Design and Synthesis of Eugenol/Isoeugenol Glycoconjugates and Other Analogues as Antifungal Agents against *Aspergillus fumigatus*

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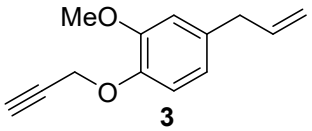
Supporting Information

General Information; All melting points were recorded on a Büchi melting point apparatus in open capillaries and are uncorrected. Flash chromatography was performed with CombiFlash *R*f 200*i* equipped with UV/VIS and ELSD (Isco Teledyne Inc., USA) using RediSep®pre-packed column (SiO_2). ^1H NMR spectra were recorded on a Bruker 200, 400 or 500 MHz spectrometer and ^{13}C NMR spectra were recorded at 50, 100 or 125 MHz, respectively. Chemical shifts are reported as δ values (ppm) relative to residual solvent peak of $CDCl_3$. HRMS (ESI) were recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. Petroleum ether and ethyl acetate were distilled by usual methods. All the starting materials and dried solvent were purchased and used without further drying.

General Procedure for the propargylation of isoeugenol/eugenol:

Compound **1** or **2** (5 g, 30.4506 mmol, 1 equiv.) was taken in a 250 ml round bottom flask and dissolved in acetone (20 ml) at room temperature under inert atmosphere. Then K_2CO_3 (6.3 g, 45.6759 mmol, 1.5 equiv.) and propargyl bromide (5.8 ml, 76.1266 mmol, 2.5 equiv.) were added to the above-mentioned solution at room temperature. After reaction was completed (monitored by TLC) the reaction mixture was filtered over Celite bed and the filtrate was evaporated *in vacuo* to furnish a residue which was purified by flash chromatography using a RediSep column (SiO_2, 12g) with EtOAc-petroleum ether mixture as eluent.

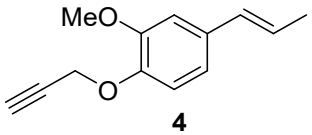
4-Allyl-2-methoxy-1-(prop-2-yn-1-yloxy) benzene (3):



3

Yellow liquid (4.5 g, 73%); R_f 0.34 (5% EtOAc in Petroleum Ether);^1H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.98-6.90 (m, 1H), 6.74-6.66 (m, 2H), 6.05-5.82 (m, 1H), 5.15-5.06 (m, 1H), 5.03 (s, 1H), 4.70 (d, J = 2.4 Hz, 2H), 3.82 (s, 3H), 3.32 (d, J = 6.7 Hz, 2H), 2.48 (t, J = 2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 149.5, 145.0, 137.3, 134.1, 120.1, 115.6, 114.6, 112.2, 78.7, 75.4, 56.8, 55.6, 39.6; LCMS: *m/z* 203.1 for $C_{13}H_{15}O_2$ $(M+H)^+$.

(*E*)-2-Methoxy-4-(prop-1-en-1-yl)-1-(prop-2-yn-1-yloxy) benzene (4):



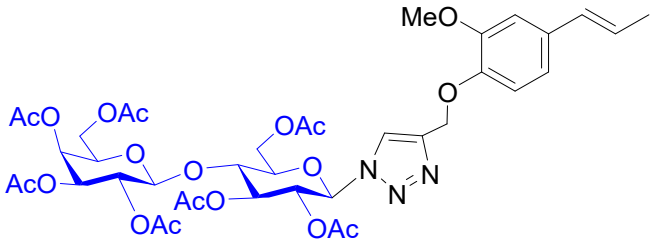
4

Colourless semisolid (4.6 g, 74%); R_f 0.34 (5% EtOAc in Petroleum Ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.99-6.81 (m, 3H), 6.41-6.25 (m, 1H), 6.22-6.03 (m, 1H), 4.75 (d, J = 2.4 Hz, 2H), 3.88 (s, 3H), 2.50 (t, J = 2.3 Hz, 1H), 1.87 (dd, J = 1.3, 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 13C NMR (50MHz ,CHLOROFORM-d) $\boldsymbol{\delta}_C$ 149.7, 145.8, 132.6, 130.5, 124.4, 118.4, 114.6, 109.1, 78.6, 75.6, 56.9, 55.8, 18.3; LCMS: *m/z* 203.1 for $C_{13}H_{15}O_2$ $(M+H)^+$.

General Procedure for the coupling of sugar azide with propargylated eugenol and isoeugenol:

To a stirred solution of propargylated eugenol/isoeugenol **3** or **4** (30 mg, 0.1485 mmol, 1 equiv.) in DCM (3 ml) azido sugars **5a-f** (0.1782 mmol, 1.2 equiv.), CuI (15.55 mg, 0.0816 mmol, 0.55 equiv.) and DIPEA (26 µl, 0.1485 mmol, 1.0 equiv.) were added and stirred for 14-24 hours under an inert atmosphere at 25 °C. After completion of reaction (monitored by TLC) the reaction mixture was concentrated *in vacuo* to obtain crude, which was purified by flash chromatography using a RediSep column (SiO_2, 12g) with EtOAc in petroleum ether to furnish desired eugenol/isoeugenol glycoconjugates **6a-j**.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-((2-methoxy-4-((*E*)-prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6a):

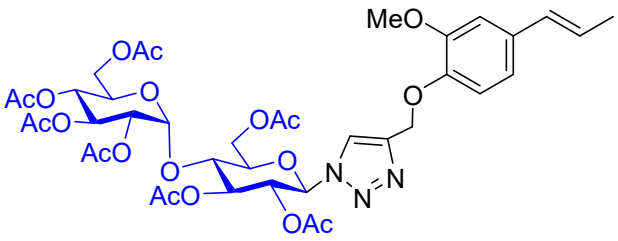


6a

Colourless solid (89.7 mg, 70%); m.p.: 85-87 ºC; R_f 0.13 (40% EtOAc in Petroleum Ether);^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.78 (s, 1H), 6.91-6.86 (m, 2H), 6.84-6.76 (m, 1H), 6.30 (dd, J = 1.5, 15.3 Hz, 1H), 6.08 (dd, J = 6.5, 15.6 Hz, 1H), 5.83-5.76 (m, 1H), 5.39 - 5.33 (m, 3H), 5.23 (s, 2H), 5.10 (dd, J = 8.0, 10.3 Hz, 1H), 4.95 (dd, J = 3.4, 10.3 Hz, 1H), 4.50 (d, J = 7.6 Hz,

1H), 4.44 (d, J = 13.0 Hz, 1H), 4.15-4.04 (m, 3H), 3.93-3.86 (m, 3H), 3.85 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 6H), 1.95 (s, 3H), 1.83 (dd, J = 1.5, 6.9 Hz, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$): $\boldsymbol{\delta}_C$ 170.5, 170.3, 170.2, 170.2, 169.6, 169.2, 149.7, 146.6, 145.1, 132.4, 130.5, 124.5, 121.6, 118.7, 114.5, 109.1, 101.2, 85.6, 75.9, 75.7, 72.7, 71.0, 70.9, 70.5, 69.1, 66.7, 63.2, 61.8, 60.9, 55.9, 20.9, 20.8, 20.7, 20.7, 20.6, 20.2, 18.5; HRMS: *m/z* for $C_{39}H_{49}O_{19}N_3Na$ $(M+Na)^+$: calcd 886.2852, found 886.2847.

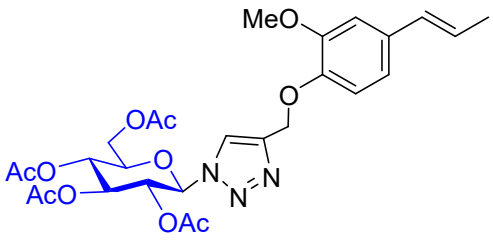
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-((2-methoxy-4-((E)-prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6b):



6b

Colourless solid (87.2 mg, 68%); m.p.: 171-173 ºC; R_f 0.20 (40% EtOAc in Petroleum Ether); ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.86-7.76 (m, 1H), 6.97-6.87 (m, 2H), 6.86-6.76 (m, 1H), 6.33 (dd, J = 1.3, 15.7 Hz, 1H), 6.22-6.02 (m, 1H), 5.90-5.77 (m, 1H), 5.47-5.34 (m, 3H), 5.26 (s, 2H), 5.13 (dd, J = 7.7, 10.4 Hz, 1H), 5.04-4.93 (m, 1H), 4.61-4.36 (m, 2H), 4.17-4.09 (m, 3H), 4.00-3.89 (m, 3H), 3.87 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06-2.04 (m, 6H), 1.97 (s, 3H), 1.86 (dd, J = 1.0, 6.4 Hz, 3H), 1.82 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.3, 170.2, 170.1, 170.0, 169.5, 169.1, 149.7, 146.5, 145.0, 132.4, 130.5, 124.3, 121.5, 118.6, 114.7, 109.3, 101.1, 85.5, 75.9, 75.6, 72.7, 70.9, 70.9, 70.5, 69.1, 66.7, 63.2, 61.8, 60.9, 60.4, 55.9, 21.0, 20.7, 20.6, 20.4, 20.1, 18.4; HRMS: *m/z* for $C_{39}H_{49}O_{19}N_3Na$ $(M+Na)^+$: 886.2852, found 886.2847.

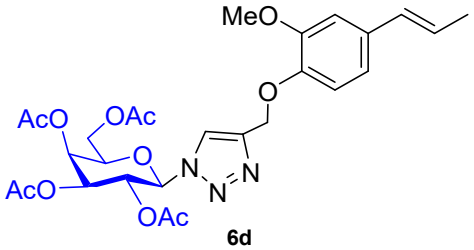
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(4-((2-methoxy-4-((*E*)-prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6c):



6c

Colourless solid (69.2 mg, 81%); m.p.: 181-183 ºC; R_f 0.25 (40% EtOAc in Petroleum Ether); ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.86 (s, 1H), 6.93-6.89 (m, 2H), 6.86-6.80 (m, 1H), 6.33 (dd, *J* = 1.5, 15.8 Hz, 1H), 6.11 (qd, *J* = 6.6, 15.7 Hz, 1H), 5.89-5.85 (m, 1H), 5.47-5.38 (m, 2H), 5.28-5.20 (m, 3H), 4.28 (dd, *J* = 5.1, 12.6 Hz, 1H), 4.14 (dd, *J* = 2.0, 12.6 Hz, 1H), 4.02-3.96 (m, 1H), 3.89-3.87 (m, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.86 (dd, *J* = 1.5, 6.6 Hz, 3H), 1.84-1.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.5, 169.9, 169.3, 168.8, 149.7, 146.5, 145.1, 132.4, 130.5, 124.4, 121.4, 118.6, 114.6, 109.1, 85.7, 75.1, 72.7, 70.2, 67.7, 63.1, 61.5, 55.9, 20.7, 20.5, 20.5, 20.1, 18.4; HRMS: *m/z* for $C_{27}H_{33}O_{11}N_3Na$ $(M+Na)^+$: calcd 598.2007, found 598.2004.

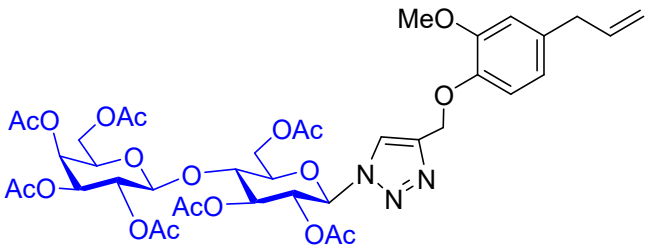
(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(4-((2-methoxy-4-((*E*)-prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6d):



6d

Yellow solid (61.4 mg, 72%); m.p.: 105-107 ºC; R_f 0.18 (40% EtOAc in Petroleum Ether); ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.92 (s, 1H), 6.93-6.88 (m, 2H), 6.85-6.78 (m, 1H), 6.31 (dd, *J* = 1.5, 15.3 Hz, 1H), 6.16-6.05 (m, 1H), 5.81 (d, *J* = 9.2 Hz, 1H), 5.58-5.51 (m, 2H), 5.27- 5.19 (m, 3H), 4.21-4.18 (m, 1H), 4.13 (dd, *J* = 6.5, 11.8 Hz, 2H), 3.87 (s, 3H), 2.20 (s, 4H), 2.03 (s, 4H), 1.99 (s, 4H), 1.86-1.83 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.5, 170.1, 169.9, 169.1, 149.7, 146.7, 145.1, 132.4, 130.5, 124.5, 121.6, 118.7, 114.7, 109.1, 86.3, 74.1, 70.9, 67.8, 66.9, 63.3, 61.3, 55.9, 20.8, 20.6, 20.3, 18.5; HRMS: *m/z* for $C_{27}H_{33}O_{11}N_3Na$ $(M+Na)^+$: calcd 598.2007, found 598.2002.

