Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Unleashing Naphthopyranopyrimidine's Anticancer Potential: A Deep Eutectic Solvent (DES) Study

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Contents

General information:

Reagents and solvent purchased for the synthesis of Naphthopyranopyrimidine were of reagent grade and had been used without any further purification. All of the reaction had been carried out in an oven dried glassware. Silica gel with the mesh size of 100-200 was used for the purification in column chromatography.^{1}H, ^{13}C, and ^{19}F NMR spectroscopies of column purified products had been recorded in Bruker 400 MHz instrument. Chemical shift (δ) values had been reported in ppm. Coupling constant (*J*) values were assigned in hertz (Hz). Peak multiplicity for proton NMR spectroscopy were assigned with s, d, t, q, m which refers to the singlet, doublet, triplet, quartet, and multiplate respectively.

General procedure for the synthesis of Naphthopyranopyrimidine:

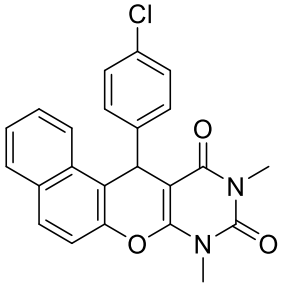
A mixture of aromatic aldehyde (1 mmol), 6-amino-1,3-dimehyl uracil (1 mmol), and β-naphthol (1 mmol) was taken in a round bottom flask and 2 ml ChCl: Chloroacetic acid (1:1) based DES was added to it. The resulting mixture was stirred at 90 ℃ for 2 hours. Progress of the reaction was monitored with thin layer chromatography at regular intervals of time. After the completion of the reaction indicated by TLC, the reaction mixture was cooled to room temperature and then worked up with ethyl acetate and water mixture. Then, the organic layer is dried over anhydrous Na_2SO_4. After that pure product was obtained through column chromatography in 100-200 mesh size silica using ethyl acetate and petroleum ether eluent, the formation of the pure product was confirmed with ^{1}H and ^{13}C NMR spectroscopic techniques.

Preparation of Deep Eutectic Solvent (DES)[1]:

ChCl: Chloroacetic acid (1:1) based deep eutectic solvent had been prepared by mixing Choline chloride and Chloroacetic acid in equimolar ratio and then heated to 70 ℃ with continuous stirring until clear and homogeneous liquid formed. Then the freshly prepared DES mixture was used without any further purification.

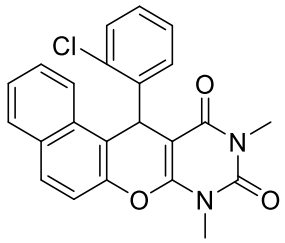
Spectroscopic data of Naphthopyranopyrimidine:

12-(4-chlorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4a**)



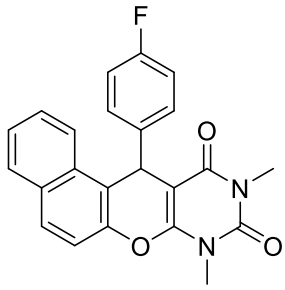
White solid, Yield: 327 mg (81%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02-7.94 (m, 3H), 7.63-7.60 (m, 1H), 7.53-7.45 (m, 2H), 7.35 (d, 2H, *J*=8.4 Hz), 7.23 (d, 2H, *J*=8.4 Hz), 5.69 (s, 1H), 3.50 (s,3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.58, 152.77, 150.56, 147.18, 143.69, 131.83, 131.57, 130.57, 130.28, 129.16, 128.61, 128.00, 125.98, 124.05, 117.48, 116.84, 90.06, 35.42, 29.45, 28.23.

12-(2-chlorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4b**)



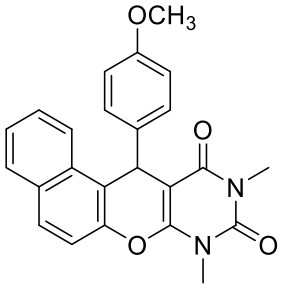
White solid, Yield: 339 mg (84%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07-8.05 (m, 1H), 7.98-7.91 (m, 2H), 7.56-7.42 (m, 3H), 7.31-7.29 (m, 2H), 7.15-7.07 (m, 2H), 5.89 (s, 1H), 3.49 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.31, 152.84, 150.52, 147.23, 141.84, 132.64, 132.41, 131.70, 130.91, 130.38, 130.03, 129.27, 128.79, 127.90, 125.91, 123.75, 117.49, 116.60, 89.54, 34.08, 29.47, 28.18.

12-(4-fluorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4c**)



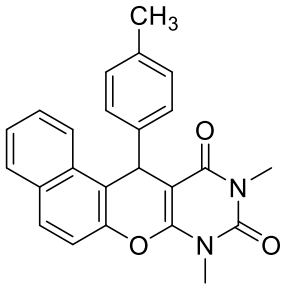
White solid, Yield: 345 mg (89%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02-7.94 (m, 3H), 7.63-7.61 (m, 1H), 7.53-7.43 (m, 2H), 7.38-7.35 (m, 2H), 7.02-6.98 (m, 2H), 5.70 (s, 1H), 3.50 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.57, 159.96, 153.98 (d, *J*= 250 Hz), 150.56, 147.19, 140.97, 131.85, 130.58, 130.19, 129.15, 127.95, 125.94, 124.14, 117.34 (d, *J*= 29 Hz), 115.37 (d, J= 21 Hz), 90.33, 35.21, 29.43, 28.22.

12-(4-methoxyphenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4d**)



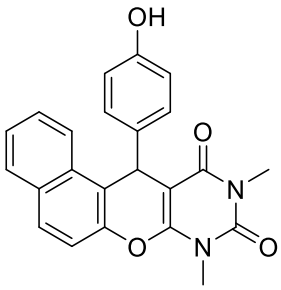
White solid, Yield: 336 mg (84%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03-7.93 (m, 3H), 7.61-7.59 (m,1H), 7.52-7.44 (m, 2H), 7.22 (d, 2H, *J*=8.4 Hz), 6.73 (d, 2H, *J*=8.4 Hz), 5.62 (s, 1H), 3.62 (s, 3H), 3.50 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.55, 158.19, 152.52, 150.55, 147.13, 136.97, 131.83, 130.66, 129.09, 129.65, 129.08, 127.81, 125.84, 124.19, 117.67, 117.43, 114.02, 90.74, 55.39, 35.07, 29.39, 28.20.

8,10-dimethyl-12-(p-tolyl)-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4e**)



White solid, Yield: 349 mg (91%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01-7.90 (m, 3H), 7.57-7.55 (m, 1H), 7.50-7.41 (m, 2H), 7.18 (d, 2H, *J*=8.0 Hz), 6.96 (d, 2H, *J*=8.0 Hz), 5.58 (s, 1H), 3.47 (s, 3H), 3.14 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.52, 152.48, 150.52, 147.04, 141.86, 136.10, 131.77, 130.60, 129.90, 129.21, 129.21, 129.03, 128.50, 127.77, 125.80, 124.07, 117.47, 117.35, 90.62, 35.51, 29.35, 28.18, 20.91.

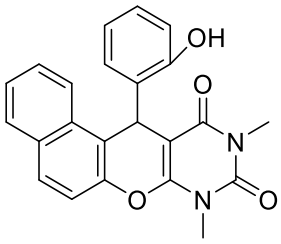
12-(4-hydroxyphenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4f**)



Yellow solid, Yield: 343 mg (89%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 1H), 8.01-7.92 (m, 3H), 7.59-7.56 (m, 1H), 7.52-7.34 (m, 2H), 7.13-7.03 (m, 2H), 6.58-6.48 (m, 2H), 5.54 (s, 1H), 3.49 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.55, 156.32, 152.47, 150.55,

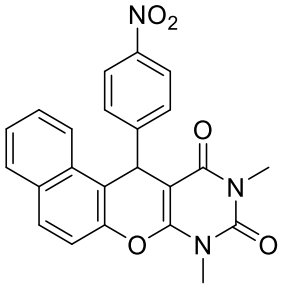
147.09, 135.33, 131.82, 130.68, 129.78, 129.62, 129.07, 127.77, 125.82, 124.22, 117.92, 117.44, 115.34, 90.92, 35.03, 29.39, 28.21.

12-(2-hydroxyphenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4g**)



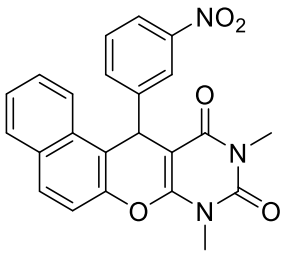
White solid, Yield: 331 mg (86%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.66 (s, 1H), 8.29-8.22 (m, 1H), 7.99-7.87 (m, 2H), 7.60-7.42 (m, 3H), 7.22-7.11 (m, 1H), 6.91-6.87 (m, 1H), 6.72-6.60 (m, 2H), 5.82 (s, 1H), 3.51 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.91, 154.57, 153.22, 150.57, 147.37, 131.63, 131.06, 130.86, 129.51, 128.09, 127.62, 125.70, 124.12, 119.75, 117.72, 117.32, 116.56, 89.89, 30.96, 29.43, 28.22.

8,10-dimethyl-12-(4-nitrophenyl)-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4h**)



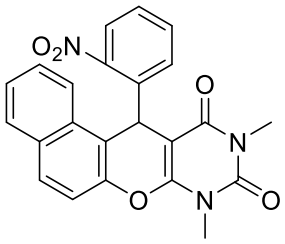
Yellow solid, Yield: 377 mg (91%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06-7.95 (m, 5H), 7.70-7.63 (m, 3H), 7.53-7.45 (m, 2H), 5.86 (s, 1H), 3.52 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.50, 152.95, 151.98, 150.52, 147.22, 146.56, 131.85, 130.65, 130.49, 130.14, 129.21, 128.13, 126.07, 124.02, 123.86, 117.55, 116.08, 89.34, 35.98, 29.50,28.23.

8,10-dimethyl-12-(3-nitrophenyl)-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4i**)



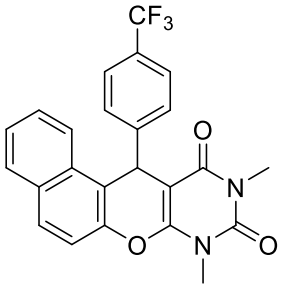
White solid, Yield: 390 mg (94%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 8.01-7.98 (m, 1H), 7.94-7.90 (m, 2H), 7.88-7.83 (m, 2H), 7.51-7.42 (m, 4H), 5.92 (s, 1H), 3.65 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.89, 152.49, 150.55, 148.54, 147.27, 145.85, 134.87, 131.93, 130.39, 129.23, 128.87, 127.86, 125.84, 123.47, 123.12, 122.08, 116.54, 115.75, 90.28, 36.06, 29.23, 28.29.

8,10-dimethyl-12-(2-nitrophenyl)-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4j**)



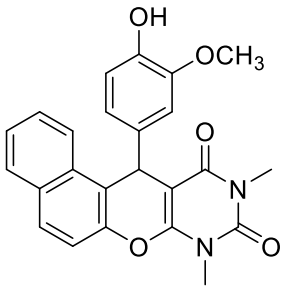
White solid, Yield: 340 mg (82%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34-8.29 (m, 1H), 8.05-8.03 (m, 1H), 7.96-7.83 (m, 2H), 7.62-7.57 (m, 1H), 7.51-7.38 (m, 3H), 7.34-7.30 (m, 1H), 7.02-7.00 (m, 1H), 6.48 (s, 1H), 3.45 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.72, 151.86, 150.50, 149.26, 147.59, 138.28, 133.07, 131.84, 131.02, 130.39, 128.42, 128.04, 127.57, 125.85, 124.80, 124.65, 116.26, 115.91, 90.49, 31.08, 29.13, 28.29.

8,10-dimethyl-12-(4-(trifluoromethyl)phenyl)-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4k**)



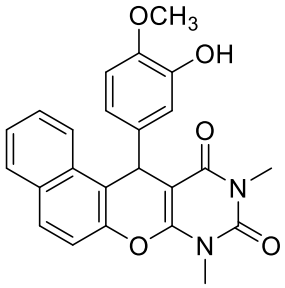
White solid, Yield: 350 mg (80%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07-7.95 (m, 3H), 7.66-7.62 (m, 1H), 7.60-7.57 (m, 4H), 7.55-7.45 (m, 2H), 5.80 (s, 1H), 3.51 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.55, 152.89, 150.54, 149.20, 147.25, 132.01, 131.84, 130.50, 130.47, 129.61, 129.19, 127.61 (q, J= 31 Hz), 125.79 (q, J= 3.9 Hz), 124.59 (q, J= 270 Hz), 124.00, 117.51, 116.49, 89.75, 35.91, 29.47, 28.23.

12-(4-hydroxy-3-methoxyphenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4l**)



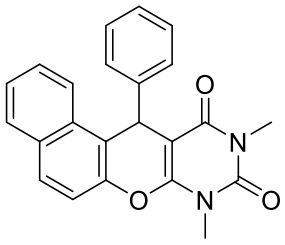
Brown solid, Yield: 374 mg (90%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 8.07-8.04 (m, 1H), 7.97-7.90 (m, 2H), 7.66-7.61 (m, 1H), 7.58-7.43 (m, 2H), 7.00 (s,1H), 6.53 (s, 2H), 5.56 (s, 1H), 3.67 (s, 3H), 3.49 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.64,152.50,150.56,147.42,147.11, 145.57, 135.91, 131.79, 130.77, 129.79, 129.02, 127.76, 125.82, 124.34, 120.81, 117.84, 117.39, 115.65, 113.29, 90.89, 56.07, 35.36, 29.39, 28.24.

12-(3-hydroxy-4-methoxyphenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4m**)



Brown solid, Yield: 361 mg (87%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 7.99-7.87 (m, 3H), 7.60-7.57 (m, 1H), 7.53-7.43 (m, 2H), 6.75-6.65 (m, 3H), 5.51 (s, 1H), 3.62 (s, 3H), 3.48 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.53, 152.42, 150.52, 147.14, 146.72, 146.55, 137.42, 131.81, 130.74, 129.82, 129.06, 127.78, 125.83, 124.16, 119.42, 117.74, 117.40, 115.86, 112.28, 90.80, 55.96, 35.15, 29.38, 28.22.

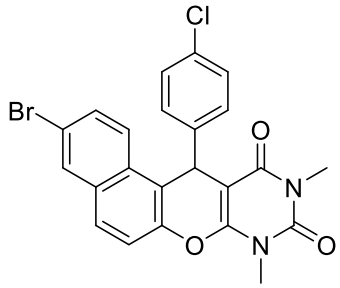
8,10-dimethyl-12-phenyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (**4n**)



White solid, Yield: 318 mg (86%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04-7.91(m, 3H), 7.60-7.58 (m, 1H), 7.51-7.42 (m, 2H), 7.33-7.31 (m, 2H), 7.19-7.15 (m, 2H), 7.08-7.02 (m, 1H), 5.65

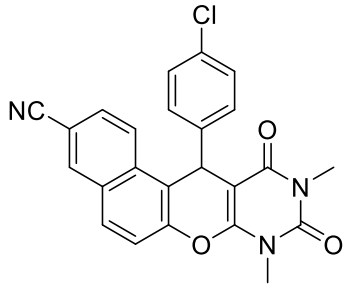
(s, 1H), 3.49 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.53, 152.67, 150.54, 147.19, 144.79, 131.81, 130.63, 130.03, 129.09, 128.68, 127.86, 126.96, 125.87, 124.11, 117.43, 90.52, 35.93, 29.41, 28.21.

3-bromo-12-(4-chlorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d] pyrimidine-9,11(10H)-dione (**4o**)



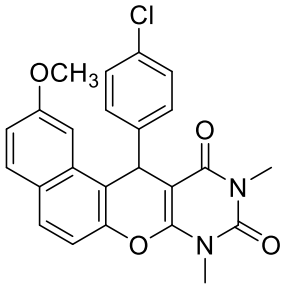
White solid, Yield: 429 mg (89%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (s, 1H), 7.97-7.88 (m, 2H), 7.64-7.55 (m, 2H), 7.31 (d, 2H, *J*= 8.0 Hz), 7.22 (d, 2H, *J*= 8.0 Hz), 5.61 (s, 1H), 3.46 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.45, 152.54, 150.47, 147.39, 143.45, 133.12, 131.68, 130.92, 130.75, 130.56, 129.52, 129.21, 128.63, 126.43, 119.22, 118.79, 117.15, 89.86, 35.32, 29.44, 28.22.

12-(4-chlorophenyl)-8,10-dimethyl-9,11-dioxo-8,10,11,12-tetrahydro-9H-benzo[5,6]chromeno [2,3-d] pyrimidine-3-carbonitrile (**4p**)



White solid, Yield: 321 mg (75%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.16-8.12 (m, 2H), 7.78-7.74 (m, 2H), 7.36-7.33 (m, 2H), 7.25-7.22 (m, 2H), 5.70 (s, 1H), 3.49 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.41, 152.46, 150.48, 149.20, 143.29, 135.29, 132.46, 131.77, 131.03, 130.66, 128.70, 128.41, 125.72, 119.52, 119.21, 117.42, 108.46, 89.91, 35.24, 29.51, 28.25.

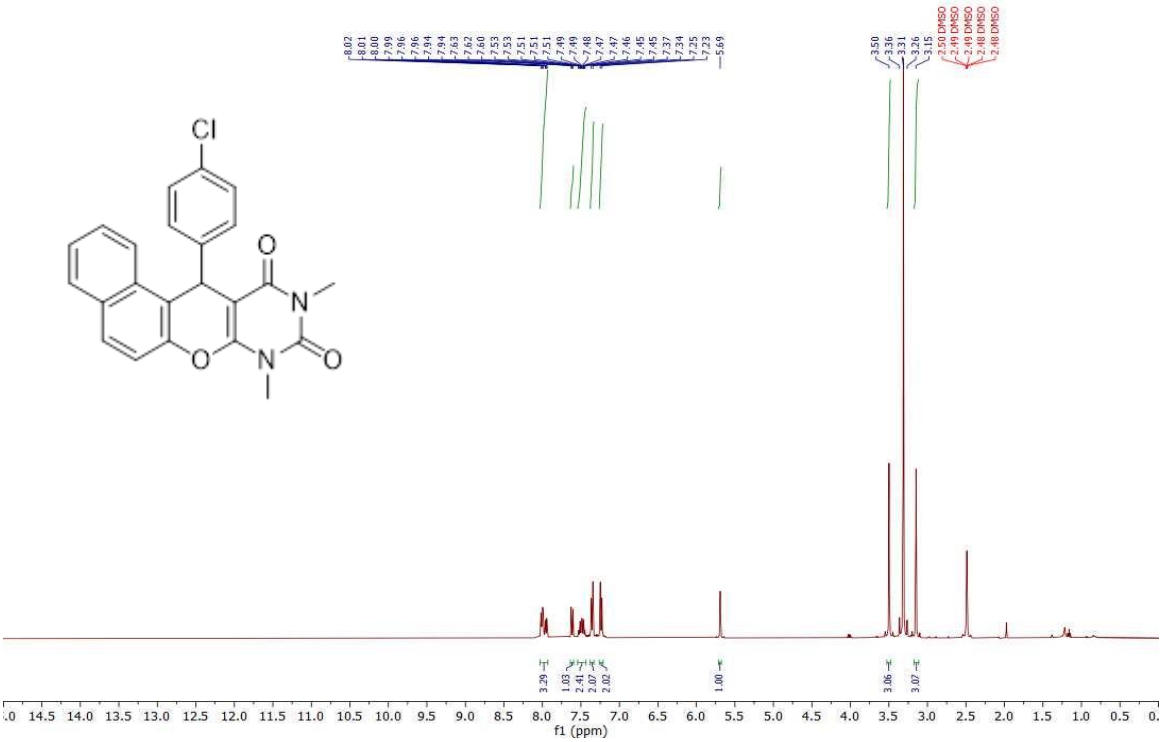
12-(4-chlorophenyl)-2-methoxy-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d] pyrimidine-9,11(10H)-dione (**4q**)

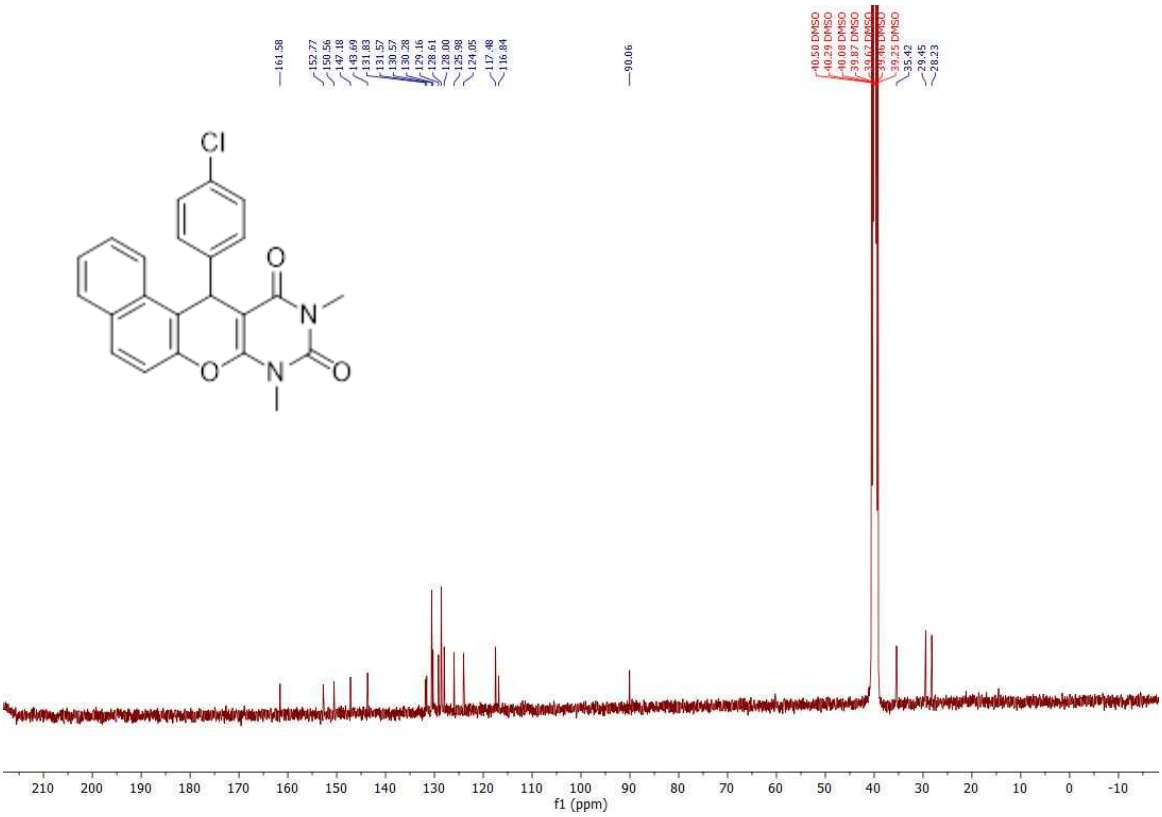


White solid, Yield: 364 mg (84%), ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.90-7.82 (m, 2H), 7.41-7.36 (m, 3H), 7.25-7.20 (m, 3H), 7.09-7.06 (m, 1H), 5.60 (s, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 161.52, 158.69, 152.60, 150.56, 147.55, 143.72, 132.11, 131.49, 130.83, 130.73, 129.88, 128.51, 126.99, 117.88, 115.88, 114.72, 103.46, 89.97, 55.74, 35.68, 29.43, 28.19.

