

## **Mannich Reaction Mediated Derivatization of Chromones and Their Biological Evaluations as Putative Multipotent Ligands for the Treatment of Alzheimer's Disease**

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## Chemistry

### General procedure for the synthesis of hydroxy chromone intermediates

A mixture of 2-Hydroxyacetophenone (1 equiv.), respective hydroxy-benzaldehyde (1 equiv.), and iodine (1 equiv.) were taken in a sealed tube in PEG-400 as solvent and heated at 140 °C for 4 to 7 h. Completion of the reaction was checked by thin-layer chromatography. On completion of the reaction, it was cooled to room temperature, iodine was quenched with 10 % sodium thiosulphate solution and extracted with ethyl acetate. The crude product was purified on silica gel by column chromatography using pet. ether/ethyl acetate (3:1 to 6:1) as eluent to give the desired product (70-84 % yield).

### General procedure for the synthesis of Mannich intermediates

A mixture of paraformaldehyde (7 mmol) and secondary amines (3 mmol) were kept on heating at 80 °C for 1 h in ethanol. The synthesized chromone derivative (1 mmol) dissolved in ethanol was mixed to the above solution of imine. The reaction mixture was heated at 80 °C for 5-7 h to give the Mannich product as intermediate. Progress of the reaction was monitored using TLC plate. After completion of the reaction, ethanol was evaporated and water was added to the crude product. Aqueous layer was extracted with ethyl acetate thrice. Organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum using a rotary evaporator. Crude product was used for next step after column chromatography to purify the compounds using ethyl acetate-pet ether as eluent.

### General procedure for the synthesis of *O*-alkylated chromone derivatives

To the solution of hydroxy-substituted Mannich intermediates (1 mmol) solubilized in minimum amount of DMF, alkyl halide (1.1 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.2 mmol) was added. The reaction mixture (RM) was heated at 80 °C and progress of the reaction was monitored using TLC plate. After completion of the reaction, water was added to the crude product. Aqueous layer was extracted with ethyl acetate thrice. Organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum using a rotary evaporator. The crude product was purified through column chromatography using acetone-pet ether as eluent to get the desired product. HRMS and NMR analysis was done for the characterization of synthesized compounds.

## Characteristic spectral data of the products

### **2-(3-methoxy-5-(morpholinomethyl)-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-1)**

White solid, 72 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (dd,  $J$ = 6 Hz, 1.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.61 (d,  $J$ = 1.8 Hz, 1H), 7.59 (d,  $J$ = 8.4 Hz, 1H), 7.43 (t,  $J$ = 7.2 Hz, 1H), 7.35 (d,  $J$ = 1.8 Hz, 1H), 6.79 (s, 1H), 4.15 (t,  $J$ = 6.0 Hz, 2H), 3.95 (s, 3H), 3.73 (t,  $J$ = 4.8 Hz, 4H), 3.61 (s, 2H), 2.52 (s, 4H), 2.49 (td,  $J$ = 2.4 Hz, 4.8 Hz, 2H), 2.03 (quintet,  $J$ = 6.0 Hz, 2H), 1.99 (t, 2.4 Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 163.3, 156.2, 153.1, 149.9, 133.6, 132.6, 127.0, 125.7, 125.2, 123.9, 121.1, 118.1, 108.9, 107.3, 83.8, 71.6, 68.8, 67.0, 56.9, 55.9, 53.7, 29.2, 15.2. HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  for  $\text{C}_{26}\text{H}_{27}\text{NO}_5$ , Calculated 434.1962; observed 434.1972.

### **2-(3-methoxy-5-(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-2)**

Off-white solid, 66 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (dd,  $J$ = 6.6 Hz, 1.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.63 (d,  $J$ = 1.8 Hz, 1H), 7.59 (d,  $J$ = 7.8 Hz, 1H), 7.42-7.45 (m, 1H), 7.36 (d,  $J$ = 1.8 Hz, 1H), 6.80 (s, 1H), 4.84 (d,  $J$ = 2.4 Hz, 2H), 3.97 (s, 3H), 3.73 (t,  $J$ = 4.8 Hz, 4H), 3.68 (s, 2H), 2.54 (s, 4H), 2.48 (t,  $J$ = 2.4 Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 163.2, 156.2, 153.0, 148.2, 133.7, 133.5, 127.7, 125.7, 125.2, 123.9, 120.8, 118.1, 108.8, 107.4, 79.1, 75.5, 67.1, 60.2, 57.1, 56.0, 53.6. HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  for  $\text{C}_{24}\text{H}_{23}\text{NO}_5$ , Calculated 406.1649; observed 406.1655.

### **2-(4-(but-3-yn-1-yloxy)-3-methoxy-5-(morpholinomethyl)phenyl)-4H-chromen-4-one (NS-3)**

White solid, 69 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (dd,  $J$ = 6.0 Hz, 4.2 Hz, 1H), 7.69-7.72 (m, 1H), 7.59-7.60 (m, 2H), 7.42-7.45 (m, 1H), 7.35 (d,  $J$ = 1.8 Hz, 1H), 6.79 (s, 1H), 4.21 (t,  $J$ = 6.6 Hz, 2H), 3.96 (s, 3H), 3.73 (t,  $J$ = 4.8 Hz, 4H), 3.64 (s, 2H), 2.70 (td,  $J$ = 4.2 Hz, 3.0 Hz, 2H), 2.53 (s, 4H), 2.05 (t,  $J$ = 3.0 Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 163.2, 156.2, 153.0, 149.4, 133.7, 132.6, 127.2, 125.7, 125.2, 123.9, 121.1, 118.1, 109.0, 107.3, 80.9, 71.1, 69.8, 67.0, 57.0, 56.0, 53.6, 20.3. HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  for  $\text{C}_{25}\text{H}_{25}\text{NO}_5$ , Calculated 420.1805; observed 420.1833.

### **2-(3-methoxy-5-(piperidin-1-ylmethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-4)**

Yellowish solid, 66 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (d,  $J$ = 8.4 Hz, 1H), 7.70 (t,  $J$ = 7.2 Hz, 1H), 7.66 (s, 1H), 7.59 (d,  $J$ = 8.4 Hz, 1H), 7.42 (t,  $J$ = 7.2 Hz, 1H), 7.34 (s, 1H), 6.81 (s, 1H),

4.84 (d, J= 1.8 Hz, 2H), 3.96 (s, 3H), 3.67 (s, 2H), 2.51 (s, 1H), 2.48 (s, 4H), 1.60 (quintet, J= 5.4 Hz, 4H), 1.45 (s, 2H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.4, 163.3, 156.2, 152.9, 148.2, 133.7, 127.6, 125.7, 125.2, 123.9, 121.1, 118.1, 108.6, 107.3, 79.1, 75.4, 60.2, 57.2, 56.0, 54.4, 25.9, 24.2. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>25</sub>H<sub>25</sub>NO<sub>4</sub>, Calculated 404.1856; observed 404.1855.

**2-(3-methoxy-4-(pent-4-yn-1-yloxy)-5-(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-5)**

White solid, 78 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (dd, J= 6.6 Hz, 1.2 Hz, 1H), 7.69-7.71 (m, 1H), 7.63 (d, J= 2.4 Hz, 1H), 7.59 (d, J= 8.4 Hz, 1H), 7.41-7.44 (m, 1H), 7.33 (d, J= 2.4 Hz, 1H), 6.80 (s, 1H), 4.13 (t, J= 6.6 Hz, 2H), 3.94 (s, 3H), 3.56 (s, 2H), 2.49 (td, J= 4.2 Hz, 3.0 Hz, 2H), 2.43 (s, 4H), 2.02 (quintet, J= 7.2 Hz, 2H), 1.98 (t, J= 2.4 Hz, 1H), 1.59 (quintet, J= 5.4 Hz, 4H), 1.45 (s, 2H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.4, 163.5, 156.2, 153.0, 149.8, 133.7, 133.6, 126.8, 125.7, 125.1, 123.9, 121.2, 118.1, 108.6, 107.2, 83.9, 71.6, 68.6, 57.2, 55.9, 54.6, 29.2, 26.1, 24.3, 15.2. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>27</sub>H<sub>29</sub>NO<sub>4</sub>, Calculated 432.2169; observed 432.2173.

**2-(3-ethoxy-5-(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-6)**

White solid, 73 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (d, J= 7.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.61 (s, 1H), 7.58 (d, J= 8.4 Hz, 1H), 7.41-7.45 (m, 1H), 7.34 (s, 1H), 6.78 (s, 1H), 4.87 (d, J= 0.6 Hz, 2H), 4.18 (q, J= 7.2 Hz, 2H), 3.73 (t, J= 4.2 Hz, 4H), 3.68 (s, 2H), 2.53 (s, 4H), 2.47 (t, J= 2.4 Hz, 1H), 1.52 (t, J= 7.2 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.3, 163.2, 156.2, 152.2, 148.4, 133.7, 133.4, 127.6, 125.7, 125.2, 123.9, 120.7, 118.0, 109.8, 107.4, 79.2, 75.4, 67.1, 64.6, 60.1, 57.1, 53.6, 14.8. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>25</sub>H<sub>25</sub>NO<sub>5</sub>, Calculated 420.1805; observed 420.1803.

**2-(4-(but-3-yn-1-yloxy)-3-ethoxy-5-(morpholinomethyl)phenyl)-4H-chromen-4-one (NS-7)**

Yellowish solid, 64 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (dd, J= 6.0 Hz, 1.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.59 (d, J= 7.8 Hz, 2H), 7.41-7.45 (m, 1H), 7.34 (d, J= 2.4 Hz, 1H), 6.78 (s, 1H), 4.23 (t, J= 6.6 Hz, 2H), 4.17 (q, J= 7.2 Hz, 2H), 3.73 (t, J= 4.2 Hz, 4H), 3.64 (s, 2H), 2.71 (td, J= 4.2 Hz, 2.4 Hz, 2H), 2.53 (s, 4H), 2.04 (t, J= 3.0 Hz, 1H), 1.52 (t, J= 6.6 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.4, 163.3, 156.2, 152.2, 149.6, 133.7, 132.5, 127.1, 125.7, 125.2, 123.9, 121.0, 118.0, 110.0, 107.3, 81.0, 71.1, 69.8, 67.0, 64.6, 57.0, 53.6, 20.4, 14.8. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>26</sub>H<sub>27</sub>NO<sub>5</sub>, Calculated 434.1962; observed 434.1966.

**2-(3-ethoxy-5-(morpholinomethyl)-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-8)**

Off-white solid, 68 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (dd,  $J$ = 6.0 Hz, 1.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.58-7.60 (m, 2H), 7.41-7.44 (m, 1H), 7.34 (dd,  $J$ = 2.4 Hz, 1H), 6.78 (s, 1H), 4.15-4.19 (m, 4H), 3.73 (t,  $J$ = 4.8 Hz, 4H), 3.60 (s, 2H), 2.52 (s, 4H), 2.49 (td,  $J$ = 4.2 Hz, 2.4 Hz, 2H), 2.03 (quintet,  $J$ = 6.6 Hz, 2H), 1.99 (t,  $J$ = 3.0 Hz, 1H), 1.52 (t,  $J$ = 6.6 Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 163.4, 156.2, 152.3, 150.0, 133.6, 132.5, 126.9, 125.7, 125.2, 123.9, 121.0, 118.0, 109.9, 107.2, 83.8, 71.6, 68.8, 67.1, 64.5, 56.9, 53.7, 29.2, 15.3, 14.8. HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  for  $\text{C}_{27}\text{H}_{29}\text{NO}_5$ , Calculated 448.2118; observed 448.2121.

**2-(3-ethoxy-4-(pent-4-yn-1-yloxy)-5-(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-9)**

Off-white solid, 69 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (dd,  $J$ = 6.0 Hz, 1.8 Hz, 1H), 7.68-7.71 (m, 1H), 7.61 (d,  $J$ = 7.58, 1H), (dd,  $J$ = 7.8 Hz, 0.6 Hz, 1H), 7.40-7.43 (m, 1H), 7.32 (d,  $J$ = 2.4 Hz, 1H), 6.78 (s, 1H), 4.14-4.17 (m, 4H), 3.55 (s, 2H), 2.49 (td,  $J$ = 4.8 Hz, 2.4 Hz, 2H), 2.44 (s, 4H), 2.02 (quintet,  $J$ = 6.0 Hz, 2H), 1.99 (t,  $J$ = 3.0 Hz, 1H), 1.59 (quintet,  $J$ = 5.4 Hz, 4H), 1.51 (t,  $J$ = 7.2 Hz, 3H), 1.45 (s, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.4, 163.7, 156.3, 152.3, 150.0, 133.7, 133.6, 126.8, 125.7, 125.2, 124.0, 121.1, 118.1, 109.6, 107.2, 83.9, 71.6, 68.7, 64.5, 57.3, 54.7, 29.3, 26.1, 24.4, 15.4, 14.9. HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  for  $\text{C}_{28}\text{H}_{31}\text{NO}_4$ , Calculated 446.2326; observed 446.2328.

**2-(3,5-bis(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-10)**

Off-white solid, 64 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (dd,  $J$ = 6.6 Hz, 1.2 Hz, 1H), 7.87 (s, 2H), 7.70-7.74 (m, 1H), 7.60 (d,  $J$ = 8.4 Hz, 1H), 7.44 (t,  $J$ = 7.2 Hz, 1H), 6.81 (s, 1H), 4.93 (d,  $J$ = 3.0 Hz, 2H), 3.73 (t,  $J$ = 4.8 Hz, 8H), 3.64 (s, 4H), 2.58 (t,  $J$ = 2.4 Hz, 1H), 2.55 (s, 8H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 163.0, 159.1, 156.2, 133.7, 133.0, 128.4, 127.6, 125.7, 125.3, 123.9, 118.1, 107.5, 79.1, 75.7, 67.0, 62.8, 57.7, 53.6. HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  for  $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_4$ , Calculated 475.2227; observed 475.2228.

**2-(3,5-bis(morpholinomethyl)-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-11)**

Off-white solid, 77 % yield,  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (dd,  $J$ = 6.6 Hz, 1.2 Hz, 1H), 7.93 (s, 2H), 7.70-7.73 (m, 1H), 7.60 (dd,  $J$ = 7.8 Hz, 0.6 Hz, 1H), 7.42-7.45 (m, 1H), 6.82 (s, 1H), 4.08 (t,  $J$ = 6.6 Hz, 2H), 3.74 (t,  $J$ = 4.2 Hz, 8H), 3.61 (s, 4H), 2.50-2.53 (m, 10H), 2.05 (quintet,  $J$ = 6.6 Hz, 2H), 2.03 (t,  $J$ = 2.4 Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.4, 163.3, 159.6, 156.2, 133.7,

132.4, 128.0, 127.2, 125.7, 125.2, 123.9, 118.1, 107.3, 83.6, 72.9, 69.3, 67.0, 57.1, 53.7, 29.0, 15.2. HRMS:  $m/z$   $[M + H]^+$  for  $C_{30}H_{34}N_2O_4$ , Calculated 503.2540; observed 503.2544.

**2-(3-(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-12)**

White solid, 69 % yield,  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  8.23 (dd,  $J= 6.6$  Hz, 1.2 Hz, 1H), 8.01 (d,  $J= 1.8$  Hz, 1H), 7.85 (dd,  $J= 6.6$  Hz, 2.4 Hz, 1H), 7.68-7.71 (m, 1H), 7.57 (d,  $J= 8.4$  Hz, 1H), 7.42 (t,  $J= 7.2$  Hz, 1H), 7.12 (d,  $J= 8.4$  Hz, 1H), 6.78 (s, 1H), 4.81 (d,  $J= 2.4$  Hz, 2H), 3.76 (t,  $J= 4.2$  Hz, 4H), 3.63 (s, 2H), 2.55-2.57 (m, 5H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  178.4, 163.4, 158.4, 156.2, 133.6, 128.5, 127.7, 126.4, 125.7, 125.1, 124.7, 123.9, 118.0, 112.3, 106.6, 77.9, 76.1, 67.1, 56.2, 56.1, 53.6. HRMS:  $m/z$   $[M + H]^+$  for  $C_{23}H_{21}NO_4$ , Calculated 376.1543; observed 376.1546.

**2-(4-(pent-4-yn-1-yloxy)-3-(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-13)**

Yellowish solid, 70 % yield,  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  8.23 (dd,  $J= 6.0$  Hz, 1.8 Hz, 1H), 8.00 (s, 1H), 7.81 (dd,  $J= 6.0$  Hz, 2.4 Hz, 1H), 7.67-7.70 (m, 1H), 7.57 (d,  $J= 7.8$  Hz, 1H), 7.70-7.42 (m, 1H), 6.98 (d,  $J= 9.0$  Hz, 1H), 6.78 (s, 1H), 4.17 (t,  $J= 6.6$  Hz, 2H), 3.58 (s, 2H), 2.45-2.49 (m, 6H), 2.06 (quintet,  $J= 6.0$  Hz, 2H), 2.00 (t,  $J= 3.0$  Hz, 1H), 1.64 (t,  $J= 5.4$  Hz, 4H), 1.47 (s, 2H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  178.4, 163.7, 159.8, 156.2, 133.5, 128.5, 126.4, 125.6, 125.0, 124.0, 123.7, 118.0, 111.3, 106.2, 83.2, 69.1, 66.5, 56.5, 54.6, 28.1, 26.0, 24.2, 15.2. HRMS:  $m/z$   $[M + H]^+$  for  $C_{26}H_{27}NO_3$ , Calculated 402.2064; observed 402.2069.

**2-(4-(pent-4-yn-1-yloxy)-3,5-bis(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-14)**

White solid, 79 % yield,  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  8.23 (dd,  $J= 6.0$  Hz, 1.8 Hz, 1H), 7.91 (s, 2H), 7.69-7.71 (m, 1H), 7.60 (d,  $J= 8.4$  Hz, 1H), 7.41-7.43 (m, 1H), 6.83 (s, 1H), 4.05 (t,  $J= 6.6$  Hz, 2H), 3.54 (s, 4H), 2.50 (td,  $J= 4.2$  Hz, 3.0 Hz, 2H), 2.45 (s, 8H), 2.04 (quintet,  $J= 6.6$  Hz, 2H), 2.01 (t,  $J= 2.4$  Hz, 1H), 1.60 (quintet,  $J= 5.4$  Hz, 8H), 1.46 (s, 4H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  178.5, 163.8, 159.5, 156.3, 133.5, 133.3, 127.6, 126.9, 125.6, 125.1, 124.0, 118.1, 107.2, 83.8, 72.7, 69.0, 57.5, 54.7, 29.1, 26.1, 24.4, 15.2. HRMS:  $m/z$   $[M + H]^+$  for  $C_{32}H_{38}N_2O_3$ , Calculated 499.2955; observed 499.2963.

**2-(3-((benzyl(methyl)amino)methyl)-5-methoxy-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-15)**

White solid, 73 % yield,  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  8.24 (dd,  $J= 6.0$  Hz, 1.8 Hz, 1H), 7.76 (d,  $J= 1.8$  Hz, 1H), 7.70-7.73 (m, 1H), 7.59 (d,  $J= 7.8$  Hz, 1H), 7.42-7.44 (m, 1H), 7.39 (d,  $J= 6.6$  Hz, 2H), 7.33-7.35 (m, 3H), 7.25 (t,  $J= 7.2$  Hz, 1H), 6.81 (s, 1H), 4.13 (t,  $J= 6.0$  Hz, 2H), 3.94 (s, 3H),

3.65 (s, 2H), 3.59 (s, 2H), 2.47 (td, J= 4.2 Hz, 2.4 Hz, 2H), 2.24 (s, 3H), 2.00 (quintet, J= 6.6 Hz, 2H), 1.98 (t, J= 3.0 Hz, 1H), <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.4, 163.5, 156.2, 152.9, 149.6, 139.2, 134.0, 133.6, 128.9, 128.3, 127.0, 127.0, 125.7, 125.1, 123.9, 120.9, 118.0, 108.6, 107.2, 83.8, 71.5, 68.7, 62.2, 55.9, 55.2, 42.5, 29.2, 15.2. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>30</sub>H<sub>29</sub>NO<sub>4</sub>, Calculated 468.2169; observed 468.2172.

**2-(3-((4-benzylpiperazin-1-yl)methyl)-5-methoxy-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-16)**

White solid, 81 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (dd, J= 6.0 Hz, 1.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.60 (d, J= 2.4 Hz, 1H), 7.58 (d, J= 8.4 Hz, 1H), 7.41-7.44 (m, 1H), 7.33 (d, J= 2.4 Hz, 1H), 7.29-7.33 (m, 4H), 7.22-7.25 (m, 1H), 6.79 (s, 1H), 4.13 (t, J= 6.0 Hz, 2H), 3.94 (s, 3H), 3.62 (s, 2H), 3.52 (s, 2H), 2.46-2.54 (m, 10H), 2.01 (quintet, J= 6.6 Hz, 2H), 1.98 (t, J= 3.0 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.4, 163.4, 156.2, 153.0, 149.8, 138.2, 133.6, 133.0, 129.2, 128.1, 127.0, 126.9, 125.7, 125.2, 123.9, 121.1, 118.1, 108.8, 107.2, 83.8, 71.6, 68.7, 63.0, 56.4, 55.9, 53.2, 53.2, 29.2, 15.2. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>33</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>, Calculated 523.2591; observed 523.2590.

**2-(4-(but-3-yn-1-yloxy)-3-methoxy-5-((4-phenylpiperazin-1-yl)methyl)phenyl)-4H-chromen-4-one (NS-17)**

White solid, 67 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (dd, J= 6.0 Hz, 1.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.64 (s, 1H), 7.59 (d, J= 8.4 Hz, 1H), 7.42-7.44 (m, 1H), 7.36 (s, 1H), 7.25-7.27 (m, 2H), 6.93 (d, J= 7.8 Hz, 2H), 6.85 (t, J= 7.2 Hz, 1H), 6.80 (s, 1H), 4.22 (t, J= 5.4 Hz, 2H), 3.97 (s, 3H), 3.72 (s, 2H), 3.22 (s, 4H), 2.70-2.73 (m, 6H), 2.04 (t, J= 2.4 Hz, 1H), <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.3, 163.3, 156.2, 153.0, 151.3, 149.5, 133.7, 132.8, 129.1, 127.2, 125.7, 125.2, 123.9, 121.2, 119.6, 118.1, 116.0, 109.0, 107.3, 80.9, 71.1, 69.8, 56.6, 56.0, 53.1, 49.2, 20.3. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>31</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>, Calculated 495.2278; observed 495.2286.