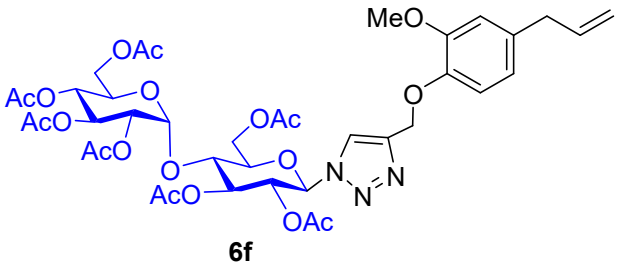
(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-((4-allyl-2-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (6e):



6e

Yellow solid (96 mg, 75%); m.p.: 73-75 ºC; R_f 0.22 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.85 (s, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.76-6.65 (m, 2H), 6.02-5.82 (m, 2H), 5.46-5.34 (m, 3H), 5.24 (s, 2H), 5.15-5.05 (m, 2H), 5.05-4.98 (m, 2H), 4.61-4.43 (m, 2H), 4.13 (td, J = 3.5, 7.2 Hz, 3H), 4.01-3.93 (m, 3H), 3.85 (s, 3H), 3.32 (d, J = 6.6 Hz, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.08-2.02 (m, 10H), 1.97 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.3, 170.2, 170.1, 170.0, 169.5, 169.1, 169.1, 149.6, 145.8, 145.0, 137.4, 134.0, 121.6, 120.5, 115.7, 114.7, 112.4, 101.0, 85.3, 75.7, 75.6, 72.6, 70.9, 70.8, 70.5, 69.0, 66.7, 63.2, 61.8, 60.9, 60.3, 55.8, 39.8, 21.0, 20.7, 20.6, 20.5, 20.1, 14.1; HRMS: *m/z* for $C_{39}H_{50}O_{19}N_3$ $(M)^+$: calcd 863.3033, found 864.3029; *m/z* for $C_{39}H_{49}O_{19}N_3Na$ $(M+Na)^+$: calcd 886.2852, found 886.2844.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-((4-allyl-2-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6f):

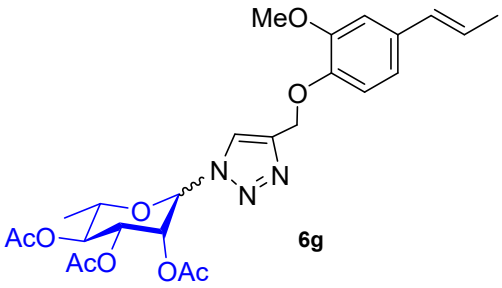


6f

Colourless solid (79 mg, 62%); m.p.: 136-138 ºC; R_f 0.26 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.82 (s, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.77-6.64 (m, 2H), 6.02-5.83 (m, 2H), 5.49-5.30 (m, 4H), 5.25 (s, 2H), 5.16-5.00 (m, 4H), 4.89 (dd, J = 3.9, 10.5 Hz, 1H), 4.54-4.42 (m, 1H), 4.31-4.19 (m, 2H), 4.18-4.05 (m, 2H), 4.04-3.93 (m, 2H), 3.85 (s, 3H), 3.33 (d, J = 6.7 Hz, 2H), 2.12 (d, J = 3.8 Hz, 6H), 2.07 (s, 3H), 2.05-2.01 (m, 9H), 1.81 (s, 3H);

^{13}C NMR (50MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.5, 170.5, 170.3, 169.9, 169.9, 169.4, 169.1, 149.6, 145.8, 145.1, 137.5, 134.0, 121.5, 120.5, 115.7, 114.7, 112.4, 95.9, 85.2, 75.2, 75.2, 72.4, 70.8, 70.0, 69.2, 68.7, 67.9, 63.3, 62.5, 61.5, 55.8, 39.8, 20.8, 20.7, 20.7, 20.6, 20.1; HRMS: *m/z* for $C_{39}H_{50}O_{19}N_3$ $(M+H)^+$: calcd 864.3033, found 864.3033; *m/z* for $C_{39}H_{49}O_{19}N_3Na$ $(M+Na)^+$: calcd 886.2852; found 886.2847.

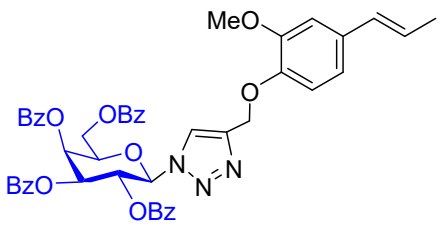
(3*R*,4*R*,5*S*,6*S*)-2-(4-((2-methoxy-4-((*E*)-prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6g):



6g

Colourless solid (57.6 mg, 75%); m.p.: 112-114 ºC; R_f 0.20 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.86 (s, 1H), 6.98-6.77 (m, 3H), 6.40-6.24 (m, 1H), 6.23-6.03 (m, 2H), 5.74-5.62 (m, 1H), 5.28 (s, 2H), 5.24-5.13 (m, 2H), 3.94-3.74 (m, 4H), 2.09 (s, 3H), 1.98 (s, 3H), 1.92 (s, 3H), 1.85 (d, J = 6.3 Hz, 3H), 1.33 (d, J = 6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 169.9, 169.2, 149.5, 146.5, 144.5, 132.2, 130.5, 124.3, 121.9, 118.6, 114.1, 109.1, 84.7, 73.9, 70.7, 69.6, 69.2, 63.1, 55.8, 20.7, 20.5, 20.2, 18.4, 17.5; HRMS: *m/z* for $C_{25}H_{32}O_9N_3$ $(M+H)^+$: calcd 518.2133, found 518.2131.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-((benzoyloxy)methyl)-6-(4-((2-methoxy-4-((*E*)-prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (6h):

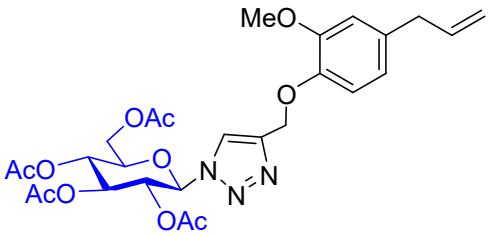


6h

Colourless solid (86.7 mg, 71%); m.p.: 130-132 ºC; R_f 0.20 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 8.02 (d, J = 8.5 Hz, 3H), 7.92 (d, J = 7.2 Hz, 2H), 7.81 (d, J

= 7.2 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.60-7.46 (m, 2H), 7.45-7.35 (m, 5H), 7.34-7.21 (m, 5H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.80-6.69 (m, 1H), 6.38-6.24 (m, 2H), 6.20-5.97 (m, 3H), 5.96-5.81 (m, 1H), 5.24 (s, 2H), 4.75-4.59 (m, 1H), 4.57-4.42 (m, 2H), 3.83 (s, 3H), 1.85 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 166.1, 165.6, 165.1, 164.7, 149.8, 146.7, 145.2, 133.7, 133.6, 133.5, 133.3, 132.3, 130.6, 129.8, 129.8, 129.4, 128.5, 128.5, 128.4, 128.0, 124.2, 121.6, 118.7, 114.7, 109.3, 86.1, 75.5, 73.1, 71.0, 68.9, 63.3, 62.7, 55.9, 18.4; HRMS: *m/z* for $C_{47}H_{42}O_{11}N_3$ $(M+H)^+$: calcd 824.2814, found 824.2814.

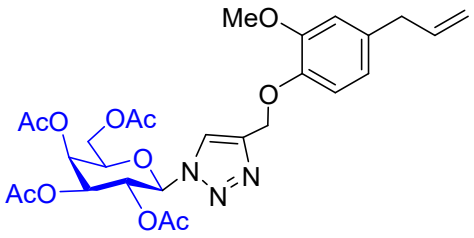
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(4-((4-allyl-2-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6i):



6i

Colourless solid (69.1 mg, 81%); m.p.: 151-153 ºC; R_f 0.21 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.88 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.76-6.65 (m, 2H), 6.03-5.84 (m, 2H), 5.52-5.35 (m, 2H), 5.30-5.18 (m, 3H), 5.13-5.07 (m, 1H), 5.03 (s, 1H), 4.36-4.24 (m, 1H), 4.13 (dd, *J* = 1.9, 12.5 Hz, 1H), 4.06-3.94 (m, 1H), 3.86 (s, 3H), 3.33 (d, *J* = 6.7 Hz, 2H), 2.08 (d, *J* = 3.3 Hz, 6H), 2.03 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.5, 169.9, 169.3, 168.8, 149.7, 145.9, 145.3, 137.5, 134.1, 121.4, 120.5, 115.8, 114.8, 112.5, 85.7, 75.1, 72.7, 70.3, 67.7, 63.3, 61.6, 55.9, 39.8, 20.7, 20.5, 20.1; HRMS: *m/z* for $C_{27}H_{33}O_{11}N_3Na$ $(M+Na)^+$: calcd 598.2007, found 598.2008.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(4-((4-allyl-2-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (6j):



6j

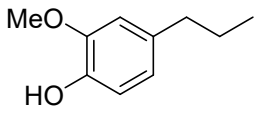
Colourless solid (55.4 mg, 65%); m.p.: 105-107 ºC; R_f 0.18 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.95 (s, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.76-6.65 (m, 2H), 6.06-

5.90 (m, 1H), 5.89-5.81 (m, 1H), 5.64-5.51 (m, 2H), 5.29-5.20 (m, 3H), 5.10 (d, J = 6.6 Hz, 1H), 5.04 (s, 1H), 4.28-4.09 (m, 3H), 3.87 (s, 3H), 3.33 (d, J = 6.7 Hz, 2H), 2.25-2.17 (m, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.4, 170.0, 169.8, 169.0, 149.7, 145.9, 145.2, 137.5, 134.1, 121.5, 120.5, 115.8, 114.9, 112.4, 86.2, 74.0, 70.9, 67.8, 66.9, 63.4, 61.3, 55.9, 39.8, 20.7, 20.5, 20.2; HRMS: *m/z* for $C_{27}H_{33}O_{11}N_3Na$ $(M+Na)^+$: calcd 598.2115, found 598.2007; *m/z* for $C_{27}H_{33}O_{11}N_3Na$ $(M+Na)^+$: calcd 598.2006., found 598.2006.

Synthesis of 7:

Compound **1** was dissolved in anhydrous methanol under argon at 0 ºC. After dissolution of compound Pd/C was added in catalytic amount and reaction mixture was kept under H_2 atmosphere for 3 hours at 25 ºC. After completion of reaction (monitored by TLC) the reaction mixture was filtered over celite bed and concentrated *in vacuo* to obtain crude, which was purified by flash chromatography using a RediSep column (silica gel, 12g) with EtOAc in petroleum ether to furnish desired compound **7**.

2-Methoxy-4-propylphenol (7):



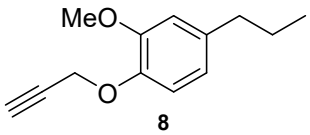
7

Brown oil (183 mg, 84%); R_f 0.40 (40% EtOAc in Petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.89-6.76 (m, 1H), 6.72-6.58 (m, 2H), 5.65 (br. s., 1H), 3.90-3.79 (m, 3H), 2.50 (t, J = 7.5 Hz, 2H), 1.60 (qd, J = 7.4, 14.9 Hz, 2H), 0.99-0.86 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 146.5, 143.6, 134.8, 121.1, 114.3, 111.2, 55.9, 37.8, 25.0, 13.9; HRMS: *m/z* for $C_{10}H_{13}O_2$ $(M+H)^+$: calcd 165.0910, found 165.0910.

Synthesis of 8:

Compound **7** (2 g, 12.0336 mmol, 1 equiv.) was dissolved in dry acetone (20 mL) at room temperature followed by addition of K_2CO_3 (2.5 g, 18.0504 mmol, 1.5 equiv.) and propargyl bromide (2.3 ml, 30.0842 mmol, 2.5 equiv.) at room temperature. After completion of reaction (monitored by TLC) reaction mixture was filtered through Celite bed and the filtrate was evaporated *in vacuo*. Residue was purified by flash chromatography using a RediSep column (silica gel, 12g) with EtOAc in petroleum ether to furnish product **8**.

2-Methoxy-1-(prop-2-yn-1-yloxy)-4-propylbenzene: (8):



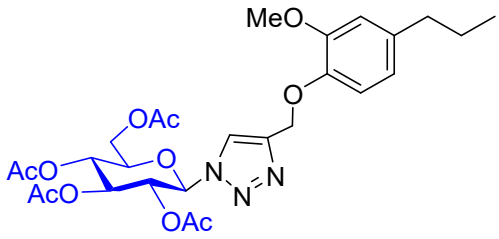
8

Brown oil (1.8 g, 75%); R_f 0.33 (2% EtOAc in Petroleum Ether);^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.94 (d, J = 8.7 Hz, 1H), 6.74-6.65 (m, 2H), 4.72 (d, J = 2.3 Hz, 2H), 3.85 (s, 3H), 2.59-2.45 (m, 3H), 1.72-1.52 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 149.6, 146.4, 137.0, 121.0, 114.8, 112.4, 79.0, 75.5, 57.0, 55.8, 37.8, 24.7, 13.8; HRMS: *m/z* for $C_{13}H_{16}O_2Na$ $(M+Na)^+$: calcd 227.1043, found 227.1043.

Synthesis of compound 9:

Compound **9** was synthesized by treating compound **8** and **5c** according the general procedure for synthesizing compounds **6a-j.**

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(4-((2-methoxy-4-propylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (9):



9

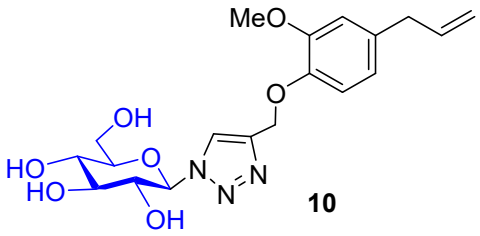
Yellowish liquid (80 mg, 63%); R_f 0.14 (40% EtOAc in Petroleum Ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.87 (s, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.71-6.69 (m, 1H), 6.66 (dd, J = 1.6, 8.1 Hz, 1H), 5.86 (d, J = 8.9 Hz, 1H), 5.47-5.36 (m, 2H), 5.27-5.19 (m, 3H), 4.25 (d, J = 5.0 Hz, 1H), 4.15-4.09 (m, 1H), 3.85 (s, 3H), 2.53-2.47 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.82 (s, 3H), 1.63-1.56 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 170.5, 169.9, 169.3, 168.8, 149.4, 145.4, 136.7, 120.3, 114.6, 112.3, 85.6, 75.0, 72.6, 70.1, 67.6, 63.2, 61.5, 55.8, 37.6, 24.6, 20.6, 20.5, 20.4, 20.1, 13.8; HRMS: *m/z* for $C_{27}H_{36}O_{11}N_3(M+H)^+$: calcd 578.2350, found 578.2347.

