

“Copper-catalyzed tandem cyclization via (C–O) arylation and oxidative acylation for the construction of chromeno fused isoxazole derivatives”

Rajnikant N. Ghoghari^[a], Anant R. Patel^[a], Parth P. Patel^[a], Kishor H. Chikhalia^{*[a]}

^[a]Department of Chemistry, Veer Narmad South Gujarat University, Surat, 395007, Gujarat, India

Email address: 1. chikhalia_kh@yahoo.com

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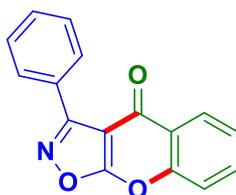
General information:

Unless otherwise noted, all the basic chemicals, catalysts, reagents and solvents were procured from university-identified suppliers and Sigma-Aldrich. Commercial reagents and solvents were used without purification. The synthesized compounds were characterized by ^1H NMR, ^{13}C NMR and mass spectral studies. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz FT NMR, Advance III Bruker model spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal standard. ESI mass spectra were recorded on a Bruker Daltonics MicroTof. The ^1H NMR chemical shifts are reported as parts per million (ppm) downfield from TMS. The splitting patterns are designated as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

General procedure for the synthesis of compound 3

To a solution of 3-phenylisoxazol-5(4*H*)-one **1** (0.5 mmol), 2-bromobenzaldehyde **2a** (0.65 mmol), metal catalyst CuI (10 mol%), ligand (20 mol%), base (1.65 mmol), and solvent (2 mL) were taken in the closed reaction vial under air atmosphere. Then the reaction mass was heated at 110 °C in a pre-heated oil bath for 10 hours and progress of the reaction was monitored continuously by TLC with ethyl acetate: hexane (2:3) eluent system. After the completion of reaction, crude was cooled to room temperature and then diluted with water. Afterward, reaction mass was extracted by ethyl acetate (3x15 ml). The organic layer was separated, dried over anhydrous MgSO_4 , concentrated under reduced pressure and purified by column chromatography to get the desired product.

1) **3-Phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3a):**

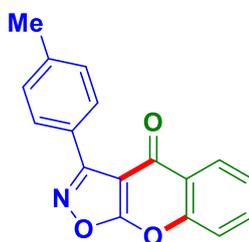


Yield: 74 %. White solid; M.P: 173-175 °C; ¹H NMR (400 MHz, DMSO-d₆) δ :8.13 (dd, J = 8.1, 1.7 Hz, 1H), 7.61-7.37 (m, 6H), 7.21-7.17 (m, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ:172.38, 159.34, 156.67, 153.49, 135.72, 129.53, 129.04, 128.76, 127.68, 126.29, 123.15, 119.57, 103.35.

Anal. calcd for C₁₆H₉NO₃: C: 73.00; H: 3.45; N: 5.32. found: C: 73.03; H: 3.42; N: 5.36.

HRMS-ESI (*m/z*) calcd for C₁₆H₉NO₃ [M + H]⁺ 264.0691, found 264.0696.

2) **3-(p-tolyl)-4H-chromeno[3,2-d]isoxazol-4-one (3b):**

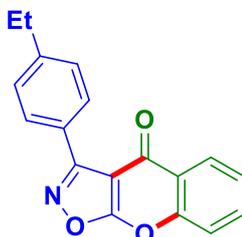


Yield: 76 %. Off-white solid; M.P: 162-164 °C; ¹H NMR (400 MHz, DMSO-d₆) δ :8.11 (dd, J = 8.0, 1.6 Hz, 1H), 7.71-7.58 (m, 3H), 7.34 (d J= 7.9 Hz, 2H), 7.16-7.13 (m, 2H). 2.39 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ:172.21, 159.83, 158.13, 152.85, 136.24, 131.56, 129.23, 127.68, 126.39, 126.07, 123.26, 120.83, 102.36, 21.32.

Anal. calcd for C₁₇H₁₁NO₃: C: 73.64; H: 4.00; N: 5.05. found: C: 73.67; H: 3.98; N: 5.03.

HRMS-ESI (*m/z*) calcd for C₁₇H₁₁NO₃ [M + H]⁺ 278.0849, found 278.0853.

3) 3-(4-ethylphenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3c):

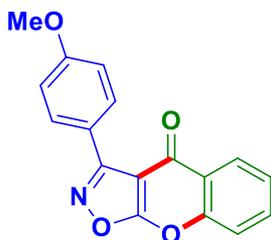


Yield: 77 %. yellowish white solid; M.P: 159-160 °C; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ :8.08 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.86-7.84 (m, 2H), 7.72-7.68 (m, 2H), 7.41-7.36 (m, 2H), 7.18-7.15 (m, 1H), 2.72 (q, $J = 7.8$ Hz, 2H), 1.33 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ :173.26, 160.15, 158.93, 155.85, 144.31, 134.96, 129.49, 127.64, 126.55, 125.84, 122.53, 120.85, 103.28, 28.71, 14.23.

Anal. calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_3$: C: 74.22; H: 4.50; N: 4.81. found: C: 74.25; H: 4.53; N: 4.79.

HRMS-ESI (m/z) calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 292.0917, found 292.0922.

4) 3-(4-methoxyphenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3d):



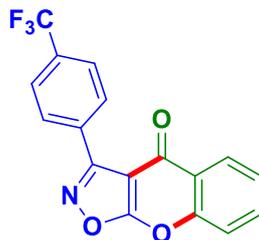
Yield: 81 %. White solid; M.P: 157-160 °C; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ :8.11 (dd, $J = 8.1, 1.4$ Hz, 1H), 7.68 (d, $J = 7.9$ Hz, 2H), 7.47-7.44 (m, 1H), 7.19-7.14 (m, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 3.89 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ :171.85, 159.87, 158.63, 154.13, 135.12, 129.24, 127.40, 125.83, 122.36, 119.28, 114.57, 104.25, 55.96.

Anal. calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_4$: C: 69.62; H: 3.78; N: 4.78. found: C: 69.65; H: 3.75; N: 4.81.

HRMS-ESI (m/z) calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 294.0724, found 294.0719.

5) 3-(4-(trifluoromethyl)phenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3e):

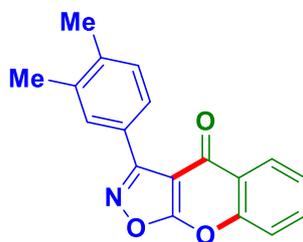


Yield: 65 %. Off-white solid; M.P: 171-173 °C; ¹H NMR (400 MHz, DMSO-d₆) δ :8.13 (dd, J = 7.9, 1.6 Hz, 1H), 7.73 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H), 7.48-7.45 (m, 1H), 7.19-7.14 (m, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ:172.32, 160.37, 158.56, 153.18, 136.71, 133.82, 131.07, 127.64, 126.47, 125.58, 124.39, 122.36, 119.42, 102.75.

Anal. calcd for C₁₇H₈F₃NO₃: C: 61.64; H: 2.43; N: 4.23. found: C: 61.62; H: 2.46; N: 4.20.

HRMS-ESI (*m/z*) calcd for C₁₇H₈F₃NO₃ [M + H]⁺ 332.0538, found 332.0543.

6) 3-(3,4-dimethylphenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3f):

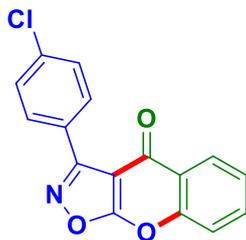


Yield: 78 %. Yellowish white solid; M.P: 189-191 °C; ¹H NMR (400 MHz, DMSO-d₆) δ:8.13 (dd, J = 8.2, 1.7 Hz, 1H), 7.59 (s, 1H), 7.50-7.45 (m, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.18-7.13 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ:172.78, 160.39, 158.67, 152.98, 137.49, 135.22, 131.07, 129.86, 126.18, 125.36, 123.56, 118.94, 101.87, 20.57, 19.64.

Anal. calcd for C₁₈H₁₃NO₃: C: 74.22; H: 4.50; N: 4.81. found: C: 74.25; H: 4.54; N: 4.78.

HRMS-ESI (*m/z*) calcd for C₁₈H₁₃NO₃ [M + H]⁺ 292.0918, found 292.0926.

7) 3-(4-chlorophenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3g):

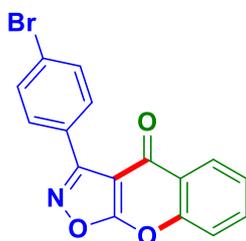


Yield: 63 %. Pale-yellow white solid; M.P: 178-180 °C; ¹H NMR (400 MHz, DMSO-d₆) δ :8.12 (dd, J = 7.8, 1.6 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.53-7.48 (m, 3H), 7.18-7.15 (m, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ:173.63, 160.49, 158.37, 153.88, 136.04, 134.67, 130.43, 128.90, 127.25, 126.51, 123.35, 120.42, 103.72.

Anal. calcd for C₁₆H₈ClNO₃: C: 64.55; H: 2.71; N: 4.71. found: C: 64.52; H: 2.69; N: 4.74.

HRMS-ESI (*m/z*) calcd for C₁₆H₈ClNO₃ [M + H]⁺ 298.0284, found 298.0288.

8) 3-(4-bromophenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3h):



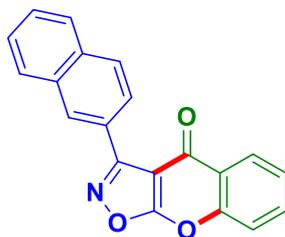
Yield: 63 %. White solid; M.P: 187-189 °C; ¹H NMR (400 MHz, DMSO-d₆) δ: 8.08 (dd, J = 7.9, 1.5 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.55-7.44 (m, 3H), 7.16-7.13 (m, 2H).

¹³C NMR (100 MHz, DMSO-d₆) δ:173.57, 160.43, 158.28, 153.77, 135.93, 134.56, 130.28, 128.84, 127.08, 126.15, 123.19, 120.35, 103.63.

Anal. calcd for C₁₆H₈BrNO₃: C: 56.17; H: 2.36; N: 4.09. found: C: 56.14; H: 2.31; N: 4.12.

HRMS-ESI (*m/z*) calcd for C₁₆H₈BrNO₃ [M + H]⁺ 343.9752, found 343.9748.

9) 3-(naphthalen-2-yl)-4H-chromeno[3,2-d]isoxazol-4-one (3i):

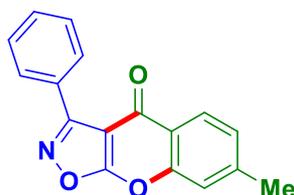


Yield: 71 %. Brown solid; M.P: 195-198 °C; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ : 8.25 (s, 1H), 8.11 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.96 (d, $J = 8.2$ Hz, 1H), 7.89-7.79 (m, 3H), 7.49-7.41 (m, 3H), 7.16-7.10 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ : 171.99, 160.52, 158.53, 153.27, 135.01, 134.55, 134.12, 133.86, 132.79, 129.49, 128.53, 128.37, 127.09, 126.74, 126.31, 126.02, 123.38, 121.91, 118.75, 102.67.

Anal. calcd for $\text{C}_{20}\text{H}_{11}\text{NO}_3$: C: 76.67; H: 3.54; N: 4.47. found: C: 76.64; H: 3.57; N: 4.50.

HRMS-ESI (m/z) calcd for $\text{C}_{20}\text{H}_{11}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 314.0872, found 314.0869.

10) 7-methyl-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3j):

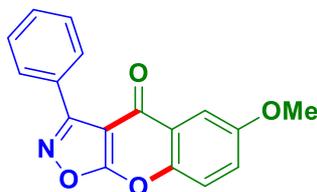


Yield: 73 %. White solid; M.P: 173-175 °C; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ : 7.98 (d, $J = 7.6$ Hz, 1H), 7.59-7.53 (m, 2H), 7.48-7.36 (m, 3H), 7.15-7.10 (m, 2H), 2.36 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ : 172.75, 160.03, 157.94, 153.35, 143.49, 129.65, 129.10, 128.71, 127.46, 125.79, 122.93, 118.84, 104.25, 21.20.

Anal. calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_3$: C: 73.64; H: 4.00; N: 5.05. found: C: 73.61; H: 3.98; N: 5.08.

HRMS-ESI (m/z) calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 278.0887, found 278.0883.

11) 6-methoxy-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3k):



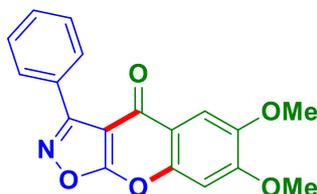
Yield: 77 %. Off-white solid; M.P: 176-178 °C; $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ : 7.72 (s, 1H), 7.46-7.35 (m, 4H), 7.30-7.24 (m, 2H), 7.16 (d J= 8.8 Hz, 1H), 3.89 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, DMSO-d₆) δ :173.48, 159.89, 158.65, 154.12, 149.47, 129.58, 128.76, 127.556, 125.11, 124.87, 119.93, 108.34, 104.57, 56.24.

Anal. calcd for C₁₇H₁₁NO₄: C: 69.62; H: 3.78; N: 4.78. found: C: 69.65; H: 3.75; N: 4.81.

HRMS-ESI (*m/z*) calcd for C₁₇H₁₁NO₄ [M + H]⁺ 294.0709, found 294.0712.

12) 6,7-dimethoxy-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3l):



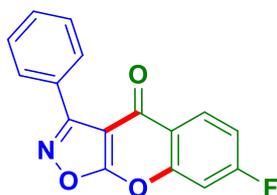
Yield: 78 %. White solid; M.P: 166-168 °C; $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ : 7.68 (s, 1H), 7.46-7.35 (m, 3H), 7.29-7.24 (m, 2H), 7.11 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, DMSO-d₆) δ :172.95, 160.18, 159.25, 155.67, 150.02, 148.34, 129.78, 128.52, 127.60, 116.15, 108.81, 104.31, 102.63, 58.35, 58.21.

Anal. calcd for C₁₈H₁₃NO₅: C: 66.87; H: 4.05; N: 4.33. found: C: 66.84; H: 4.09; N: 4.31.

HRMS-ESI (*m/z*) calcd for C₁₈H₁₃NO₅ [M + H]⁺ 324.0837, found 324.0840.

13) 7-fluoro-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3m):



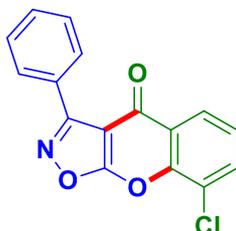
Yield: 66 %. Pale-yellow solid; M.P: 188-190 °C; $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ : 8.13 (dd, J = 8.5, 1.7 Hz, 1H) 7.43-7.36 (m, 3H), 7.31-7.26 (m, 2H), 7.21-7.13 (m, 1H), 7.02 (s, 1H).

$^{13}\text{C NMR}$ (100 MHz, DMSO-d₆) δ : 172.72, 166.83, 160.53, 158.96, 155.75, 132.65, 129.10, 128.71, 127.46, 115.85, 122.37, 108.58, 103.93.

Anal. calcd for C₁₆H₈FNO₃: C: 68.33; H: 2.87; N: 4.98. found: C: 68.31; H: 2.91; N: 4.95.

HRMS-ESI (m/z) calcd for C₁₆H₈FNO₃ [M + H]⁺ 282.0568, found 282.0574.

14) 8-chloro-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3n):



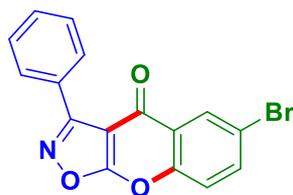
Yield: 62 %. Off-white solid; M.P: 175-176 °C; $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ : 7.95 (dd, J = 8.2, 1.4 Hz, 1H), 7.65 (d J = 8.2 Hz, 1H), 7.56-7.49 (m, 1H) 7.42-7.25 (m, 5H).

$^{13}\text{C NMR}$ (100 MHz, DMSO-d₆) δ : 172.38, 159.29, 158.36, 150.27, 135.89, 129.82, 129.12, 128.79, 127.53, 125.06, 123.13, 121.27, 102.92.

Anal. calcd for C₁₆H₈ClNO₃: C: 64.55; H: 2.71; N: 4.71. found: C: 64.53; H: 2.69; N: 4.74.

HRMS-ESI (m/z) calcd for C₁₆H₈ClNO₃ [M + H]⁺ 298.0284, found 298.0290.

15) 6-bromo-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3o):



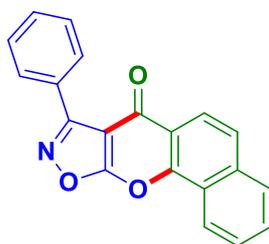
Yield: 65 %. White solid; M.P: 188-190 °C; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ : 8.33 (s, 1H), 7.70-7.61 (m, 3H), 7.47-7.37 (m, 3H), 7.14 (d J = 8.3 Hz, 1H).

$^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ : 173.15, 160.75, 158.49, 155.16, 138.09, 129.87, 129.10, 128.68, 127.46, 124.32, 122.28, 119.19, 103.58.

Anal. calcd for $\text{C}_{16}\text{H}_8\text{BrNO}_3$: C: 56.17; H: 2.36; N: 4.09. found: C: 56.13; H: 2.40; N: 4.13.

HRMS-ESI (m/z) calcd for $\text{C}_{16}\text{H}_8\text{BrNO}_3$ $[\text{M} + \text{H}]^+$ 343.9733, found 343.9739.

16) 8-phenyl-7H-benzo[7,8]chromeno[3,2-d]isoxazol-7-one (3p):



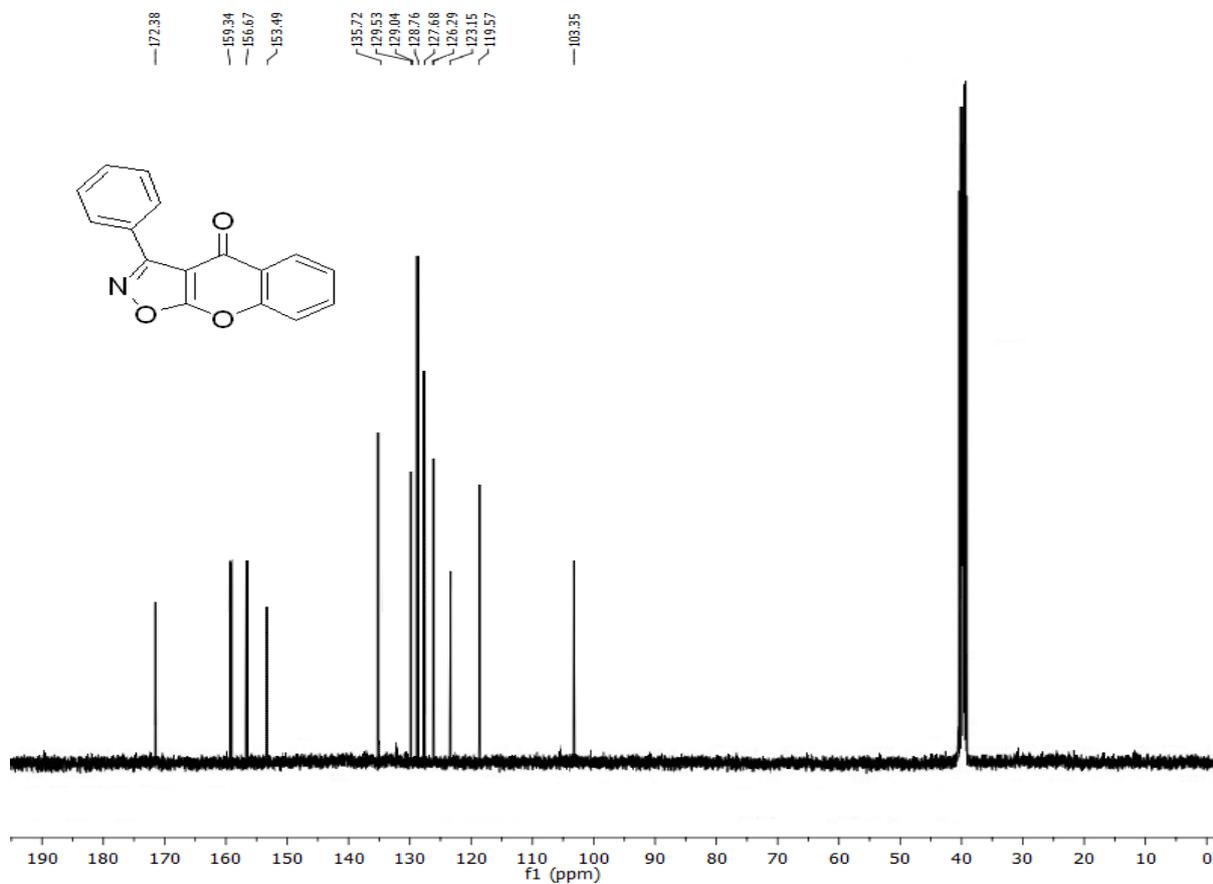
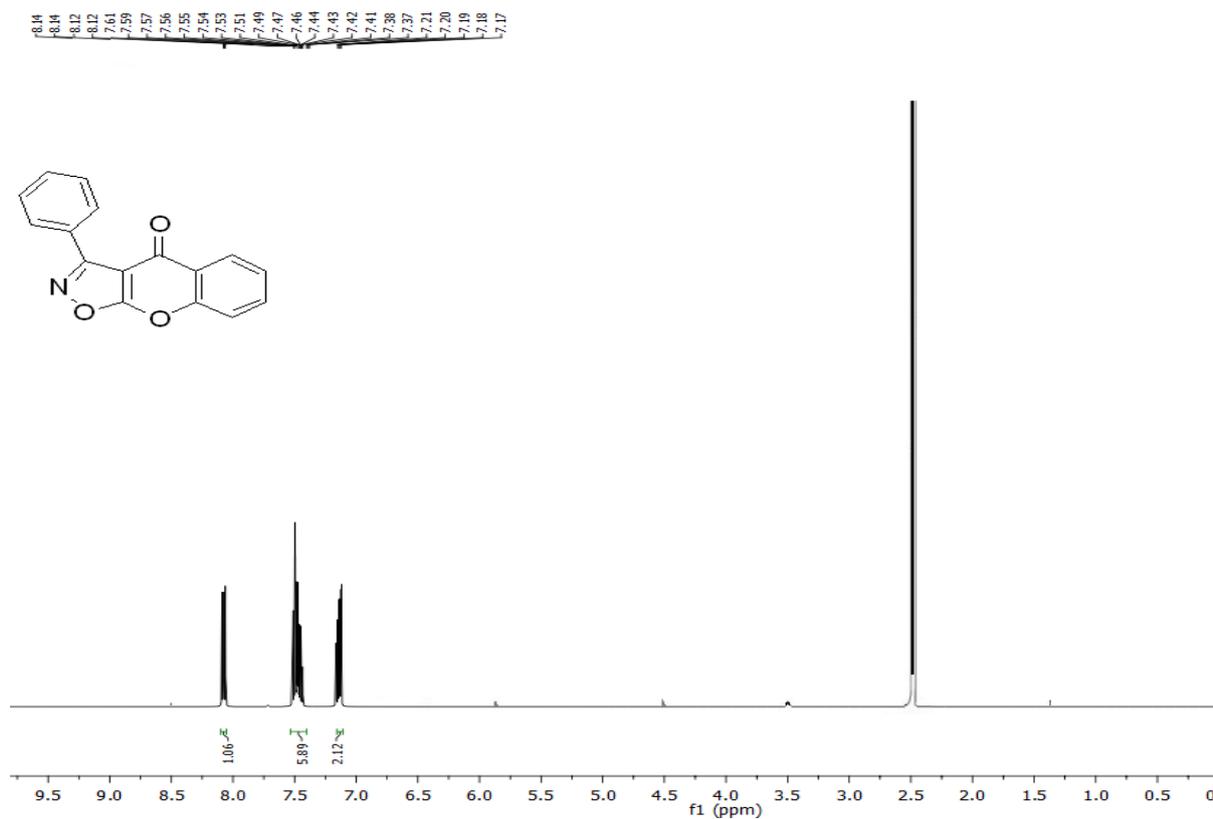
Yield: 70 %. Off-white solid; M.P: 192-194 °C; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ : 8.39- 8.36 (m, 1H), 8.26 (d J = 8.1 Hz, 1H), 8.17-8.14 (m, 2H), 7.84-7.81 (m, 1H), 7.69-7.63 (m, 1H), 7.36-7.28 (m, 5H).

