Supporting information

E Enamine Barbiturates and Thiobarbiturates as a New Class of Bacterial Urease Inhibitors

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Experimental

General methods

Compounds **3a, 3d, 3h, 3j-p, 4, and** 5 are prepared according to our reported method [1]. Melting points were determined using Mel-Temp apparatus and are uncorrected. Thin Layer Chromatography (TLC) was conducted on silica gel (Kiesel gel G, Merck) and spots were detected under UV light at 254 nm. IR spectra were recorded in a KBr matrix with a Bruker Tensor 37 FTIR spectrophotometer. ^{1}H-NMR spectra were recorded with a JEOL spectrophotomer at400 MHz, ^{13}C-NMR were recorded using JEOL spectrophotometers at 100MHz. Chemical shifts (δ) are given in ppm. The X-ray crystallographic analysis was collected by using a Bruker SMART APEX II D8 Venture diffractometer at Karachi University".

General procedure for the synthesis of 3a-p

A solution of **1** or **2** (1 equiv.) with different amines (1 equiv.) in MeOH (10 ml) was mixed and stirred at room temperature for 10 min for up to 2 h (TLC 20% EtOAc/n-hexane). The solvent was evaporated slowly to provide the corresponding solid products in quantitative yield.

1,3-Dimethyl-5-(((2-morpholinoethyl)amino)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3a

3a was synthesized from **1** and 4-(2-aminoethyl)morpholine following the general procedure and obtained as a yellow powder in 83% yield; m.p: 162°C; IR (KBr, cm^{-1}): 3637, 3423, 3197, 2960, 2935, 1583, 1570, 1510, 1462; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.28 (brs, 1H, NH), 8.15 (d, 1H, *J* = 14.8 Hz, CH=), 3.66 (q, 2H, $NHCH_2$), 3.48 (q, 4H, $2OCH_2$), 2.28(s, 3H, $2CH_3$), 2.54(t, 2H, *J* = 6.8 Hz, CH_2), 2.44(t, 4H, *J* = 4.4 Hz, $2CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.8, 163.0, 152.1, 90.8, 66.8, 57.6, 53.4, 46.7, 27.8, 27.1; LC/MS (ESI): 297.33 $[M+1]^+$; Anal. for $C_{13}H_{20}N_4O_4$; Calcd: C, 52.69; H, 6.80; N, 18.91; Found: C, 52.70; H, 6.81; N, 18.92.

1,3-Dimethyl-5-(((4-methylpyridin-2-yl)amino)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3b

3b was synthesized from **1** and 2-amino-4-picoline following the general procedure and obtained as a pink powder in 90% yield; m.p: 239°C; IR (KBr, cm^{-1}): 3215, 3045, 2958, 2908, 2866, 1614, 1598, 1544,1463; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.02 (d, 1H, *J* = 11.6Hz, NH), 9.36 (d, 1H,

J = 13.2 Hz, CH=), 8.24 (d, 1H, *J* = 4.4 Hz, Ph), 6.95 (d, 1H, *J* = 5.2 Hz, Ph), 6.81 (s, 1H, Ph), 3.33 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.0, 162.4, 151.8, 151.3, 150.4, 149.7, 148.7, 122.4, 113.1, 93.9, 27.9, 27.3, 21.0; LC/MS (ESI): 275.28 $[M+1]^+$; Anal. for $C_{13}H_{14}N_4O_3$; Calcd: C, 56.93; H, 5.15; N, 20.43; Found: C, 56.92; H, 5.16; N, 20.45.

4-(((1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)methyl)amino)-*N*-(pyrimidin-2-yl)benzenesulfonamide 3c

3c was synthesized from **1** and sulfadiazine following the general procedure and obtained as a white powder in 91% yield; m.p: 259°C; IR (KBr, cm^{-1}): 3421, 3116, 2958, 2860, 1618, 1591, 1508, 1440; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.94 (brs, 1H, NH), 11.28(brs, 1H, NH), 8.47 (d, 1H, *J* = 5.2 Hz, CH=), 7.99 (d, 1H, *J* = 8.8 Hz, pyrimidine), 7.72 (d, 1H, *J* = 8.8 Hz, pyrimidine), 7.61 (d, 2H, *J* = 8.8 Hz, Ph), 6.99 (t, 1H, *J* = 8.8 Hz, pyrimidine), 6.55(d, 2H, *J* = 8.8 Hz, Ph), 3.35 (s, 6H, $2CH_3$);^{13}C-NMR (100 MHz, DMSO-d_6):δ= 163.9, 158.2, 157.2, 142.0, 129.8, 129.3, 124.9, 118.5, 115.5, 112.1, 94.0, 30.7; LC/MS (ESI): 417.41 $[M+1]^+$; Anal. for $C_{17}H_{16}N_6O_5S$; Calcd: C, 49.03; H, 3.87; N, 20.18; Found: C, 49.03; H, 3.87; N, 20.20.

1,3-Dimethyl-5-((*p*-tolylamino)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3d

3d was synthesized from **1** and 4-methylanline following the general procedure and obtained as a white powder in 84% yield; m.p: 172°C; IR (KBr, cm^{-1}): 3448, 3215, 3169, 2953, 2866, 1595, 1570, 1554, 1476, 1435, 1440; ^{1}H-NMR (400 MHz, $CDCl_3$): δ =11.93 (brs, 1H, NH), 8.59 (d, 1H, *J* = 13.6 Hz, CH=), 7.15-7.00 (m, 4H, Ph), 3.26 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ =164.9, 162.6, 151.8, 136.6, 135.5, 130.5, 92.5, 27.9, 27.2, 20.8; LC/MS (ESI): 274.29 $[M+1]^+$; Anal. for $C_{14}H_{15}N_3O_3$; Calcd: C, 61.53; H, 5.53; N, 15.38; Found: C, 61.52; H, 5.54; N, 15.40.

5-((Cyclohexylamino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3e

3e was synthesized from **1** and cyclohexylamine following the general procedure and obtained as a white powder in 86% yield; m.p: 220°C; IR (KBr, cm^{-1}): 3423, 3197, 2960, 2908, 2858, 1583, 1570, 1510, 1435; ^{1}H-NMR (400 MHz, DMSO-d_6): δ =10.28 (brs, 1H, NH), 8.18 (d, 1H, *J* = 13.6 Hz,

CH=), 3.31 (m, 1H, cyclohexyl), 3.24 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 1.98(m, 2H, cyclohexyl), 1.76(m, 2H, cyclohexyl), 1.60(m, 1H, cyclohexyl), 1.42-1.15(m, 5H, cyclohexyl); ^{13}C-NMR (100 MHz, DMSO-d_6): δ =165.0, 163.0, 157.4, 152.1, 90.3, 58.8, 33.3, 24.8, 24.1; LC/MS (ESI): 266.31 $[M+1]^+$; Anal. for $C_{13}H_{19}N_3O_3$; Calcd: C, 58.85; H, 7.22; N, 15.84; Found: C, 58.84; H, 7.21; N, 15.85.

5-(((2-Chlorophenyl)amino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3f

3f was synthesized from **1** and 2-chloroanline following the general procedure, affording the product as a white powder in 85% yield; m.p: 202°C; IR (KBr, cm^{-1}): 3637, 3423, 3197, 2960, 2935, 1583, 1570, 1510, 1462;^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.44 (d, 1H, *J* = 12.8Hz, NH), 8.73 (d, 1H, *J* = 13.2 Hz, CH=), 7.48-7.45 (m, 2H, Ph), 7.36 (t, 1H, *J* = 7.2 Hz, Ph), 7.20 (t, 1H, *J* = 8.8 Hz, Ph), 3.38 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ =164.9, 162.7, 151.9, 151.1, 135.4, 130.6, 128.5, 126.9, 124.7, 116.6, 94.4, 28.2, 27.5; LC/MS (ESI): 294.71 $[M+1]^+$; Anal. for $C_{13}H_{12}ClN_3O_3$; Calcd: C, 53.16; H, 4.12; N, 14.31; Found: C, 53.17; H, 4.11; N, 14.29.

5-(((2-Iodophenyl)amino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3g

3g was synthesized from **1** and 2-iodoanline following the general procedure, affording the product as a white powder in 85% yield; m.p: 285°C; IR (KBr, cm^{-1}): 3086, 3053, 2953, 2885,1598, 1560, 1516, 1463, 1371;^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.77 (d, 1H, *J* = 14.8Hz, NH), 8.55 (d, 1H, *J* = 14.0 Hz, CH=), 7.77 (d, 1H, *J* = 7.2 Hz, Ph), 7.57 (d, 1H, *J* = 8.0 Hz, Ph), 7.49 (t, 1H, *J* = 7.6 Hz, Ph), 7.26 (t, 1H, *J* = 7.2 Hz, Ph), 3.20 (s, 3H, CH_3), 3.20 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.3, 162.9, 152.2, 151.9, 138.3, 136.4, 131.3, 128.1, 125.9, 118.5, 93.9, 28.2, 27.6; LC/MS (ESI): 386.16 $[M+1]^+$; Anal. for $C_{13}H_{12}IN_3O_3$; Calcd: C, 40.54; H, 3.14; N, 10.91; Found: C, 40.55; H, 3.15; N, 10.90.

1,3-Dimethyl-5-((pyridin-2-ylamino)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3h

3h was synthesized from **1** and 2-aminopyridine following the general procedure, affording the product as a white powder in 87% yield; m.p: 287-290°C; IR (KBr, cm^{-1}): 3420, 2999, 2960, 2908, 2870, 1624, 1591, 1456;^{1}H-NMR (400 MHz, $CDCl_3$): 12.11 (d, 1H, *J* = 11.6Hz, NH), 9.41 (d, 1H, *J* =

13.2 Hz, CH=), 8.43 (d, 1H, *J* = 4.4 Hz, Ph), 7.75 (dd, 1H, *J* = 8.0, 2.4 Hz, pyridine), 7.16 (t, 1H, *J* = 7.6, Hz, pyridine), 6.99 (d, 2H, *J* = 8.0 Hz, pyridine), 3.36 (s, 6H, $2CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.3, 162.6, 152.0, 151.3, 149.7, 149.3, 138.9, 121.4, 112.7, 94.3, 28.2, 27.5; LC/MS (ESI): 261.25 $[M+1]^+$; Anal. for $C_{12}H_{12}N_4O_3$; Calcd: C, 55.38; H, 4.65; N, 21.53; Found: C, 55.38; H, 4.64; N, 21.51.

5-(((1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 3i

3i was synthesized from **1** and 6-amino-1,3-dimethyl uracil following the general procedure and obtained as a white powder in 92% yield; m.p: 194°C; IR (KBr, cm^{-1}): 3215,3157, 3045, 2958, 2908, 2866, 1614, 1598, 1544, 1463; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.76 (s, 1H, CH=), 4.68 (s, 1H, CH=), 3.35(s, 6H, $2CH_3$), 3.22(s, 3H, CH_3), 3.05(s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 161.5, 154.9, 151.6, xxxx; LC/MS (ESI): 322.29 $[M+1]^+$; Anal. for $C_{13}H_{15}N_5O_5$; Calcd: C, 48.60; H, 4.71; N, 21.80; Found: C, 48.61; H, 4.70; N, 21.77.