Procedure for the synthesis of compound 10 and 11 *via* deprotection of 6i and 9:

Compound **6i** or **9** (1.0 equiv.) was dissolved in MeOH (10 ml) at room temperature followed by addition of NaOMe (0.5 equiv.). After 2 hours of stirring, the reaction mixture was quenched with 10% HCl with the pH attains 7. The solvent was removed *in vacuo* to afford crude mixture which was purified using silica gel (230-400) flash column chromatography (MeOH/DCM) to furnish deprotected compound **10 or 11**.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-((4-allyl-2-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (10):

Synthesized from compound **6i** following the general procedure.

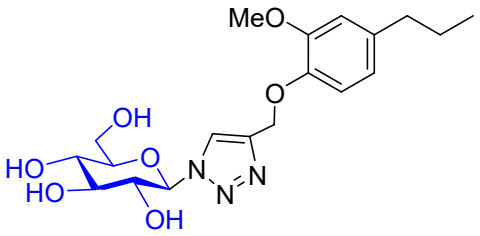


10

Colorless semisolid (76 %); R_f 0.06 (70% EtOAc in petroleum ether); ^{1}H NMR (400 MHz, Methanol-d$_4$): δ_H 8.27 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.83-6.81 (m, 1H), 6.73 (dd, J = 1.7, 8.2 Hz, 1H), 5.65 (d, J = 9.1 Hz, 1H), 5.16 (s, 2H), 5.12-5.03 (m, 2H), 3.98-3.88 (m, 2H), 3.80 (s, 3H), 3.75 (s, 1H), 3.64-3.58 (m, 2H), 3.57-3.51 (m, 1H), 3.34 (d, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, Methanol-d$_4$): δ_C 151.3, 147.5, 145.4, 139.2, 135.7, 125.0, 121.9, 116.4, 116.0, 114.1, 89.7, 81.2, 78.5, 74.1, 70.9, 63.9, 62.5, 56.5, 40.9; HRMS: *m/z* for $C_{19}H_{26}O_7N_3(M+H)^+$: calcd 408.1766, found 408.1766.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(hydroxymethyl)-6-(4-((2-methoxy-4-propylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triol (11):

Synthesized from compound **9** following the general procedure.



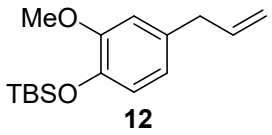
11

Colorless semisolid (79 %); m.p.: 128-130 °C; R_f 0.06 (70% EtOAc in petroleum ether); ^{1}H NMR (400 MHz, Methanol-d_4): $\boldsymbol{\delta}_H$ 8.25 (s, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.69 (dd, J = 1.8, 8.1 Hz, 1H), 5.62 (d, J = 9.1 Hz, 1H), 5.13 (s, 2H), 3.95-3.85 (m, 2H), 3.79 (s, 3H), 3.73 (s, 1H), 3.62-3.55 (m, 2H), 3.55-3.48 (m, 1H), 2.52 (t, J = 7.6 Hz, 2H), 1.67-1.56 (m, 2H), 1.15 (d, J = 6.1 Hz, 1H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, Methanol-d_4): $\boldsymbol{\delta}_C$ 151.2, 147.2, 138.3, 125.0, 121.8, 116.4, 114.0, 89.7, 81.2, 78.5, 74.1, 71.0, 64.0, 62.5, 56.5, 38.8, 26.0, 14.2; HRMS: *m/z* for $C_{19}H_{28}O_7N_3(M+H)^+$: calcd 410.1922, found 410.1924.

Procedure for the OTBDMS protection (12):

Eugenol **1** (10 g, 60.9756 mmol, 1 equiv.) was dissolved in DCM and to this solution imidazole (4.6 g, 67.0731 mmol, 1.1 equiv.) DMAP (1.1 g, 9.1463 mmol, 0.15 equiv.) and TBDMSCl (10 g, 67.0731 mmol, 1.1 equiv.) were added sequentially and stirred for 12 hours at 25 °C. After completion of reaction (monitored by TLC) the reaction mixture was concentrated *in vacuo* to obtain crude, which was purified using silica gel (230-400) flash column chromatography (EtOAc/pet.ether) to furnish the desired product **12**.

(4-allyl-2-methoxyphenoxy)(*tert*-butyl)dimethylsilane (12):



12

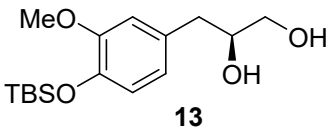
Yellow oil (12.8 g, 77%); R_f 0.77 (10% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.68-6.57 (m, 1H), 6.55-6.43 (m, 2H), 5.92-5.70 (m, 1H), 4.93 (d, J = 4.9 Hz, 1H), 4.87 (s, 1H), 3.62 (s, 3H), 3.16 (d, J = 6.6 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 150.8, 143.3, 137.8, 133.5, 120.8, 115.6, 112.6, 55.5, 40.0, 25.8, 18.5, -4.6; HRMS: *m/z* for $C_{16}H_{25}O_2Si$ $(M-H)^+$: calcd 277.1618, found 277.1617.

Procedure for the dihydroxylation (13):

To a solution of *tert*-butanol and water (total 120 mL, 1:1 v/v ratio) AD-mix β (22.4 g, 28.7769 mmol, 1.0 equiv.) was added and resulting mixture was cooled to 0°C. Compound **12** (8 g, 28.7769 mmol, 1.0 equiv.) was added to this slurry and reaction mixture was stirred 8 h at 25 °C. After completion of reaction (monitored by TLC) the reaction was quenched by addition of sodium sulphite (43 g). Then the reaction mixture was extracted with ethyl acetate (3X40 mL) and combined organic layers were washed with brine and dried over anhydrous sodium

sulphate and concentrated *in vacuo*. Crude obtained was purified using silica gel (230-400) flash column chromatography (EtOAc/pet. ether) to furnish the desired product **13**.

(S)-3-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)propane-1,2-diol (13):



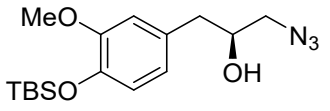
13

Yellow oil (6.3 g, 71%); R_f 0.02 (50% EtOAc in petroleum ether);^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.68-6.47 (m, 3H), 3.76 (d, J = 5.3 Hz, 1H), 3.64 (s, 3H), 3.52 (br. s., 1H), 3.38 (d, J = 6.9 Hz, 1H), 2.62-2.48 (m, 2H), 2.12 (br. s., 2H), 0.89-0.80 (m, 9H), 0.03-0.05 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 151.0, 143.8, 131.0, 121.4, 121.0, 113.2, 73.0, 66.0, 55.5, 39.6, 25.7, 18.5, -4.6; HRMS: *m/z* for $C_{16}H_{28}O_4SiNa$ $(M+Na)^+$: calcd 335.1649, found 335.1647.

Synthesis of compound (14):

Compound **13** (1 g, 3.2051 mmol, 1 equiv.) was dissolved in DCM and resulting solution was cooled to 0 °C. To this reaction mixture triethyl amine (431.62 µl, 3.2051 mmol, 1 equiv.), DMAP (234 mg, 1.9230 mmol, 0.6 equiv.) and *p*-toluene sulfonyl chloride (730 mg, 3.8461 mmol, 1.2 equiv.) was added at 0°C. Reaction mixture was stirred for 10 h at 25 °C. After completion of reaction (monitored by TLC) the reaction mixture was diluted with DCM and washed with $CuSO_4$, $NaHSO_4$ and NaCl solutions subsequently. Organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to furnish tosylated product which was directly used for next without further purification. A solution of monotosylate, TBAI (59 mg, 0.1602 mmol, 0.05 equiv.) and NaN_3 (624.9 mg, 9.6153 mmol, 3 equiv.) in DMF was heated at 95°C for 3-4 h. After completion of reaction (monitored by TLC) the reaction mixture was cooled at 0 °C and was diluted with water. The aqueous layer was extracted three times with ethyl acetate. Combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to obtain crude, which was purified using silica gel (230-400) flash column chromatography (EtOAc/pet.ether) to furnish the desired product.

(*S*)-1-Azido-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)propan-2-ol (14):



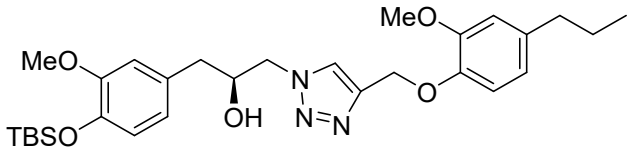
14

Yellow oil (845 mg, 78%); R_f 0.05 (50% EtOAc in petroleum ether);^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 6.68-6.45 (m, 3H), 3.88-3.73 (m, 1H), 3.64 (s, 3H), 3.23-3.02 (m, 2H), 2.57 (d, *J* = 6.7 Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 151.1, 144.0, 130.3, 121.5, 121.1, 113.2, 71.8, 55.9, 55.5, 40.6, 25.7, 18.5, -4.6; HRMS: *m/z* for $C_{16}H_{27}O_3N_3NaSi$ $(M+Na)^+$: calcd 360.1714, found 360.1712.

General procedure for the synthesis of compounds 15-17:

Compound **15-17** were synthesized by treating compound **14** with compound **8**, **3** and **4** respectively, according the general procedure for synthesizing compounds **6a-j**.

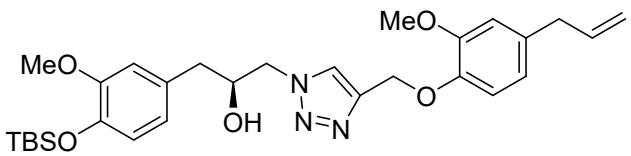
(*S*)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)-3-(4-((2-methoxy-4-propylphenoxy)- methyl)-1*H*-1,2,3-triazol-1-yl)propan-2-ol (15):



15

Colourless semisolid (112.8 mg, 85%); R_f 0.25 (40% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.61 (s, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.66-6.60 (m, 1H), 6.59-6.53 (m, 3H), 6.52-6.46 (m, 1H), 5.07 (s, 2H), 4.32 (d, *J* = 10.7 Hz, 1H), 4.09 (d, *J* = 9.3 Hz, 2H), 3.65 (d, *J* = 8.8 Hz, 7H), 2.84 (br. s., 1H), 2.63-2.52 (m, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 1.541.38 (m, 2H), 0.85 (s, 9H), 0.82-0.74 (m, 4H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 151.1, 149.4, 145.6, 144.2, 144.0, 136.6, 130.0, 124.6, 121.5, 121.0, 120.4, 114.4, 113.2, 112.3, 71.3, 63.3, 55.8, 55.5, 55.1, 40.6, 37.7, 25.7, 24.7, 18.4, 13.9, -4.6; HRMS: *m/z* for $C_{29}H_{44}O_5N_3Si$ $(M+H)^+$: calcd 542.3045, found 542.3044, *m/z* for $C_{29}H_{43}O_5N_3NaSi$ $(M+Na)^+$: calcd 564.2864, found 564.2859.

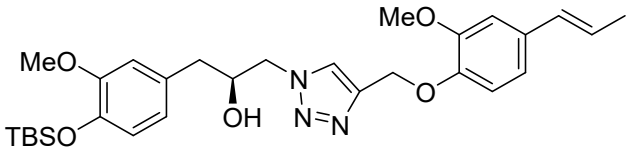
(*S*)-1-(4-((4-allyl-2-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)propan-2-ol (16):



16

Yellowish semisolid (115.6 mg, 73%); R_f 0.14 (40% EtOAc in petroleum ether);^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.60 (s, 1H), 6.83-6.60 (m, 4H), 6.58-6.44 (m, 2H), 6.14 (s, 1H), 6.05-5.86 (m, 1H), 5.10 (s, 2H), 4.37-4.25 (m, 1H), 4.19-4.01 (m, 2H), 3.70 (s, 3H), 3.63 (s, 3H), 2.64-2.49 (m, 2H), 1.71 (d, J = 6.4 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 151.1, 149.6, 146.6, 144.0, 132.2, 130.5, 129.9, 124.6, 124.3, 121.5, 121.1, 118.6, 114.3, 113.2, 109.0, 71.3, 63.1, 55.8, 55.5, 55.1, 40.6, 25.7, 18.4, -4.6; HRMS: *m/z* for $C_{29}H_{42}O_5N_3Si$ $(M+H)^+$: calcd 540.2888, found 540.2888, *m/z* for $C_{29}H_{41}O_5N_3NaSi$ $(M+Na)^+$: calcd 562.2708, found 562.2703.

(*S*,*E*)-1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)-3-(4-((2-methoxy-4-(prop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propan-2-ol (17):



17

Yellowish semisolid (97.2 mg, 73%); R_f 0.20 (40% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\boldsymbol{\delta}_H$ 7.61 (s, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.67-6.45 (m, 5H), 5.79 (tdd, J = 6.7, 10.2, 16.7 Hz, 1H), 5.07 (s, 2H), 4.99-4.92 (m, 1H), 4.88 (s, 1H), 4.32 (d, J = 10.9 Hz, 1H), 4.16-4.04 (m, 2H), 3.63 (s, 3H), 3.68 (s, 3H), 3.17 (d, J = 6.6 Hz, 2H), 2.78 (brs, 1H), 2.69-2.47 (m, 2H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\boldsymbol{\delta}_C$ 151.1, 149.5, 145.9, 144.1, 144.0, 137.5, 133.8, 130.0, 124.5, 121.5, 121.0, 120.5, 115.8, 114.5, 113.2, 112.3, 71.3, 63.3, 55.8, 55.5, 55.1, 40.6, 39.8, 25.7, 18.5, -4.6; HRMS: *m/z* for $C_{29}H_{42}O_5N_3Si$ $(M+H)^+$: calcd 540.2888, found 540.2887, *m/z* for $C_{29}H_{41}O_5N_3NaSi$ $(M+Na)^+$: calcd 562.2708, found 562.2700.