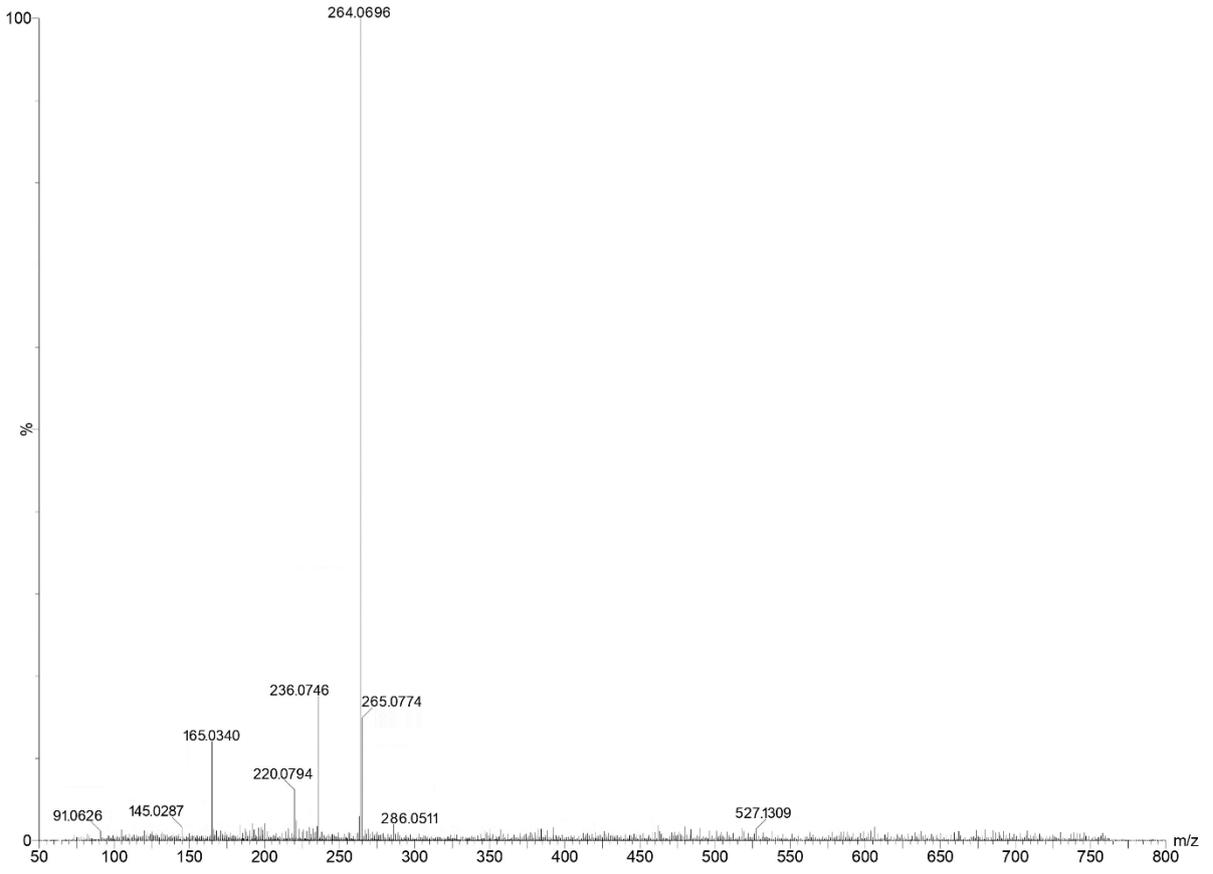
$^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ : 172.29, 160.23, 159.45, 153.18, 134.27, 129.82, 129.58, 128.66, 128.29, 127.84, 127.72, 127.56, 125.12, 123.54, 120.83, 117.85, 103.16.

Anal. calcd for $\text{C}_{20}\text{H}_{11}\text{NO}_3$: C: 76.67; H: 3.54; N: 4.47. found: C: 76.70; H: 3.51; N: 4.50.

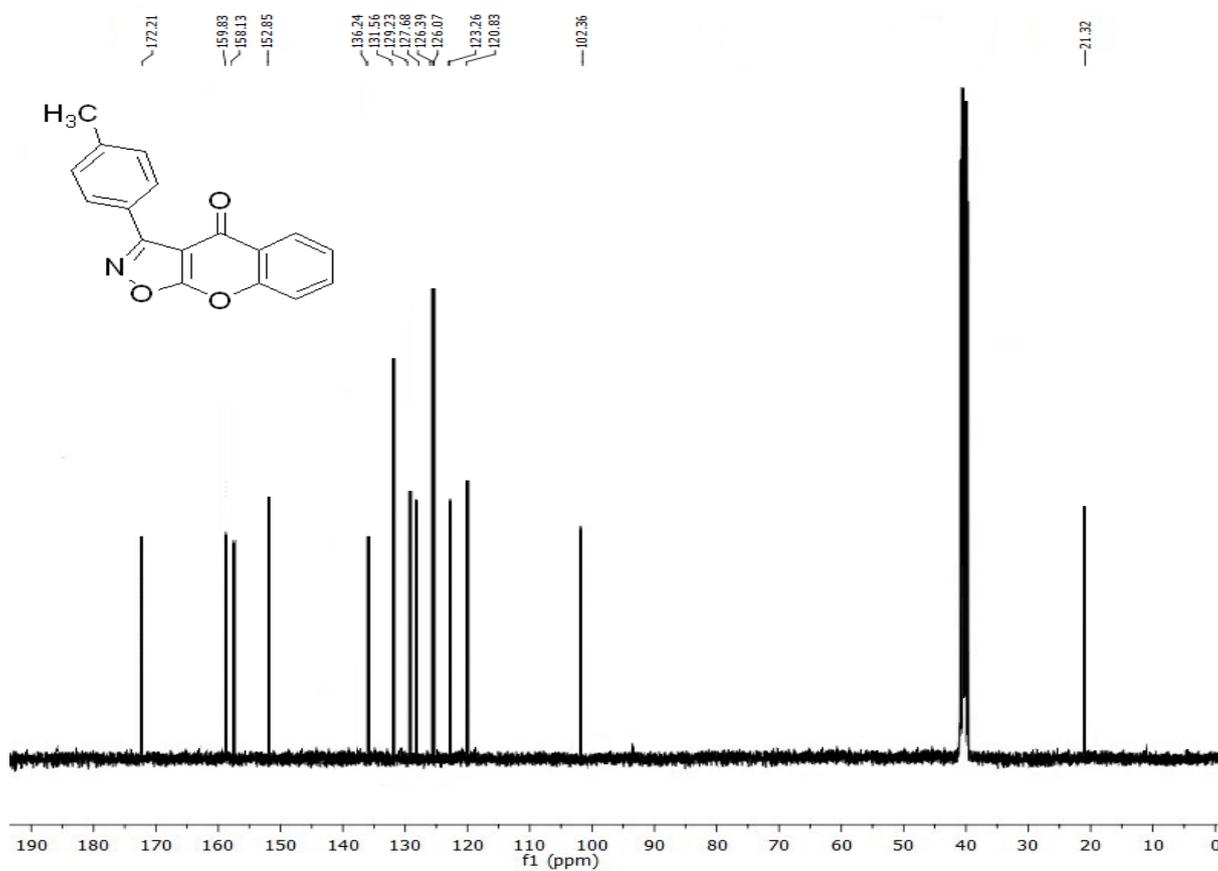
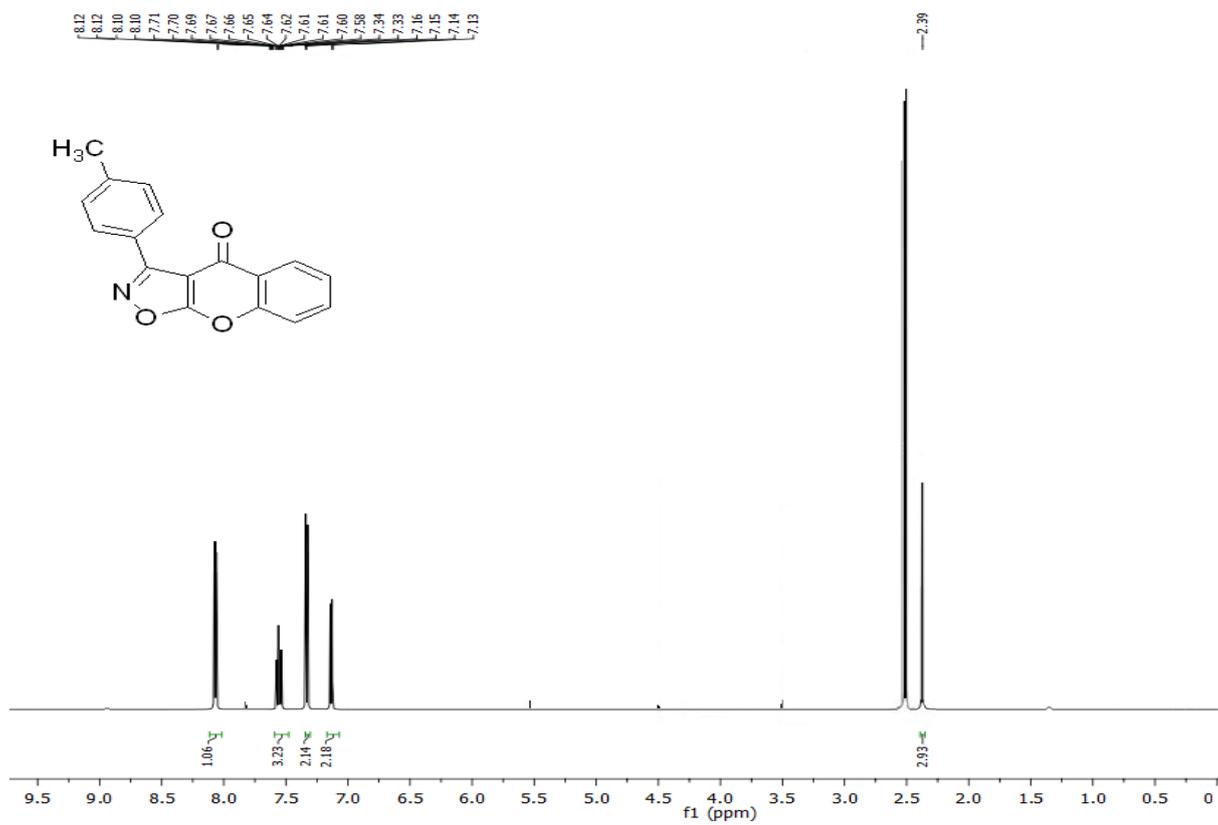
HRMS-ESI (m/z) calcd for $\text{C}_{20}\text{H}_{11}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 314.0859, found 314.0866.

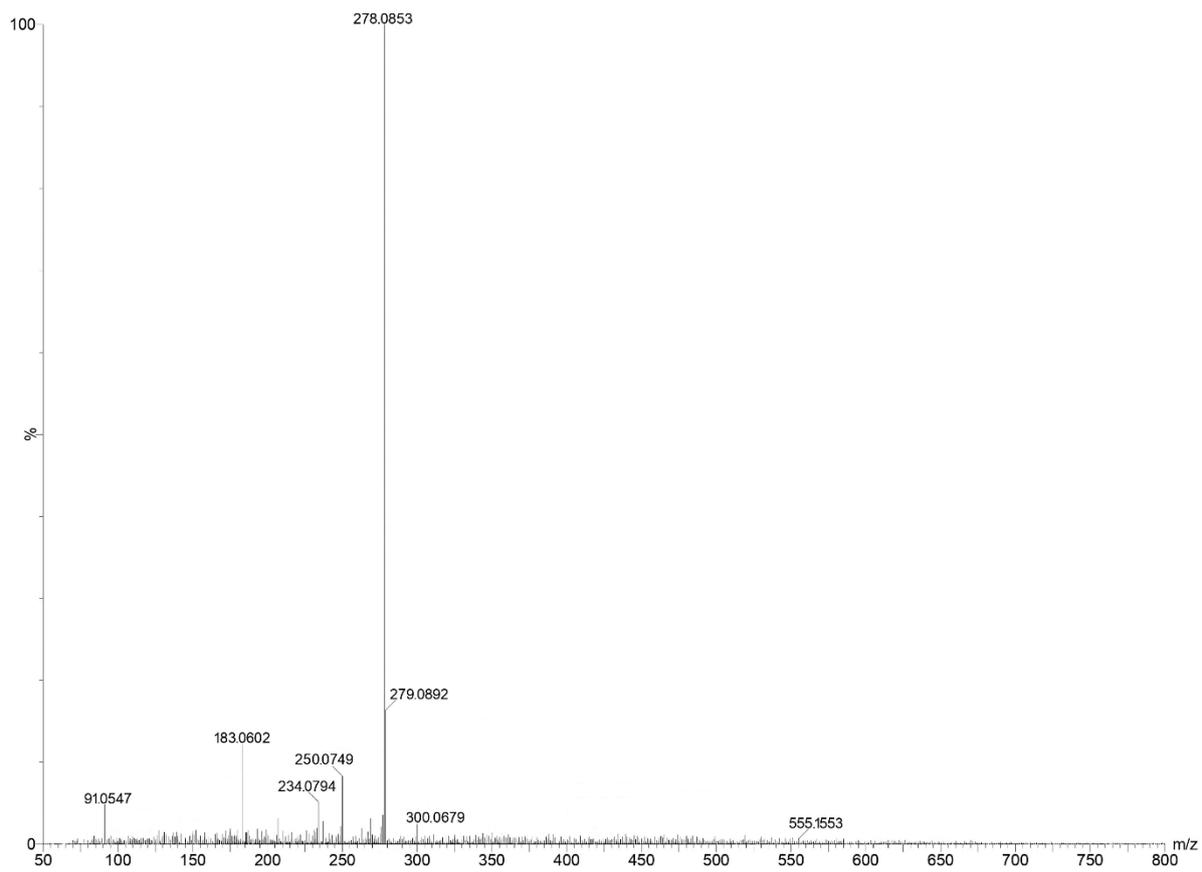
1) 3-Phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3a):



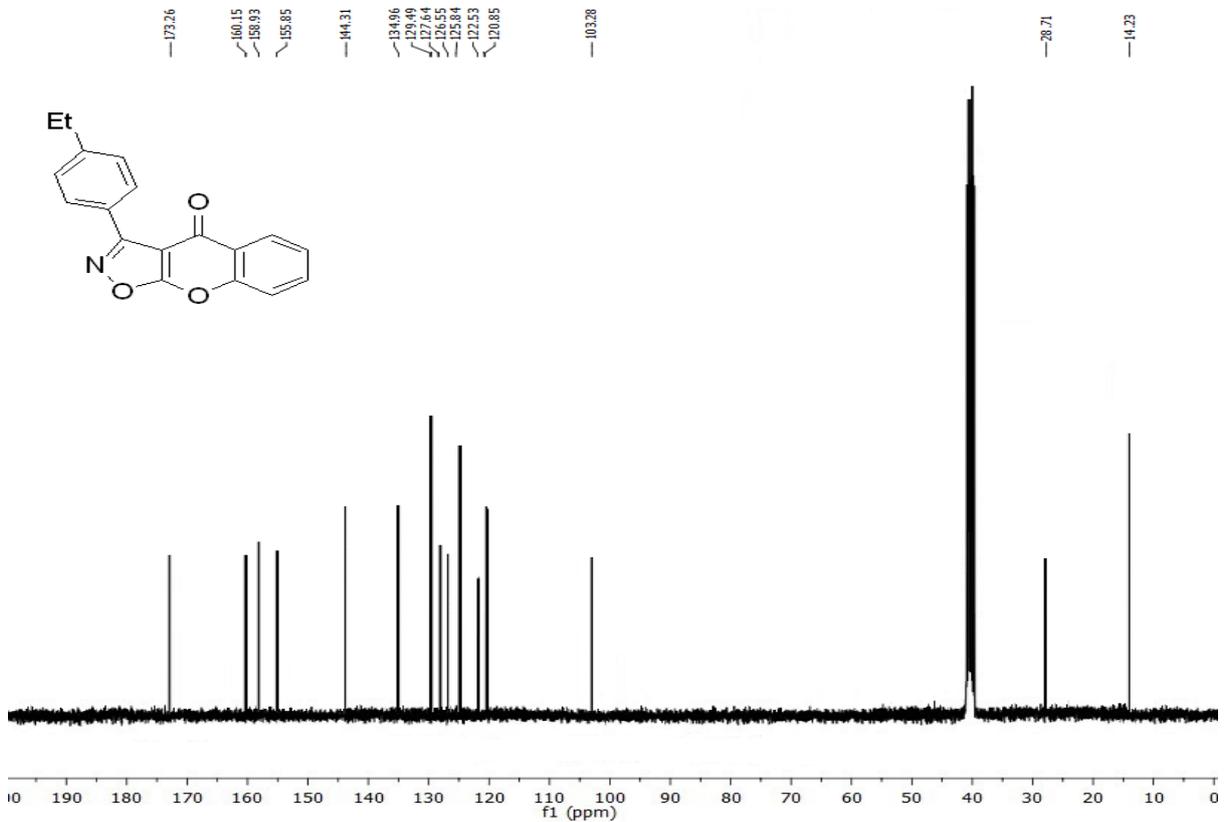
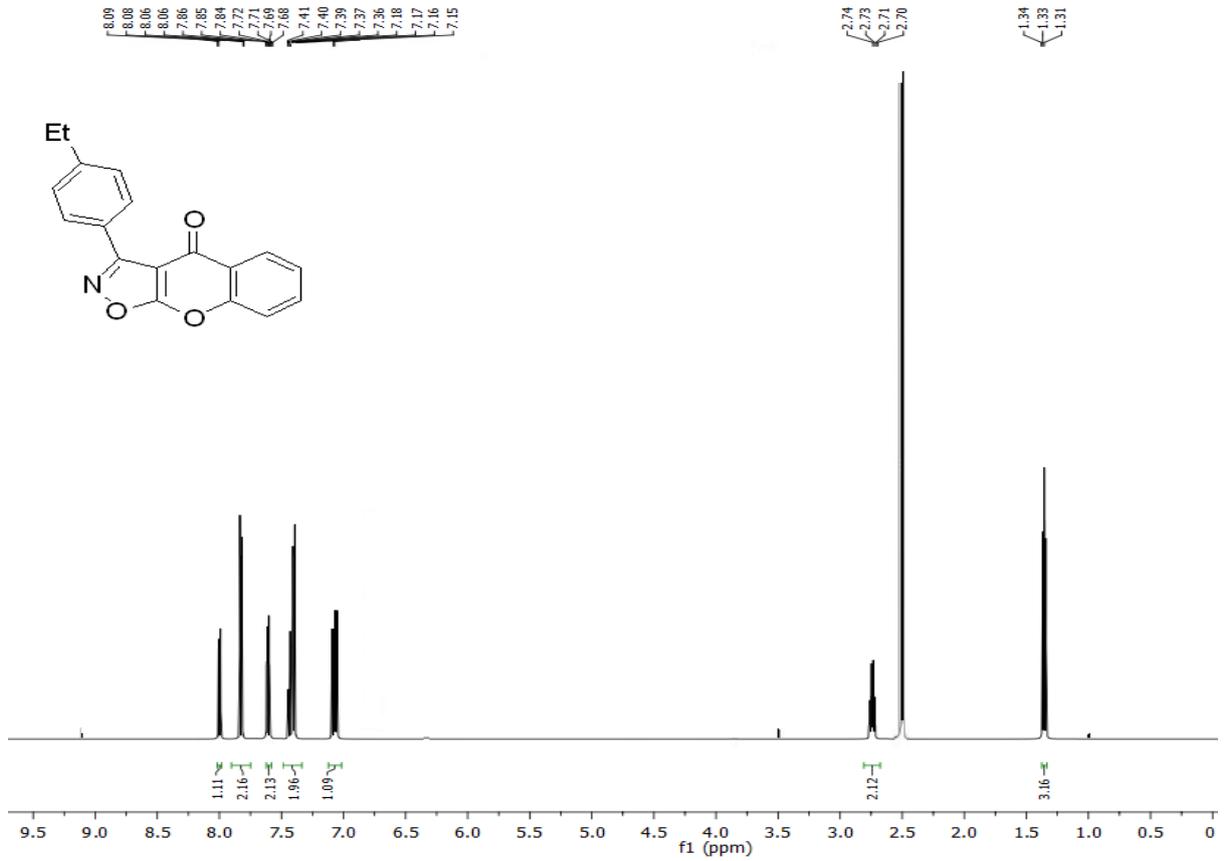