1,3-Diethyl-5-(((pyridin-2-ylmethyl)amino)methylene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione 3j

3j was synthesized from **2** and 2-picolylamine following the reported procedure [1]. All spectrum was fit with the reported.

1,3-Diethyl-5-(((4-methylpyridin-2-yl)amino)methylene)-2-thioxodihydropyrimidine-4,6(*1H*,*5H*)-dione 3k

3k was synthesized from **2** and 2-amino-4-picoline following the the reported procedure [1]. All spectrum was fit with the reported.

1,3-Diethyl-2-thioxo-5-((*p*-tolylamino)methylene)dihydropyrimidine-4,6(*1H,5H*)-dione 3l

3l was synthesized from **2** and 4-methylanline uracil following the reported procedure [1]. All spectrum was fit with the reported.

5-(((4-Chlorophenyl)amino)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione 3m

3m was synthesized from **2** and 4-chloroanline following the reported procedure [1]. All spectrum was fit with the reported.

5-(((2-Chlorophenyl)amino)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione 3n

3n was synthesized from **2** and 2-chloroanline following the reported procedure [1]. All spectrum was fit with the reported.

1,3-Diethyl-5-(((2-iodophenyl)amino)methylene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione 3o

3o was synthesized from **2** and 2-iodoanline following the reported procedure [1]. All spectrum was fit with the reported.

2-(((1,3-Diethyl-4,6-dioxo-2-thioxotetrahydropyrimidin-5(2*H*)-ylidene)methyl)amino)benzenesulfonic acid 3p

3p was synthesized from **2** and 2-aminobenzenesulfonic acid following the reported procedure [1]. All spectrum was fit with the reported.

5-(((4-(((1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)methyl) amino)benzyl)amino)methylene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 4

Compound **4** was synthesized from **1** (2 equiv.) and 4-aminobenzylamine (1 equiv.) following the reported procedure [1]. All spectrum was fit with the reported.

5-(((4-(((1,3-Diethyl-4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene)methyl) amino)benzyl)amino)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione 5

Compound **5** was synthesized from **3** (2 equiv.) and 4-aminobenzylamine (1 equiv.) following the reported procedure [1]. All spectrum was fit with the reported.

Urease assay and inhibition

***In-vitro* Urease Inhibition Assay protocol:**

The urease inhibition assay was performed spectrophotometrically. The final volume of reaction mixture was 200 μL, comprising 25 μL of urease enzyme solution (Jack bean Urease; 1 U/well, is defined as the release of 1 μM of substrate per unit time under the specified conditions). This mixture was incubated with 5 μL of test compound (500 μM) for 15 min at 30°C, which proved to be sufficient in our studies. (urease enzyme was preparing in Phosphate buffer pH 6.8, concentration 4 mM). Thereafter, 55 μL of urea (substrate) at a concentration of 100 mM was added, and the plate was again incubated for 15 min at 30°C. After incubation, 45 μL of phenol reagents (1 % w/v phenol and 0.005 % w/v sodium nitroprusside), and 70 μL of alkali reagents (0.5 % w/v sodium hydroxide and 0.1 % sodium hypochlorite) were added to each well. The plate was re-incubated for 50 min at 30 °C. The continuous production of ammonia by urease was monitored following the Weatherburn method, and absorbance was recorded at 630 nm on an ELISA plate reader (Spectra Max M2, Molecular Devices, CA, USA). Acetohydroxamic acid was used as a reference compound (Standard Drug, available under the brand name Lithostate) [3-6].

Single crystal X-ray diffraction analysis of 3b and 3k

To study the structure of the compounds synthesized, we performed X-ray structure determination of **3b** and **3k**. The former (Figure S2) comprises a planar methyl substituted pyridine ring (N1/C1-C6) and dimethyl pyrimidine trione ring (N3-N4/C8-C13/O1-O3), which are linked along C1 and C8 *via* enamine (N2/C7) bridged. The dihedral angle between the pyridine ring (N1/C1-C5) and substituted pyrimidine ring (N3-N4/C8-C11) is 0.47°, with maximum deviation of N3 atom from the r.m.s plane. The asymmetric unit of **3k** (Figure S2) consists of two independent molecules composed of a planar methyl substituted pyridine ring (N1/C1-C5/C15) and diethyl thio pyrimidine dione ring (N3-N4/S1/O1-O2/C7-C14) linked along C5 and C7 *via* enamine (N2/C6) bridged. The dihedral angle between the pyridine ring (N1/C1-C5) and substituted pyrimidine ring (N3-N4/C7-C10) is 2.62°, with maximum deviation of C9 atom from the r.m.s plane.

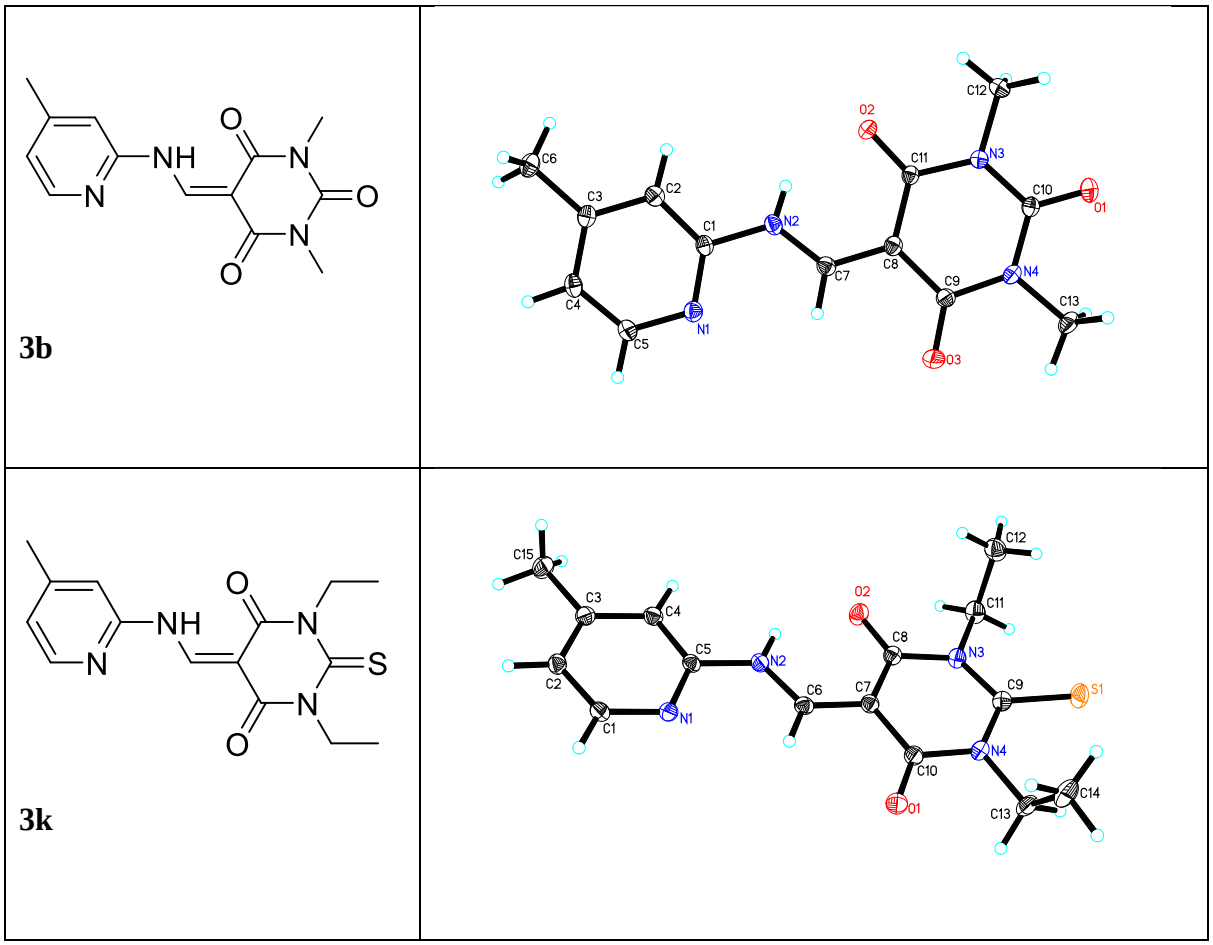

Figure S1. ORTEP diagram of the compounds **3b** and **3k**. Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

Table S1. Experimental details

Crystal data	**3b**	**3k**
Chemical formula	$C_{13}H_{14}N_4O_3$	$C_{15}H_{18}N_4O_2S$
Mr	274.28	318.40
Crystal system, space group	Monoclinic, *Cc*	Monoclinic, $P2_1/n$
Temperature (K)	173	173
a, *b*, *c* (Å)	8.2687 (6), 11.2813 (6), 13.7137 (7)	16.1065 (7), 8.0762 (4), 24.3959 (11)
β	94.141 (2)°	104.470 (2)°
V (Å^3)	1275.90 (13)	3072.7 (2)
Z	4	8
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.87	1.99
Crystal size (mm)	0.30 × 0.20 × 0.20	0.12 × 0.08 × 0.04
θ_{max} / θ_{min}	68.1°/8.5°	68.3°/3.7°
No. of measured, independent and observed [I > 2σ(I)] reflections	16420, 2261, 2253	87979, 5635, 4990
R_{int}	0.020	0.056
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.027, 0.076, 1.06	0.033, 0.087, 1.02
No. of reflections	2261	5635
No. of parameters	188	411
No. of restraints	2	0
$\Delta\varrho_{max}$, $\Delta\varrho_{min}$ (e Å^{-3})	0.14, −0.13	0.24, −0.29
CCDC no.	1967430	1967287

The molecules in the crystal lattice of **3b** are connected in a two-dimensional pattern *via* H2…O3, H4…O1, H13C…O2 intermolecular interactions with a donor-acceptor distance of 3.3750(2)Å, 3.3344(2)Å, and 3.2781(2)Å, respectively. The $\pi ... \pi$ interaction and C O…π interactions further strengthen the crystal structure with Cg1(N1/C1-C5)…Cg2(N3-N4/C8-C11) with a donor-acceptor distance of 3.476Å and O1-Cg1(N1/C1-C5) with a distance of 3.7893(3)Å, respectively. (Figure 3) While the molecules in the crystal lattice of **3k** are connected in a two-dimensional pattern *via* H4…O3, H19…O1, H30A…O1 intermolecular interactions, with donor-acceptor distances of 3.3269(2)Å, 3.3548(2)Å, 3.4316(2)Å, respectively. The $\pi ... \pi$ and C-S…π interactions further strengthen the crystal structure with Cg1(N1/C1-C5)…Cg4(N7-N8/C22-C25) with donor-acceptor distance of 3.5878(2)Å, Cg2(N3-N4/C7-C10)…Cg3(N5/C16-C20) distance 3.5535(2)Å and S2-Cg4(N7-N8/C22-C25) distance 3.6688(2)Å, respectively (Figure 4). The details of selected hydrogen bonding geometry Å in **3b** and **3k** are given in Table **2** and **3**.

