

## ***Supporting information***

### **Water Triggered Union of Multi-Component Reactions towards Synthesis of 4H-Chromene Hybrid Scaffold**

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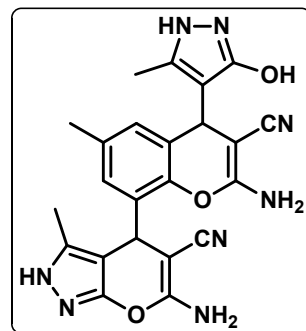
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**General procedure for Compound 9a-9l:**

To a stirred aqueous (25 mL of water) mixture of hydrazine hydrate 96% **1** (107 mg, 2 mmol), ethyl acetoacetate **2** (260 mg, 2 mmol), malononitrile **3** (132 mg, 2 mmol), respective 2-hydroxyisophthalaldehyde **4** (1 mmol) and 5 mol % of piperidine catalyst were added successively at room temperature under open atmosphere with vigorous stirring for 5–10 min. The solid thrown out from the reaction mixture was filtered, washed with water and then with ethyl acetate and/or cold ethanol. The products obtained were pure on TLC, NMR spectra and diastereoselectivity calculated by was calculated based on well separated <sup>1</sup>H NMR signals of 4H proton of chromene/pyran moiety or methyl protons of any one of pyrazole ring.

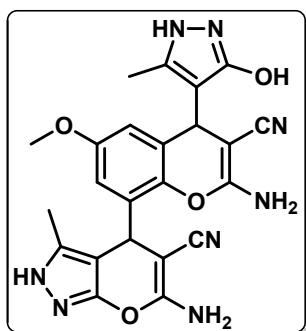
**4-(4-(1*H*-pyrazol-4-yl)-4*H*-chromen-8-yl)-2*H*,4*H*-dihydropyrano[2,3-*c*]pyrazoles S<sub>16a-k</sub>  
6-Amino-4-(2-amino-3-cyano-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-6-methyl-4*H*-  
chromen-8-yl)-3-methyl-2*H*,4*H*-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile 9a:**

White solid (isolated as a 68:32 mixture of diastereomers), yield 82%; IR (KBr):  $\nu_{\max}$  = 3424, 3342, 3191, 2188, 1645, 1598, 1485, 1398, 1215, 1148, 1049  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.08 (br s,  $\approx$  1H + 1H), 11.10 (br s,  $\approx$  1H + 1H), 9.54 (br s,  $\approx$  1H + 1H), 6.92 (s, 1H + 1H), 6.90 (s, 1H + 1H), 6.69 (s, 2H + 2H), 6.65 (s, 2H), 6.64 (s, 2H), 5.14 (s, 1H + 1H), 4.61 (s, 1H), 4.60 (s, 1H), 2.12 (s, 3H + 3H), 1.99 (s, 3H), 1.88 (s, 3H), 1.87 (s, 3H), 1.83 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 161.57, 161.40, 160.14, 159.88, 154.68, 154.64, 143.42, 135.61, 135.36, 133.02, 130.95, 127.50, 127.37, 127.18, 127.13, 123.28, 123.09, 120.87 (CN), 120.81 (CN), 120.77 (CN), 120.58 (CN), 105.32 (C + C), 97.58 (C), 97.44 (C), 55.97 (C), 55.88 (C), 54.95 (C), 54.84 (C), 28.78 (CH + CH), 28.02 (CH + CH), 20.40 (CH<sub>3</sub>), 18.50 (CH<sub>3</sub>), 9.87 (CH<sub>3</sub>), 9.52 (CH<sub>3</sub>), 9.45 (CH<sub>3</sub> + CH<sub>3</sub>) ppm; HRMS (ESI-TOF) Calcd. for C<sub>23</sub>H<sub>20</sub>N<sub>8</sub>NaO<sub>3</sub><sup>+</sup> (M+Na)<sup>+</sup>: 479.1556, found: 479.1552.



**6-Amino-4-(2-amino-3-cyano-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-6-methoxy-4*H*-  
chromen-8-yl)-3-methyl-2*H*,4*H*-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile**

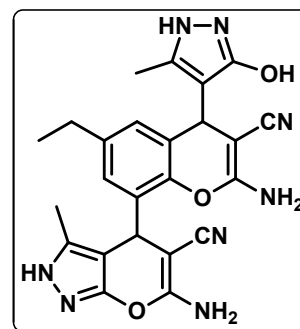
**9b:** White solid (isolated as a 62:38 mixture of diastereomers), yield 73%; IR (KBr):  $\nu_{\max}$  = 3328, 3183, 2188, 1650, 1600, 1482, 1400, 1203, 1053  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.11 (br s,  $\approx$  1H + 1H), 10.97 (br s,  $\approx$  1H + 1H), 10.02 (br s,  $\approx$  1H + 1H), 6.95 (s, 2H), 6.93 (s, 2H), 6.65 (s, 2H), 6.63 (s, 2H), 6.45–6.37 (m, 2H + 2H), 5.13 (s, 1H + 1H), 4.63 (s, 1H), 4.62 (s, 1H), 3.58 (s, 3H), 3.57 (s, 3H + 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.88 (s, 3H), 1.84 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 161.67, 161.48, 160.26, 160.02, 155.49, 155.38, 154.69, 139.65, 135.63, 135.40, 132.52, 124.81, 124.66, 120.76 (CN), 120.64 (CN), 120.48 (CN + CN), 112.52, 112.42, 11.33, 111.07, 105.06 (C), 104.75 (C), 97.30 (C), 97.16 (C), 55.69 (C), 55.66 (C), 55.13 (OCH<sub>3</sub>), 55.11 (OCH<sub>3</sub>), 54.65 (C), 54.54 (C), 29.26 (CH + CH), 28.48 (CH + CH),



9.86 (CH<sub>3</sub> + CH<sub>3</sub>), 9.52 (CH<sub>3</sub>), 9.45 (CH<sub>3</sub> + CH<sub>3</sub>) ppm; HRMS (ESI-TOF) Calcd. for C<sub>23</sub>H<sub>20</sub>N<sub>8</sub>NaO<sub>4</sub><sup>+</sup> (M+Na)<sup>+</sup>: 495.1505, found: 495.1509.

**6-Amino-4-(2-amino-3-cyano-6-ethyl-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9c:**

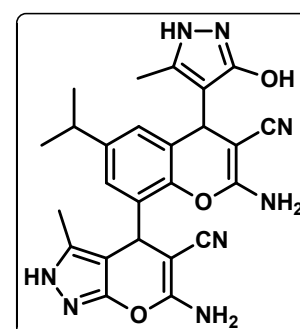
White solid (isolated as a 91:9 mixture of diastereomers), yield 92%; IR (KBr):  $\nu_{\max}$  = 3424, 338, 3285, 3175, 2188, 1650, 1595, 1488, 1400, 1212, 1149, 1052 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.08 (br s,  $\approx$  1H + 1H), 10.41 (br s,  $\approx$  2H + 2H), 6.93 (s, 2H), 6.90 (s, 2H), 6.75 (s, 1H + 1H), 6.69 (s, 3H + 3H), 5.15 (s, 1H + 1H), 4.63 (s, 1H + 1H), 2.44–2.42 (m, 2H + 2H), 1.99 (s, 3H



+ 3H), 1.89–1.83 (m, 3H + 3H), 1.02 (t, 3H + 3H, *J* = 8.8 Hz) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 161.61, 161.40, 160.17, 159.92, 159.3, 154.76, 143.67, 139.51, 136.83, 135.60, 135.35, 130.88, 126.18, 126.01, 125.94, 123.41, 123.21, 120.77 (2CN + 2CN), 105.27 (C + C), 97.56 (C), 97.39 (C), 55.97 (C), 55.88 (C), 54.95 (C + C), 28.89 (CH + CH), 28.19 (CH + CH), 27.29 (CH<sub>2</sub> + CH<sub>2</sub>), 15.35 (CH<sub>3</sub>), 15.23 (CH<sub>3</sub>), 9.91 (CH<sub>3</sub> + CH<sub>3</sub>), 9.55 (CH<sub>3</sub>), 9.48 (CH<sub>3</sub>) ppm; HRMS (ESI-TOF) Calcd. for C<sub>24</sub>H<sub>22</sub>N<sub>8</sub>NaO<sub>3</sub><sup>+</sup> (M+Na)<sup>+</sup>: 493.1712, found: 493.1709.

**6-Amino-4-(2-amino-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-6-isopropyl-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9d:** White

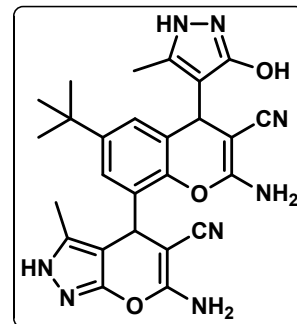
solid (isolated as a 50:50 mixture of diastereomers), yield 66%; IR (KBr):  $\nu_{\max}$  = 3481, 3379, 3315, 3203, 2963, 2190, 1648, 1596, 1488, 1399, 1214, 1166, 1044 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.06 (br s,  $\approx$  1H + 1H), 10.96 (br s,  $\approx$  1H + 1H), 9.61 (br s,  $\approx$  1H + 1H), 6.92 (s, 2H), 6.89 (s, 2H), 6.80 (s, 1H), 6.74 (s, 2H), 6.73 (s, 1H), 6.62 (s, 2H + 2H), 5.13 (s, 1H), 5.128 (s, 1H), 4.63 (s,



1H), 4.62 (s, 1H), 2.74–2.67 (m, 1H + 1H), 1.97 (s, 3H), 1.88 (s, 3H), 1.85 (s, 3H), 1.81 (s, 3H), 1.06–1.02 (s, 6H + 6H) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 161.66, 161.39, 160.21, 159.99, 154.84, 154.74, 144.12, 143.95, 135.56, 135.33, 130.76, 130.72, 124.51, 123.78, 120.74 (2CN + 2CN), 105.02 (C + C), 97.53 (C), 97.33 (C), 56.04 (C), 55.08 (C + C), 32.55 (C + C), 29.02 (2CH + 2CH), 23.91 (CH<sub>3</sub>), 23.79 (CH<sub>3</sub>), 23.76 (CH<sub>3</sub>), 23.61 (CH<sub>3</sub>), 9.92 (CH<sub>3</sub> + CH<sub>3</sub>), 9.57 (CH<sub>3</sub>), 9.48 (CH<sub>3</sub>) ppm; HRMS (ESI-TOF) Calcd. for C<sub>25</sub>H<sub>24</sub>N<sub>8</sub>NaO<sub>3</sub><sup>+</sup> (M+Na)<sup>+</sup>: 507.1869, found: 507.1864.

