ANTI PROLIFERATIVE ACTIVITY OF NITROQUINOLONE FUSED ACYLHYDRAZONES AS NON-SMALL CELL HUMAN LUNG CANCER AGENTS

Vandana Nandakumar[a], Amsaveni Sundarasamy[a] , Kaviyarasu Adhigaman[a], Sentamil Selvi Ramasamy[a] , Manickam Paulpandi[c] , Gothandam Kodiveri Muthukaliannan[b], Narayanasamy Arul[c] ,Suresh Thangaraj[a]**

**Corresponding Author, mail id: suresh@buc.edu.in

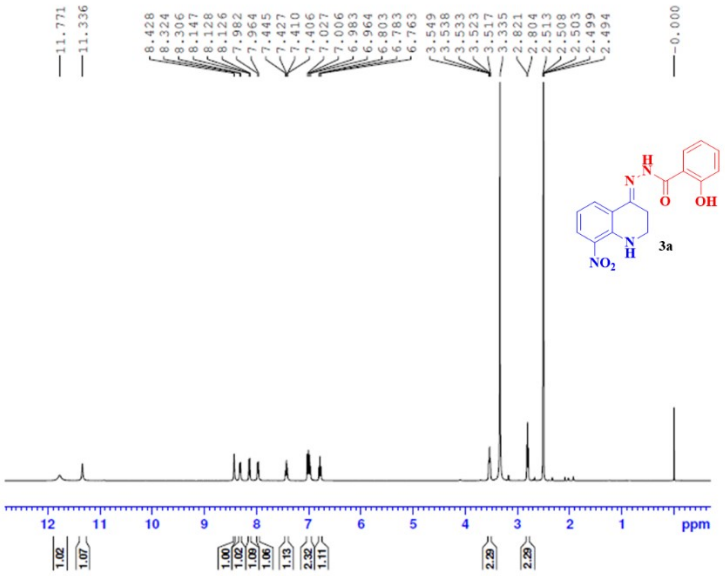
[a] School of Chemical Sciences, Department of Chemistry, Bharathiar University, Coimbatore, Tamilnadu, 641046, India

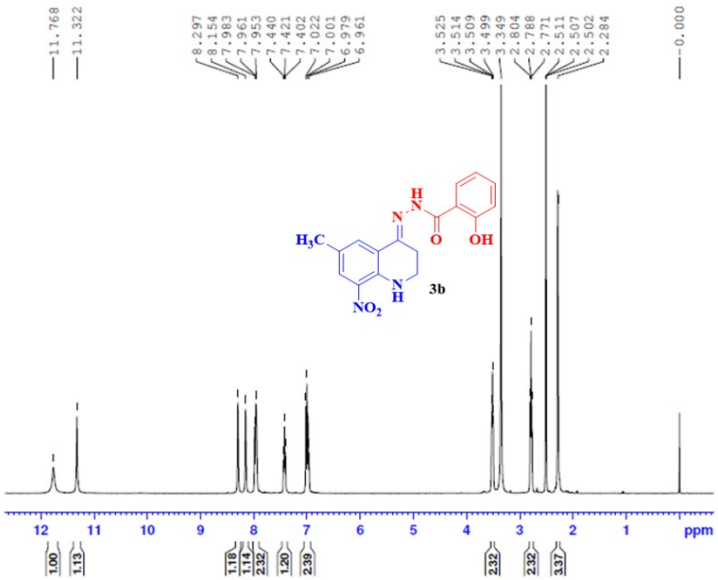
[b]School of BioSciences and Technology, Vellore Institute of Technology, Vellore 632014, Tamil Nadu, India

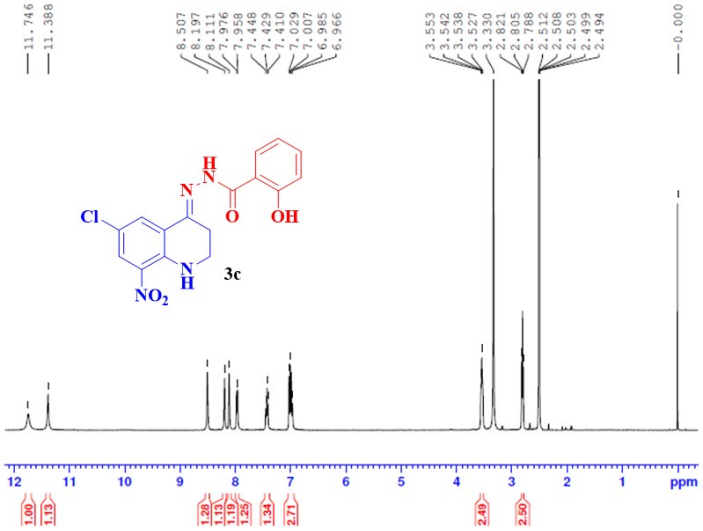
[c] School of Life Sciences, Department of Zoology , Bharathiar University, Coimbatore, Tamilnadu, 641046, India

