# Synthesis and characterizations of novel isatin-*s*-triazine hydrazone derivatives; X-ray structure, Hirshfeld analysis and DFT calculations

Hessa H. Al-Rasheed [1], Sarah, A. AL-khamis, Assem Barakat [1,] Ayman El-Faham [2,]*, Matti Haukka[3], Saied M. Soliman[2]*

[1] Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia

[2] Department of Chemistry, Faculty of Science, Alexandria University, P.O. Box 426, Ibrahimia, Alexandria 21321, Egypt

3Department of Chemistry, University of Jyväskylä, P.O. Box 35, FI-40014 Jyväskylä, Finland

*****Correspondence: ayman.elfaham@alexu.edu.eg (A.E-F) and saeed.soliman@alexu.edu.eg (S.M.S.).

**Method S1**

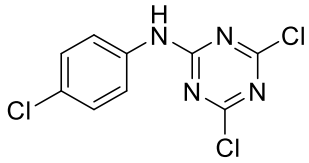
The solvents used were of analytical reagent grade. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a JEOL 500 MHz spectrometer at room temperature. The chemical shifts were measured using internal standard δ= 0 ppm (TMS). Elemental analyses were

performed on Perkin-Elmer 2400 elemental analyzer. Melting points were recorded on a Mel-Temp apparatus in an open capillary and are uncorrected. Fourier transform infrared spectroscopy (FTIR) spectra were recorded on Nicolet 560 spectrophotometer from KBr discs. The reaction was followed-up and checks for the purity were detected using TLC on silica gel-protected aluminum sheets (Type 60 GF254, Merck).

**Method S2**

*Synthesis of 4,6-Dichloro-N-(4-chlorophenyl)-1,3,5-triazin-2-amine,* ***2***

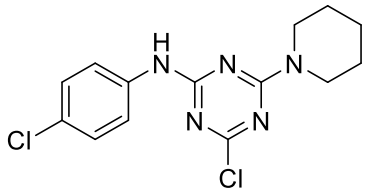
The target product was prepared following the reported method [22].



The desired product **2** was collected *via* filtration as brown solid in 95% yield, m.p. 191-194 $^{o}$C using the reported method[21]; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (s, 1H, NH), 7.49 (d, $J$ = 8.8 Hz, 2H, H-2, H-6), 7.39 – 7.27 (d, $J$ = 8.8 Hz, 2H, H-3, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 122.8, 129.5, 131.3, 134.4, 164.2, 170.5,171.6.

*Synthesis of 4-Chloro-N-(4-chlorophenyl)-6-(piperidin-1-yl)-1,3,5-triazin-2-amine,* ***3***

The target product was prepared following the reported method [22].



The target compound **3** was obtained as a white solid in 94% yield; m.p. 189-193 °C using the reported method [21]; $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.15 (s, 1H, NH), 7.66 (d, $J$ = 8.4 Hz, 2H, H-2, H-6), 7.37 (d, $J$ = 9.2 Hz, 2H, H-3, H-5), 3.72 (dt, $J$ = 14.8, 5.2 Hz, 4H, 2$NCH_2$-), 1.62 (q, $J$ = 5.7, 5.3 Hz, 2H, -$CH_2$-), 1.55 – 1.45 (m, 4H, 2-$CH_2$-); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 24, 25.8, 44.8, 122.2, 127.2, 129.1, 164.1 , 169.

*Synthesis of 2-hydrazino-4,6-disubstituted-1,3,5-triazine derivatives,* ***4***

2-Chloro-4,6-disubstituted-1,3,5-triazine derivatives were synthesized following the

strategies and method reported [21] to give the expected product **4** as a white solid in a high yield and purity to be used without further purification for the next step.

**Method S3**

The crystal of **6c** was immersed in cryo-oil, mounted in a loop, and measured at a temperature of 120 K. The X-ray diffraction data was collected on a Rigaku Oxford Diffraction Supernova diffractometer using Cu Kα radiation. The *CrysAlisPro* [23] software package was used for cell refinement and data reduction. A Multi-scan, absorption correction (*CrysAlisPro* [23]) was applied to the intensities before structure solution. Structure was solved by intrinsic phasing (*SHELXT* [24]) method. Structural refinement was carried out using *SHELXL* [25] software with *SHELXLE* [26] graphical user interface. The NH were located from the difference Fourier map and refined isotropically. All other hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms, with C-H = 0.95 – 0.99 Å and $U_{iso}$ = 1.2-1.5·$U_{eq}$(parent atom).

**Method S4**

The topology analyses were performed using Crystal Explorer 17.5 program [27]. All DFT calculations were performed using Gaussian 09 software package [28] utilizing B3LYP/6-31G(d,p) method. Natural bond orbital analyses were performed using NBO 3.1 program as implemented in the Gaussian 09W package [29].

**Table S1** Selected bond angles [°] for **6c**.

| Bonds | Angle | Bonds | Angle |
|---|---|---|---|
| C7-N1-C6 | 130.4917 | C13-C12-C11 | 111.0616 |
| C7-N2-C8 | 114.3415 | N5-C13-C12 | 110.8015 |

| | | | |
|---|---|---|---|
| C14-N3-C8 | 113.4716 | N4-C14-N3 | 128.6016 |
| C14-N4-C7 | 111.7716 | N4-C14-N6 | 119.0817 |
| C8-N5-C13 | 121.9315 | N3-C14-N6 | 112.3316 |
| C8-N5-C9 | 121.7516 | N7-C15-C22 | 125.6117 |
| C13-N5-C9 | 115.4315 | N7-C15-C16 | 128.0617 |
| N7-N6-C14 | 121.7716 | C22-C15-C16 | 106.3114 |
| C15-N7-N6 | 116.1016 | O1-C16-N8 | 126.4217 |
| C16-N8-C17 | 110.9915 | O1-C16-C15 | 127.0916 |
| C6-C1-C2 | 119.4119 | N8-C16-C15 | 106.4916 |
| C3-C2-C1 | 120.3619 | C18-C17-N8 | 128.6117 |
| C2-C3-C4 | 120.7417 | C18-C17-C22 | 121.6218 |
| C2-C3-Cl1 | 119.9816 | N8-C17-C22 | 109.7716 |
| C4-C3-Cl1 | 119.2816 | C17-C18-C19 | 117.9417 |
| C3-C4-C5 | 119.42 | C18-C19-C20 | 120.3018 |
| C4-C5-C6 | 120.4219 | C19-C20-C21 | 122.3319 |
| C1-C6-C5 | 119.6217 | C19-C20-Cl2 | 118.5415 |
| C1-C6-N1 | 124.6618 | C21-C20-Cl2 | 119.1315 |
| C5-C6-N1 | 115.7017 | C22-C21-C20 | 117.1217 |
| N2-C7-N4 | 126.8917 | C21-C22-C17 | 120.6817 |
| N2-C7-N1 | 119.8815 | C21-C22-C15 | 132.8916 |
| N4-C7-N1 | 113.2216 | C17-C22-C15 | 106.4316 |
| N5-C8-N2 | 117.7415 | C25-O2-C24 | 116.9014 |
| N5-C8-N3 | 117.5317 | O2-C24-C23 | 107.0016 |
| N2-C8-N3 | 124.7317 | O3-C25-O2 | 123.3918 |
| N5-C9-C10 | 110.6916 | O3-C25-C26 | 125.4519 |
| C11-C10-C9 | 111.2616 | O2-C25-C26 | 111.1616 |
| C10-C11-C12 | 109.9417 | | |

