Electronic Supplementary Information

One-flask synthesis of pyrazolone thioethers involving catalyzed and uncatalyzed thioetherification pathways of pyrazolones

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Materials and method:

^{1}H-NMR and ^{13}C-NMR spectral analysis were carried out on 300 MHz, 75 MHz instruments where tetramethylsilane (TMS) was used as internal standard. Infrared spectra were recorded in KBr pallets in reflection mode on a FTIR spectrophotometer. High Resolution Mass Spectra were obtained using a mass spectrometer. Elemental analyses were done using an autoanalyzer. Suitable single crystals of compound **2s** and **3a** were mounted on a X-ray diffractometer equipped with a graphite monochromator. All the reactions were monitored by thin layer chromatography carried out on aluminum-blocked silica gel plates coated with silica gel G under UV light and also by exposure to iodine vapor for detection. Melting points were recorded on a Köfler Block apparatus and are uncorrected. Synthetic grade chemicals from available companies were used for carrying out the organic reactions. For column chromatography 100-200 mesh silica gel was used. All the organic solvents, used in the reaction, were appropriately dried and distilled prior to use.

General Procedure for the Synthesis of Pyrazolone Derivatives:

Sodium acetate (328 mg, 4.0 mmol) was added in a suspension of aromatic hydrazine hydrochloride derivatives (4.0 mmol) in 5 ml of EtOH and 1 ml of water, and the mixture was stirred at rt for 5 min. Then, to the mixture ethyl acetoacetate (521 mg, 4.0 mmol) was added, and the resultant mixture was heated to reflux for 3 h. After that, the mixture was poured dropwise onto crushed ice (50 g) with vigorous stirring, and the resulting precipitate was then filtered off and crystallized from EtOH. These pyrazolone derivatives were then employed for the synthesis of pyrazolonethioethers without further purification.

General Procedure for the Palladium Catalyzed Synthesis of Pyrazolone thioethers (2a-s):

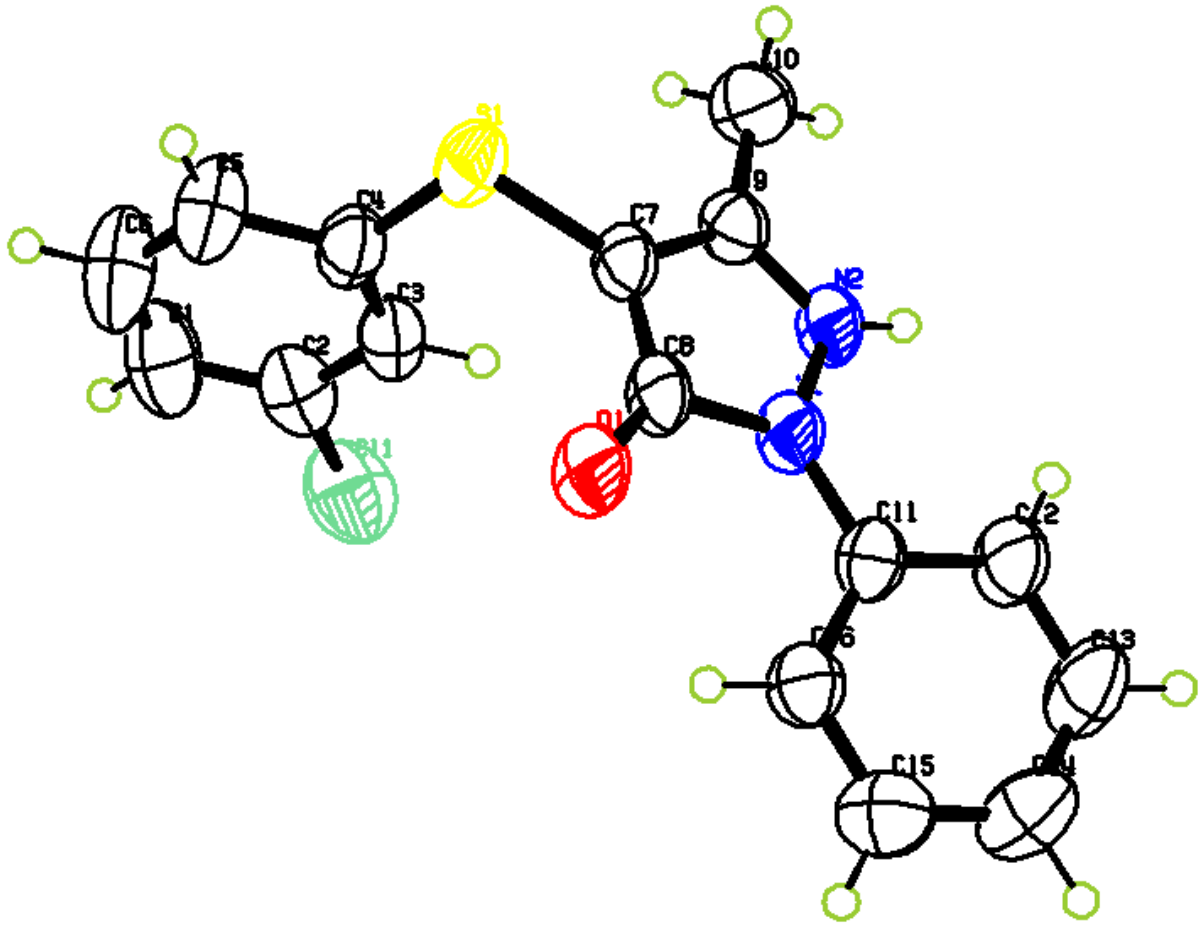
In a 25 ml double neck RB flask fitted with a rubber septum and condenser, were added pyrazolone derivatives (1.5 mmol), elemental sulfur (1.3 equiv, 62 mg), triethylamine (1 drop) and 2 ml ethanol. The resulting mixture was then heated to reflux for 40 min. After that the volatiles were removed under vacuo followed by the addition of Cs_2CO_3 (1.2 equiv, 391 mg). The reaction vial was then evacuated and backfilled with argon (3 times) and 1.0 mmol of iodobenzene derivatives, a solution of $Pd(OAc)_2$ (2 mol%, 4 mg) and Xantphos (2 mol%, 12 mg) in 1 ml DMSO and additional 1 ml of DMSO were added to the reaction vial through a syringe. Solid iodobenzene derivatives were taken into the reaction vial prior to evacuation and backfilling with argon. The resulting mixture was then stirred at 130 ^oC in a preheated oil bath for 2.5 h. After completion of the reaction (monitored by TLC) the mixture was cooled to rt and quenched by addition of H_2O followed by the extraction with EtOAc (3 × 10 ml). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo and the residue was purified by column chromatography over silica gel (100-200 mesh) with ethyl acetate and petroleum ether (1:4−3:2, v/v) as the eluent to afford the pyrazolone thioethers.

General Procedure for the Synthesis of Pyrazolone thioethers (3a-f) from 2,3-dichloropyrazine:

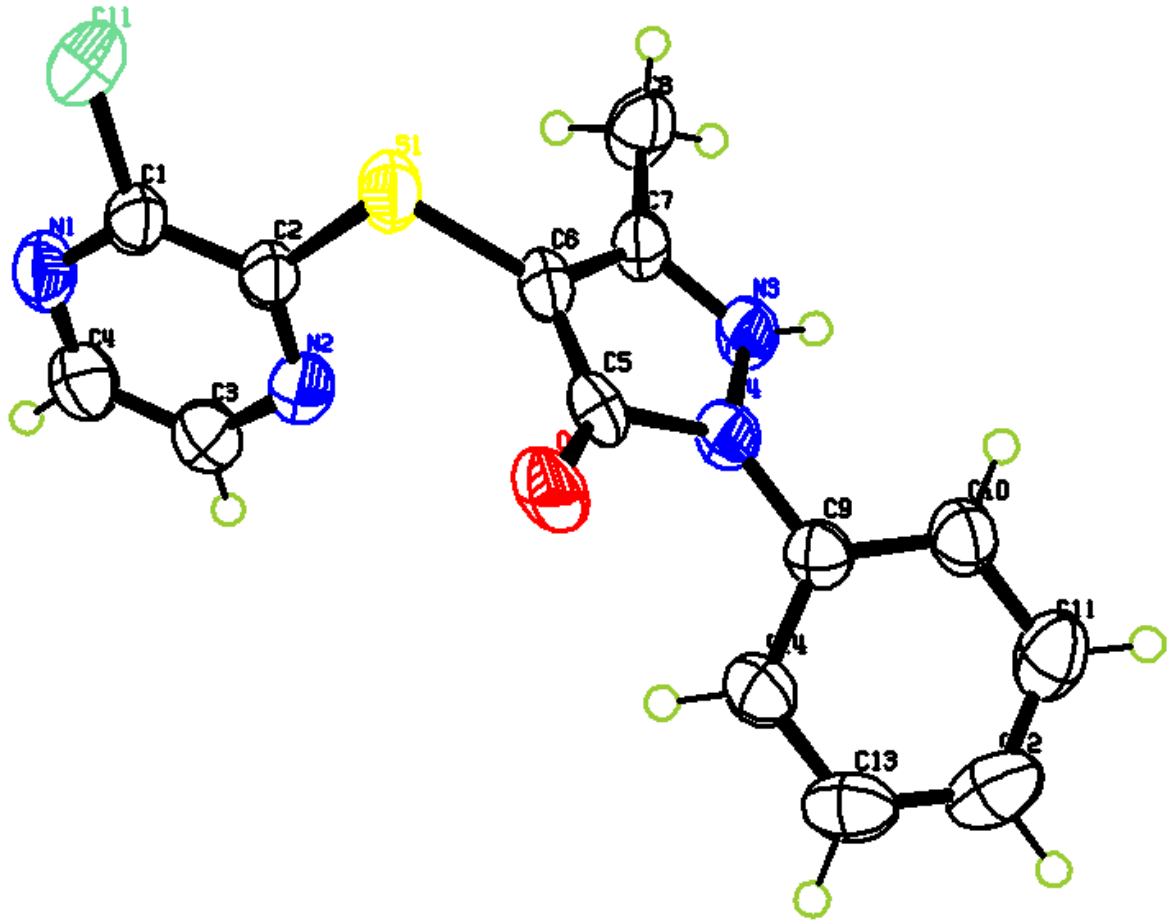
In a 25 ml RB flask fitted with a condenser, were added pyrazolone derivatives (1.5 mmol), elemental sulfur (1.3 equiv, 62 mg), triethylamine (1 drop) and 2 ml ethanol. The resulting mixture was then heated to reflux for 40 min. After that the volatiles were removed under vacuo followed by the addition of 2,3-dichloropyrazine (1.0 mmol, 149 mg), Cs_2CO_3 (1.2 equiv, 391 mg) and DMSO (2 ml). The resulting mixture was then stirred at 80 ^oC for 20 min. After completion of the reaction (monitored by TLC) the mixture was cooled to rt and quenched by

addition of H_2O followed by the extraction with EtOAc (3 × 10 ml). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo and the residue was purified by column chromatography over silica gel (100-200 mesh) with ethyl acetate and petroleum ether (1:4−3:2, v/v) as the eluent to afford the pyrazolone thioethers.

II. X-ray Crystallography Data of Compound 2s (CCDC 1557690) and 3a (CCDC 1557692):



The X-ray structure of **2s**. The ellipsoid contour percent probability level is 50%.



The X-ray structure of **3a**. The ellipsoid contour percent probability level is 50%.

Single crystal X-ray data for compound 2s (CCDC 1557690) and 3a (CCDC 1557692):

Single crystals suitable for X-ray diffraction of **2s** and **3a** were grown from ethyl acetate. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. In all the cases the data were collected at 296(2) K on a CCD diffractometer with graphite monochromated Mo-Kα radiation (0.71073 Å). The data were processed using the package SAINT.[1] Structures were solved by direct and Fourier methods and refined by full-matrix least squares based on F2 using SHELXTL[2] and SHELXL-97[3] packages.

Table S1. Crystallographic data for the compound **2s** and **3a**

Compounds	**2s**	**3a**
empirical formula	C_{16} H_{13} Cl N_2 O S	C_{14} H_{11} Cl N_4 O S
fw	316.79	320.79
crystal system	Monoclinic	Monoclinic
space group	*C 2/c*	*P 21/c*
a (Å)	42.263(6)	9.676(5)
b(Å)	5.9743(8)	12.483(6)
c (Å)	11.7282(16)	11.857(6)
α (°)	90.00	90.00
β (°)	91.856(5)	98.414(16)
γ (°)	90.00	90.00
V (Å^3)	2959.7(7)	1416.7(12)
Z	8	4
T, K	296(2)	296(2)
Wavelength (Å)	0.71073	0.71073
2θ (°)	1.92–51.82	4.26-51.84
μ (mm^{-1})	0.398	0.421
ρ_{calcd} (g cm^{-3})	1.422	1.504
F(000)	1312	664
absorption correction	multi-Scan	multi-Scan
index ranges	$-51 \le h \le 51$	$-10 \le h \le 11$
	$-6 \le k \le 7$	$-15 \le k \le 15$

	$-14 \le l \le 14$	$-13 \le l \le 14$
reflections collected	16616	16684
independent reflections (R_{int})	2843 (0.0443)	2740 (0.0638)
Goodness-of-fit on F^2	0.997	0.970
$R_1{}^a$ /w$R_2{}^b$ ($I > 2\sigma(I)$)	0.0472/ 0.1303	0.0442/ 0.1182
$R_1{}^a$/w$R_2{}^b$ (for all data)	0.0722/ 0.1479	0.0818/ 0.1393
Largest diff. peak/hole / e Å^{-3}	0.384/ -0.310	0.301/ -0.286

$^aR_1 = [\sum||F_o| - |F_c||/\sum|F_o|]$. $^bwR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2}$

References:

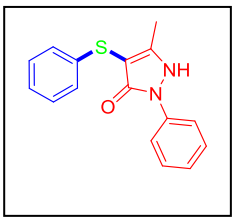
1. *APEX-II*, *SAINT-Plus*, and *TWINABS;* Bruker-Nonius AXS Inc.: Madison, WI, 2004.

2 *SHELXTL*, version 6.10; Bruker AXS Inc.: Madison, WI, 2002.

3. Sheldrick, G. M. *SHELXL-97, Crystal Structure Refinement Program;* University of Göttingen: Göttingen, Germany, 1997.

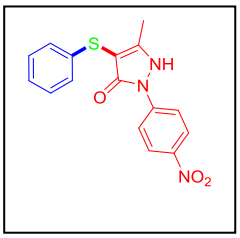
III. Characterization data for the products of Table 2 and 3

5-methyl-2-phenyl-4-(phenylthio)-1,2-dihydro-3H-pyrazol-3-one 2a[6b]



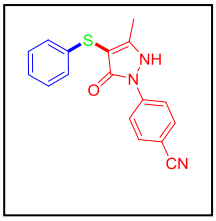
Off-white solid (254 mg, 90%); Mp: 188-190 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.04 (s, 3H), 6.98-7.19 (m, 6H), 7.38 (t, J=7.4 Hz, 2H), 7.66 (d, J=7.5 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ12.6, 87.9, 114.1, 121.0, 125.3, 126.1, 127.5, 129.3, 129.4, 129.44, 129.8, 138.4, 138.7, 152.4, 157.3; IR (KBr): 3340, 2869, 1578, 1489, 1326, 1311, 1208, 1172, 1122, 1018, 822, 740, 690, 591, 540 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{14}N_2OS + H]^{+}$: 283.0900, found: 283.0911.

5-methyl-2-(4-nitrophenyl)-4-(phenylthio)-1,2-dihydro-3H-pyrazol-3-one 2b



Yellow solid (301 mg, 92%); Mp: 210-212 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.04 (s, 3H), 7.16 (s, 3H), 7.32 (d, J=6.3 Hz, 2H), 8.16 (d, J=8.1 Hz, 2H), 8.41 (d, J=8.7 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 11.9, 88.3, 118.5, 118.9, 124.4, 124.6, 124.8, 128.2, 128.6, 128.7, 128.9, 129.4, 137.3, 142.6, 142.8, 143.2, 153.9, 158.0; IR (KBr): 3342, 2612, 1623, 1519, 1328, 1185, 1071, 855, 820, 737, 689, 597, 535cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{13}N_3O_3S + H]^{+}$: 328.0750, found: 328.0752.

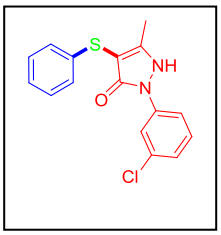
4-(3-methyl-5-oxo-4-(phenylthio)-2,5-dihydro-1H-pyrazol-1-yl)benzonitrile 2c



Off-white solid (280 mg, 91%); Mp: 202-204 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.12 (s, 3H), 7.05-7.12 (m, 3H), 7.25 (t, J=7.2 Hz, 2H), 7.91 (d, J=7.5 Hz, 2H), 7.99 (d, J=8.7 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.4, 88.9, 107.4, 118.7, 119.9, 125.1, 129.2, 133.5, 137.9, 141.6, 154.0, 158.2; IR

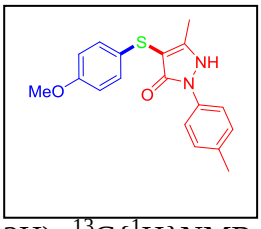
(KBr): 3330, 2595, 2227, 1628, 1545, 1506, 1398, 1334, 1305, 1181, 1072, 838, 736, 690, 546cm^{-1}; HRMS (ESI-TOF) m/z Calcd for [$C_{17}H_{13}N_3OS$ +H]$^+$: 308.0852, found: 308.0861.

2-(3-chlorophenyl)-5-methyl-4-(phenylthio)-1,2-dihydro-3H-pyrazol-3-one 2d



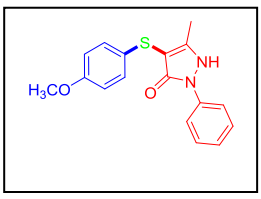
Off-white solid (285 mg, 90%); Mp: 188-190 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.50 (s, 3H), 7.44-7.51 (m, 3H), 7.62-7.71 (m, 3H), 7.87 (t, J=8.1 Hz, 1H), 8.14 (d, J=8.1 Hz, 1H), 8.22 (s, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 17.6, 87.3, 123.7, 123.9, 125.1, 130.3, 130.6, 134.4, 136.1, 138.7, 143.4, 144.6, 154.5, 158.2; IR (KBr):3346, 2579, 1620,1540,1493, 1393, 1335, 1194, 1140, 1043, 827, 738, 538, 500 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for [$C_{16}H_{13}ClN_2OS$ +H]$^+$: 317.0510, found: 317.0516.

4-((4-methoxyphenyl)thio)-5-methyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one 2e[6b]



Light yellow solid (313 mg, 96%); Mp: 180-182 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.47 (s, 3H), 2.67 (s, 3H), 4.05 (s, 3H), 7.22 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H), 7.95 (d, J=8.4 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.9, 21.1, 55.7, 85.6, 115.4, 121.3, 128.3, 129.3, 129.9, 132.9, 135.5, 138.1, 148.7, 158.1, 160.2; IR (KBr): 3348, 2698, 1510, 1450, 1396, 1328, 1244, 1135, 1089, 1038, 838, 781, 689, 587, 520cm^{-1}; HRMS (ESI-TOF) m/z Calcd for [$C_{18}H_{18}N_2O_2S$ +H]$^+$: 327.1162, found: 327.1158.

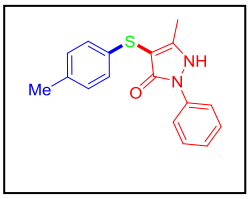
4-((4-methoxyphenyl)thio)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 2f[6b]



Off-white solid (294 mg, 94%); Mp: 200-202 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.49 (s, 3H), 4.05 (s, 3H), 7.23 (d, J=8.7 Hz, 2H),

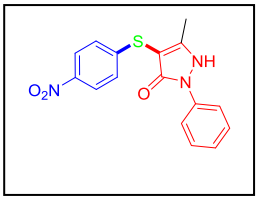
7.44 (d, J=8.4 Hz, 2H), 7.61 (t, J=7.4 Hz, 1H), 7.81 (t, J=7.8 Hz, 2H), 8.08 (d, J=7.8 Hz, 2H); $^{13}C\{^{1}H\}$NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.9, 55.8, 87.6, 115.4, 121.3, 126.2, 128.3, 129.2, 129.5, 137.2, 137.4, 146.4, 151.5, 158.2; IR (KBr): 3352, 2398, 1519, 1449, 1401, 1331, 1254, 1137, 1090, 1045, 833, 788, 691, 591, 521, 448cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{17}H_{18}N_2O_2S +H]^+$: 313.1005, found: 313.1002.

5-methyl-2-phenyl-4-(p-tolylthio)-2,4-dihydro-3H-pyrazol-3-one 2g[6b]



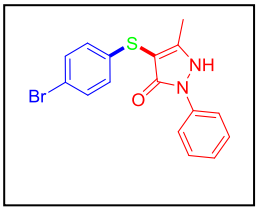
Off-white solid (273 mg, 92%); Mp: 202-204 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.12 (s, 3H), 2.28 (s, 3H), 6.99 (d, J=7.5 Hz, 2H), 7.09 (d, J=7.2 Hz, 2H), 7.28 (d, J=6.9 Hz, 1H), 7.47 (t, J=7.1 Hz, 2H), 7.75 (d, J=7.8 Hz, 2H); $^{13}C\{^{1}H\}$NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 20.7, 88.0, 121.1, 125.7, 126.0, 129.2, 129.3, 130.0, 134.7, 135.1, 138.5, 152.5, 157.1; IR (KBr): 3347, 2622, 1611, 1396, 1198, 837, 734, 680cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{17}H_{16}N_2OS +H]^+$: 297.1056, found: 297.1052.

5-methyl-4-((4-nitrophenyl)thio)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 2h



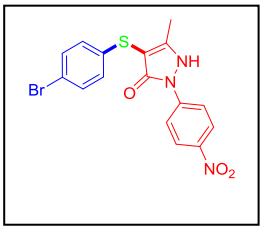
Yellow solid (321 mg, 98%); Mp: 208-210 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 1.99 (s, 3H), 7.21 (d, J=8.7 Hz, 3H), 7.40 (t, J=7.5 Hz, 2H), 7.68 (d, J=7.8 Hz, 2H), 8.05 (d, J=8.7 Hz, 2H); $^{13}C\{^{1}H\}$NMR (75 MHz; DMSO d_6; Me_4Si): δ 7.5, 80.5, 116.1, 118.8, 119.4, 120.1, 121.2, 124.2, 133.2, 139.9, 144.1, 147.1, 152.3, 158.4; IR (KBr): 3348, 2568, 1618, 1531, 1396, 1340, 1202, 835, 732, 685cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{13}N_3O_3S +H]^+$: 328.0750, found: 328.0748.

4-((4-bromophenyl)thio)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 2i[6b]



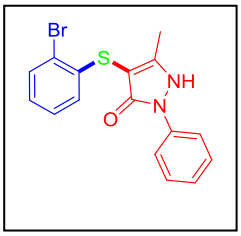
Off-white solid (325 mg, 90%); Mp: 188-190 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.10 (s, 3H), 7.00 (d, J=7.2 Hz, 2H), 7.26 (t, J=6.9 Hz, 1H), 7.45 (t, J=6.9 Hz, 4H), 7.72 (d, J=7.5 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.6, 88.2, 118.0, 121.1, 126.2, 127.2, 129.2, 129.3, 132.1, 138.5, 140.3, 152.3, 158.01; IR (KBr): 3335, 2622, 1621, 1600, 1201, 1066, 810, 735, 593, 480cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{13}BrN_2OS + H]^+$: 361.0005, found: 361.0011.

4-((4-bromophenyl)thio)-5-methyl-2-(4-nitrophenyl)-2,4-dihydro-3H-pyrazol-3-one 2j



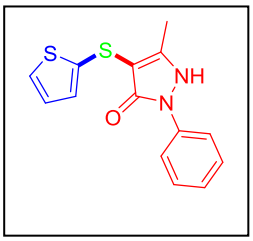
Yellow solid (374 mg, 92%); Mp: 220-222 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.06 (s, 3H), 6.96 (d, J=7.2 Hz, 2H), 7.36 (d, J=6.9 Hz, 2H), 8.00 (d, J=7.8 Hz, 2H), 8.25 (d, J=7.8 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 88.6, 118.2, 119.8, 125.3, 127.4, 132.2, 137.9, 143.4, 144.1, 154.6, 158.9; IR (KBr): 3336, 2603,1629,1596,1512,1324,1183,1074,807,736,593,479 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{12}BrN_3O_3S + H]^+$: 405.9856, found: 405.9851.

4-((2-bromophenyl)thio)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 2k



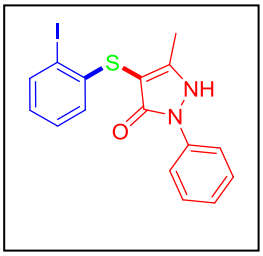
Yellow solid (340 mg, 94%); Mp: 180-182 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.11 (s, 3H), 6.75 (d, J=8.1 Hz, 1H), 7.07 (t, J=7.5 Hz, 1H), 7.29 (t, J=7.4 Hz, 2H), 7.48 (t, J=7.4 Hz, 2H), 7.59 (d, J=7.8 Hz, 1H), 7.76 (d, J=7.8 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.4, 87.2, 118.8, 120.9, 125.3, 125.9, 126.4, 128.3, 128.9, 129.0, 132.8, 138.2, 139.2, 152.0, 156.8; IR (KBr): 3341, 2638, 1589, 1482, 1328, 1312, 1220, 1152, 1115, 1011, 802, 686, 493cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{13}BrN_2OS + H]^+$: 361.0005, found: 361.0025.

