

1 **Supporting Information**

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3 **Anti-Hepatocellular Carcinoma Activities of Novel Hydrazone Derivatives Via**
4 **Downregulation of Interleukin-6**
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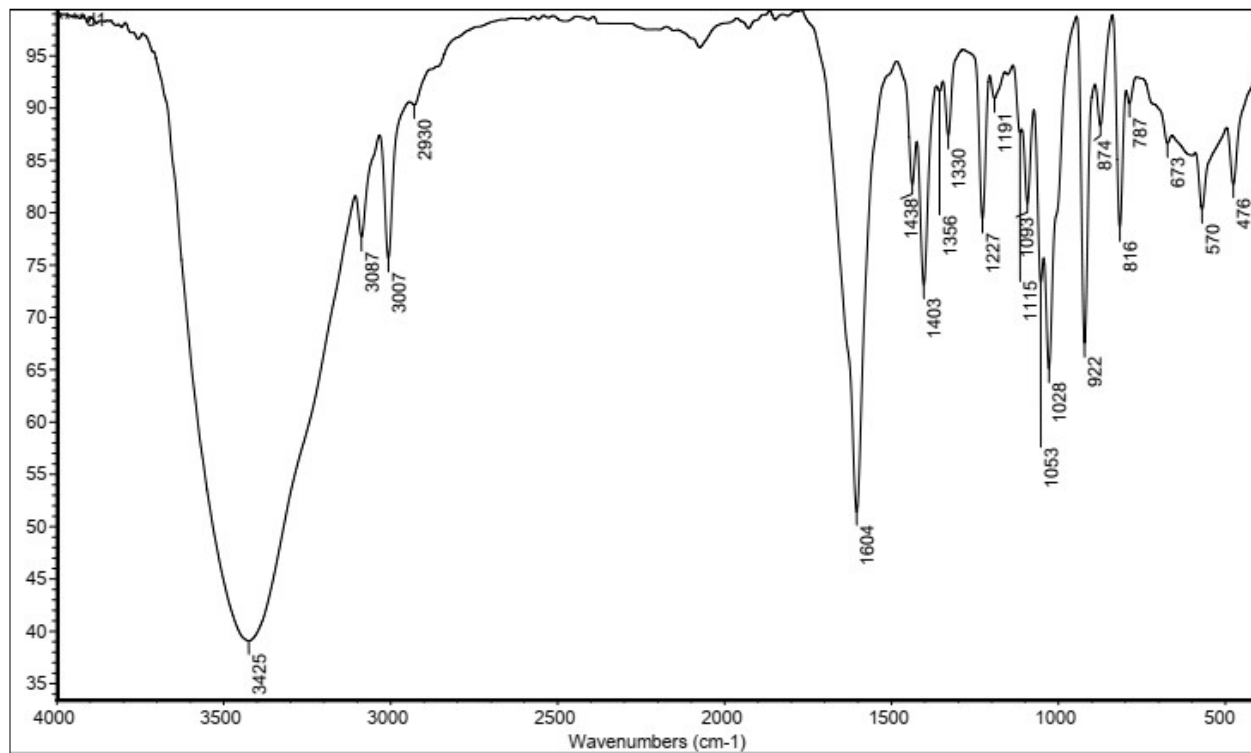
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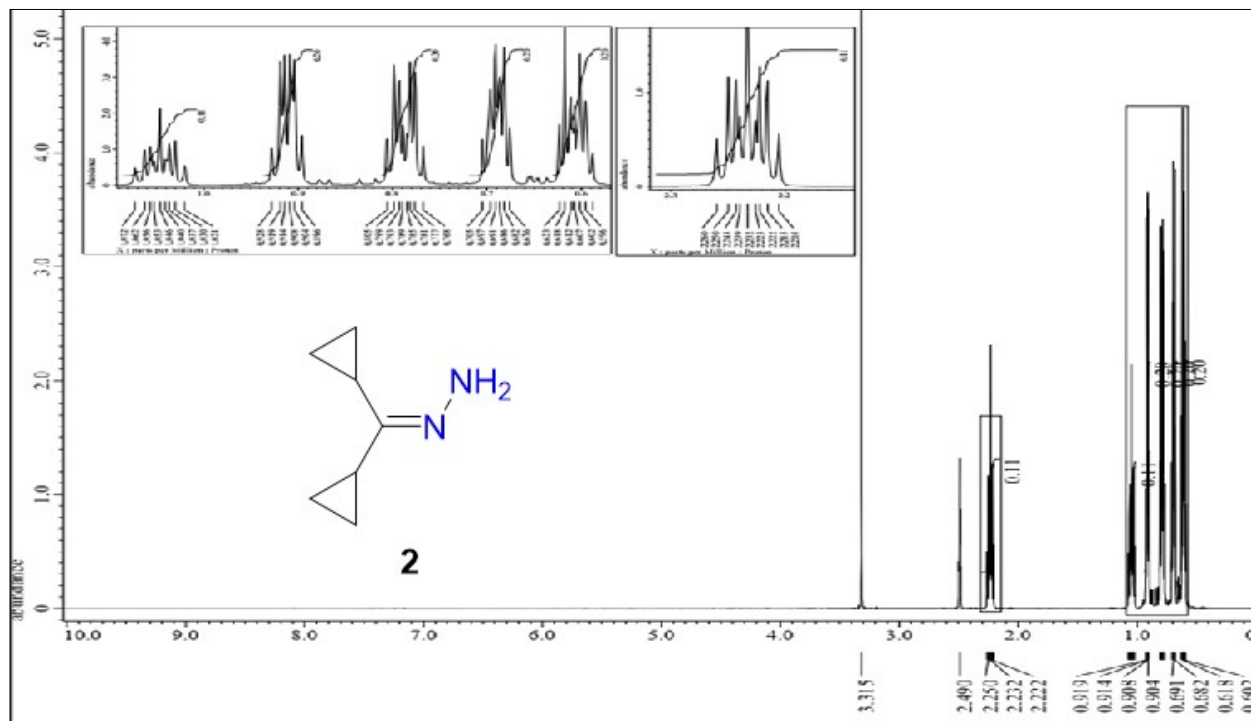
74 **Figure S1. Spectral analyses of different hydrazone derivatives.**



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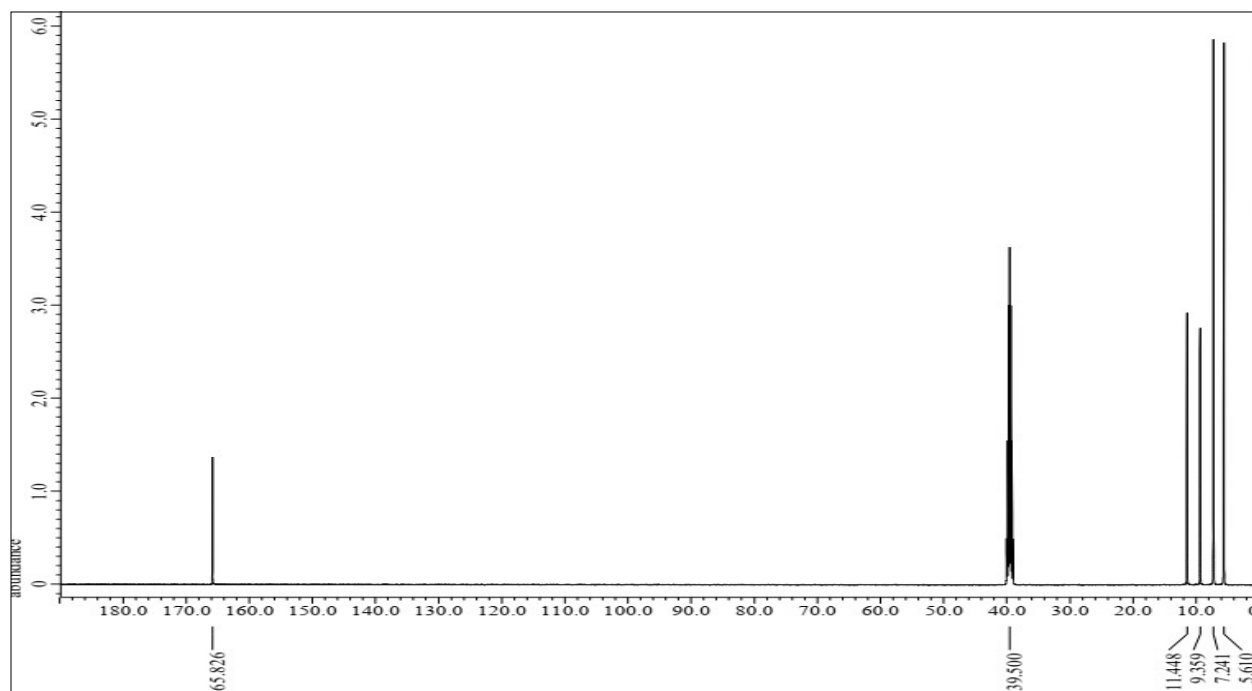
FTIR spectrum of compound 2.



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$^1\text{H-NMR}$ (500 MHz, DMSO) spectrum of compound 2.



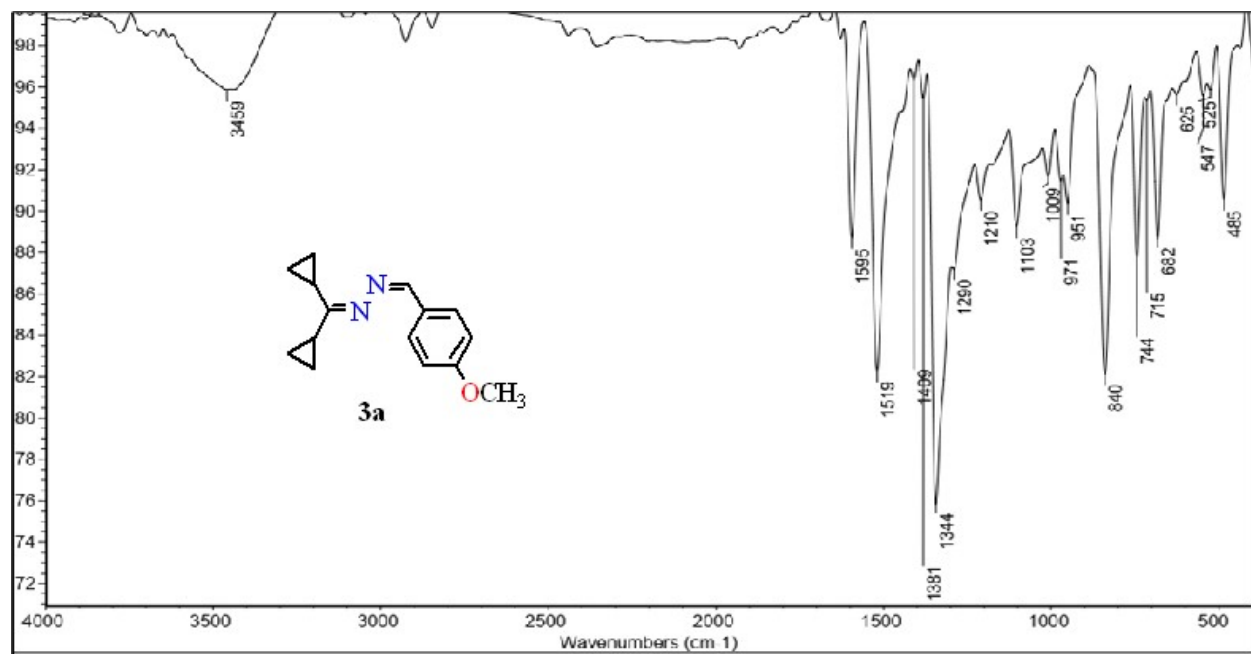
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$^{13}\text{C-NMR}$ spectrum (125 MHz, DMSO) spectrum of compound 2.

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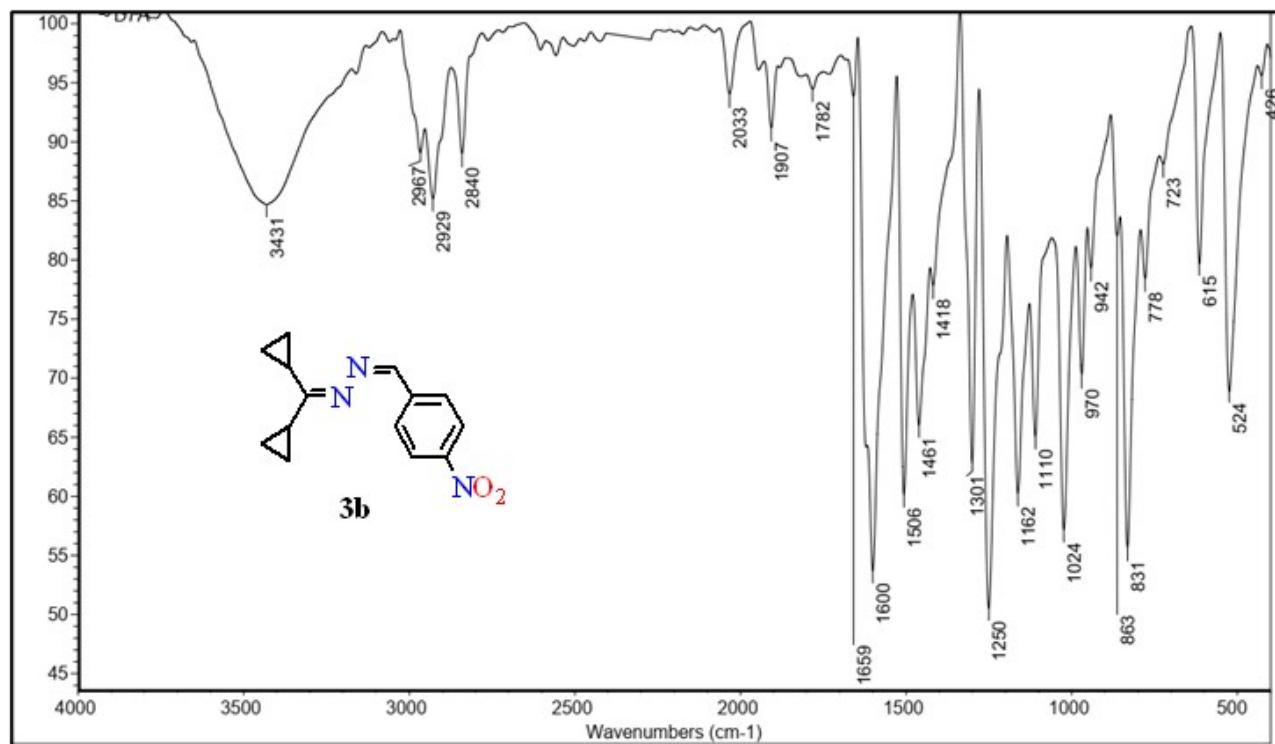
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FTIR spectrum of compound 3a.

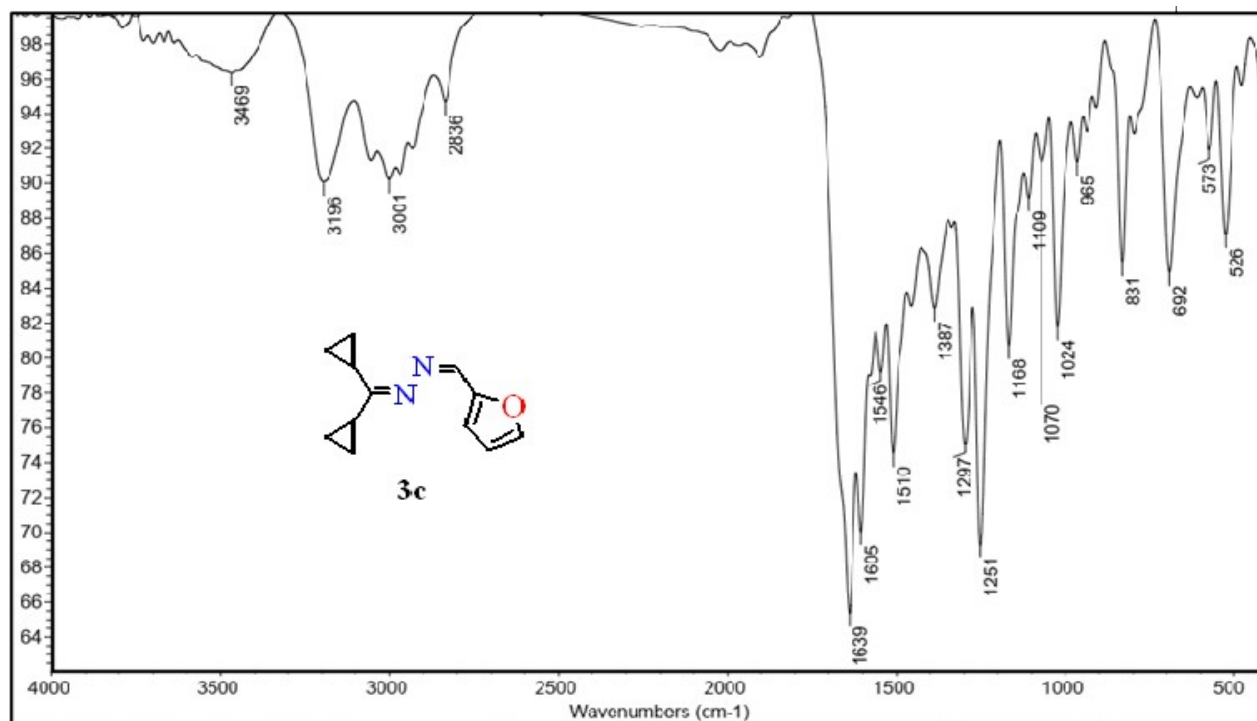


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FTIR spectrum of compound 3b.

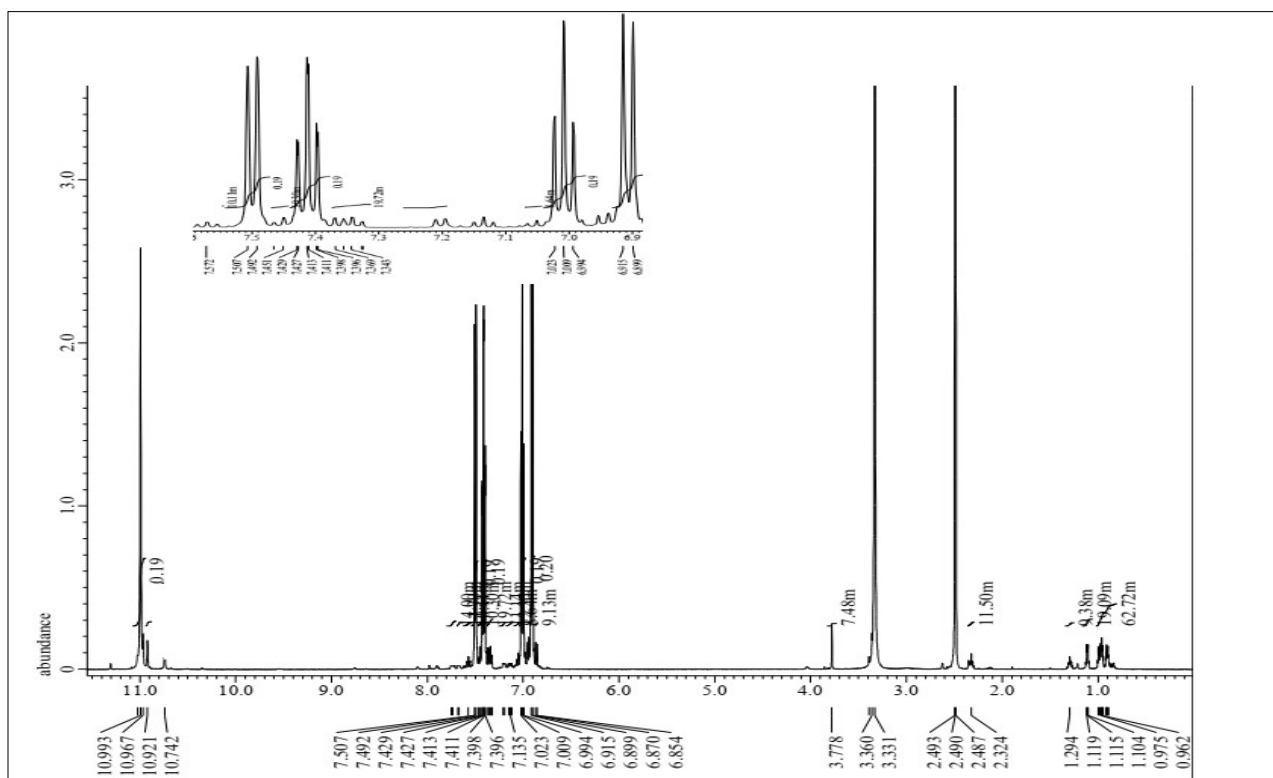
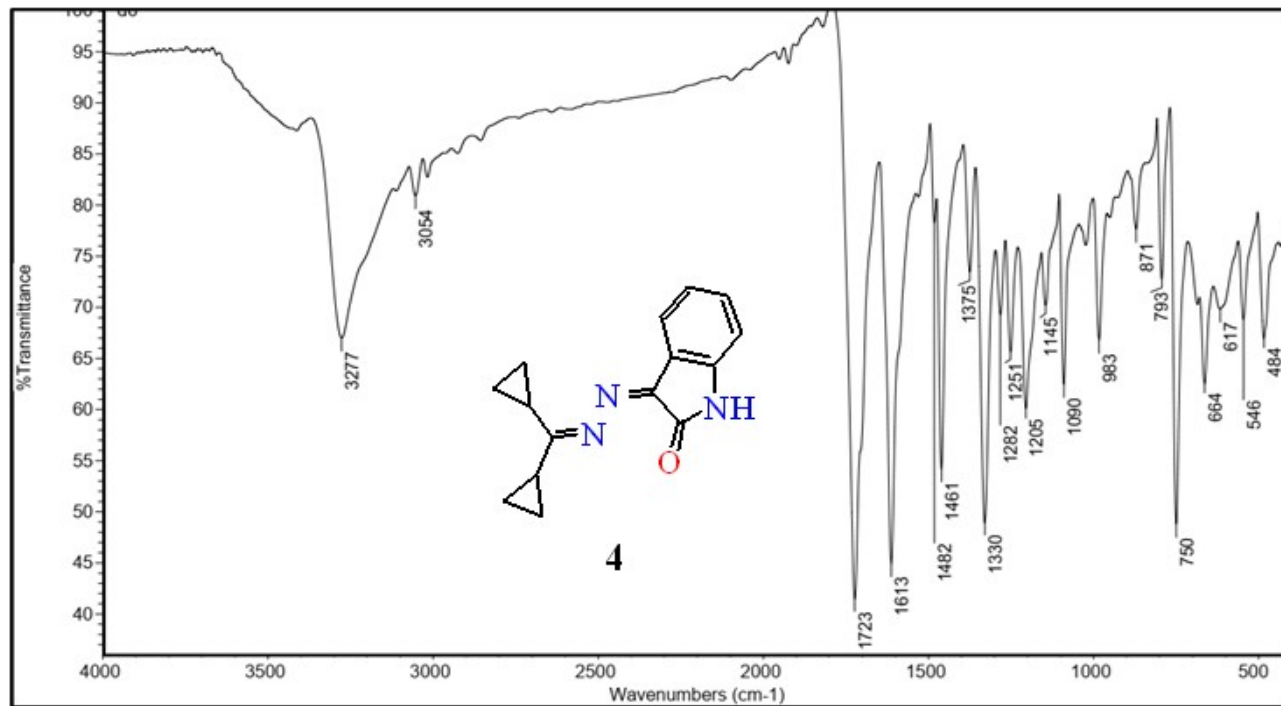
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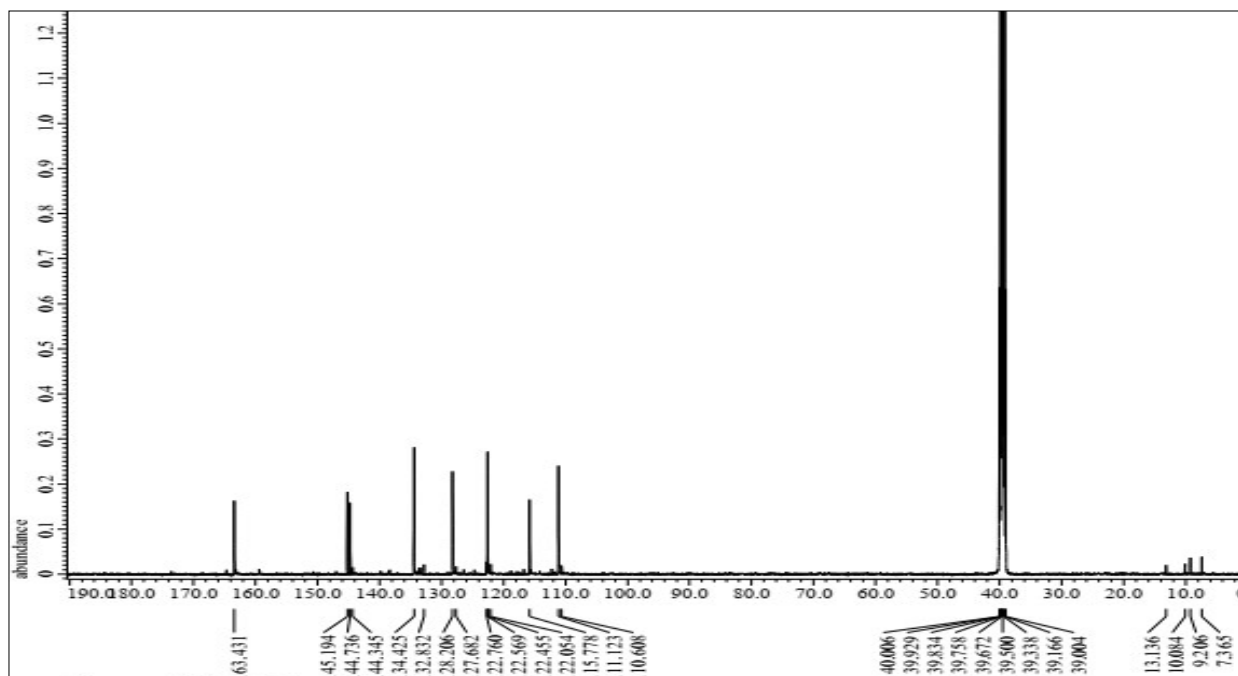


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FTIR and ¹H-NMR (500 MHz, DMSO) spectra of compound 3c.