**6-Amino-4-(2-amino-6-(tert-butyl)-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9e:** White solid (isolated as a 53:47 mixture of diastereomers), yield 58%; IR

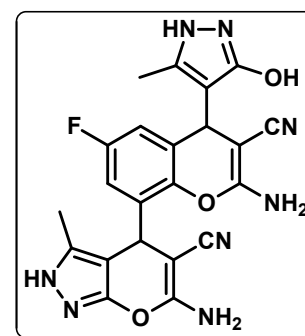
(KBr):  $\nu_{\max}$  = 3343, 3373, 3197, 2967, 2190, 1650, 1596, 1487, 1398, 1193, 1045  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 12.09 (br s,  $\approx$  1H + 1H), 10.47 (br s,  $\approx$  1H + 1H), 9.54 (br s,  $\approx$  1H + 1H), 6.99-6.93 (m, 4H + 4H), 6.64 (s, 2H + 2H), 5.13 (s, 1H + 1H), 4.65 (s, 1H + 1H), 1.99 (s, 3H), 1.91 (s, 3H), 1.87 (s, 3H), 1.82 (s, 3H),



1.12 (s, 9H + 9H) ppm;  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 161.75, 161.42, 160.27, 159.08, 154.88, 154.76, 146.40, 146.24, 143.56, 143.50, 136.32, 135.32, 135.29, 130.36, 130.30, 123.66, 123.53, 123.32, 123.13, 122.96, 120.83 (CN), 120.76 (CN), 120.70 (CN), 120.54 (CN), 105.15 (C), 104.97 (C), 97.56 (C), 97.31 (C), 56.06 (C), 55.84 (C), 54.99 (C + C), 33.81 (C + C), 30.97 (3CH<sub>3</sub> + 3CH<sub>3</sub>), 29.12 (CH + CH), 28.77 (CH + CH), 9.93 (CH<sub>3</sub> + CH<sub>3</sub>), 9.61 (CH<sub>3</sub>), 9.51 (CH<sub>3</sub>) ppm; HRMS (ESI-TOF) Calcd. for C<sub>26</sub>H<sub>26</sub>N<sub>8</sub>NaO<sub>3</sub><sup>+</sup> (M+Na)<sup>+</sup>: 521.2025, found: 521.2021.

**6-Amino-4-(2-amino-3-cyano-6-fluoro-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9f:**

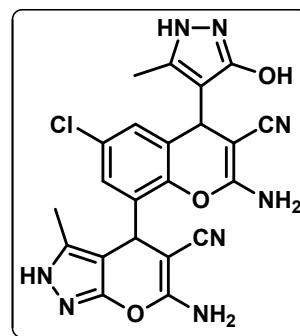
White solid (isolated as a 63:37 mixture of diastereomers), yield 91%; IR (KBr):  $\nu_{\max}$  = 3479, 3440, 3329, 3183, 2190, 1645, 1601, 1480, 1398, 1199, 1051  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 12.13 (br s,  $\approx$  1H + 1H), 11.13 (br s,  $\approx$  1H + 1H), 9.74 (br s,  $\approx$  1H + 1H), 7.01 (s, 2H), 6.98 (s, 2H), 6.75 (s, 2H + 2H), 6.67-6.63 (m, 2H + 2H), 5.19 (s, 1H + 1H), 4.673 (s, 1H), 4.666 (s, 1H), 2.04 (s, 3H),



1.92 (s, 3H), 1.90 (s, 3H), 1.85 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 161.74, 161.57, 159.73, 159.40, 157.01, 154.60, 141.86, 135.80, 135.51, 133.71, 125.78, 120.52 (2CN + 2CN), 113.31 ( $^2J_{CF}$  = 9.6 Hz), 104.41 (C + C), 96.86 (C), 96.70 (C), 55.21 (C + C), 54.57 (C + C), 29.18 (CH + CH), 28.40 (CH + CH), 9.77 (CH<sub>3</sub>), 9.49 (CH<sub>3</sub>), 9.44 (CH<sub>3</sub> + CH<sub>3</sub>) ppm; HRMS (ESI-TOF) Calcd. for C<sub>22</sub>H<sub>17</sub>FN<sub>8</sub>NaO<sub>3</sub><sup>+</sup> (M+Na)<sup>+</sup>: 483.1305, found: 483.1309.

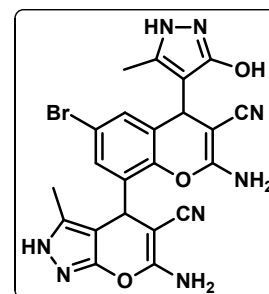
**6-Amino-4-(2-amino-6-chloro-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9g:**

White solid (isolated as a 80:20 mixture of diastereomers), yield 88%; IR (KBr):  $\nu_{\max}$  = 3423, 3334, 3275, 3154, 2187, 1658, 1594, 1497, 1403, 1197, 1050  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 12.18 (br s,  $\approx$  1H + 1H), 10.62 (br s,  $\approx$  2H + 2H), 7.04 (s, 2H), 7.02 (s, 2H), 6.92 (s, 1H), 6.91 (s, 1H), 6.86-6.84 (m, 3H + 3H), 5.19 (s, 1H + 1H), 4.68 (s, 1H + 1H), 2.06 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H), 1.86 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 161.75, 161.59, 159.76, 154.61, 133.72, 127.96, 126.59, 126.37, 126.14, 125.95, 120.32 (2CN+ 2CN), 104.63 (C), 104.50 (C), 96.84 (C), 96.68 (C), 55.16 (C + C), 54.84 (C), 54.64 (C), 28.89 (CH + CH), 28.82 (CH + CH), 9.85 ( $\text{CH}_3$ ), 9.74 ( $\text{CH}_3$ ), 9.50 ( $\text{CH}_3$ ), 9.45 ( $\text{CH}_3$ ) ppm; HRMS (ESI-TOF) Calcd. for  $\text{C}_{22}\text{H}_{17}\text{ClN}_8\text{NaO}_3^+$  (M+Na) $^+$ : 499.1009, found: 499.1006.



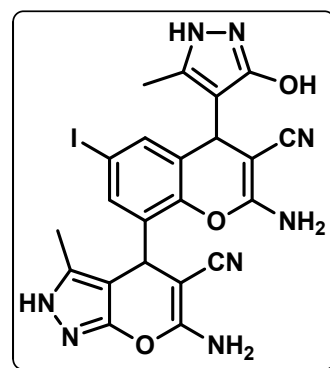
**6-Amino-4-(2-amino-6-bromo-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9h:**

White solid (isolated as a 84:16 mixture of diastereomers), yield 73%; IR (KBr):  $\nu_{\max}$  = 3424, 3338, 3272, 3158, 2188, 1655, 1593, 1497, 1401, 1194, 1048  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 12.18 (br s,  $\approx$  1H + 1H), 11.15 (br s,  $\approx$  1H + 1H), 9.79 (br s,  $\approx$  1H + 1H), 7.03 (s, 3H + 3H), 6.95 (s, 1H + 1H), 6.83 (s, 2H + 2H), 5.17 (s, 1H + 1H), 4.67 (s, 1H + 1H), 2.06 (s, 3H), 1.93 (s, 3H), 1.91 (s, 3H), 1.86 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 161.59, 159.71, 159.39, 158.66, 154.62, 144.71, 135.55, 134.02, 129.50, 129.22, 126.51, 120.33 (CN + CN), 120.33 (CN + CN), 115.91, 104.68 (C + C), 96.71 (C + C), 55.51 (C + C), 54.67 (C + C), 28.71 (CH + CH), 28.27 (CH + CH), 9.84 ( $\text{CH}_3$  +  $\text{CH}_3$ ), 9.46 ( $\text{CH}_3$  +  $\text{CH}_3$ ) ppm; HRMS (ESI-TOF) Calcd. for  $\text{C}_{22}\text{H}_{17}\text{BrN}_8\text{NaO}_3^+$  (M+Na) $^+$ : 543.0504, found: 543.0510.



**6-Amino-4-(2-amino-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-6-iodo-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9i:**

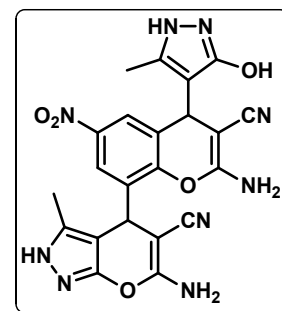
White solid (isolated as a 54:46 mixture of diastereomers), yield 68%; IR (KBr):  $\nu_{\max}$  = 3329, 3269, 2190, 1648, 1602, 1397, 1246, 1210, 1158, 1045  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 12.08 (br s,  $\approx$  1H + 1H), 11.13 (br s,  $\approx$  1H + 1H), 9.59 (br s,  $\approx$  1H + 1H), 7.41 (s, 1H), 7.31 (s, 1H), 6.94 (s, 1H), 6.90 (s, 2H + 2H), 6.80 (s, 1H), 6.74 (s, 2H + 2H), 4.64 (s, 1H), 4.63 (s, 1H), 4.53 (s, 1H + 1H), 1.97 (s, 3H), 1.88 (s, 3H), 1.72 (s, 3H), 1.59 (s, 3H)



ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 161.19, 160.88, 159.96, 159.87, 154.51, 154.20, 146.80, 146.20, 141.72, 136.17, 135.75, 135.55, 128.32, 127.83, 124.45, 124.14, 120.62 (CN), 120.53 (CN), 120.34 (CN), 120.27 (CN), 104.42 (C), 104.22 (C), 97.13 (C), 96.73 (C), 84.52, 84.20, 56.42 (C), 55.92 (C), 55.73 (C), 55.71 (C), 35.07 (CH), 34.73 (CH), 29.49 (CH), 29.44 (CH), 9.83 ( $\text{CH}_3$ ), 9.68 ( $\text{CH}_3$ ), 9.37 ( $\text{CH}_3$  +  $\text{CH}_3$ ) ppm; HRMS (ESI-TOF) Calcd. for  $\text{C}_{22}\text{H}_{17}\text{IN}_8\text{NaO}_3^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 591.0366, found: 591.0370.

**6-Amino-4-(2-amino-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-6-nitro-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9j:**

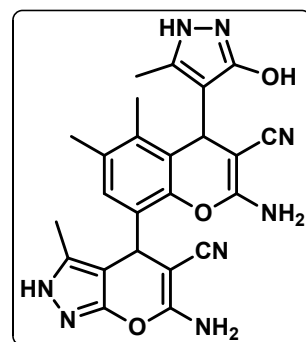
White solid (isolated as a 59:41 mixture of diastereomers), yield 72%; IR (KBr):  $\nu_{\max}$  = 3452, 3329, 3191, 2191, 1652, 1599, 1528, 1450, 1399, 1340, 1279, 1211, 1155, 1088, 1047  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 12.24 (br s,  $\approx$  1H + 1H), 11.11 (br s,  $\approx$  1H + 1H), 9.87 (br s,  $\approx$  1H + 1H), 7.78 (s, 1H), 7.74 (s, 1H), 7.68 (s, 2H), 7.16 (s, 2H), 7.13 (s, 2H), 7.08 (s, 2H + 2H), 5.30 (s, 1H + 1H), 4.83



(s, 1H), 4.82 (s, 1H), 2.13 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H), 1.87 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 161.87, 161.72, 159.15, 158.87, 154.70, 149.99, 143.71, 143.55, 136.02, 135.72, 133.35, 125.62, 125.41, 122.96, 121.98, 120.34 (CN), 120.18 (CN), 119.89 (CN + CN), 104.45 (C), 104.37 (C), 96.41 (C), 96.25 (C), 59.71 (C + C), 55.06 (C), 54.79 (C), 28.92 (CH + CH), 28.83 (CH + CH), 9.88 ( $\text{CH}_3$ ), 9.73 ( $\text{CH}_3$ ), 9.53 ( $\text{CH}_3$  +  $\text{CH}_3$ ) ppm; HRMS (ESI-TOF) Calcd. for  $\text{C}_{22}\text{H}_{17}\text{N}_9\text{NaO}_5^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 510.1250, found: 510.1248.