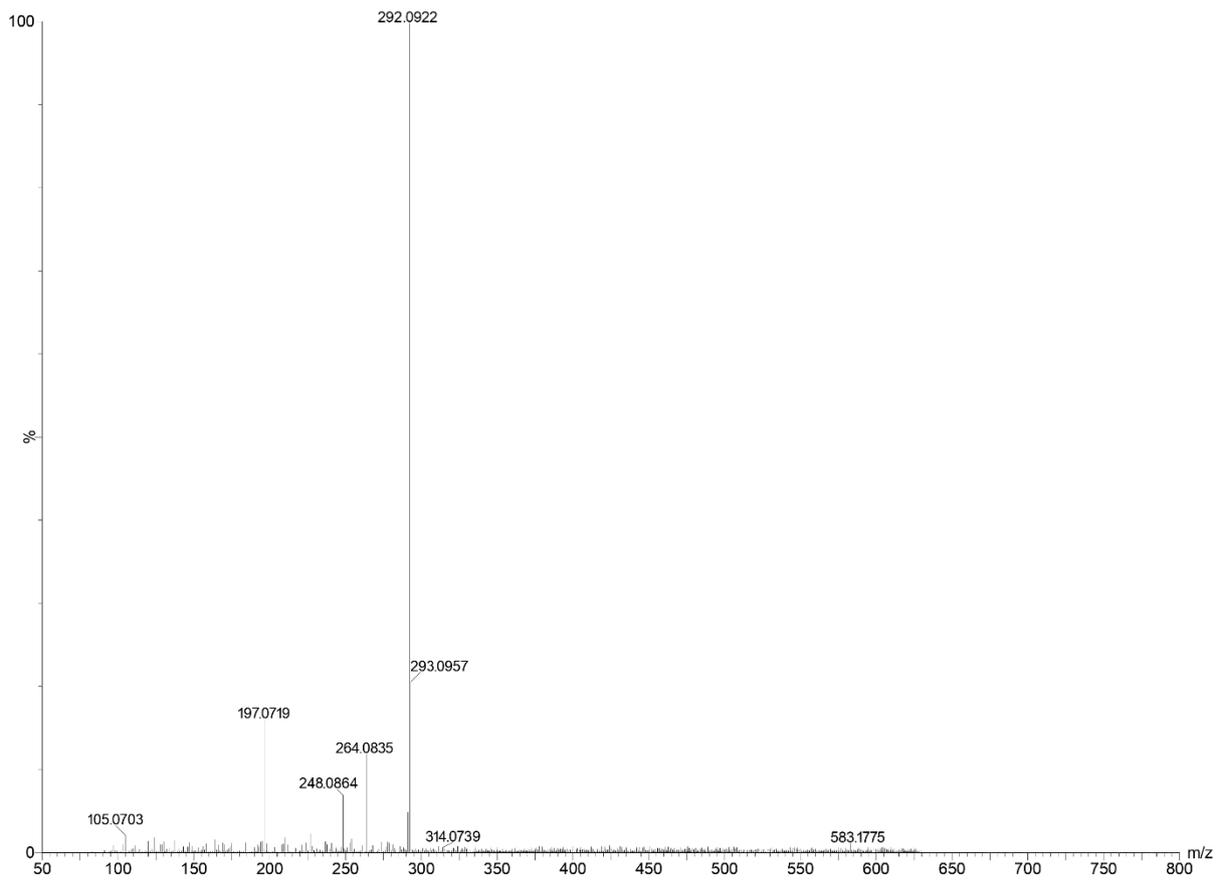
2) 3-(p-tolyl)-4H-chromeno[3,2-d]isoxazol-4-one (3)



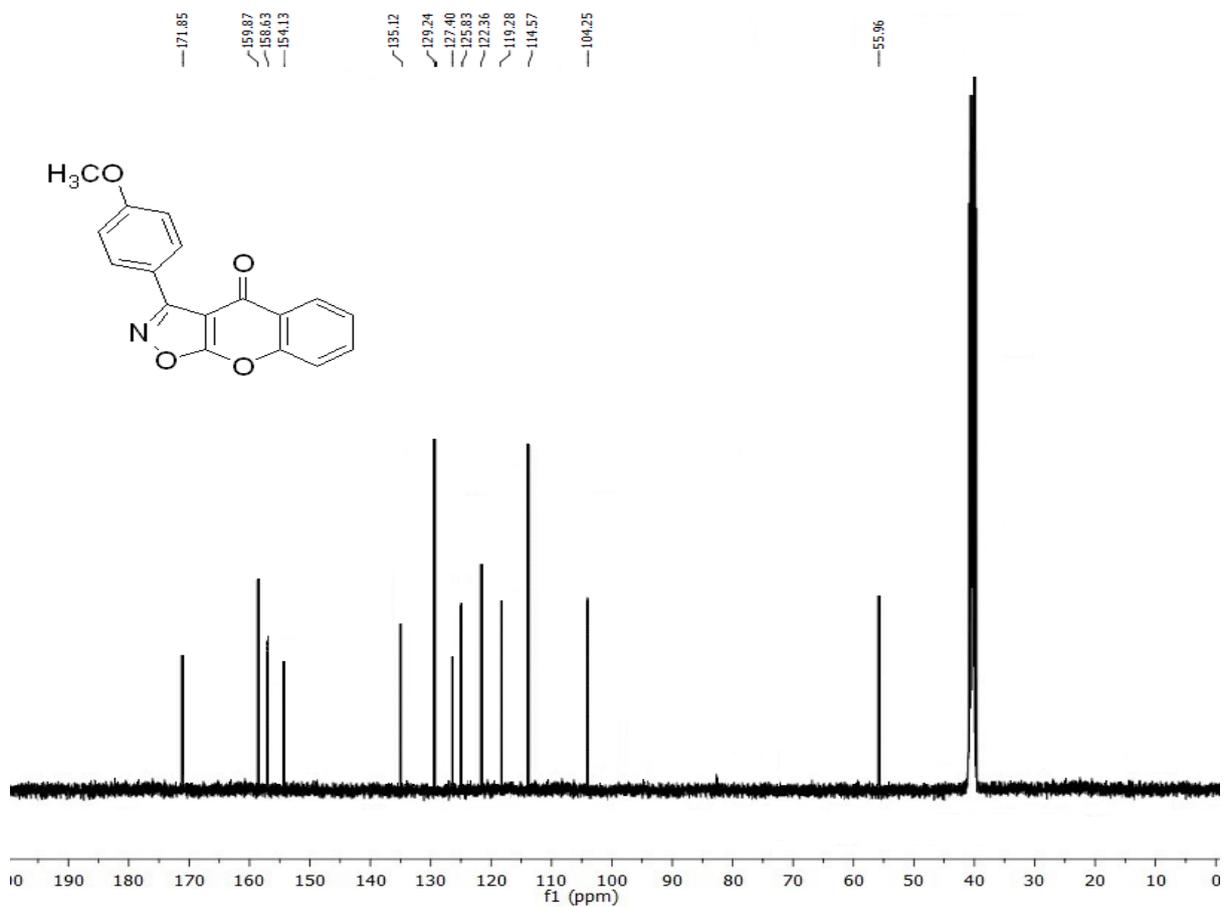
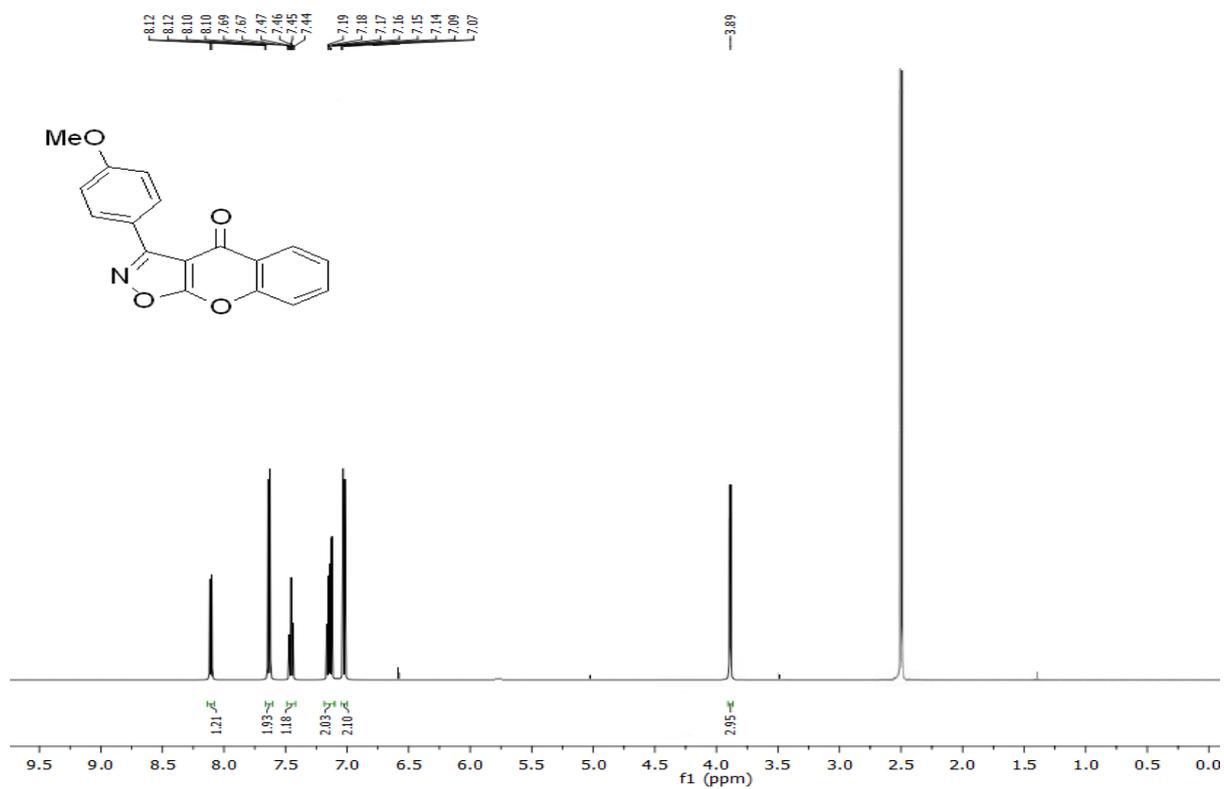


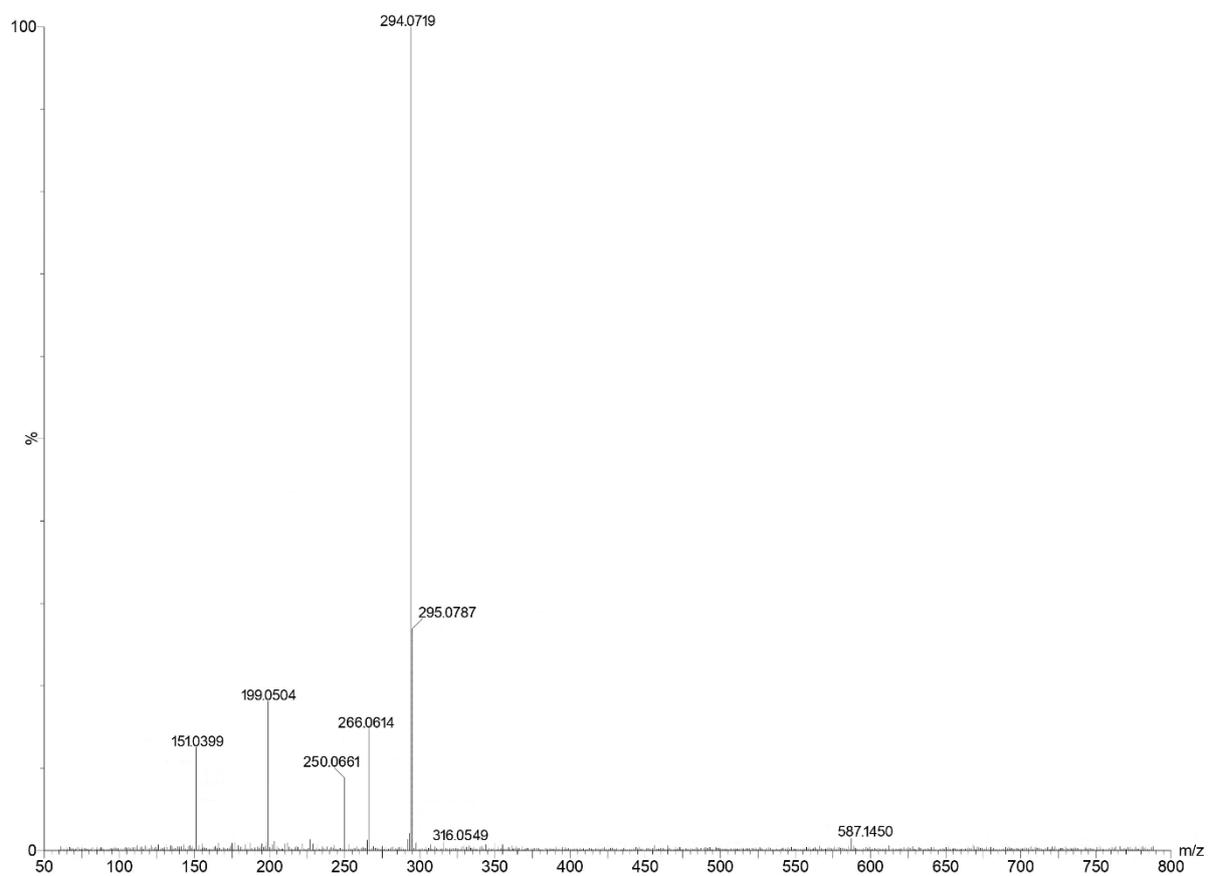
3) 3-(4-Ethylphenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3c):



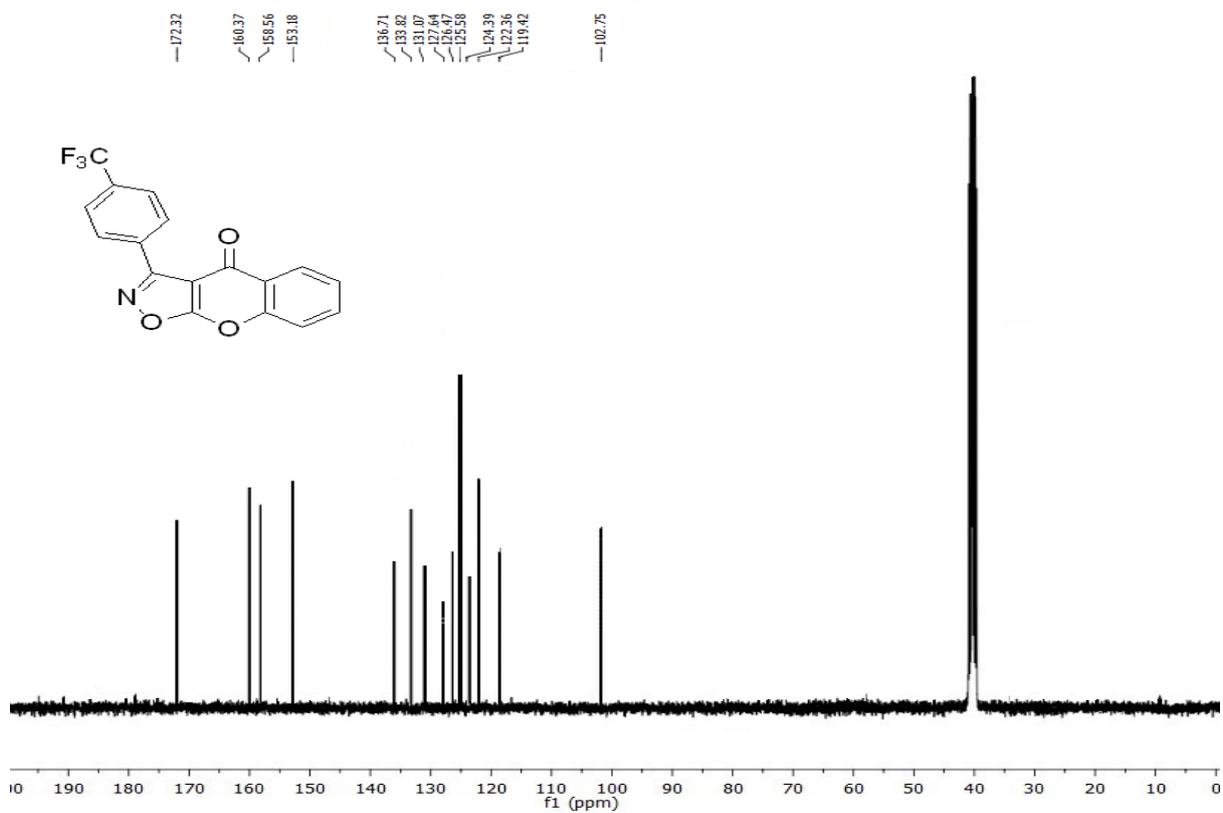
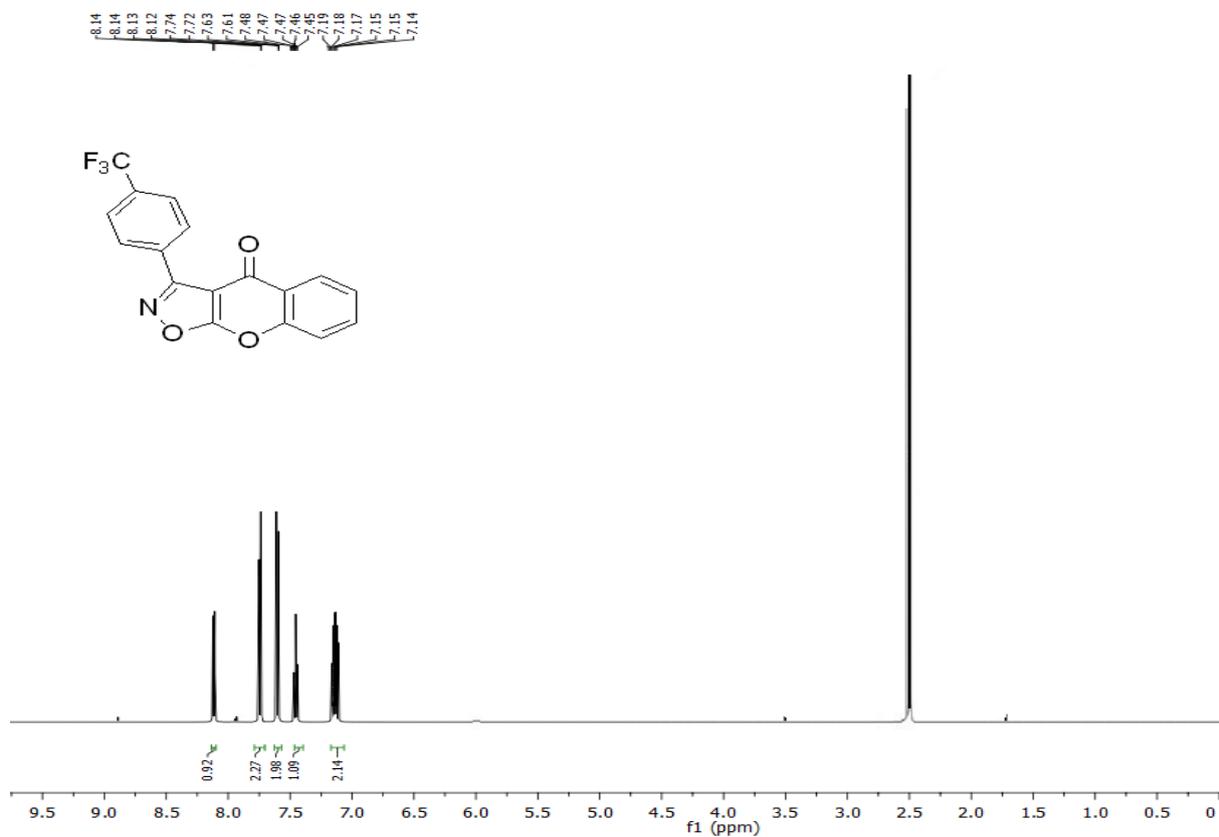