**Table S2** The calculated geometric parameters of **6c**[a].

| Parameter | Calc. | Exp. | Parameter | Calc. | Exp. |
|---|---|---|---|---|---|
| R(1-19) | 1.763 | 1.746 | A(1-19-17) | 119.8 | 120.0 |
| R(2-50) | 1.762 | 1.747 | A(1-19-20) | 119.7 | 119.3 |

| | | | | | |
|---|---|---|---|---|---|
| R(3-44) | 1.230 | 1.235 | A(2-50-48) | 118.9 | 118.6 |
| R(4-24) | 1.405 | 1.413 | A(2-50-51) | 119.0 | 119.1 |
| R(4-25) | 1.363 | 1.363 | A(3-44-13) | 126.6 | 126.4 |
| R(6-25) | 1.337 | 1.329 | A(3-44-43) | 127.9 | 127.1 |
| R(6-26) | 1.352 | 1.349 | A(44-3-11) | 95.2 | 92.1 |
| R(7-26) | 1.352 | 1.350 | A(5-4-24) | 115.6 | 113.5 |
| R(7-42) | 1.335 | 1.332 | A(5-4-25) | 113.2 | 115.6 |
| R(8-25) | 1.358 | 1.359 | A(4-5-55) | 169.4 | 175.3 |
| R(8-42) | 1.325 | 1.325 | A(24-4-25) | 131.1 | 130.5 |
| R(9-26) | 1.359 | 1.347 | A(4-24-15) | 124.4 | 124.7 |
| R(9-27) | 1.463 | 1.466 | A(4-24-22) | 116.7 | 115.7 |
| R(9-39) | 1.464 | 1.462 | A(4-25-6) | 120.9 | 119.9 |
| R(10-12) | 1.326 | 1.335 | A(4-25-8) | 113.5 | 113.2 |
| R(10-42) | 1.393 | 1.386 | A(25-6-26) | 115.1 | 114.4 |
| R(12-43) | 1.301 | 1.301 | A(6-25-8) | 125.6 | 126.9 |
| R(13-44) | 1.382 | 1.363 | A(6-26-7) | 124.5 | 124.7 |
| R(13-45) | 1.403 | 1.399 | A(6-26-9) | 117.9 | 117.8 |
| R(15-17) | 1.394 | 1.398 | A(26-7-42) | 113.8 | 113.5 |
| R(15-24) | 1.404 | 1.393 | A(7-26-9) | 117.5 | 117.5 |
| R(17-19) | 1.392 | 1.375 | A(7-42-8) | 128.0 | 128.6 |
| R(19-20) | 1.394 | 1.383 | A(7-42-10) | 113.0 | 112.3 |
| R(20-22) | 1.390 | 1.391 | A(25-8-42) | 113.0 | 111.8 |
| R(22-24) | 1.407 | 1.395 | A(8-42-10) | 119.0 | 119.1 |
| R(27-30) | 1.535 | 1.522 | A(26-9-27) | 122.7 | 121.7 |
| R(30-33) | 1.536 | 1.520 | A(26-9-39) | 122.6 | 121.9 |
| R(33-36) | 1.536 | 1.524 | A(27-9-39) | 114.7 | 115.4 |
| R(36-39) | 1.536 | 1.524 | A(9-27-28) | 108.5 | 109.5 |
| R(43-44) | 1.496 | 1.493 | A(9-27-29) | 108.2 | 109.5 |
| R(43-53) | 1.458 | 1.457 | A(9-27-30) | 110.7 | 110.7 |
| R(45-46) | 1.387 | 1.378 | A(9-39-36) | 110.5 | 110.8 |
| R(45-53) | 1.413 | 1.403 | A(9-39-40) | 108.3 | 109.5 |

| | | | | | |
|---|---|---|---|---|---|
| R(46-48) | 1.400 | 1.388 | A(9-39-41) | 108.4 | 109.5 |
| R(48-50) | 1.397 | 1.388 | A(11-10-12) | 120.1 | 119.1 |
| R(50-51) | 1.397 | 1.391 | A(11-10-42) | 117.8 | 119.1 |
| R(51-53) | 1.393 | 1.384 | A(10-11-3) | 131.8 | 137.4 |
| R(54-60) | 1.459 | 1.458 | A(12-10-42) | 122.1 | 121.8 |
| R(54-63) | 1.339 | 1.337 | A(10-12-43) | 118.0 | 116.1 |
| R(55-63) | 1.220 | 1.214 | A(12-43-44) | 127.0 | 128.1 |
| R(56-60) | 1.516 | 1.498 | A(12-43-53) | 126.0 | 125.6 |
| R(63-64) | 1.508 | 1.494 | A(14-13-44) | 122.5 | 124.5 |
| | | | A(14-13-45) | 125.8 | 124.5 |
| | | | A(44-13-45) | 111.7 | 111.0 |
| | | | A(13-44-43) | 105.5 | 106.5 |
| | | | A(13-45-46) | 129.3 | 128.6 |
| | | | A(13-45-53) | 109.1 | 109.8 |
| | | | A(16-15-17) | 120.3 | 120.3 |
| | | | A(16-15-24) | 119.5 | 120.3 |
| | | | A(17-15-24) | 120.2 | 119.4 |
| | | | A(15-17-18) | 120.0 | 119.9 |
| | | | A(15-17-19) | 120.1 | 120.4 |
| | | | A(15-24-22) | 118.9 | 119.6 |
| | | | A(18-17-19) | 120.0 | 119.8 |
| | | | A(17-19-20) | 120.5 | 120.7 |
| | | | A(19-20-21) | 120.2 | 120.3 |
| | | | A(19-20-22) | 119.5 | 119.5 |
| | | | A(21-20-22) | 120.3 | 120.3 |
| | | | A(20-22-23) | 119.9 | 119.8 |
| | | | A(20-22-24) | 120.8 | 120.4 |
| | | | A(23-22-24) | 119.3 | 119.8 |
| | | | A(28-27-29) | 107.8 | 108.1 |
| | | | A(28-27-30) | 112.1 | 109.5 |
| | | | A(29-27-30) | 109.5 | 109.5 |

| | | | |
|---|---|---|---|
| | A(27-30-31) | 109.3 | 109.4 |
| | A(27-30-32) | 108.8 | 109.4 |
| | A(27-30-33) | 110.9 | 111.3 |
| | A(31-30-32) | 107.2 | 108.0 |
| | A(31-30-33) | 110.7 | 109.4 |
| | A(32-30-33) | 109.9 | 109.3 |
| | A(30-33-34) | 110.5 | 109.7 |
| | A(30-33-35) | 109.1 | 109.6 |
| | A(30-33-36) | 110.9 | 110.0 |
| | A(34-33-35) | 106.6 | 108.2 |
| | A(34-33-36) | 110.5 | 109.7 |
| | A(35-33-36) | 109.2 | 109.7 |
| | A(33-36-37) | 110.7 | 109.4 |
| | A(33-36-38) | 109.8 | 109.4 |
| | A(33-36-39) | 111.4 | 111.1 |
| | A(37-36-38) | 107.1 | 108.0 |
| | A(37-36-39) | 109.1 | 109.4 |
| | A(38-36-39) | 108.7 | 109.4 |
| | A(36-39-40) | 109.7 | 109.5 |
| | A(36-39-41) | 111.8 | 109.5 |
| | A(40-39-41) | 108.1 | 108.0 |
| | A(44-43-53) | 107.0 | 106.3 |
| | A(43-53-45) | 106.8 | 106.4 |
| | A(43-53-51) | 132.9 | 132.9 |
| | A(46-45-53) | 121.6 | 121.6 |
| | A(45-46-47) | 121.6 | 121.0 |
| | A(45-46-48) | 118.0 | 118.0 |
| | A(45-53-51) | 120.4 | 120.7 |
| | A(47-46-48) | 120.4 | 121.0 |
| | A(46-48-49) | 120.1 | 119.9 |
| | A(46-48-50) | 120.2 | 120.3 |