**2-(3-methoxy-4-(pent-4-yn-1-yloxy)-5-((4-phenylpiperazin-1-yl)methyl)phenyl)-4H-chromen-4-one (NS-18)**

White solid, 79 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (d, J= 7.8 Hz, 1H), 7.70 (t, J= 8.4 Hz, 1H), 7.65 (d, J= 1.8 Hz, 1H), 7.58 (d, J= 8.4 Hz, 1H), 7.42 (t, J= 7.8 Hz, 1H), 7.35 (d, J= 1.8 Hz, 1H), 7.26 (t, J= 8.4 Hz, 2H), 6.93 (d, J= 8.4 Hz, 2H), 6.85 (t, J= 7.8 Hz, 1H), 6.80 (s, 1H), 4.17 (t, J= 6.0 Hz, 2H), 3.96 (s, 3H), 3.68 (s, J= 2H), 3.23 (t, J= 4.8 Hz, 4H), 2.69 (t, J= 4.2 Hz, 4H), 2.49 (td, J= 3.6 Hz, 3.0 Hz, 2H), 2.03 (quintet, J= 6.0 Hz, 2H), 1.97 (t, J= 2.4 Hz, 1H); <sup>13</sup>C NMR (150

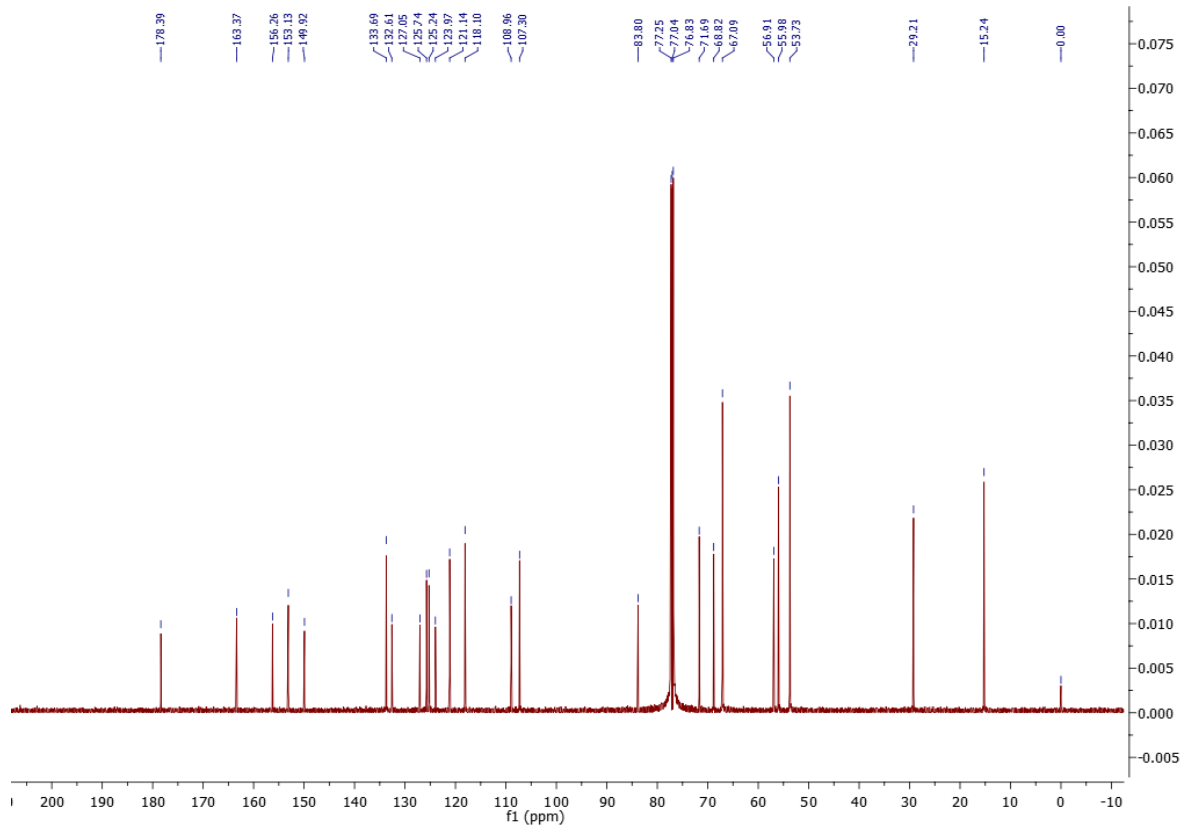
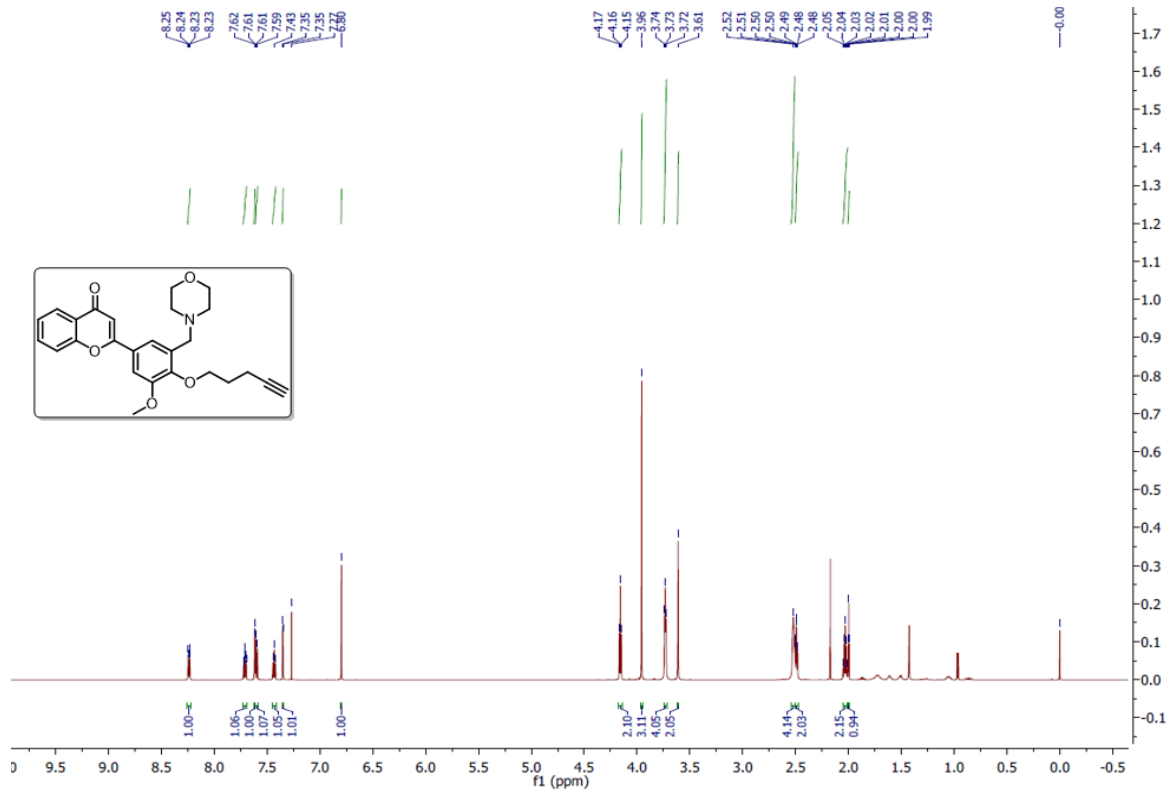
MHz, CDCl<sub>3</sub>) δ 178.4, 163.3, 156.2, 153.1, 151.3, 149.9, 133.6, 132.8, 129.1, 127.0, 125.7, 125.2, 123.9, 121.1, 119.6, 118.1, 116.0, 108.9, 107.2, 83.8, 71.7, 68.8, 56.5, 55.9, 53.2, 49.2, 29.2, 15.2. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>, Calculated 509.2435; observed 509.2443.

**2-(3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-5-methoxy-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-19)**

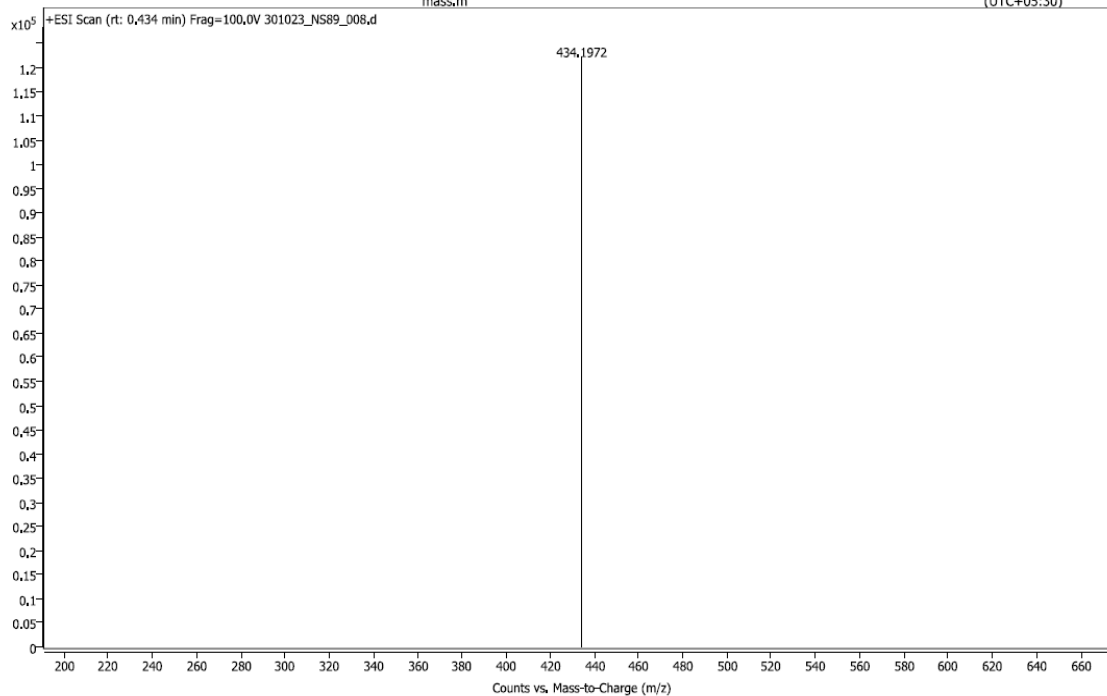
Yellowish solid, 74 % yield, <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.22 (dd, J= 6.6 Hz, 1.2 Hz, 1H), 7.72 (d, J= 2.4 Hz, 1H), 7.67-7.70 (m, 1H), 7.57 (d, J= 8.4 Hz, 1H), 7.41 (t, J= 7.2 Hz, 1H), 7.35 (d, J= 1.8 Hz, 1H), 7.09-7.14 (m, 3H), 7.00 (d, J= 7.2 Hz, 1H), 6.77 (s, 1H), 4.16 (t, J= 6.0 Hz, 2H), 3.96 (s, 3H), 3.80 (s, 2H), 3.72 (s, 2H), 2.93 (t, J= 6.0 Hz, 2H), 2.81 (t, J= 6.0 Hz, 2H), 2.47 (td, J= 4.8 Hz, 2.4 Hz, 2H), 2.01 (quintet, J= 6.6 Hz, 2H), 1.94 (t, J= 2.4 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 178.4, 163.4, 156.2, 153.1, 149.8, 134.8, 134.3, 133.6, 133.2, 128.7, 127.1, 126.5, 126.1, 125.6, 125.6, 125.1, 123.9, 121.0, 118.1, 108.9, 107.3, 83.7, 71.7, 68.7, 56.2, 56.1, 55.9, 50.8, 29.2, 29.2, 15.2. HRMS: *m/z* [M + H]<sup>+</sup> for C<sub>31</sub>H<sub>29</sub>NO<sub>4</sub>, Calculated 480.2169; observed 480.2177.

**2-(3-methoxy-5-(morpholinomethyl)-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-1)**

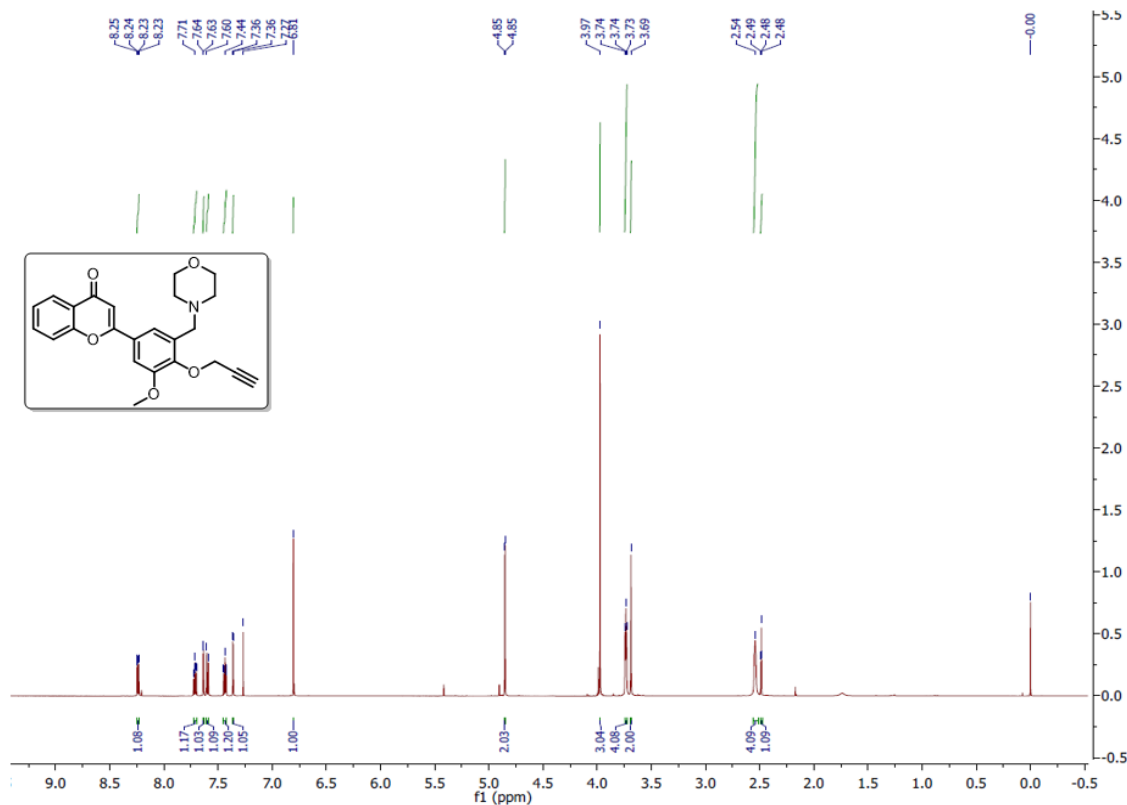


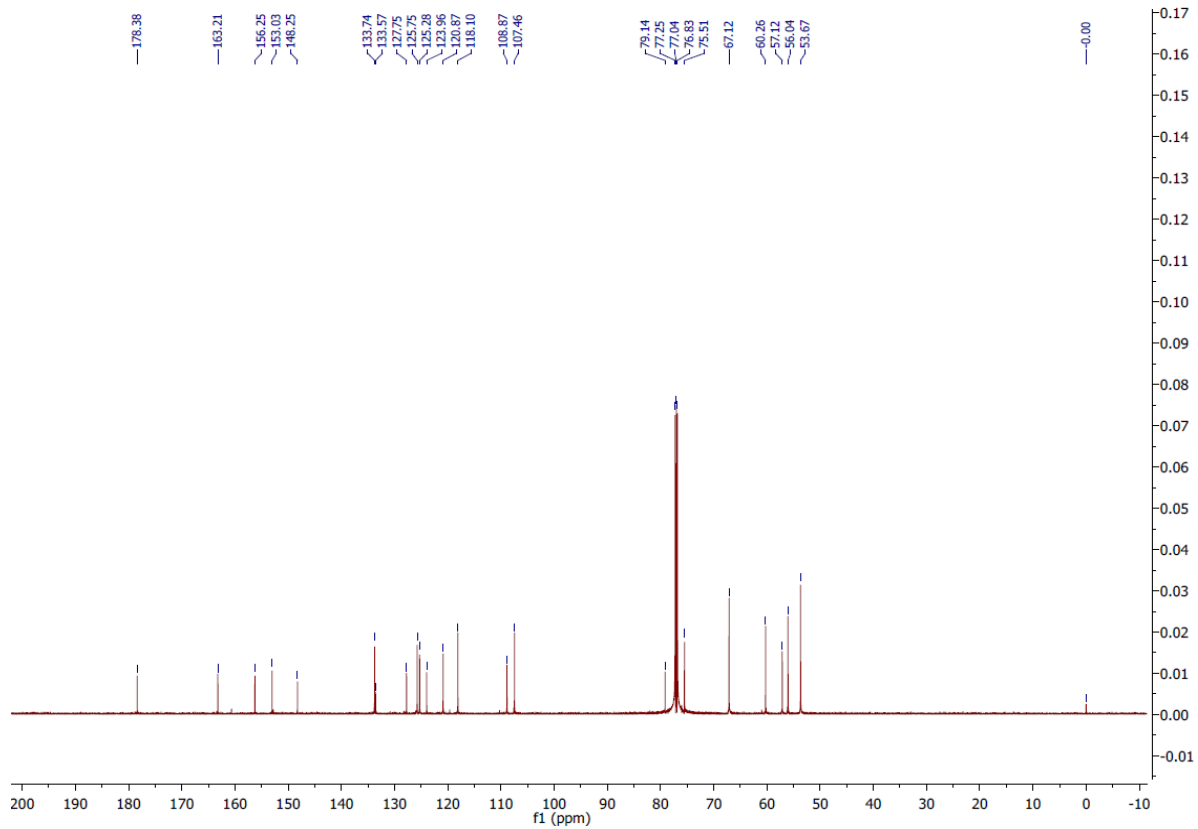


Name		Rack Pos.		Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	2	Plate Pos.		IRM Status	Success		
Data File	301023_NS89_008.d	Method (Acq)	vinod231023 low mass,m	Comment		Acq. Time (Local)	30-10-2023 12:31:09 (UTC+05:30)