5-methyl-2-phenyl-4-(thiophen-2-ylthio)-1,2-dihydro-3H-pyrazol-3-one 2l



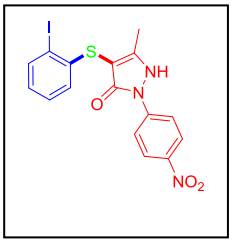
Yellow solid (254 mg, 88%); Mp: 178-180 ^{o}C ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.17 (s, 3H), 6.90 (s, 1H), 7.06 (s, 1H), 7.20 (d, J=6.6 Hz, 1H), 7.39 (s, 3H), 7.64 (d, J=8.1 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 84.7, 121.0, 126.0, 128.1, 128.3, 129.3, 129.4, 131.2, 133.7, 137.7, 138.3, 151.5, 156.6; IR (KBr): 3342, 2923, 2854, 1620, 1545, 1493, 1366, 1294, 1074, 814, 751, 686, 493cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{14}H_{12}N_2OS_2 + H]^+$: 289.0464, found: 289.0461.

4-((2-iodophenyl)thio)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 2m



Off-white solid (367 mg, 90%); Mp: 180-182 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.02 (s, 3H), 6.62 (d, J=7.5 Hz, 1H), 6.81 (t, J=7.2 Hz, 1H), 7.18-7.25 (m, 2H), 7.40 (t, J=7.8 Hz, 2H), 7.66-7.73 (m, 3H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.6, 88.4, 94.7, 121.2, 124.9, 126.2, 126.7, 129.2, 129.3, 132.1, 138.5, 139.5, 142.8, 152.3, 158.5; IR (KBr): 3335, 2622, 1621, 1478, 1202, 1088, 737, 598cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{13}IN_2OS+H]^+$: 408.9866, found: 408.9862.

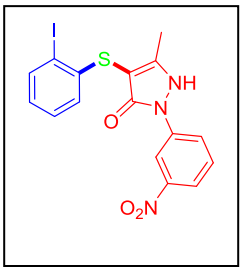
4-((2-iodophenyl)thio)-5-methyl-2-(4-nitrophenyl)-2,4-dihydro-3H-pyrazol-3-one 2n



Yellow solid (417 mg, 92%); Mp: 204-206 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.03 (s, 3H), 6.65 (d, J=8.1 Hz, 1H), 6.79 (t, J=7.4 Hz, 1H), 7.20 (t, J=7.4 Hz, 1H), 7.70 (d, J=7.5 Hz, 1H), 8.01 (d, J=9.0 Hz, 2H), 8.25 (d, J=9.0 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 89.5, 94.8, 119.8, 125.0, 125.3, 126.8, 129.2, 139.5, 142.3, 143.4, 144.1, 154.6, 158.9; IR (KBr): 3332,

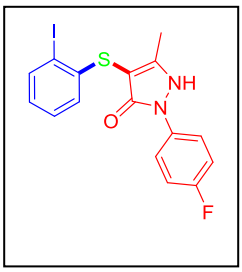
2590, 1622, 1535, 1490, 1350, 1196, 1091, 731, 600cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{12}IN_3O_3S+H]^+$: 453.9717, found: 453.9720.

4-((2-iodophenyl)thio)-5-methyl-2-(3-nitrophenyl)-2,4-dihydro-3H-pyrazol-3-one 2o



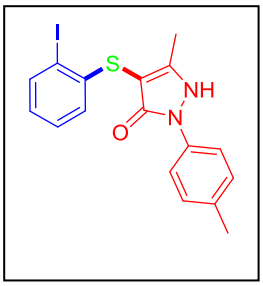
Yellow solid (408 mg, 90%); Mp: 190-192 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.01 (s, 3H), 6.64 (d, J=7.2 Hz, 1H), 6.77 (s, 1H), 7.18 (s, 1H), 7.66 (d, J=7.5 Hz, 2H), 7.99 (d, J=6.6 Hz, 1H), 8.17 (d, J=7.2 Hz, 1H), 8.54 (s, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 88.9, 94.7, 114.5, 120.1, 125.0, 126.1, 126.8, 129.2, 130.9, 139.3, 139.5, 142.5, 148.4, 153.7, 158.2; IR (KBr): 3330, 2595, 1624, 1530, 1482, 1348, 1198, 1081, 737, 597cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{12}IN_3O_3S+H]^+$: 453.9717, found: 453.9712.

2-(4-fluorophenyl)-4-((2-iodophenyl)thio)-5-methyl-2,4-dihydro-3H-pyrazol-3-one 2p



Off-white solid (401 mg, 94%); Mp: 178-180 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.03 (S, 3H), 6.65 (d, J=8.1 Hz, 1H), 6.82 (t, J=7.5 Hz, 1H), 7.22-7.29 (m, 3H), 7.70-7.75 (m, 3H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.6, 88.7, 94.7, 115.9, 116.2, 123.3, 124.9, 126.7, 129.2, 129.9, 134.8, 139.5, 139.6, 142.7, 152.2, 158.6; IR (KBr): 3400, 2482, 1588, 1503, 1400, 1240, 1182, 1030, 822, 738, 600, 520cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{12}FIN_2OS+H]^+$: 426.9772, found: 426.9768.

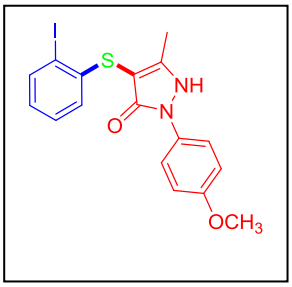
4-((2-iodophenyl)thio)-5-methyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one 2q



Off-white solid (397 mg, 94%); Mp: 176-178 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.09 (s, 3H), 2.33 (s, 3H), 6.70 (d, J=7.8 Hz, 1H),

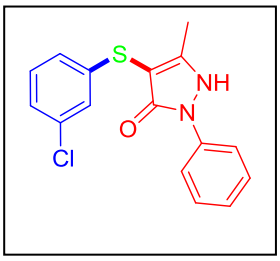
6.88 (t, J=7.5 Hz, 1H), 7.28 (d, J=6.9 Hz, 3H), 7.63 (d, J=8.1 Hz, 2H), 7.79 (d, J=7.8 Hz, 1H); $^{13}C\{^{1}H\}$NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.4, 20.6, 87.8, 94.4, 121.0, 124.7, 126.4, 128.9, 129.4, 135.3, 135.8, 139.2, 142.6, 151.6, 157.5; IR (KBr): 3345, 2620, 1620, 1486, 1200, 1090, 732, 600cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{17}H_{15}IN_2OS+H]^+$: 423.0023, found: 423.0018.

4-((2-iodophenyl)thio)-2-(4-methoxyphenyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one 2r



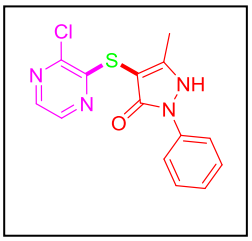
Off-white solid (416 mg, 95%); Mp: 184-186 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 1.99 (s, 3H), 3.70 (s, 3H), 6.60 (d, J=7.5 Hz, 1H), 6.80 (t, J=7.5 Hz, 1H), 6.95 (d, J=8.1 Hz, 2H), 7.22 (t, J=7.4 Hz, 1H), 7.53 (d, J=7.8 Hz, 2H), 7.71 (d, J=7.8 Hz, 1H); $^{13}C\{^{1}H\}$NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.6, 55.7, 87.6, 94.7, 114.4, 123.3, 124.9, 126.7, 129.1, 131.6, 139.4, 142.9, 151.5, 157.7; IR (KBr): 3340, 2486, 1602, 1509, 1399, 1248, 1174, 1028, 828, 741, 593, 517cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{17}H_{15}IN_2O_2S+H]^+$: 438.9972, found: 438.9968.

4-((3-chlorophenyl)thio)-5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one 2s[6e]



Off-white solid (301 mg, 95%); Mp: 184-186 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.07 (s, 3H); 6.98 (d, J=9.6 Hz, 2H), 7.10 (d, J=7.5 Hz, 1H), 7.23 (t, J=6.9 Hz, 2H), 7.41 (t, J=7.2 Hz, 2H), 7.69 (d, J=8.1 Hz, 2H); $^{13}C\{^{1}H\}$NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.3, 86.8, 120.9, 123.6, 124.2, 125.0, 125.9, 129.0, 129.1, 130.8, 134.0, 138.1, 141.4, 152.1, 157.2; IR (KBr): 3332, 2587, 1621, 1548, 1499, 1398, 1355, 1299, 1074, 826, 733, 684, 589cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{16}H_{13}ClN_2OS+H]^+$: 317.0510, found: 317.0521.

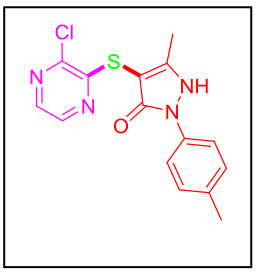
4-((3-chloropyrazin-2-yl)thio)-5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one 3a



Off-white solid (287 mg, 90%); Mp: 190-192 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.09 (s, 3H), 7.26 (t, J=6.8 Hz, 1H), 7.46 (t, J=6.8 Hz, 2H), 7.73 (d, J=7.2 Hz, 2H), 8.21 (d, J=2.4 Hz, 1H), 8.43 (d, J=2.4 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 85.1, 120.9, 126.1, 129.3, 129.32, 129.5, 138.4, 139.4, 139.8, 143.5, 144.7, 152.8, 155.5, 159.2, 161.5; IR (KBr): 3330, 2794, 1619, 1544, 1495, 1397, 1335, 1299, 1139, 1045, 830, 729, 683cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{14}H_{11}ClN_4OS + H]^{+}$: 319.0415, found: 319.0414.

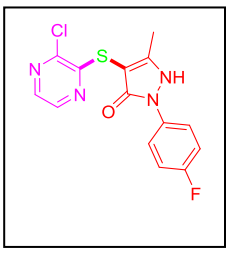
4-((3-chloropyrazin-2-yl)thio)-5-methyl-2-(p-tolyl)-1,2-dihydro-3H-pyrazol-3-one 3b

Off-white solid (306 mg, 92%); Mp: 182-184 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.08 (s, 3H), 2.32 (s, 3H), 7.26 (d, J=8.1 Hz, 2H), 7.60 (d, J=8.1 Hz, 2H), 8.21 (s, 1H), 8.44 (s, 1H);



^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 20.8, 83.9, 120.9, 129.7, 135.3, 136.1, 139.8, 143.5, 144.7, 152.3, 155.6, 159.2, 162.2; IR (KBr): 3350, 2577, 1615, 1509, 1397, 1338, 1196, 1140, 1044, 817, 730, 504cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{15}H_{13}ClN_4OS + H]^{+}$: 333.0571, found: 333.0560.

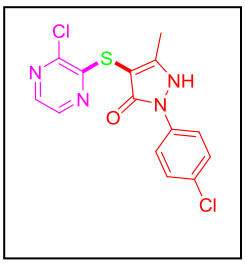
4-((3-chloropyrazin-2-yl)thio)-2-(4-fluorophenyl)-5-methyl-1,2-dihydro-3H-pyrazol-3-one 3c



Off-white solid (310 mg, 92%); Mp: 168-170 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.08 (s, 3H), 7.31 (t, J=8.7 Hz, 2H), 7.72-7.76 (m, 2H), 8.21 (s, 1H), 8.44 (s, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.7, 84.1, 115.9, 116.2, 123.0, 123.1, 134.8, 139.8, 143.5, 144.7, 152.8, 155.4,

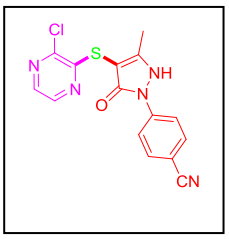
158.5, 161.7; IR (KBr): 3346, 2602, 1571, 1507, 1409, 1334, 1223, 1139, 1047, 838, 592, 512cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{14}H_{10}ClFN_4OS+H]^+$: 337.0321, found: 337.0350.

2-(4-chlorophenyl)-4-((3-chloropyrazin-2-yl)thio)-5-methyl-1,2-dihydro-3H-pyrazol-3-one 3d



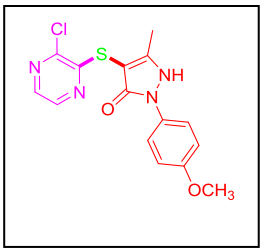
Off-white solid (318 mg, 90%); Mp: 198-200 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.01 (s, 3H), 7.44 (d, J=9.0 Hz, 2H), 7.70 (d, J=6.9 Hz, 2H), 8.13 (s, 1H), 8.35 (s, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.8, 84.5, 122.2, 129.3, 130.0, 137.3, 139.8, 143.5, 144.7, 153.3, 155.4, 157.5, 161.6; IR (KBr): 3336, 2650, 1566, 1512, 1395, 1332, 1219, 1135, 1051, 840, 734, 588, 510cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{14}H_{10}Cl_2N_4OS+H]^+$: 353.0025, found: 353.0042.

4-(4-((3-chloropyrazin-2-yl)thio)-3-methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)benzonitrile 3e



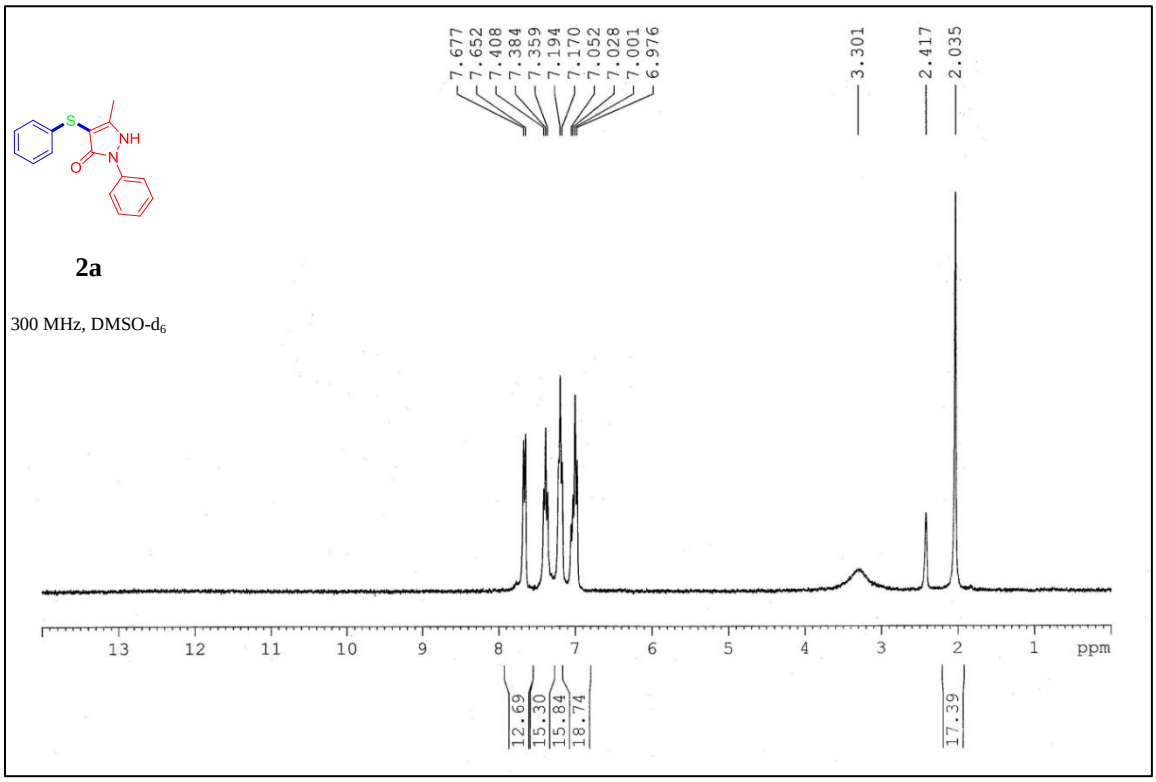
Yellow solid (309 mg, 90%); Mp: 230-232 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 2.07 (s, 3H),7.93 (dd, J=18.5 and 7.7 Hz, 4H), 8.19 (s, 1H), 8.40 (s, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 12.9, 84.0, 107.7, 119.1, 120.1, 133.9, 140.1, 141.9, 143.6, 144.8, 153.4, 155.2, 160.0, 162.4; IR (KBr): 3330, 2583, 2223, 1721, 1627, 1594, 1504, 1422, 1377, 1327, 1121, 1007, 837, 573, 604, 546cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{15}H_{10}ClN_5OS+H]^+$: 344.0367, found: 344.0359.

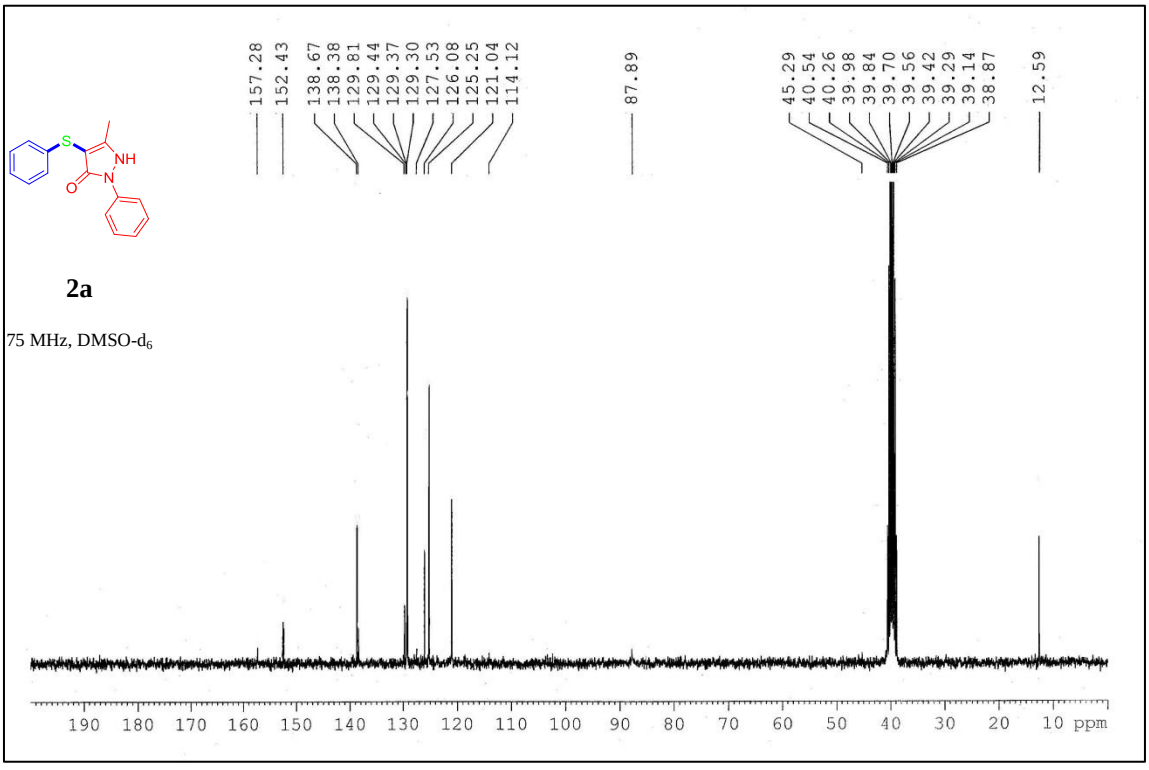
4-((3-chloropyrazin-2-yl)thio)-2-(4-methoxyphenyl)-5-methyl-1,2-dihydro-3H-pyrazol-3-one 3f

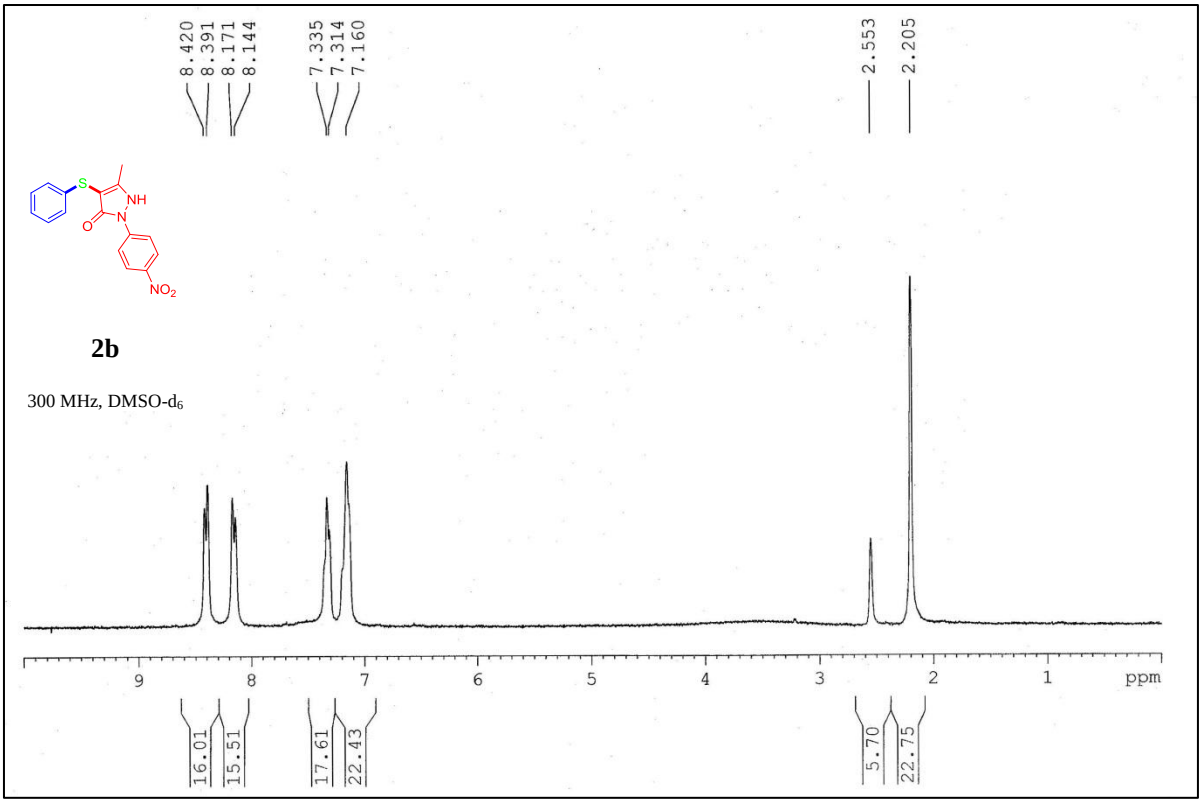


Off-white solid (328 mg, 94%); Mp: 180-182 ^{o}C; ^{1}H NMR (300 MHz; DMSO d_6; Me_4Si): δ 1.99 (s, 3H), 3.70 (s, 3H), 6.95 (d, J=9.0 Hz, 2H), 7.52 (d, J=8.7 Hz, 2H), 8.14 (s, 1H), 8.37 (d, J=2.1 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO d_6; Me_4Si): δ 7.6, 50.6, 84.3, 109.3, 117.9, 126.7, 134.7, 138.4, 139.6, 147.0, 150.5, 152.5, 156.5, 161.0; IR (KBr): 3340, 2690, 1720, 1622, 1588, 1502, 1418, 1350, 1320, 1126, 1012, 835, 570, 596, 550 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{15}H_{13}ClN_4O_2S+H]^+$: 349.0521, found: 349.0544.