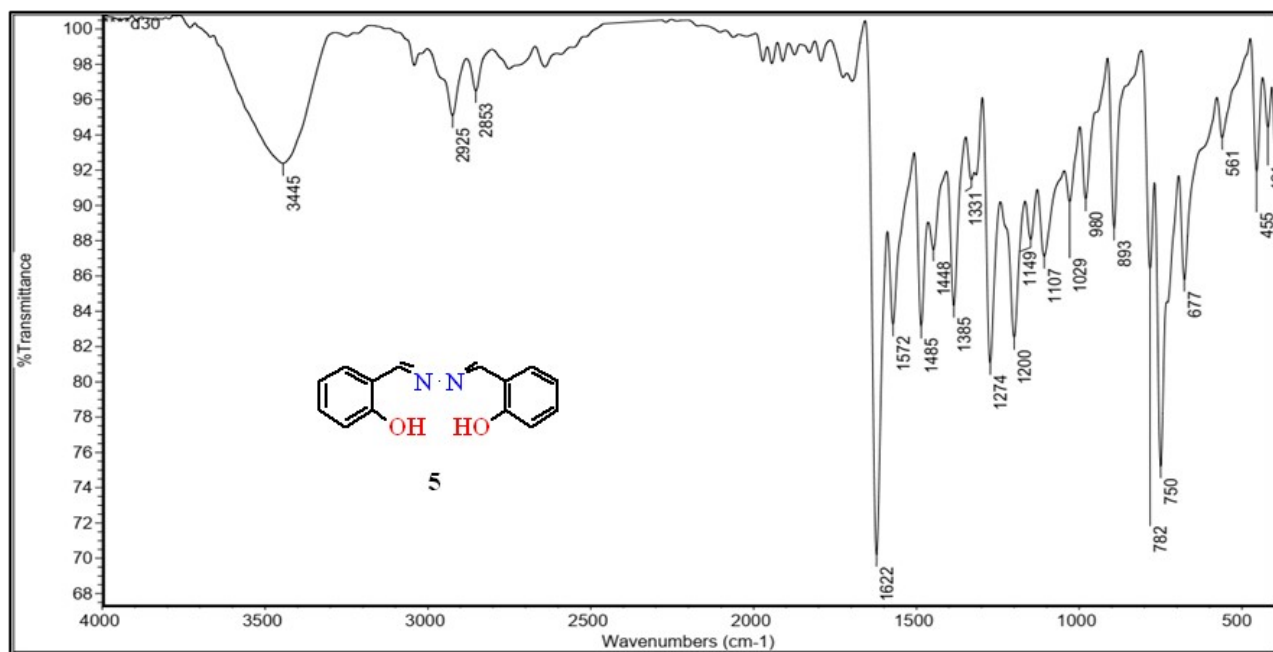


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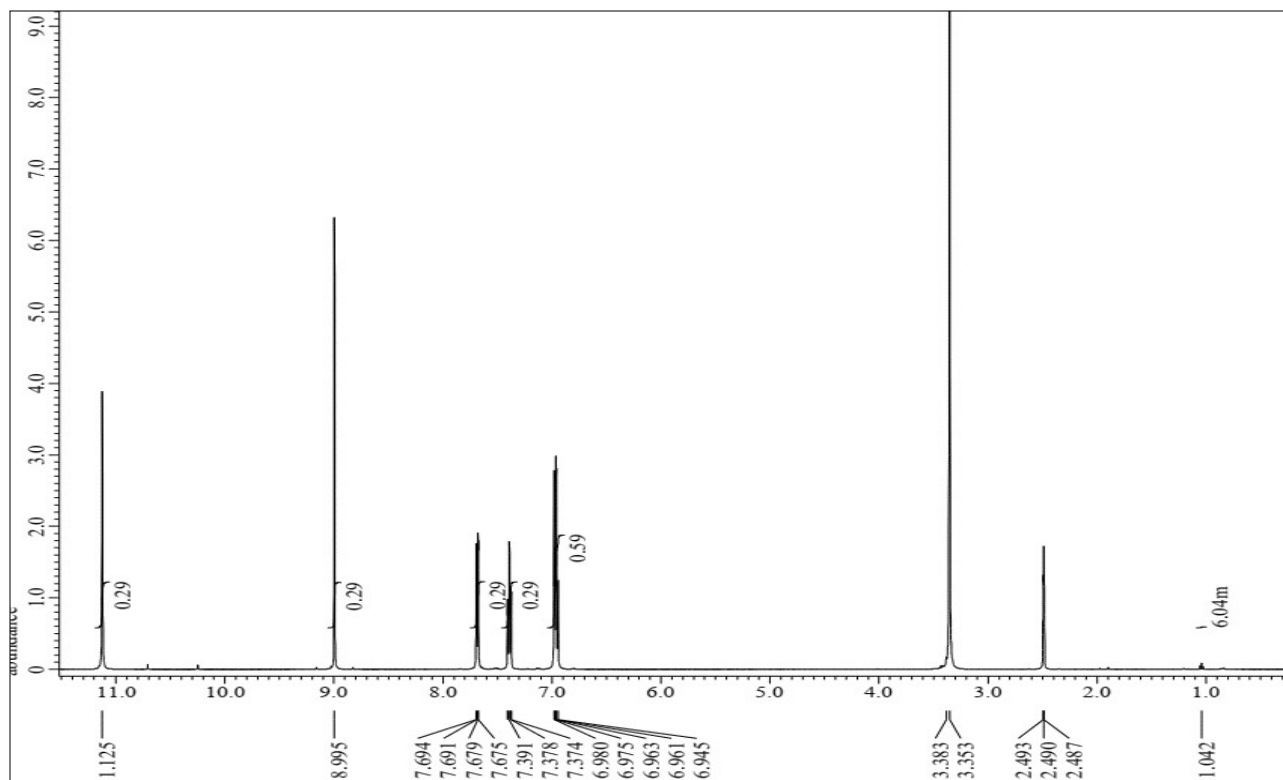
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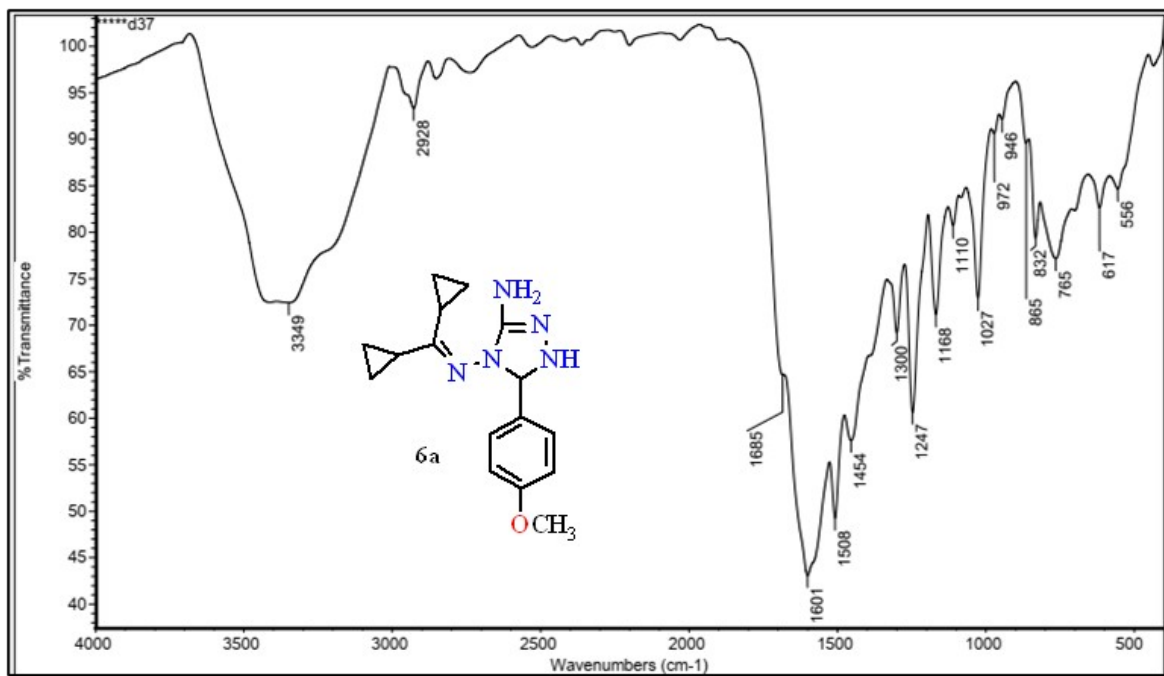
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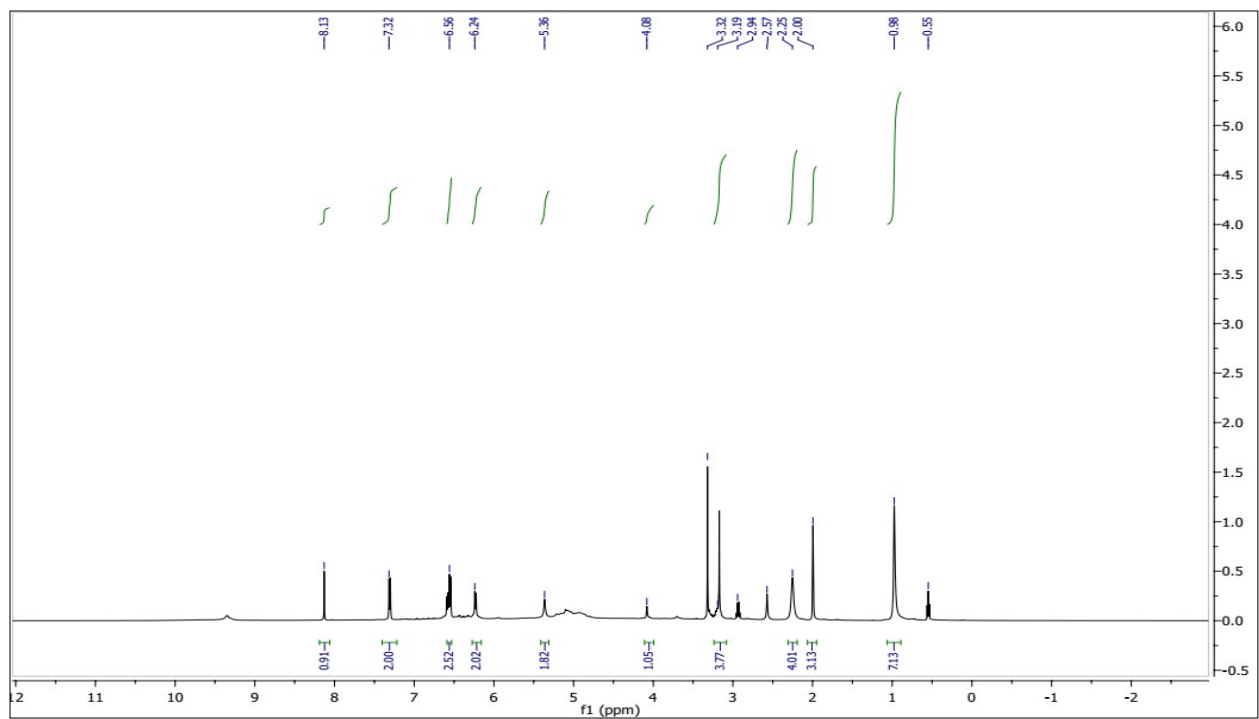
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FTIR and ¹H-NMR (500 MHz, DMSO) spectra of compound 5.



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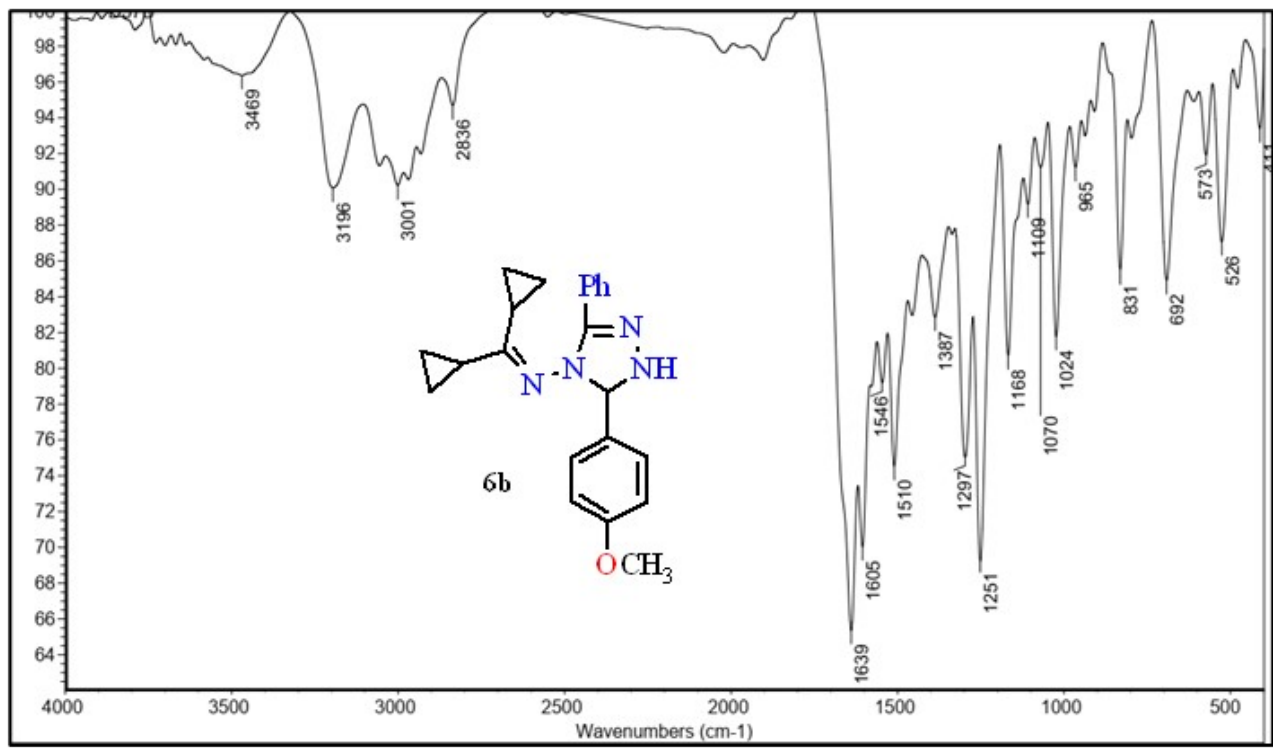


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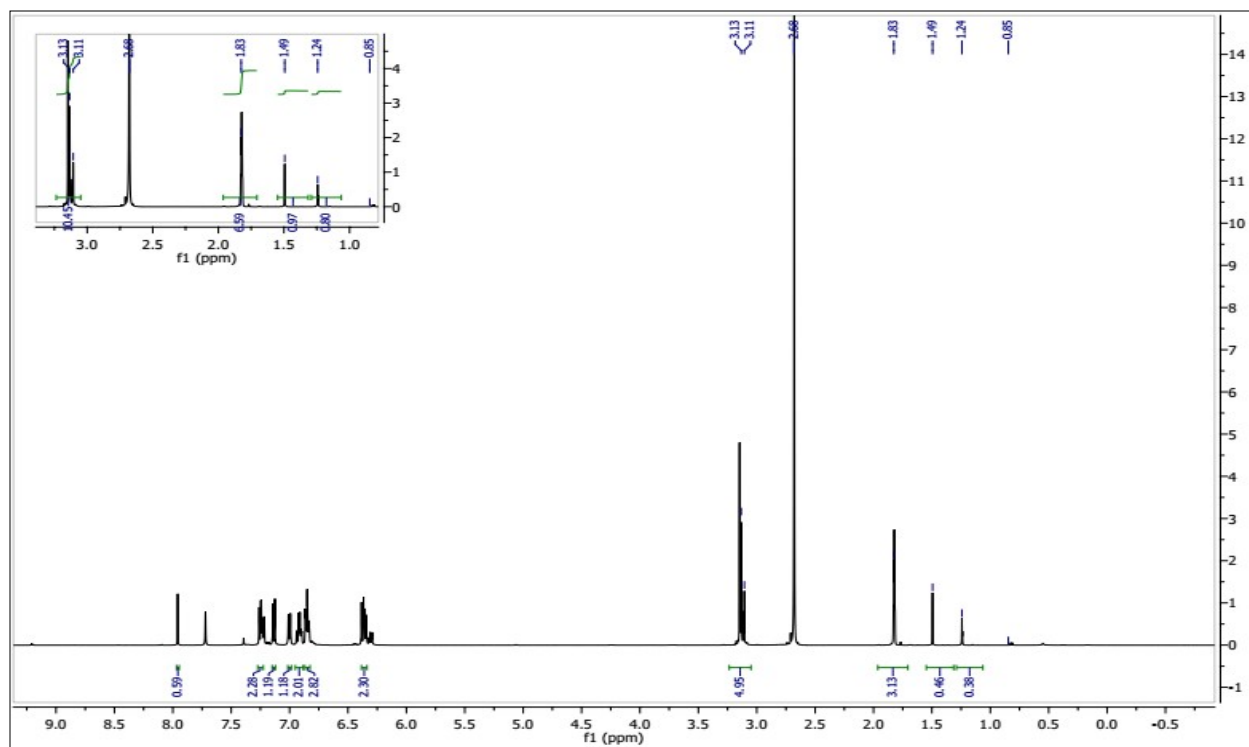
FTIR and ¹H-NMR (500 MHz, DMSO) spectra of compound 6a.