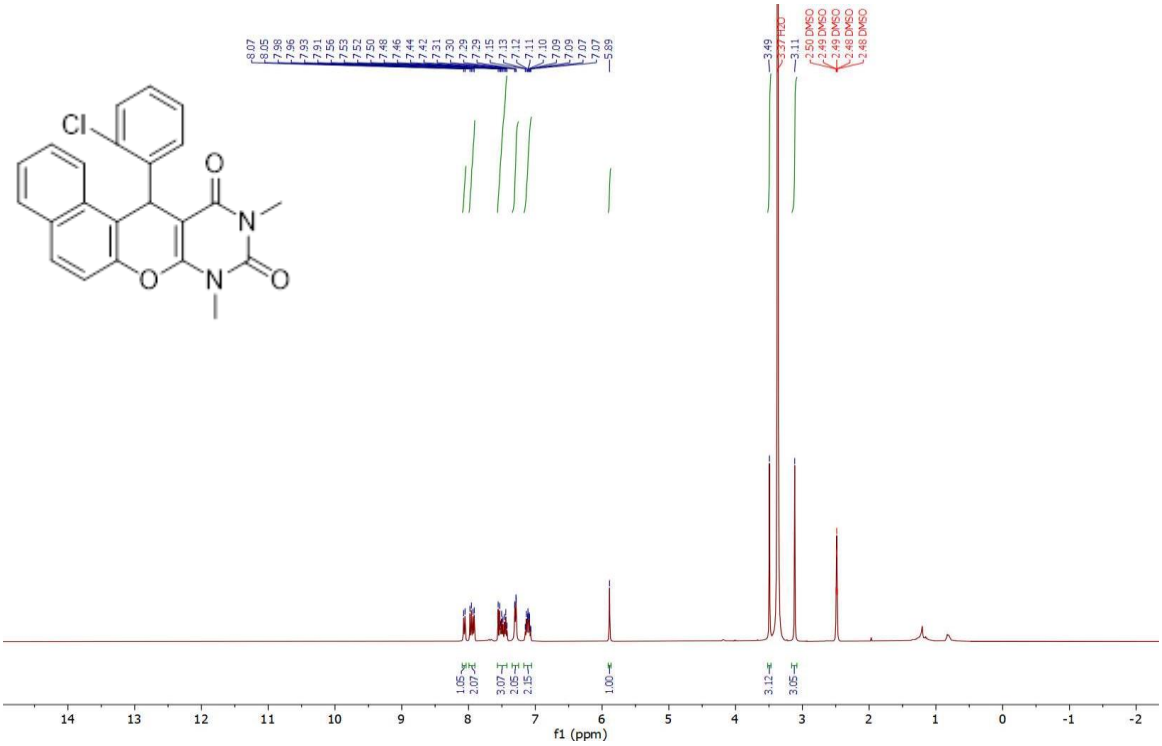
Copies of NMR spectra

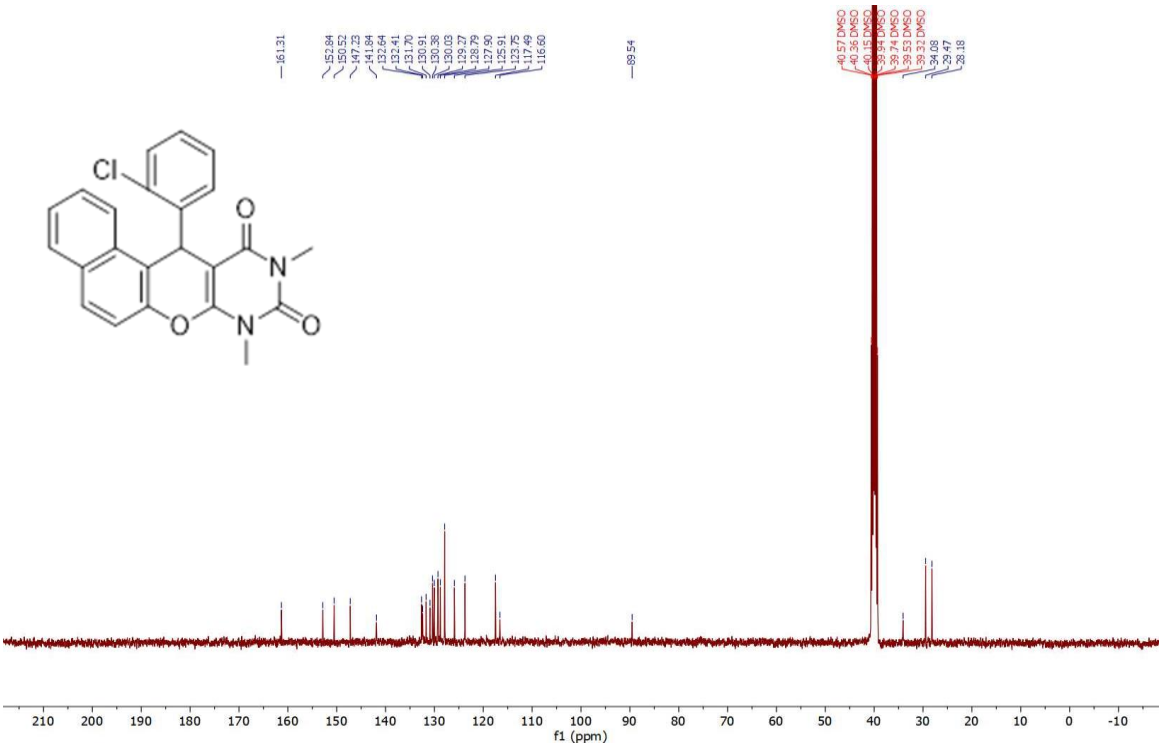
^{1}H and ^{13}C NMR spectra of **4a**



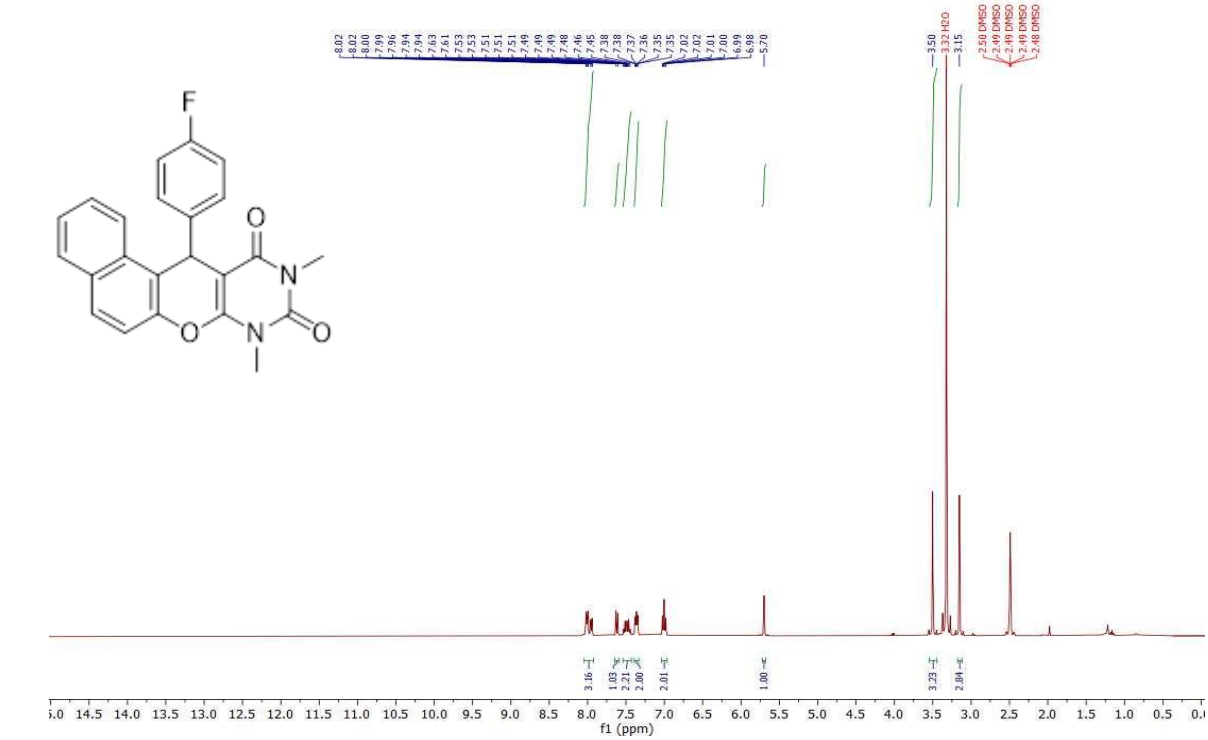


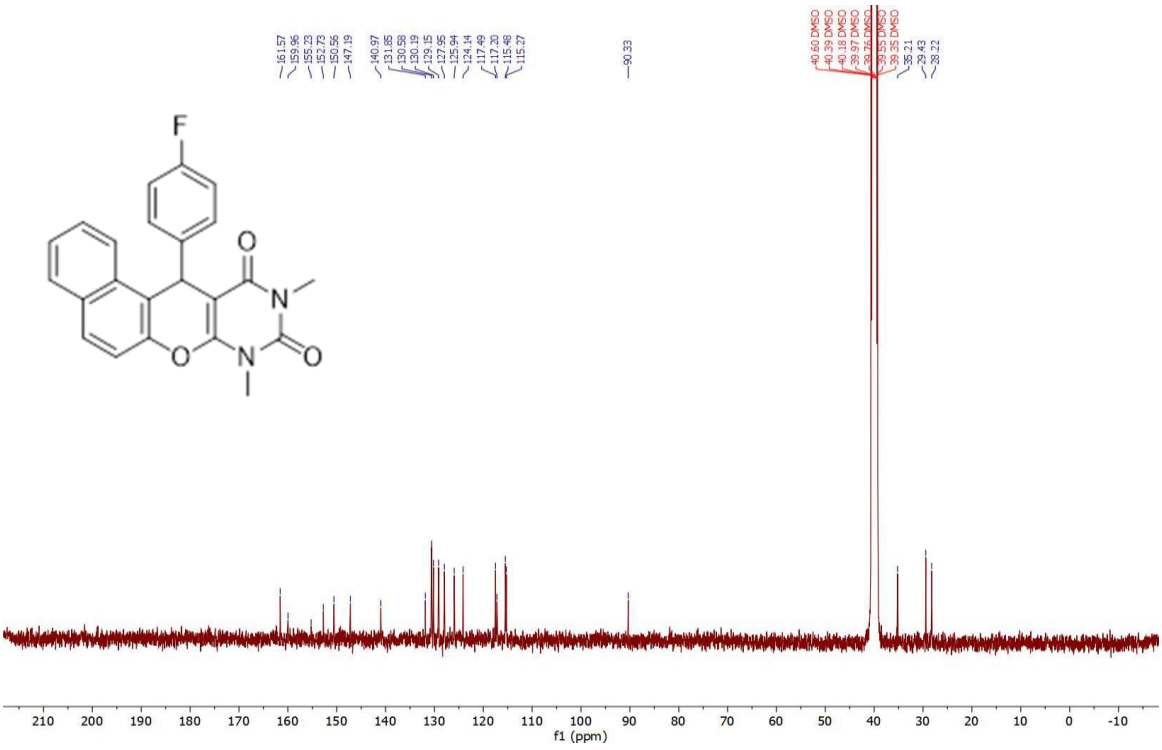
^{1}H and ^{13}C NMR spectra of **4b**

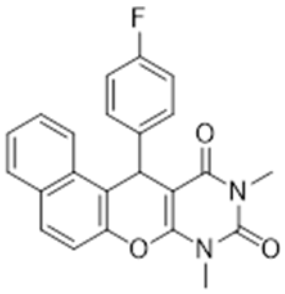




^{1}H ,^{13}C NMR and ^{19}F spectra of **4c**

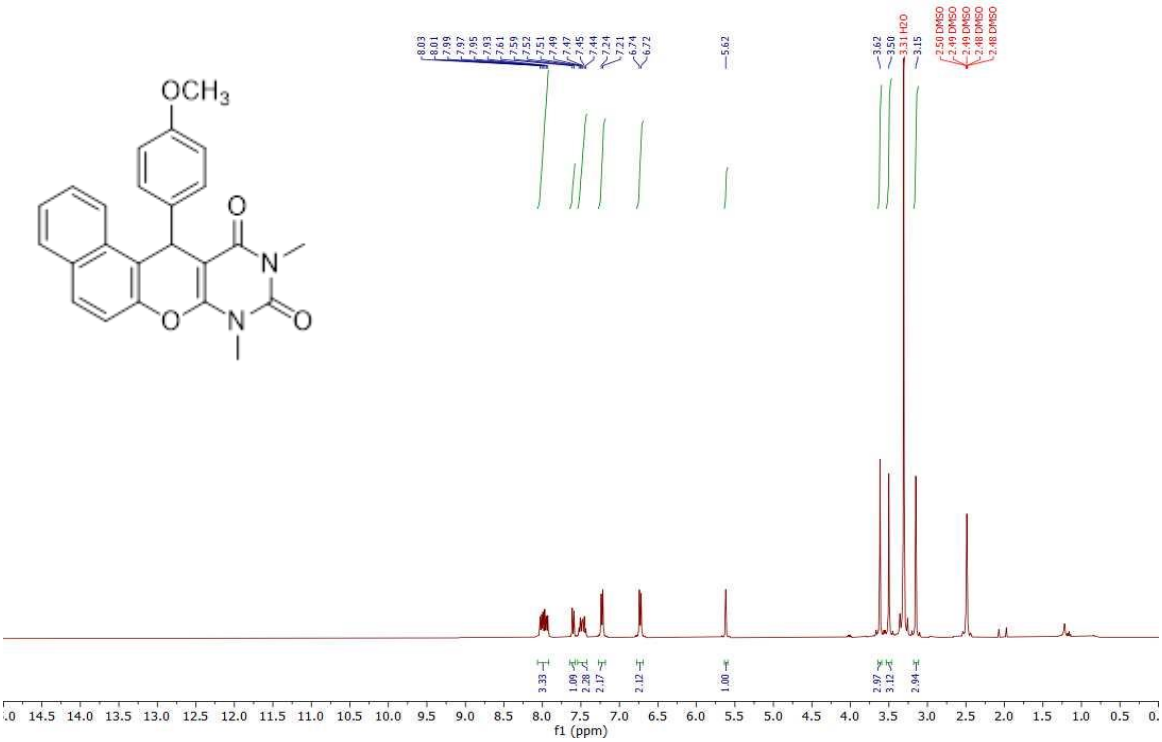


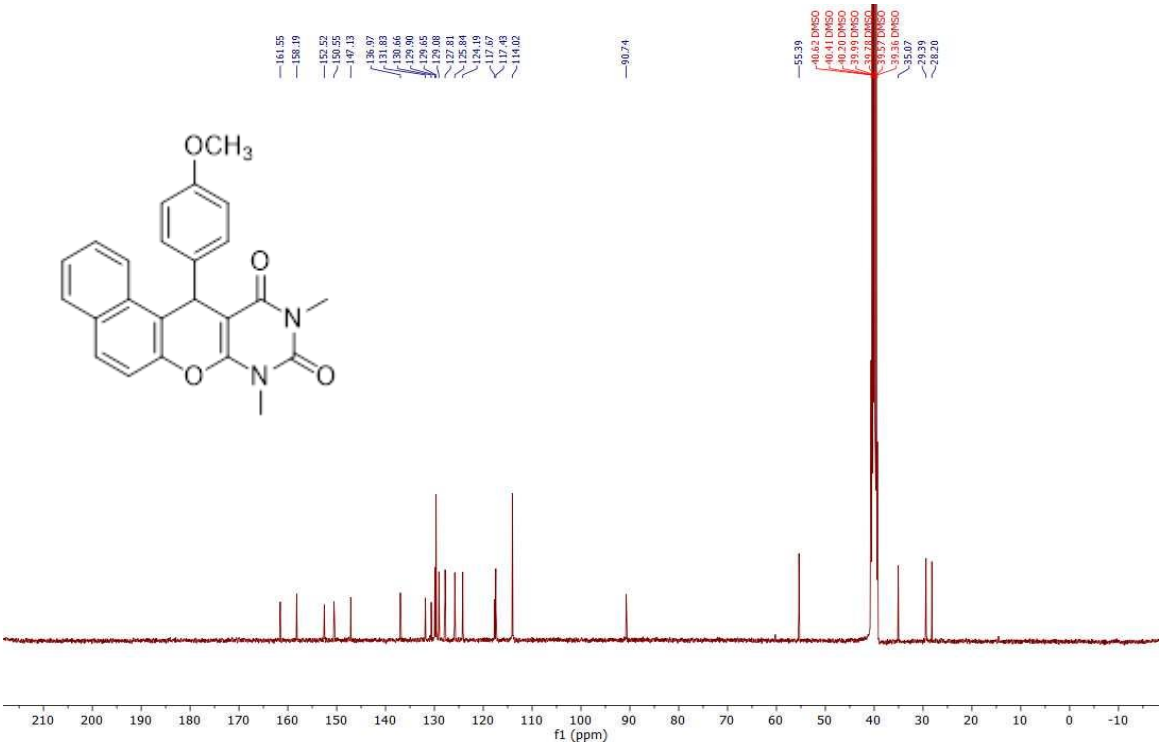



F
O
N
O
N
O

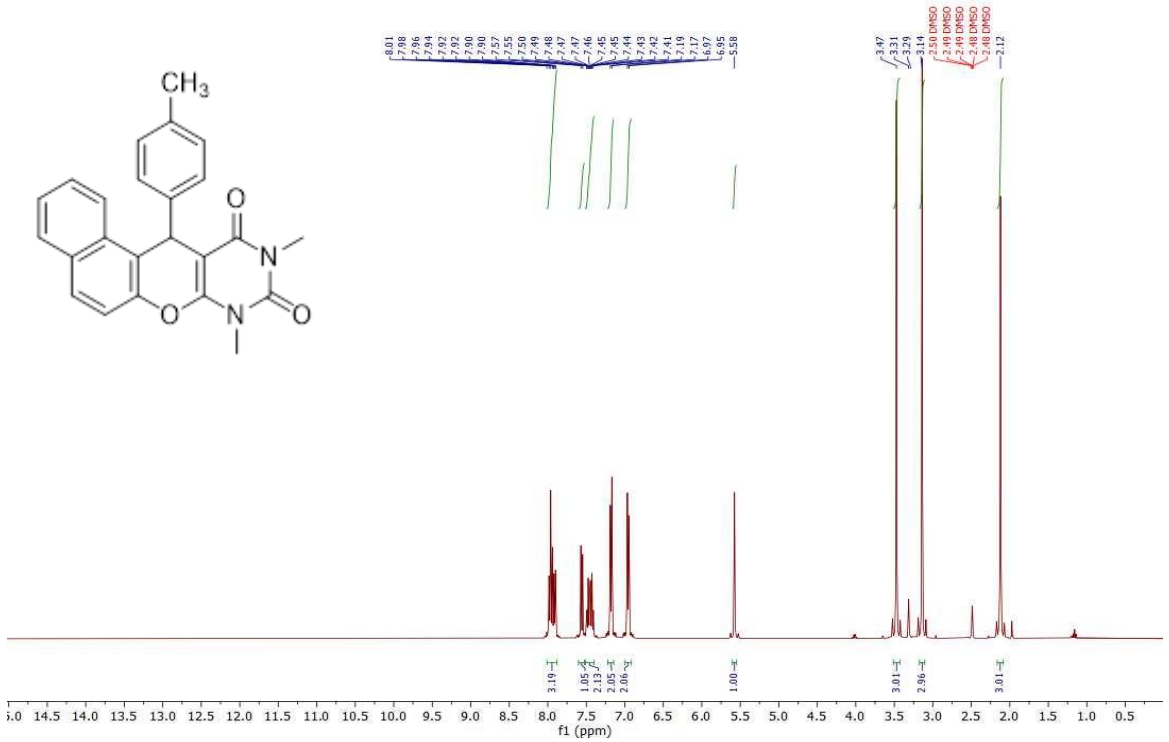
-116.13
-5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)