IV. ^{1}H and ^{13}C NMR spectra for the products of Table 2 and 3



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8.144
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7.314
7.160
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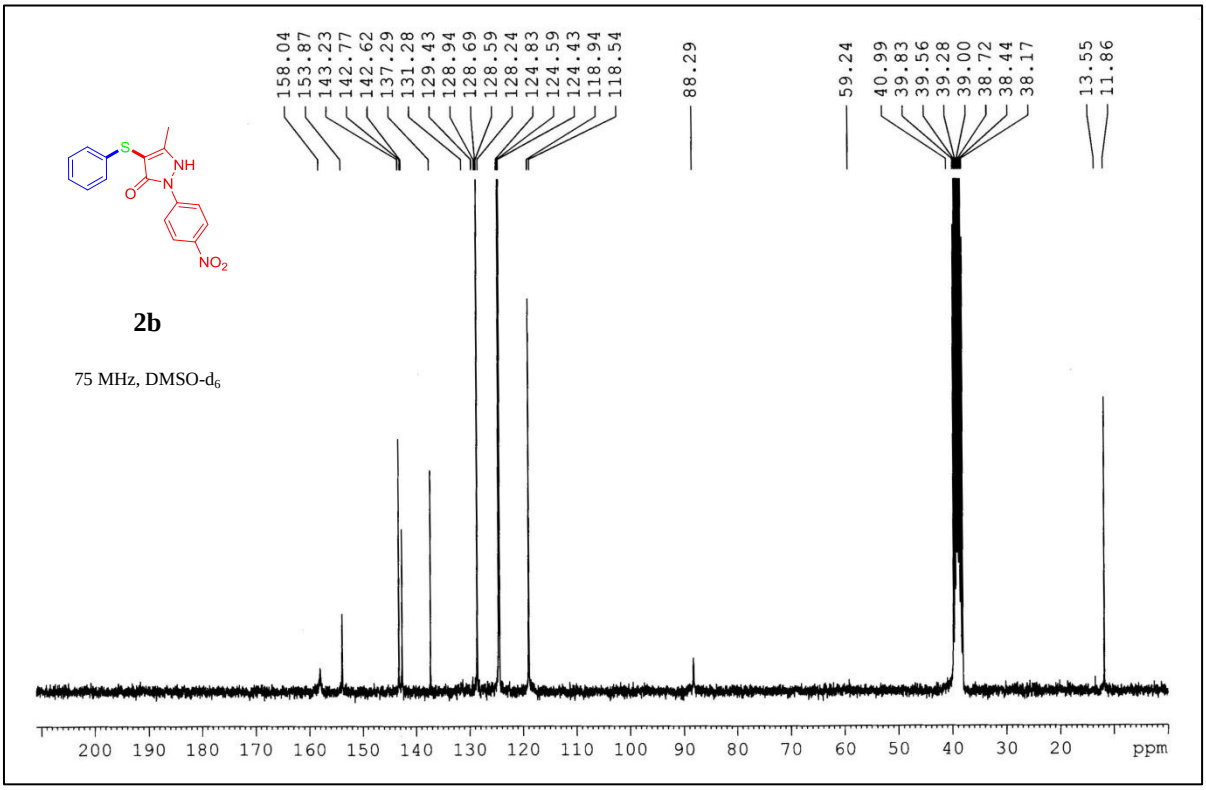
S
O
N
NO2
2b
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
16.01
15.51
17.61
22.43
5.70
22.75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129.43
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124.59
124.43
118.94
118.54
88.29
59.24
40.99
39.83
39.56
39.28
39.00
38.72
38.44
38.17
13.55
11.86
NH
S
O
N
NO2
2b
75 MHz, DMSO-d6
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160
150
140
130
120
110
100
90
80
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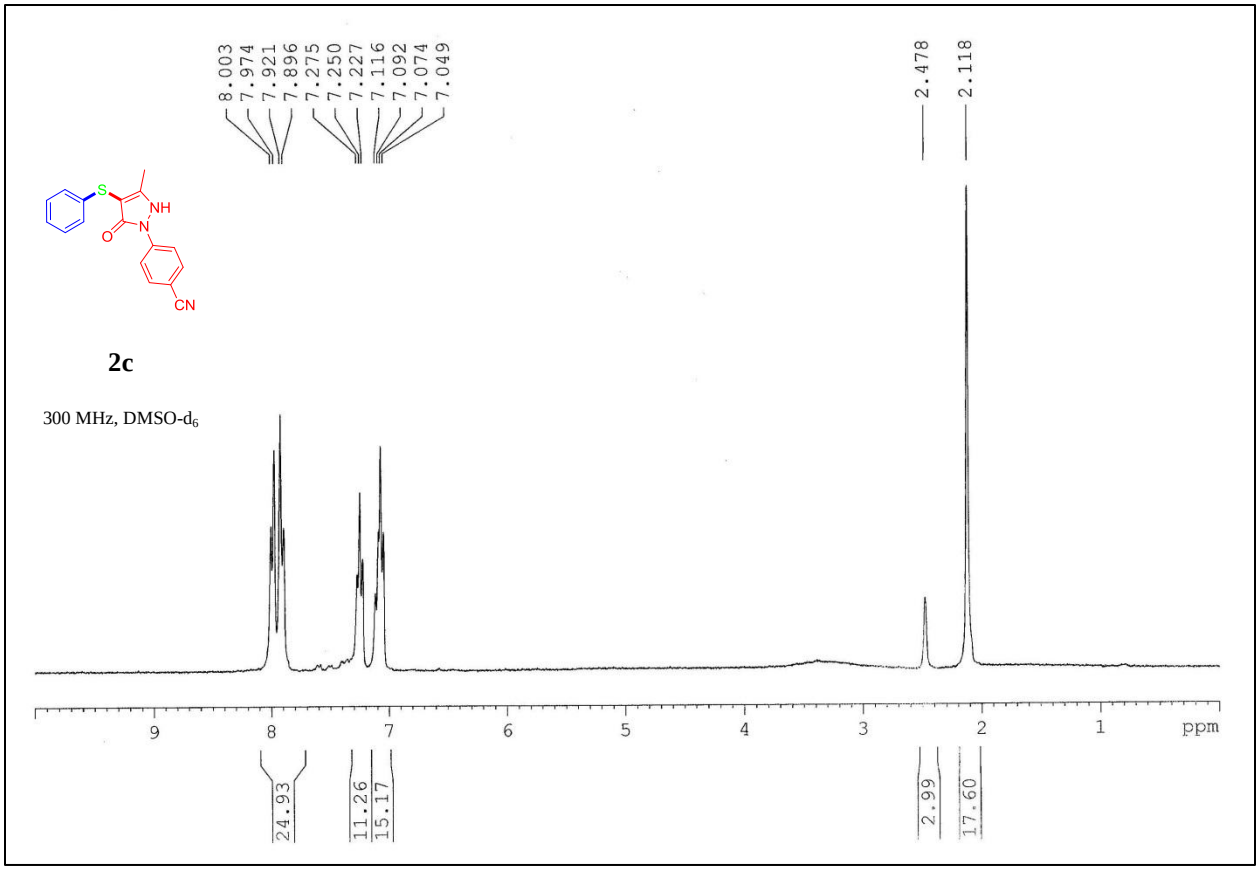
30
20
ppm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7.092
7.074
7.049
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O
N
CN
2c
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ppm
24.93
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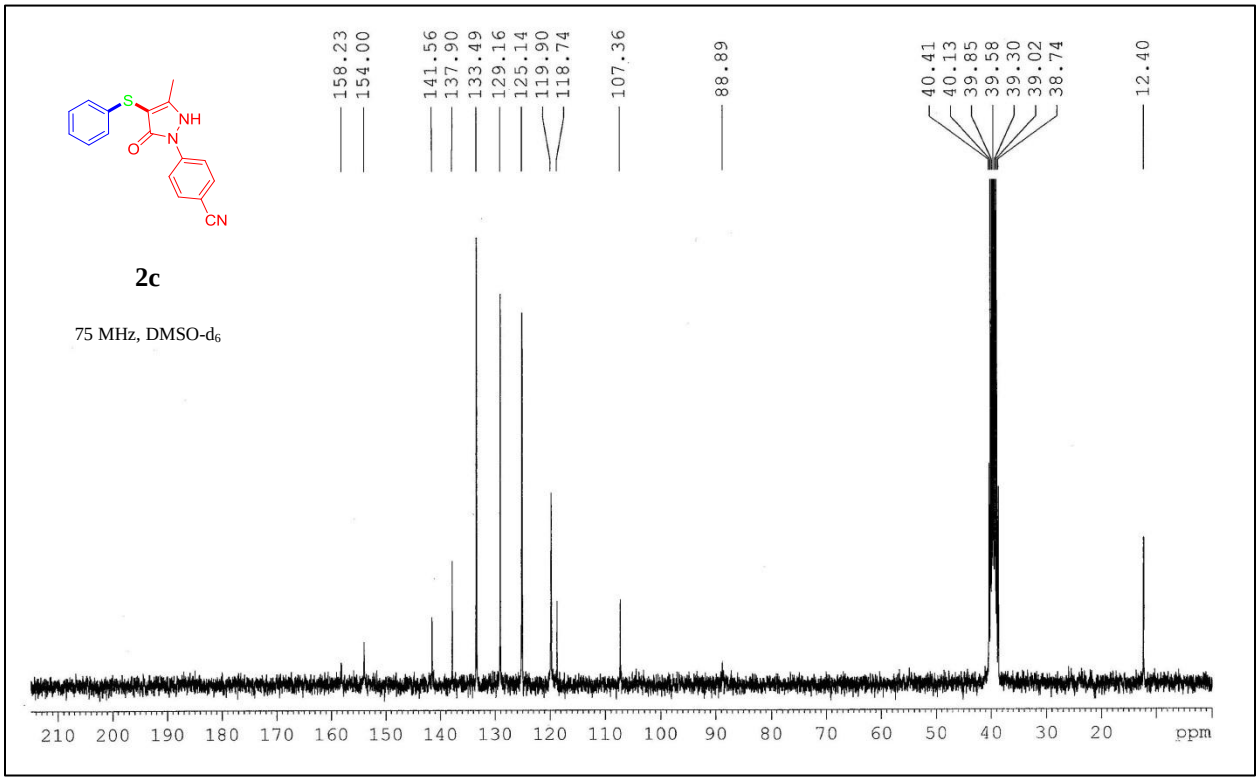
15.17
2.99
17.60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125.14
119.90
118.74
107.36
88.89
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40.13
39.85
39.58
39.30
39.02
38.74
12.40
S
NH
O
N
CN
2c
75 MHz, DMSO-d6
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150
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90
80
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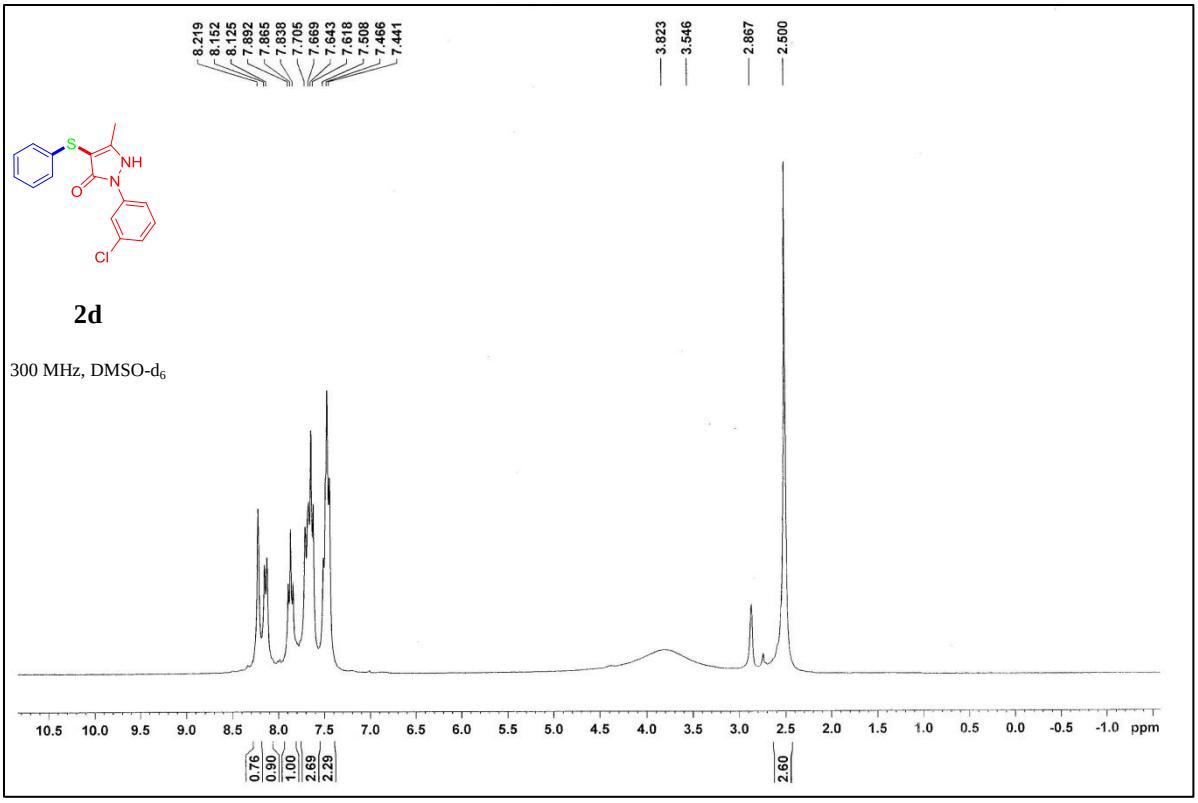
40
30
20
ppm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7.838
7.705
7.669
7.643
7.618
7.508
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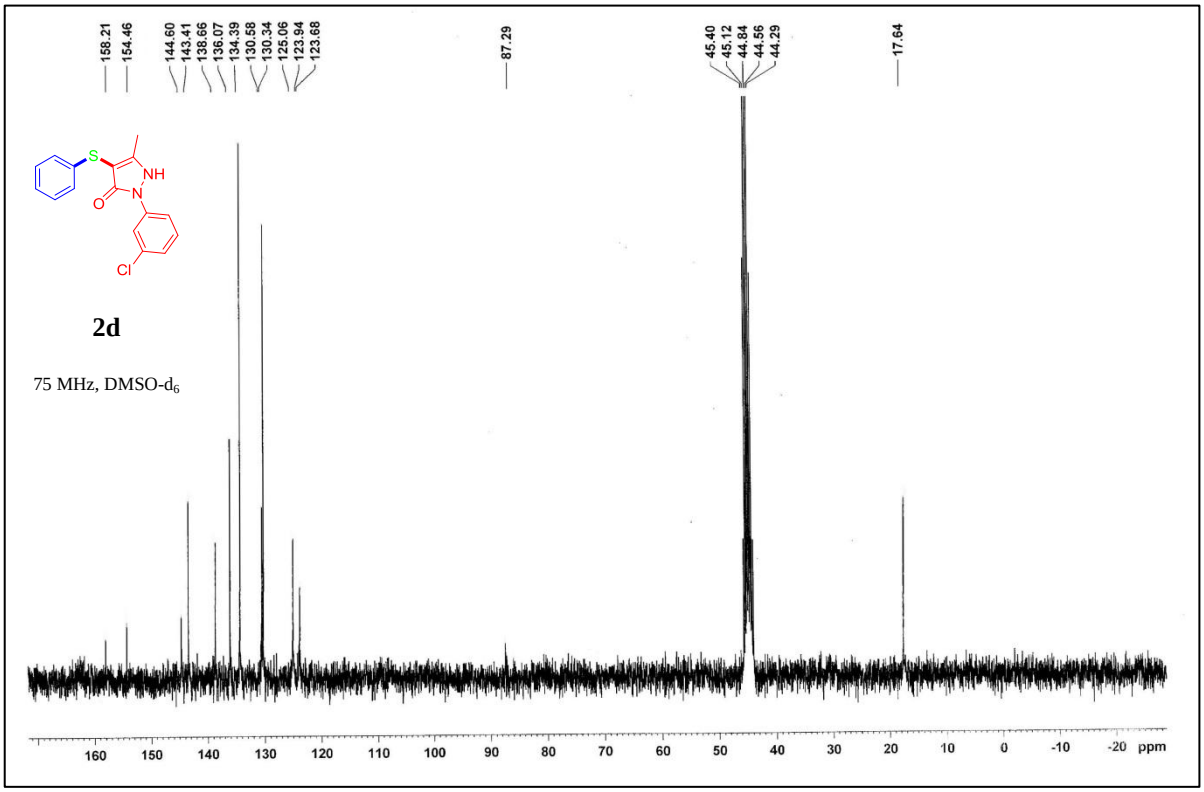
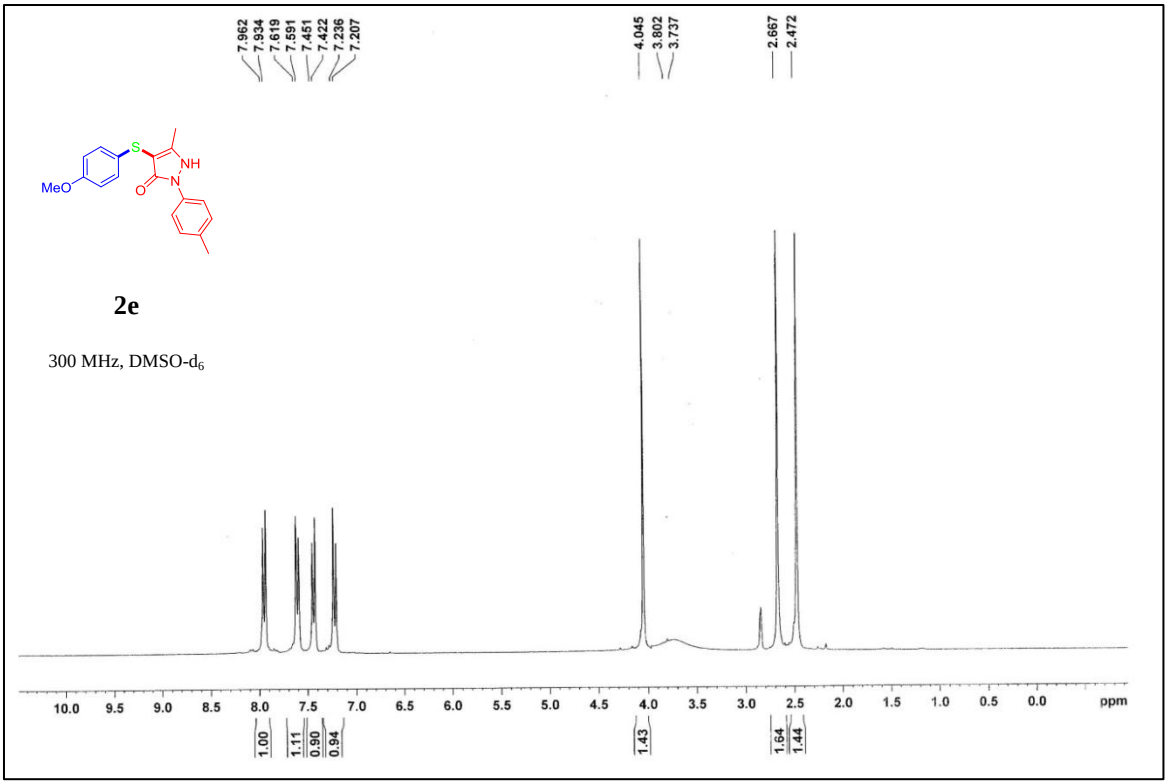
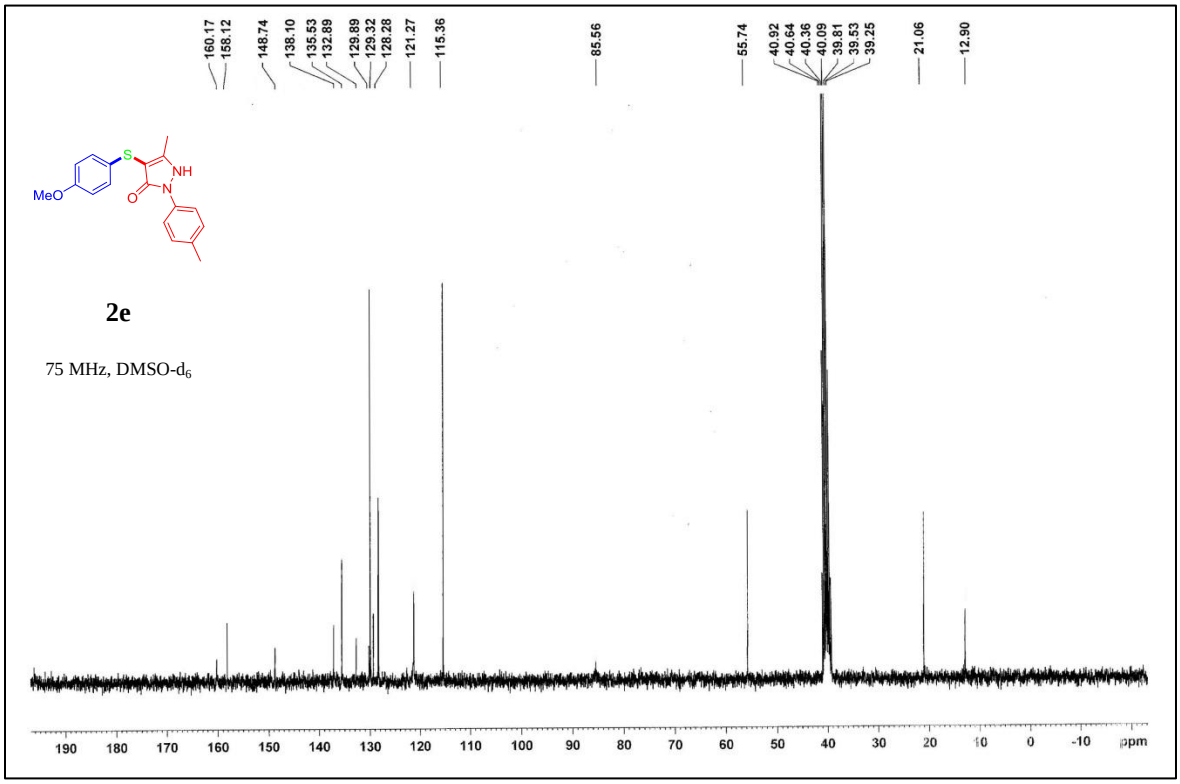
7.441
3.823
3.546
2.867
2.500
S
NH
N
O
Cl
2d
300 MHz, DMSO-d6
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 ppm
0.76
0.90
1.00
2.69
2.29
2.60


158.21
154.46
144.60
143.41
138.66
136.07
134.39
130.58
130.34
125.06
123.94
123.68
87.29
45.40
45.12
44.84
44.56
44.29
17.64
S
NH
N
O
Cl
2d
75 MHz, DMSO-d6
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 ppm