| | | | |
|---|---|---|---|
| | A(49-48-50) | 119.7 | 119.8 |
| | A(48-50-51) | 122.1 | 122.3 |
| | A(50-51-52) | 121.2 | 121.4 |
| | A(50-51-53) | 117.7 | 117.2 |
| | A(52-51-53) | 121.2 | 121.4 |
| | A(60-54-63) | 116.9 | 116.9 |
| | A(54-60-56) | 107.5 | 107.0 |
| | A(54-60-61) | 108.1 | 110.3 |
| | A(54-60-62) | 107.7 | 110.3 |
| | A(54-63-55) | 124.0 | 123.4 |
| | A(54-63-64) | 111.8 | 111.2 |
| | A(55-63-64) | 124.1 | 125.4 |
| | A(63-55-5) | 135.8 | 121.2 |
| | A(57-56-58) | 108.3 | 109.5 |
| | A(57-56-59) | 108.5 | 109.5 |
| | A(57-56-60) | 111.3 | 109.5 |
| | A(58-56-59) | 108.1 | 109.5 |
| | A(58-56-60) | 109.4 | 109.5 |
| | A(59-56-60) | 111.2 | 109.4 |
| | A(56-60-61) | 112.0 | 110.3 |
| | A(56-60-62) | 112.6 | 110.3 |
| | A(61-60-62) | 108.8 | 108.5 |
| | A(63-64-65) | 108.7 | 109.5 |
| | A(63-64-66) | 109.5 | 109.5 |
| | A(63-64-67) | 111.3 | 109.5 |
| | A(65-64-66) | 108.4 | 109.5 |
| | A(65-64-67) | 107.9 | 109.5 |
| | A(66-64-67) | 110.9 | 109.5 |

[a]Atom numbering refer to **Fig. 8**

**Table S3** The calculated natural charges of **6c**[a].

| Atom | Charge | Atom | Charge |
|---|---|---|---|
| Cl 1 | -0.0194 | H35 | 0.2292 |
| Cl 2 | -0.0115 | C36 | -0.4770 |
| O 3 | -0.6137 | H37 | 0.2467 |
| N 4 | -0.5995 | H38 | 0.2375 |
| H 5 | 0.4610 | C39 | -0.2677 |
| N 6 | -0.6331 | H40 | 0.2245 |
| N 7 | -0.6206 | H41 | 0.2769 |
| N 8 | -0.6084 | C42 | 0.6201 |
| N 9 | -0.4342 | C43 | 0.0655 |
| N10 | -0.3829 | C44 | 0.6400 |
| H11 | 0.4458 | C45 | 0.1700 |
| N12 | -0.1597 | C46 | -0.2633 |
| N13 | -0.6235 | H47 | 0.2495 |
| H14 | 0.4450 | C48 | -0.2373 |
| C15 | -0.2508 | H49 | 0.2596 |
| H16 | 0.2639 | C50 | -0.0580 |
| C17 | -0.2437 | C51 | -0.2215 |
| H18 | 0.2532 | H52 | 0.2739 |
| C19 | -0.0599 | C53 | -0.0906 |
| C20 | -0.2448 | O54 | -0.5538 |
| H21 | 0.2553 | O55 | -0.6515 |
| C22 | -0.2487 | C56 | -0.7118 |
| H23 | 0.2603 | H57 | 0.2394 |
| C24 | 0.1582 | H58 | 0.2444 |
| C25 | 0.6465 | H59 | 0.2418 |
| C26 | 0.6497 | C60 | -0.1306 |
| C27 | -0.2649 | H61 | 0.2248 |
| H28 | 0.2701 | H62 | 0.2554 |
| H29 | 0.2258 | C63 | 0.8603 |
| C30 | -0.4770 | C64 | -0.7867 |

| | | | |
|---|---|---|---|
| H31 | 0.2464 | H65 | 0.2688 |
| H32 | 0.2374 | H66 | 0.2616 |
| C33 | -0.4716 | H67 | 0.2627 |
| H34 | 0.2465 | H35 | 0.2292 |