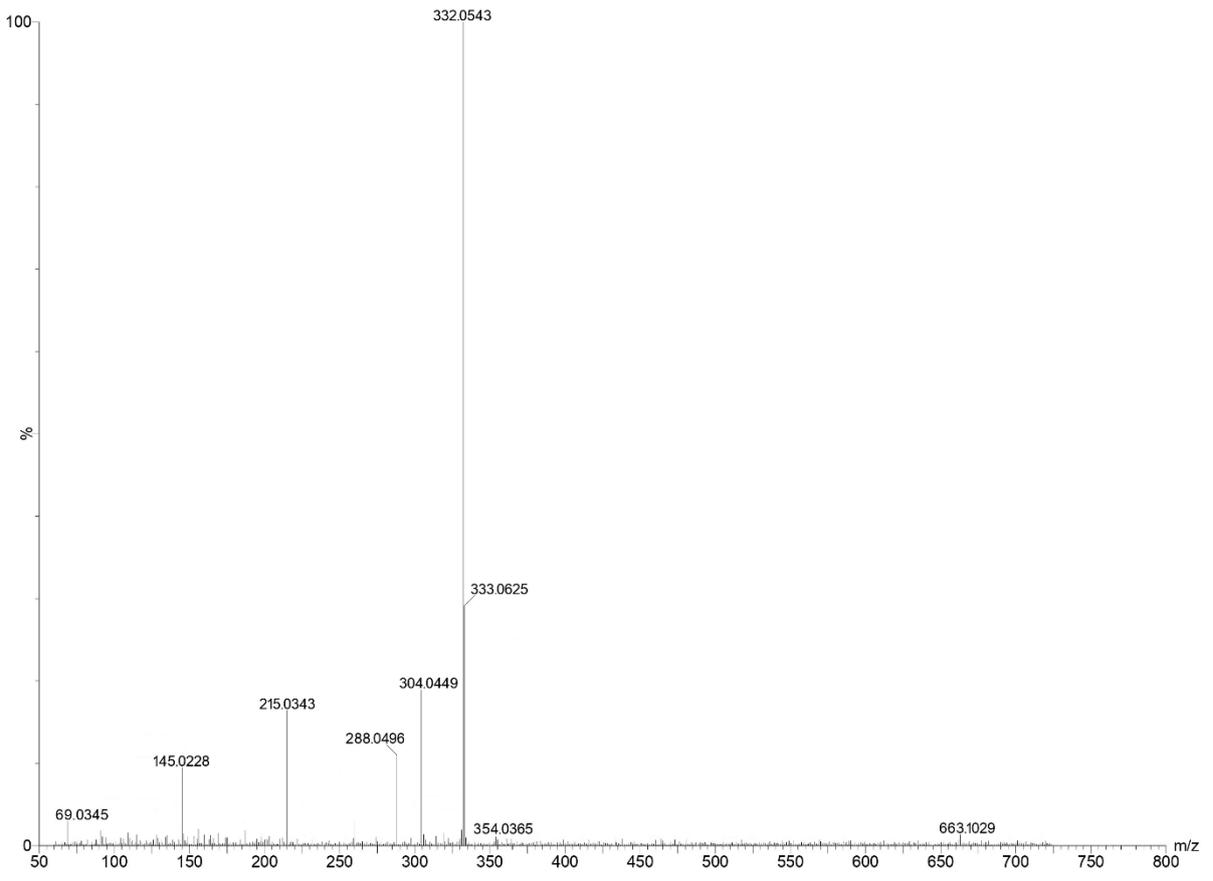
4) 3-(4-Methoxyphenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3d):



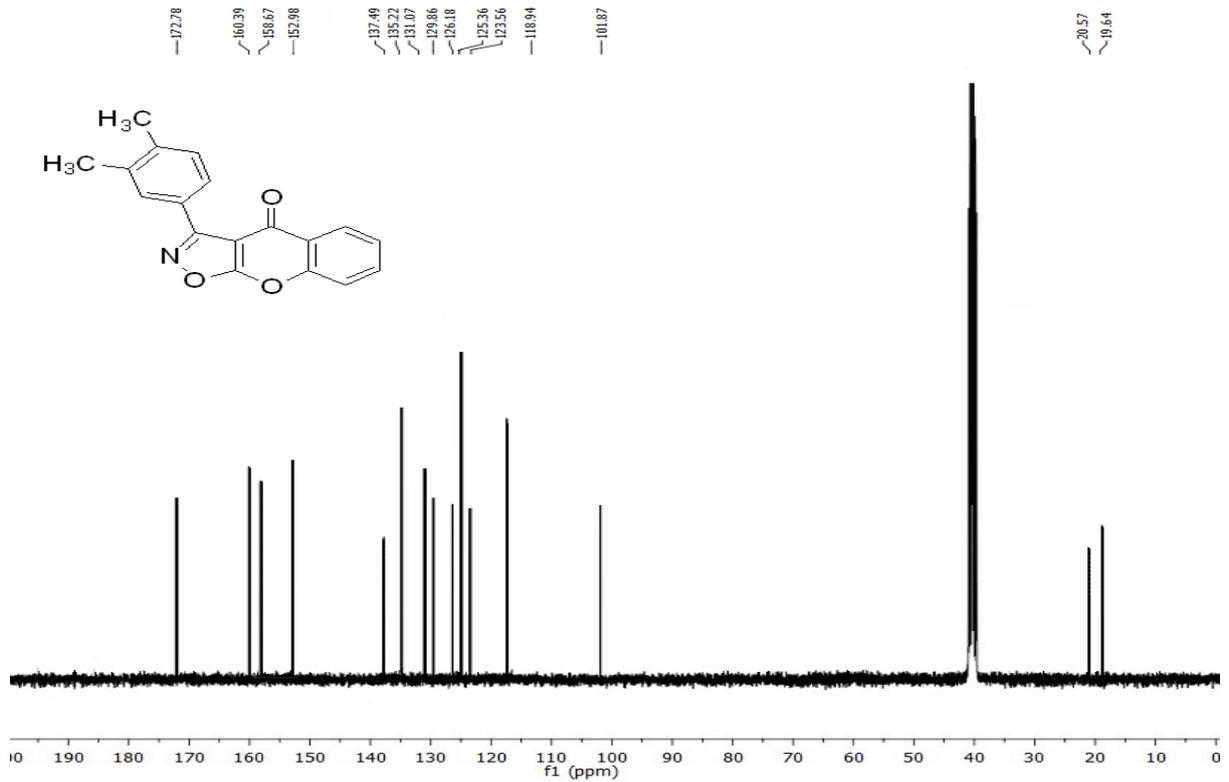
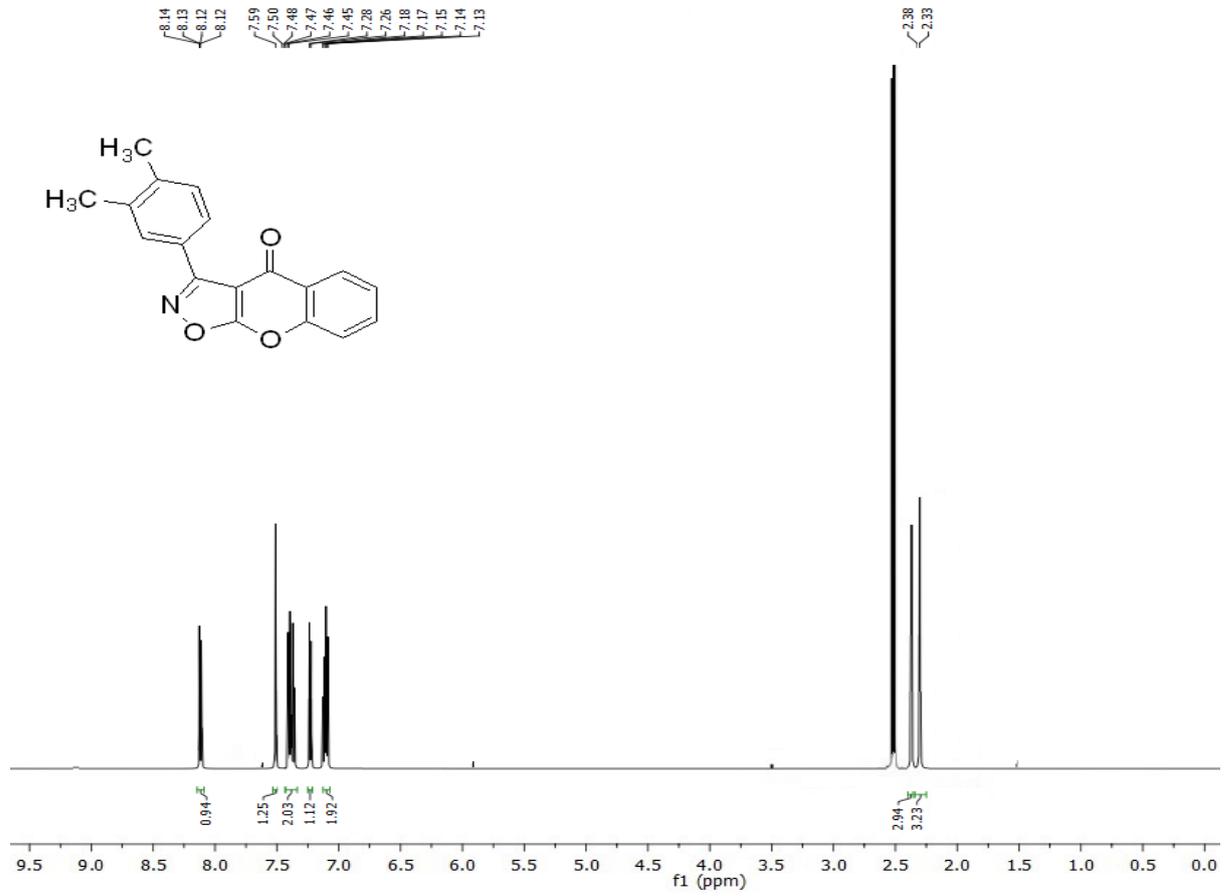


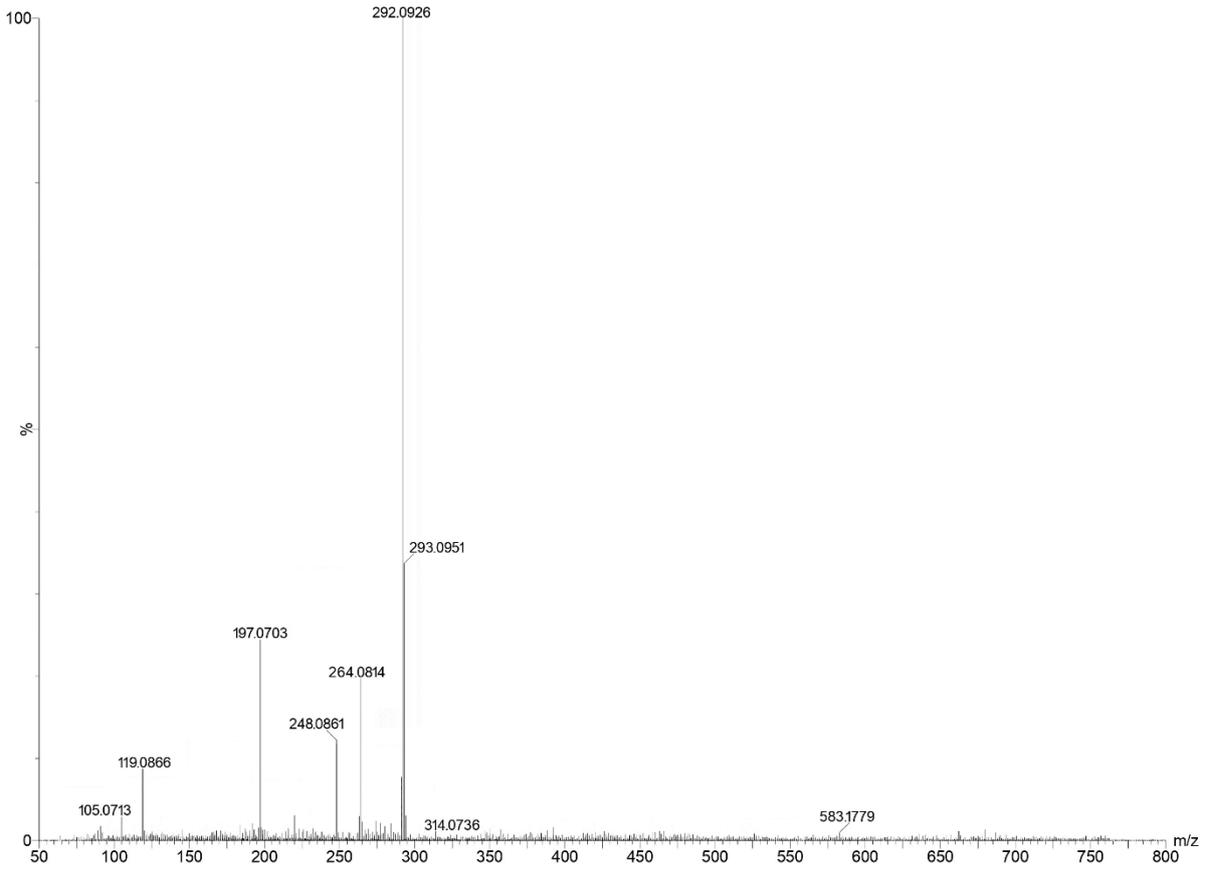
5) 3-(4-(Trifluoromethyl) phenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3e):



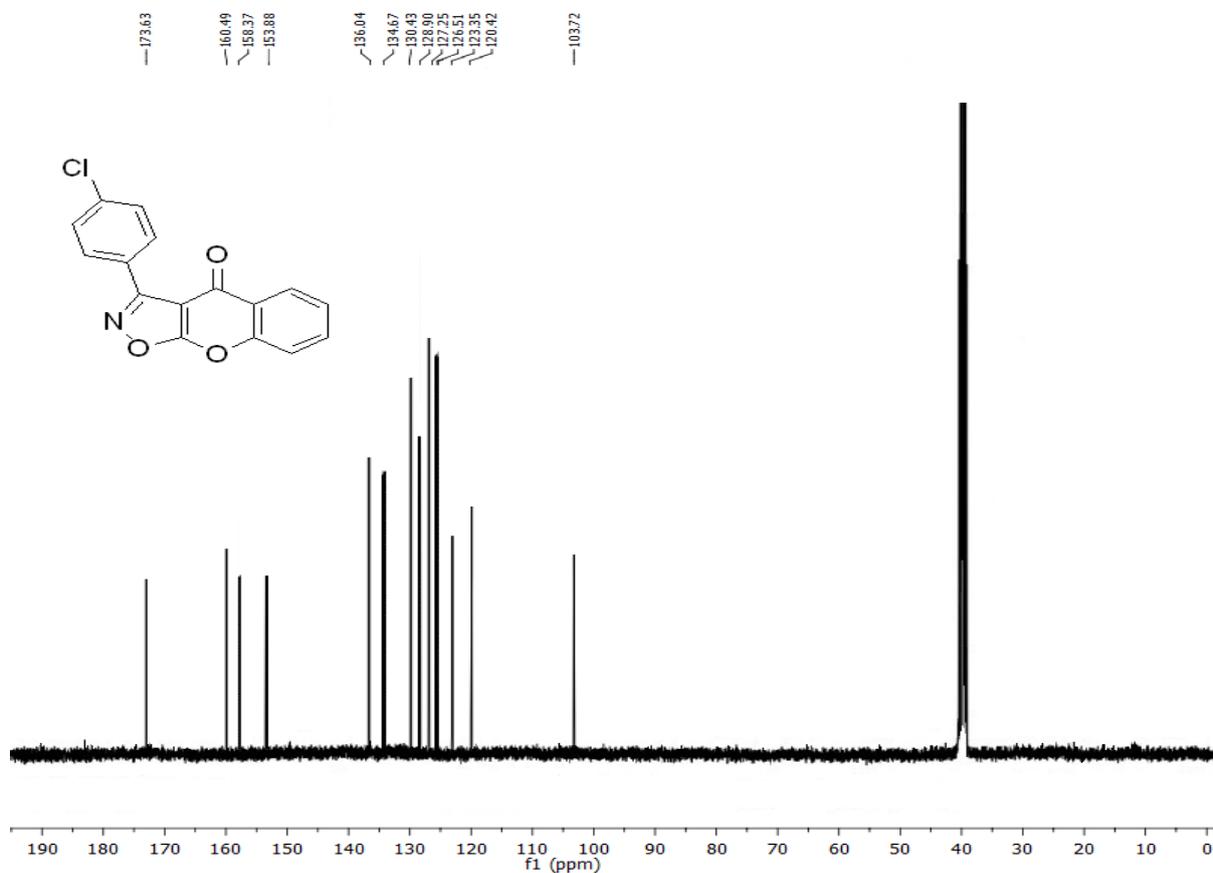
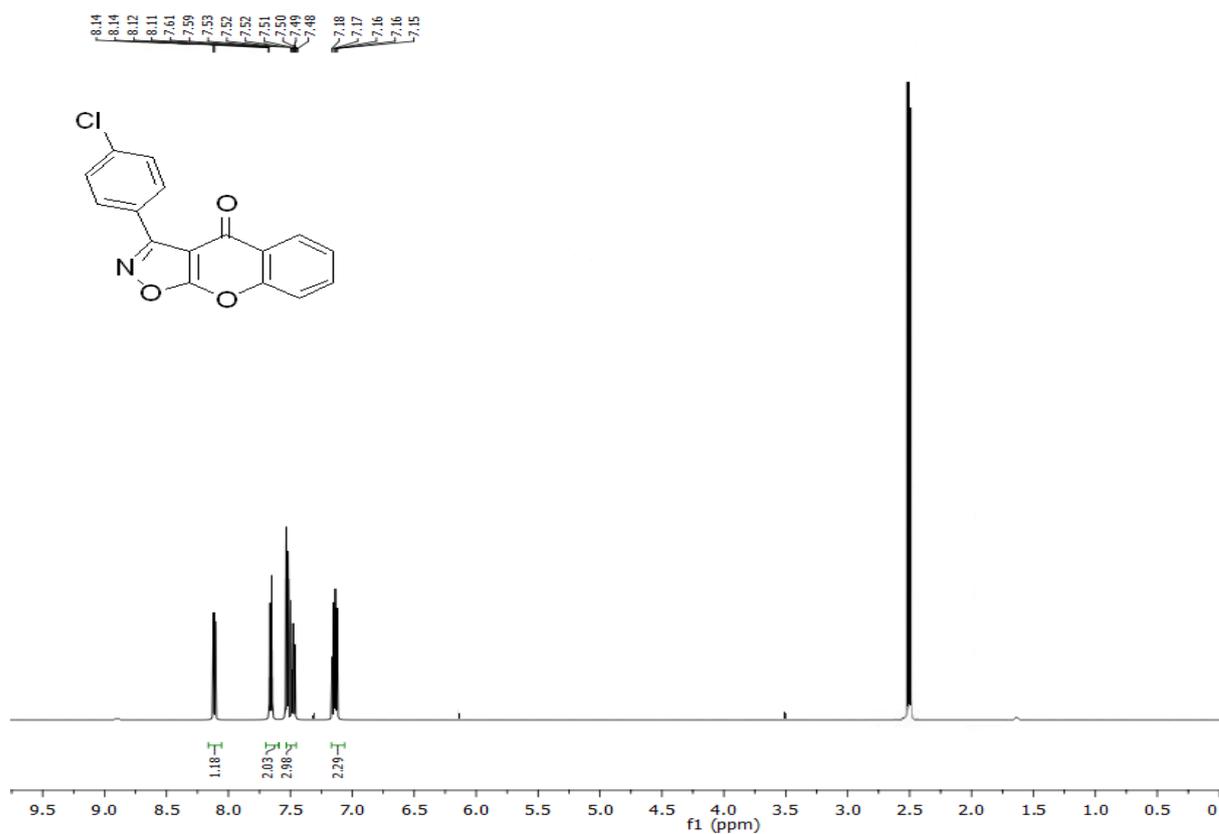


