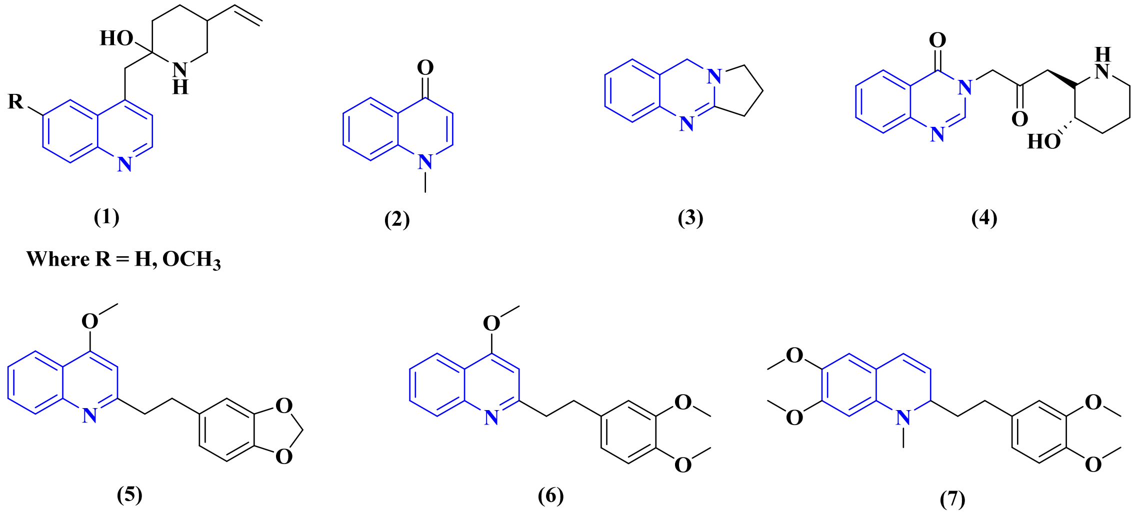
Chapter 1

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

1.1 Introduction

Quinoline is heterocyclic compound made of a pyridine heterocyclic system fused with a benzene ring.[1] Quinoline is sometimes referred to as 1-azanaphthalene and benzo[*b*]pyridine because it only have one nitrogen atom in one benzene ring and none in the other or at the ring junction.[2] High and intriguing therapeutic and pharmacological qualities are possessed by heterocycles that include a nitrogen atom.[3] Quinoline and its derivatives represent a substantial class of chemicals that garner attention because to the vast range of microbiological and pharmacological studies documented for this category.[4] Pure quinoline is a colourless, hygroscopic liquid with a strong odor and a pKa of 4.85 in water at 20°C. Quinoline is a weak tertiary base capable of forming salts with various acids and exhibits reactions akin to those of pyridine and benzene. It also demonstrates both electrophilic and nucleophilic substitution processes. It is non-toxic to humans upon oral ingestion and inhalation.[5] Quinoline can be obtained from several natural sources, naturally occurring quinoline alkaloids such as cinchona (**1**), echinopsine (**2**), vasicine (**3**), fabrifugine (**4**), cusparine (**5**), galipine (**6**), and cuspareine (**7**) were found to contain quinoline nucleus (**Figure 1**).[6-10]



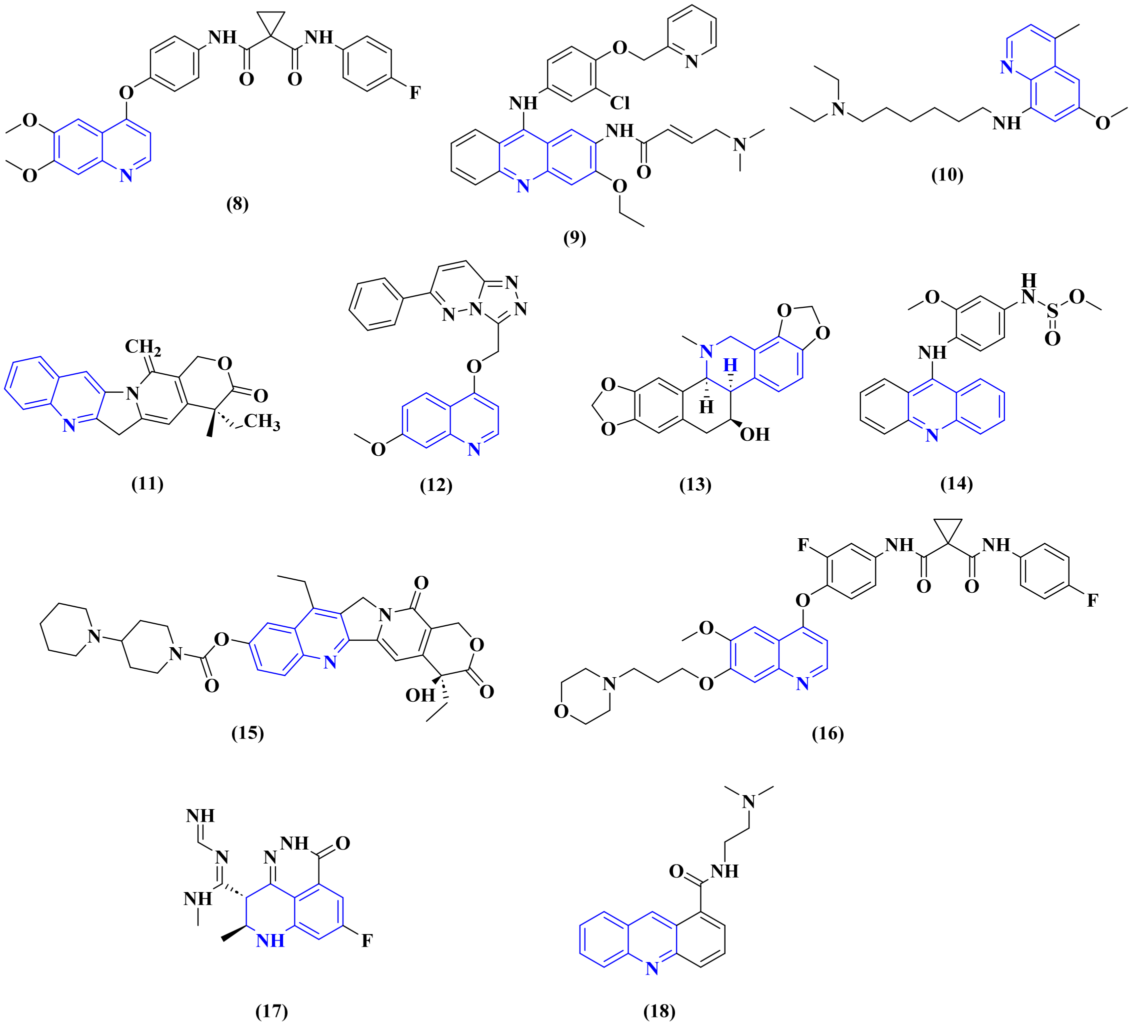
(1) **(2)** **(3)** **(4)**

Where R = H, OCH$_3$

(5) **(6)** **(7)**

Figure 1: Natural sources of quinolines.

Quinoline containing numerous drugs that are sold in the market which display a wide range of the biological activities like insecticidal (**8**),[11] antimicrobial (**9**),[12] antimalarial (**10**),[13] anti-amoebic (**11**),[14] analgesic (**12**),[15] vaso-relaxing (**13**),[16] anti-diabetic (**14**),[17] anti-mycobacterial (**15**),[18] anti-cancer (**16**),[19] anti-inflammatory (**17**),[20] anti-hypertensive (**18**),[21] and anti-HIV activities.[22] Additionally, quinoline's counterpart has demonstrated its critical potential as an anticancer agent in numerous drugs and depicted in figure **2**.[23]



(8) **(9)** **(10)**

(11) **(12)** **(13)** **(14)**

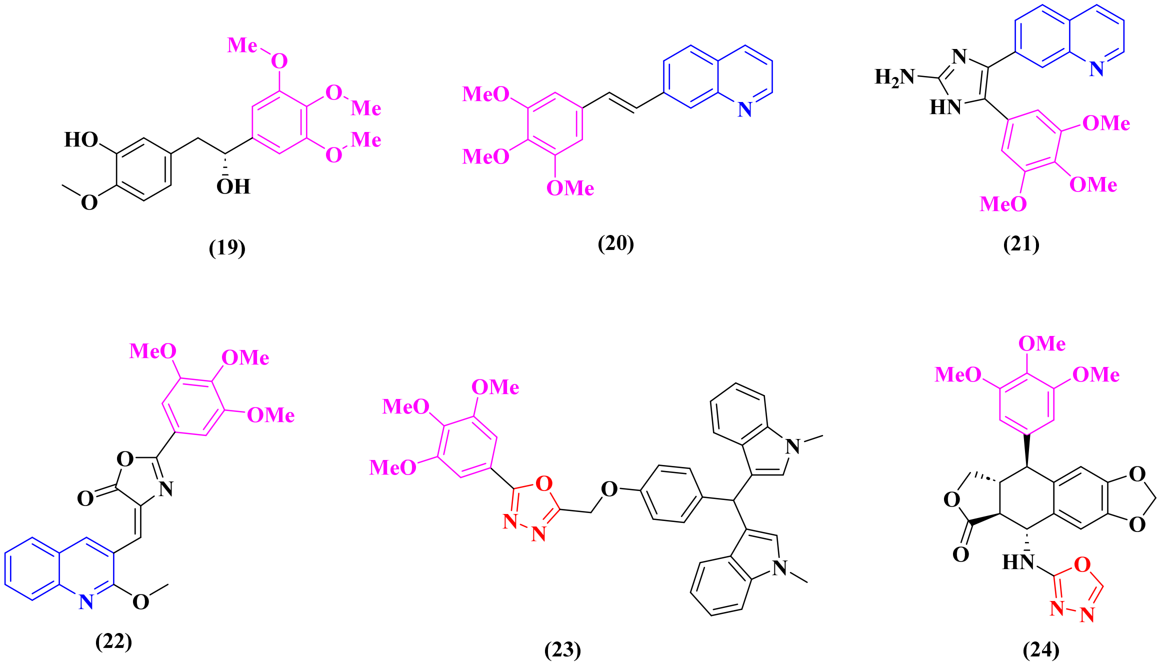
(15) **(16)**

(17) **(18)**

Figure 2: Biologically active compounds with quinoline bases.

Apart from quinoline-containing compounds, the numerous analogues of anti-cancer agent Combretastatin A-4 (CA-4, **Figure 3**) are also in clinical studies for the treatment of several tumors such as thyroid cancer, ovarian cancer, bladder cancer, colorectal cancer, and breast cancer.[24] Considering its metabolic profile and capacity to generate hydrogen bonds with receptor sites, the 1,2,4-oxadiazole nucleus

is also considered as a "bioisosteres" to the cis-alkene double bond of CA-4.[25] Some of the recent research has demonstrated that 1,2,4-oxadiazole derivatives exhibited potent anticancer activity by inhibiting a variety of targets, including combretastatin site (**19**), telomerase (**20**), histone deacetylase (HDAC) (**21**), glycogen synthase kinase-3 (GSK-3) (**22**), epidermal growth factor (EGF) (**23**), and vascular endothelial growth factor (VEGF) (**24**).[26]



(19) **(20)** **(21)**

(22) **(23)** **(24)**

Figure 3: Some CA-4 analogues of quinoline and oxadiazole core.

1.1.1 Synthetic methodologies for the substituted quinoline framework and its biological significance

The acetylation of aromatic amines (**1**) with acetic anhydride yielded the corresponding substituted *N*-phenyl acetamides (**2**), which were subsequently utilized in the synthesis of quinolines following the Meth-Cohn technique[27,28] employing the Vilsmeier formylation agent produced from the reaction of dimethyl formamide (DMF) with phosphorus oxychloride treating with **2** at 80 °C for 12 h yielded 2-chloro-3-formylquinolines **(3)** (**Figure 1.1**).

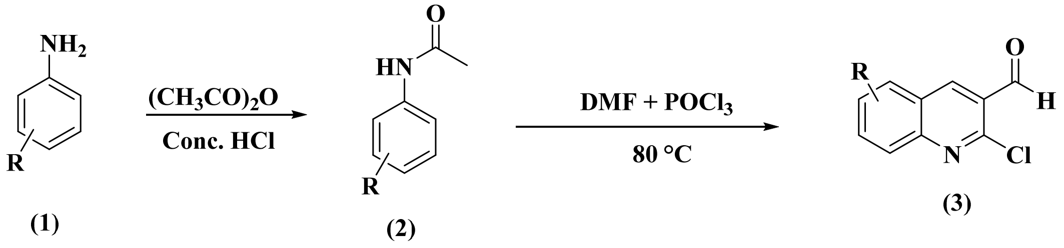


Figure 1.1

The Friedlander synthesis is a chemical process involving 2-aminobenzaldehydes (**4**) and ketones that yields quinoline derivatives (**5**). It is named in honour of German chemist Paul Friedlander. This reaction has been catalyzed by trifluoroacetic acid, toluene sulfonic acid, iodine, and various Lewis acids (**Figure 1.2**).[29]

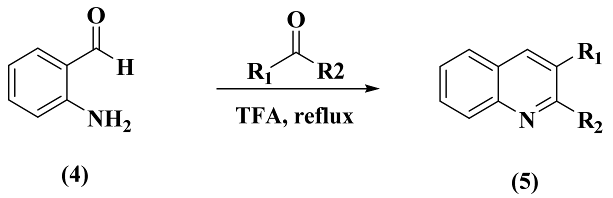


Figure 1.2

The Knorr quinoline synthesis is an intramolecular organic reaction that transforms a β-ketoanilide (**6**) into a 2-hydroxyquinoline (**7**) utilizing sulfuric acid. This reaction was initially delineated by Ludwig Knorr in 1886 (**Figure 1.3**).[30]

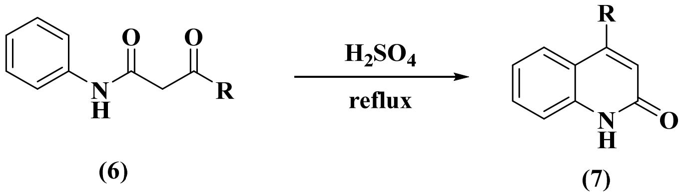
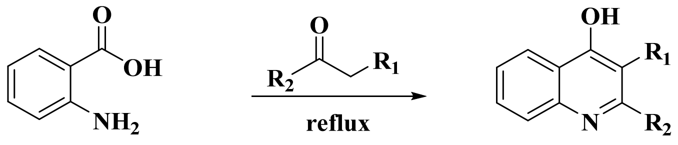


Figure 1.3

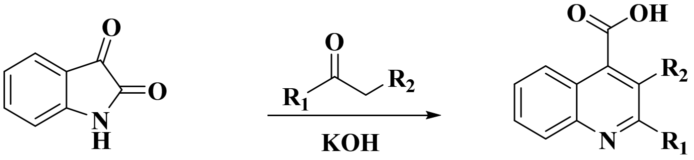
Derivatives of 2-phenyl-4-hydroxyquinoline (**9**) were produced by heating anthranilic acid (**8**) with substituted acetophenones at temperatures ranging from 120 to 130 °C. Notably, it was subsequently carried out at elevated temperatures, approximately 200 °C, the reaction exhibited distinct behaviour, possibly resulting in alterations to the product or reaction mechanism (**Figure 1.4**).[31]



(8) **(9)**

Figure 1.4

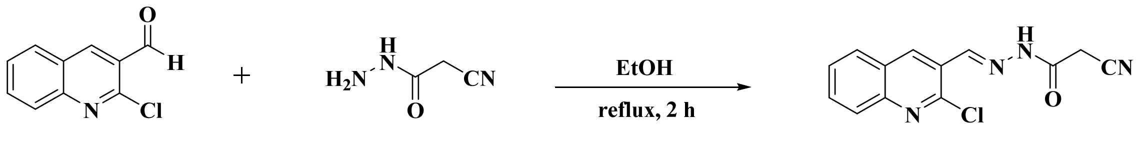
The amide bond is hydrolyzed by isatin's (**10**) interaction with a base, like potassium hydroxide, to produce a keto-acid. Although it is not often done, this intermediate can be isolated. The keto or aldehyde group in the structure will react with an amine to produce an imine and subsequently an enamine. To produce the required quinoline (**11**), the enamine will cyclize and undergo dehydration, resulting in the formation of the fused heterocyclic structure of quinolines (**Figure 1.5**).[32]



(10) **(11)**

Figure 1.5

The condensation of **3** with cyanoacetic acid hydrazide **12** in refluxing ethanol yielded the corresponding acetohydrazide. 2-cyano-*N'*-((2-oxo1,2-dihydroquinolin-3-yl)methylene)aceto-hydrazide **13** was regarded as a reactive synthetic precursor for the synthesis of many heterocycles, including pyrazoles, pyridines, coumarins, and pyrazines (**Figure 1.6**).[33]



(3) **(12)** **(13)**

Figure 1.6

The condensation of quinoline **3** with hydroxylamine hydrochloride in ethanol to get compound **14**, followed by treatment with thionyl chloride in DMF, yielded the corresponding

2-chloro-3-cyanoquinoline (**15**). The reduction of the nitrile group of compound **15** using $LiAlH_4$ in THF produced the required (2-chloroquinolin-3-yl)methanamine (**16**) with a favourable yield (**Figure 1.7**).[34]

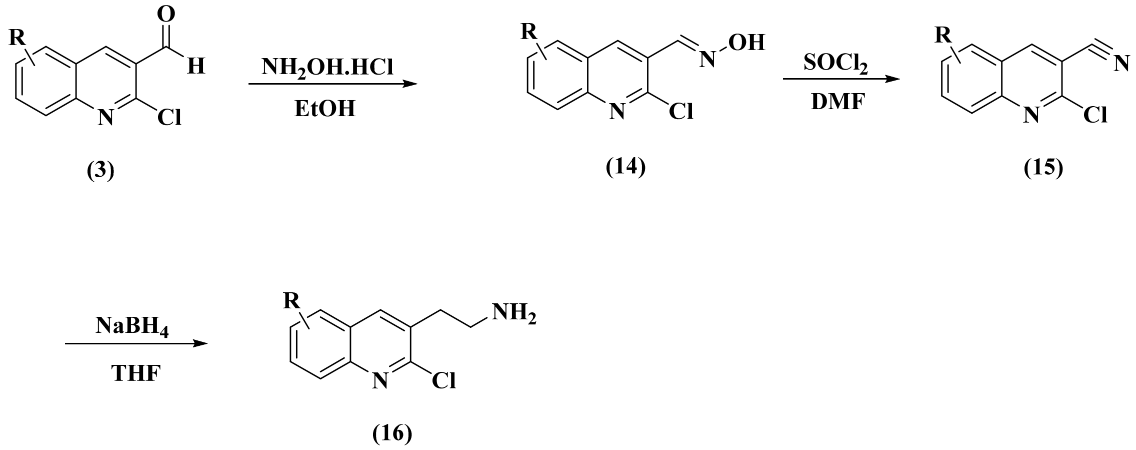


Figure 1.7

The condensation of **3** with substituted anilines **1** in acetone yielded the corresponding 1-(2-chloro-quinolin-3-yl)-*N*-(substituted phenyl)methanamine **17**.[35] Schiff base **18** was produced through the condensation of quinoline **3** with phenyl hydrazine utilizing natural surfactant (Acacia pods) over a brief reaction period.[36] The condensation of quinoline **3** with hydrazine hydrate yielded 2-chloro-3-(hydrazonomethyl)quinoline **19**, which subsequently reacted with both 2-naphthaldehyde and 1*H*-indole-3-carbaldehyde through condensation in refluxing ethanol to give the target hydrazono-quinolines **20** and **21**, respectively shown in **Figure 1.8**.[34]

The reaction of quinoline (**3**) with morpholine, facilitated by a catalytic quantity of dimethyl aminopyridine, yielded 2-morpholinoquinoline-3-carbaldehydes (**22**). Subsequent refluxing of compound **22** with 2-amino-5-methyl-thiophene-3-carbonitrile (**23**) in isopropyl alcohol, followed by the reduction of the resultant imine (C=NH) bond using sodium borohydride in methanol, yielded substituted 3-cyano-5-methyl-2-(((2-morpholinoquinolin-3-yl)methyl)amino)-thiophenes **24** (**Figure 1.9**). The 6-bromo derivative of compound **24** demonstrated the most significant antibacterial action against *Escherichia coli, Staphylococcus aureus*, and *Bacillus spizizenii*, as well as antifungal activity against *Aspergillus niger, Aspergillus brasiliensis,* and *Curvularia lunata*.[37]

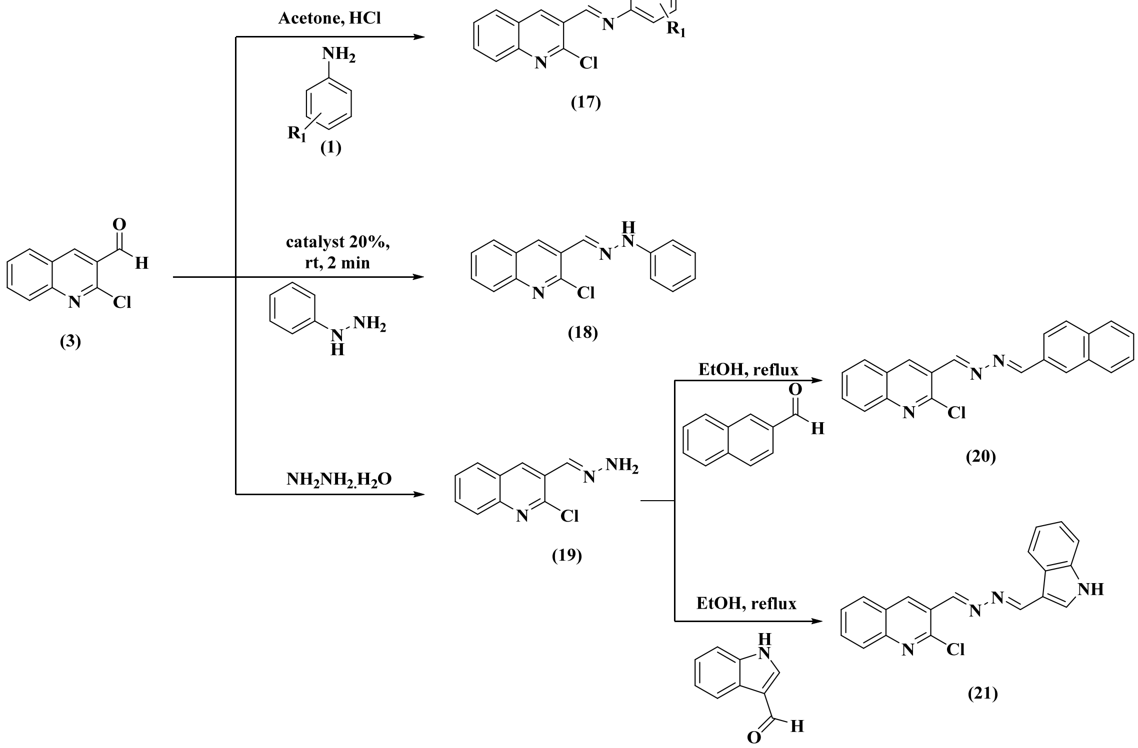


Figure 1.8

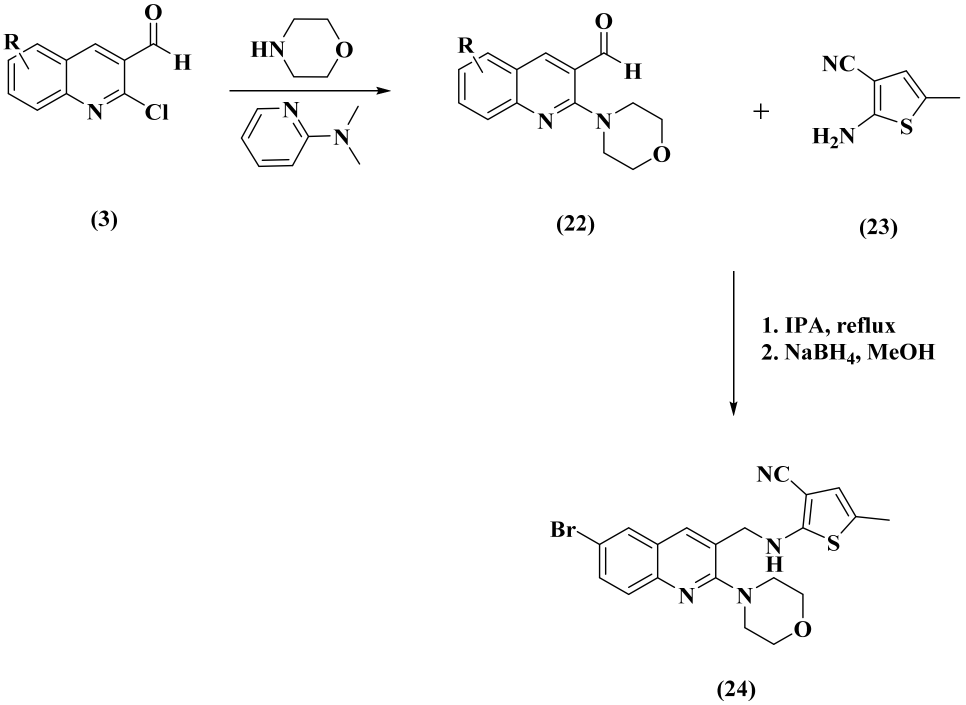


Figure 1.9

Compound **3** was reduced using $NaBH_4$ to get the corresponding alcohols **25**. This was succeeded by bromination in dichloromethane (DCM) utilizing phosphorus tribromide (PBr_3) to yield the bromo methylene intermediate **26**. The compound **26** was subsequently reacted with 2-aryl-2*H*-1,2,4-triazol-3(4*H*)-ones (**27**) in the presence of anhydrous K_2CO_3 to get the compounds 4-[(2-chloro-6-substituted quinolin-3-yl)methyl]-2-aryl-2*H*-1,2,4-triazol-3(4*H*)-one **28**. Analogous sequences of procedures were executed subsequent to the introduction of the hydroxyl group at the second position of quinoline in compounds **3** to synthesize compounds **29**. The compound **29** was utilized to synthesize another series of compounds, specifically 4-[(2-hydroxy-6-substituted-quinolin-3-yl)methyl].-2-aryl-2*H*-1,2,4-triazol-3(4*H*)- one **32** as depicted in **Figure 1.10.**[38,39] The most potent molecules with MIC90 value in the range 0.070–0.080 µM against anti-tuberculosis activity. The quinoline-triazole hybrid found within this framework represents a potentially viable option for the development of novel anticancer and antitubercular medicines, constructed in accordance with structure-activity relationships (SAR).

The condensation of quinolines **3** with 2-oxo-2*H*-chromene-3-carbohydrazide (**32**) in DMF, supplemented with catalytic amounts of glacial acetic acid, yielded the corresponding Schiff bases **33**. Compounds **33** exhibit antifungal action against *A. niger* and *A. clavatus bacteria* (**Figure 1.11**).[40]

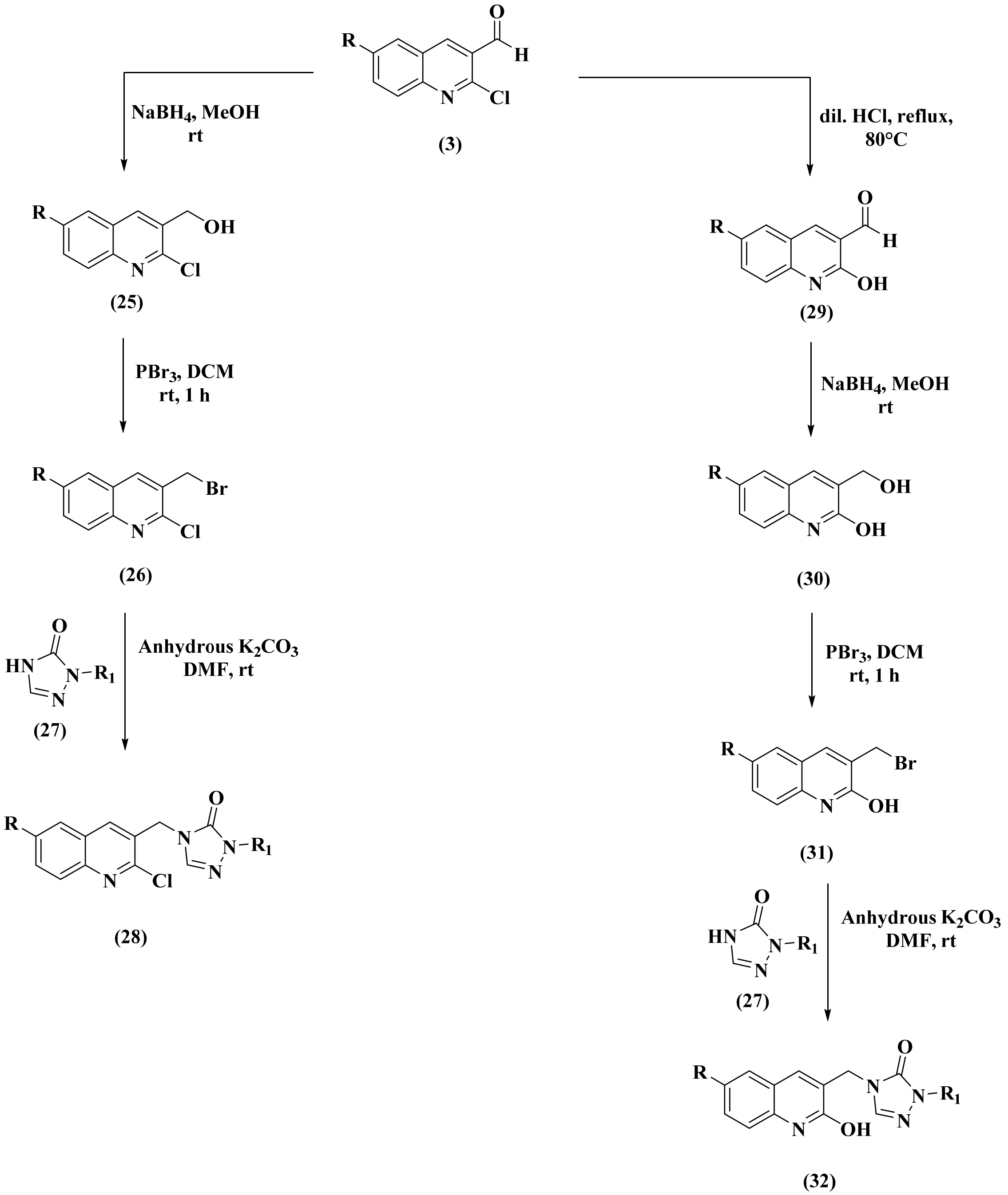


Figure 1.10

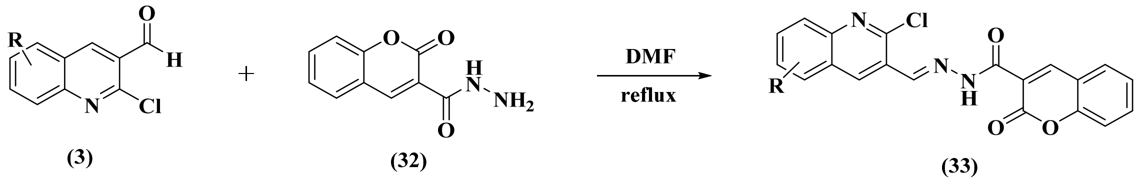
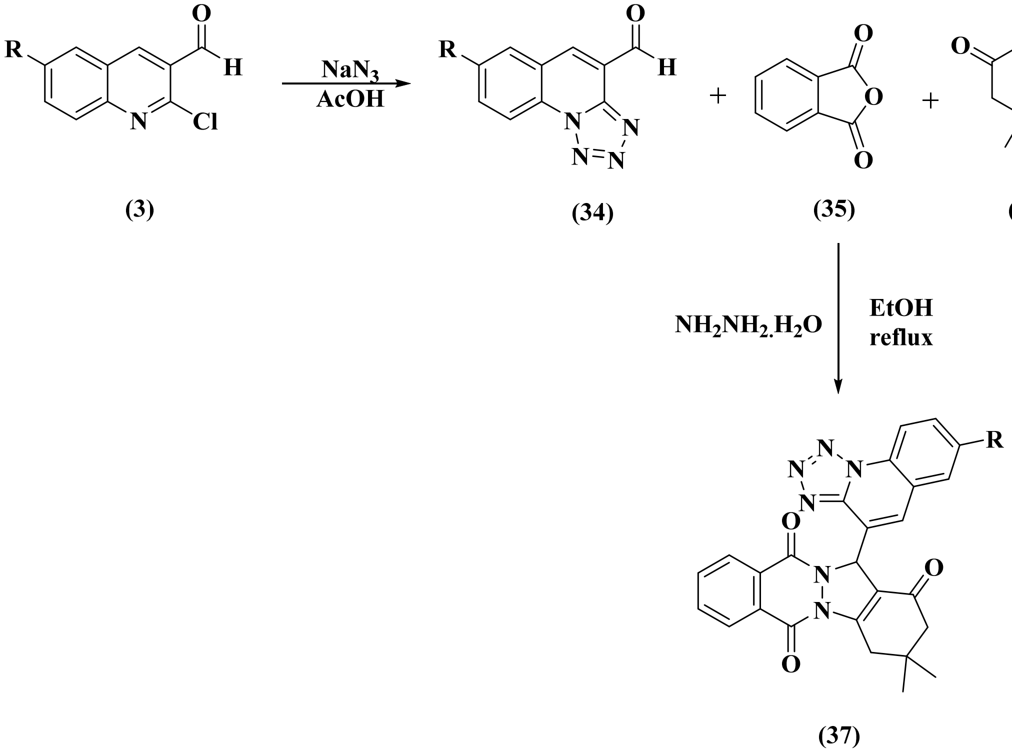
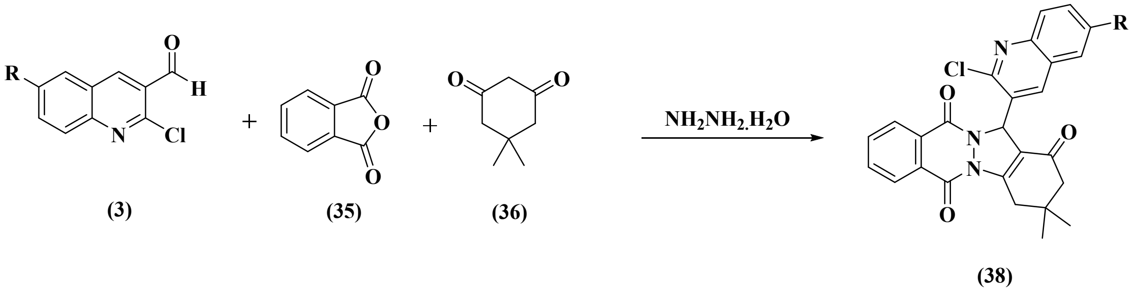


Figure 1.11

Tetrazolo[1,5-*a*]quinoline-4-carbaldehydes **34** was synthesized via the reaction of 2-chloroquinoline-3-carbaldehydes **3** with sodium azide in acetic acid. The multicomponent reaction involving phthalic anhydride (**35**), 5,5-dimethylcyclohexane-1,3-dione (**36**), and either quinolines **3** or tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **34**, conducted in refluxing ethanol with Pr_x-$CoFe_{2-x}O_4$ (5 mol%) nanoparticles as a catalyst, produced tetrazolo[1,5-*a*]quinolinyl-indazolo[1,2-*b*]phthalazine-triones **(37)** and quinolinyl-indazolo[1,2-*b*]phthalazine-triones (**38)**, respectively (**Scheme 1.12**). The synthesized chemicals **37** and **38** are regarded as inhibitors of amalgamation biofilm formation. Quinolines 6-methoxy derivative **37e** (IC_{50} = 46.5 μM), 6-H **38a** (IC_{50} = 30 μM) and 6-methyl derivative **38b** (IC_{50} = 46.5 μM), and exhibit greater antibacterial potency than the antibiotic standard ciprofloxacin.[41]



Where, R = H, CH_3, Br, Cl, NO_2, OCH_3



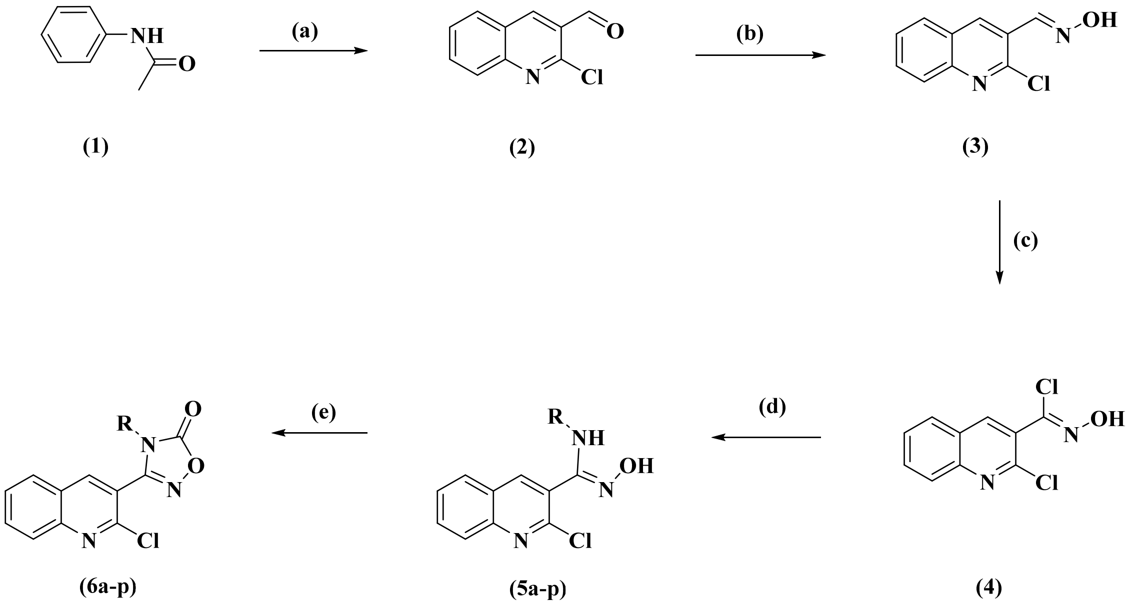
Where, R = H, CH_3, Br, Cl, NO_2, OCH_3

Figure 1.12

1.2 Results and Discussion

1.2.1 Chemistry

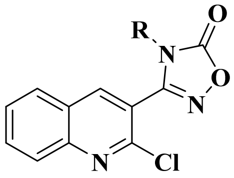
The synthesis of quinoline derivatives containing substituted 1,2,4-oxadiazol-5(4*H*)-one **(6a-p)** as a potent anticancer agent is portrayed in scheme-1. The required intermediate 2-chloroquinoline-3-carbaldehyde (**2**) was prepared from acetanilide (**1**) by reacting it with Vilsmeier–Haack reagent prepared from DMF and $POCl_3$ at 80°C in accordance with the method described in the literature.[42] The reaction of intermediate **2** with hydroxylamine hydrochloride in methanol, and Na_2CO_3 in water at ambient temperature yielded quinoline aldoxime (**3**) using reported method.[43] Further reaction of quinoline aldoxime (**3**) is carried out with *N*-chlorosuccinimide (NCS) in DMF at 0°C, followed by ambient temperature to achieve (*Z*)-2-chloro-*N*-hydroxyquinoline-3-carbimidoyl chloride (**4**). Compounds **5a-p** was prepared from intermediate **4** by reaction with substituted aniline in H_2O:THF(1:1) as a solvent, and $NaHCO_3$ at 60°C using reported protocoals.[44] Compounds **5a-p** were then treated with 1,1'-carbonyldiimidazole (CDI) in 1,4-dioxane at 100 °C to produce the required 1,2,4-oxadiazol-5(4*H*)-one derivatives **(6a-p)**.[45]



Reaction condition: a) DMF, $POCl_3$, 80°C, 24 h; b) Hydroxylamine hydrochloride, Na_2CO_3, MeOH/water (2:1), rt, 1 h; c) NCS, DMF, rt, 12 h; d) THF/H_2O (1:1), substituted aniline, $NaHCO_3$, 60°C, 4 h; e) CDI, 1,4-Dioxane, 100°C, 2 h;

Scheme 1: Synthesis of the quinoline containing oxadiazole derivatives.