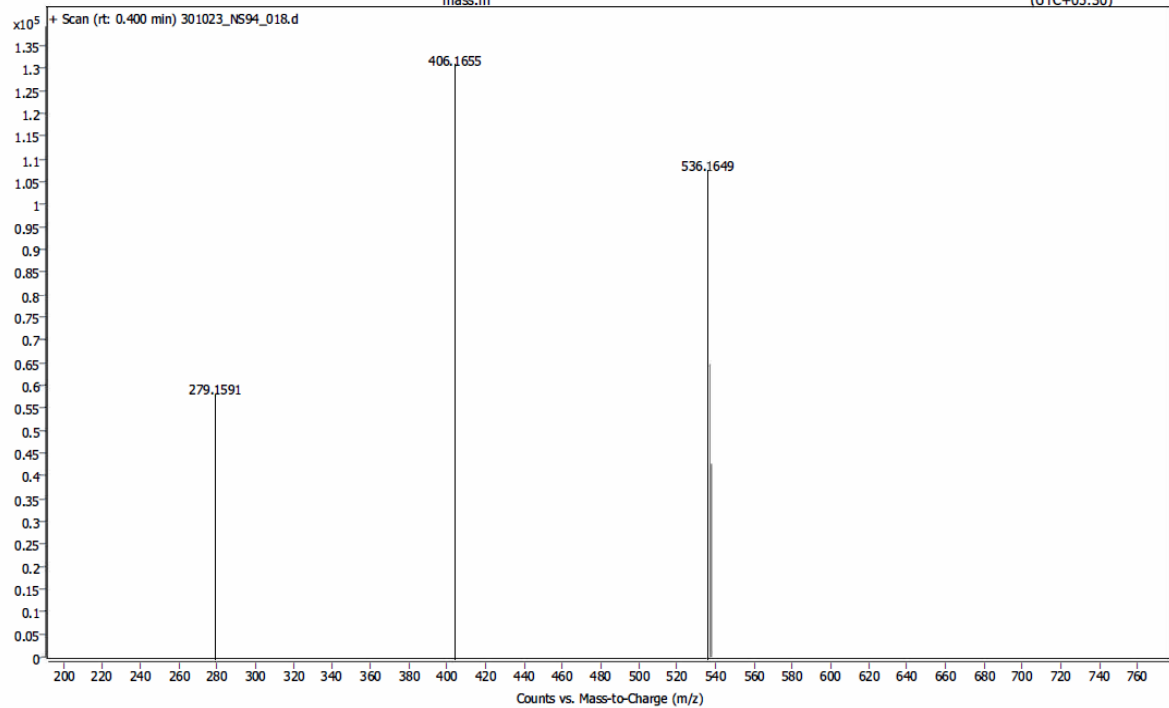


*2-(3-methoxy-5-(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-2)*

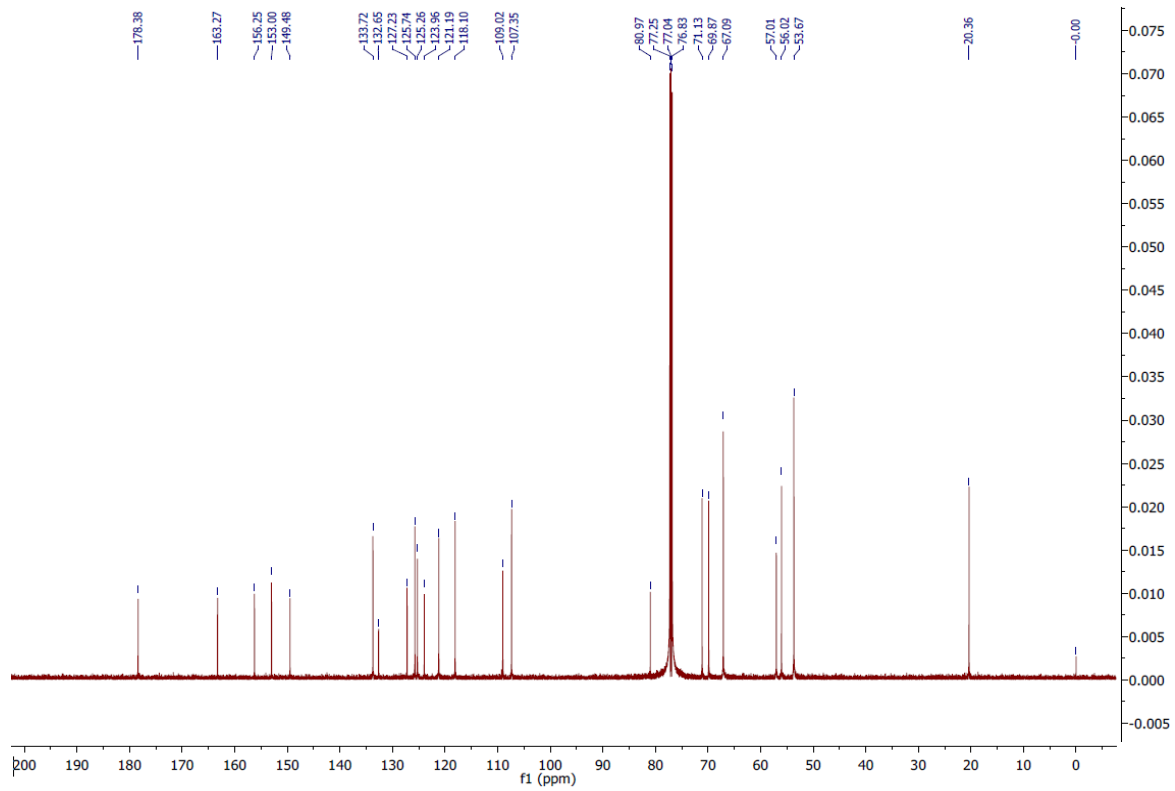
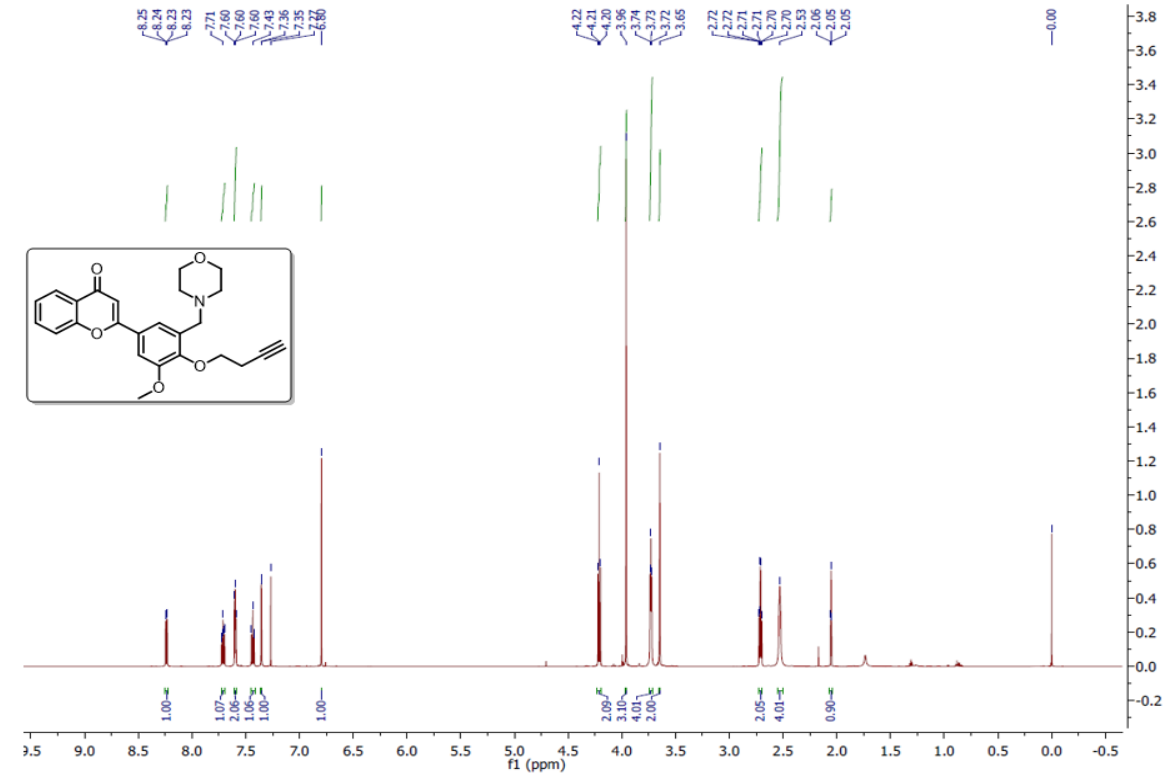




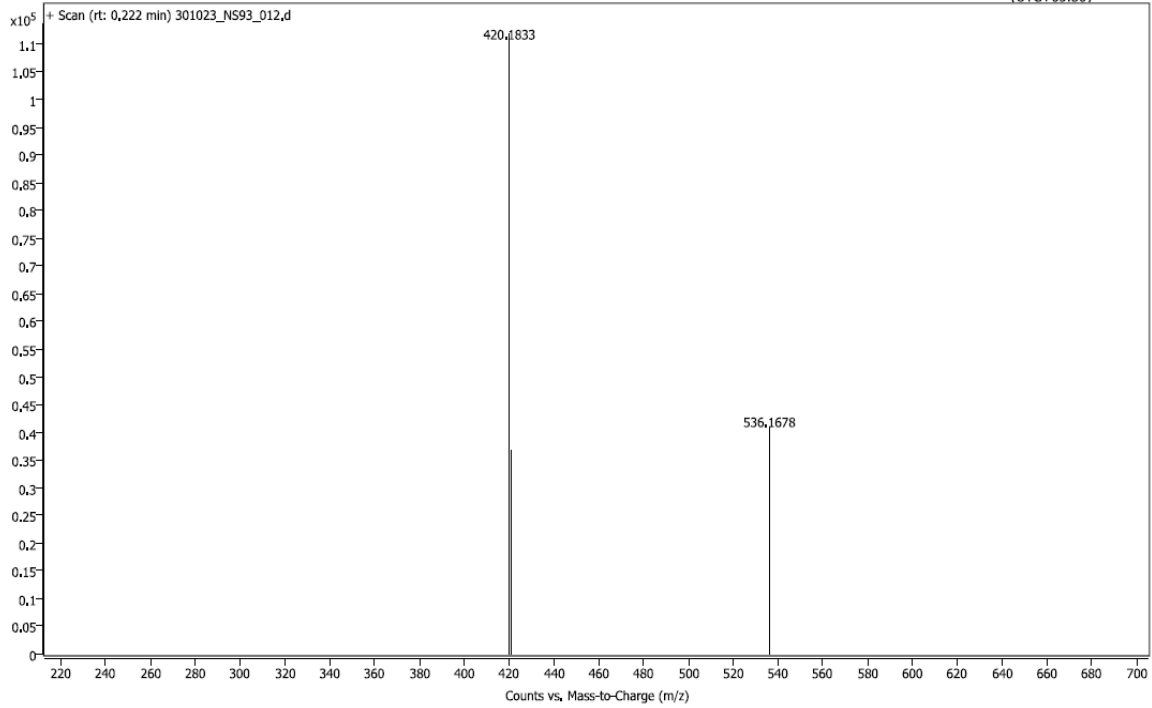
Name	Inj. Vol. (ul)	Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
301023_NS90_001.d	3	Plate Pos.	vinod231023 low mass.m	Success		
		Method (Acq)			Acq. Time (Local)	30-10-2023 16:58:58 (UTC+05:30)



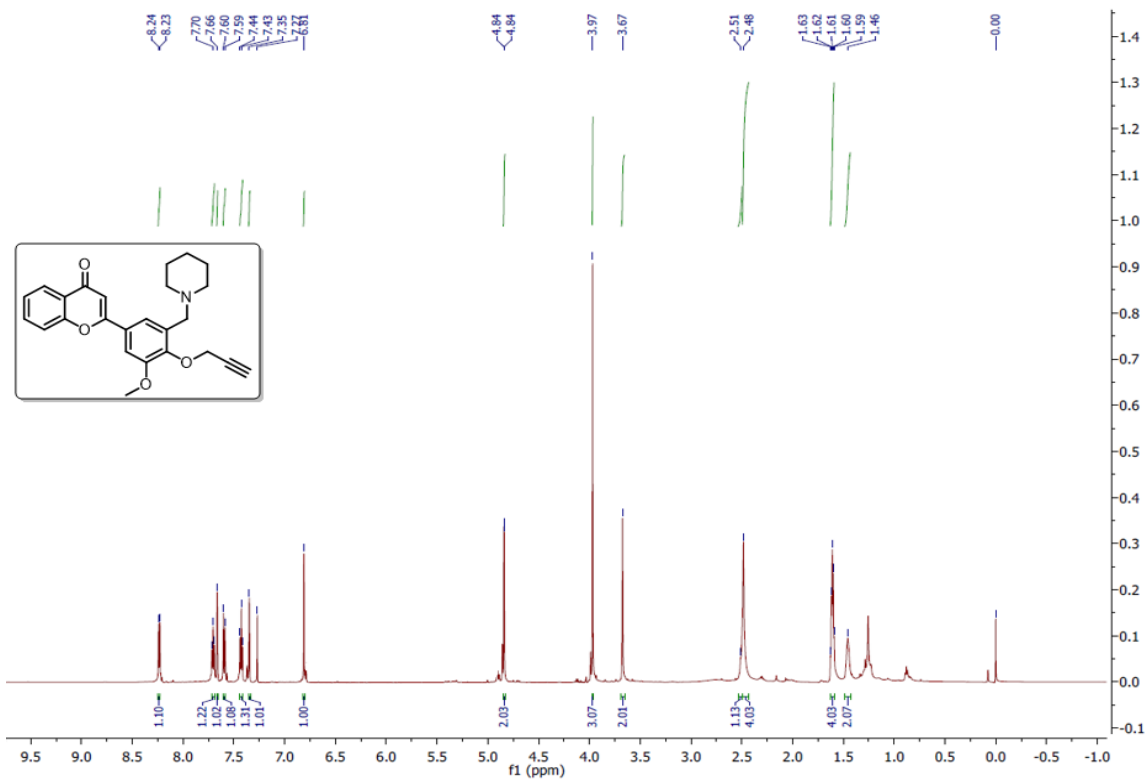
2-(4-(but-3-yn-1-yloxy)-3-methoxy-5-(morpholinomethyl)phenyl)-4H-chromen-4-one (NS-3)

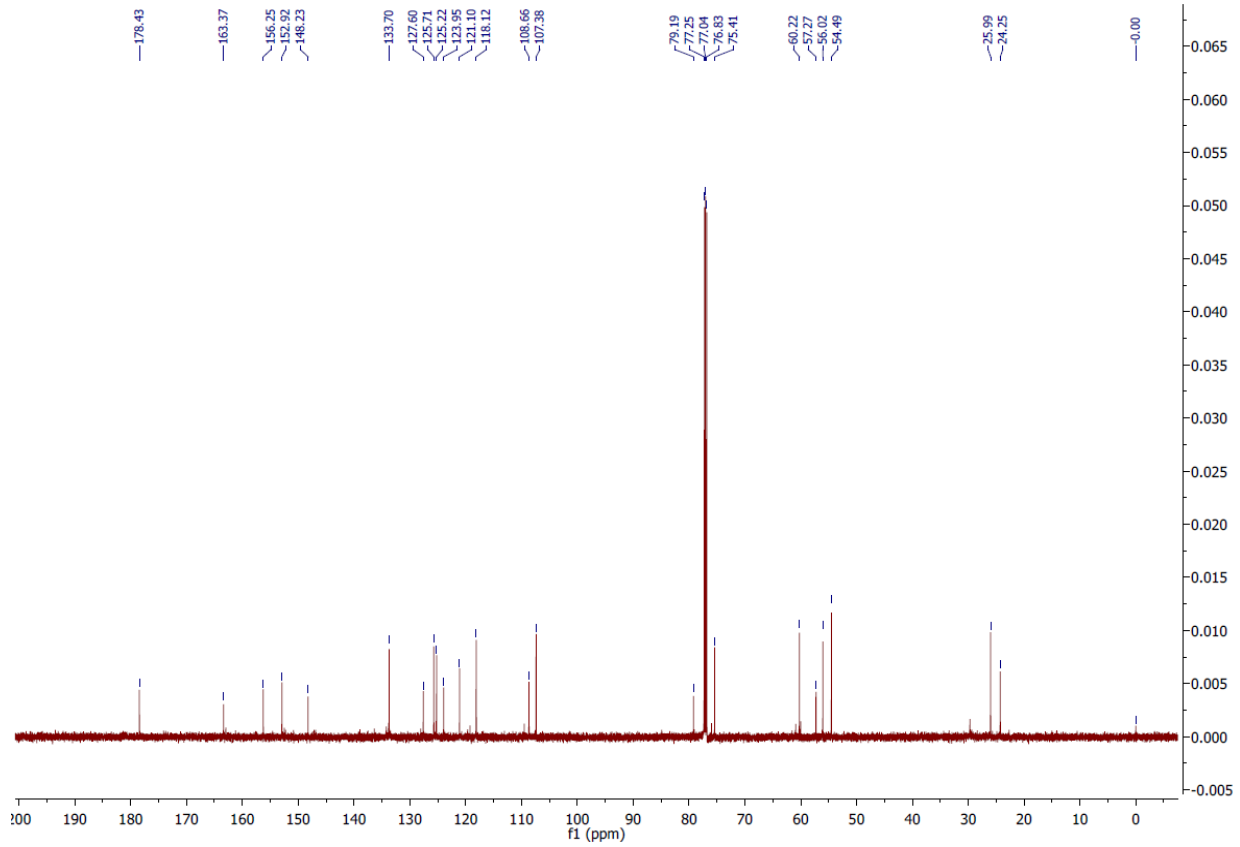


Name	1	Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.	IRM Status	Success		
Data File	301023_NS93_012.d	Method (Acq)	trial_211023.m	Comment	Acq. Time (Local)	30-10-2023 15:25:20 (UTC+05:30)

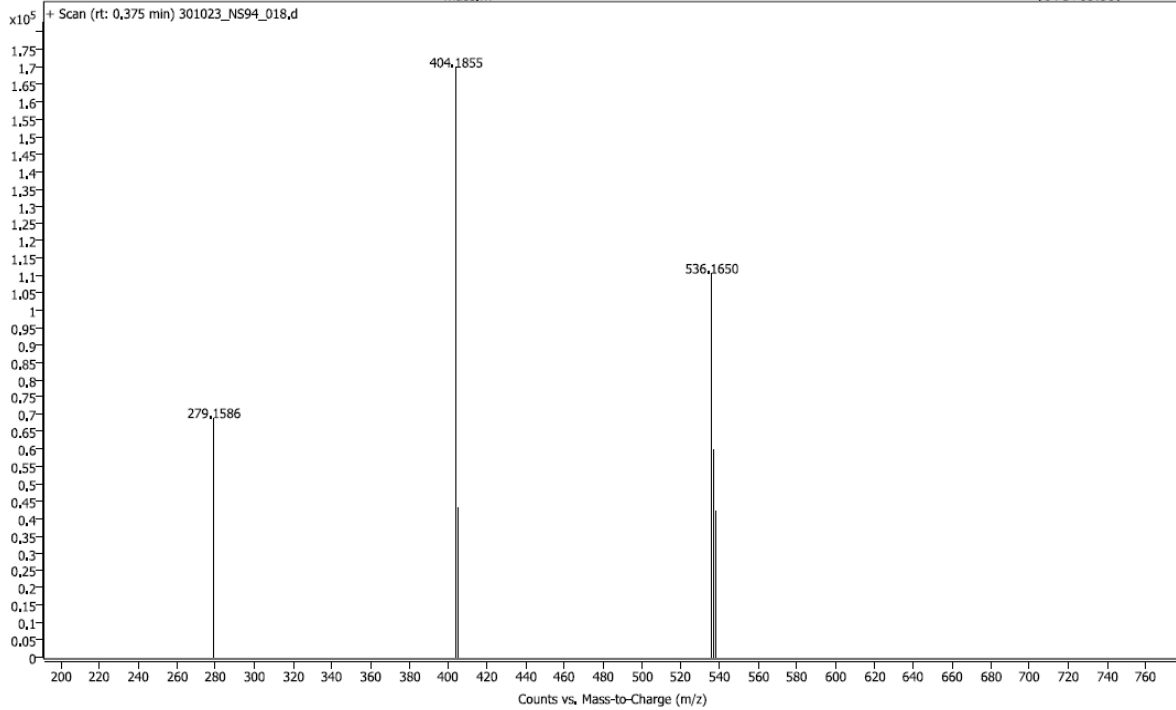


**2-(3-methoxy-5-(piperidin-1-ylmethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-4)**

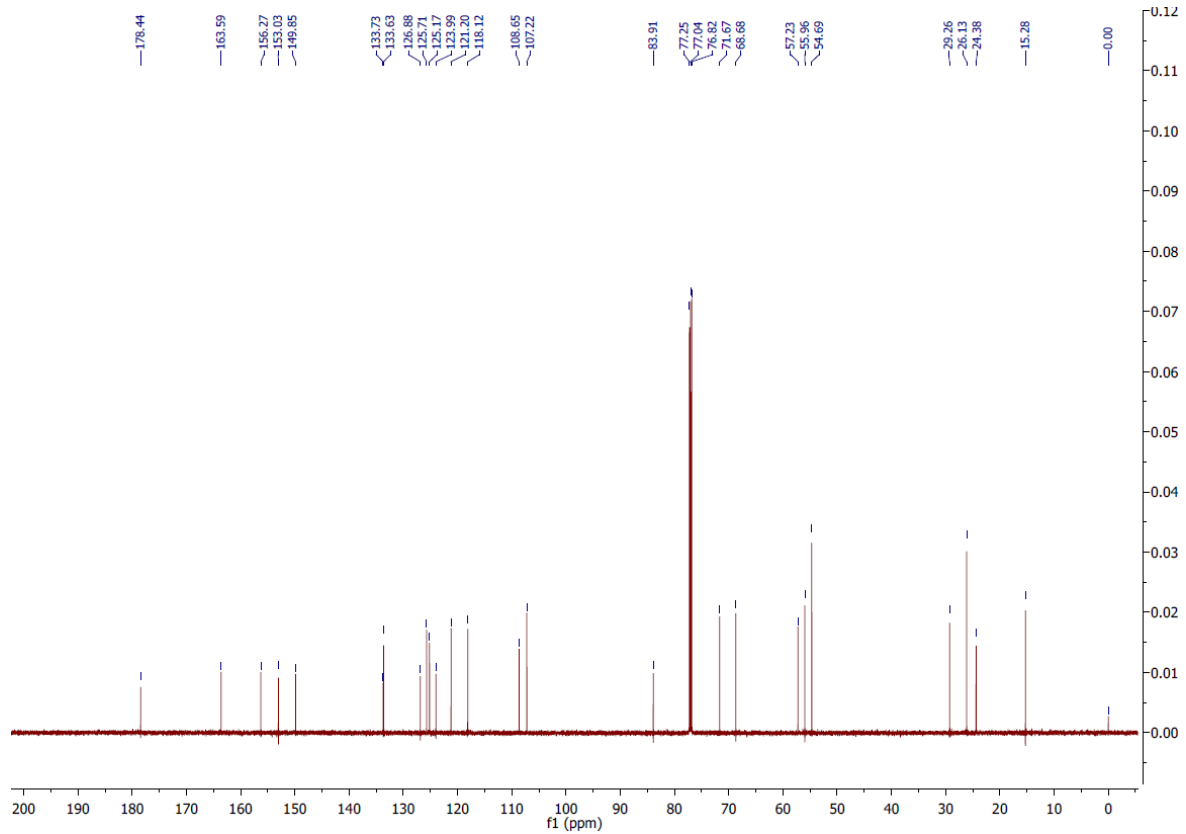
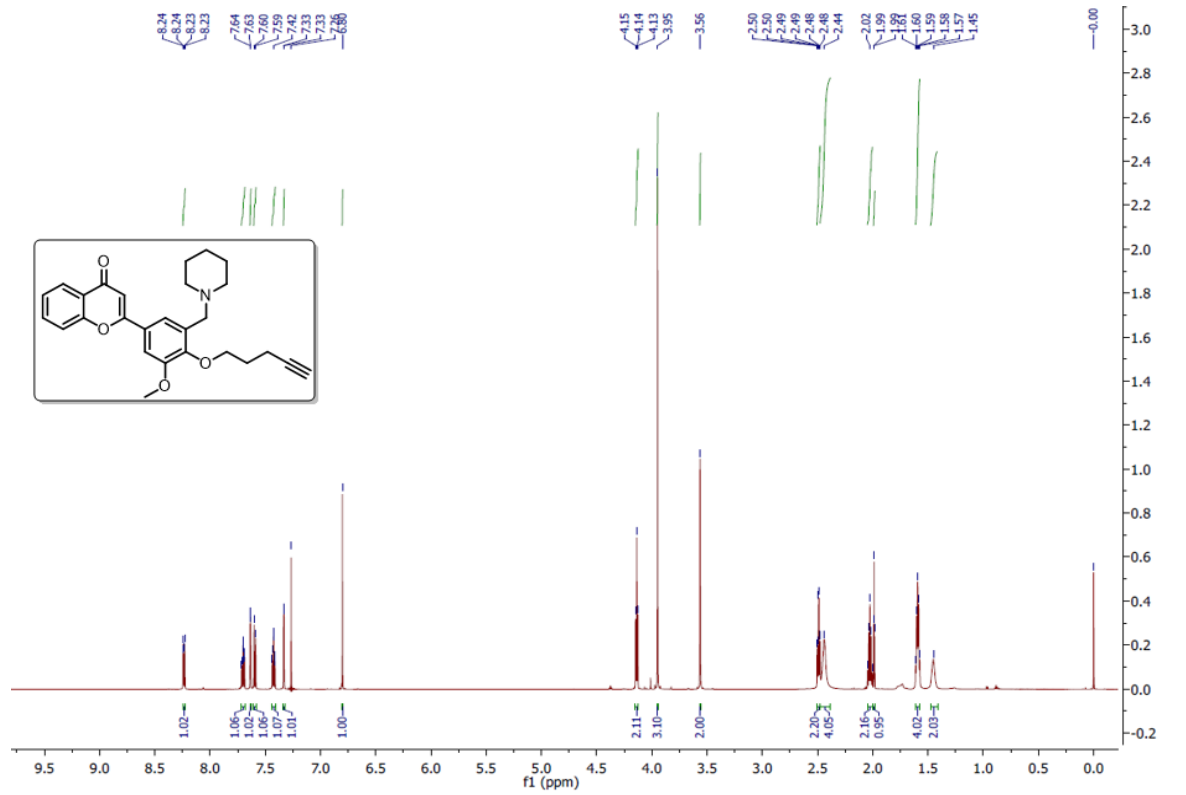