[a]Atom numbering refer to **Fig. 8**

**Figure S1 $^{1}$H and $^{13}$C-NMR Compound 2**

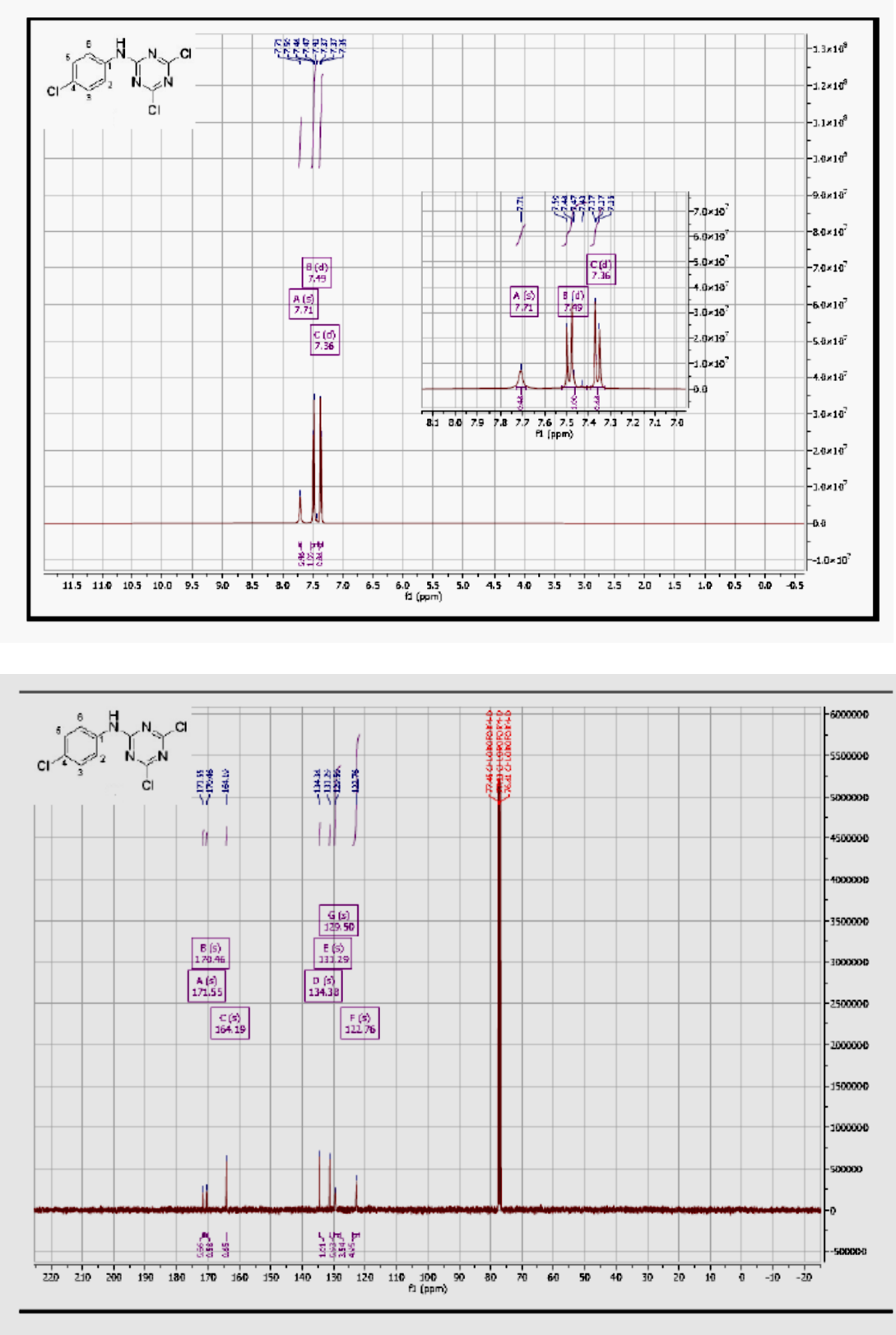
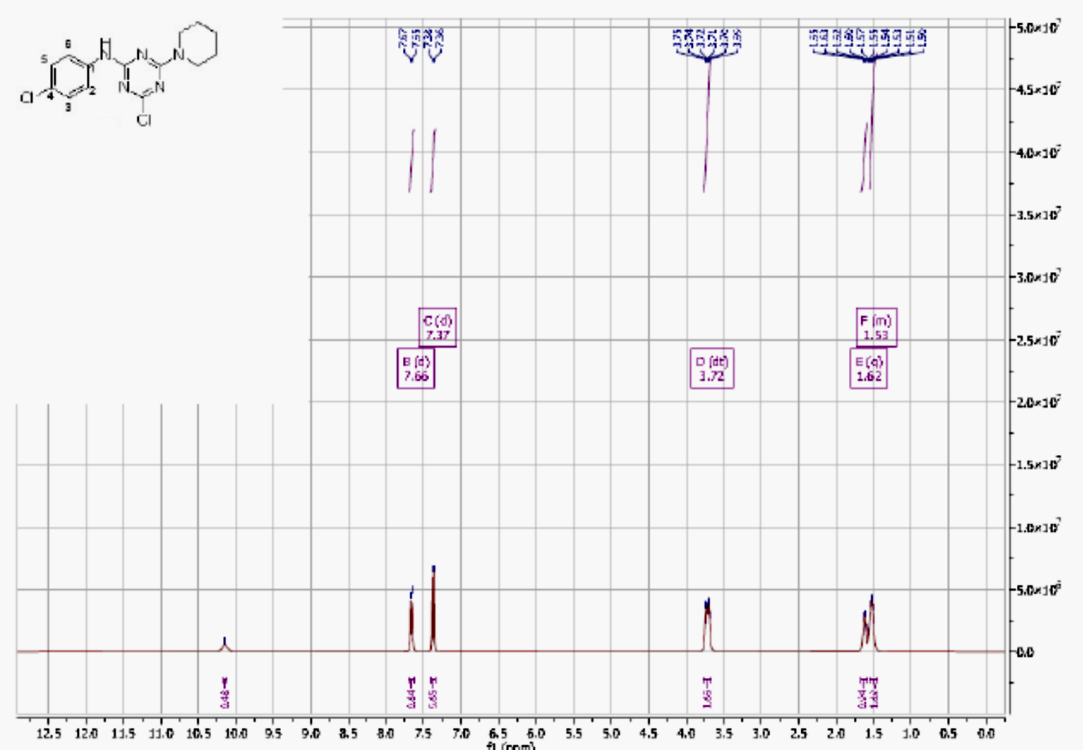



**Figure S2 $^{1}$H and $^{13}$C-NMR Compound 3**



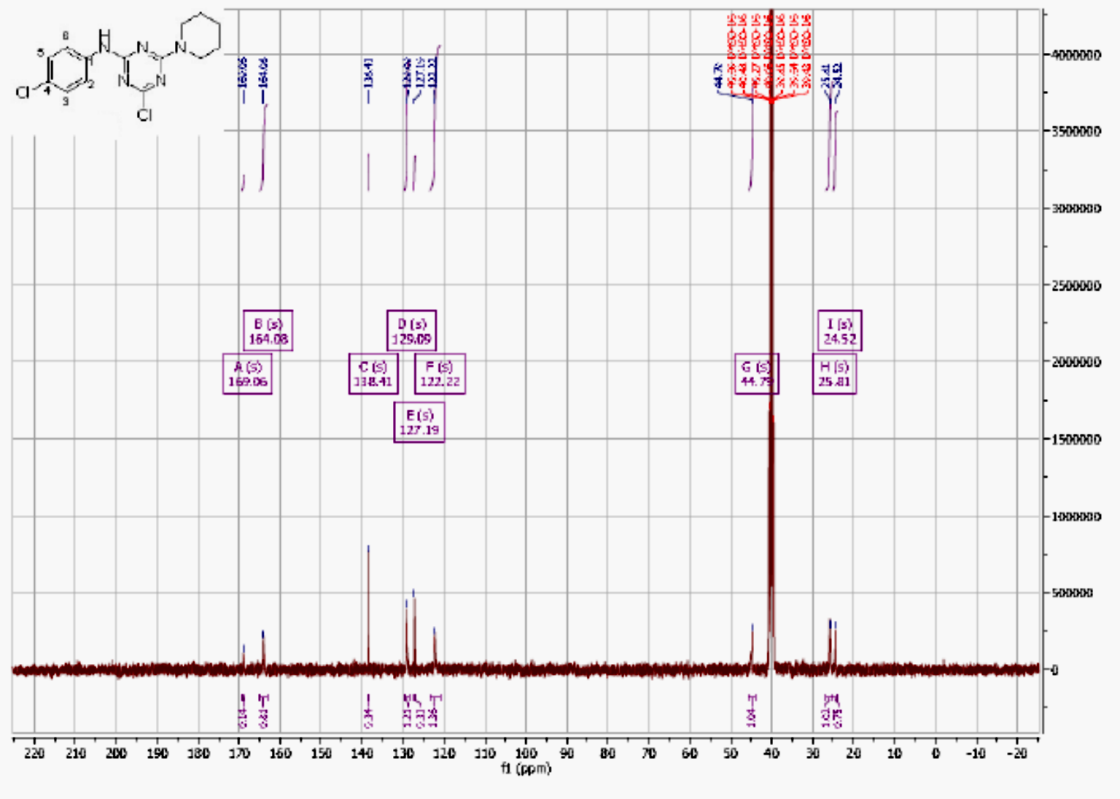
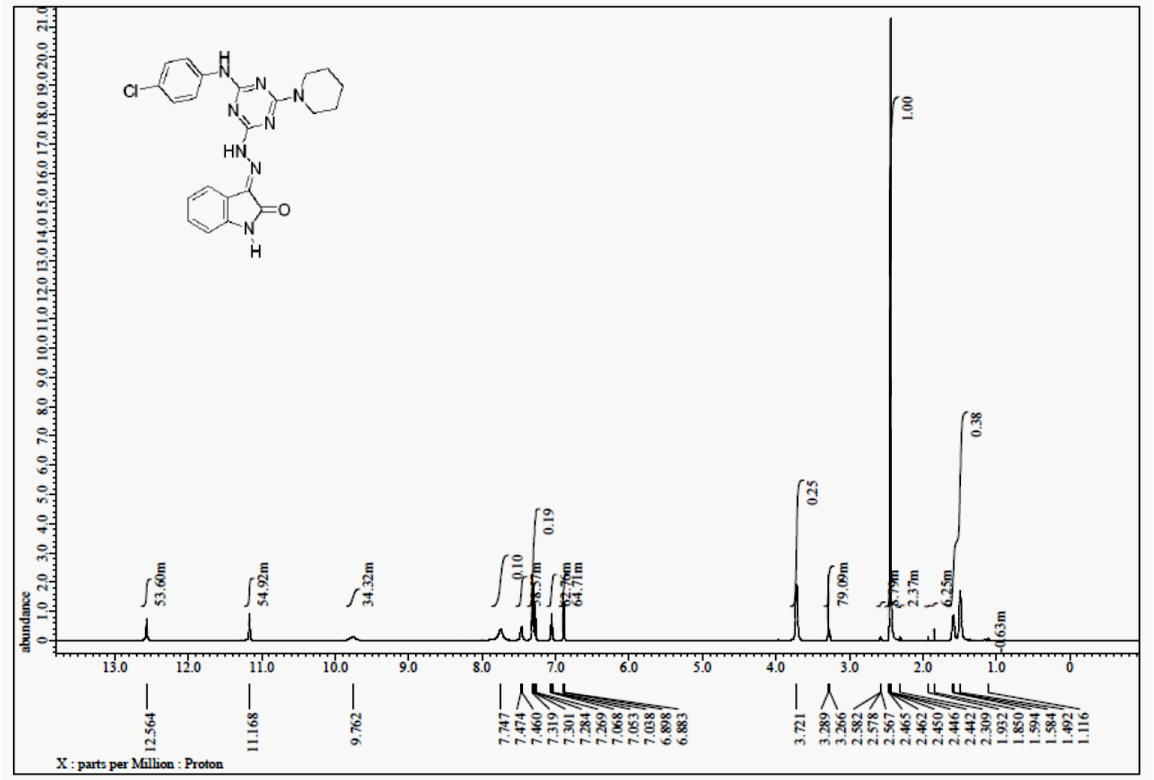