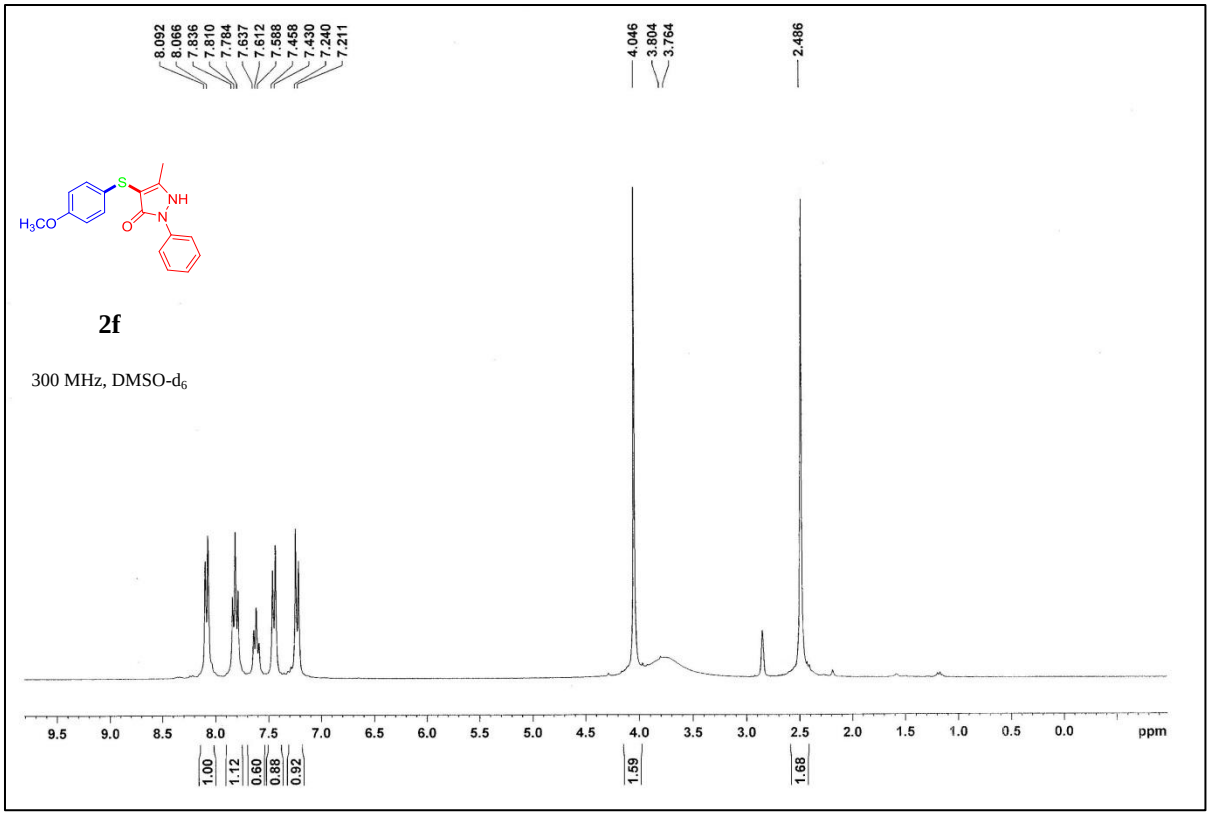
2e

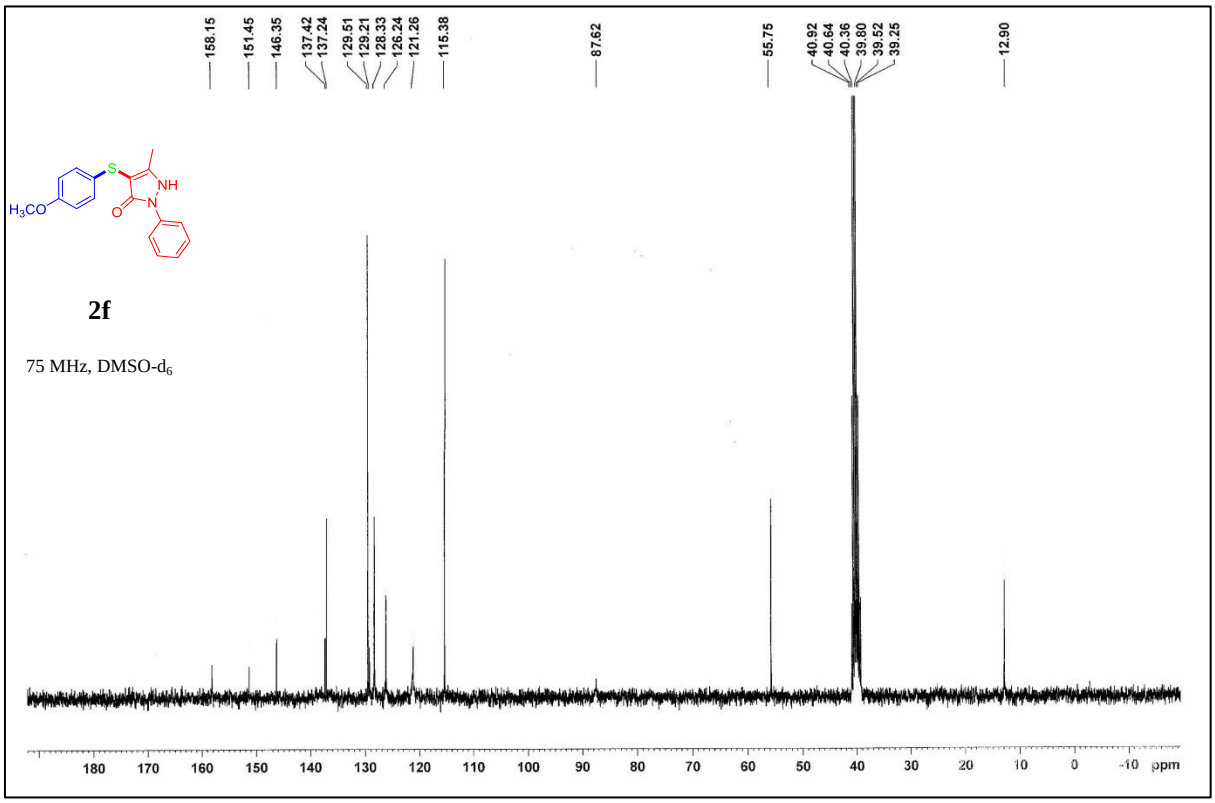
300 MHz, DMSO-d_6

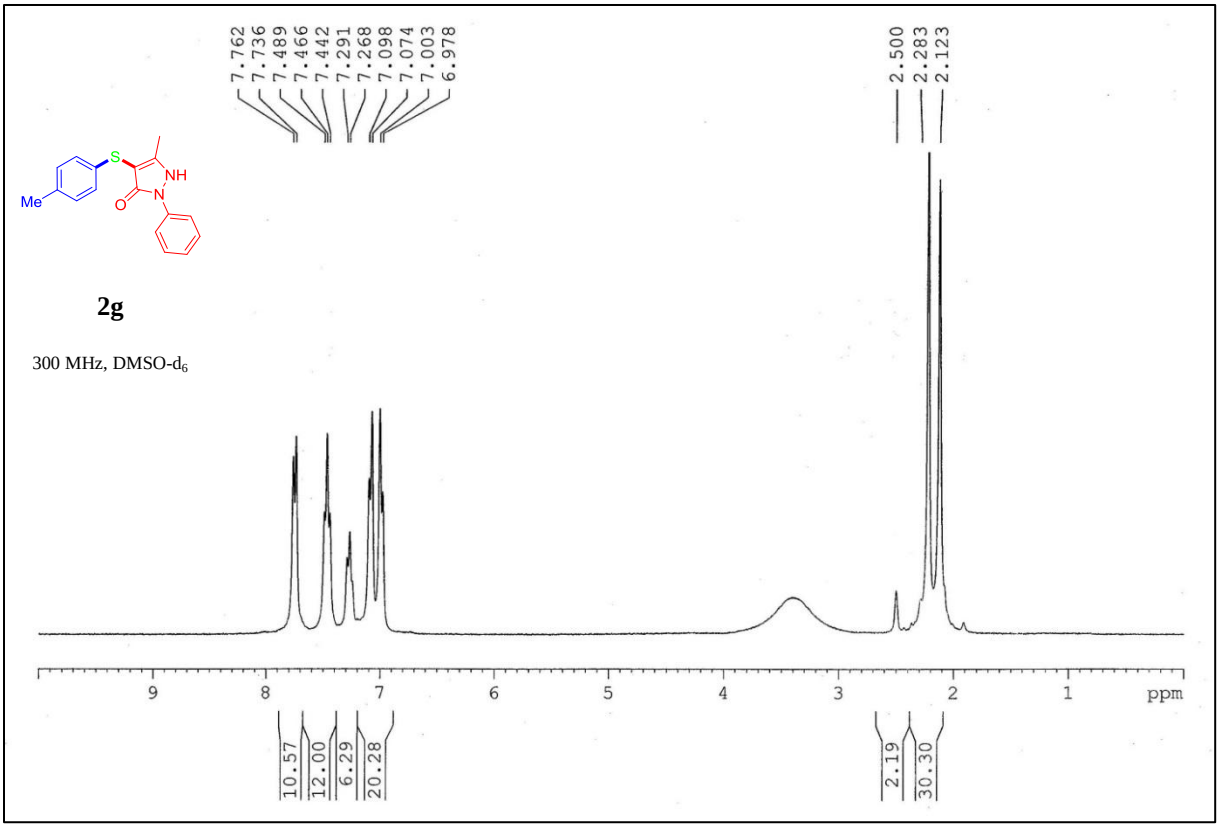


2e

75 MHz, DMSO-d_6

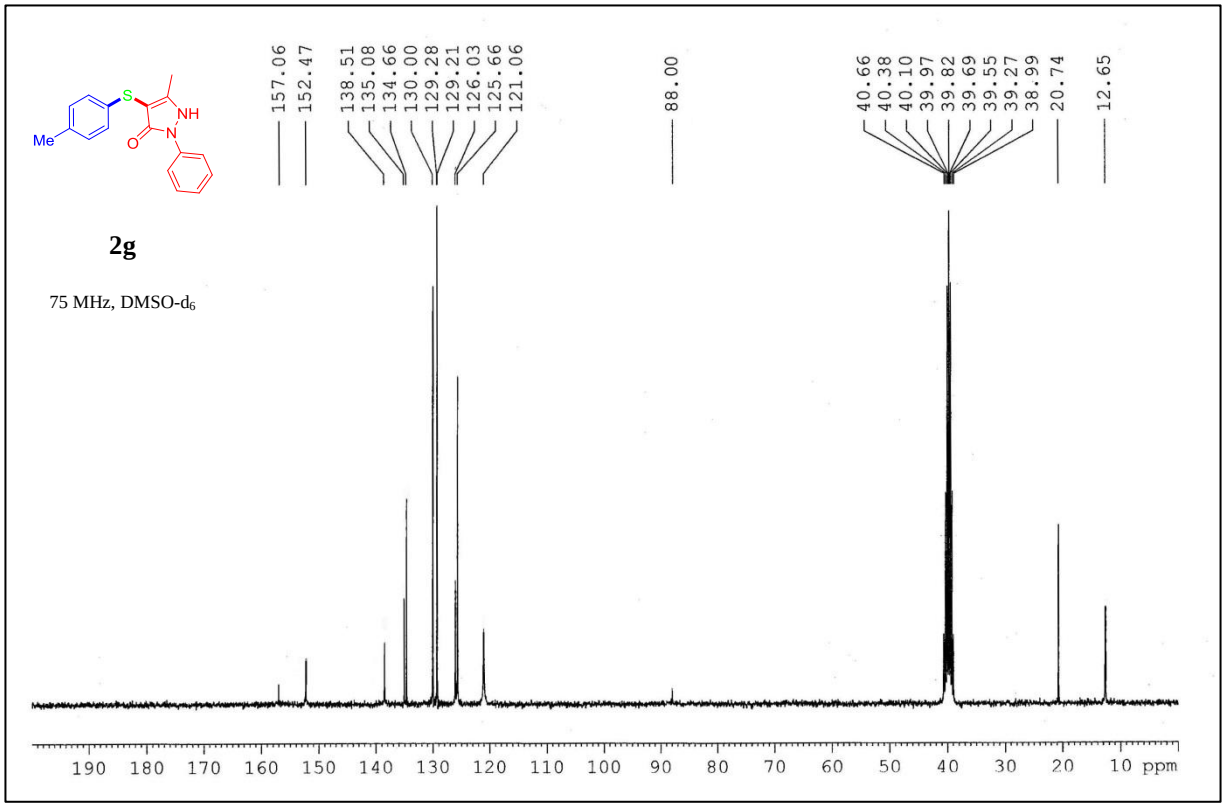

8.092
8.066
7.836
7.810
7.784
7.637
7.612
7.588
7.458
7.430
7.240
7.211
4.046
3.804
3.764
2.486
S
NH
N
O
H3CO
2f
300 MHz, DMSO-d6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.12
0.60
0.88
0.92
1.59
1.68


158.15
151.45
146.35
137.42
137.24
129.51
129.21
128.33
126.24
121.26
115.38
87.62
55.75
40.92
40.64
40.36
39.80
39.52
39.25
12.90
S
NH
N
O
H3CO
2f
75 MHz, DMSO-d6
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



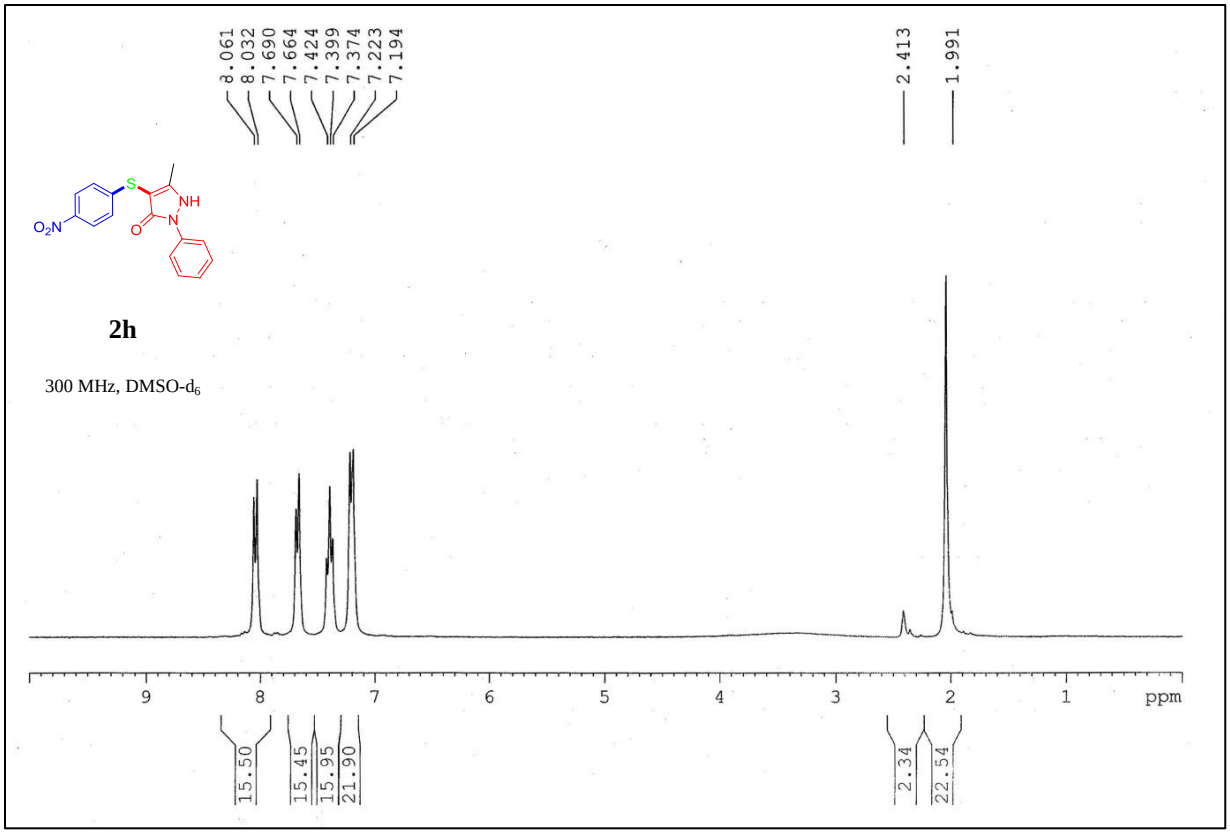
2g

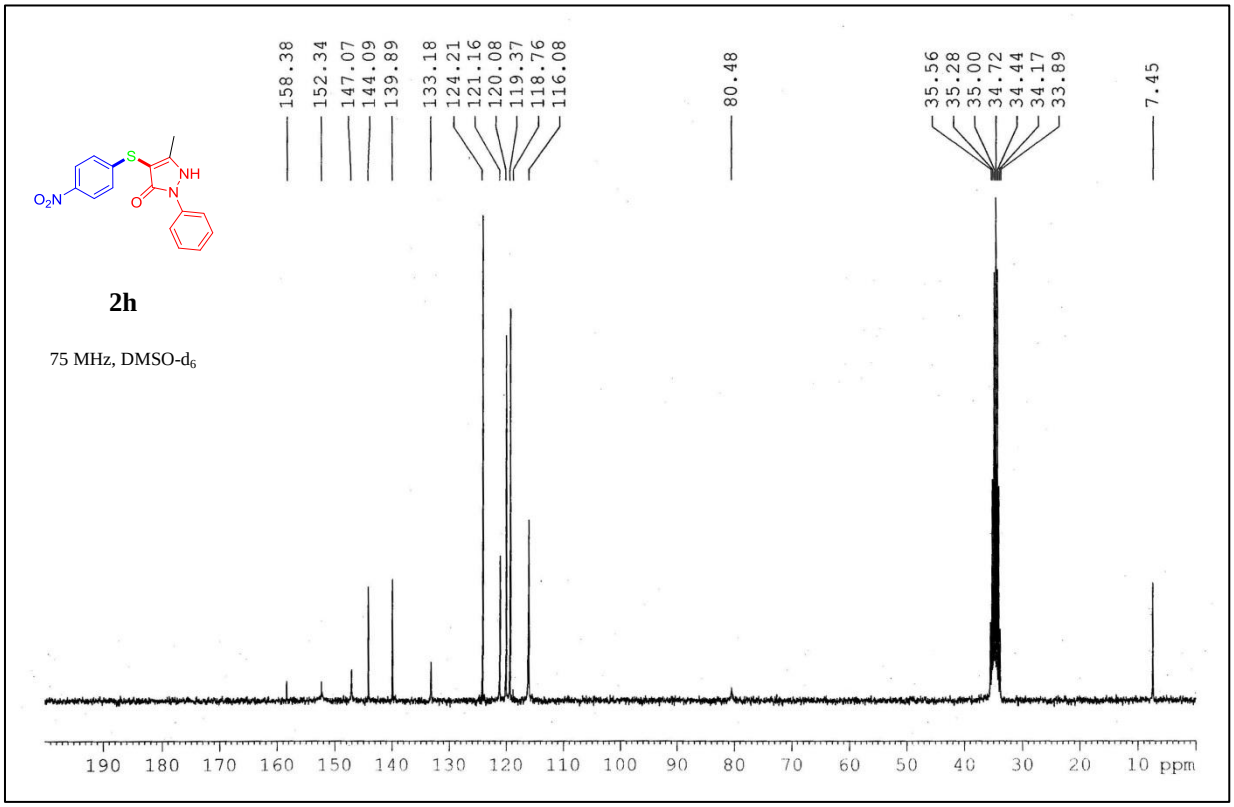
300 MHz, DMSO-d_6

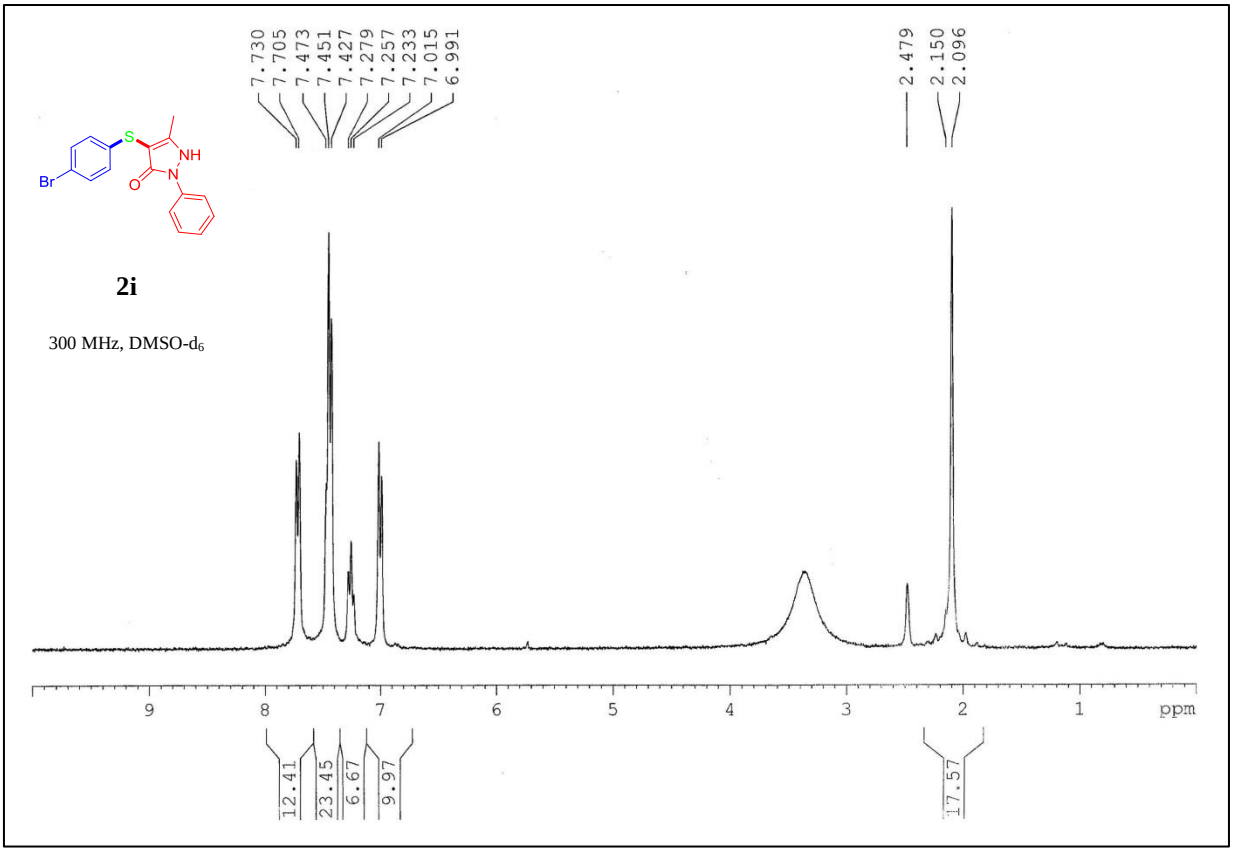


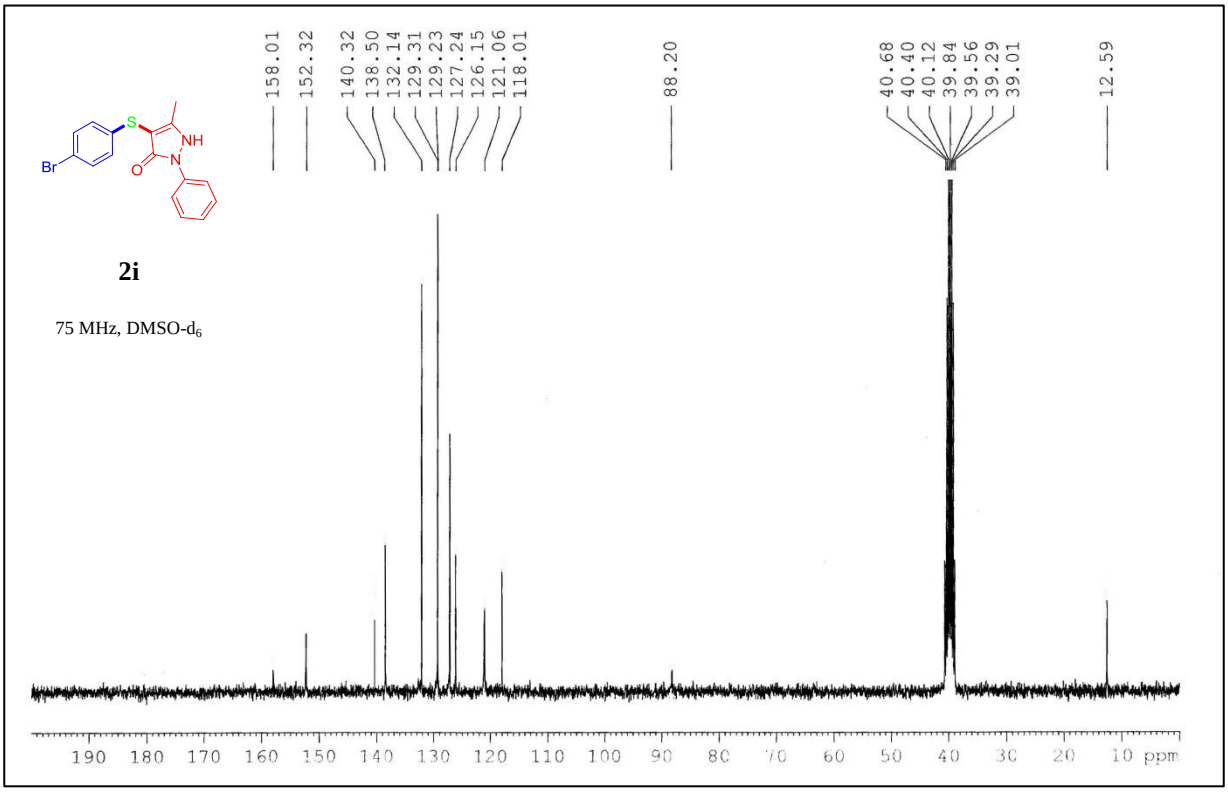
2g

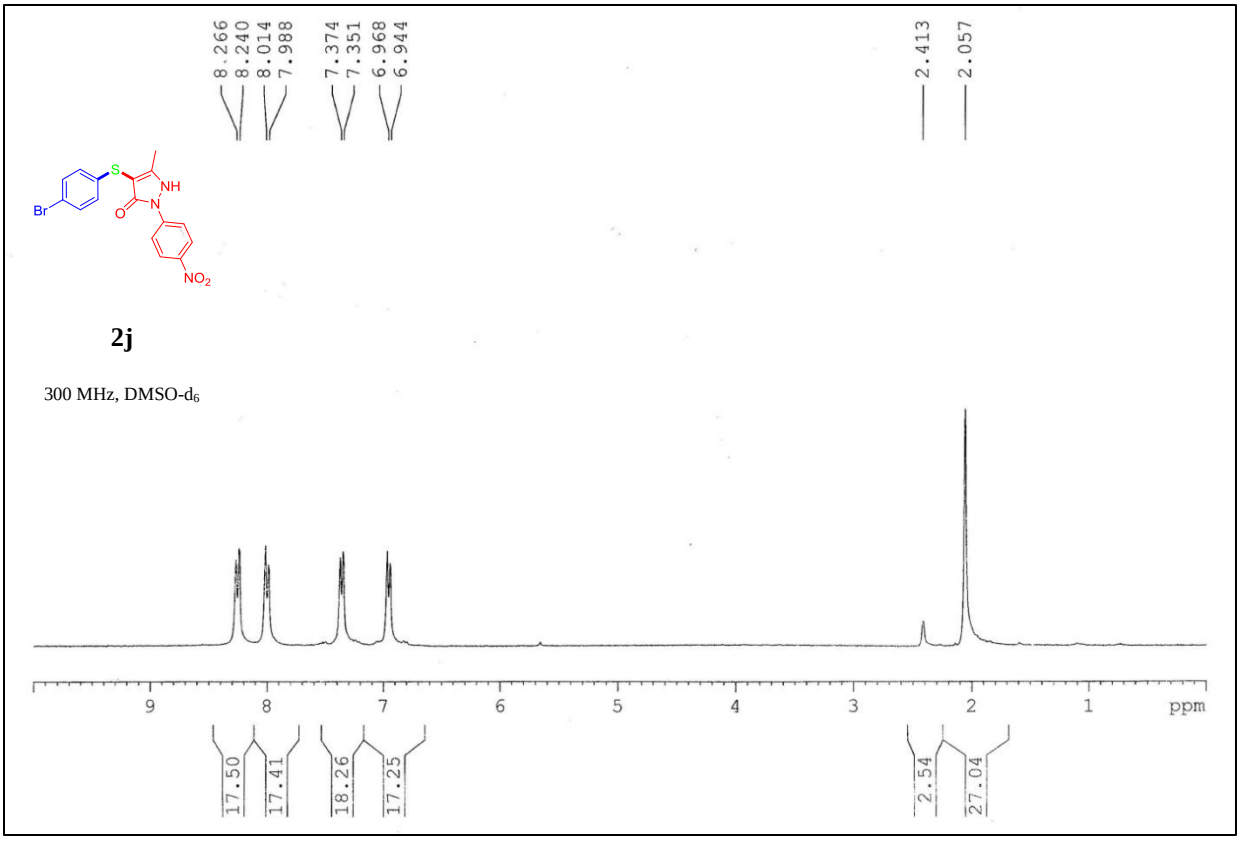
75 MHz, DMSO-d_6

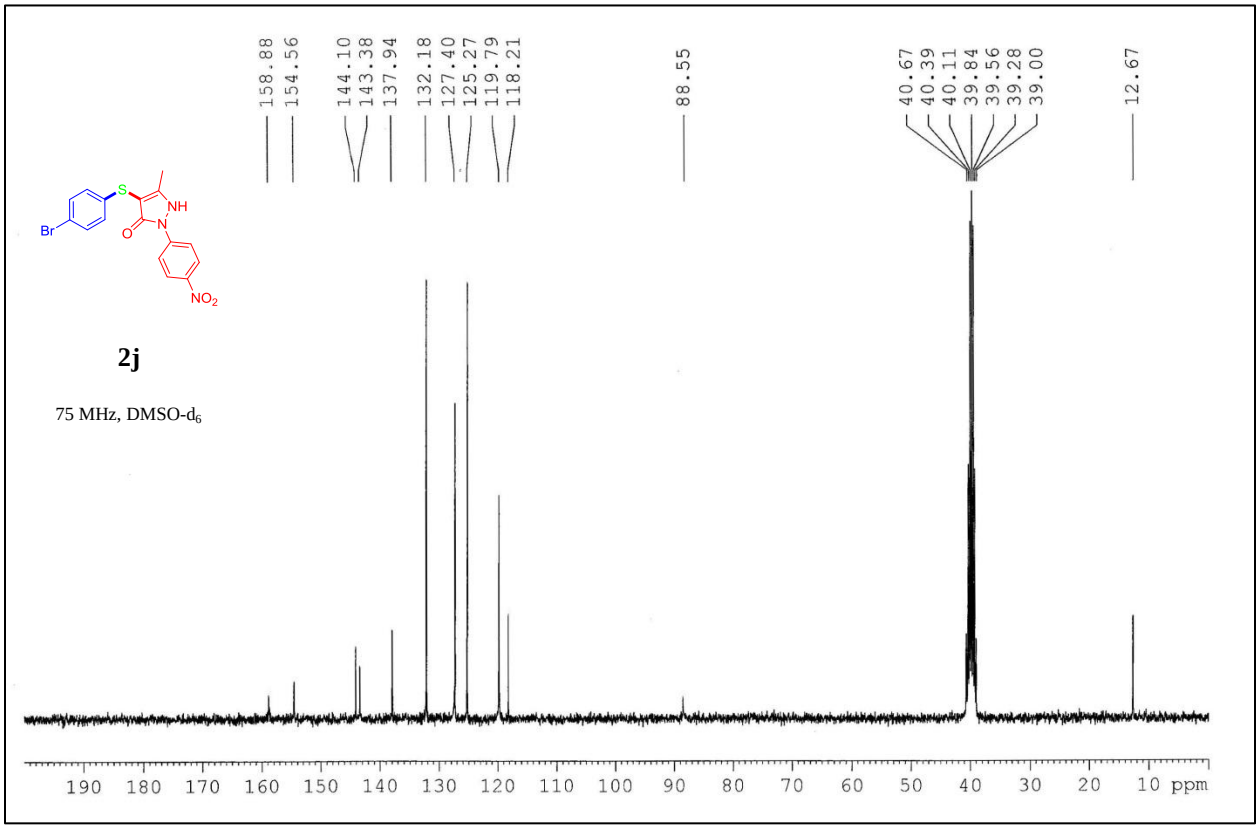

8.061
8.032
7.690
7.664
7.424
7.399
7.374
7.223
7.194
2.413
1.991
O2N
S
NH
N
O
2h
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
15.50
15.45
15.95
21.90
2.34
22.54