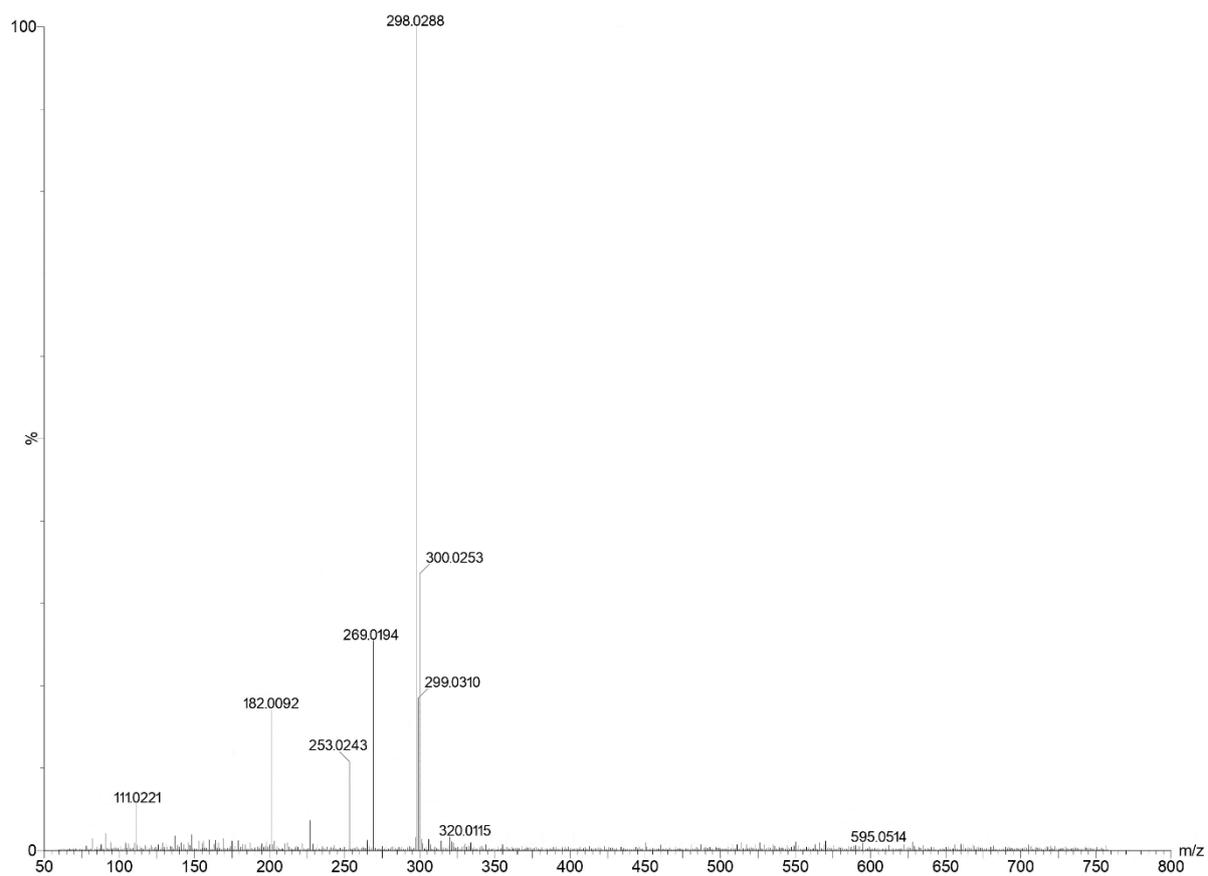
6) 3-(3,4-Dimethylphenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3f):



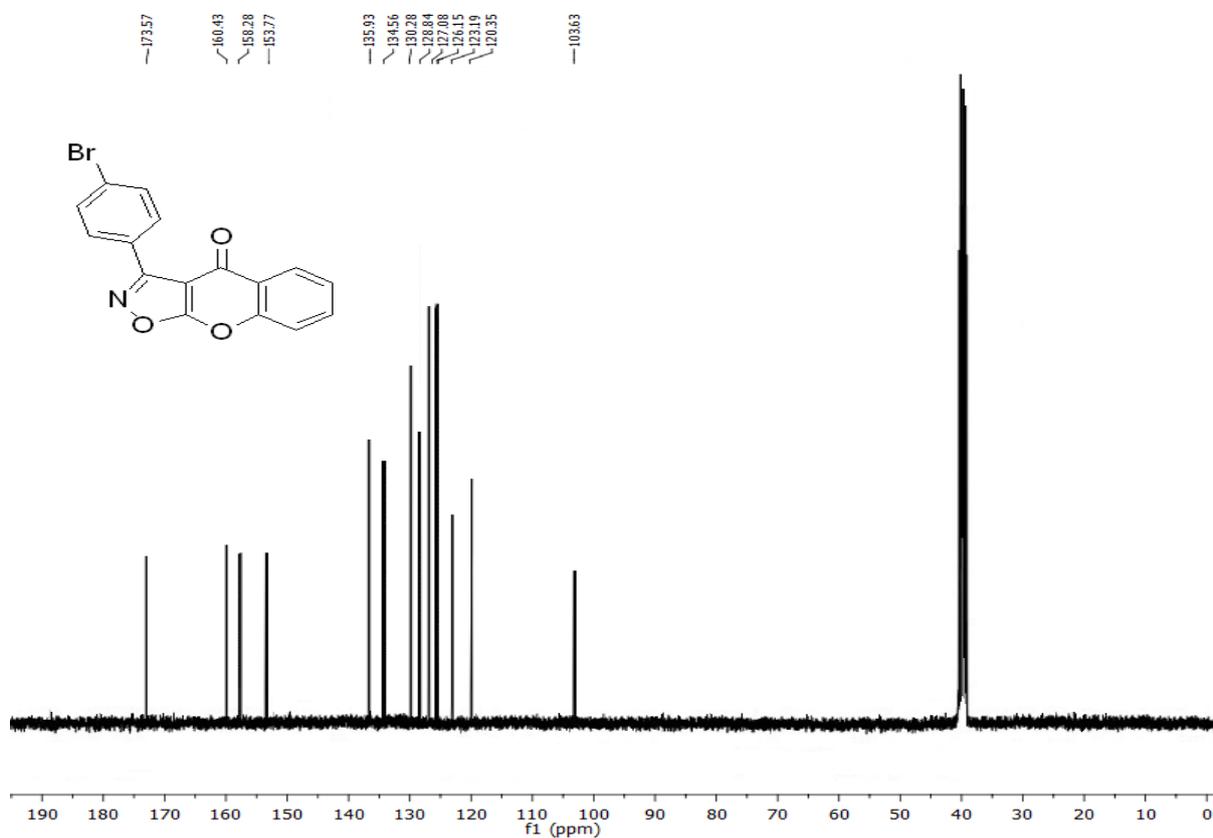
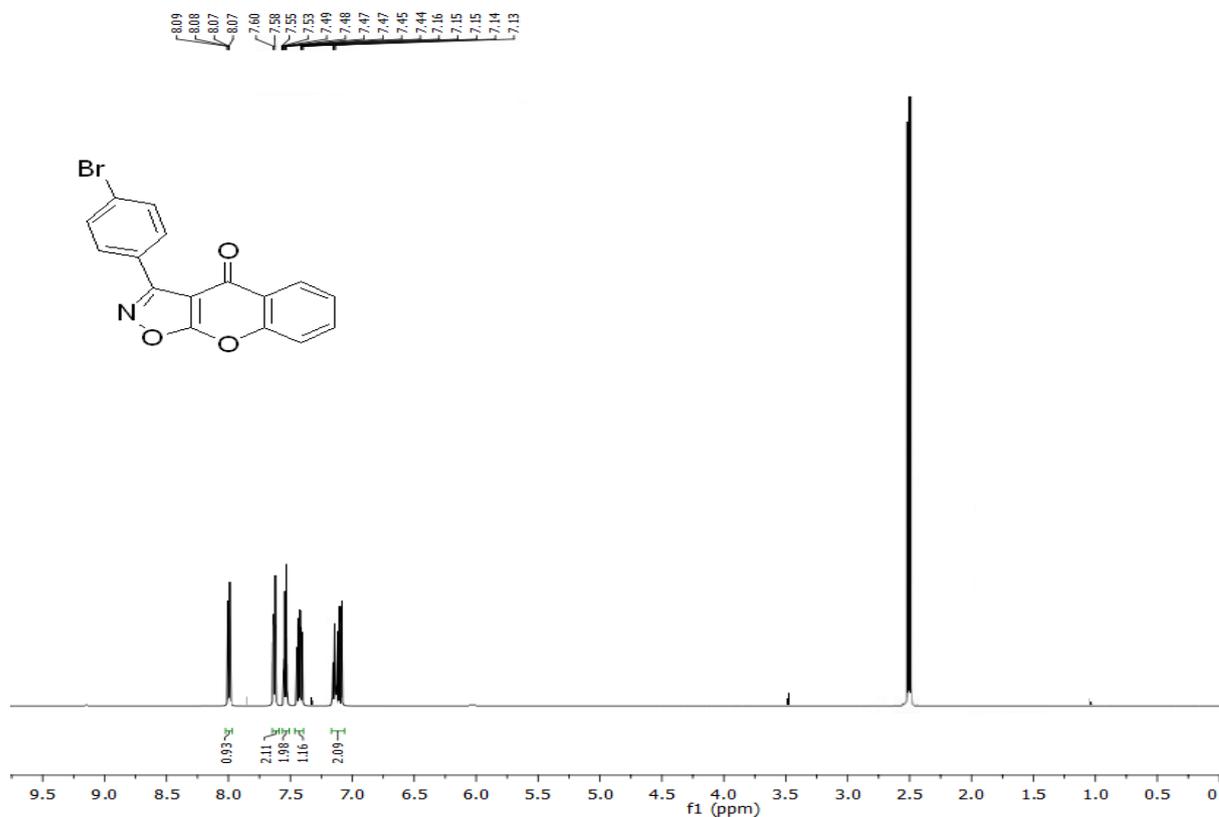


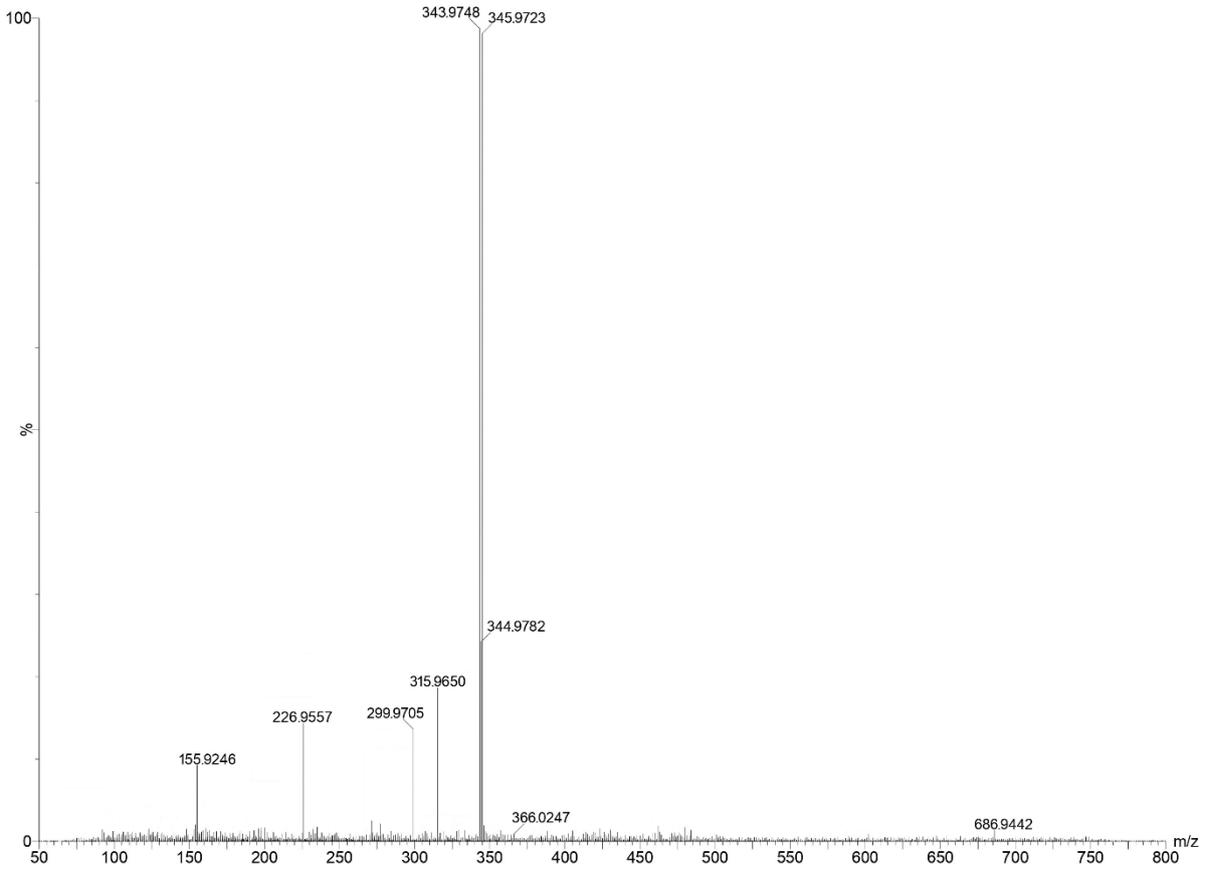
7) 3-(4-Chlorophenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3g):



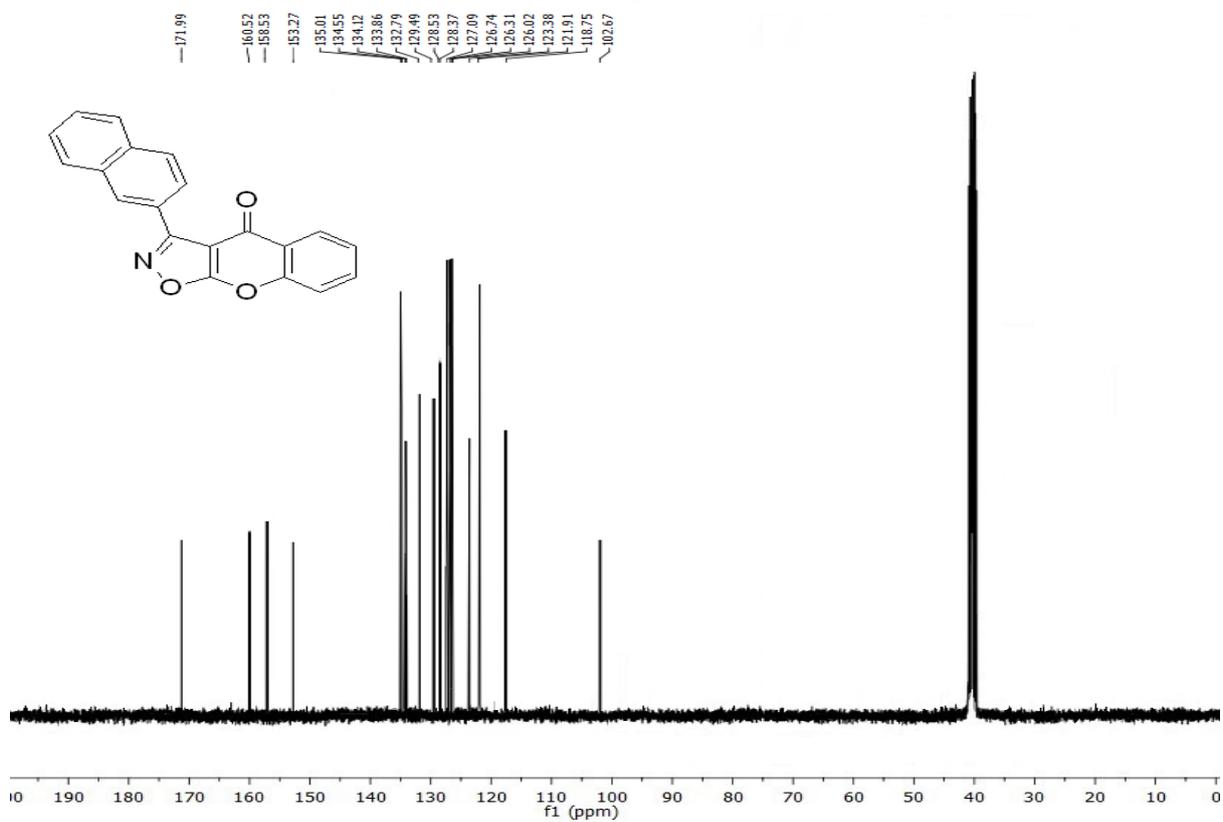
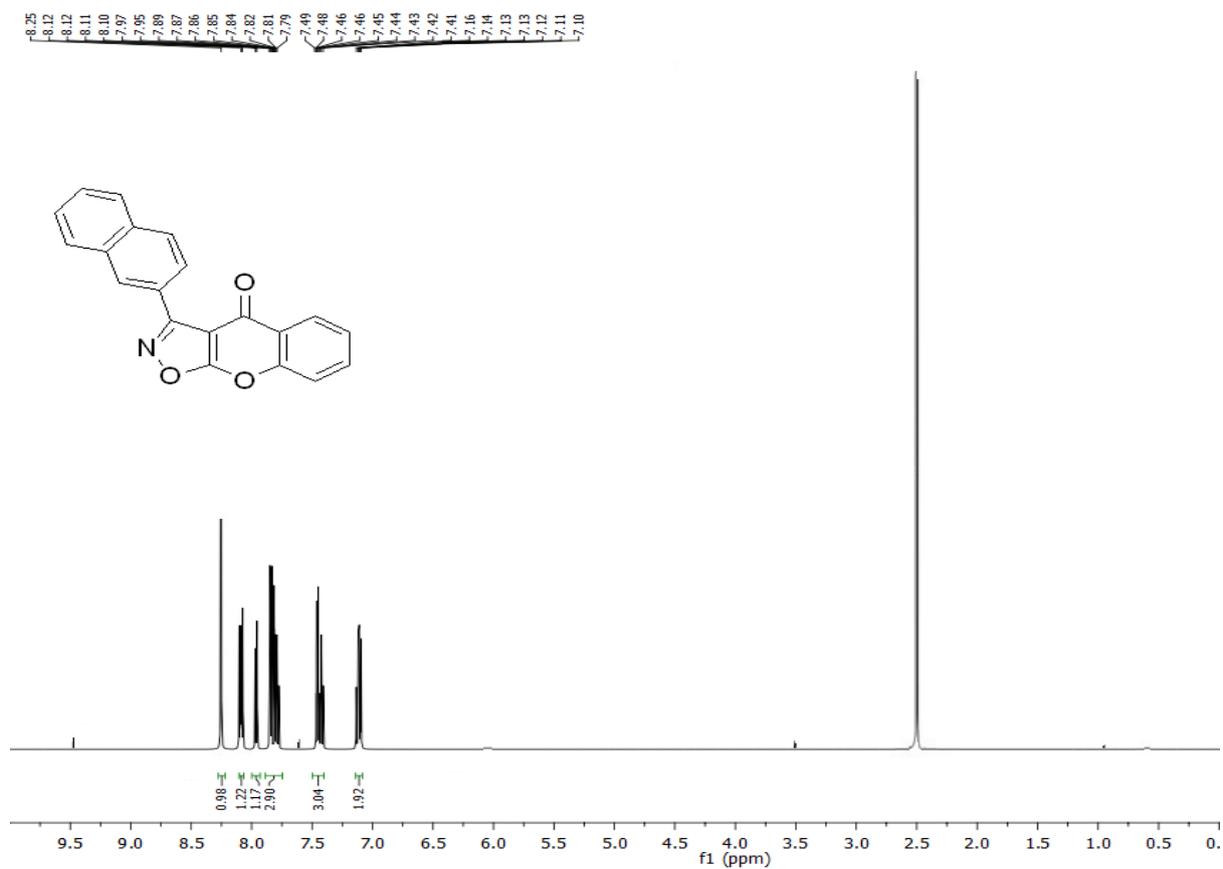