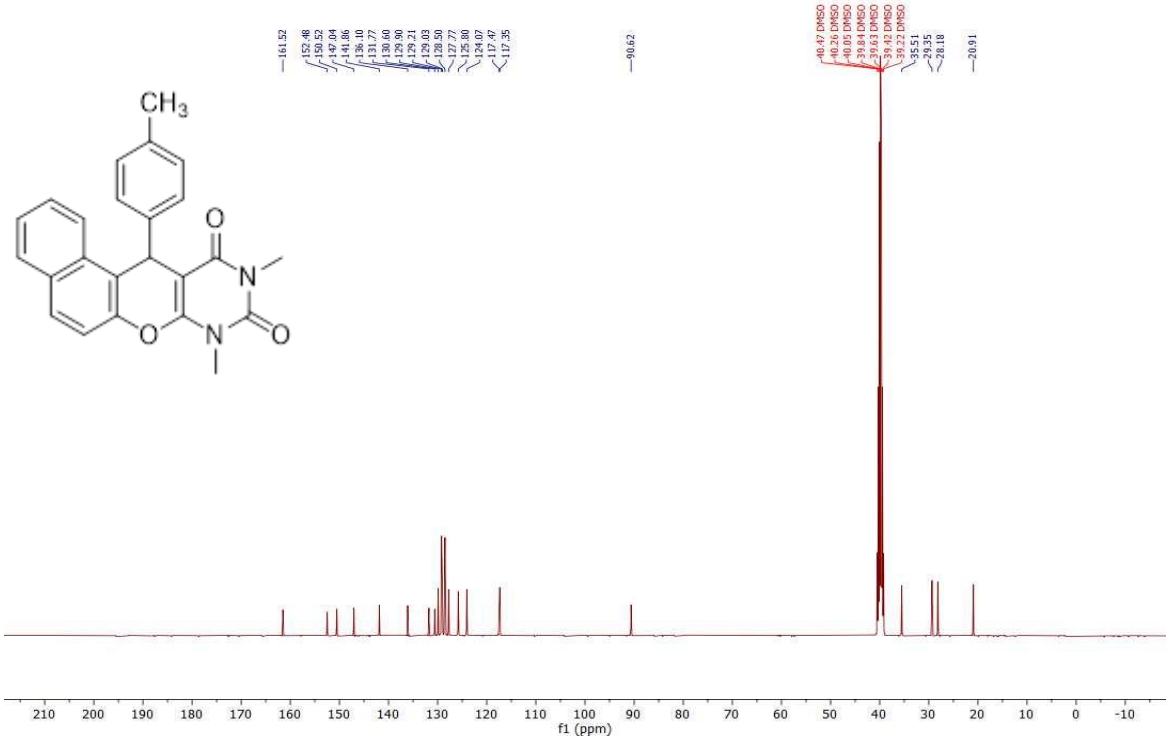
^{1}H and ^{13}C NMR spectra of **4d**



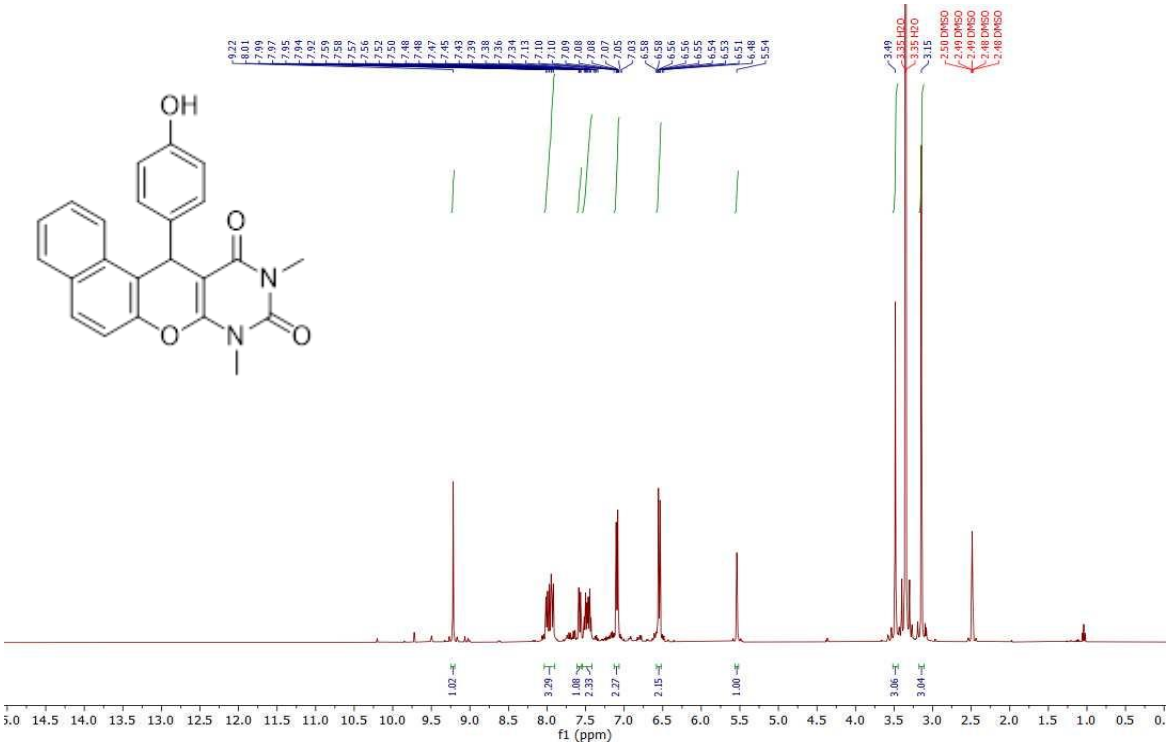


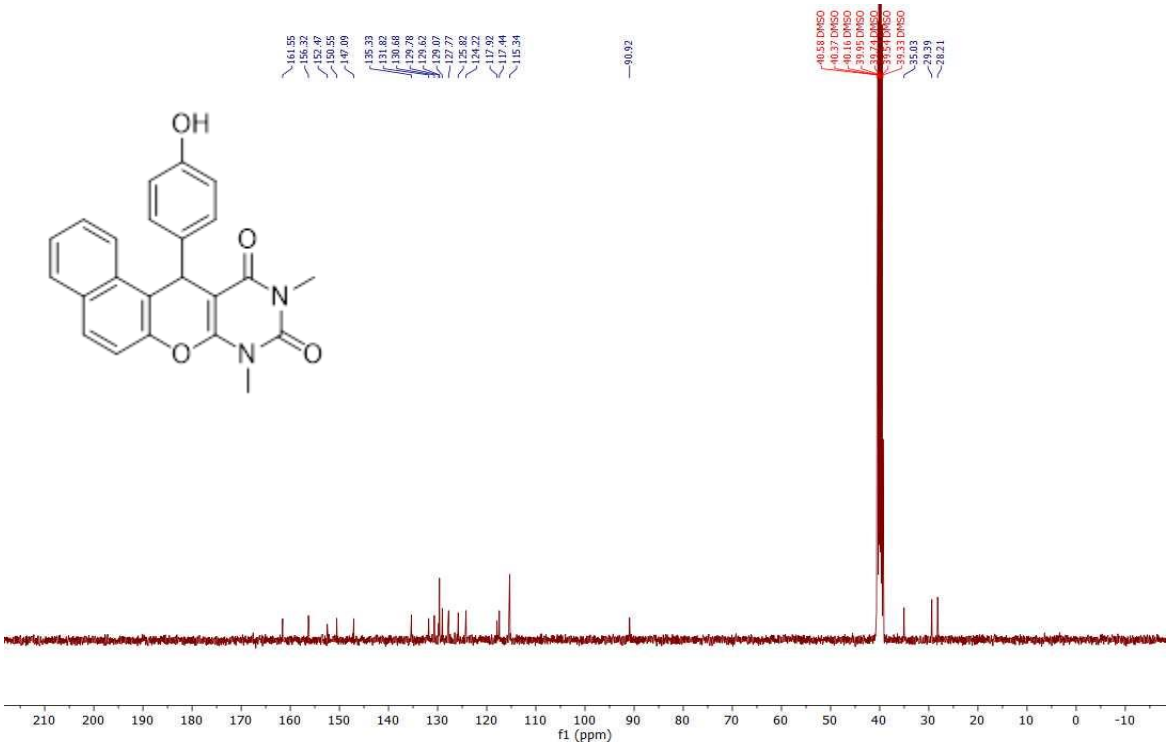
^{1}H and ^{13}C NMR spectra of **4e**



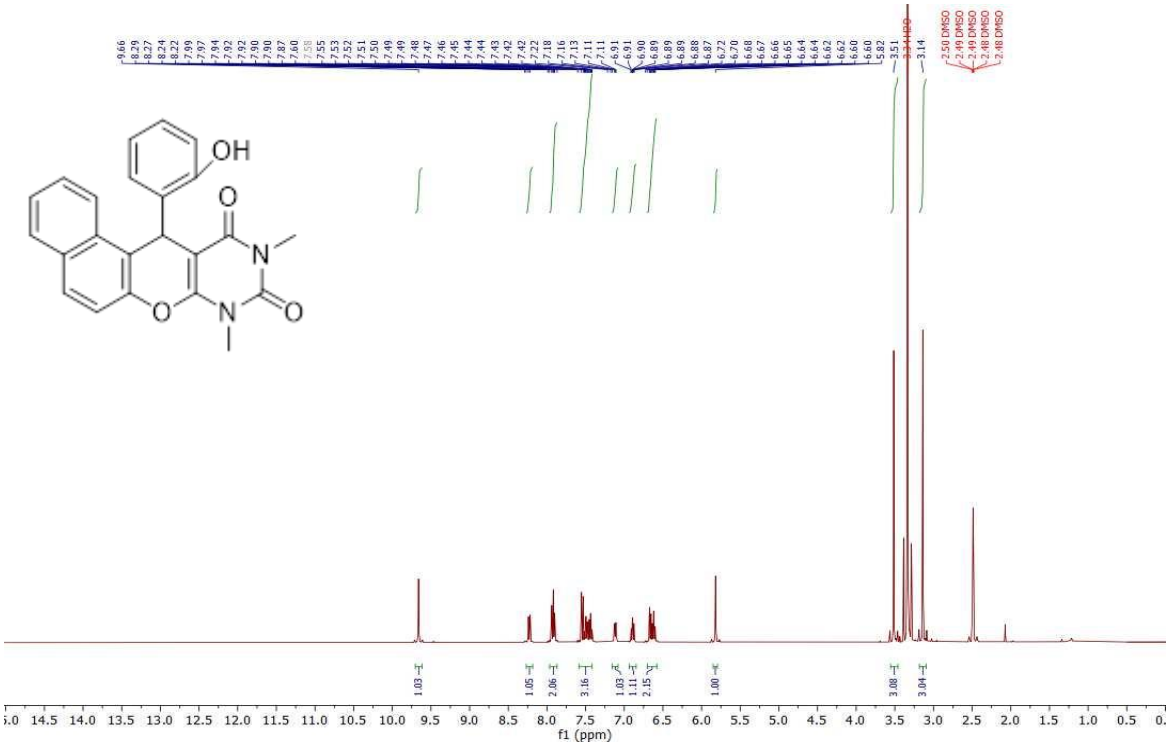


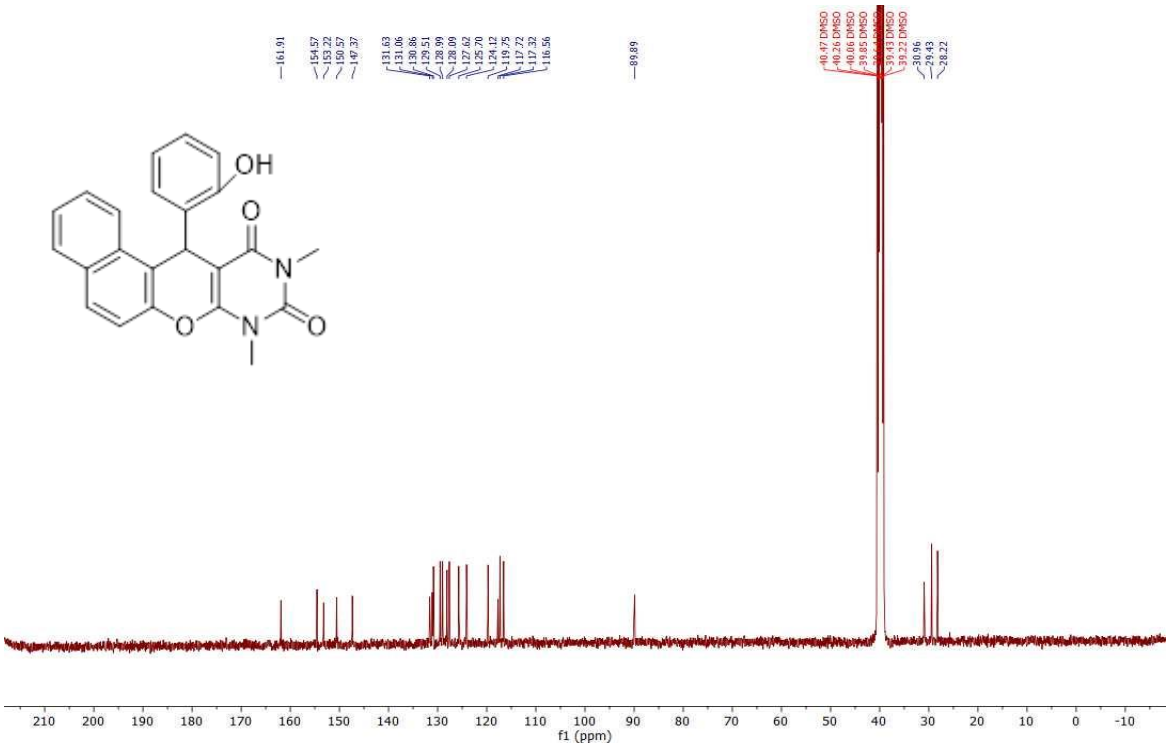
^{1}H and ^{13}C NMR spectra of **4f**



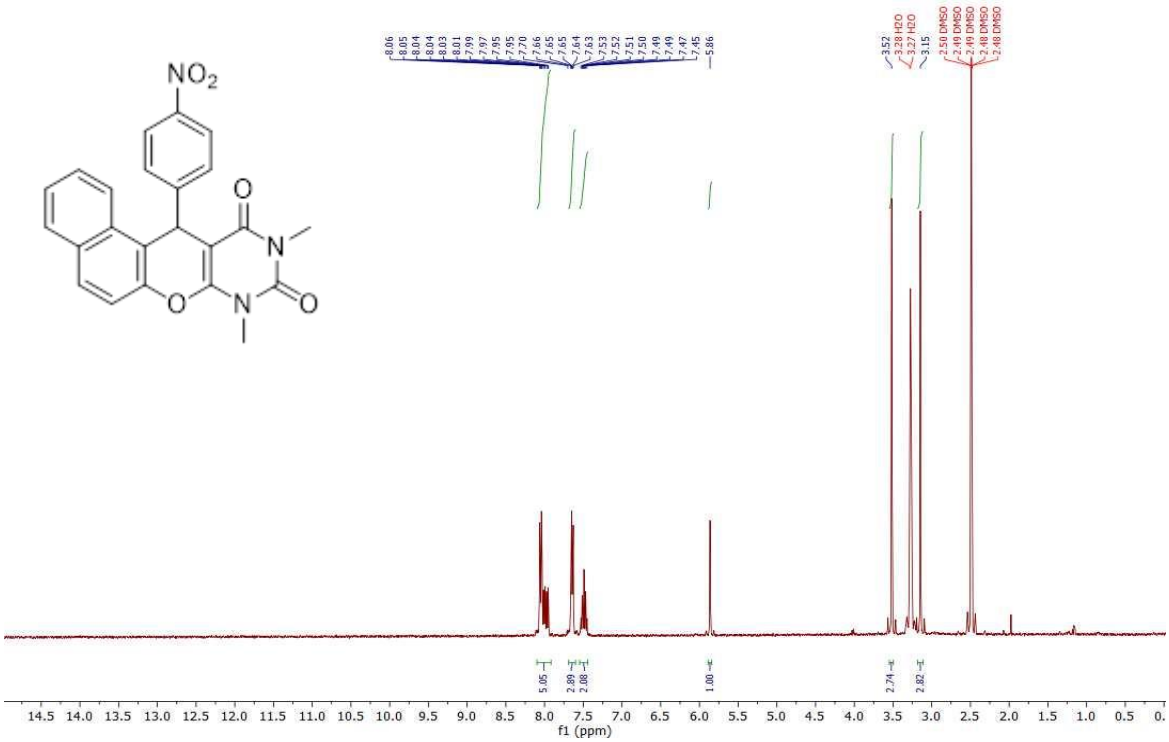


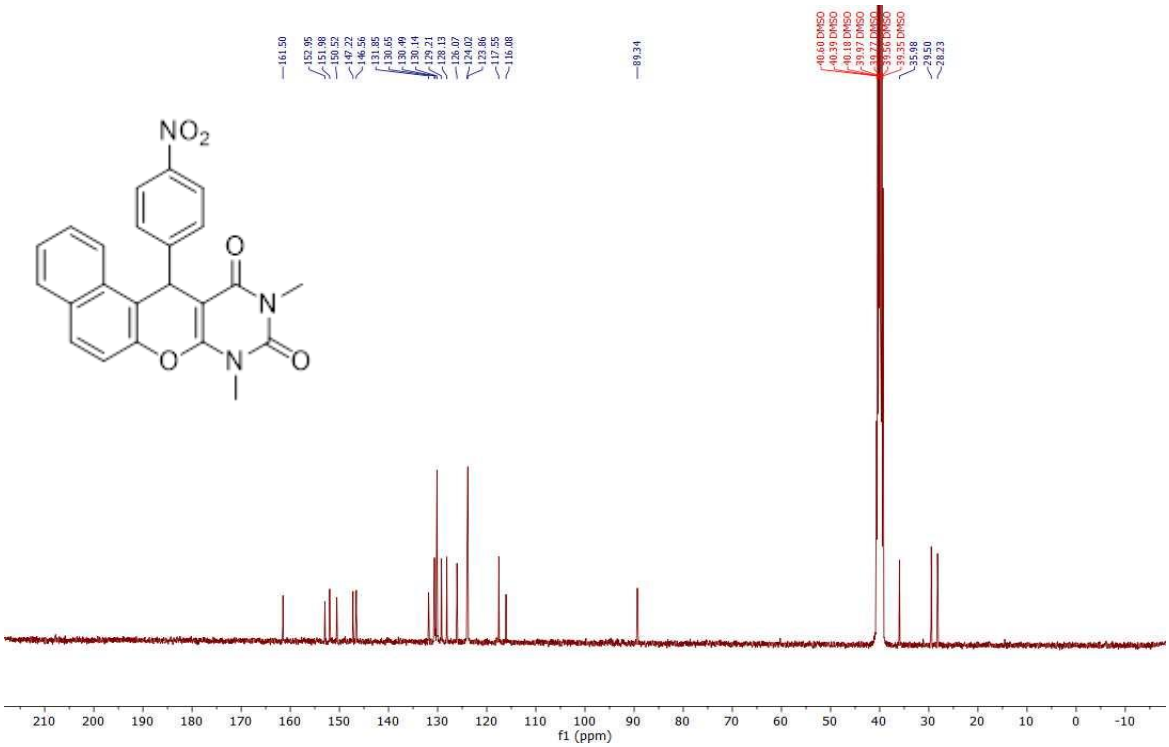
^{1}H and ^{13}C NMR spectra of **4g**



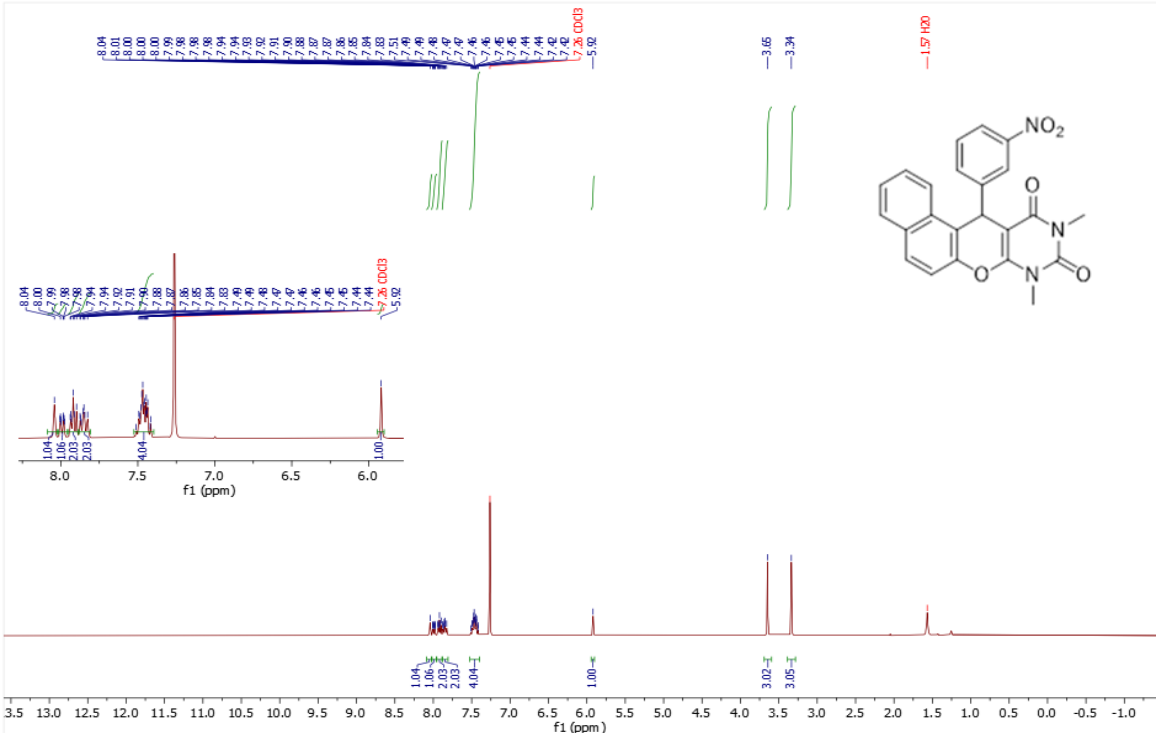