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



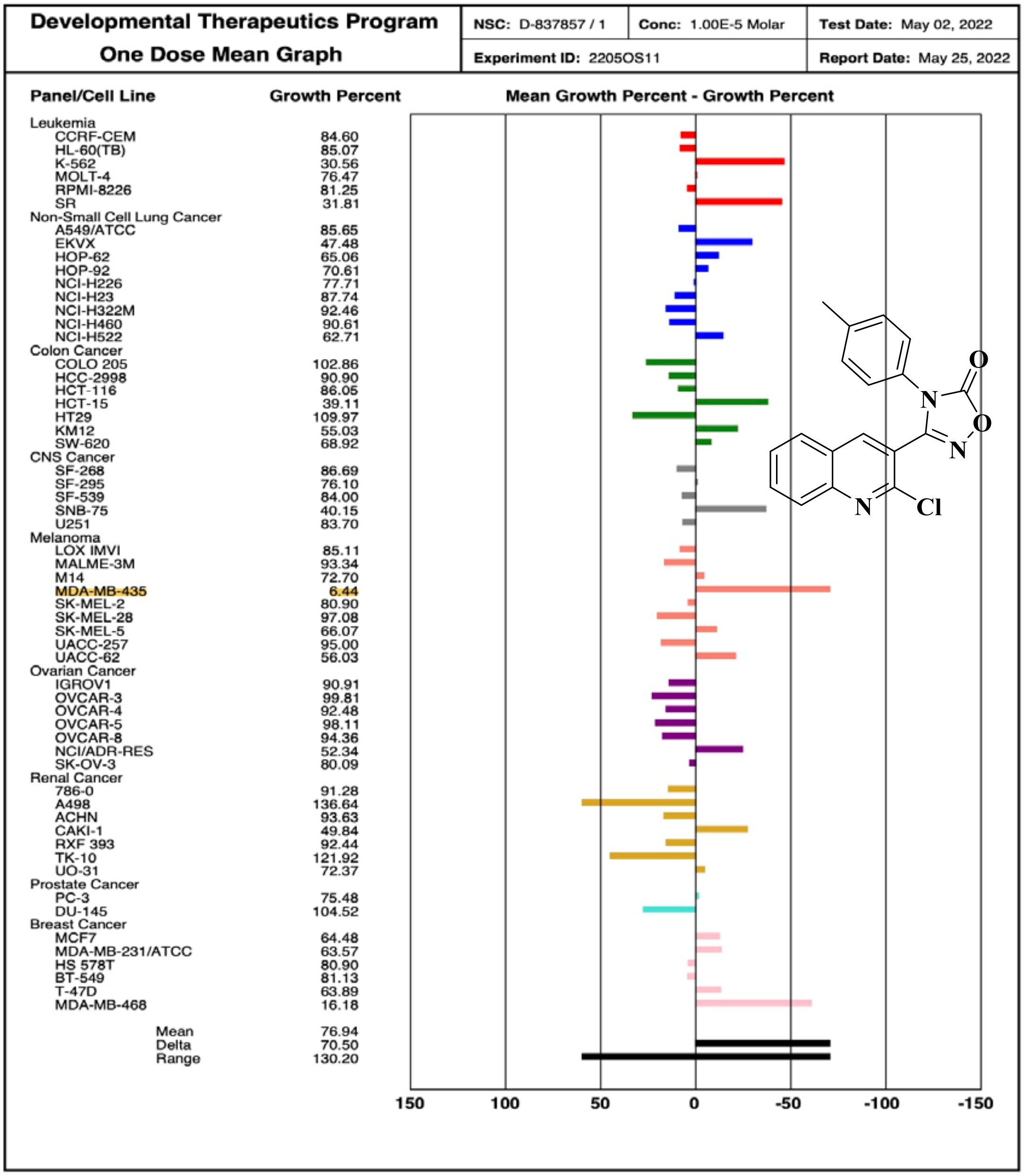
Compounds	R	Molecular Weight	Molecular Formula	Yield (%)	Melting Point (°C)
6a	4-OCH_3-C_6H_4-	353.762	$C_{18}H_{12}ClN_3O_3$	94	137-139
6b	C_6H_5-	323.736	$C_{17}H_{10}ClN_3O_2$	92	152-154
6c	4-Br-C_6H_4-	402.632	$C_{17}H_9BrClN_3O_2$	96	170-172
6d	4-CH_3-C_6H_4-	337.76	$C_{18}H_{12}ClN_3O_2$	92	126-128
6e	4-Cl-C_6H_4-	358.16	$C_{17}H_9Cl_2N_3O_2$	95	164-166
6f	2-$OCH_3C_6H_4$-	353.76	$C_{18}H_{12}ClN_3O_3$	95	138-140

6g	2-$C_{10}H_8$-	373.80	$C_{21}H_{12}ClN_3O_2$	91	160-162
6h	4-F-C_6H_4-	371.73	$C_{17}H_9ClFN_3O_2$	80	159-161
6i	3-Cl-C_6H_4-	358.16	$C_{17}H_9Cl_2N_3O_2$	92	160-162
6j	1-$C_{10}H_8$-	373.80	$C_{21}H_{12}ClN_3O_2$	98	155-157
6k	2,4-CH_3-C_6H_3-	351.79	$C_{19}H_{14}ClN_3O_2$	96	130-132
6l	2,6-CH_3-C_6H_3-	351.79	$C_{19}H_{14}ClN_3O_2$	97	134-136
6m	2,3-CH_3-C_6H_3-	351.79	$C_{19}H_{14}ClN_3O_2$	97	120-122
6n	2-CH_3-C_6H_4-	337.76	$C_{18}H_{12}ClN_3O_2$	96	129-131
6o	2,5-CH_3-C_6H_3-	351.79	$C_{19}H_{14}ClN_3O_2$	95	125-127
6p	3,4,5-OCH_3-C_6H_2-	413.81	$C_{20}H_{16}ClN_3O_5$	98	174-176

1.3 Biological Activity

The newly synthesized samples of quinoline containing substituted 1,2,4-oxadiazol-5(4*H*)-one **(6a-p)** were analyzed by Developmental Therapeutics Program, that falls under Division of Cancer Treatment & Diagnosi (DCTD) of National Cancer Institute, National Institute of Health (NIH), Germantown, USA. All sixteen novel derivatives (**6a-p**) were selected for the *In vitro* cell-based screening at a single dose is the first step in the search for the cytotoxic activity. Out of them compound **6d**, **6g**, **6j**, **6o** were showing moderate efficacy to inhibit the cell's growth in different types of cancer's sub cell-lines. The sample data are represented as One Dose Mean Graph showing the growth of cancerous cell lines under the effect of 1.00E-5 molar concentration.[46]

Compound **6d** (sample no: **837857-2205OS11**) showed efficacy to inhibit the cell's growth in Melanoma Cell Line: MDA-MB 435 and Breast Cancer Cell Line: MDA-MB-468. Significantly, the samples have evidently reported the promising anti-cancer property by having the depreciable cell growth in their least factor concentration that makes them the lead compounds to be explored for cancer therapeutics.



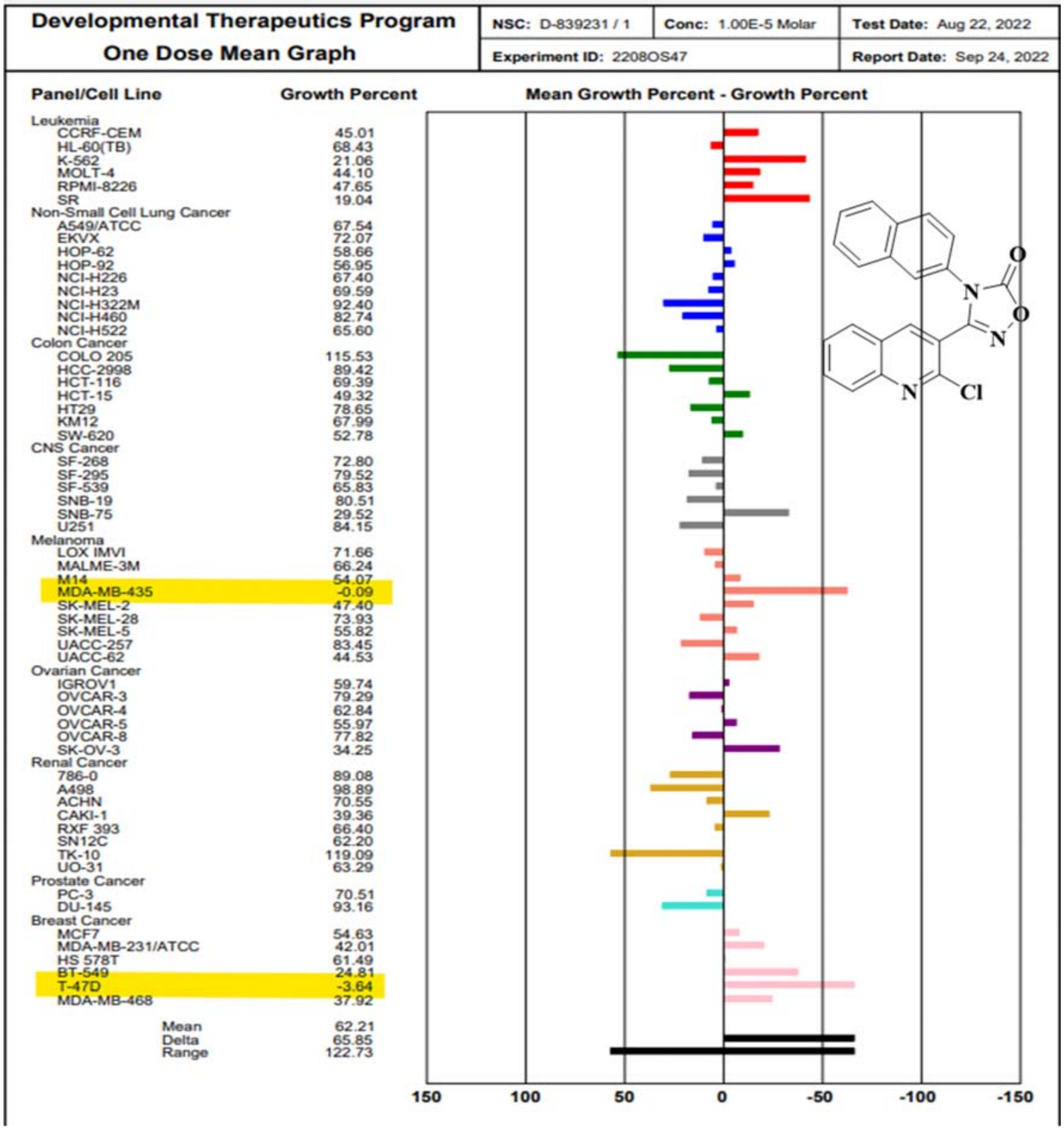
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-837857 / 1
Conc: 1.00E-5 Molar
Test Date: May 02, 2022
Experiment ID: 2205OS11
Report Date: May 25, 2022

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	84.60
HL-60(TB)	85.07
K-562	30.56
MOLT-4	76.47
RPMI-8226	81.25
SR	31.81
Non-Small Cell Lung Cancer	
A549/ATCC	85.65
EKVX	47.48
HOP-62	65.06
HOP-92	70.61
NCI-H226	77.71
NCI-H23	87.74
NCI-H322M	92.46
NCI-H460	90.61
NCI-H522	62.71
Colon Cancer	
COLO 205	102.86
HCC-2998	90.90
HCT-116	86.05
HCT-15	39.11
HT29	109.97
KM12	55.03
SW-620	68.92
CNS Cancer	
SF-268	86.69
SF-295	76.10
SF-539	84.00
SNB-75	40.15
U251	83.70
Melanoma	
LOX IMVI	85.11
MALME-3M	93.34
M14	72.70
MDA-MB-435	6.44
SK-MEL-2	80.90
SK-MEL-28	97.08
SK-MEL-5	66.07
UACC-257	95.00
UACC-62	56.03
Ovarian Cancer	
IGROV1	90.91
OVCAR-3	99.81
OVCAR-4	92.48
OVCAR-5	98.11
OVCAR-8	94.36
NCI/ADR-RES	52.34
SK-OV-3	80.09
Renal Cancer	
786-0	91.28
A498	136.64
ACHN	93.63
CAKI-1	49.84
RXF 393	92.44
TK-10	121.92
UO-31	72.37
Prostate Cancer	
PC-3	75.48
DU-145	104.52
Breast Cancer	
MCF7	64.48
MDA-MB-231/ATCC	63.57
HS 578T	80.90
BT-549	81.13
T-47D	63.89
MDA-MB-468	16.18
Mean	76.94
Delta	70.50
Range	130.20

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

Compound **6g** (sample no: **839231-2208OS47**) showed its biological impact by inhibiting the cells' growth in Melanoma Cell Line: MDA-MB 435 and in Breast Cancer Cell Line: T- 47D.



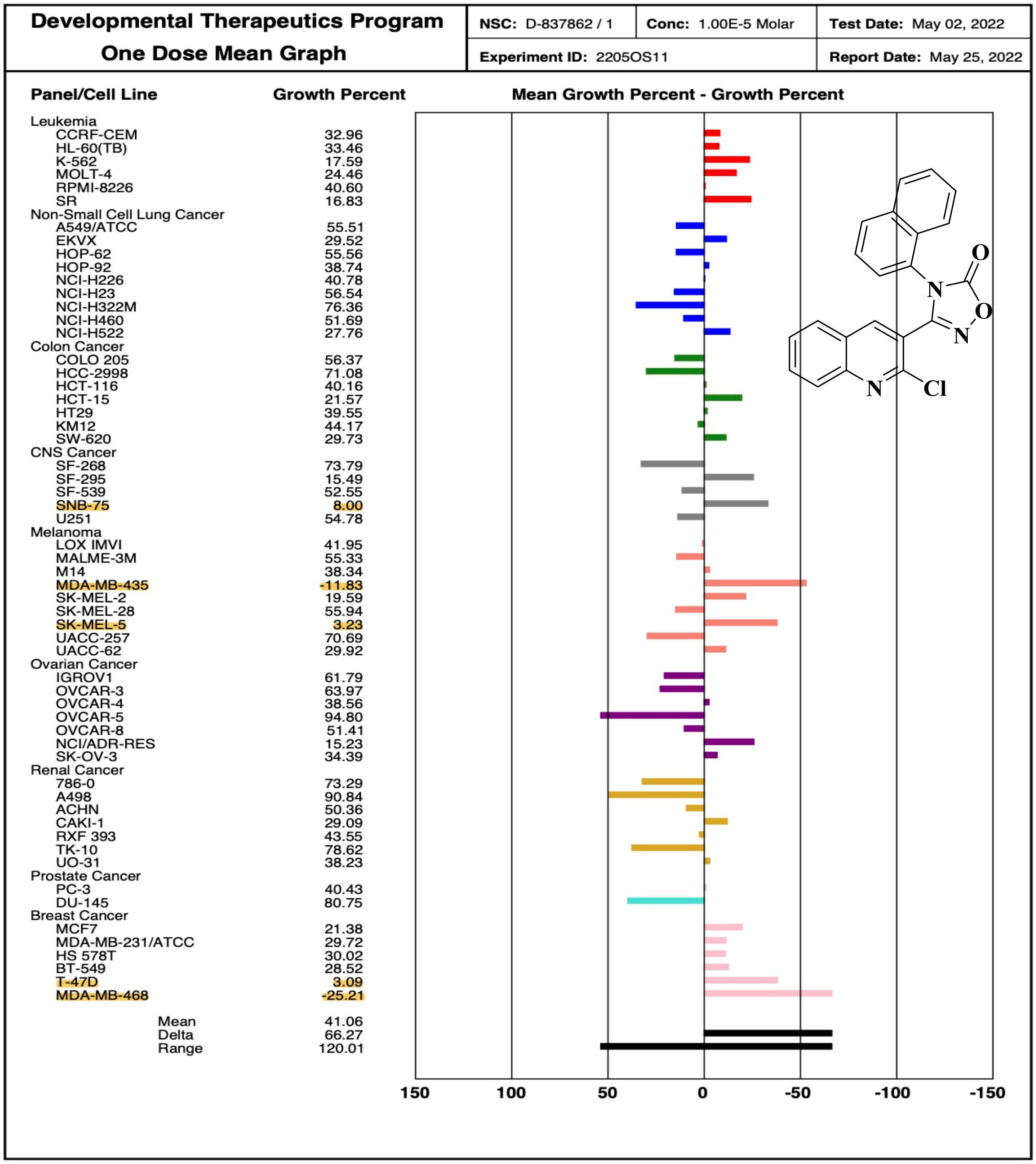
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-839231 / 1
Conc: 1.00E-5 Molar
Test Date: Aug 22, 2022
Experiment ID: 2208OS47
Report Date: Sep 24, 2022

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	45.01
HL-60(TB)	68.43
K-562	21.06
MOLT-4	44.10
RPMI-8226	47.65
SR	19.04
Non-Small Cell Lung Cancer	
A549/ATCC	67.54
EKVX	72.07
HOP-62	58.66
HOP-92	56.95
NCI-H226	67.40
NCI-H23	69.59
NCI-H322M	92.40
NCI-H460	82.74
NCI-H522	65.60
Colon Cancer	
COLO 205	115.53
HCC-2998	89.42
HCT-116	69.39
HCT-15	49.32
HT29	78.65
KM12	67.99
SW-620	52.78
CNS Cancer	
SF-268	72.80
SF-295	79.52
SF-539	65.83
SNB-19	80.51
SNB-75	29.52
U251	84.15
Melanoma	
LOX IMVI	71.66
MALME-3M	66.24
M14	54.07
MDA-MB-435	-0.09
SK-MEL-2	47.40
SK-MEL-28	73.93
SK-MEL-5	55.82
UACC-257	83.45
UACC-62	44.53
Ovarian Cancer	
IGROV1	59.74
OVCAR-3	79.29
OVCAR-4	62.84
OVCAR-5	55.97
OVCAR-8	77.82
SK-OV-3	34.25
Renal Cancer	
786-0	89.08
A498	98.89
ACHN	70.55
CAKI-1	39.36
RXF 393	66.40
SN12C	62.20
TK-10	119.09
UO-31	63.29
Prostate Cancer	
PC-3	70.51
DU-145	93.16
Breast Cancer	
MCF7	54.63
MDA-MB-231/ATCC	42.01
HS 578T	61.49
BT-549	24.81
T-47D	-3.64
MDA-MB-468	37.92
Mean	62.21
Delta	65.85
Range	122.73

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

Compound **6j** (sample no: **837862-2205OS11**) showed its biological impact by inhibiting the cells' growth in CNS (Central Nervous System) Cancer Cell Line: SNB-75, in Melanoma Cell Line: MDA-MB 435 & SK-MEL 5 and in Breast Cancer Cell Line: T- 47D & MDA-MB-468.



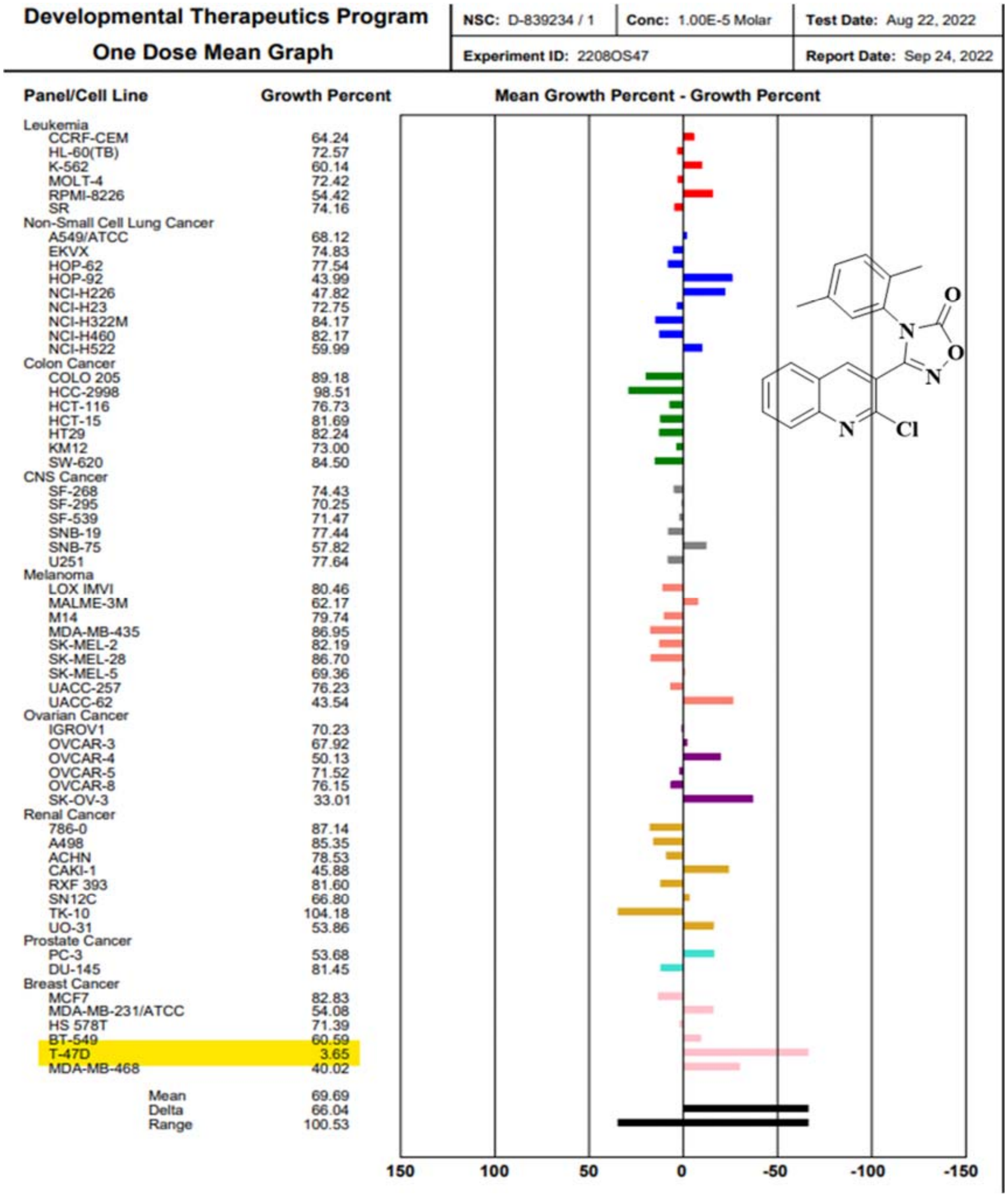
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-837862 / 1
Conc: 1.00E-5 Molar
Test Date: May 02, 2022
Experiment ID: 2205OS11
Report Date: May 25, 2022

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	32.96
HL-60(TB)	33.46
K-562	17.59
MOLT-4	24.46
RPMI-8226	40.60
SR	16.83
Non-Small Cell Lung Cancer	
A549/ATCC	55.51
EKVX	29.52
HOP-62	55.56
HOP-92	38.74
NCI-H226	40.78
NCI-H23	56.54
NCI-H322M	76.36
NCI-H460	51.69
NCI-H522	27.76
Colon Cancer	
COLO 205	56.37
HCC-2998	71.08
HCT-116	40.16
HCT-15	21.57
HT29	39.55
KM12	44.17
SW-620	29.73
CNS Cancer	
SF-268	73.79
SF-295	15.49
SF-539	52.55
SNB-75	8.00
U251	54.78
Melanoma	
LOX IMVI	41.95
MALME-3M	55.33
M14	38.34
MDA-MB-435	-11.83
SK-MEL-2	19.59
SK-MEL-28	55.94
SK-MEL-5	3.23
UACC-257	70.69
UACC-62	29.92
Ovarian Cancer	
IGROV1	61.79
OVCAR-3	63.97
OVCAR-4	38.56
OVCAR-5	94.80
OVCAR-8	51.41
NCI/ADR-RES	15.23
SK-OV-3	34.39
Renal Cancer	
786-0	73.29
A498	90.84
ACHN	50.36
CAKI-1	29.09
RXF 393	43.55
TK-10	78.62
UO-31	38.23
Prostate Cancer	
PC-3	40.43
DU-145	80.75
Breast Cancer	
MCF7	21.38
MDA-MB-231/ATCC	29.72
HS 578T	30.02
BT-549	28.52
T-47D	3.09
MDA-MB-468	-25.21
Mean	41.06
Delta	66.27
Range	120.01

Figure 3. Anti-cancer activity of molecule **6j** as a mean graph plot of GI_{50} values against NCI-60 cell line panels.

Compound **6o** (sample no: **839234-2208OS47**) showed its biological impact by inhibiting the cells' growth in Breast Cancer Cell Line: T- 47D.



Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-839234 / 1 | **Conc:** 1.00E-5 Molar | **Test Date:** Aug 22, 2022

Experiment ID: 2208OS47 | **Report Date:** Sep 24, 2022

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	64.24
HL-60(TB)	72.57
K-562	60.14
MOLT-4	72.42
RPMI-8226	54.42
SR	74.16
Non-Small Cell Lung Cancer	
A549/ATCC	68.12
EKVX	74.83
HOP-62	77.54
HOP-92	43.99
NCI-H226	47.82
NCI-H23	72.75
NCI-H322M	84.17
NCI-H460	82.17
NCI-H522	59.99
Colon Cancer	
COLO 205	89.18
HCC-2998	98.51
HCT-116	76.73
HCT-15	81.69
HT29	82.24
KM12	73.00
SW-620	84.50
CNS Cancer	
SF-268	74.43
SF-295	70.25
SF-539	71.47
SNB-19	77.44
SNB-75	57.82
U251	77.64
Melanoma	
LOX IMVI	80.46
MALME-3M	62.17
M14	79.74
MDA-MB-435	86.95
SK-MEL-2	82.19
SK-MEL-28	86.70
SK-MEL-5	69.36
UACC-257	76.23
UACC-62	43.54
Ovarian Cancer	
IGROV1	70.23
OVCAR-3	67.92
OVCAR-4	50.13
OVCAR-5	71.52
OVCAR-8	76.15
SK-OV-3	33.01
Renal Cancer	
786-0	87.14
A498	85.35
ACHN	78.53
CAKI-1	45.88
RXF 393	81.60
SN12C	66.80
TK-10	104.18
UO-31	53.86
Prostate Cancer	
PC-3	53.68
DU-145	81.45
Breast Cancer	
MCF7	82.83
MDA-MB-231/ATCC	54.08
HS 578T	71.39
BT-549	60.59
T-47D	3.65
MDA-MB-468	40.02
Mean	69.69
Delta	66.04
Range	100.53

Figure 4. Anti-cancer activity of molecule **6o** as a mean graph plot of GI_{50} values against NCI-60 cell line panels.

1.4 Conclusion

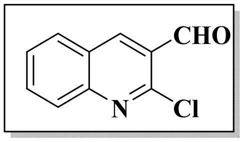
A series of hybrid quinoline derivatives featuring substituted oxadiazole-5(4*H*)-one (**6a-p**) was produced and characterized using NMR, mass spectrometry, FTIR, and LCMS investigation. All produced compounds were assessed for their anticancer characteristics. Among the produced compounds, the inclusion of the electron donating group (CH_3) lies on the *para* position in compound **6d** showing moderate anticancer activity. A β-naphthyl ring system in compound **6g** showed good activity compare to **6d**. Compound **6j** having α-naphthyl as a substitution exhibited excellent efficacy against five cell lines (CNS Cancer Cell Line: SNB-75, in Melanoma Cell Line: MDA-MB 435 & SK-MEL 5 and in Breast Cancer Cell Line: T-47D & MDA-MB-468), and Compound **6o** having two methyl on *ortho* and *meta*, respectively exhibited modest anticancer activity.

1.5 Experimental Section

1.5.1 Chemistry

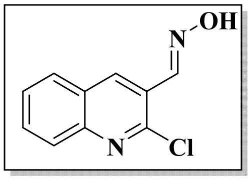
The open-capillary method was used to determine all the melting points on an electrothermal device, and the results are uncorrected. Compounds were detected in thin-layer chromatography with UV light at 254 nm, 365 nm and/or with iodine vapour on precoated silica gel 60 F254 (Merck). IR spectra were recorded using Shimadzu FTIR spectrometer with ATR method. A Bruker AVANCE III (400 MHz) spectrometer was used to capture ^1H 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. An ACQUITY LCMS ultra perfomence system was used to capture purity and mass. All reagents purchased from Sigma-Aldrich, Alfa Aesar, Loba Chemie, Molychem, and Sisco Research Laboratories Pvt. Ltd. (SRL) and used without further purification.

Procedure for the synthesis of 2-chloroquinoline-3-carbaldehyde (2):



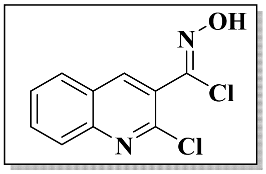
$POCl_3$ (9 mL, 98.28 mmol) was added dropwise from an addition funnel to DMF (2.7 mL, 34.65 mmol) taken in a round bottom flask while maintaining the temperature at 0–5 °C. The resulting mixture was allowed to stir for about 5 min. To the resulting solution acetanilide (**1**, 1.4 g, 10.37 mmol) was added in small portions. The obtained solution was heated at 80 °C for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and poured onto crushed ice, and pale-yellow precipitate was obtained. The precipitate was collected by filtration with suction and washed thoroughly with water to remove all the acid and dried. The crude precipitate was then recrystallized from ethyl acetate to obtain an analytically pure compound. Yield: 0.84 gm, 60%, mp: 147–149 °C. (reported mp: 148-150).[42]

Procedure for the synthesis of (*E*)-2-chloroquinoline-3-carbaldehyde oxime (3):



To a stirred solution of 2-chloroquinoline-3-carbaldehyde (**2**, 500 mg, 2.61 mmol) in methanol (30 mL) and water (8 mL), $NH_2OH.HCl$ (261 mg, 3.76 mmol) was added in portions. To the resulting mixture, a solution of Na_2CO_3 (331.77 mg, 3.13 mmol) in water (8 mL) was added in a dropwise manner and the mixture was allowed to stir at rt for an additional 1 h. After completion, of the reaction (monitored by TLC), water (30 mL) was added and the formed precipitate was filtered with suction and washed with water to give the title compound a white solid, which was then recrystallized from methanol to obtain an analytically pure compound. Yield: 0.49 gm, 98%, mp: 130-132 °C (reported mp: 130-132).[43]

Procedure for synthesis of (*Z*)-2-chloro-N-hydroxyquinoline-3-carbimidoyl chloride (4):

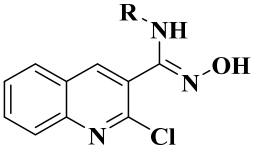


To a well stirred solution of (*E*)-2-chloroquinoline-3-carbaldehyde oxime (**3**, 500 mg, 2.42 mmol) in DMF (10 mL), *N*-Chlorosuccinimide (NCS) (323.11 mg, 2.42 mmol) was added in a small portion while maintaining the temperature at 0 °C. The mixture was then allowed to attain rt and stirred for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured onto ice-cold water (30 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to dryness to provide the title compound as a white solid, the obtained residue was recrystallized from Etc to give an analytically pure compound. Yield: 0.46 gm, 92%, mp: 146-148 °C (reported mp: 146-148).[44]

General procedure for the synthesis of compound (5a-p):[44]

To a well stirred mixture of (*Z*)-2-chloro-*N*-hydroxyquinoline-3-carbimidoyl chloride (**4**, 0.83 mmol) and substituted aniline (0.83 mmol) in H_2O:THF (1:1, 12 mL), $NaHCO_3$ (1 mmol) was added in portions and the mixture was stirred at 60 °C for 4 h, after completion of the reaction (monitored by TLC), the reaction mixture was then poured onto crushed ice. The precipitate thus appeared was collected by filtration with suction and washed with water, and dried. The obtained residue was slurry washed with diethyl ether to give title compounds **(5a-p)**, which are sufficiently pure to use in the next step.

Table 2: Physicochemical characteristics of the quinoline derivatives (**5a-p**).

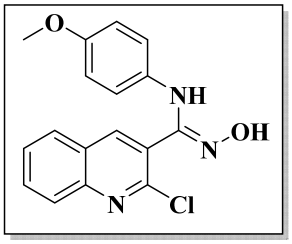


Compound	R	Molecular Weight	Molecular Formula	Yield (%)	Melting Point (°C)
5a	4-OCH3-C6H4-	327.77	$C_{17}H_{14}ClN_3O_2$	92	182-184
5b	C6H5-	297.74	$C_{16}H_{12}ClN_3O$	88	146-148
5c	4-Br-C6H4-	376.64	$C_{16}H_{11}BrClN_3O$	90	172-174
5d	4-CH3-C6H4-	311.77	$C_{17}H_{14}ClN_3O$	91	166-168
5e	4-Cl-C6H4-	332.18	$C_{16}H_{11}Cl_2N_3O$	90	178-180
5f	2-OCH3C6H4-	327.77	$C_{17}H_{14}ClN_3O_2$	94	174-176
5g	2-C10H8-	347.80	$C_{18}H_{16}ClN_3O$	60	192-194
5h	4-F-C6H4-	315.73	$C_{16}H_{11}ClFN_3O$	86	182-184
5i	3-Cl-C6H4-	332.18	$C_{16}H_{11}Cl_2N_3O$	88	177-179
5j	1-C10H8-	347.80	$C_{18}H_{16}ClN_3O$	97	167-169
5k	2,4-CH3-C6H3-	325.80	$C_{18}H_{16}ClN_3O$	94	183-185

5l	2,6-CH_3-C_6H_3-	325.80	$C_{18}H_{16}ClN_3O$	96	183-185
5m	2,3-CH_3-C_6H_3-	298.73	$C_{18}H_{16}ClN_3O$	96	177-179
5n	2-CH_3-C_6H_4-	311.77	$C_{17}H_{14}ClN_3O$	94	169-171
5o	2,5-CH_3-C_6H_3-	339.78	$C_{18}H_{16}ClN_3O$	96	186-188
5p	3,4,5-OCH_3-C_6H_2-	387.82	$C_{19}H_{18}ClN_3O_4$	90	193-195

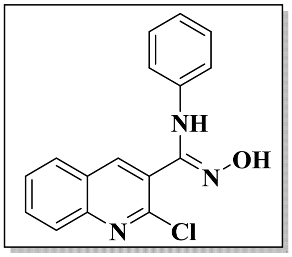
By using the same general synthetic procedure for **5a-p**, the following compounds were prepared:

(*Z*)-2-chloro-*N′*-hydroxy-*N*-(4-methoxyphenyl)quinoline-3-carboximidamide (5a):



Compound **5a** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 4-methoxy aniline (0.10 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (92% yield); mp: 182-184 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.33 (s, 1H, Ar-H), 8.01 (d, J = 8.5 Hz, 1H, Ar-H), 7.86 (d, J = 8.1 Hz, 1H, Ar-H), 7.79 (t, J = 8.6 Hz, 1H, Ar-H), 7.61 (t, J = 7.6 Hz, 1H, Ar-H), 6.77 (d, J = 8.8 Hz, 2H, 2 × Ar-H), 6.61 (d, J = 8.9 Hz, 2H, 2 × Ar-H), 3.67 (s, 3H, OCH_3). Mass spectrum: 327 *m/z*.