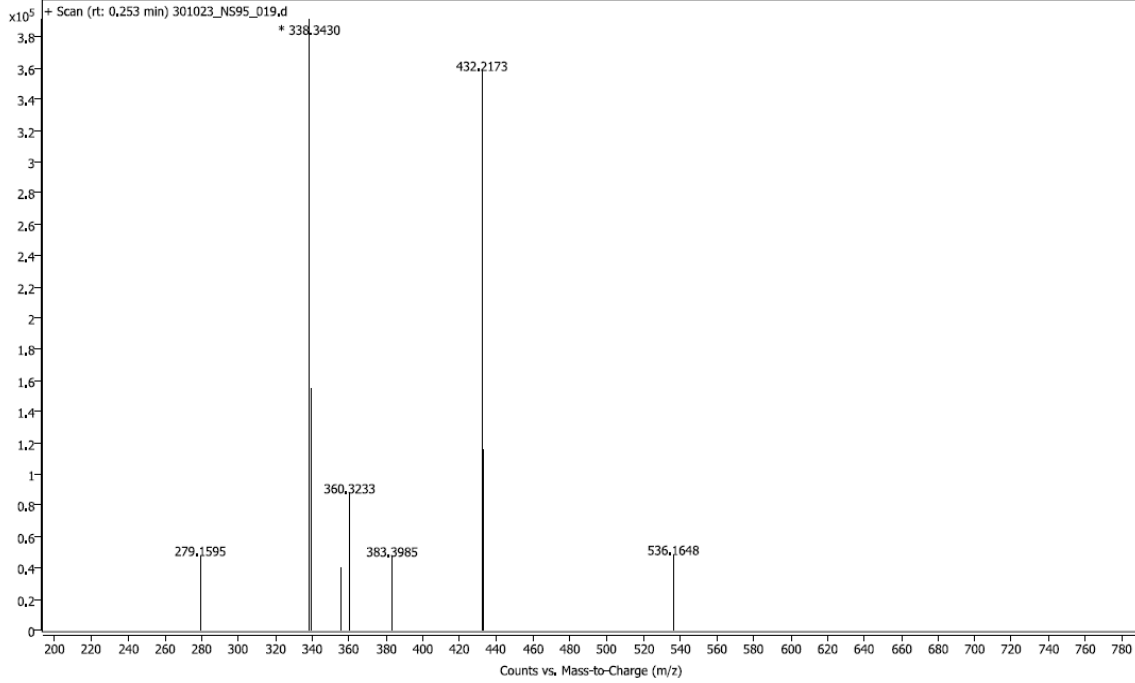
Name		Rack Pos.		Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	3	Plate Pos.		IRM Status	Success		
Data File	301023_NS94_018.d	Method (Acq)	vinod231023_low mass.m	Comment		Acq. Time (Local)	30-10-2023 16:15:53 (UTC+05:30)



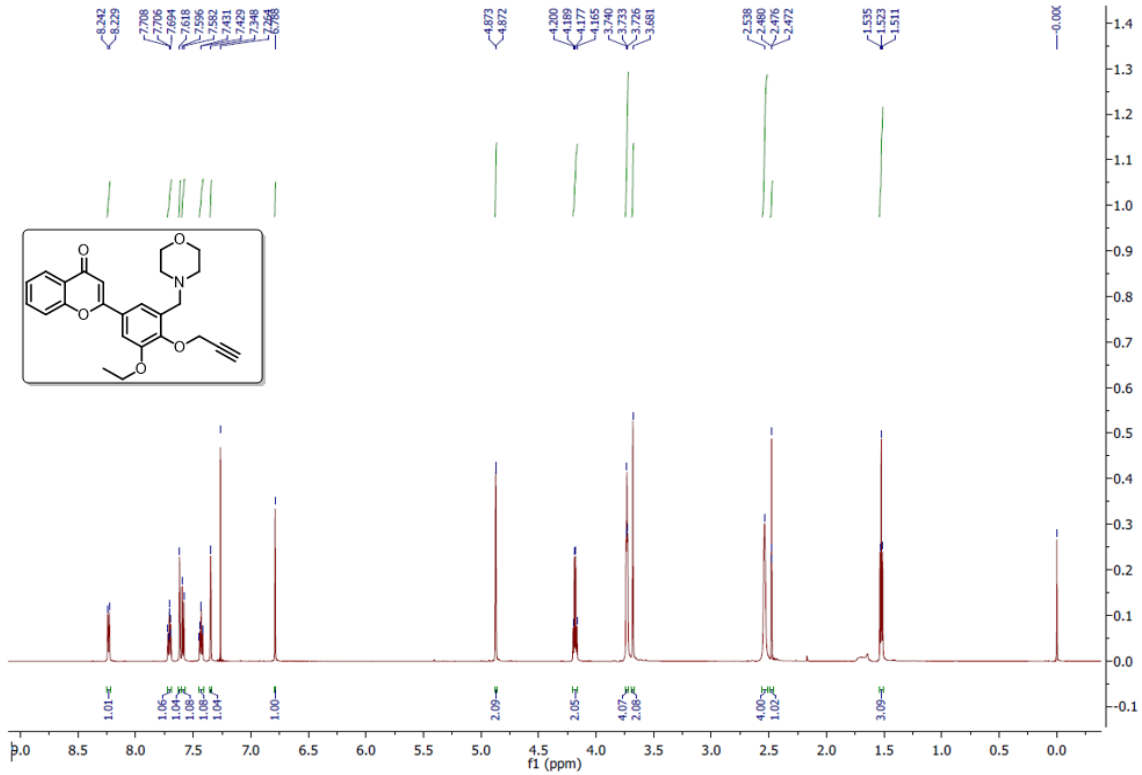
2-(3-methoxy-4-(pent-4-yn-1-yloxy)-5-(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-5)



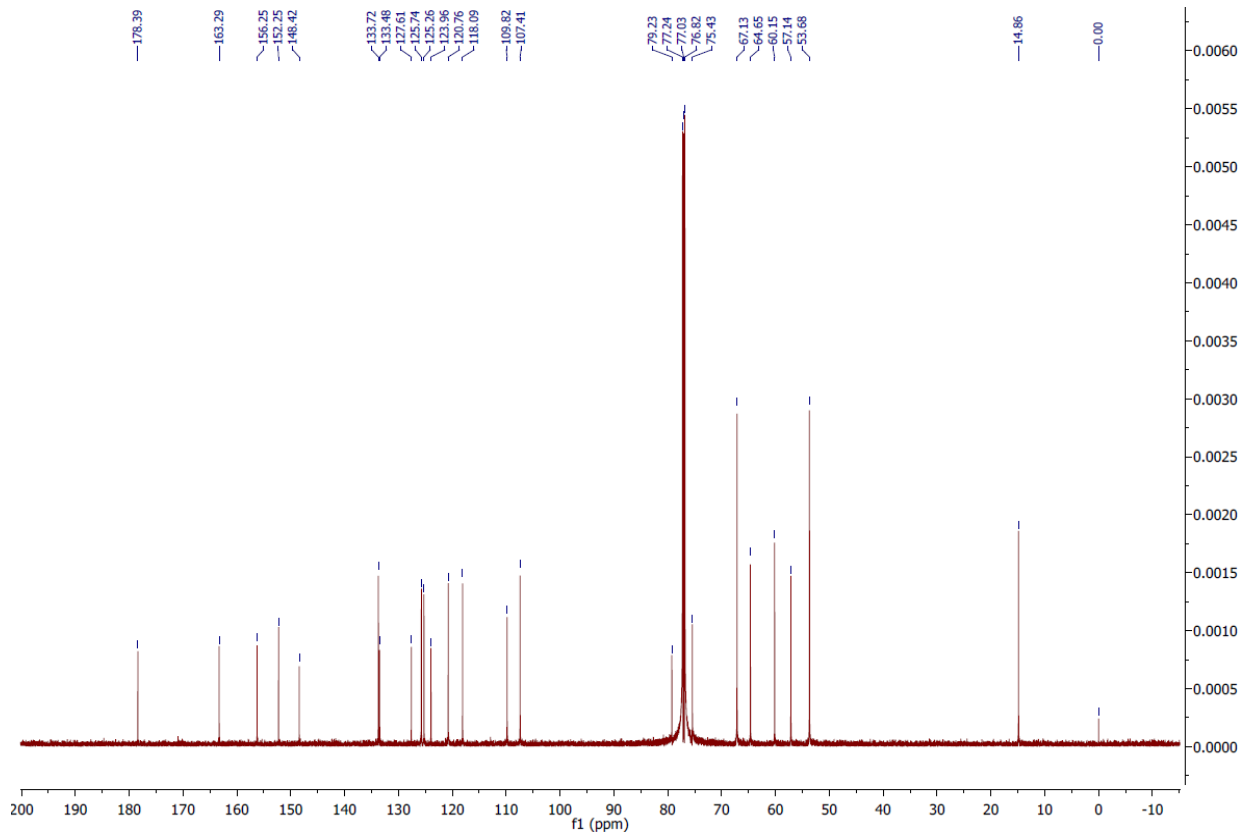
Name	Inj. Vol. (ul)	Rack Pos.	Plate Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
1	301023_NS95_019.d	Method (Acq)	vinod231023 low mass.m	IRM Status	Success	Acq. Time (Local)	30-10-2023 16:20:32 (UTC+05:30)



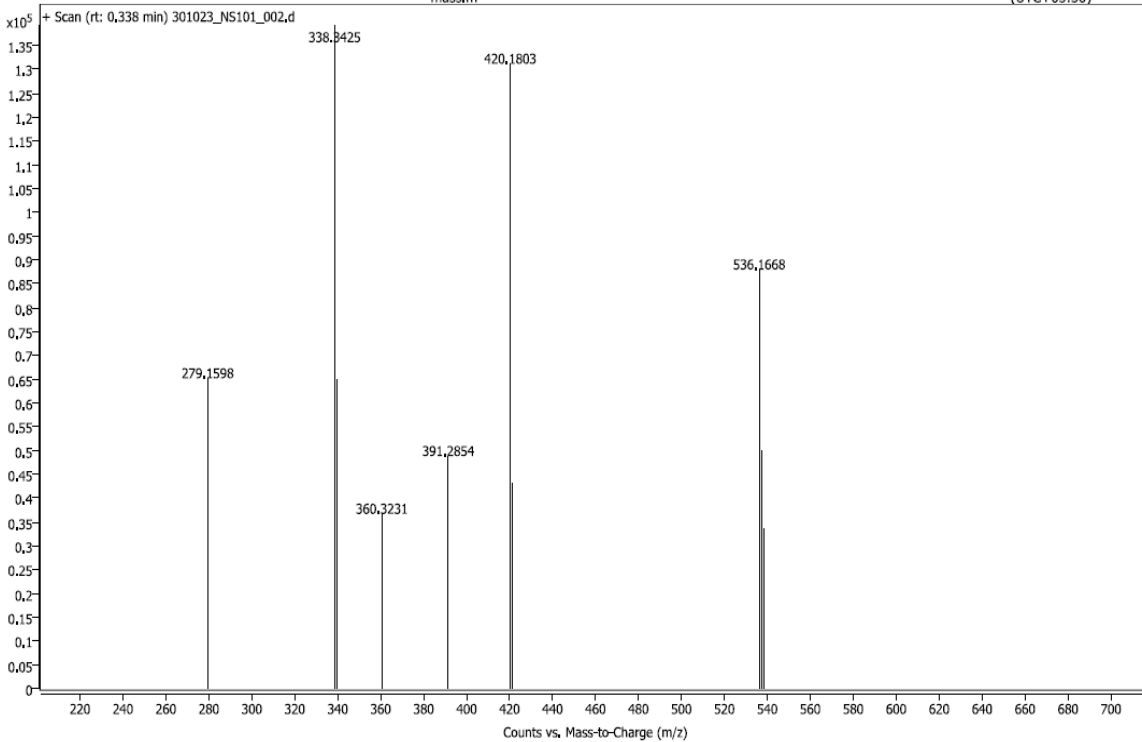
**2-(3-ethoxy-5-(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-6)**



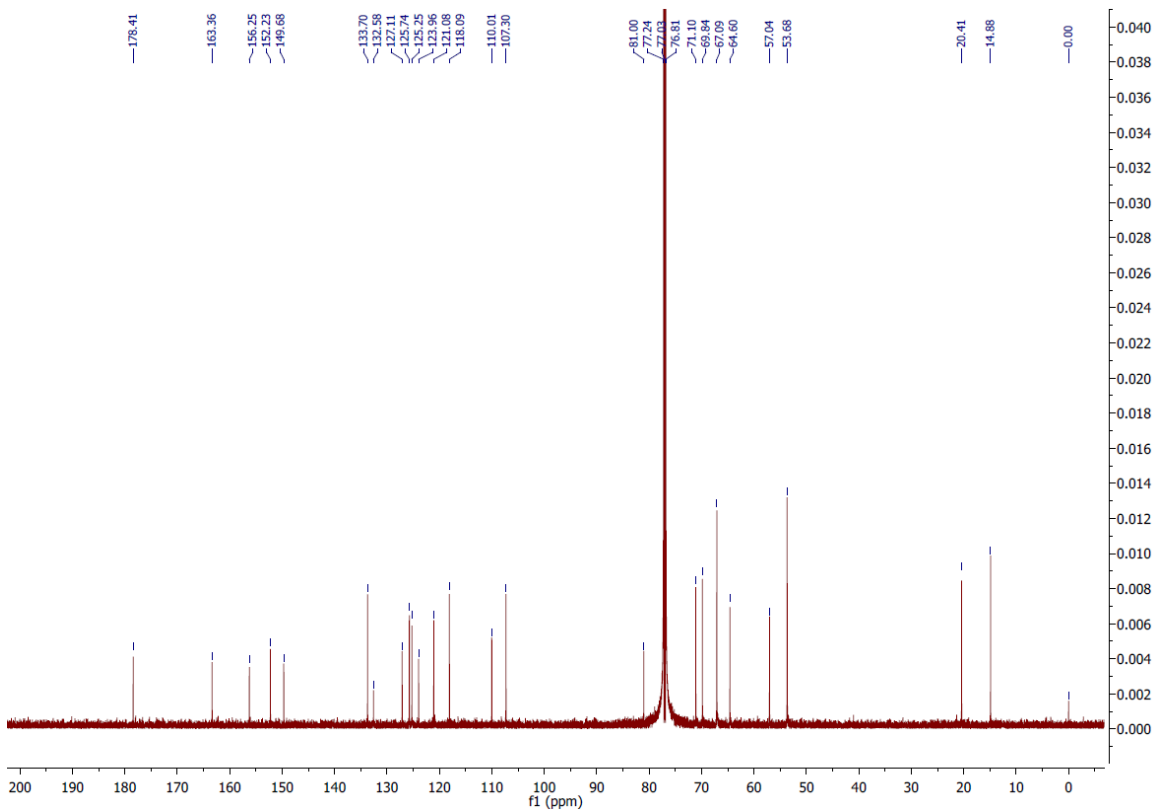
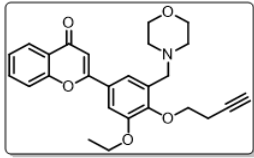
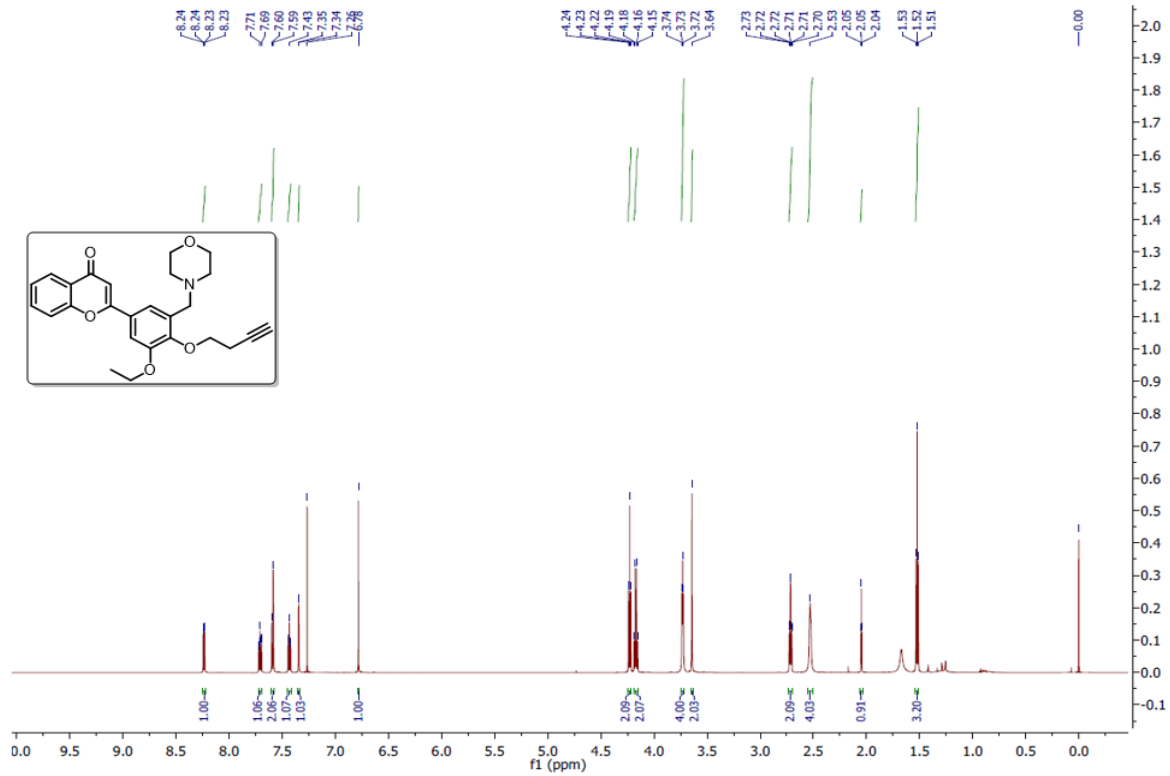




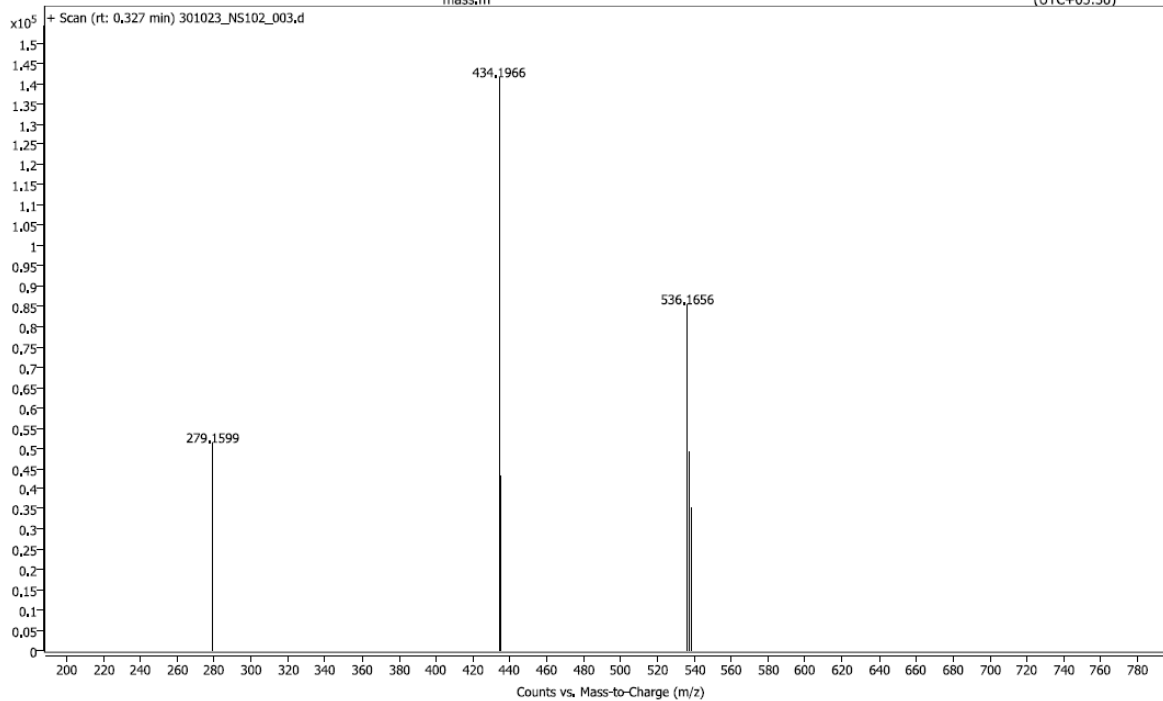
Name	1	Rack Pos.		Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.		IRM Status	Success		
Data File	301023_NS101_002.d	Method (Acq)	vinod231023 low mass.m	Comment		Acq. Time (Local)	30-10-2023 17:00:53 (UTC+05:30)



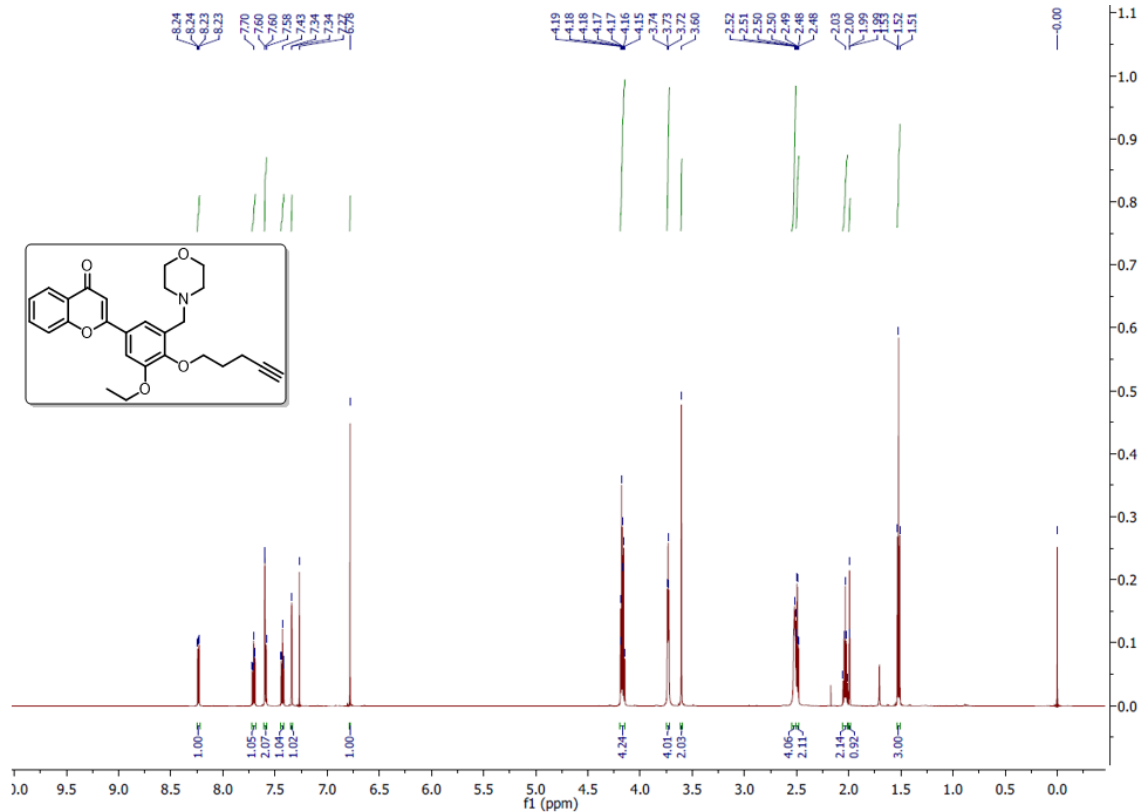
2-(4-(but-3-yn-1-yloxy)-3-ethoxy-5-(morpholinomethyl)phenyl)-4H-chromen-4-one (NS-7)