**Figure S3 $^{1}$H and $^{13}$C-NMR Compound 6a**



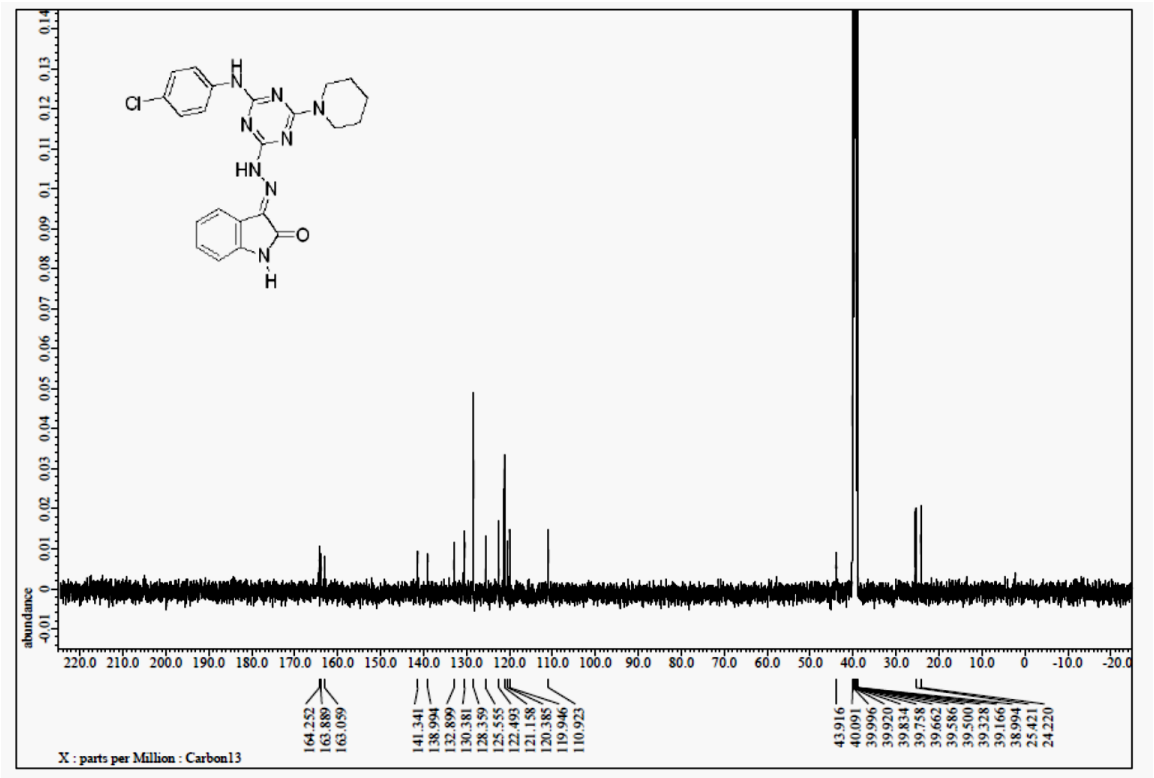
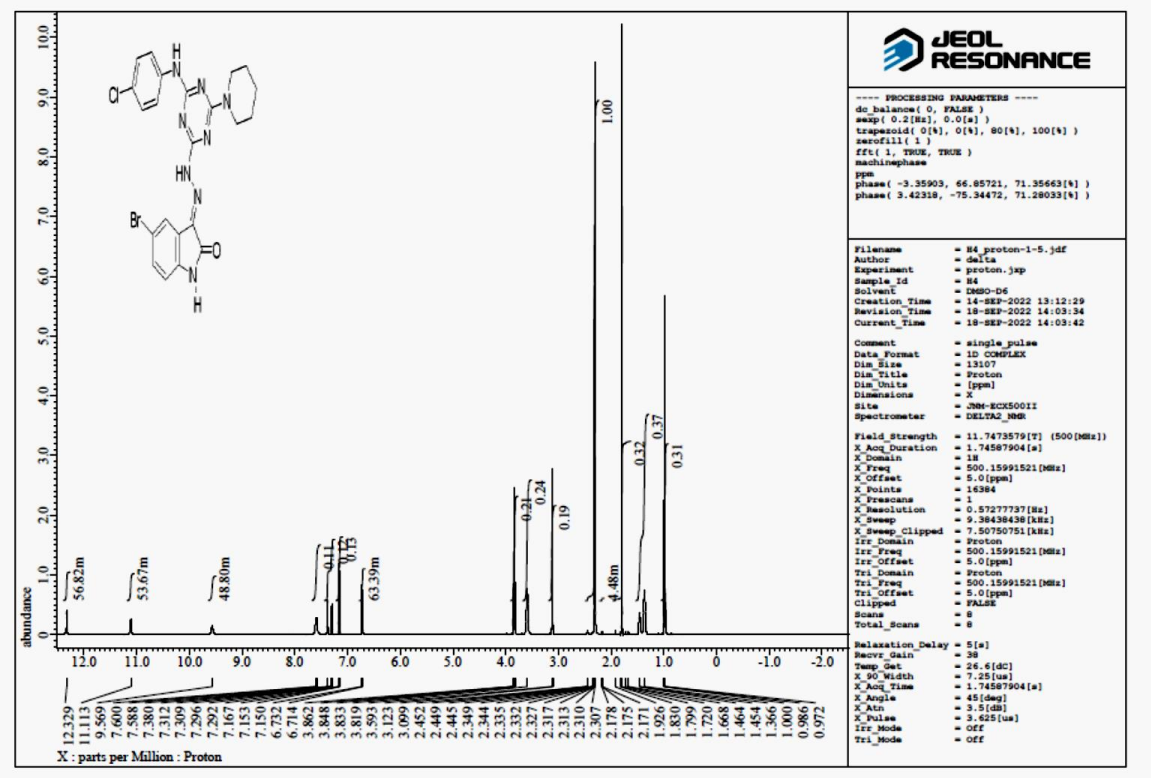