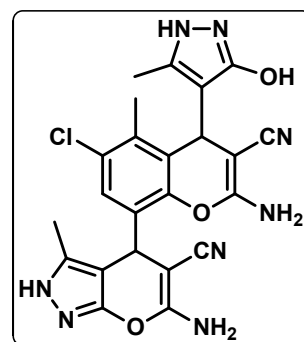
**6-Amino-4-(2-amino-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-5,6-dimethyl-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9k:** White

solid (isolated as a 59:41 mixture of diastereomers), yield 71%; IR (KBr):  $\nu_{\max}$  = 3440, 3332, 3191, 2192, 1652, 1599, 1490, 1400, 1217, 1054  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 12.05 (br s,  $\approx$  1H + 1H), 10.99 (br s,  $\approx$  1H + 1H), 9.65 (br s,  $\approx$  1H + 1H), 6.87 (s, 2H), 6.84 (s, 2H), 6.72 (s, 1H), 6.65 (s, 1H), 6.61 (br s, 2H), 6.52 (br s, 2H), 5.15 (s, 1H), 5.12 (s, 1H), 4.55 (s, 1H), 4.52 (s, 1H), 2.07 (s, 6H), 1.96–1.89 (m, 6H + (3H + 3H)), 1.81 (s, 3H), 1.70 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 161.42, 161.16, 159.78, 159.70, 155.03, 144.97, 135.72, 133.18, 132.04, 128.08, 127.99, 127.86, 121.13 (CN), 120.94 (CN), 120.74 (CN), 120.68 (CN), 104.45 (C + C), 97.58 (C + C), 57.03 (C), 56.85 (C), 56.44 (C), 56.17 (C), 28.06 (CH), 27.93 (CH), 27.62 (CH + CH), 19.93 ( $\text{CH}_3$ ), 19.85 ( $\text{CH}_3$ ), 14.40 ( $\text{CH}_3$  +  $\text{CH}_3$ ), 9.78 ( $\text{CH}_3$ ), 9.72 ( $\text{CH}_3$ ), 9.47 ( $\text{CH}_3$ ), 9.43 ( $\text{CH}_3$ ) ppm; HRMS (ESI-TOF) Calcd. for  $\text{C}_{24}\text{H}_{22}\text{N}_8\text{NaO}_3^+$  (M+Na) $^+$ : 493.1713, found: 493.1712.



**6-Amino-4-(2-amino-6-chloro-3-cyano-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-5-methyl-4H-chromen-8-yl)-3-methyl-2H,4H-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 9l:** White solid (isolated as a 61:39 mixture of diastereomers), yield

59%; IR (KBr):  $\nu_{\max}$  = 3432, 332, 3196, 2193, 1651, 1600, 1494, 1450, 1399, 1207, 1064  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 12.13 (br s,  $\approx$  1H + 1H), 11.01 (br s,  $\approx$  1H + 1H), 9.77 (br s,  $\approx$  1H + 1H), 7.06 (s, 2H), 7.02 (s, 2H), 6.91 (s, 1H), 6.87 (s, 1H), 6.75 (br s, 2H), 6.70 (br s, 2H), 5.19 (s, 1H), 5.17 (s, 1H), 4.59 (s, 1H), 4.58 (s, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 1.93 (s, 3H), 1.83 (s, 3H), 1.77 (s, 3H), ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 161.59, 161.43, 159.22, 154.84, 154.51, 145.46, 135.95, 135.53, 132.44, 130.75, 129.03, 128.66, 126.72, 123.57, 120.69 (CN + CN), 120.48 (CN + CN), 103.87 (C), 103.59 (C), 97.06 (C), 96.85 (C), 56.15 (C), 55.95 (C), 55.24 (C + C), 28.44 (CH + CH), 28.04 (CH + CH), 15.18 ( $\text{CH}_3$ ), 15.13 ( $\text{CH}_3$ ), 9.67 ( $\text{CH}_3$  +  $\text{CH}_3$ ), 9.38 ( $\text{CH}_3$  +  $\text{CH}_3$ ) ppm; HRMS (ESI-TOF) Calcd. for  $\text{C}_{23}\text{H}_{19}\text{ClN}_8\text{NaO}_3^+$  (M+Na) $^+$ : 513.1166, found: 513.1171.





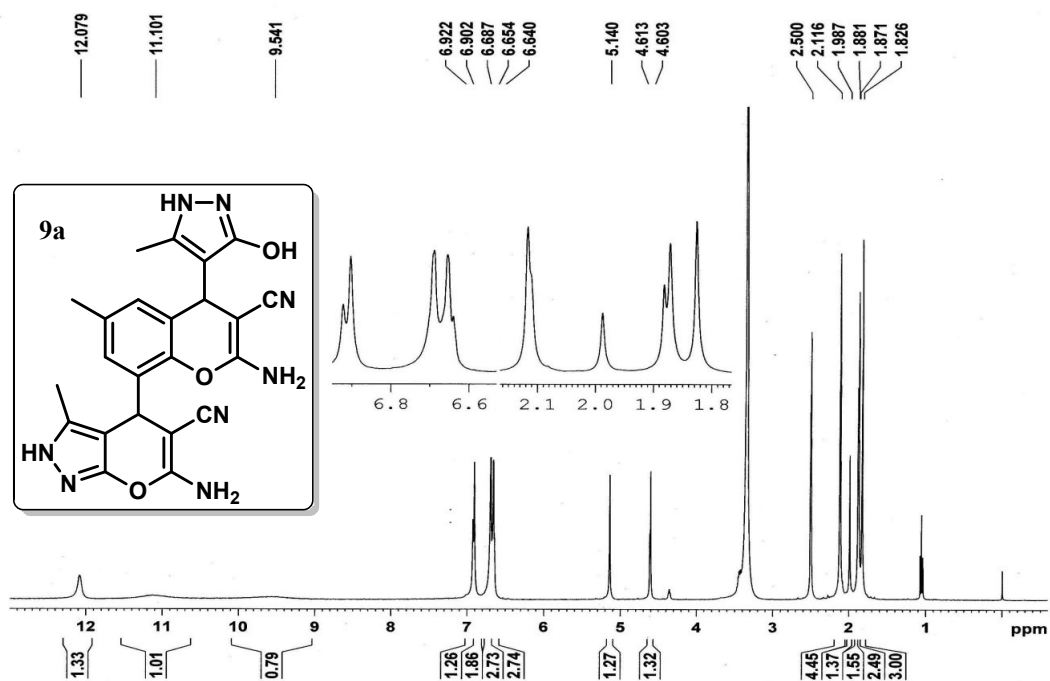


Figure 1 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9a

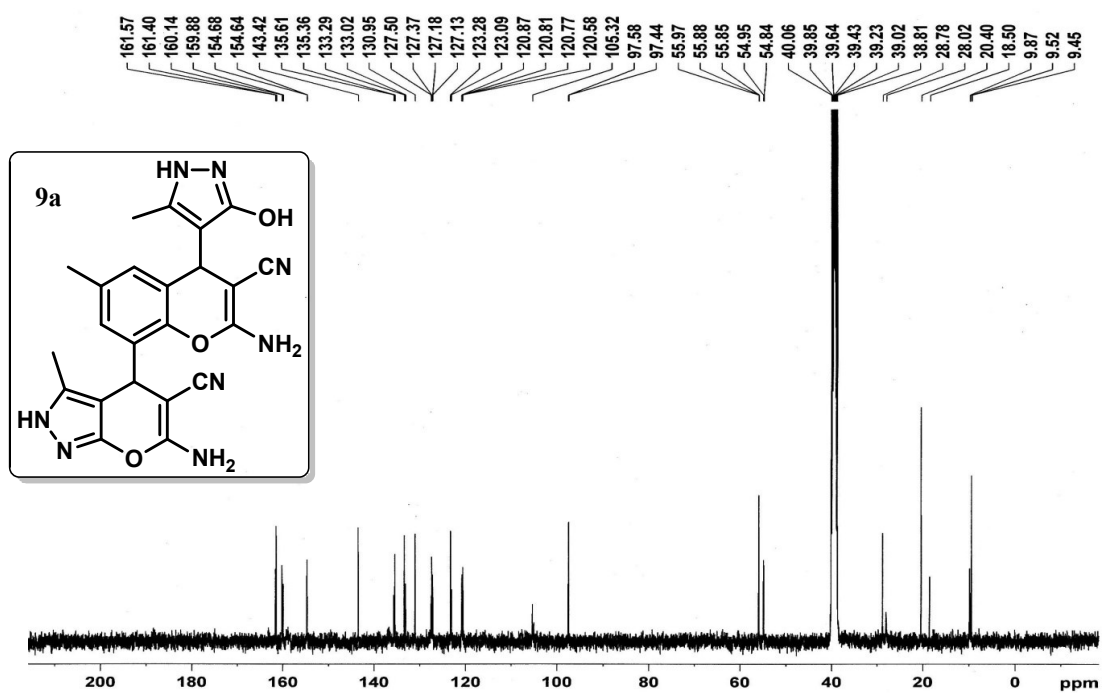
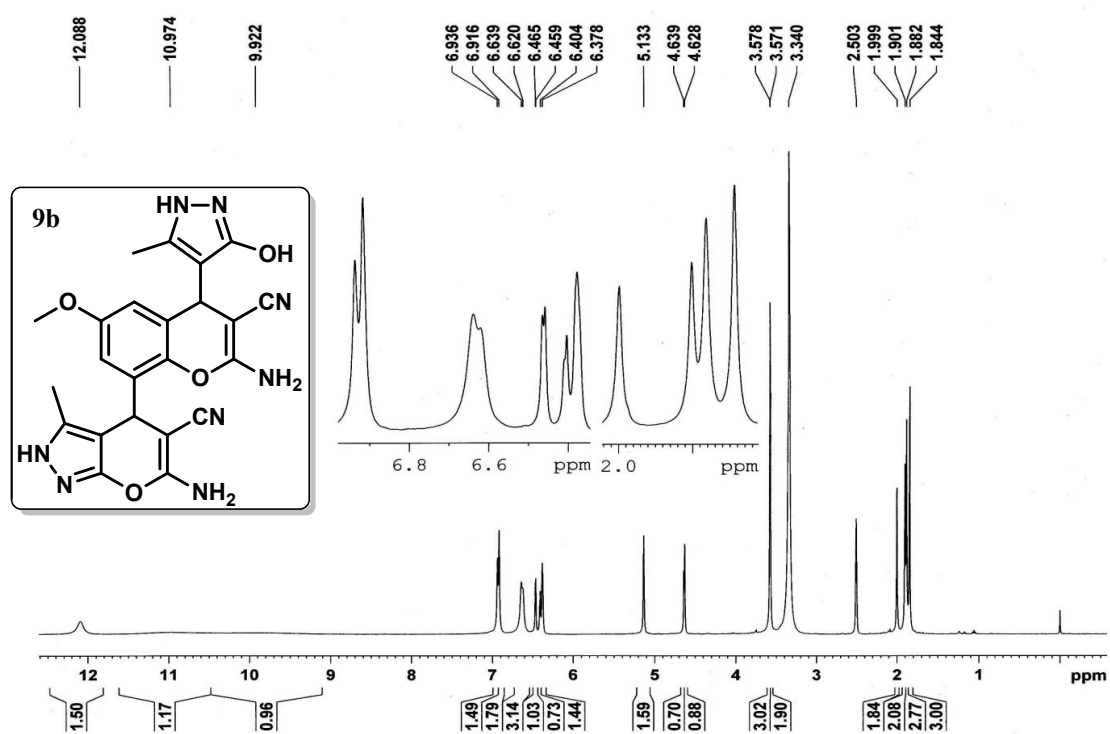
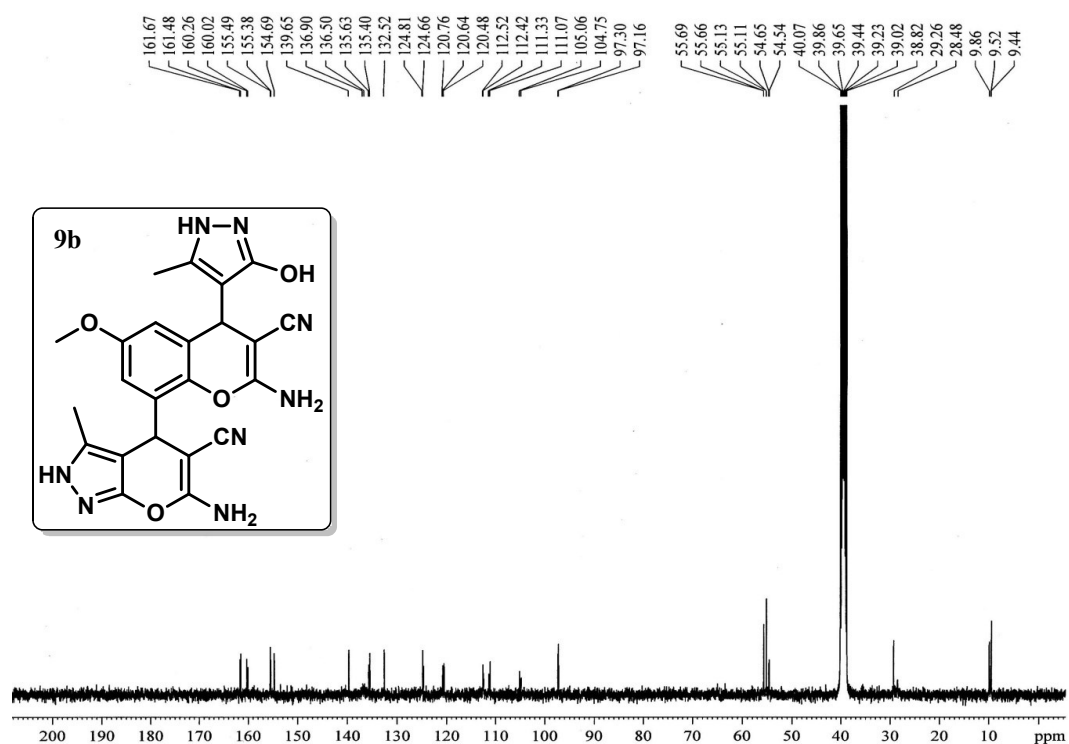