Biological Evaluation

Fungal strain, culture maintenance and inoculum preparation. *Aspergillus fumigatus* (ATCC-46645) strain was a gift from Prof. Axel Brakhage, Department of Molecular and Applied Microbiology, Leibnitz Institute for Natural Product Research, and Infection Biology-

HKI, Germany. It was maintained by subculturing on Czapek Dox Agar (CzA), grown at 28 ± 2°C for 5 days. The *A. fumigatus* spores were harvested in sterile phosphate buffered saline (1xPBS) supplemented with 0.05% Tween 20. The conidial suspension was adjusted to 10^6 conidia/ml (0.1 OD) at 530 nm wavelength, further diluted in Czapek Dox Broth (CzB;1:50 ratio) to adjust the final suspension to 5×10^4 conidia/ml according to CLSI M38-A2 reference method (CLSI, 2008).

***In-vitro* antifungal activity of synthesized analogues of compounds 1 and 2.** Minimum inhibitory concentration (MIC) and IC_{50} was calculated according to the CLSI M38-A2 microbroth dilution method for filamentous fungi (CLSI, 2008). The experiment was carried out in triplicates in a 96-well polystyrene plate (Tarsons, India). All the twenty three synthesized analogues of compound **1** and **2** (compound **3, 4, 6a-j, 7-17**), amphotericin B (Amp B) were dissolved in DMSO. Two-fold dilutions of synthesized analogues and parent compounds were prepared in growth media CzB. Prepared conidial suspension (100 µL) was added to each well except negative control. The plates were incubated statically for 5 days at 28 ± 2°C. The MIC and IC_{50} were defined as the lowest concentration of the compound, which completely inhibit the microbial growth and 50% inhibition of microbial growth, respectively (CLSI, 2008). The results were expressed in micromolar value.

Assessment of cytotoxicity of synthetic analogues in normal lung epithelial cell line L-132.

Cytotoxicity analysis of selected analogues, which showed antifungal results at lowest concentrations against *A. fumigatus*, was performed. The selected analogues **6i and 7** were taken forward for all experiments**.**

The lung epithelial normal cell line L-132 was procured from National Centre for Cell Science (NCCS), Pune, India. Cells were grown in T-25 vented neck flask in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% foetal bovine serum (FBS), 1% penicillin/ streptomycin and 1% L-glutamine in a humidified atmosphere of 5% CO_2 and 95% air at 37°C. L-132 cells were seeded at density 1 x 10^5 cells per well in 100 µl culture medium containing 10% FBS on 96 multi-well culture plates and incubated overnight for adherence. After that, the medium was removed, and cells were incubated in FBS free medium containing different concentrations of **6i and 7** and drug amp B for another 24 h. The wells containing media plus cells as positive control and only media as negative control. After 24 h, the reaction medium was removed, and the adhering cells washed with PBS. 100 µl of MTT solution (0.5g/L in

medium) was added to each culture well and incubated for 4 h at 37^{o}C. Next, MTT reaction medium was removed, and formazan blue was solubilised in 100 µl of DMSO. The formazan-blue formation absorbance was recorded at 570 nm using micro-plate reader (Cloud-Clone smart microplate reader, Model no. SMR-16.1). All experiments were performed in triplicates. The percentage relative cell viability was calculated as (A_{570} of treated samples/A_{570} of untreated samples) * 100 (Venkatraman et al. 2005).

The selectivity index (SI) was determined by CC_{50}/IC_{50} ratio against *A. fumigatus*. The SI is an indirect measure of the therapeutic window, and it can serve as a predictor of safety during *in vivo* trials for a given pathogen infection (Insuasty et al. 2019). (CC_{50} -cytotoxic concentration 50)

***In-silico* screening of analogues for therapeutic activity.** *In-silico* study was conducted to determine drug-likeness and health effect prediction profile of synthetic analogues **6i and 7**. The structures of compounds were drawn manually using ChemSketch (Advanced Chemistry Development, inc., ACD/Labs, freeware 12.0, Toronto, Canada). Molecular property and drug likeness were analysed using online software ACD/I-Lab version 4.5 and MolSoft LLC 3.5-0, San Diego, CA, respectively. The parameters deployed to predict the physicochemical properties of the compound and describe its disposition within the host organism are summarized in Table 3 (Lipinski et al., 2001).

Evaluating the effect of the analogues on cell wall associated virulence factors in *A. fumigatus*.

A) Conidiation- The effect of selected analogues at their respective IC_{50} on fungal conidiation was estimated spectrophotometrically (CLSI 2008). One cubic centimeter of agar block containing treated and untreated fungal culture was excised from CzA media plate supplemented with IC_{50} using a sterile surgical blade and transferred to a sterile test tube. Phosphate buffer supplemented with 0.25% Tween-20 (5 ml) was added to each tube, shaken vigorously and absorbance was observed. The absorbance of treated (**2, 6i, 7**, amp B), and positive control (untreated) samples of *A. fumigatus* conidia were measured at 530nm using UV- vis spectrophotometer.

B) M*elanin pigment-* The isolation and estimation of cell wall associated melanin was performed at the calculated IC_{50} of analogues (**6i and 7**) and compound **2** treated conidia using the modified protocol of Kumar et al. (2011) and Gupta et al (2022). Briefly, in 12 well tissue culture plate, 1 x 10^4 conidia with IC_{50} of analogues (**6i and 7**), **2** and AmpB was added and

incubated at 28°C for 5 days. After incubation, conidia from treated as well as untreated culture were harvested using 1×PBS and centrifuged (5000 *g*) for 10 min, followed by washing twice with sterile distilled water. The conidia melanin was extracted with 1M NaOH (2 mL) and further autoclaved at 120°C for 20 mins. The autoclaved suspension was further centrifuged (5000 *g*) for 5 min to recover the supernatant containing the pigment. The alkaline pigmented supernatant was acidified to pH 2 with 7M HCl (2 mL) in a sealed glass vial and kept for 2 h at 100 °C. After cooling, precipitate was recovered by centrifugation (5000*g*; 10 min). Precipitate was suspended in 100 mM borate buffer and the extracted melanin was scanned by UV-Vis absorption spectrum between 250-800 nm on a UV-Vis spectrophotometer. 100 mM borate buffer was used as a blank.

C) Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) of the treated *A. fumigatus* conidial surface- Synthesized compounds (**6i and 7**) and compound **2** treated conidial surfaces of *A. fumigatus* were analysed by electron microscopy. For SEM, conidia were harvested, washed, and fixed in 4% glutaraldehyde in 1x PBS under vacuum for 24 hours. After washing, the cells were post-fixed with 1% osmium tetroxide for 60 min and dehydrated by passage through ethanol solutions of increasing concentration. The sample were then mounted on aluminium sheet and coated with gold-palladium alloy. The observations were made using a Zeiss SEM, MA EVO -18 Special Edition (Pihet, 2009). For TEM analysis, conidia were harvested, washed, and fixed overnight at room temperature with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4). Conidia were incubated for 1.5 h at 20°C in a solution of 4% formaldehyde and 1% glutaraldehyde in 0.1% PBS and then incubated in 2% osmium tetraoxide for 1.5 h. Dehydration was accomplished by serial washings in graded ethanol solutions of 50-95% for 10 min, followed by two final washes in 100% ethanol for 15 min. The cells were embedded in Spurr's resin, sectioned onto nickel grids, and examined on a JEOL 2100F transmission electron microscope to obtain micrographs (Graham, 2007).

Effect of compounds on of *A. fumigatus* biofilm

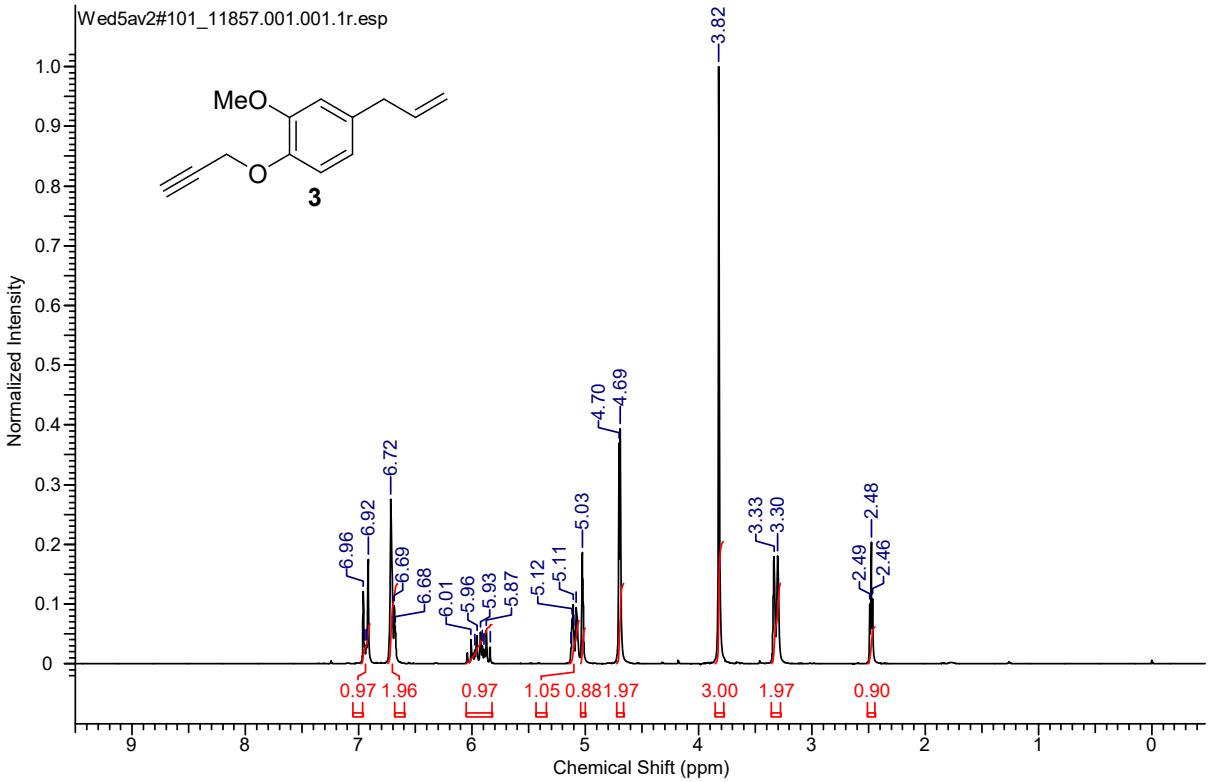
The minimal biofilm-eradicating concentration (MBEC) of synthesized compounds (**6i and 7**) on pre-formed *A. fumigatus* biofilm was calculated by performing MTT assay in a 96-well flat bottom microtiter plate with minor modifications (Sav et al., 2018). Briefly, conidia in RPMI + 2% glucose (100µL) were added to each well and incubated at 37 ºC for 24 h without agitation for biofilm formation. After 24 h, non-adherent conidia were removed by washing with 1× PBS

and treated with synthesized compounds (**6i and 7**) and compound **2**. Microtiter plate was further incubated at 37 ºC statically for an additional 24 h. The wells with preformed biofilms (without any treatment) were considered as positive control. After 24 h, the reaction medium was removed, and the fungal biofilm washed with PBS. 100 µl of MTT solution (0.5g/L in medium) was added to each well and incubated for 4 h at 37ºC. Subsequently, MTT was removed, and formazan blue was solubilised in 100 µl of DMSO. The formazan-blue formation absorbance was recorded at 570 nm using micro-plate reader (Cloud-Clone smart microplate reader, Model no. SMR-16.1).

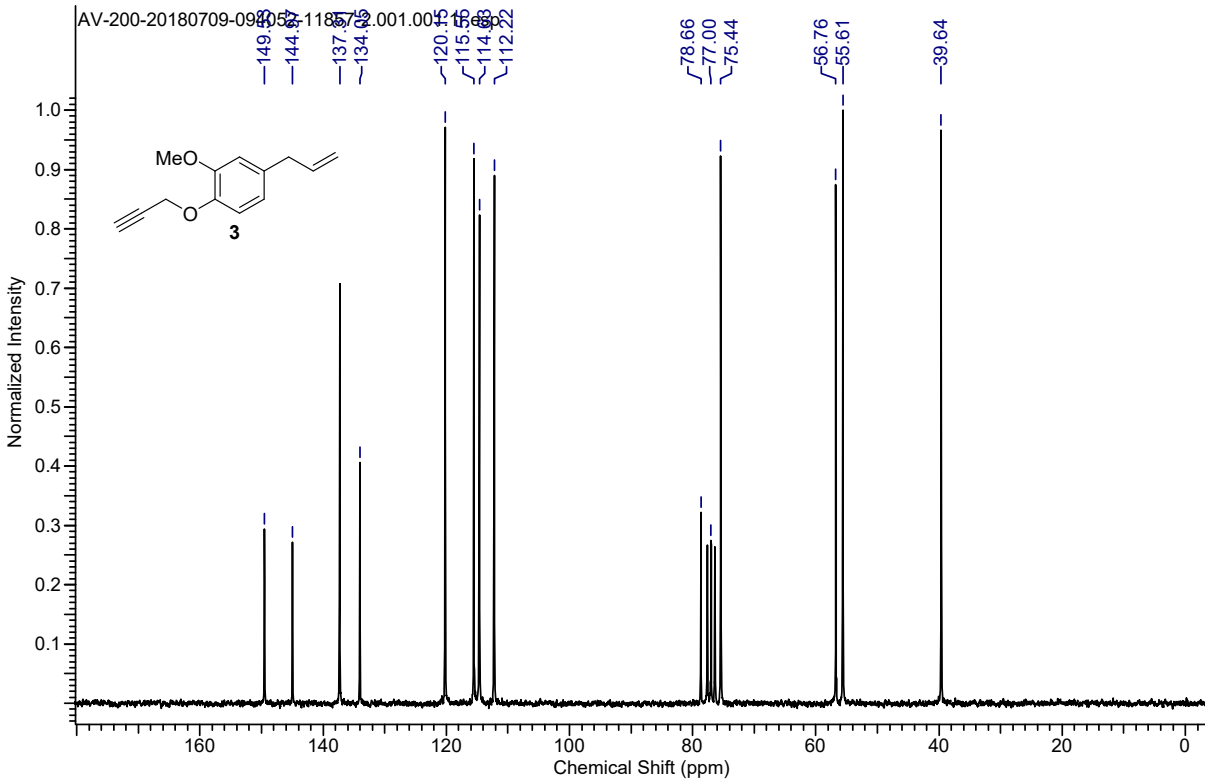
Statistical analyses

For the statistical analyses, one-way ANOVA was used, comparing the results of conidiation for compounds and isoeugenol treated culture with wild type, antifungal drug treated strain. All experiments were conducted in biological triplicates. All the statistics was performed using GraphPad Prism software 8.0.2.263 version and Microsoft Excel. $p<0.05$ was considered statistically significant.