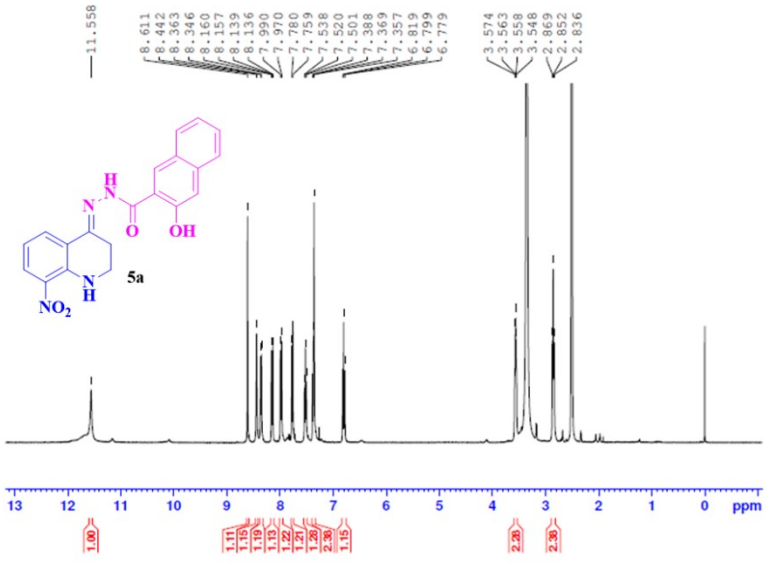
SUPPLIMENTARY INFORMATION

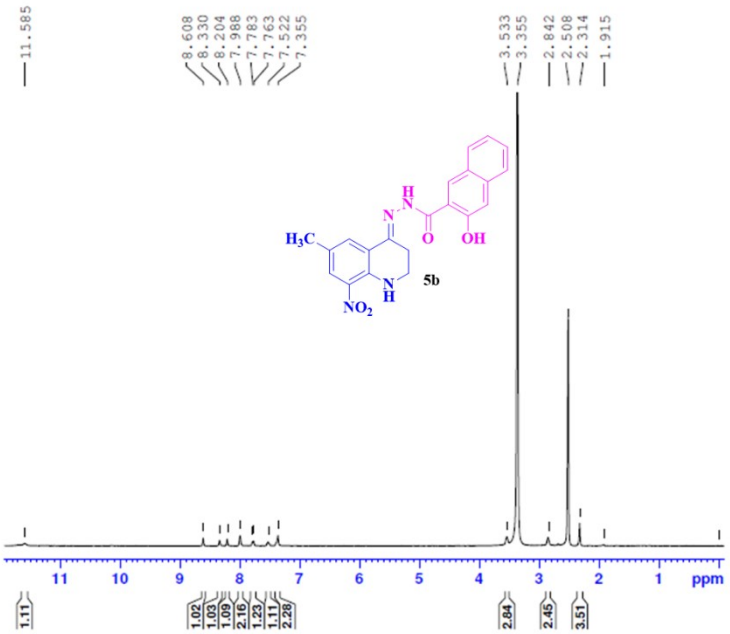
I. ^{1}H NMR SPECTRA

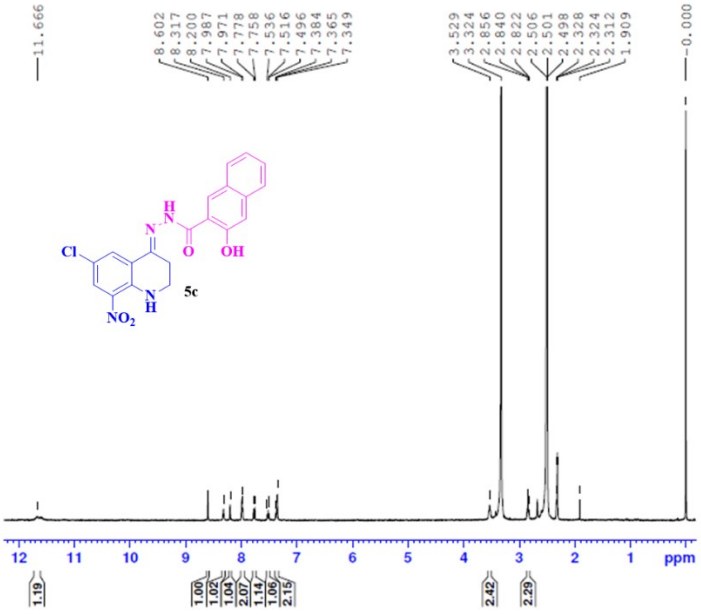


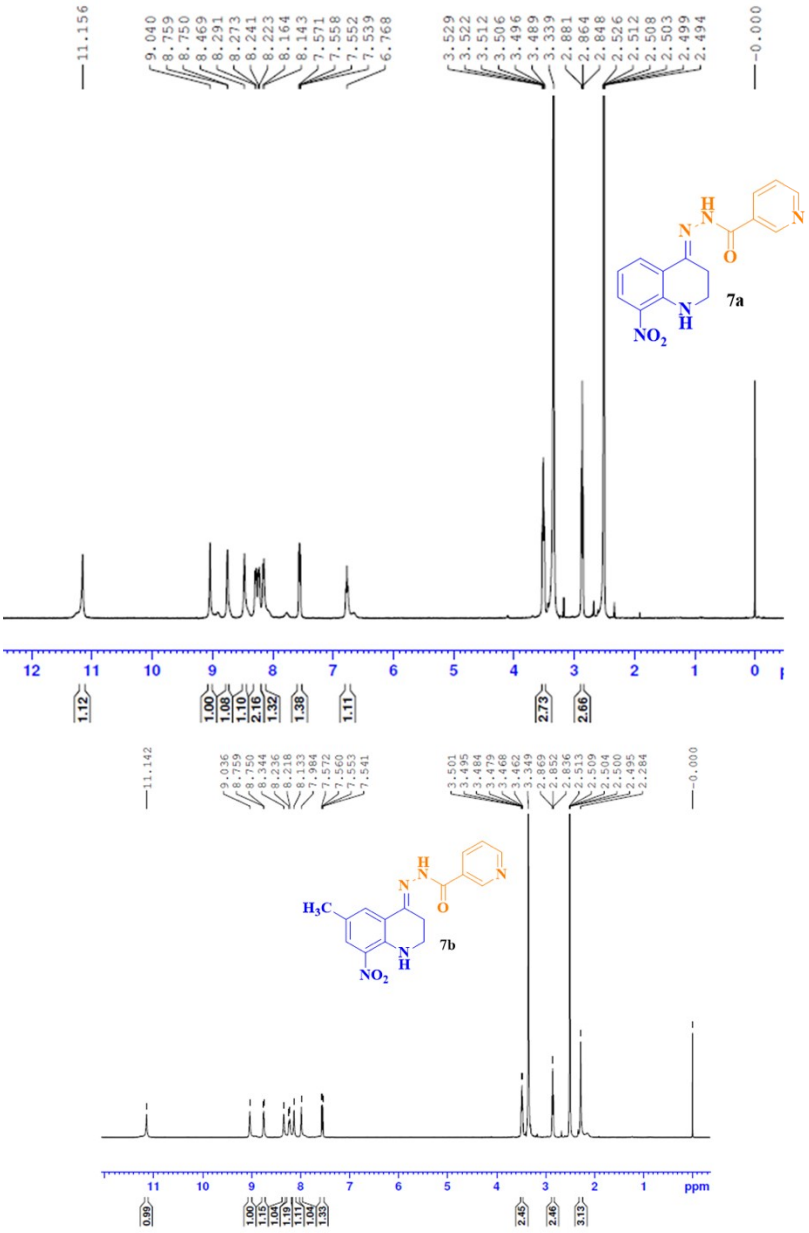

11.768
11.322
8.297
8.154
7.983
7.961
7.953
7.440
7.421
7.402
7.022
7.001
6.979
6.961
3.525
3.514
3.509
3.499
3.349
2.804
2.788
2.771
2.511
2.507
2.502
2.284
0.000
3b
ppm

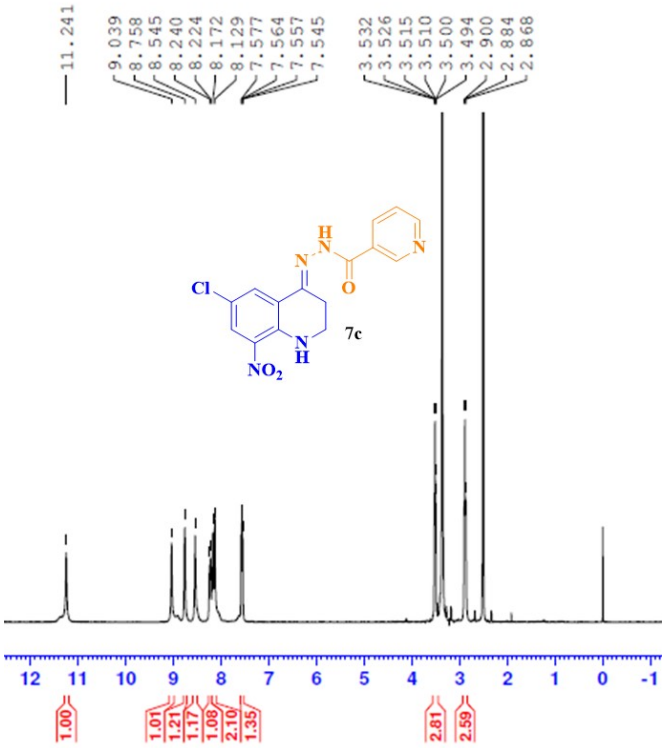

11.746
11.388
8.507
8.197
8.111
7.976
7.958
7.448
7.429
7.410
7.029
7.007
6.985
6.966
3.553
3.542
3.538
3.527
3.330
2.821
2.805
2.788
2.512
2.508
2.503
2.499
2.494
0.000
3c
ppm

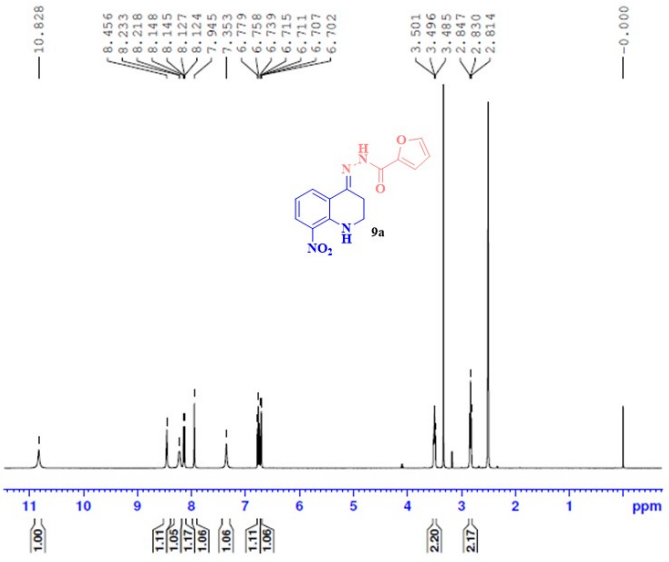

11.558
8.611
8.442
8.363
8.346
8.160
8.157
8.139
8.136
7.990
7.970
7.780
7.759
7.538
7.520
7.501
7.388
7.369
7.357
6.819
6.799
6.779
3.574
3.563
3.558
3.548
2.869
2.852
2.836
5a
ppm