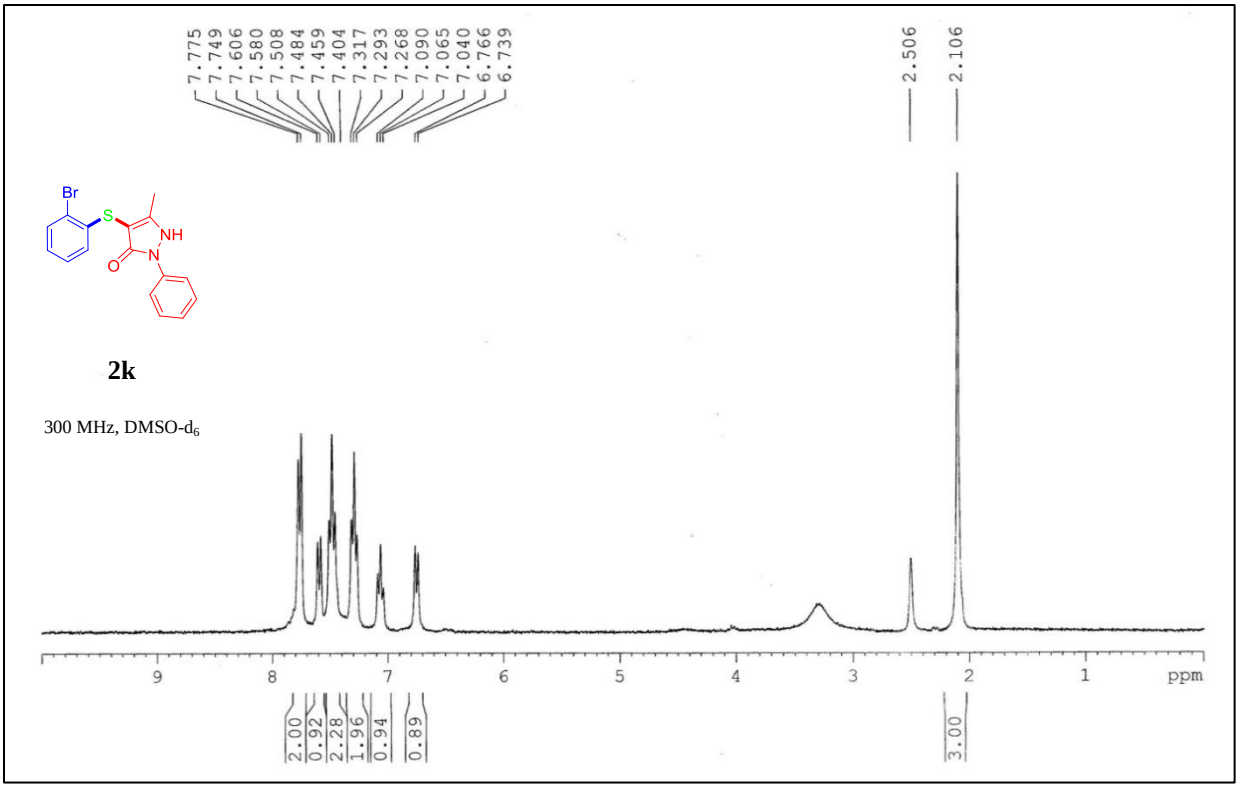

158.38
152.34
147.07
144.09
139.89
133.18
124.21
121.16
120.08
119.37
118.76
116.08
80.48
35.56
35.28
35.00
34.72
34.44
34.17
33.89
7.45
O2N
S
NH
N
O
2h
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

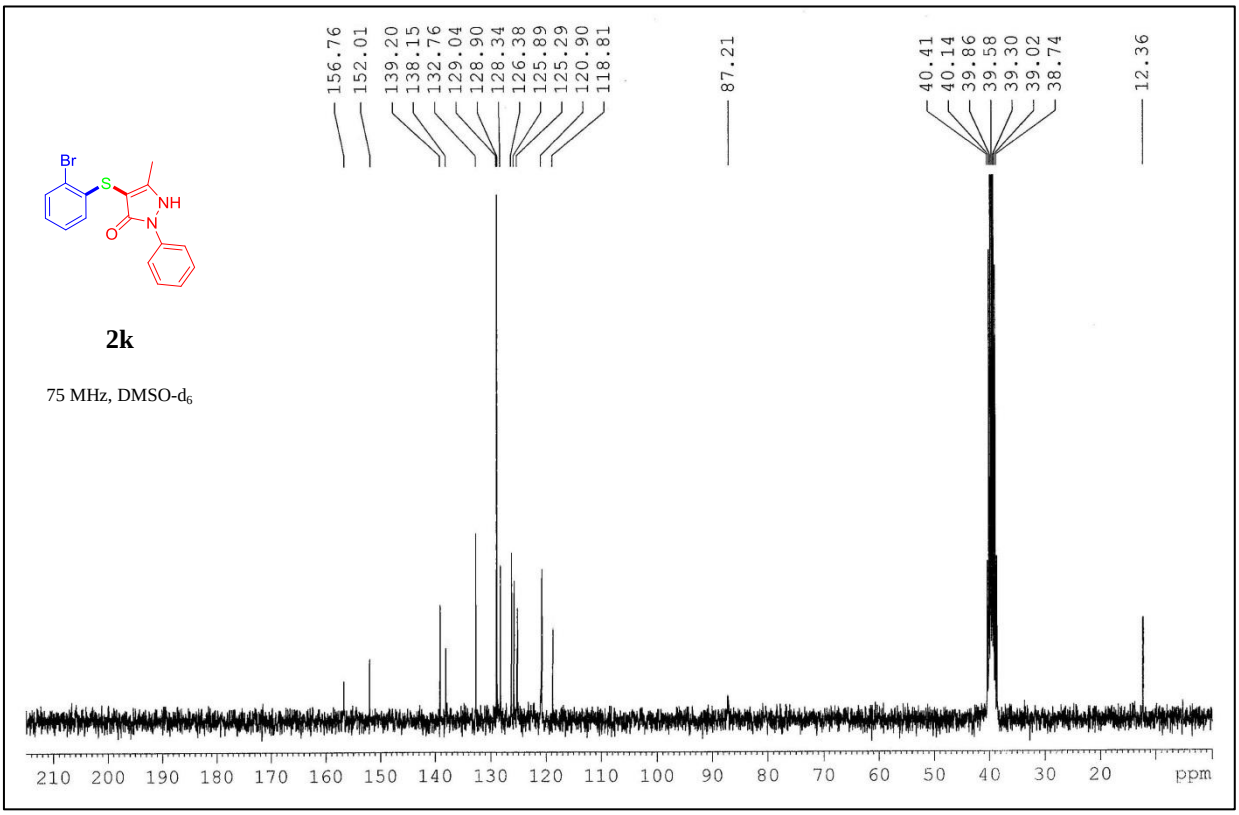

7.730
7.705
7.473
7.451
7.427
7.279
7.257
7.233
7.015
6.991
2.479
2.150
2.096
Br
S
NH
N
O
2i
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
12.41
23.45
6.67
9.97
17.57

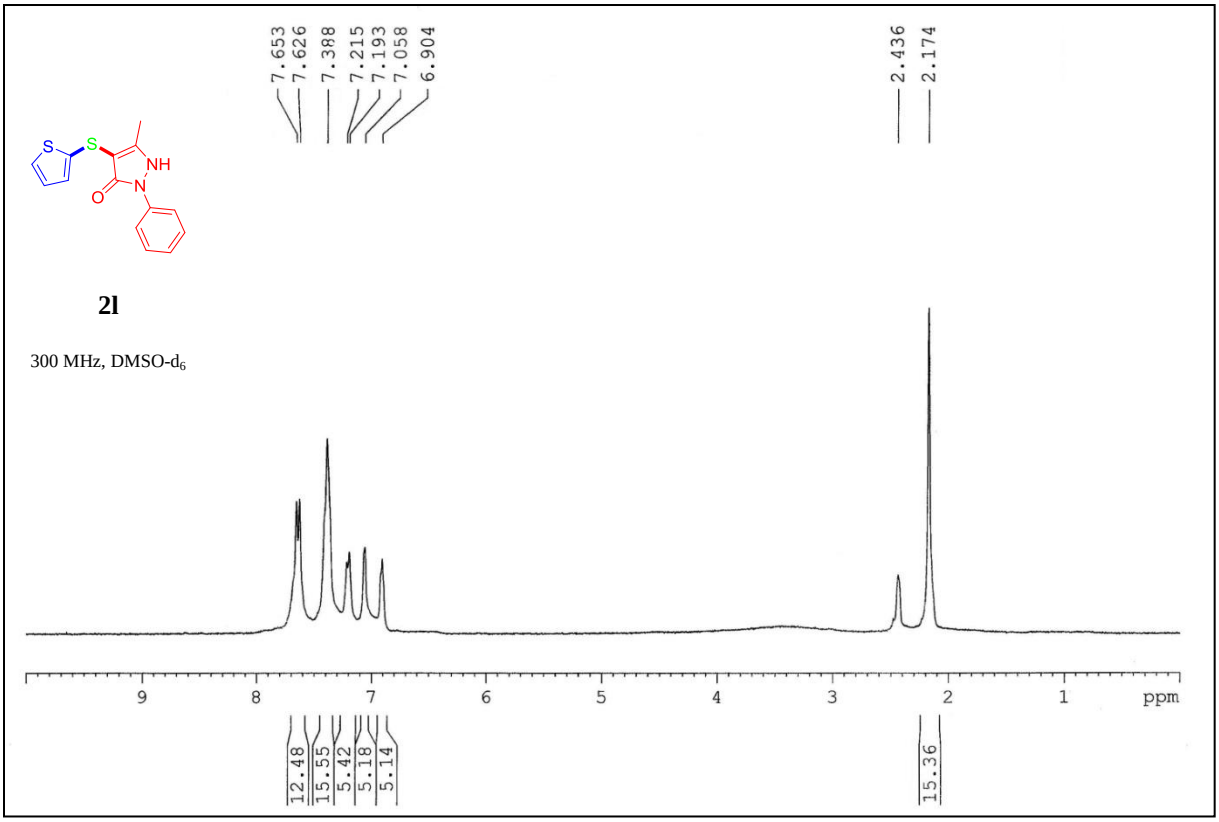

158.01
152.32
140.32
138.50
132.14
129.31
129.23
127.24
126.15
121.06
118.01
88.20
40.68
40.40
40.12
39.84
39.56
39.29
39.01
12.59
Br
S
NH
N
O
2i
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm


8.266
8.240
8.014
7.988
7.374
7.351
6.968
6.944
2.413
2.057
Br
S
NH
N
O
NO2
2j
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
17.50
17.41
18.26
17.25
2.54
27.04


158.88
154.56
144.10
143.38
137.94
132.18
127.40
125.27
119.79
118.21
88.55
40.67
40.39
40.11
39.84
39.56
39.28
39.00
12.67
Br
S
NH
N
O
NO2
2j
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

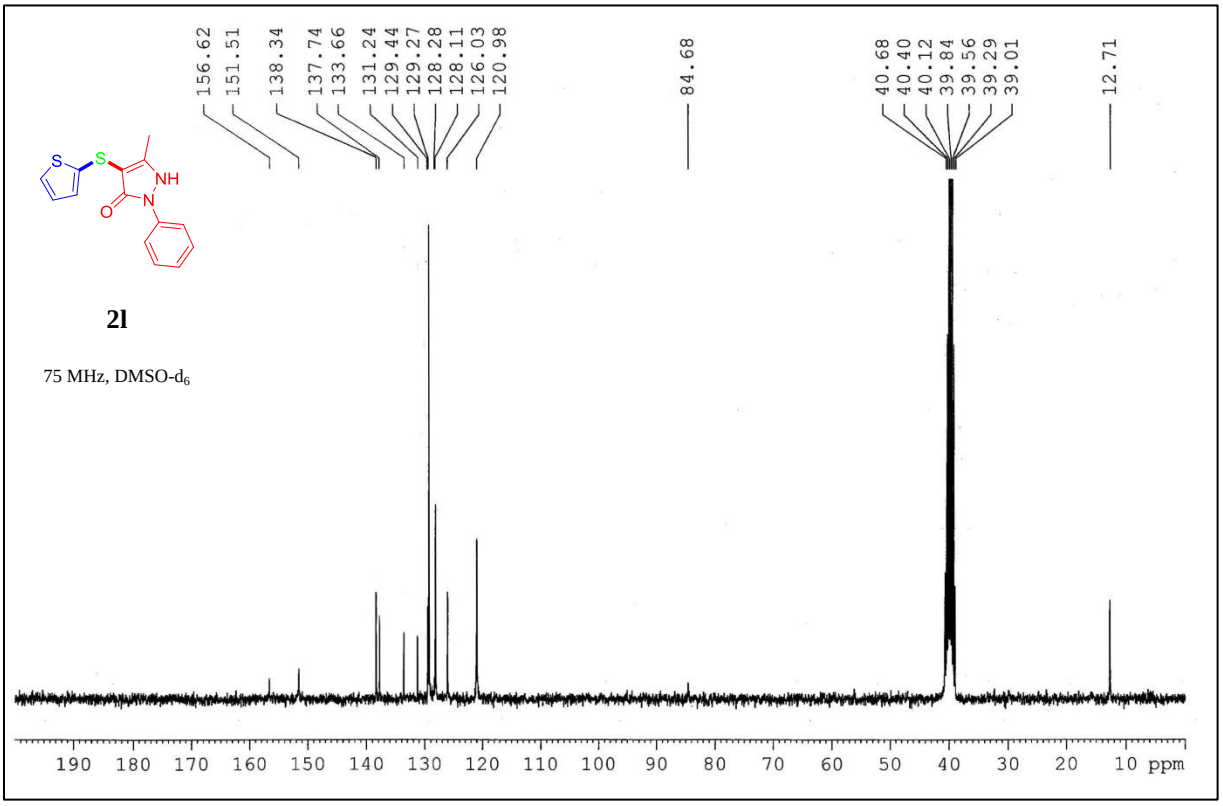

7.775
7.749
7.606
7.580
7.508
7.484
7.459
7.404
7.317
7.293
7.268
7.090
7.065
7.040
6.766
6.739
2.506
2.106
Br
S
NH
N
O
2k
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
2.00
0.92
2.28
1.96
0.94
0.89
3.00


156.76
152.01
139.20
138.15
132.76
129.04
128.90
128.34
126.38
125.89
125.29
120.90
118.81
87.21
40.41
40.14
39.86
39.58
39.30
39.02
38.74
12.36
Br
S
NH
N
O
2k
75 MHz, DMSO-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