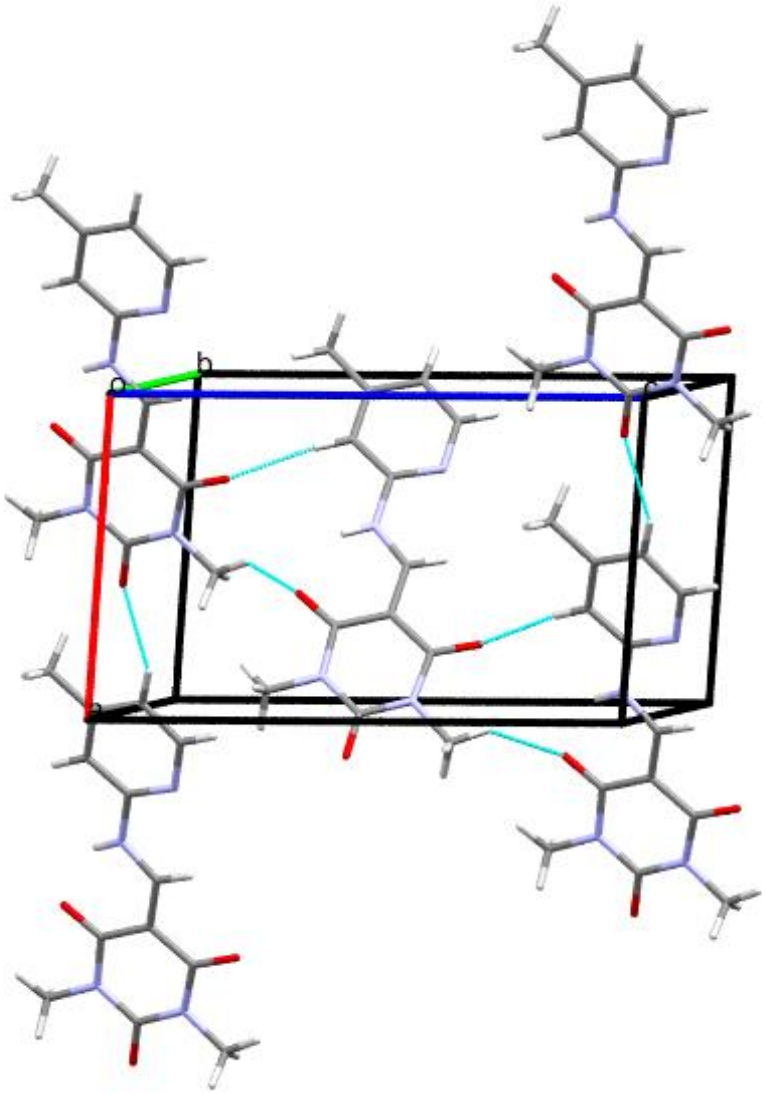

Figure S2: Crystal packing diagram of compound **3b** along b-axis.

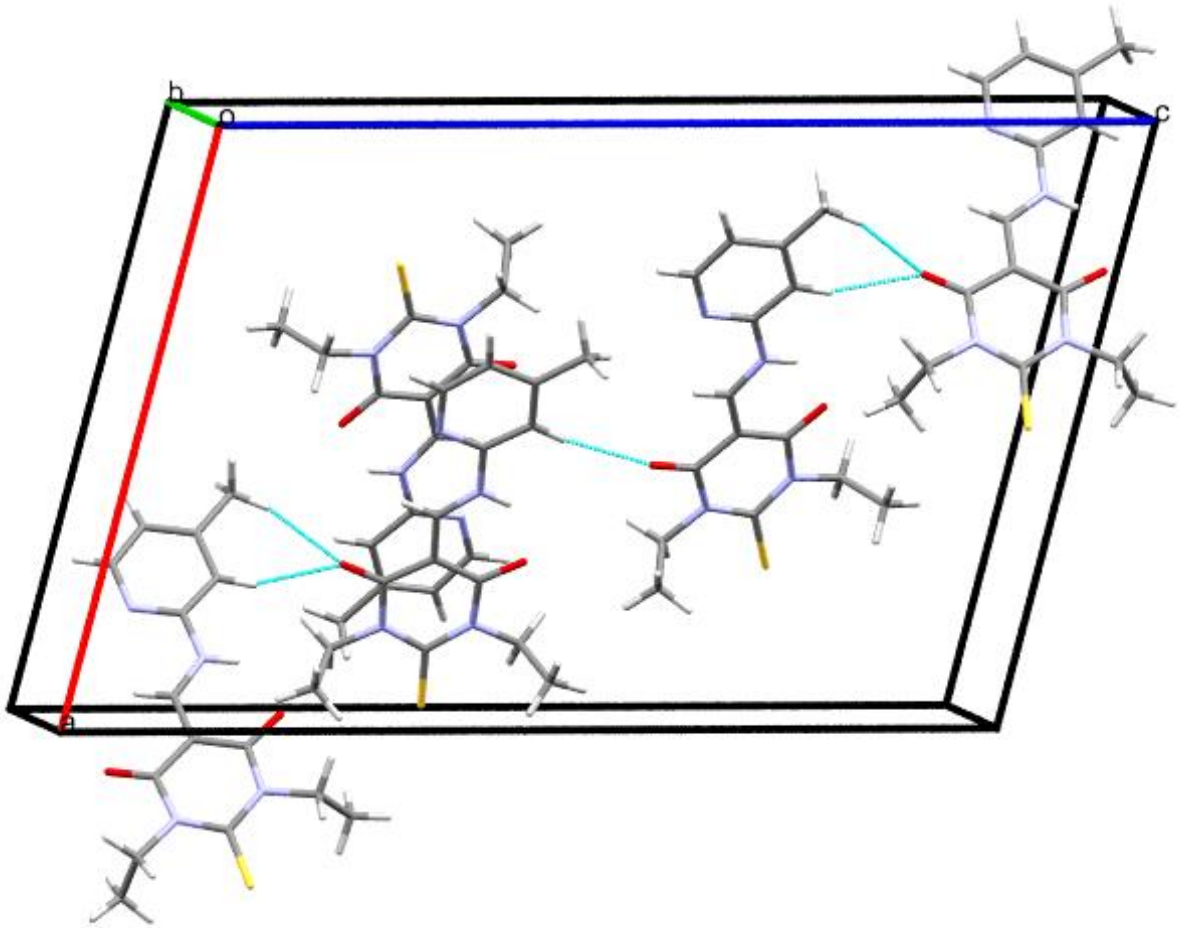

Figure S3: Crystal packing diagram of compound **3k** along c-axis.

Table S2: The list of selected hydrogen bonding geometry Å in compound **3b** is given below:

D	**H**	**A**	**D-H**	**H…A**	**D…A**	**D-H…A**
C2	H2	O3	0.95	2.43	3.3750(2)	172
C4	H4	O1	0.95	2.46	3.3344(2)	153
C13	H13C	O2	0.98	2.47	3.2781(2)	139

Symmetric codes: x, -y, z+1/2

Table S3: The list of selected hydrogen bonding geometry Å in compound **3k** is given below:

D	**H**	**A**	**D-H**	**H…A**	**D…A**	**D-H…A**
C4	H4	O3	0.95	2.43	3.3269(2)	157
C19	H19	O1	0.95	2.49	3.3548(2)	152

C30	H30A	O1	0.98	2.50	3.4316(2)	158

Symmetric codes: -x+1/2, y+1/2, -z+1/2

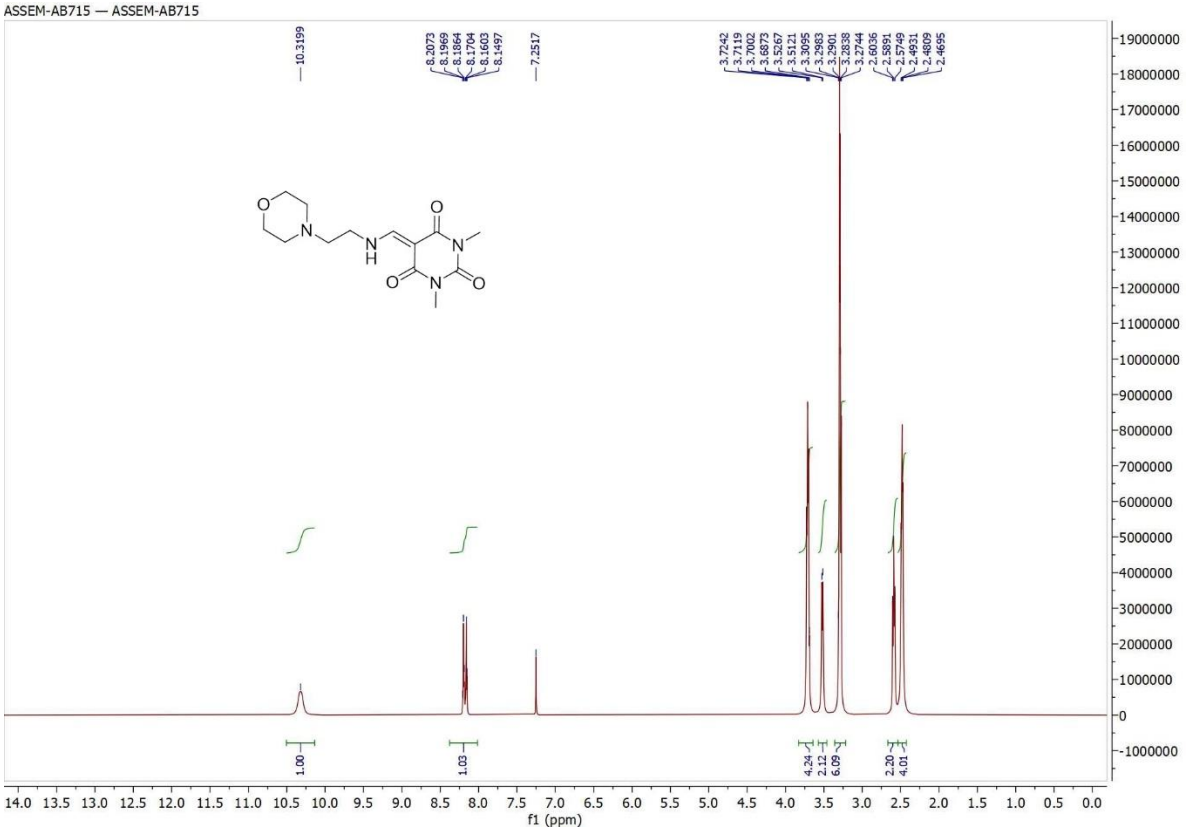

Figure S4: ^{1}HNMR ($CDCl_3$) **3a**

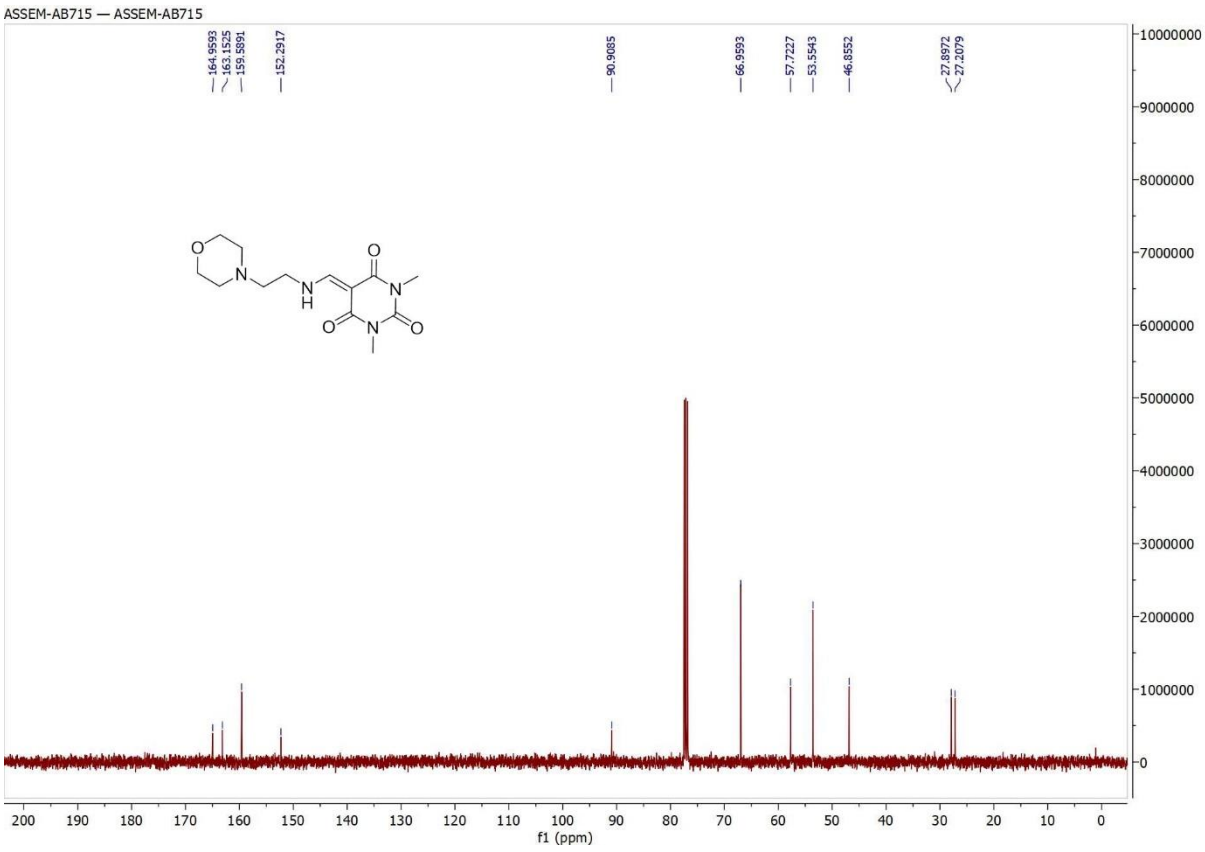