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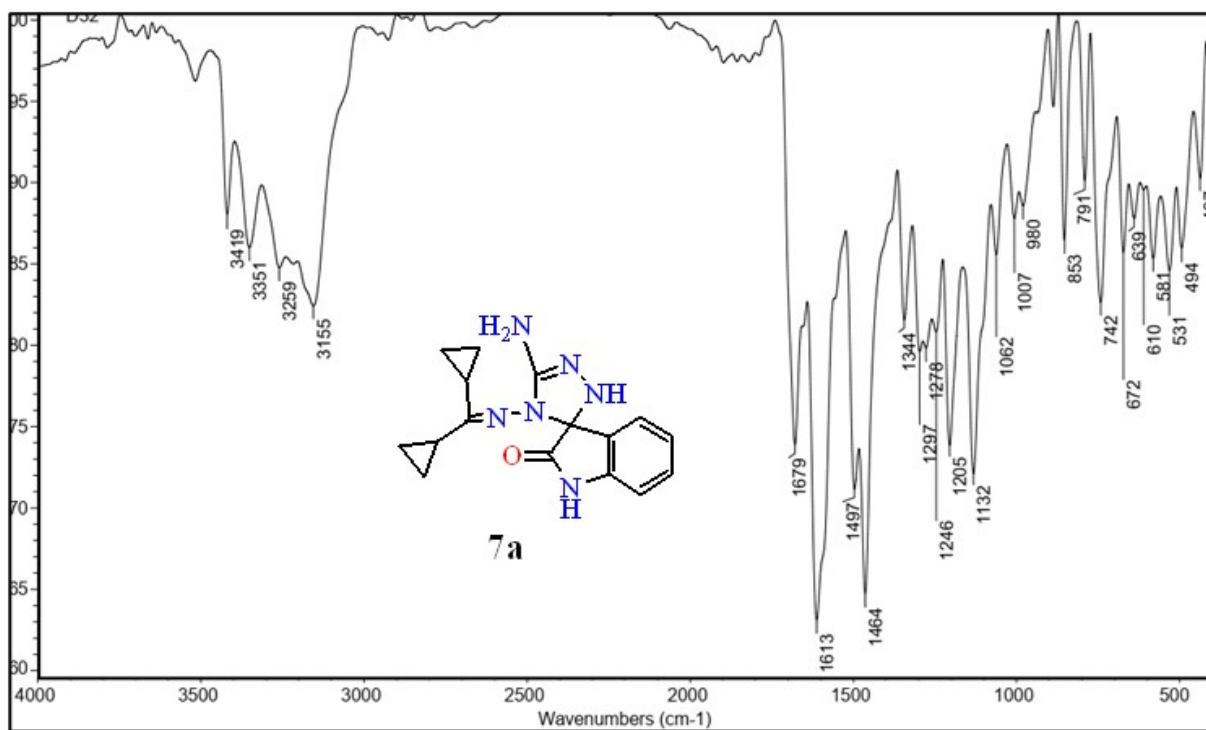
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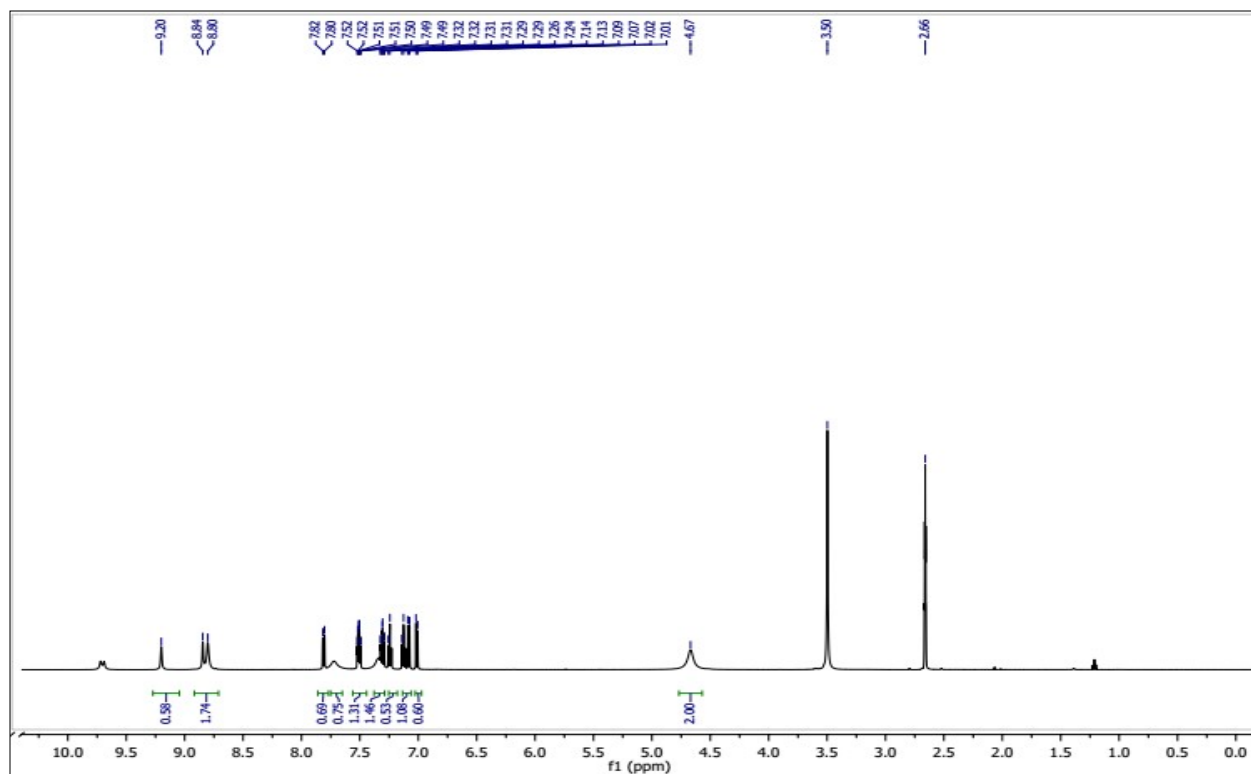
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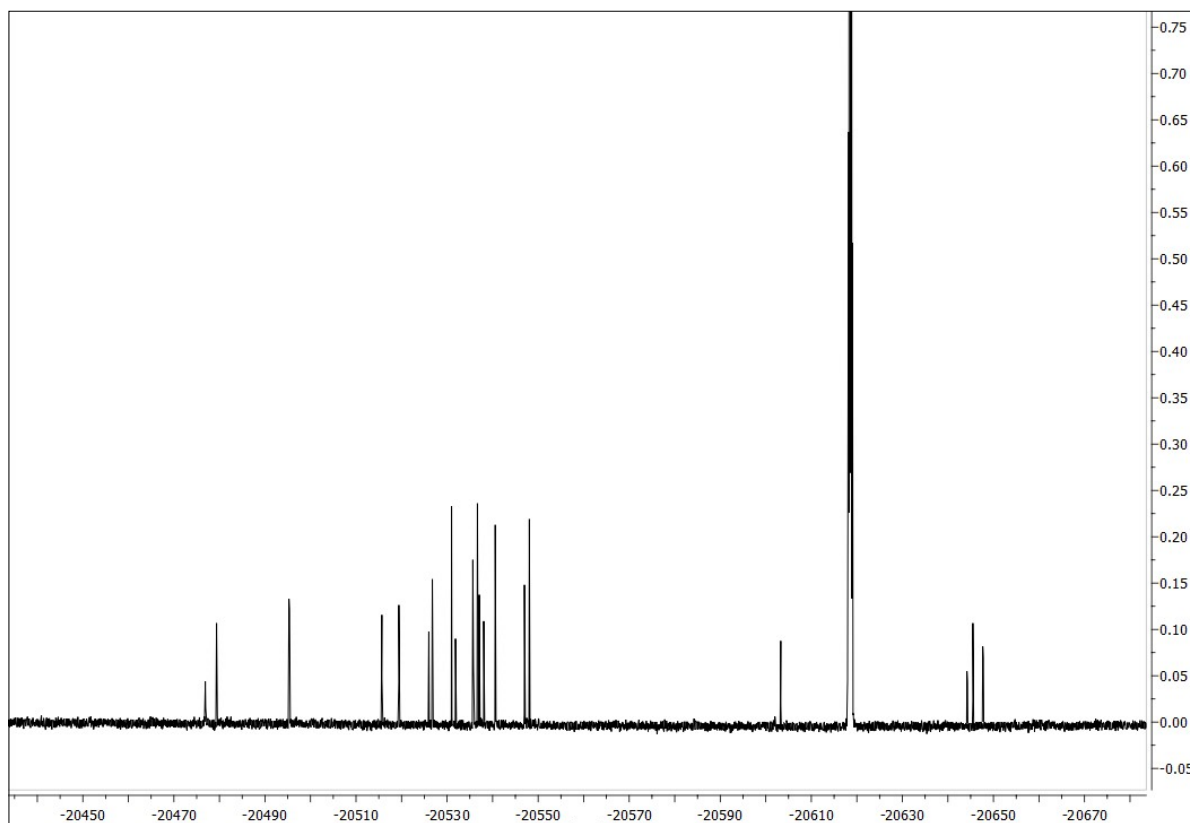
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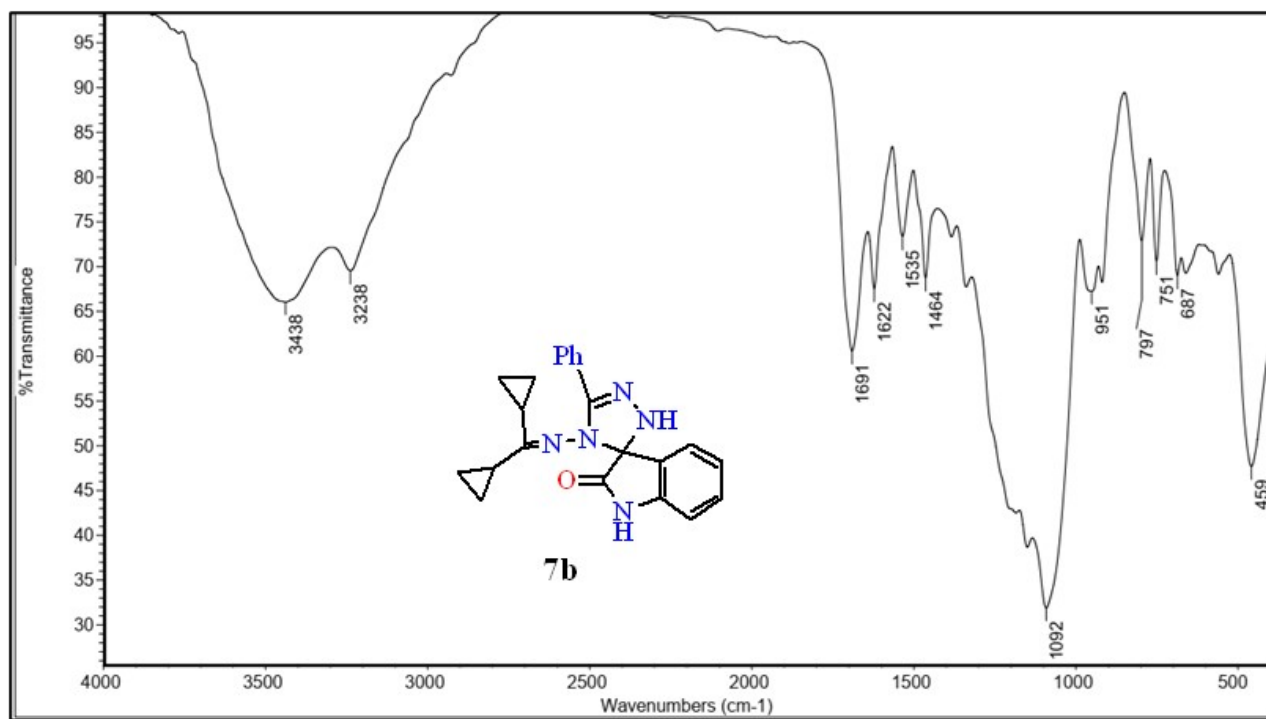


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FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) spectra of compound 7a.

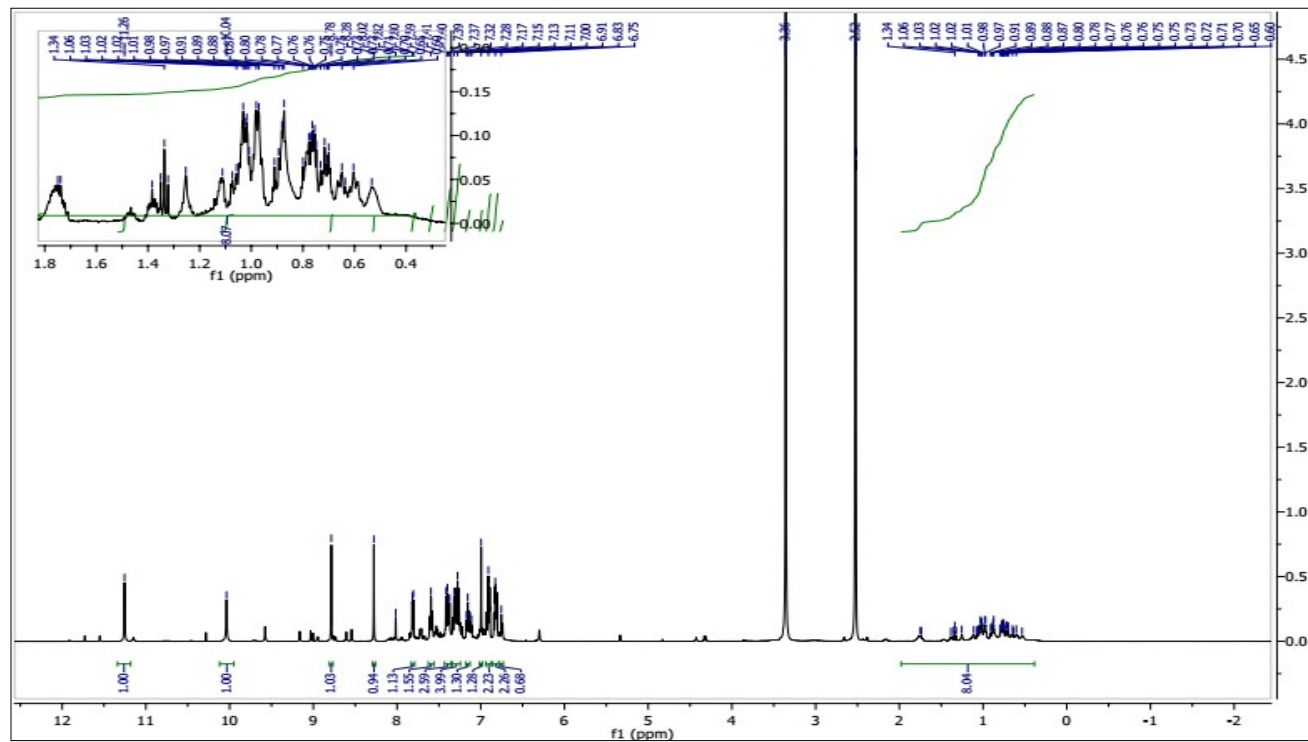
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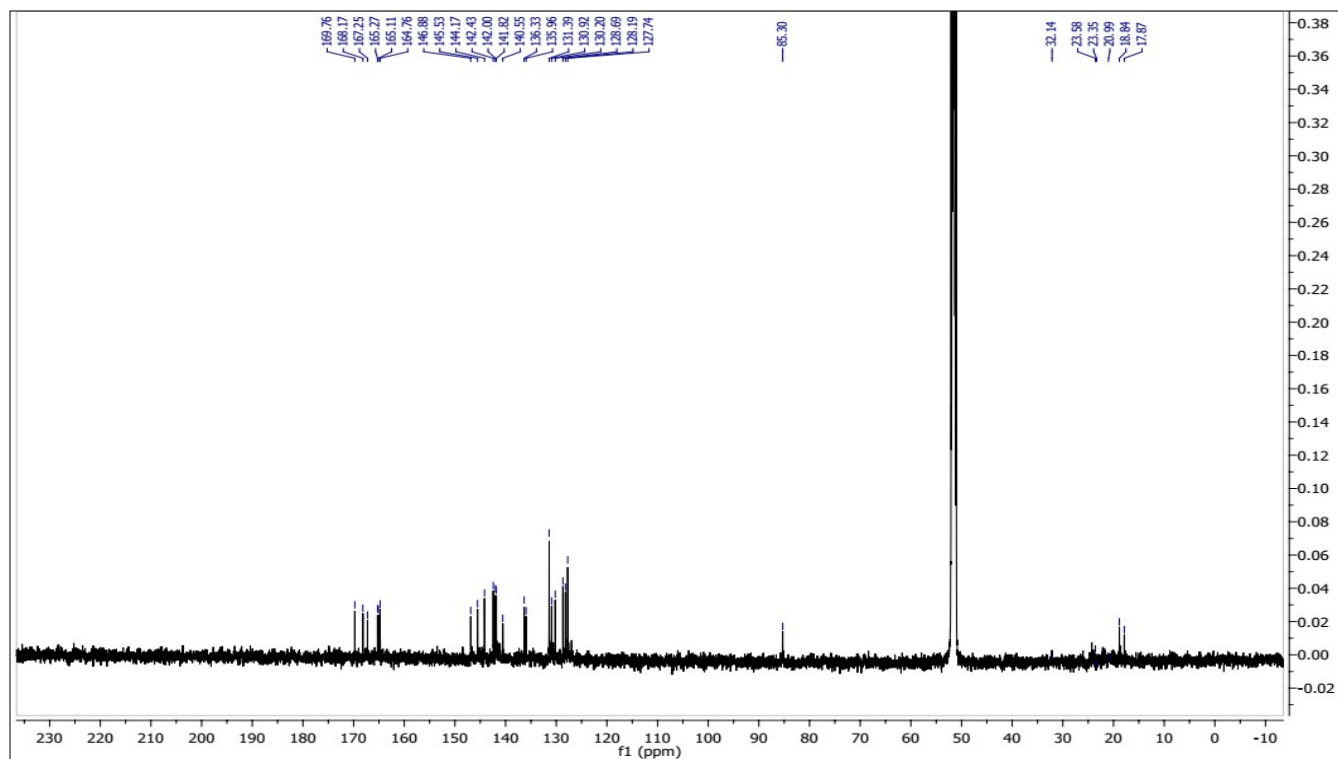


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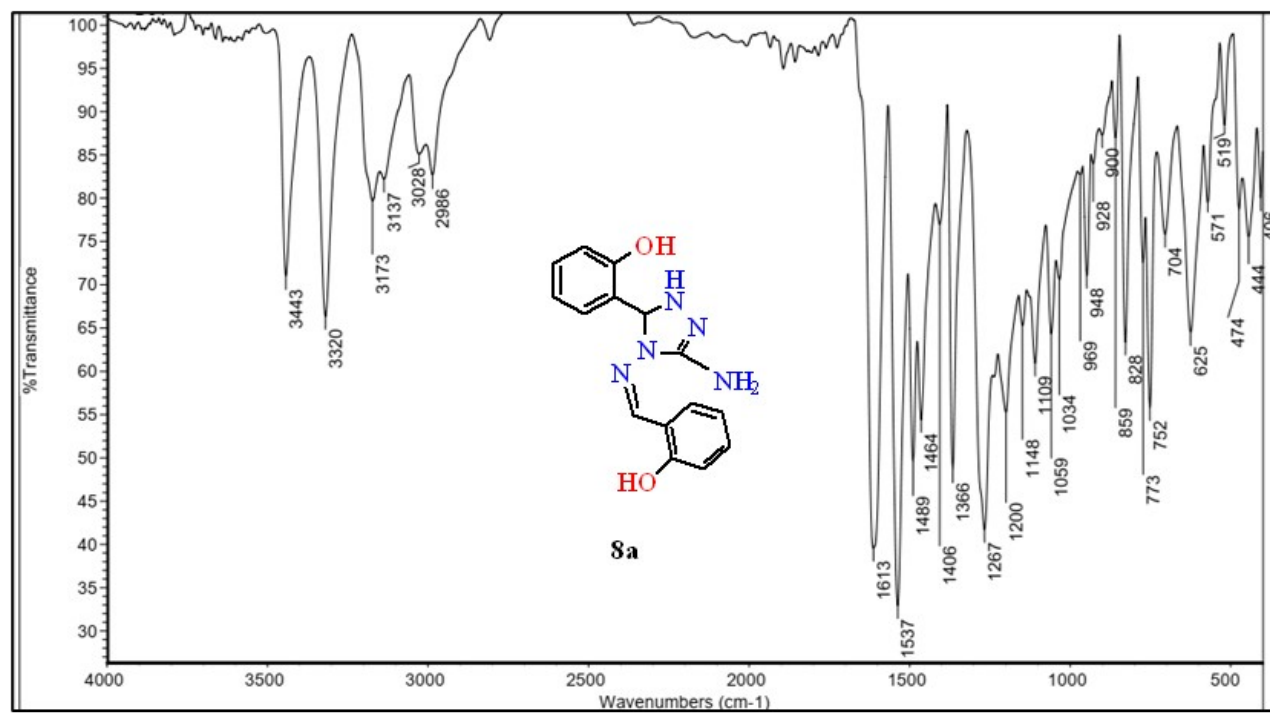


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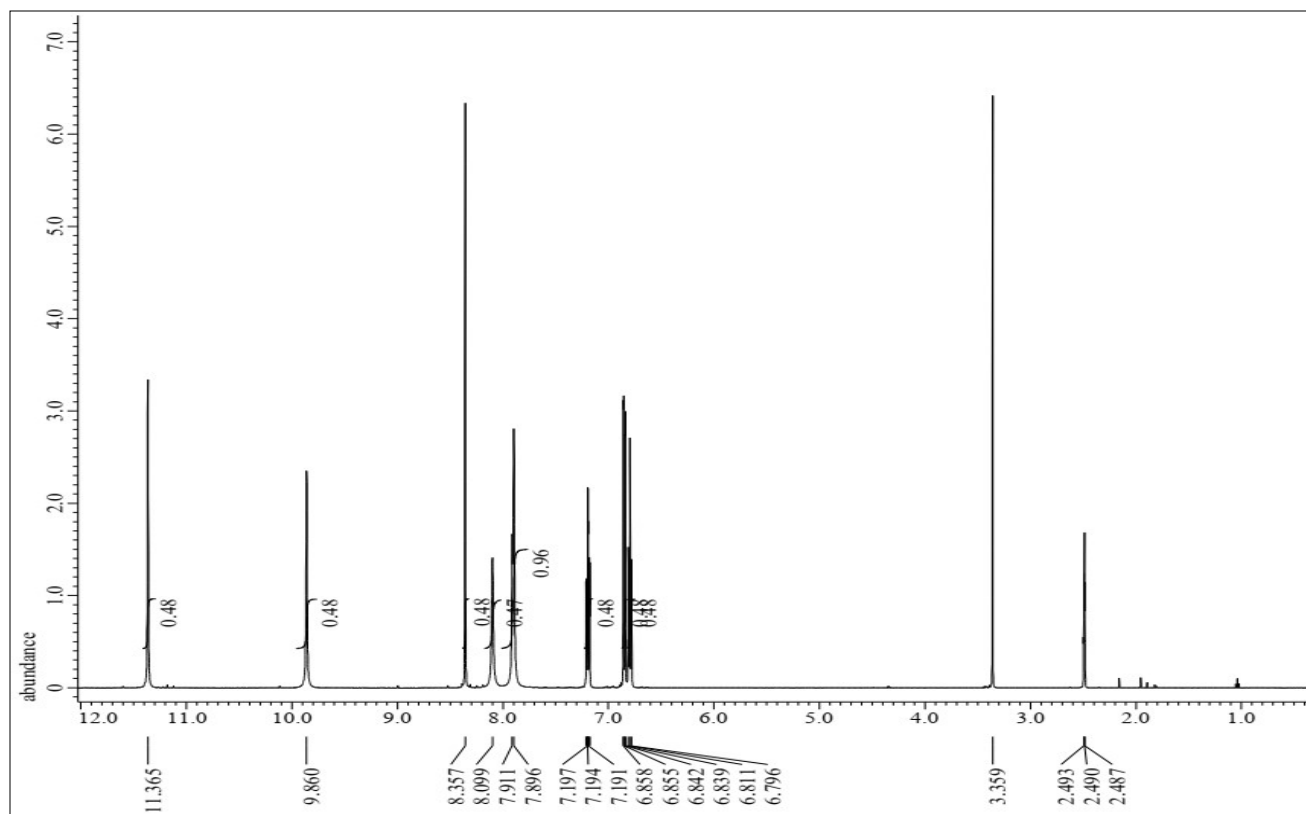
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FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) spectra of compound 7b.