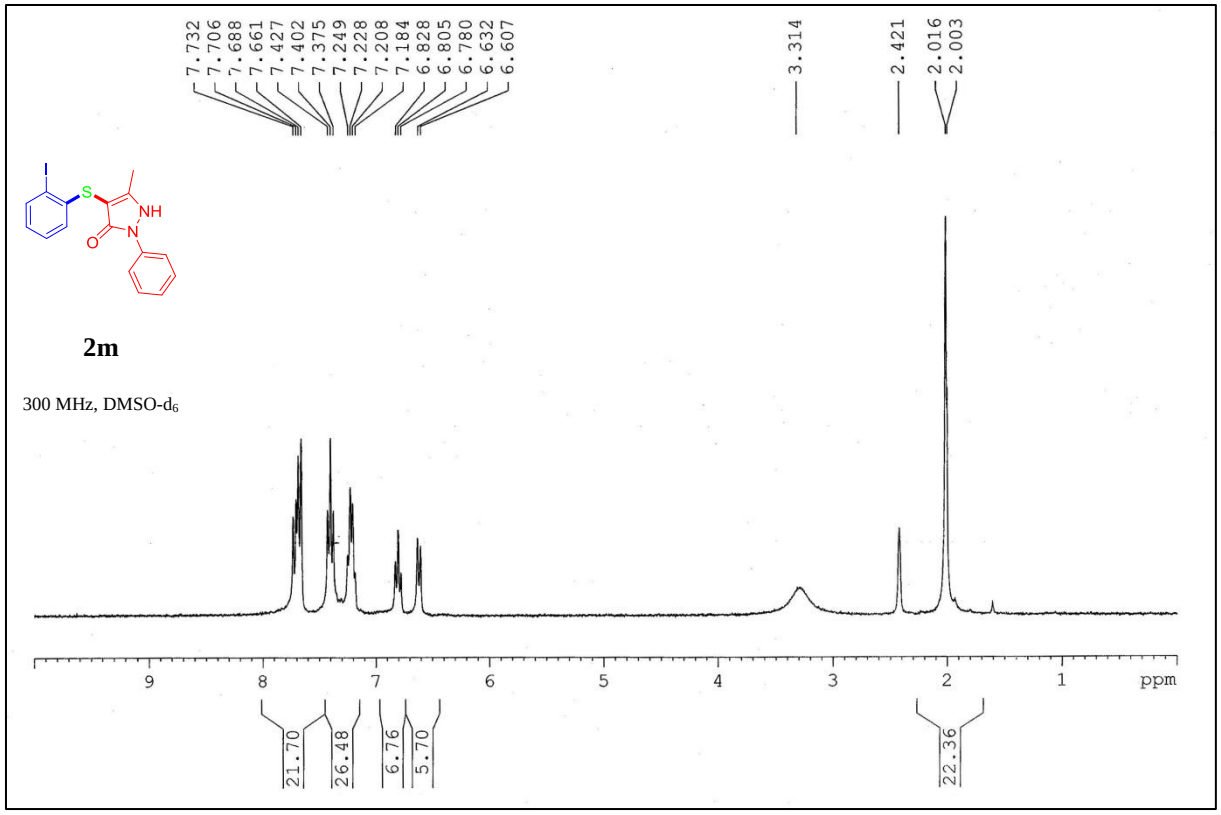
2l

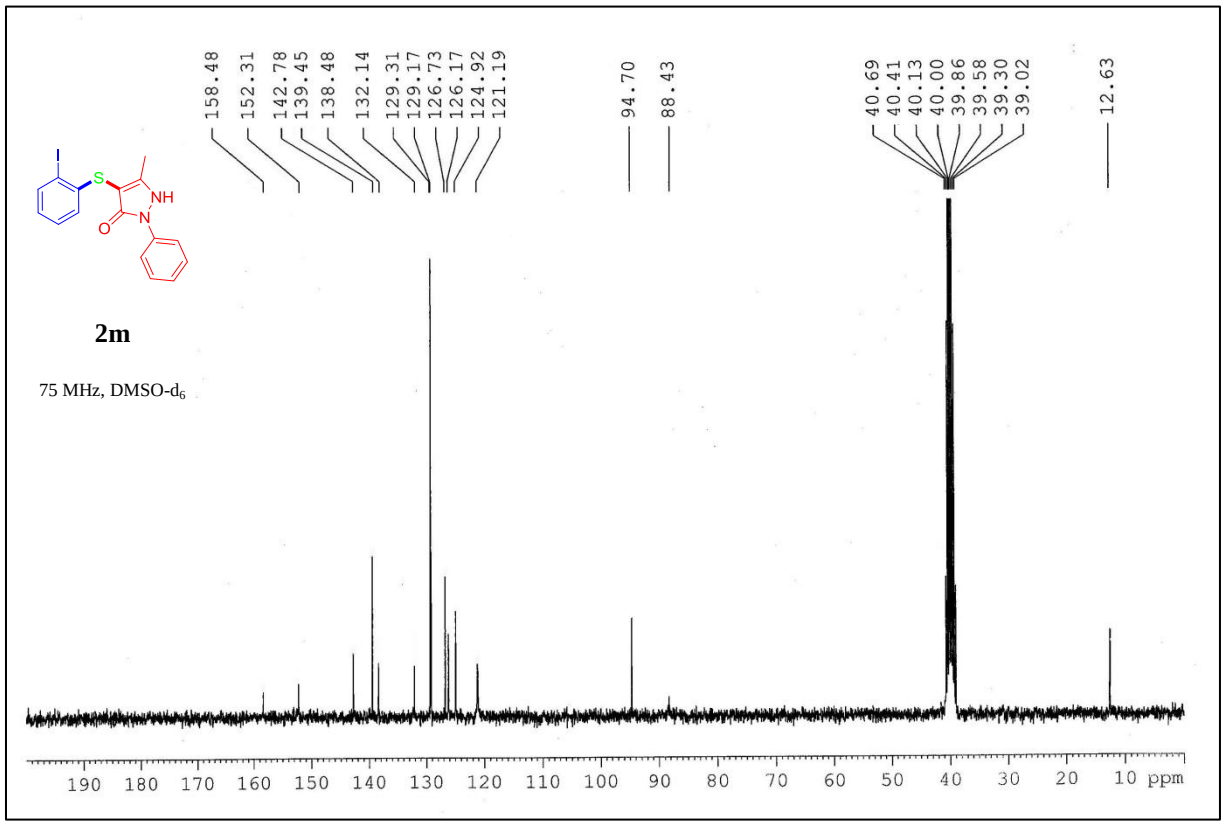
300 MHz, DMSO-d_6

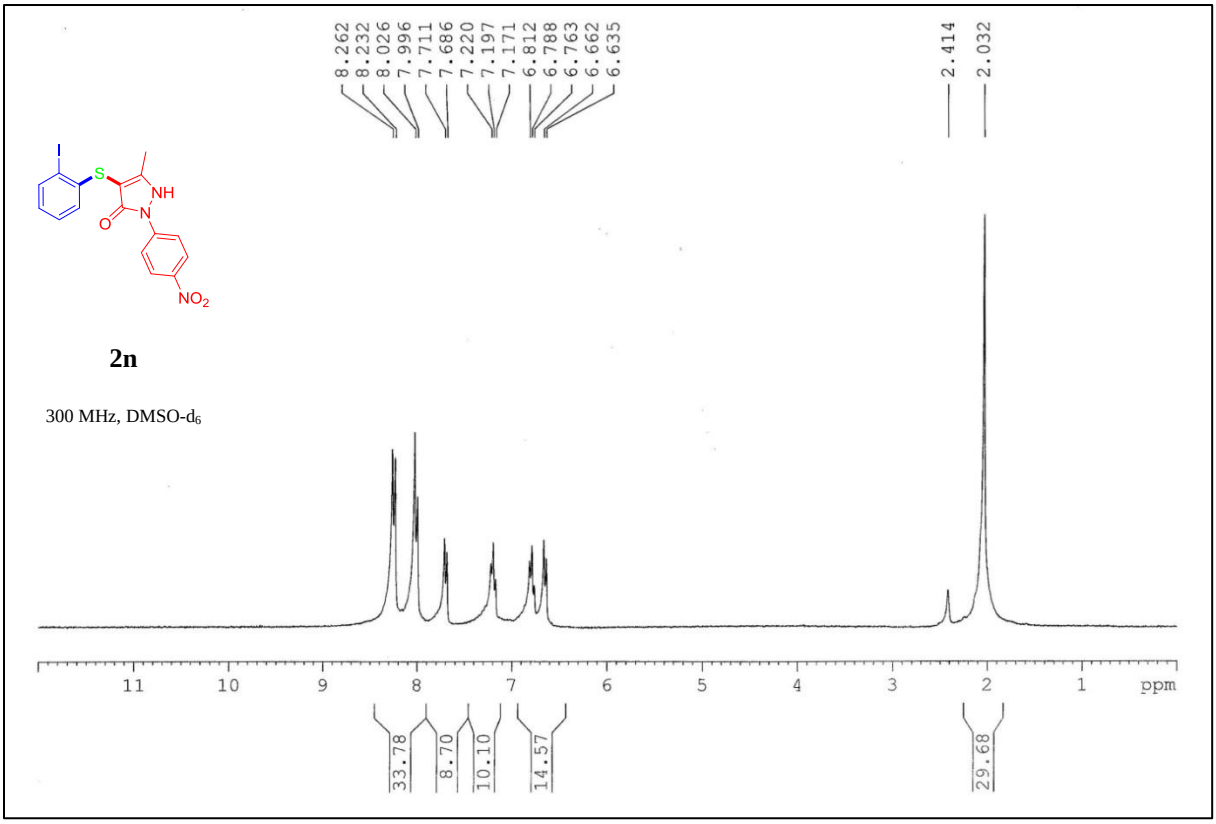


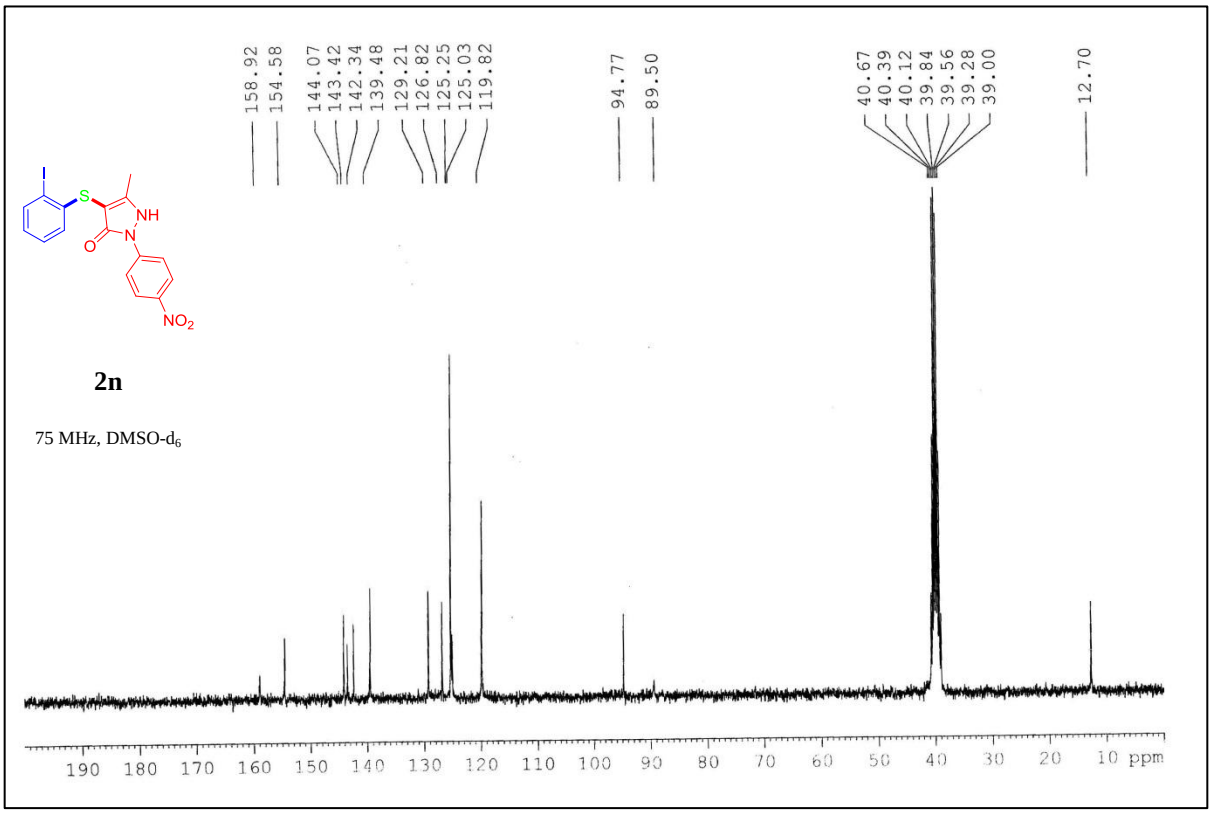
2l

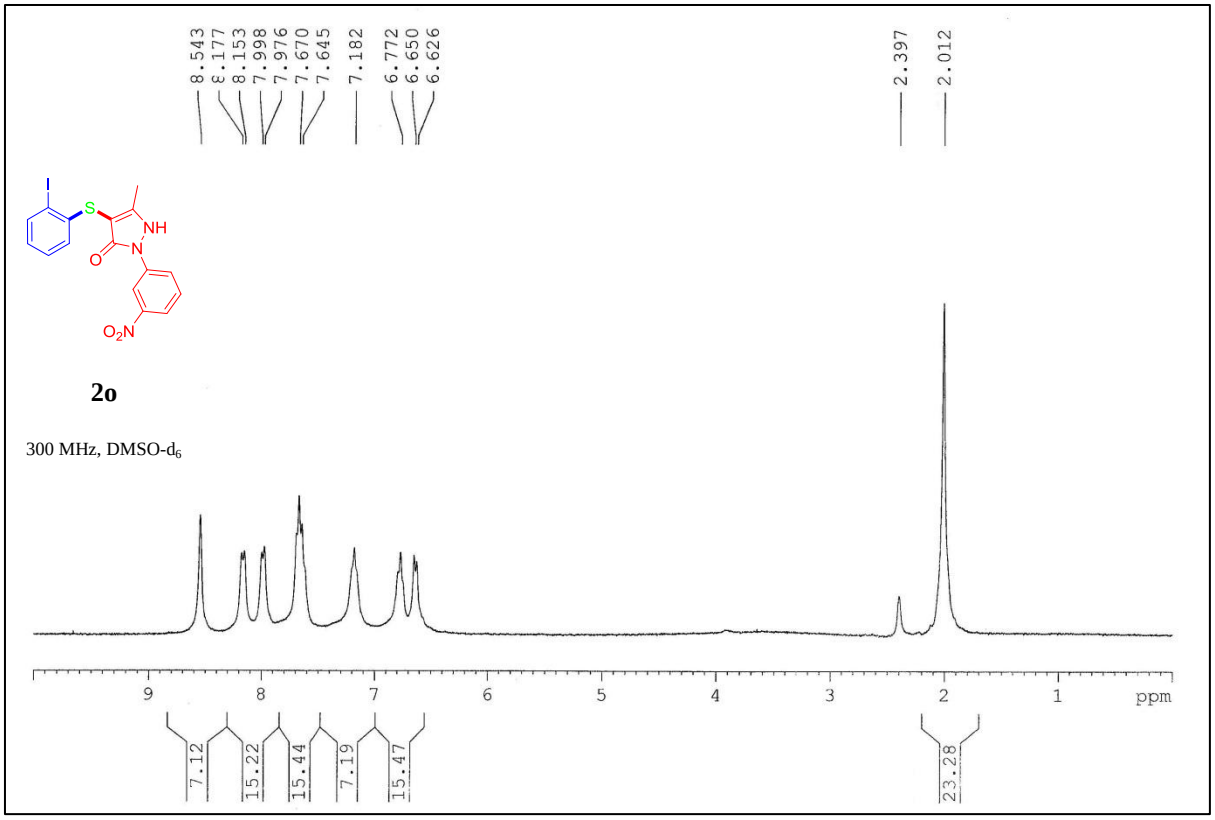
75 MHz, DMSO-d_6


7.732
7.706
7.688
7.661
7.427
7.402
7.375
7.249
7.228
7.208
7.184
6.828
6.805
6.780
6.632
6.607
3.314
2.421
2.016
2.003
I
S
NH
N
O
2m
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
21.70
26.48
6.76
5.70
22.36


158.48
152.31
142.78
139.45
138.48
132.14
129.31
129.17
126.73
126.17
124.92
121.19
94.70
88.43
40.69
40.41
40.13
40.00
39.86
39.58
39.30
39.02
12.63
I
S
NH
N
O
2m
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

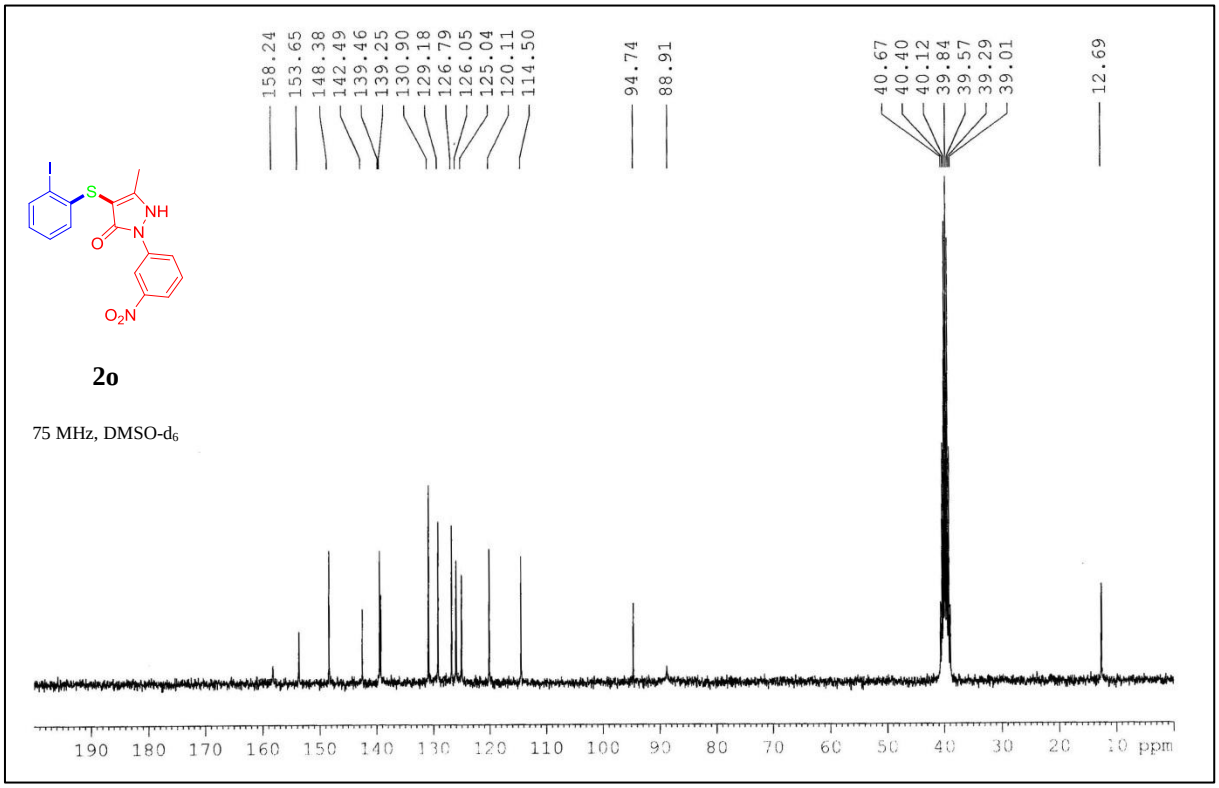

8.262
8.232
8.026
7.996
7.711
7.686
7.220
7.197
7.171
6.812
6.788
6.763
6.662
6.635
2.414
2.032
I
S
NH
O
N
NO2
2n
300 MHz, DMSO-d6
11
10
9
8
7
6
5
4
3
2
1
ppm
33.78
8.70
10.10
14.57
29.68


158.92
154.58
144.07
143.42
142.34
139.48
129.21
126.82
125.25
125.03
119.82
94.77
89.50
40.67
40.39
40.12
39.84
39.56
39.28
39.00
12.70
I
S
NH
O
N
NO2
2n
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm



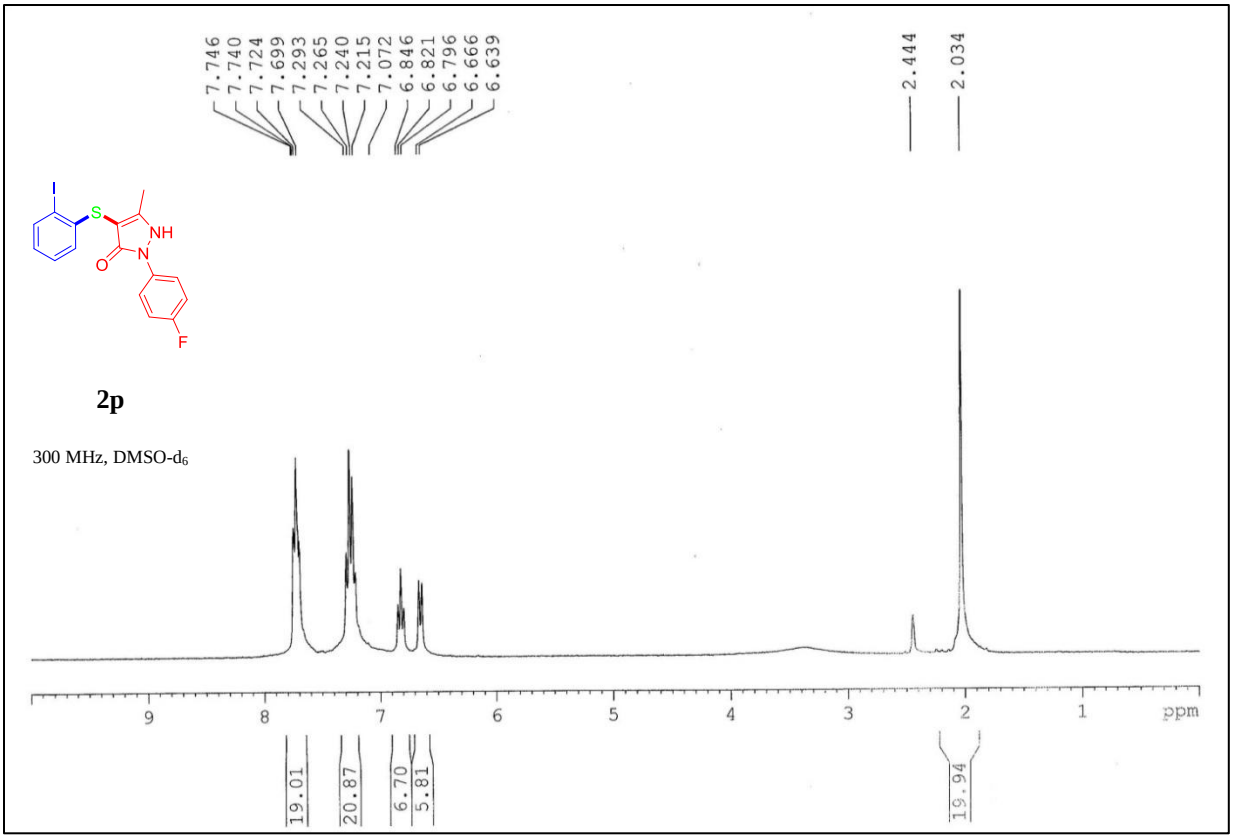
2o

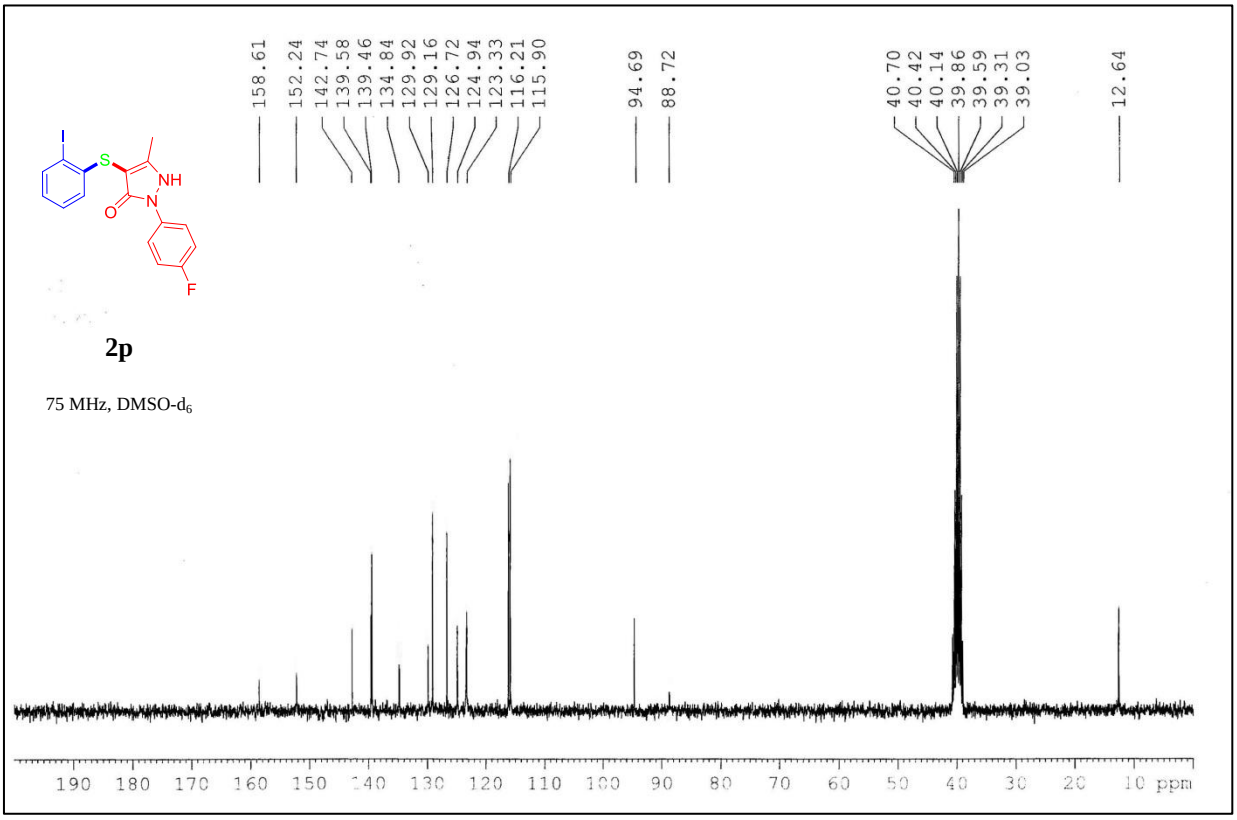
300 MHz, DMSO-d_6

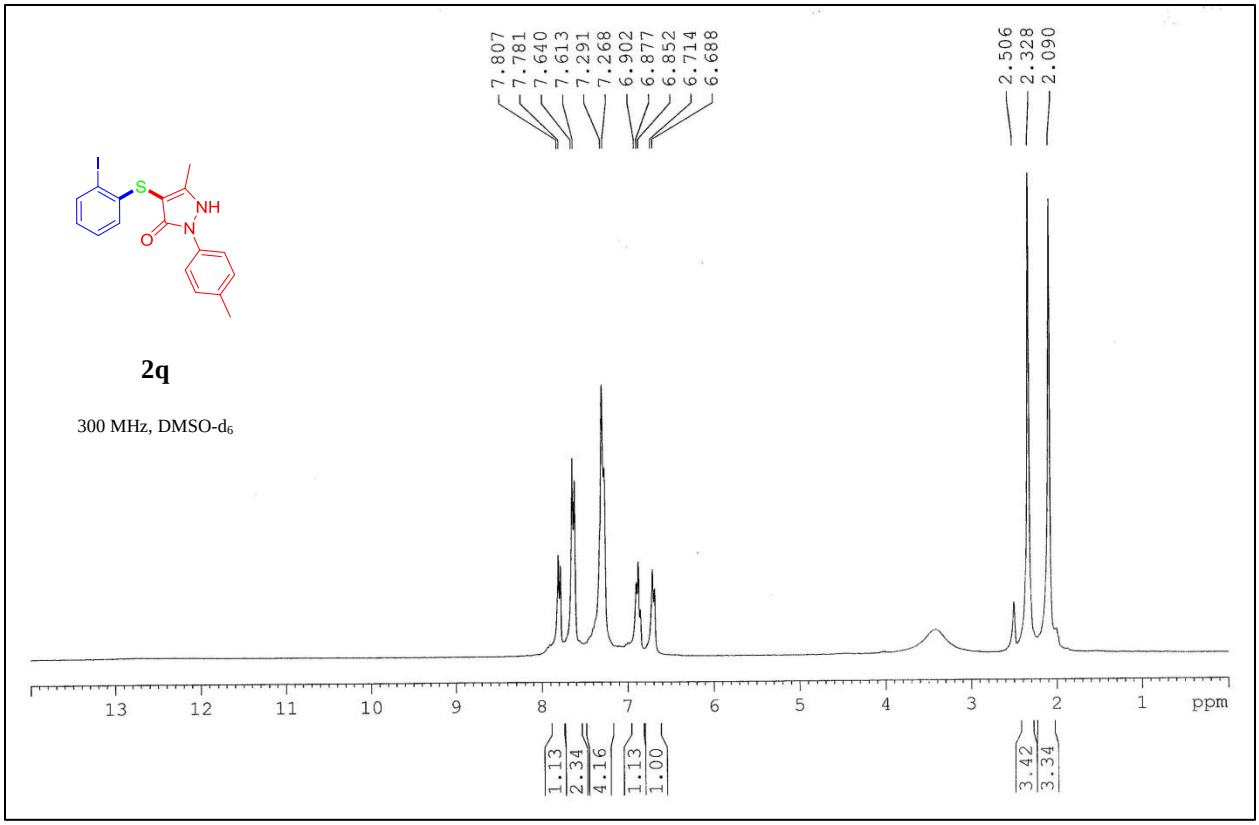


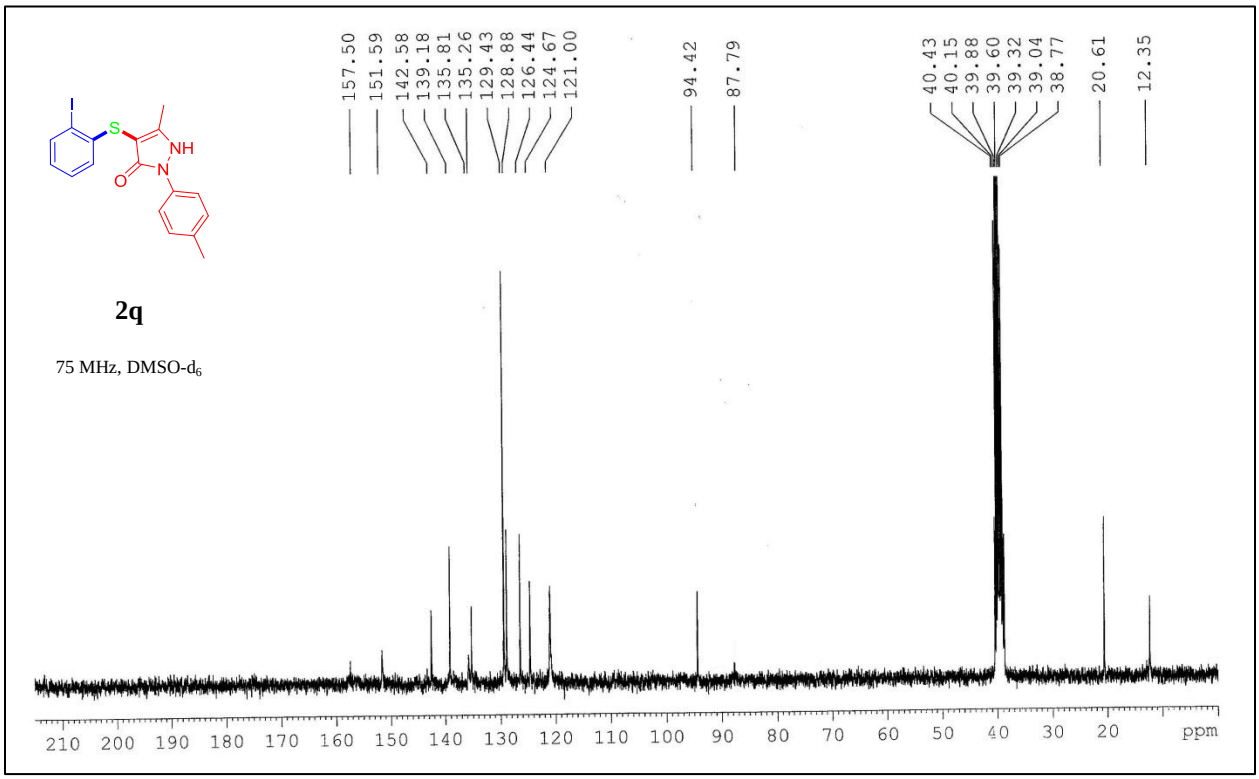
2o

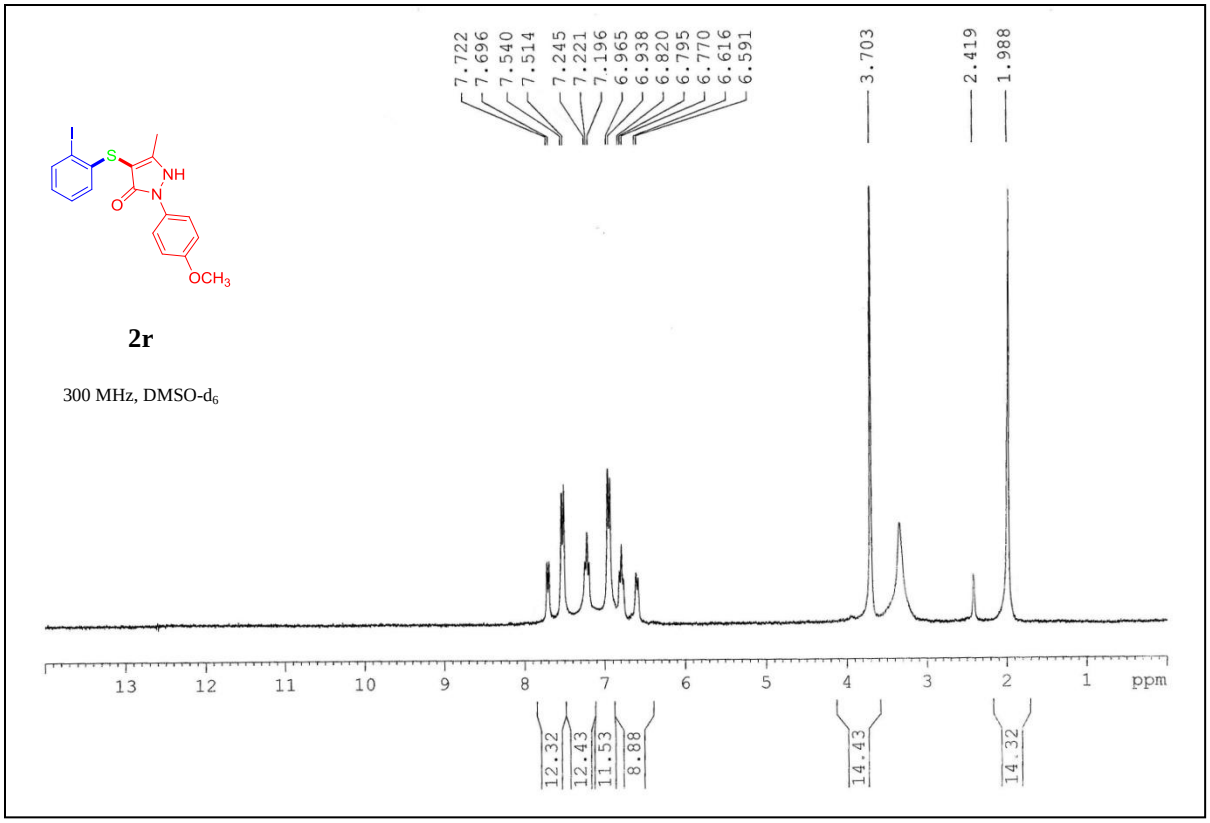
75 MHz, DMSO-d_6


7.746
7.740
7.724
7.699
7.293
7.265
7.240
7.215
7.072
6.846
6.821
6.796
6.666
6.639
2.444
2.034
I
S
NH
N
O
F
2p
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
19.01
20.87
6.70
5.81
19.94