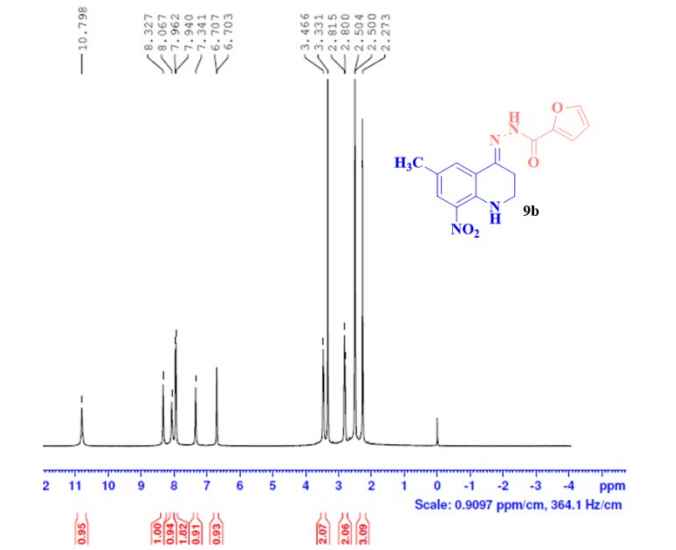

11.585
8.608
8.330
8.204
7.988
7.783
7.763
7.522
7.355
3.533
3.355
2.842
2.508
2.314
1.915
H3C
NO2
5b
11
10
9
8
7
6
5
4
3
2
1
ppm
1.11
1.02
1.03
1.09
2.16
1.23
1.11
2.28
2.84
2.45
3.51

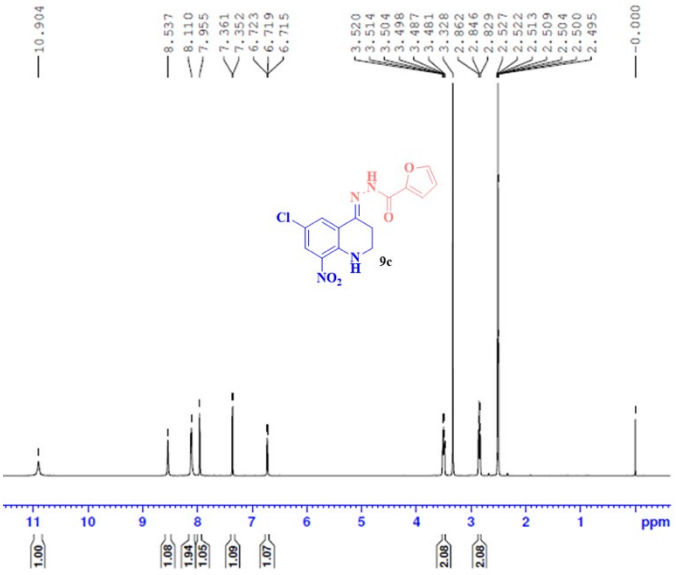

11.666
8.602
8.317
8.200
7.987
7.971
7.778
7.758
7.536
7.516
7.496
7.384
7.365
7.349
3.529
3.324
2.856
2.840
2.822
2.506
2.501
2.498
2.328
2.324
2.312
1.909
0.000
Cl
NO2
5c
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.19
1.00
1.02
1.04
2.07
1.14
1.06
2.15
2.42
2.29

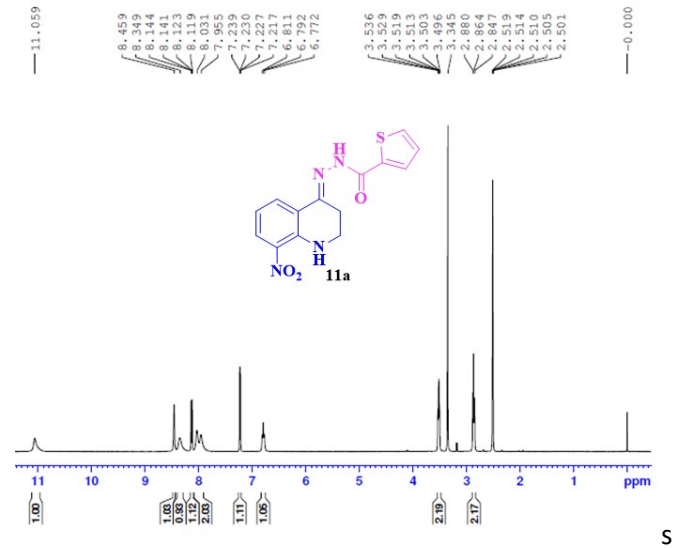

11.156
9.040
8.759
8.750
8.469
8.291
8.273
8.241
8.223
8.164
8.143
7.571
7.558
7.552
7.539
6.768
3.529
3.522
3.512
3.506
3.496
3.489
3.339
2.881
2.864
2.848
2.526
2.512
2.508
2.503
2.499
2.494
0.000
7a
11.142
9.036
8.759
8.750
8.344
8.236
8.218
8.133
7.984
7.572
7.560
7.553
7.541
3.501
3.495
3.484
3.479
3.468
3.462
3.348
2.869
2.852
2.836
2.513
2.509
2.504
2.500
2.495
2.284
0.000
7b
ppm


11.241
9.039
8.758
8.545
8.240
8.224
8.172
8.129
7.577
7.564
7.557
7.545
3.532
3.526
3.515
3.510
3.500
3.494
2.900
2.884
2.868
7c
12 11 10 9 8 7 6 5 4 3 2 1 0 -1
1.00
1.01
1.21
1.17
1.08
2.10
1.35
2.81
2.59

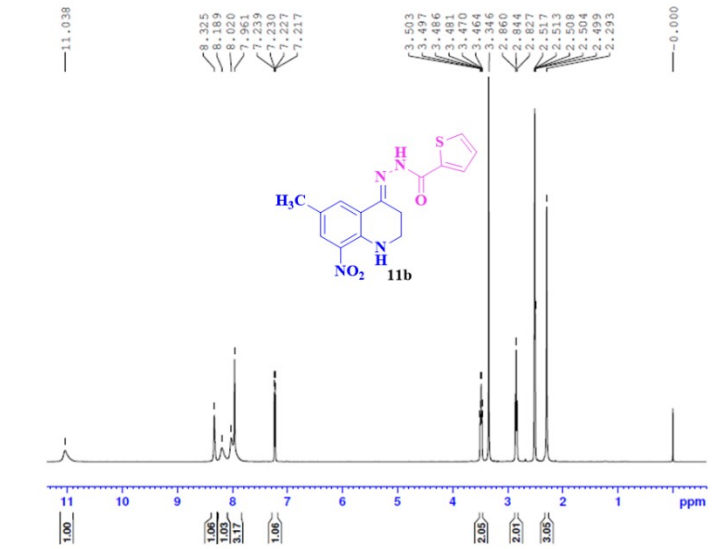

10.828
8.456
8.233
8.218
8.148
8.145
8.127
8.124
7.945
7.353
6.779
6.758
6.739
6.715
6.711
6.707
6.702
3.501
3.496
3.485
2.847
2.830
2.814
-0.000
9a
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.11
1.05
1.17
1.06
1.06
1.11
1.06
2.20
2.17

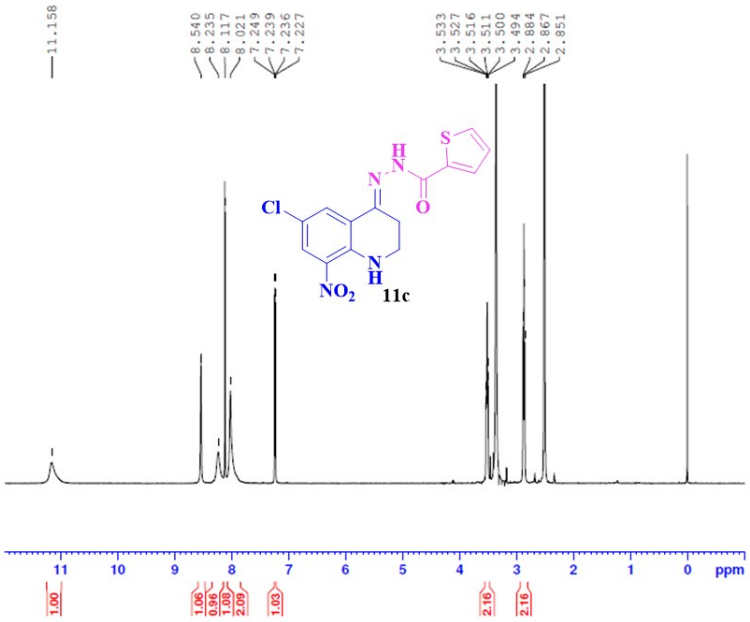

10.798
8.327
8.067
7.962
7.940
7.341
6.707
6.703
3.466
3.331
2.815
2.800
2.504
2.500
2.273
9b
Scale: 0.9097 ppm/cm, 364.1 Hz/cm