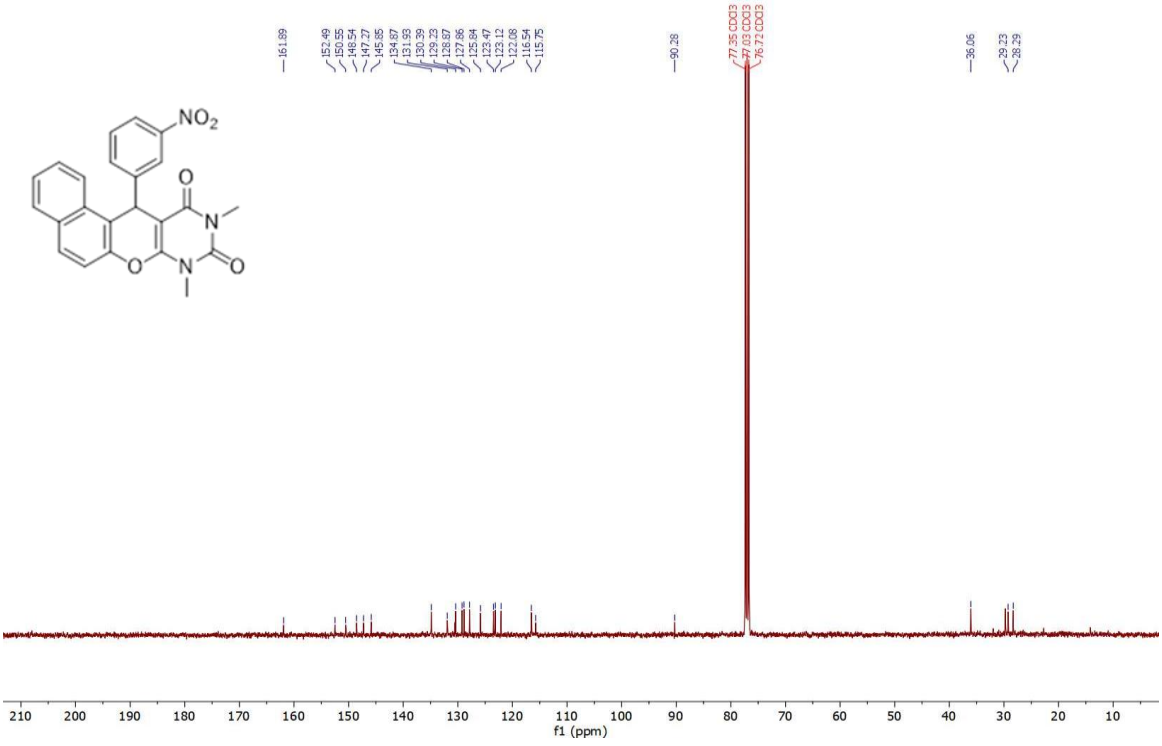
^{1}H and ^{13}C NMR spectra of **4h**



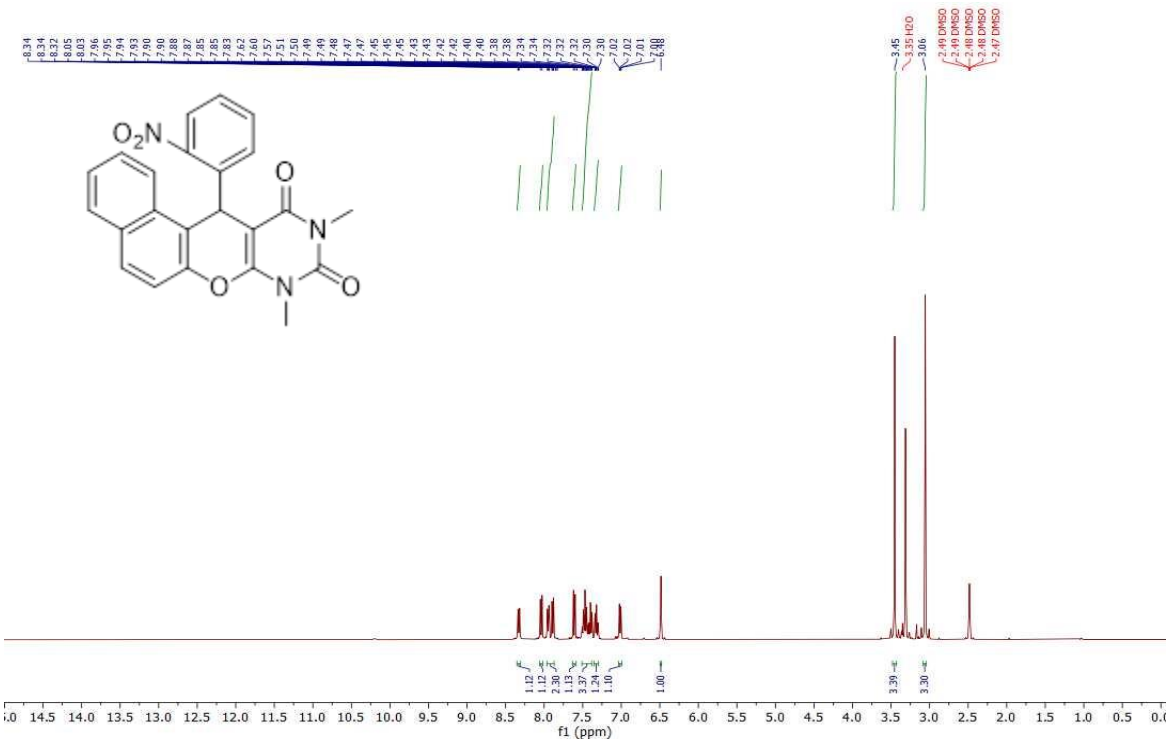


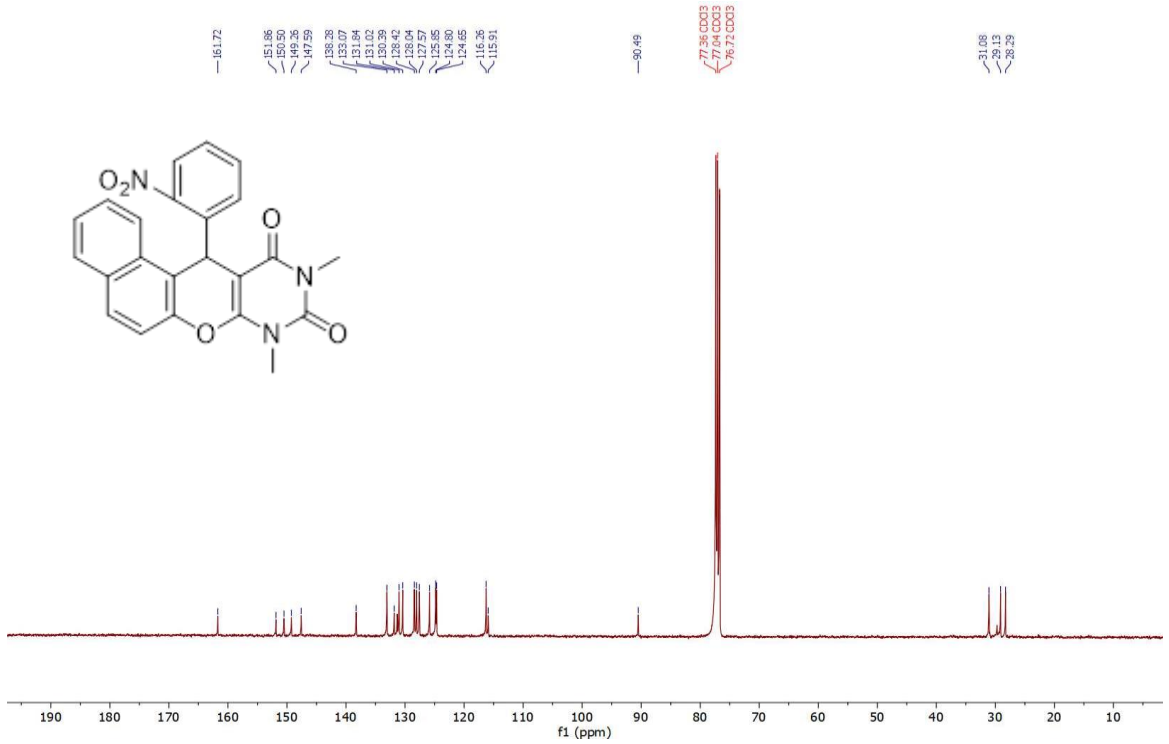
^{1}H and ^{13}C NMR spectra of **4i**



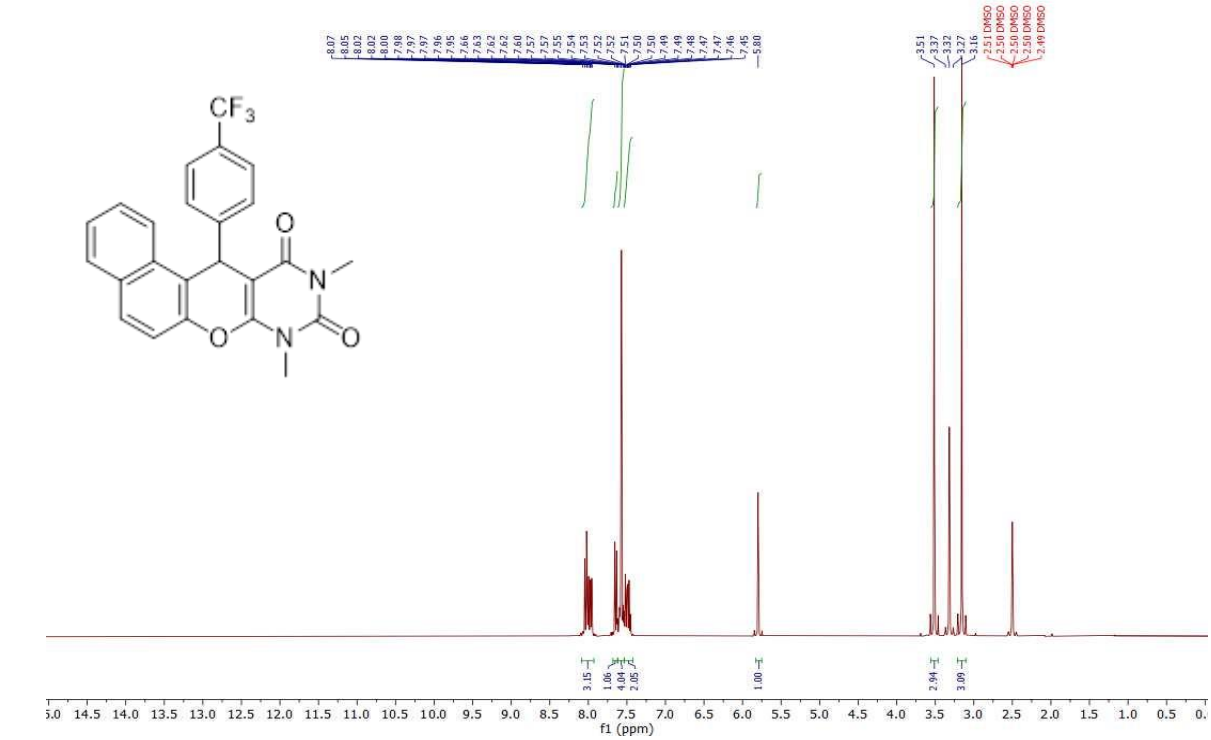


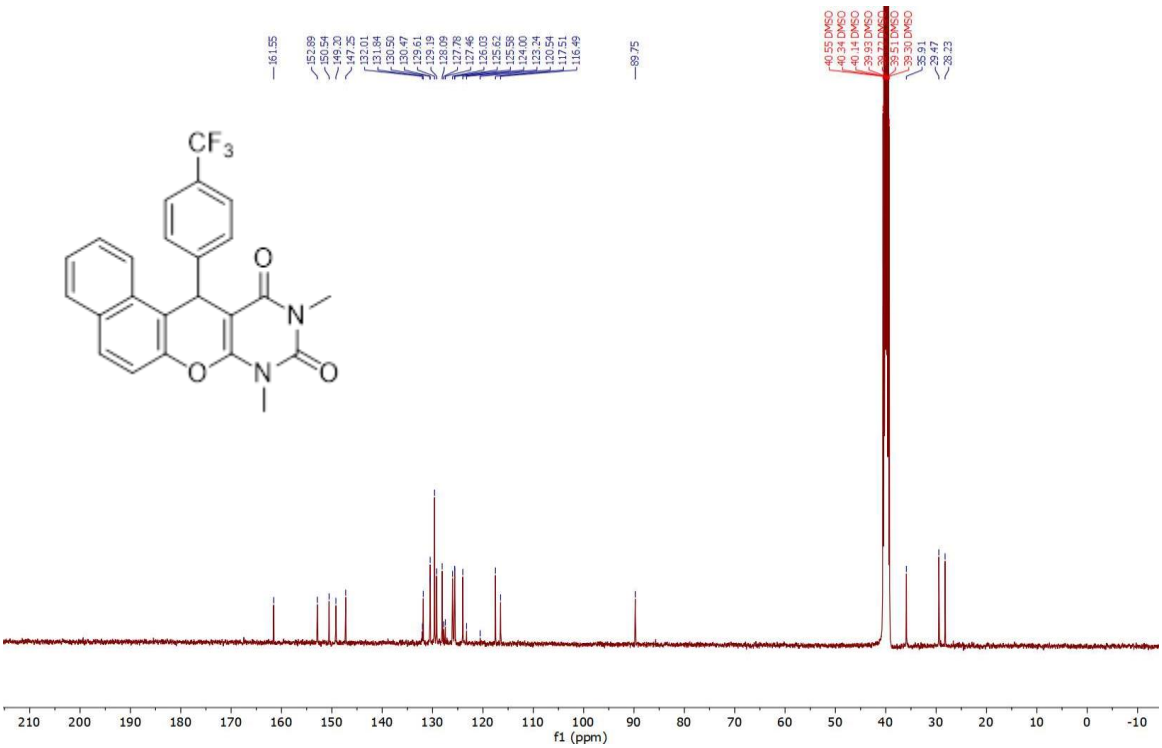
^{1}H and ^{13}C NMR spectra of **4j**

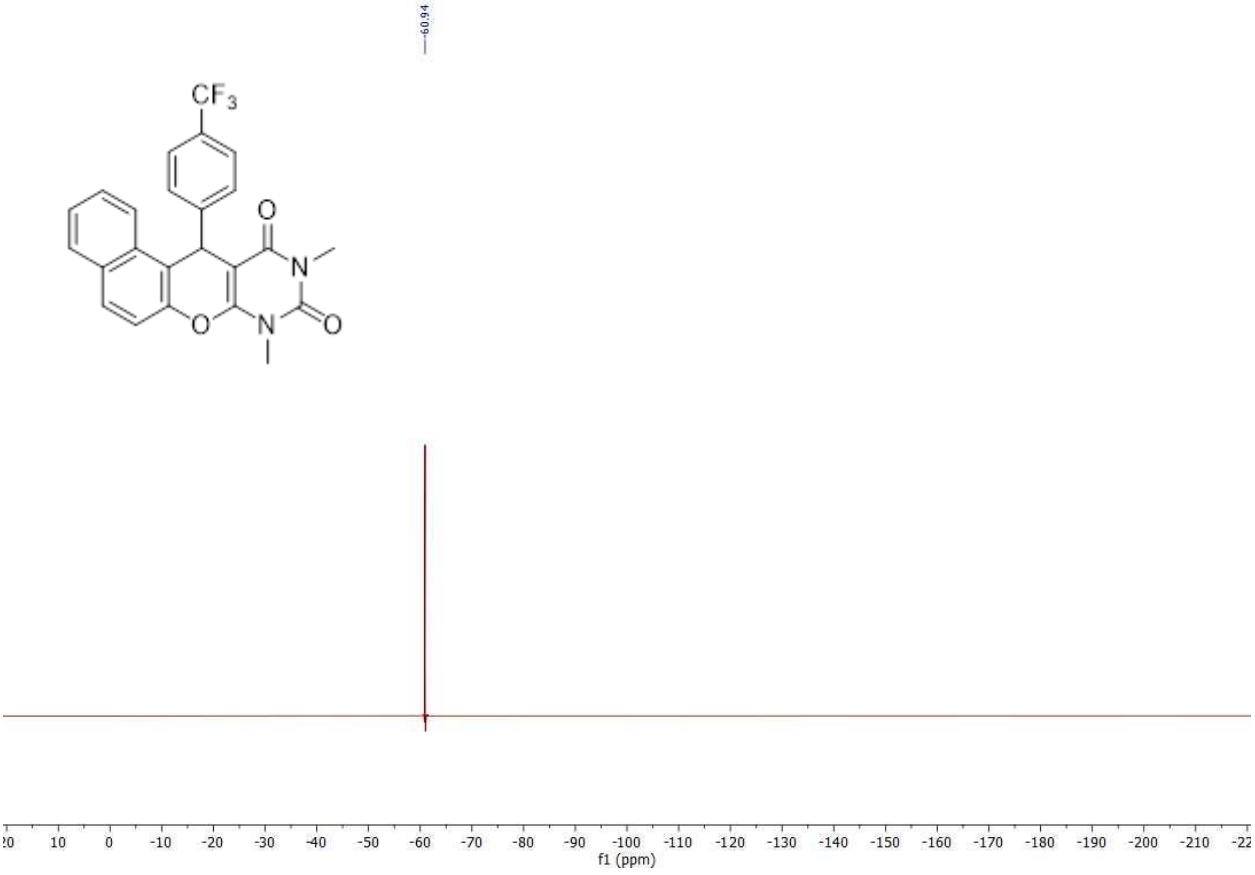




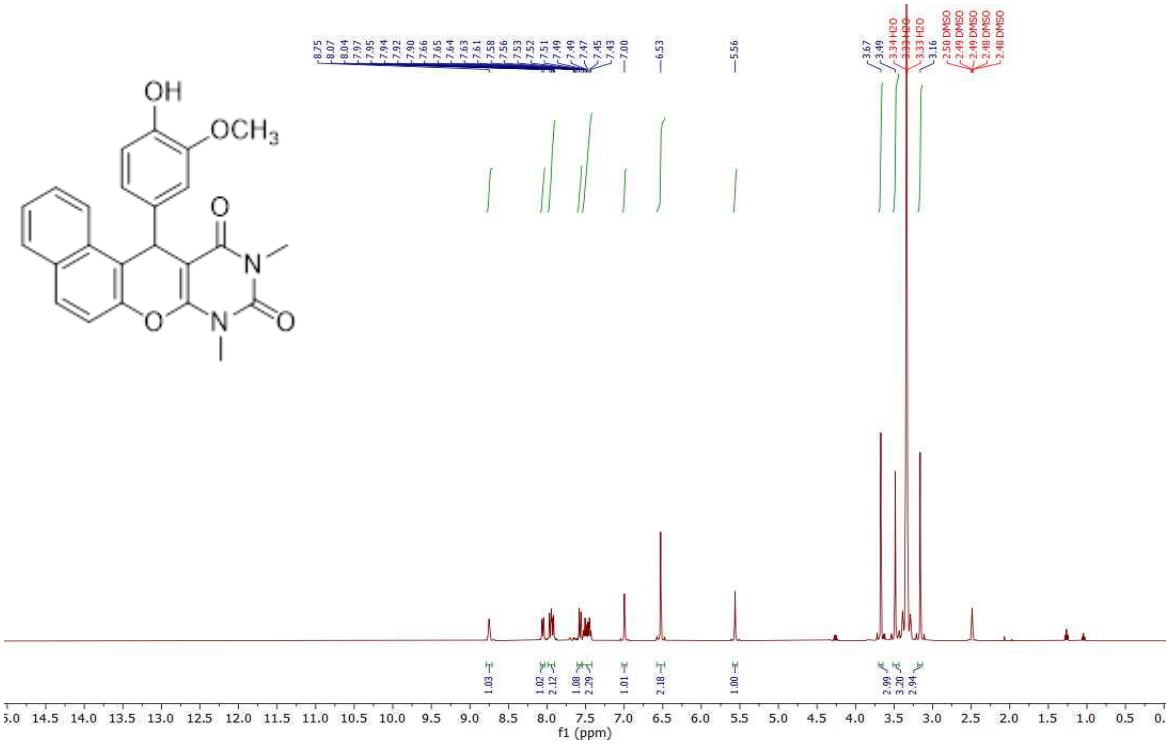
^{1}H,^{13}C NMR and ^{19}F spectra of **4k**