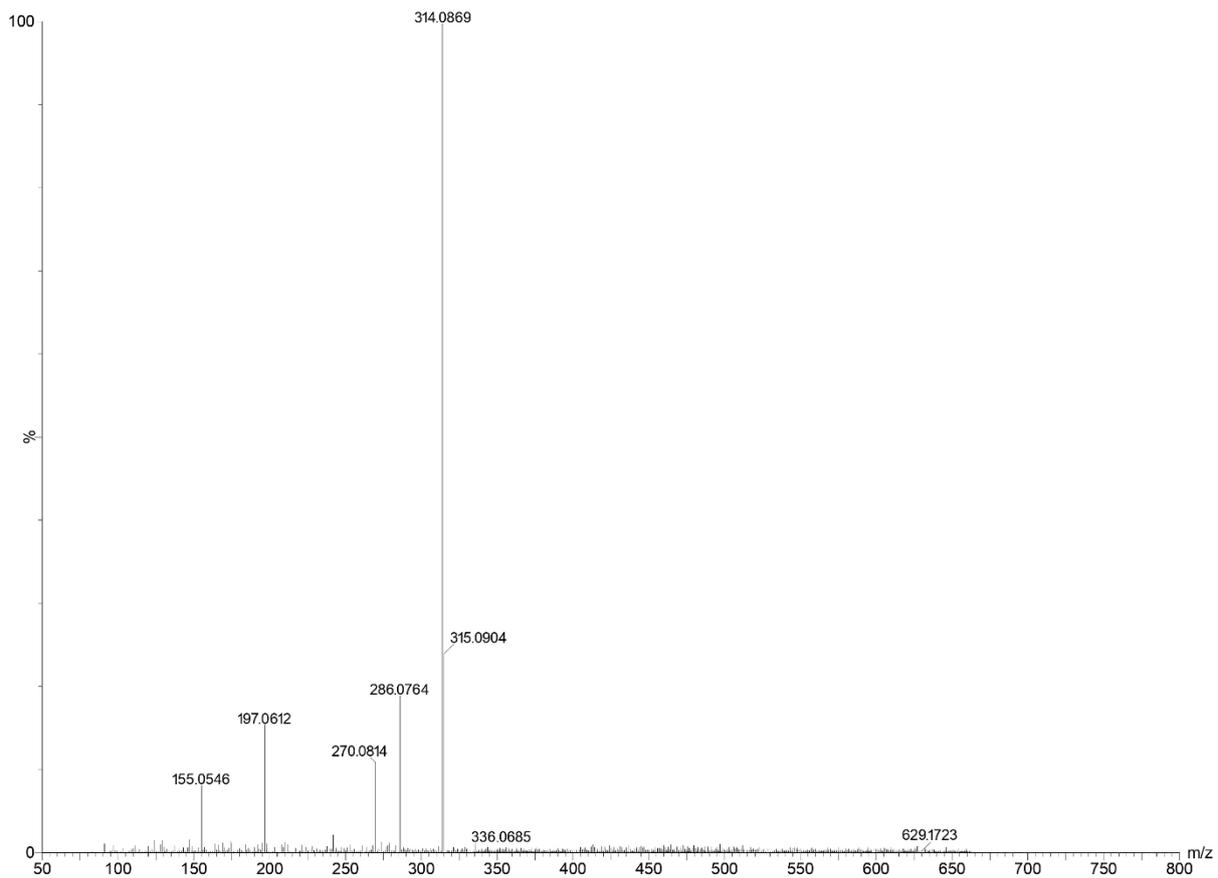
8) 3-(4-Bromophenyl)-4H-chromeno[3,2-d]isoxazol-4-one (3h):



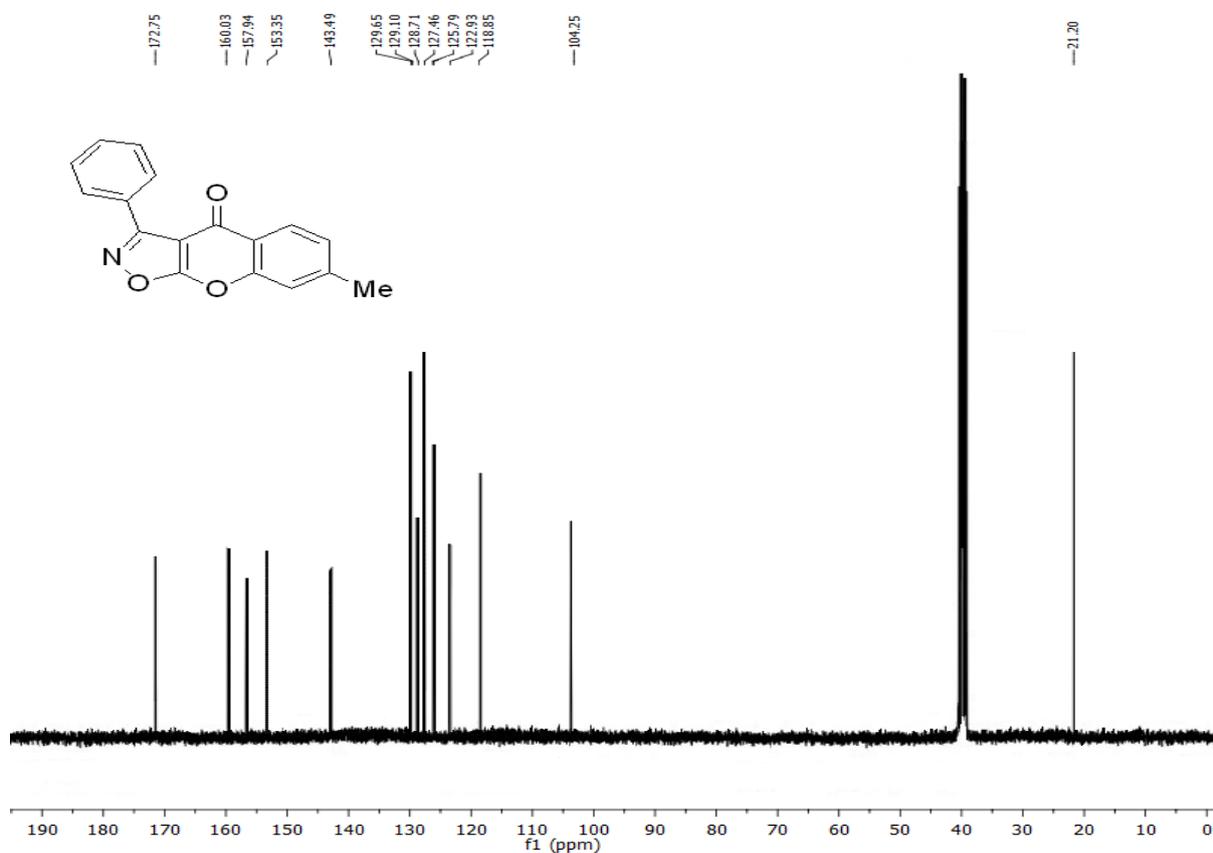
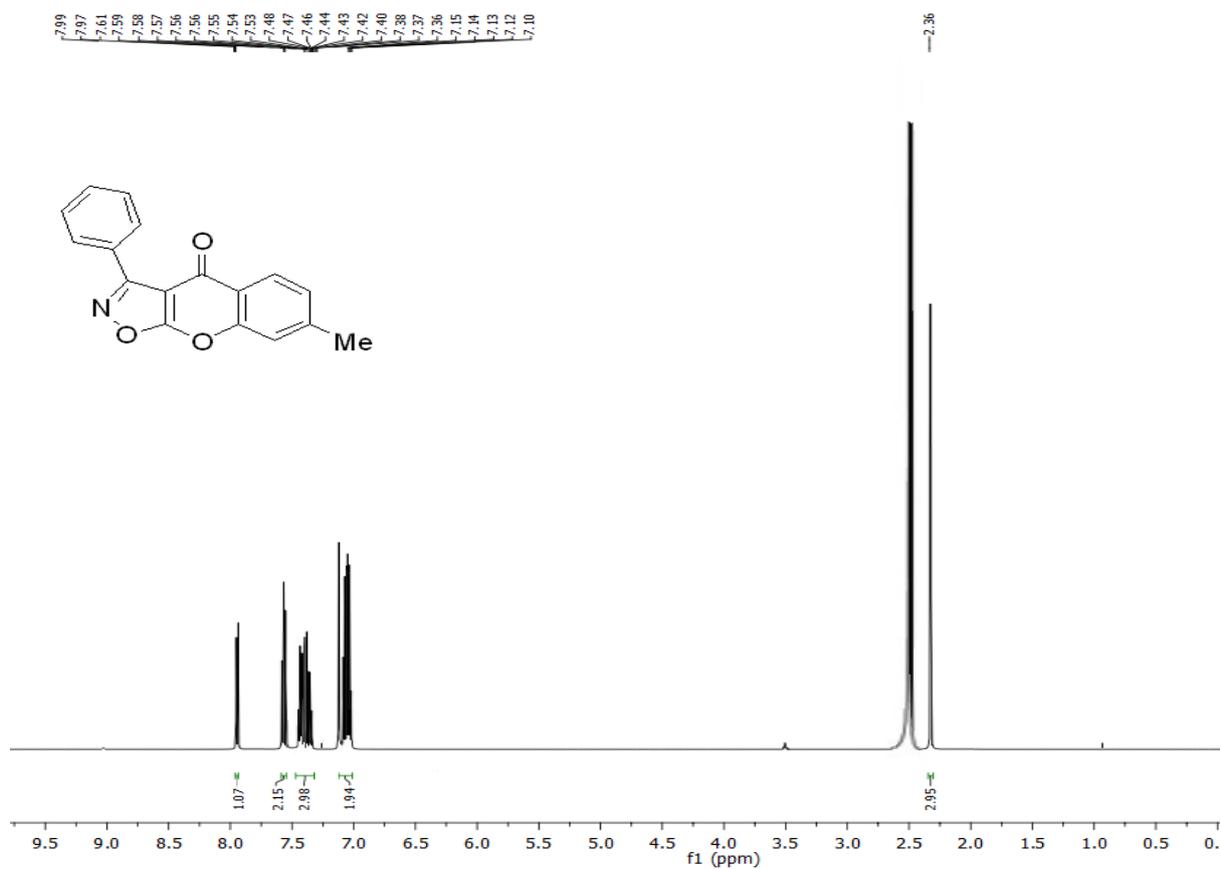


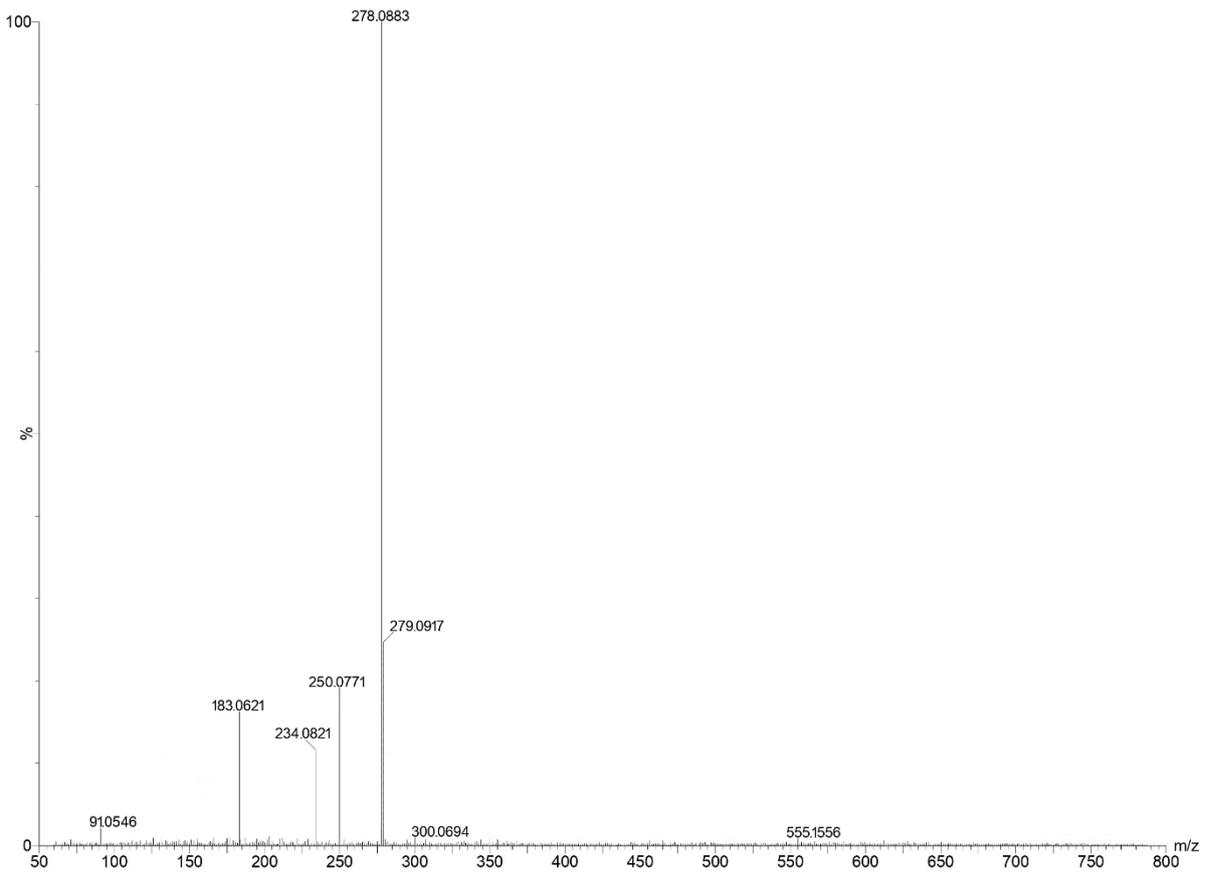
9) 3-(Naphthalen-2-yl)-4H-chromeno[3,2-d]isoxazol-4-one (3i):



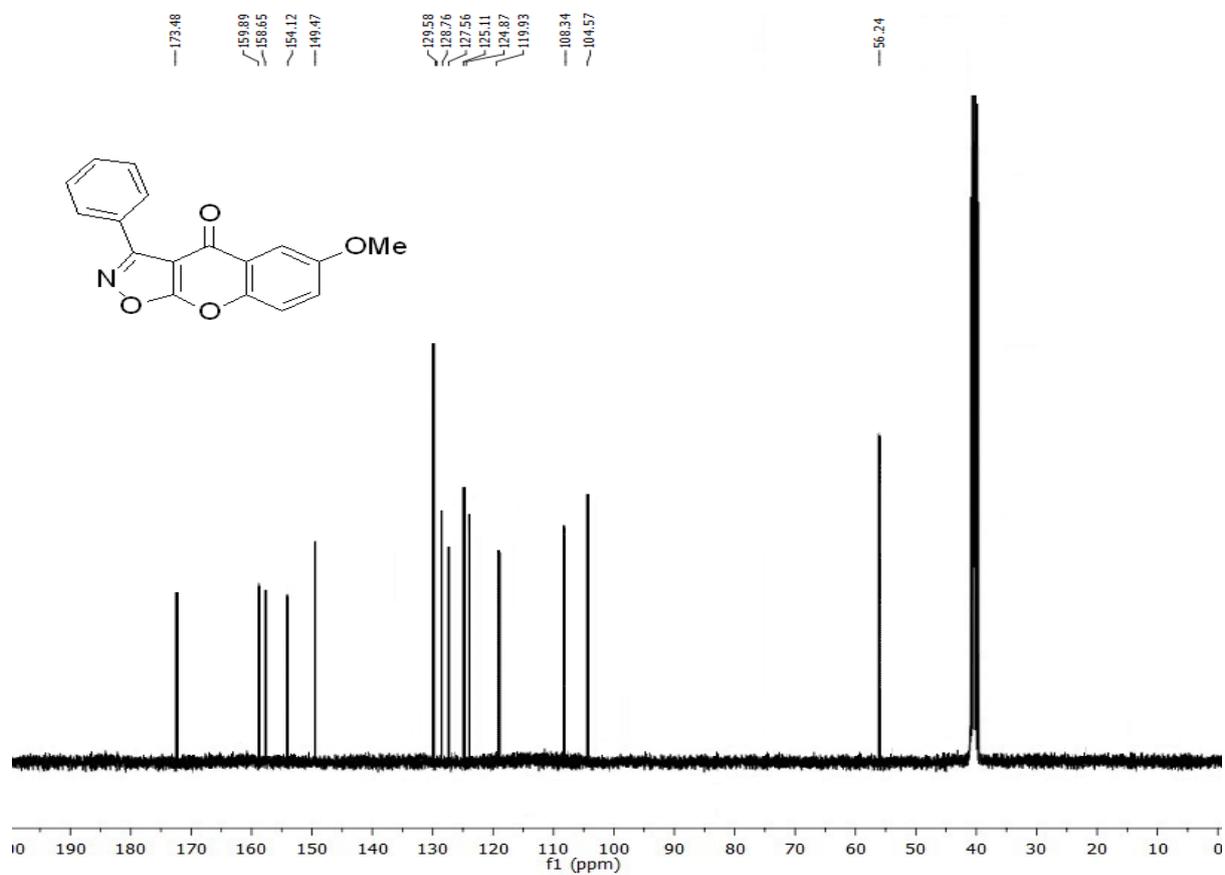
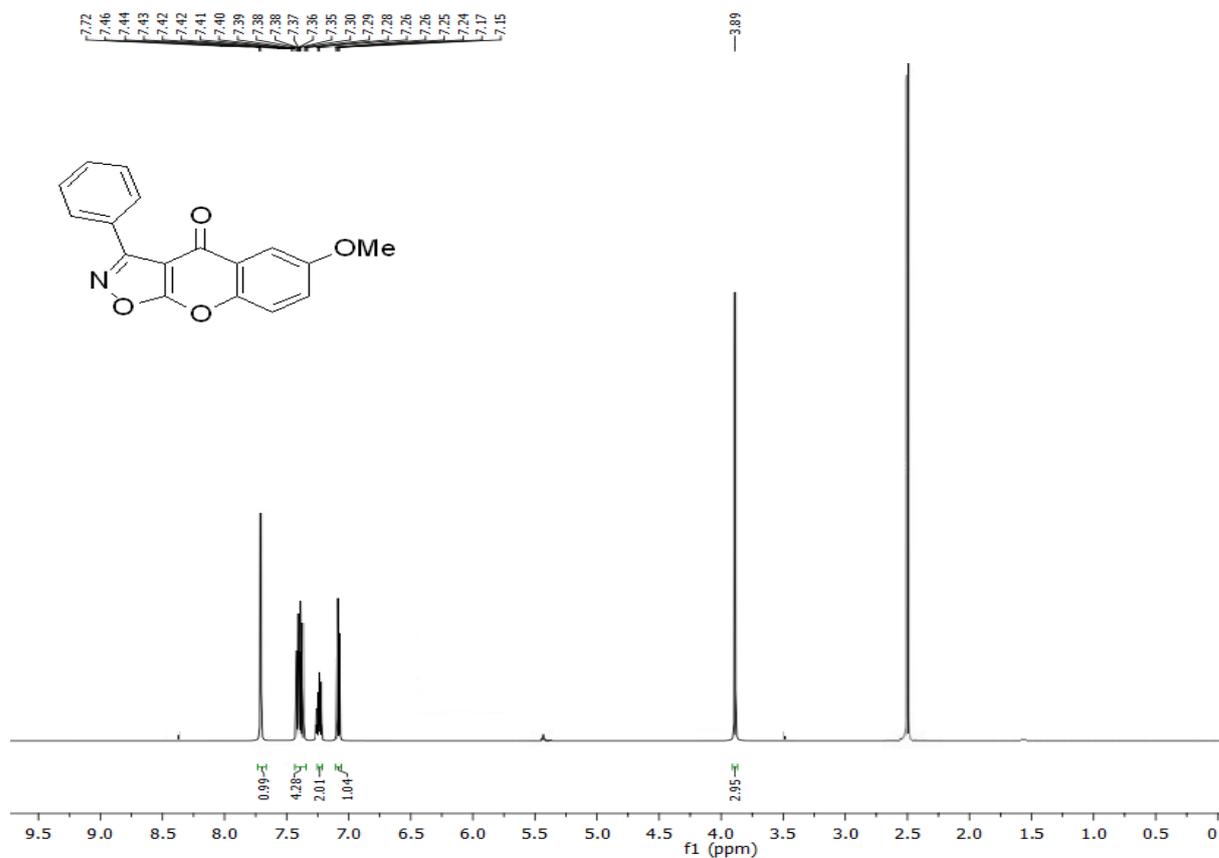


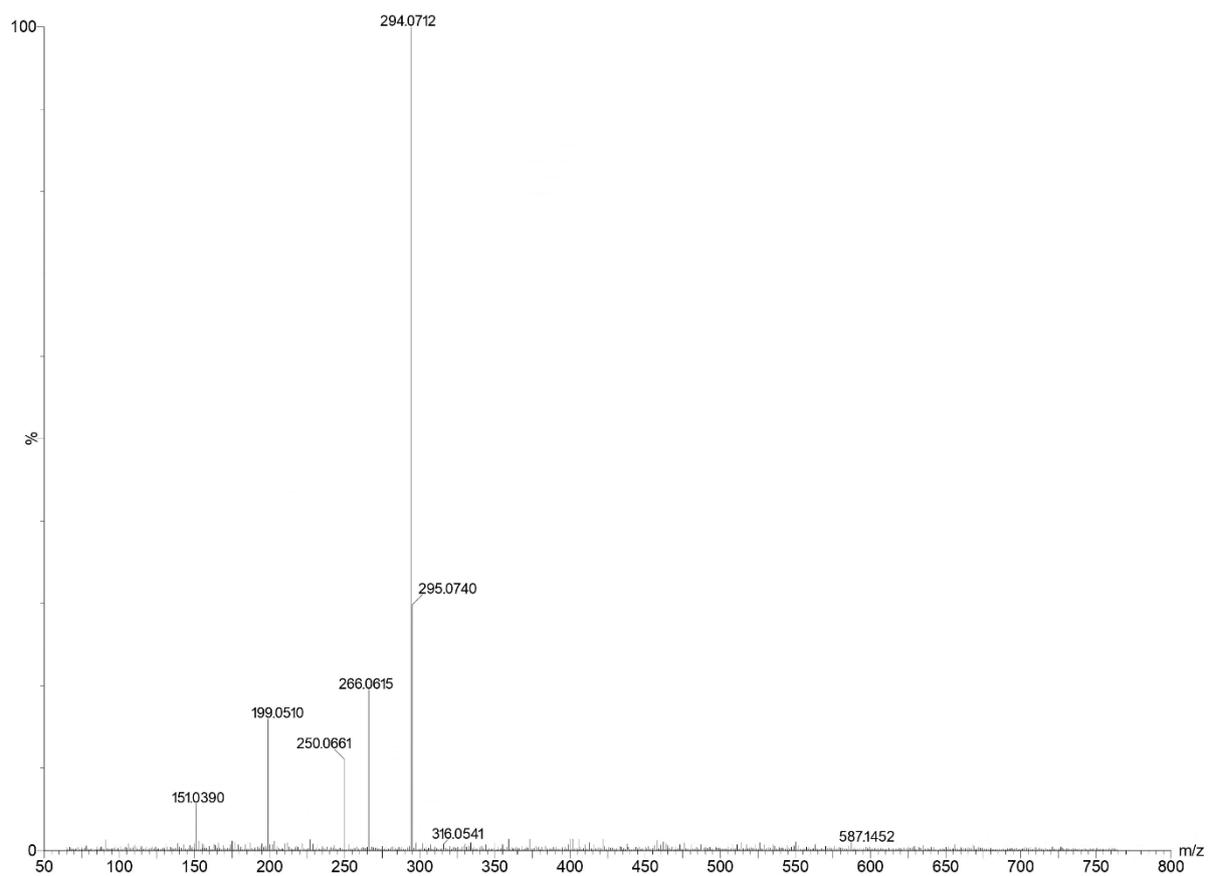
10) 7-Methyl-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3j):