Figure S5: ^{13}CNMR ($CDCl_3$) **3a**

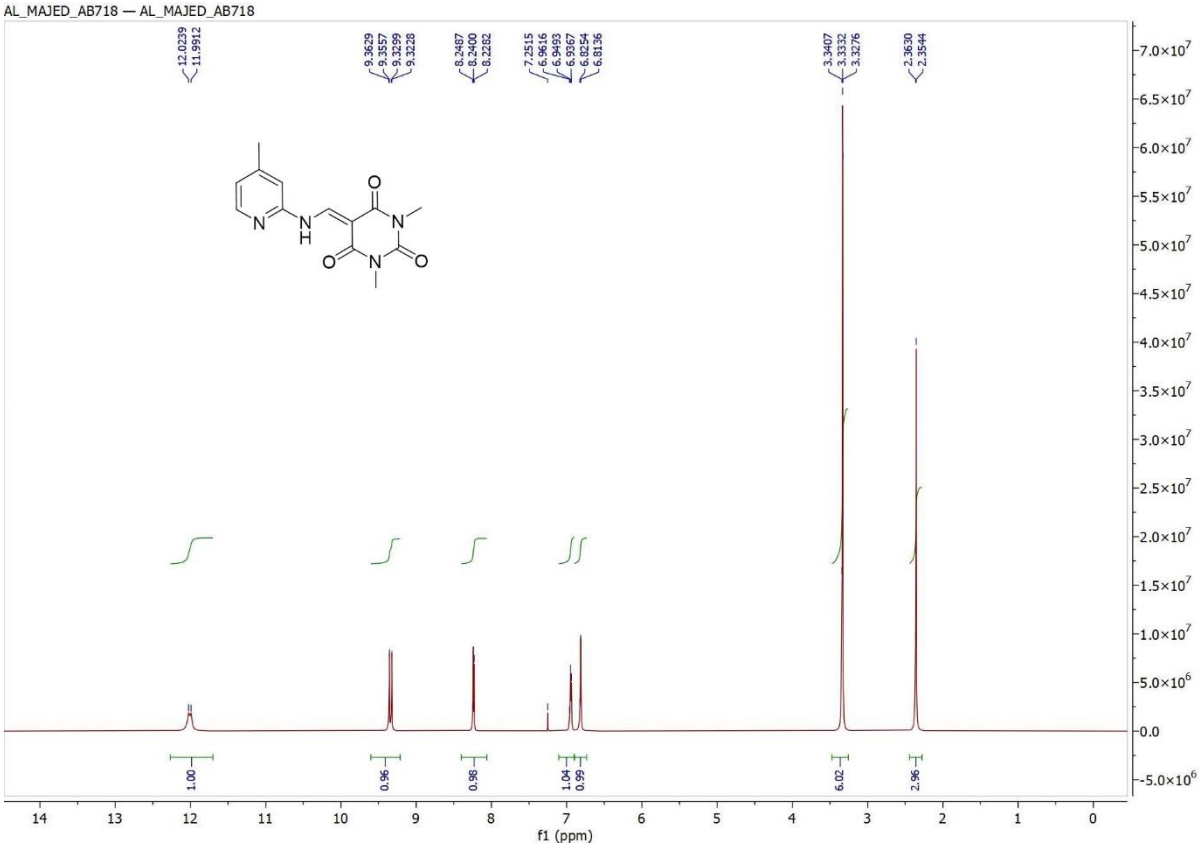

Figure S6: ^{1}HNMR ($CDCl_3$) **3b**

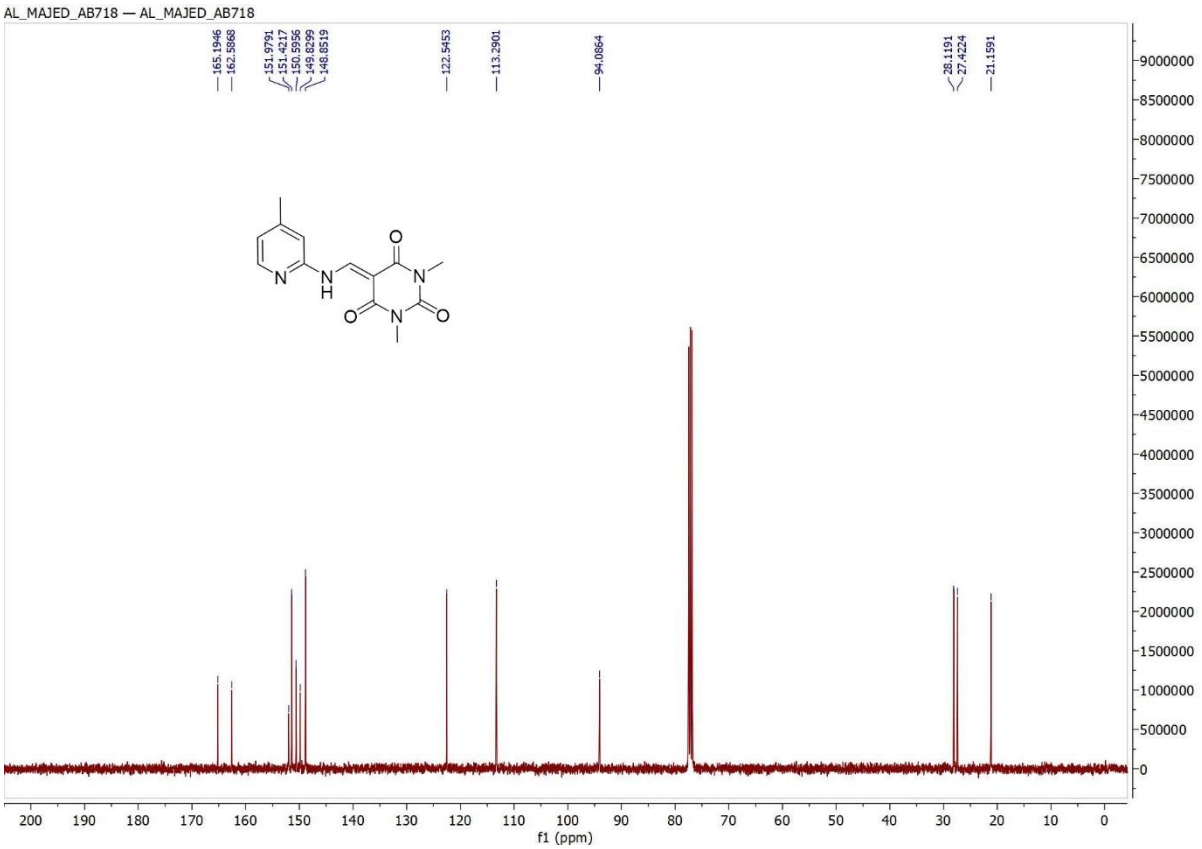

Figure S7: ^{13}CNMR ($CDCl_3$) **3b**

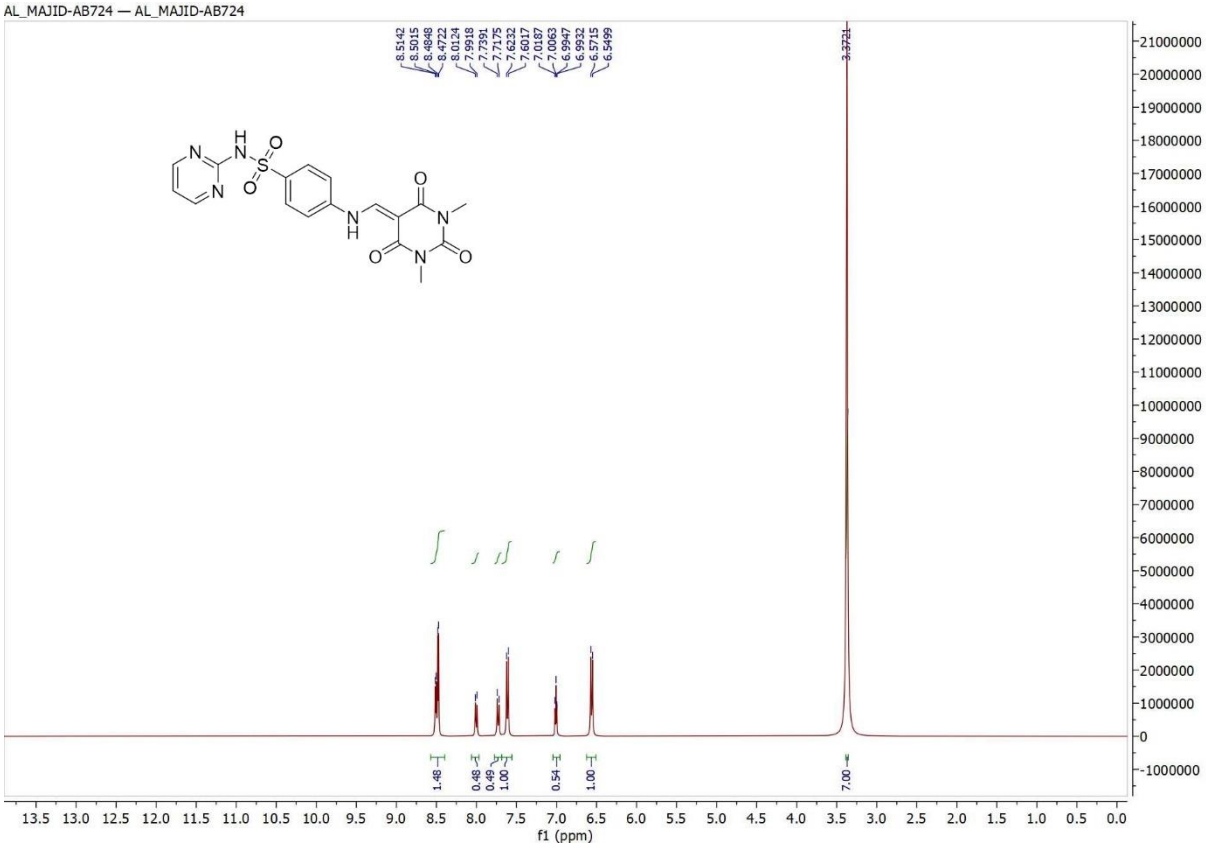

Figure S8: [1]HNMR (DMSO-d_6) **3c**

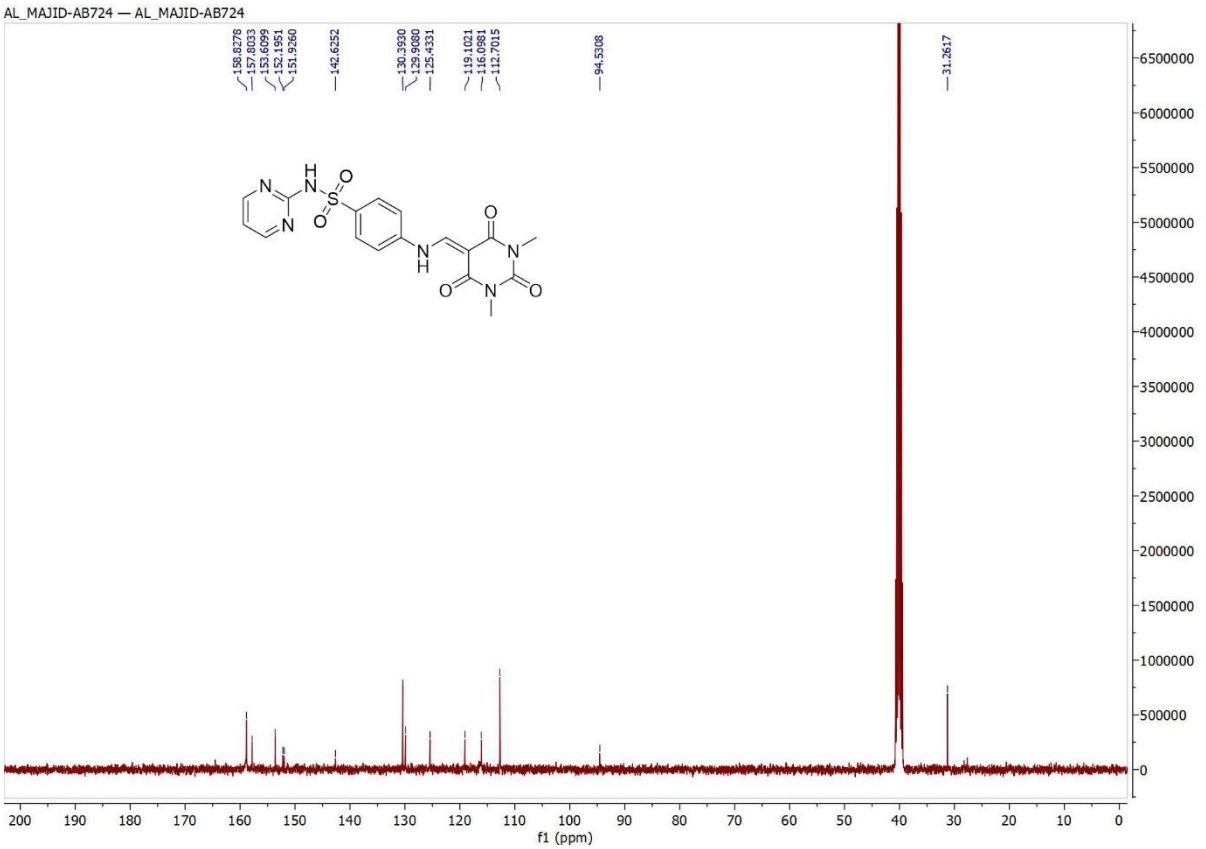

Figure S9: [13]CNMR (DMSO-d_6) **3c**