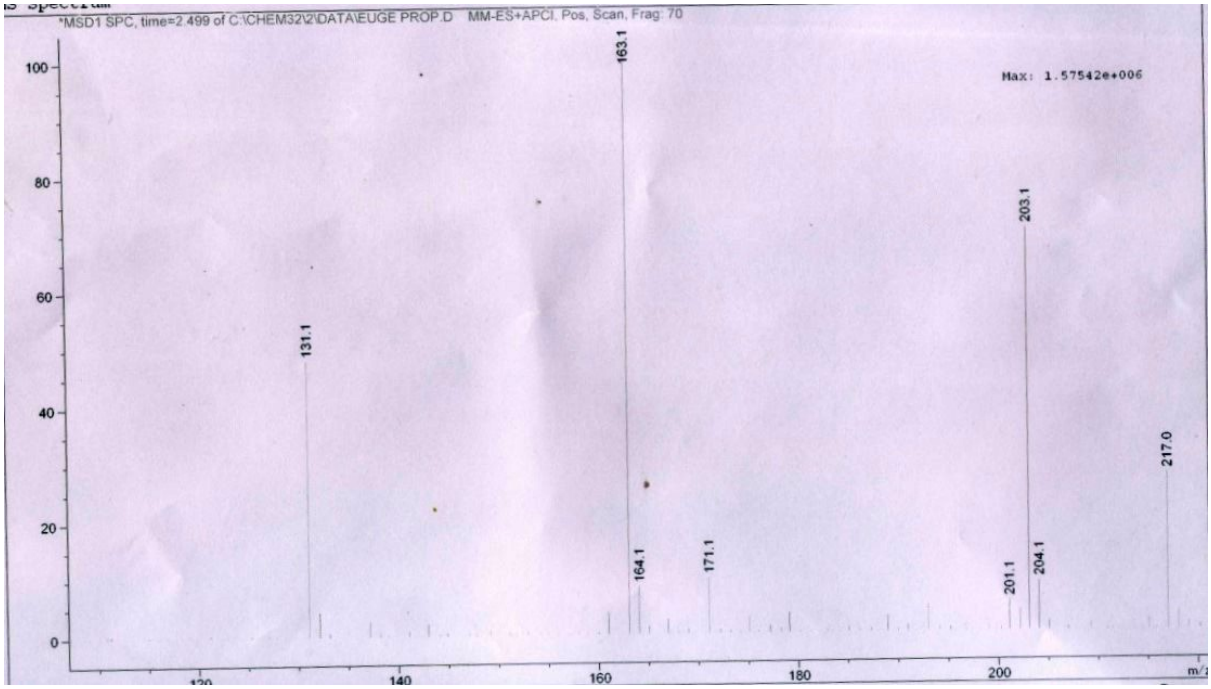
^{1}H, ^{13}C and Mass spectra of all the synthesized compounds