Figure 2 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9a



**Figure 3**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound **9b**



**Figure 4**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound **9b**

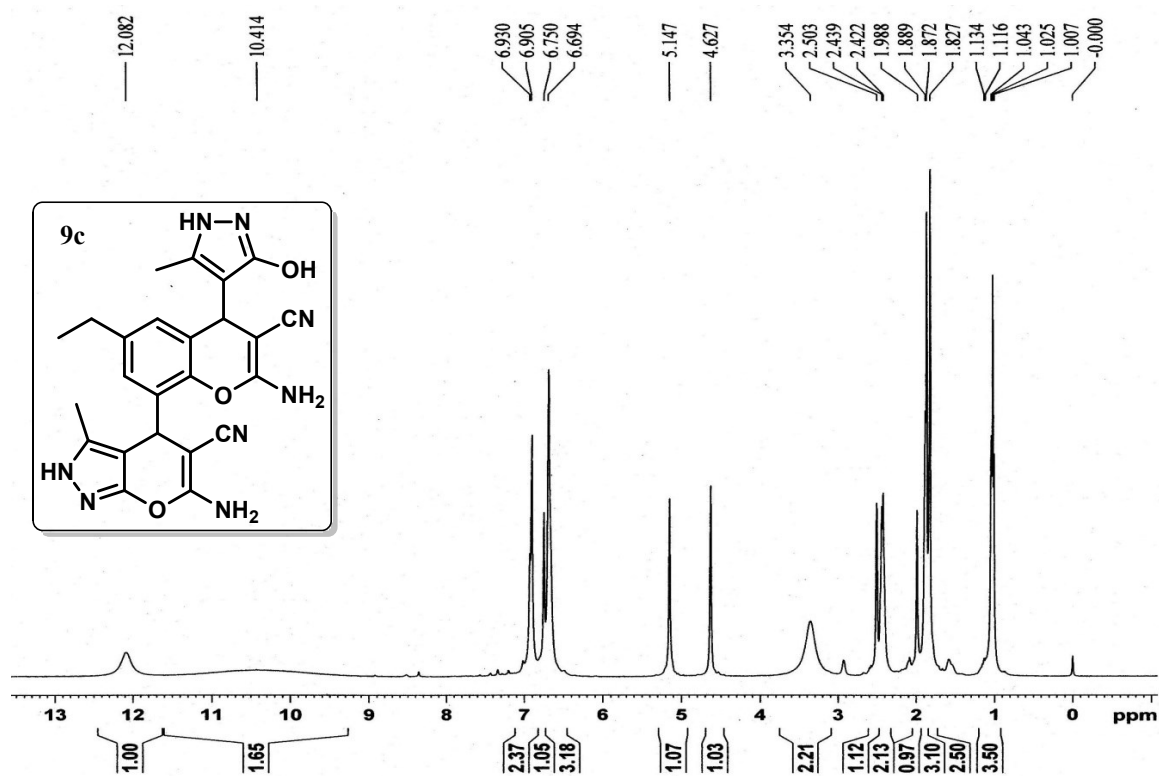


Figure 5 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9c