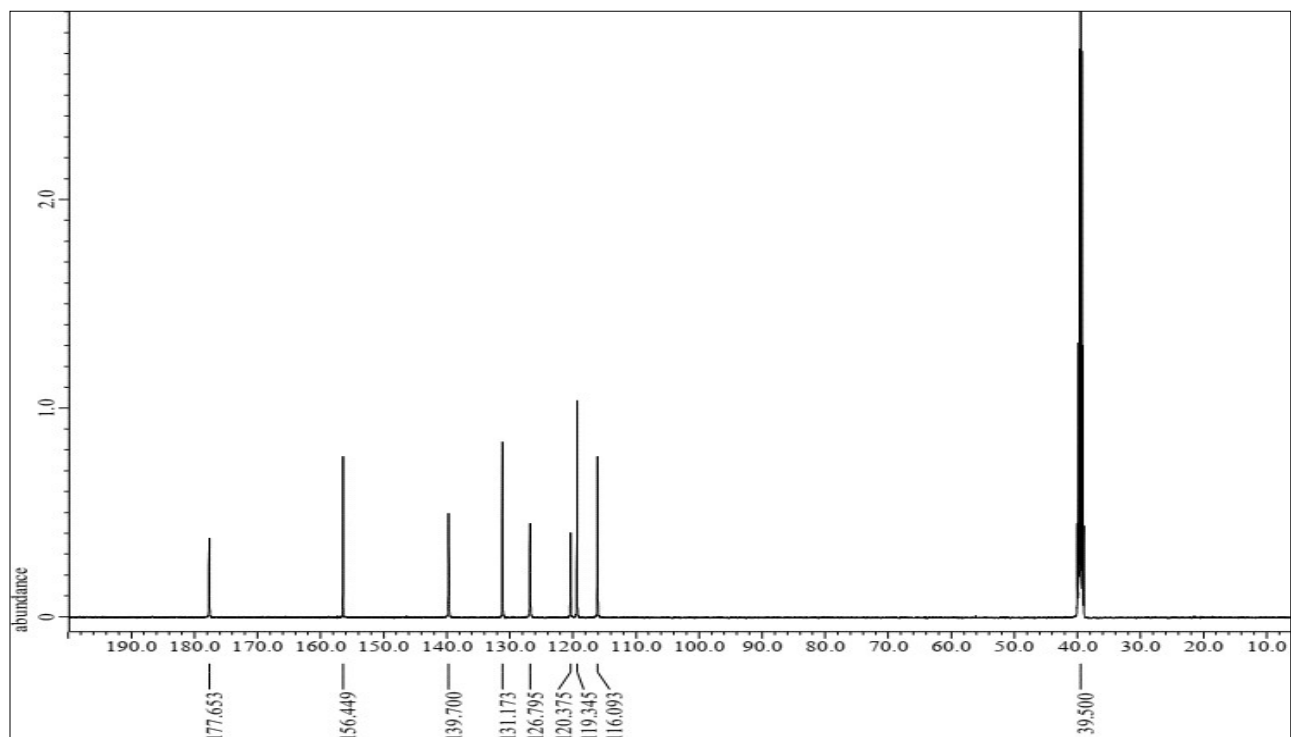


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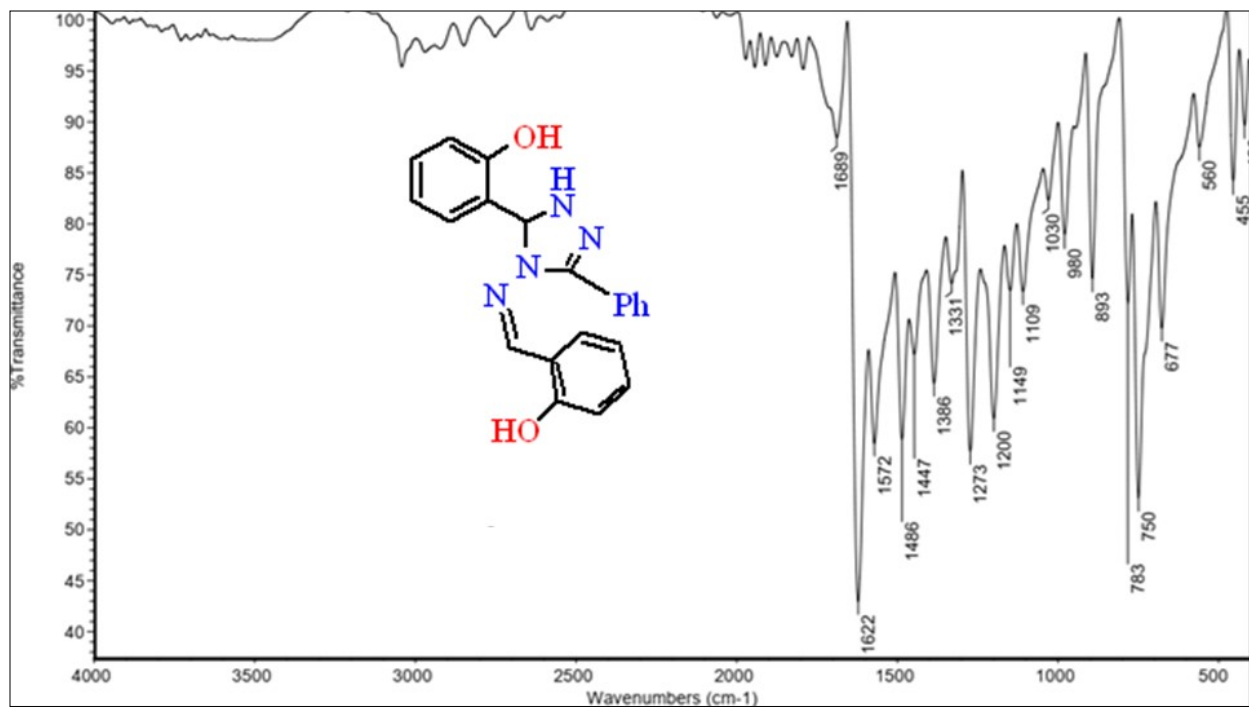
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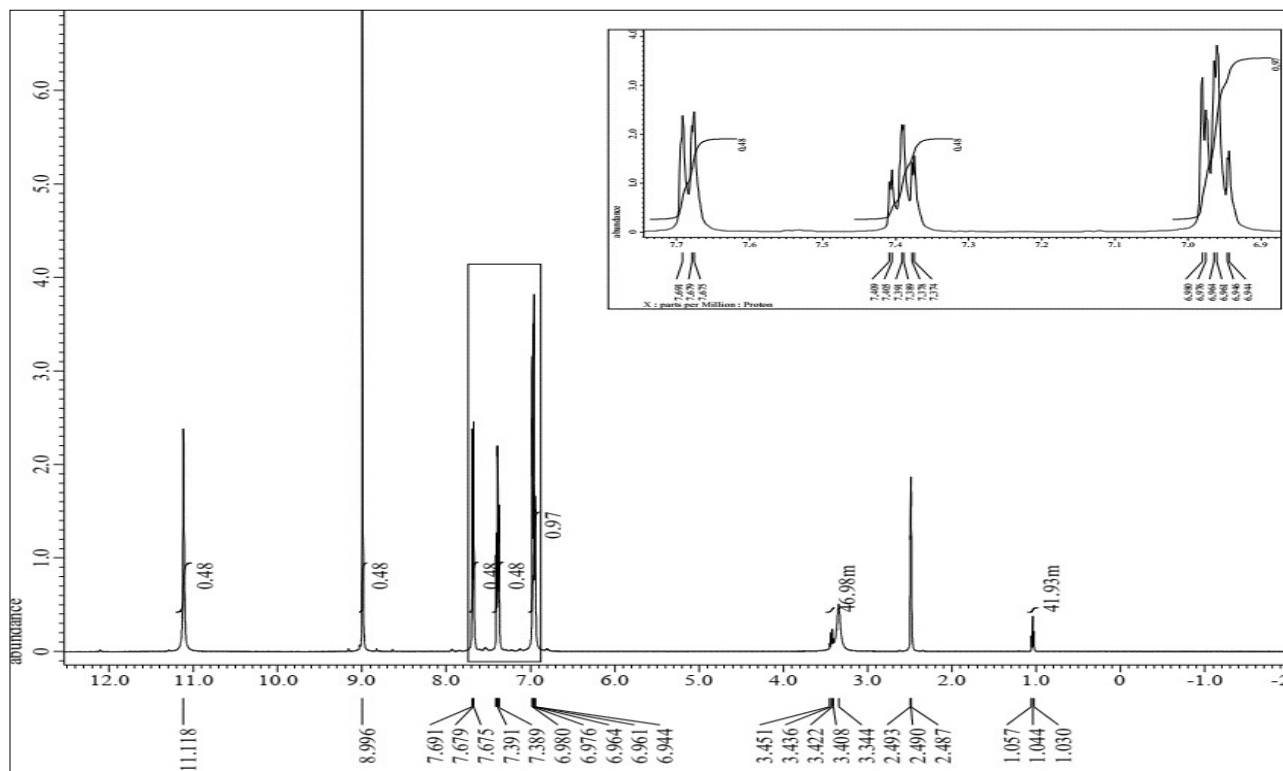
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FTIR, $^1\text{H-NMR}$ (500 MHz, DMSO), and $^{13}\text{C-NMR}$ (125 MHz, DMSO) spectra of compound 8a.

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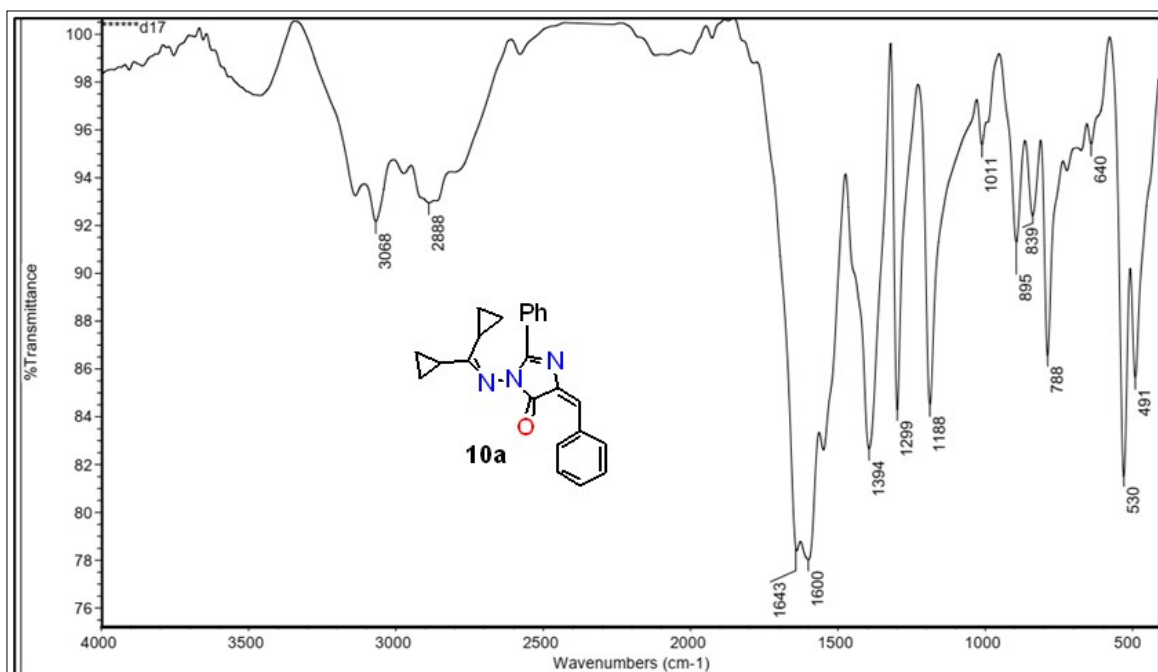


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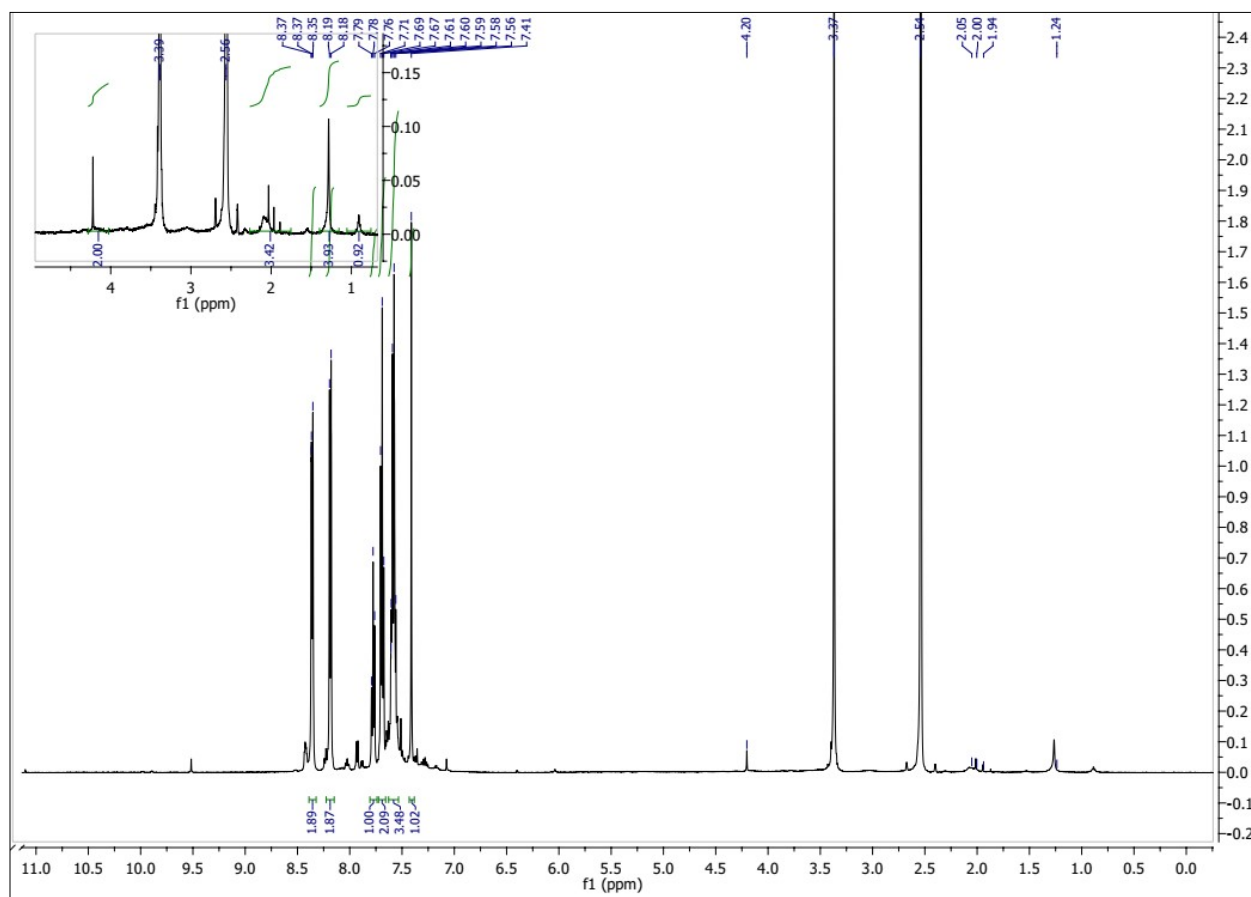
FTIR, and $^1\text{H-NMR}$ (500 MHz, DMSO) of compound 8b.

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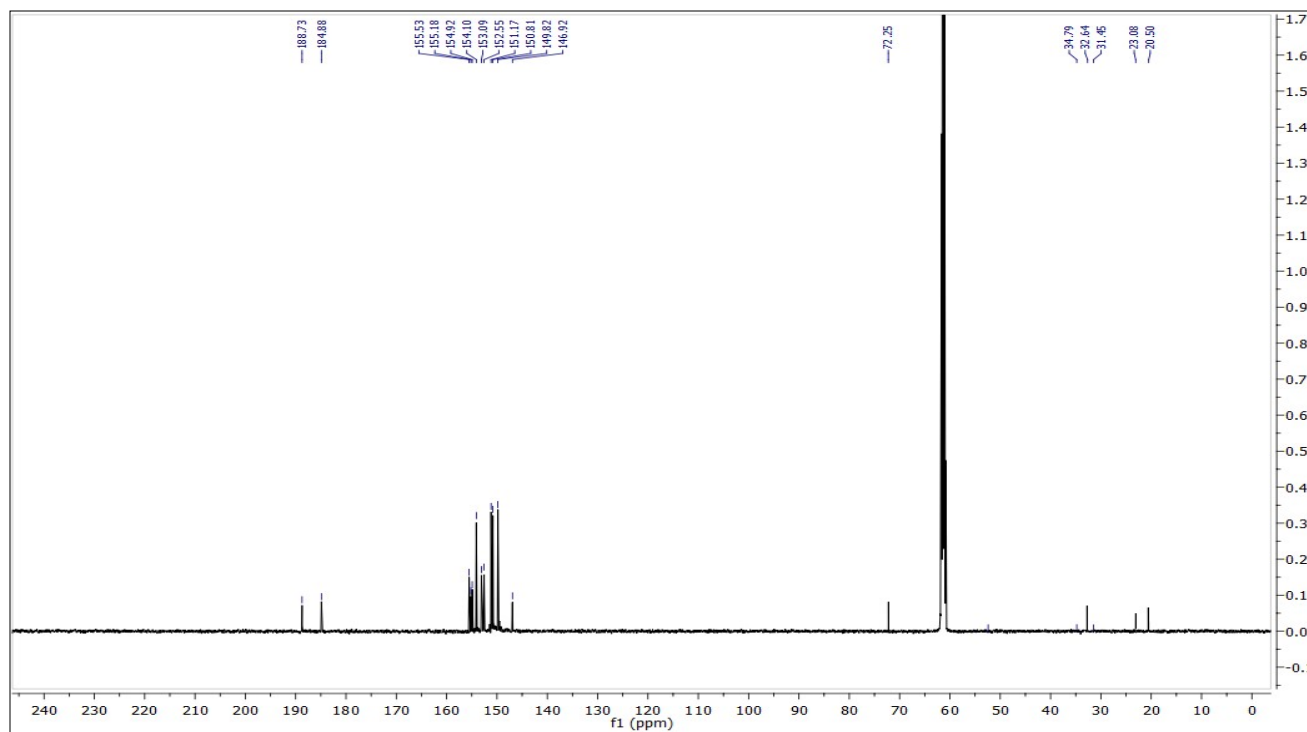


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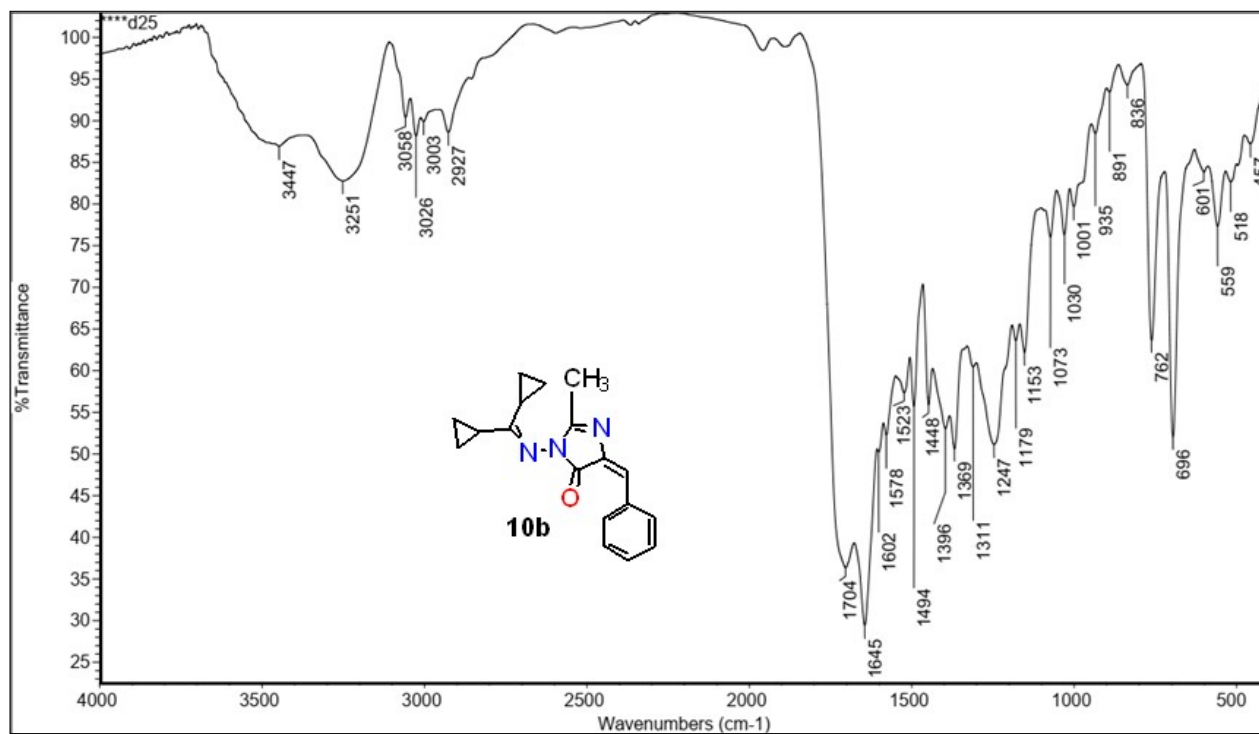
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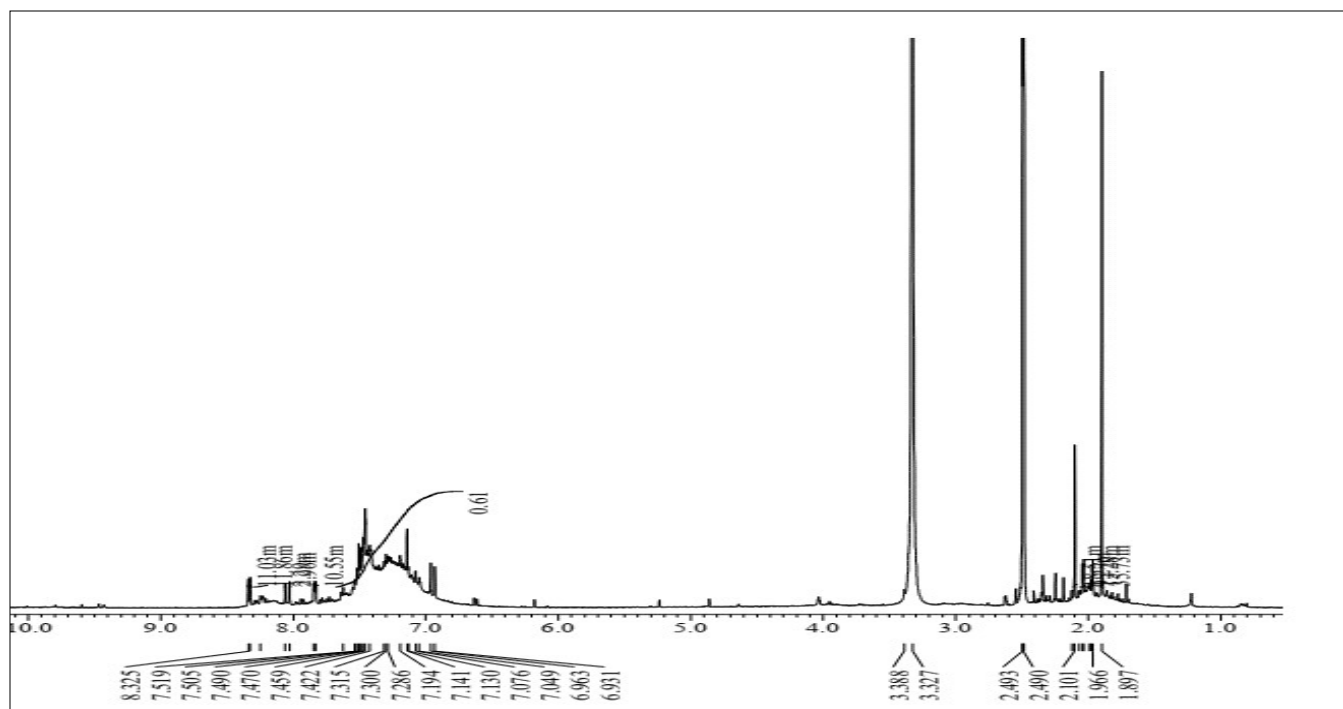
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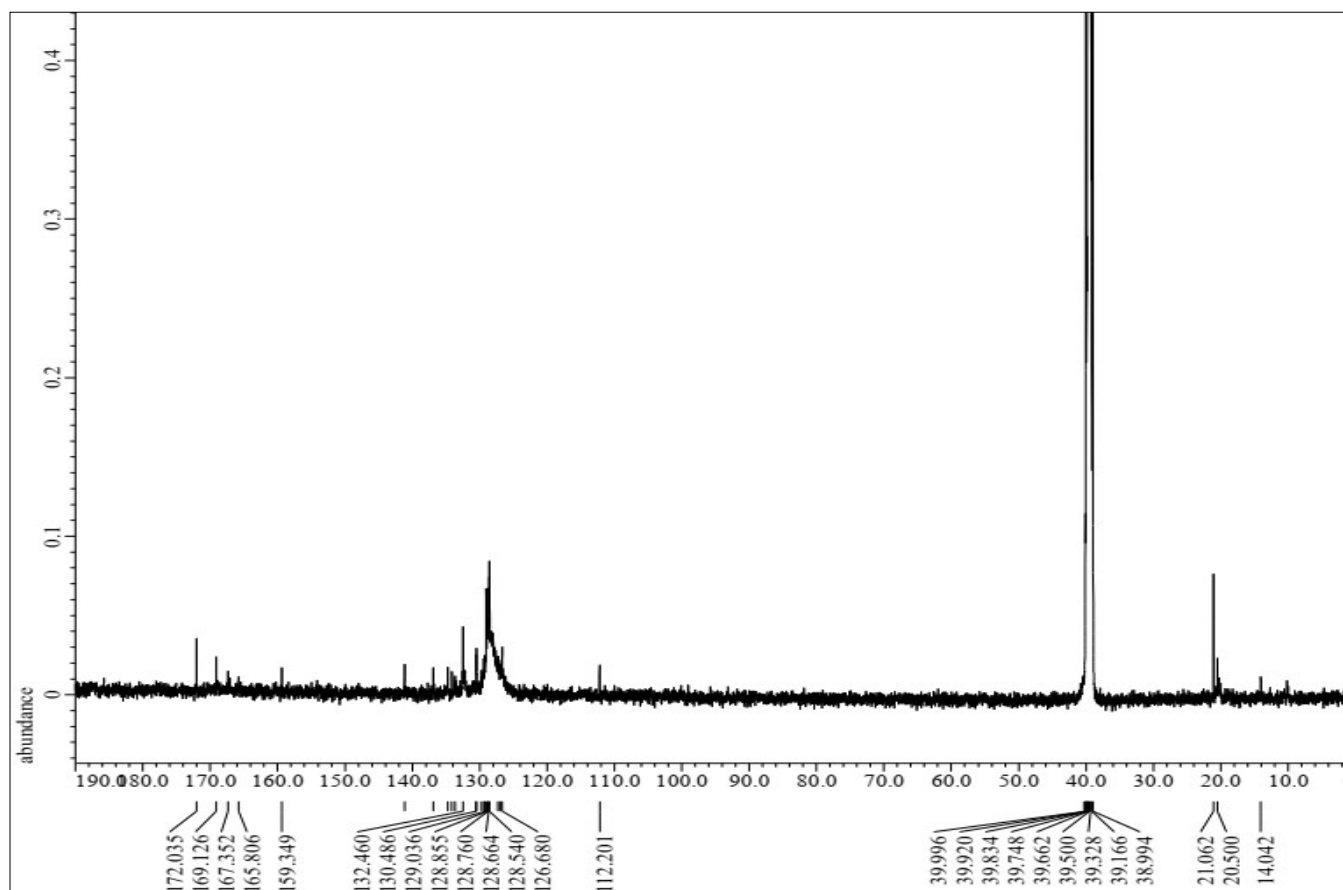
133 FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 10a.