**Figure S4 $^{1}$H and $^{13}$C-NMR Compound 6b**



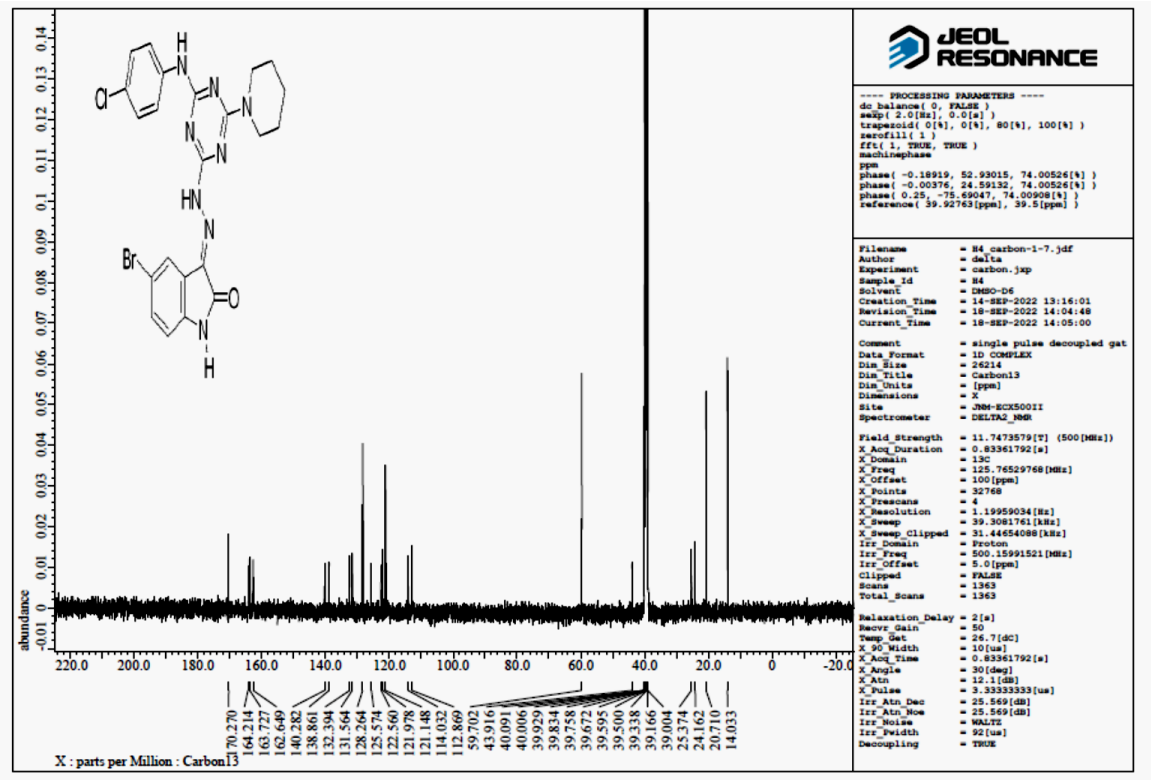
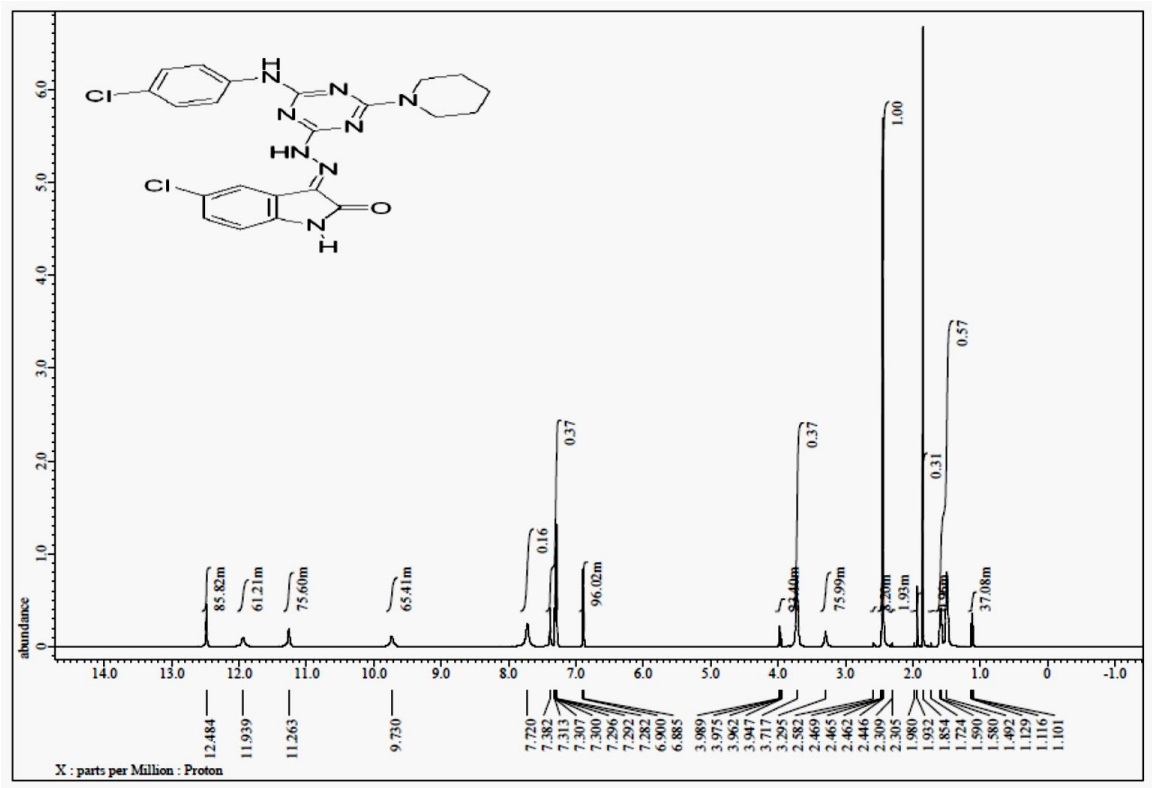