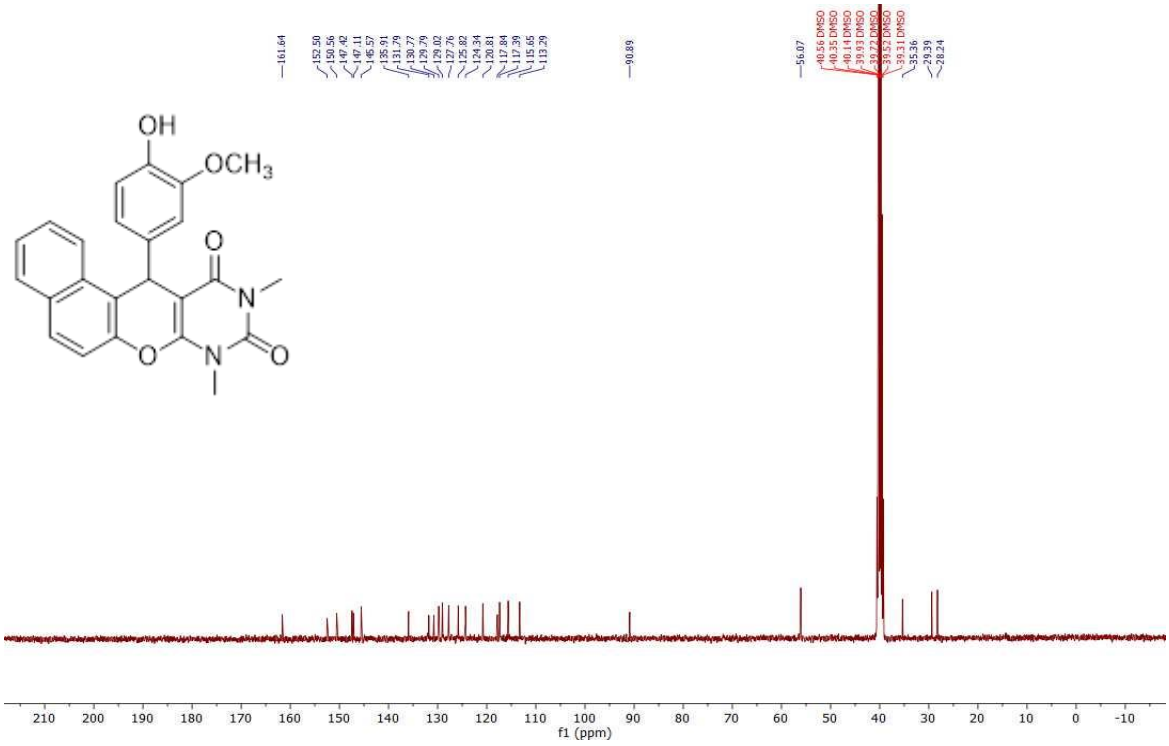




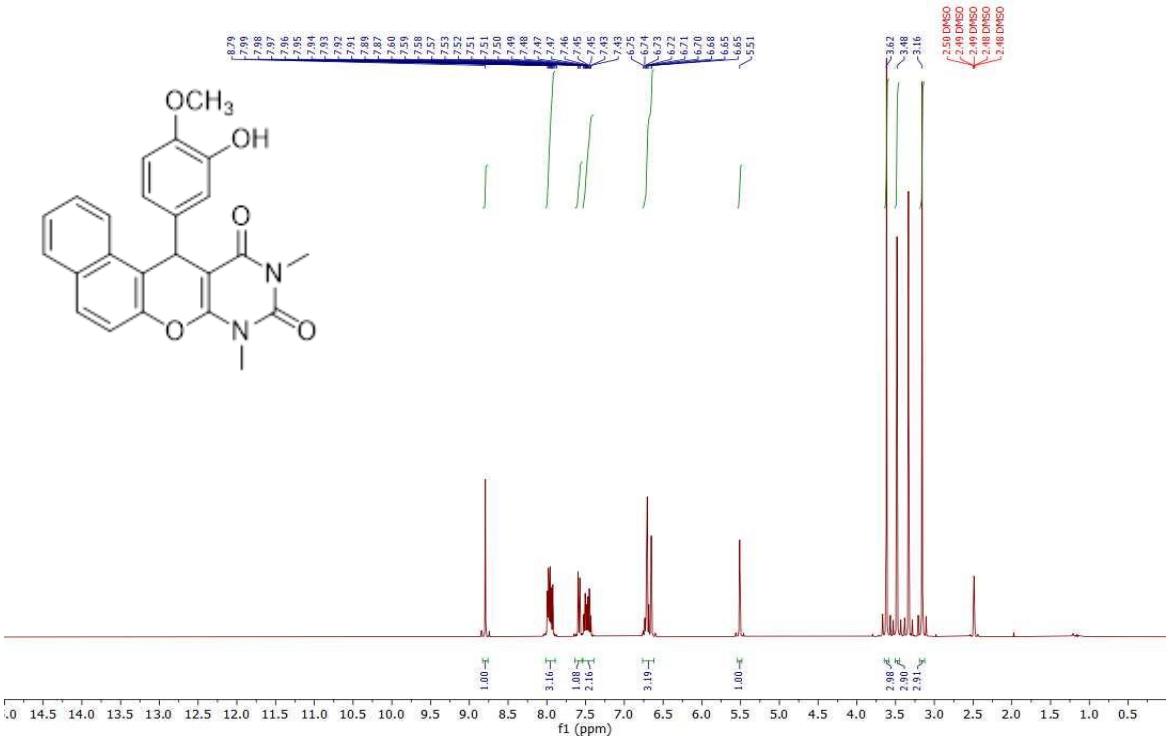

-60.84
CF3
O
N
O
N
O
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

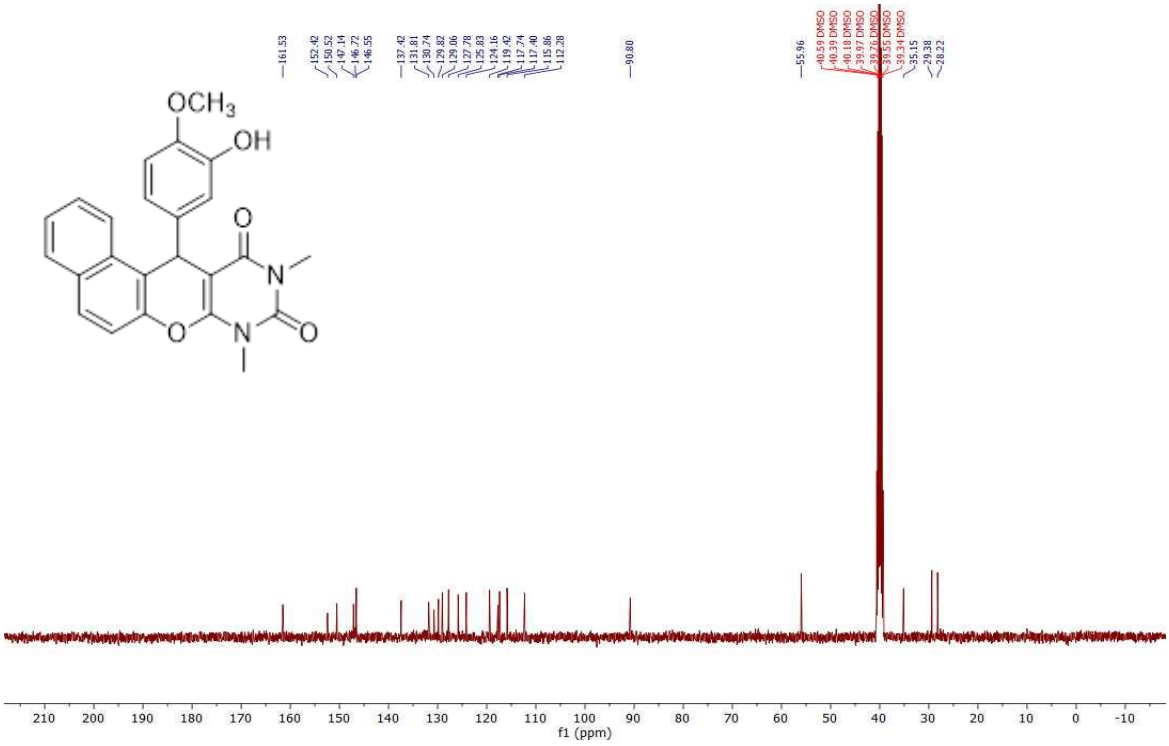
^{1}H and ^{13}C NMR spectra of **4l**



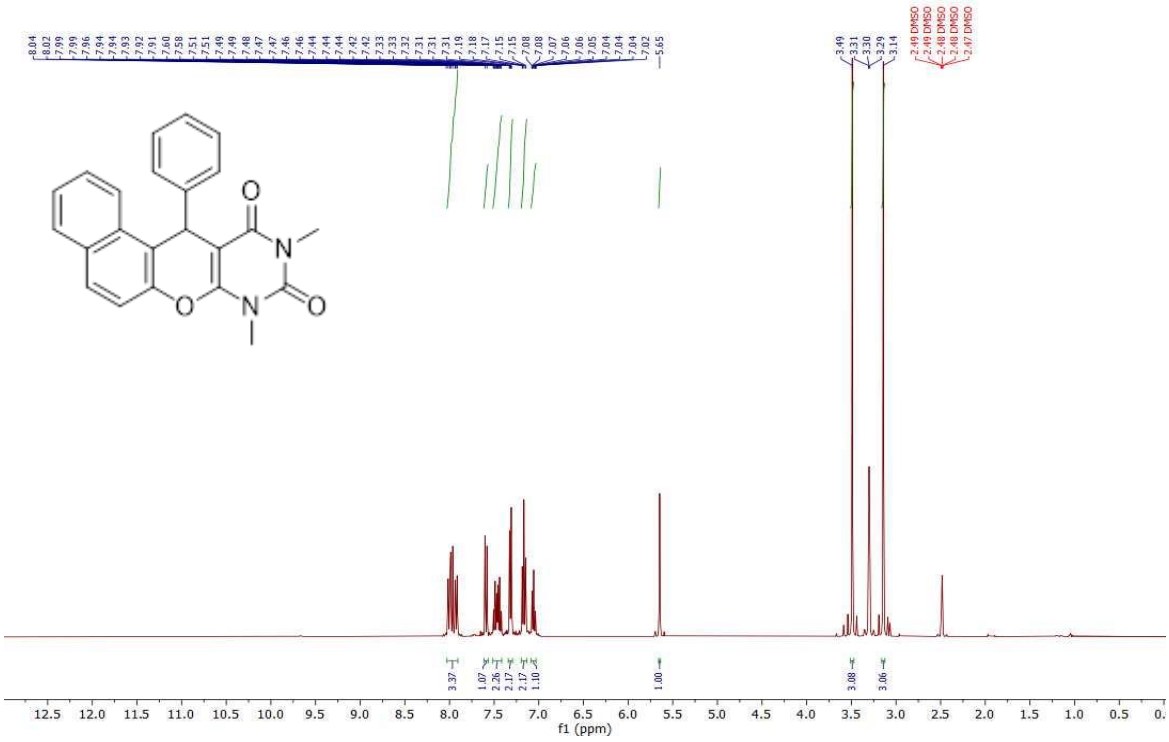


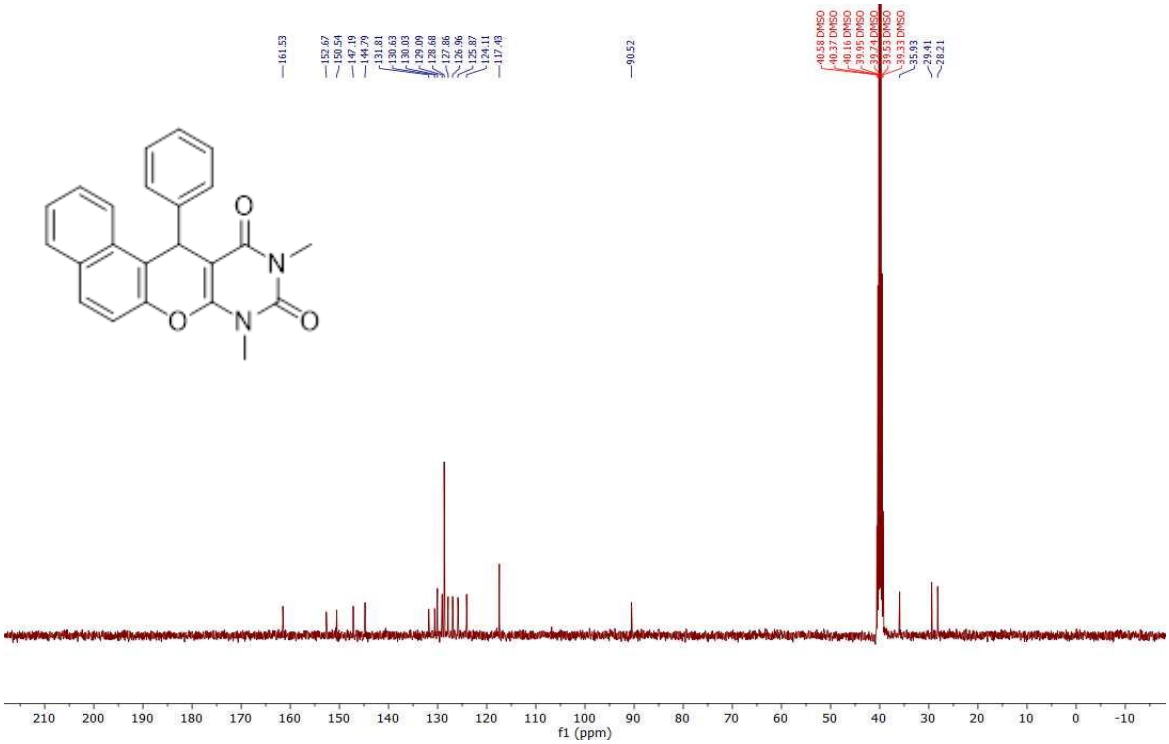
^{1}H and ^{13}C NMR spectra of **4m**



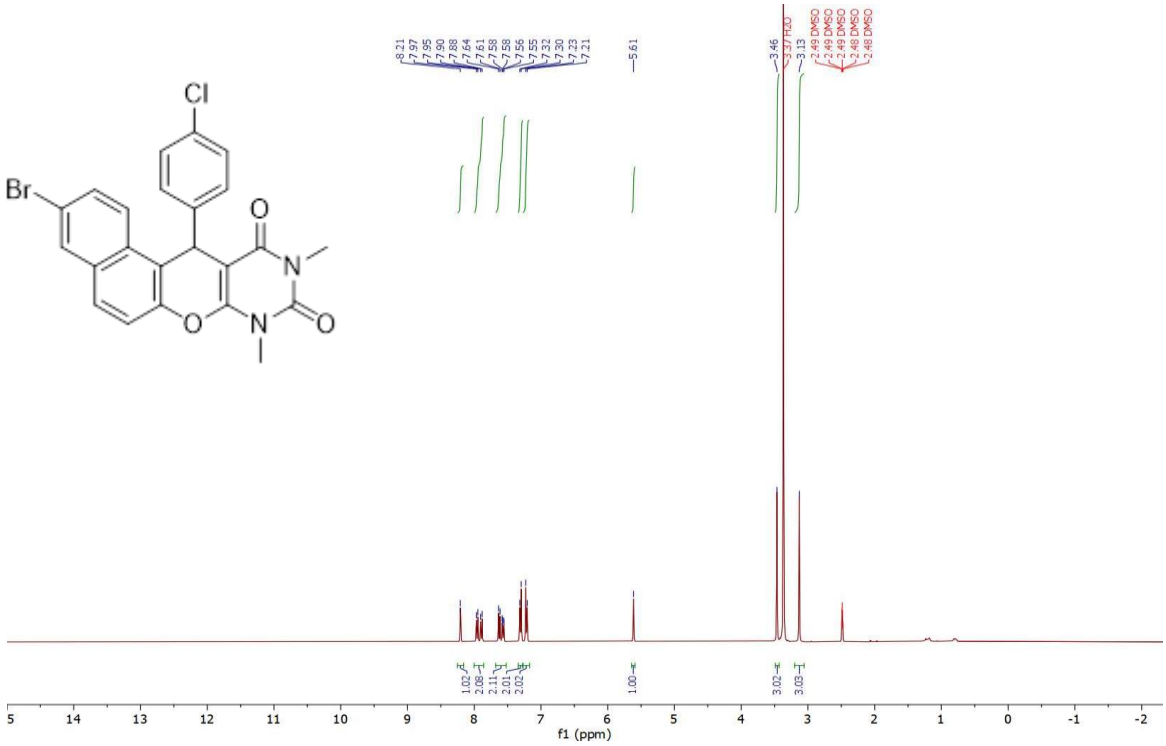


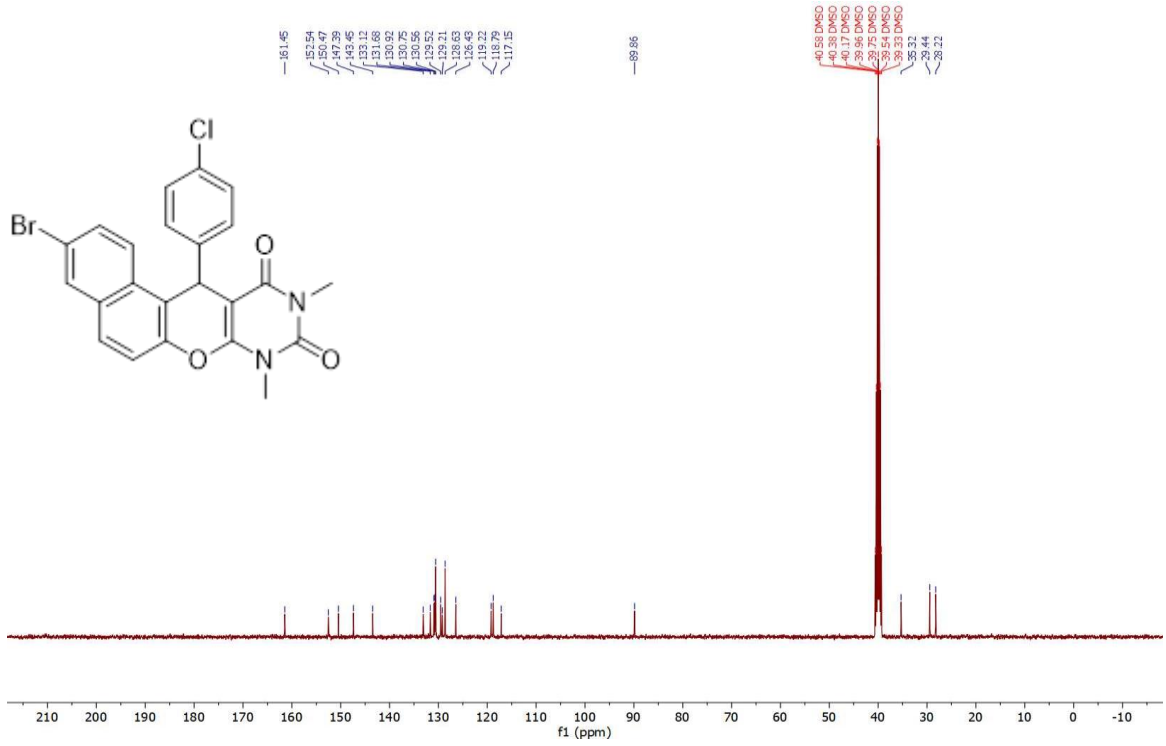
^{1}H and ^{13}C NMR spectra of **4n**



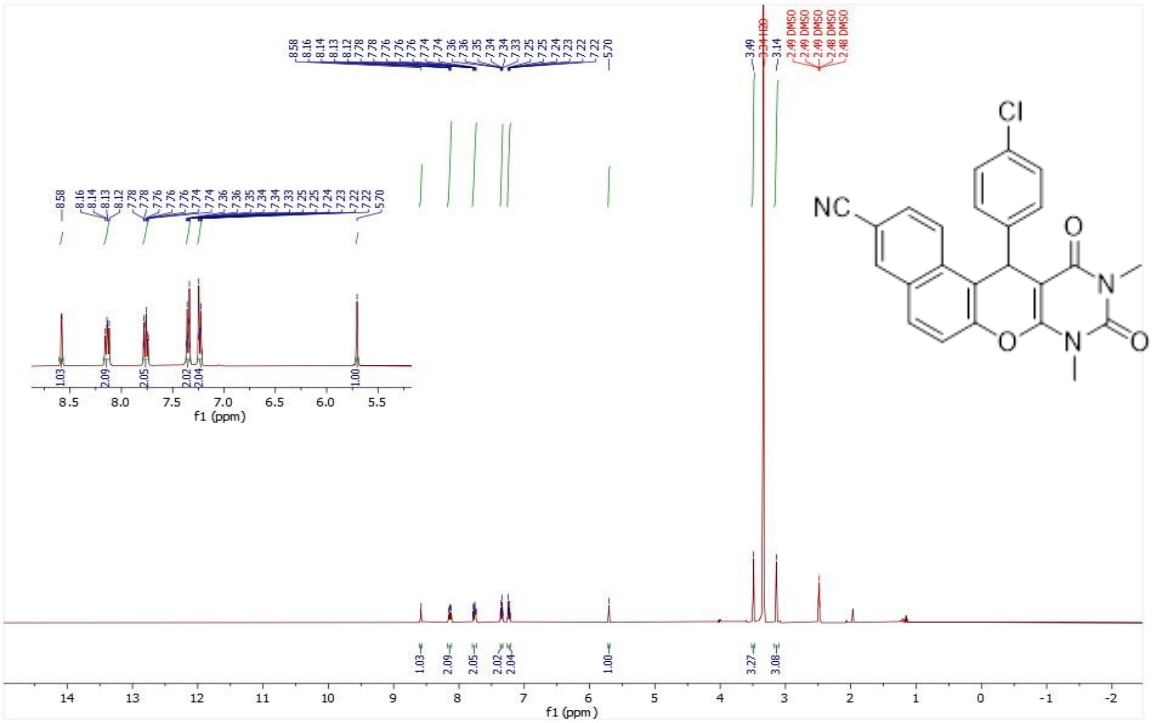


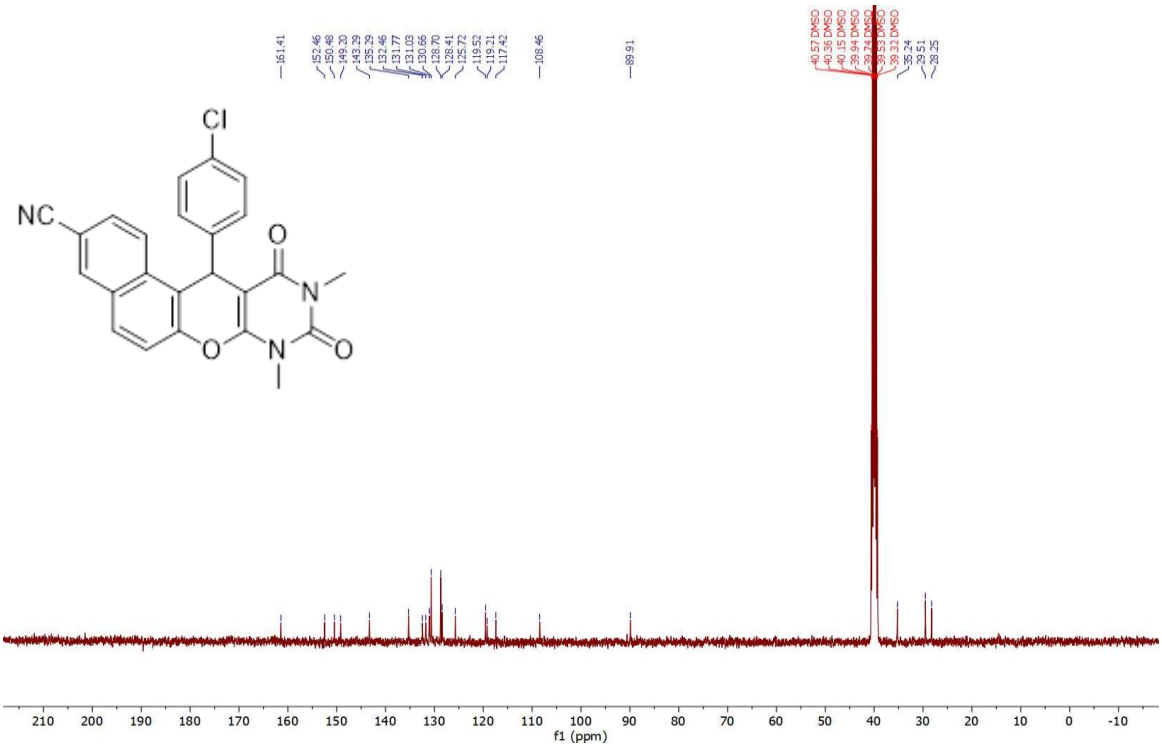
^{1}H and ^{13}C NMR spectra of **4o**



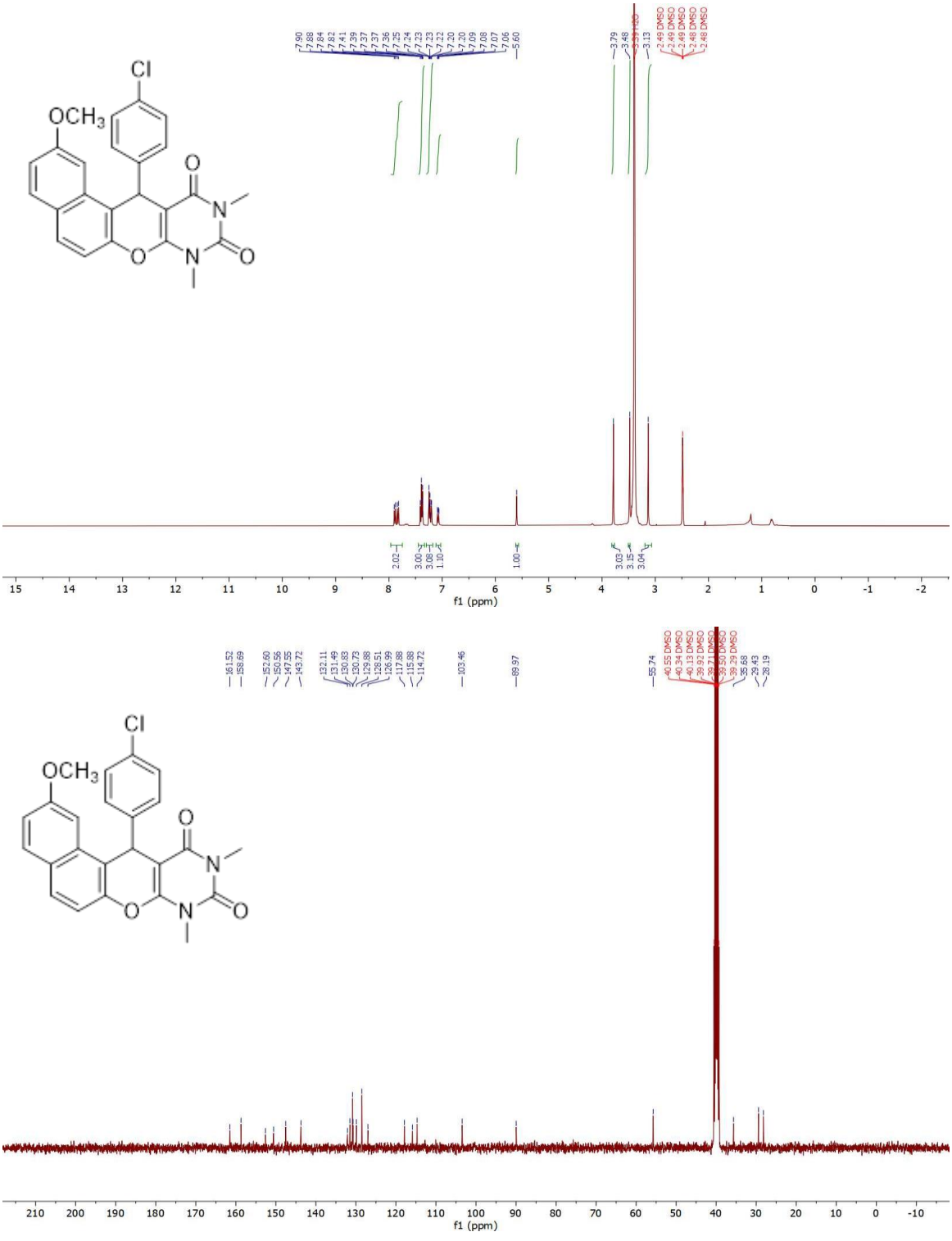


^{1}H and ^{13}C NMR spectra of **4p**





^{1}H and ^{13}C NMR spectra of **4q**



Theoretical calculations:

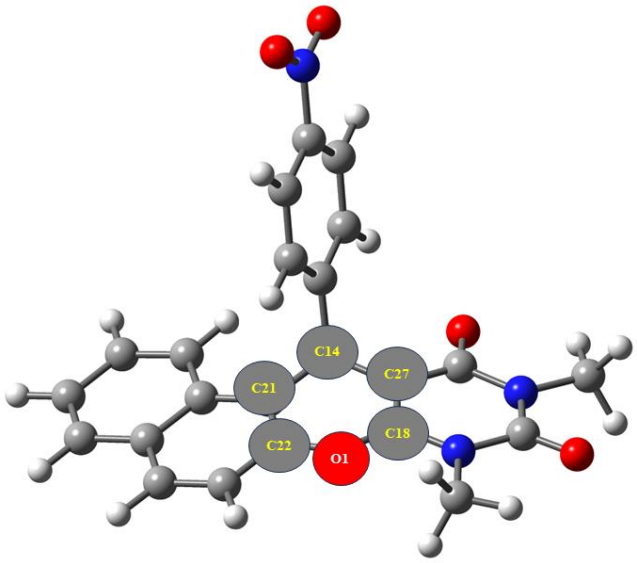


Figure S1: Geometrical parameters used for comparing theoretical and experimental results of phenol product are marked with atomic symbols and labels.

Table S1: Comparison of theoretical bond length data with crystal structure data.

Bond length (Å)		C14-C21	C14-C27	C27-C18	C21-C22	O1-C18	O1-C22	RMSD value
Experimental		1.515	1.513	1.348	1.373	1.348	1.402	
Basis Sets	6-31G	1.525	1.519	1.36	1.381	1.372	1.423	0.006
	6-31G(d)	1.521	1.515	1.357	1.378	1.35	1.396	0.002
	6-31+G(d,p)	1.521	1.516	1.358	1.378	1.35	1.398	0.002
	6-311G	1.524	1.519	1.357	1.377	1.375	1.426	0.006
	6-311G(d)	1.519	1.514	1.354	1.374	1.349	1.396	0.001

The vibrational energy is evaluated using the equation

$$E_{vib} = N\sum_{i=1}^{s}\left(\frac{h\nu_i}{2} + \frac{h\nu_i}{e^{\frac{h\nu_i}{k_B T}} - 1}\right)$$

where s is the vibrational degree of freedom, ν_i are the vibrational frequencies, N is the Avogadro number, k_B is the Boltzmann constant, and T is the temperature.

Co-ordinates of reactants, transition states and intermediates

β-naphthol

0 1

C	-2.92323700	0.39478900	-0.00004200
C	-1.86168800	1.26612400	-0.00000800
C	-0.52623500	0.78709300	0.00003600
C	-0.29069900	-0.62581100	0.00001900
C	-1.41235800	-1.49843600	0.00000100
C	-2.69265200	-1.00160800	-0.00002900
H	0.42806900	2.72968100	-0.00001600
H	-3.94060000	0.77232700	-0.00008600
H	-2.03242300	2.33908200	-0.00002700
C	0.59348300	1.65633600	0.00002800
C	1.03937600	-1.10923800	0.00015500
H	-1.24101800	-2.57088400	-0.00000500
H	-3.53755300	-1.68319600	-0.00006400
C	2.10184600	-0.23485800	0.00014200
C	1.87471900	1.16402200	-0.00002100
H	1.23487900	-2.17634800	0.00029300
H	2.72256500	1.84565100	-0.00031600
O	3.36739200	-0.75148400	-0.00038800
H	4.01162100	-0.03492800	0.00163700

Absolute energy= -461.208674 a.u.

Imaginary frequency= 0

Phenol

0 1

C	-1.13133700	1.21630100	0.00002100
C	-1.85491500	0.02705100	0.00000100
C	-1.16920100	-1.18857000	0.00002800
C	0.22035500	-1.22067000	-0.00001000

C	0.26216500	1.19687500	-0.00003800
H	-1.64941800	2.17010700	0.00005700
H	-2.93932400	0.04529200	0.00001600
H	-1.72173500	-2.12288100	0.00005400
H	0.76619800	-2.15759200	0.00001200
H	0.82119400	2.13009300	-0.00001800
C	0.94013900	-0.02386800	-0.00010100
O	2.30440200	-0.11038100	0.00001100
H	2.68462700	0.77532200	0.00038500

Absolute energy= -307.536364 a.u.