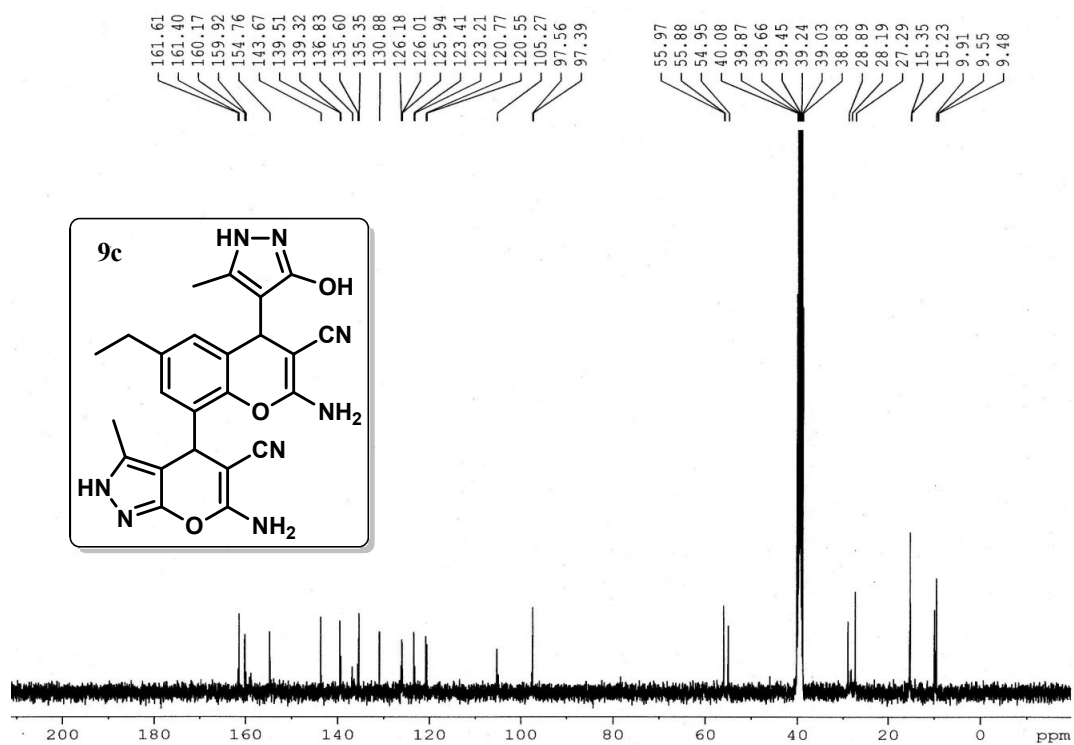
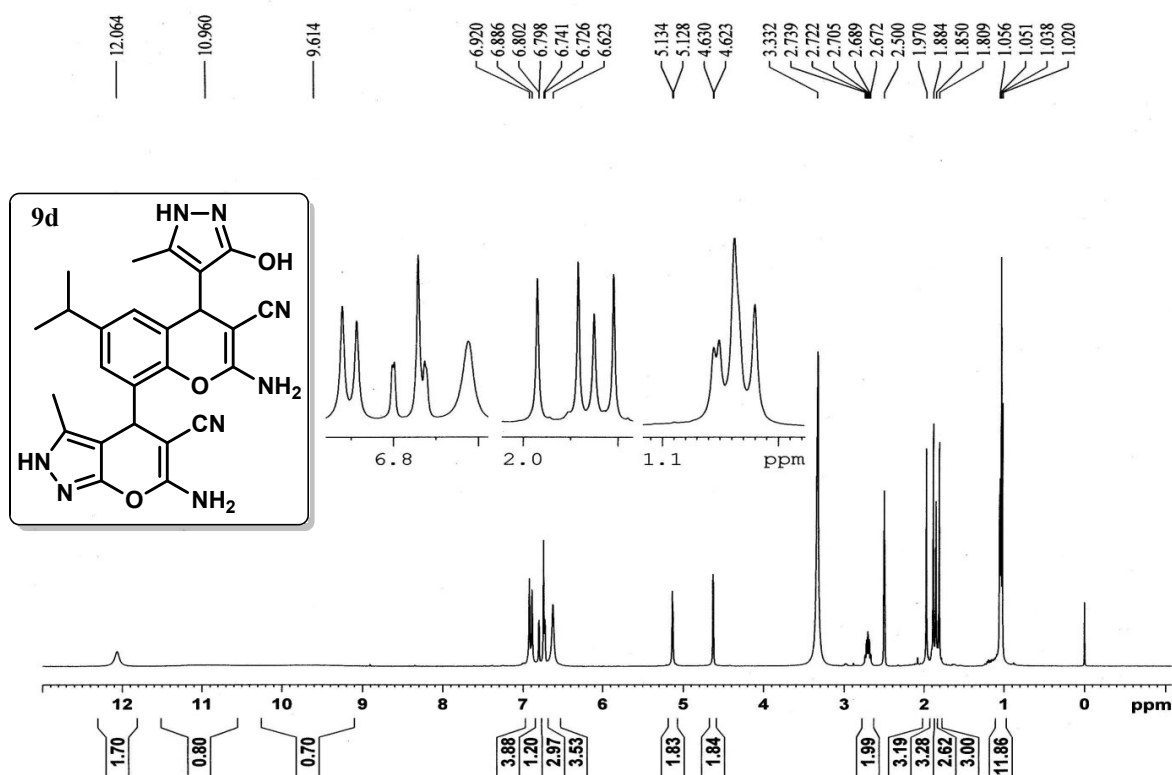
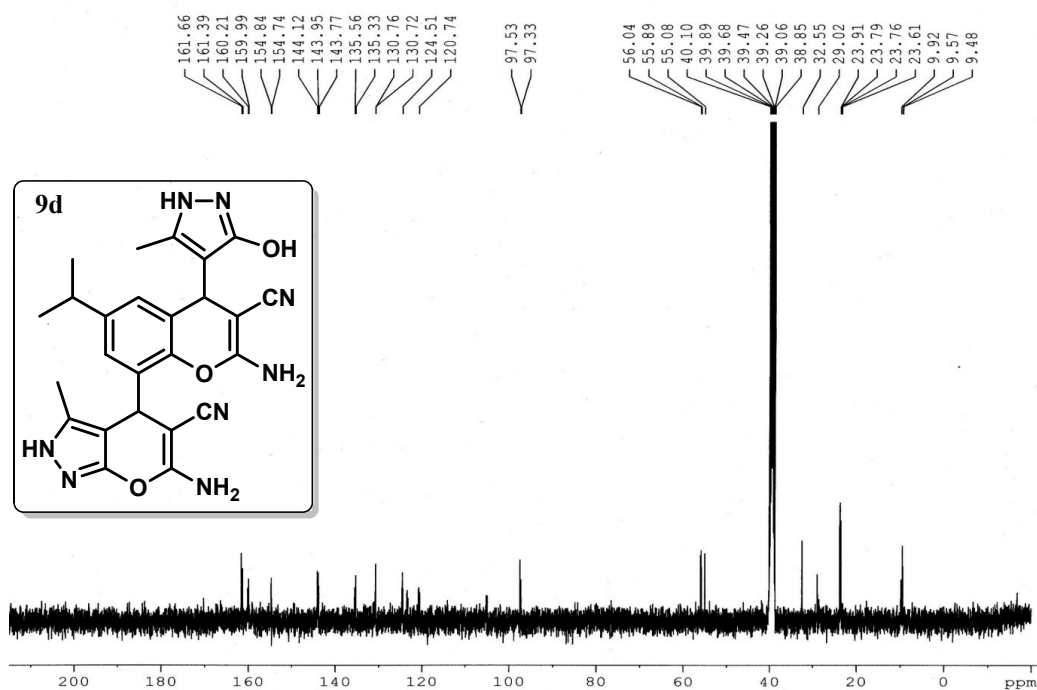
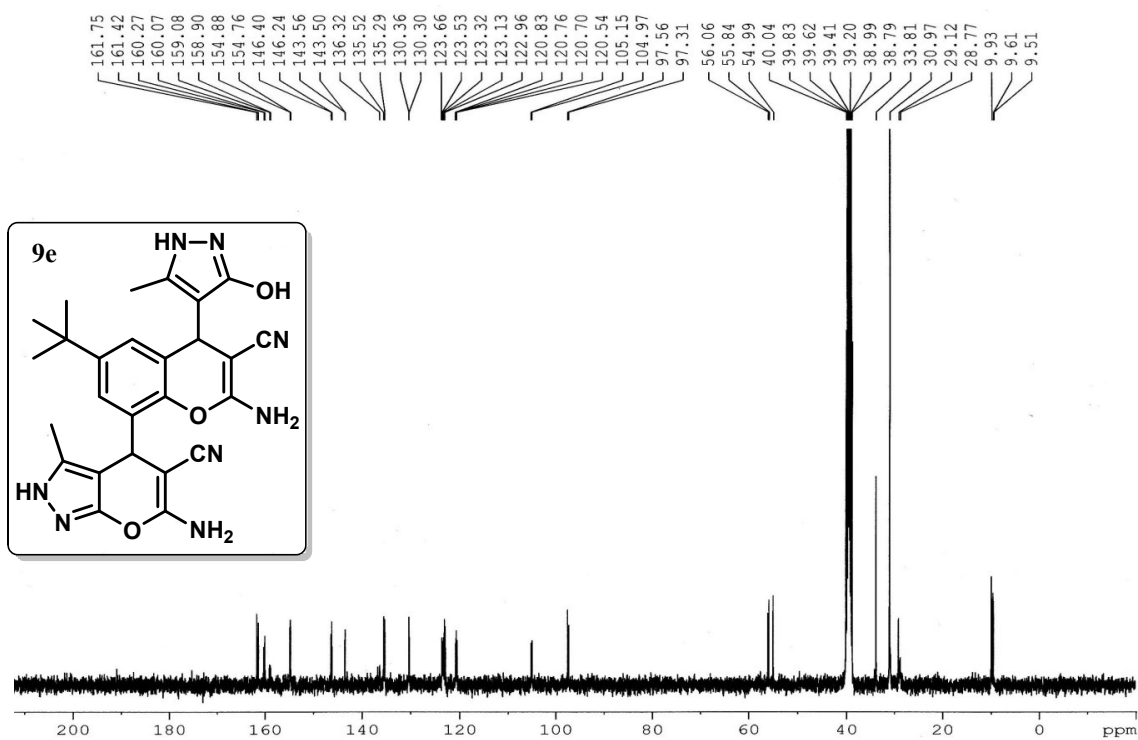
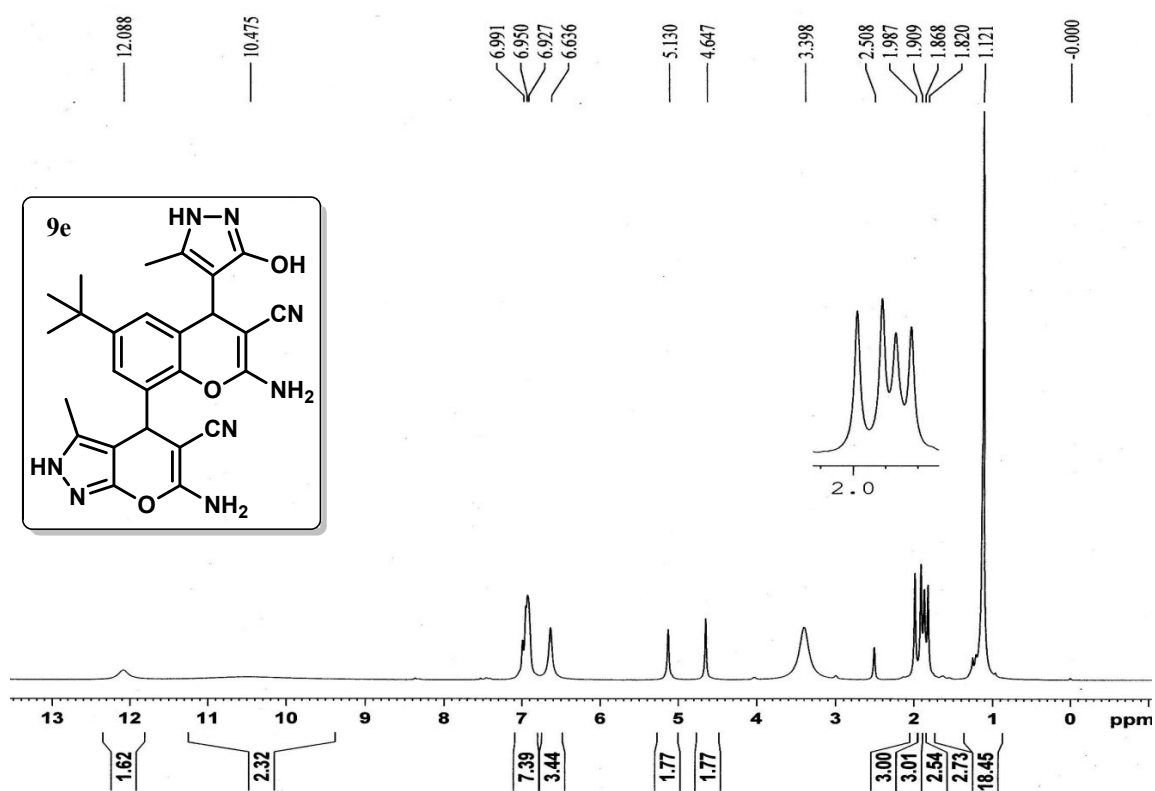
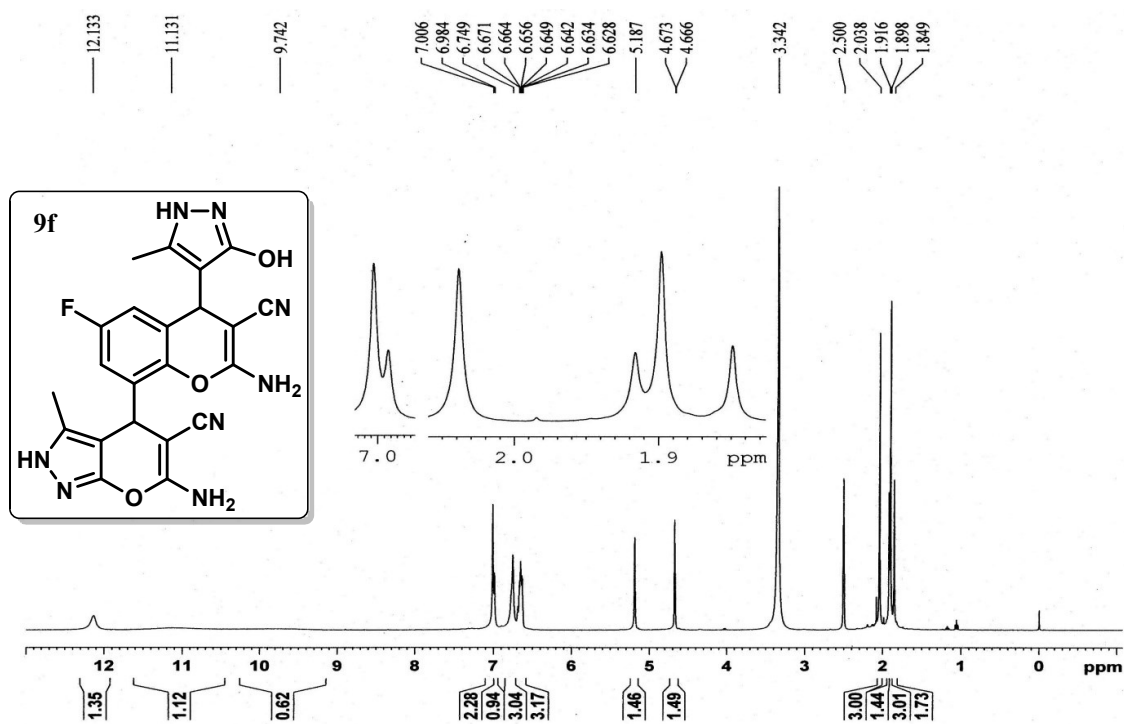
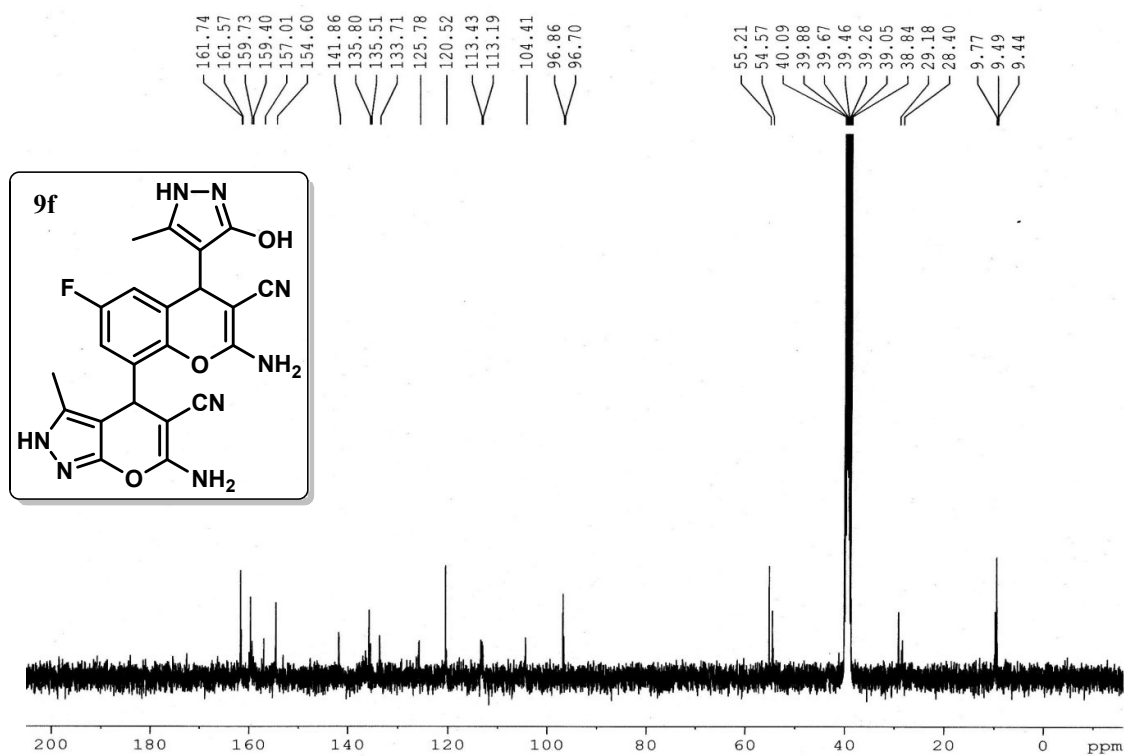
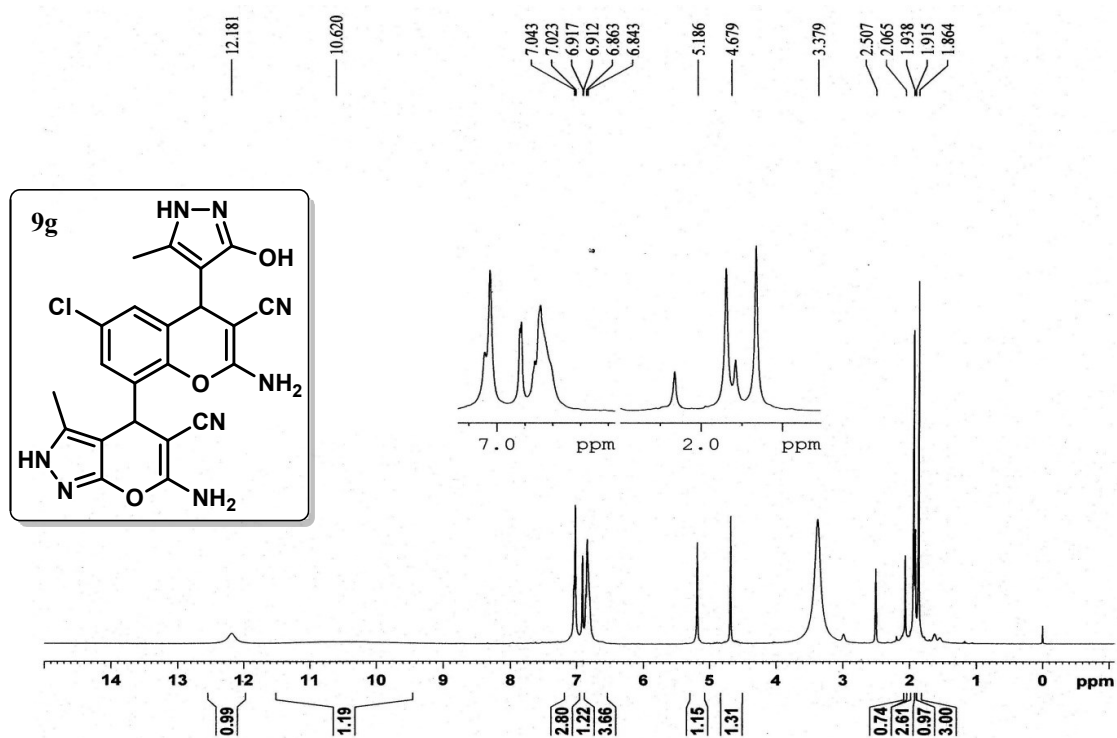
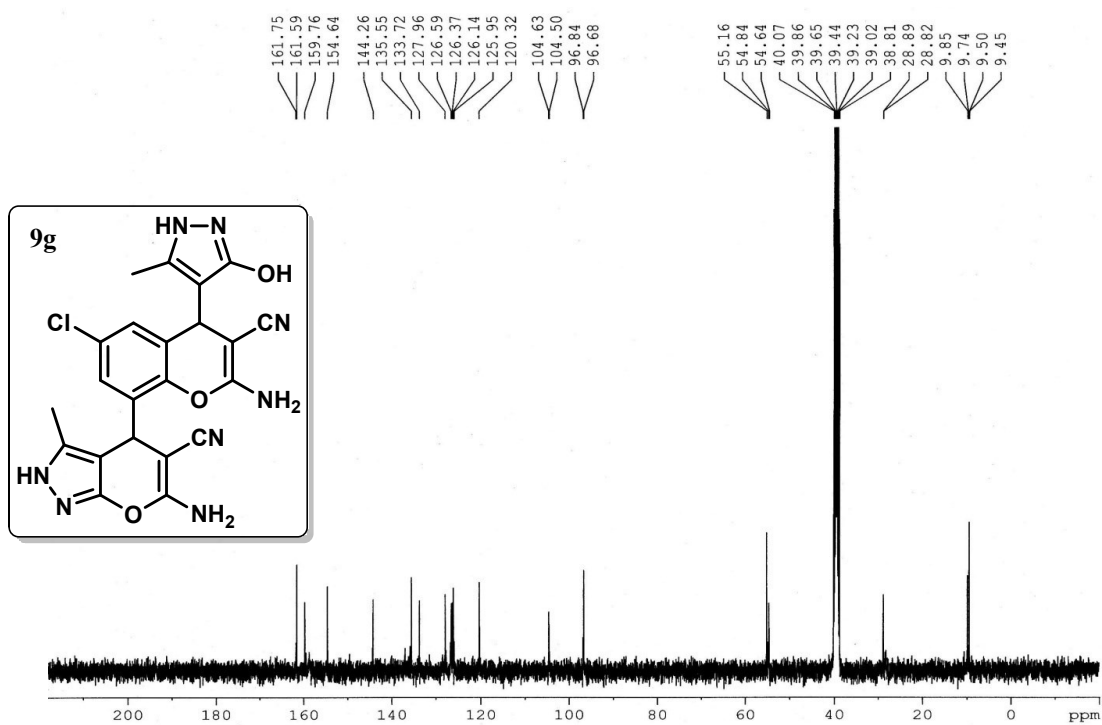