10.904
8.537
8.110
7.955
7.361
7.352
6.723
6.719
6.715
3.520
3.514
3.504
3.498
3.487
3.481
3.328
2.862
2.846
2.829
2.527
2.522
2.513
2.509
2.504
2.500
2.495
0.000
9c

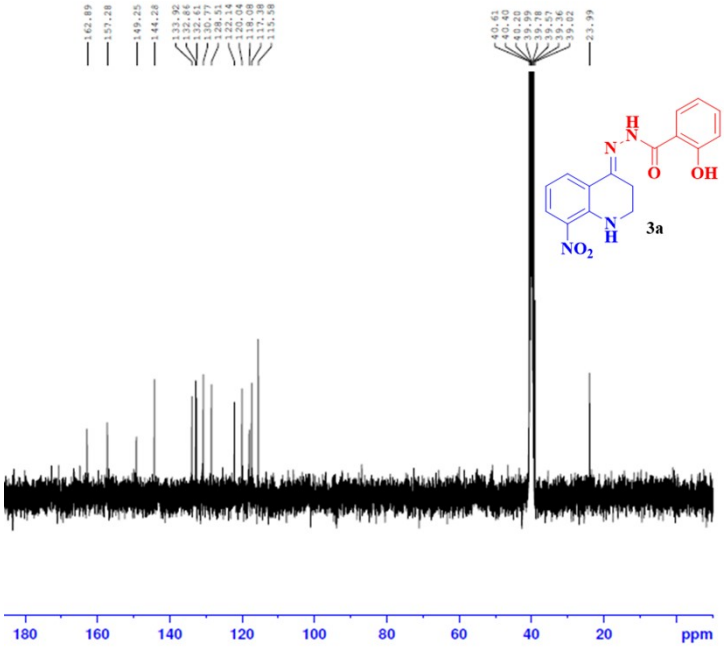

11.059
8.459
8.349
8.144
8.141
8.123
8.119
8.031
7.955
7.239
7.230
7.227
7.217
6.811
6.792
6.772
3.536
3.529
3.519
3.513
3.503
3.496
3.345
2.880
2.864
2.847
2.519
2.514
2.510
2.505
2.501
0.000
11a

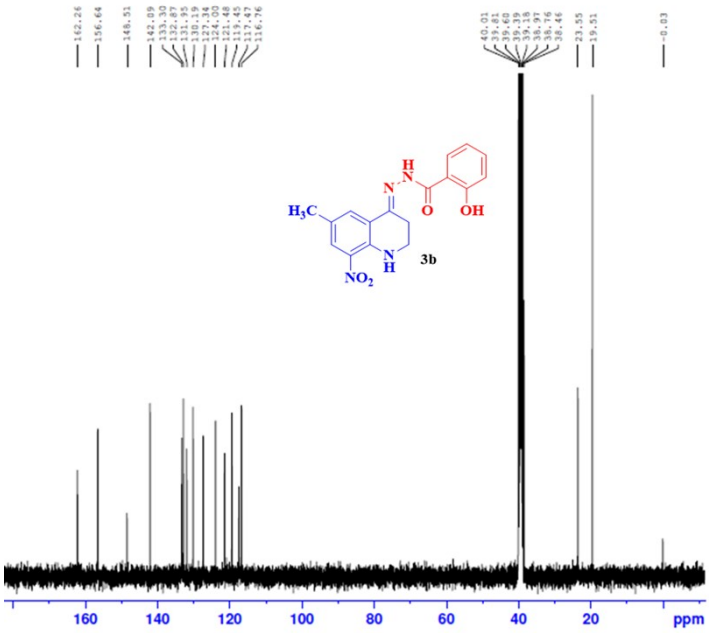
s

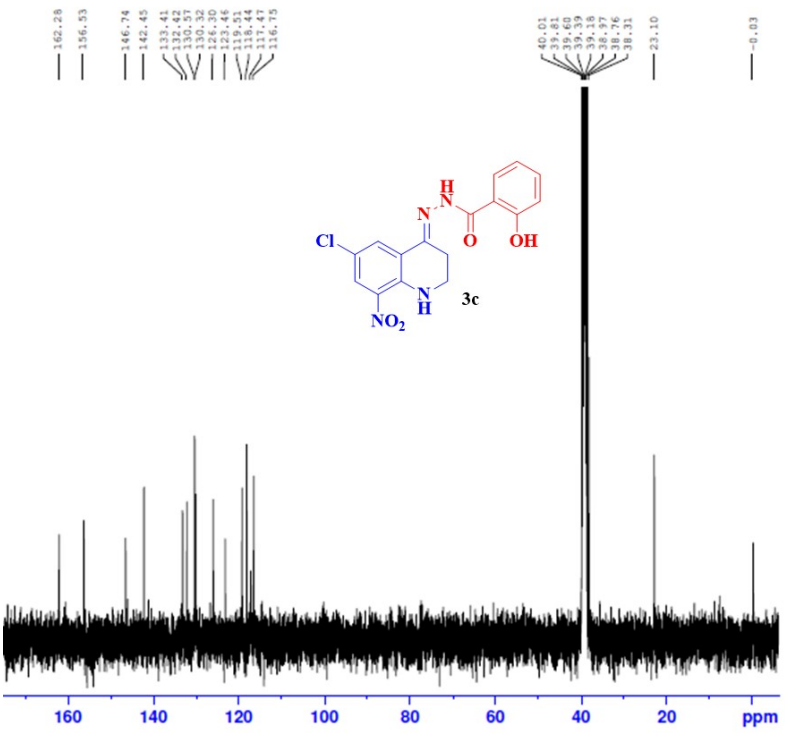

11.038
8.325
8.189
8.020
7.961
7.239
7.230
7.227
7.217
3.503
3.497
3.486
3.481
3.470
3.464
3.346
2.860
2.844
2.827
2.517
2.513
2.508
2.504
2.499
2.293
0.000
H3C
NO2
11b
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00 1.06 1.03 3.17 1.06 2.05 2.07 3.05

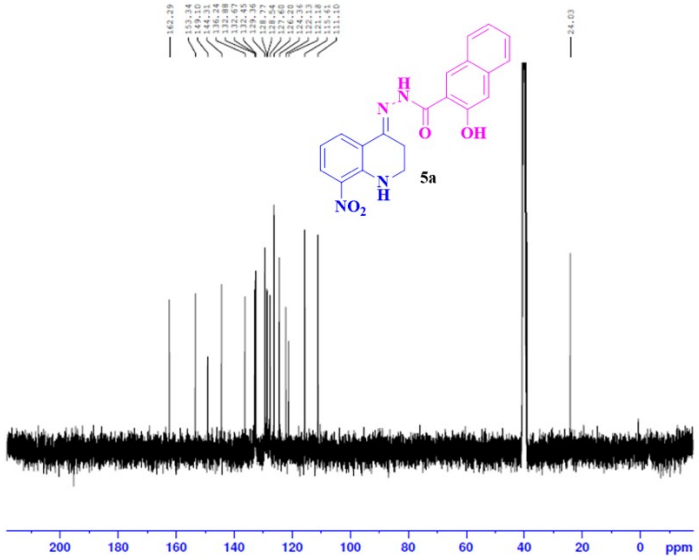

11.158
8.540
8.235
8.117
8.021
7.249
7.239
7.236
7.227
3.533
3.527
3.516
3.511
3.500
3.494
2.884
2.867
2.851
Cl
NO2
11c
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.06 0.96 1.08 2.09 1.03 2.16 2.16