Imaginary frequency= 0

p-Nitro-benzaldehyde

0 1

O	-3.00241500	-1.22656700	0.00137200
N	-2.52349200	-0.10217300	-0.00003700
O	-3.16731100	0.93707600	-0.00166300
C	-1.04367600	0.01024000	-0.00000400
C	1.10013600	-1.04520500	-0.00026500
H	1.73166700	-1.92599100	-0.00044600
C	-0.28190300	-1.15646600	-0.00030400
H	-0.77798100	-2.11752000	-0.00060500
C	-0.47080200	1.27674900	0.00044700
H	-1.10656500	2.15154300	0.00078200
C	0.91581000	1.37279500	0.00073600
H	1.38782900	2.35062100	0.00125400
C	1.70434700	0.21836300	0.00017200
C	3.18718100	0.33324600	0.00025900
H	3.57527000	1.37408500	0.00117100

O	3.94318500	-0.60749100	-0.00072600

Absolute energy= -550.207043 a.u.

Imaginary frequency= 0

6-amino-1,3-dimehyl uracil

0 1

O	0.23681100	2.33139300	-0.02885000
O	2.24593900	-1.78140100	0.02132400
N	1.25122900	0.29163200	-0.00201300
N	-1.10873600	0.47752300	-0.00449700
C	1.21166500	-1.13610100	0.01026100
C	0.14819800	1.11750900	-0.01562100
C	-2.29192400	1.33487300	0.05446100
H	-2.84347100	1.31978500	-0.89148300
H	-1.94937000	2.34925700	0.23014000
H	-2.94718900	1.01891100	0.86731400
C	2.55564700	0.95805100	-0.00373000
H	3.31215100	0.17973300	0.00097300
H	2.65660000	1.59189800	0.87788800
H	2.65788600	1.58360700	-0.89104400
C	-0.11127400	-1.69152300	-0.01154200
H	-0.19348500	-2.76949100	-0.03200800
C	-1.22004300	-0.89979800	-0.01175900
N	-2.50327700	-1.40601000	0.04899600
H	-3.22281400	-0.90885000	-0.45344700
H	-2.56044600	-2.40486200	-0.07795400

Absolute energy= -548.934002 a.u.

Imaginary frequency= 0

Transition state for β-naphthol + *p*-nitro-benzaldehyde + 6-amino-1,3-dimehyl uracil reaction

0 1

C	-2.57982900	3.21450100	-0.01435900
C	-1.98076000	2.52502800	1.02329100
C	-1.88976400	1.11932200	0.99609400
C	-2.40999500	0.40657900	-0.11721100
C	-3.03017100	1.12845500	-1.15407300
C	-3.11342500	2.50948400	-1.10507500
H	-0.94301700	0.93380400	2.94132600
H	-2.64638900	4.29672700	0.01669900
H	-1.57808800	3.06372000	1.87596700
C	-1.32545200	0.37516500	2.09128300
C	-2.27813400	-1.03293400	-0.15476600
H	-3.45118800	0.58888600	-1.99778700
H	-3.59755400	3.05009700	-1.91189700
C	-1.77602500	-1.74123900	0.98626000
C	-1.26497000	-0.98264700	2.09748400
H	-2.95640900	-1.58231600	-0.79818900
H	-0.84218200	-1.53568300	2.92845500
O	-1.66670200	-3.01981700	0.94518500
H	-1.22978100	-3.23673700	-0.23126400
O	4.97199500	0.22729100	0.80155100
N	4.15062500	0.89261800	0.18517500
O	4.29002700	2.07062100	-0.11702500
C	2.89556800	0.22553600	-0.22143800
C	1.52267600	-1.73260600	-0.27122800
H	1.35308100	-2.77692600	-0.04063800
C	2.70256200	-1.11227000	0.11215400
H	3.47274200	-1.64335400	0.65494800

C	1.94644400	0.95301700	-0.93239200
H	2.14005700	1.98831900	-1.17774200
C	0.77098700	0.32051000	-1.31295700
H	0.02414900	0.87412400	-1.87143700
C	0.54382100	-1.02240900	-0.98067100
C	-0.70258200	-1.70437200	-1.40967300
H	-1.20191400	-1.25394700	-2.27072000
O	-0.81827000	-2.99181500	-1.28099600

Absolute energy= -1011.383805 a.u.

Imaginary frequency= 1

Transition state for phenol + *p*-nitro-benzaldehyde + 6-amino-1,3-dimehyl uracil reaction

0 1

H	-1.00584600	2.81816700	1.81363800
C	-1.52781800	2.10669800	1.18059200
C	-2.84574900	0.29916400	-0.50133300
C	-2.62487800	-0.04403000	0.89011200
C	-1.91626500	0.90211800	1.70064500
H	-3.63786400	-0.23732600	-1.01112300
H	-1.71947800	0.63230600	2.73216200
O	-2.95597100	-1.20115700	1.31994100
H	-2.52927500	-2.01799600	0.31099000
O	4.35640500	-0.43396500	1.18070000
N	3.84009800	0.17836300	0.25607300
O	4.38510900	1.06544900	-0.38740900
C	2.45228500	-0.17797500	-0.10990300
C	0.50056600	-1.51124400	0.25700400
H	-0.02153000	-2.29849900	0.78610700
C	1.80077000	-1.17994000	0.60501100

H	2.31877500	-1.68451200	1.40926700
C	1.84136300	0.49313300	-1.16363700
H	2.38774300	1.25846800	-1.69775400
C	0.53890200	0.15310700	-1.50279400
H	0.05076600	0.66477700	-2.32479000
C	-0.14522500	-0.84555100	-0.79578600
C	-1.51862800	-1.23014600	-1.18765400
H	-1.78607300	-1.02488200	-2.22465300
O	-2.08680400	-2.27776500	-0.65678000
C	-1.79559500	2.46183500	-0.17501100
H	-1.49211000	3.43625300	-0.54161100
C	-2.47585700	1.59147900	-0.98058300
H	-2.73894700	1.87231600	-1.99634500

Absolute energy= -857.701086 a.u.

Imaginary frequency= 1

Intermediates for β-naphthol + *p*-nitro-benzaldehyde + 6-amino-1,3-dimehyl uracil reaction

0 1

C	-3.20822100	2.89200900	-0.09696000
C	-2.63142600	2.29954400	1.01829400
C	-2.21632900	0.95957800	0.98453700
C	-2.36981300	0.20989000	-0.19870400
C	-2.97115100	0.81227000	-1.30380900
C	-3.38768900	2.14139800	-1.25870100
H	-1.55857600	0.94220300	3.05962600
H	-3.52732100	3.92797900	-0.06030000
H	-2.50488000	2.87064000	1.93314800
C	-1.67100500	0.32317300	2.17301400
C	-1.89856200	-1.22431400	-0.26483000

H	-3.12315700	0.23649600	-2.21214900
H	-3.85481700	2.58921500	-2.12956600
C	-1.46979800	-1.84607500	1.06263800
C	-1.33510600	-0.98174500	2.22821900
H	-2.71265100	-1.84753200	-0.65203900
H	-0.95688400	-1.44352100	3.13343000
O	-1.19892400	-3.04422200	1.10738700
H	-0.74269600	-3.31501600	-0.72920100
O	5.13429900	0.30767900	0.67761900
N	4.25821300	1.02660300	0.21551700
O	4.35981800	2.23695100	0.05942800
C	2.98526400	0.38956600	-0.17858800
C	1.63318300	-1.57430000	-0.38858800
H	1.51177100	-2.64528000	-0.29317000
C	2.83411500	-0.98250300	-0.01526200
H	3.64969800	-1.56551200	0.39088800
C	1.97243600	1.17736100	-0.71520700
H	2.13238900	2.23931300	-0.84407500
C	0.77822500	0.57029600	-1.08159800
H	-0.01041500	1.17774300	-1.51134100
C	0.58733300	-0.80723800	-0.91076800
C	-0.73195800	-1.46279100	-1.31347300
H	-1.06024800	-1.00765300	-2.25208800
O	-0.60102900	-2.84066000	-1.56731800

Absolute energy= -1011.412657 a.u.

Imaginary frequency= 0

Intermediates for phenol + *p*-nitro-benzaldehyde + 6-amino-1,3-dimehyl uracil reaction

0 1

H	-2.41685300	3.14841600	1.60789600
C	-2.45636100	2.22186000	1.04230600
C	-2.54056700	-0.17408000	-0.55858900
C	-2.52955800	-0.22182800	0.97231100
C	-2.48365800	1.04142700	1.69965600
H	-3.48641500	-0.64494200	-0.86587000
H	-2.46218700	0.97908400	2.78194300
O	-2.55095100	-1.30637900	1.55095800
H	-2.08357200	-2.47754700	0.12176200
O	4.48158400	-0.27317900	1.20920600
N	3.93551000	0.35645200	0.31323300
O	4.44457600	1.28970700	-0.29441700
C	2.56100500	-0.03507500	-0.06056800
C	0.65542200	-1.45063300	0.25116100
H	0.17925000	-2.28545000	0.74839000
C	1.94898600	-1.08836600	0.60847900
H	2.48704500	-1.61070900	1.38804200
C	1.91624000	0.65401600	-1.08203800
H	2.43026200	1.45693200	-1.59296200
C	0.62377100	0.27934800	-1.42462200
H	0.12365100	0.80385100	-2.23191100
C	-0.02842600	-0.76456500	-0.75684900
C	-1.45261100	-1.15633600	-1.14490400
H	-1.53175200	-1.09480100	-2.23544000
O	-1.77226500	-2.48226700	-0.80064600
C	-2.47605500	2.30741400	-0.40828200
H	-2.46976200	3.28886400	-0.87020500
C	-2.50609500	1.19597800	-1.15842200

H	-2.53433500	1.26310900	-2.24291000

Absolute energy= -857.724314 a.u.

Imaginary frequency= 0

Final Product

0 1

O	-1.58563300	-1.62491300	-1.31978900
O	-5.39563600	0.69653200	-0.39189100
O	-1.78727100	1.34934200	2.34580100
O	3.31950800	5.09315100	-0.12917500
N	-3.60104600	1.03866500	0.97329800
N	3.08685500	4.22238600	-0.95738800
O	3.46662800	4.24803700	-2.12125100
N	-3.46972700	-0.45550400	-0.85402900
C	-2.25806800	0.81039300	1.35486300
C	2.42794500	-1.85249500	1.52570500
H	2.19181500	-0.92592500	2.03370200
C	-4.23993900	0.45369200	-0.10935700
C	1.57006000	-2.33409800	0.50221100
C	-0.04663400	-0.33700900	0.76089900
H	0.07455900	-0.41447000	1.84505000
C	3.91527800	-3.73990200	1.22540100
H	4.81729100	-4.26946100	1.51331600
C	-2.16039300	-0.69963100	-0.52467500
C	-0.04157200	-3.38645400	-1.56138100
H	-0.69535500	-3.75275100	-2.34427800
C	0.37385100	-1.64669700	0.11577300
C	-0.38809300	-2.19751000	-0.88666000
C	2.29097600	3.05706900	-0.52198700

C	0.80245400	0.85764800	0.29689300
C	1.08813900	1.89657200	1.19131000
H	0.69786100	1.85042000	2.20047700+
C	-1.51752900	-0.09043000	0.49927900
C	3.11255000	-4.23092500	0.22486900
H	3.37381700	-5.15292100	-0.28594800
C	1.83228900	2.99939800	0.78911800
H	2.05929500	3.80764900	1.47131700
C	2.02101500	2.04350900	-1.43490600
H	2.39660800	2.12175900	-2.44625000
C	1.93158600	-3.55010700	-0.16317900
C	3.56687400	-2.53841900	1.87824700
H	4.20606000	-2.14938600	2.66403400
C	1.27615100	0.94812300	-1.01691100
H	1.07553500	0.14914200	-1.72200700
C	1.10086600	-4.04680100	-1.20223400
H	1.38080500	-4.96490900	-1.70879700
C	-4.10764000	-1.15303300	-1.97699900
H	-3.56605100	-0.95746200	-2.90232500
H	-5.11992900	-0.77025000	-2.05262700
H	-4.12997500	-2.22791000	-1.79528500
C	-4.41397000	1.96313600	1.77164100
H	-3.79083900	2.32564200	2.58254900
H	-5.28875700	1.44588100	2.16554300
H	-4.75325100	2.79274400	1.15127800

Absolute energy= -1427.348901 a.u.

Imaginary frequency= 0

Network pharmacology results for the target prediction:

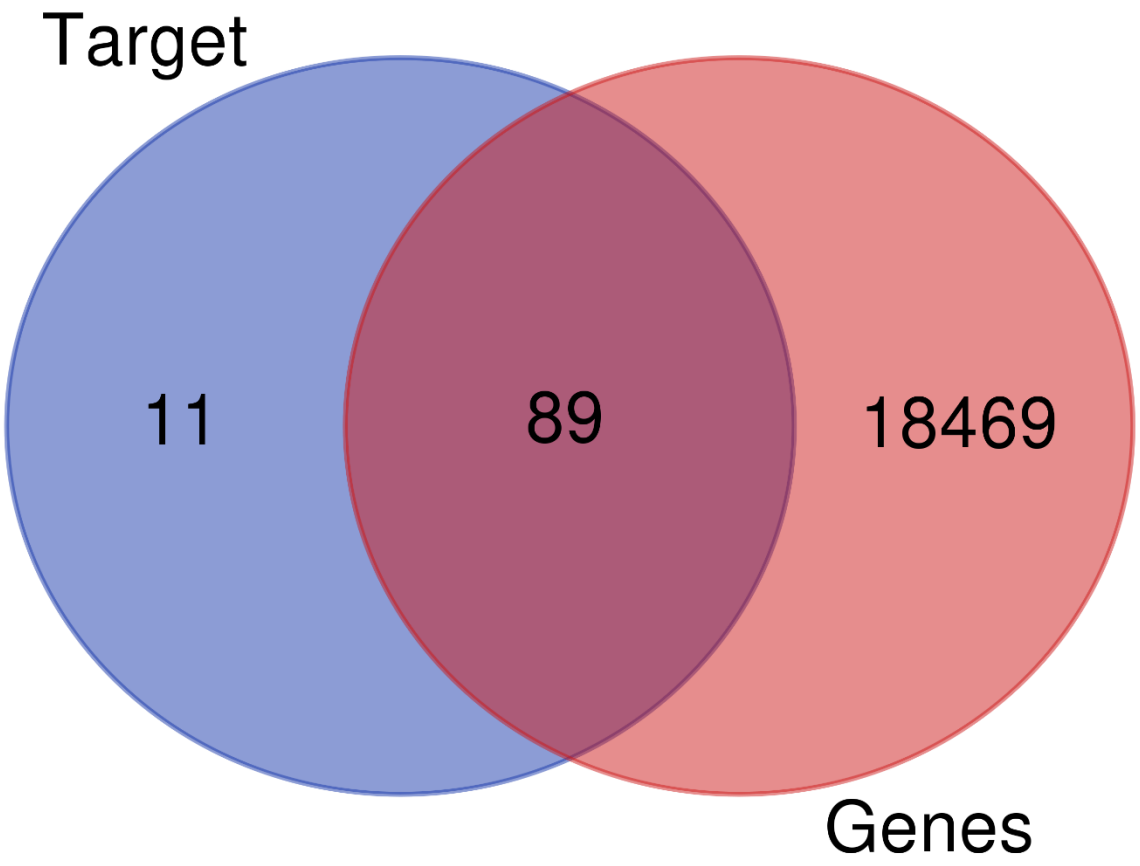


Figure S2: Venn diagram of potential target between target compounds and liver cancer genes

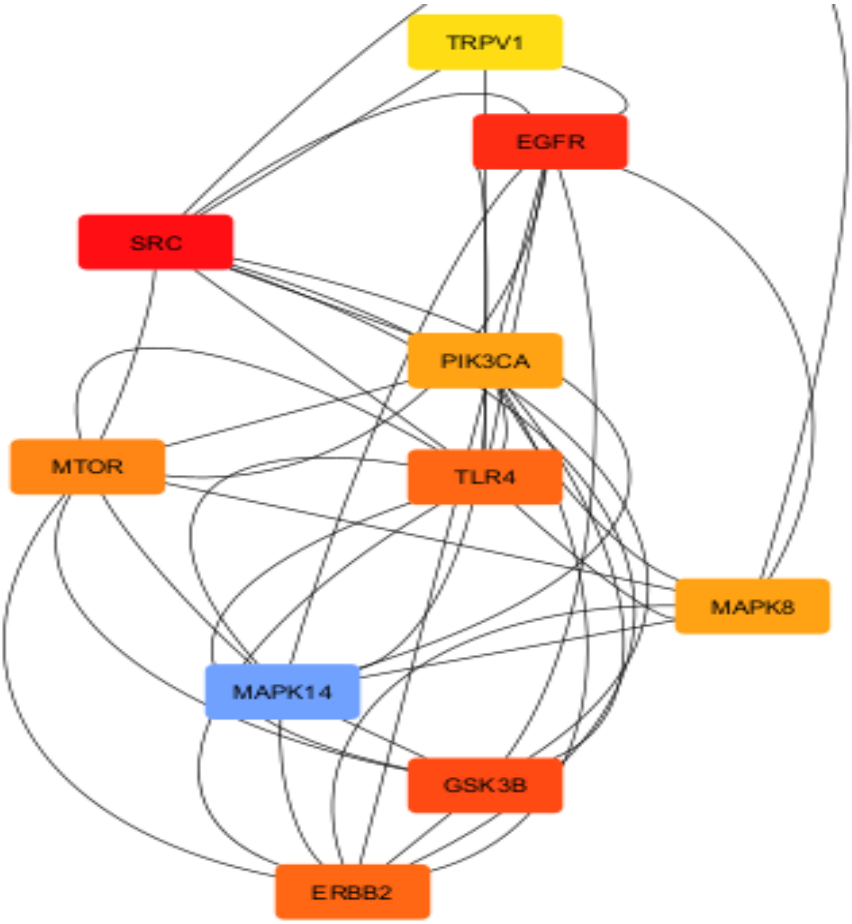


Figure S3: String interaction top 10 hub genes network for liver cancer

Table S2: Top 10 genes ranked with the help of string network for liver cancer

Rank	**Name**	**Score**
1	SRC	45
2	EGFR	32
3	GSK3B	24
4	TLR4	23
4	ERBB2	23
6	MTOR	21
7	PIK3CA	19
7	MAPK8	19
9	MAPK14	18
10	TRPV1	16

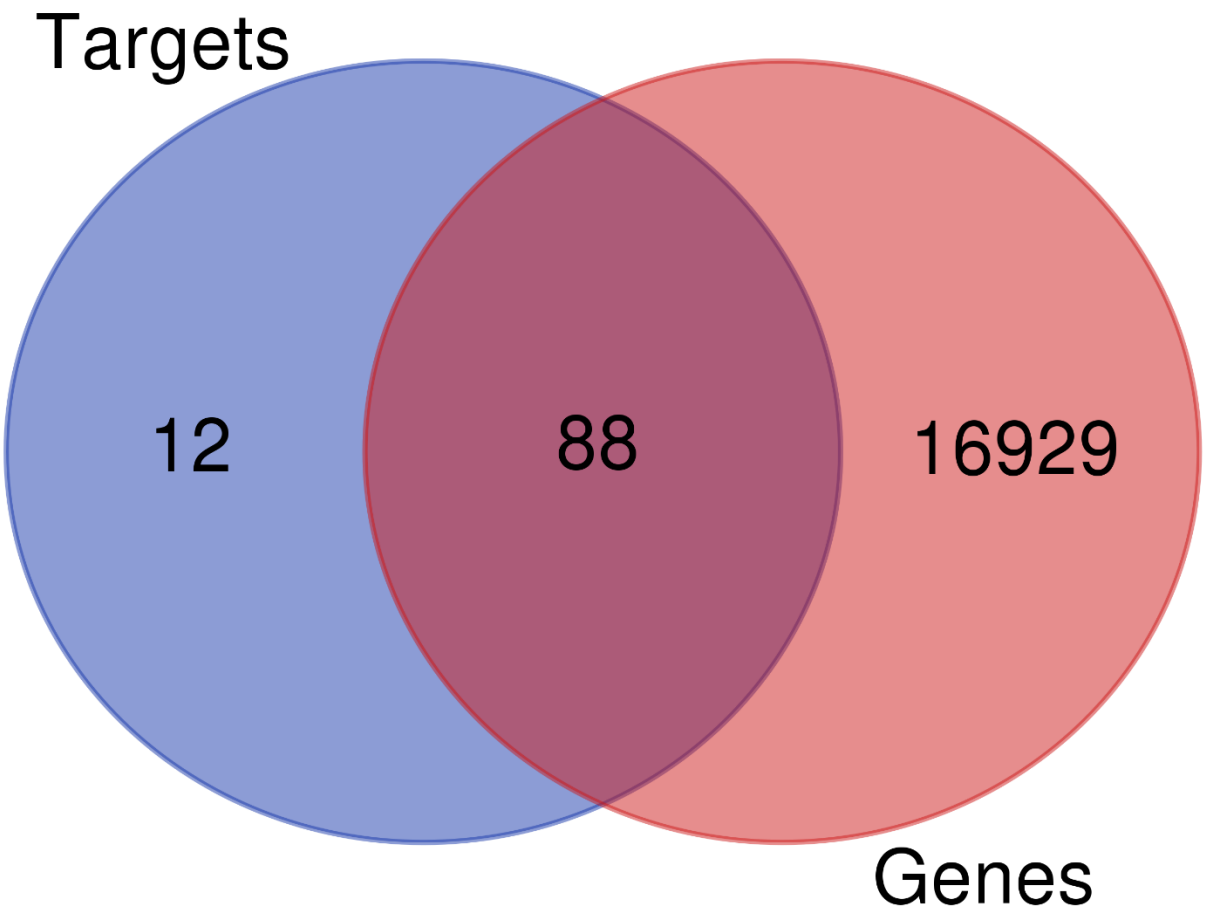


Figure S4: Venn diagram of potential target between target compounds and breast cancer genes