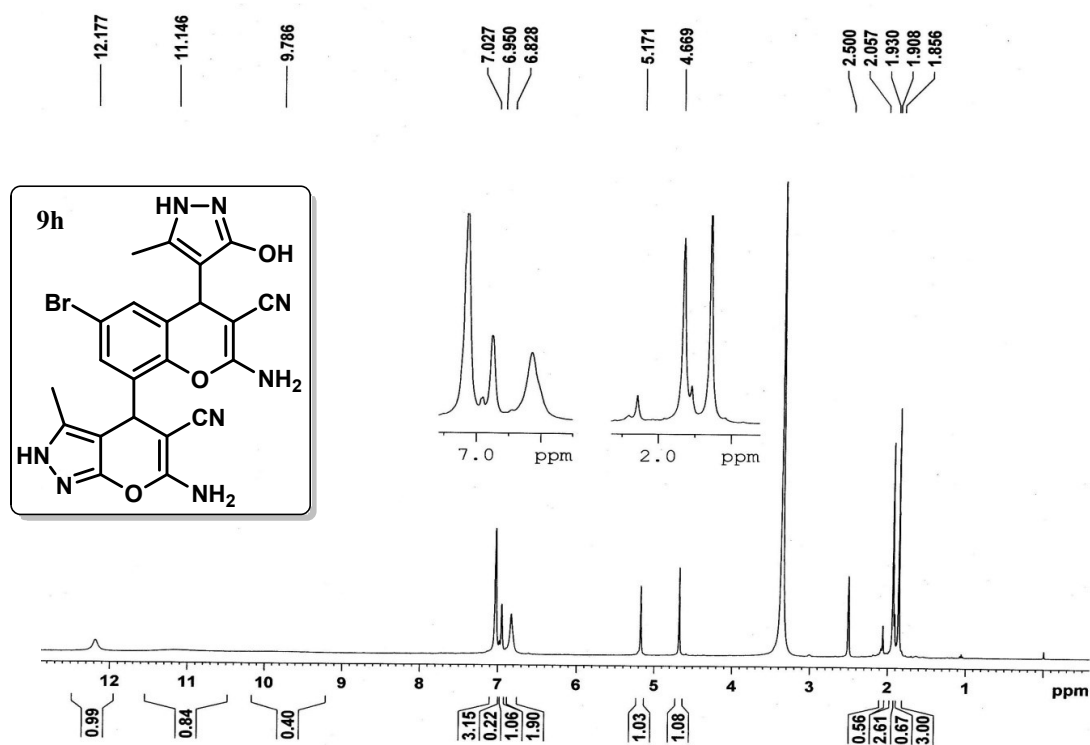
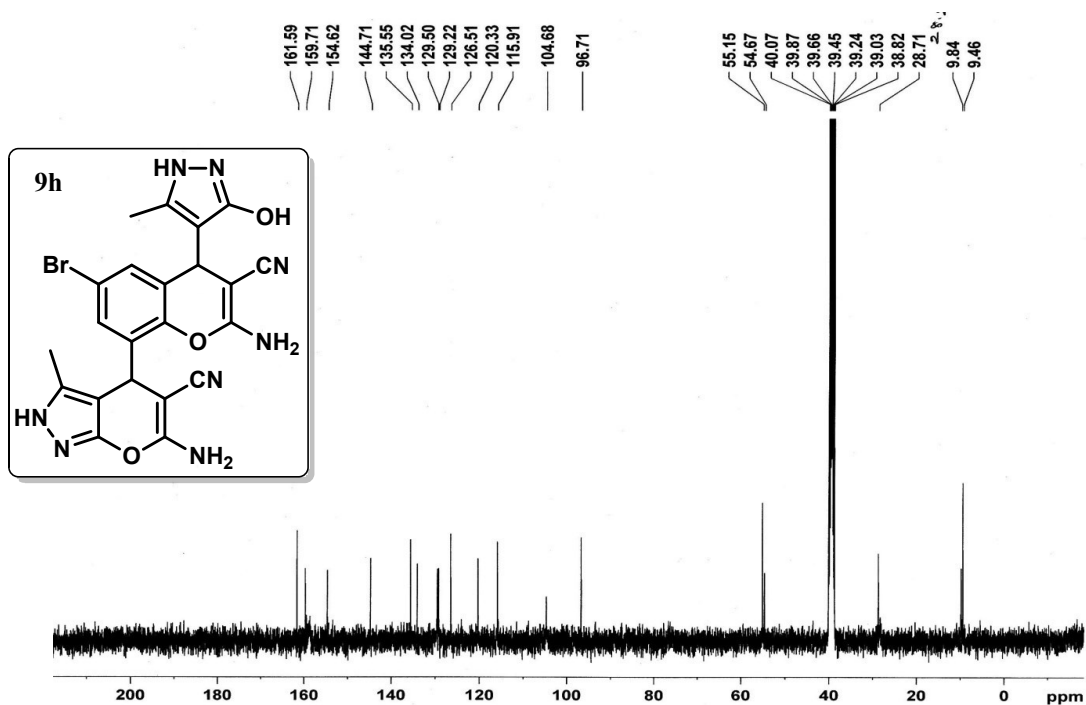
Figure 6 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9c

Figure 7  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound 9dFigure 8  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound 9d



Figure 11 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9fFigure 12 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9f

Figure 13 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9gFigure 14 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9g

Figure 15  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound 9hFigure 16  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound 9h