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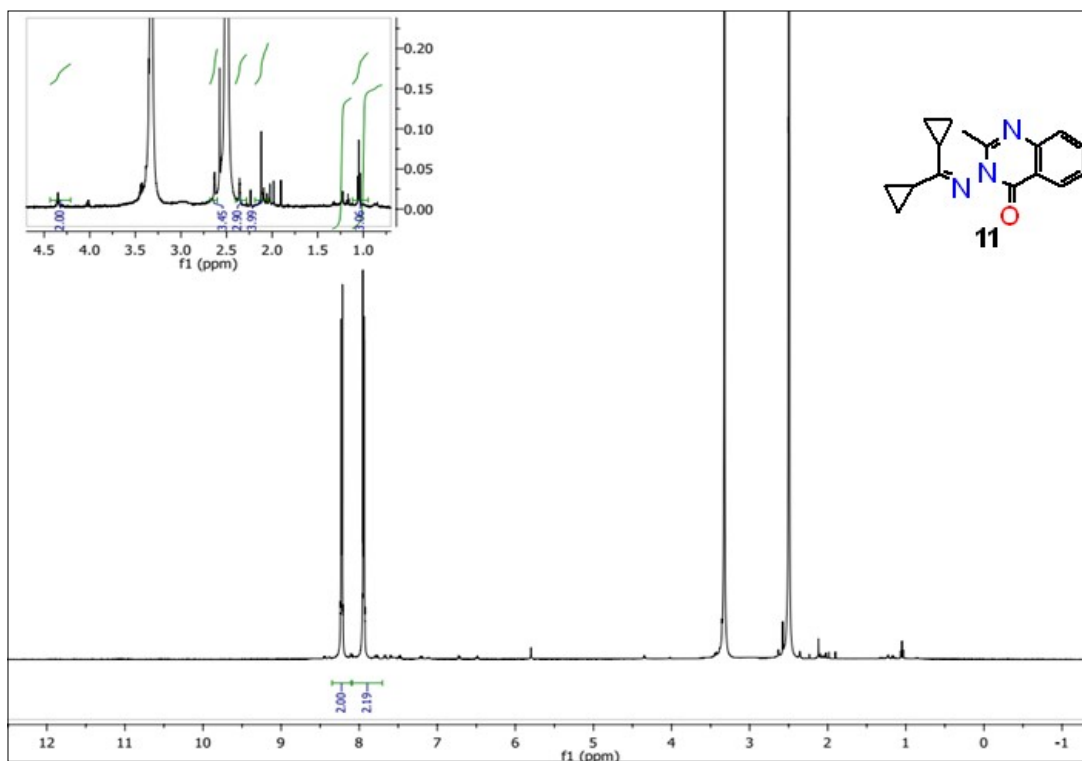


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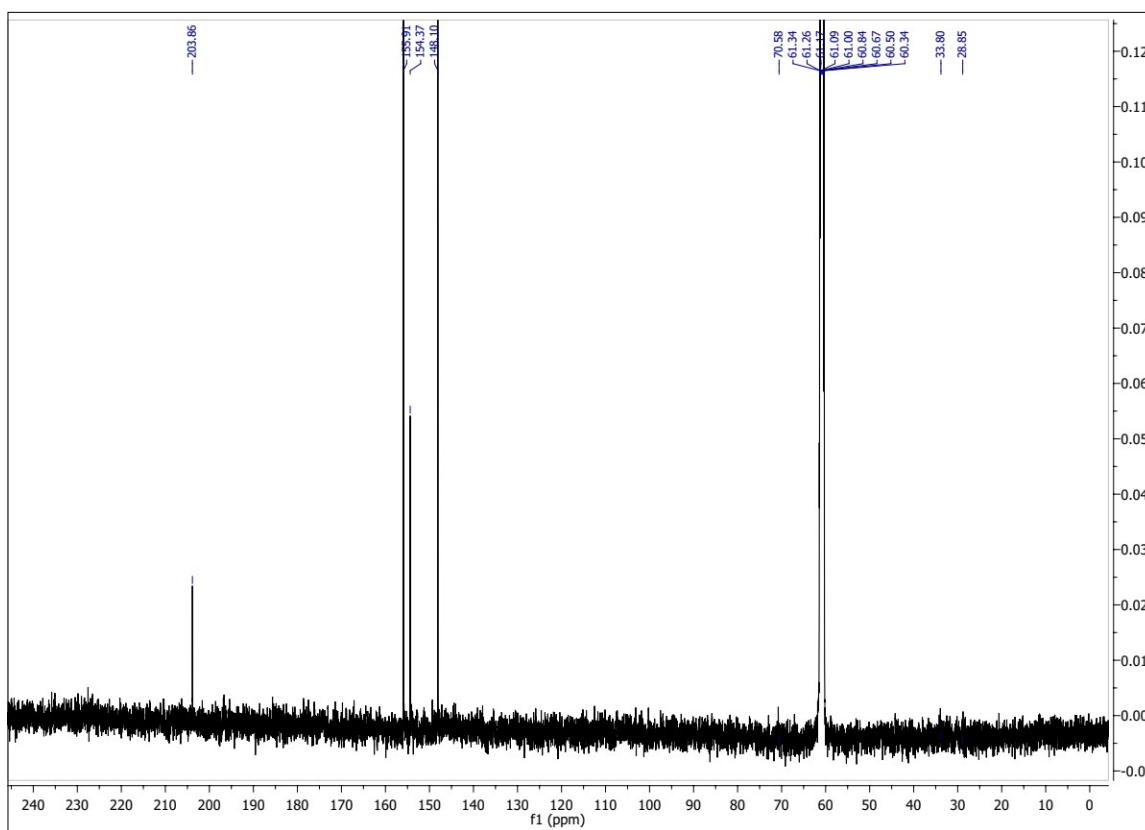


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FTIR, $^1\text{H-NMR}$ (500 MHz, DMSO), and $^{13}\text{C-NMR}$ (125 MHz, DMSO) of compound 10b.



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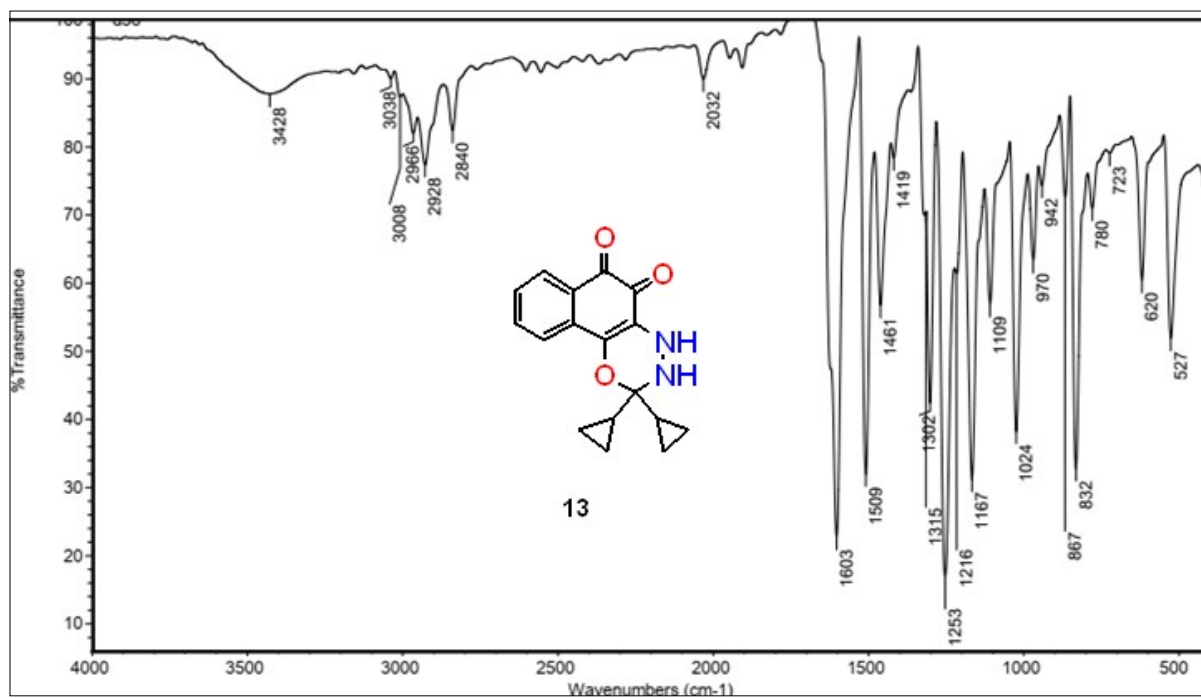


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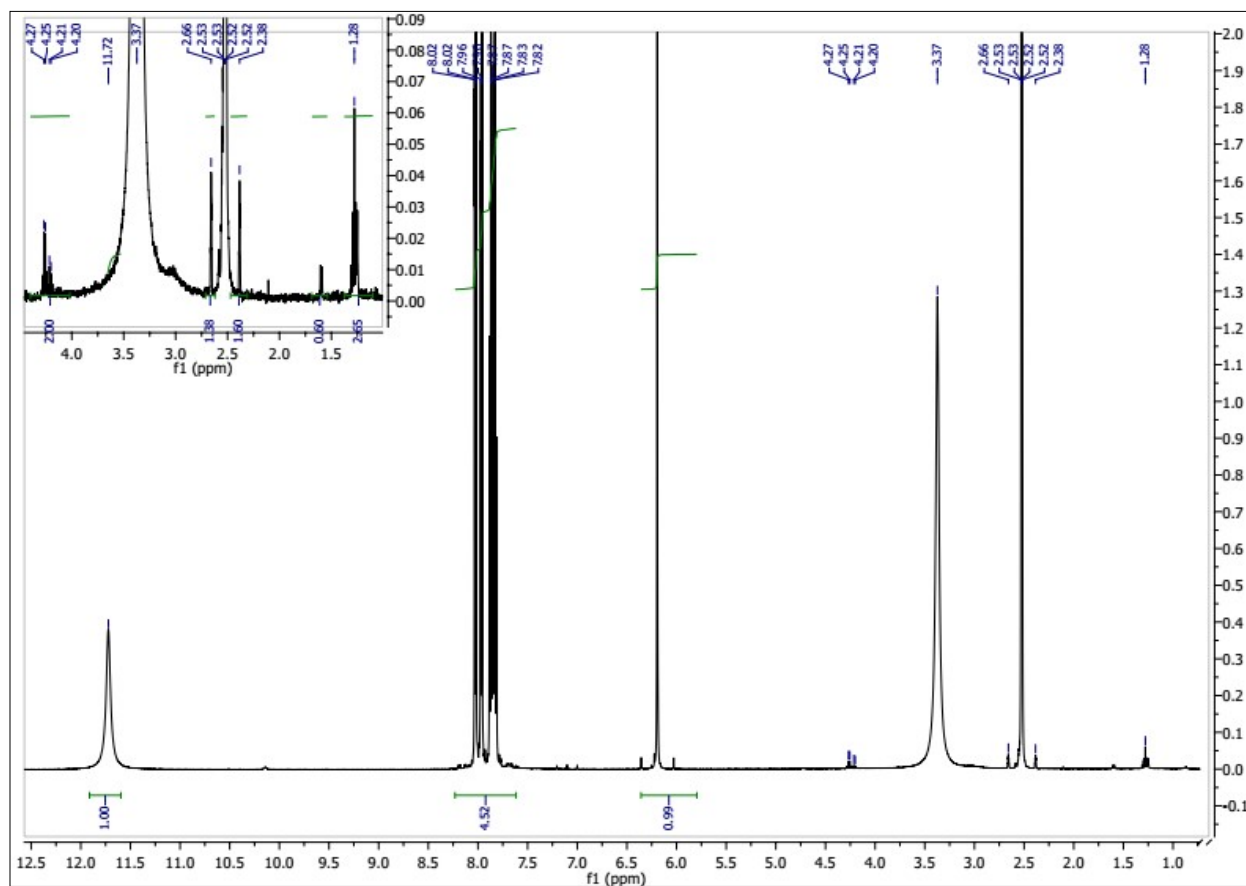
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¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 11.

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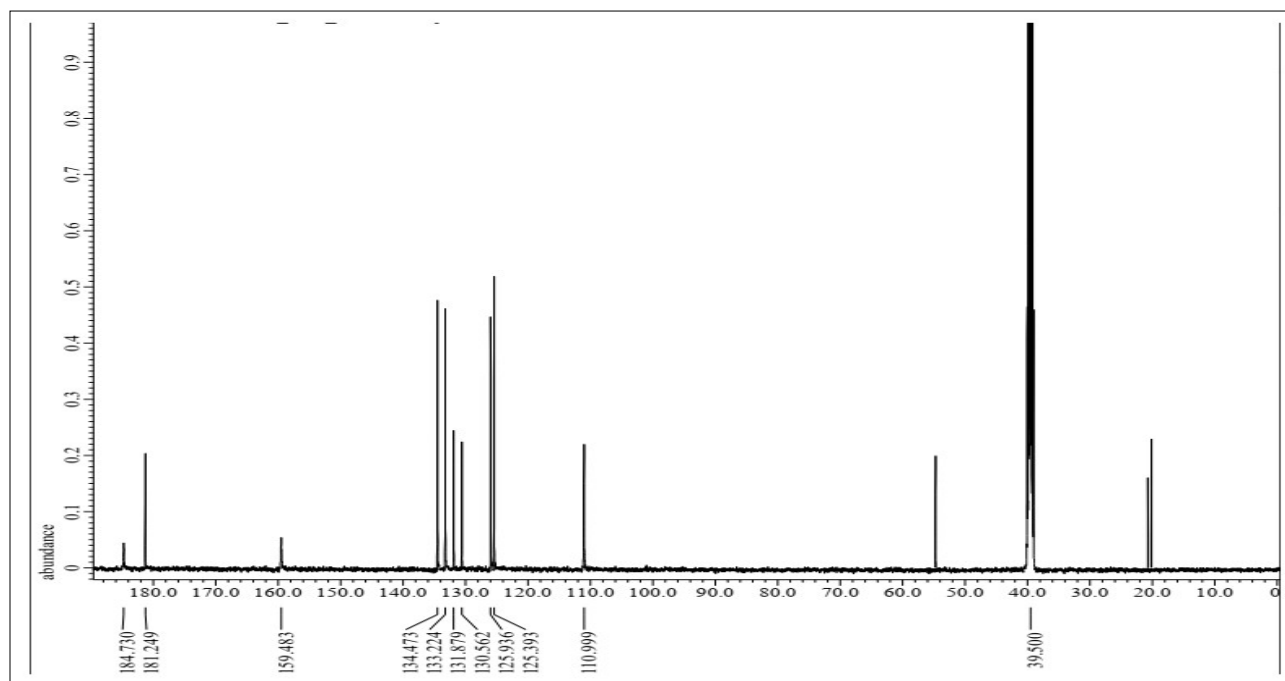
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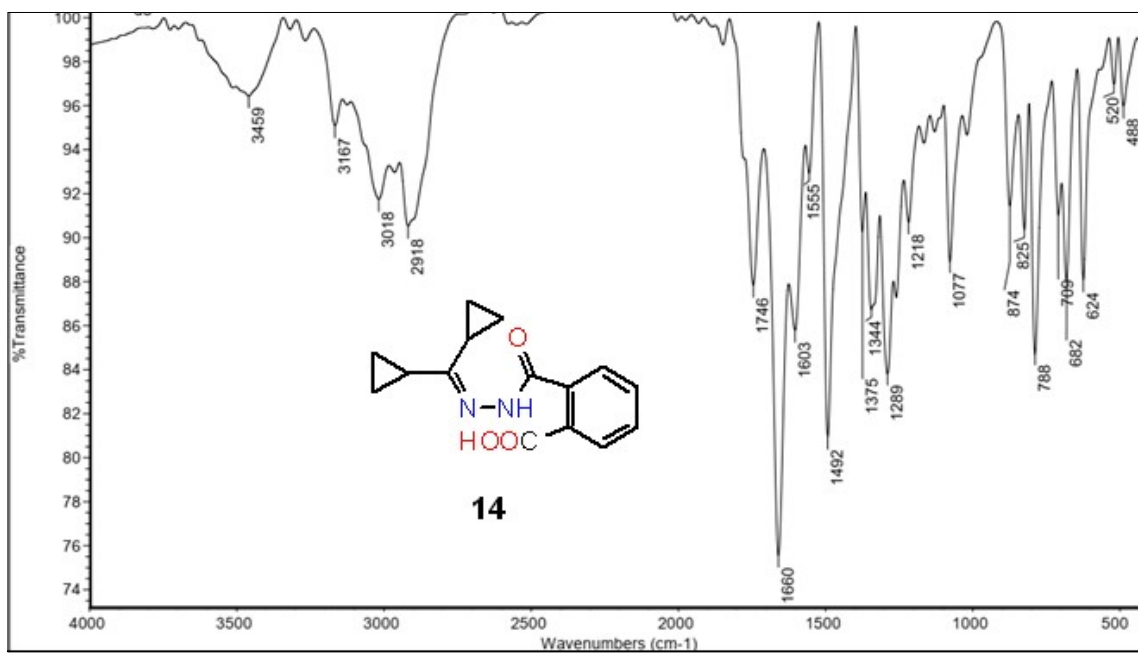


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148 FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 13.