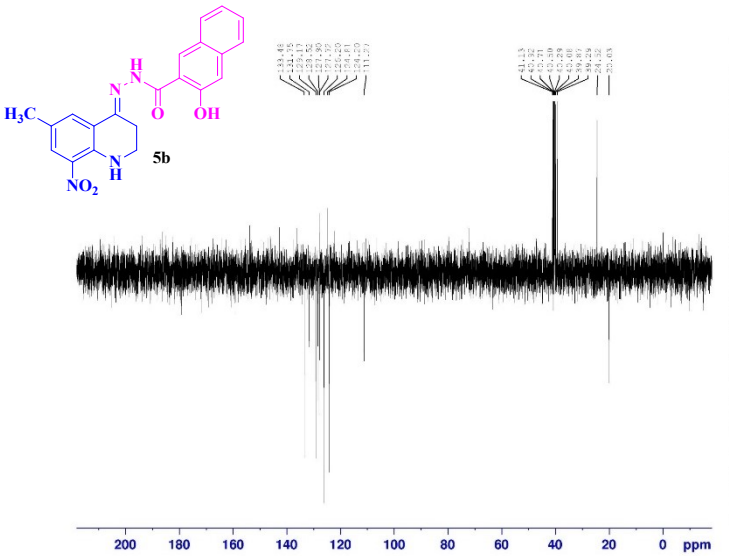
II. ^{13}C NMR SPECTRA

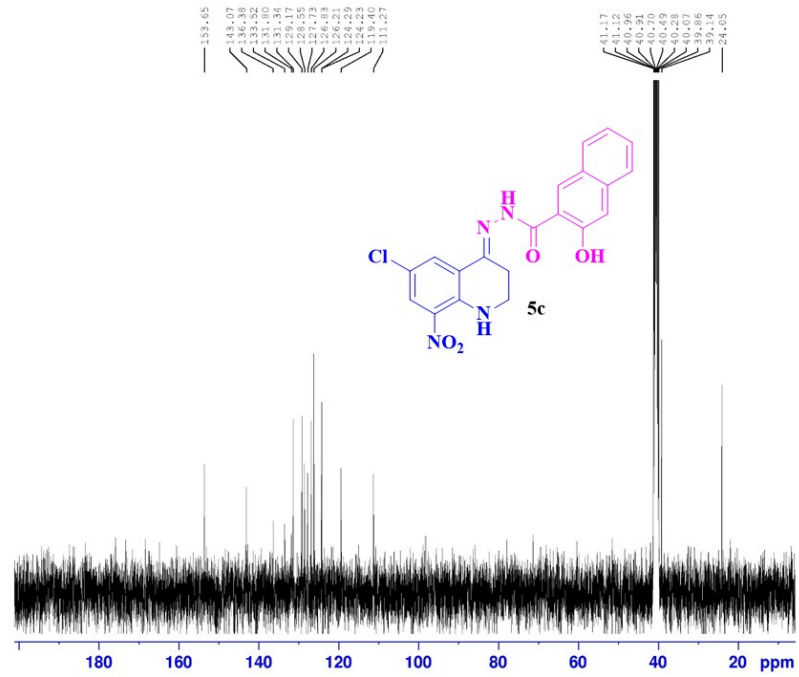


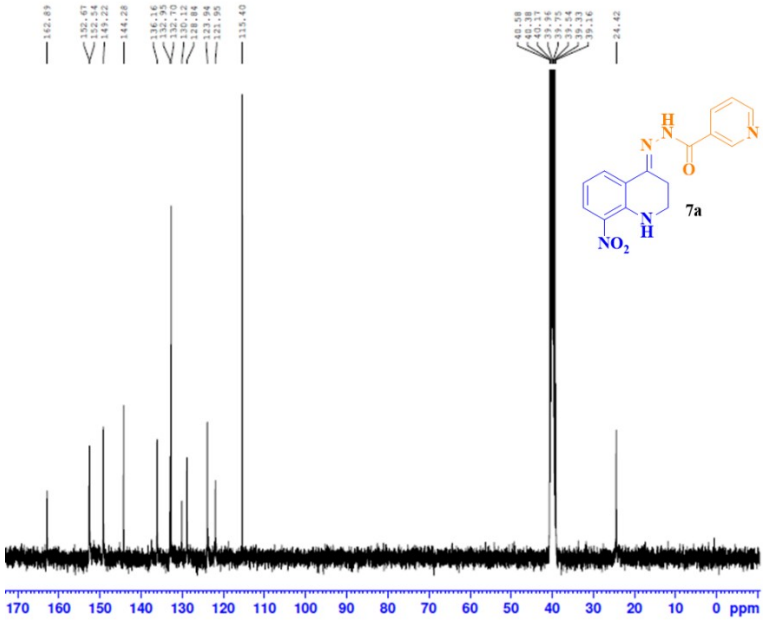


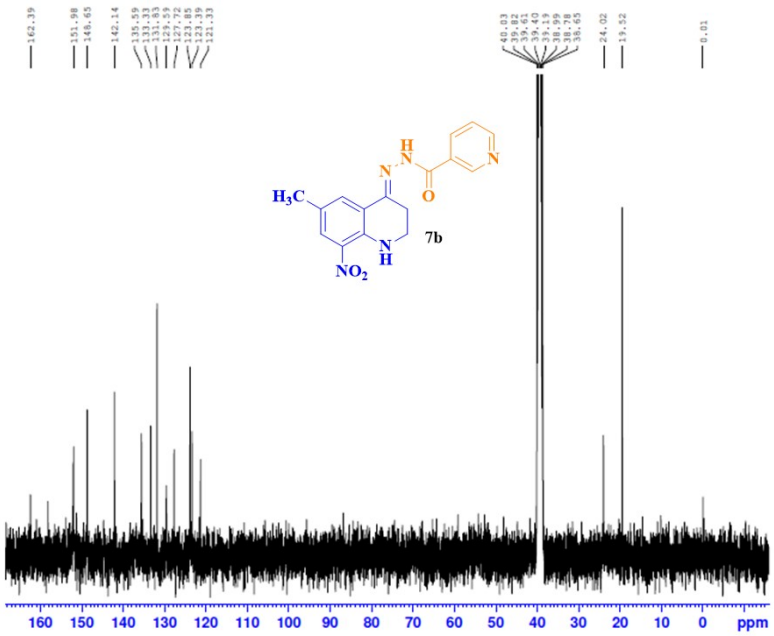

Cl
NO2
OH
3c
160
140
120
100
80
60
40
20
ppm

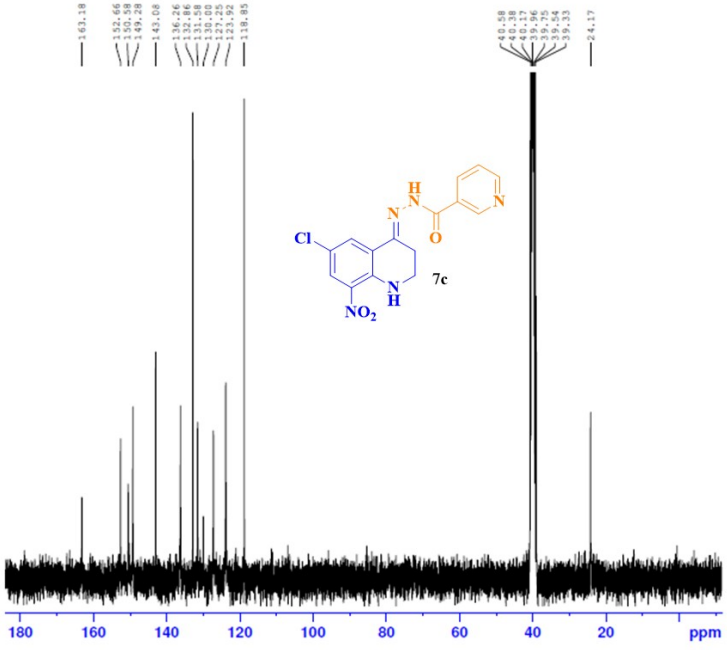

NO2
OH
5a
200
180
160
140
120
100
80
60
40
20
0
ppm

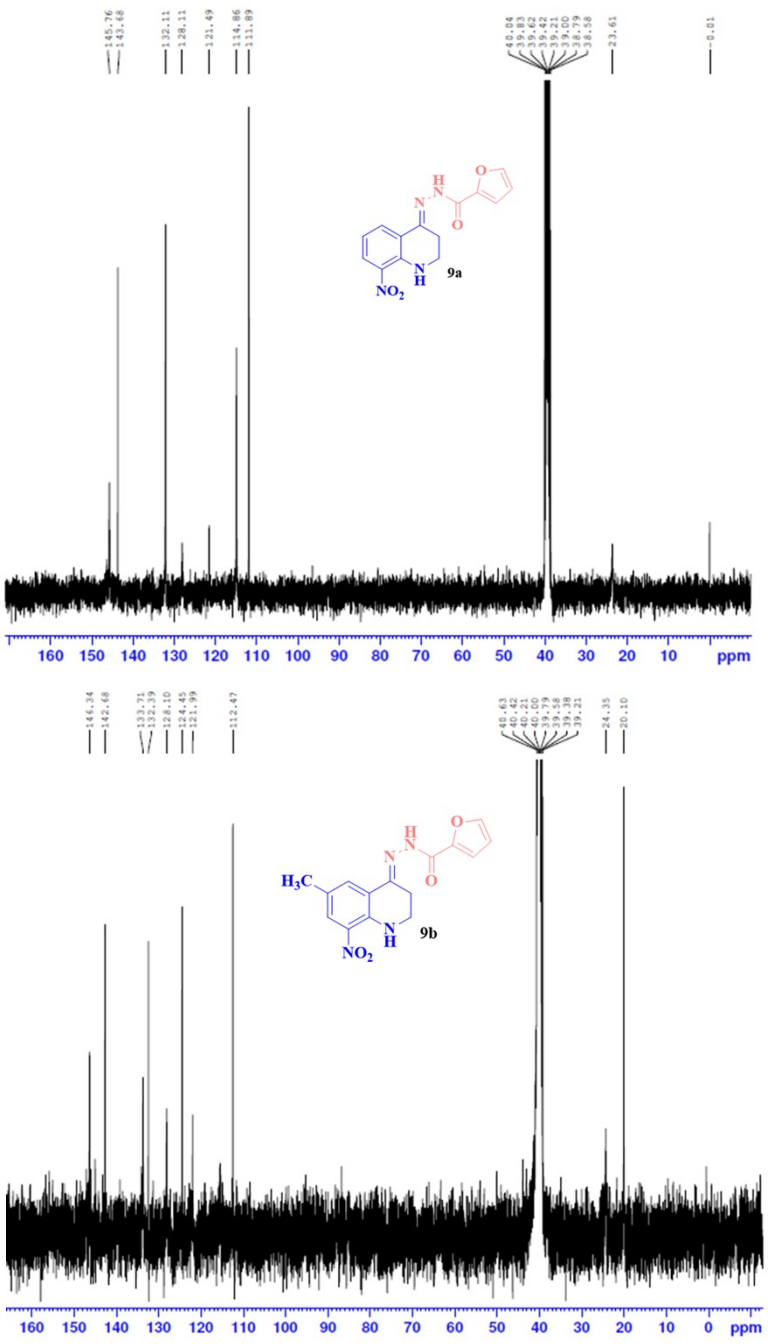

H3C
NO2
OH
5b
200
180
160
140
120
100
80
60
40
20
0
ppm

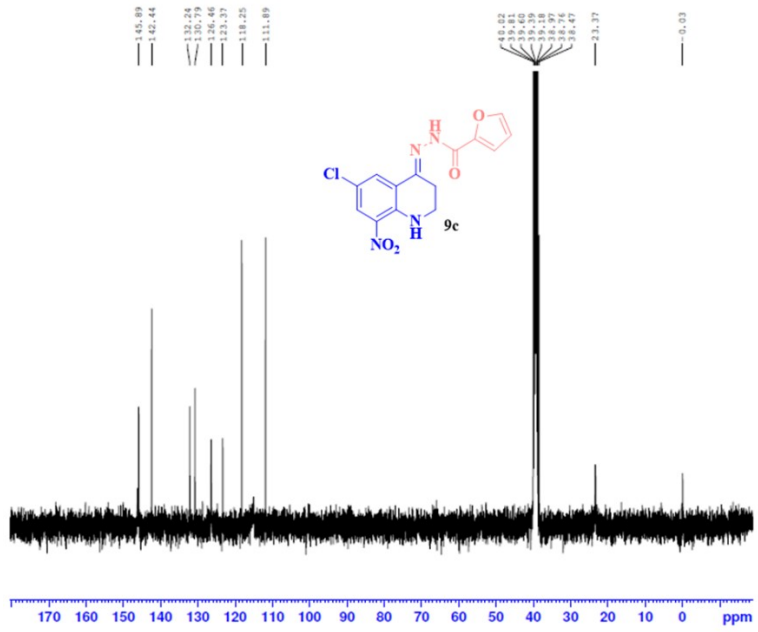

153.65