**Figure S5 $^{1}$H and $^{13}$C-NMR Compound 6c**



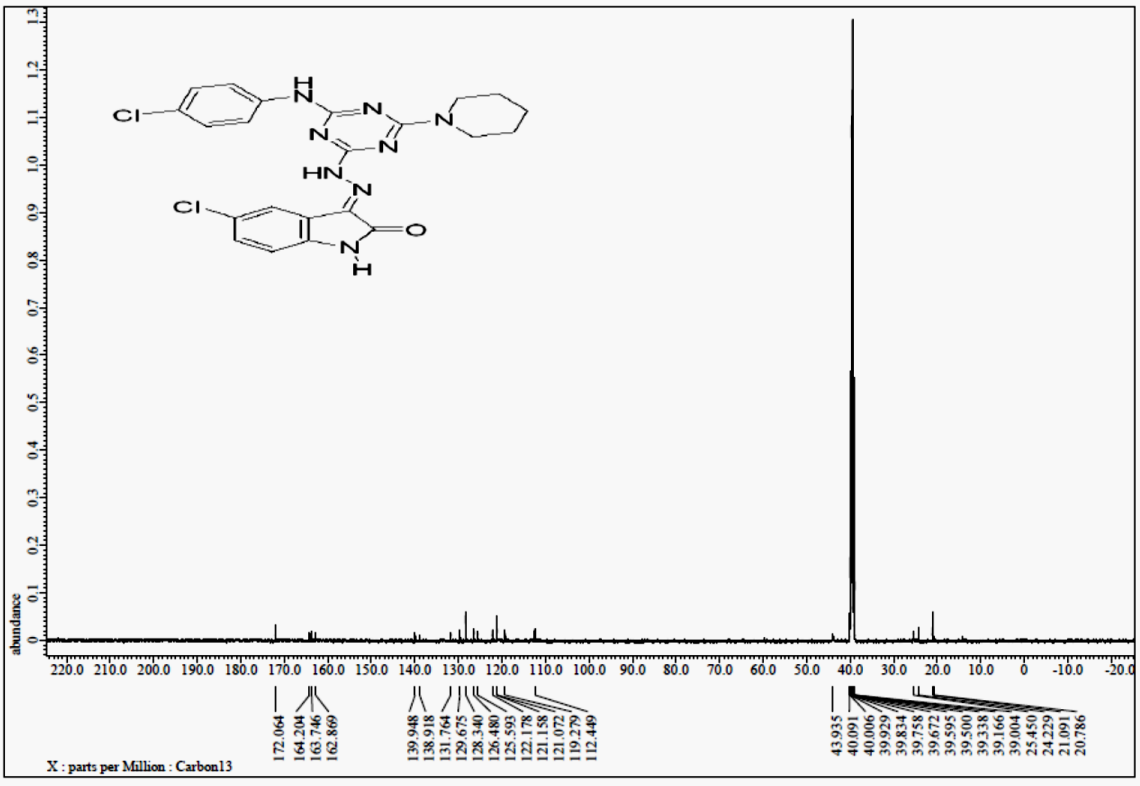
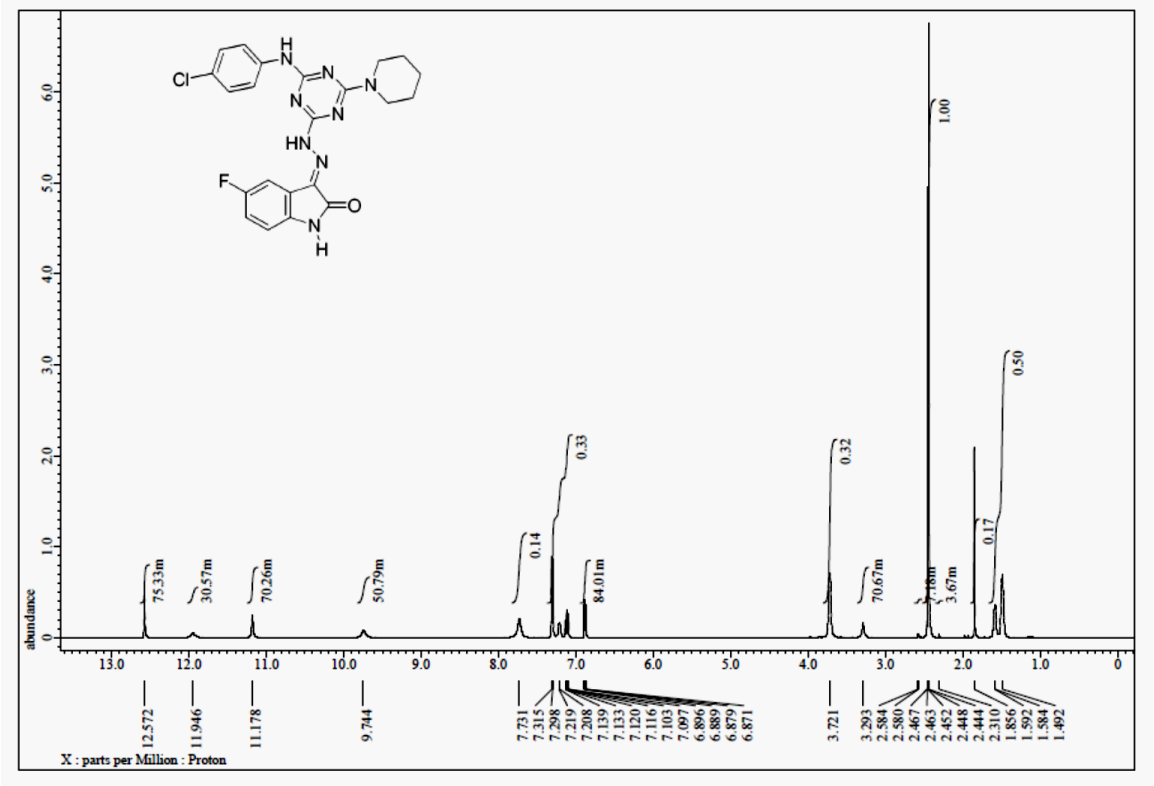