158.61
152.24
142.74
139.58
139.46
134.84
129.92
129.16
126.72
124.94
123.33
116.21
115.90
94.69
88.72
40.70
40.42
40.14
39.86
39.59
39.31
39.03
12.64
I
S
NH
N
O
F
2p
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

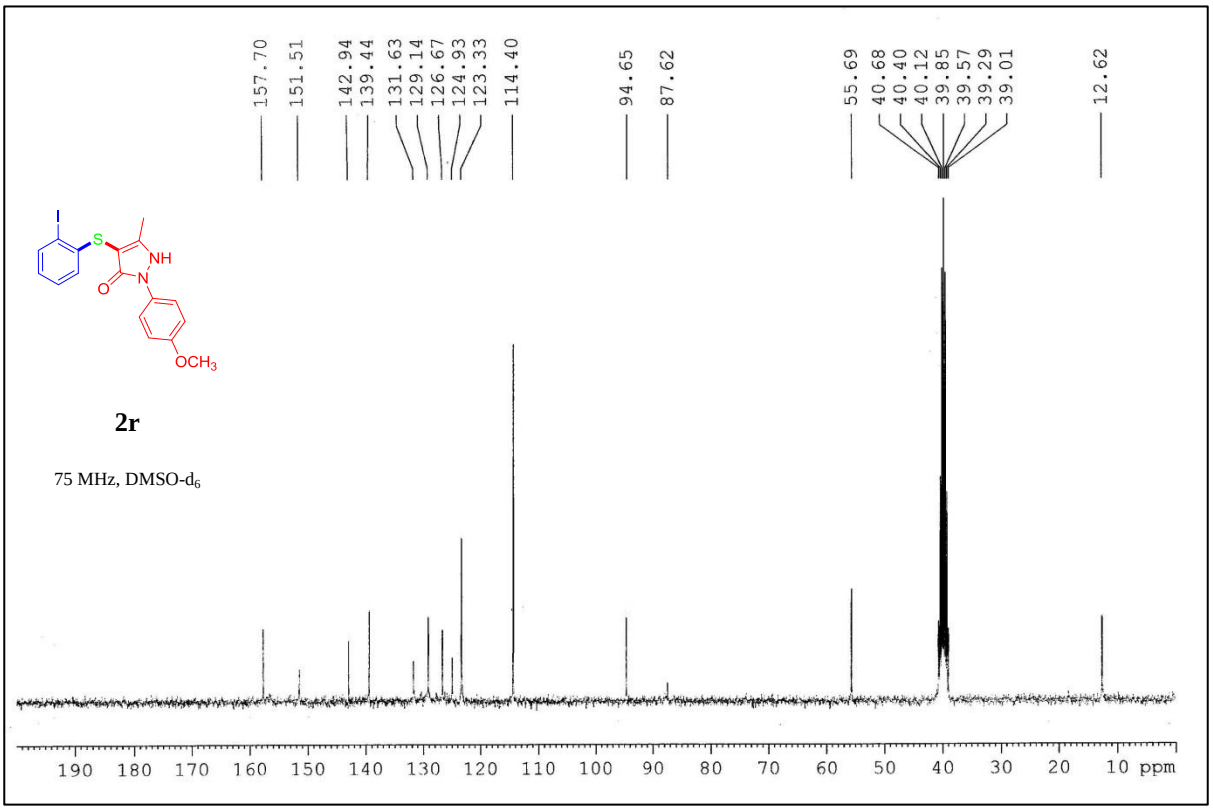

7.807
7.781
7.640
7.613
7.291
7.268
6.902
6.877
6.852
6.714
6.688
2.506
2.328
2.090
NH
O
N
S
I
2q
300 MHz, DMSO-d6
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.13
2.34
4.16
1.13
1.00
3.42
3.34


157.50
151.59
142.58
139.18
135.81
135.26
129.43
128.88
126.44
124.67
121.00
94.42
87.79
40.43
40.15
39.88
39.60
39.32
39.04
38.77
20.61
12.35
NH
O
N
S
I
2q
75 MHz, DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