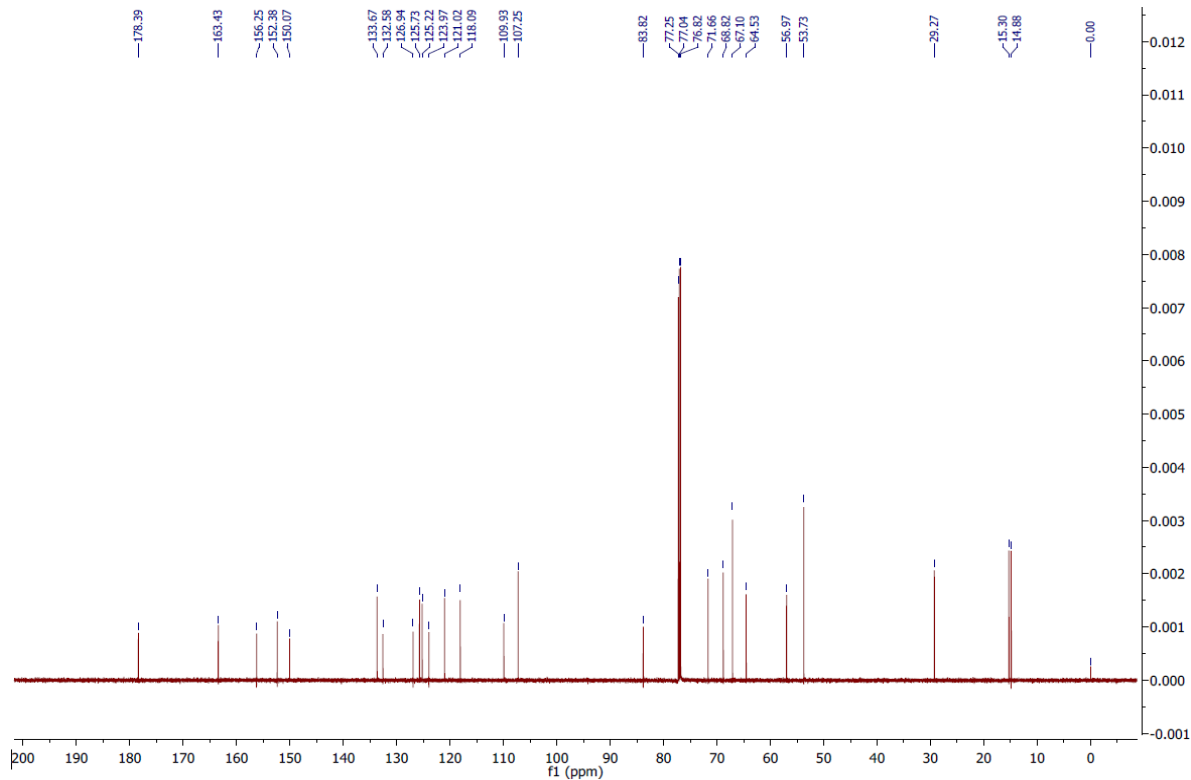


Name	Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	IRM Status	Success		
Data File	301023_NS102_003.d	Method (Acq)	vinod231023 low mass.m	Acq. Time (Local)	30-10-2023 17:07:43 (UTC+05:30)

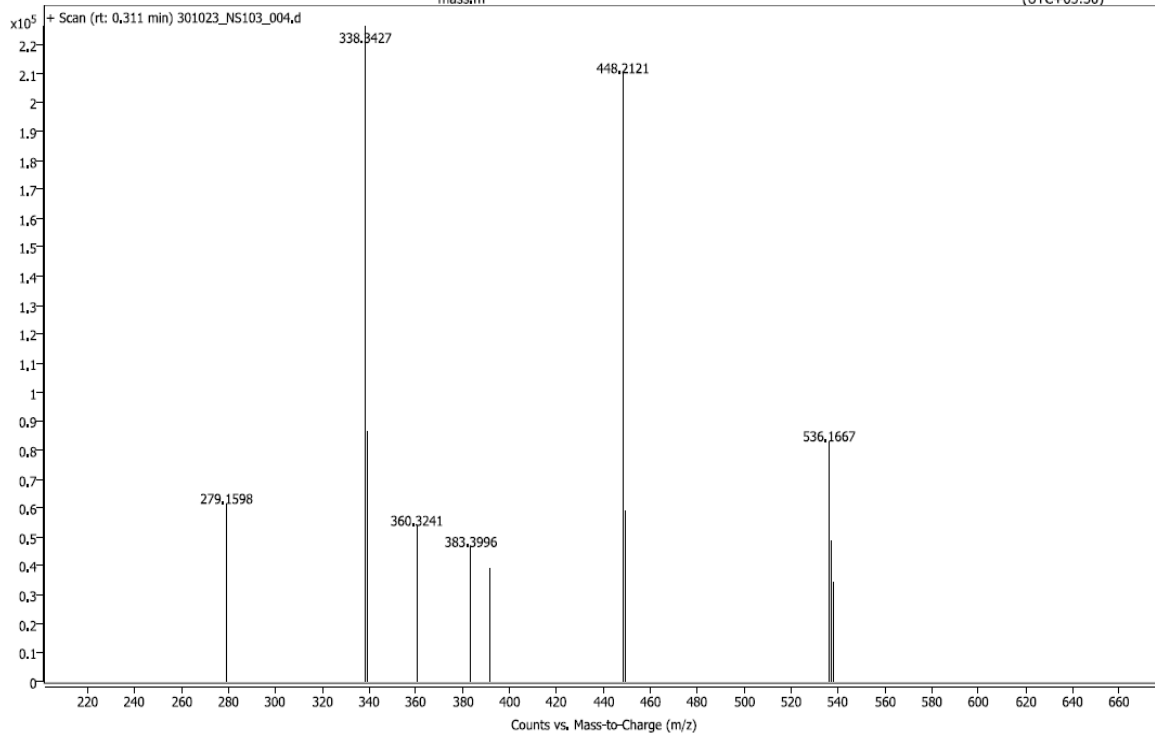


**2-(3-ethoxy-5-(morpholinomethyl)-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-8)**

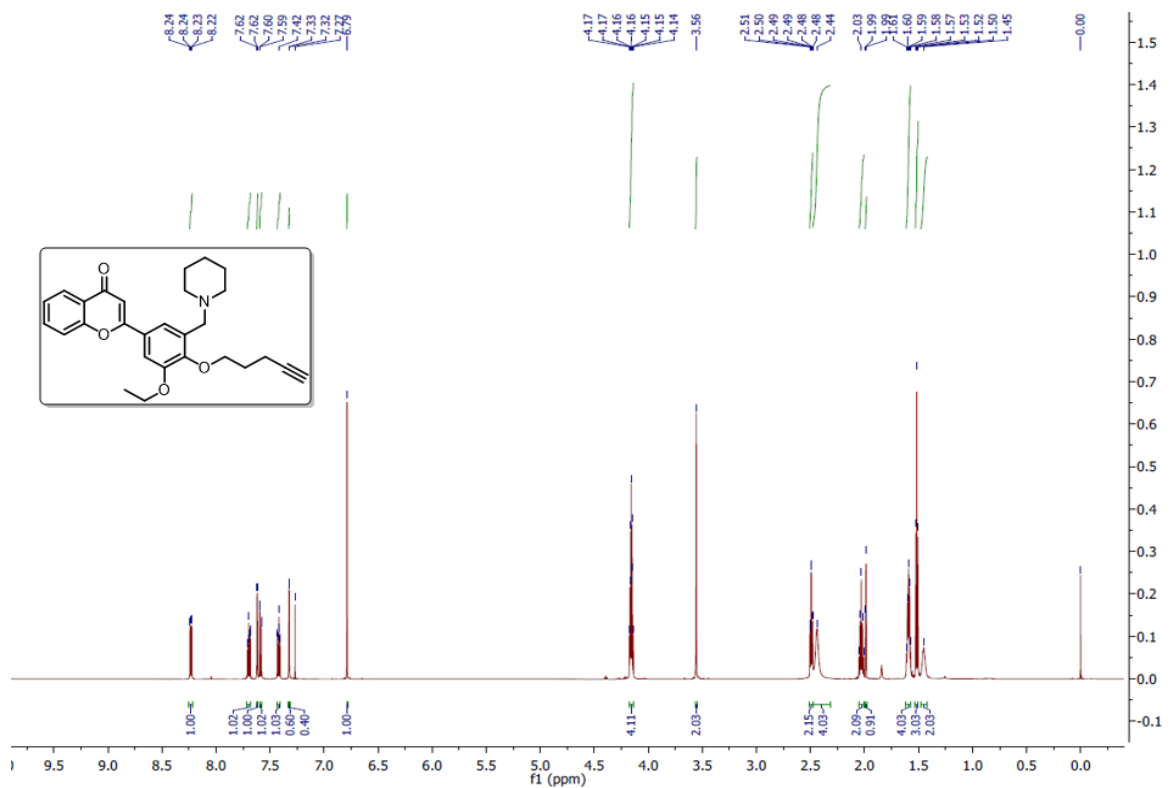




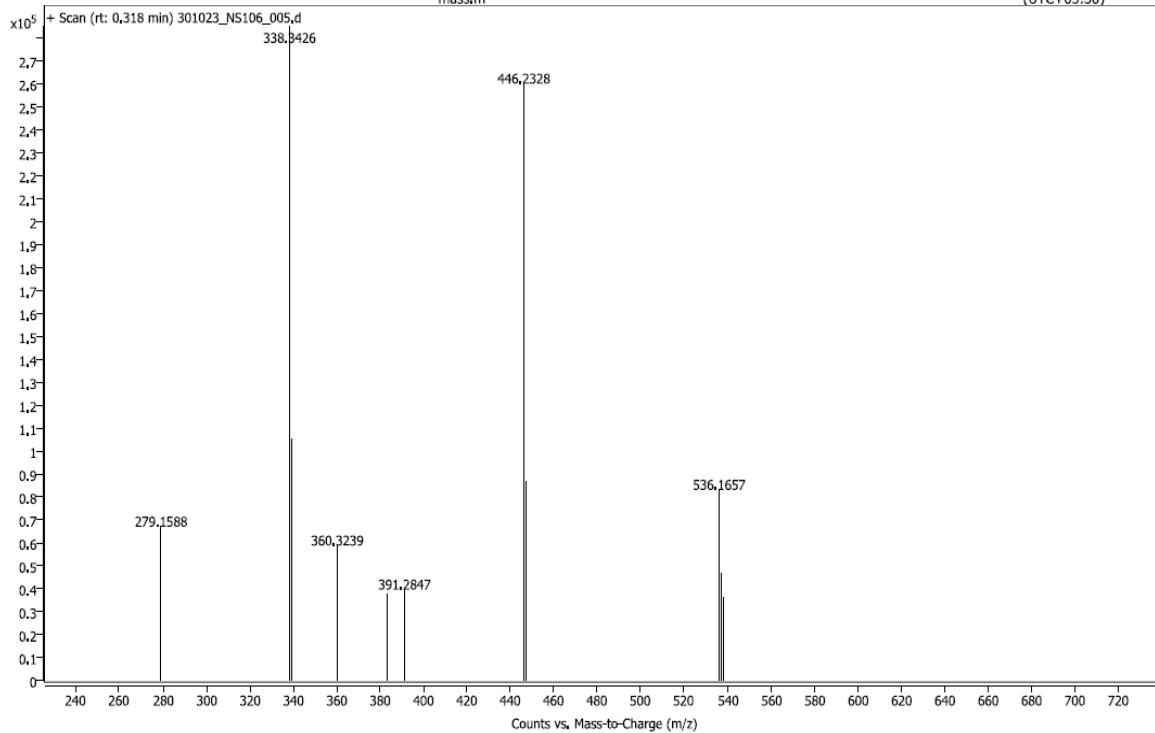
Name	Inj. Vol. (ul)	Rack Pos.	Plate Pos.	Instrument	DESKTOP-77LK19J	Operator	SYSTEM (SYSTEM)
Data File	1	301023_NS103_004.d	Method (Acq)	vinod231023 low mass.m	Success	Acq. Time (Local)	30-10-2023 17:09:37 (UTC+05:30)



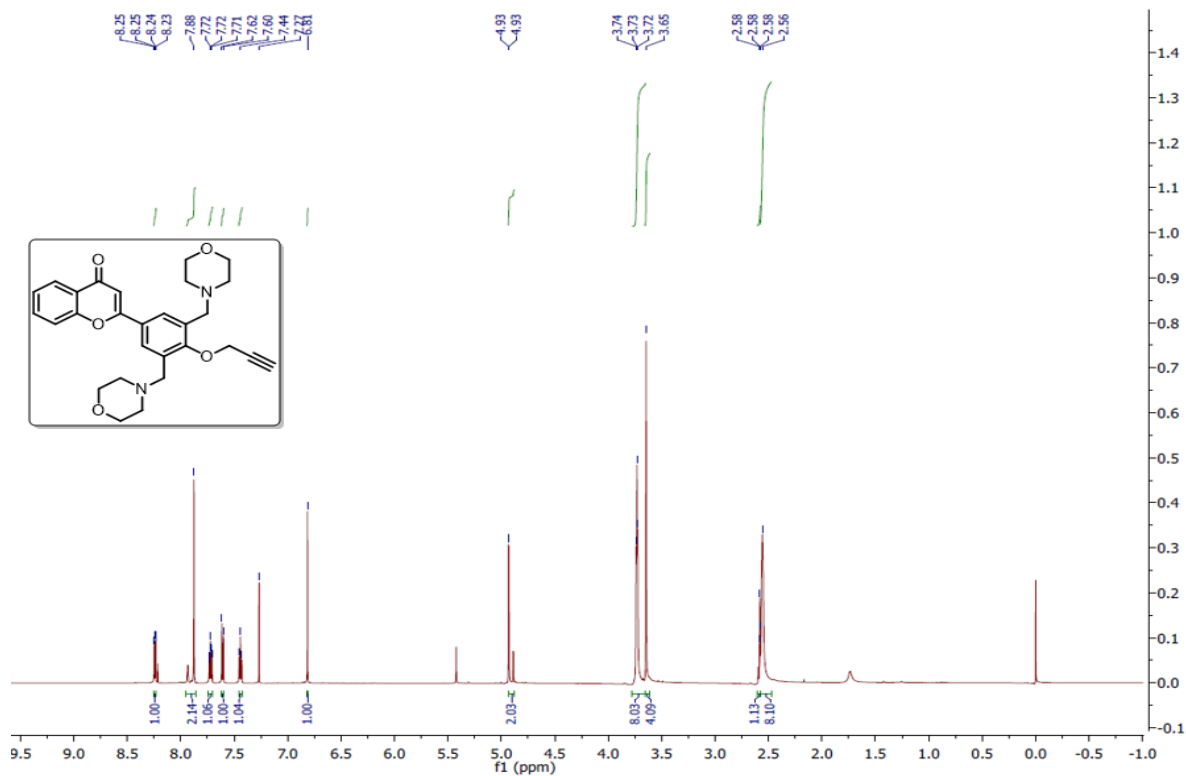
2-(3-ethoxy-4-(pent-4-yn-1-yloxy)-5-(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-9)

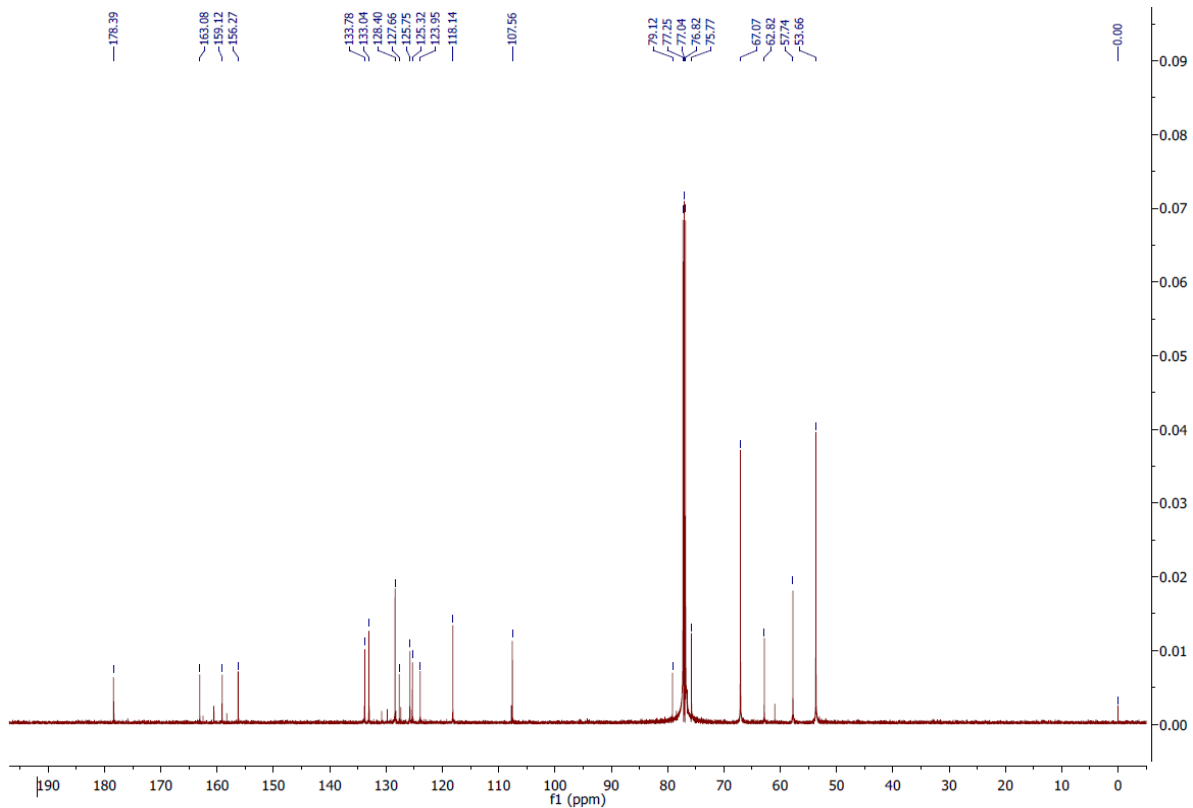


Name	1	Rack Pos.		Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)		Plate Pos.		IRM Status	Success		
Data File	301023_NS106_005.d	Method (Acq)	vinod231023 low mass.m	Comment		Acq. Time (Local)	30-10-2023 17:11:53 (UTC+05:30)

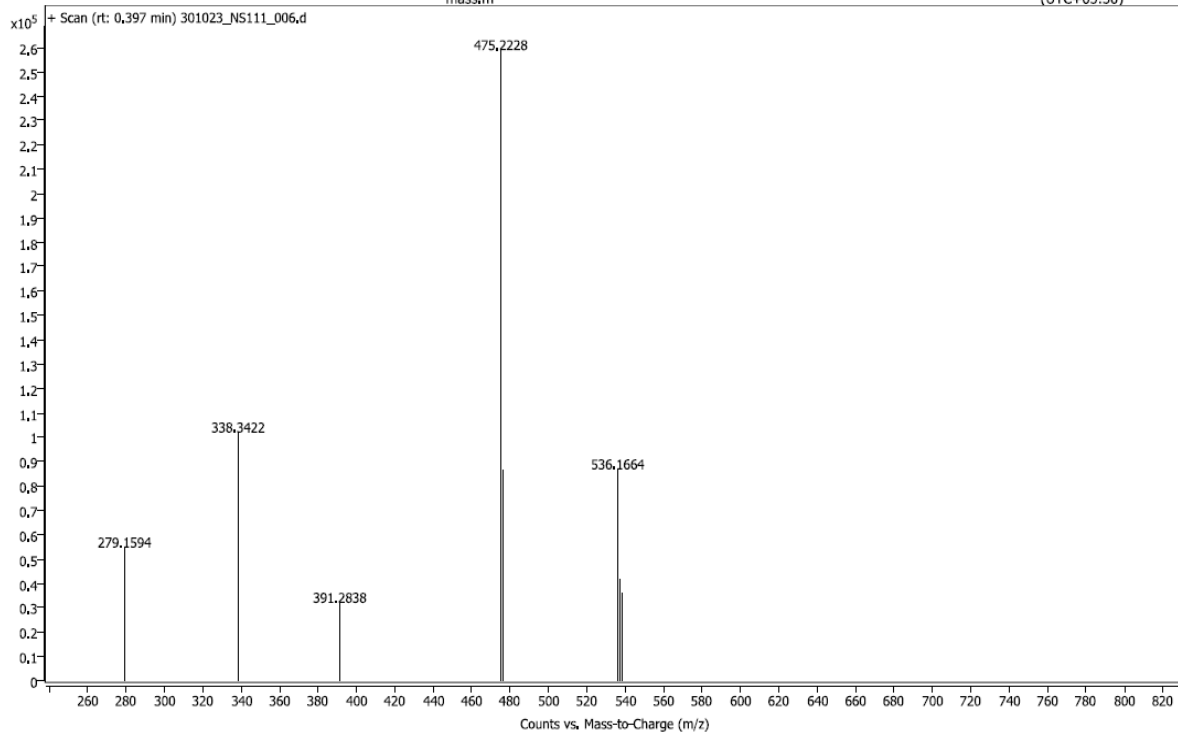


**2-(3,5-bis(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-10)**

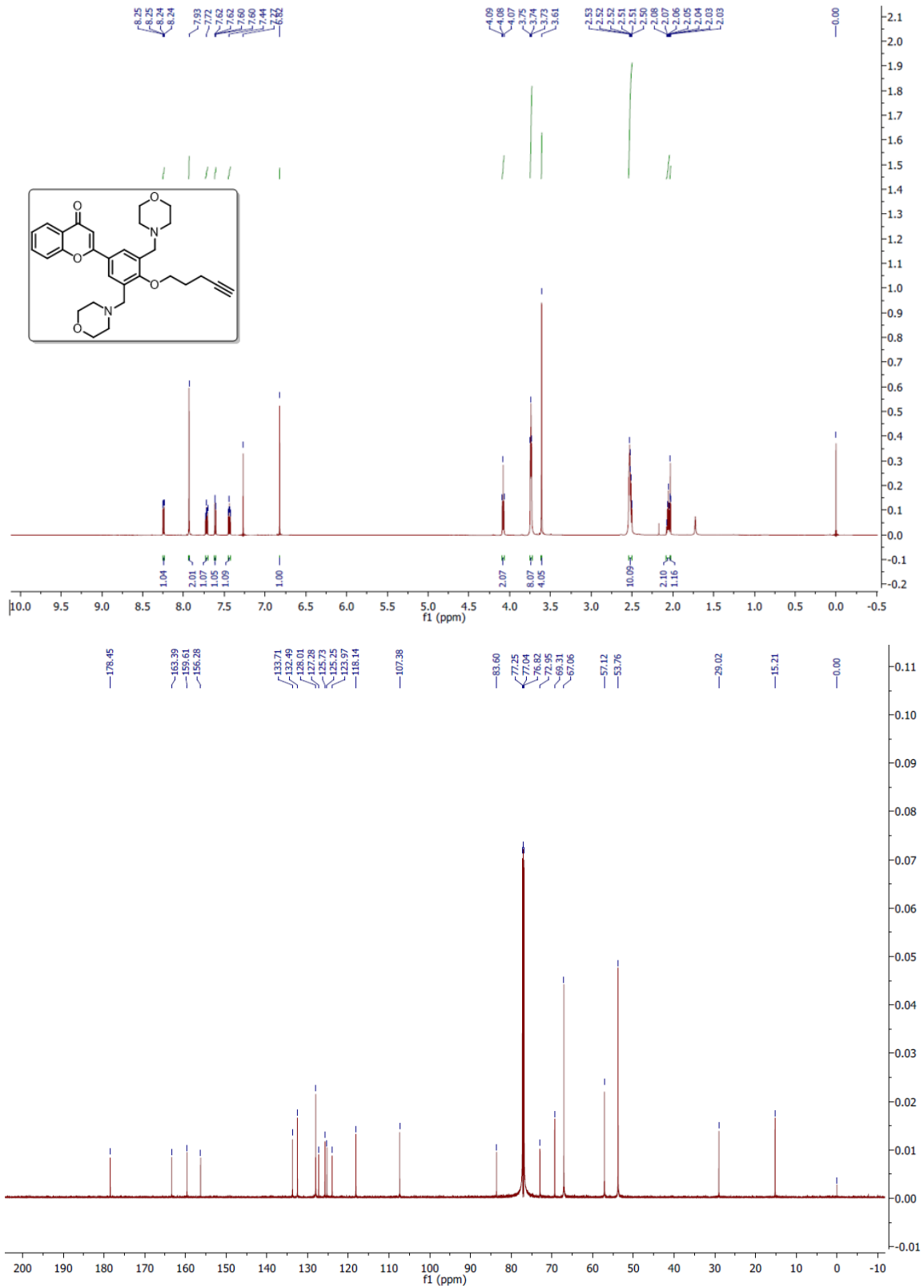




Name	Inj. Vol. (ul)	Rack Pos.	Plate Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Data File	1	301023_NS111_006.d	Method (Acq)	vinod231023 low mass.m	Success	Acq. Time (Local)	30-10-2023 17:13:49 (UTC+05:30)