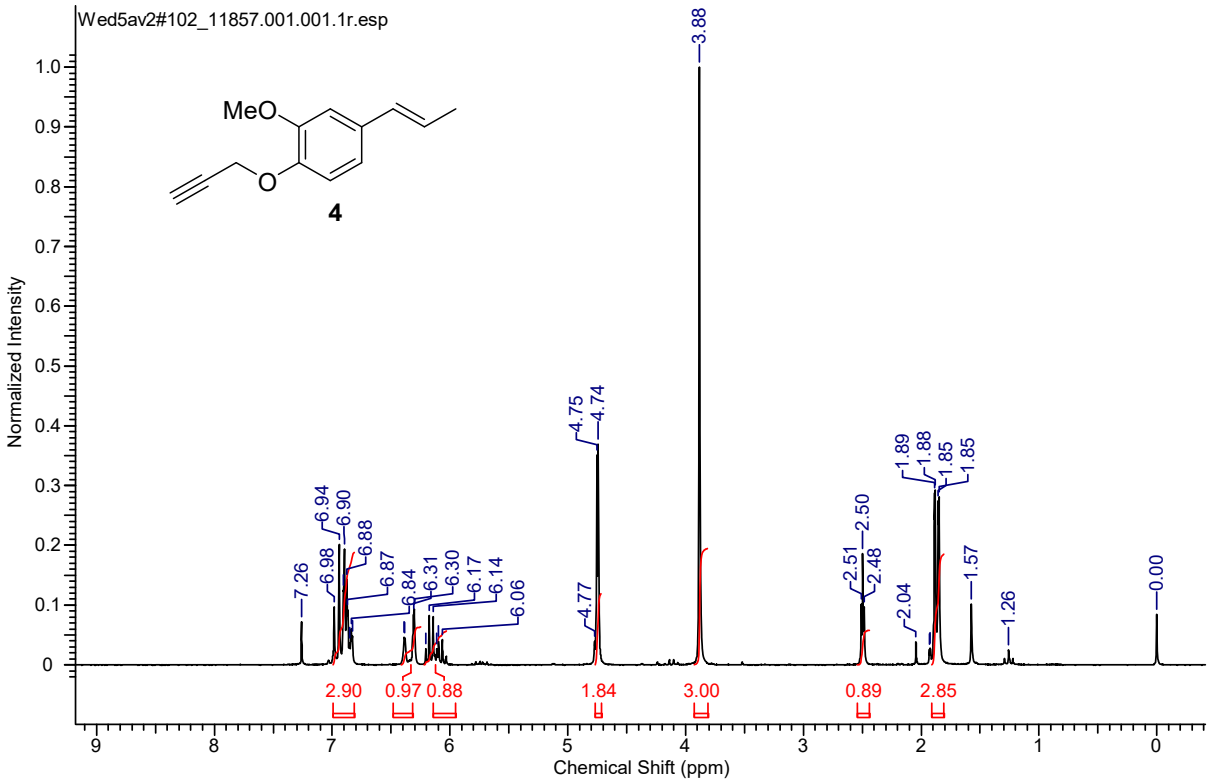
^{1}H NMR ($CDCl_3$, 200 MHz) of **3**



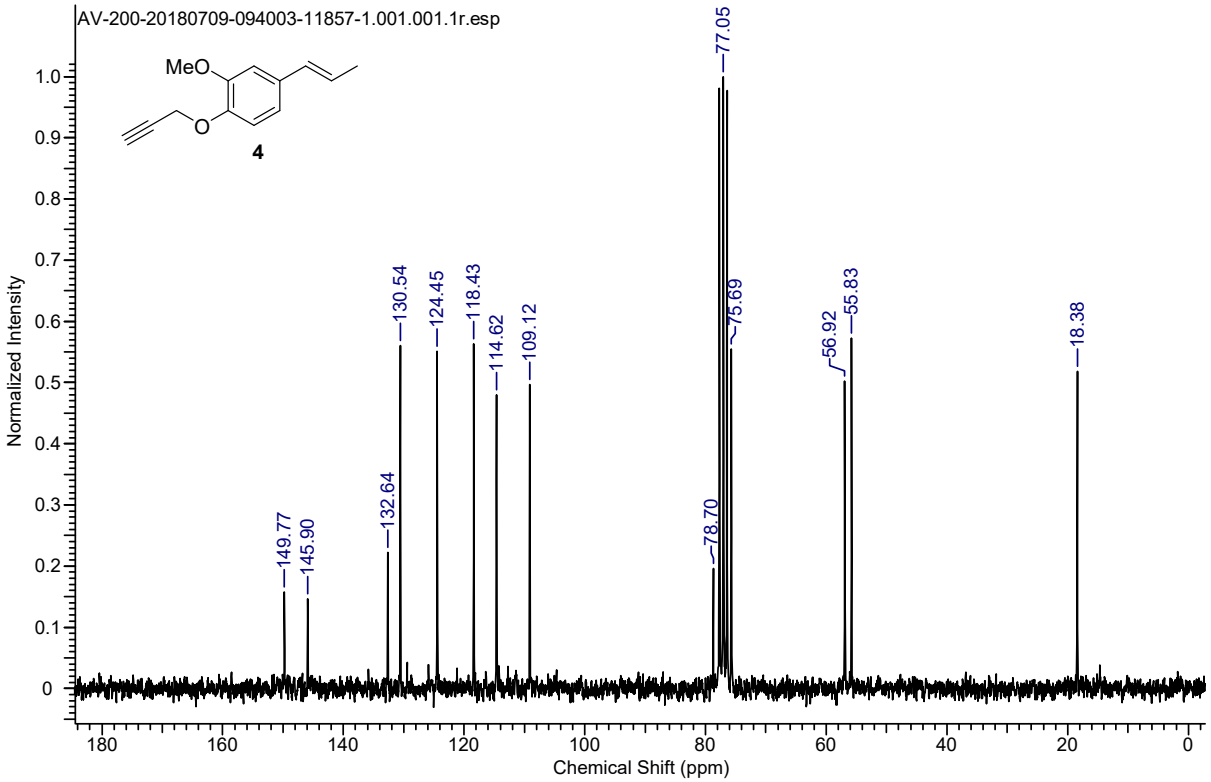
^{13}C NMR ($CDCl_3$, 50 MHz) of **3**



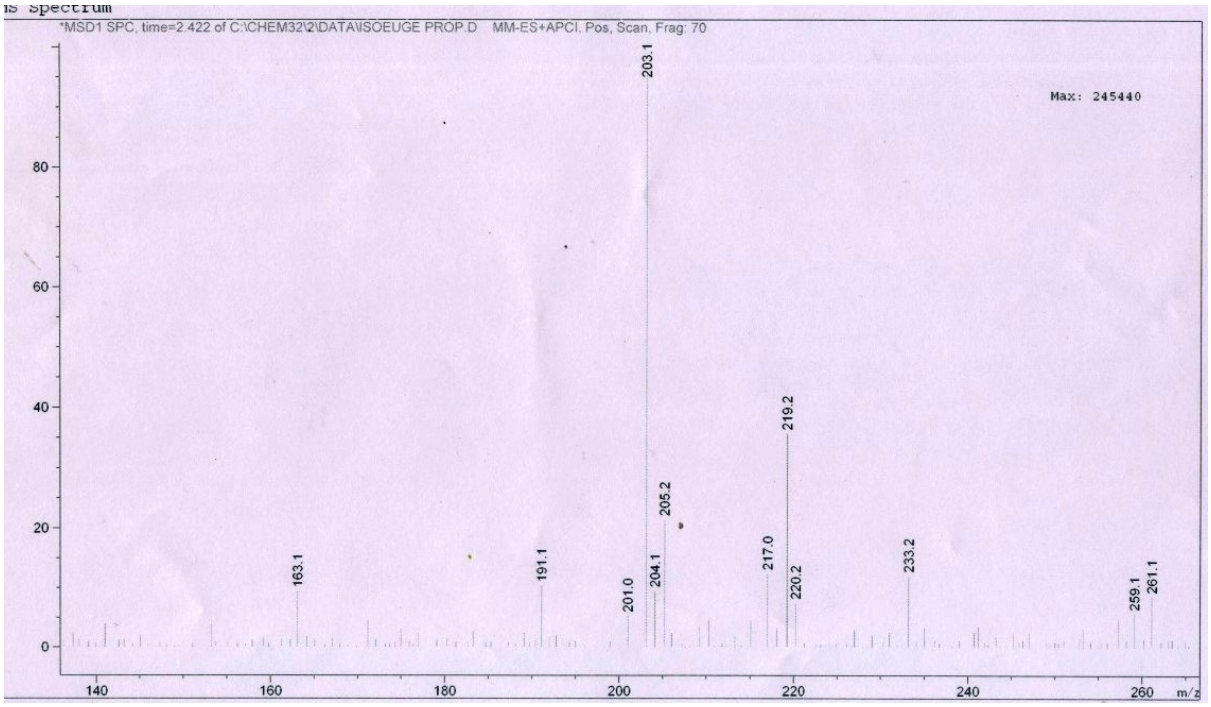
LCMS of **3**



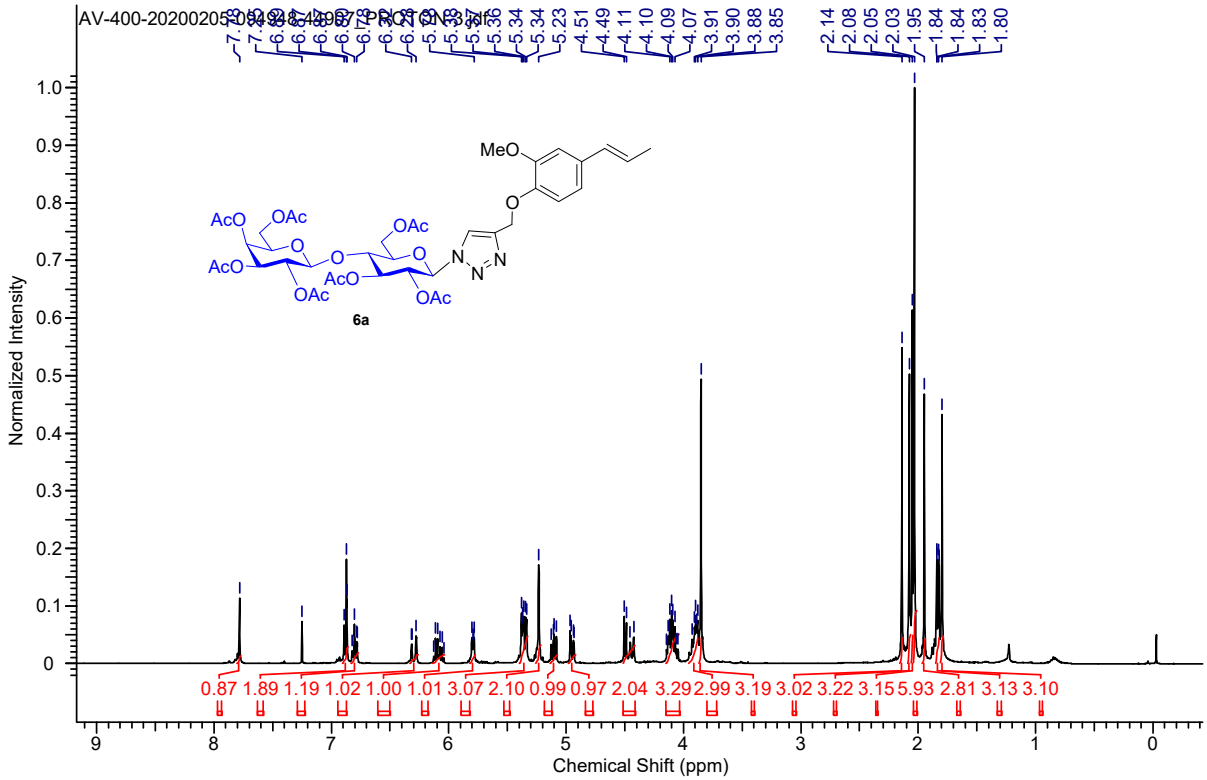
^{1}H NMR ($CDCl_3$, 200 MHz) of **4**



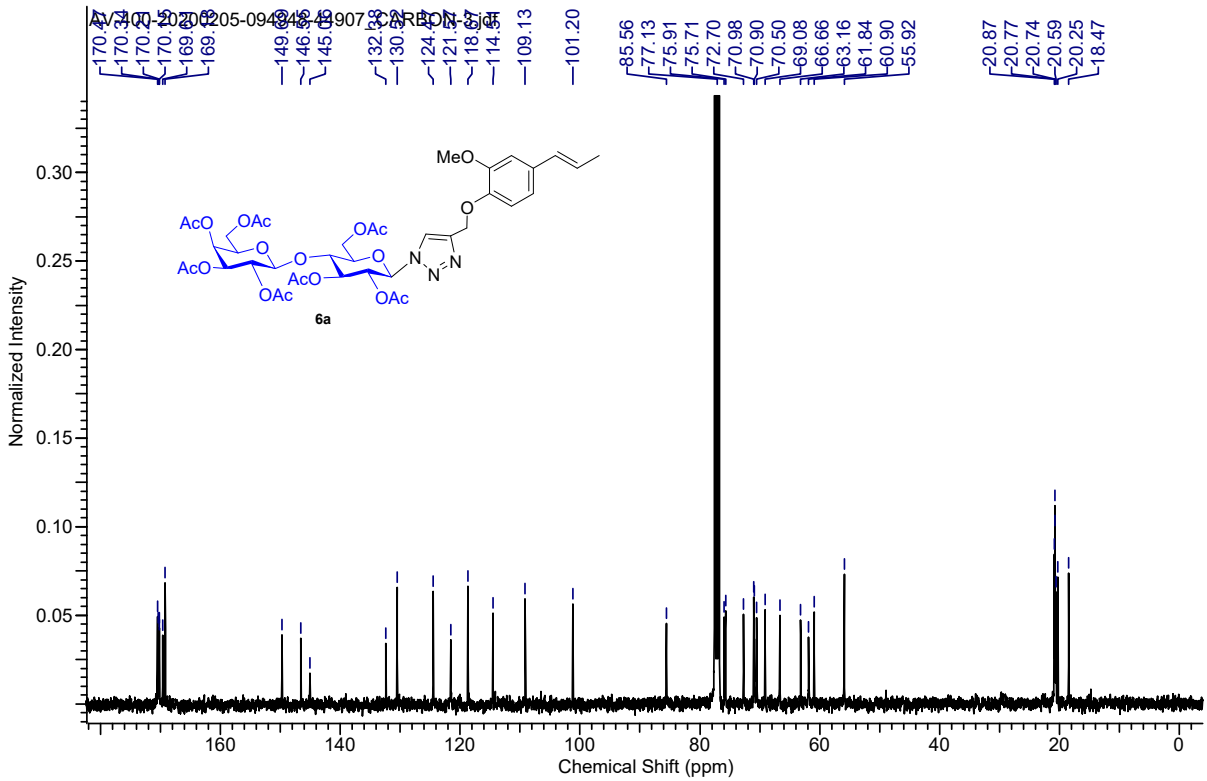
^{13}C NMR ($CDCl_3$, 50 MHz) of **4**



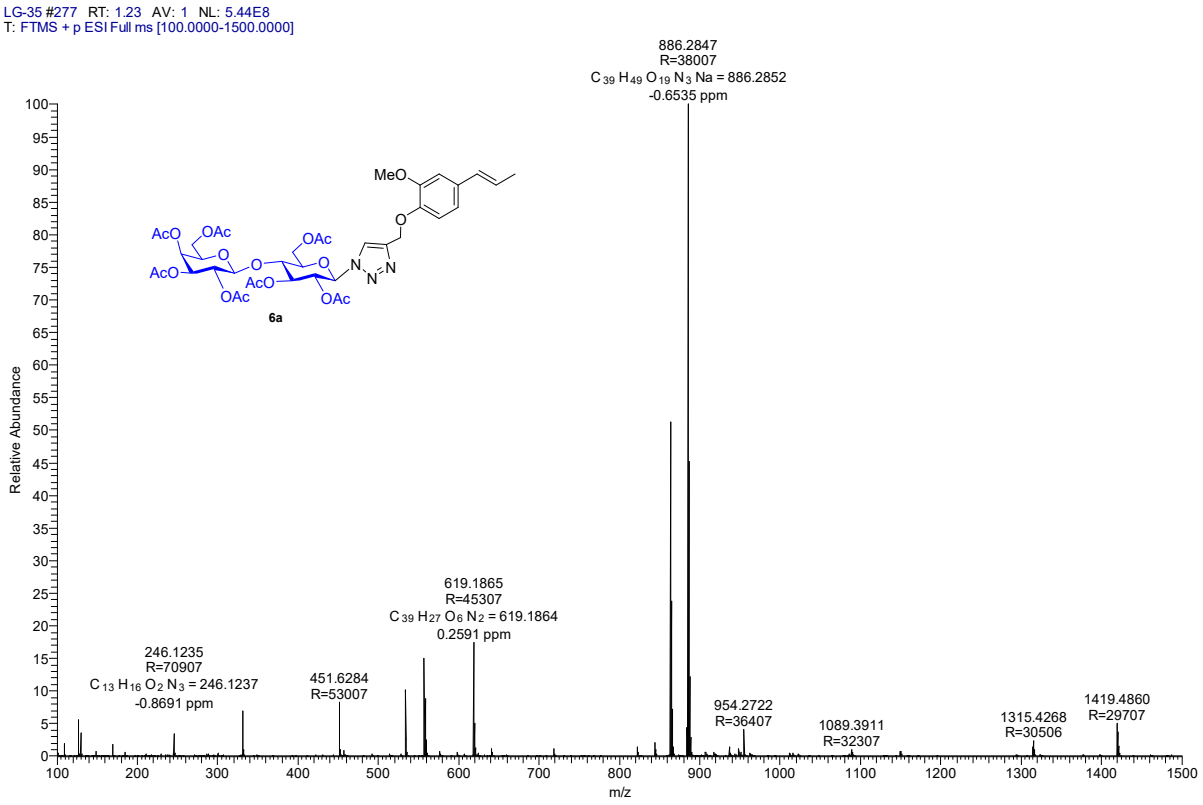