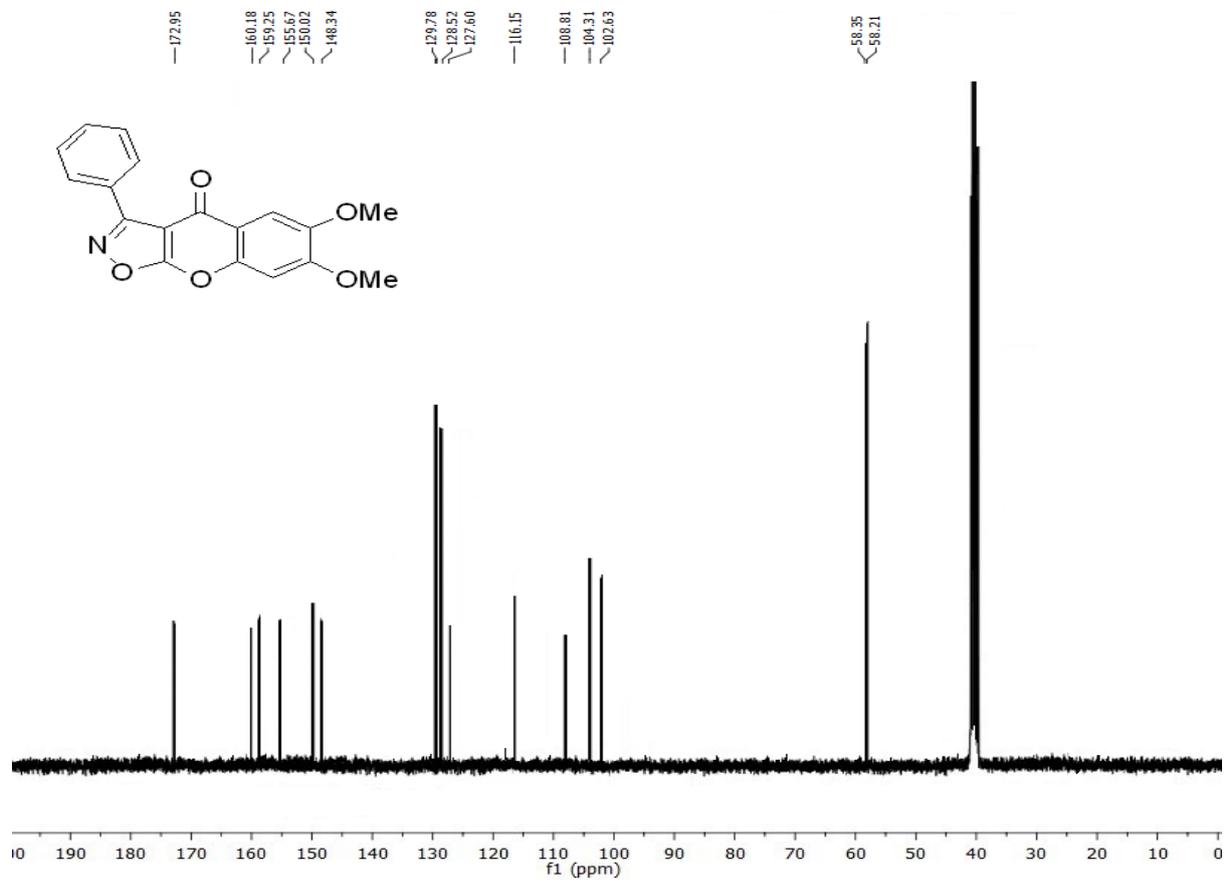
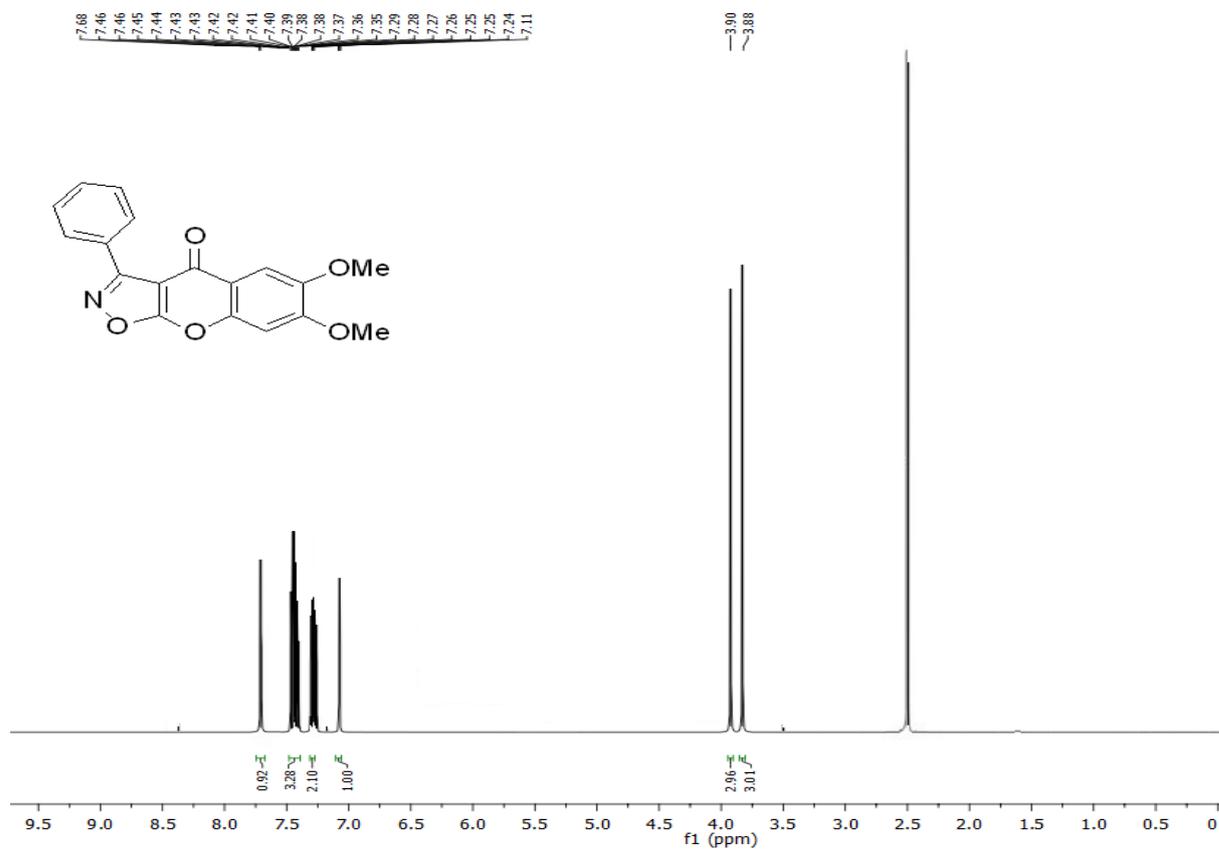


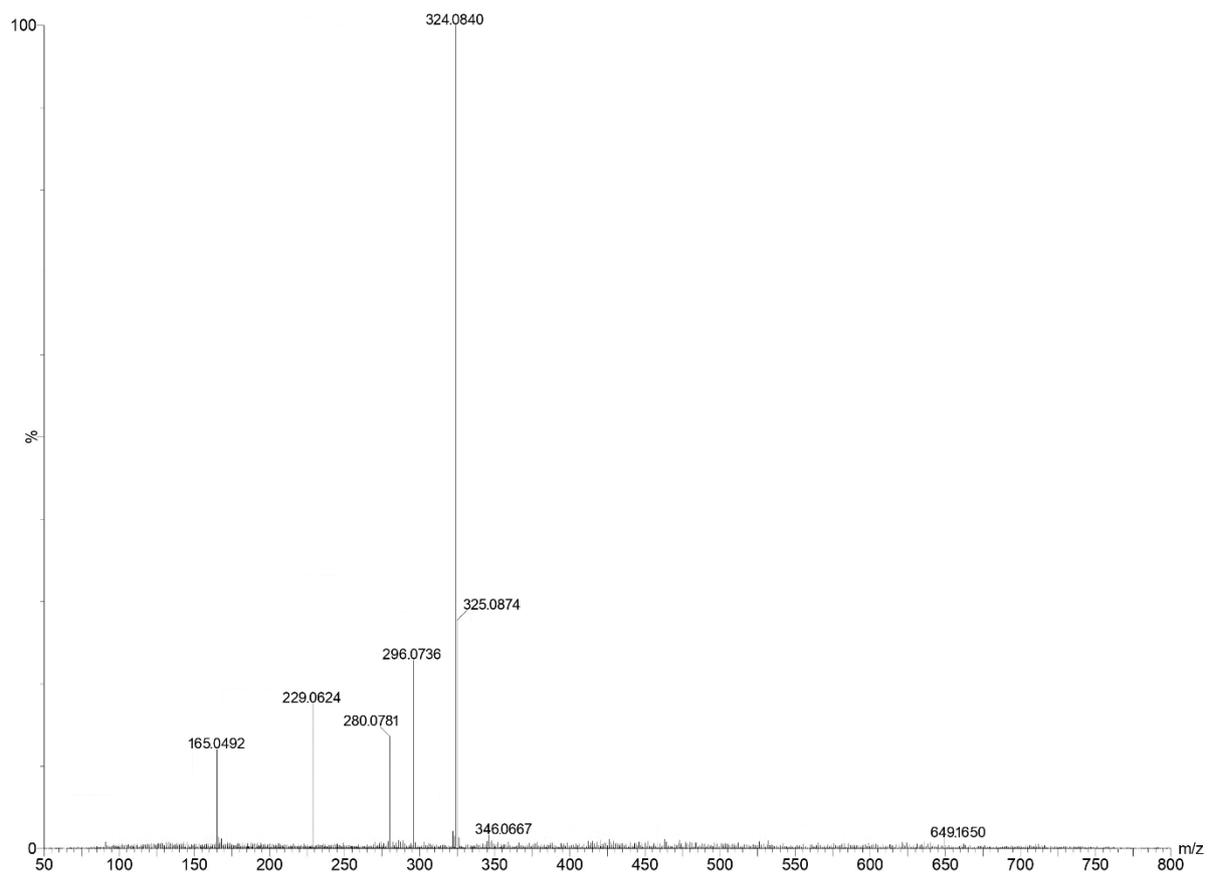
11) 6-Methoxy-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3k):



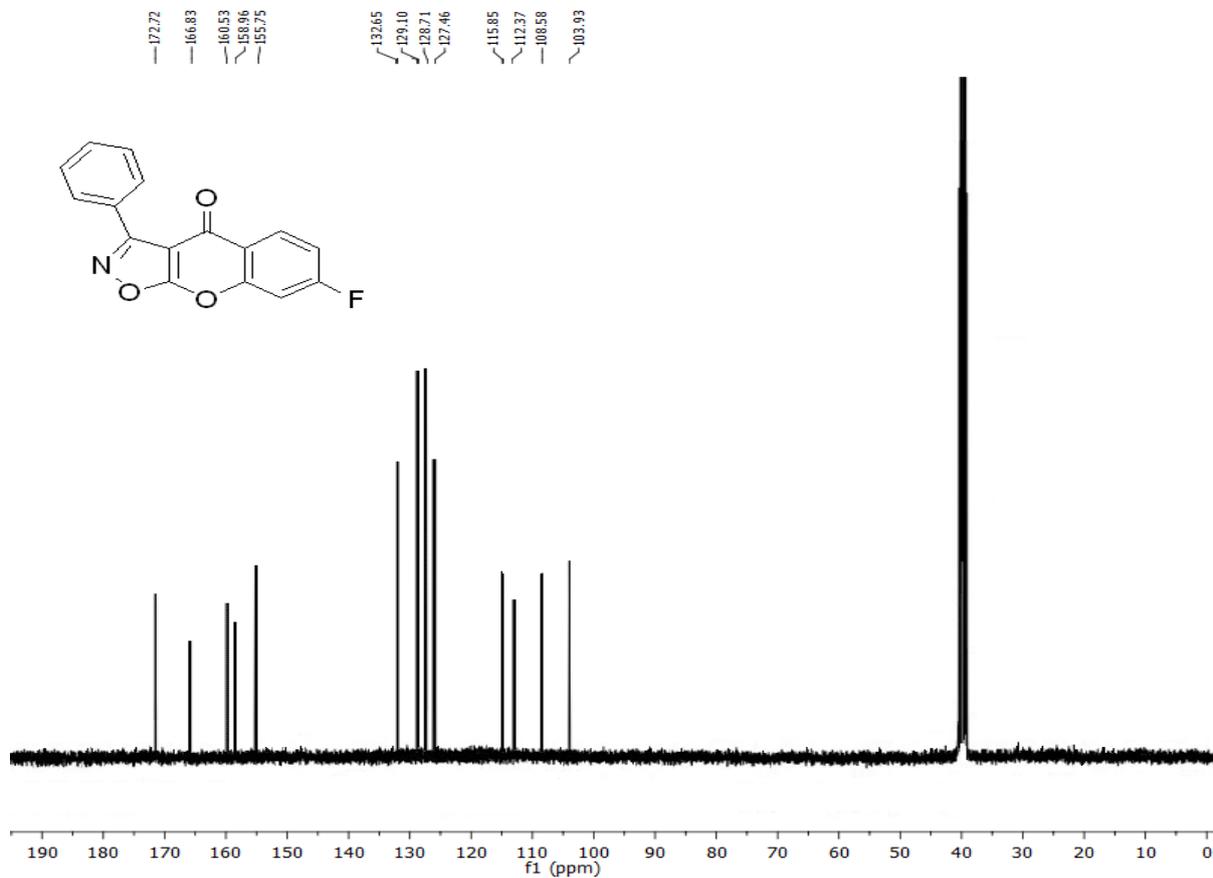
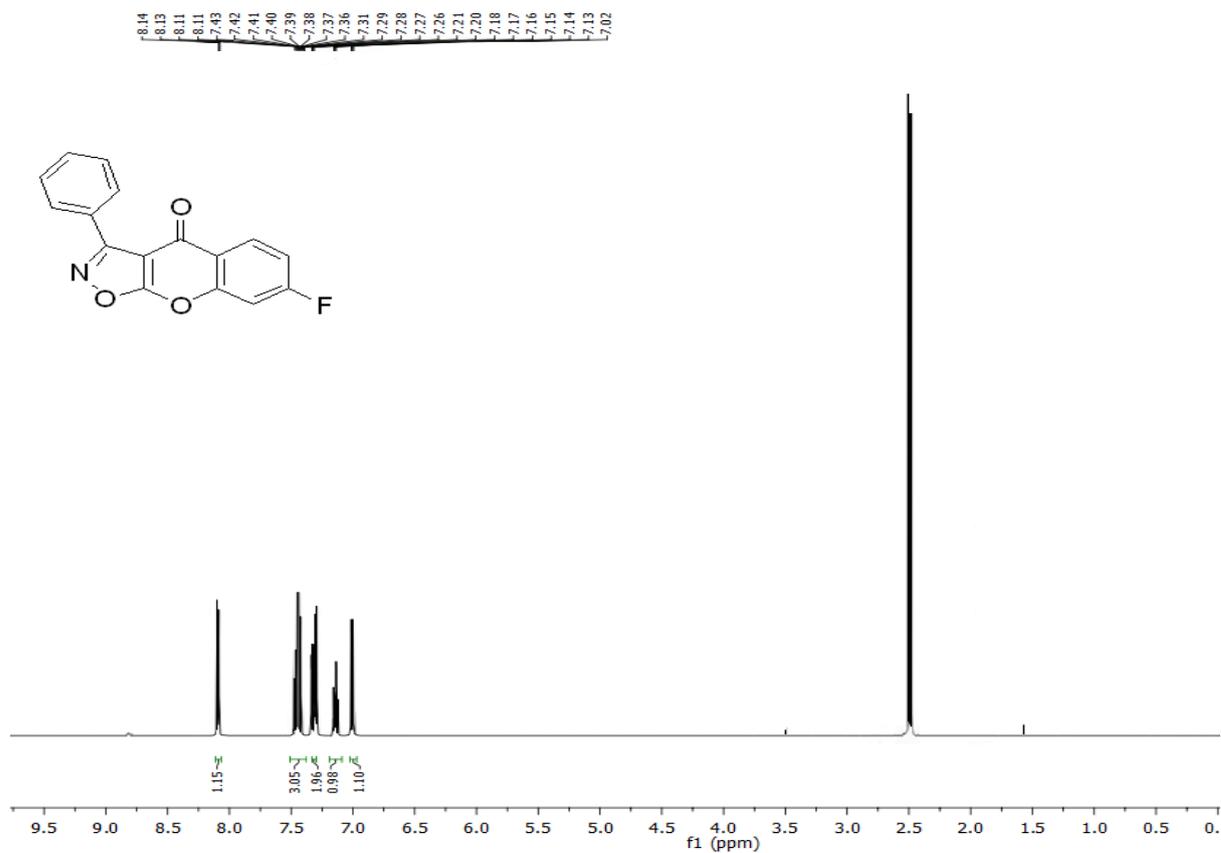


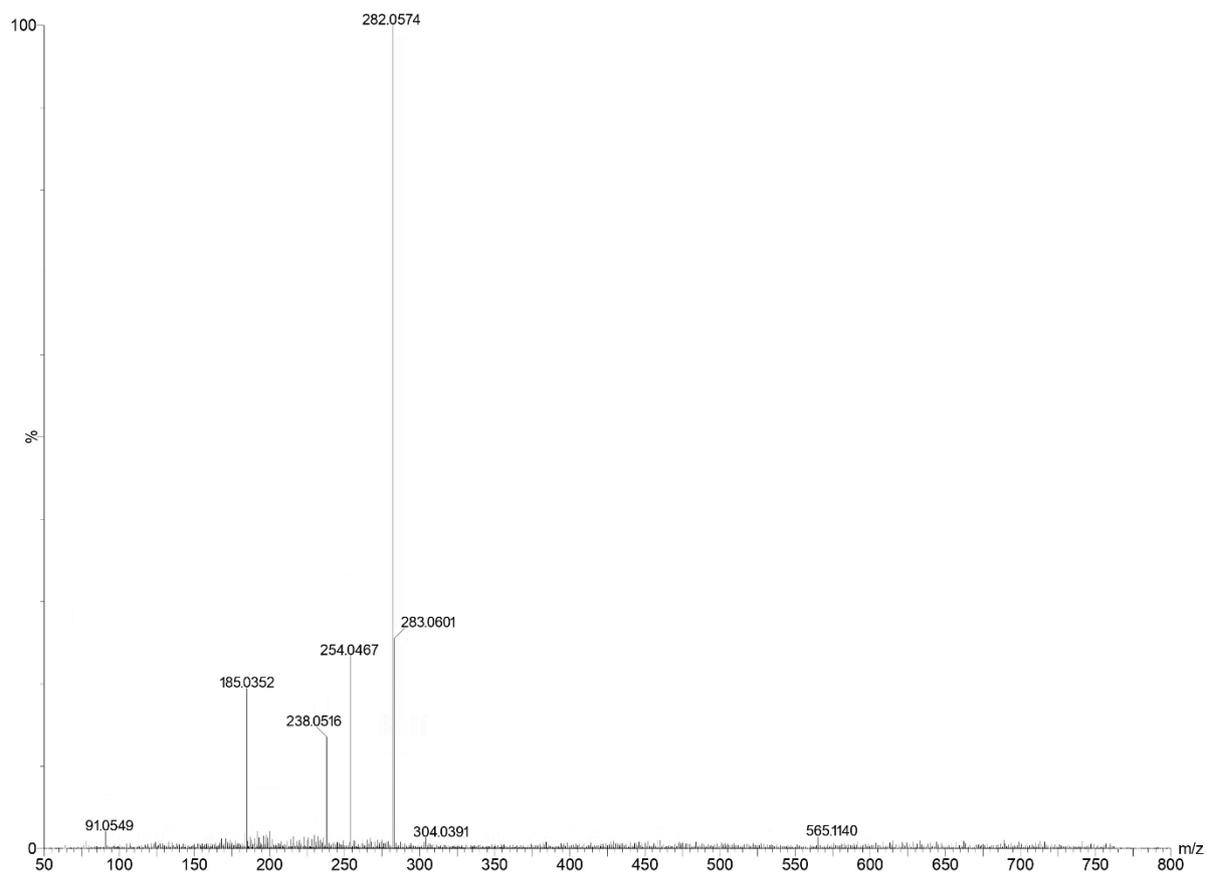
12) 6,7-Dimethoxy-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3I):