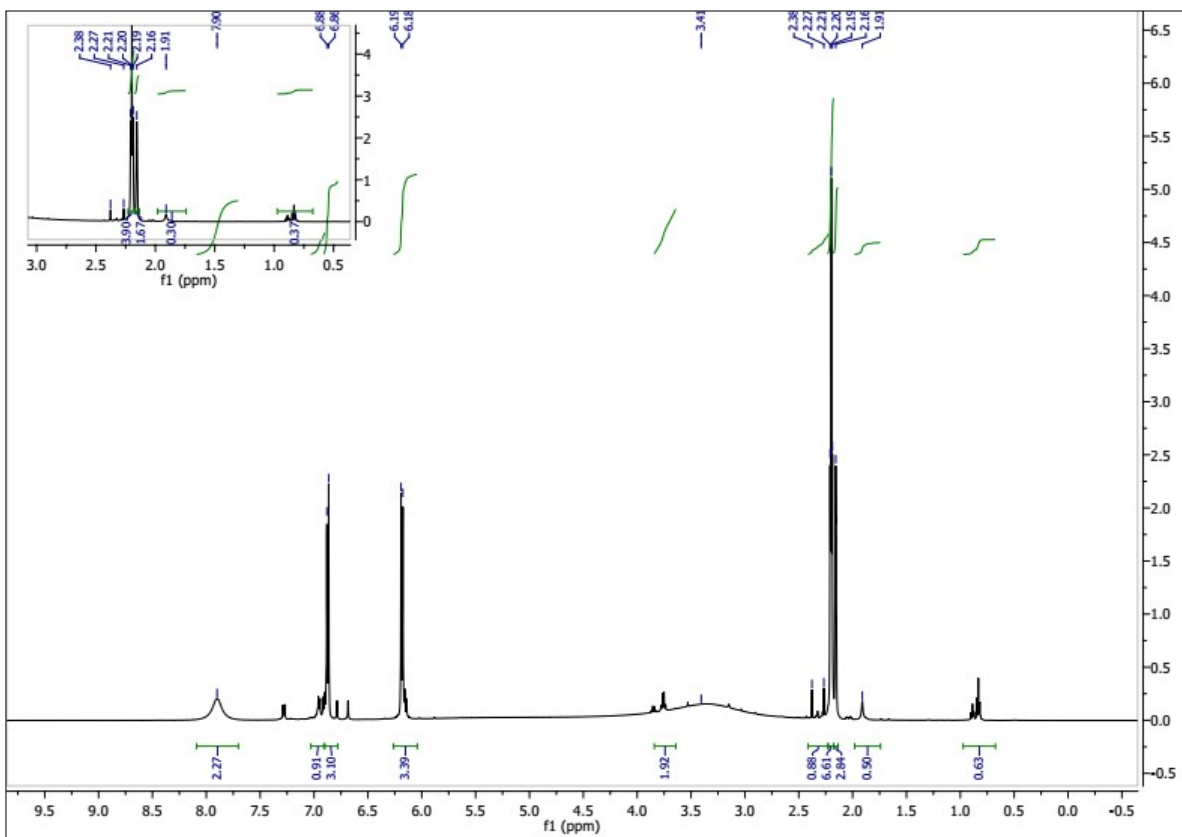
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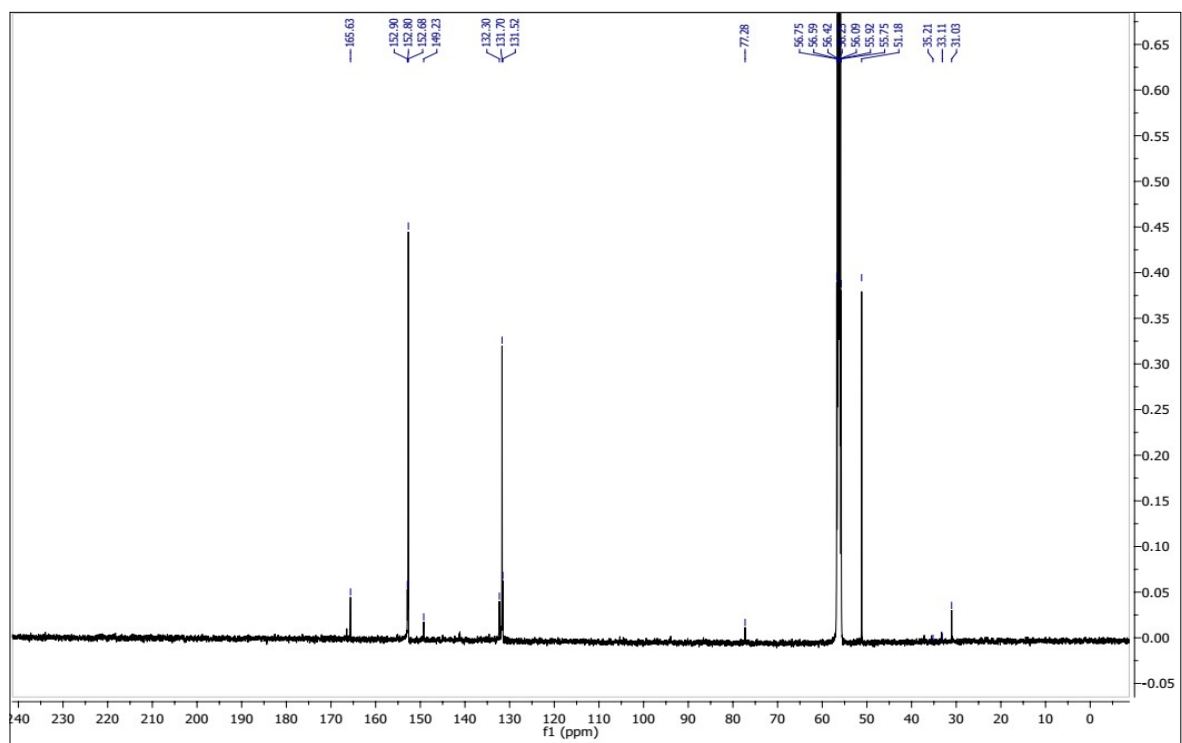
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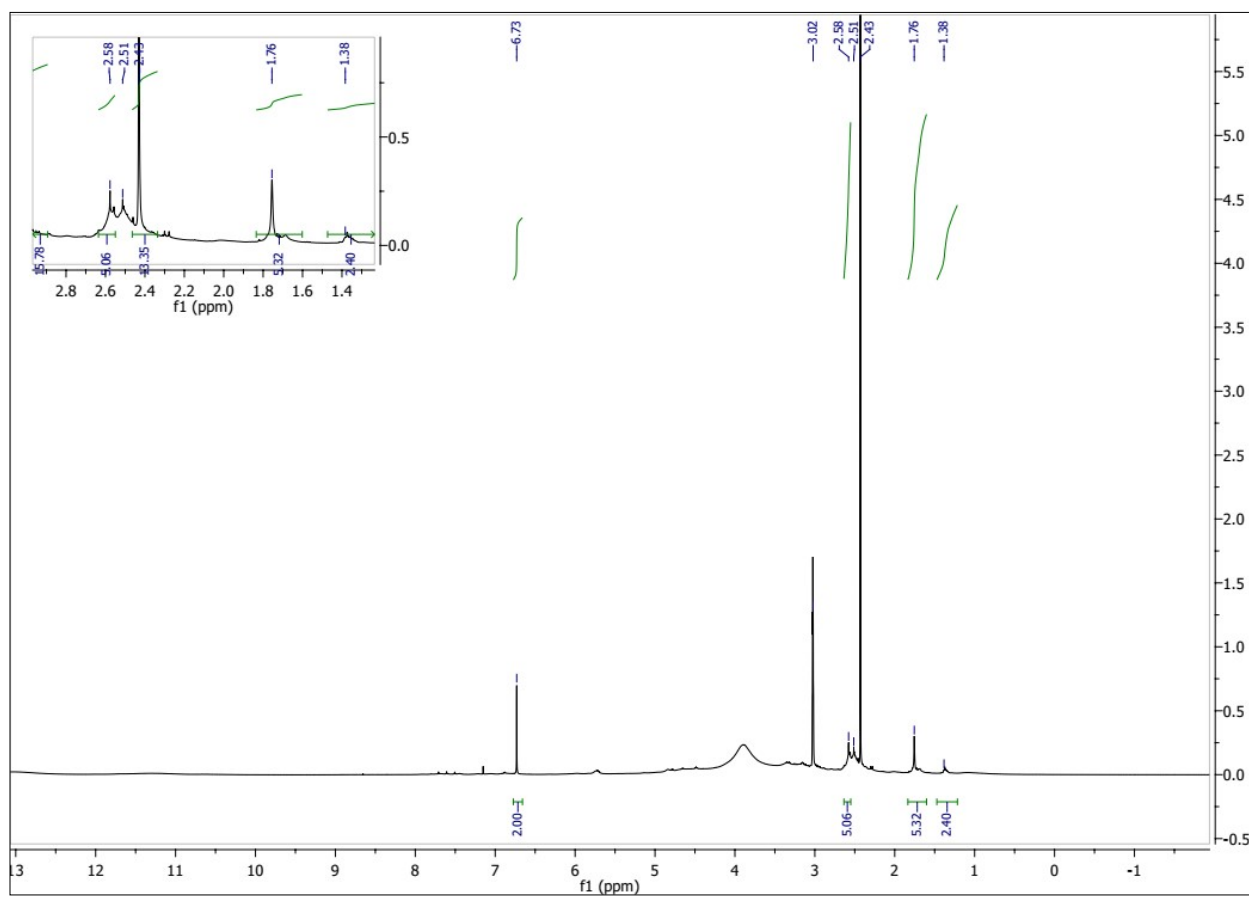
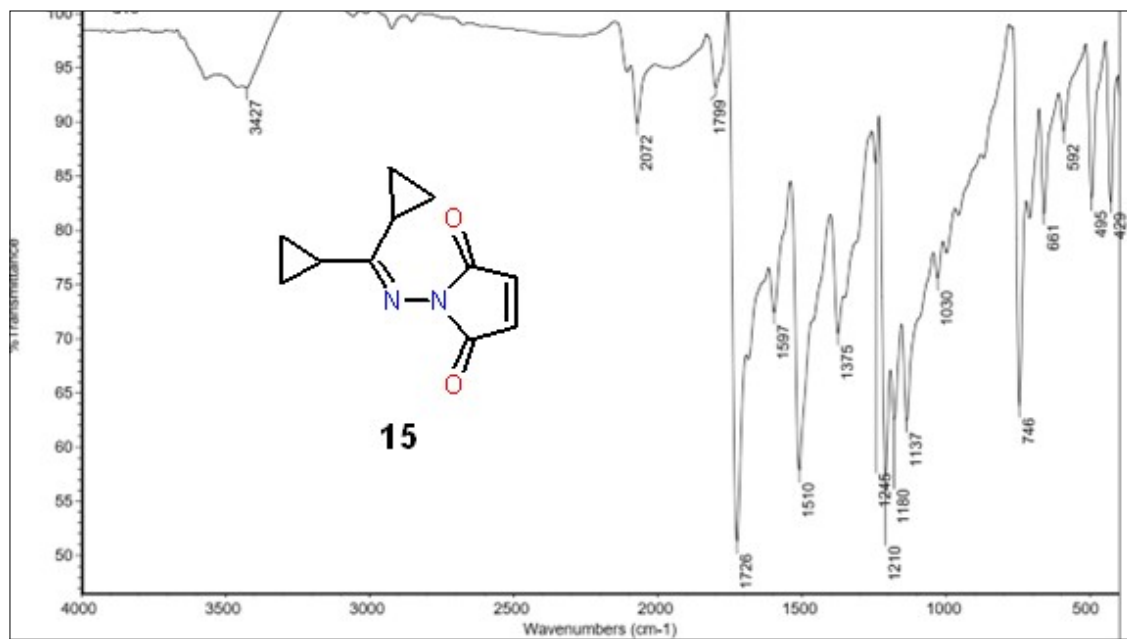
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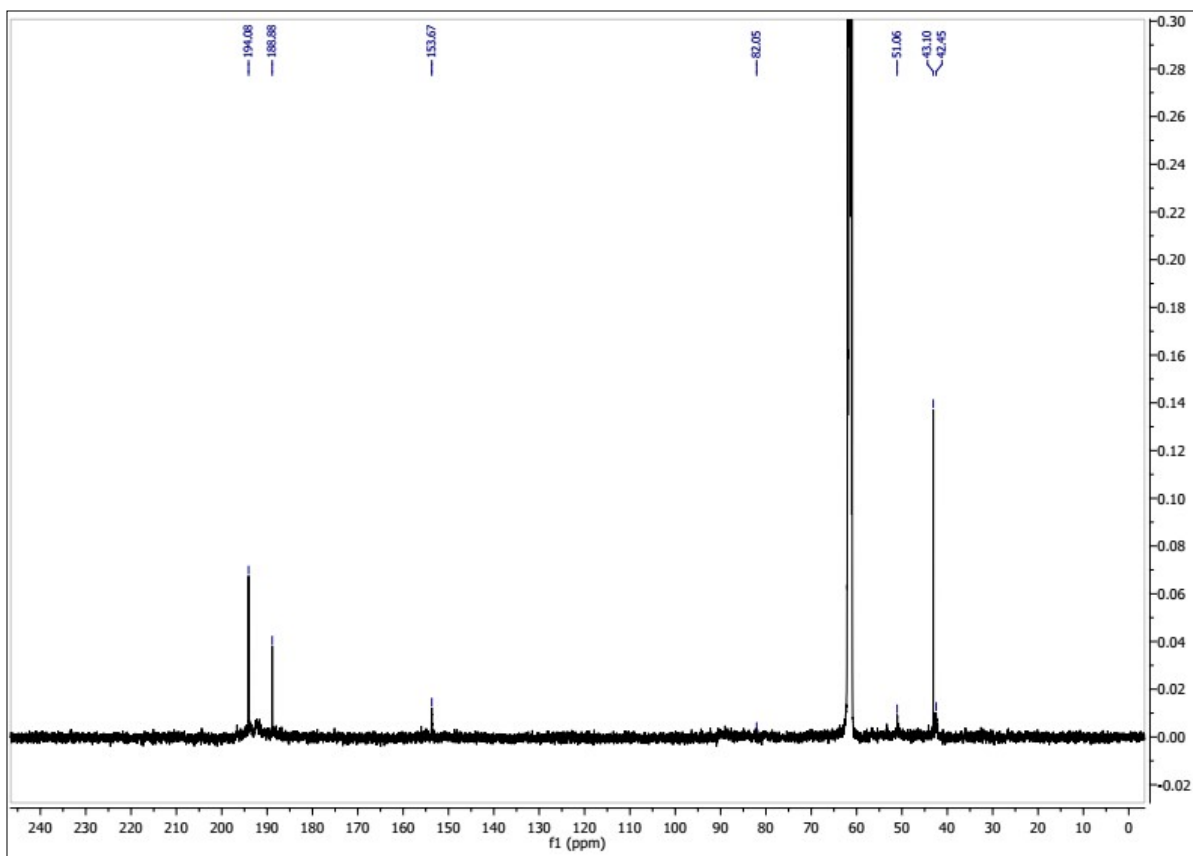


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155 FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 14.

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161 **FTIR, ^1H -NMR (500 MHz, DMSO), and ^{13}C -NMR (125 MHz, DMSO) of compound 15.**

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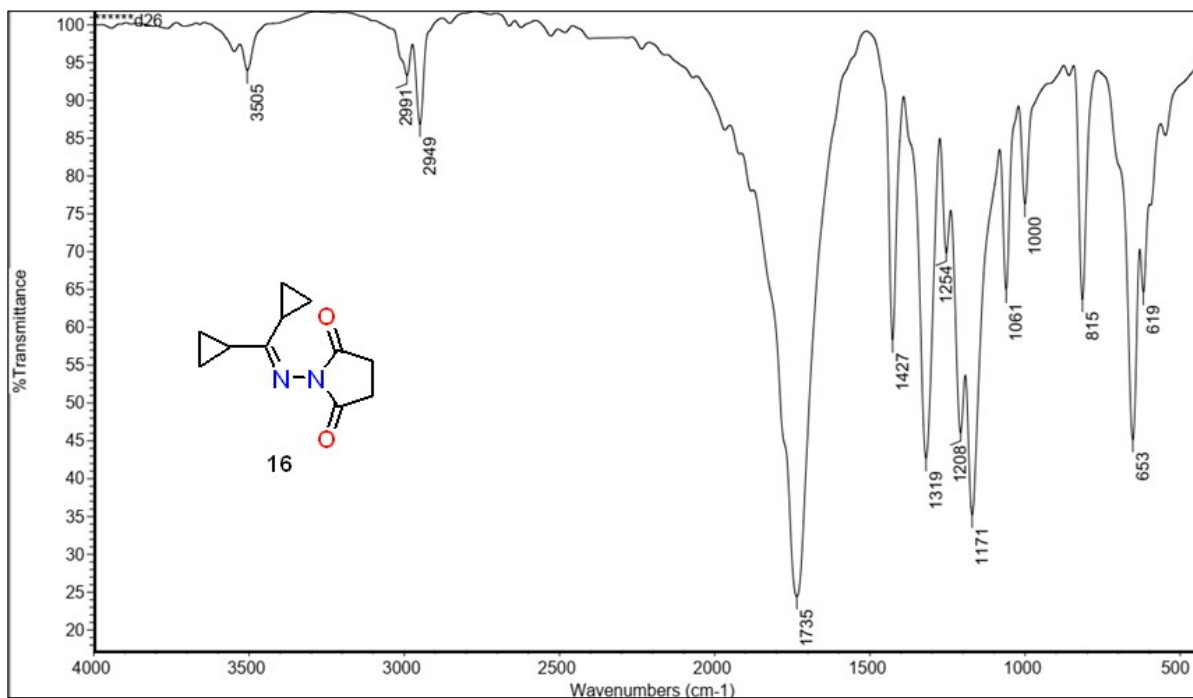
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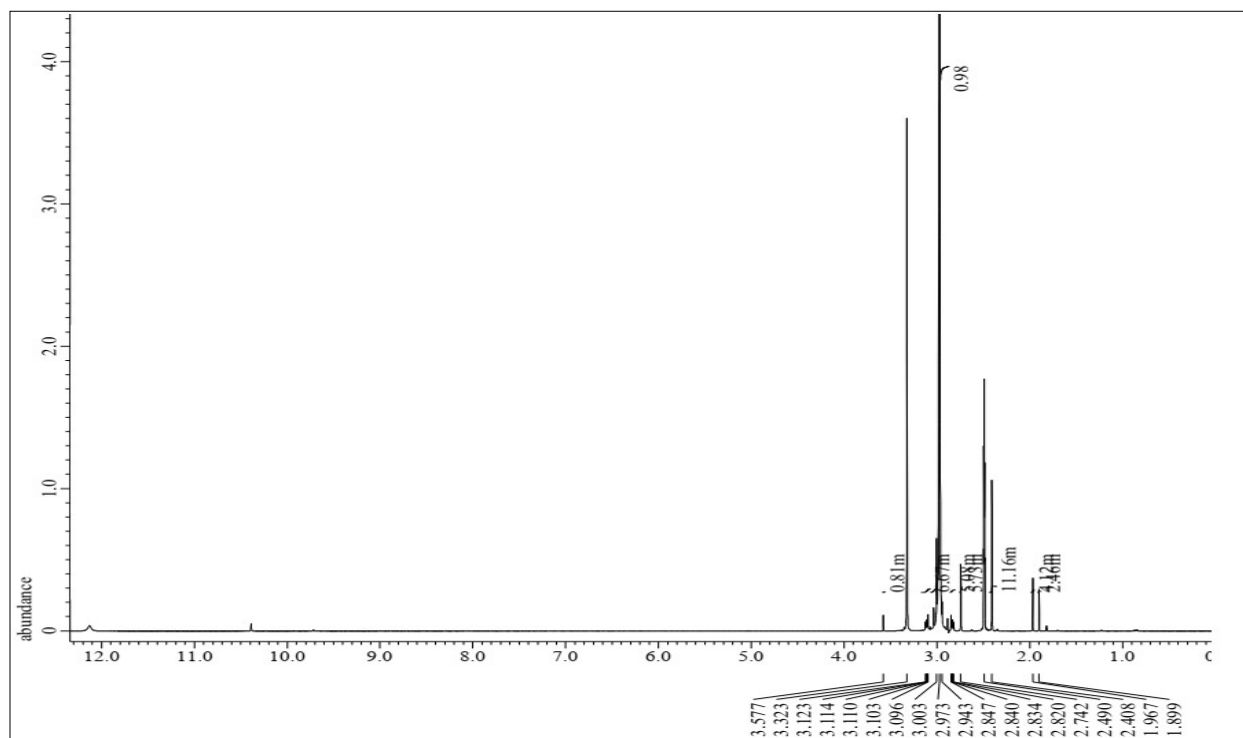
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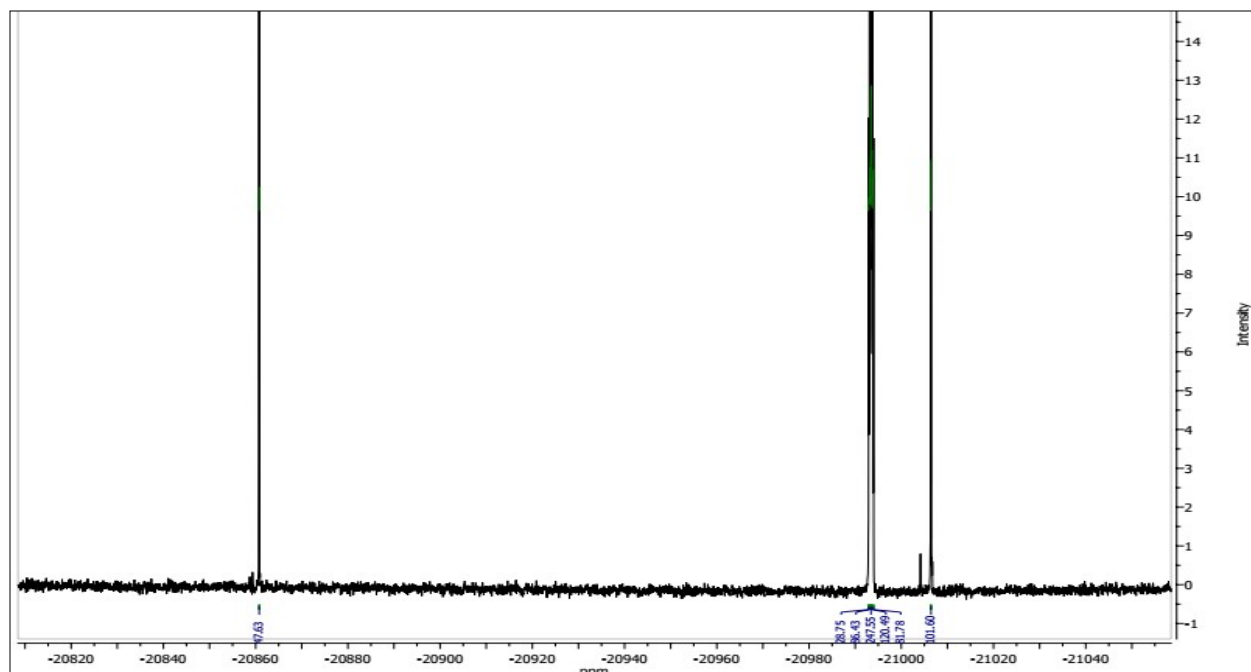


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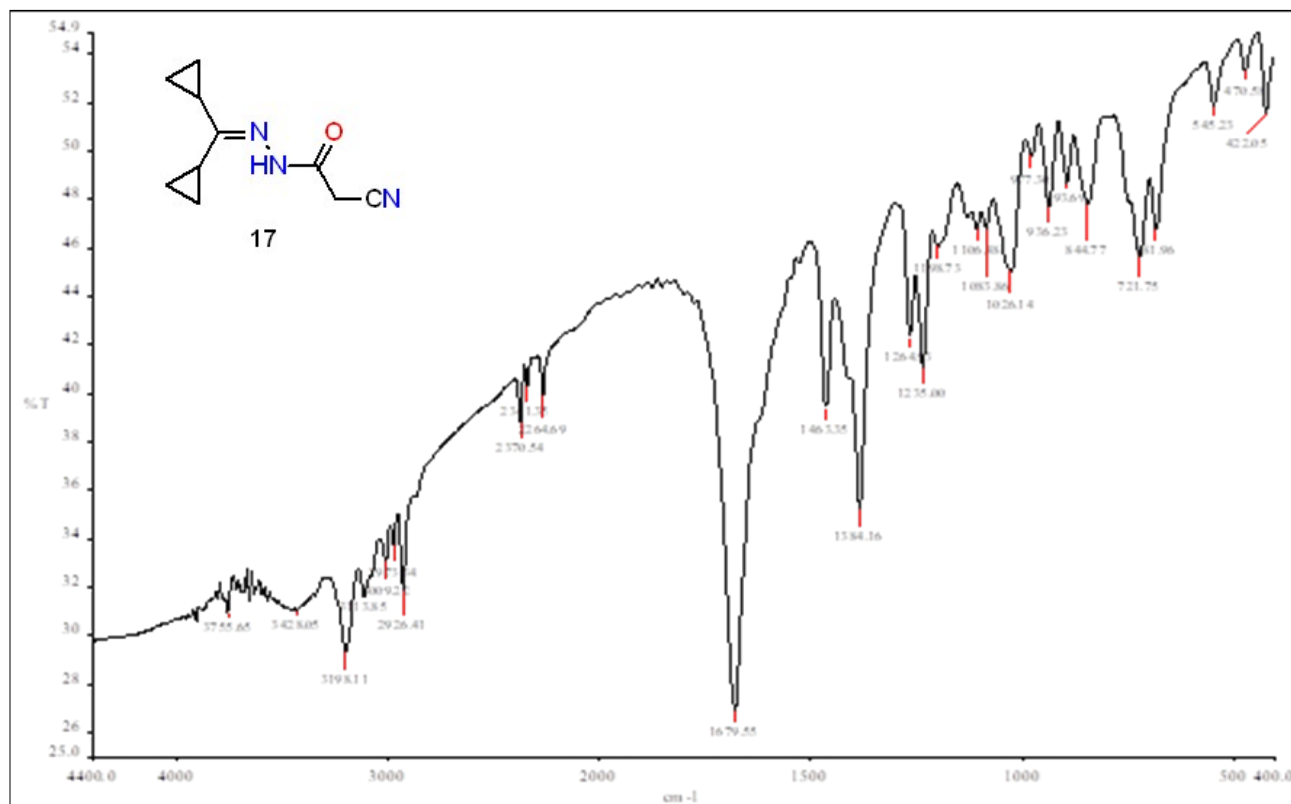
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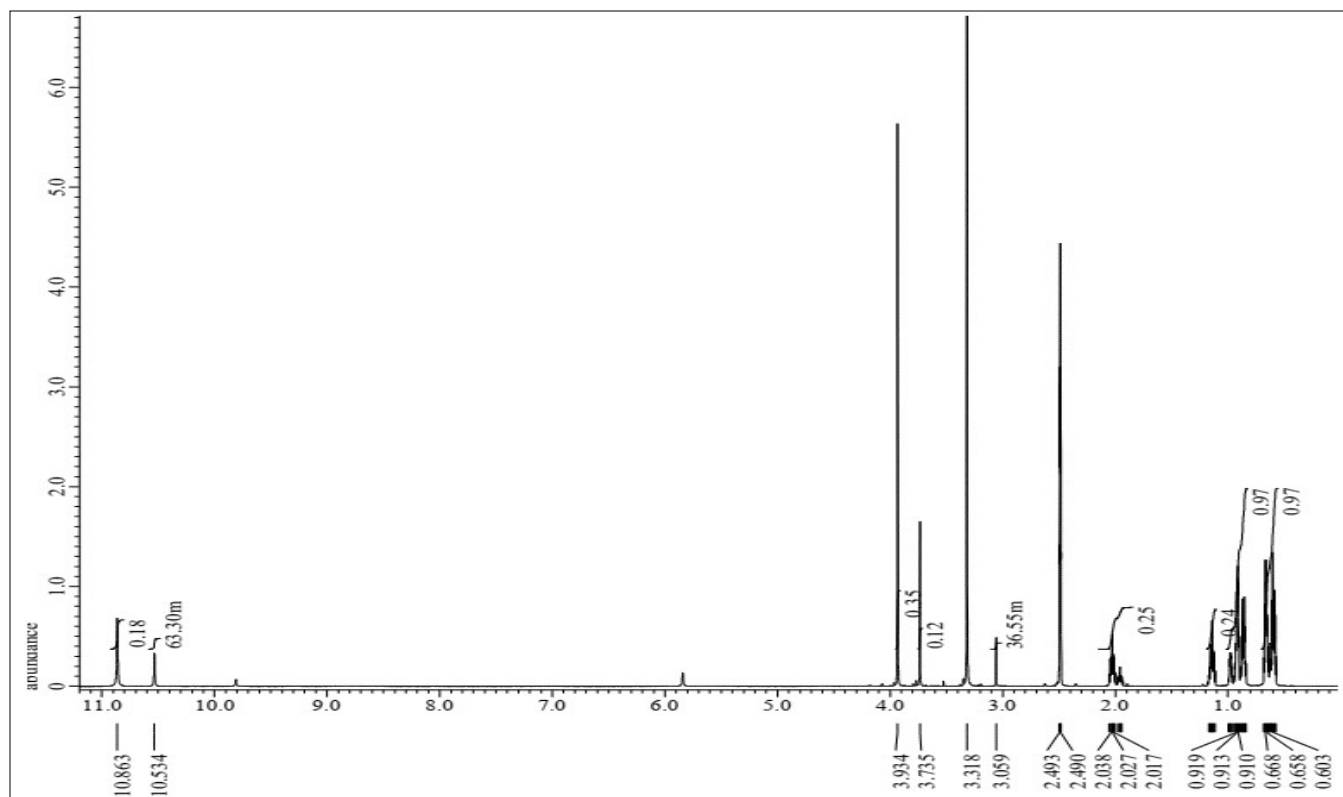
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179 FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 16.