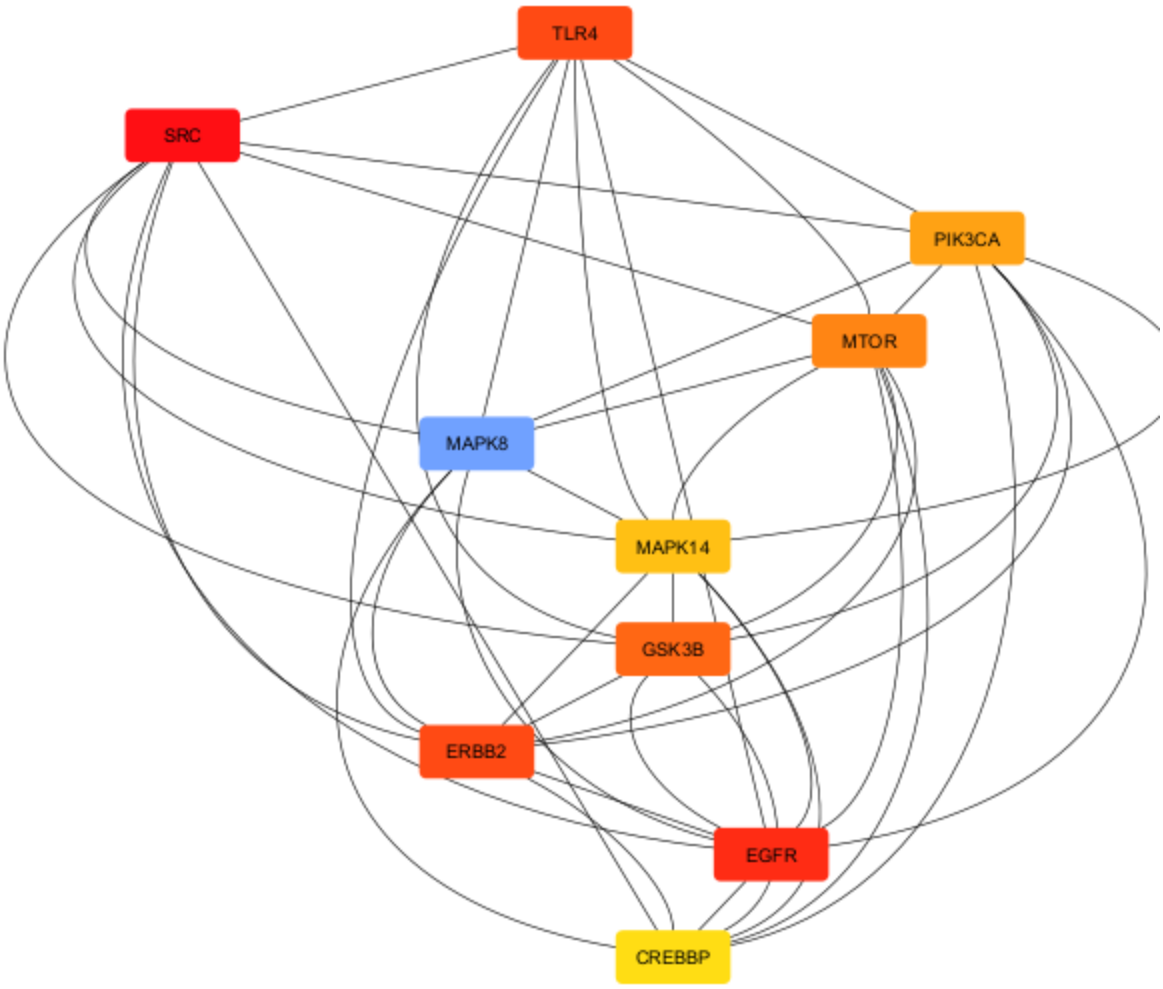


Figure S5: String interactions of top 10 hub genes network for breast cancer

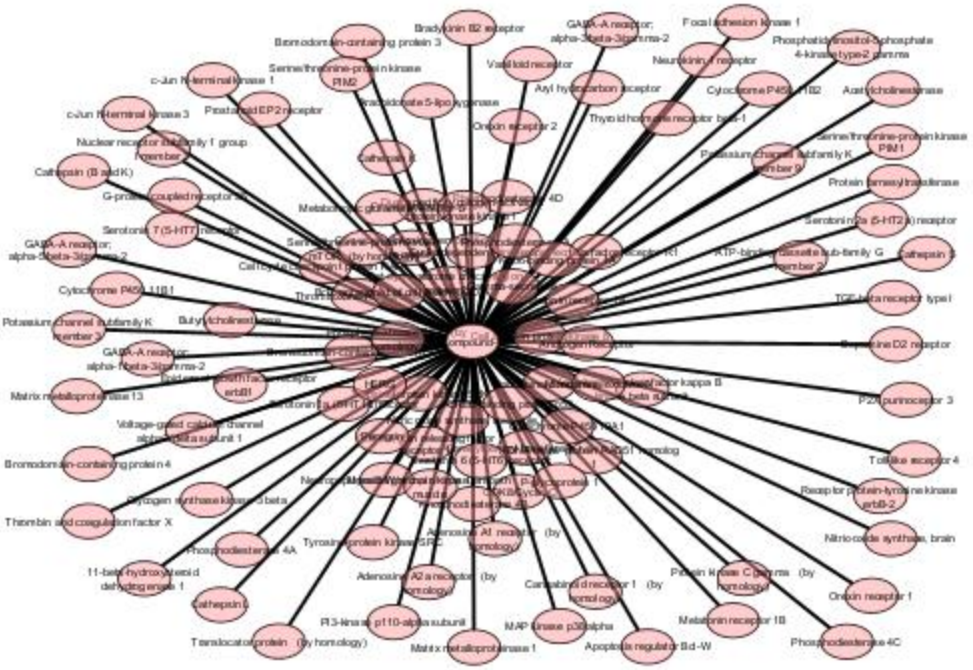


Figure S6: Protein- protein interaction for liver cancer

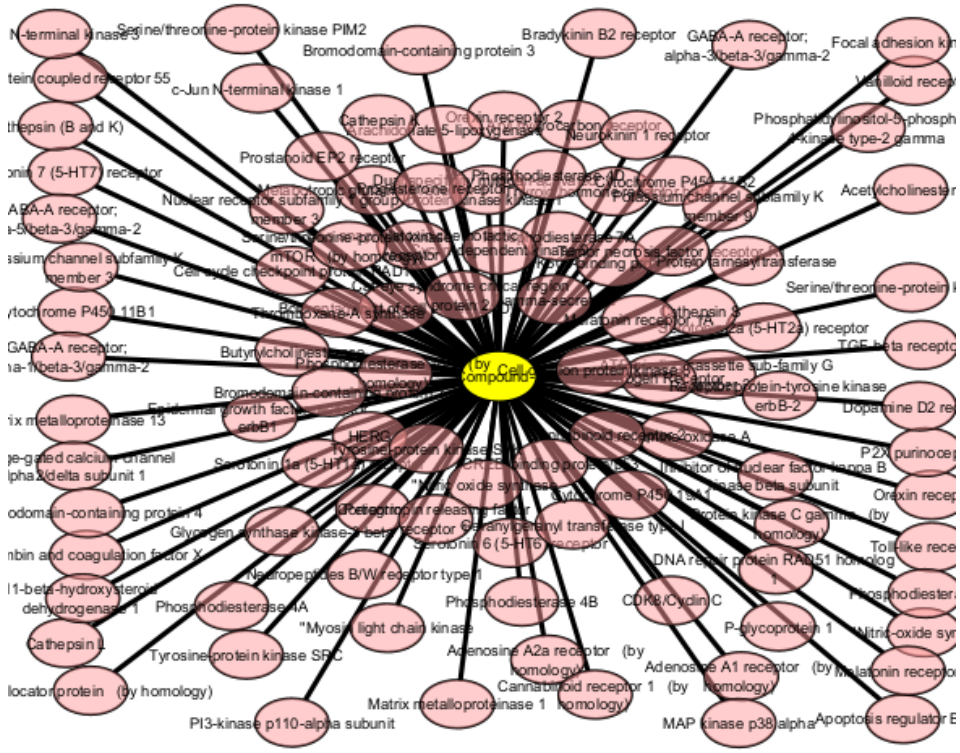


Figure S7: Protein- protein interaction for breast cancer

Table S3: Top 10 genes ranked with the help of string network for breast cancer

Rank	Name	Score
1	SRC	44
2	EGFR	32
3	TLR4	23
3	ERBB2	23
5	GSK3B	22
6	MTOR	21
7	PIK3CA	19
8	MAPK14	18
8	MAPK8	18
10	CREBBP	15

Docking studies:

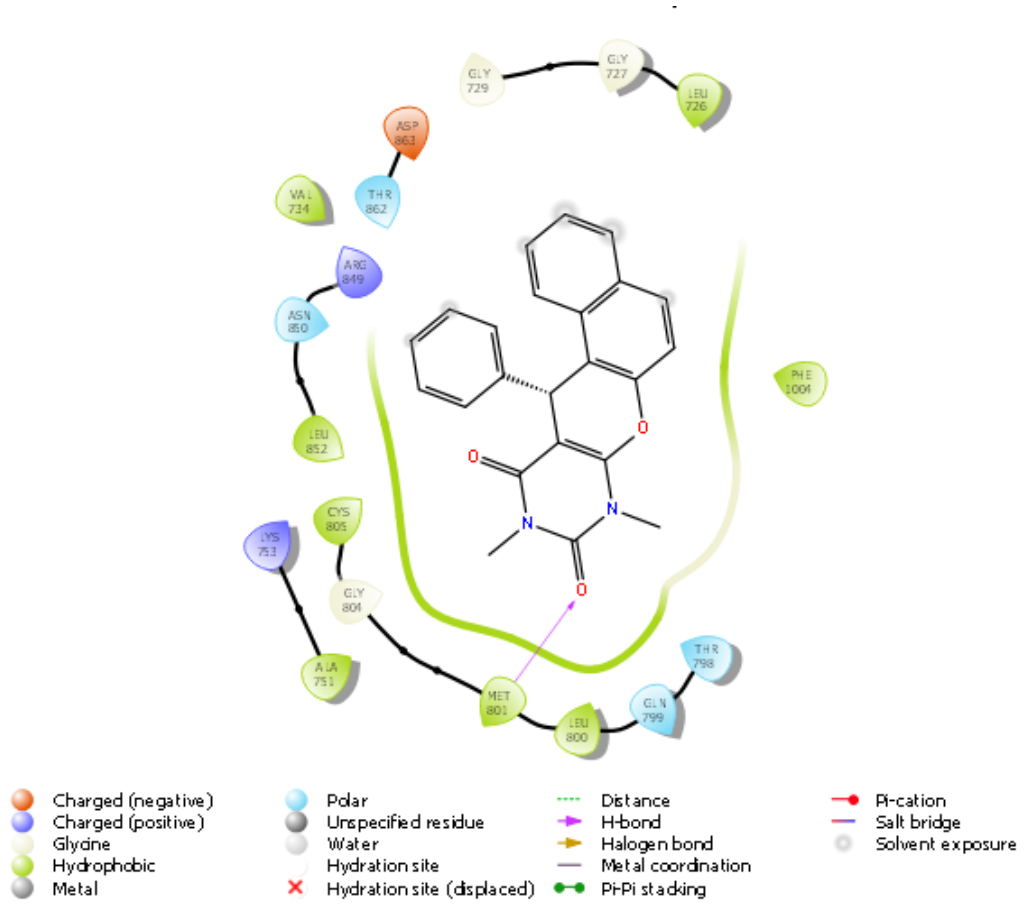


Figure S8: 2-D interaction of compound **4n** (PDB id: 3RCD)

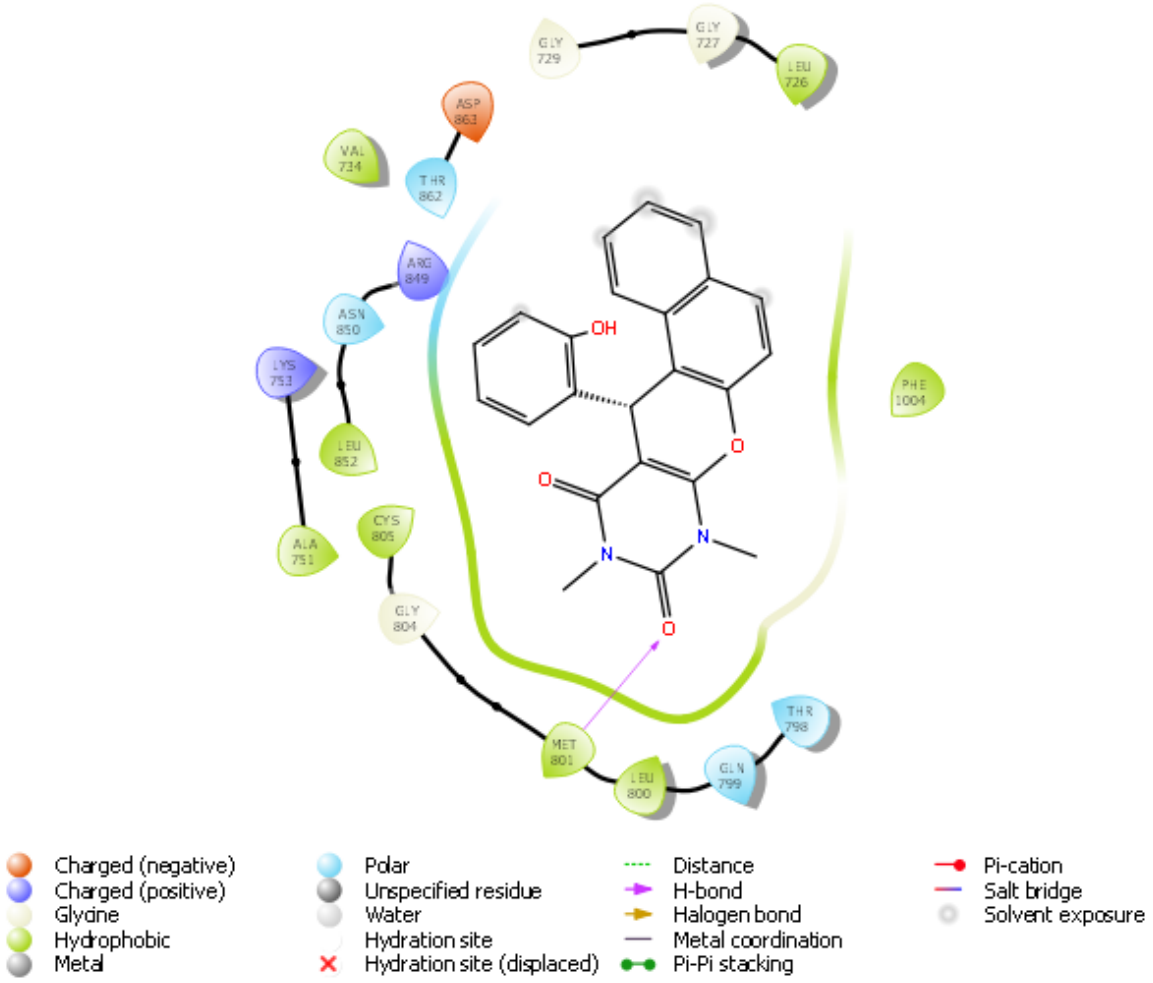


Figure S9: 2-D interaction of compound **4g** (PDB id: 3RCD)

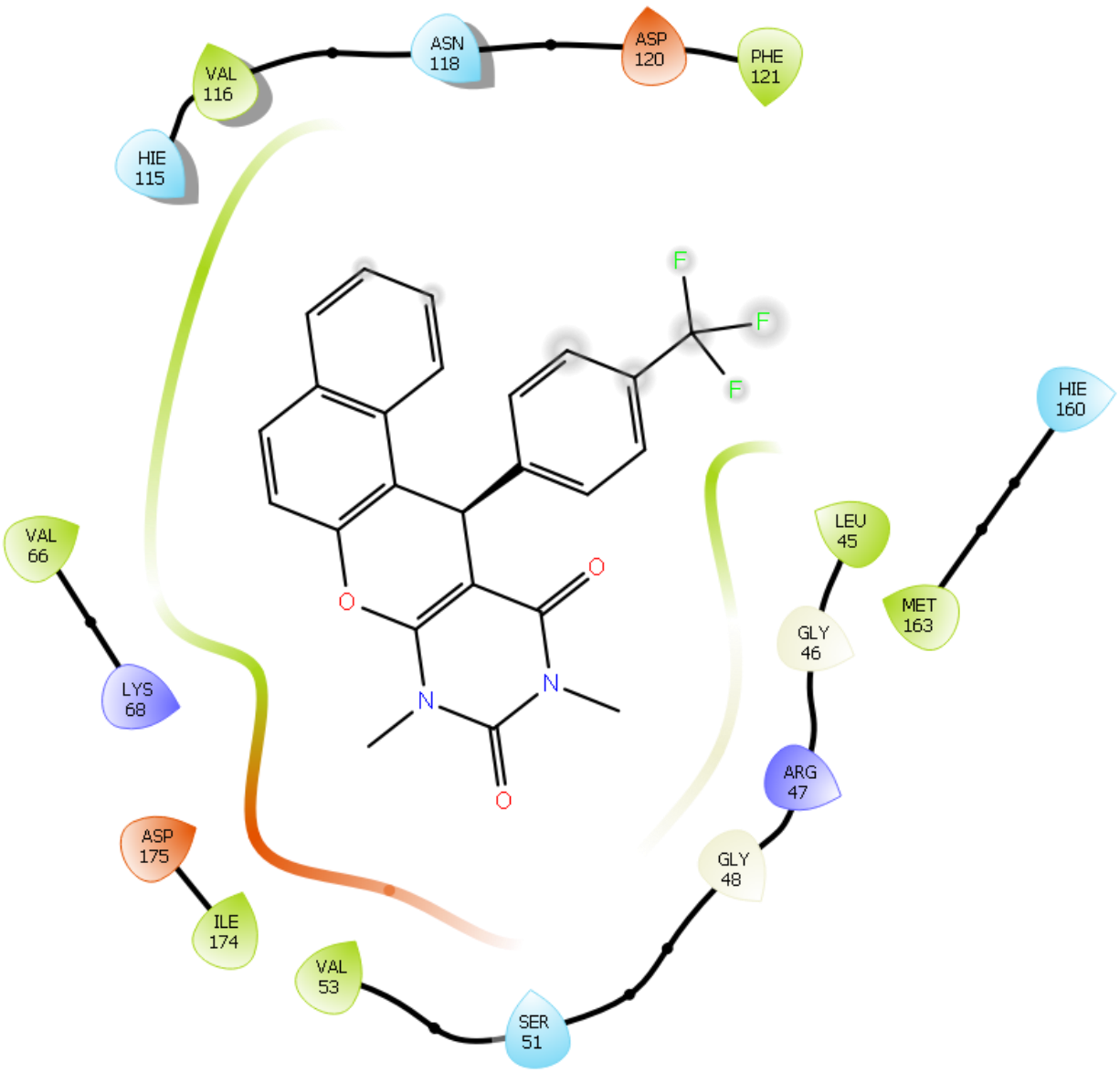


Figure S10: 2-D interaction of compound **4k** (PDB id: 6HNY)

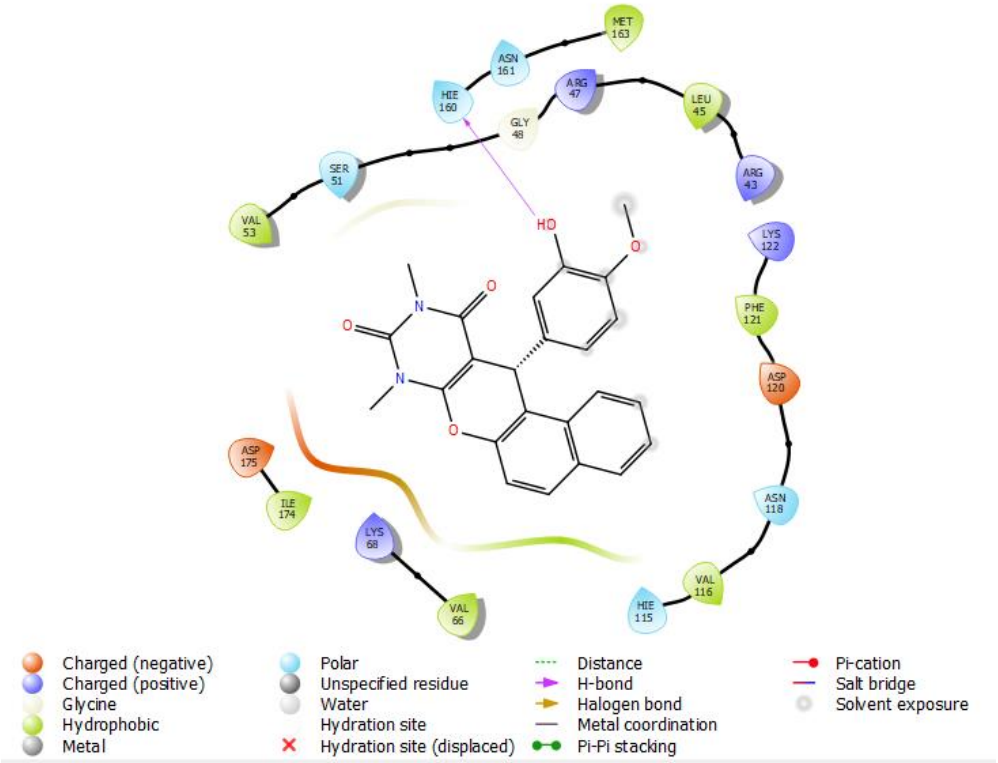


Figure S11: 2-D interaction of compound **4m** (PDB id: 6HNY)

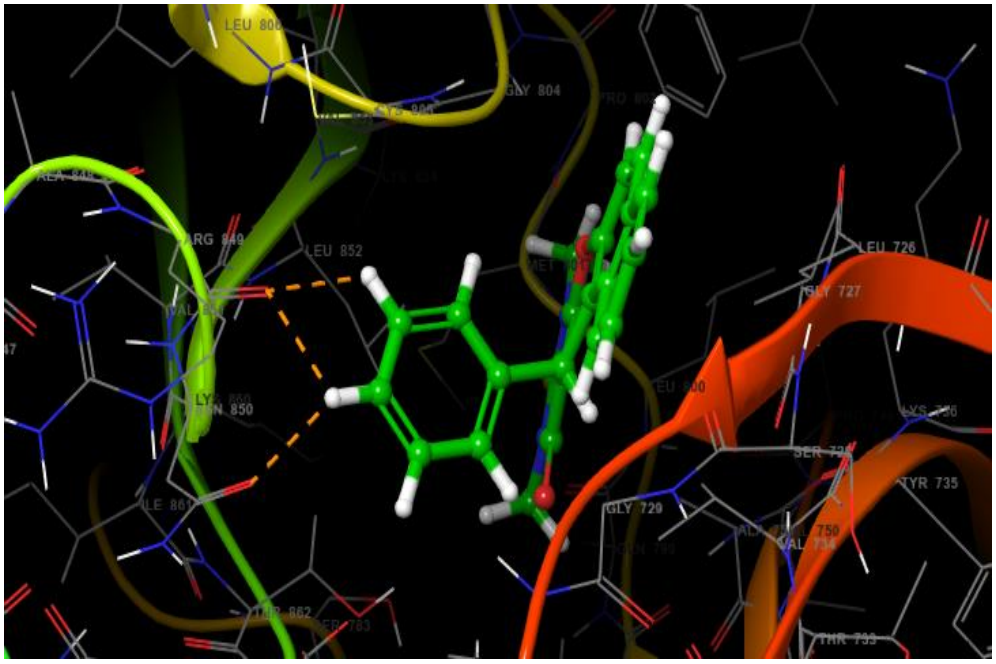


Figure S12: 3-D interaction of compound **4n** (PDB id: 3RCD)

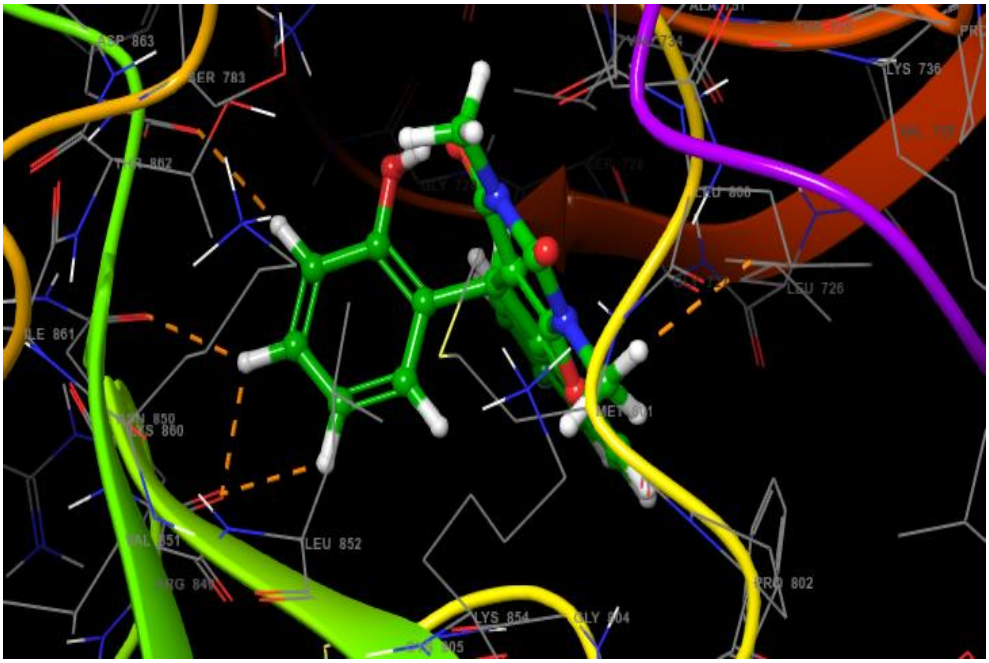


Figure S13: 3-D interaction of compound **4g** (PDB id: 3RCD)