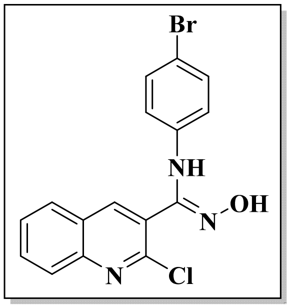
(*Z*)-2-chloro-*N′*-hydroxy-*N*-phenylquinoline-3-carboximidamide (5b):



Compound **5b** was prepared from compound **4** (0.20 gm, 0.61 mmol) and aniline (0.08 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (88% yield); mp: 146-148 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.36 (s, 1H, Ar-H), 8.00 (d, J = 8.5 Hz, 1H, Ar-H), 7.94 – 7.76 (m, 2H, 2 × Ar-H), 7.62 (d, J = 8.1 Hz, 1H, Ar-H), 7.13 –

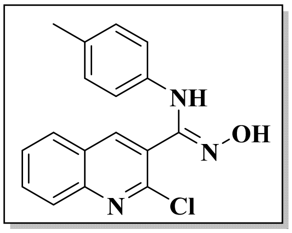
7.03 (m, 2H, 2 × Ar-H), 6.96 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.75 – 6.67 (m, 2H, 2 × Ar-H). Mass spectrum: 298 *m/z*.

(*Z*)-*N*-(4-bromophenyl)-2-chloro-*N'*-hydroxyquinoline-3-carboximidamide (5c):



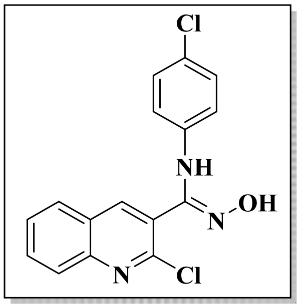
Compound **5c** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 4-bromo aniline (0.14 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (90% yield); mp: 172-174 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.39 (s, 1H, Ar-H), 7.98 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.87 – 7.81 (m, 2H, 2 × Ar-H), 7.62 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.17 (d, *J* = 8.9 Hz, 2H, 2 × Ar-H), 6.62 (d, *J* = 8.7 Hz, 2H, 2 × Ar-H). Mass spectrum: 377 *m/z*.

(*Z*)-2-chloro-*N'*-hydroxy-*N*-(*p*-tolyl)quinoline-3-carboximidamide (5d):



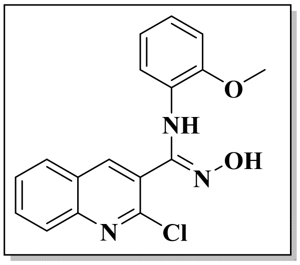
Compound **5d** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 4-methyl aniline (0.09 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (91% yield); mp: 166-168 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.36 (s, 1H, Ar-H), 8.02 (d, *J* = 8 Hz, 1H, Ar-H), 7.87 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.80 (t, *J* = 8.6 Hz, 1H, Ar-H), 7.62 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.38 (s, 1H, Ar-NH), 6.87 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H), 6.65 (d, *J* = 8.9 Hz, 2H, 2 × Ar-H), 2.19 (s, 3H, CH_3).). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 148.95, 147.79, 140.85, 133.61, 131.53, 129.64, 128.49, 127.94, 127.55, 126.34, 121.90, 67.99, 20.65. Mass spectrum: 312 *m/z*.

(*Z*)-2-chloro-*N*-(4-chlorophenyl)-*N′*-hydroxyquinoline-3-carboximidamide (5e):



Compound **5e** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 4-chloro aniline (0.11 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (90% yield); mp: 178-180 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.38 (s, 1H, Ar-H), 7.97 (d, J = 8.4 Hz, 1H, Ar-H), 7.87 – 7.81 (m, 2H, 2 × Ar-H), 7.62 (t, J = 7.6 Hz, 1H, Ar-H), 7.02 (d, J = 8.9 Hz, 2H, 2 × Ar-H), 6.68 (d, J = 8.7 Hz, 2H, 2 × Ar-H). Mass spectrum: 332 *m/z*.

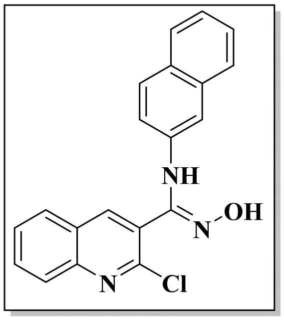
(*Z*)-2-chloro-*N′*-hydroxy-*N*-(2-methoxyphenyl)quinoline-3-carboximidamide (5f):



Compound **5f** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 2-methoxy aniline (0.10 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (94% yield); mp: 174-176 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.39 (s, 1H, Ar-H), 8.06 (d, J = 8.4 Hz, 1H, Ar-H), 7.88 (d, J = 8.3 Hz, 1H, Ar-H), 7.81 (m, 2H, 2 × Ar-H), 7.77 (s, 1H, Ar-NH), 7.63 (t, J = 6.9 Hz, 1H, Ar-H), 6.93 – 6.81 (m, 2H, 2 × Ar-H), 6.50 (t, J = 6.7 Hz, 1H, Ar-H), 6.31 (d, J = 8.1 Hz, 1H, Ar-H), 3.90 (s, 3H, OCH_3). ^{13}C NMR (101 MHz,

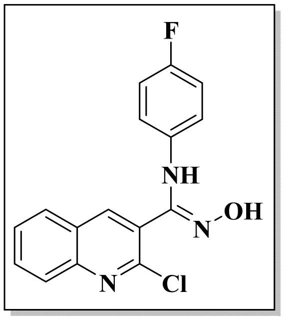
$CDCl_3$) δppm: 149.83, 149.08, 148.90, 147.78, 140.72, 131.55, 128.51, 128.09, 128.00, 127.56, 126.42, 125.54, 123.44, 120.44, 119.36, 110.81, 68.02, 55.71, 25.62. Mass spectrum: 328 *m/z*.

(*Z*)-2-chloro-*N′*-hydroxy-*N*-(naphthalen-2-yl)quinoline-3-carboximidamide (5g):



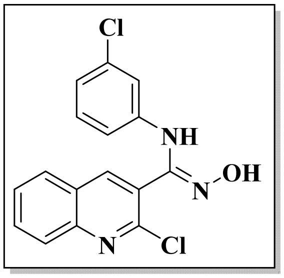
Compound **5g** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 2-napthyl amine (0.12 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (60% yield); mp: 192-194 °C. Mass spectrum: 348 *m/z*.

(*Z*)-2-chloro-*N*-(4-fluorophenyl)-*N′*-hydroxyquinoline-3-carboximidamide (5h):



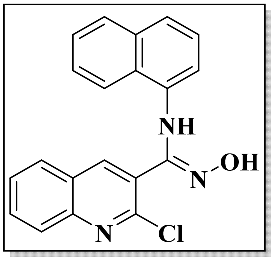
Compound **5h** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 4-fluro aniline (0.09 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (86% yield); mp: 182-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.45 (s, 1H, Ar-H), 8.09 – 7.74 (m, 3H, 3 × Ar-H), 7.62 (m, 2H, 2 × Ar-H), 6.98 (d, *J* = 8.5 Hz, 2H, 2 × Ar-H), 6.69 (d, *J* = 55.2 Hz, 2H, 2 × Ar-H). Mass spectrum: 316 *m/z*.

(*Z*)-2-chloro-*N*-(3-chlorophenyl)-*N*'-hydroxyquinoline-3-carboximidamide (5i):



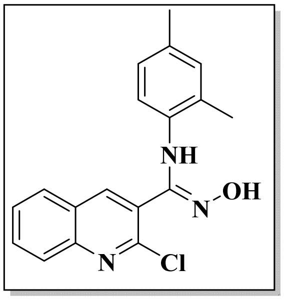
Compound **5i** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 3-chloro aniline (0.11 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (88% yield); mp: 177-179 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.38 (s, 1H, Ar-H), 7.96 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.87 – 7.76 (m, 2H, 2 × Ar-H), 7.60 (t, *J* = 6.9 Hz, 1H, Ar-H), 6.97 – 6.90 (m, 2H, 2 × Ar-H), 6.81 (s, 1H, Ar-H), 6.52 (d, *J* = 6.7 Hz, 1H, Ar-H). Mass spectrum: 332 *m/z*.

(*Z*)-2-chloro-*N′*-hydroxy-*N*-(naphthalen-1-yl)quinoline-3-carboximidamide (5j):



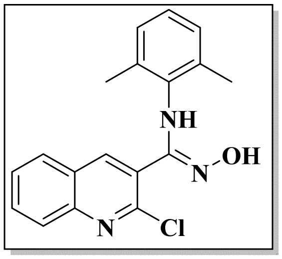
Compound **5j** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 1-napthyl amine (0.12 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (97% yield); mp: 177-179 °C. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.32 (s, 1H, Ar-H), 7.95 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.86 (s, 3H, 3 × Ar-H), 7.81 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.66 – 7.49 (m, 4H, 4 × Ar-H), 7.07 (t, *J* = 7.9 Hz, 1H, Ar-H), 6.82 (d, *J* = 7.5 Hz, 1H, Ar-H). Mass spectrum: 348 *m/z*.

(*Z*)-2-chloro-*N*-(2,4-dimethylphenyl)-*N′*-hydroxyquinoline-3-carboximidamide (5k):



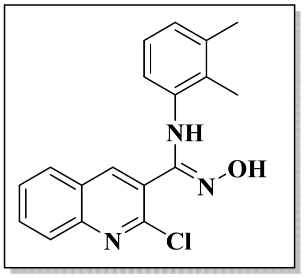
Compound **5k** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 2,4-xylidine (0.10 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (94% yield); mp: 183-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.34 (s, 1H, Ar-H), 8.01 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.86 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.80 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.61 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.54 (s, 1H, Ar-NH), 6.76 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.61 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.38 (d, *J* = 8.1 Hz, 1H, Ar-H), 2.06 (d, *J* = 12.6 Hz, 6H, 2 × CH_3). Mass spectrum: 326 *m/z*.

(*Z*)-2-chloro-*N*-(2,6-dimethylphenyl)-*N*′-hydroxyquinoline-3-carboximidamide (5l):



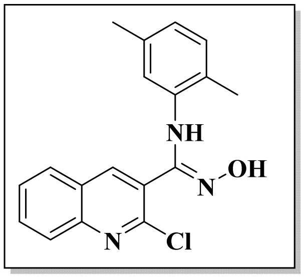
Compound **5l** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 2,6-xylidine (0.10 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (96% yield); mp: 183-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.37 (s, 1H, Ar-H), 7.99 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.87 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.80 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.62 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.36 (s, 1H, Ar-NH), 7.00 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.71 (d, *J* = 7.3 Hz, 1H, Ar-H), 6.33 – 6.28 (m, 1H, Ar-H), 2.32 (s, 3H, CH_3), 1.89 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 148.37, 147.71, 140.99, 135.95, 131.79, 130.63, 128.40, 128.01, 127.68, 126.03, 125.76, 124.08, 29.72, 20.76, 17.51. Mass spectrum: 326 *m/z*.

(*Z*)-2-chloro-*N*-(2,3-dimethylphenyl)-*N*′-hydroxyquinoline-3-carboximidamide (5m):



Compound **5m** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 2,3-xylidine (0.10 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (96% yield); mp: 177-179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.35 (s, 1H, Ar-H), 7.96 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.86 (d, *J* = 9.8 Hz, 1H, Ar-H), 7.79 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.60 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-NH), 6.81 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.65 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.41 (d, *J* = 7.9 Hz, 1H, Ar-H), 2.29 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). Mass spectrum: 326 *m/z*.

(*Z*)-2-chloro-*N*-(2,5-dimethylphenyl)-*N'*-hydroxyquinoline-3-carboximidamide (5o):



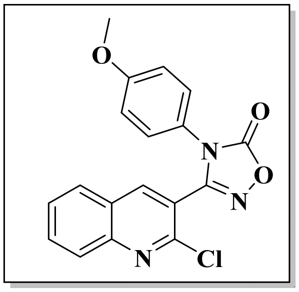
Compound **5o** was prepared from compound **4** (0.20 gm, 0.61 mmol) and 2,5-xylidine (0.10 gm, 0.61 mmol) and $NaHCO_3$ (0.05 gm, 0.61 mmol) in H_2O:THF (1:1, 12 mL). An off-white solid (96% yield); mp: 186-188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.40 (s, 1H, Ar-H), 7.97 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.89 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.82 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.66 – 7.59 (m, 2H, 4 × Ar-H), 7.01 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.75 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.32 (d, *J* = 1.8 Hz, 1H, Ar-H), 2.31 (s, 3H, CH_3), 1.89 (s, 3H, CH_3). Mass spectrum: 326 *m/z*.

General procedure for the synthesis of compound (6a-p):[45]

To a well stirred solution of compound **5** (1 mmol) in a 1,4-dioxane (10 mL), 1,1'-carbonyldiimidazole (CDI) (2 mmol) was added, and the mixture was stirred under reflux for 2 h 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.

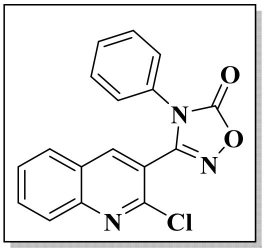
By using the same general synthetic procedure for **6a-p**, the following compounds were prepared:

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



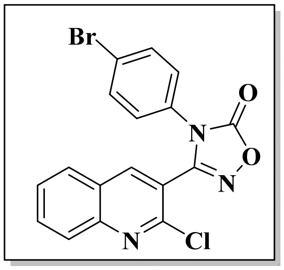
CDI (0.18 gm, 1.11 mmol) was added to a solution of (Z)-2-chloro-*N'*-hydroxy-*N*-(4-methoxyphenyl)-quinoline-3-carboximidamide **5a** (0.2 gm, 0.57 mmol) in 1,4-dioxane (10 mL), and the reaction was heated at 100 °C for 2 h with stirring. The mixture was poured into ice water and the formed precipitate was filtered off, washed with water to give **6a** the title compound as an off-white solid (94% yield); mp: 137-139 °C. IR (KBr) ν_{max}/cm^{-1}: 3535 (NH), 3043 (Ar-C-H), 2115 (C=N), 1774 (C=O, amide), 1595 (Aromatic ring), 1511 (C-N), 941 (C-Cl) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δppm: 9.02 (s, 1H, Ar-H), 8.20 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.06 –7.94 (m, 2H, Ar-H), 7.81 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.37 (d, *J* = 9.0 Hz, 2H, 2 × Ar-H), 6.95 (d, *J* = 9.0 Hz, 2H, 2 × Ar-H), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δppm: 159.70, 157.40, 156.08, 147.80, 146.31, 143.89, 133.50, 129.05, 128.68, 128.46, 127.90, 125.37, 123.34, 116.80, 114.63, 55.34. LCMS: 353.80 *m/z*, Purity: 99.78%.

3-(2-chloroquinolin-3-yl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-one (6b):



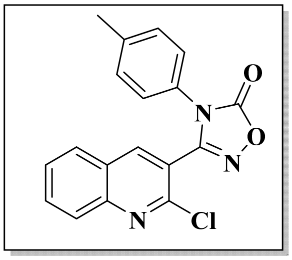
Compound **6b** was prepared from **5b** (0.2 gm, 0.62 mmol) and CDI (0.20 gm, 1.23 mmol) in 1,4-dioxane (10 mL). A white solid (92% yield); mp: 152-154 °C. IR (KBr) ν_{max}/cm^{-1}: 3525 (NH), 3076 (Ar-C-H), 2344 (C=N), 1897 (C=O, amide), 1612 (Aromatic ring), 1567 (C-N), 689 (C-Cl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.51 (s, 1H, Ar-H), 8.07 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.98 – 7.96 (d, *J* = 8.3 Hz, 1H, 1 × Ar-H), 7.94-7.90 (t, *J* = 8.2, 1H, Ar-H), 7.75-7.71 (t, *J* = 1.1 Hz, 1H, Ar-H), 7.37 – 7.36 (m, 3H, 3 × Ar-H), 7.17 (m, 2H, 2 × Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.05, 155.37, 148.21, 146.61, 141.63, 132.66, 130.87, 129.31, 128.98, 128.26, 128.03, 127.83, 125.20, 125.19, 116.99. Mass spectrum: 323 *m/z*.

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



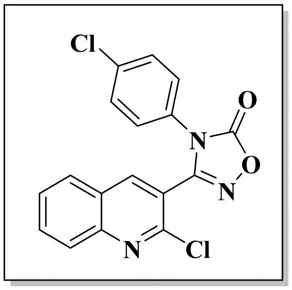
Compound **6c** was prepared from **5c** (0.2 gm, 0.5 mmol) and CDI (0.16 gm, 0.1 mmol) in 1,4-dioxane (10 mL). An off-white solid (96% yield); mp: 170-172 °C. IR (KBr) ν_{max}/cm^{-1}: 3529 (NH), 3054 (Ar-C-H), 2327 (C=N), 1768 (C=O, amide), 1567 (Aromatic ring), 1489 (C-N), 762 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.52 (s, 1H, Ar-H), 8.08 (d, *J* = 9.3 Hz, 1H, Ar-H), 8.00 – 7.97 (d, *J* = 8.04 Hz, 1H, Ar-H), 7.94-7.92 (t, *J* = 1.5 Hz, 2H, 2 × Ar-H), 7.74 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.51-7.47 (d, *J* = 2.1 Hz, 2H, 2 × Ar-H), 7.12-7.10 (d, *J* = 2.1 Hz, 2H, 2 × Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 156.66, 155.07, 148.31, 146.33, 141.70, 132.86, 132.59, 129.92, 128.32, 128.19, 127.86, 126.60, 125.18, 123.11, 116.62. Mass spectrum: 403 *m/z*.

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



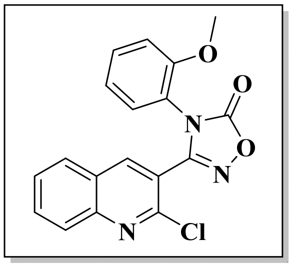
Compound **6d** was prepared from **5d** (0.2 gm, 0.59 mmol) and CDI (0.19 gm, 1.18 mmol) in 1,4-dioxane (10 mL). An off-white solid (96% yield); mp: 126-128 °C. IR (KBr) ν_{max}/cm^{-1}: 3490 (NH), 3054 (Ar-C-H), 1757 (C=O, amide), 1511 (Aromatic ring), 1427 (C-N), 756 (C-Cl) cm^{-1}. ^{1}H NMR ($CDCl_3$) δppm: 8.48 (s, 1H, Ar-H), 8.06 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.96 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.91 (t, *J* = 7.1 Hz, 1H, Ar-H), 7.72 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.15 (d, *J* = 8.5 Hz, 2H, 2 × Ar-H), 7.10 (d, *J* = 8.5 Hz, 2H, 2 × Ar-H), 2.31 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.72, 156.00, 148.69, 147.22, 142.07, 139.80, 133.10, 130.40, 128.75, 128.67, 128.48, 128.33, 125.68, 125.63, 117.61, 21.13. LCMS (m/z): 337.75 (M+); 100 % purity.

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



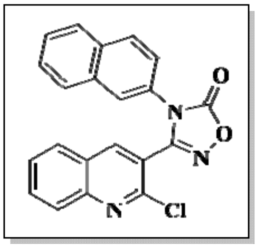
Compound **6e** was prepared from **5e** (0.2 gm, 0.56 mmol) and CDI (0.18 gm, 1.11 mmol) in 1,4-dioxane (10 mL). A white solid (93% yield); mp: 164-166 °C. IR (KBr) ν_{max}/cm^{-1}: 3529 (NH), 2327 (C=N), 1768 (C=O, amide), 1567 (Aromatic ring), 1494 (C-N), 762 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.52 (s, 1H, Ar-H), 8.07 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.97 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.93 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.73 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.33 (d, *J* = 8.3 Hz, 2H, 2 × Ar-H), 7.17 (d, *J* = 8.3 Hz, 2H, 2 × Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.24, 155.64, 148.81, 146.83, 142.23, 135.59, 133.35, 130.10, 129.87, 128.81, 128.68, 128.37, 126.92, 125.68, 117.12. LCMS: 357.70 *m/z* (M+); 98.30 % purity.

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



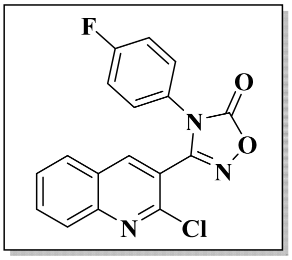
Compound **6f** was prepared from **5f** (0.2 gm, 0.57 mmol) and CDI (0.18 gm, 1.11 mmol) in 1,4-dioxane (10 mL). A white solid (94% yield); mp: 138-140 °C. IR (KBr) ν_{max}/cm^{-1}: 3552 (NH), 3065 (Ar-C-H), 2361 (C=N), 1779 (C=O, amide), 1600 (Aromatic ring), 1427 (C-N), 756 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.35 (s, 1H, Ar-H), 8.03 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.89-7.85 (t, *J* = 8.0 Hz, 2H, 2 × Ar-H), 7.67 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.44 (d, *J* = 9.7 Hz, 1H, Ar-H), 7.35 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.02 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.82 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.67 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.37, 156.27, 153.58, 147.96, 146.85, 141.23, 132.38, 131.38, 128.88, 128.16, 127.80, 127.61, 125.01, 120.85, 118.85, 117.33, 111.68, 55.05. Mass spectrum: 353 *m/z*.

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



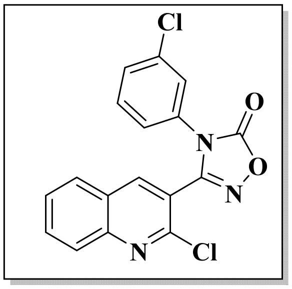
Compound **6g** was prepared from **5g** (0.2 gm, 0.54 mmol) and CDI (0.18 gm, 1.15 mmol) in 1,4-dioxane (10 mL). An off-white solid (96% yield); mp: 160-162 °C. IR (KBr) ν_{max}/cm^{-1}: 3065 (Ar-C-H), 2378 (C=N), 1785 (C=O, amide), 1561 (Aromatic ring), 1472 (C-N), 807 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.36 (s, 1H, Ar-H), 7.96 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.94 – 7.77 (m, 5H, 5× Ar-H), 7.70 – 7.58 (m, 2H, 2 × Ar-H), 7.62 – 7.52 (m, 1H, Ar-H), 7.46 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.45 – 7.37 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.32, 156.32, 147.99, 146.87, 141.33, 133.92, 132.53, 130.73, 128.74, 128.32, 128.12, 127.83, 127.65, 127.56, 126.73, 126.52, 126.26, 124.89, 124.58, 121.11, 116.75. Mass spectrum: 374 *m/z*.

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



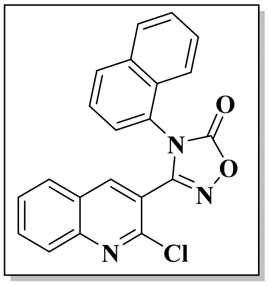
Compound **6h** was prepared from **5h** (0.2 gm, 0.63 mmol) and CDI (0.21 gm, 1.27 mmol) in 1,4-dioxane (10 mL). A white solid (95% yield); mp: 159-161 °C. IR (KBr) ν_{max}/cm^{-1}: 3546 (NH), 3054 (Ar-C-H), 1763 (C=O, amide), 1572 (Aromatic ring), 1382 (C-N), 756 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.51 (s, 1H, Ar-H), 8.06 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.96 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.92 (t, *J* = 1.5 Hz, 1H, Ar-H), 7.72 (t, *J* = 1.3 Hz, 1H, Ar-H), 7.23 (dd, *J* = 9.0, 4.6 Hz, 2H, 2 × Ar-H), 7.05 (dd, *J* = 9.1, 7.8 Hz, 2 × Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 163.84, 161.34, 157.49, 155.82, 148.78, 146.88, 142.25, 133.31, 128.78, 128.64, 128.36, 127.93, 127.84, 127.30, 127.27, 125.67, 117.16, 117.12, 116.89. Mass spectrum: 372 *m/z*.

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



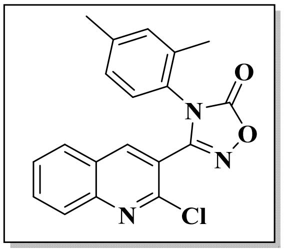
Compound **6i** was prepared from **5i** (0.2 gm, 0.56 mmol) and CDI (0.18 gm, 1.11 mmol) in 1,4-dioxane (10 mL). A white solid (94% yield); mp: 160-162 °C. IR (KBr) ν_{max}/cm^{-1}: 3559 (NH), 3065 (Ar-C-H), 2327 (C=N), 2115 (C=O, amide), 1656 (Aromatic ring), 1483 (C-N), 751 (C-Cl) cm^{-1}. ^1H NMR (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, $CDCl_3$) δppm: 157.10, 155.52, 148.83, 146.84, 142.20, 135.55, 133.36, 132.45, 130.72, 129.85, 128.82, 128.67, 128.38, 126.06, 125.67, 123.71, 117.09. Mass spectrum: 358 *m/z*.

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



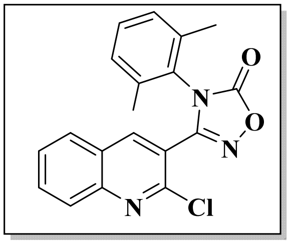
Compound **6j** was prepared from **5j** (0.2 gm, 0.54 mmol) and CDI (0.18 gm, 1.15 mmol) in 1,4-dioxane (10 mL). A sepia solid (88% yield); mp: 155-157 °C. IR (KBr) ν_{max}/cm^{-1}: 3065 (Ar-C-H), 2378 (C=N), 1785 (C=O, amide), 1561 (Aromatic ring), 1472 (C-N), 807 (C-Cl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.35 (s, 1H, Ar-H), 7.95 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.92 – 7.75 (m, 5H, 5 × Ar-H), 7.68 – 7.51 (m, 3H, 3 × Ar-H), 7.46 (d, *J* = 6.3 Hz, 1H, 1× Ar-H), 7.40 (t, *J* = 7.8 Hz, 1H, 1× Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.85, 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. LCMS: 373.85 *m/z* (M+); 91.73 % purity.

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



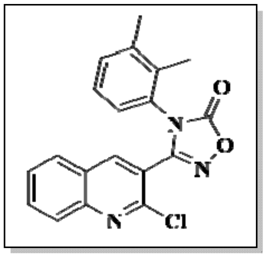
Compound **6k** was prepared from **5k** (0.2 gm, 0.54 mmol) and CDI (0.18 gm, 1.15 mmol) in 1,4-dioxane (10 mL). A white solid (98% yield); mp: 130-132 °C. IR (KBr) ν_{max}/cm^{-1}: 3060, 2920 (Ar-C-H), 2341 (C=N), 1763 (C=O, amide), 1617 (Aromatic ring), 1427 (C-N), 756 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.40 (s, 1H, Ar-H), 8.03 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.96 – 7.83 (m, 2H, 2 × Ar-H), 7.69 (t, *J* = 7.6 Hz, 1H, Ar-H), δ 7.08 (s, 1H, 1 × Ar-H) 6.96 – 6.85 (m, 2H, 2 × Ar-H), 2.33 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.41, 156.51, 148.58, 147.18, 142.11, 140.62, 135.74, 133.08, 132.59, 128.67, 128.43, 128.28, 127.78, 127.55, 127.01, 125.58, 117.53, 21.05, 17.87. Mass spectrum: 352 *m/z*.

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



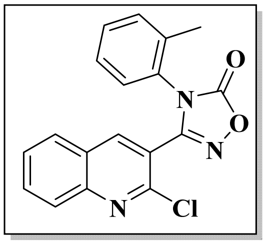
Compound **6l** was prepared from **5l** (0.2 gm, 0.54 mmol) and CDI (0.18 gm, 1.15 mmol) in 1,4-dioxane (10 mL). A white solid (98% yield); mp: 134-136 °C. 3519 (NH), 3065 (Ar-C-H), 2327 (C=N), 1779 (C=O, amide), 1584 (Aromatic ring), 1472 (C-N), 756 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.12 (s, 1H, Ar-H), 8.04 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.87 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.79 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.65 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.09 (d, *J* = 7.6 Hz, 2H, 2 × Ar-H), 2.27 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.25, 155.99, 148.39, 147.14, 141.58, 136.39, 133.22, 130.51, 129.30, 128.69, 128.65, 128.42, 128.17, 125.32, 117.20, 18.33. Mass spectrum: 352 *m/z*.

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



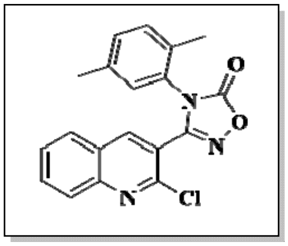
Compound **6m** was prepared from **5m** (0.2 gm, 0.54 mmol) and CDI (0.18 gm, 1.15 mmol) in 1,4-dioxane (10 mL). A gray solid (97% yield); mp: 120-122 °C. 3680 (NH), 3037 (Ar-C-H), 2372 (C=N), 1691 (C=O, amide), 1584 (Aromatic ring), 1511 (C-N), 678 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.41 (s, 1H, Ar-H), 8.04 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.99 – 7.85 (m, 2H, 2 × Ar-H), 7.70 (t, *J* = 1.2 Hz, 1H, Ar-H), 7.17 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.00 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.88 (d, *J* = 6.7 Hz, 1H, Ar-H), 2.29 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 156.99, 155.99, 148.09, 146.71, 141.55, 138.96, 134.30, 132.57, 131.29, 129.12, 128.21, 127.92, 127.74, 125.91, 125.08, 124.90, 117.07, 19.81, 14.39. Mass spectrum: 352 *m/z*.

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



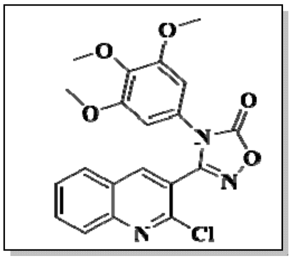
Compound **6n** was prepared from **5n** (0.2 gm, 0.59 mmol) and CDI (0.19 gm, 1.18 mmol) in 1,4-dioxane (10 mL). An off-white solid (97% yield); mp: 129-131 °C. 3552 (NH), 3060 (Ar-C-H), 2372 (C=N), 1785 (C=O, amide), 1606 (Aromatic ring), 1427 (C-N), 751 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.41 (s, 1H, Ar-H), 8.02 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.95 – 7.84 (m, 2H, 2 × Ar-H), 7.69 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.33 – 7.23 (m, 2H, 2 × Ar-H), 7.10 (t, *J* = 2.4 Hz, 1H, Ar-H), 7.03 (d, *J* = 7.6 Hz, 1H, Ar-H), 2.39 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 157.22, 156.40, 148.59, 147.07, 142.18, 136.20, 133.16, 132.00, 130.40, 129.66, 128.68, 128.49, 128.29, 127.76, 127.09, 125.58, 117.39, 17.99. Mass spectrum: 338 *m/z*.

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



Compound **6o** was prepared from **5o** (0.2 gm, 0.54 mmol) and CDI (0.18 gm, 1.15 mmol) in 1,4-dioxane (10 mL). An off-white solid (98% yield); mp: 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.39 (s, 1H, Ar-H), 8.05 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.93 – 7.86 (m, 2H, 2 ×Ar-H), 7.70 (t, *J* = 8.2 Hz, 1H), Ar-H, 7.16 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.10 (d, *J* = 9.8 Hz, 1H,), 6.91 (s, 1H, Ar-H), 2.30 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 156.92, 155.83, 148.08, 146.73, 141.45, 136.66, 132.60, 132.31, 131.16, 130.85, 128.92, 128.21, 127.95, 127.83, 127.71, 125.03, 117.02, 20.16, 16.98. Mass spectrum: 352 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazol-5(4*H*)-one (6p):



Compound **6p** was prepared from **5p** (0.2 gm, 0.48 mmol) and CDI (0.17 gm, 0.97 mmol) in 1,4-dioxane (10 mL). An off-white solid (99% yield); mp: 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.33 (s, 1H, Ar-H), 8.05 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.89 – 7.77 (m, 2H, 2 × Ar-H), 7.62 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.00 (s, 1H, Ar-H), 3.73 (S, 3H, OCH_3), 3.51 (s, 6H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 152.78, 148.60, 147.18, 141.29, 140.08, 133.94, 132.77, 131.26, 128.32, 128.16, 127.97, 127.64, 127.30, 127.26, 125.77, 124.86, 103.12, 98.98, 60.41, 55.29. Mass spectrum: 414 *m/z*.

1.5.2 Protocol of the biological activity

The NCI anticancer screening methodology is thoroughly detailed in other sources (http://www.dtp.nci.nih.gov). In summary, the principal anticancer experiment utilized approximately sixty human tumor cell lines derived from nine neoplastic diseases, in accordance with the guidelines issued by the drug evaluation branch of the national cancer institute bethesda, United states. The chemicals being studied were introduced to the cells at a singular concentration of 10^{-5} M, incubated for 48 h. Assessment of endpoints were conducted utilizing sulforhodamine B (SRB), a protein-binding dye. The results of each molecule were articulated. As a percentage of growth inhibition in treated cells compared to untreated controls, quantified using spectrophotometry in comparison to controls that were not subjected to the test chemicals. Utilizing in doses ranging from 10^{-4} to 10^{-8} M, the most active compound was subjected to additional growth testing. Inhibitory and/or cytotoxic effects across a comprehensive panel of around 60 human tumor cells lines. A continuous drug exposure protocol lasting 48 h was implemented, and SRB protein Assays were employed to assess cellular viability or proliferation. The growth percentage was computed.