143.07
136.38
133.52
131.80
131.34
129.17
128.55
127.73
126.83
126.21
124.29
124.23
119.40
111.27
61.17
41.12
40.96
40.91
40.70
40.49
40.28
40.07
39.86
39.14
24.05
Cl
H
N
N
O
OH
N
H
NO2
5c
180
160
140
120
100
80
60
40
20
ppm

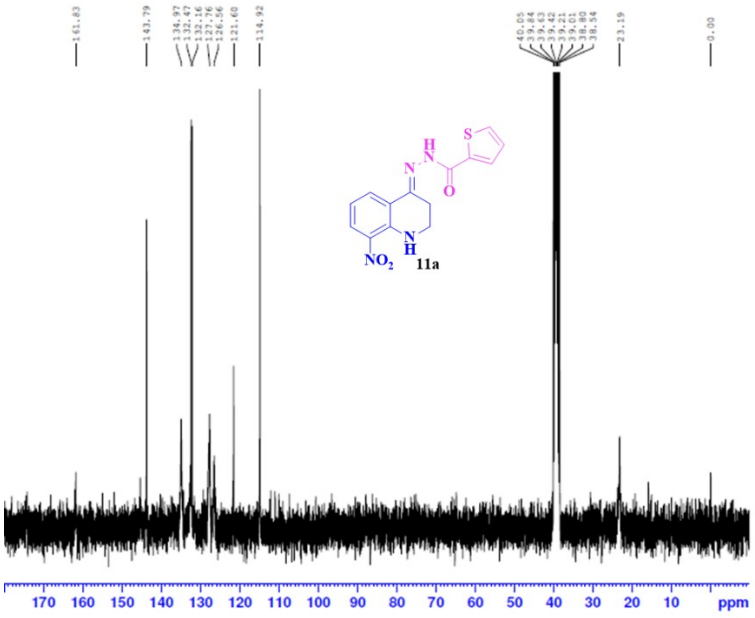

162.89
152.67
152.54
149.22
144.28
136.16
132.95
132.70
130.72
128.84
123.94
121.95
115.40
40.58
40.38
40.17
39.96
39.75
39.54
39.33
39.12
24.42
H
N
N
O
N
N
H
NO2
7a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