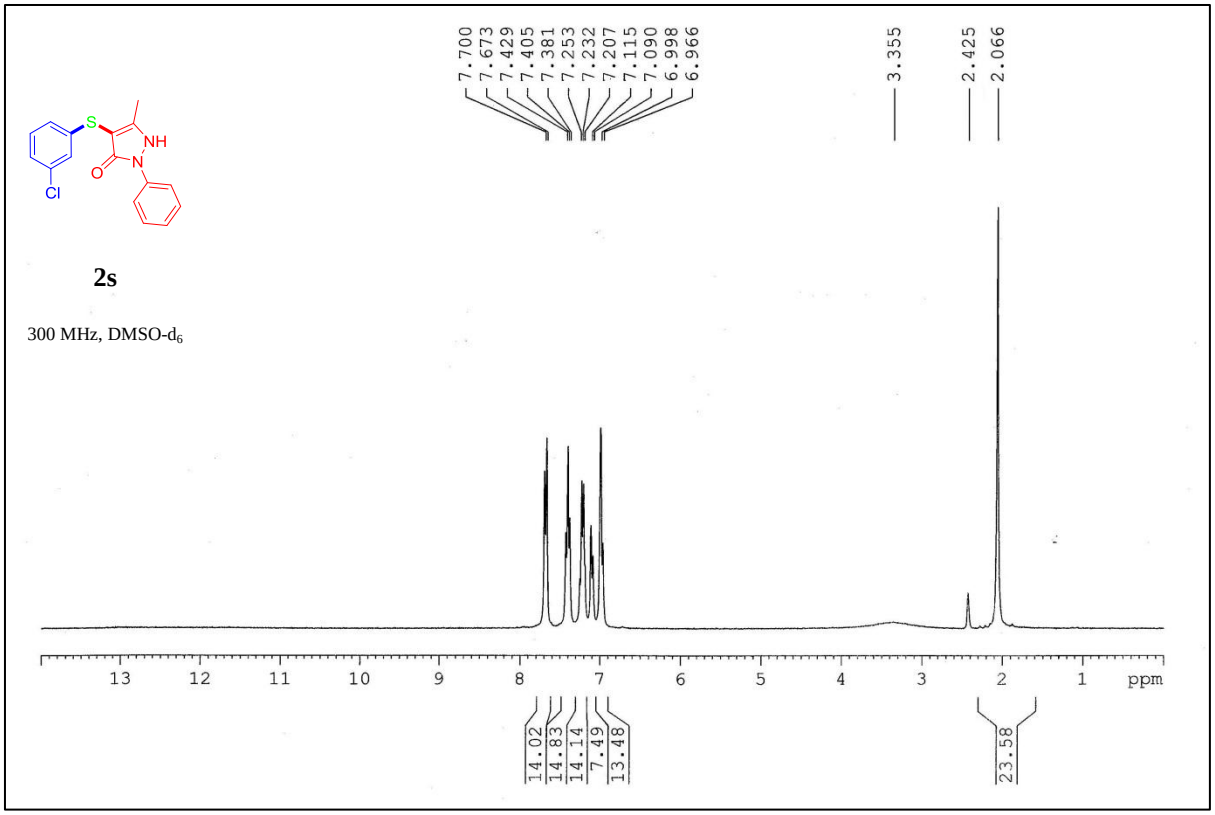
2r

300 MHz, DMSO-d_6



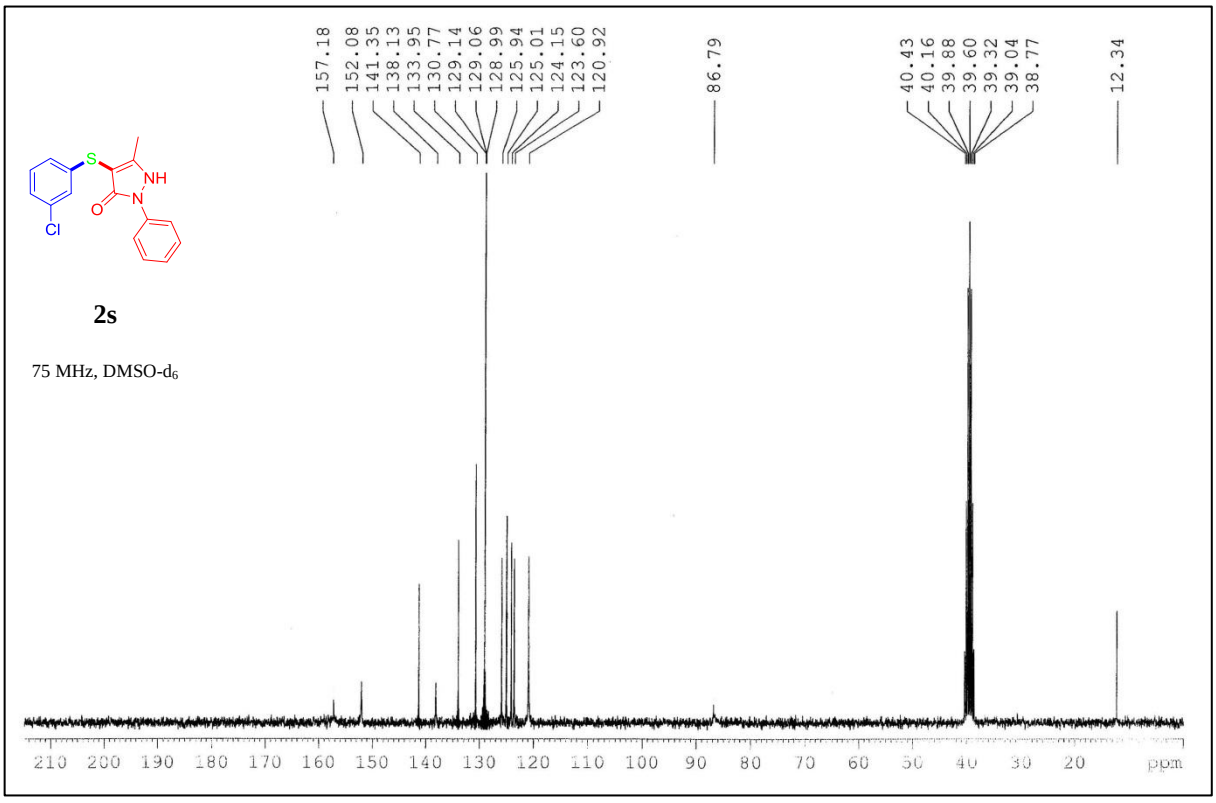
2r

75 MHz, DMSO-d_6



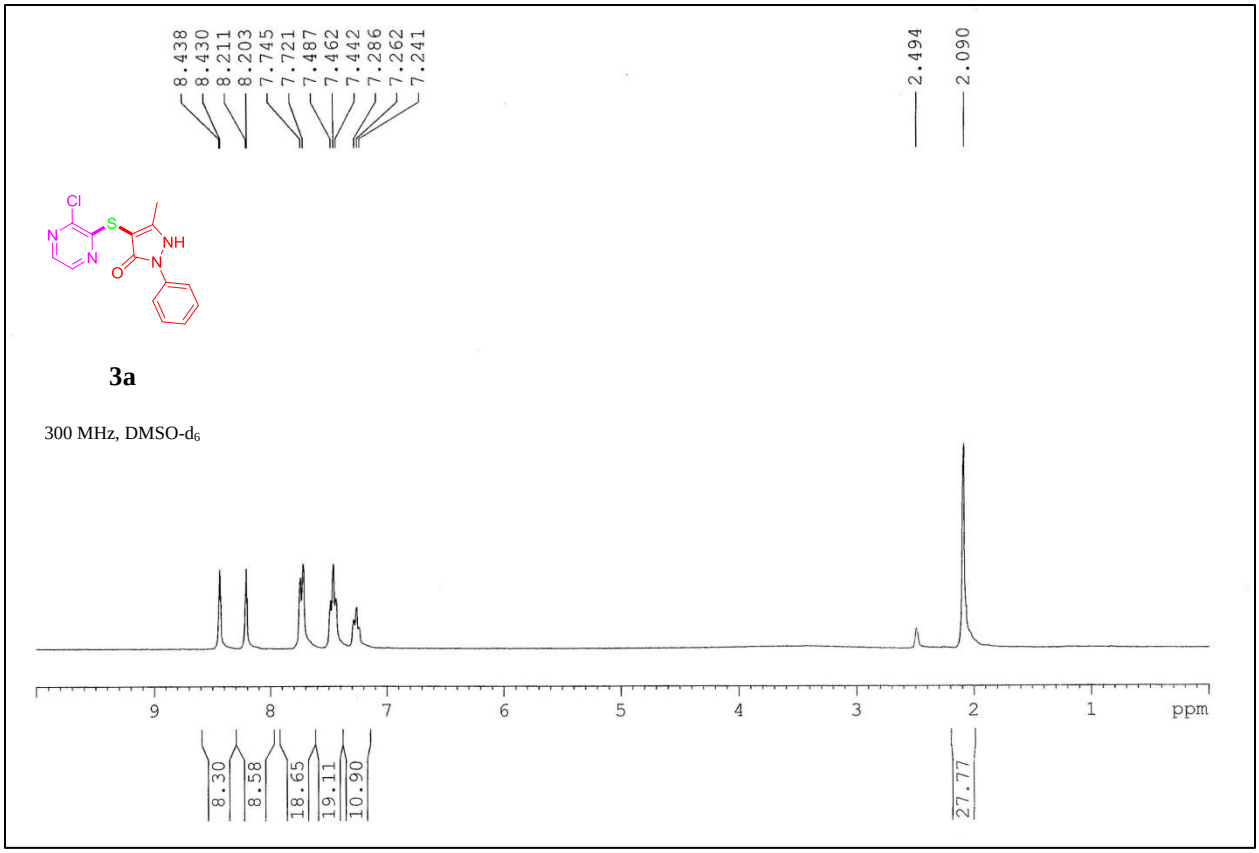
2s

300 MHz, DMSO-d_6



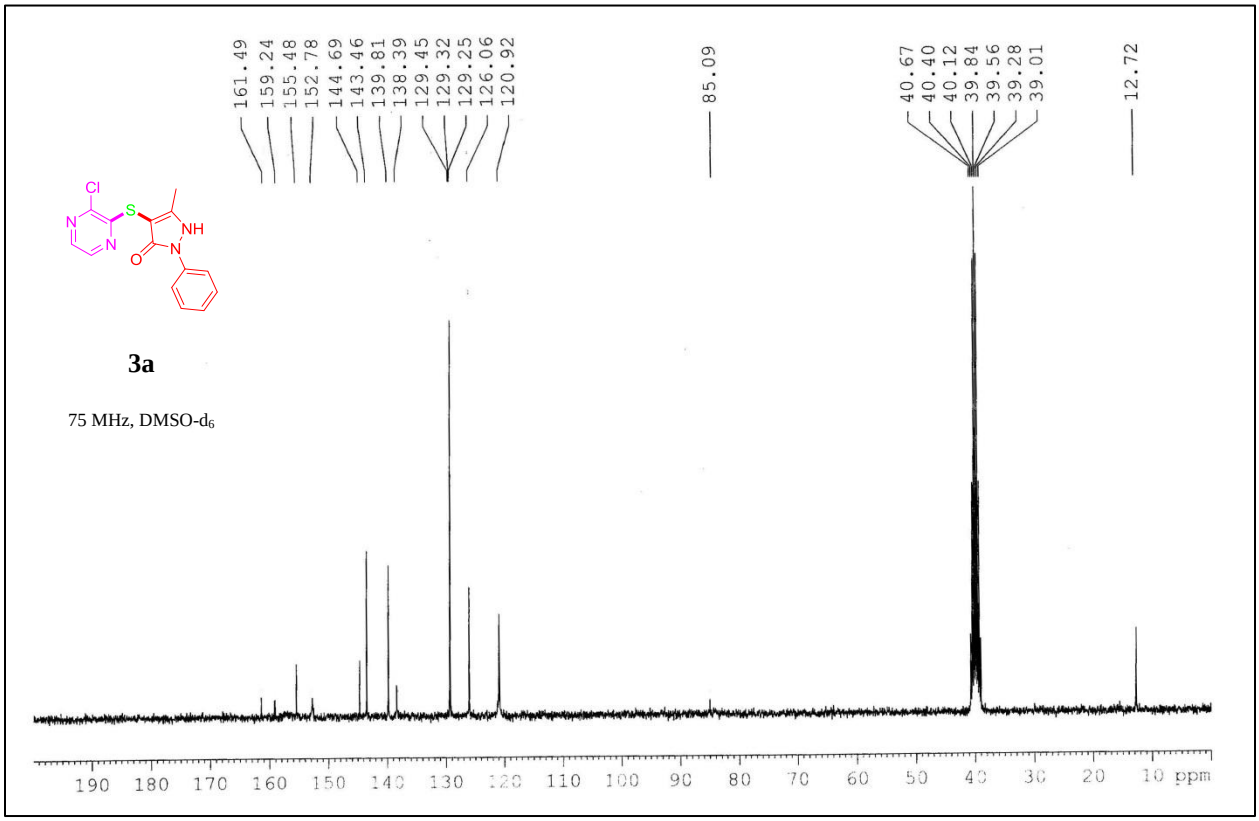
2s

75 MHz, DMSO-d_6



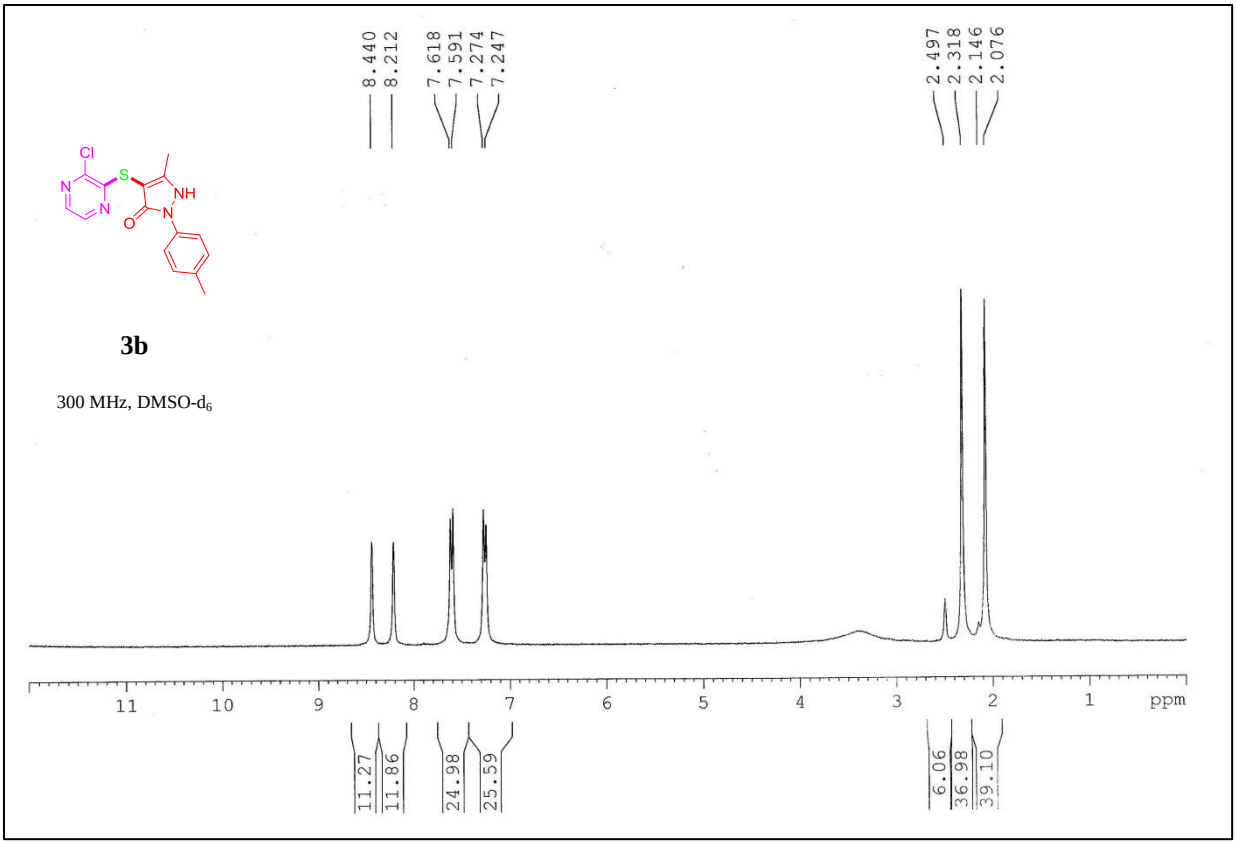
3a

300 MHz, DMSO-d_6



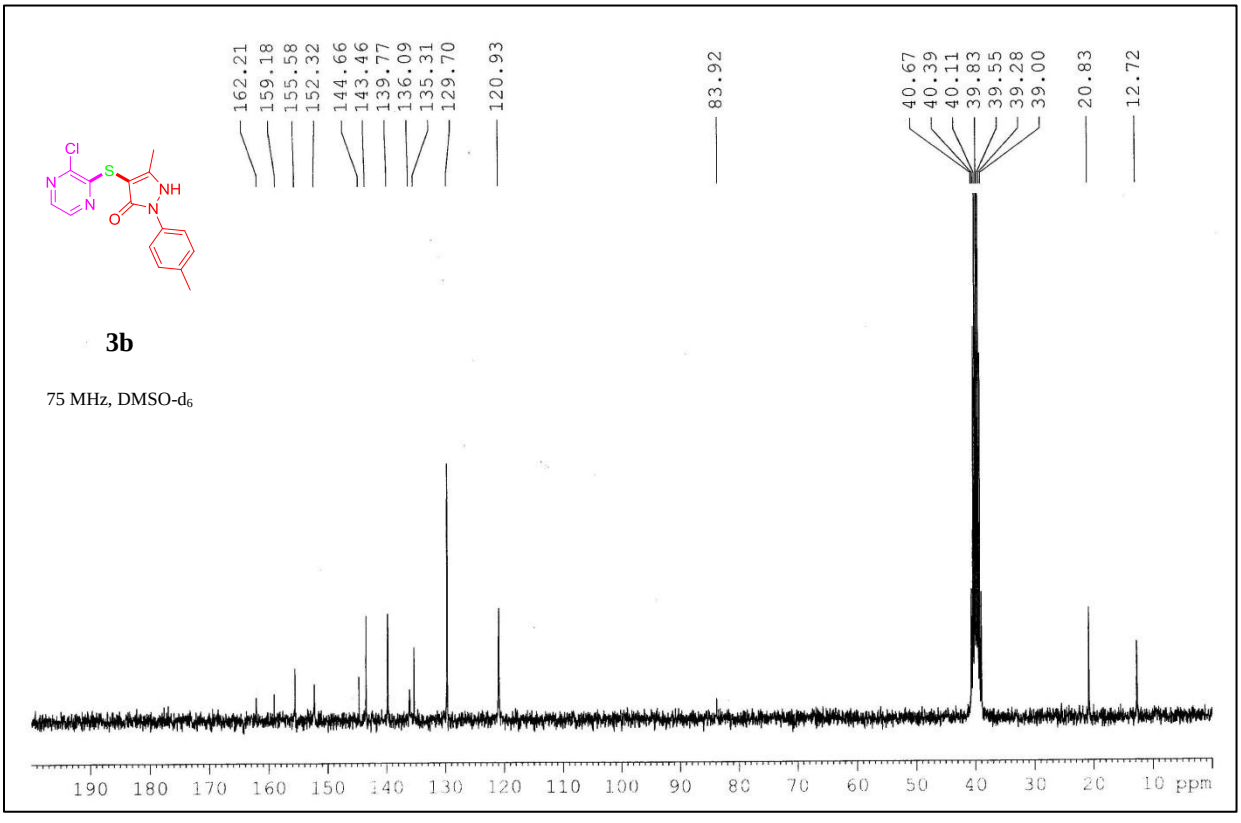
3a

75 MHz, DMSO-d_6



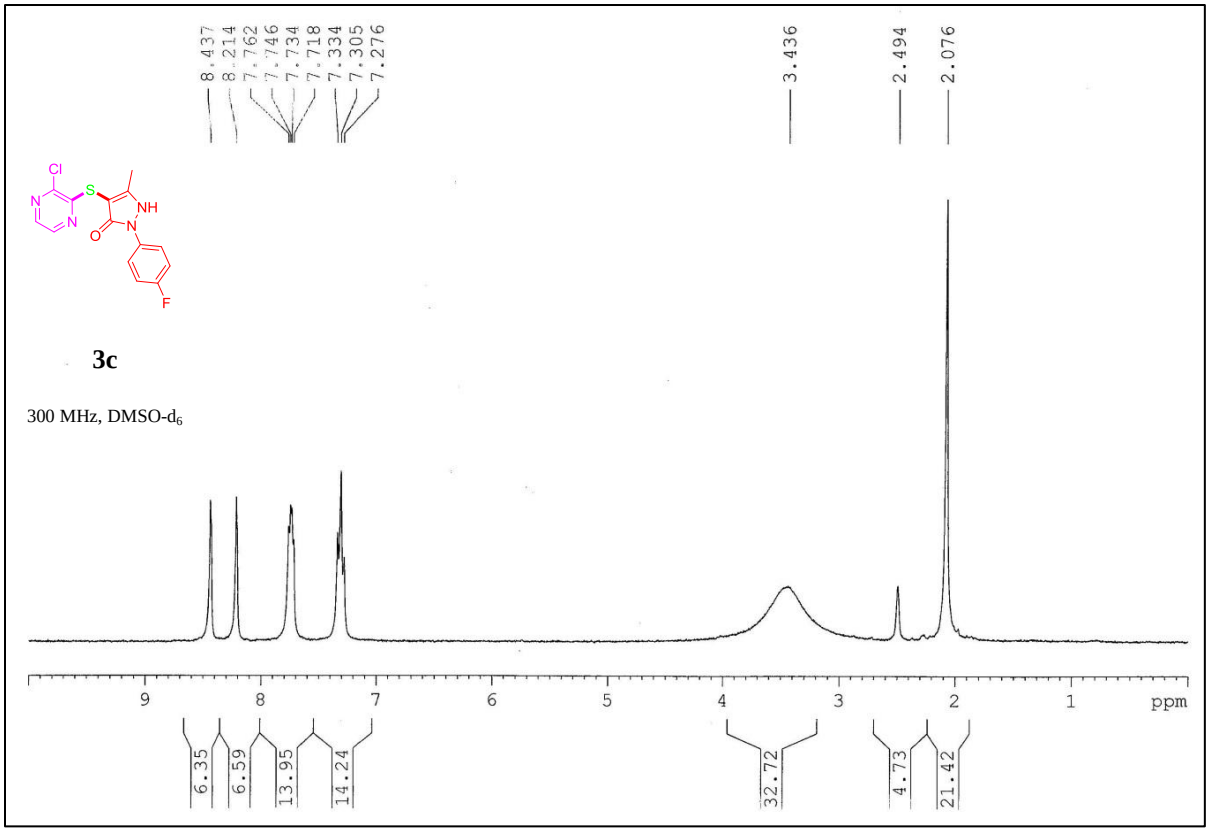
3b

300 MHz, DMSO-d_6



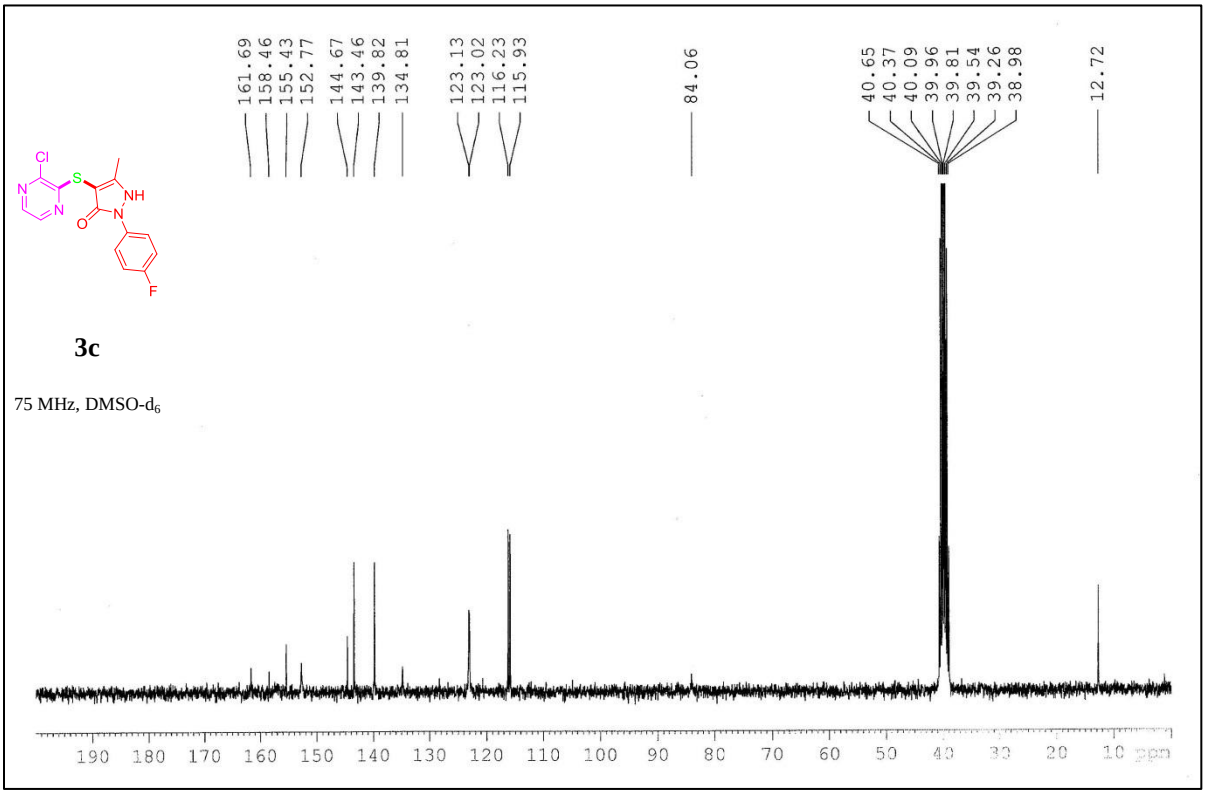
3b

75 MHz, DMSO-d_6



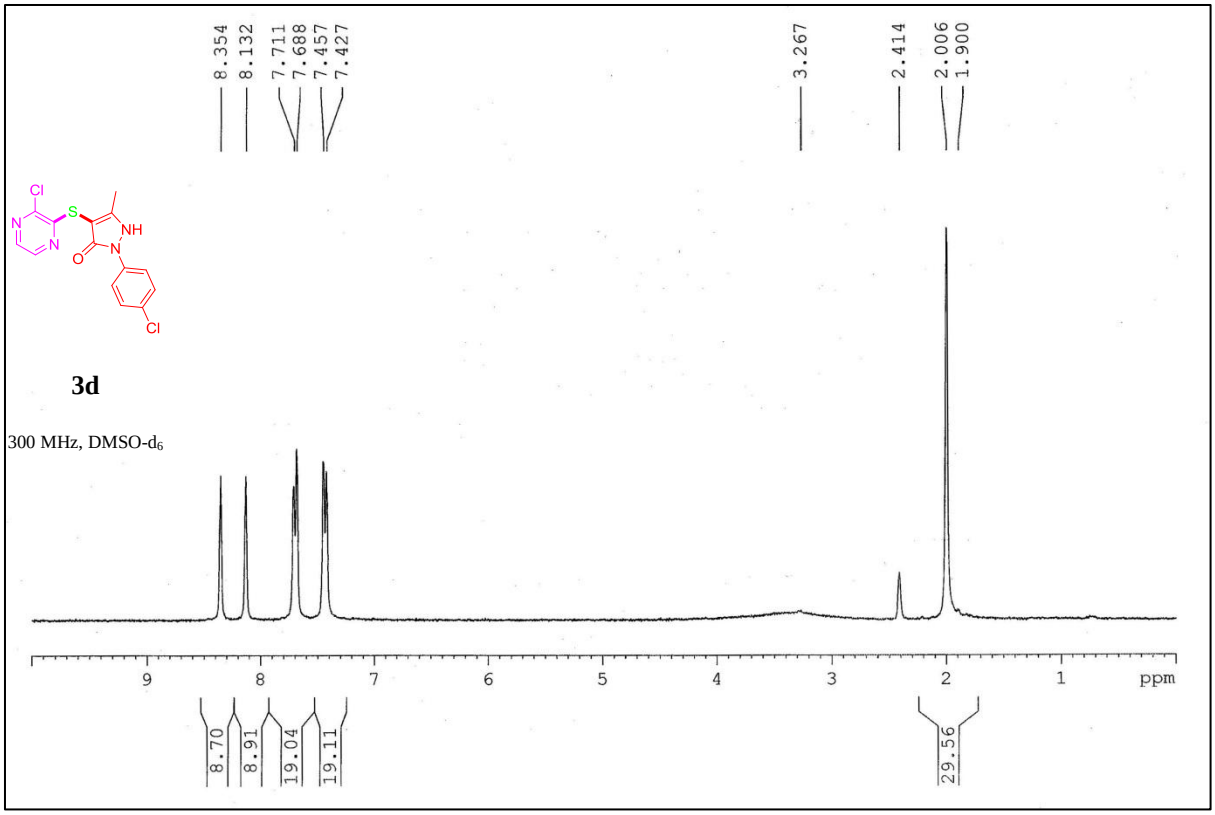
3c

300 MHz, DMSO-d_6



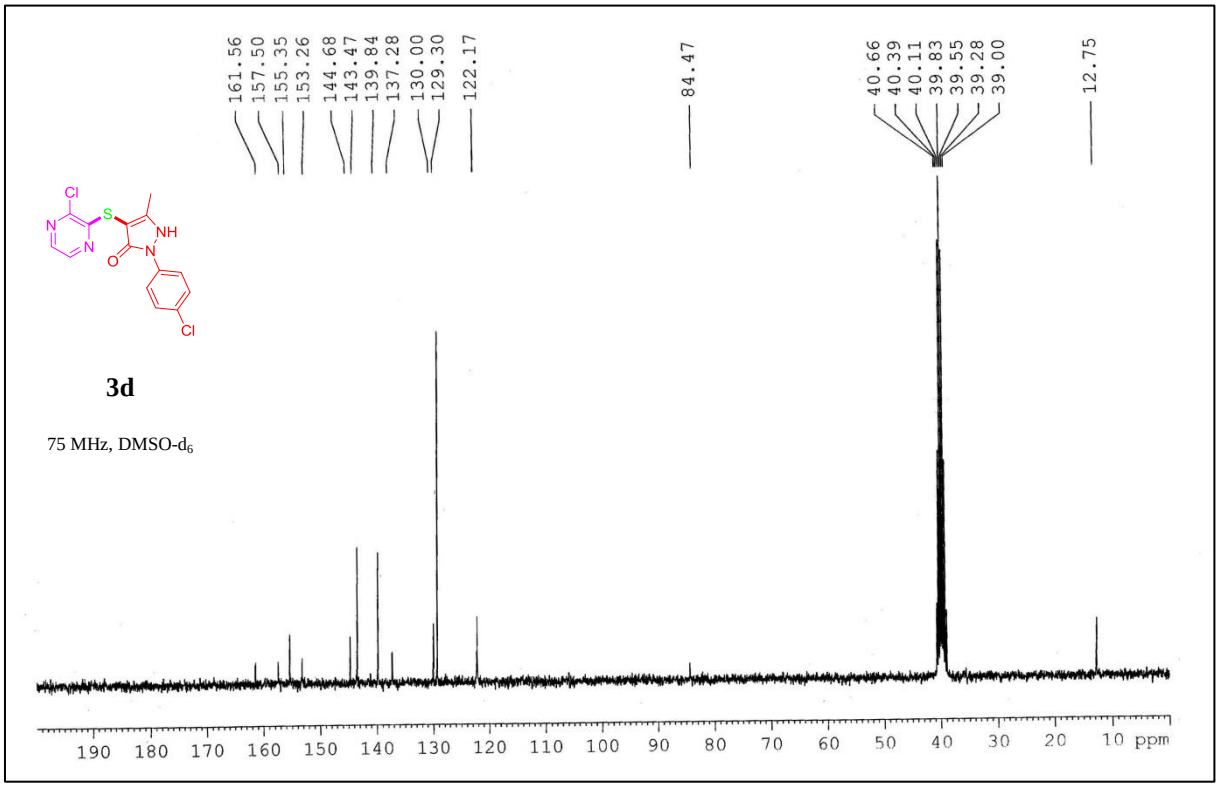
3c

75 MHz, DMSO-d_6



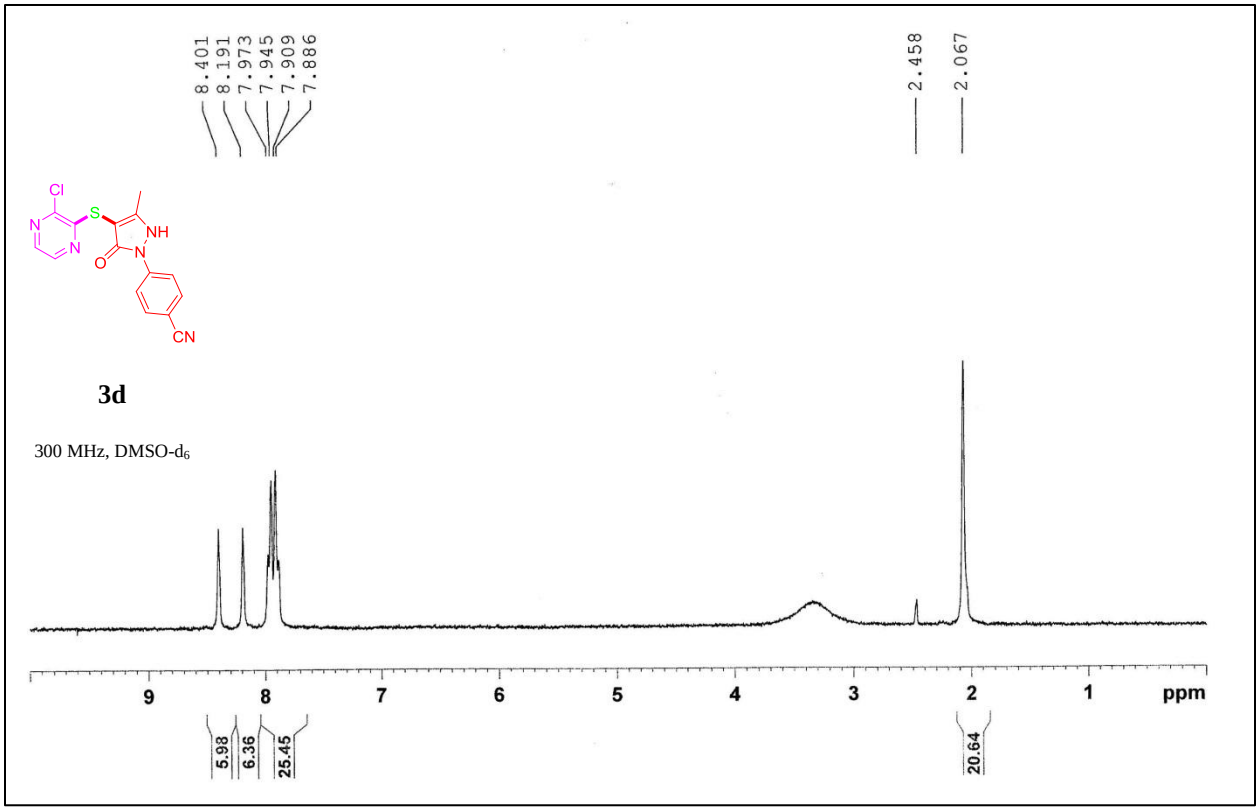
3d

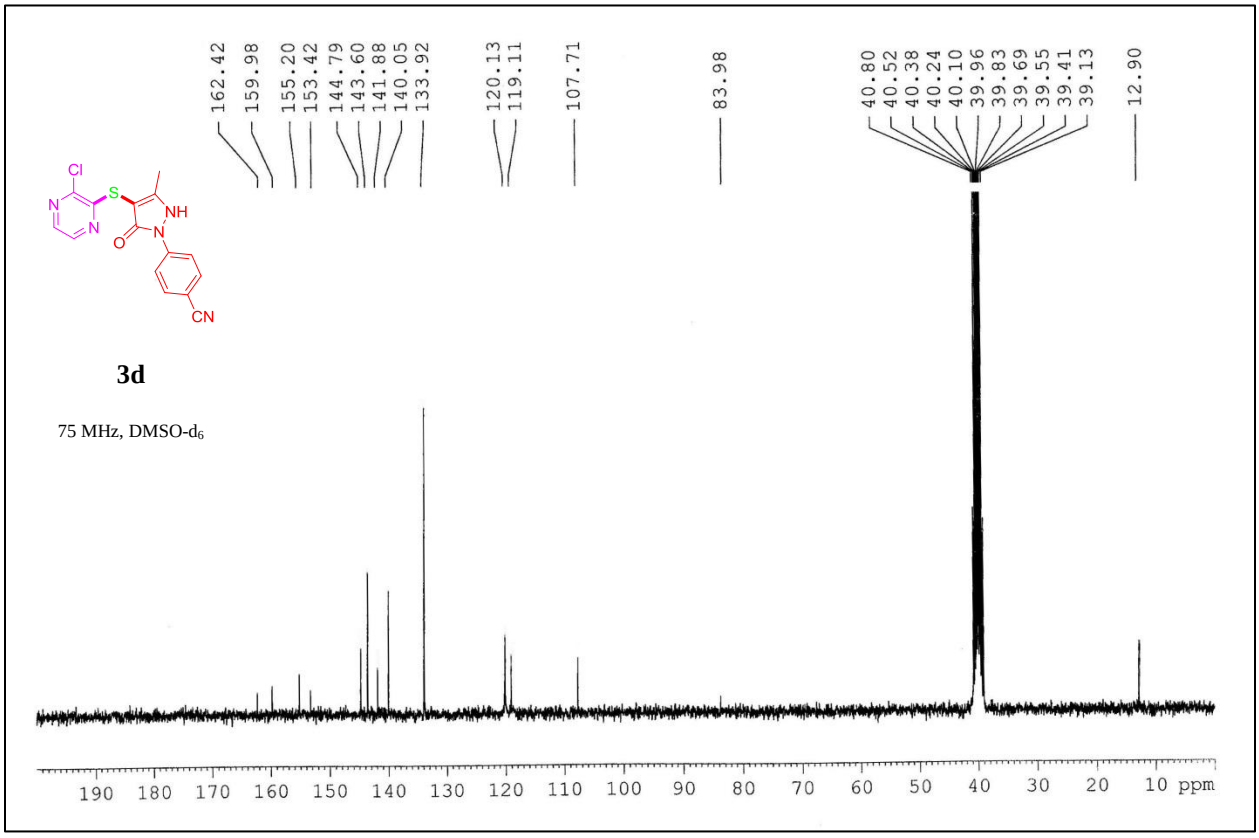
300 MHz, DMSO-d_6

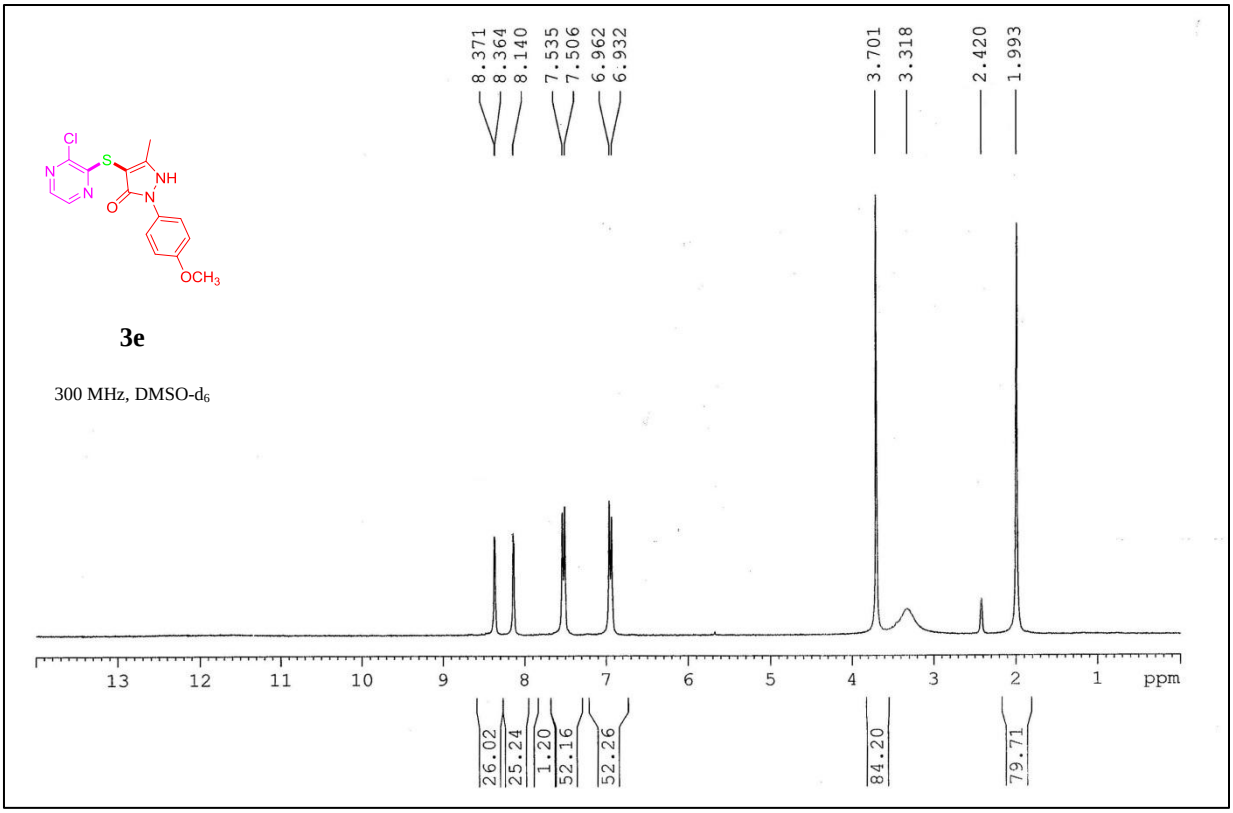


3d

75 MHz, DMSO-d_6

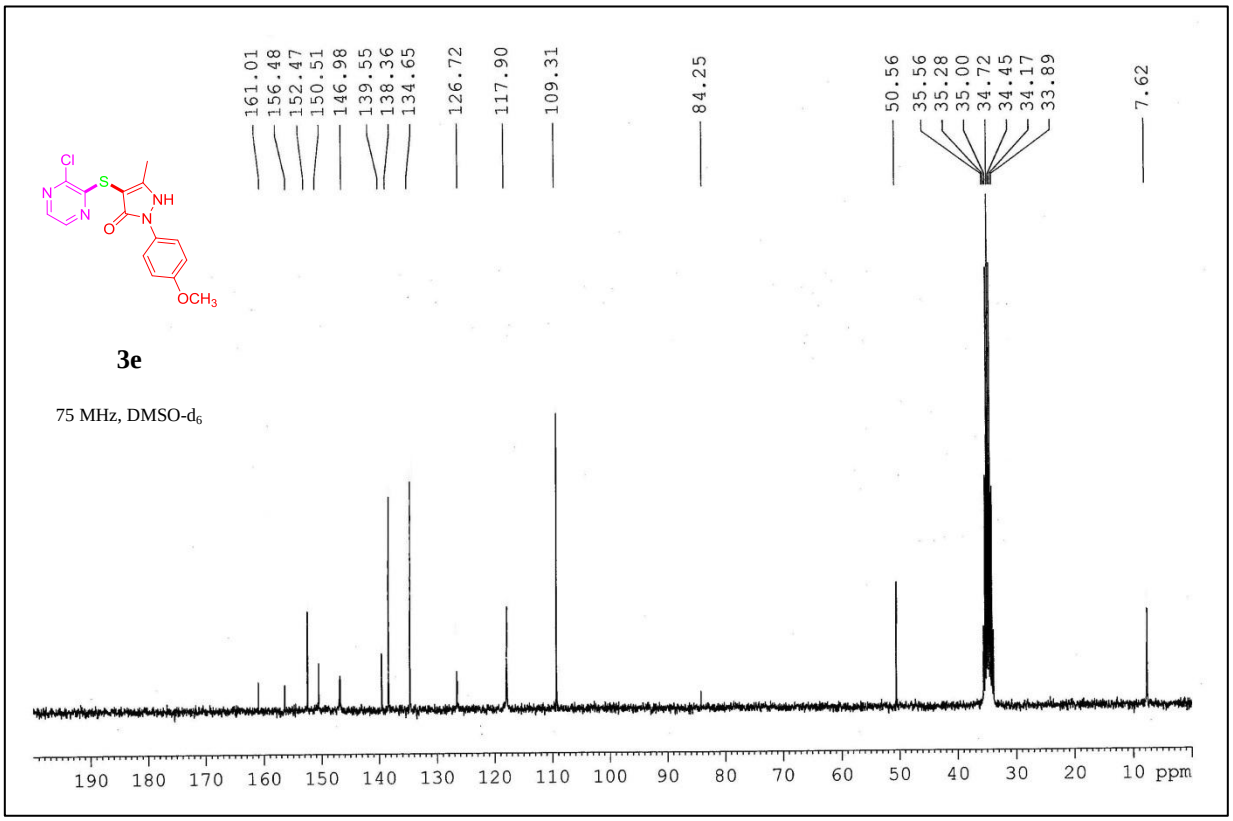

8.401
8.191
7.973
7.945
7.909
7.886
2.458
2.067
Cl
S
NH
N
O
N
CN
3d
300 MHz, DMSO-d6
9
8
7
6
5
4
3
2
1
ppm
5.98
6.36
25.45
20.64


162.42
159.98
155.20
153.42
144.79
143.60
141.88
140.05
133.92
120.13
119.11
107.71
83.98
40.80
40.52
40.38
40.24
40.10
39.96
39.83
39.69
39.55
39.41
39.13
12.90
Cl
S
NH
N
O
N
CN
3d
75 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm



3e

300 MHz, DMSO-d_6



3e

75 MHz, DMSO-d_6