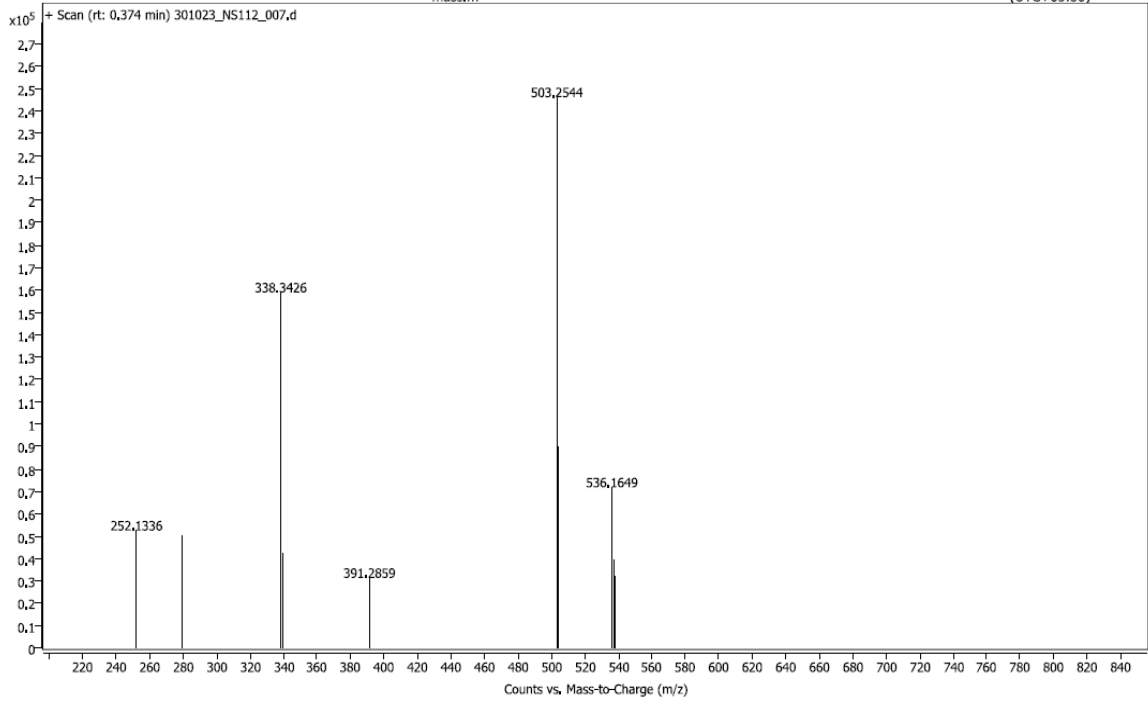


2-(3,5-bis(morpholinomethyl)-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-11)

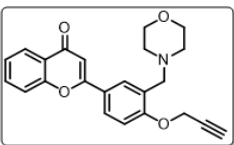
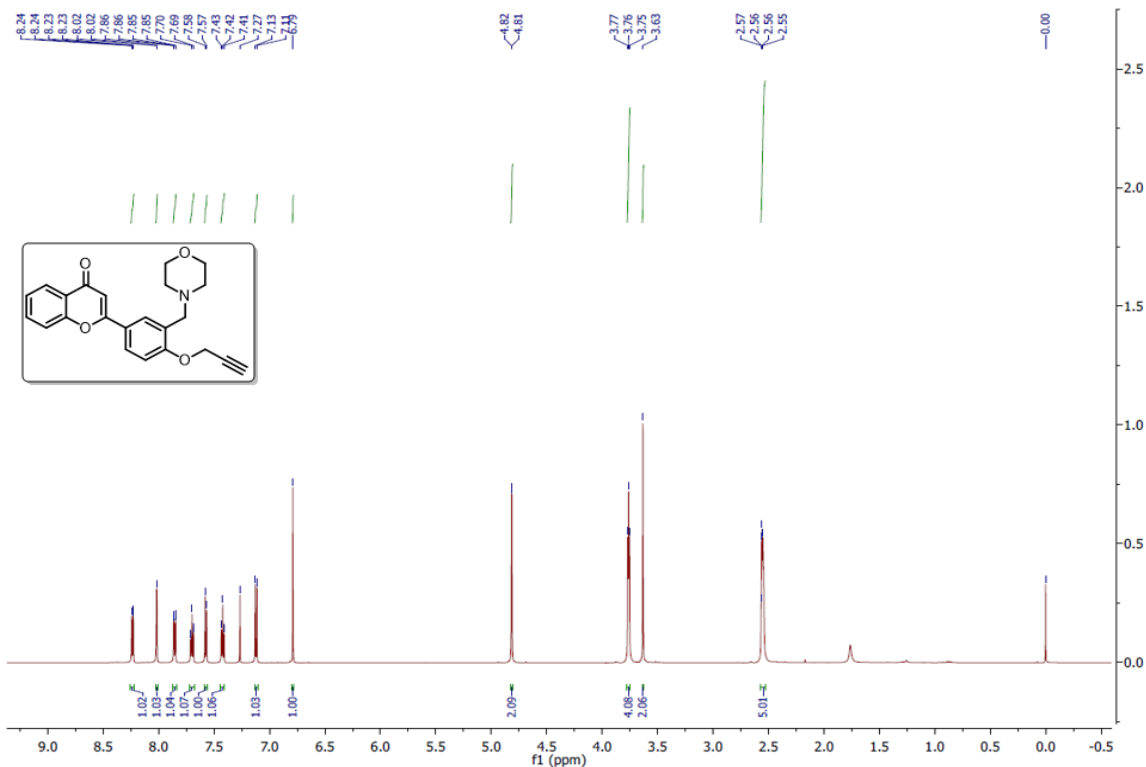


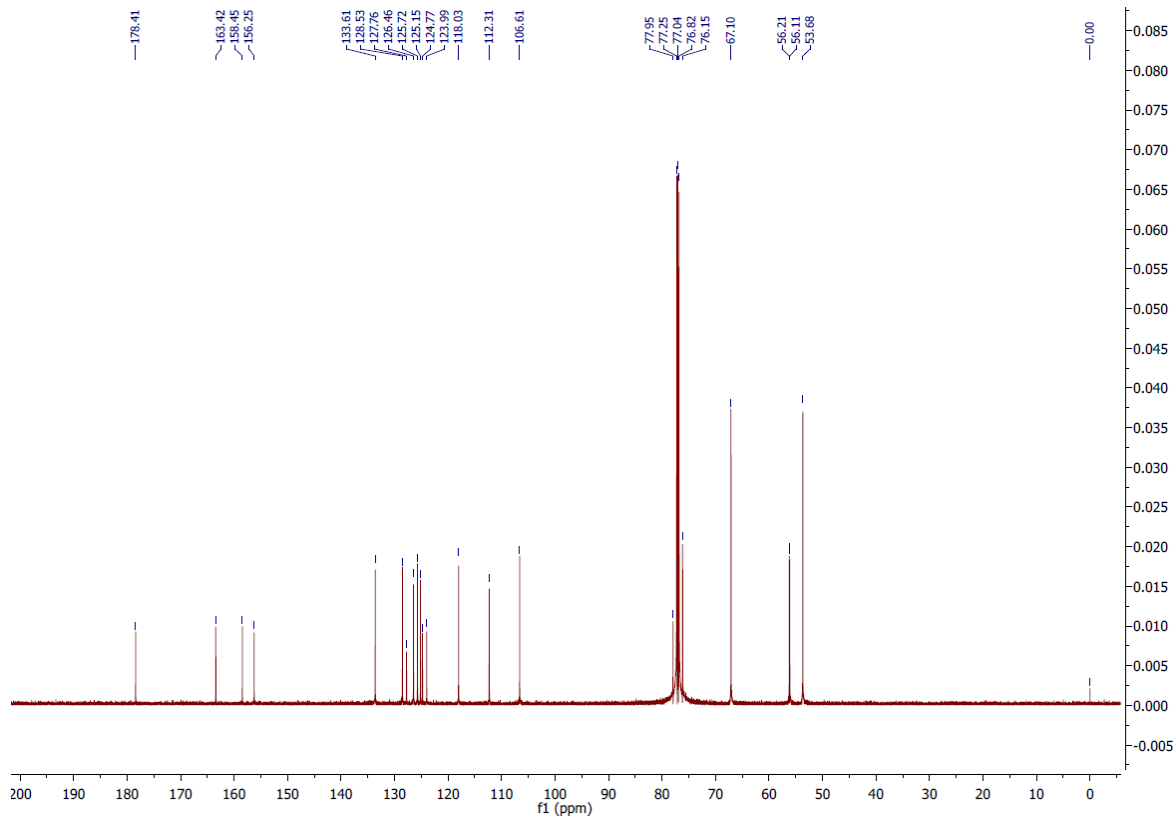


Name	1	Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	301023_NS112_007.d	Plate Pos.	IRM Status	Success		
Data File	301023_NS112_007.d	Method (Acq)	vinod231023 low mass.m	Comment	Acq. Time (Local)	30-10-2023 17:15:42 (UTC+05:30)

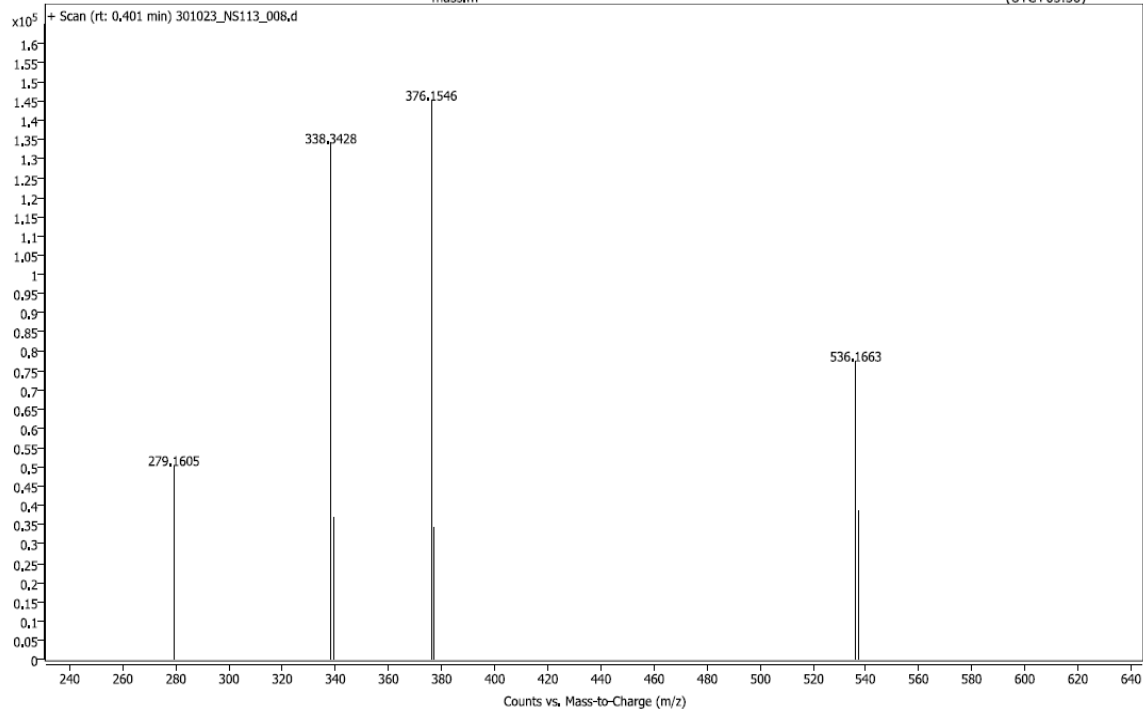


*2-(3-(morpholinomethyl)-4-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-12)*

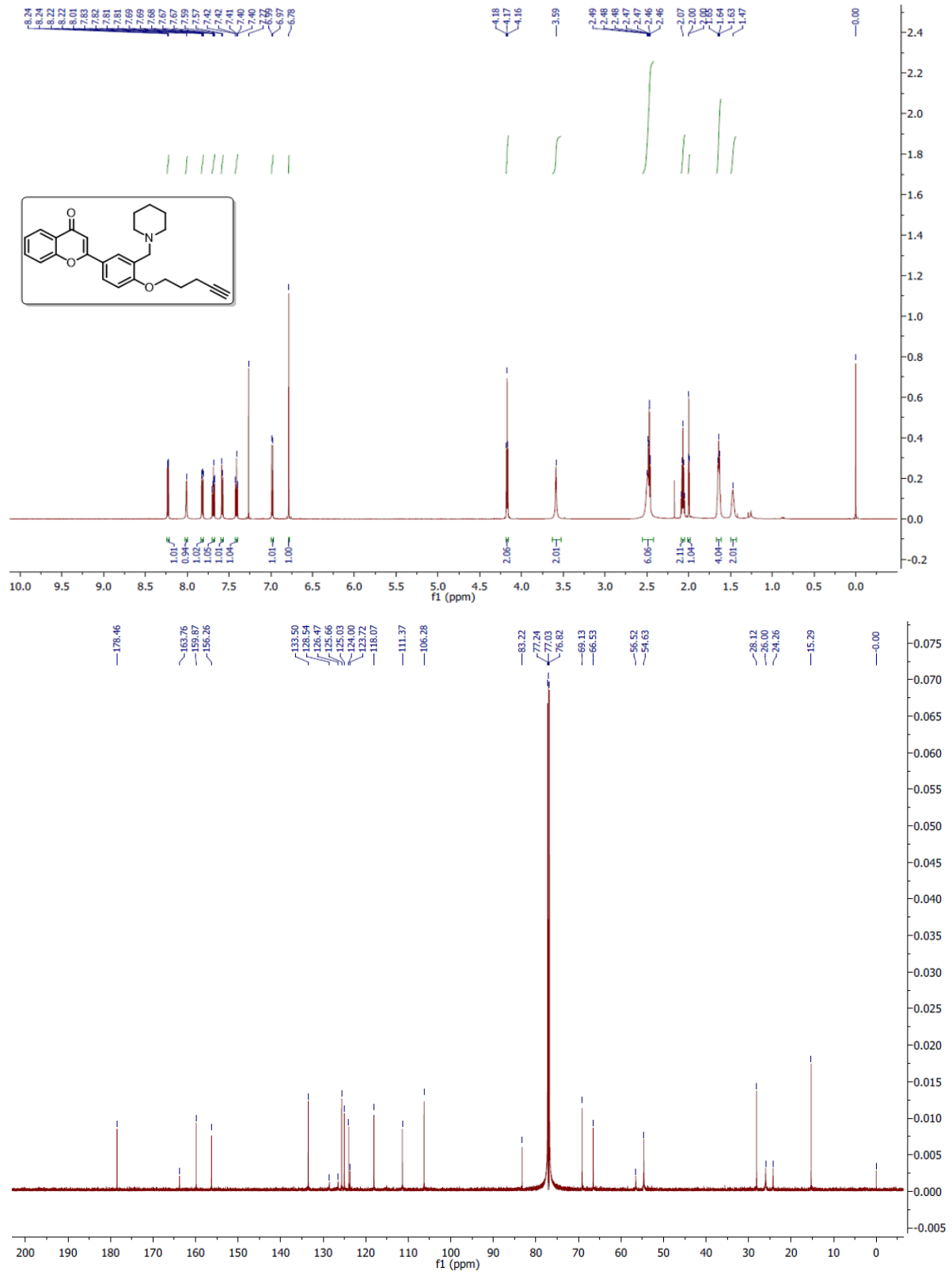




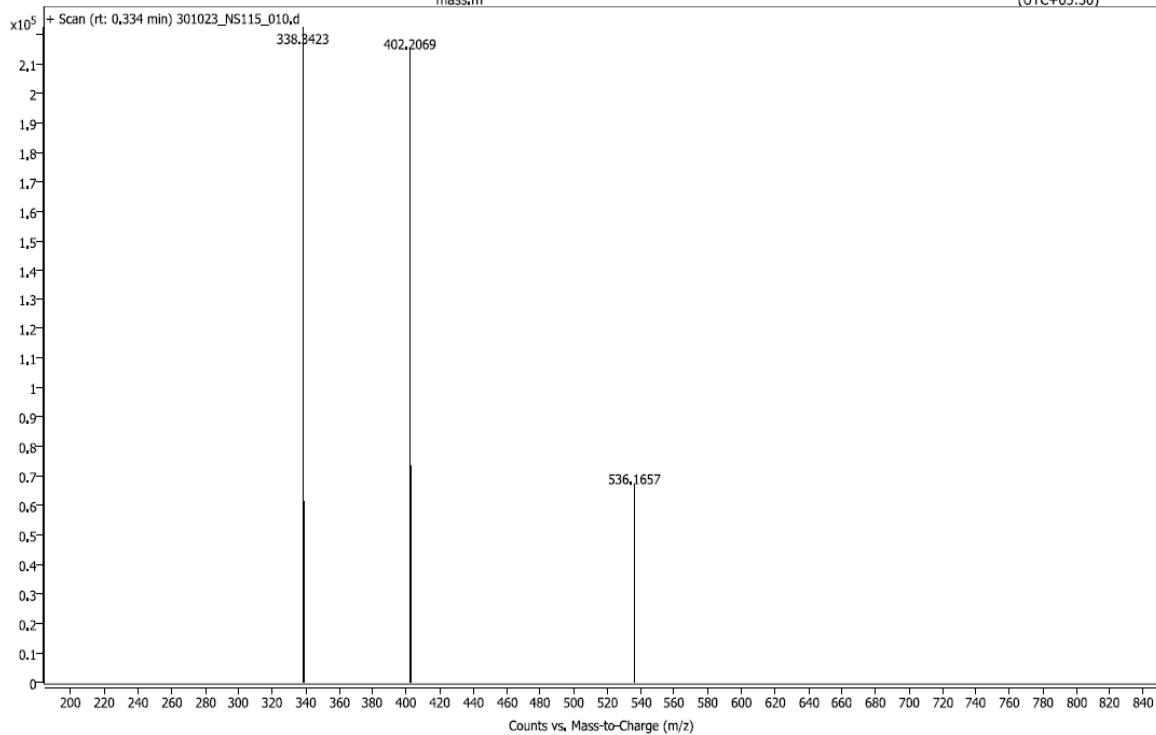
Name		Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.	IRM Status	Success		
Data File	301023_NS113_008.d	Method (Acq)	vinod231023 low mass.m	Comment	Acq. Time (Local)	30-10-2023 17:17:34 (UTC+05:30)