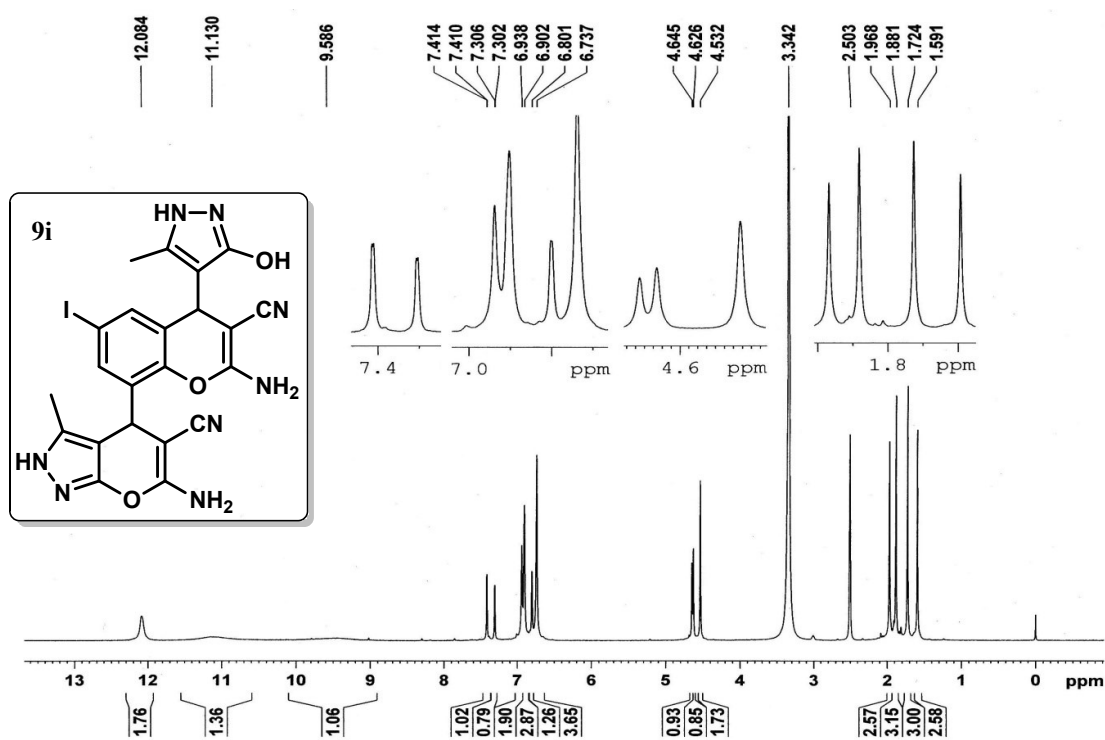


Figure 17  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound 9i

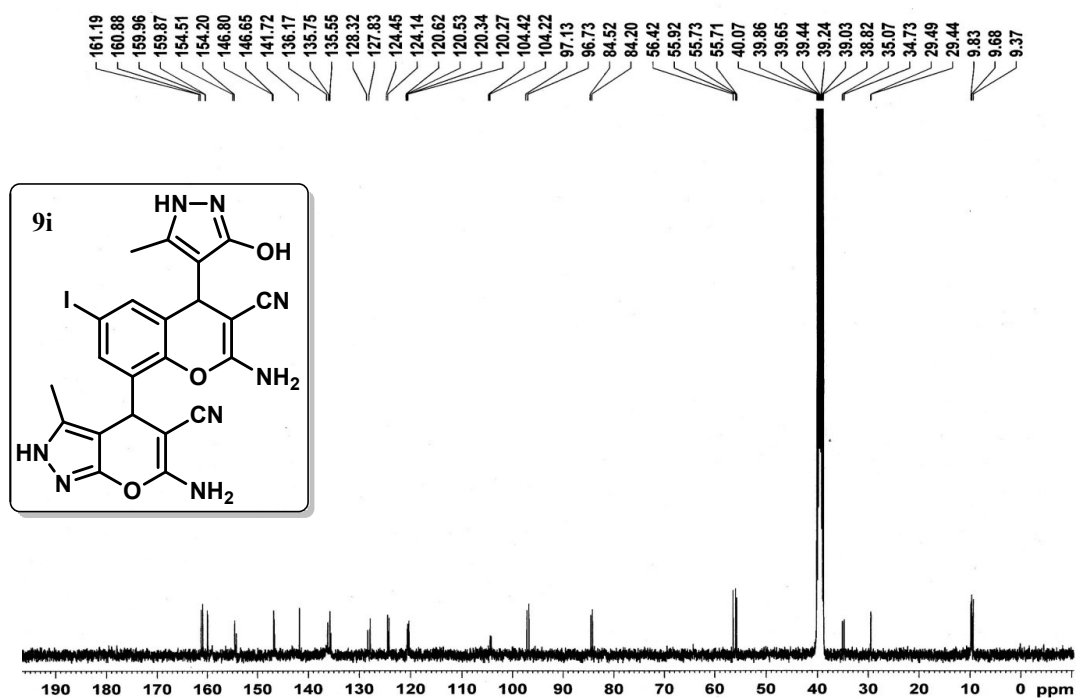
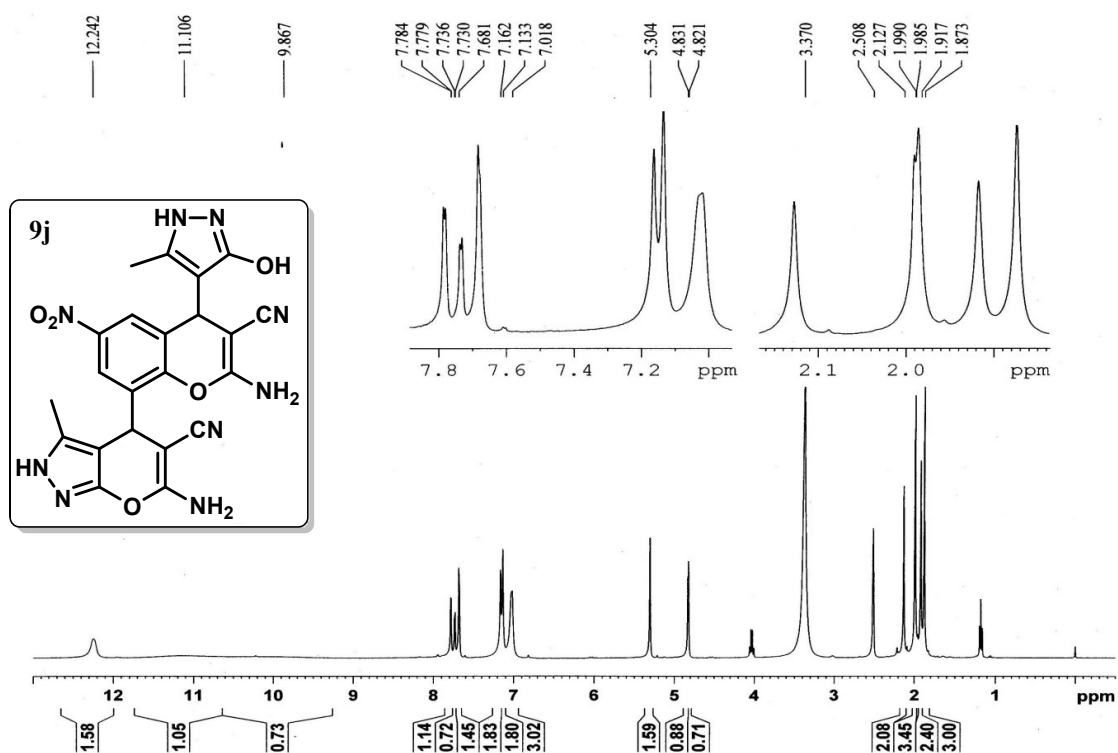
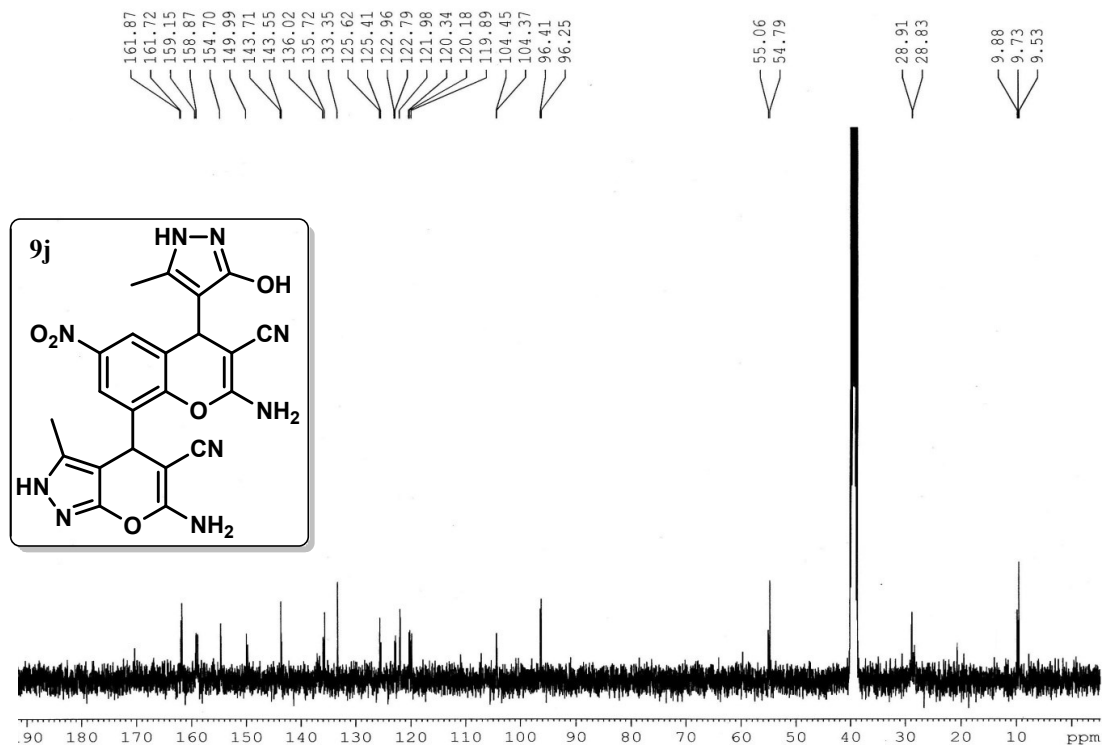
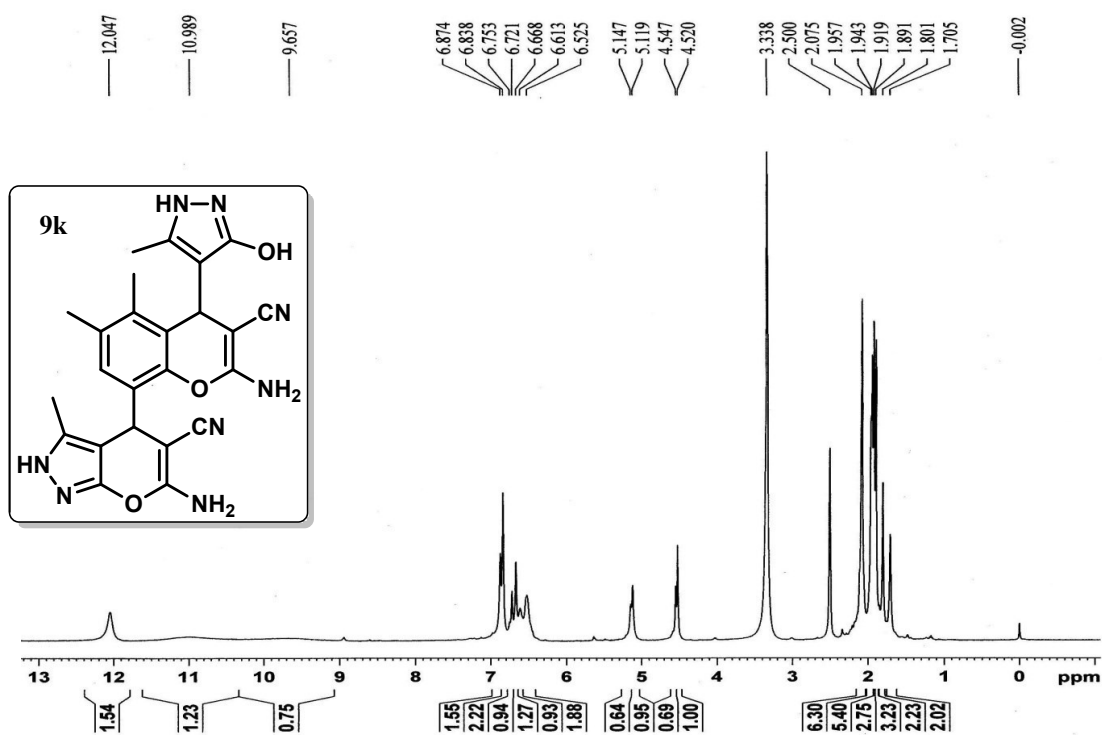
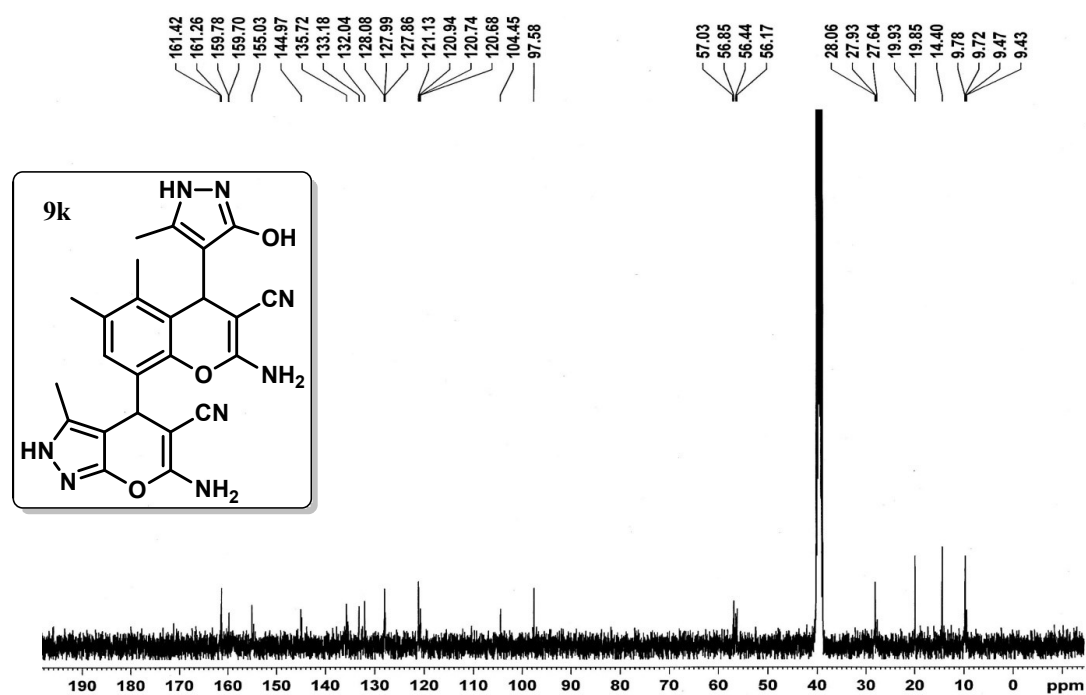
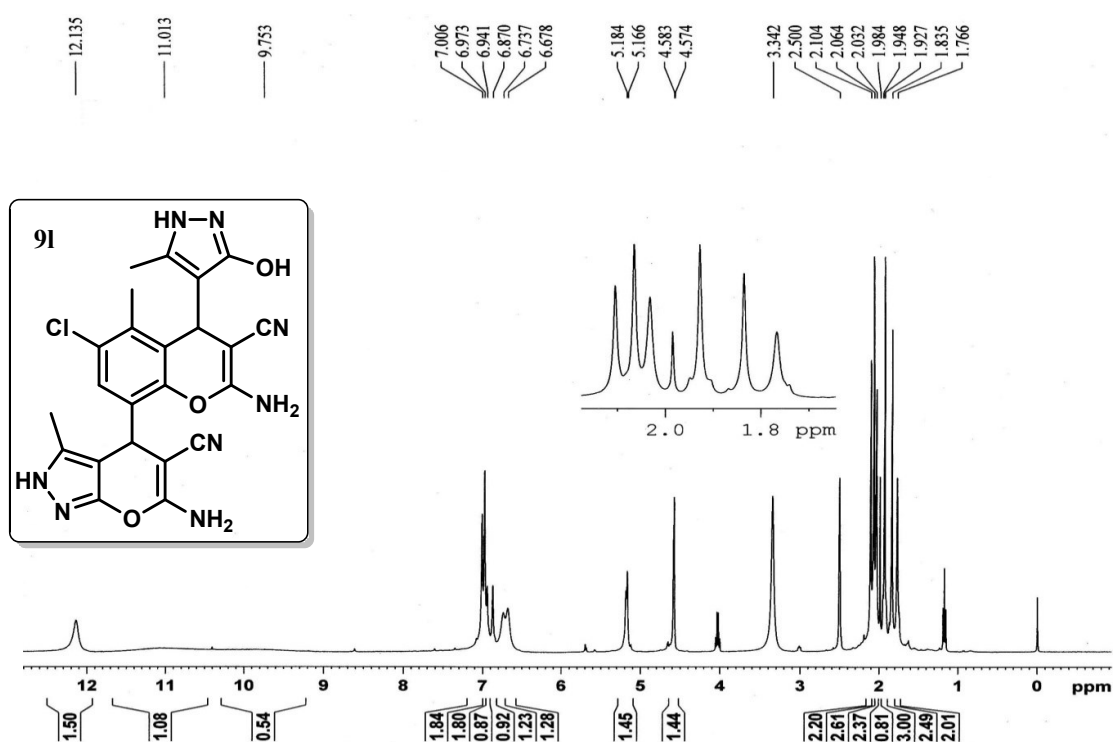
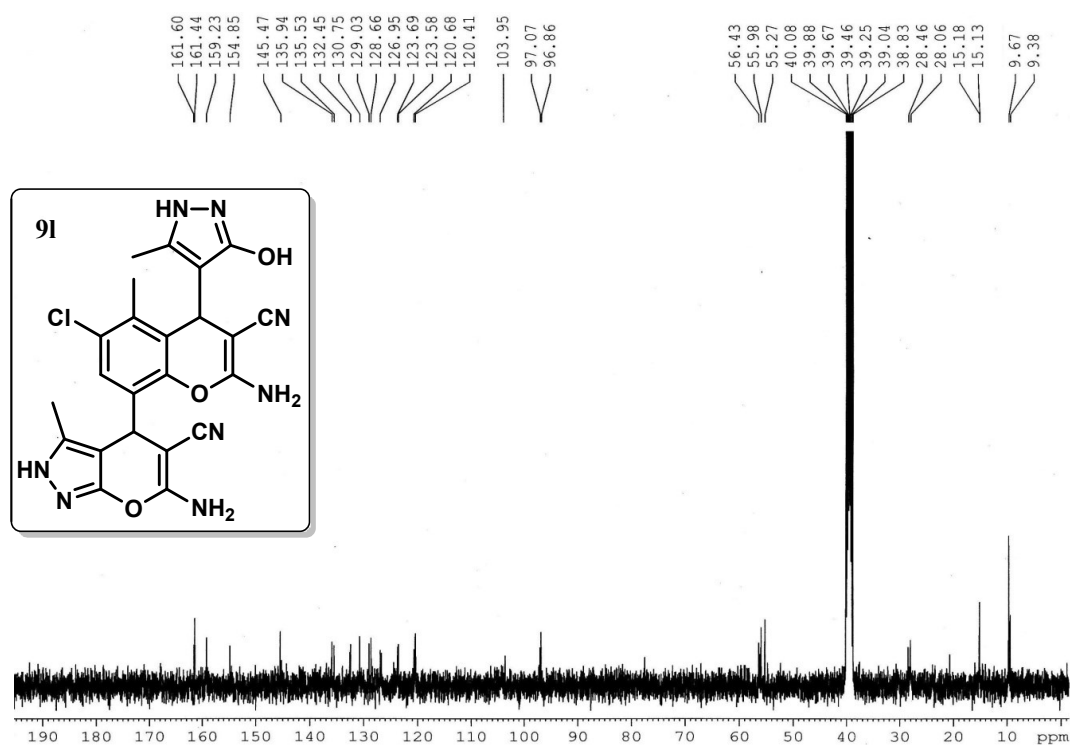