LCMS of **4**



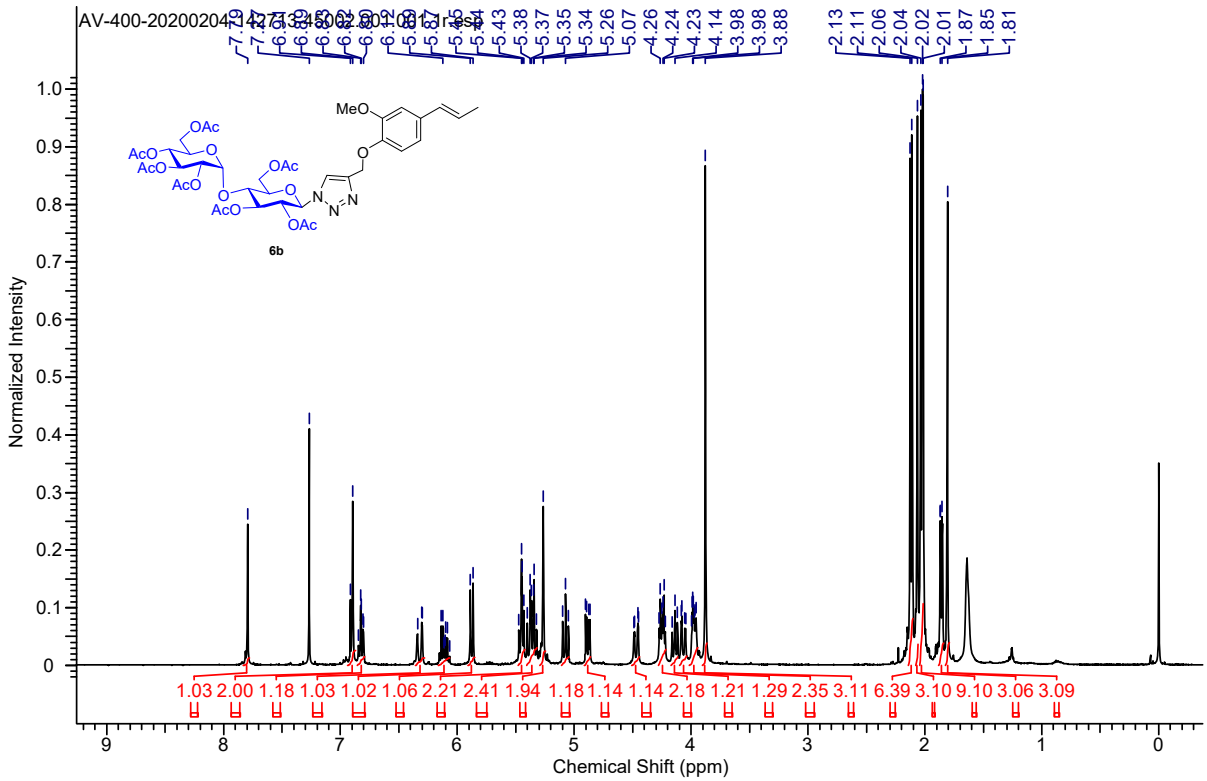
^{1}H NMR ($CDCl_3$, 200 MHz) of **6a**



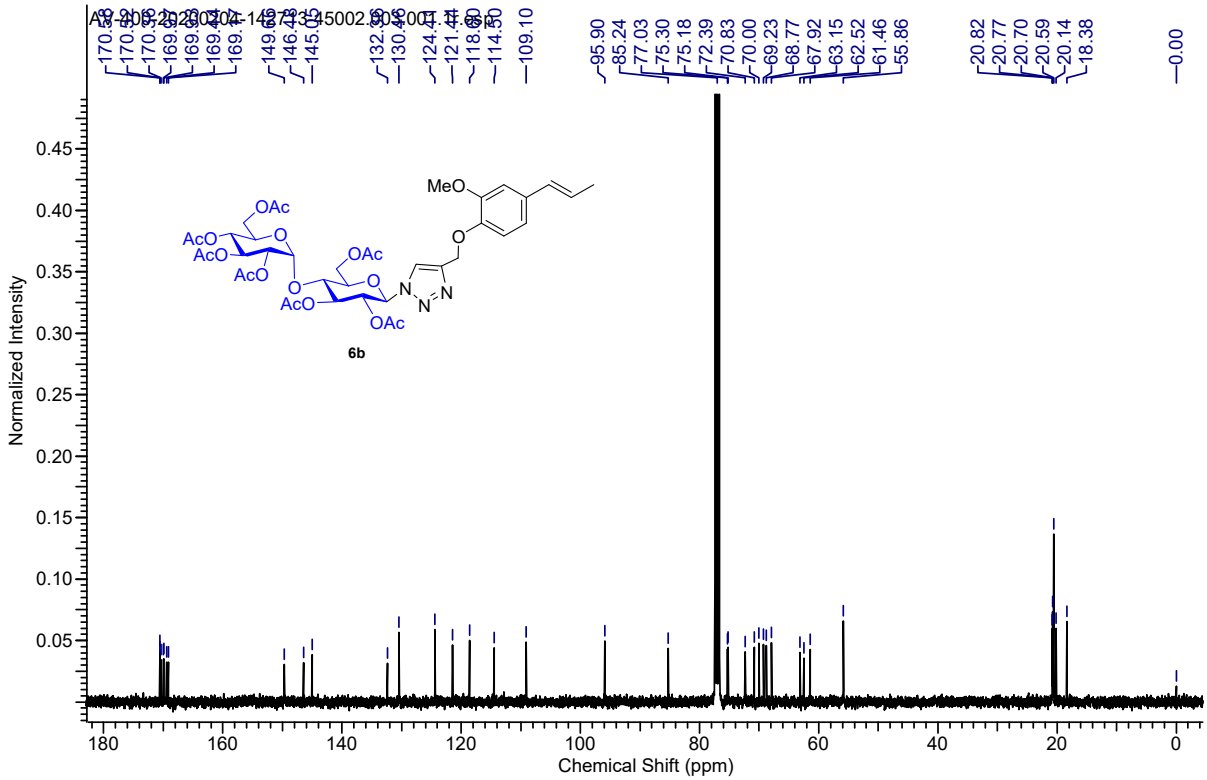
^{13}C NMR ($CDCl_3$, 50 MHz) of **6a**



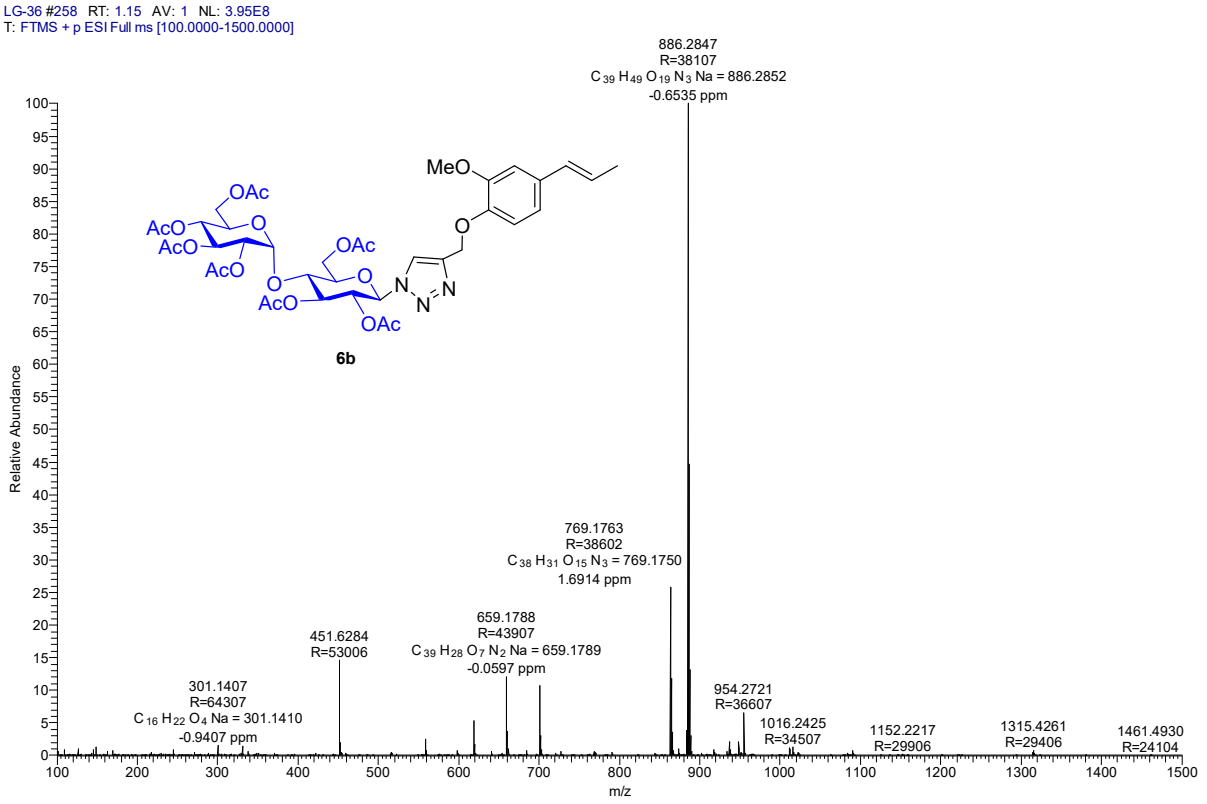
HRMS of **6a**



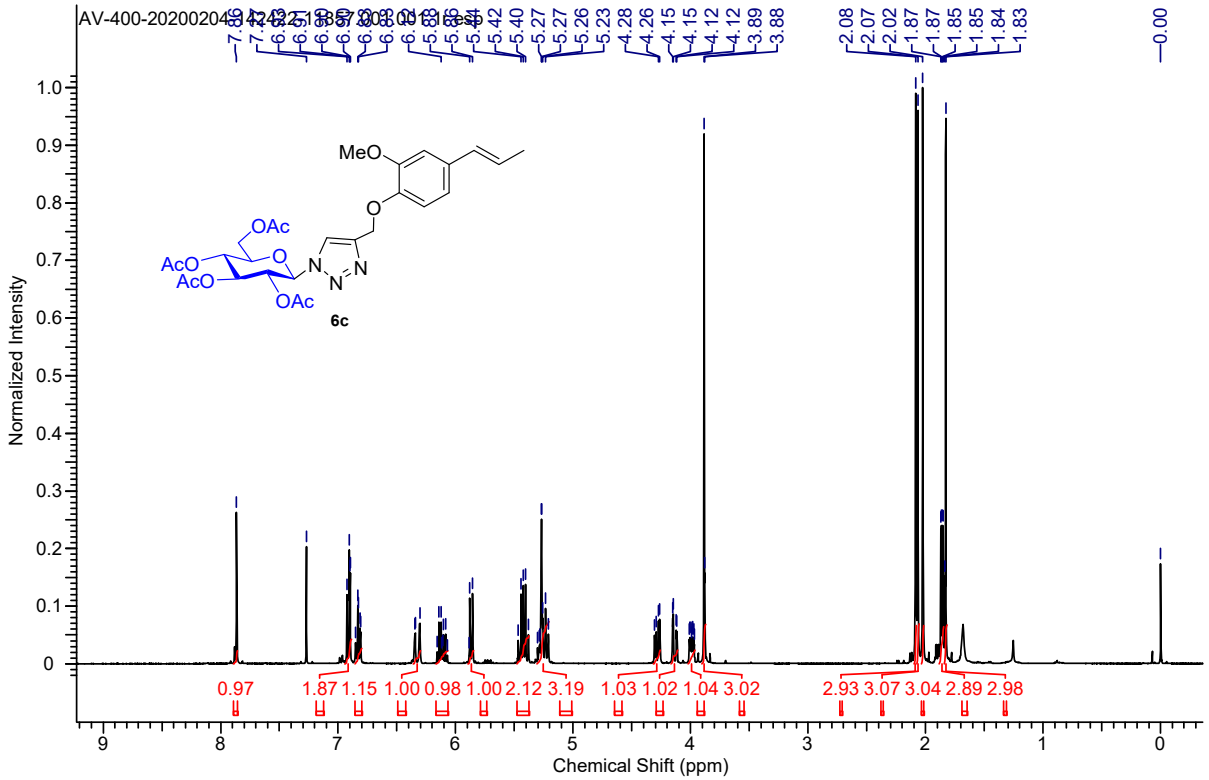
^{1}H NMR ($CDCl_3$, 200 MHz) of **6b**



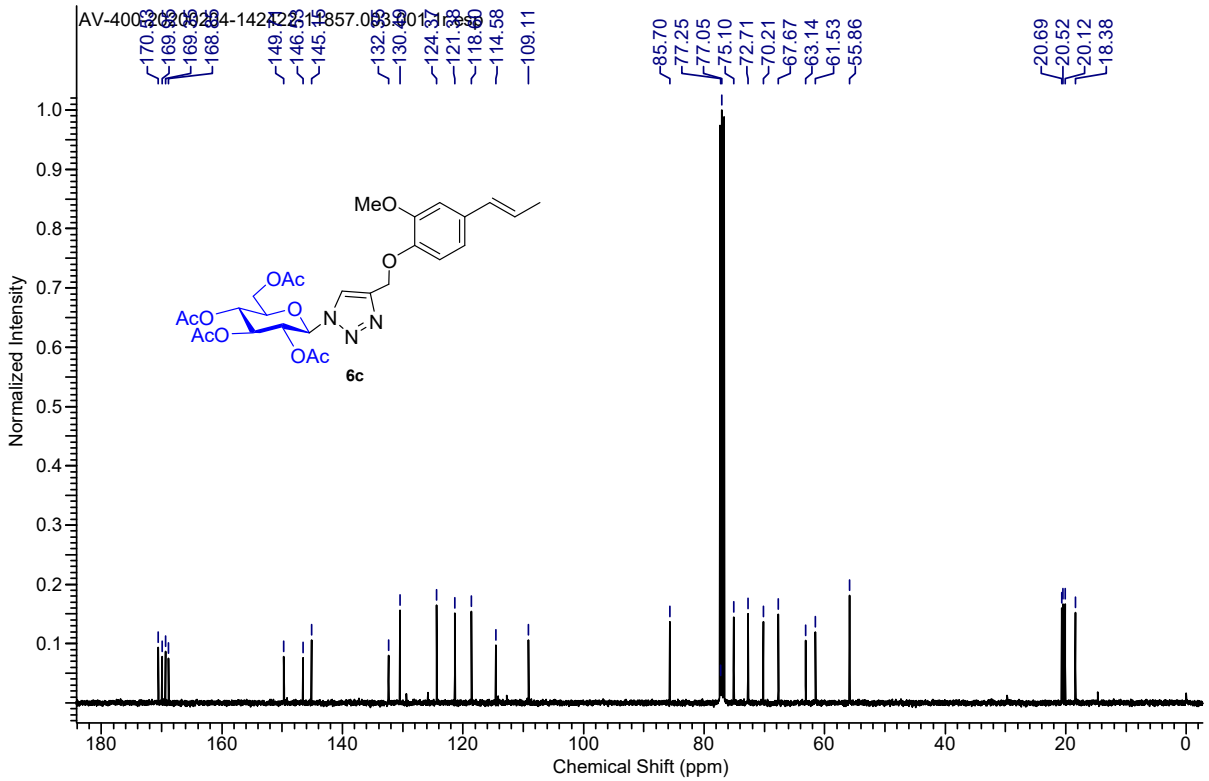
^{13}C NMR ($CDCl_3$, 50 MHz) of **6b**



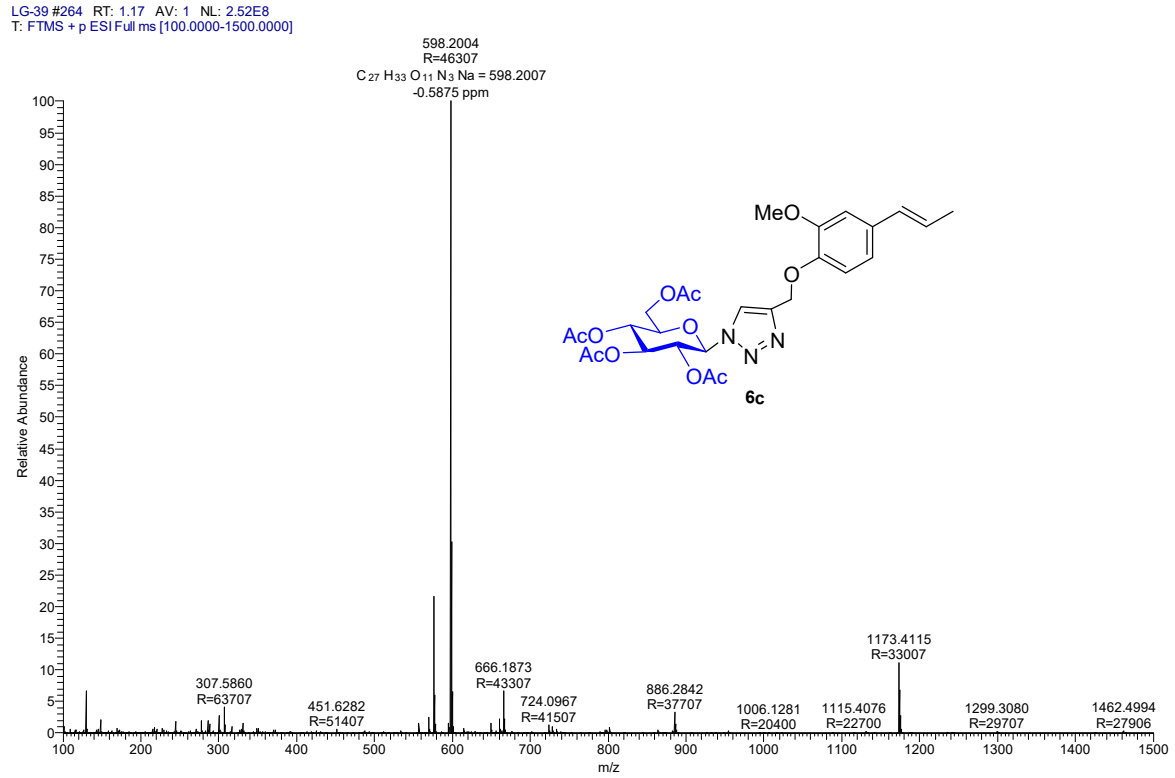