1.6 Spectral data

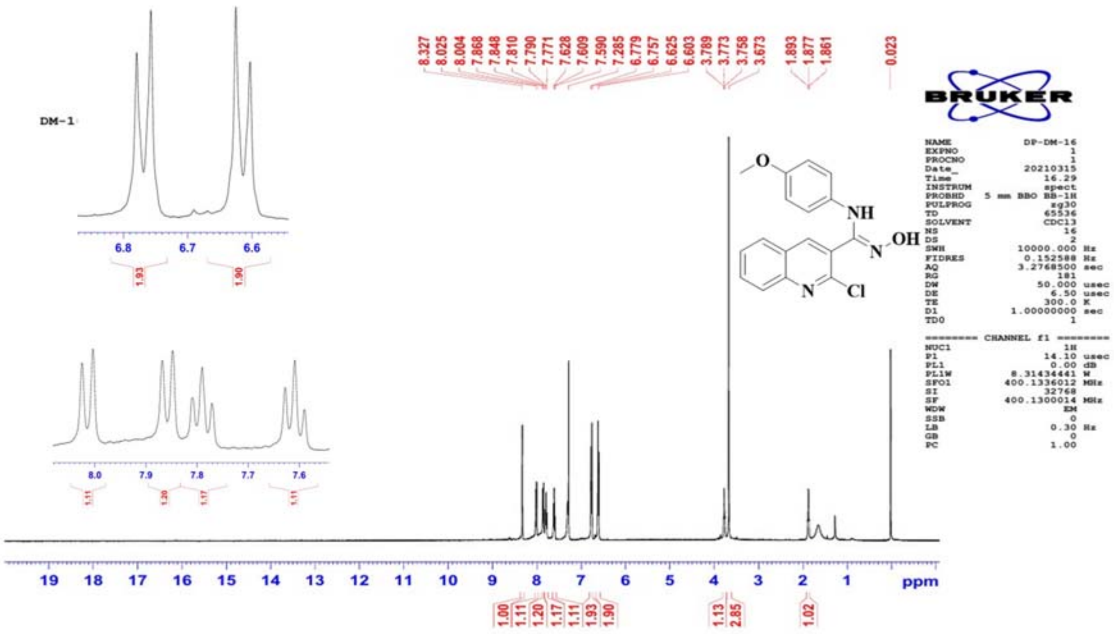


Figure 1: ^{1}H NMR of compound **5a**

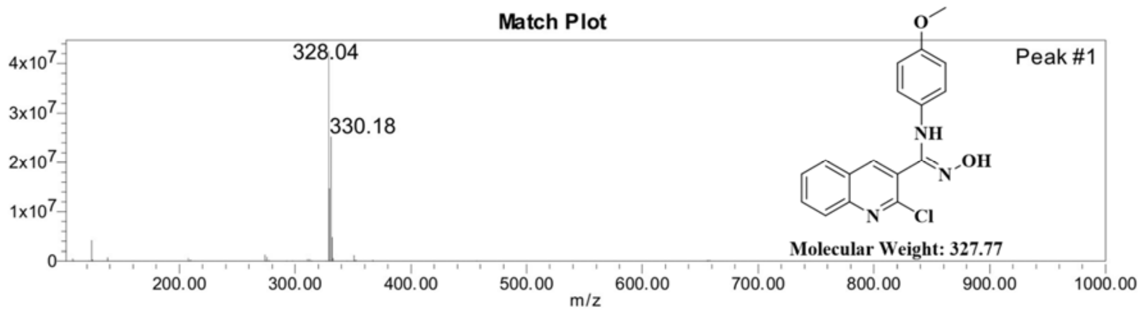
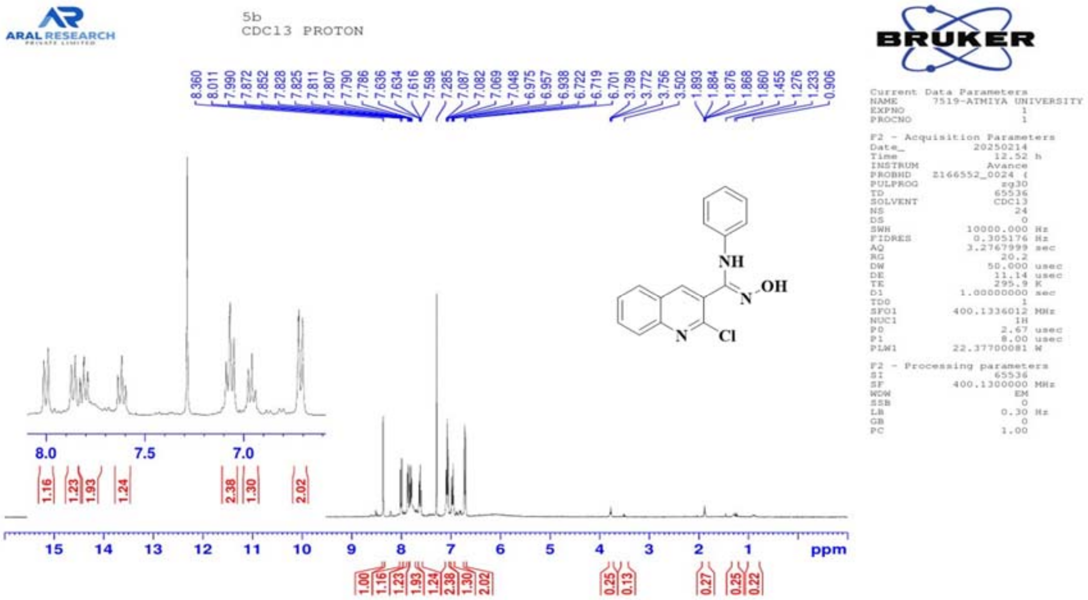


Figure 2: Mass spectrum of compound **5a**



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PROCNO                      1

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TD                    65536
SOLVENT               CDCl3
NS                       24
DS                        0
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FIDRES            0.305176 Hz
AQ               3.2767999 sec
RG                     20.2
DW                  50.000 usec
DE                   11.14 usec
TE                   295.9 K
D1              1.00000000 sec
TD0                       1
SFO1           400.1336012 MHz
NUC1                     1H
P0                     2.67 usec
P1                     8.00 usec
PLW1           22.37700081 W

F2 - Processing parameters
SI                    65536
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WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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Figure 3: ^{1}H NMR of compound **5b**

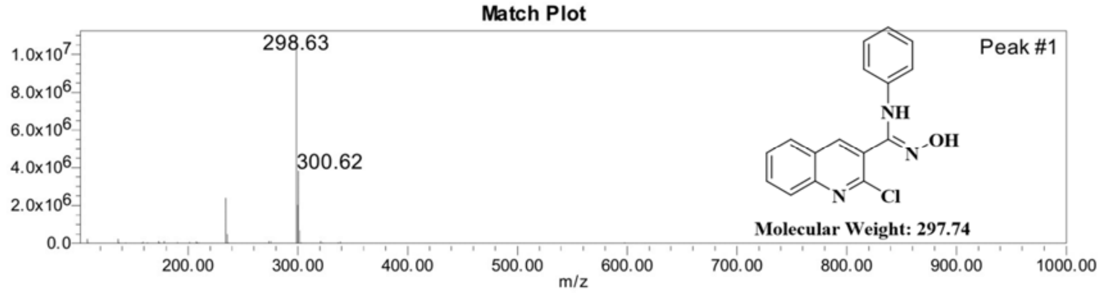
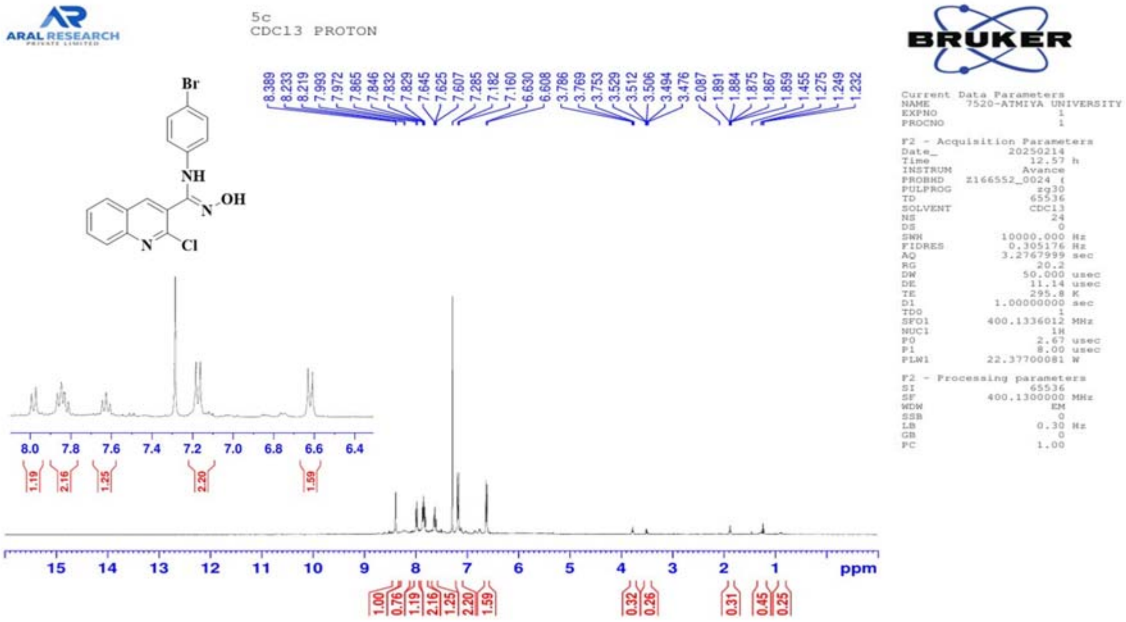


Figure 4: Mass spectrum of compound **5b**



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PROCNO                       1

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PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          24
DS                           0
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FIDRES                0.305176 Hz
AQ                   3.2767999 sec
RG                        20.2
DW                      50.000 usec
DE                       11.14 usec
TE                       295.8 K
D1                  1.00000000 sec
TD0                          1
SFO1               400.1336012 MHz
NUC1                        1H
P0                        2.67 usec
P1                        8.00 usec
PLW1               22.37700081 W

F2 - Processing parameters
SI                       65536
SF                 400.1300000 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
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Figure 5: ^{1}H NMR of compound **5c**

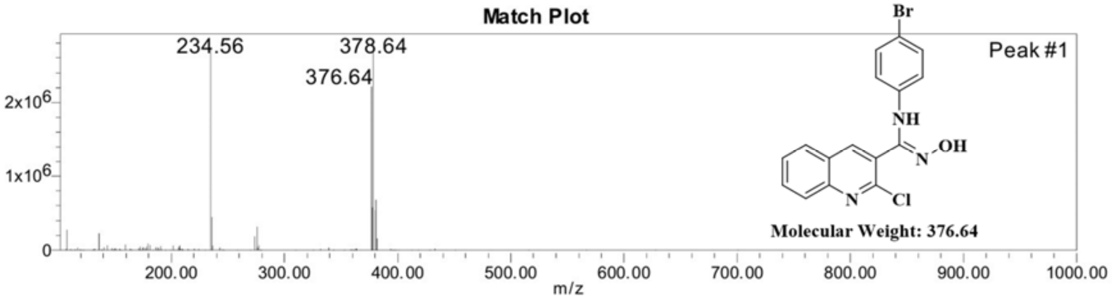


Figure 6: Mass spectrum of compound **5c**

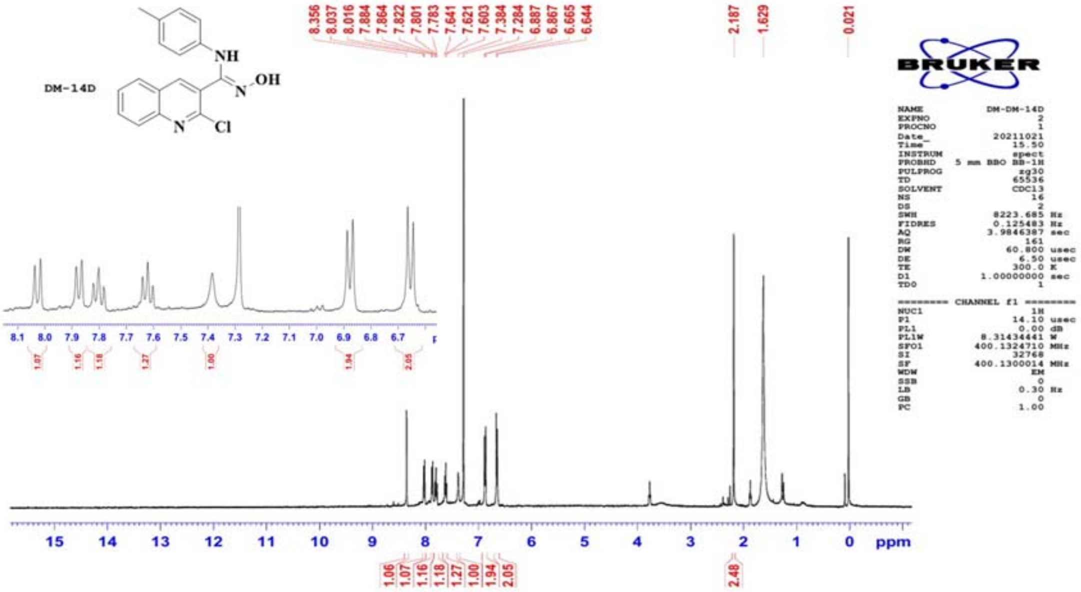


Figure 7: ^{1}H NMR of compound **5d**

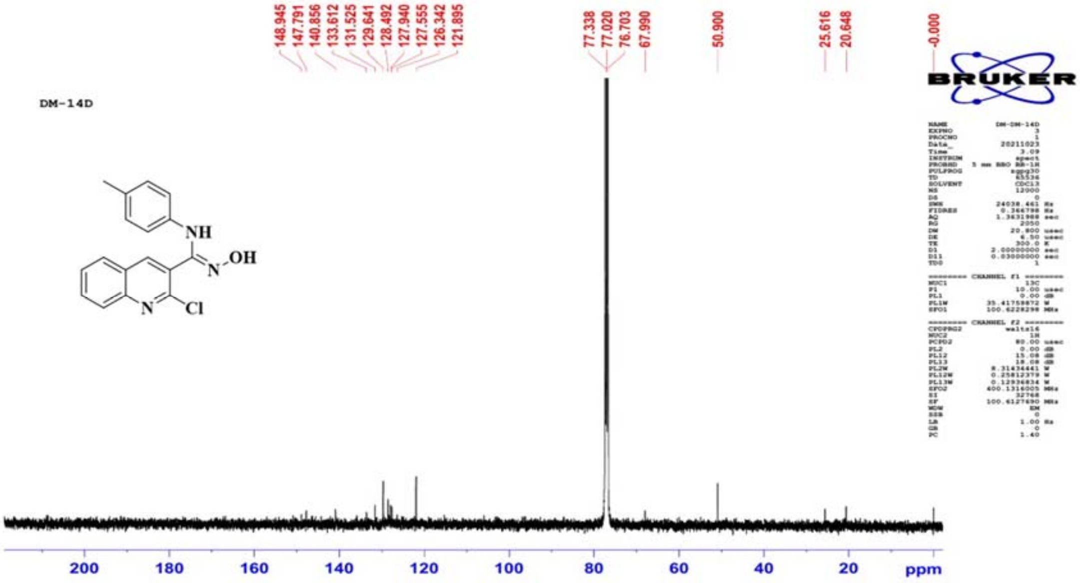


Figure 8: ^{13}C NMR of compound **5d**

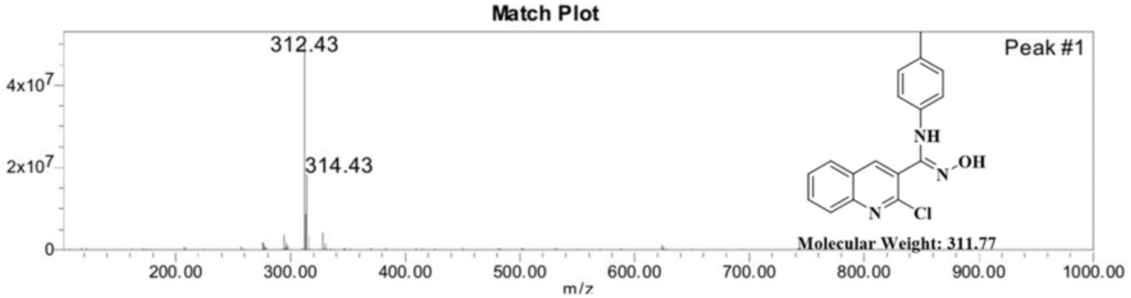
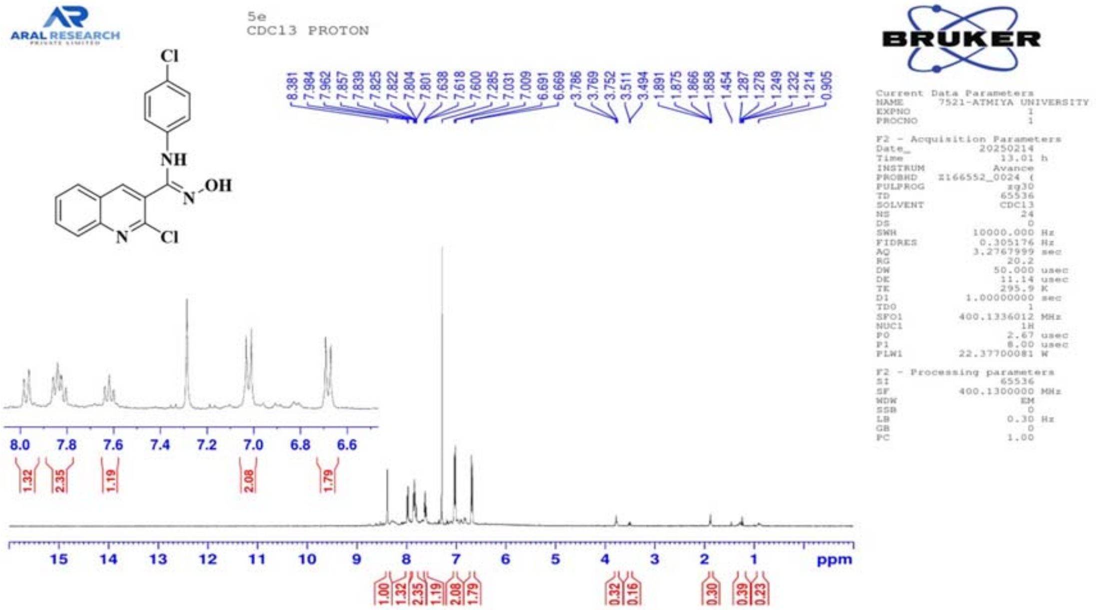


Figure 9: Mass spectrum of compound **5d**



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PROCNO                      1

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PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       24
DS                        0
SWH               10000.000 Hz
FIDRES             0.305176 Hz
AQ                3.2767999 sec
RG                     20.2
DW                   50.000 usec
DE                    11.14 usec
TE                    295.9 K
D1               1.00000000 sec
TD0                       1
SFO1            400.1336012 MHz
NUC1                     1H
P0                     2.67 usec
P1                     8.00 usec
PLW1            22.37700081 W

F2 - Processing parameters
SI                    65536
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WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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Figure 10: ^{1}H NMR of compound **5e**

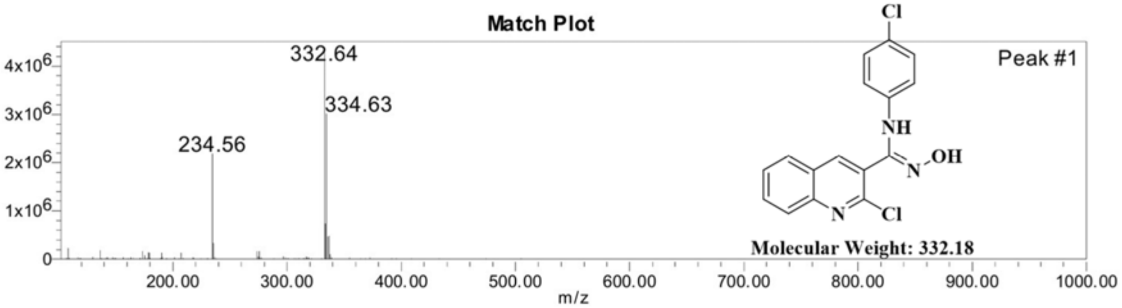
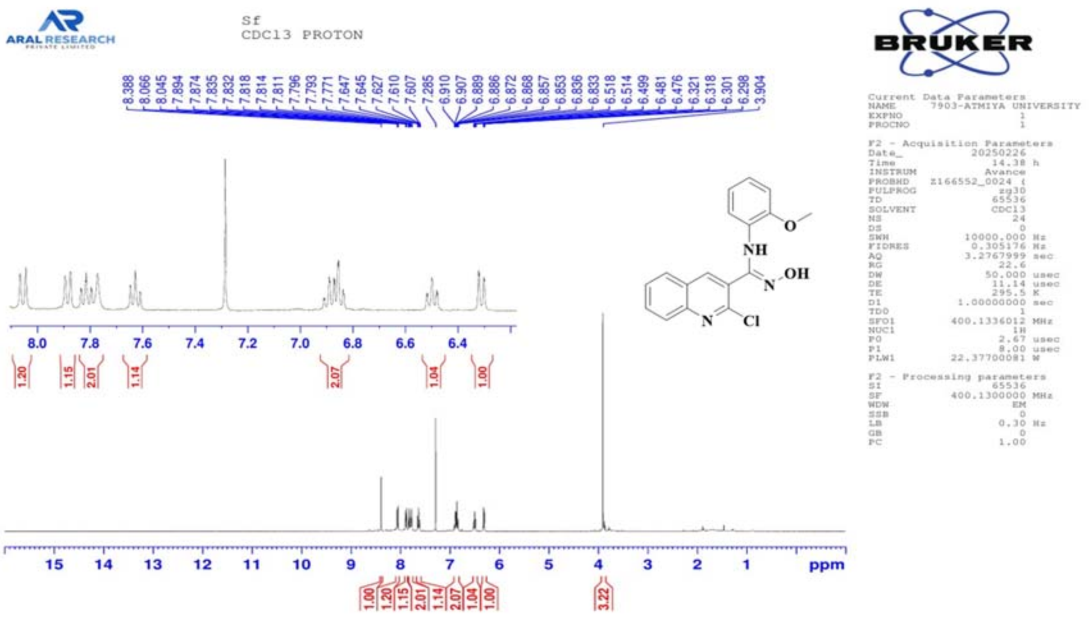


Figure 11: Mass spectrum of compound **5e**



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EXPNO                         1
PROCNO                        1

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PULPROG                    zg30
TD                        65536
SOLVENT                   CDC13
NS                           24
DS                            0
SWH                   10000.000 Hz
FIDRES                 0.305176 Hz
AQ                    3.2767999 sec
RG                         22.6
DW                       50.000 usec
DE                        11.14 usec
TE                        295.5 K
D1                   1.00000000 sec
TD0                           1
SFO1                400.1336012 MHz
NUC1                         1H
P0                         2.67 usec
P1                         8.00 usec
PLW1                22.37700081 W

F2 - Processing parameters
SI                        65536
SF                  400.1300000 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
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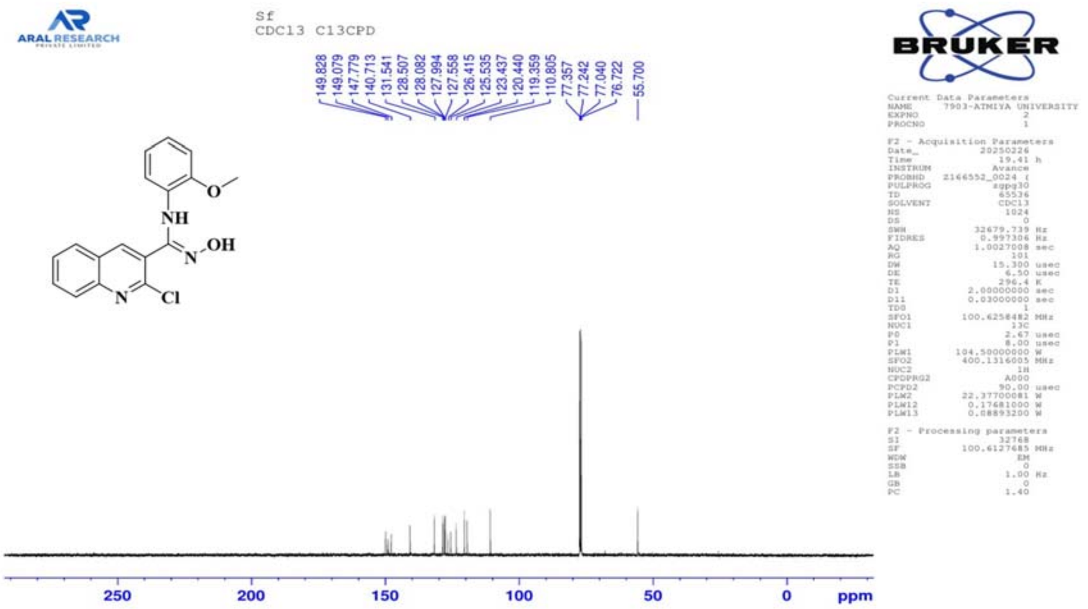
Figure 12: ^{1}H NMR of compound **5f**



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PROCNO                        1

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PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDC13
NS                         1024
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FIDRES                 0.997306 Hz
AQ                    1.0027008 sec
RG                          101
DW                       15.300 usec
DE                         6.50 usec
TE                        296.4 K
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D11                  0.03000000 sec
TD0                           1
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NUC1                        13C
P0                         2.67 usec
P1                         8.00 usec
PLW1               104.50000000 W
SFO2                400.1316005 MHz
NUC2                         1H
CPDPRG2                    A000
PCPD2                     90.00 usec
PLW2                22.37700081 W
PLW12                0.17681000 W
PLW13                0.08893200 W

F2 - Processing parameters
SI                        32768
SF                  100.6127685 MHz
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SSB                           0
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Figure 13: ^{13}C NMR of compound **5f**

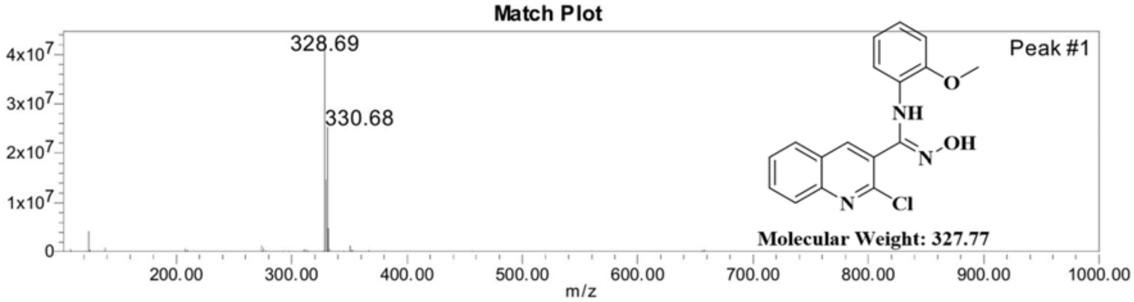


Figure 14: Mass spectrum of compound **5f**

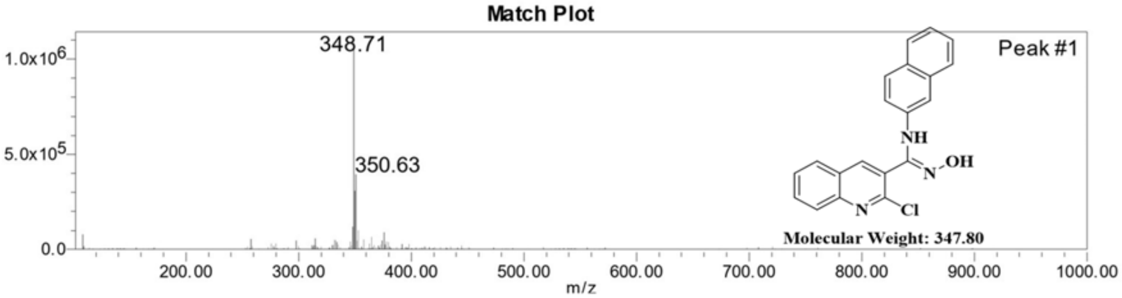
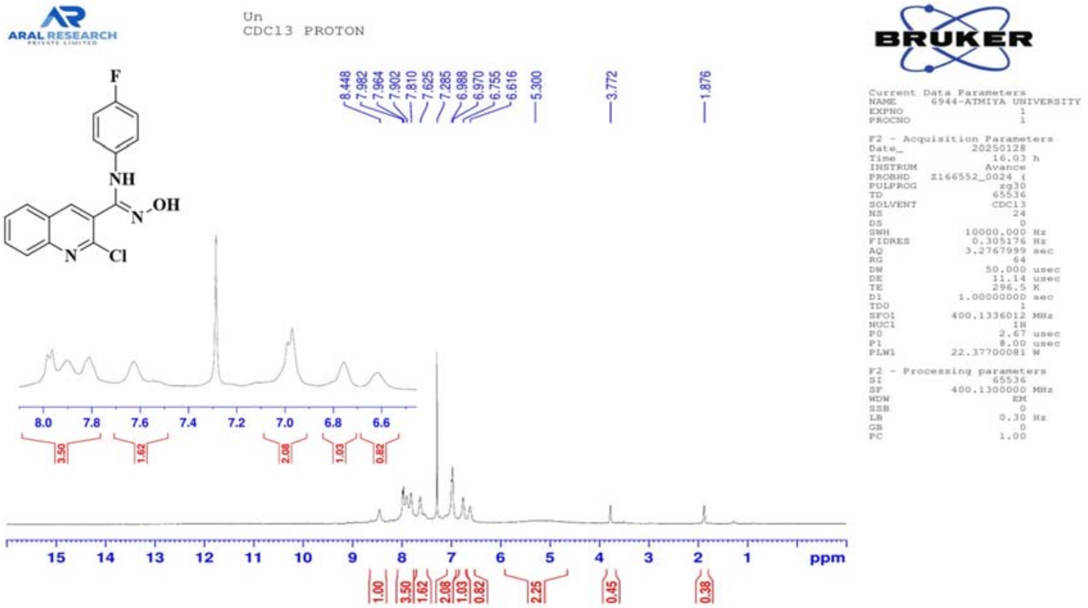


Figure 15: Mass spectrum of compound **5g**



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PROCNO                    1

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TD                    65536
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FIDRES             0.305176 Hz
AQ                3.2767999 sec
RG                       64
DW                   50.000 usec
DE                    11.14 usec
TE                    296.5 K
D1               1.00000000 sec
TD0                       1
SFO1            400.1336012 MHz
NUC1                     1H
P0                     2.67 usec
P1                     8.00 usec
PLW1            22.37700081 W

F2 - Processing parameters
SI                    65536
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SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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Figure 16: ^{1}H NMR of compound **5h**

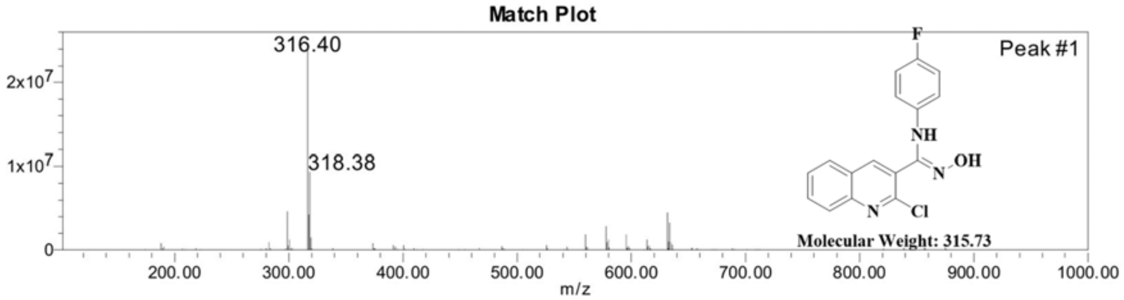
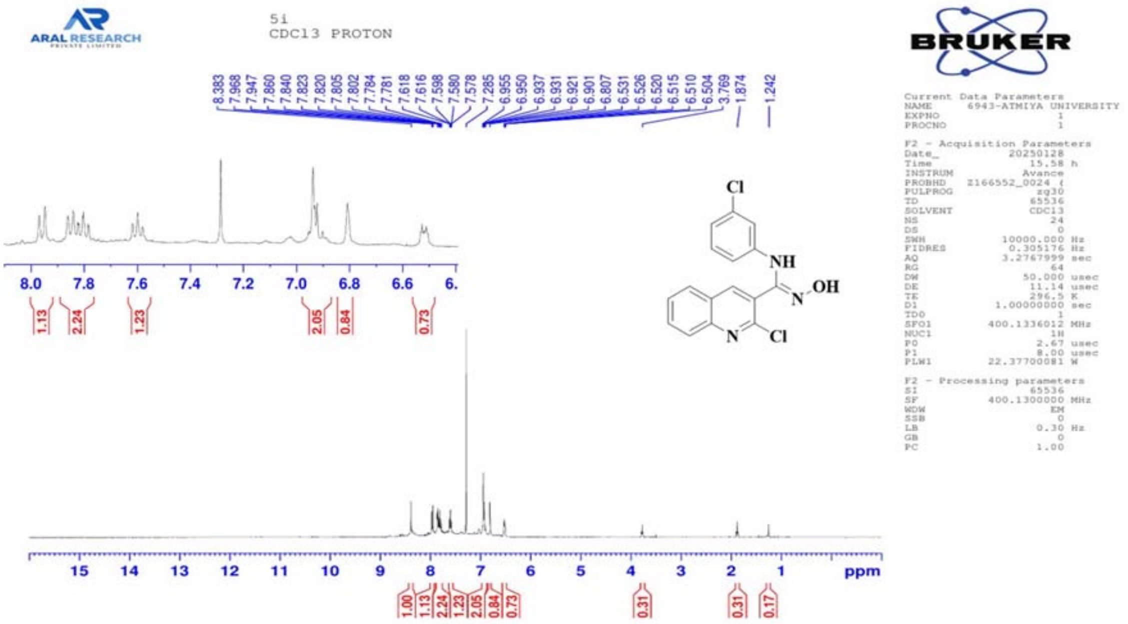


Figure 17: Mass spectrum of compound **5h**



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PROCNO                       1

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PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      24
DS                       0
SWH            10000.000 Hz
FIDRES          0.305176 Hz
AQ             3.2767999 sec
RG                      64
DW                50.000 usec
DE                 11.14 usec
TE                 296.5 K
D1            1.00000000 sec
TD0                      1
SFO1         400.1336012 MHz
NUC1                    1H
P0                  2.67 usec
P1                  8.00 usec
PLW1         22.37700081 W

F2 - Processing parameters
SI                   65536
SF           400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

Figure 18: ^{1}H NMR of compound **5i**

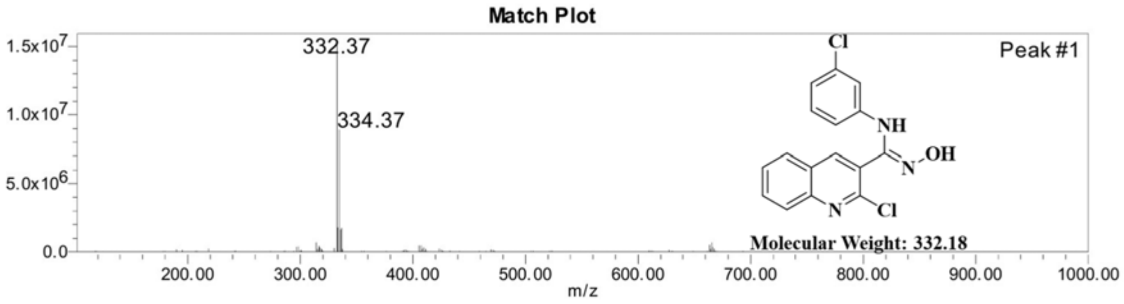


Figure 19: Mass spectrum of compound **5i**

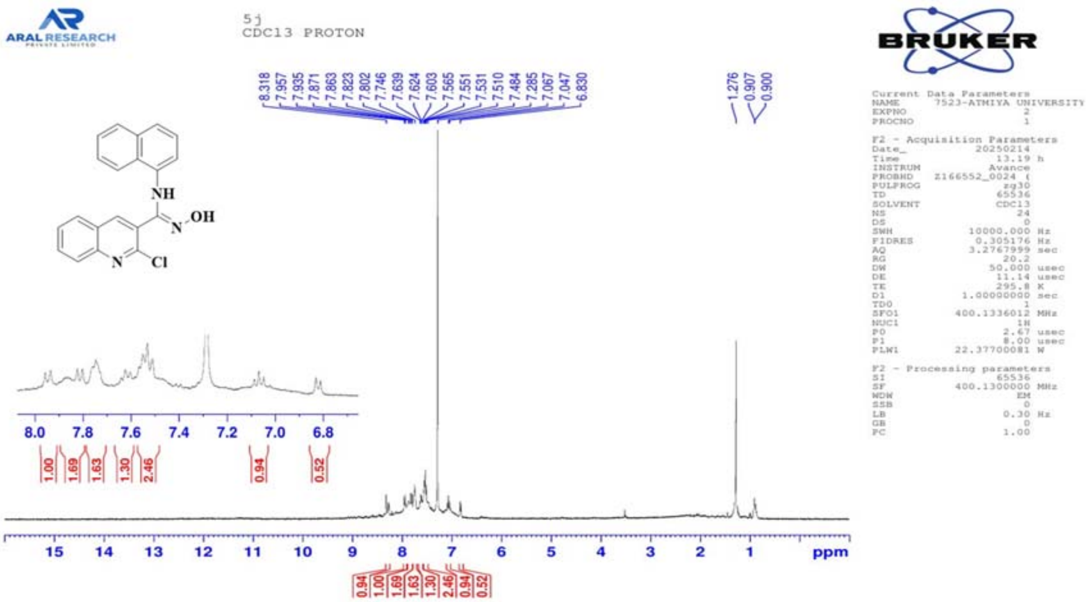


Figure 20: ^{1}H NMR of compound **5j**

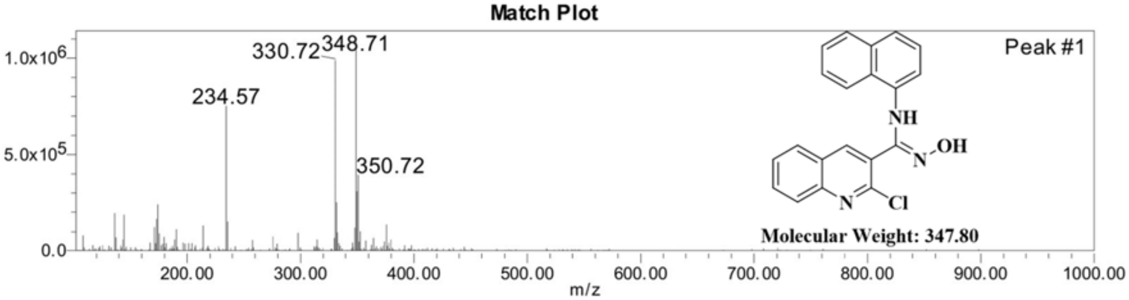


Figure 21: Mass spectrum of compound **5j**

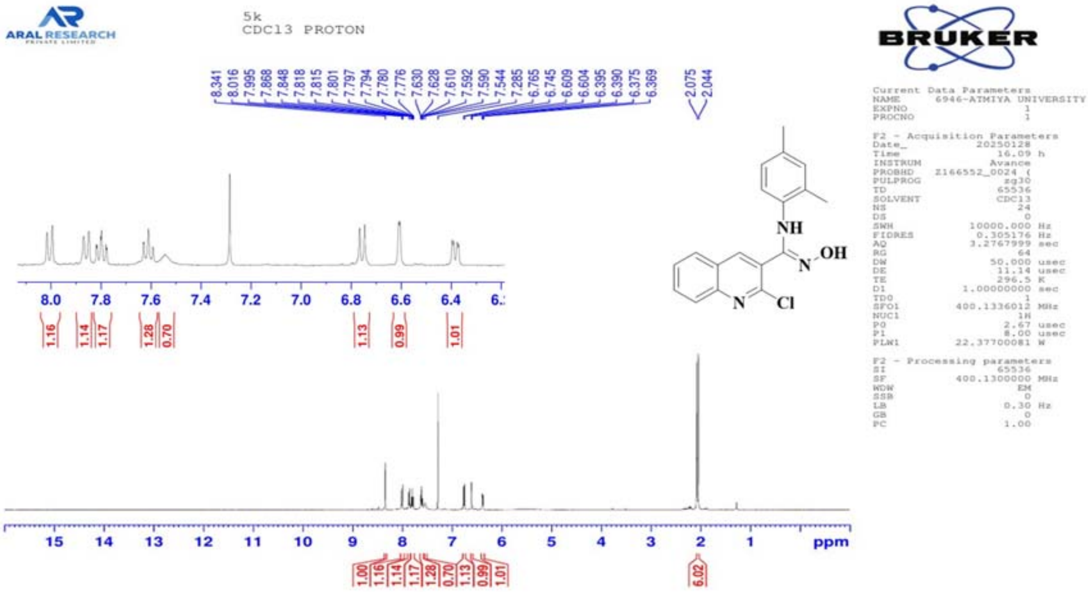


Figure 22: ^{1}H NMR of compound **5k**

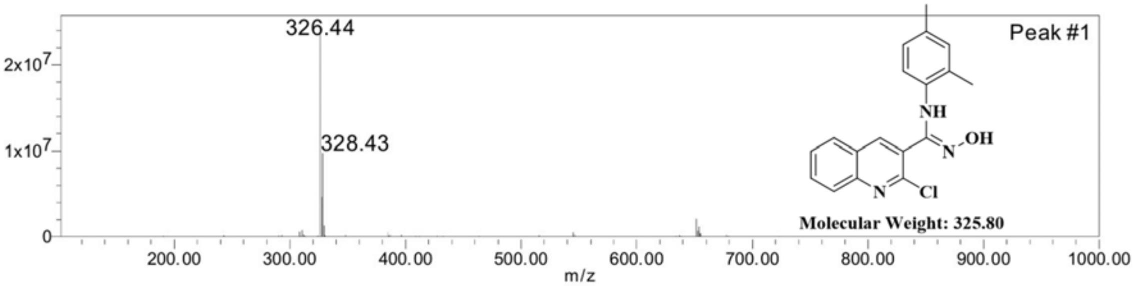
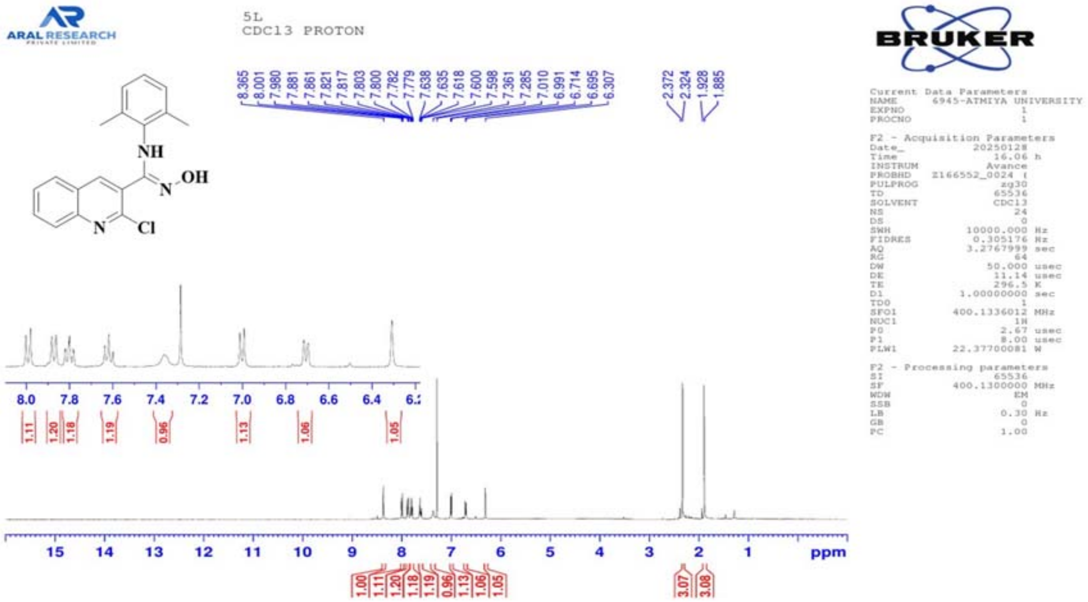