**Figure S6 $^{1}$H and $^{13}$C-NMR Compound 6d**



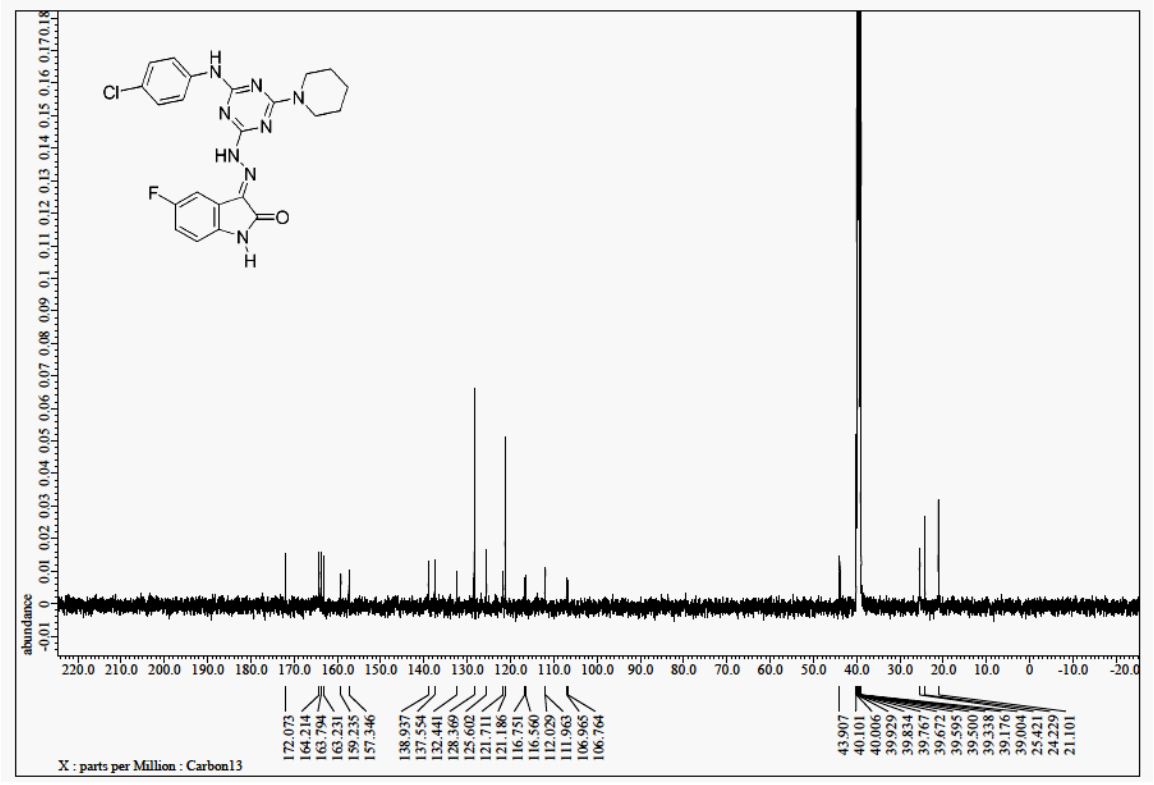
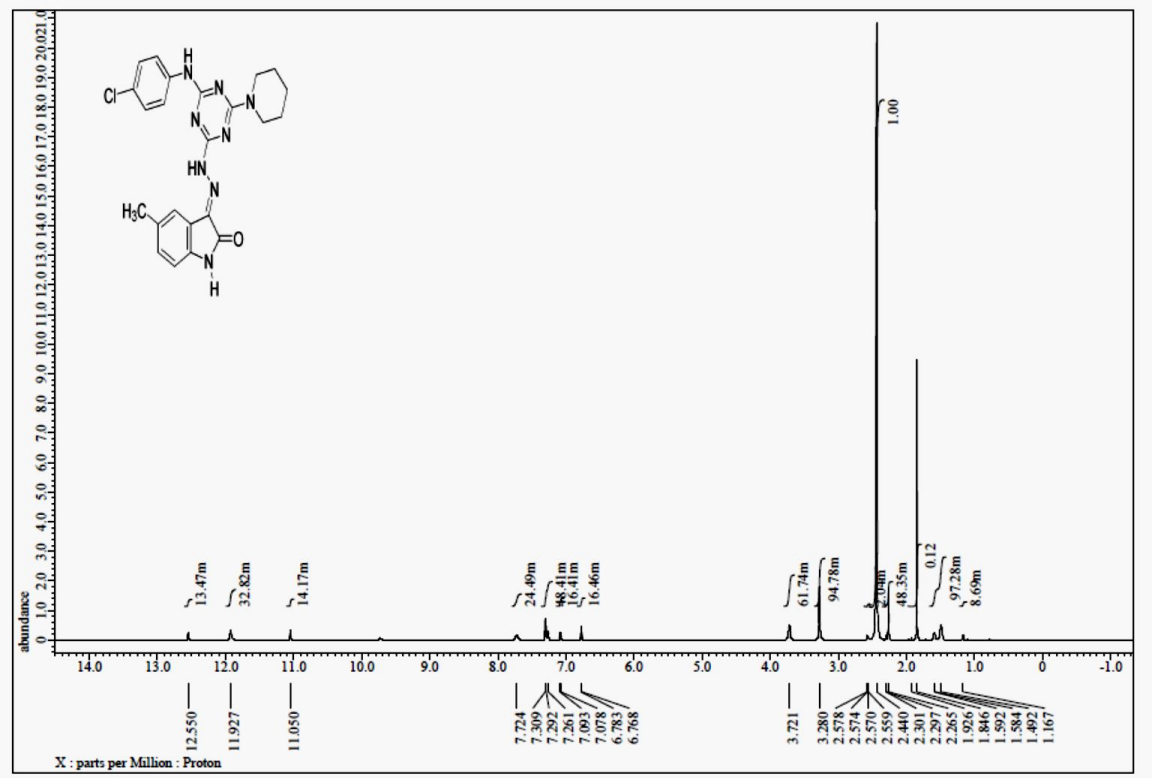
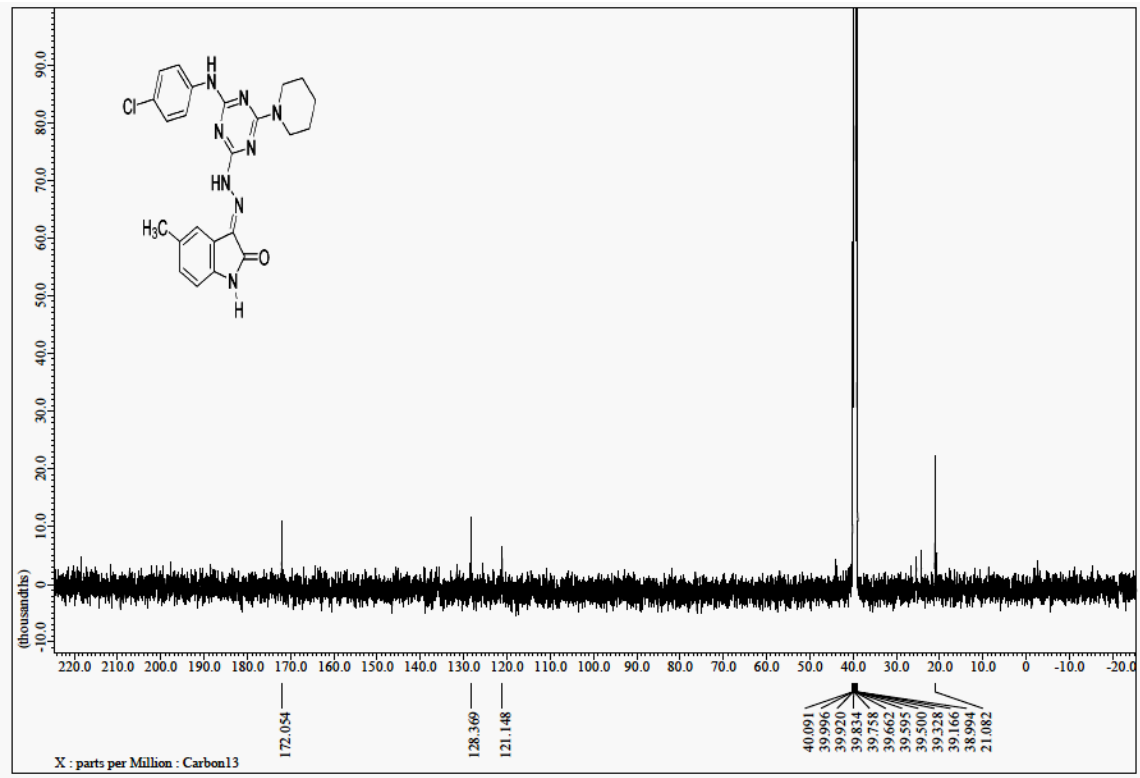




**Figure S7 $^{1}$H and $^{13}$C-NMR Compound 6e**


abundance
1.00
13.47m
32.82m
14.17m
24.49m
16.46m
61.74m
94.78m
48.35m
0.12
97.28m
8.69m
12.550
11.927
11.050
7.724
7.309
7.292
7.261
7.093
7.078
6.783
6.768
3.721
3.280
2.578
2.574
2.570
2.559
2.440
2.301
2.297
2.265
1.926
1.846
1.592
1.584
1.492
1.167
X : parts per Million : Proton


(thousandths)
172.054
128.369
121.148
40.091
39.996
39.920
39.834
39.758
39.662
39.595
39.500
39.328
39.166
38.994
21.082
X : parts per Million : Carbon13