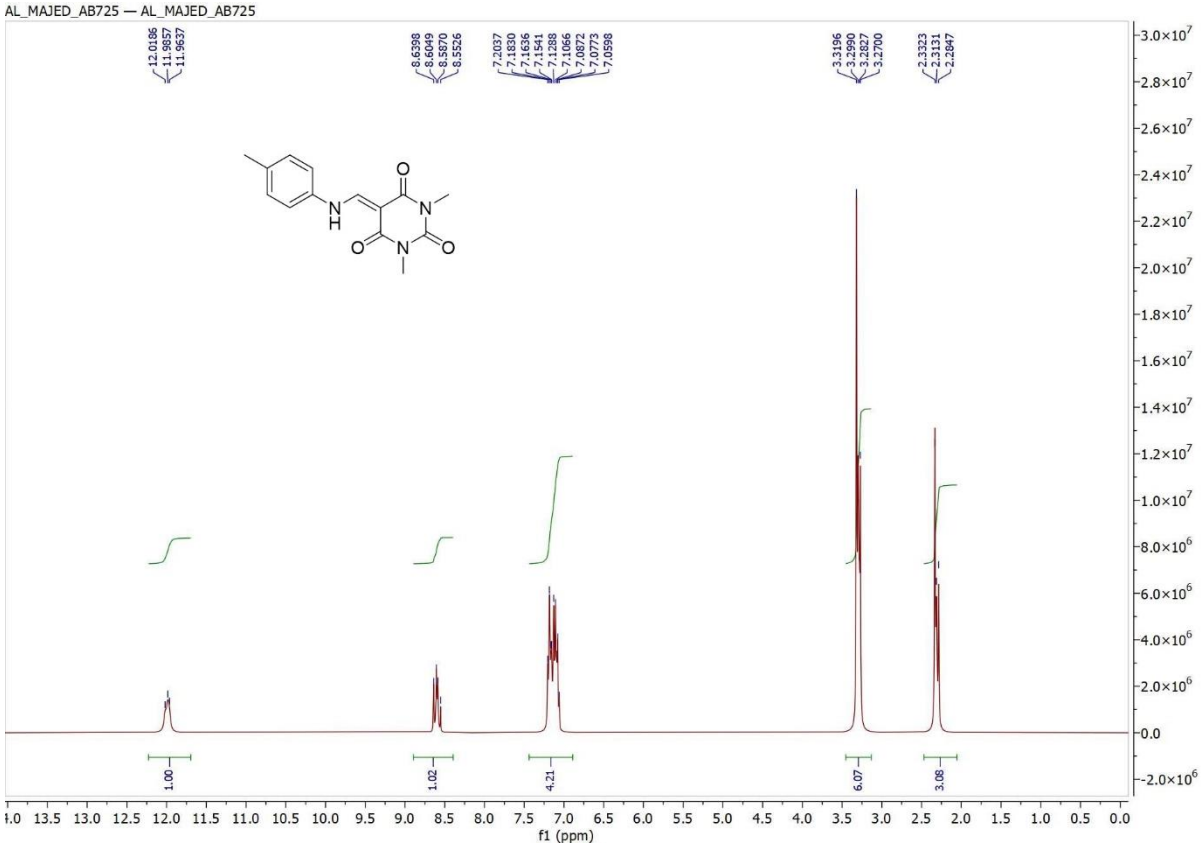

Figure S10: ^{1}HNMR ($CDCl_3$) **3d**

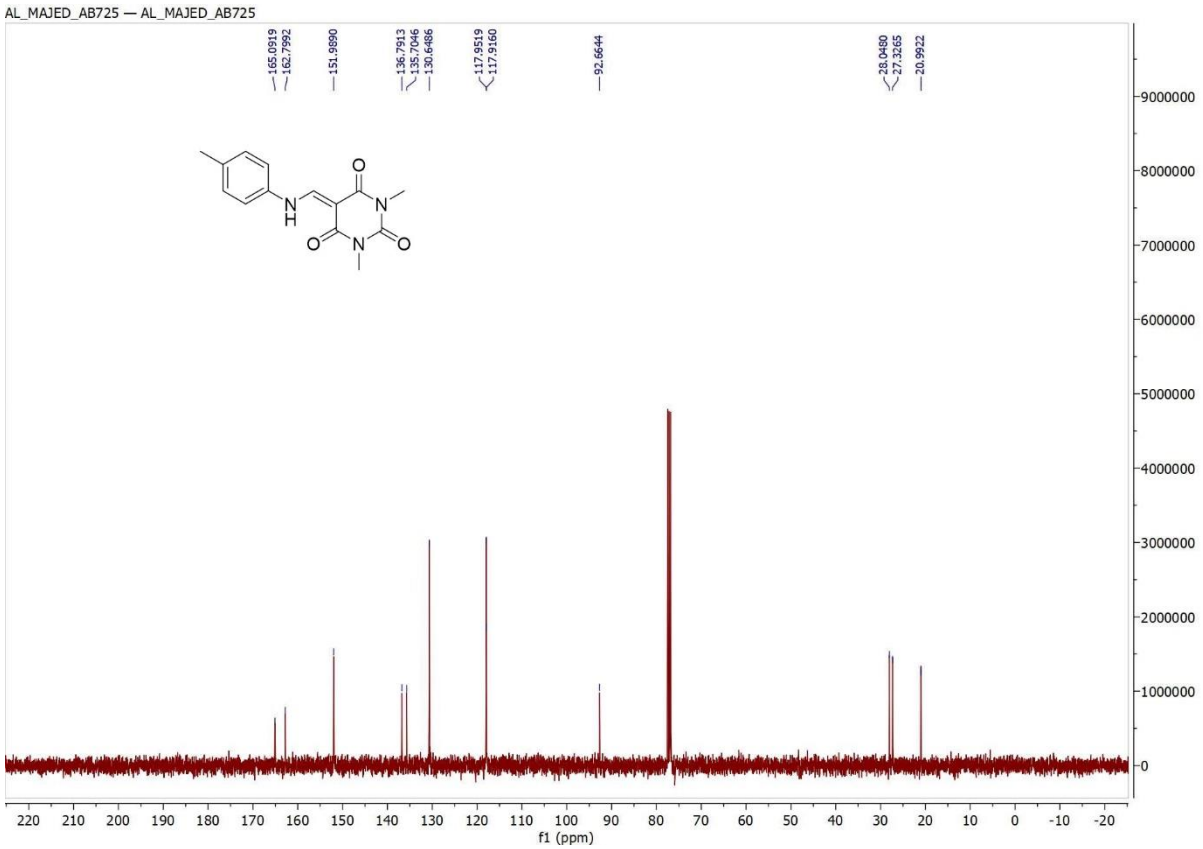

Figure S11: ^{13}CNMR ($CDCl_3$) **3d**

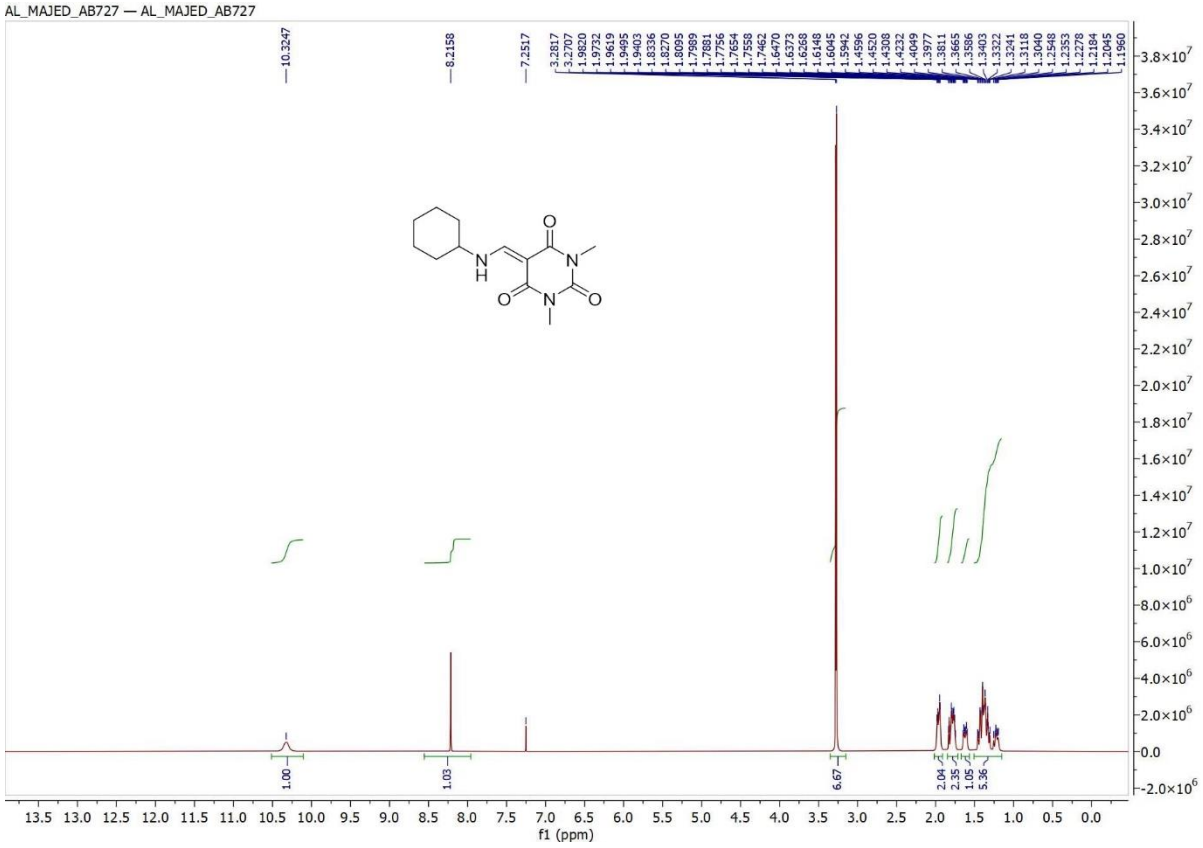

Figure S12: ^{1}HNMR ($CDCl_3$) **3e**

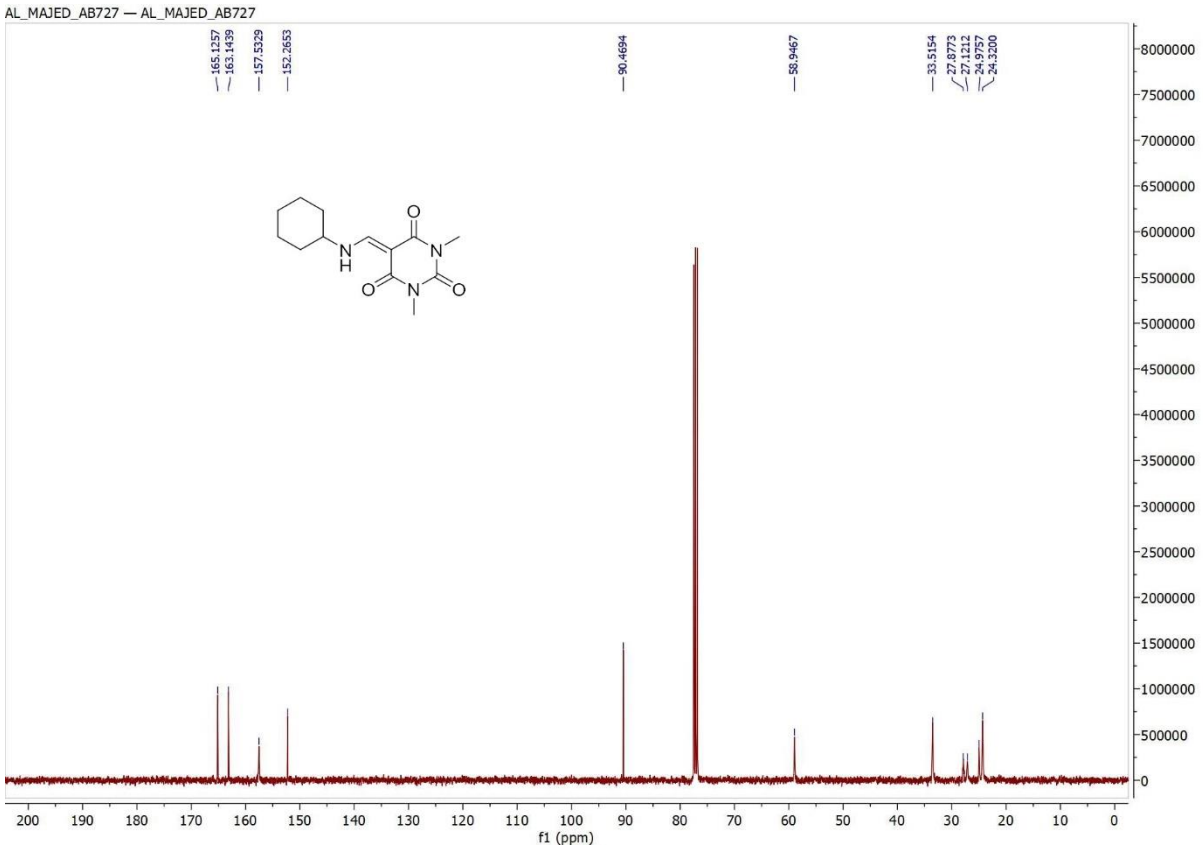

Figure S13: ^{13}CNMR ($CDCl_3$) **3e**