Figure 23: Mass spectrum of compound **5k**

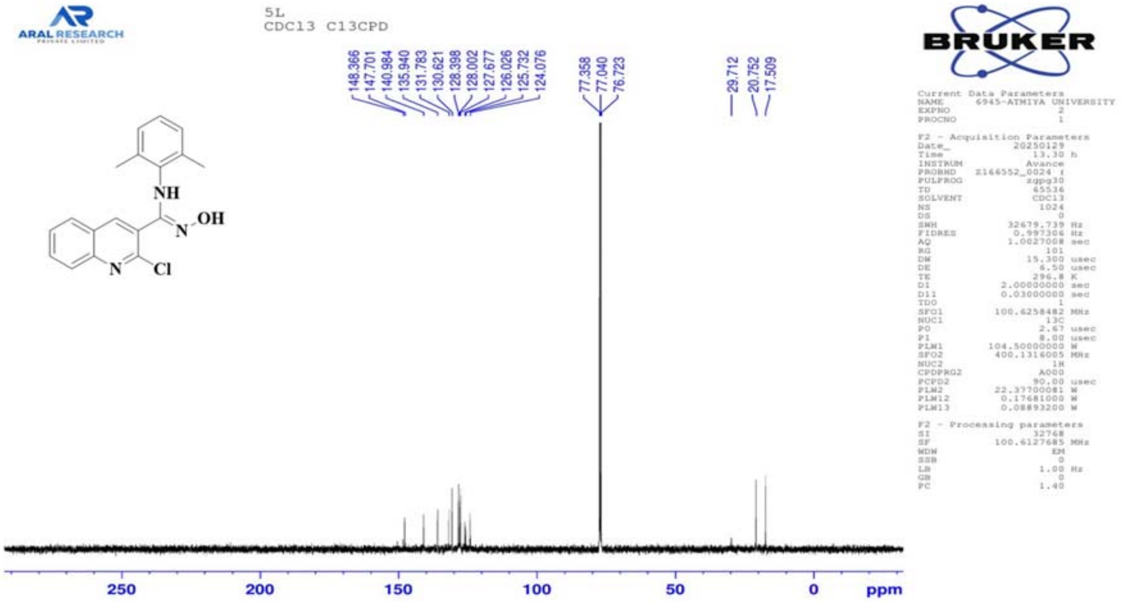


```
Current Data Parameters
NAME       6945-ATMIYA UNIVERSITY
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20250128
Time                       16.06 h
INSTRUM                   Avance
PROBHD    Z166552_0024 (
PULPROG                     zg30
TD                         65536
SOLVENT                    CDCl3
NS                            24
DS                             0
SWH                    10000.000 Hz
FIDRES                  0.305176 Hz
AQ                     3.2767999 sec
RG                            64
DW                        50.000 usec
DE                         11.14 usec
TE                         296.5 K
D1                    1.00000000 sec
TD0                            1
SFO1                 400.1336012 MHz
NUC1                          1H
P0                          2.67 usec
P1                          8.00 usec
PLW1                 22.37700081 W

F2 - Processing parameters
SI                         65536
SF                   400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

Figure 24: ^{1}H NMR of compound **5l**



```
Current Data Parameters
NAME       6945-ATMIYA UNIVERSITY
EXPNO                          2
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20250129
Time                       13.30 h
INSTRUM                   Avance
PROBHD    Z166552_0024 (
PULPROG                   zgpg30
TD                         65536
SOLVENT                    CDCl3
NS                          1024
DS                             0
SWH                    32679.739 Hz
FIDRES                  0.997306 Hz
AQ                     1.0027008 sec
RG                           101
DW                        15.300 usec
DE                          6.50 usec
TE                         296.8 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1
SFO1                 100.6258482 MHz
NUC1                         13C
P0                          2.67 usec
P1                          8.00 usec
PLW1                104.50000000 W
SFO2                 400.1316005 MHz
NUC2                          1H
CPDPRG2                     A000
PCPD2                      90.00 usec
PLW2                 22.37700081 W
PLW12                 0.17681000 W
PLW13                 0.08893200 W

F2 - Processing parameters
SI                         32768
SF                   100.6127685 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

Figure 25: ^{13}C NMR of compound **5l**

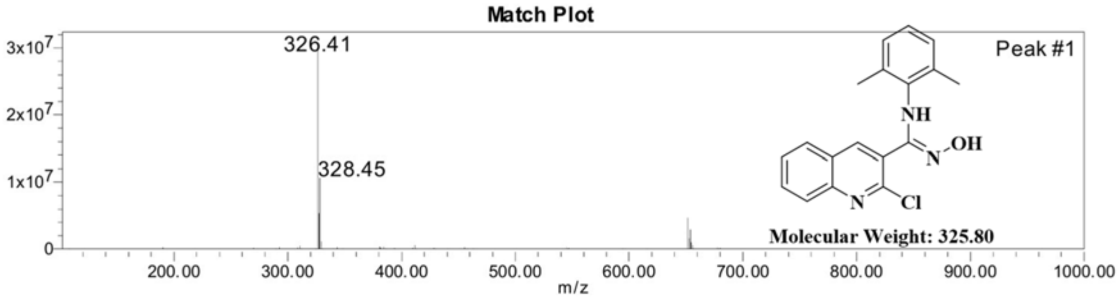
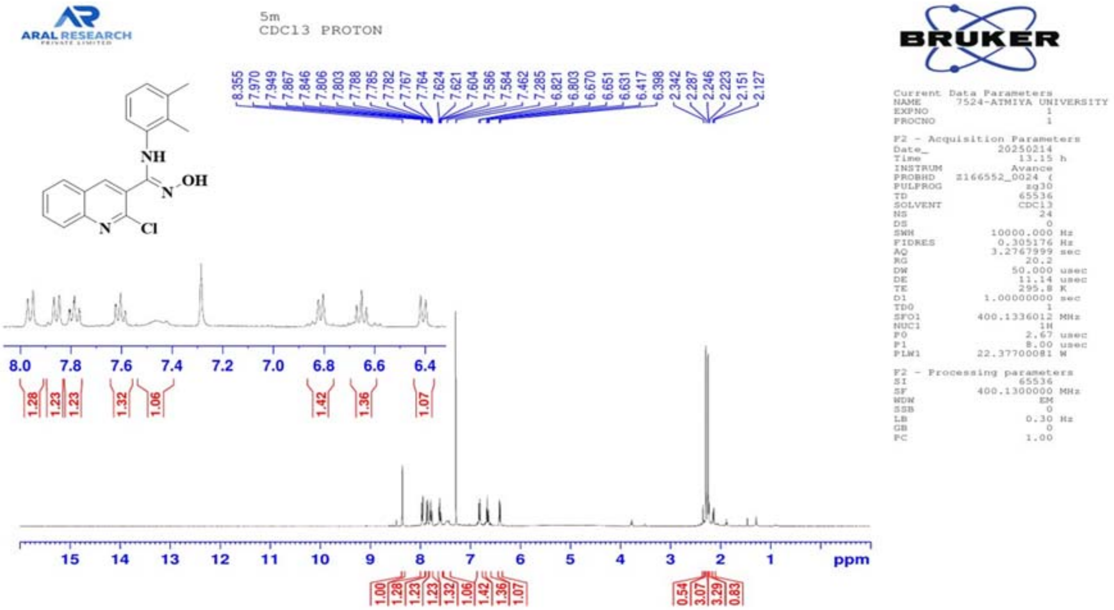


Figure 26: Mass spectrum of compound **5l**



```
Current Data Parameters
NAME       7524-ATMIYA UNIVERSITY
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20250214
Time                13.15 h
INSTRUM            Avance
PROBHD   Z166552_0024 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     24
DS                      0
SWH             10000.000 Hz
FIDRES           0.305176 Hz
AQ              3.2767999 sec
RG                   20.2
DW                 50.000 usec
DE                  11.14 usec
TE                  295.8 K
D1             1.00000000 sec
TD0                     1
SFO1          400.1336012 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          22.37700081 W

F2 - Processing parameters
SI                  65536
SF            400.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

Figure 27: ^{1}H NMR of compound **5m**

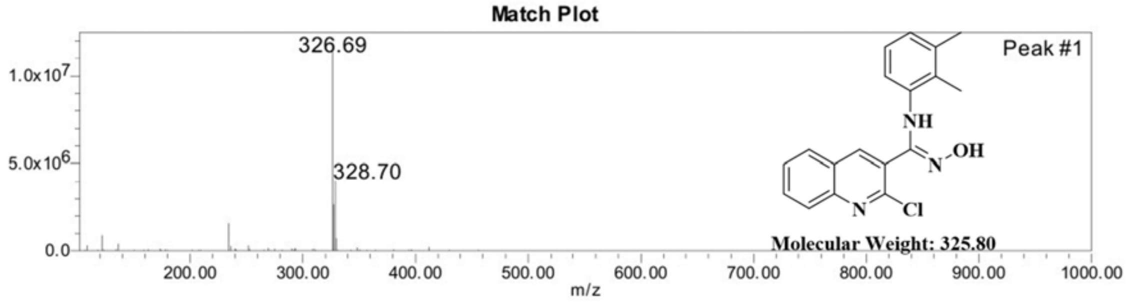
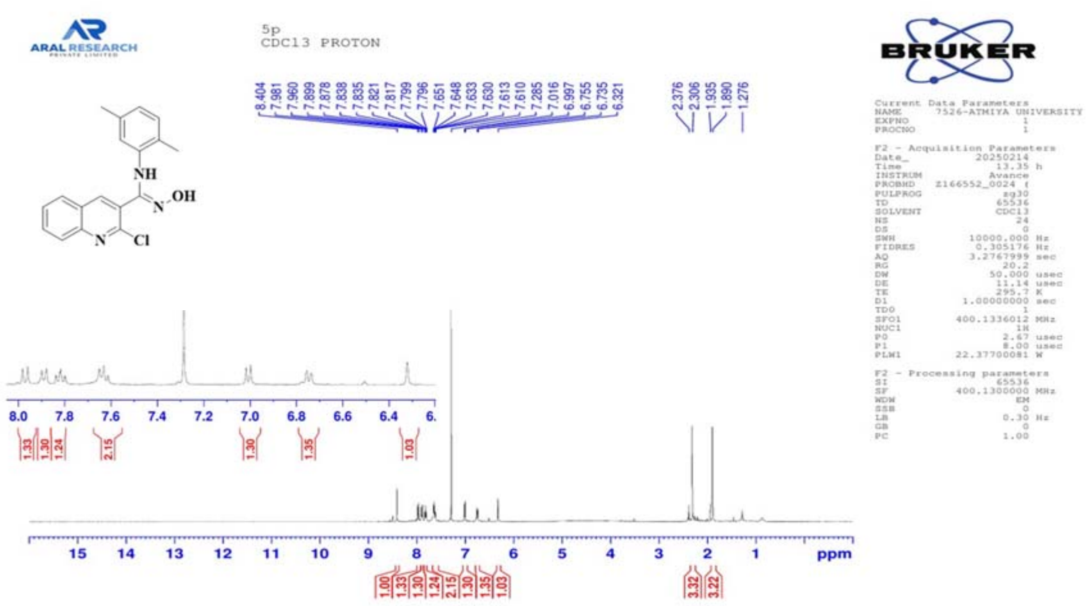


Figure 28: Mass spectrum of compound **5m**



```
Current Data Parameters
NAME       7526-ATMIYA UNIVERSITY
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20250214
Time               13.35 h
INSTRUM            Avance
PROBHD   Z166552_0024 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     24
DS                      0
SWH             10000.000 Hz
FIDRES           0.305176 Hz
AQ              3.2767999 sec
RG                   20.2
DW                 50.000 usec
DE                  11.14 usec
TE                  295.7 K
D1             1.00000000 sec
TD0                     1
SFO1          400.1336012 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          22.37700081 W

F2 - Processing parameters
SI                  65536
SF            400.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

Figure 29: ^{1}H NMR of compound **5o**

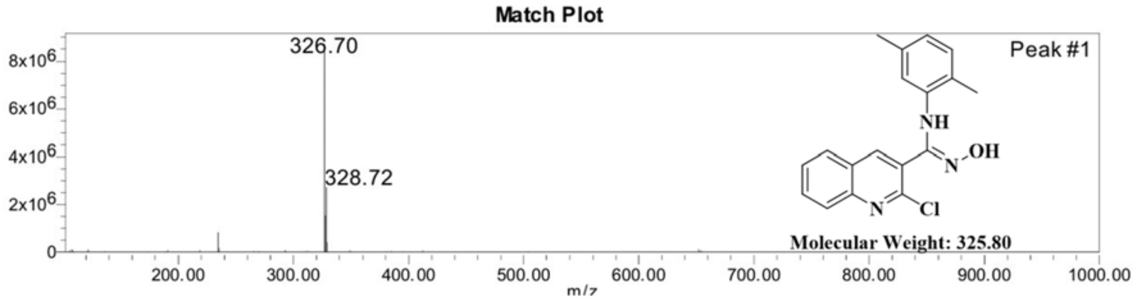


Figure 30: Mass spectrum of compound **5o**

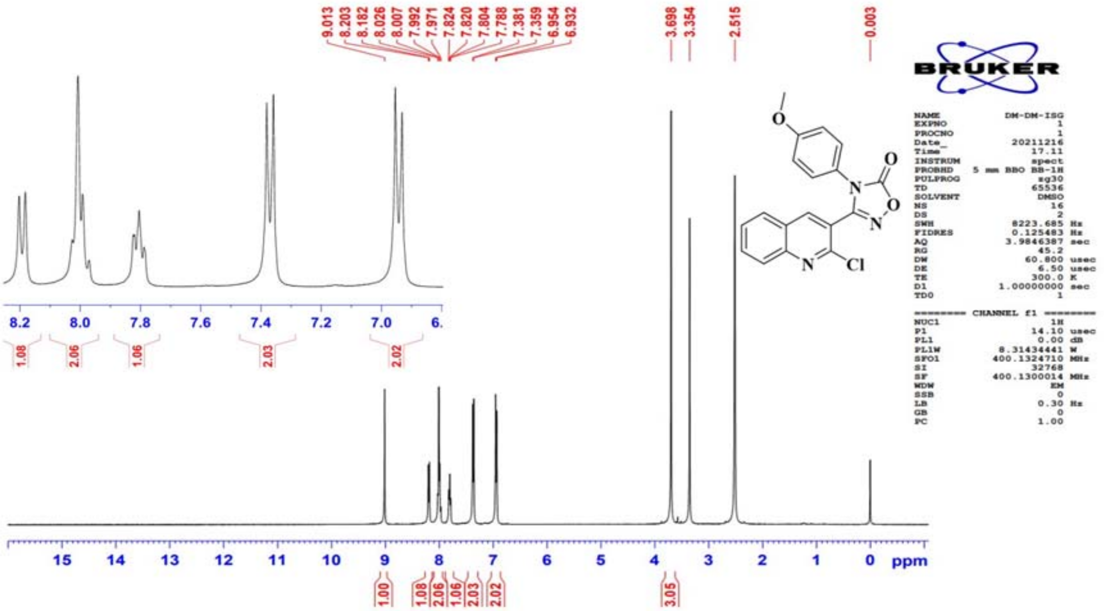


Figure 31: ^{1}H NMR of compound **6a**

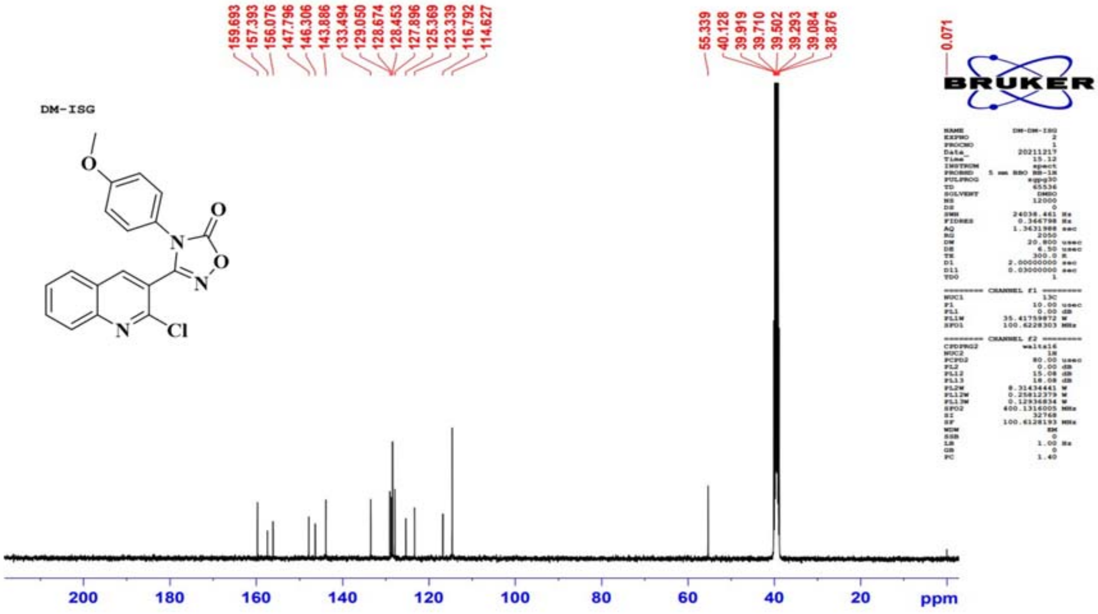
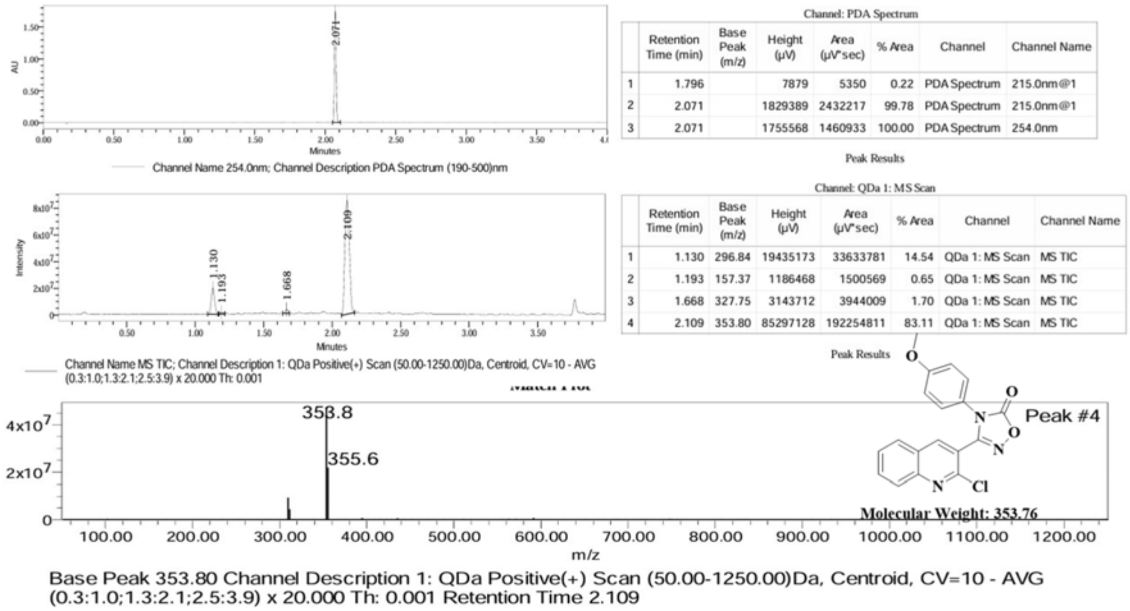


Figure 32: ^{13}C NMR of compound **6a**



Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.796		7879	5350	0.22	PDA Spectrum	215.0nm@1
2	2.071		1829389	2432217	99.78	PDA Spectrum	215.0nm@1
3	2.071		1755568	1460933	100.00	PDA Spectrum	254.0nm

Peak Results

Channel: QDa 1: MS Scan

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.130	296.84	19435173	33633781	14.54	QDa 1: MS Scan	MS TIC
2	1.193	157.37	1186468	1500569	0.65	QDa 1: MS Scan	MS TIC
3	1.668	327.75	3143712	3944009	1.70	QDa 1: MS Scan	MS TIC
4	2.109	353.80	85297128	192254811	83.11	QDa 1: MS Scan	MS TIC

Peak Results

Base Peak 353.80 Channel Description 1: QDa Positive(+) Scan (50.00-1250.00)Da, Centroid, CV=10 - AVG (0.3:1.0;1.3:2.1;2.5:3.9) x 20.000 Th: 0.001 Retention Time 2.109

Figure 33: LCMS of compound **6a**

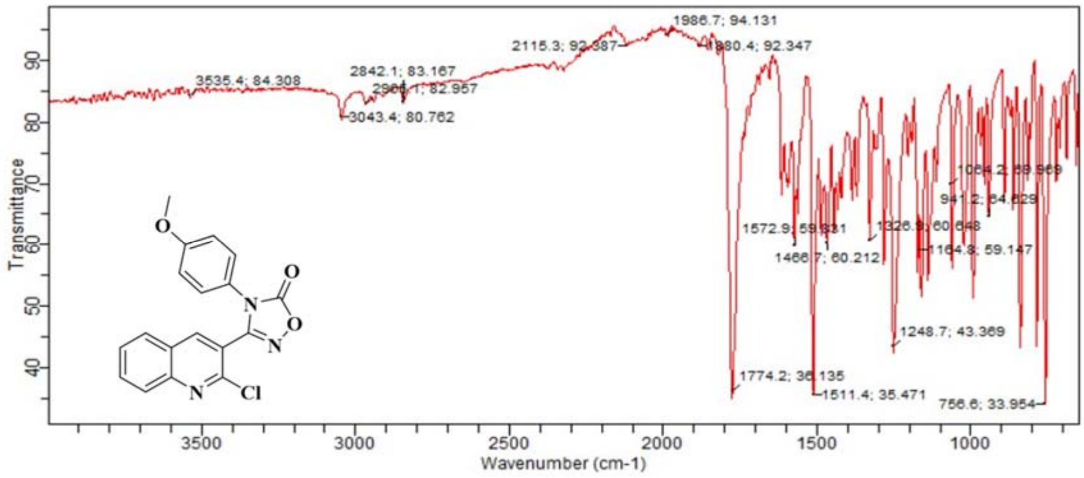


Figure 34: IR spectra of compound **6a**

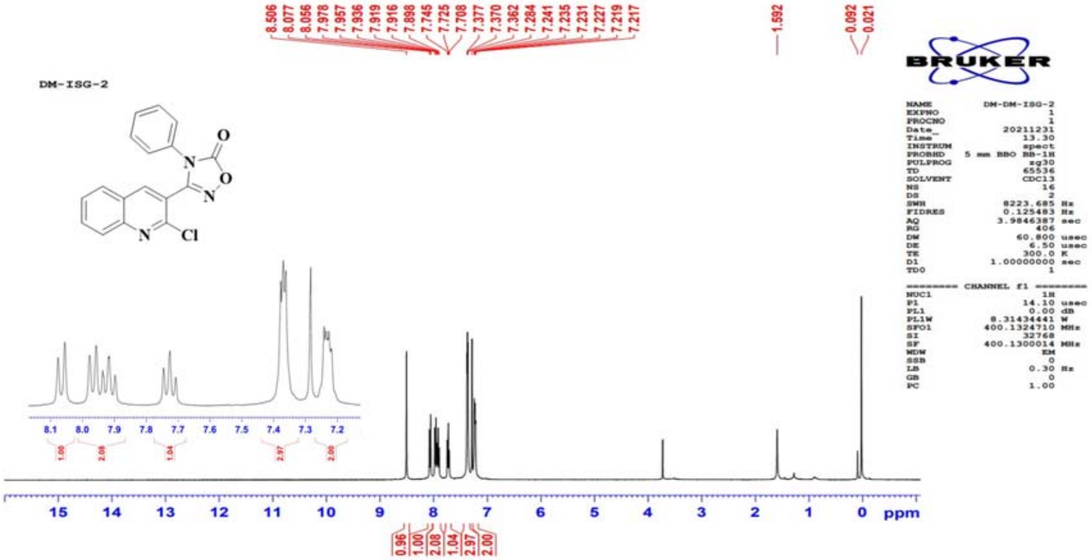


Figure 35: ^{1}H NMR of compound **6b**

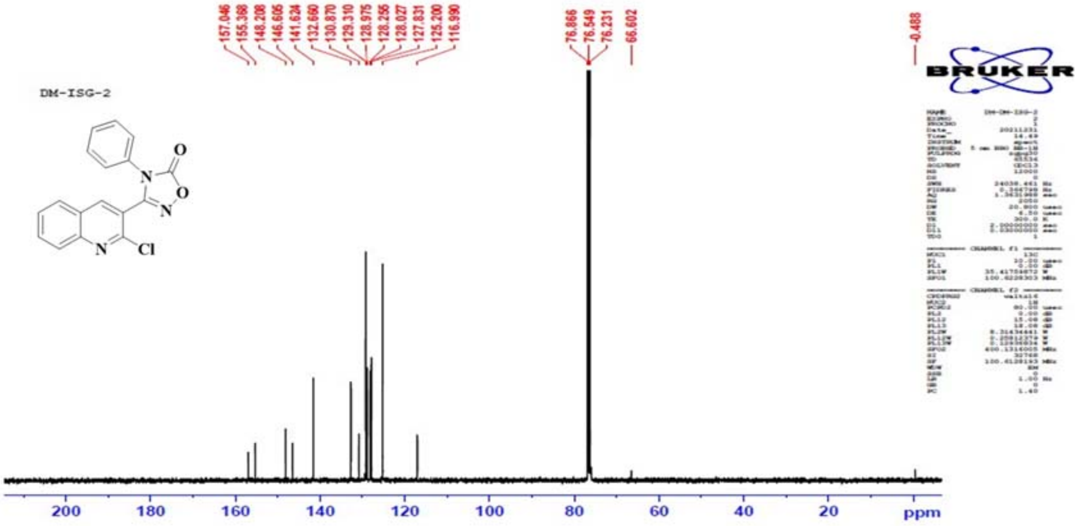


Figure 36: ^{13}C NMR of compound **6b**

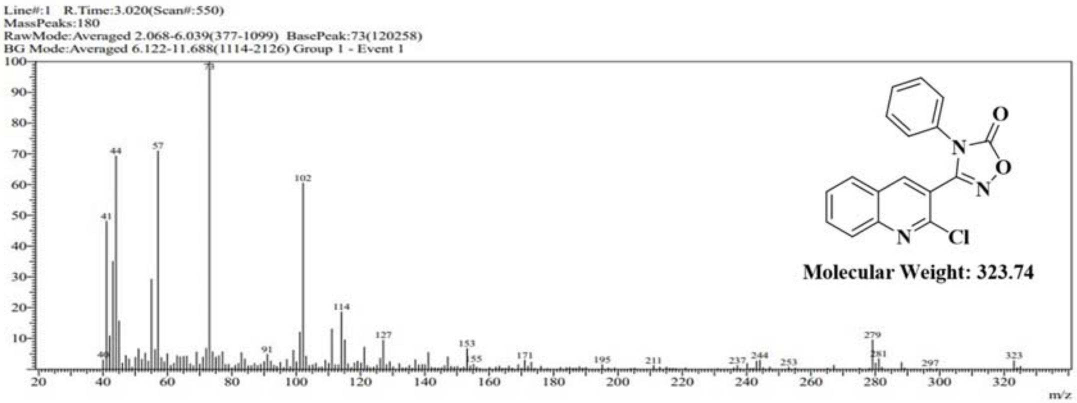


Figure 37: Mass spectrum of compound **6b**

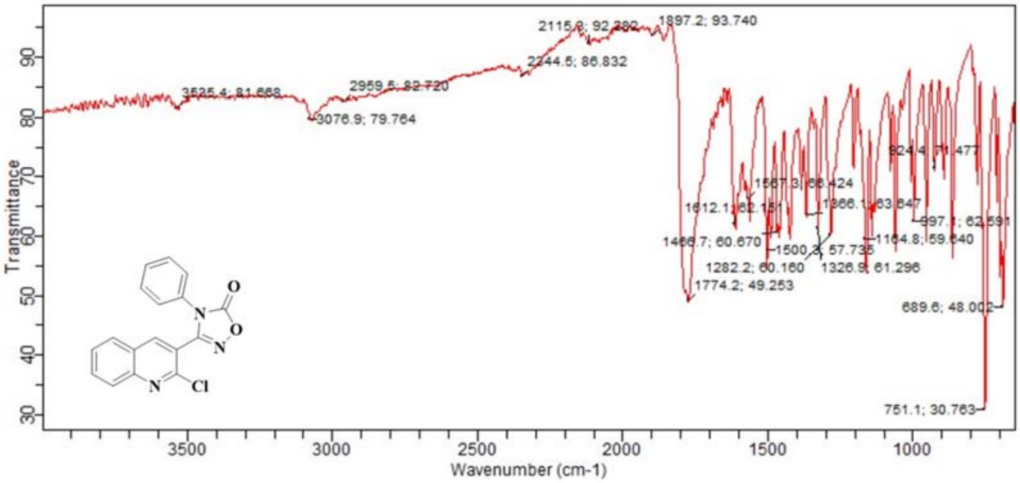


Figure 38: IR spectra of compound **6b**

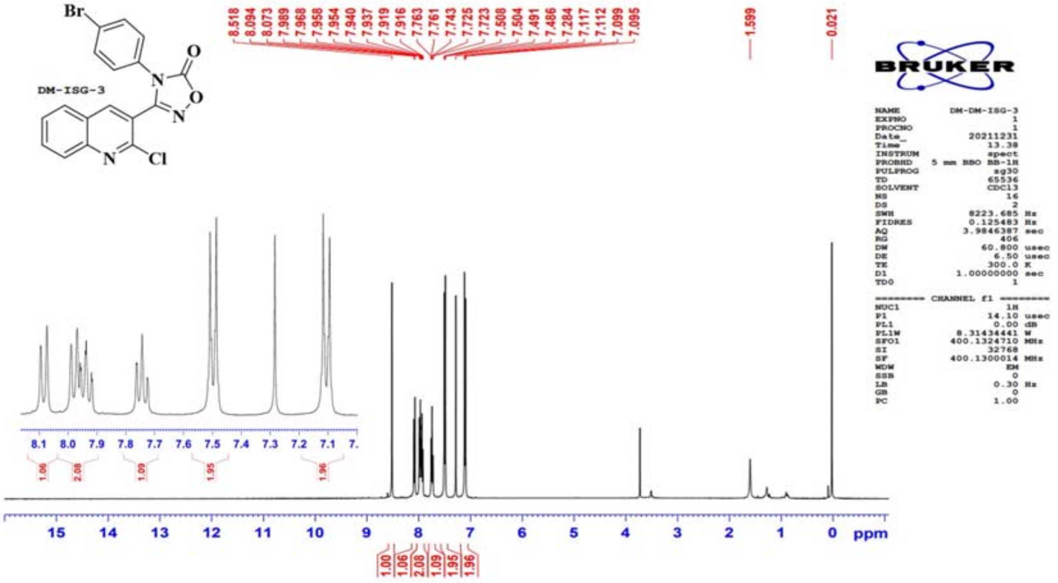


Figure 39: ^{1}H NMR of compound **6c**

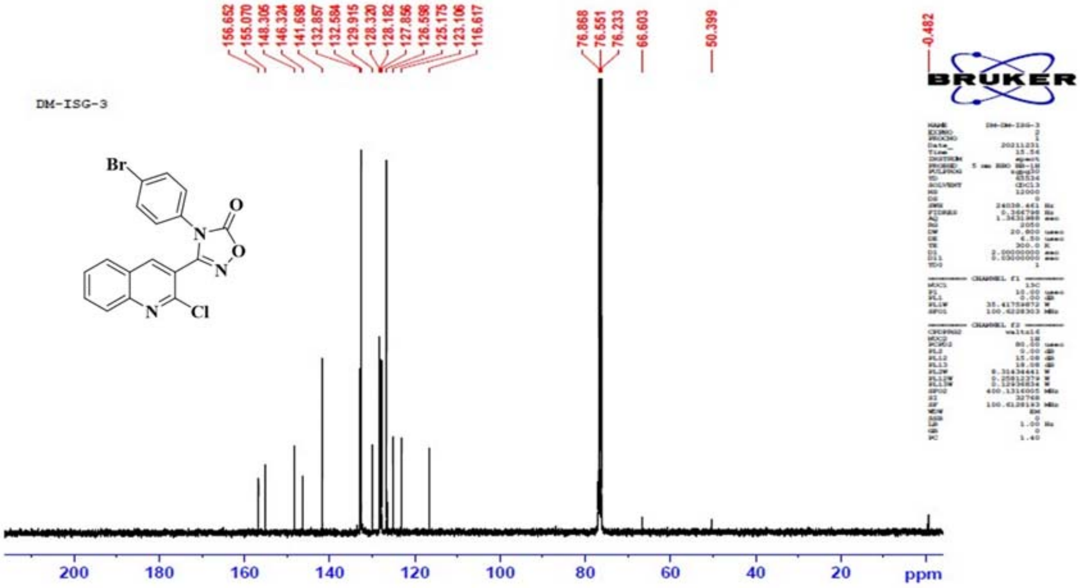


Figure 40: ^{13}C NMR of compound **6c**

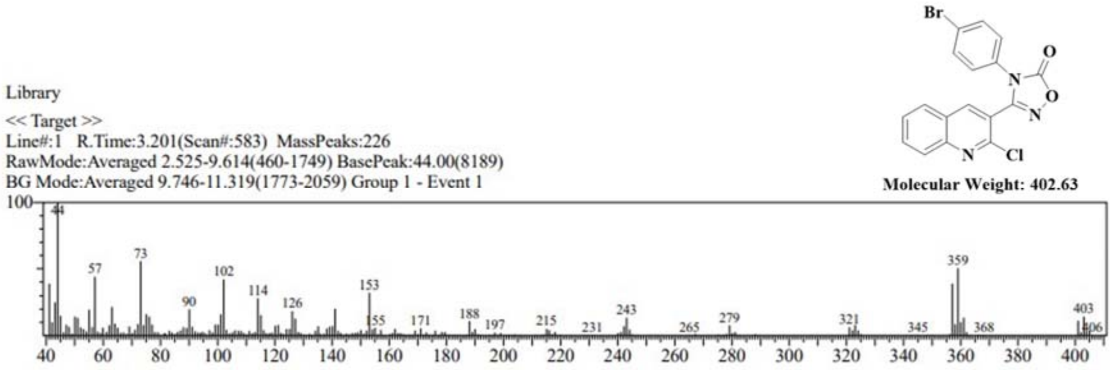


Figure 41: Mass spectrum of compound **6c**

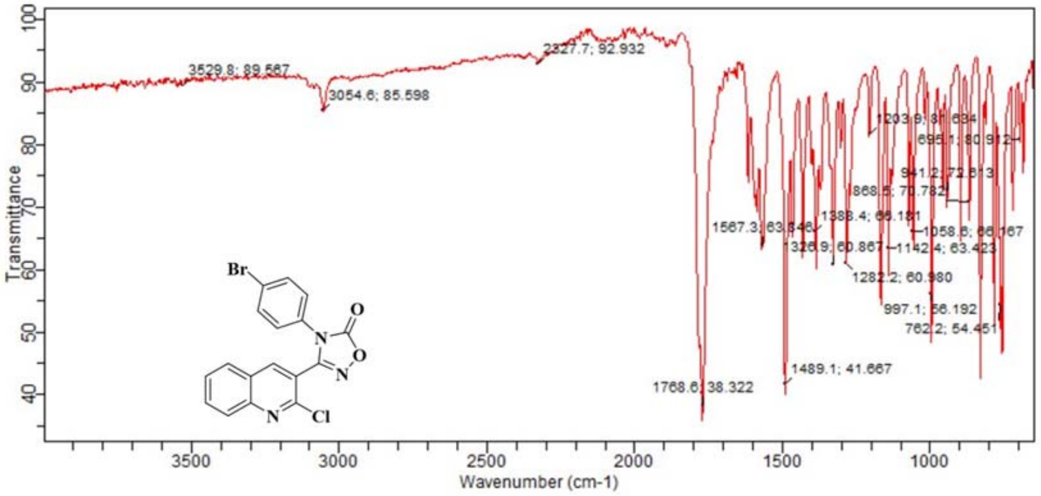
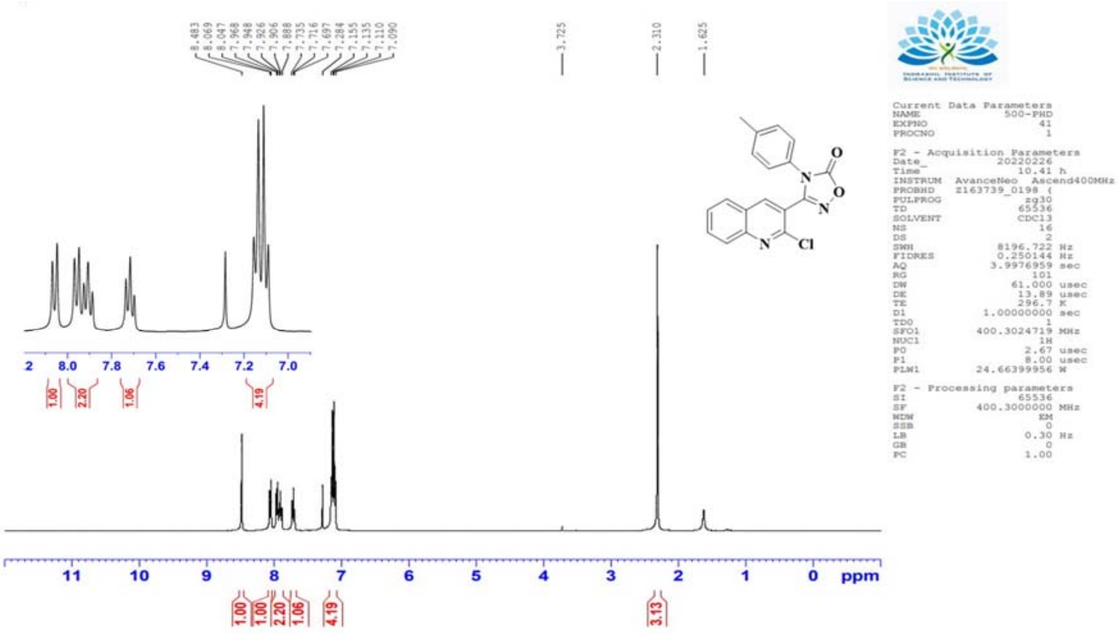