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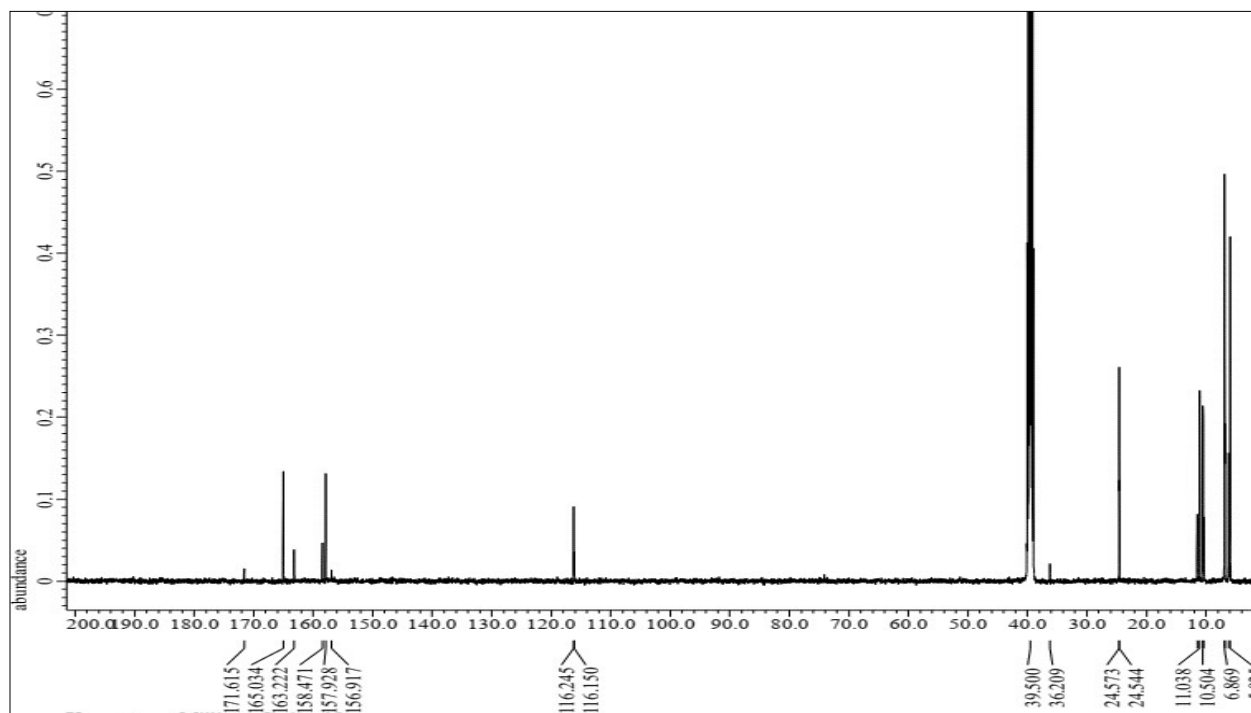


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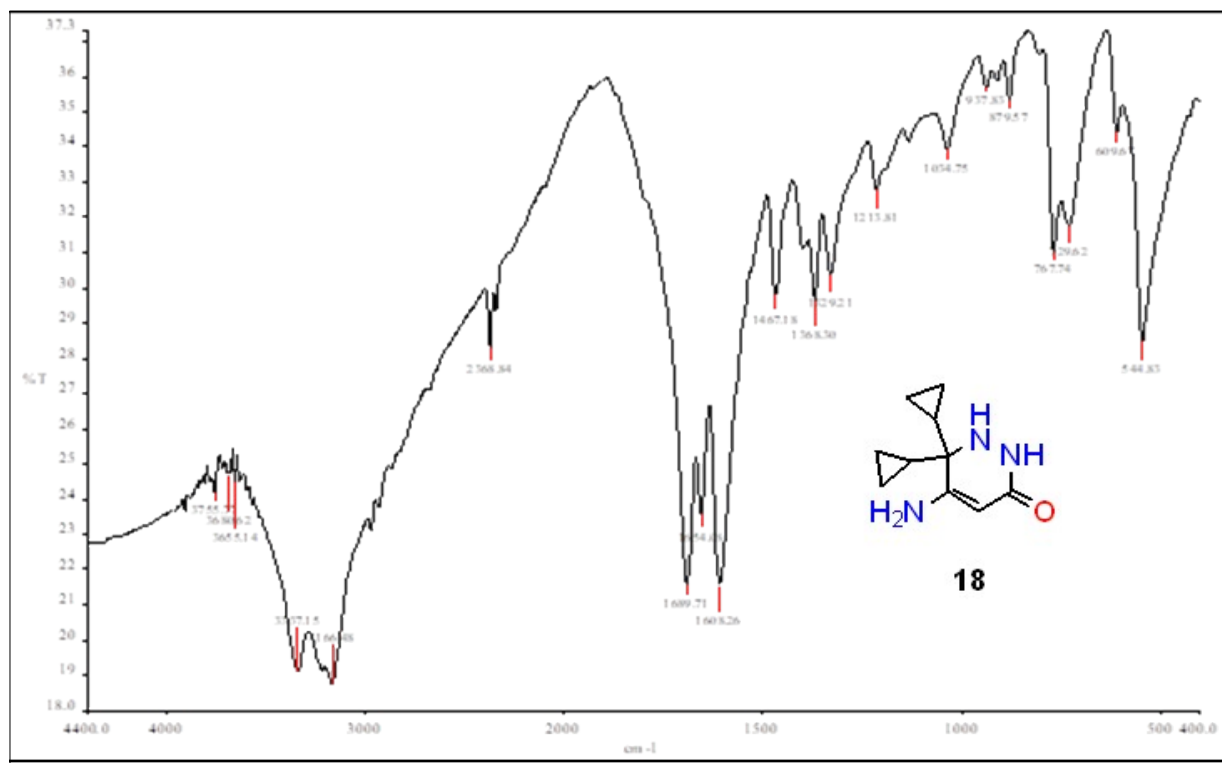


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185 FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 17.

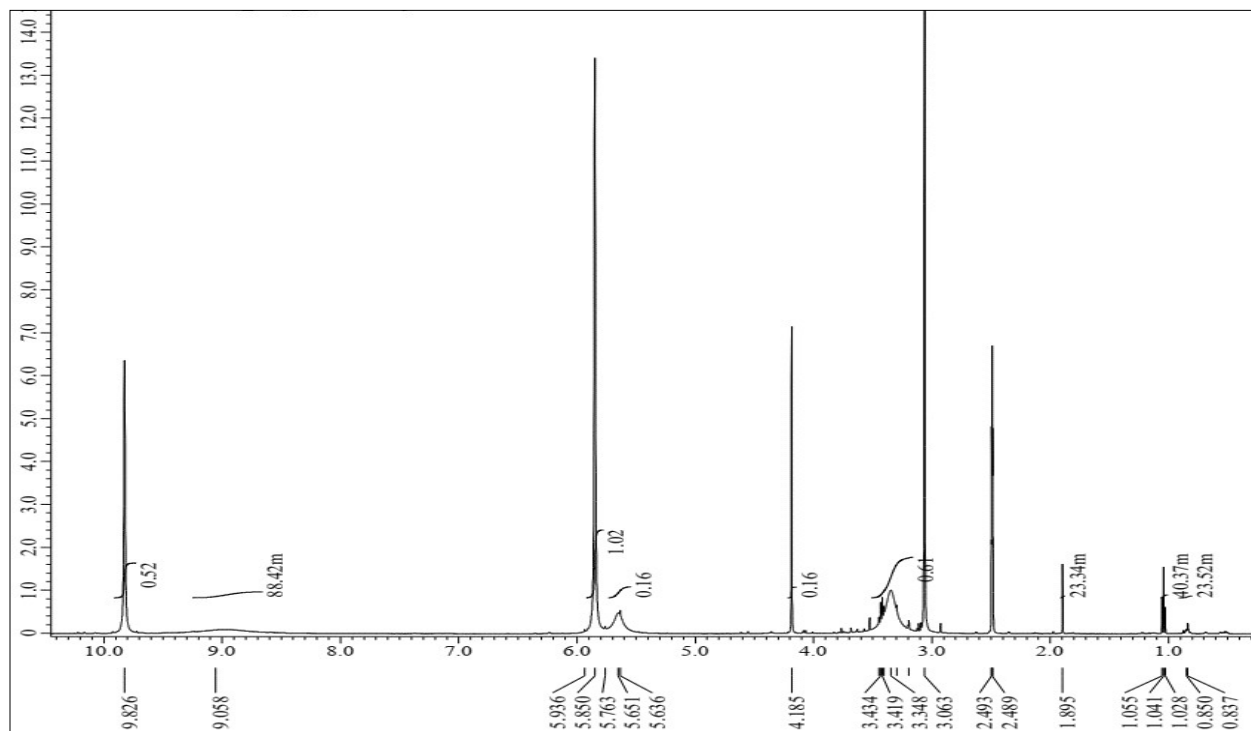
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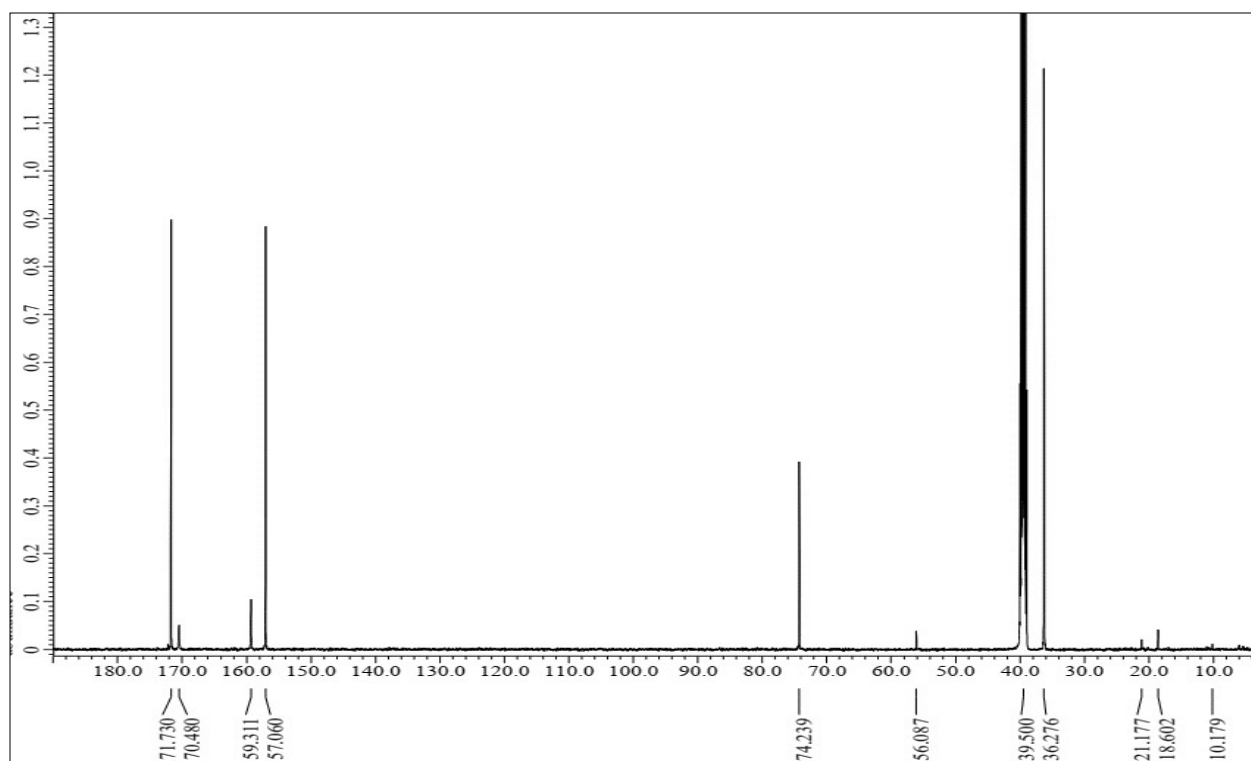
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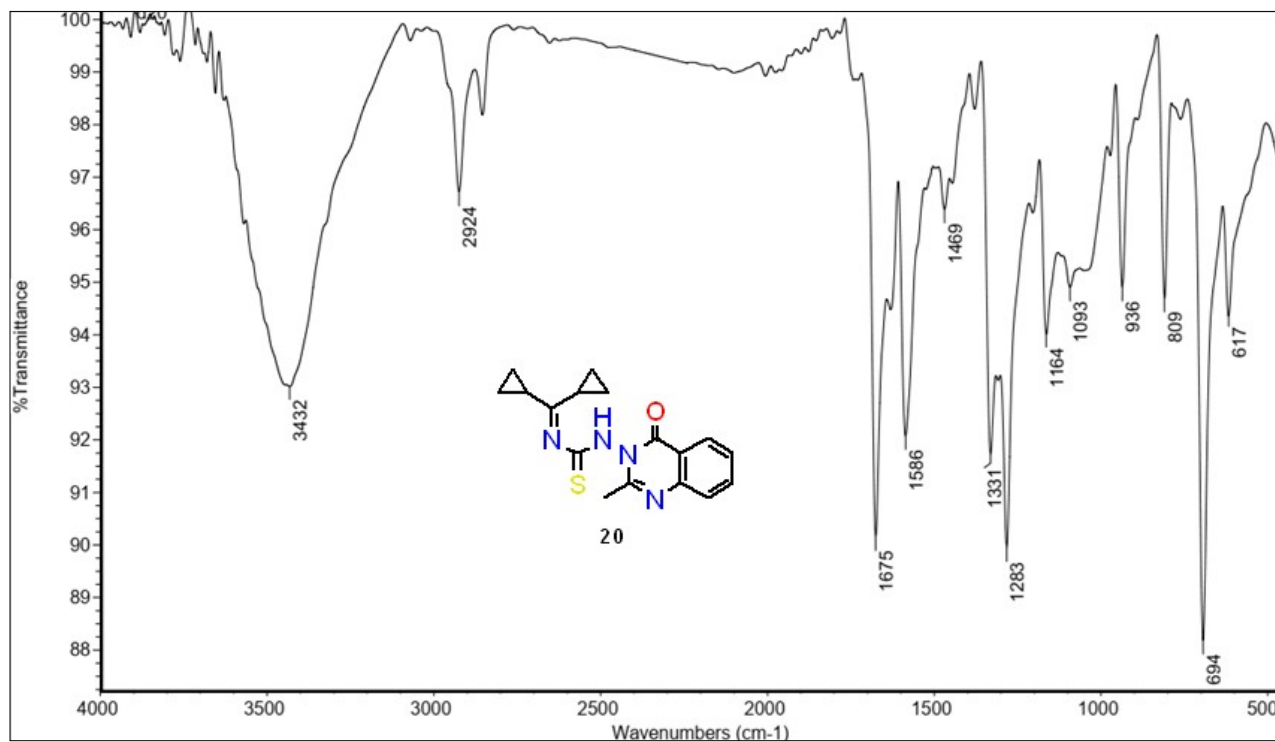
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193 **FTIR, ¹H-NMR (500 MHz, DMSO), and ¹³C-NMR (125 MHz, DMSO) of compound 18.**

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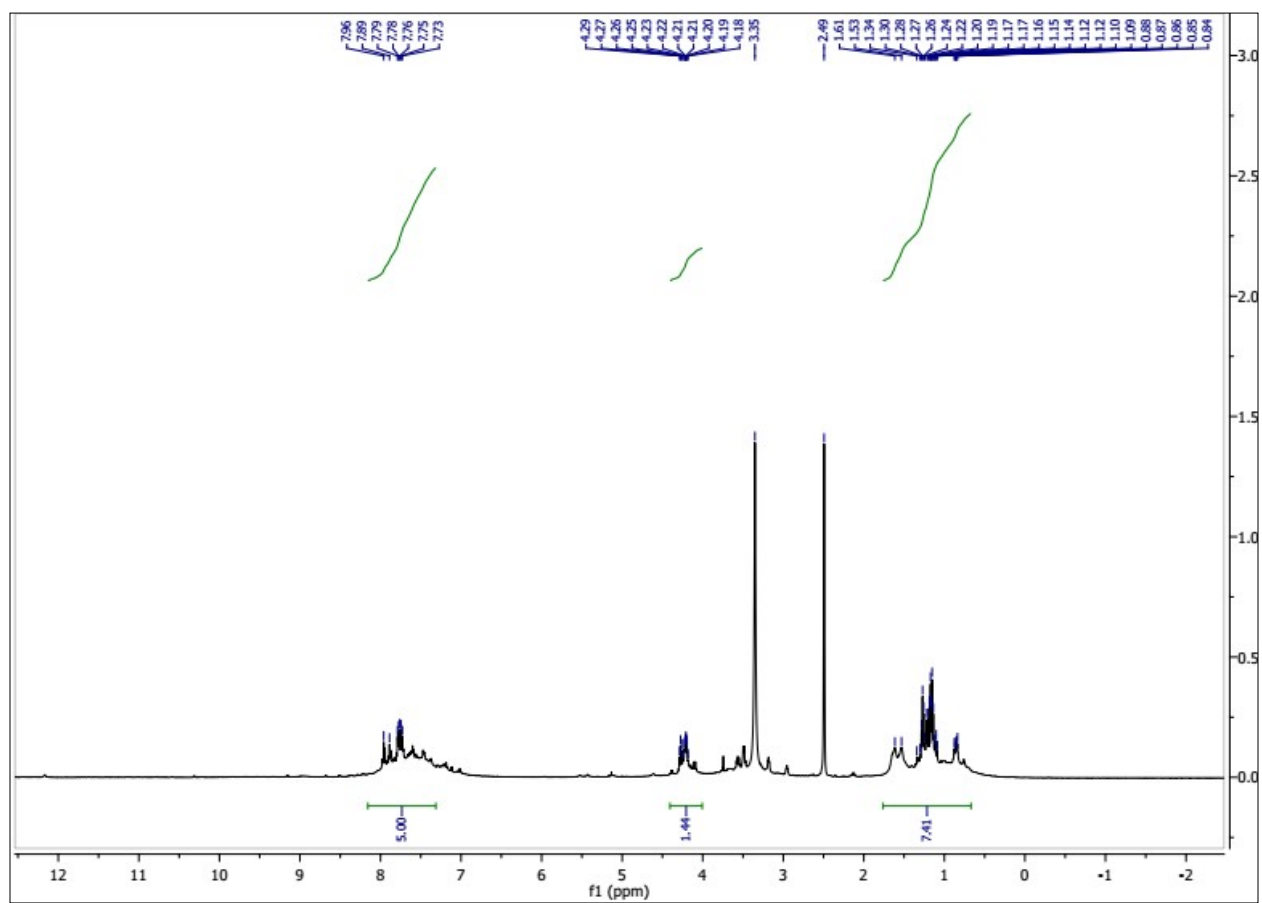


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201 **FTIR, and ¹H-NMR (500 MHz, DMSO) of compound 20**

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Table S1: Physicochemical properties and spectroscopy data of the synthesized compounds.

compound	Color Recrystallization solvent	Yield %	Mp C	IR (KBr, v/cm⁻¹), ¹H, ¹³C NMR (DMSO-d₆, δ ppm). MS (EI): (m/z, %)
2	White needles (ethanol)	92%;	85	IR : 3425, 3395 (NH₂), 1604 (C=N). ¹H NMR: 0.6-1.07 (m, 8H, 4CH₂), 2.25 (m, 4H, 2CH, NH₂). ¹³C-NMR: 5.6, 7.24, 9.36, 11.45 and 165.8. MS (EI): (m/z, %), 124 (M⁺-1, 1), 108 (100).
3a	yellow needles (Ethanol)	78	164-6	IR: 2967-2840 (CH aliphatic), 1659, 1600 (2C=N). MS (EI): (m/z, %), 241 (M⁺-1, 9.08), 160 (100).
3b	Yellow crystals (Ethanol)	92	>250	IR: 2961-2830 (CH aliphatic), 1609 (2C=N). MS (EI): (m/z, %), 257 (M⁺, 23)
3c	buff needles (Ethanol)	81	104	IR: 2927-2850 (CH aliphatic), 1656-1651 (2C=N). MS (EI): (m/z, %), 202 (M⁺, 60).
4	Dark red crystals (Ethanol)	88	>300	IR: 3277(NH), 1723, 1613 (C=O, C=N). ¹H NMR : 0.9-1.3 (m, 10H, H-aliph), 6.8-7.5 (m, 4H, H-Ar) and 10.9(s, 1H, NH). ¹³C-NMR: 7.36, 9.2, 13.13, 110.6, 111.12, 122.05, 127.8, 128.2, 134.4, 144.73, 145.19 and 163.4. MS (EI): (m/z, %), 253 (M⁺, 100).
5	Bright yellow crystals (Ethanol)	95	205-7	IR: 3445(OH), 1622 (2 C=N). ¹H NMR : 6.9-7.6(m, 8H, H-Ar), 8.9(s, 2H, CH=N), and 11.1(s, 2H, OH).