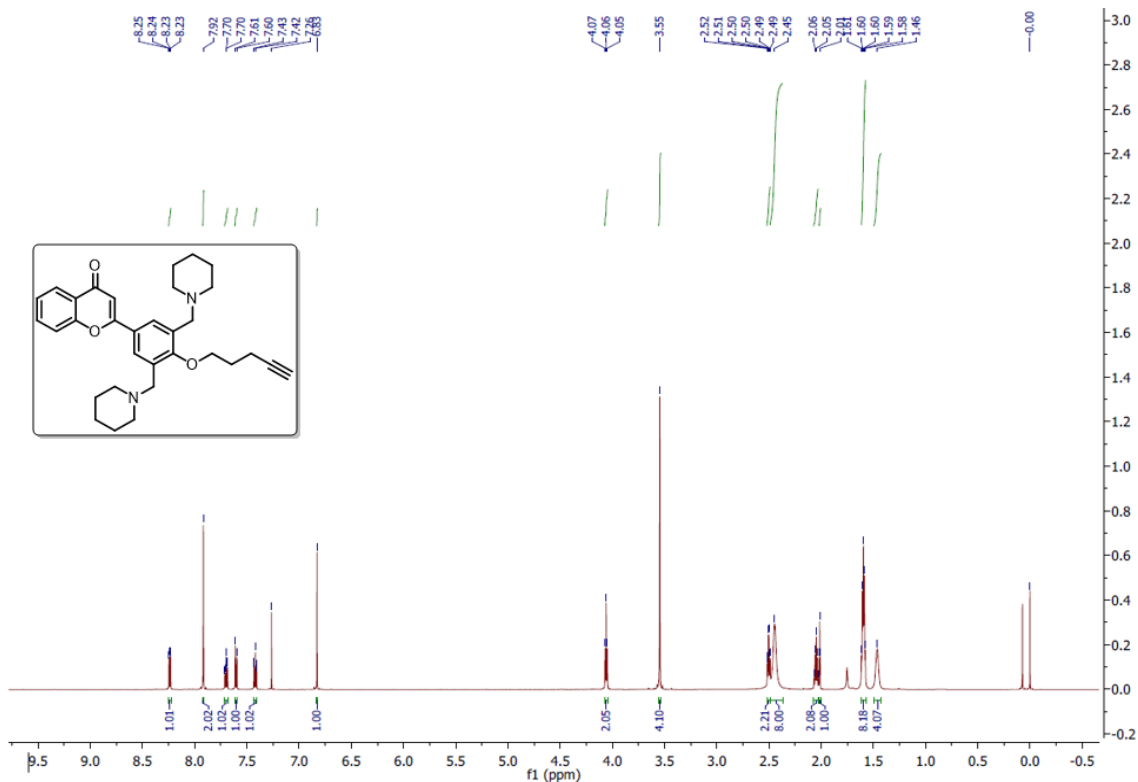
2-(4-(pent-4-yn-1-yloxy)-3-(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-13)

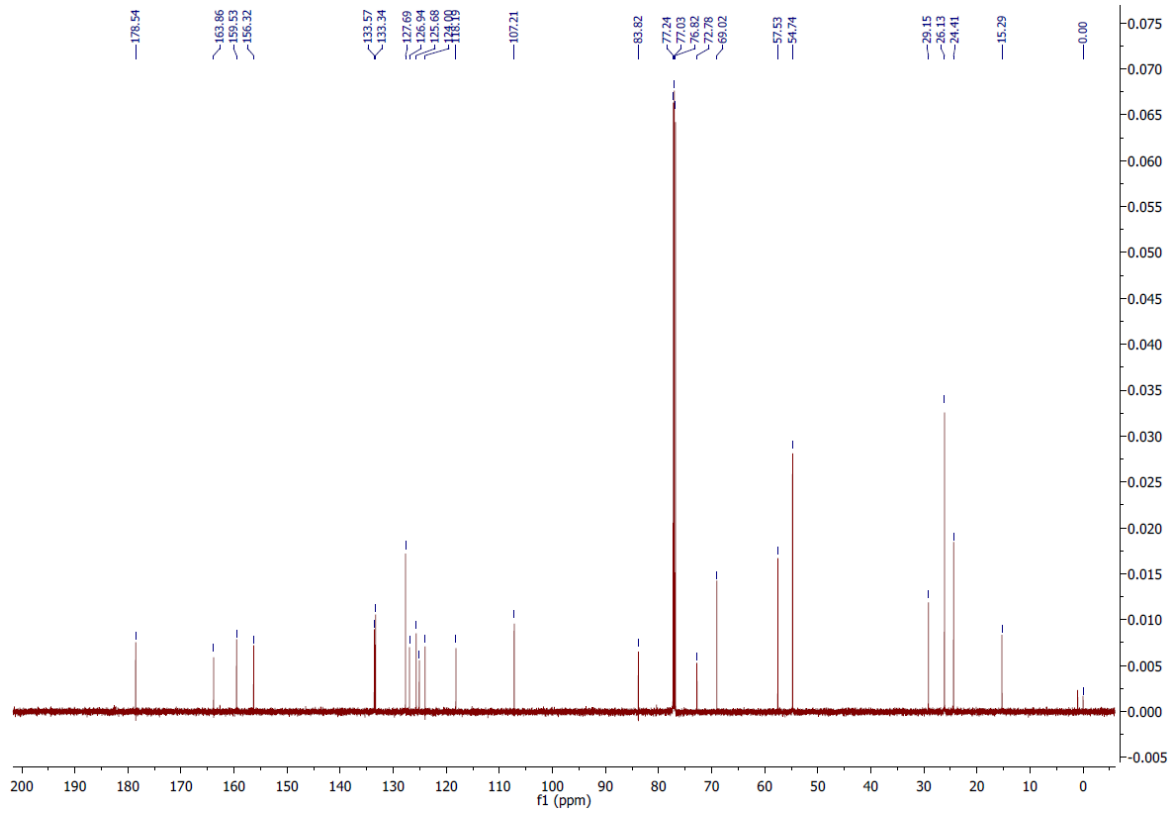


Name	1	Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.	IRM Status	Success		
Data File	301023_NS115_010.d	Method (Acq)	vinod231023 low mass.m		Acq. Time (Local)	30-10-2023 17:22:05 (UTC+05:30)

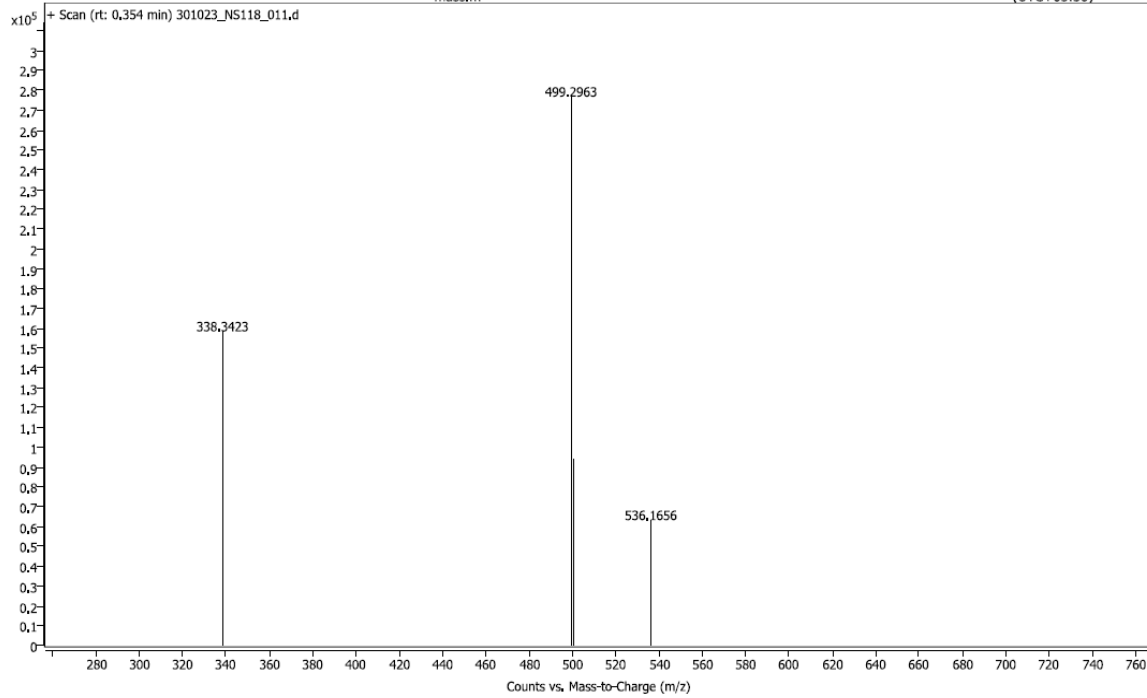


**2-(4-(pent-4-yn-1-yloxy)-3,5-bis(piperidin-1-ylmethyl)phenyl)-4H-chromen-4-one (NS-14)**

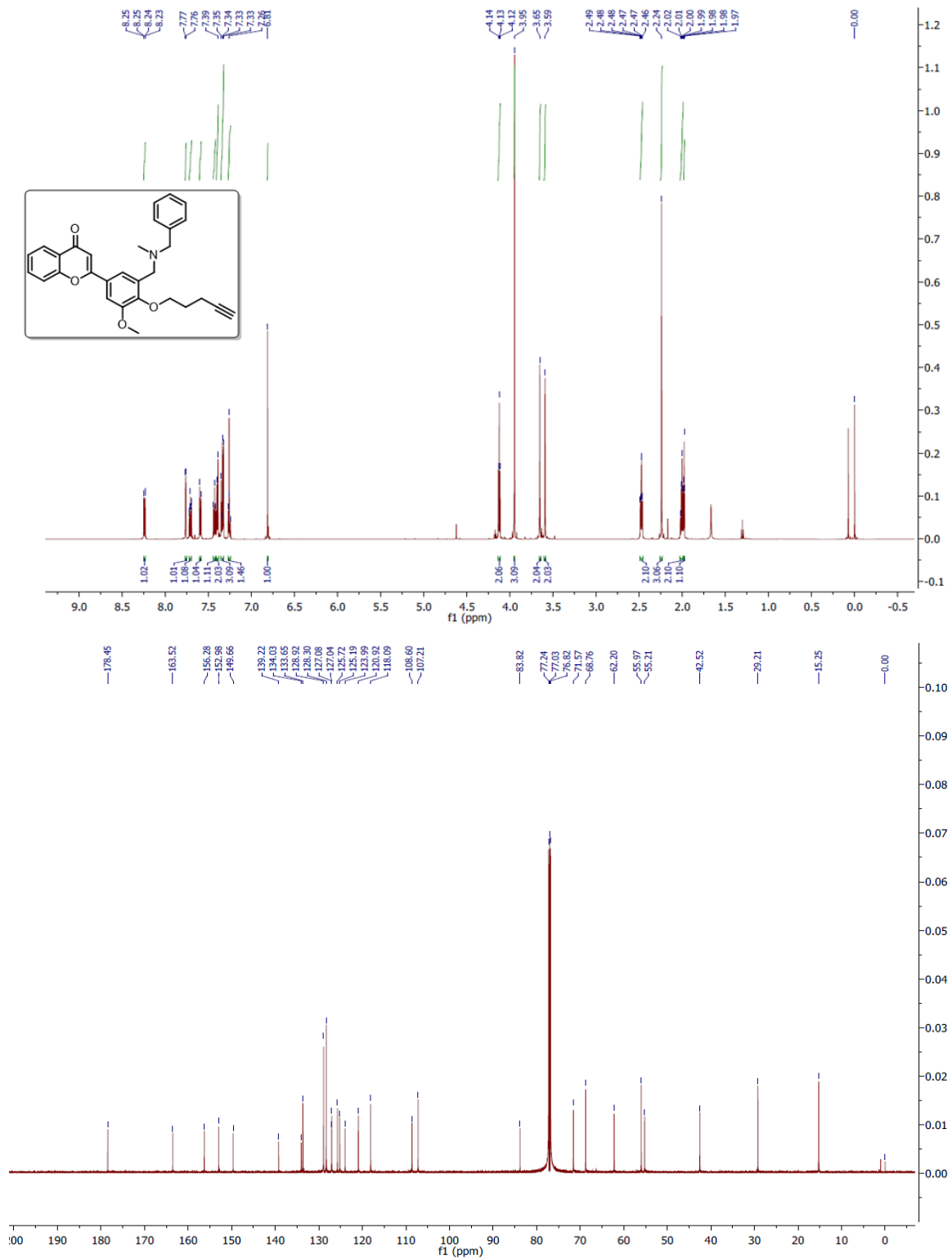




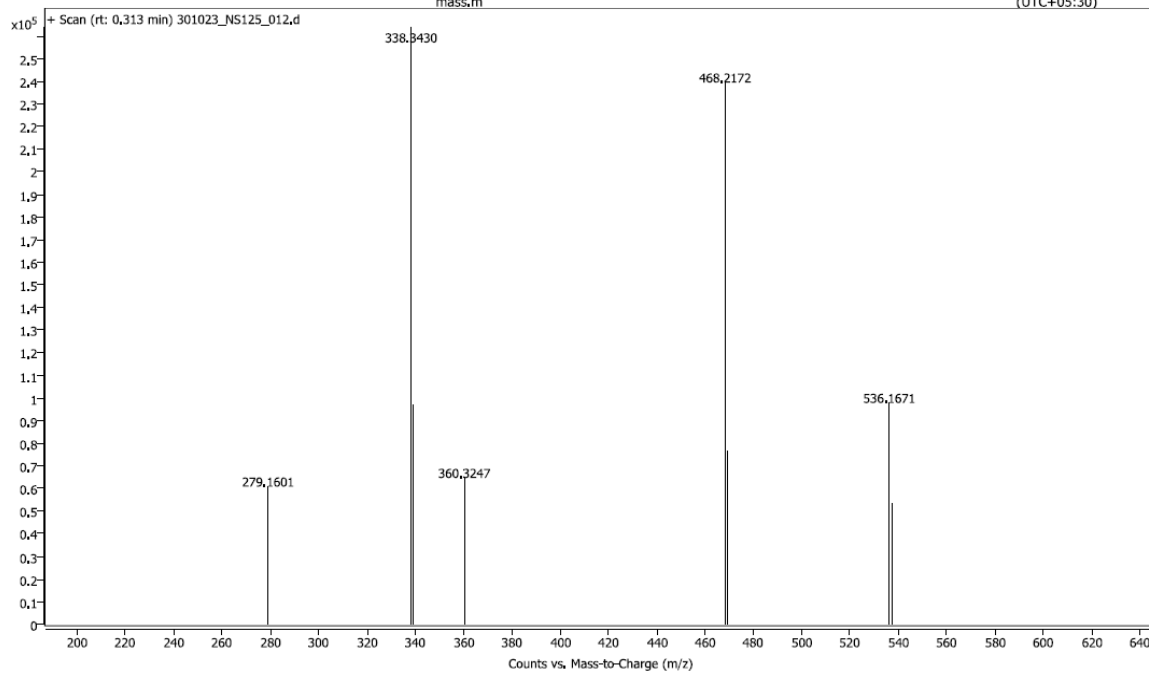
Name	Inj. Vol. (ul)	Rack Pos.	Plate Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Data File	1	301023_NS118_011.d	Method (Acq)	vinod231023 low mass.m	Success	Acq. Time (Local)	30-10-2023 17:24:16 (UTC+05:30)



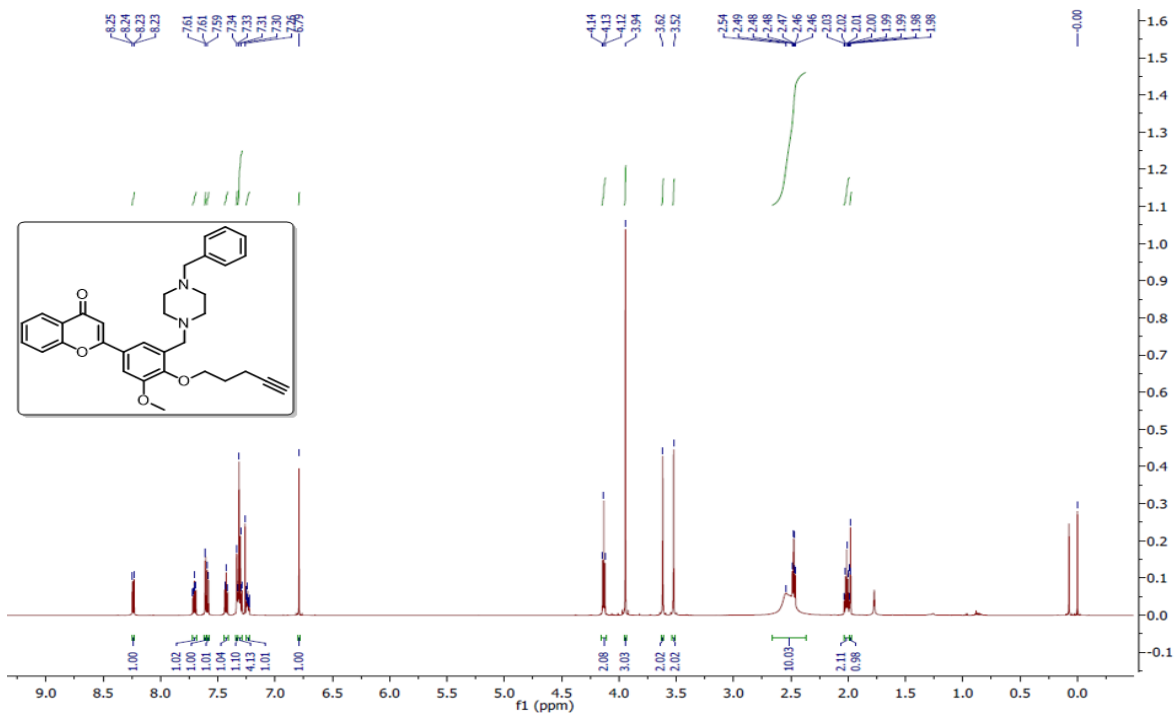
2-(3-((benzyl(methyl)amino)methyl)-5-methoxy-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-15)

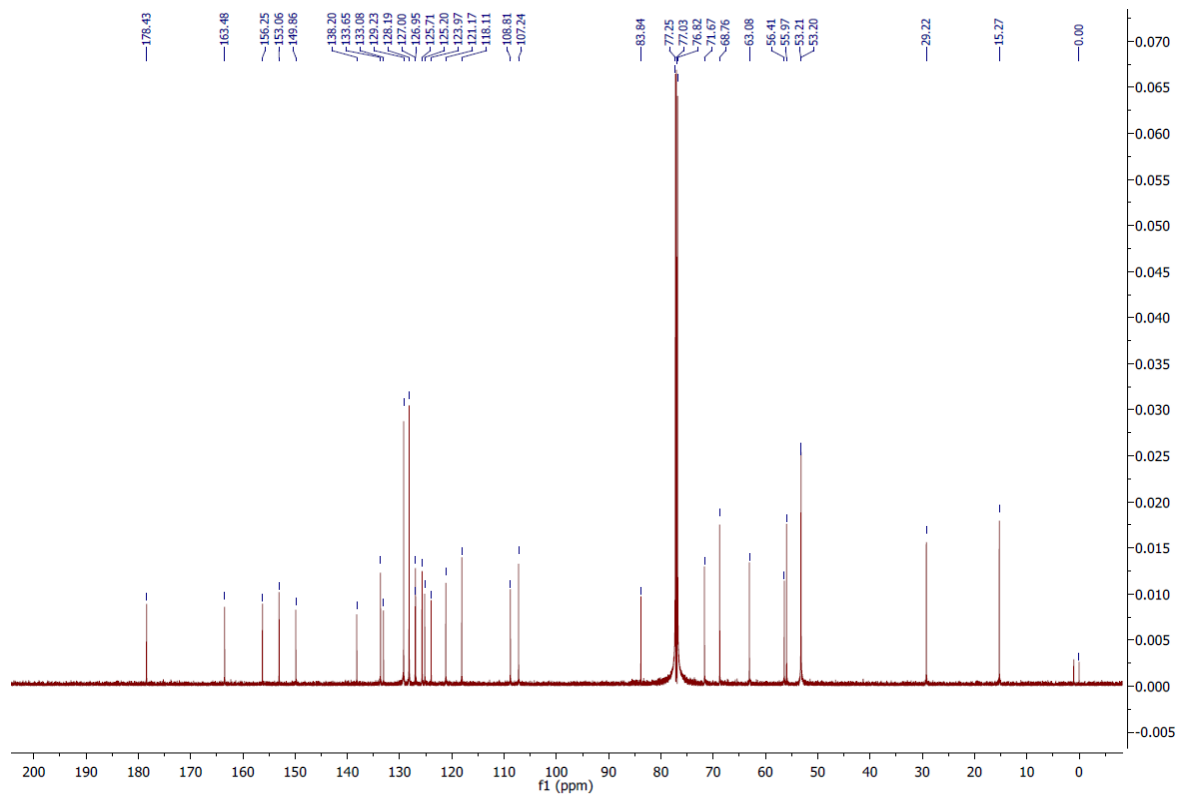


Name	1	Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.	IRM Status	Success		
Data File	301023_NS125_012.d	Method (Acq)	vinod231023 low mass.m	Comment	Acq. Time (Local)	30-10-2023 17:26:11 (UTC+05:30)

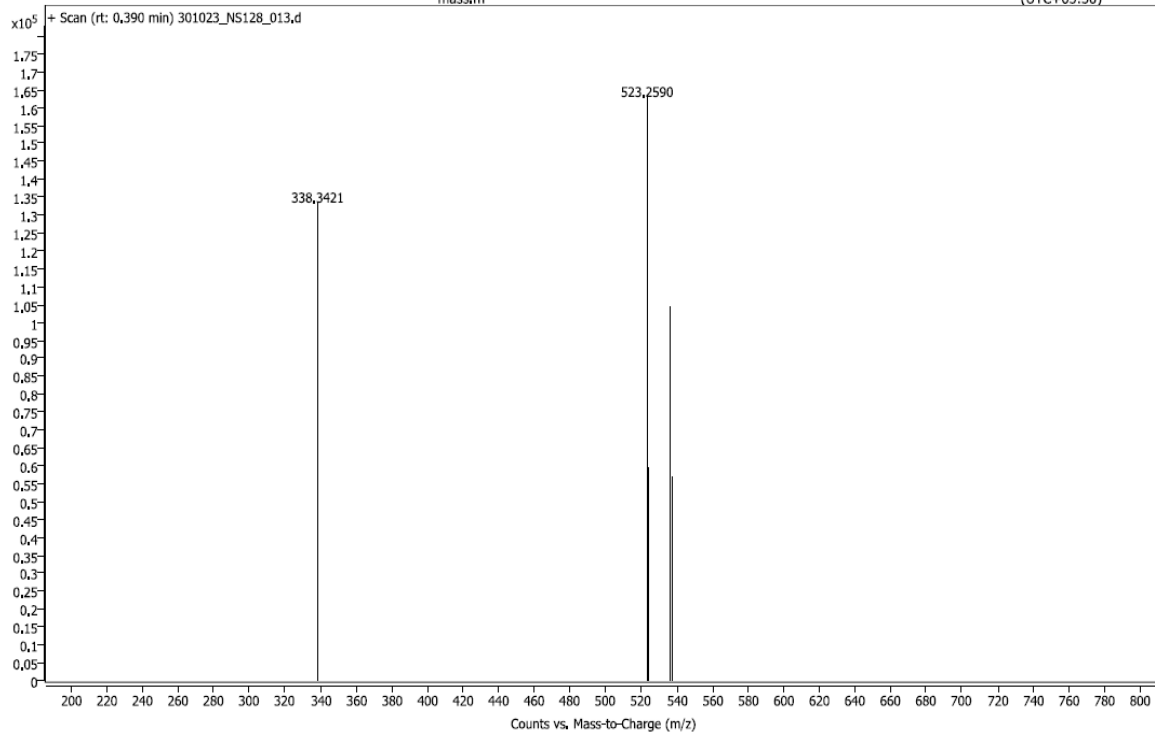


*2-(3-((4-benzylpiperazin-1-yl)methyl)-5-methoxy-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-16)*