Figure 42: IR spectra of compound **6c**

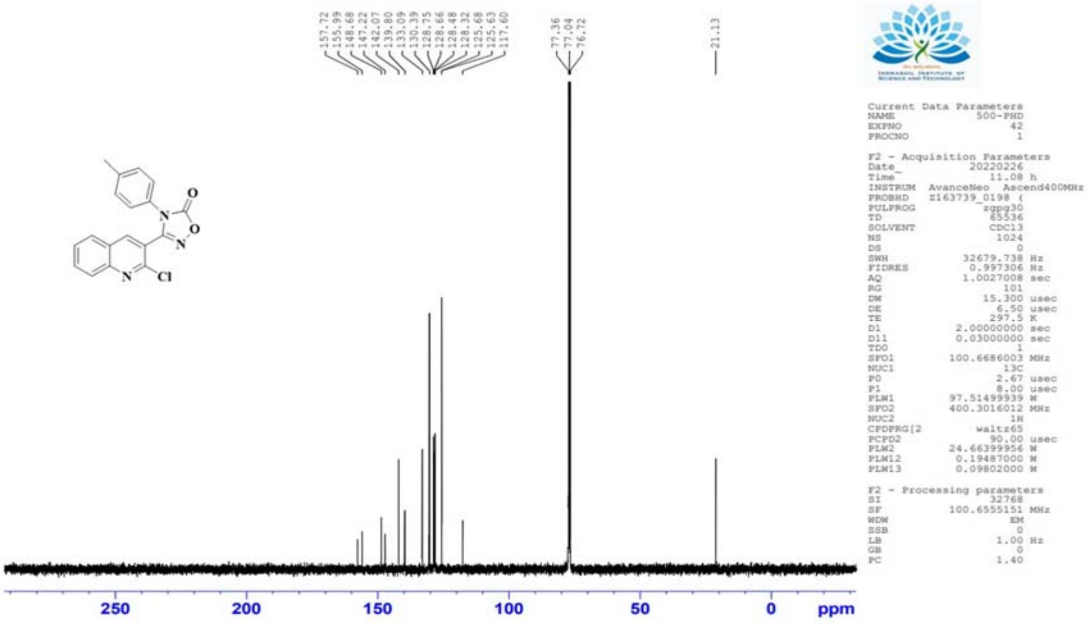


```
Current Data Parameters
NAME             500-PHD
EXPNO                 41
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220226
Time               10.41 h
INSTRUM   AvanceNeo  Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8196.722 Hz
FIDRES          0.250144 Hz
AQ             3.9976959 sec
RG                   101
DW                61.000 usec
DE                 13.89 usec
TE                 296.7 K
D1            1.00000000 sec
TDO                    1
SFO1         400.3024719 MHz
NUC1                  1H
P0                  2.67 usec
P1                  8.00 usec
PLW1         24.66399956 W

F2 - Processing parameters
SI                 65536
SF           400.3000000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

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

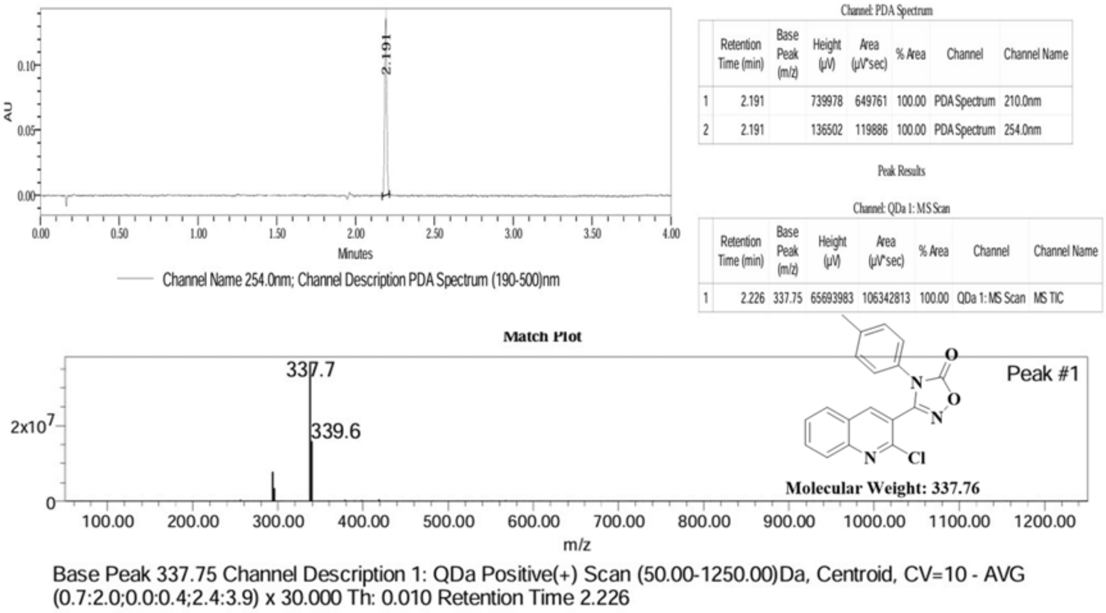


```
Current Data Parameters
NAME             500-PHD
EXPNO                 42
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220226
Time               11.08 h
INSTRUM   AvanceNeo  Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     0
SWH            32679.738 Hz
FIDRES          0.997306 Hz
AQ             1.0027008 sec
RG                   101
DW                15.300 usec
DE                  6.50 usec
TE                 297.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TDO                    1
SFO1         100.6686003 MHz
NUC1                 13C
P0                  2.67 usec
P1                  8.00 usec
PLW1         97.51499939 W
SFO2         400.3016012 MHz
NUC2                  1H
CPDPRG[2         waltz65
PCPD2              90.00 usec
PLW2         24.66399956 W
PLW12         0.19487000 W
PLW13         0.09802000 W

F2 - Processing parameters
SI                 32768
SF           100.6555151 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

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



Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	2.191		739978	649761	100.00	PDA Spectrum	210.0nm
2	2.191		136502	119886	100.00	PDA Spectrum	254.0nm

Peak Results

Channel: QDa 1: MS Scan

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	2.226	337.75	65693983	106342813	100.00	QDa 1: MS Scan	MS TIC

Base Peak 337.75 Channel Description 1: QDa Positive(+) Scan (50.00-1250.00)Da, Centroid, CV=10 - AVG (0.7:2.0;0.0:0.4;2.4:3.9) x 30.000 Th: 0.010 Retention Time 2.226

Figure 45: LCMS of compound **6d**

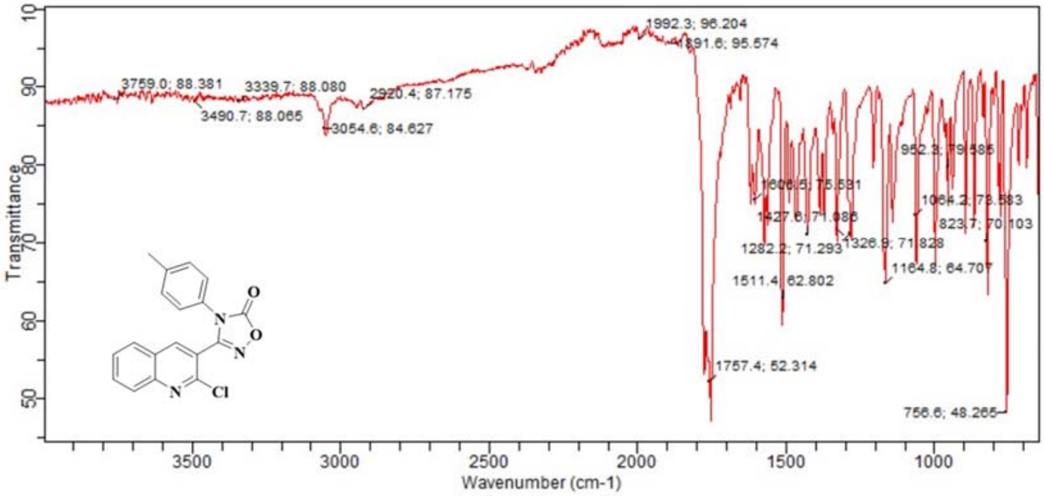
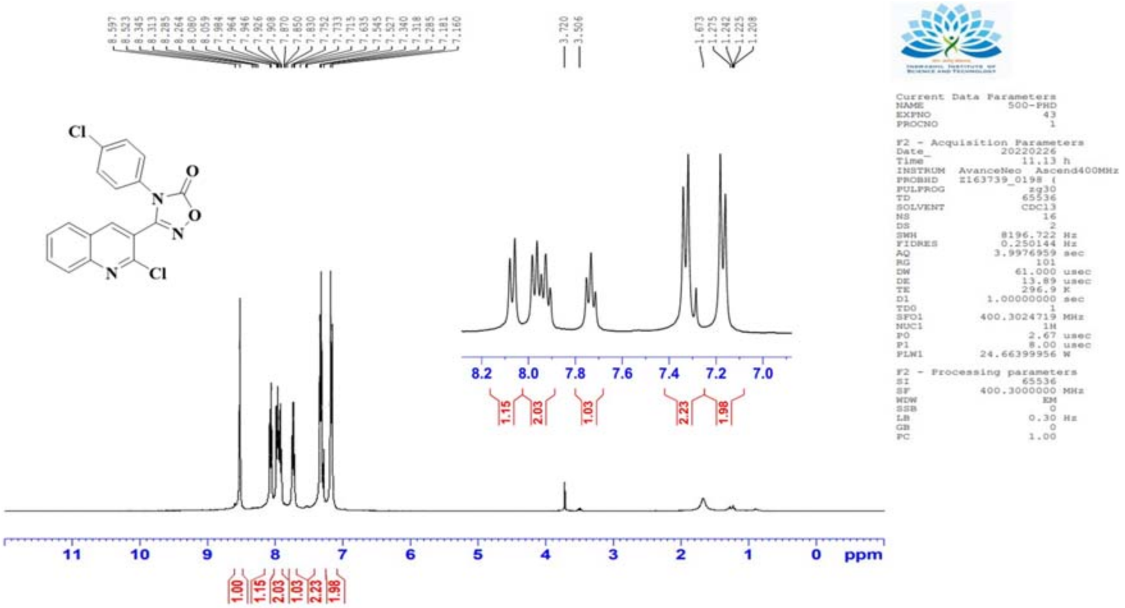


Figure 46: IR spectra of compound **6d**

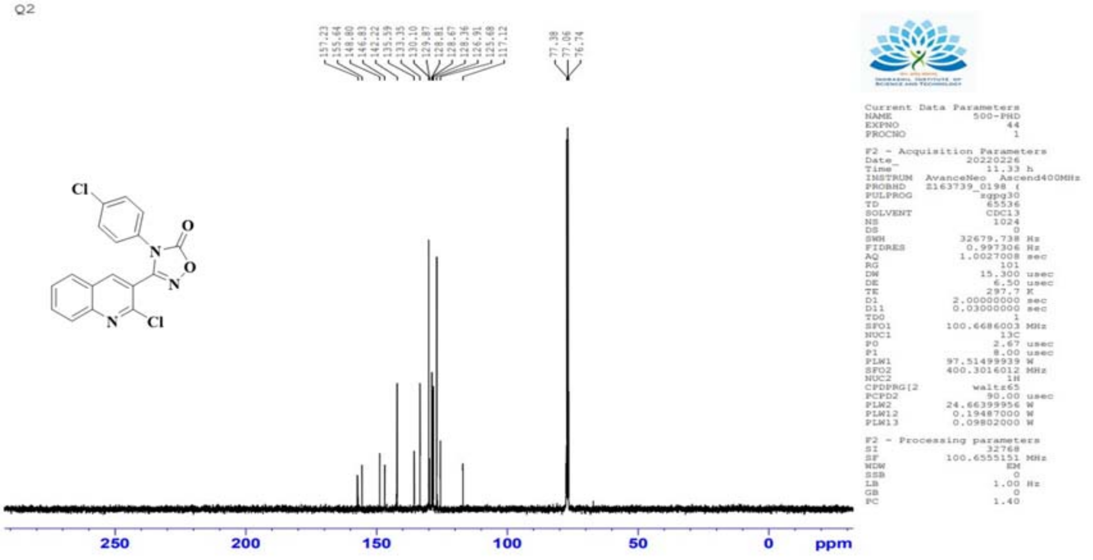


```
Current Data Parameters
NAME              500-PHD
EXPNO                  43
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                11.13 h
INSTRUM  AvanceNeo  Ascend400MHz
PROBHD   Z163739_0198 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.250144 Hz
AQ              3.9976959 sec
RG                    101
DW                 61.000 usec
DE                  13.89 usec
TE                  296.9 K
D1             1.00000000 sec
TD0                     1
SFO1          400.3024719 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          24.66399956 W

F2 - Processing parameters
SI                  65536
SF            400.3000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

Figure 47: ^{1}H NMR of compound **6e**

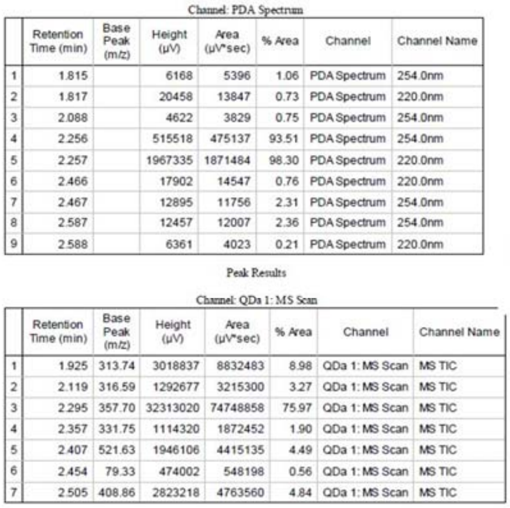


```
Current Data Parameters
NAME              500-PHD
EXPNO                  44
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                11.33 h
INSTRUM  AvanceNeo  Ascend400MHz
PROBHD   Z163739_0198 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      0
SWH             32679.738 Hz
FIDRES           0.997306 Hz
AQ              1.0027008 sec
RG                    101
DW                 15.300 usec
DE                   6.50 usec
TE                  297.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6686003 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          97.51499939 W
SFO2          400.3016012 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          24.66399956 W
PLW12          0.19487000 W
PLW13          0.09802000 W

F2 - Processing parameters
SI                  32768
SF            100.6555151 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

Figure 48: ^{13}C NMR of compound **6e**



Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.815		6168	5396	1.06	PDA Spectrum	254.0nm
2	1.817		20458	13847	0.73	PDA Spectrum	220.0nm
3	2.088		4622	3829	0.75	PDA Spectrum	254.0nm
4	2.256		515518	475137	93.51	PDA Spectrum	254.0nm
5	2.257		1967335	1871484	98.30	PDA Spectrum	220.0nm
6	2.466		17902	14547	0.76	PDA Spectrum	220.0nm
7	2.467		12895	11756	2.31	PDA Spectrum	254.0nm
8	2.587		12457	12007	2.36	PDA Spectrum	254.0nm
9	2.588		6361	4023	0.21	PDA Spectrum	220.0nm

Peak Results

Channel: QDa 1: MS Scan

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.925	313.74	3018837	8832483	8.98	QDa 1: MS Scan	MS TIC
2	2.119	316.59	1292677	3215300	3.27	QDa 1: MS Scan	MS TIC
3	2.295	357.70	32313020	74748858	75.97	QDa 1: MS Scan	MS TIC
4	2.357	331.75	1114320	1872452	1.90	QDa 1: MS Scan	MS TIC
5	2.407	521.63	1946106	4415135	4.49	QDa 1: MS Scan	MS TIC
6	2.454	79.33	474002	548198	0.56	QDa 1: MS Scan	MS TIC
7	2.505	408.86	2823218	4763560	4.84	QDa 1: MS Scan	MS TIC

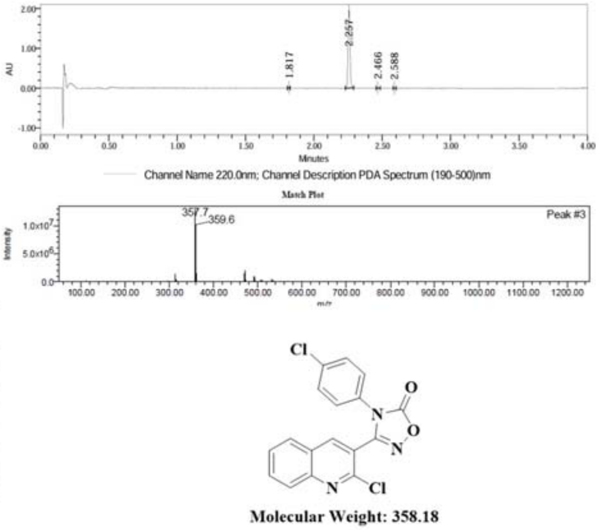


Figure 49: LCMS of compound **6e**

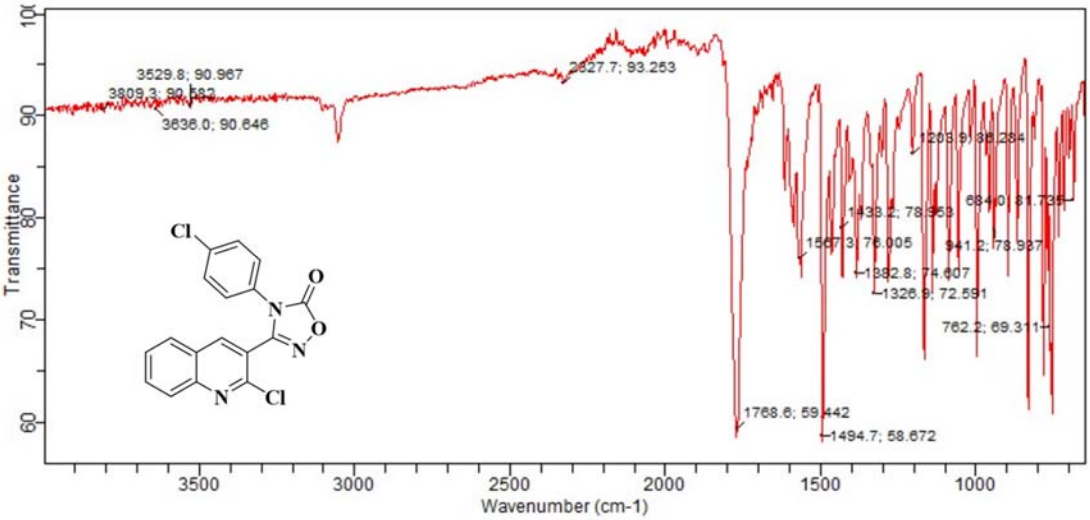


Figure 50: IR spectra of compound **6e**

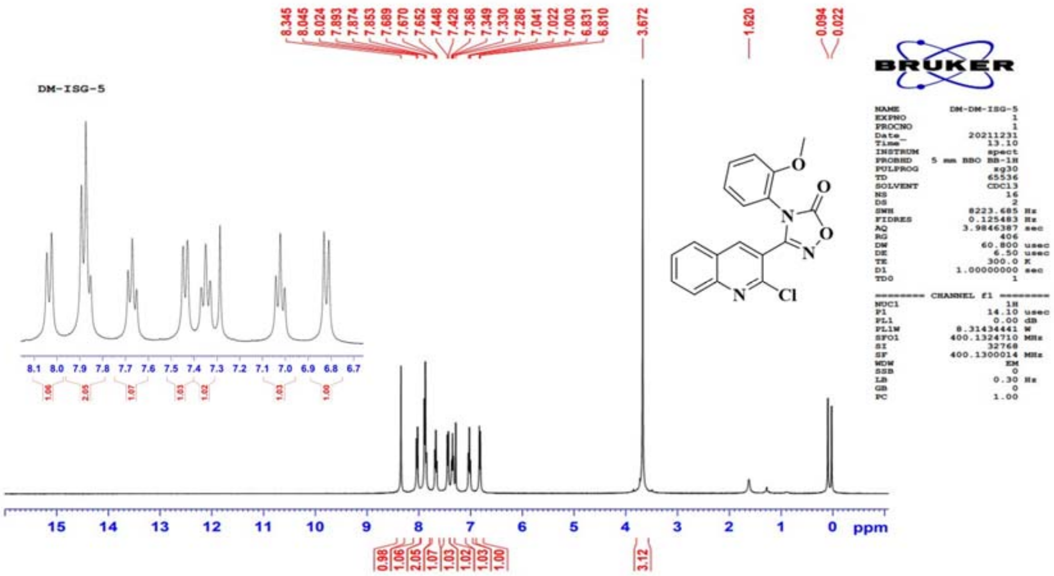


Figure 51: ^{1}H NMR of compound **6f**

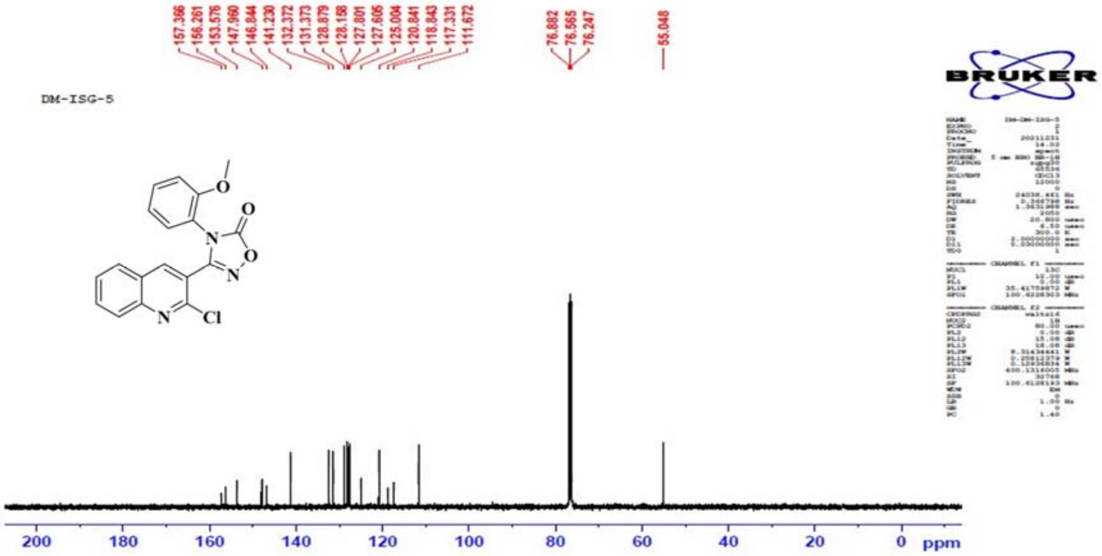


Figure 52: ^{13}C NMR of compound **6f**

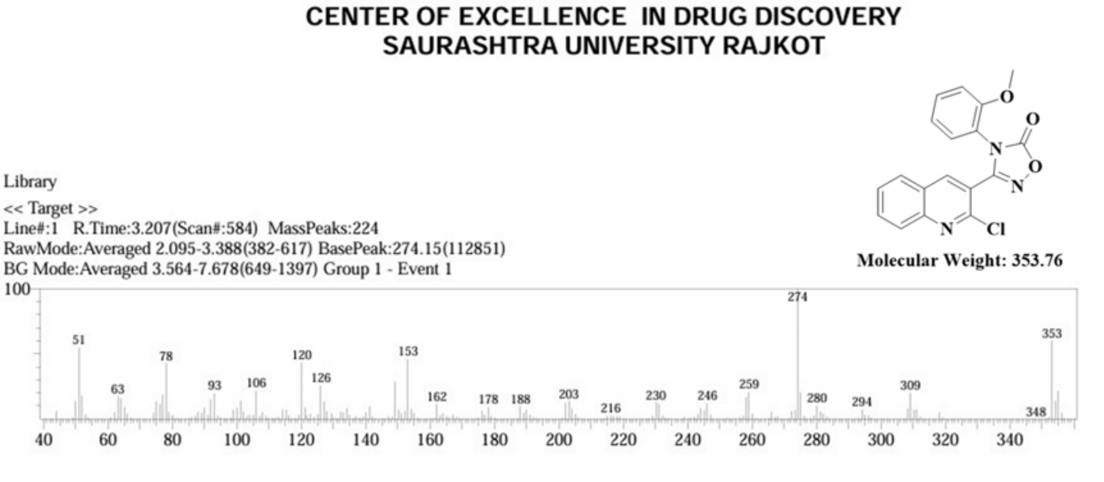


Figure 53: Mass spectrum of compound **6f**

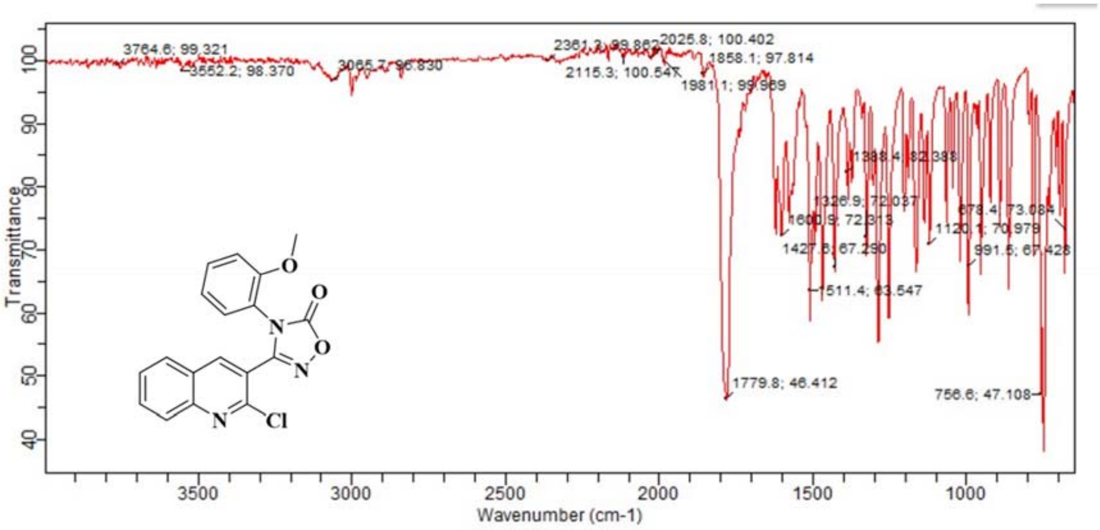


Figure 54: IR spectra of compound **6f**

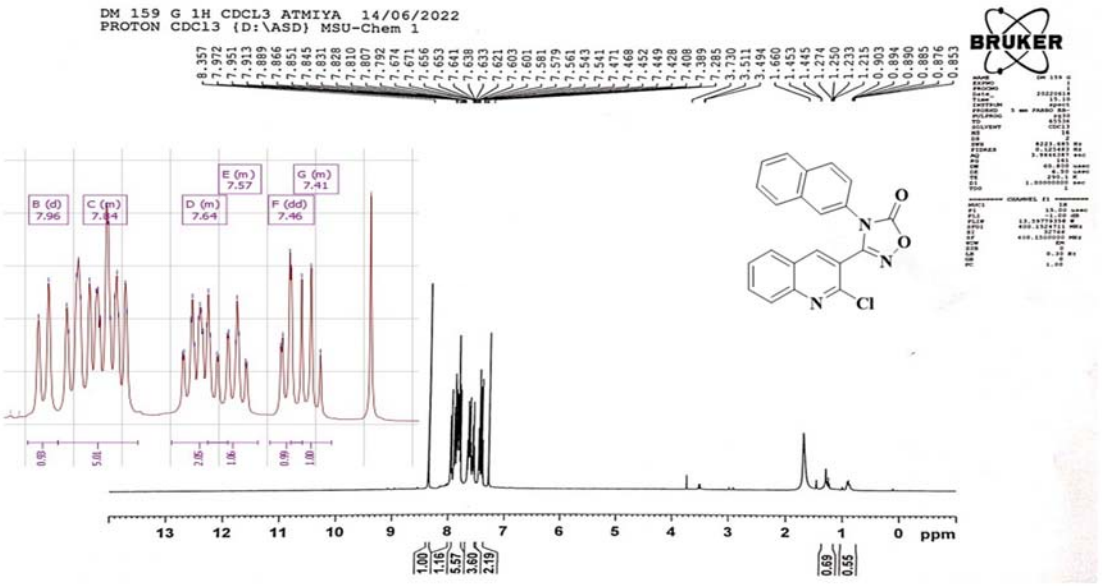


Figure 55: ^{1}H NMR of compound **6g**

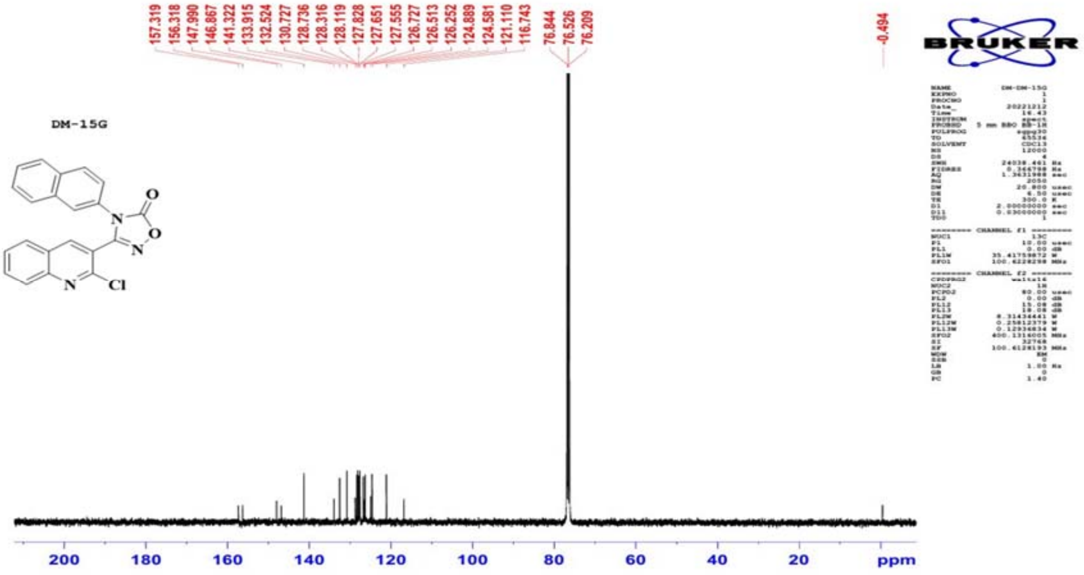


Figure 56: ^{13}C NMR of compound **6g**

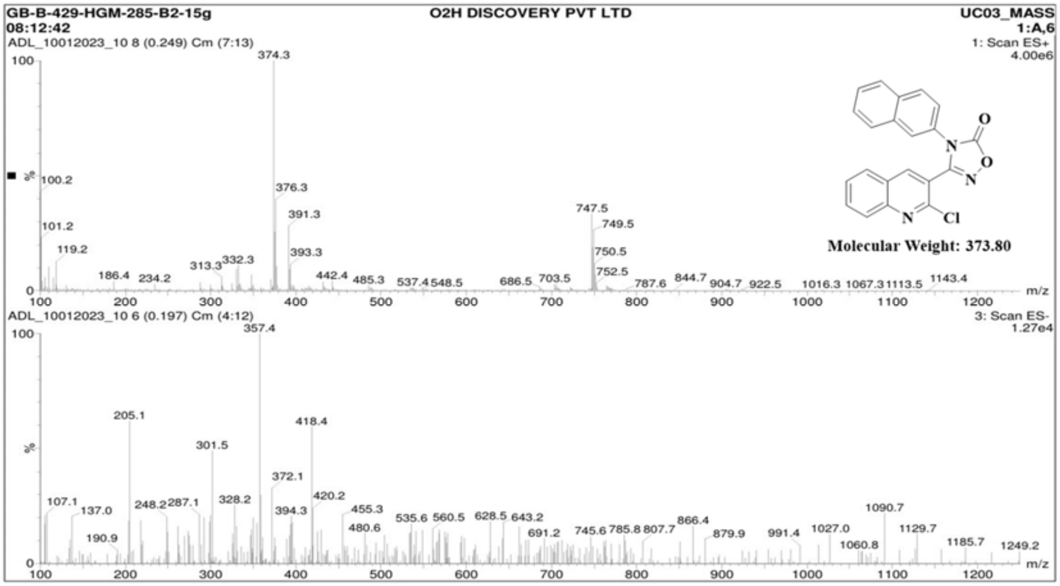


Figure 57: Mass spectrum of compound **6g**

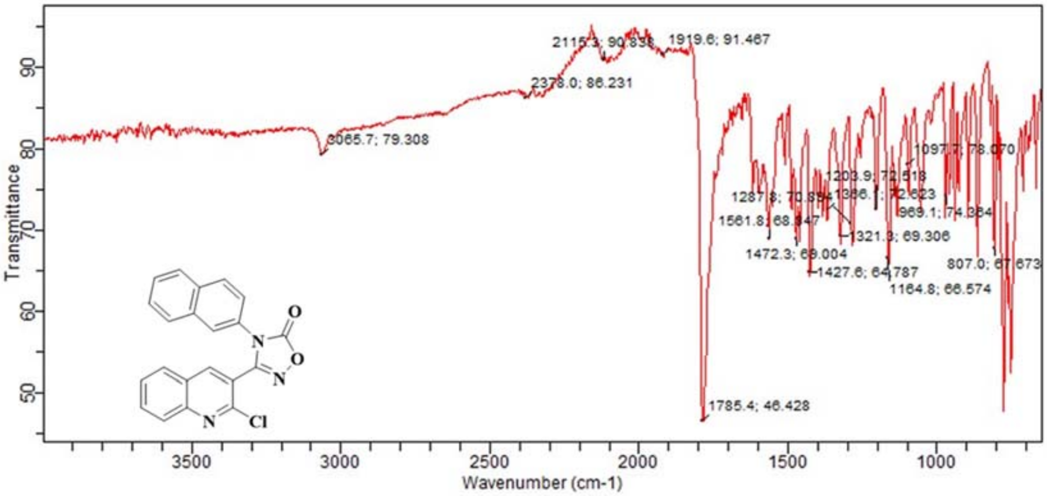
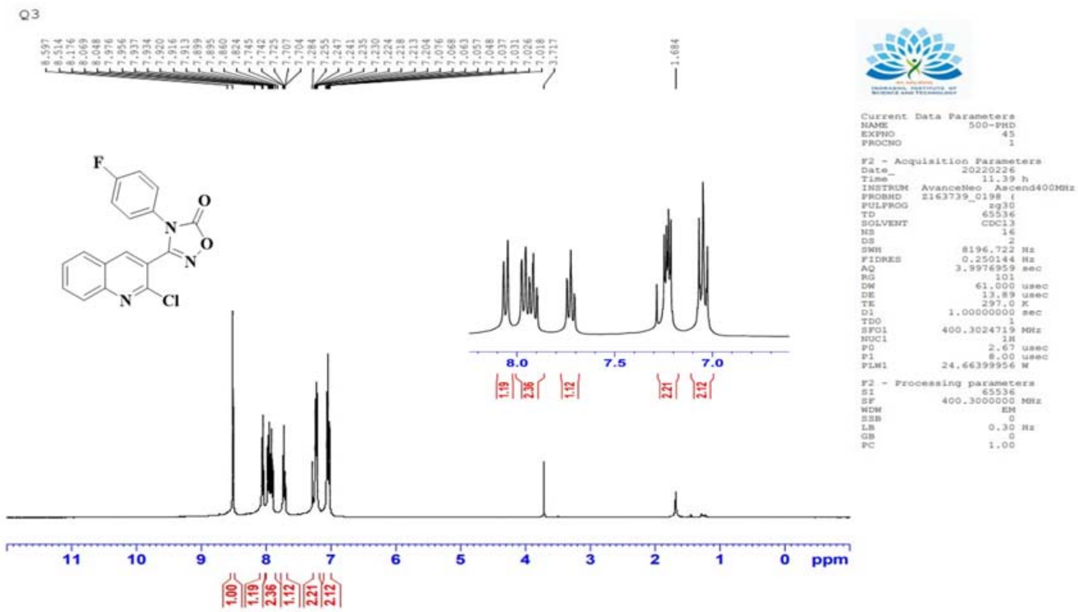