Figure 18  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) Spectrum of compound 9i

Figure 19 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9jFigure 20 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9j

Figure 21 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9kFigure 22 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9k

Figure 23 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9lFigure 24 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) Spectrum of compound 9l

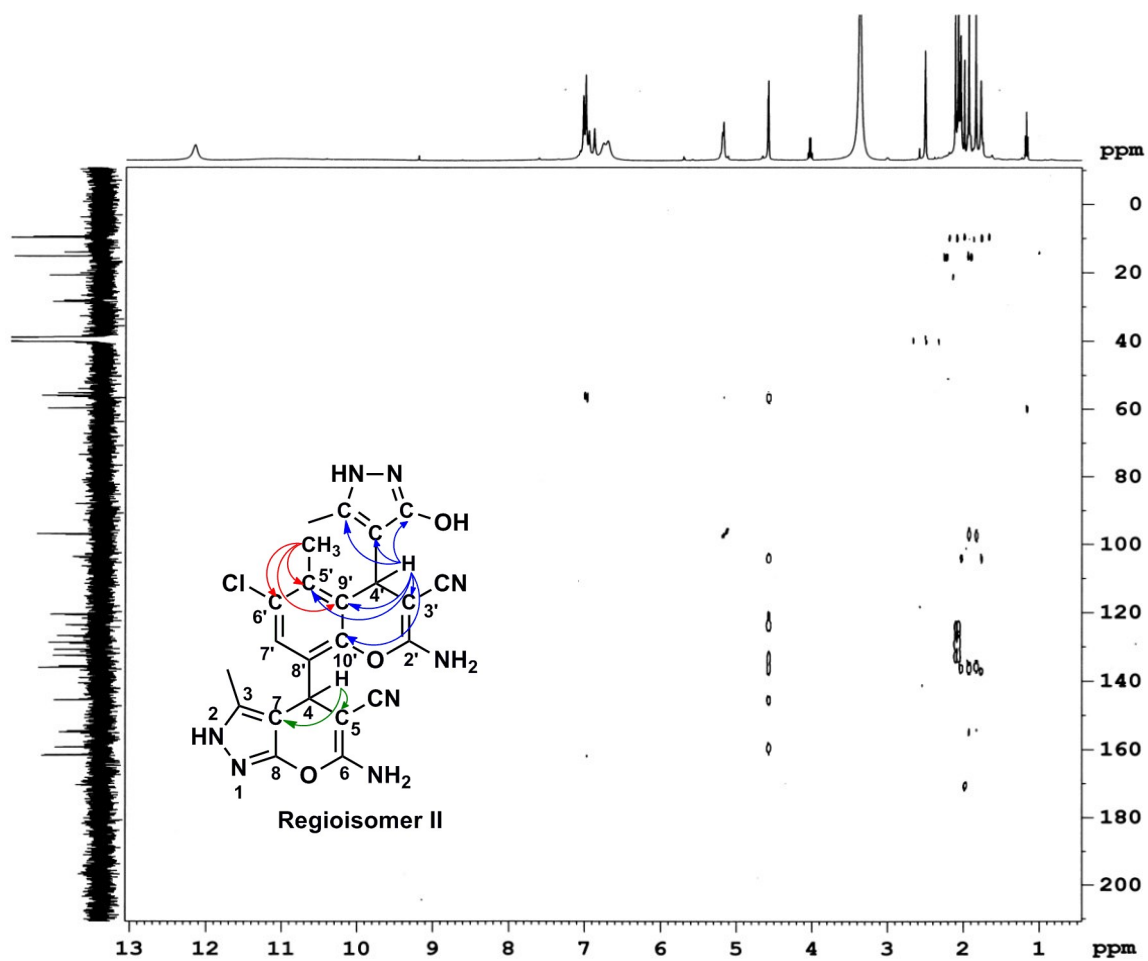


Fig. 25 HMBC correlations spectrum of compound 9I