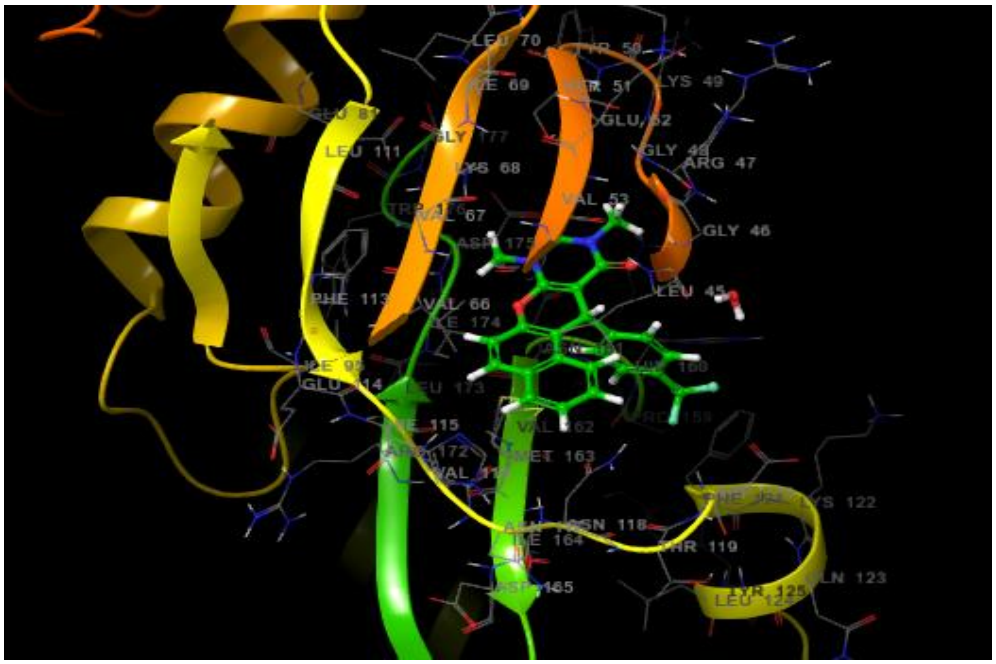


Figure S14: 3-D interaction of compound **4k** (PDB id: 6HNY)

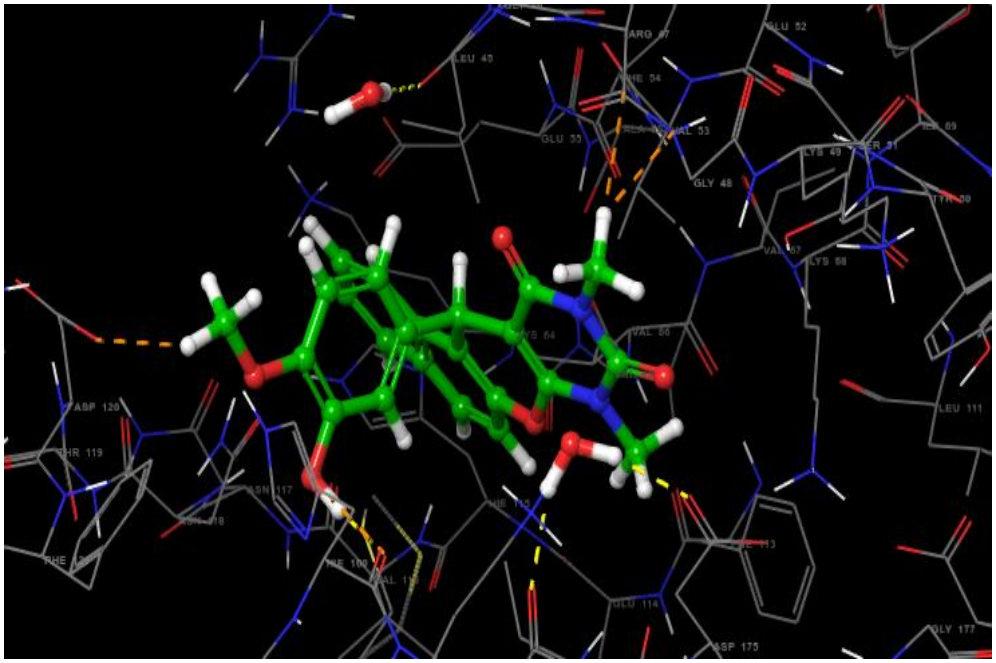


Figure S15: 3-D interaction of compound **4m** (PDB id: 6HNY)

Table S4: Docking score and binding energy (kcal/mol) of the naphthopyranopyrimidines compounds with proteins for liver cancer

S.no	**PDB id: 4HJO**			**PDB id: 5FL4**			**PDB id: 3RCD**		
	Comp.	**DS**	**BE**	**Comp.**	**DS**	**BE**	**Comp.**	**DS**	**BE**
1	Sorafenib.mol	-7.761	-56.735	Sorafenib.mol	-4.518	-48.589	4n	-8.499	-44.91
2	4f	-5.268	-38.48	Neratinib.mol	-3.941	-48.189	4g	-8.464	-45.987
3	4l	-5.144	-42.286	4f	-3.465	-30.551	Neratinib.mol	-7.8	-69.478
4	4m	-4.885	-39.562	4m	-3.373	-33.486	4i	-6.859	-42.999
5	4n	-4.701	-35.286	4i	-3.261	-31.809	Sorafenib.mol	-6.413	-52.99
6	4e	-4.685	-35.978	4g	-3.224	-31.525	4m	-5.644	-43.745
7	4k	-4.628	-35.939	4l	-3.108	-32.116	4d	-5.639	-42.382
8	4d	-4.623	-36.704	4d	-2.921	-29.539	4f	-5.257	-39.495
9	4i	-4.589	-41.53	4a	-2.868	-29.684	4a	-5.212	-40.091
10	4a	-4.405	-34.252	4n	-2.776	-24.102	4k	-5.031	-34.253
11	4g	-4.05	-38.441	4k	-2.659	-29.53	4e	-4.987	-36.365
12	-	-	-	4e	-2.381	-21.091	4l	-4.828	-40.645

Table S5: Docking score and binding energy (kcal/mol) of the naphthopyranopyrimidines compounds with proteins for breast cancer

S.no	PDB id: 6S9B			PDB id: 4MBC			PDB id: 6HNY			PDB id: 4NUS		
	Comp.	DS	BE	Comp.	DS	BE	Comp.	DS	BE	Comp	DS	BE
1	Neratinib.mol	-7.938	-63.33	Neratinib.mol	-5.827	-53.43	4k	-7.14	-43.67	Neratinib.mol	-6.361	-52.91
2	Sorafenib.mol	-7.013	-56.676	4m	-4.964	-37.008	4m	-6.534	-42.413	Sorafenib.mol	-6.169	-45.597
3	4n	-6.448	-41.935	Sorafenib.mol	-4.908	-47.851	4l	-6.455	-42.847	4n	-3.755	-29.045
4	4e	-6.356	-41.674	4g	-4.865	-36.27	4g	-6.361	-41.505	4f	-3.528	-27.152
5	4d	-6.217	-41.993	4i	-4.836	-34.836	4a	-6.236	-44.853	4g	-3.189	-27.71
6	4i	-6.042	-40.321	4n	-4.807	-33.784	4i	-6.211	-45.41	4m	-3.164	-29.475
7	4g	-5.636	-40.897	4f	-4.804	-33.806	4f	-6.138	-40.881	4l	-3.086	-29.068
8	4a	-5.328	-37.174	4a	-4.78	-34.881	4d	-6.085	-44.871	4e	-2.711	-25.492
9	4k	-5.025	-36.623	4k	-4.759	-35.086	Neratinib.mol	-5.914	-52.326	4d	-2.628	-25.396
10	4m	-4.816	-39.425	4d	-4.641	-34.005	4e	-5.758	-39.856	4i	-2.458	-28.893

11	4f	-4.598	-35.814	4l	-4.559	-34.649	4n	-5.668	-38.272	4a	-2.435	-26.365
12	4l	-4.478	-35.531	4e	-4.367	-33.134	Sorafenib.mol	-4.77	-39.79	4k	-2.35	-27.166

Table S6: Docking results for isomer of best docking score compounds in liver cancer

PDB id: 3RCD			
S.no.	**Compound name**	**Docking score**	**Binding Energy**
1	4g wedged	-8.713	-45.197
2	4g dashed	-8.685	-45.284
3	4n Wedged	-8.477	-45.791
4	4n dashed	-7.558	-44.502

Table S7: Docking results for isomer of best docking score compounds in breast cancer

PDB id: 6HNY			
S.no	**Compound name**	**Docking score**	**Binding Energy**
1	4k wedged	-6.791	-42.840
2	4k dashed	-6.774	-42.672
3	4m wedged	-6.549	-44.817
4	4m dashed	-6.361	-41.906

Table S8: Docking results of topoisomerase inhibitor against naphthopyranopyrimidine compounds

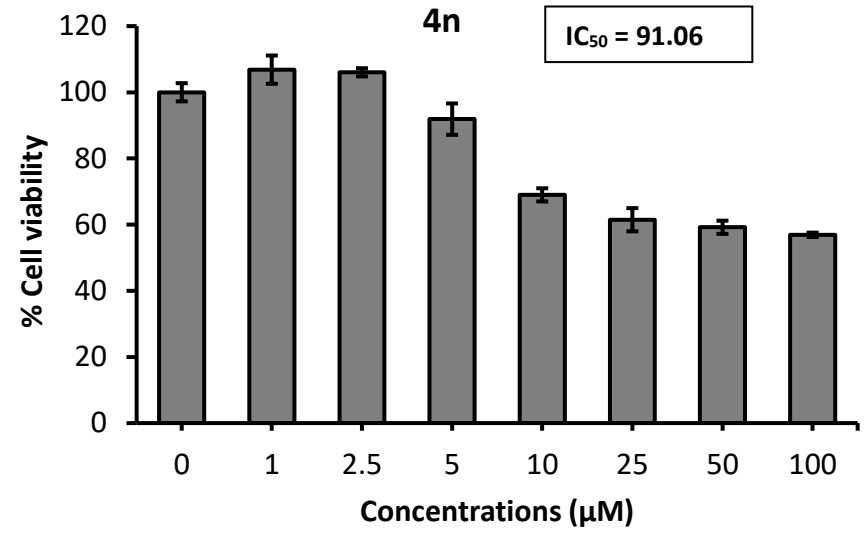
S.no	**Compounds**	**Docking score**	**Binding energy**
1	Camptothecin.1	-5.102	-41.347
2	4m	-4.888	-38.578
3	4g	-4.888	-38.578

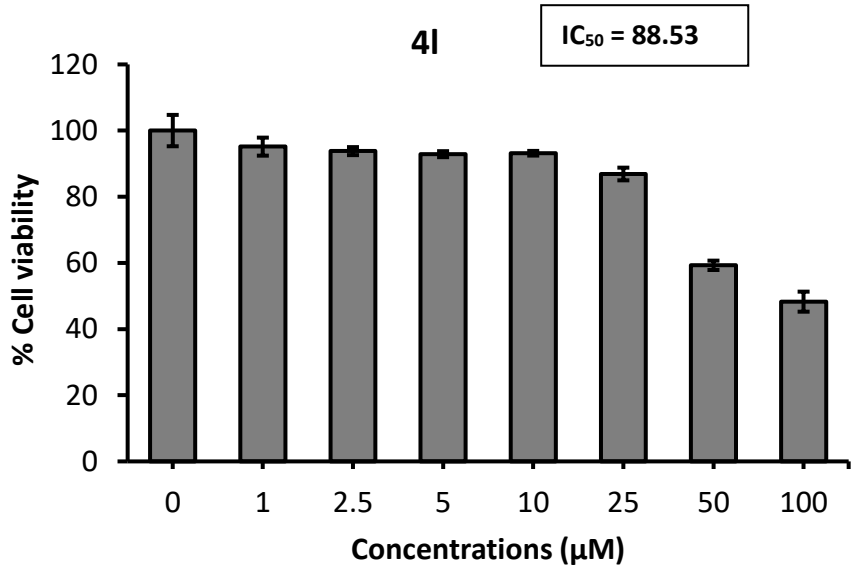
4	4d	-4.764	-36.449
5	4h	-4.72	-37.064
6	4c	-4.37	-32.677
7	4l	-4.332	-38.281
8	4n	-4.325	-29.776
9	4e	-4.238	-30.457
10	4f	-4.186	-34.873
11	Sorafenib	-4.139	-49.041
12	4k	-4.081	-32.846
13	4a	-3.45	-32.869
14	4i	-3.112	-35.052
15	4j	-2.576	-33.472
16	4b	-2.468	-32.353

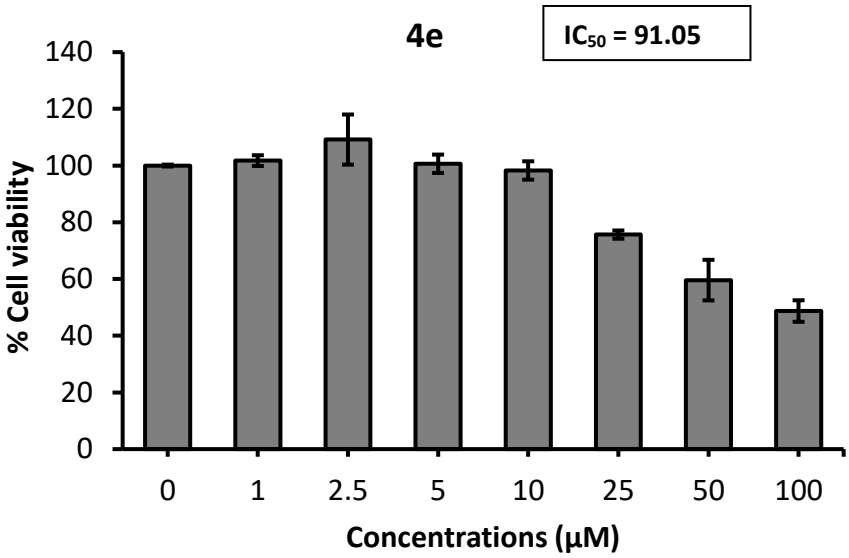
In vitro anti-proliferative activity

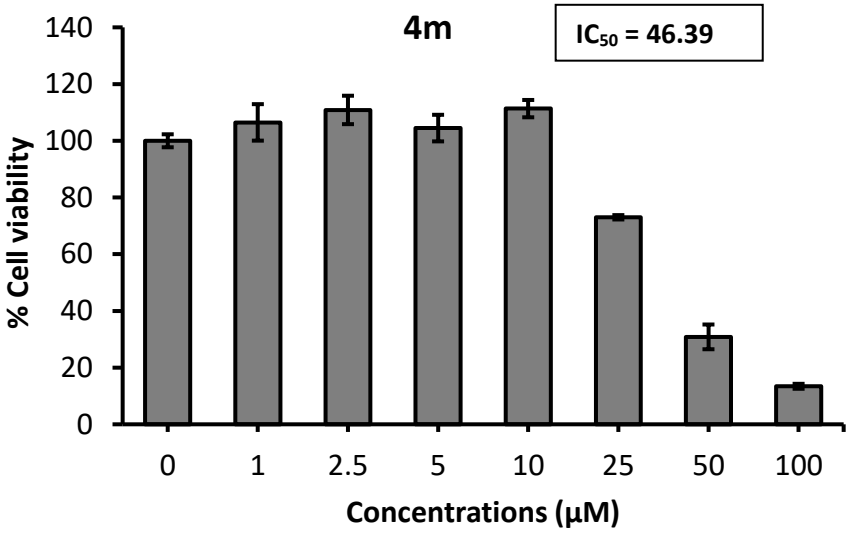
The anti-proliferative activity of the synthesized compound against MCF7 and HepG2 cell lines where evaluated using MTT assay. The IC_{50} value of the tested compound where determined. Initially, 100 ul of 10^4 Cells were seeded with 10% PBS in each well of 96-well and incubated for 24 h. Then, cells were treated with the test compounds and incubated for 48 h. Then 0.5 mg/ml of MTT dye (3-(4,5-dimethylthiazolyl-2)-2,5 diphenyltetrazolium bromide, sigma-aldrich) was added to each well and was further incubated for 4 h and the supernatant was removed and 100 µl of DMSO was added then the absorbance was recorded at 570 nm wavelength using Multimode Reader (Synergy Biotek) and DMSO alone was used as control.

HepG2 cell lines data

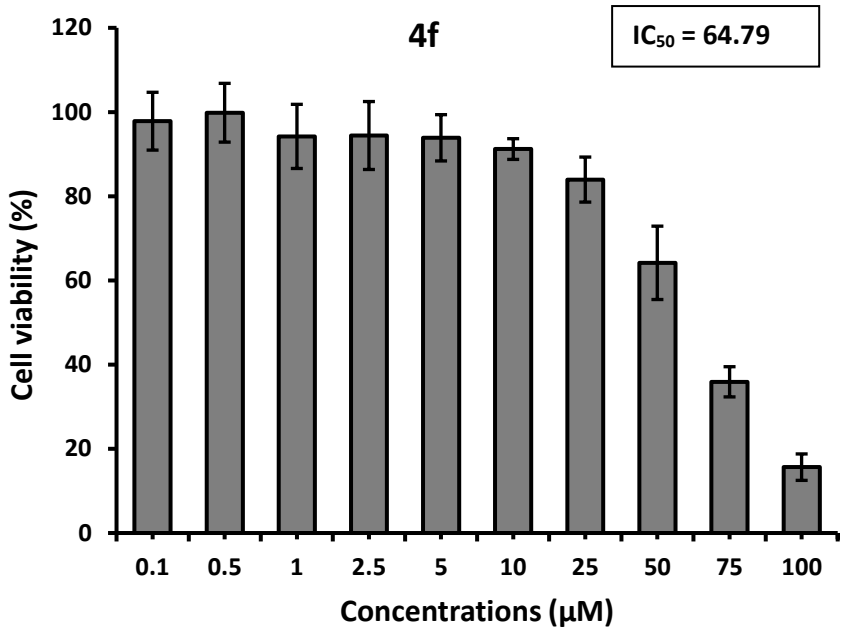


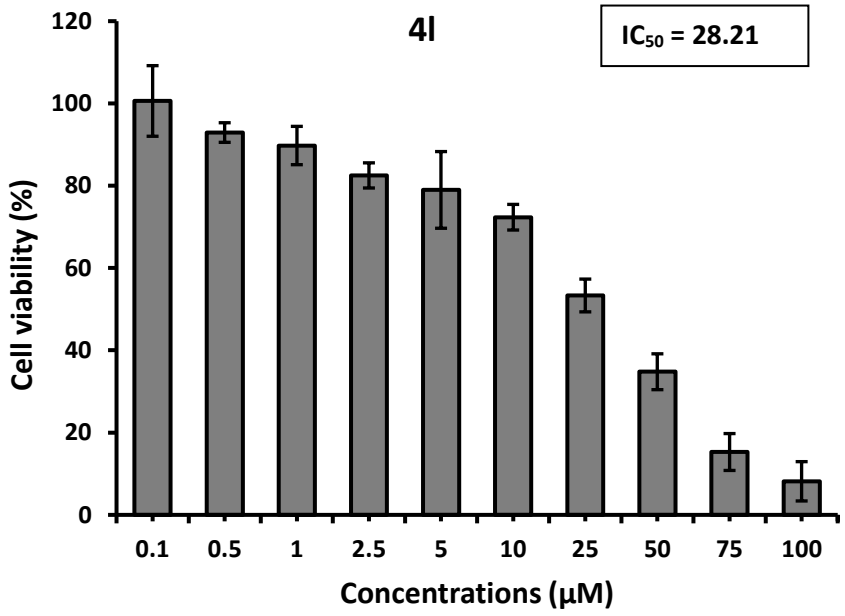


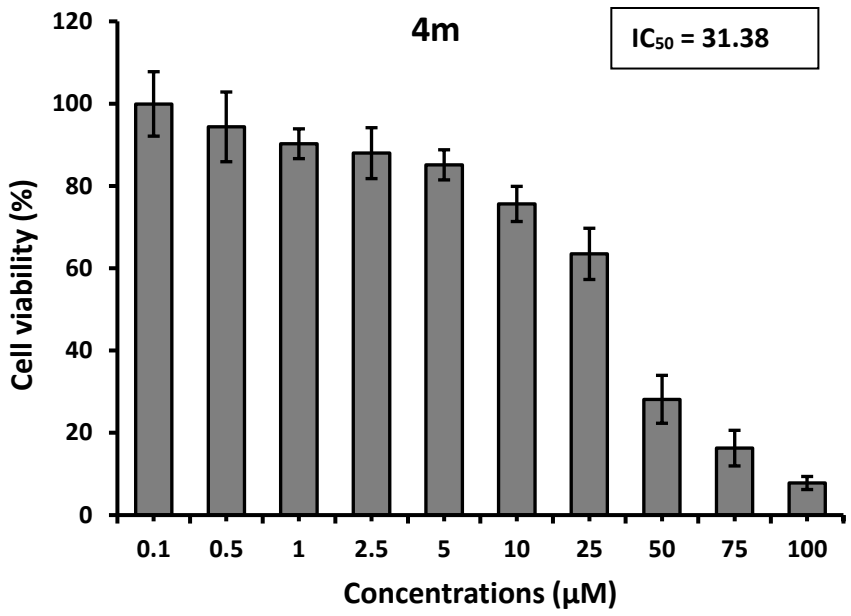

4e
IC50 = 91.05
% Cell viability
140
120
100
80
60
40
20
0
0
1
2.5
5
10
25
50
100
Concentrations (µM)


4m
IC50 = 46.39
% Cell viability
140
120
100
80
60
40
20
0
0
1
2.5
5
10
25
50
100
Concentrations (µM)

MCF7 cell line data







Crystallographic experimental data for compound 4h

Identification code	SD10054_auto
Empirical formula	$C_{23}H_{17}N_3O_5$
Formula weight	415.39
Temperature/K	100.01(10)
Crystal system	orthorhombic
Space group	Pbca
a/Å	9.31509(6)
b/Å	19.69557(13)
c/Å	20.17380(14)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3701.21(4)
Z	8
ρ_{calc}g/cm^3	1.491

μ/mm^{-1}	0.890
F(000)	1728.0
Crystal size/mm^3	0.002 × 0.002 × 0.001
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.766 to 136.372
Index ranges	$-11 \leq h \leq 11$, $-23 \leq k \leq 23$, $-24 \leq l \leq 24$
Reflections collected	44160
Independent reflections	3378 [$R_{int} = 0.0982$, $R_{sigma} = 0.0277$]
Data/restraints/parameters	3378/0/283
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	$R_1 = 0.0361$, $wR_2 = 0.0971$
Final R indexes [all data]	$R_1 = 0.0372$, $wR_2 = 0.0982$
Largest diff. peak/hole / e $Å^{-3}$	0.25/-0.23

References:

1. A. r. Momeni, H. A. Samimi and H. Vaezzadeh, Eutectic Mixture Choline Chloride–Chloroacetic acid: a New and Efficient Catalyst for Synthesis of 3,4-Dihydropyrimidin-2-ones, *Chem. Methodol.*, 2018, **2**, 260-269.