Figure 58: IR spectra of compound **6g**



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Current Data Parameters
NAME              500-PHD
EXPNO                  45
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                11.39 h
INSTRUM  AvanceNeo  Ascend400MHz
PROBHD   Z163739_0198 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.250144 Hz
AQ              3.9976959 sec
RG                    101
DW                 61.000 usec
DE                  13.89 usec
TE                  297.0 K
D1             1.00000000 sec
TD0                     1
SFO1          400.3024719 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          24.66399956 W

F2 - Processing parameters
SI                  65536
SF            400.3000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```
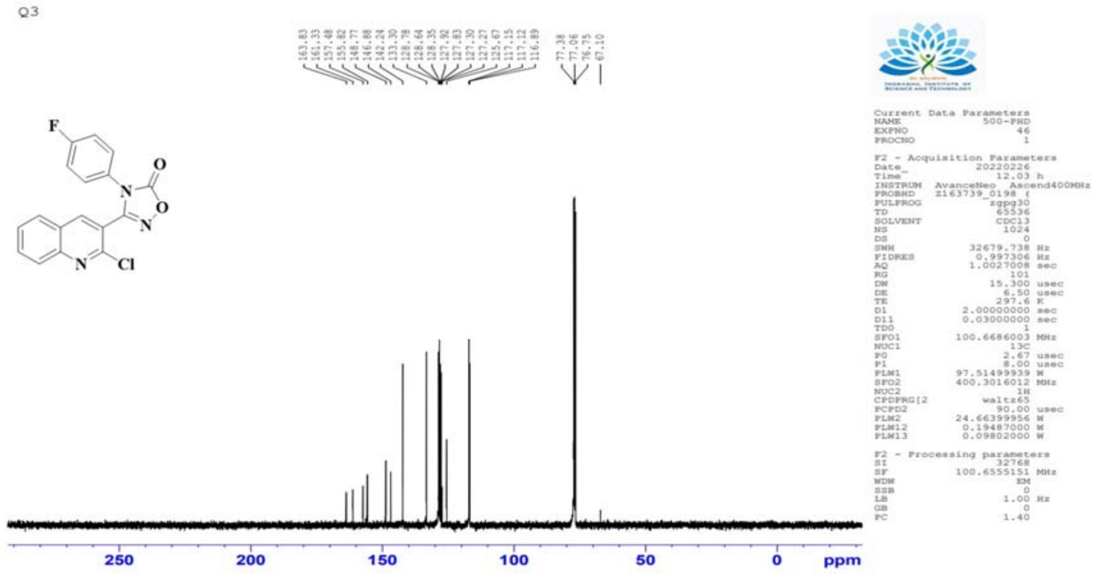

Figure 59: ^{1}H NMR of compound **6h**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  46
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                12.03 h
INSTRUM  AvanceNeo  Ascend400MHz
PROBHD   Z163739_0198 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      0
SWH             32679.738 Hz
FIDRES           0.997306 Hz
AQ              1.0027008 sec
RG                    101
DW                 15.300 usec
DE                   6.50 usec
TE                  297.6 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6686003 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          97.51499939 W
SFO2          400.3016012 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          24.66399956 W
PLW12          0.19487000 W
PLW13          0.09802000 W

F2 - Processing parameters
SI                  32768
SF            100.6555151 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

Figure 60: ^{13}C NMR of compound **6h**

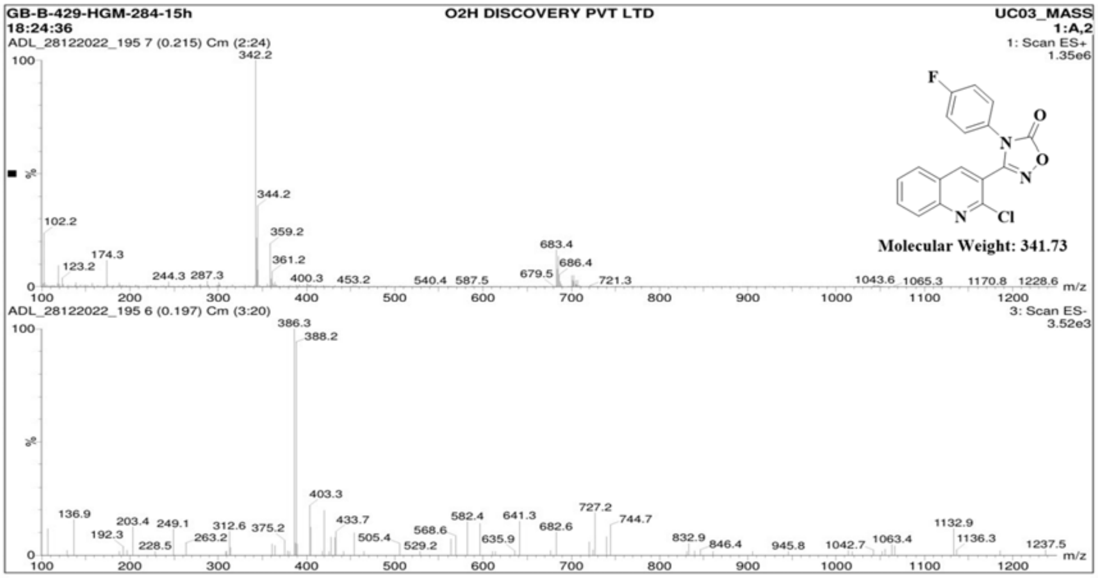


Figure 61: Mass spectrum of compound **6h**

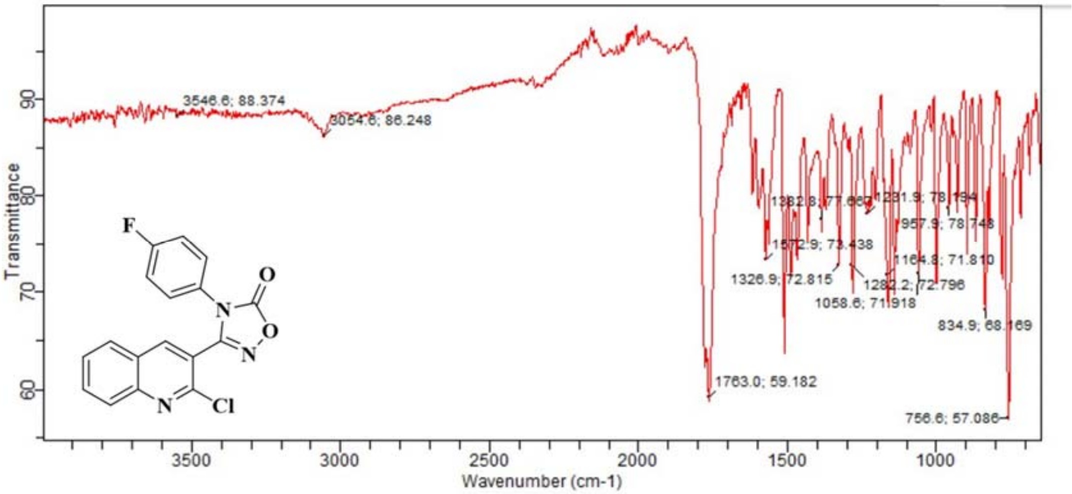


Figure 62: IR spectra of compound **6h**

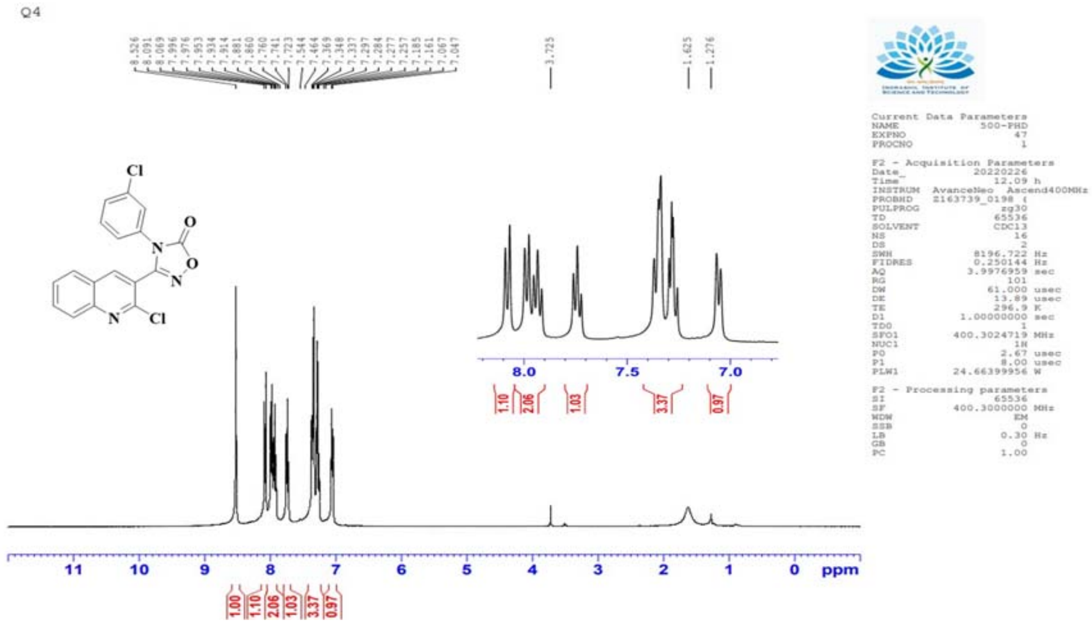


Figure 63: ^{1}H NMR of compound **6i**

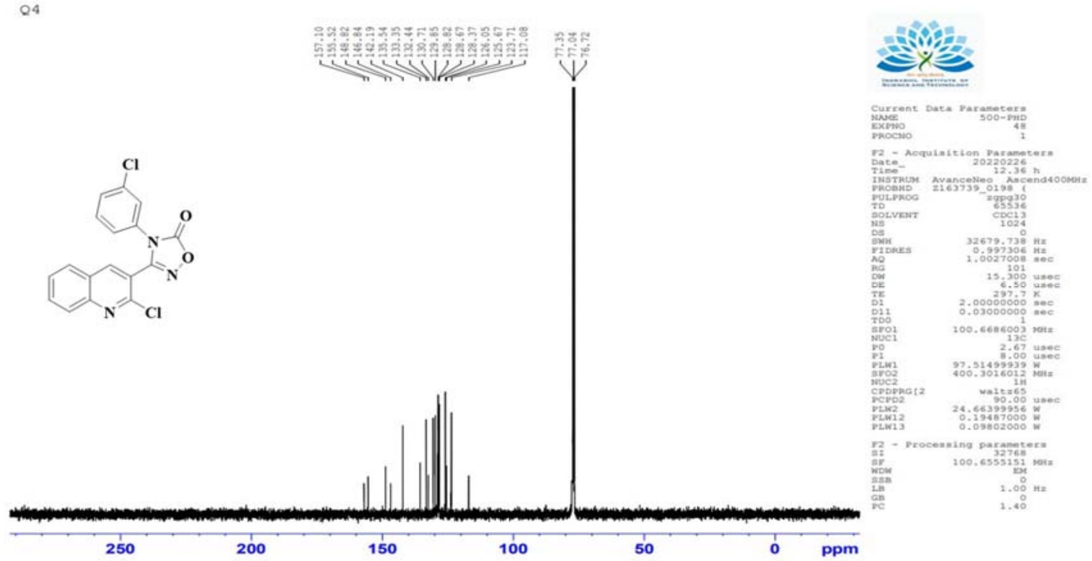


Figure 64: ^{13}C NMR of compound **6i**

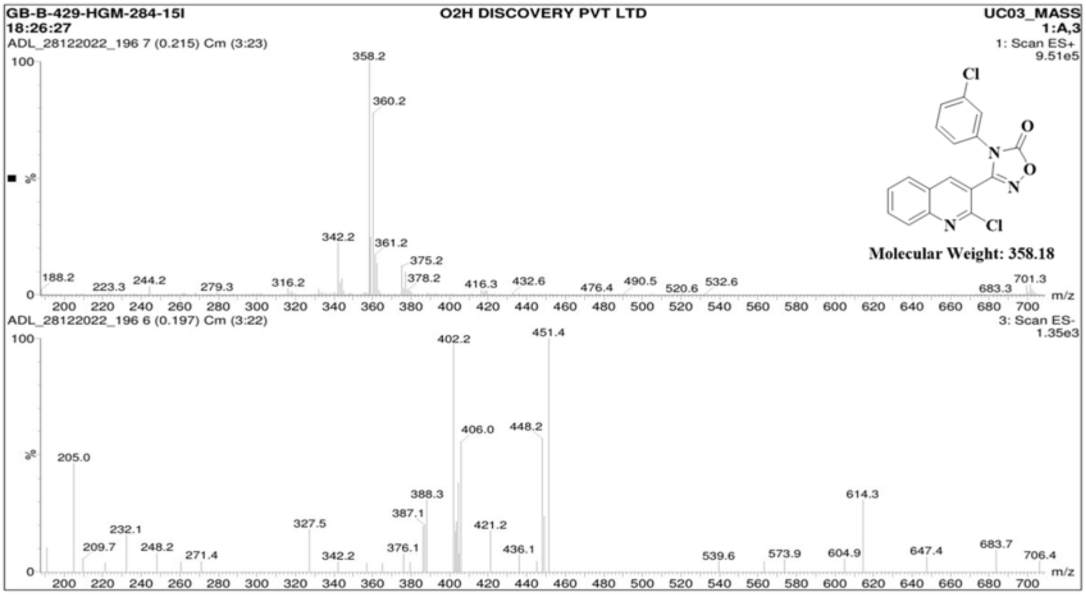


Figure 65: Mass spectrum of compound **6i**

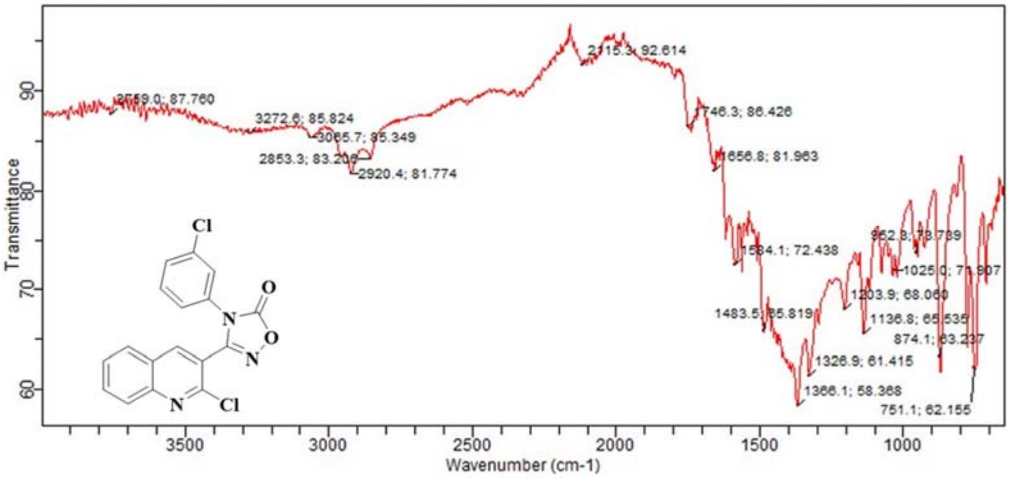
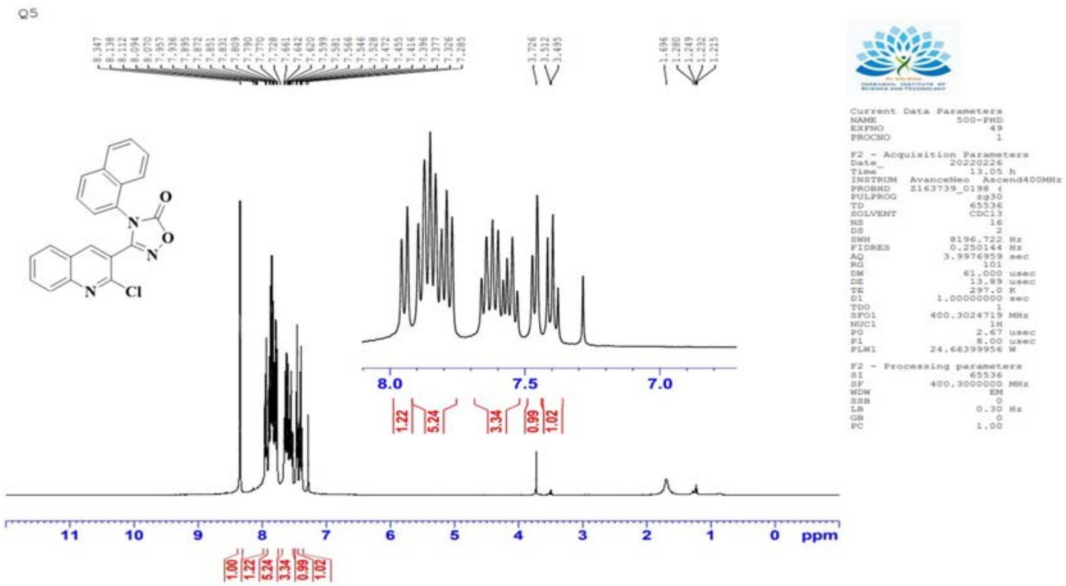
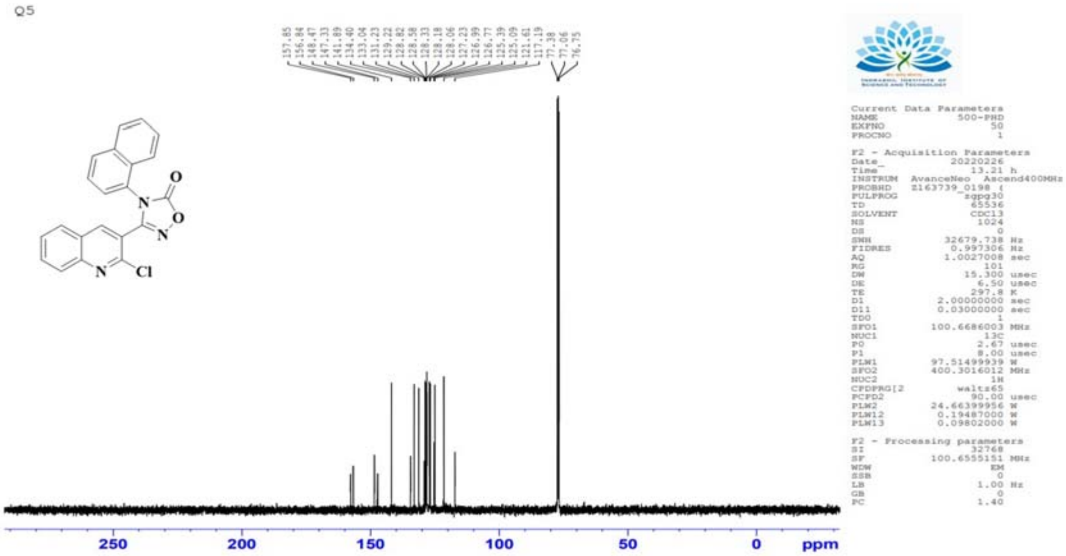


Figure 66: IR spectra of compound **6i**



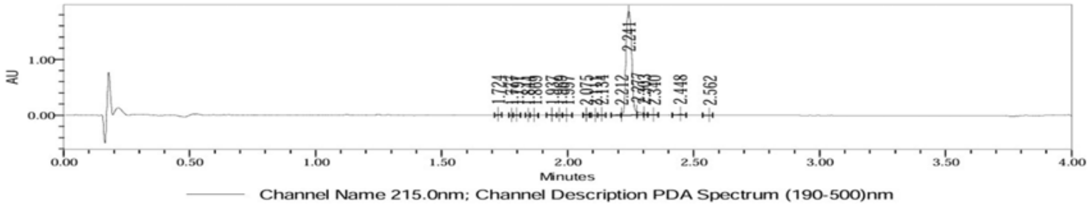
```
Current Data Parameters
NAME             500-PHD
EXPNO                 49
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220226
Time               13.05 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8196.722 Hz
FIDRES          0.250144 Hz
AQ             3.9976959 sec
RG                   101
DW                61.000 usec
DE                 13.89 usec
TE                 297.0 K
D1            1.00000000 sec
TD0                    1
SFO1         400.3024719 MHz
NUC1                  1H
P0                  2.67 usec
P1                  8.00 usec
PLW1         24.66399956 W

F2 - Processing parameters
SI                 65536
SF           400.3000000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

Figure 67: ^{1}H NMR of compound **6j**



```
Current Data Parameters
NAME             500-PHD
EXPNO                 50
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220226
Time               13.21 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     0
SWH            32679.738 Hz
FIDRES          0.997306 Hz
AQ             1.0027008 sec
RG                   101
DW                15.300 usec
DE                  6.50 usec
TE                 297.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         100.6686003 MHz
NUC1                 13C
P0                  2.67 usec
P1                  8.00 usec
PLW1         97.51499939 W
SFO2         400.3016012 MHz
NUC2                  1H
CPDPRG[2         waltz65
PCPD2              90.00 usec
PLW2         24.66399956 W
PLW12         0.19487000 W
PLW13         0.09802000 W

F2 - Processing parameters
SI                 32768
SF           100.6555151 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

Figure 68: ^{13}C NMR of compound **6j**



2.217	13374	9310	0.76	PDA Spectrum	254.0nm
2.241	1862854	2874550	92.35	PDA Spectrum	215.0nm
2.243	1318117	1117715	91.73	PDA Spectrum	254.0nm
2.274	10455	9434	0.77	PDA Spectrum	254.0nm

Match Plot

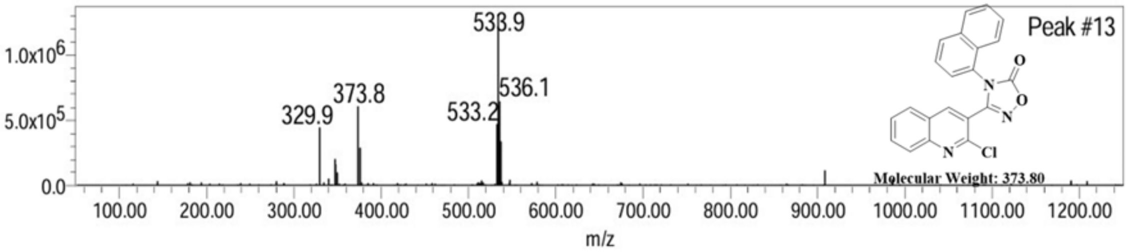


Figure 69: LCMS of compound **6j**

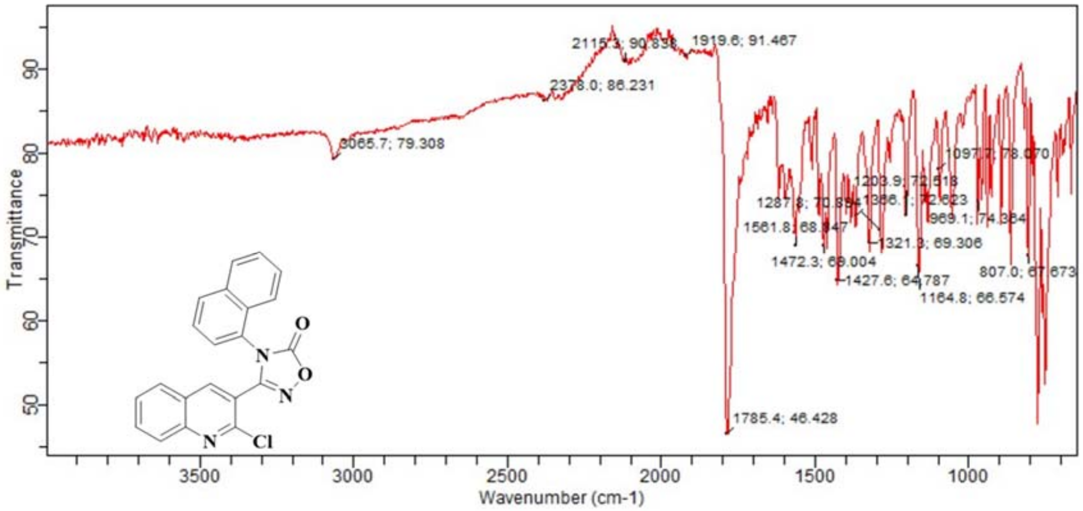
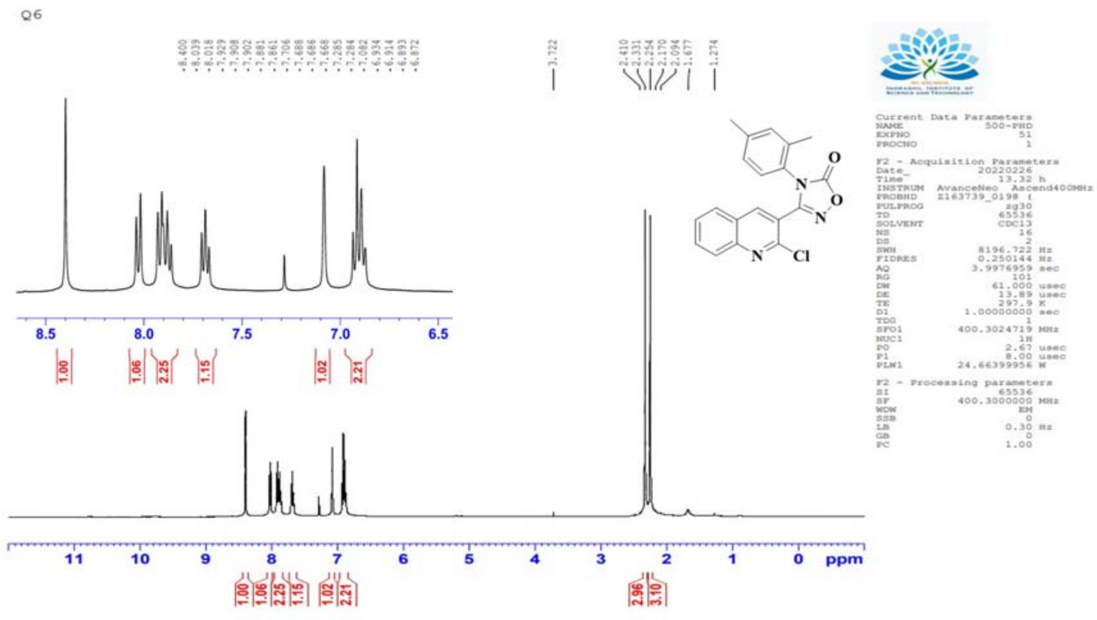
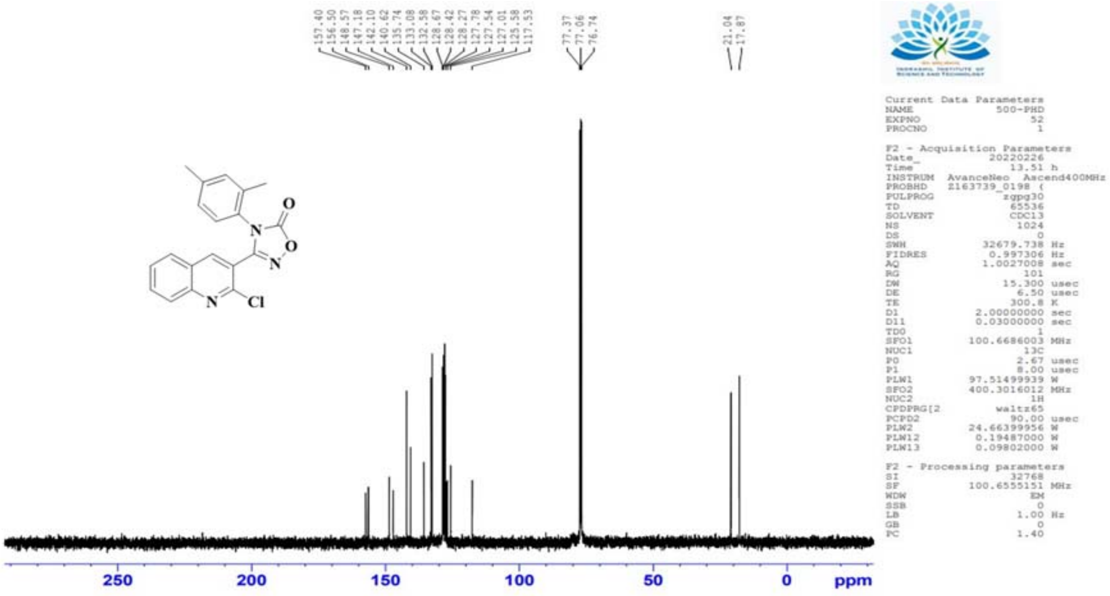


Figure 70: IR spectra of compound **6j**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  51
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                13.32 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD   Z163739_0198 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.250144 Hz
AQ              3.9976959 sec
RG                    101
DW                 61.000 usec
DE                  13.89 usec
TE                  297.9 K
D1             1.00000000 sec
TD0                     1
SFO1          400.3024719 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          24.66399956 W

F2 - Processing parameters
SI                  65536
SF            400.3000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

Figure 71: ^{1}H NMR of compound **6k**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  52
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                13.51 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD   Z163739_0198 (
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      0
SWH             32679.738 Hz
FIDRES           0.997306 Hz
AQ              1.0027008 sec
RG                    101
DW                 15.300 usec
DE                   6.50 usec
TE                  300.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6686003 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          97.51499939 W
SFO2          400.3016012 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          24.66399956 W
PLW12          0.19487000 W
PLW13          0.09802000 W

F2 - Processing parameters
SI                  32768
SF            100.6555151 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

Figure 72: ^{13}C NMR of compound **6k**

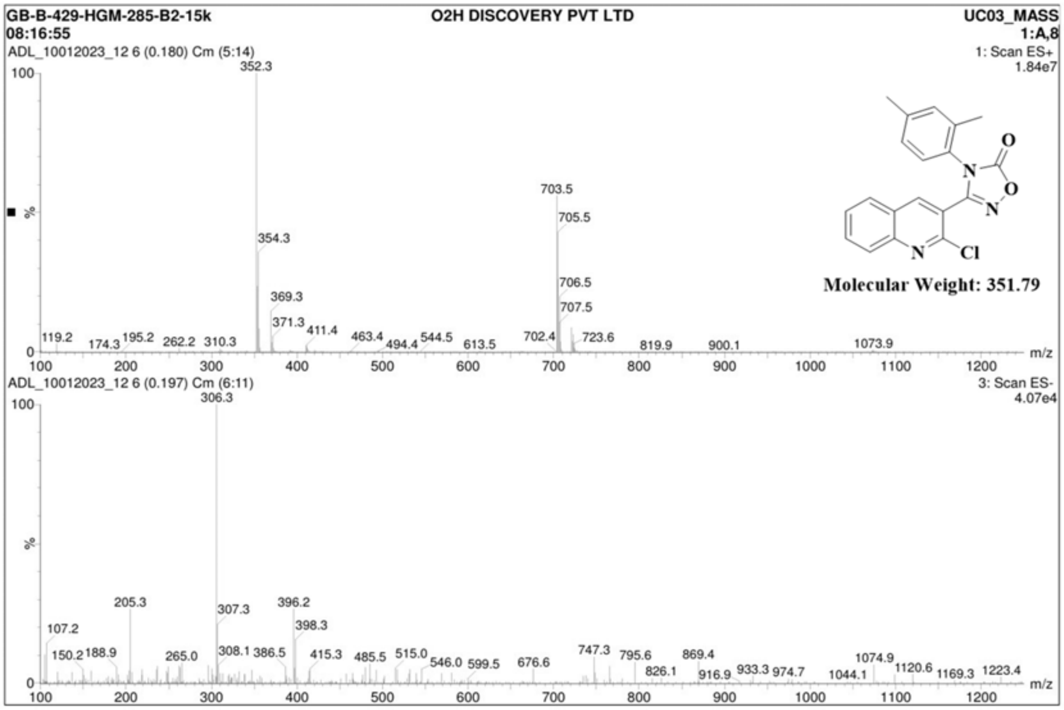


Figure 73: Mass spectrum of compound **6k**

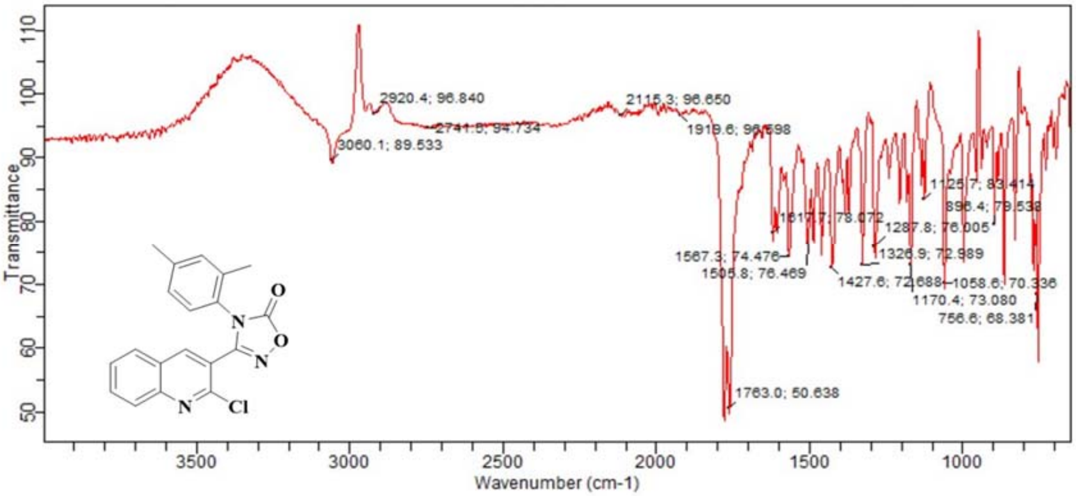
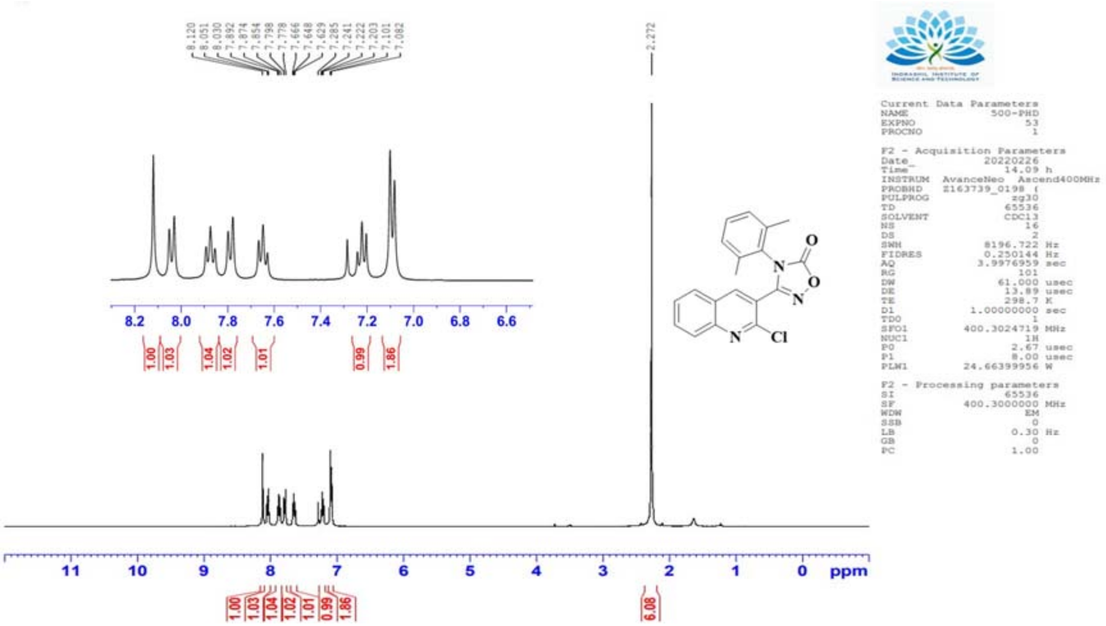
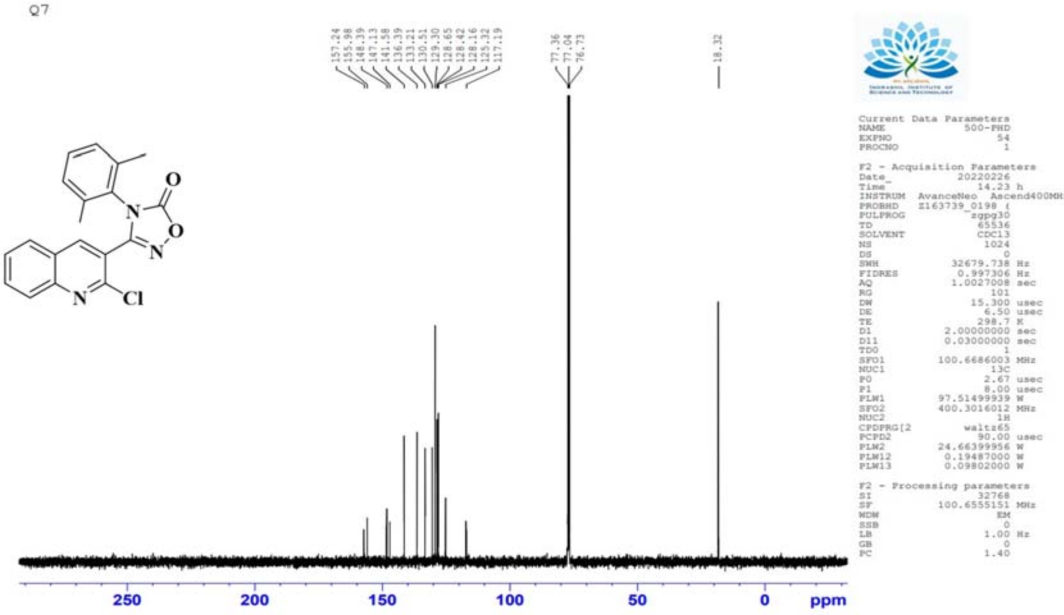