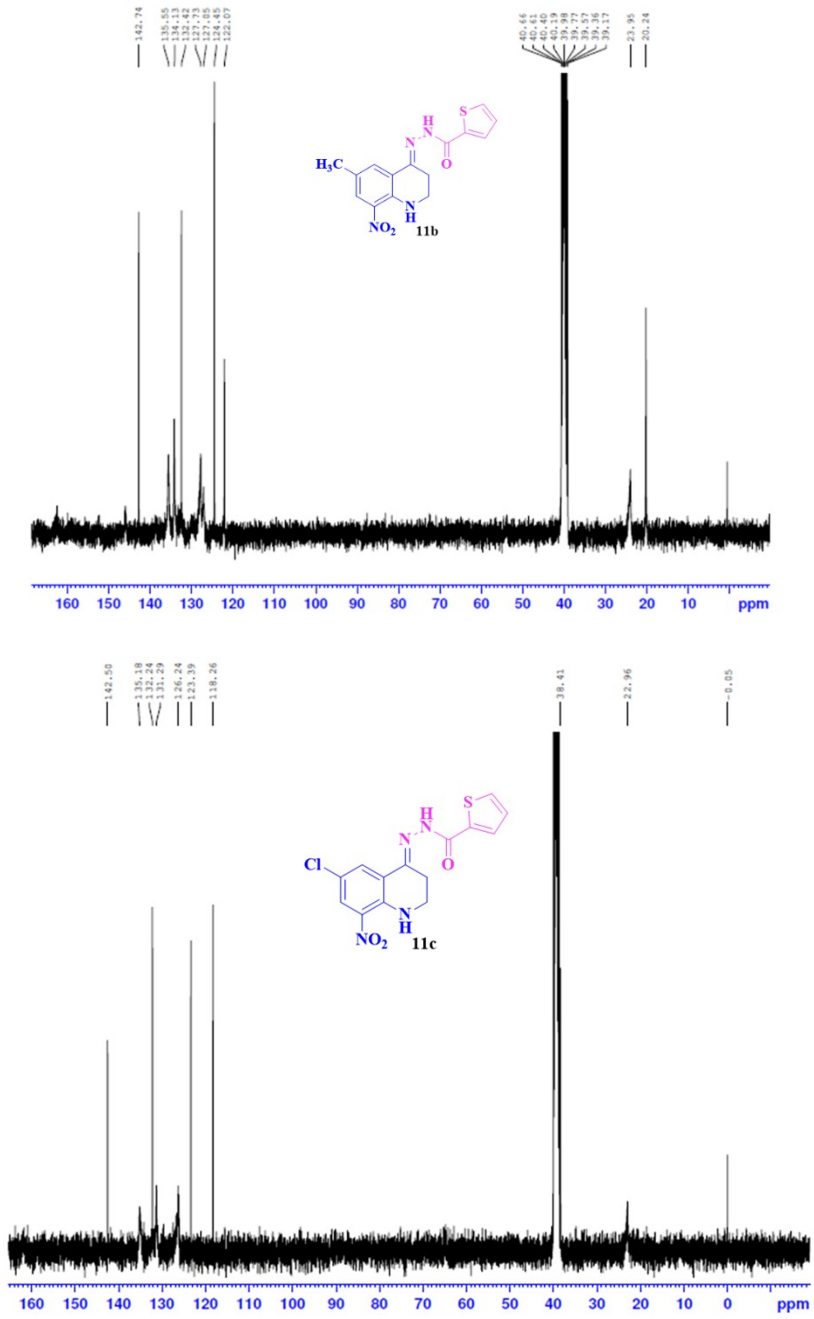

162.39
151.98
148.65
142.14
135.59
133.23
131.83
129.59
127.72
123.35
121.39
121.33
40.03
39.82
39.61
39.40
39.19
38.99
38.78
38.65
24.02
19.52
0.01
H
N
N
O
N
H3C
N
H
NO2
7b
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


163.18
152.66
150.98
149.28
143.08
136.26
132.86
131.88
130.00
127.25
123.92
118.85
40.58
40.38
40.17
39.96
39.75
39.54
39.33
24.17
H
N
N
O
N
Cl
N
H
NO2
7c
180 160 140 120 100 80 60 40 20 ppm


145.76
143.68
132.11
128.11
121.49
114.86
111.89
40.04
39.83
39.62
39.42
39.21
39.00
38.79
38.58
23.61
8.61
9a
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
146.34
142.68
133.71
132.39
128.10
124.45
121.99
112.47
40.63
40.42
40.21
40.00
39.79
39.58
39.38
39.21
24.35
20.10
9b
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


145.89
142.44
132.24
130.79
126.46
123.37
118.25
111.89
49.02
39.81
39.60
39.39
39.18
38.97
38.76
38.47
23.37
0.03
Cl
O
H
N
N
O
N
H
NO2
9c
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


161.63
143.79
134.97
132.47
132.16
127.76
126.56
121.60
114.92
40.05
39.84
39.63
39.42
39.21
39.01
38.80
38.59
23.19
0.00
S
H
N
N
O
N
H
NO2
11a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

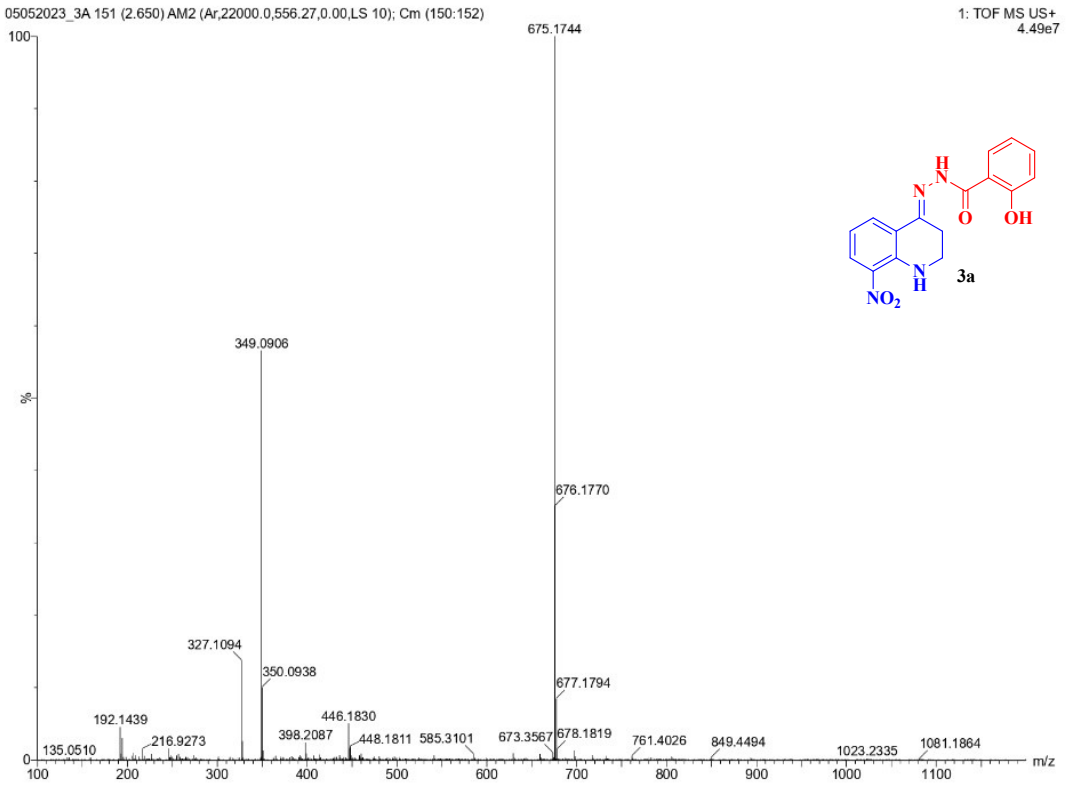


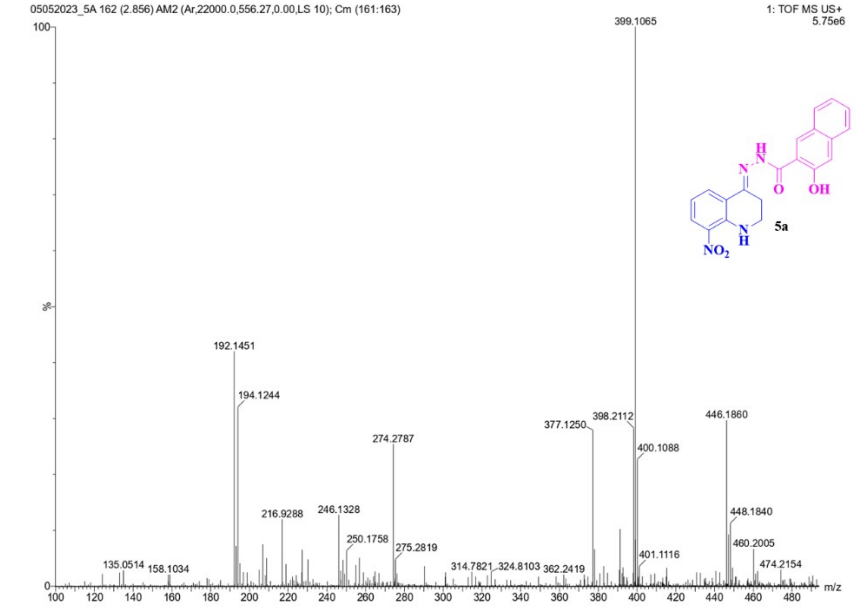
III. CRYSTALLOGRAPHIC DATA:

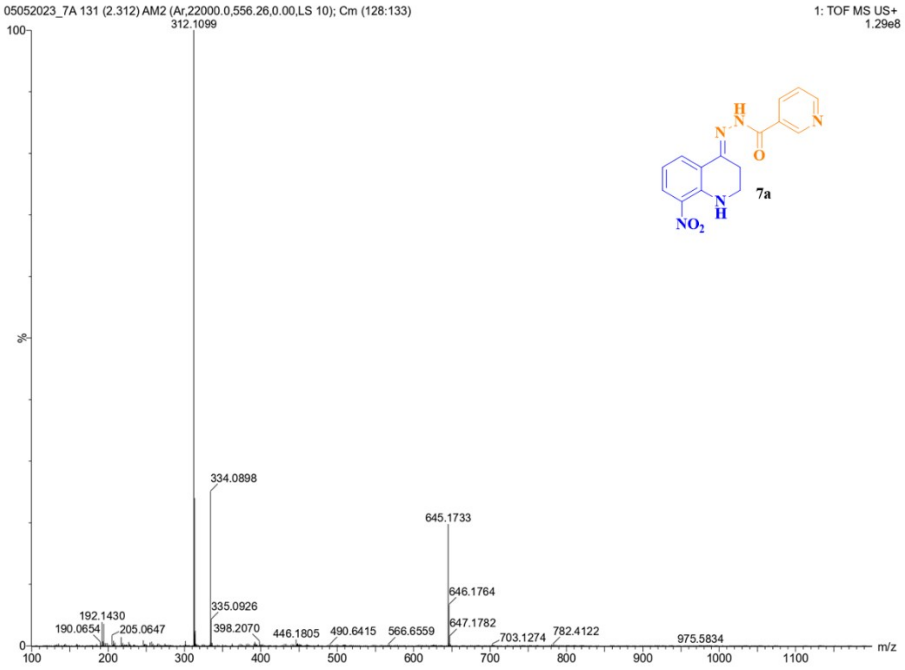
Parameters	**9b**	**11a**
Bond precision	C-C = 0.0028 A	C-C = 0.0028 A
Wavelength	0.71073	0.71073
Cell	a=10.1670(5) b=10.1947(4) c=14.5421(6) alpha=78.485(3) beta=78.991(4) gamma=86.483(4)	a=9.0301(4), b=13.7515(7), c=11.0994(7) alpha=90, beta=94.892(5), gamma=90
Temperature:	295 K	295 K
Volume	1449.34(11)	1373.27(13)