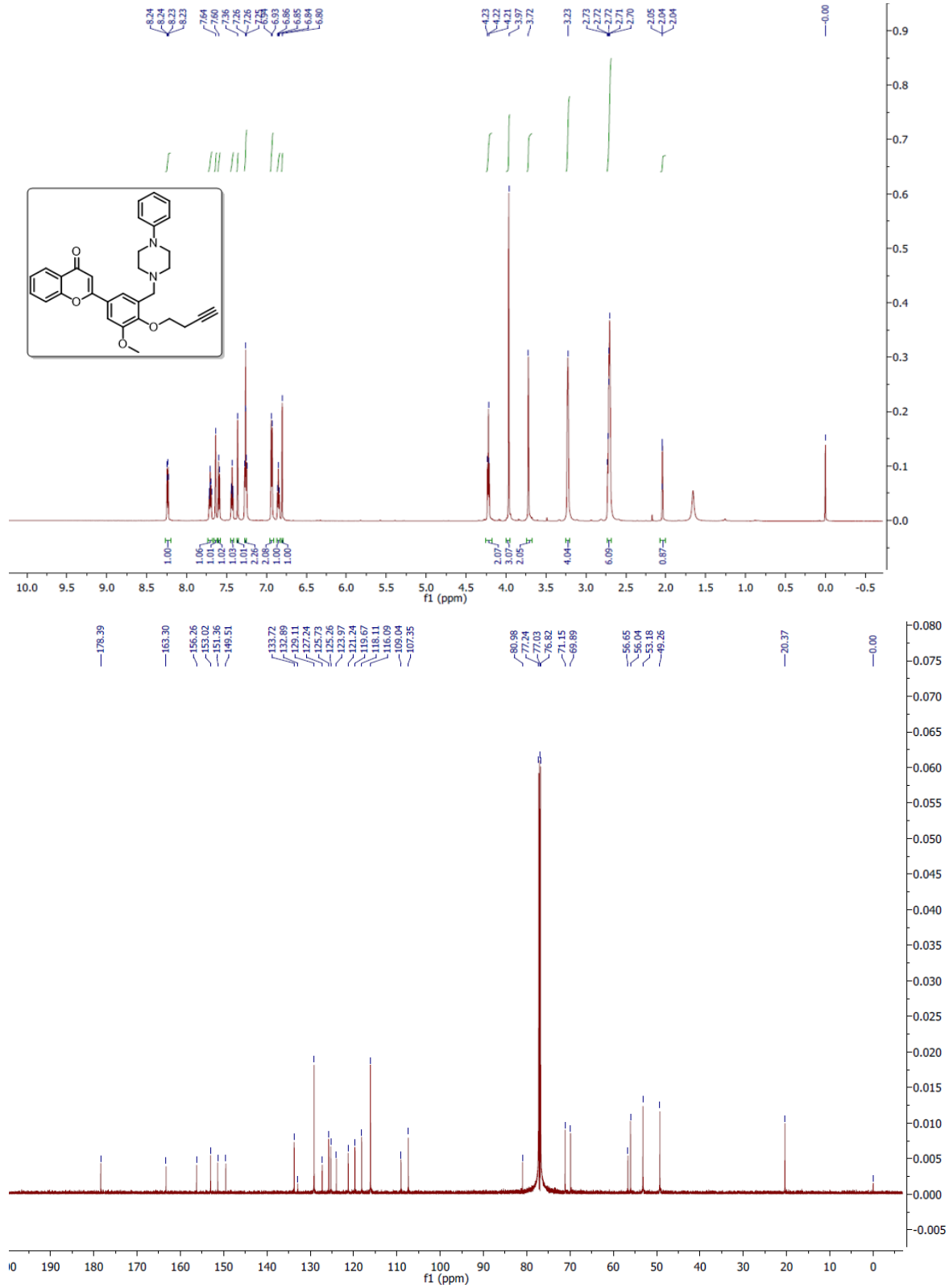


Name	Inj. Vol. (ul)	Rack Pos.	Plate Pos.	Method (Acq)	Instrument	IRM Status	Comment	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Data File	1	301023_NS128_013.d	vinod231023 low mass.m					Success	Acq. Time (Local)	30-10-2023 17:28:10 (UTC+05:30)

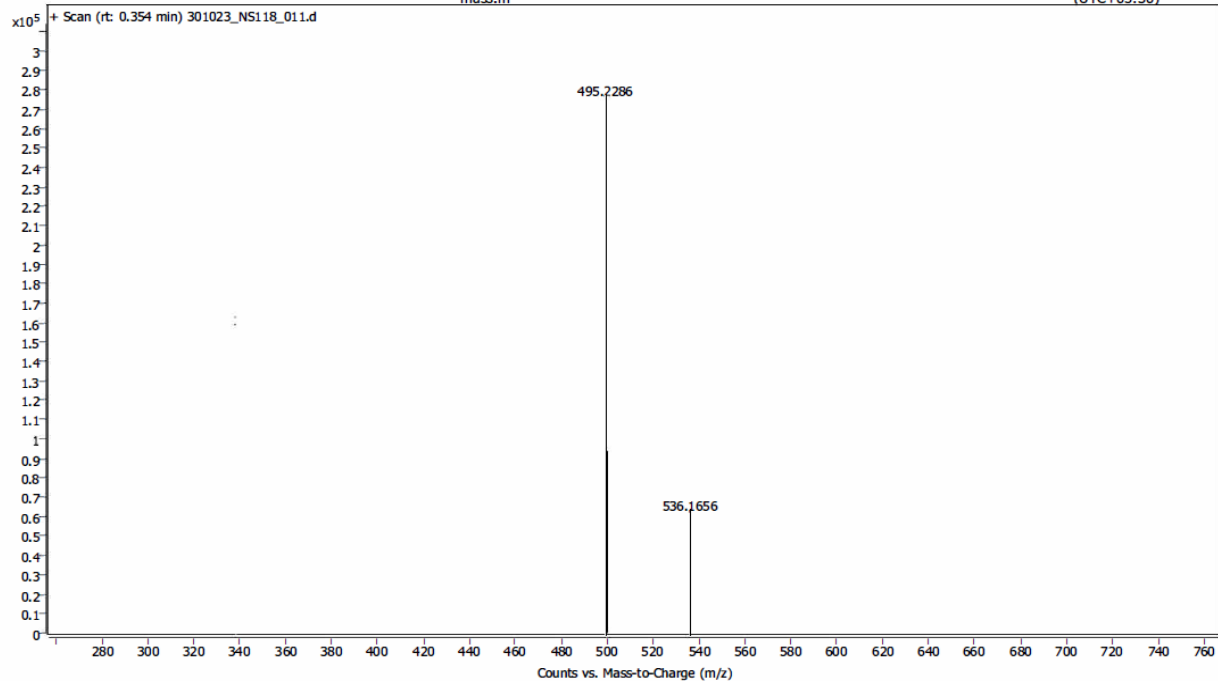




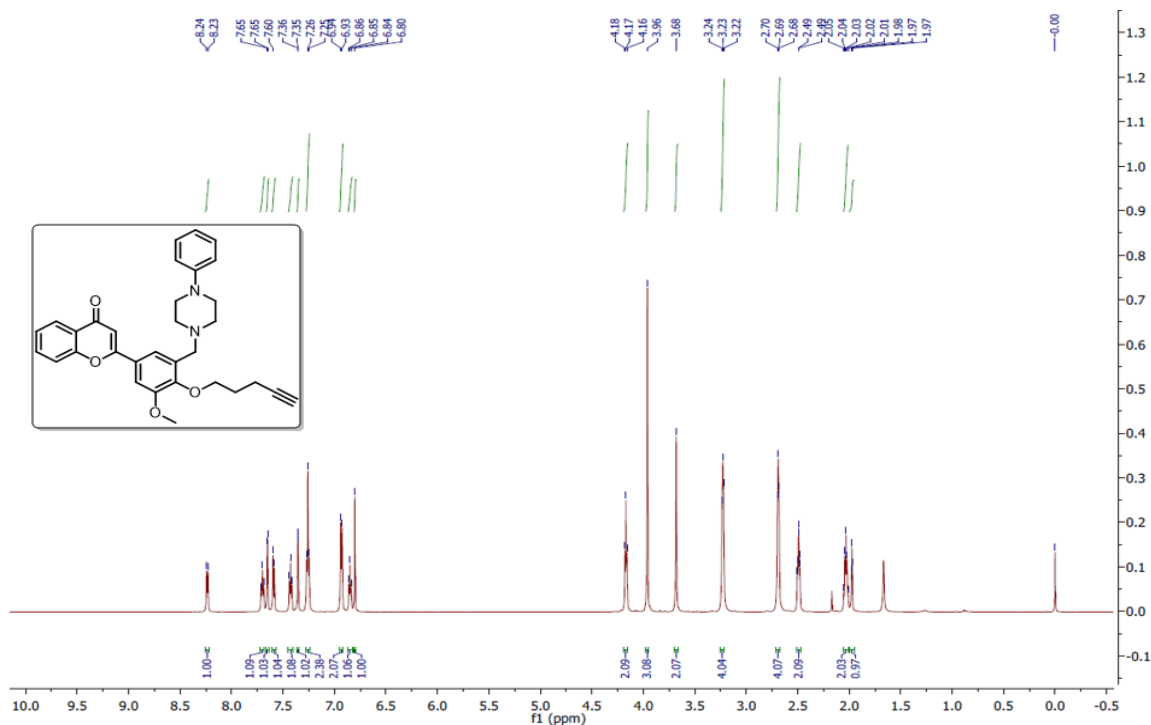
2-(3-methoxy-4-(pent-4-yn-1-yloxy)-5-((4-phenylpiperazin-1-yl)methyl)phenyl)-4H-chromen-4-one (NS-17)

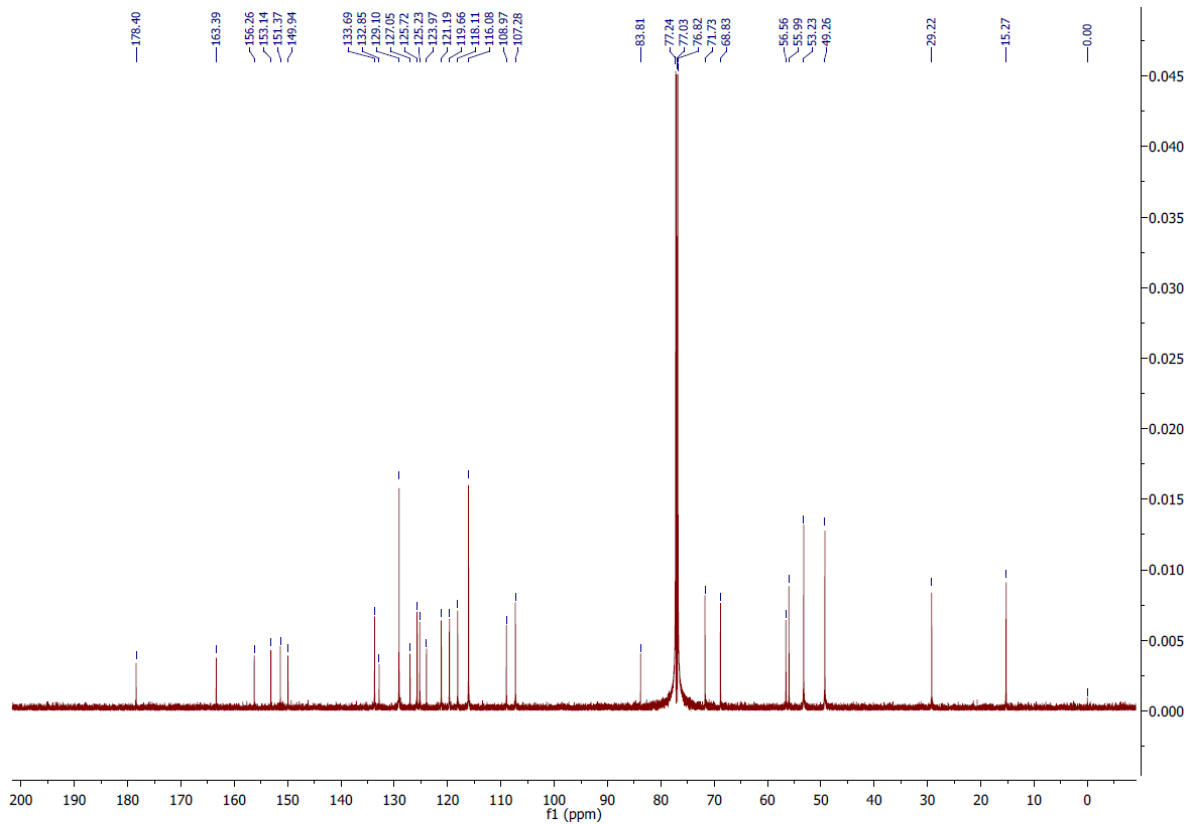


Name	Inj. Vol. (ul)	Rack Pos.	Plate Pos.	Instrument	IRM Status	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Data File	301023_NS131.d	Method (Acq)	vinod231023 low mass.m	Comment	Success	Acq. Time (Local)	30-10-2023 17:54:26 (UTC+05:30)	

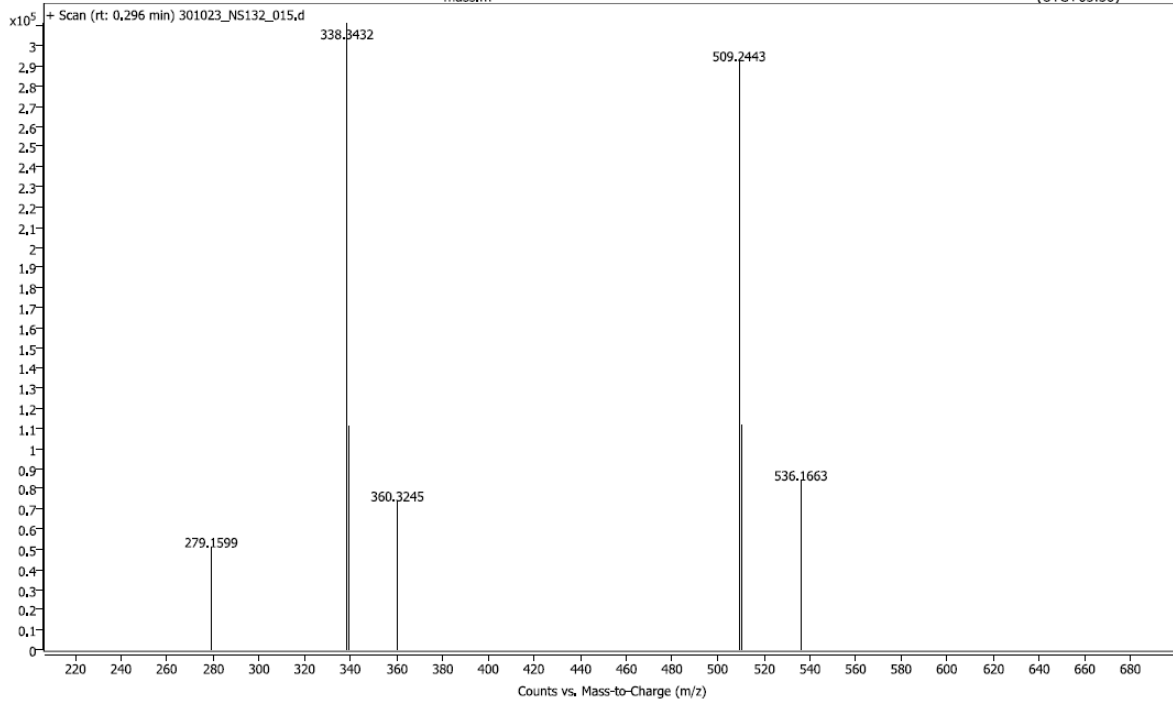


*2-(3-methoxy-4-(pent-4-yn-1-yloxy)-5-((4-phenylpiperazin-1-yl)methyl)phenyl)-4H-chromen-4-one (NS-18)*

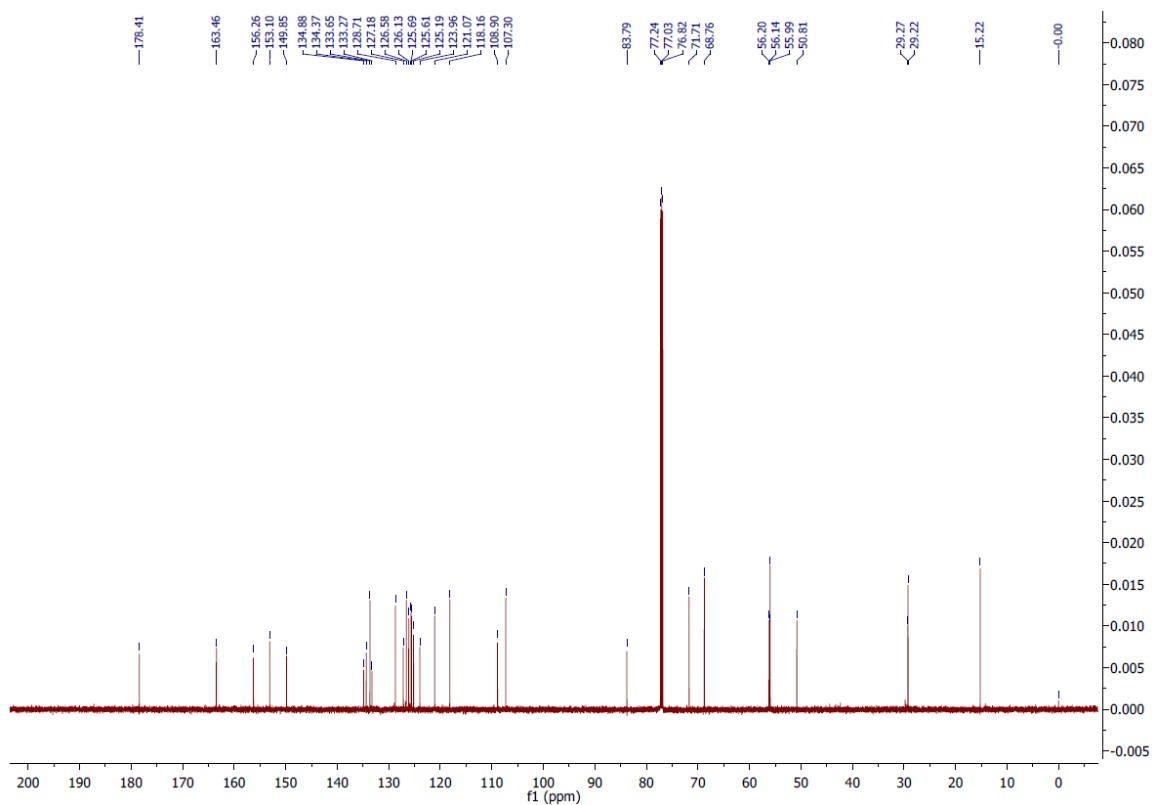
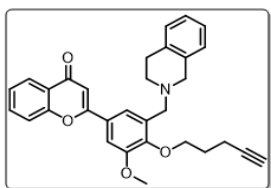
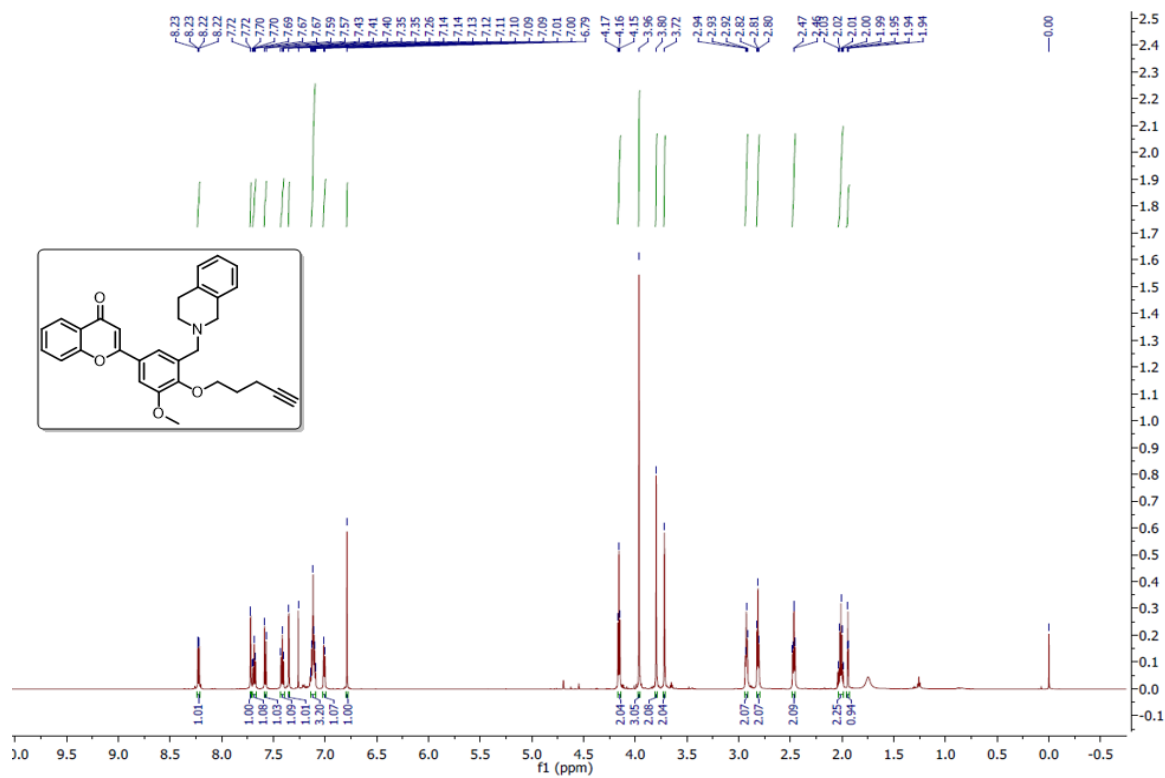




Name	1	Rack Pos.		Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.		IRM Status	Success		
Data File	301023_NS132_015.d	Method (Acq)	vinod231023 low mass.m	Comment		Acq. Time (Local)	30-10-2023 17:32:37 (UTC+05:30)



2-(3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-5-methoxy-4-(pent-4-yn-1-yloxy)phenyl)-4H-chromen-4-one (NS-19)



Name		Rack Pos.	Instrument	DESKTOP-7TLK19J	Operator	SYSTEM (SYSTEM)
Inj. Vol. (ul)	1	Plate Pos.	IRM Status	Success		
Data File	301023_NS148_016.d	Method (Acq)	vinod231023 low mass.m		Acq. Time (Local)	30-10-2023 17:34:43 (UTC+05:30)