Figure 74: IR spectra of compound **6k**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  53
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                14.09 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.250144 Hz
AQ              3.9976959 sec
RG                    101
DW                 61.000 usec
DE                  13.89 usec
TE                  298.7 K
D1             1.00000000 sec
TD0                     1
SFO1          400.3024719 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          24.66399956 W

F2 - Processing parameters
SI                  65536
SF            400.3000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

Figure 75: ^{1}H NMR of compound **6l**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  54
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                14.23 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      0
SWH             32679.738 Hz
FIDRES           0.997306 Hz
AQ              1.0027008 sec
RG                    101
DW                 15.300 usec
DE                   6.50 usec
TE                  298.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6686003 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          97.51499939 W
SFO2          400.3016012 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          24.66399956 W
PLW12          0.19487000 W
PLW13          0.09802000 W

F2 - Processing parameters
SI                  32768
SF            100.6555151 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

Figure 76: ^{13}C NMR of compound **6l**

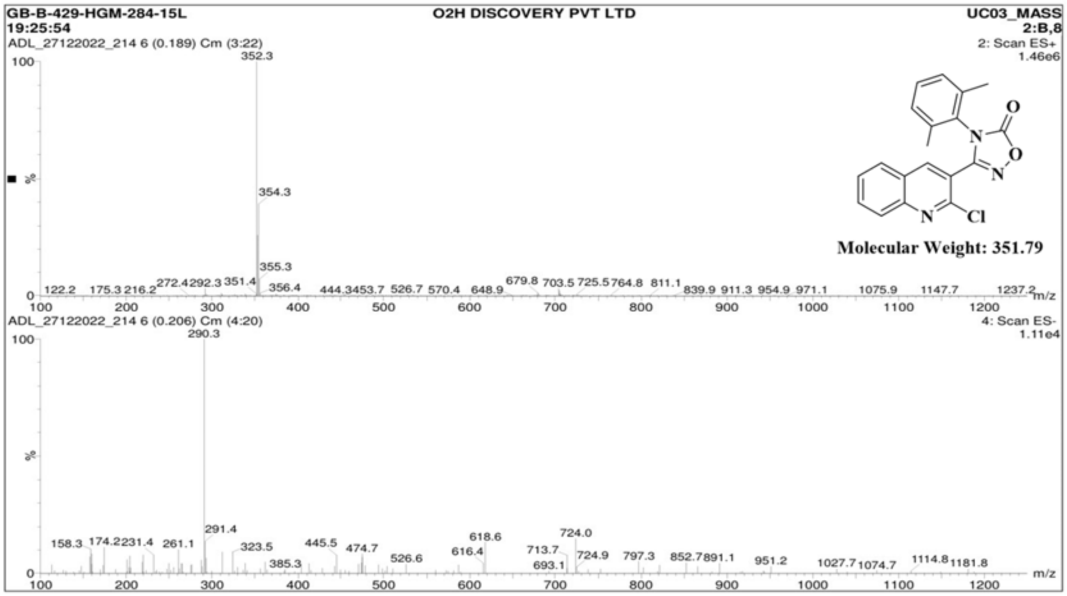


Figure 77: Mass spectrum of compound **6l**

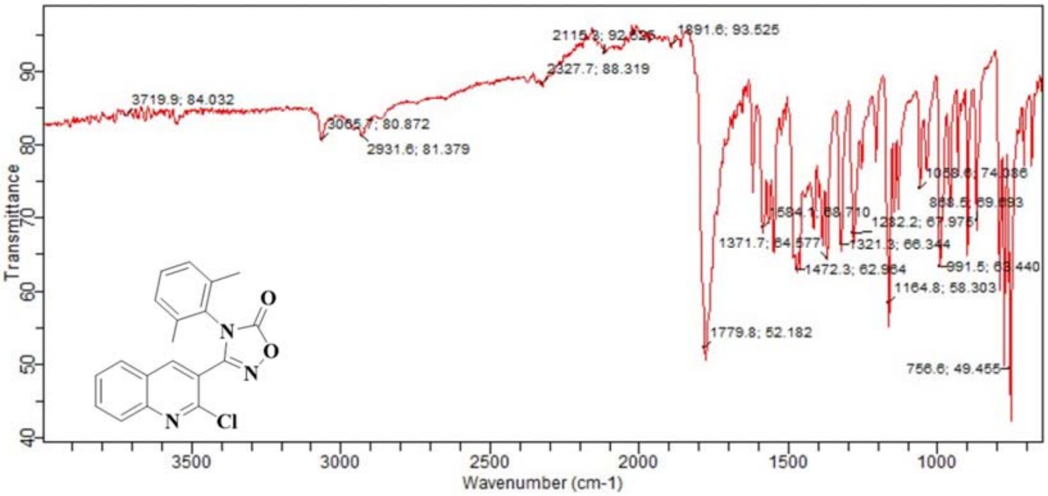


Figure 78: IR spectra of compound **6l**

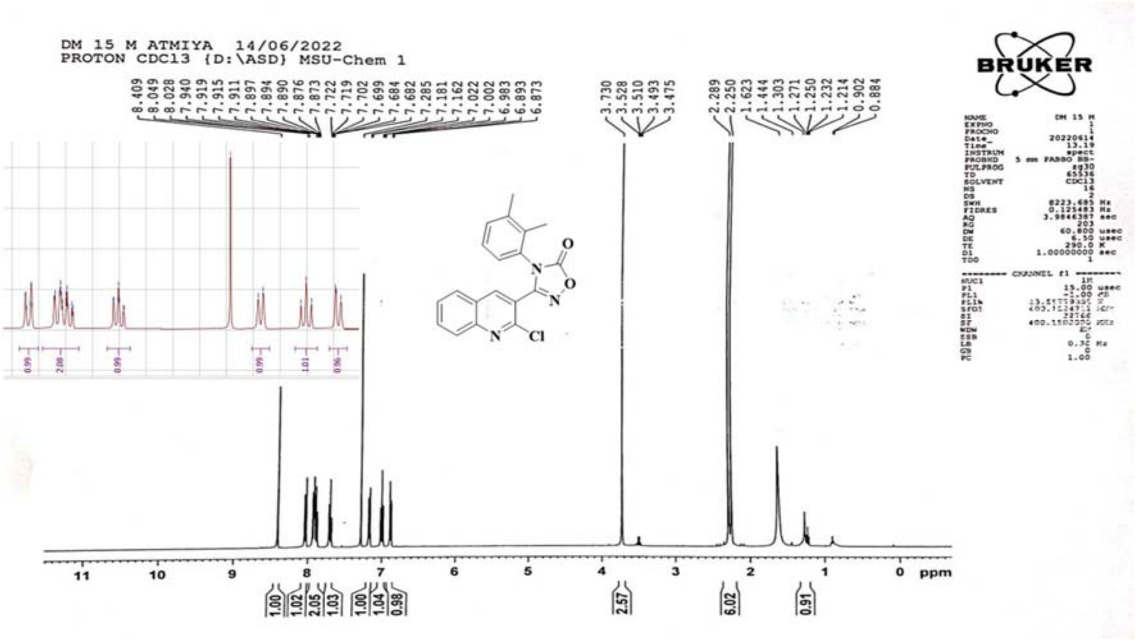


Figure 79: ^{1}H NMR of compound **6m**

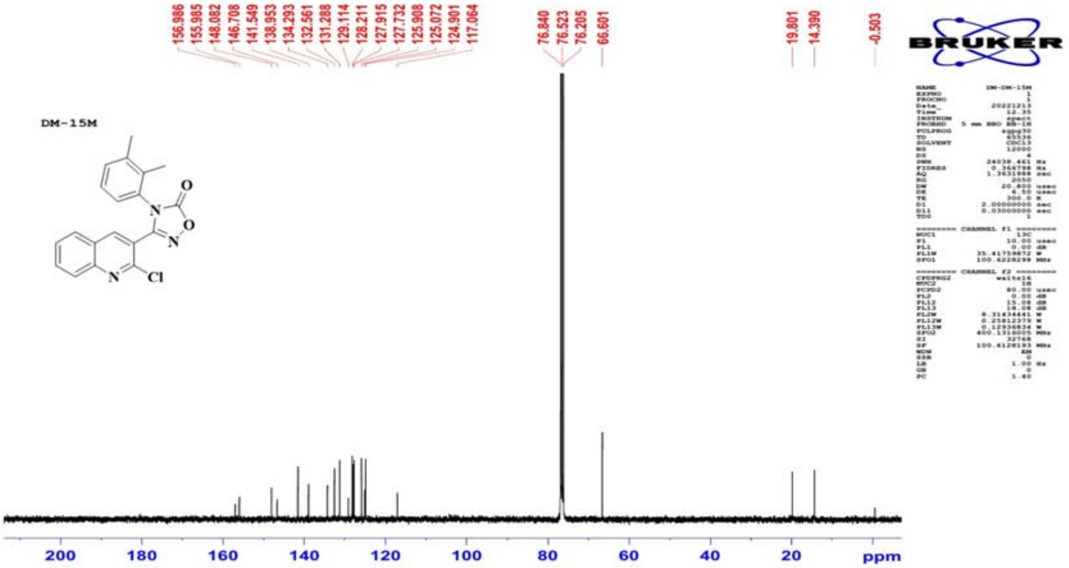


Figure 80: ^{13}C NMR of compound **6m**

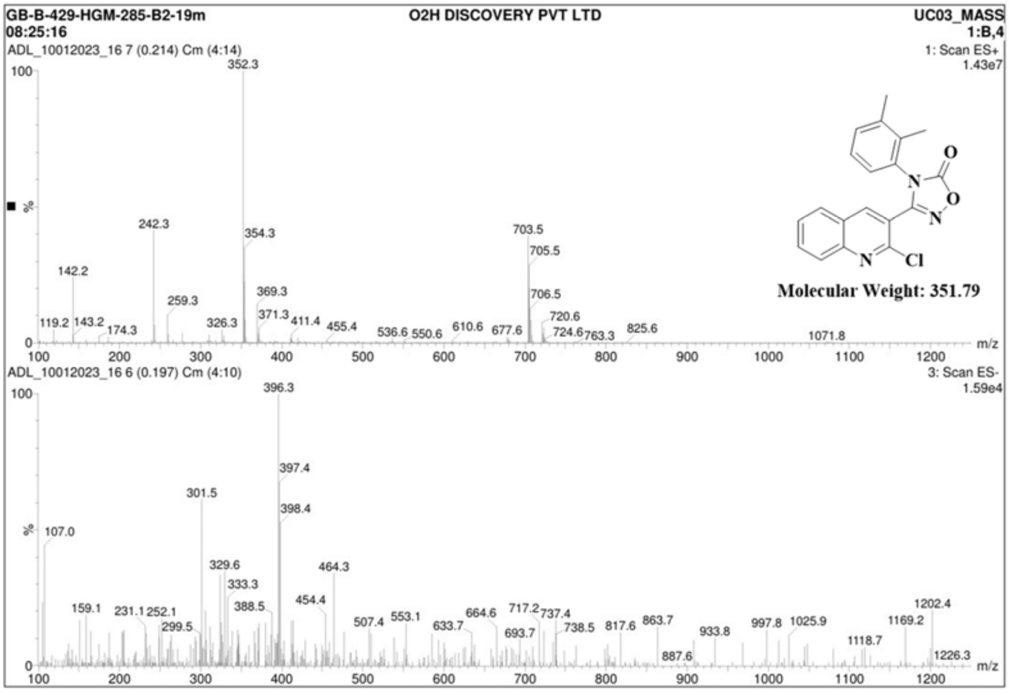


Figure 81: Mass spectrum of compound **6m**

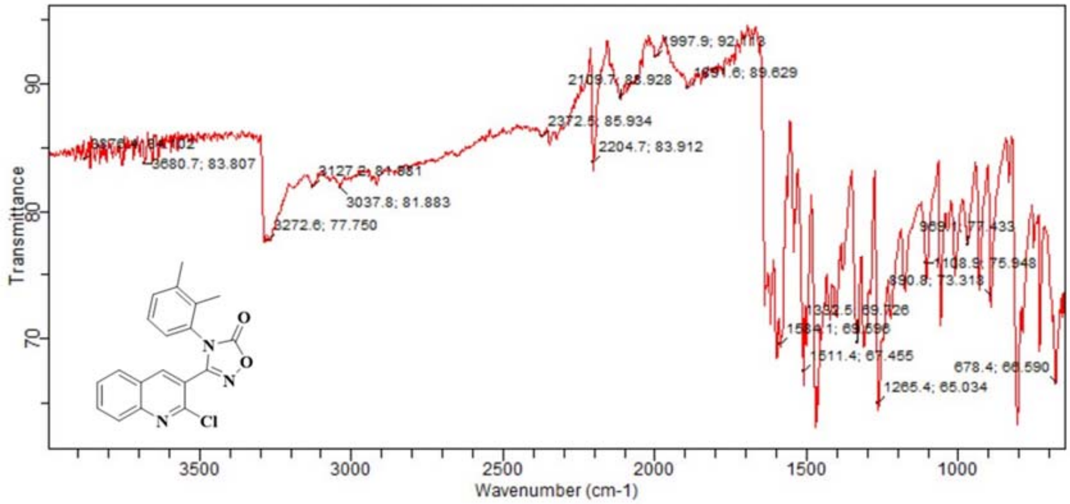
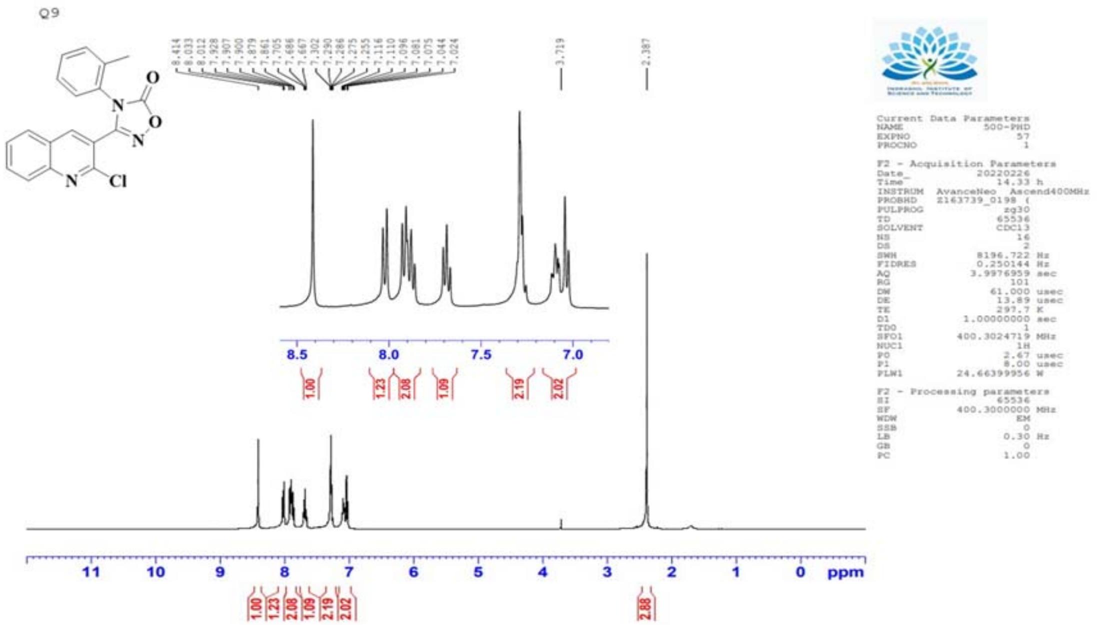
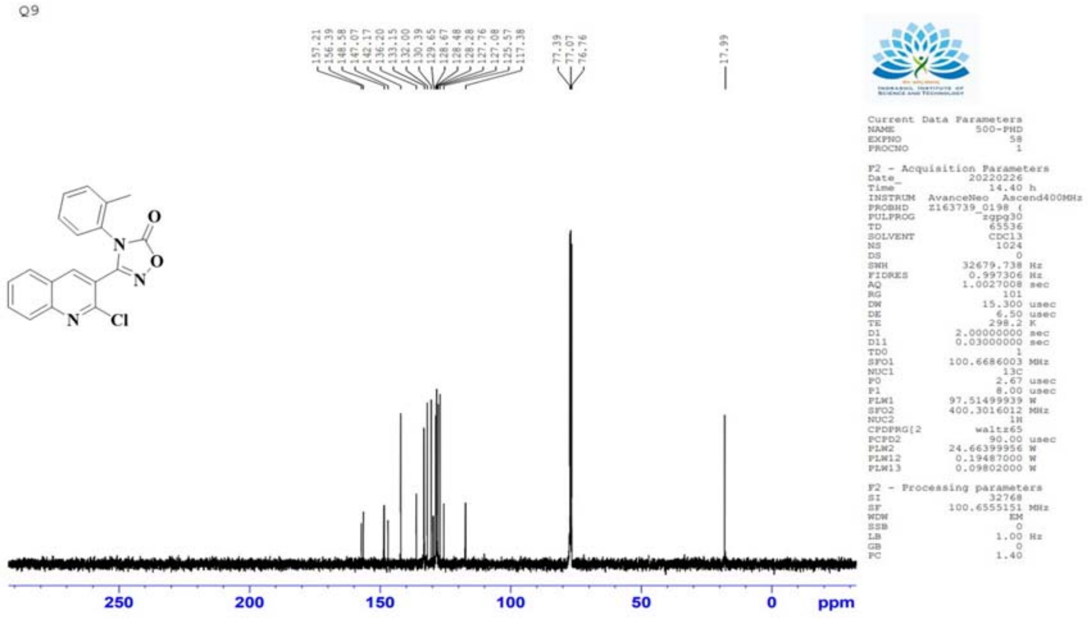


Figure 82: IR spectra of compound **6m**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  57
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                14.33 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.250144 Hz
AQ              3.9976959 sec
RG                    101
DW                 61.000 usec
DE                  13.89 usec
TE                  297.7 K
D1             1.00000000 sec
TD0                     1
SFO1          400.3024719 MHz
NUC1                   1H
P0                   2.67 usec
P1                   8.00 usec
PLW1          24.66399956 W

F2 - Processing parameters
SI                  65536
SF            400.3000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

Figure 83: ^{1}H NMR of compound **6n**



```
Current Data Parameters
NAME              500-PHD
EXPNO                  58
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220226
Time                14.40 h
INSTRUM   AvanceNeo   Ascend400MHz
PROBHD    Z163739_0198 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      0
SWH             32679.738 Hz
FIDRES           0.997306 Hz
AQ              1.0027008 sec
RG                    101
DW                 15.300 usec
DE                   6.50 usec
TE                  298.2 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6686003 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          97.51499939 W
SFO2          400.3016012 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          24.66399956 W
PLW12          0.19487000 W
PLW13          0.09802000 W

F2 - Processing parameters
SI                  32768
SF            100.6555151 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

Figure 84: ^{13}C NMR of compound **6n**

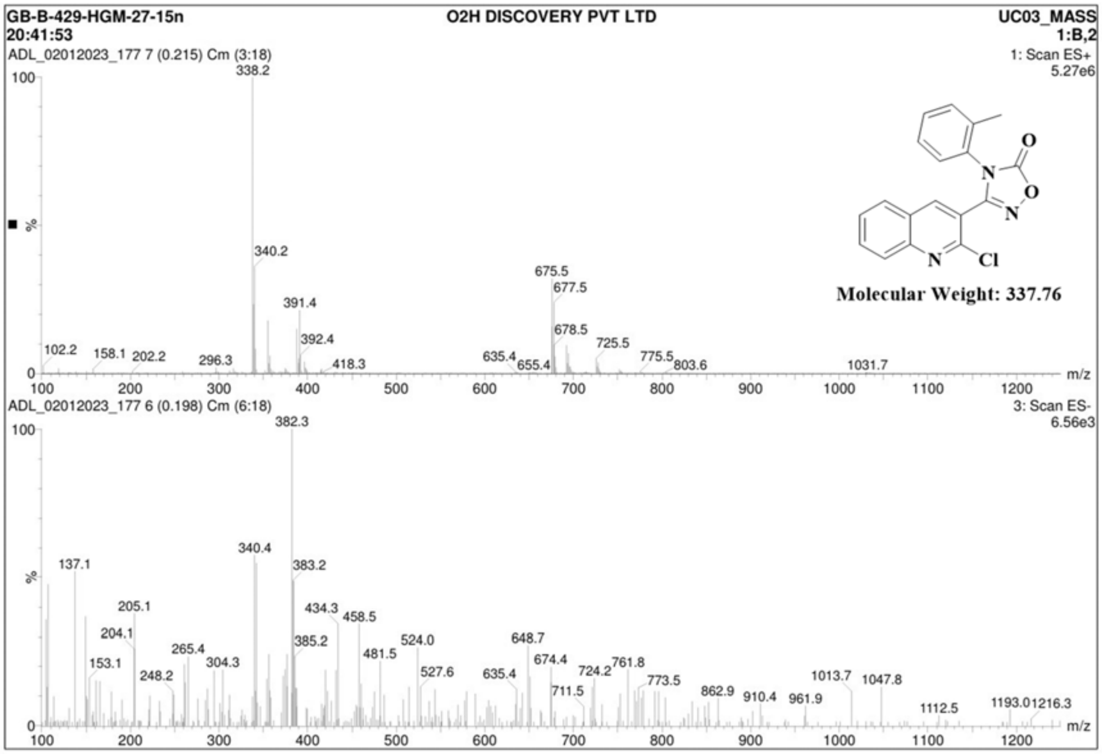


Figure 85: Mass spectrum of compound **6n**

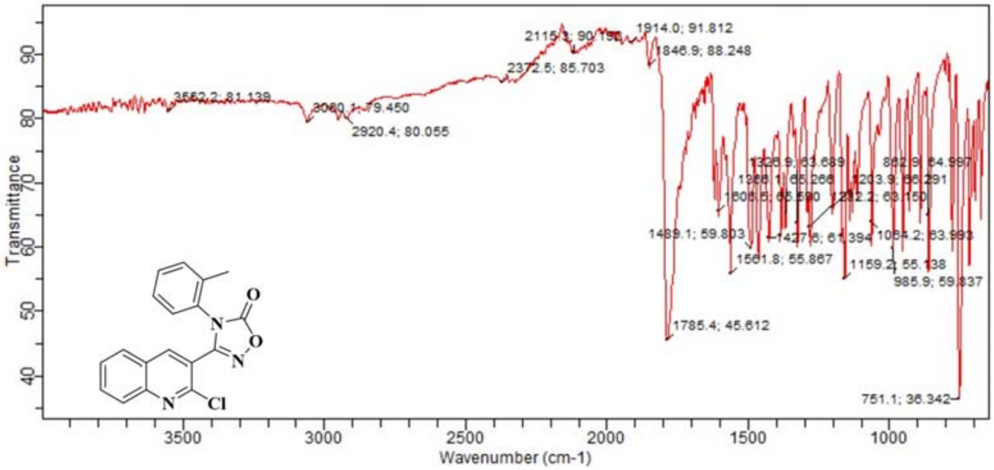


Figure 86: IR spectra of compound **6n**

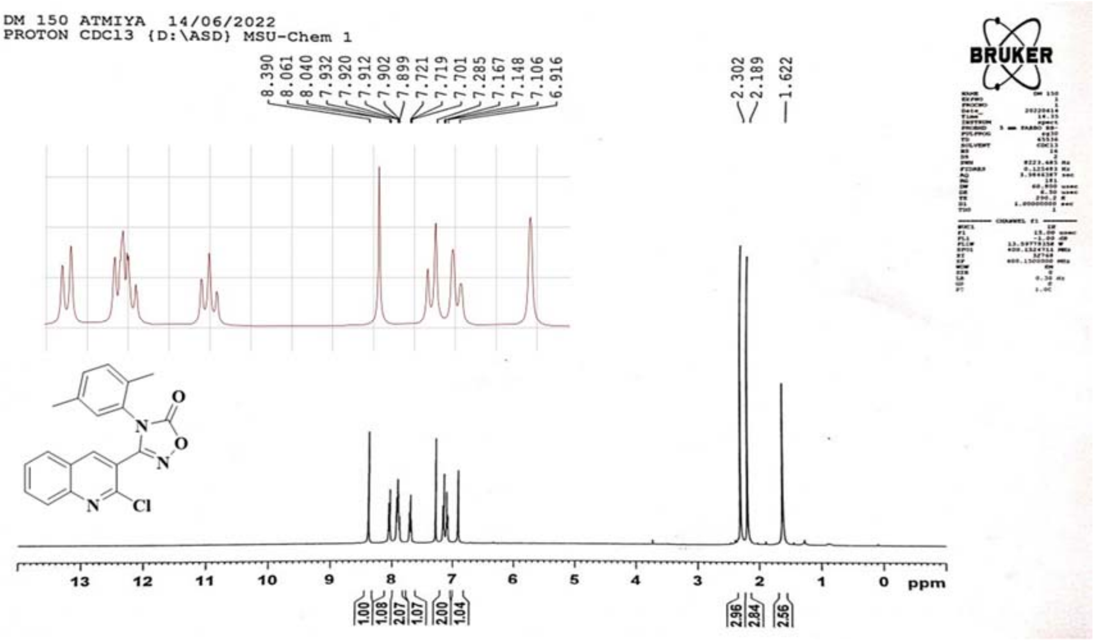


Figure 87: ^{1}H NMR of compound **6o**

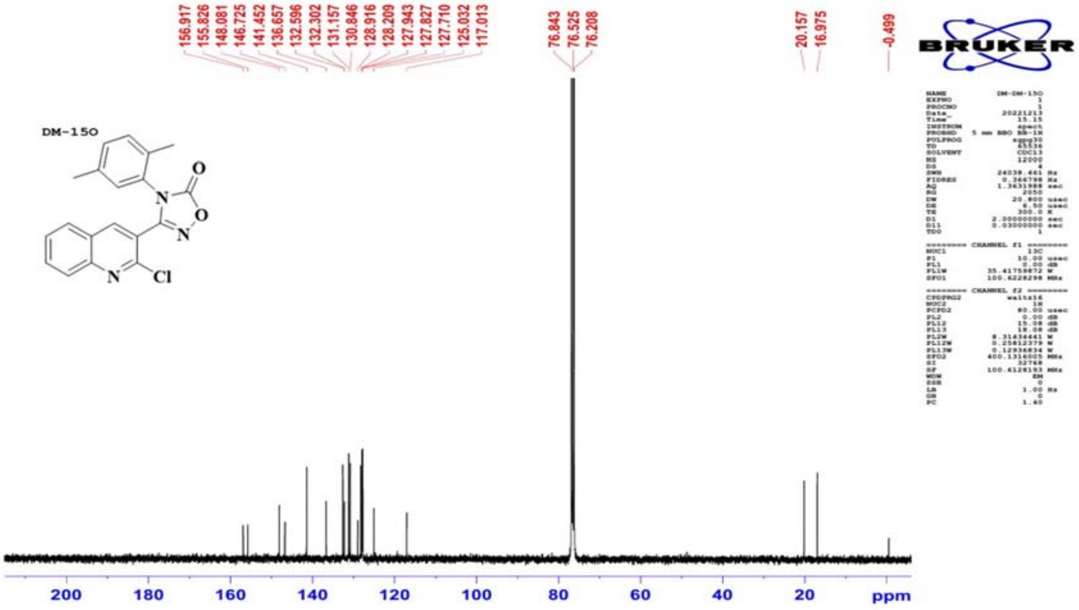


Figure 88: ^{13}C NMR of compound **6o**

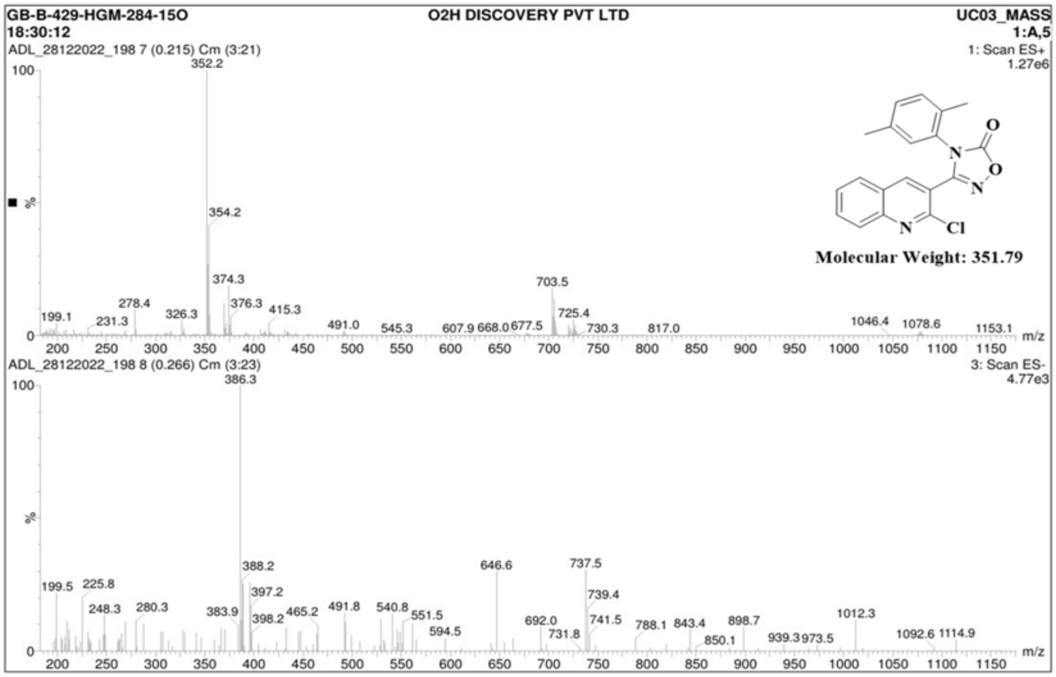


Figure 89: Mass spectrum of compound **6o**

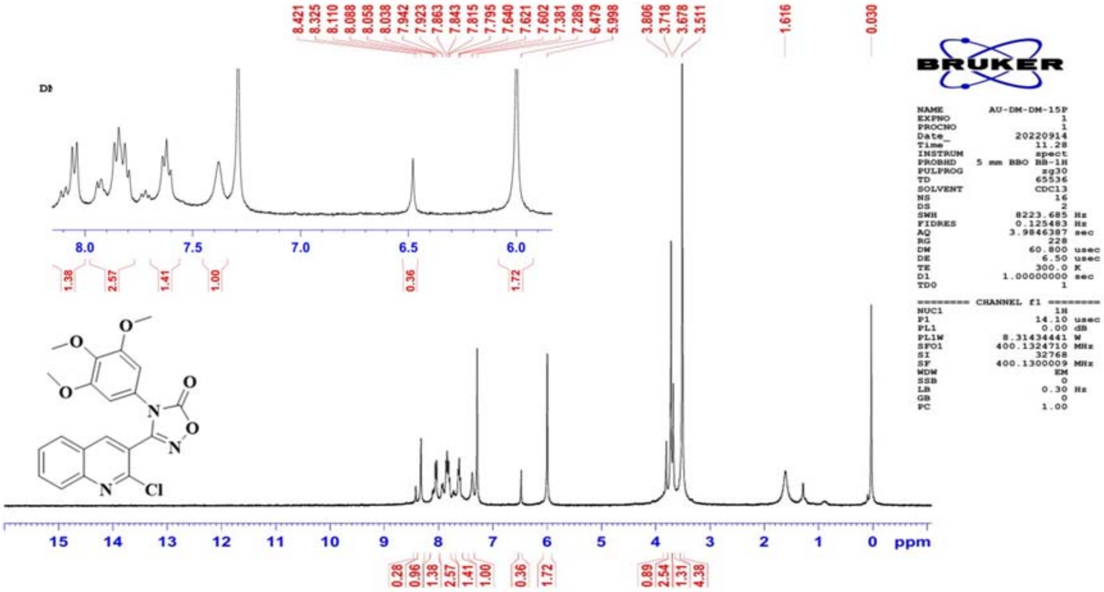


Figure 90: ^{1}H NMR of compound **6p**

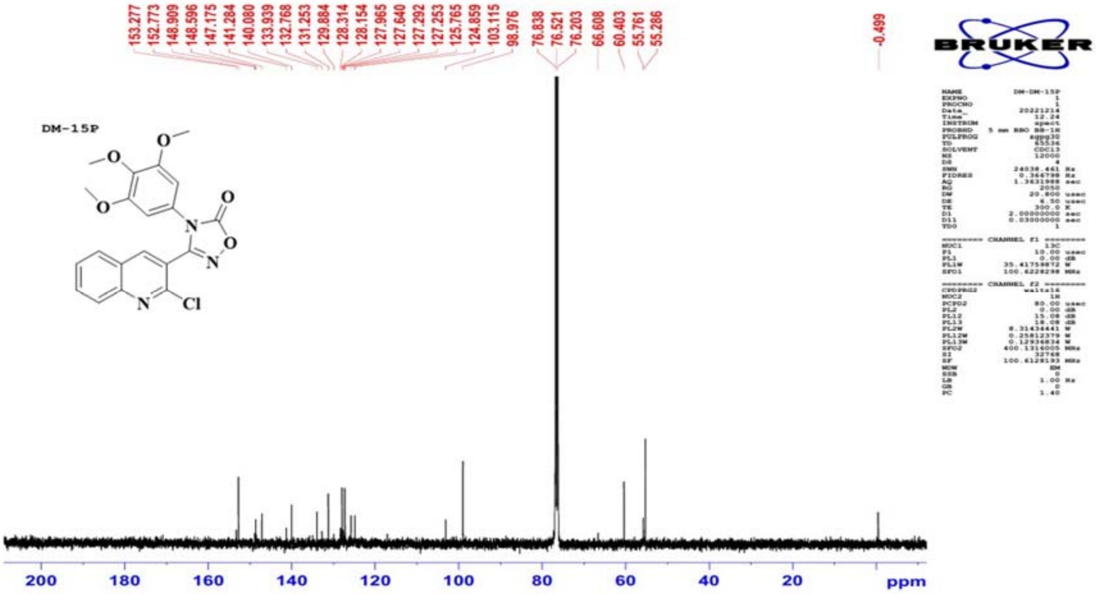


Figure 91: ^{13}C NMR of compound **6p**

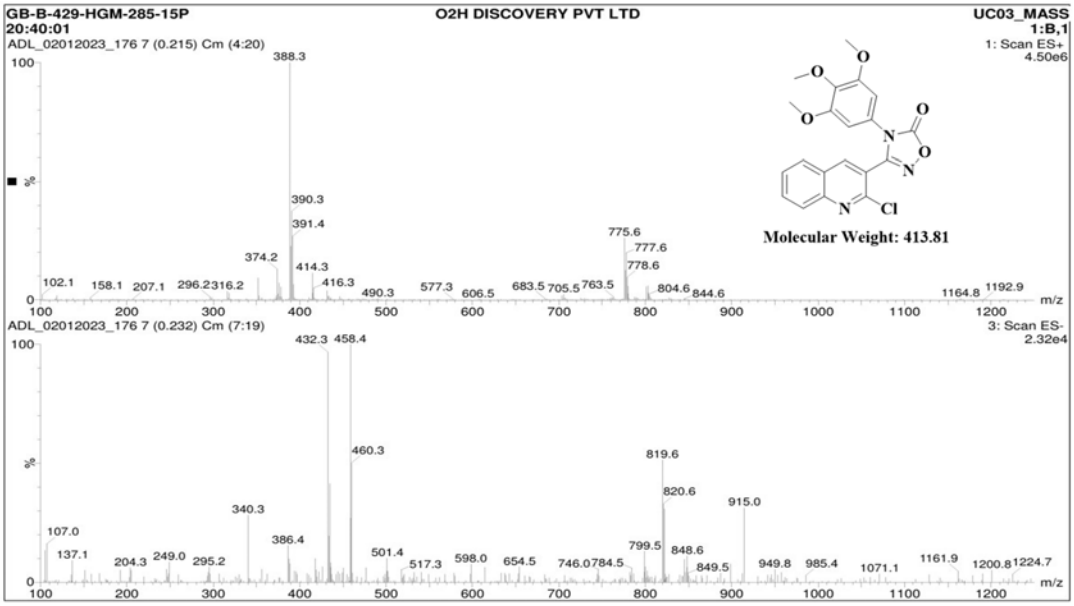


Figure 92: Mass spectrum of compound **6p**