Space group		P -1	P 21/n
Hall group		-P 1	-P 2yn
Moiety formula		C15 H14 N4 O4	C14 H12 N4 O3 S
Sum formula		C15 H14 N4 O4	C14 H12 N4 O3 S
Mr		314.30	316.34
Dx,g cm-3		1.440	1.530
Z		4	4
Mu (mm-1)		0.108	0.255
F000		656.0	656.0
F000’		656.32	656.77
h,k,lmax		13,14,19	12,18,15
Nref		7869	3773
Tmin,Tmax		0.976,0.991	0.964,0.990
Tmin’		0.972	0.933
Data completeness		0.870	0.858
Theta(max)		29.259	29.343
R(reflections)	0.0512(4391)	0.0447(2338)	
wR2(reflections)	0.1472(6848)	0.1203(3238)	
S	1.015	1.025	
Npar	453	207	

IV. HRMS SPECTRA







V. THEORETICAL ADMET PARAMETERS:

A. PHYSICO- CHEMICAL PARAMETERS:

Compounds	Molecular Weight	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA
3a	326.31	0.12	4	5	3	119.54
3b	340.33	0.18	4	5	3	119.54

3c	360.75	0.12	4	5	3	119.54
5a	376.37	0.1	4	5	3	119.54
5b	390.39	0.14	4	5	3	119.54
5c	410.81	0.1	4	5	3	119.54
7a	311.3	0.13	4	5	2	112.2
7b	325.32	0.19	4	5	2	112.2
7c	345.74	0.13	4	5	2	112.2
9a	300.27	0.14	4	5	2	112.45
9b	314.3	0.2	4	5	2	112.45
9c	334.71	0.14	4	5	2	112.45
11a	316.34	0.14	4	4	2	127.55
11b	330.36	0.2	4	4	2	127.55
11c	350.78	0.14	4	4	2	127.55

B. LIPOHILICITY:

Compound	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
3a	1.98	2.86	1.68	0.91	0.24	1.53
3b	2.29	3.23	1.99	1.15	0.75	1.88
3c	2.12	3.49	2.33	1.42	0.89	2.05
5a	2.56	4.11	2.83	1.67	1.26	2.49
5b	2.63	4.48	3.14	1.89	1.78	2.78
5c	2.42	4.74	3.49	2.16	1.91	2.94
7a	1.83	1.6	1.37	1.2	0.17	1.23
7b	1.84	1.96	1.68	0.64	0.68	1.36
7c	1.71	2.22	2.02	1.72	0.81	1.7

9a	2.12	2.06	1.57	0.98	0.12	1.37
9b	2.35	2.43	1.87	0.43	0.62	1.54
9c	2.15	2.69	2.22	1.51	0.77	1.87
11a	2.2	2.68	2.03	1.77	1.37	2.01
11b	2.17	3.04	2.34	1.22	1.87	2.13
11c	1.99	3.31	2.69	2.3	2.02	2.46

C. WATER SOLUBILITY

Compound	ESOL Log S	ESOL Class	Ali Log S	Ali Class	Silicos-IT LogSw	Silicos-IT class
3a	-3.77	Soluble	-5.03	Moderately soluble	-4.61	Moderately soluble
3b	-4.08	Moderately soluble	-5.41	Moderately soluble	-4.99	Moderately soluble
3c	-4.37	Moderately soluble	-5.68	Moderately soluble	-5.2	Moderately soluble
5a	-4.92	Moderately soluble	-6.33	Poorly soluble	-6.25	Poorly soluble
5b	-5.23	Moderately soluble	-6.71	Poorly soluble	-6.63	Poorly soluble
5c	-5.52	Moderately soluble	-6.98	Poorly soluble	-6.84	Poorly soluble
7a	-2.9	Soluble	-3.57	Soluble	-4.82	Moderately soluble
7b	-3.2	Soluble	-3.94	Soluble	-5.2	Moderately soluble
7c	-3.49	Soluble	-4.21	Moderately soluble	-5.42	Moderately soluble
9a	-3.11	Soluble	-4.05	Moderately soluble	-4.41	Moderately soluble
9b	-3.41	Soluble	-4.43	Moderately soluble	-4.79	Moderately soluble
9c	-3.7	Soluble	-4.7	Moderately soluble	-5.01	Moderately soluble
11a	-3.6	Soluble	-5.01	Moderately soluble	-4.46	Moderately soluble
11b	-3.89	Soluble	-5.38	Moderately soluble	-4.84	Moderately soluble
11c	-4.19	Moderately soluble	-5.66	Moderately soluble	-5.05	Moderately soluble

D. PHARMACOKINETICS

	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
3a	High	No	No	Yes	No	Yes	No	No	-6.26
3b	High	No	No	Yes	No	Yes	No	Yes	-6.08
3c	High	No	No	Yes	No	Yes	No	Yes	-6.02
5a	High	No	No	Yes	No	Yes	No	Yes	-5.68
5b	High	No	No	Yes	No	Yes	No	Yes	-5.5
5c	High	No	No	Yes	No	Yes	No	Yes	-5.44
7a	High	No	Yes	No	No	No	No	No	-7.06
7b	High	No	Yes	Yes	No	No	No	Yes	-6.89
7c	High	No	No	Yes	No	No	No	No	-6.83
9a	High	No	No	Yes	No	No	No	No	-6.67
9b	High	No	No	Yes	No	Yes	No	Yes	-6.49
9c	High	No	No	Yes	No	Yes	No	Yes	-6.43
11a	High	No	No	Yes	Yes	Yes	No	No	-6.33
11b	High	No	No	Yes	Yes	Yes	No	Yes	-6.16
11c	High	No	No	Yes	Yes	Yes	No	Yes	-6.09

E. DRUG LIKENESS:

Compound	Lipinski violation	Ghose violation	Veber violation	Egan violation	Muegge violation	Bioavailability Score
3a	0	0	0	0	0	0.55
3b	0	0	0	0	0	0.55
3c	0	0	0	0	0	0.55
5a	0	0	0	0	0	0.55
5b	0	0	0	0	0	0.55
5c	0	0	0	0	0	0.55

7a	0	0	0	0	0	0.55
7b	0	0	0	0	0	0.55
7c	0	0	0	0	0	0.55
9a	0	0	0	0	0	0.55
9b	0	0	0	0	0	0.55
9c	0	0	0	0	0	0.55
11a	0	0	0	0	0	0.55
11b	0	0	0	0	0	0.55
11c	0	0	0	0	0	0.55

F. TOXICITY:

Toxicity parameter	**3a**	**3b**	**3c**	**5a**	**5b**	**5c**
AMES toxicity	YES	Yes	No	Yes	Yes	Yes
Maximum tolerated dose (human) in mg/kg/day	-0.138	-0.146	-0.127	0.304	0.168	0.181
hERG I inhibitor	No	No	No	No	No	No
hERG II inhibitor	No	Yes	No	Yes	Yes	Yes
Oral rate acute toxicity (LD50) in mol/kg	2.34	3.123	3.142	2.765	2.648	2.665
Oral rat chronic toxicity (LOAEL) in mg/kg_bw/day	2.532	2.36	2.407	2.402	2.403	2.45
Hepatotoxicity	No	No	No	Yes	Yes	Yes
Skin sensitisation	No	No	No	No	No	No
T.pyriforms toxicity in log ug/l	0.752	0.513	0.504	0.327	0.307	0.305
Minnow toxicity in log mM	1.073	0.068		1.86	-0.502	-0.719