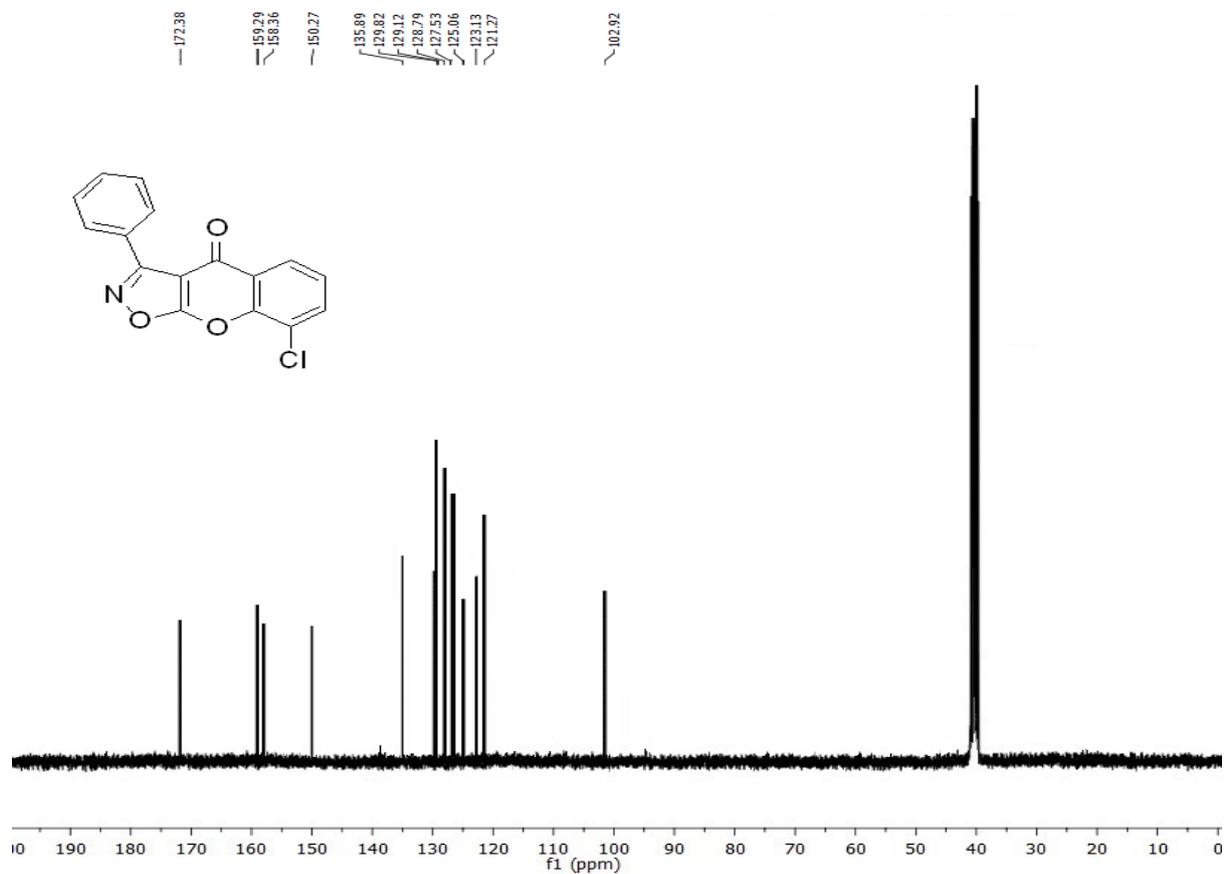
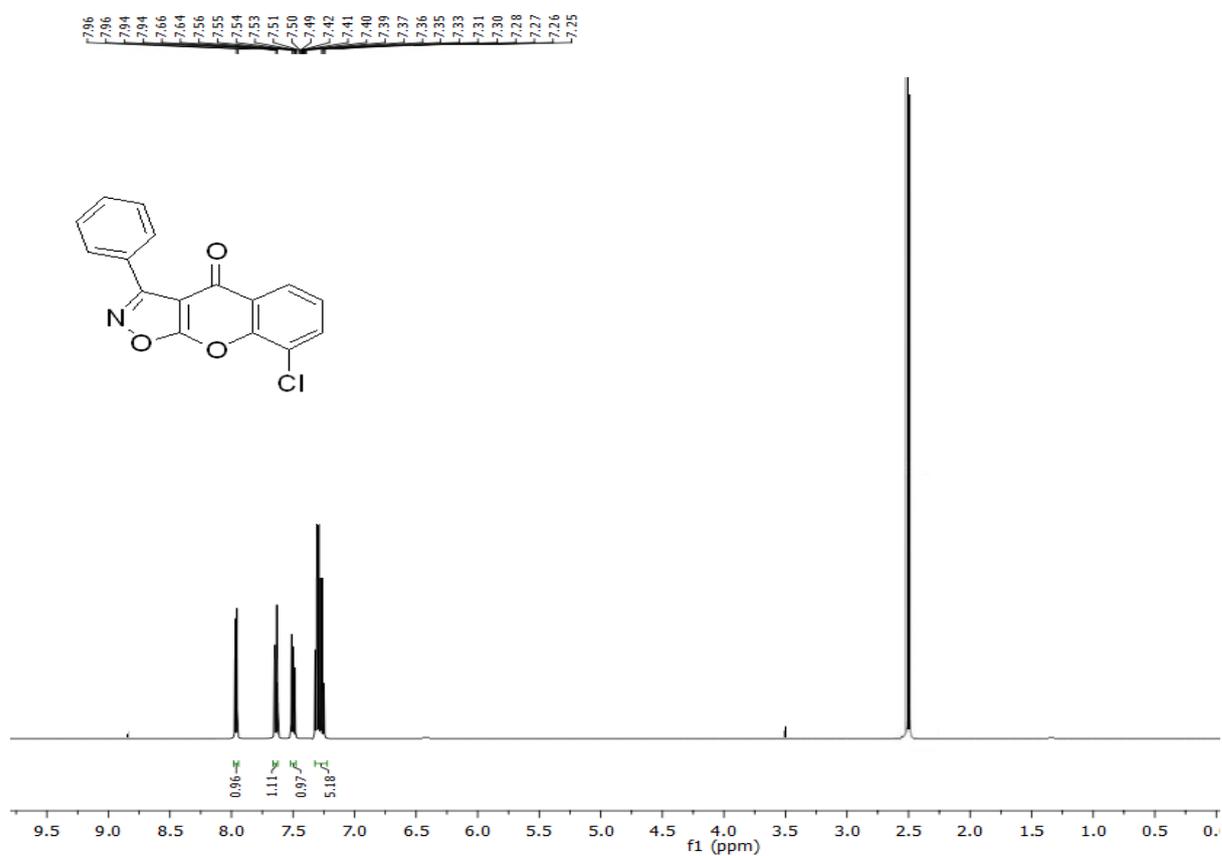


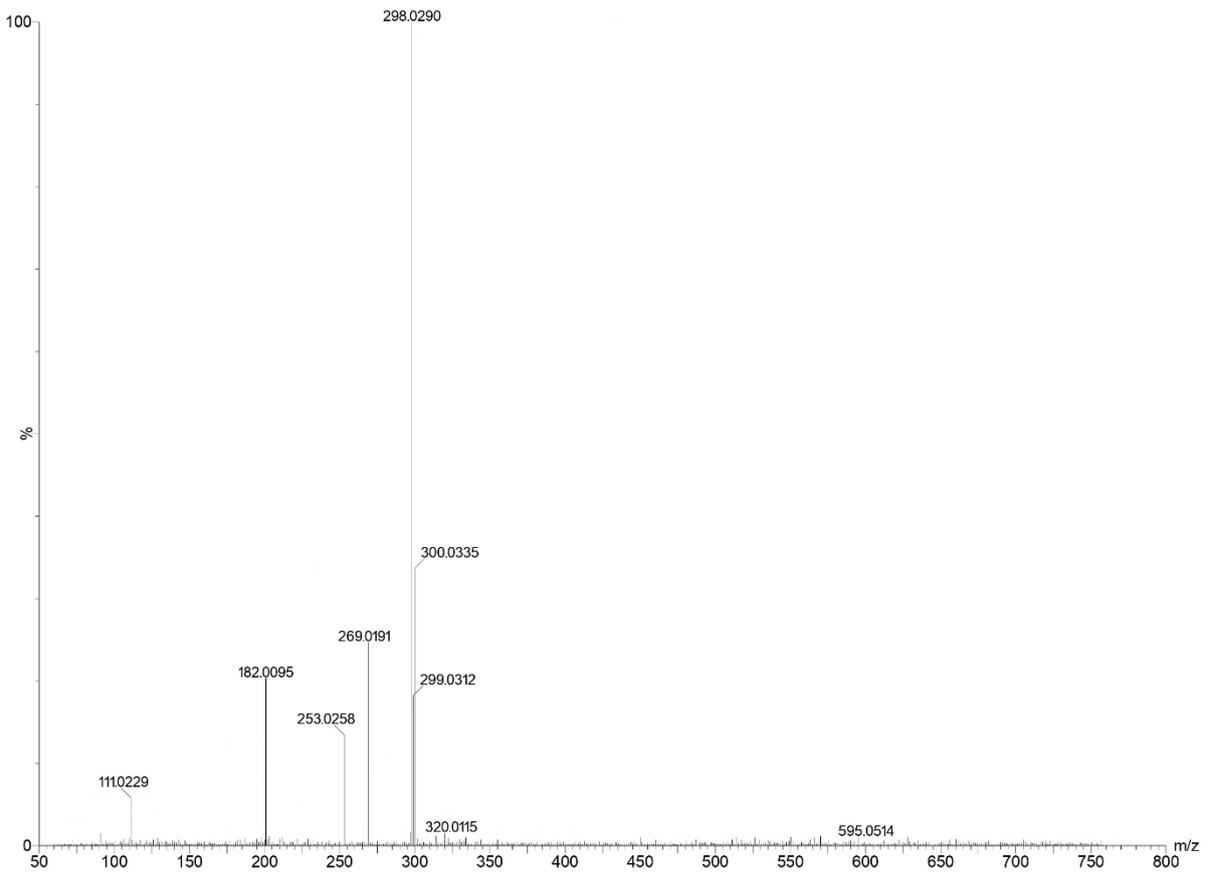
13) 7-Fluoro-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3m):



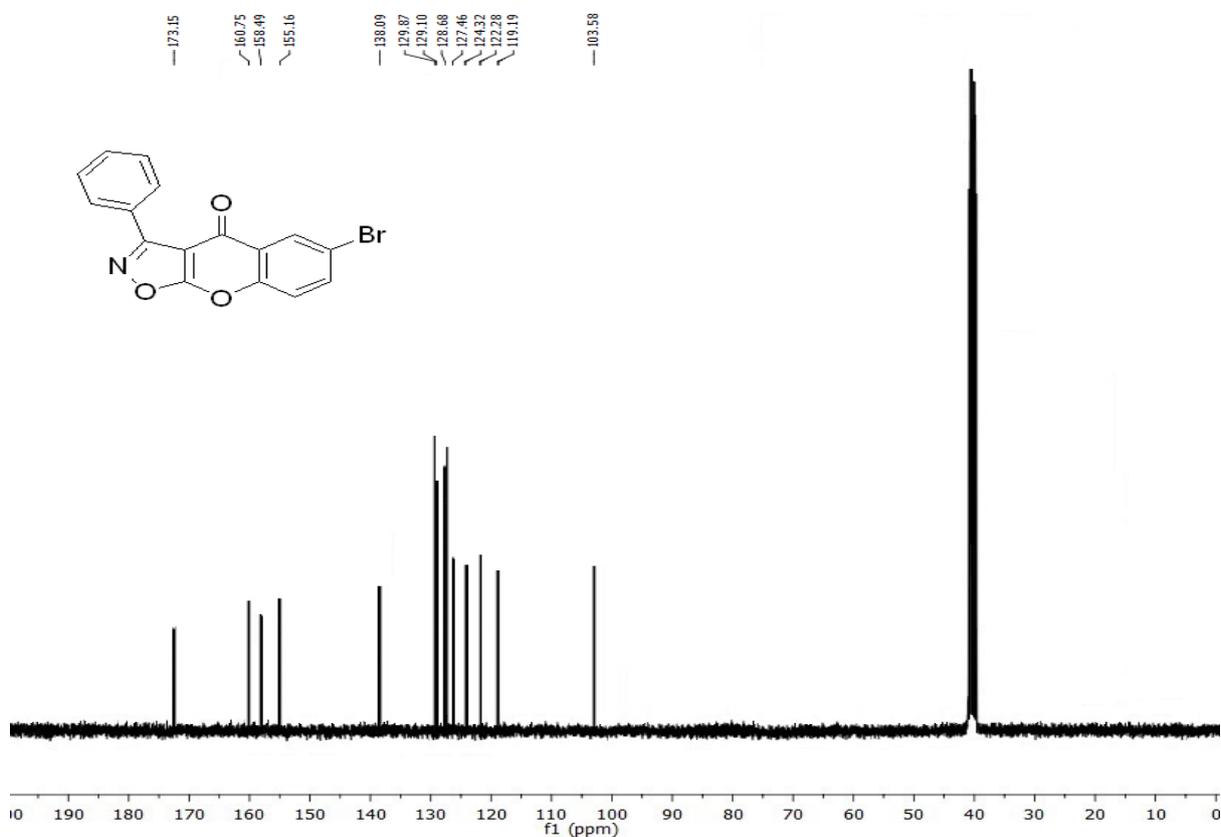
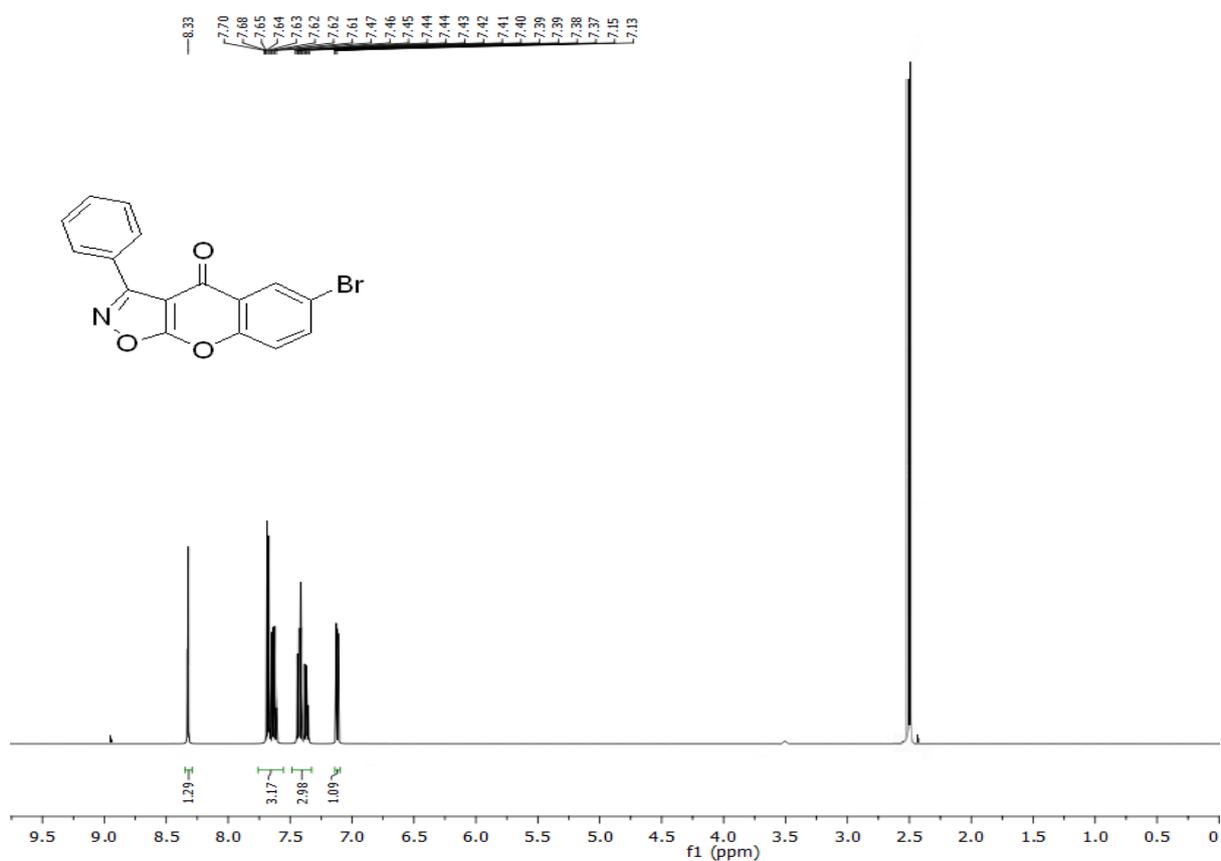


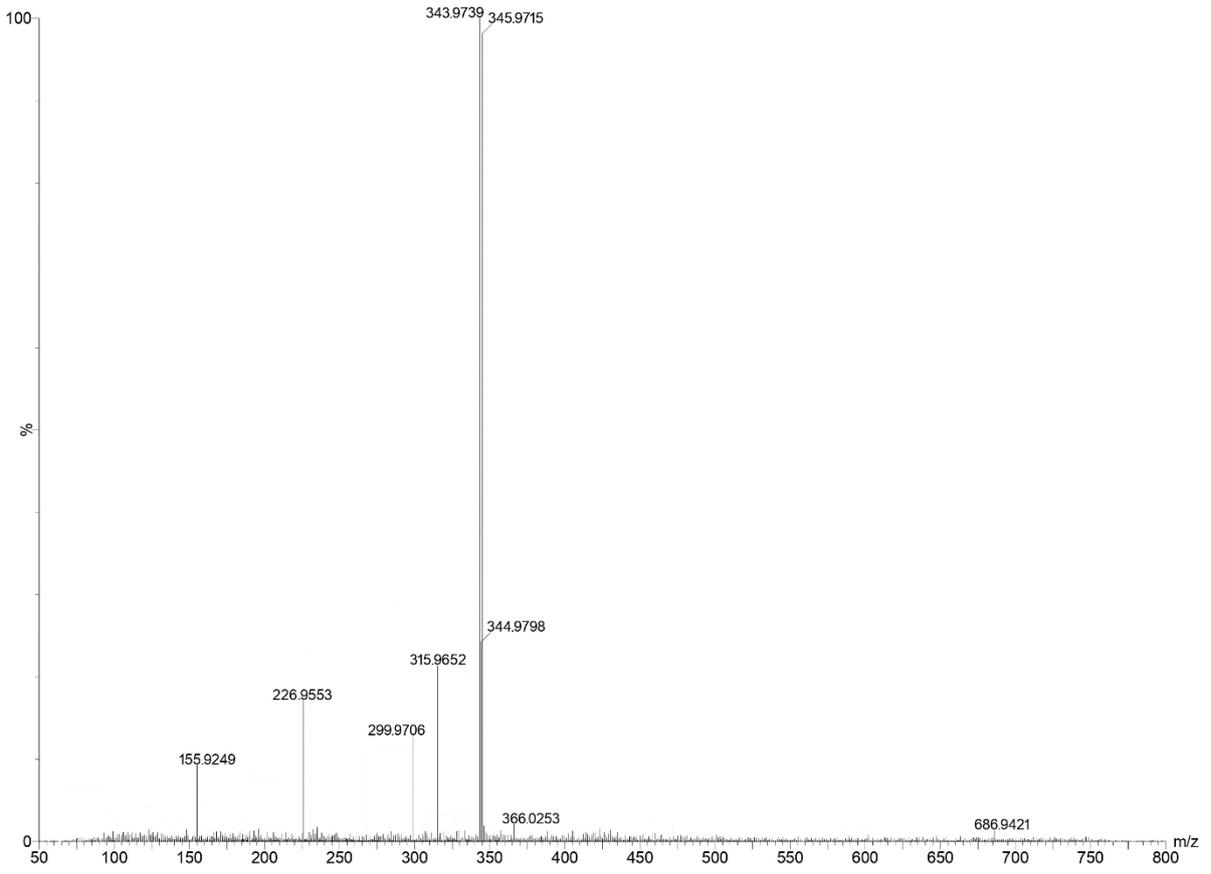
14) 8-Chloro-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3n):





15) 6-Bromo-3-phenyl-4H-chromeno[3,2-d]isoxazol-4-one (3o):





16) 8-Phenyl-7H-benzo[7,8]chromeno[3,2-d]isoxazol-7-one (3p):