				MS (EI): (m/z, %), 240 (M⁺, 17), and 185(100).
6a	White crystals (Ethanol)	62	160-162	IR (KBr, v/cm⁻¹): 1601, 1685 (2 C=N), 3349 broad (NH₂, NH). ¹H NMR: 1.02 1.4 (m, 10H, H-aliphatic) and 3.8(s, 3H, OCH₃), 5.8 (s, 1H, CH), 6.7, 7.8 (m, 4H, H-Ar), 8.6 (s, 2H, NH₂) and 9.8 (s, 1H, NH). MS (EI): (m/z, %), 268 (M⁺-OCH₃, 6.6).
7a	Yellow crystals (Ethanol)	75	238-240	IR (KBr, v/cm⁻¹): 3419, 3351 (2NH), 3259, 3190 (NH₂), 1679, 1613 (C=O, C=N). ¹H NMR: 1.0-1.055 (m, 10H, H-aliphatic), 6.8-7.3 (m, 4H, H-Ar), 10.5 (s, 1H, NH), 10.6 (s, 1H, NH) and 11.1 (s, 2H, NH₂) . ¹³C-NMR: 10-20, 109.9, 111.03, 117.4, 119.98,162.7, 178.66 and 181.13. MS (EI): (m/z, %), 313 (M⁺+2, 8.4).
6b	Brown crystals (Ethanol)	62	>250 ^o c	IR: 3469 (NH), 3196, 3351(CH aromatic), 1639, 1605 (C=N). ¹H NMR: 1.0-1.055 (m, 10H, H-aliphatic), 3.1(s, 3H, OCH₃), 6.8-7.3 (m, 4H, H-Ar), 8.5 (s, 1H, NH). MS (EI): (m/z, %), 313 (M⁺+2, 8.4)
7b	Bage crystals (Ethanol)	62	262-264	IR: 3438, 3238 (2NH), 1691, 1622 (C=O, C=N). ¹H NMR: 0.9-2.1 (m, 10H, H-aliphatic), 10.11 (s, 1H, NH), 11.2 (s, 1H, NH) and 6.7-

				<p>8.2 (m, 9H, H-Ar).</p> <p>¹³C-NMR: 17.8, 18.9, 23.3, 23.5, 32.14, 85.3, 127.7, 128.6, 130.2, 140.5, 141.8, 142.0, 146.5, 164.7, 165.2, 167.2, and 169.7.</p> <p>MS (EI): (m/z, %) 360 (M⁺- 1, 15.1).</p>
8a	Faint yellow crystals (Methanol)	95	226-8	<p>IR: 3443, 3320 (NH₂), 3173, 3137 (2CH=N), 1650, 1613 (C=N).</p> <p>¹H NMR: 6.7-8.0 (m, 8H, H-Ar), 8.3 (s, 1H, CH=N), 9.8(s, 1H, NH₂) and 11.3 (s, 1H, OH).</p> <p>¹³C-NMR: 116, 119.34, 120.37, 126.7, 131.17, 139.7, 156.4 and 177.6.</p> <p>MS (EI): (m/z, %), 297 (M⁺, 2.5), 195(100).</p>
8b	Yellow crystals (methanol)	55	198-200	<p>IR: 1689,1623 (2 C=N).</p> <p>¹H NMR: 6.9-7.6 (m, 8H, H-Ar), 8.99 (s, H, CH=N) and 11.1(s, 2H, 2OH).</p> <p>MS (EI): (m/z, %), 356 (M⁺, 20).</p>
10a	Brown crystals (Ethanol)	62	152-154	<p>IR: 1704, 1643, 1600 (C=O, 2C=N).</p> <p>¹H NMR: 1.9-2.0 (m, 13H, H-aliphatic, CH₃) and 6.9-8.3 (m, 6H, H-Ar).</p> <p>¹³C-NMR: 20.5, 23.8, 31.4,32.6, 34.7, 72.25, 146.9, 149.8, 150.8, 151.1, 152.5, 153.09, 154.1, 154.9, 155.18, 155.53, 184.8, and 18873.</p> <p>MS (EI): (m/z, %), 289 (M⁺- 4, 10.6).</p>
10b	Yellow crystals (acetic acid)	74	158-160	<p>IR: 1704,116455 (C=O,2 C=N).</p> <p>¹H NMR: 0.8-2.1 (m, 10H, H-aliphatic), 1.8 (s,3H, CH₃) and 7.4-8.3 (m, 11H, H-Ar,</p>

				CH=C).
				¹³ C-NMR (DMSO-d ₆): δ ppm 10-20, 14.02, 20.5, 21.06, 125.1-133.7 Ar-C, 163.06, 165.8, 167.3, 169.12, and 172.03.
				MS (EI): (m/z, %), 352 (M ⁺ , 1.9).
11	Faint yellow needles (Ethanol)	82	230-232	IR: 1675, 1660 (C=O, C=N).
				¹ H NMR: 1.02-2.1 (m, 13H, H-aliphatic, CH ₃) and 7.9-8.2 (m, 4H, H-Ar).
				¹³ C-NMR: 10.55-70.5, 148.1, 154.37, 155.9, and 203.8.
				MS (EI): (m/z, %), 267 (M ⁺ , 3.6).
13	Buff crystals (Methanol)	89	185-186	IR: 3450 (2NH), 3428 (NH), 1687, 1603 (2C=O).
				¹ H NMR: 1.2-1.5 (m, 10H, H-aliphatic), 6.1(s, 1H, NH), 7.7-8.01 (m, 1H, H-Ar), and 11.52(s, 1H, NH).
				¹³ C-NMR: 16.6-77, 18.1, 20.1, 20.9, 110.99, 125.3, 125.93, 130.56, 131.87, 134.47, 159.48, 181.24 and 184.73.
				MS (EI): (m/z, %), 296 (M ⁺ , 1.5).
14	White crystals (Acetic acid)	72	>250	IR: 3459(OH), 1746, 1660, 1605 (2C=O, C=N). ¹ H NMR: 0.6-1.8 (m, 10H, H-aliphatic), 7.8-8.1 (m, 5H, H-Ar) 77.9 (s, 1H, NH) and 11.5 (s, 1H, COOH).
				¹³ C-NMR: 18.6, 77.28, 131.5, 131.7, 132.3, 149.2, 152.6, 152.8, 152.9, and 165.6.
				MS (EI): (m/z, %), 272 (M ⁺ , 25).

15	Brown crystals (Methanol)	55	>260°	IR: 1799, 1728, 1634 (2C=O, C=N). ¹H NMR: 0.8-2.1 (m, 10H, H-aliphatic), 6.7 (dd, 2H, H-Ar). ¹³C-NMR: 34.2-82.8, 175.01, 153.65, 188.85 and 194.0. MS (EI): (m/z, %), 204 (M⁺, 56).
16	White needles (DMF)	82	245-8	IR: 1735 (2C=O). ¹H-NMR (DMSO-d6) δ ppm 1.8-3.5 (m, 14H, H-aliph). ¹³C-NMR: 26.3-72, 172.0 and 172.2. MS (EI): (m/z, %), 206 (M⁺, 62).
17	White crystals (Ethanol)	65	125-126	IR (KBr, v/cm⁻¹):3198 (NH), 2264(—C≡N), 1679 (C=N). ¹H NMR : 0.6-2.03 (m, 10H, H-aliphatic), 3.9 (s, 2H, CH₂) and 10.86 (s, 1H, NH). ¹³C-NMR (DMSO-d6): δ ppm 5.92, 6.86, 10.5, 11.03, 24.57, 36.2, 116.24, 157.92, 163.2, 165.3, and 171.6. MS (EI): (m/z, %), 191 (M⁺, 13), 123(100).
18	Brown pellets (Ethanol)	33	210-11	IR: 3337(NH), 3166, 3100 (NH₂), 1689, 1654 (C=O, C=N). ¹H NMR : 0.8-1.8 (m, 10H, H-aliphatic), 4.1(s, 1H, CH-N), 5.6 (s, 1H, NH), 5.8 (S, 1H, H-Ar) and 9.8(s, 2H, NH₂). ¹³C-NMR: 10.17, 18.6, 21.17, 36.27, 56.08, 74.23, 157.0, 159.3 and 171.7. MS (EI): (m/z, %), 193 (M⁺, 1.5), 69 (100).

20	Brown needles (Ethanol)	45	135-2°c	IR: 3432 (NH), 1675, 1660 (C=O, C=N). ¹H NMR: 0.8 -1.8 (m, 13H, H-aliphatic, CH₃), 7.7-7.9 (m, 4H, H-Ar) and 8.2 (s, 1H, NH). MS (EI): (m/z, %), 326 (M⁺, 100).
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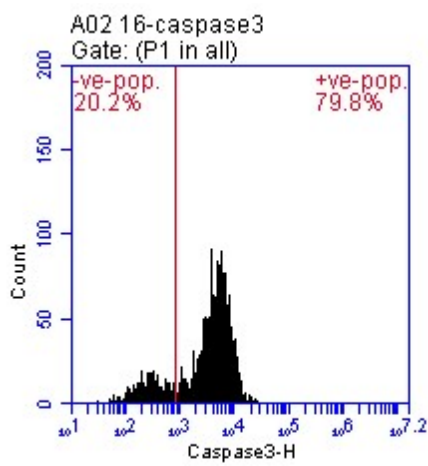
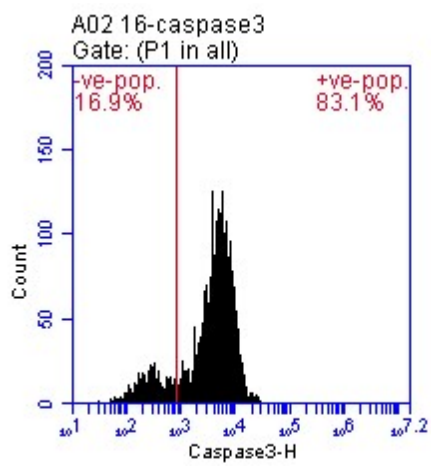
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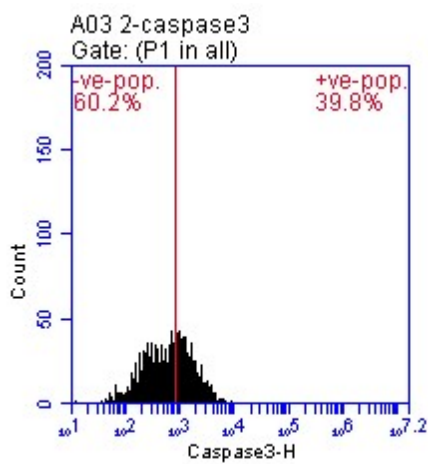
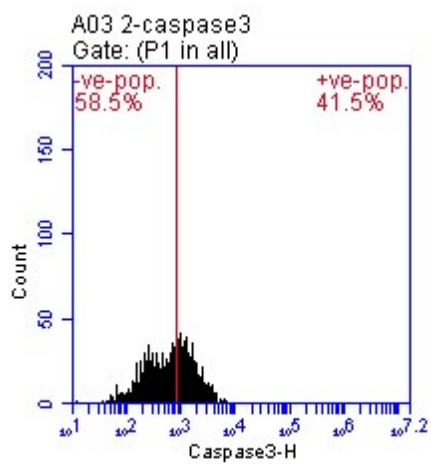
223 **Figure S2. Caspase 3 assay.**

224 **Compound 16**



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226 **Compound 2**



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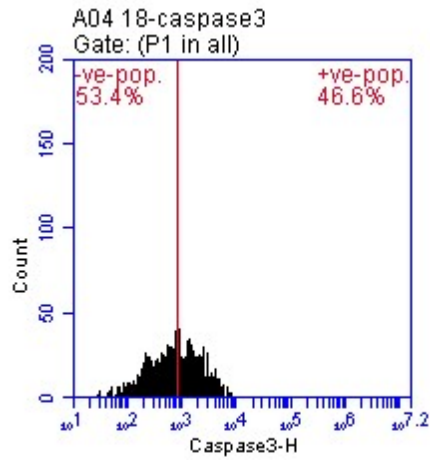
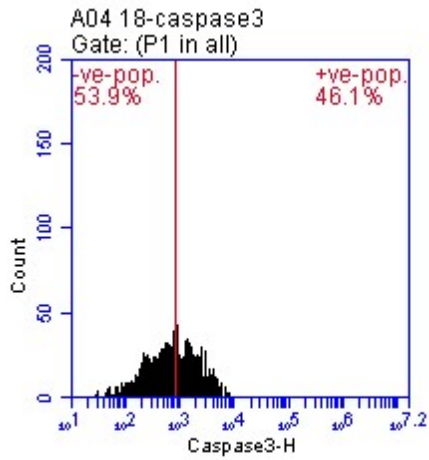
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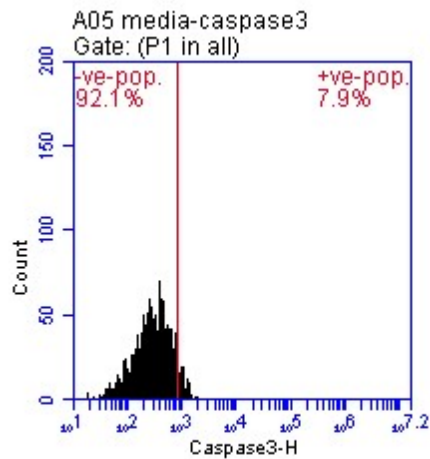
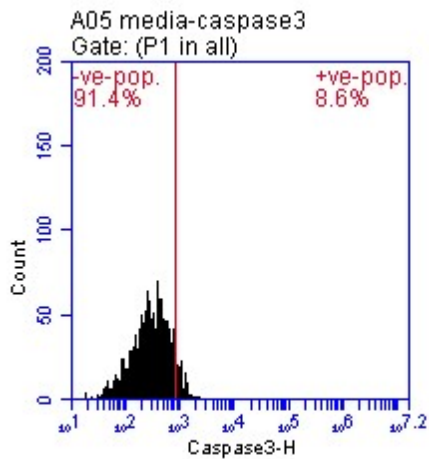
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233 **Compound 18**



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235 **Media (No treatment)**



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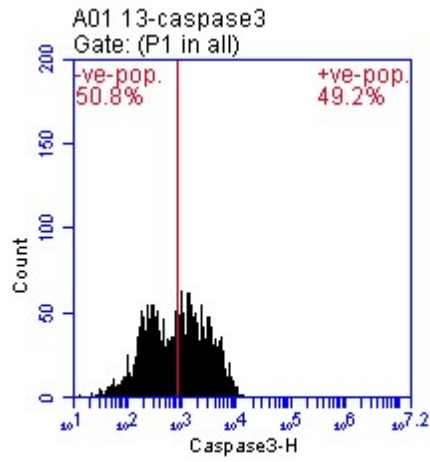
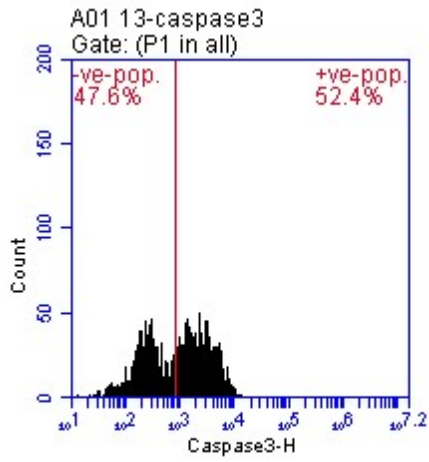
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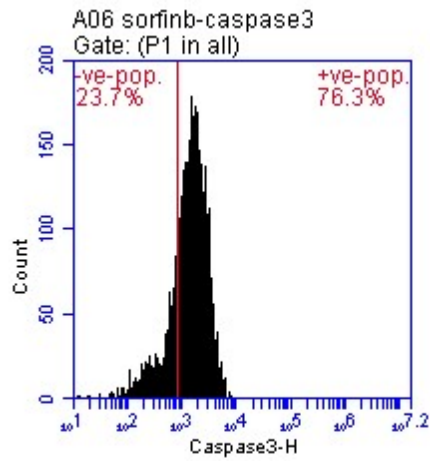
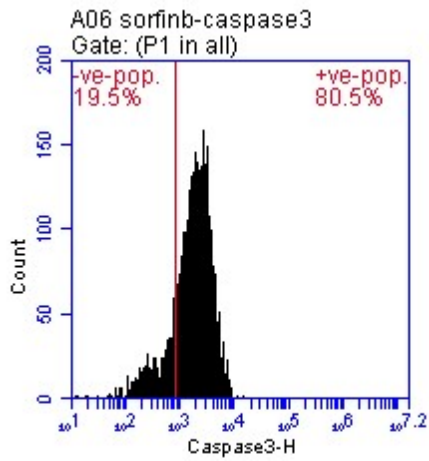
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244 **Compound 13**



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246 **Sorafenib**



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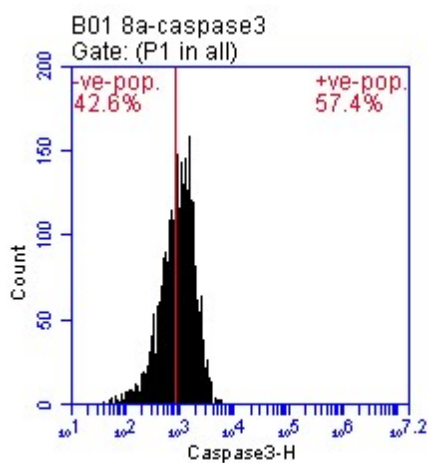
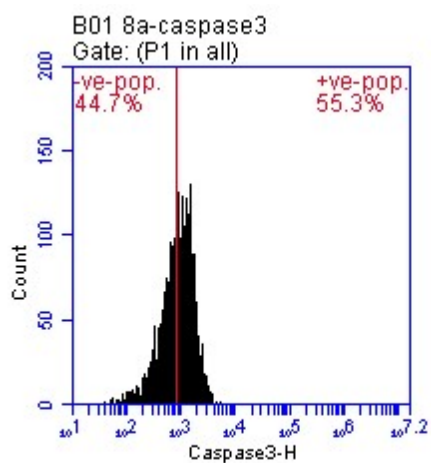
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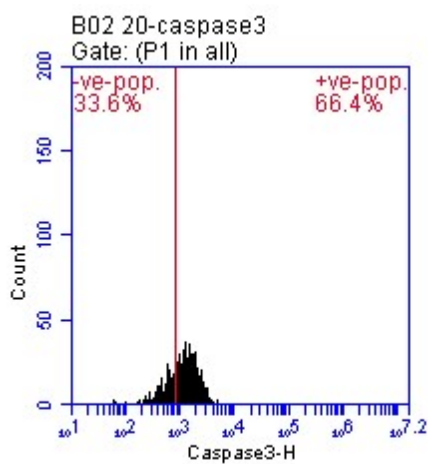
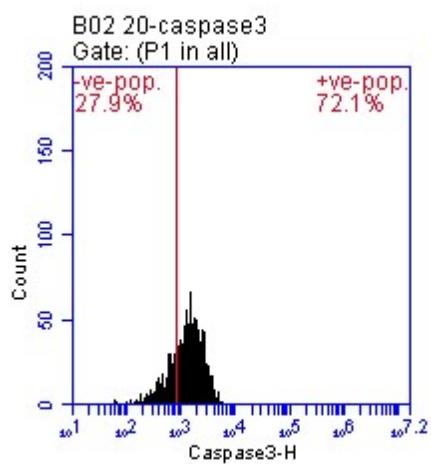
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255 **Compound 8a**



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257 **Compound 20**



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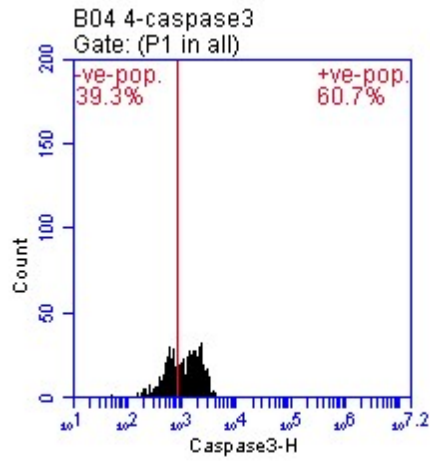
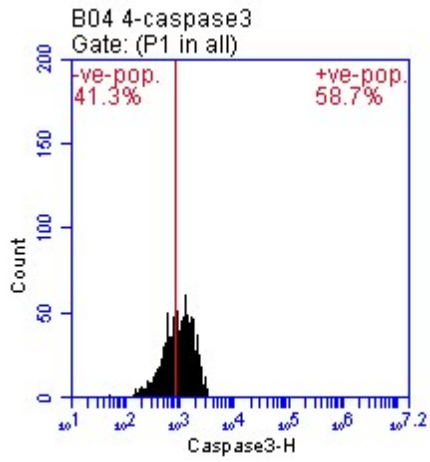
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266 **Compound 4**



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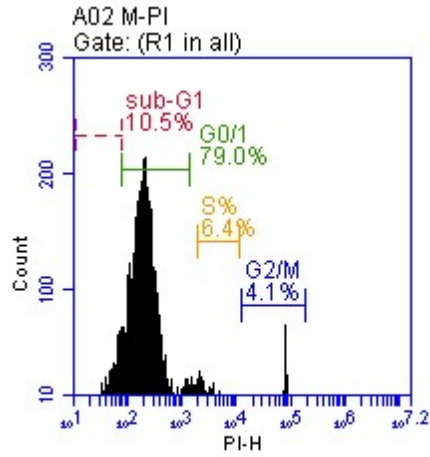
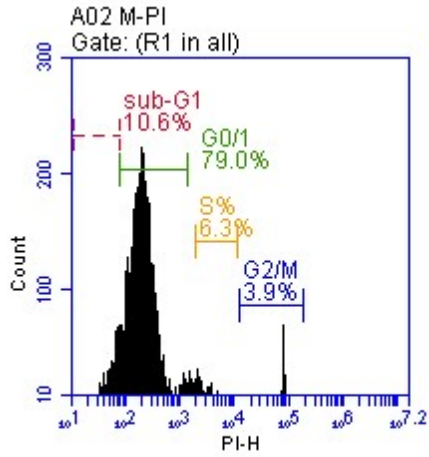
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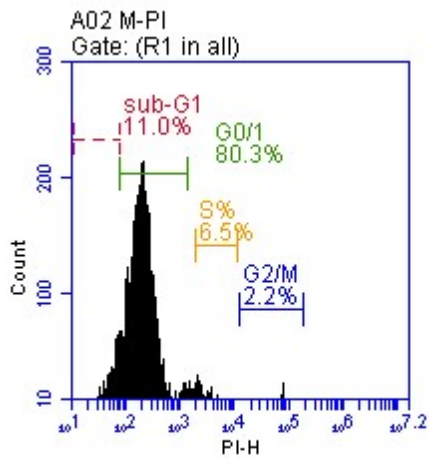
281 **Figure S3. Cell cycle analysis.**

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283 **Media (No treatment)**



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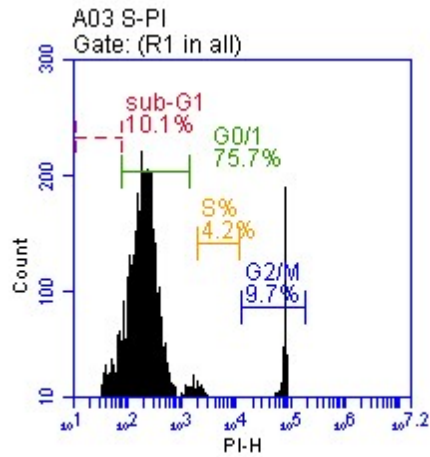
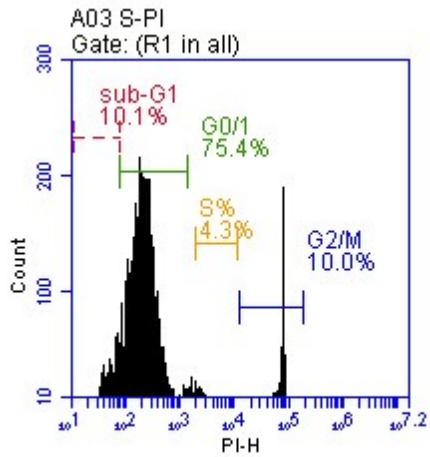
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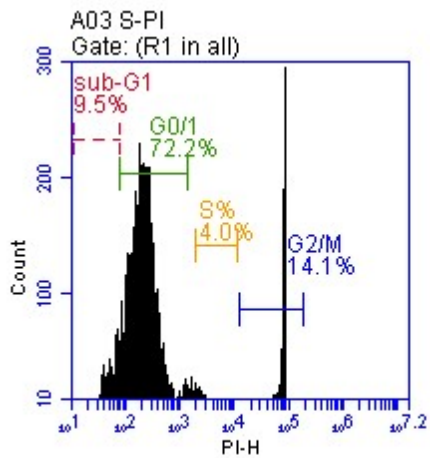
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295 **Sorafenib**



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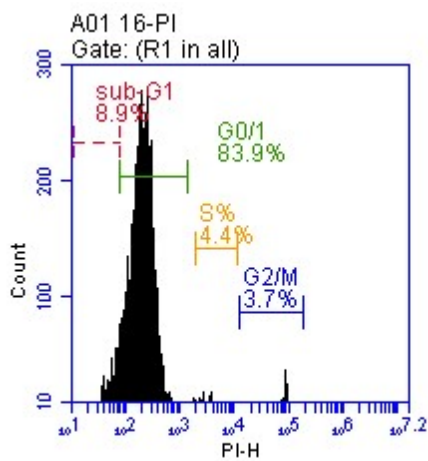
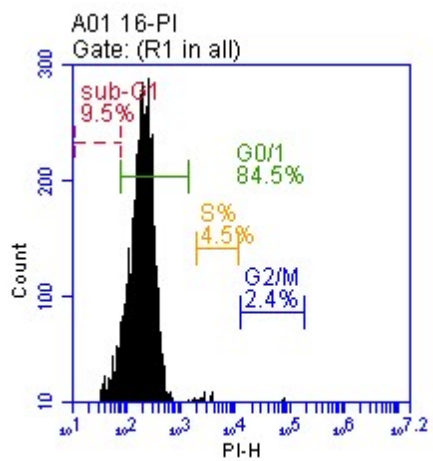
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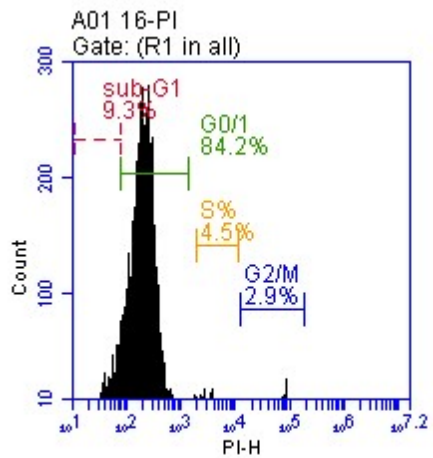
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306 **Compound 16**

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