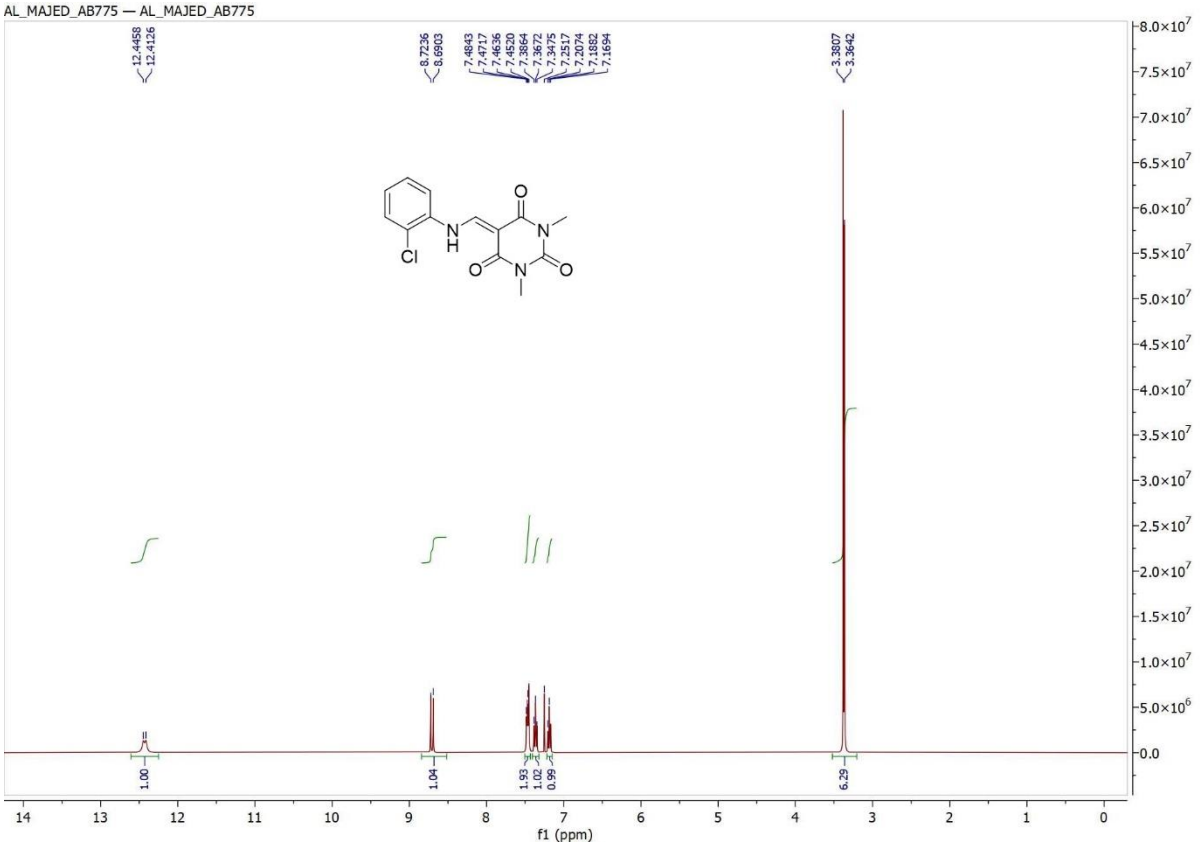

Figure S14: ^{1}HNMR ($CDCl_3$) **3f**

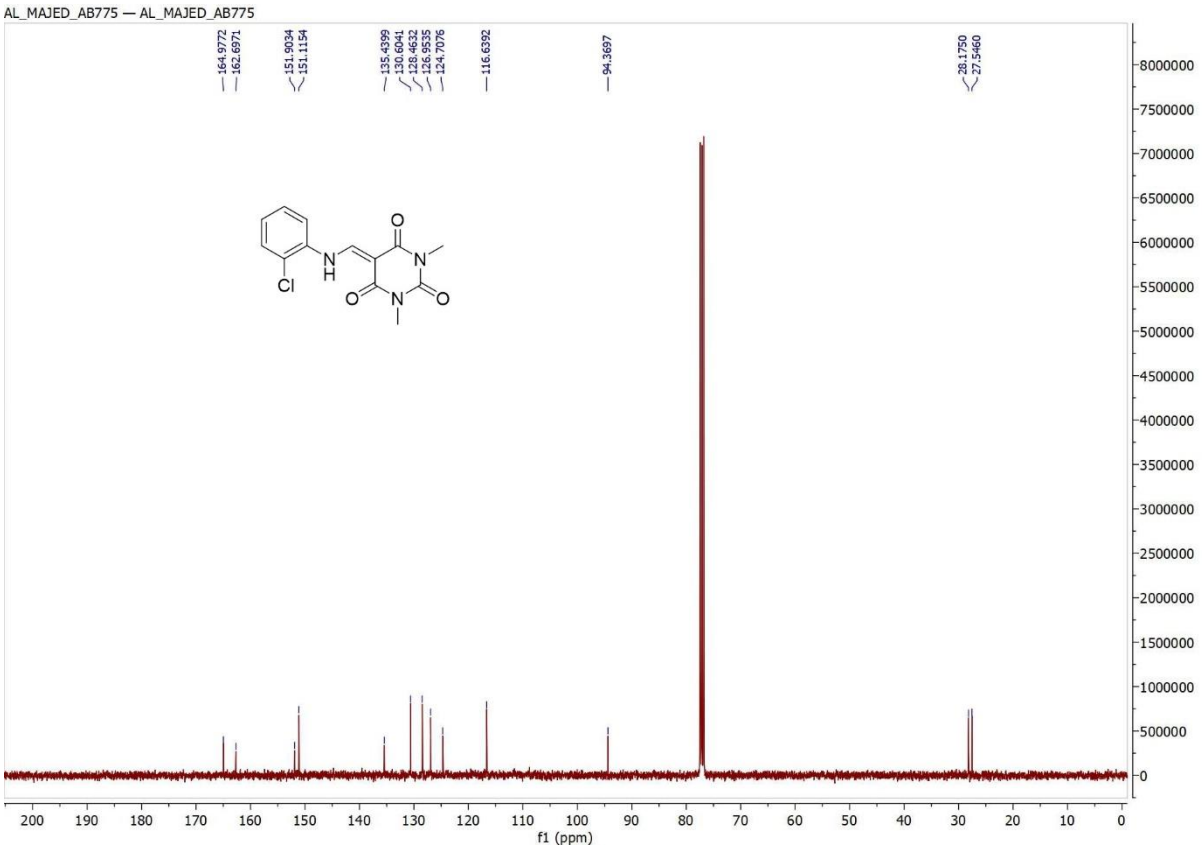

Figure S15: ^{13}CNMR ($CDCl_3$) **3f**

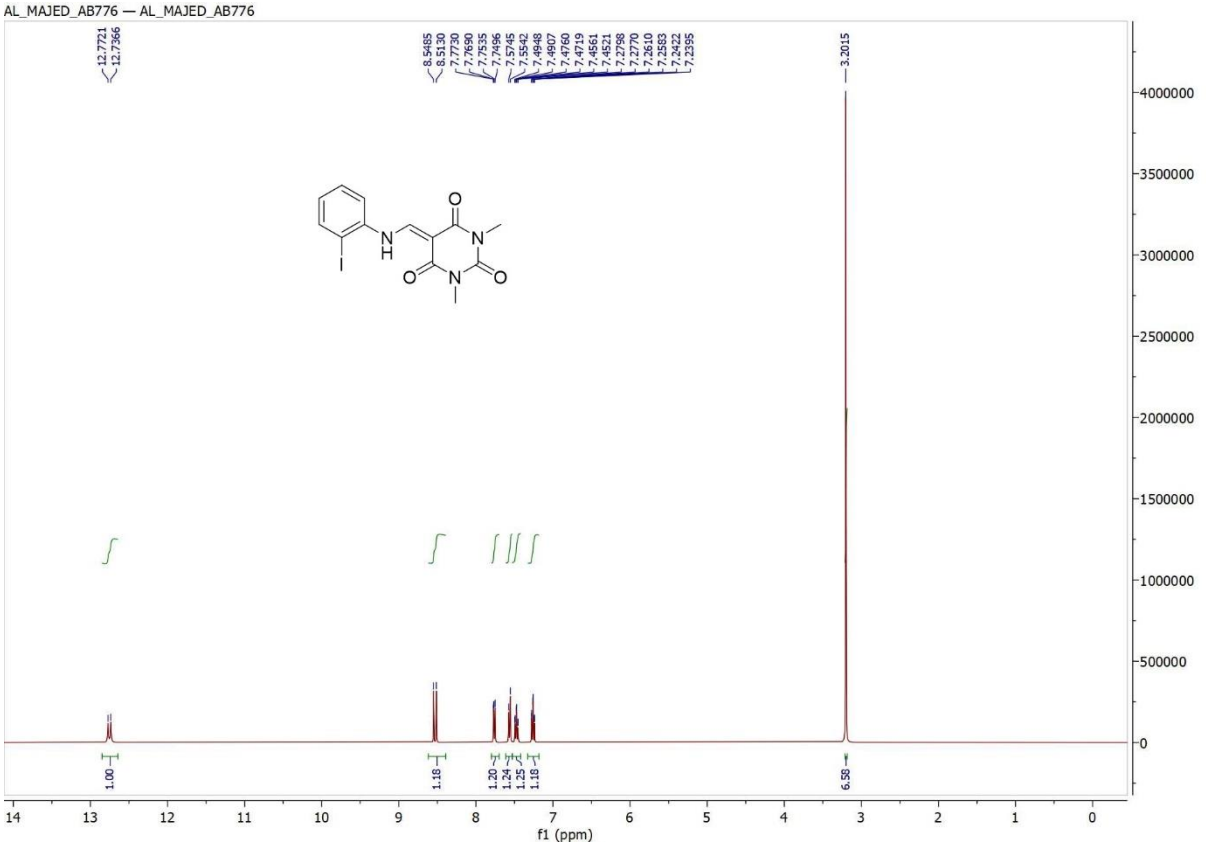

Figure S16: [1]HNMR (DMSO-d_6) **3g**

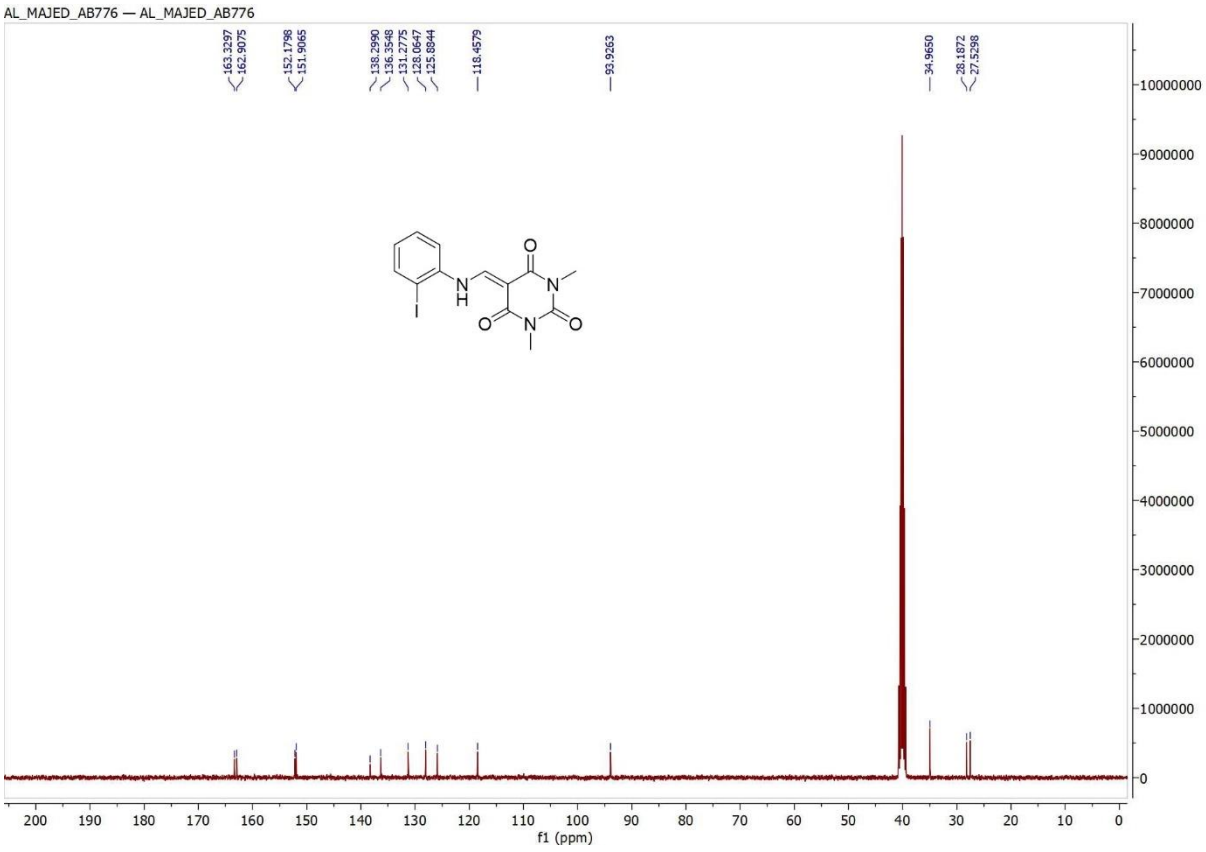

Figure S17: [13]CNMR (DMSO-d_6) **3g**

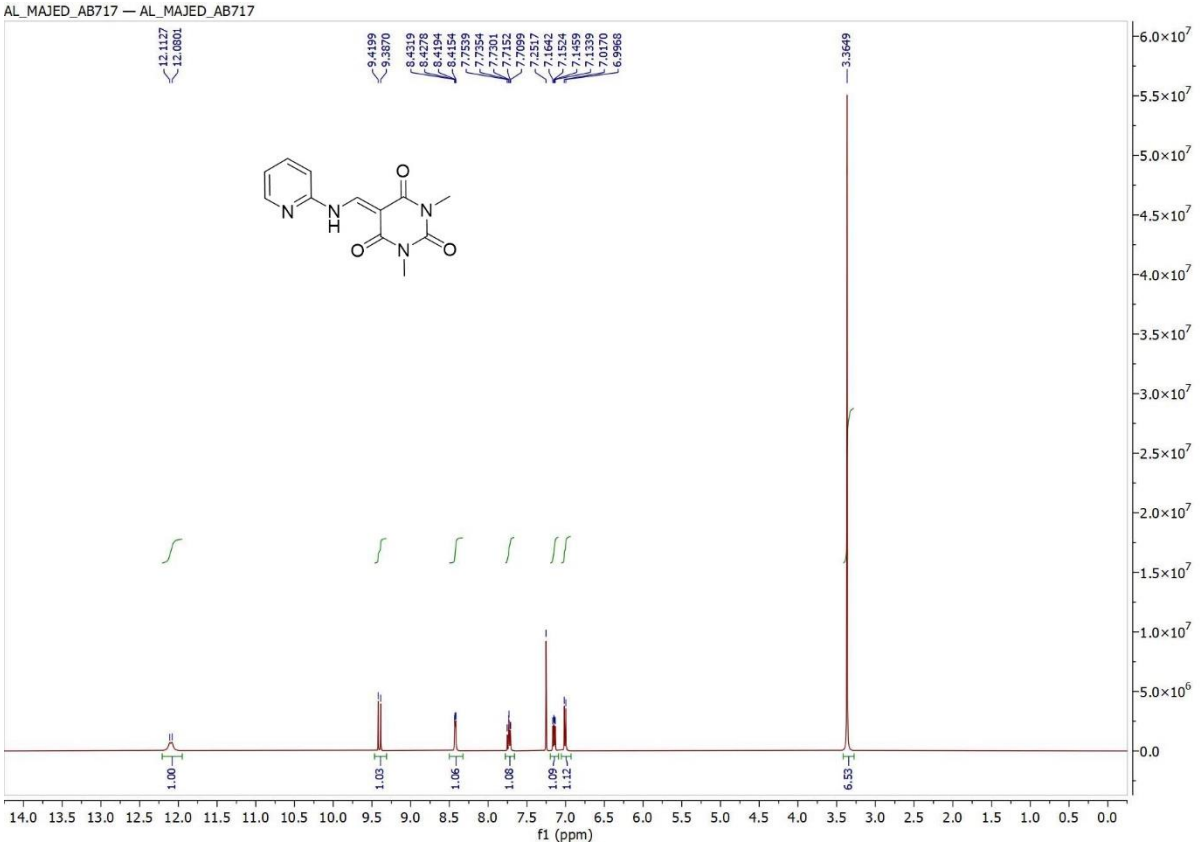

Figure S18: ^{1}HNMR ($CDCl_3$) **3h**

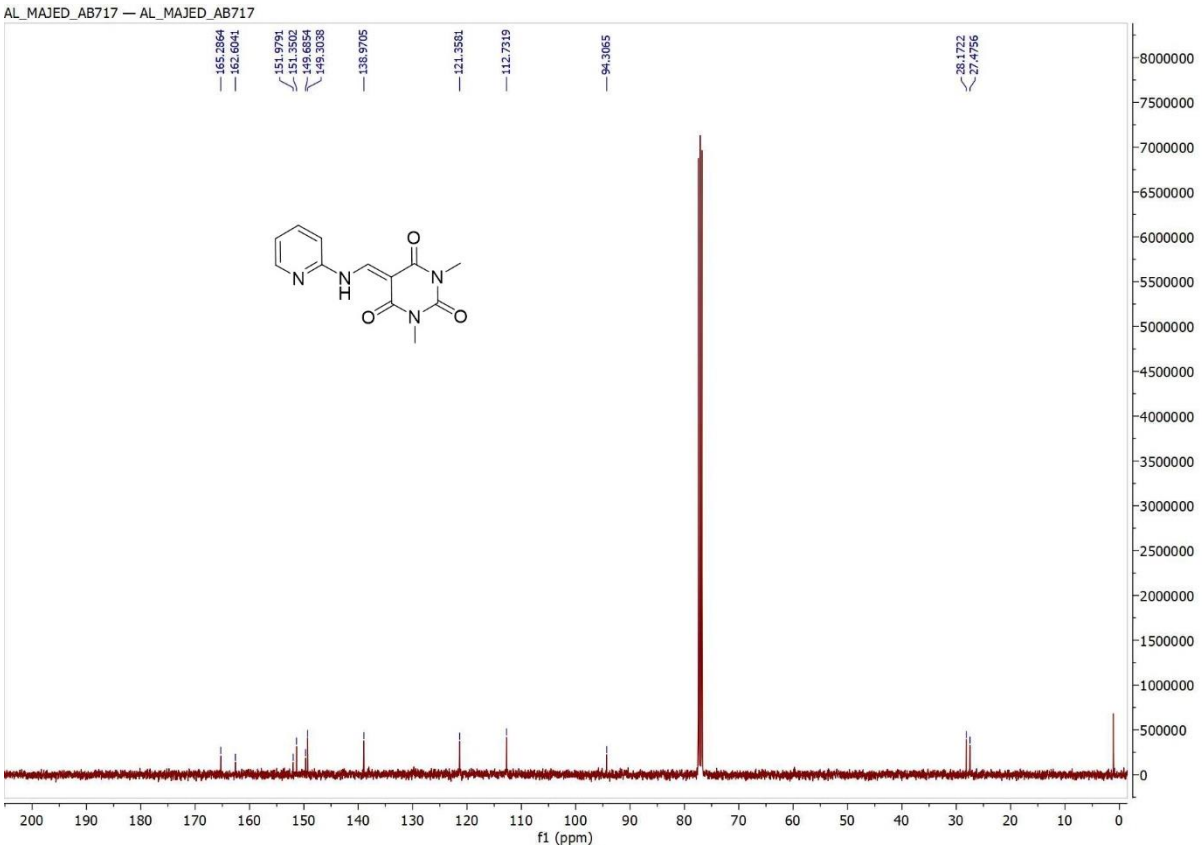

Figure S19: ^{13}CNMR ($CDCl_3$) **3h**

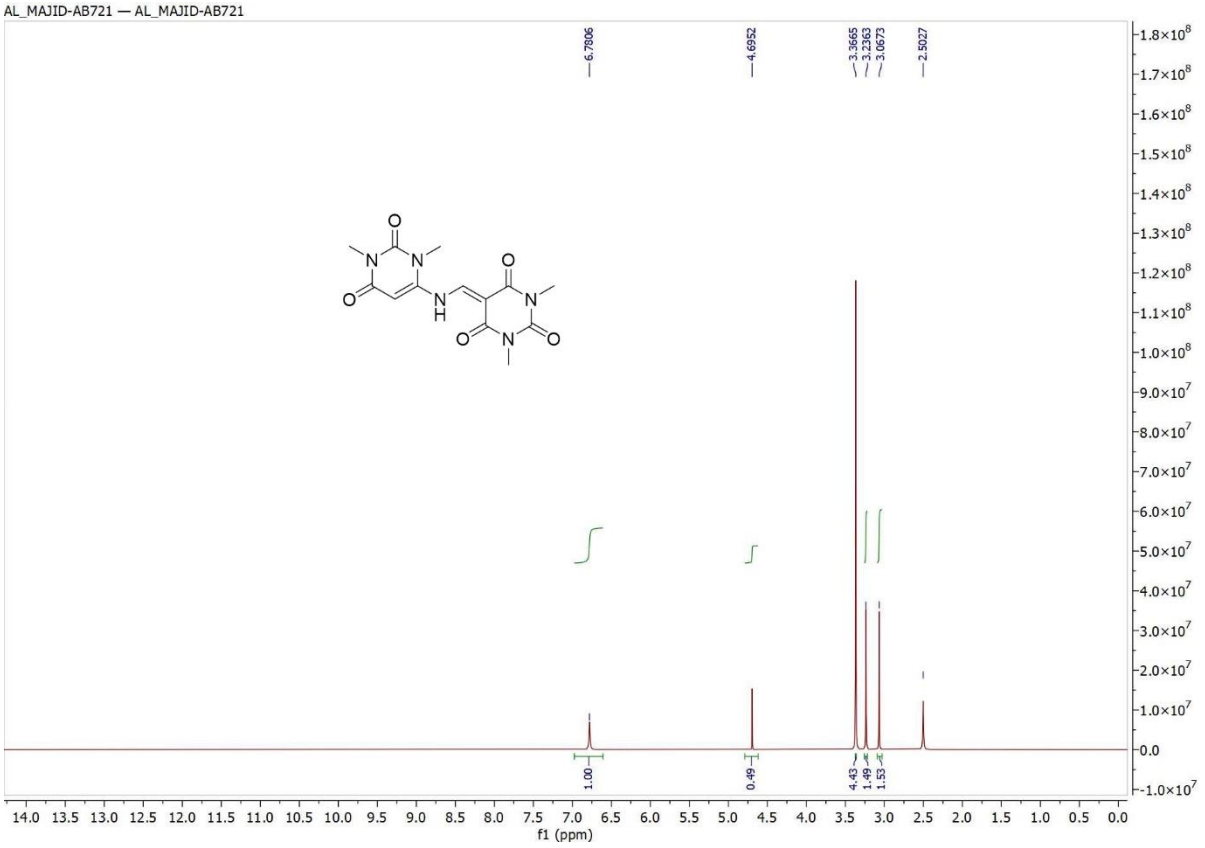

Figure S20: ^{1}HNMR (DMSO-d_6) **3i**

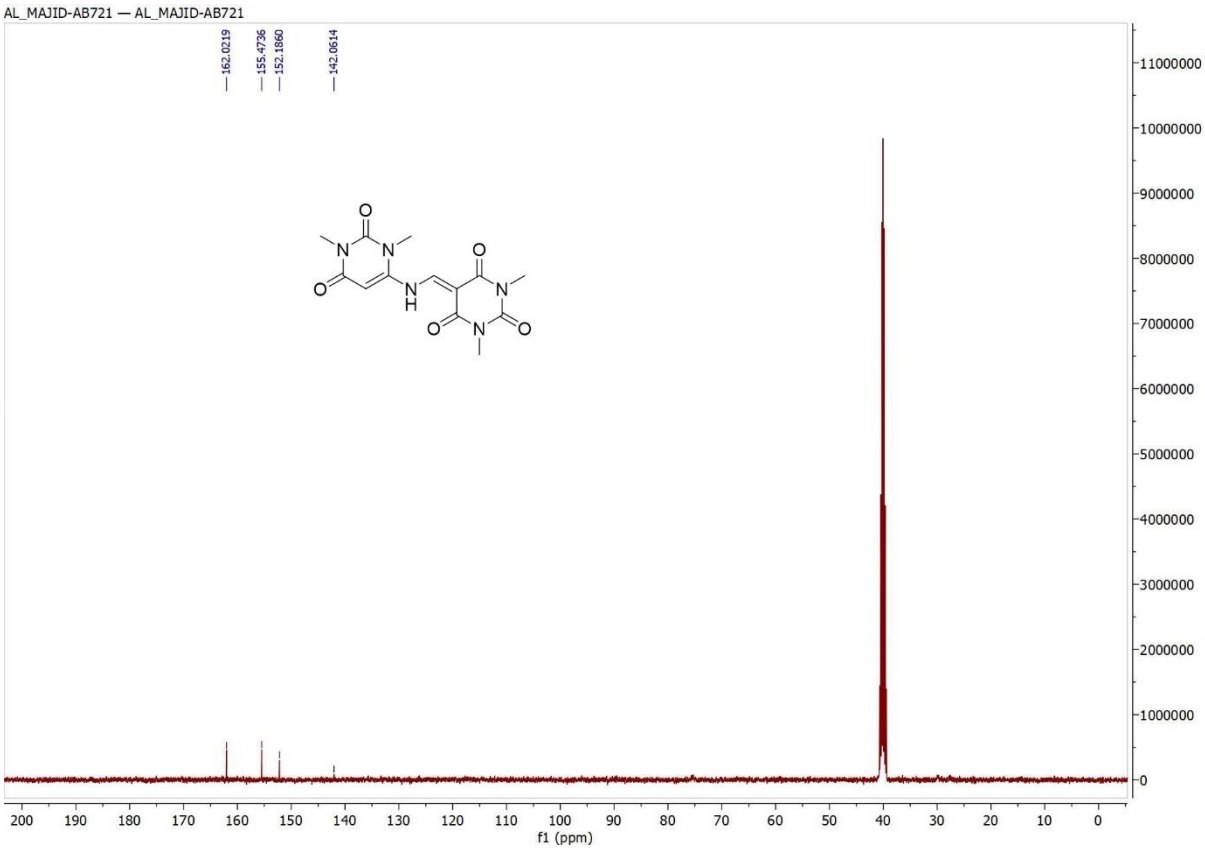

Figure S21: ^{13}CNMR (DMSO-d_6) **3i**