HRMS of **6b**



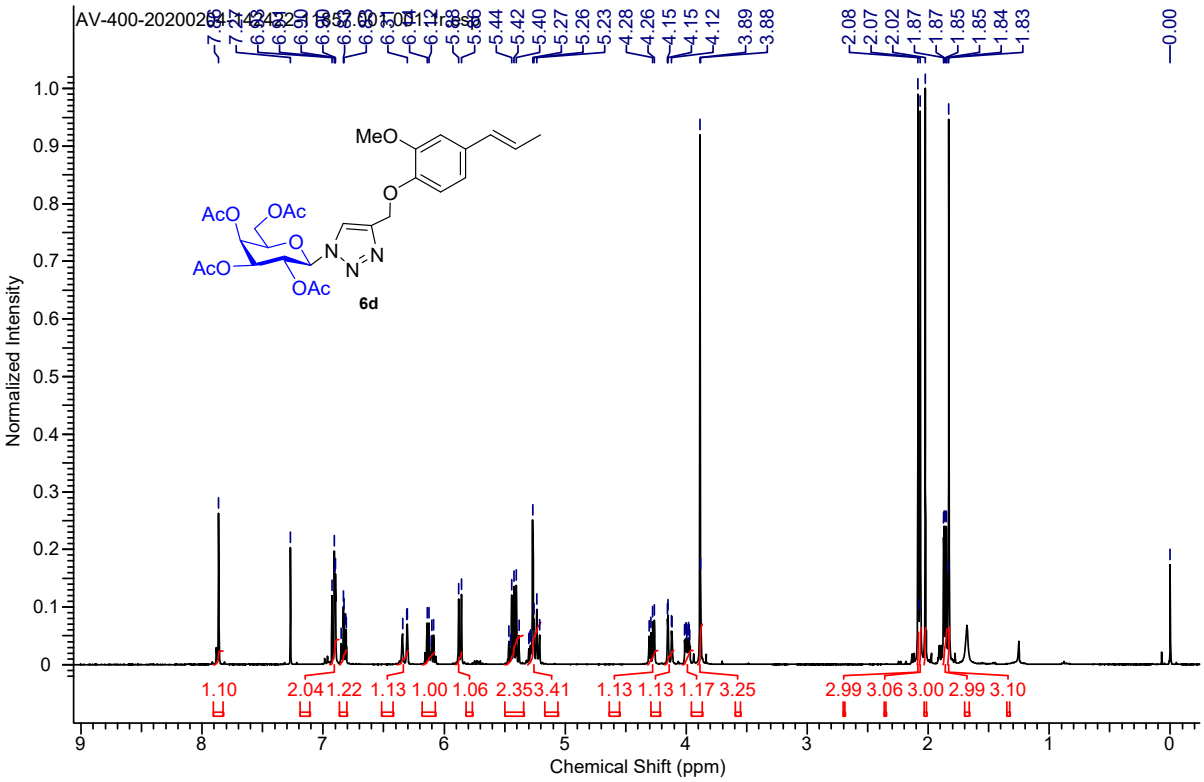
^{1}H NMR ($CDCl_3$, 200 MHz) of **6c**



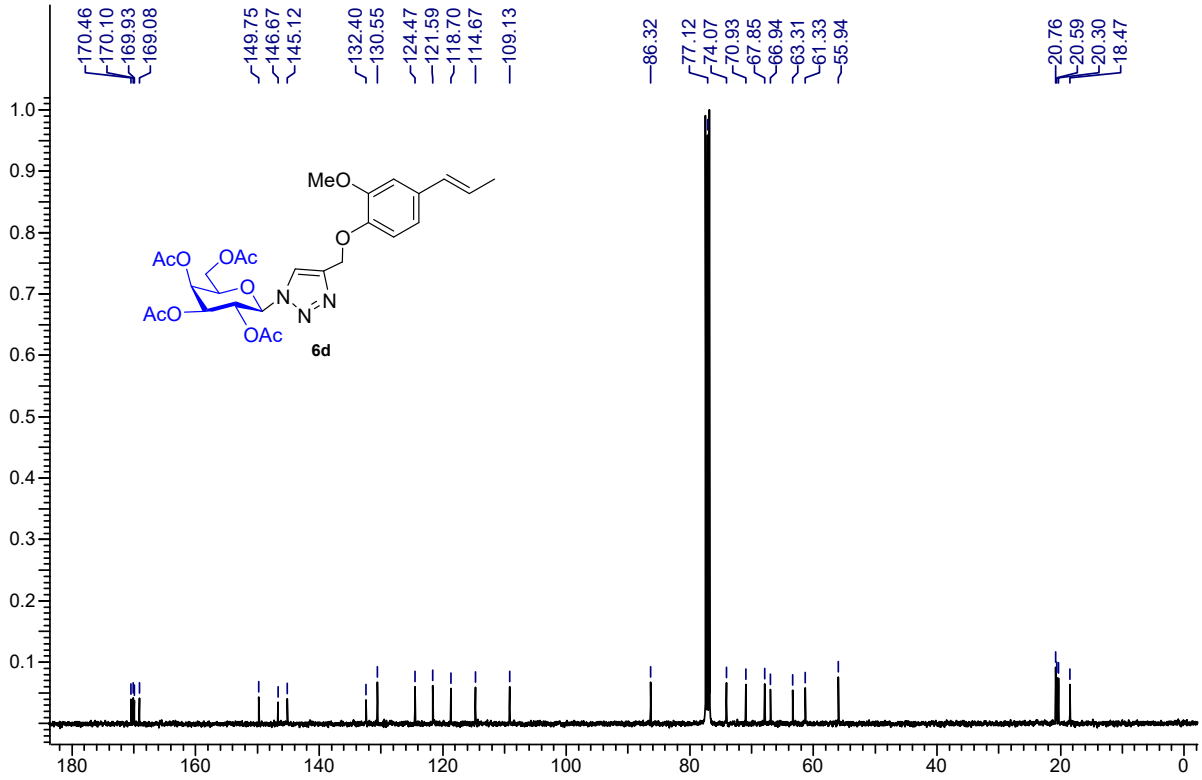
^{13}C NMR ($CDCl_3$, 50 MHz) of **6c**



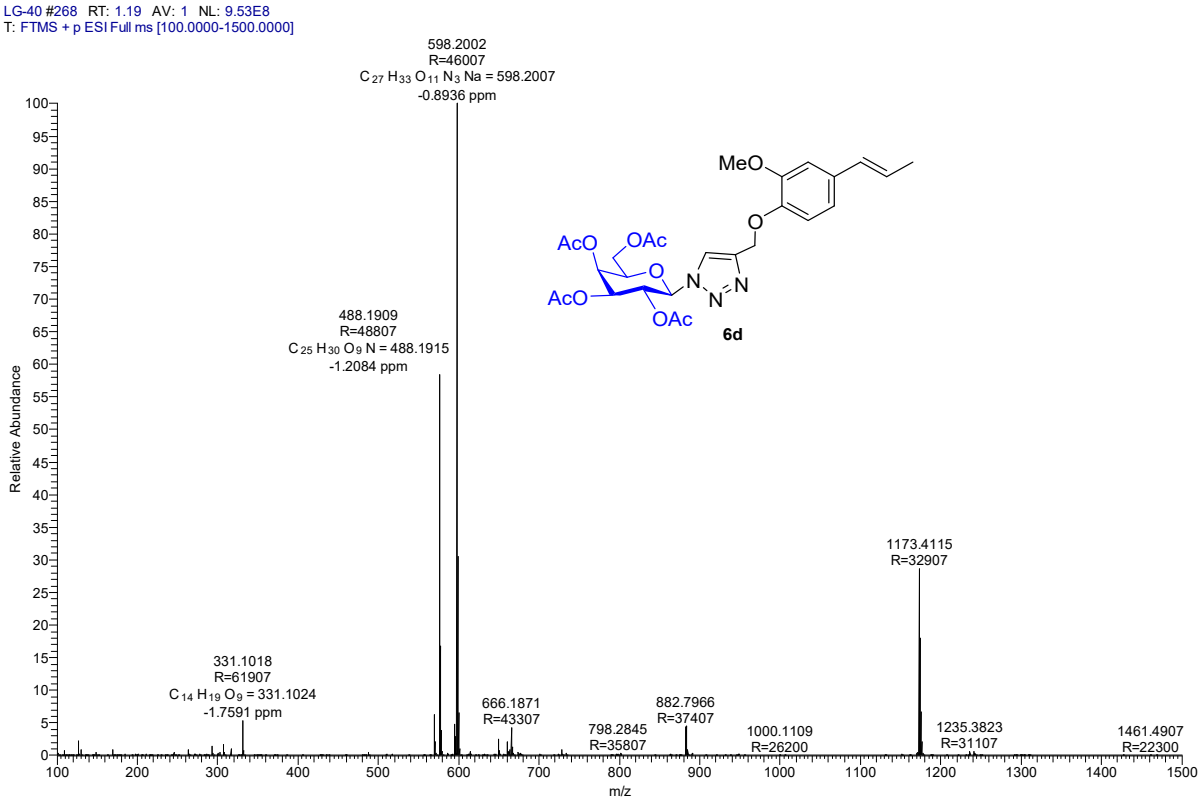
HRMS of **6c**



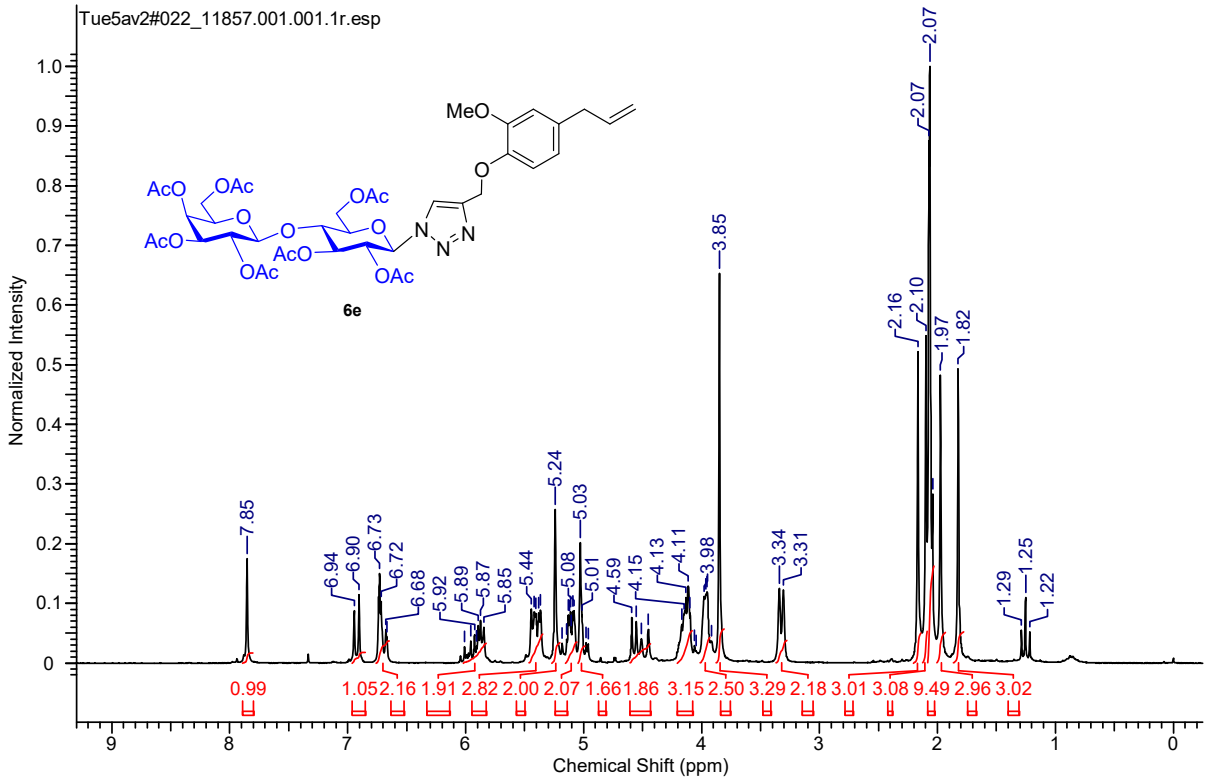
^{1}H NMR ($CDCl_3$, 400 MHz) of **6d**



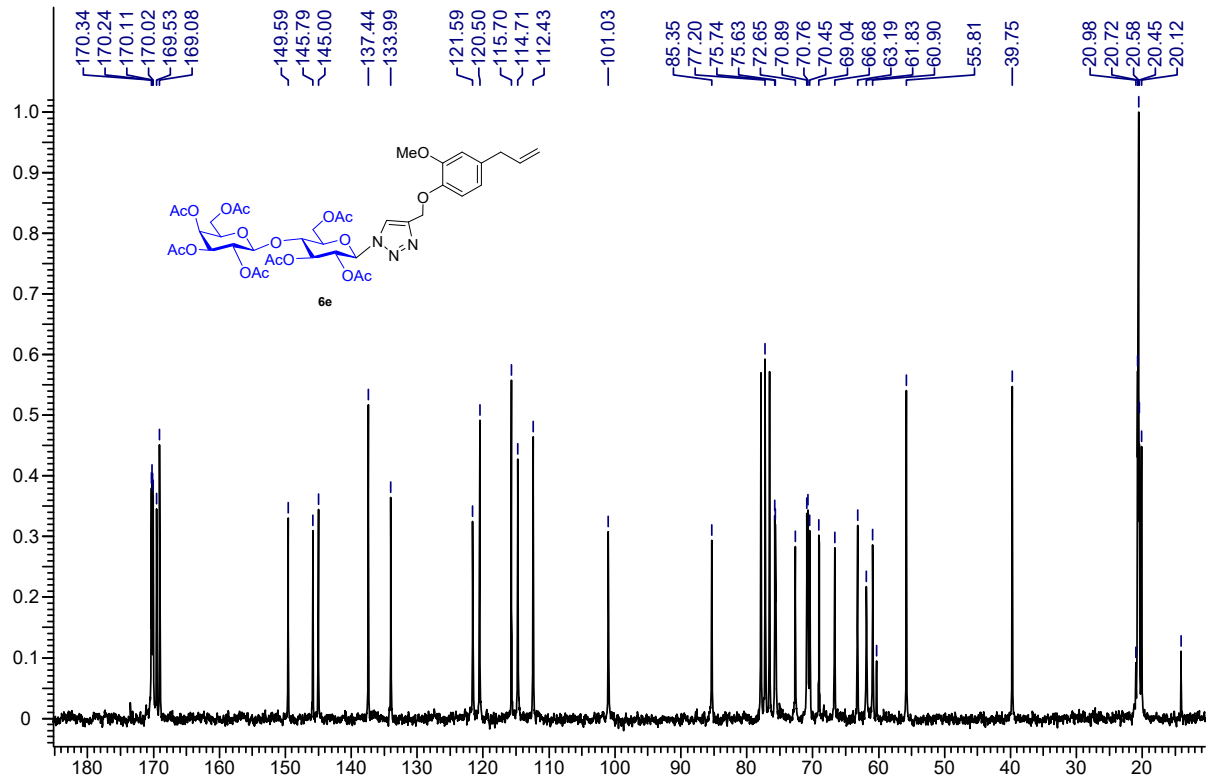
^{13}C NMR ($CDCl_3$, 100 MHz) of **6d**



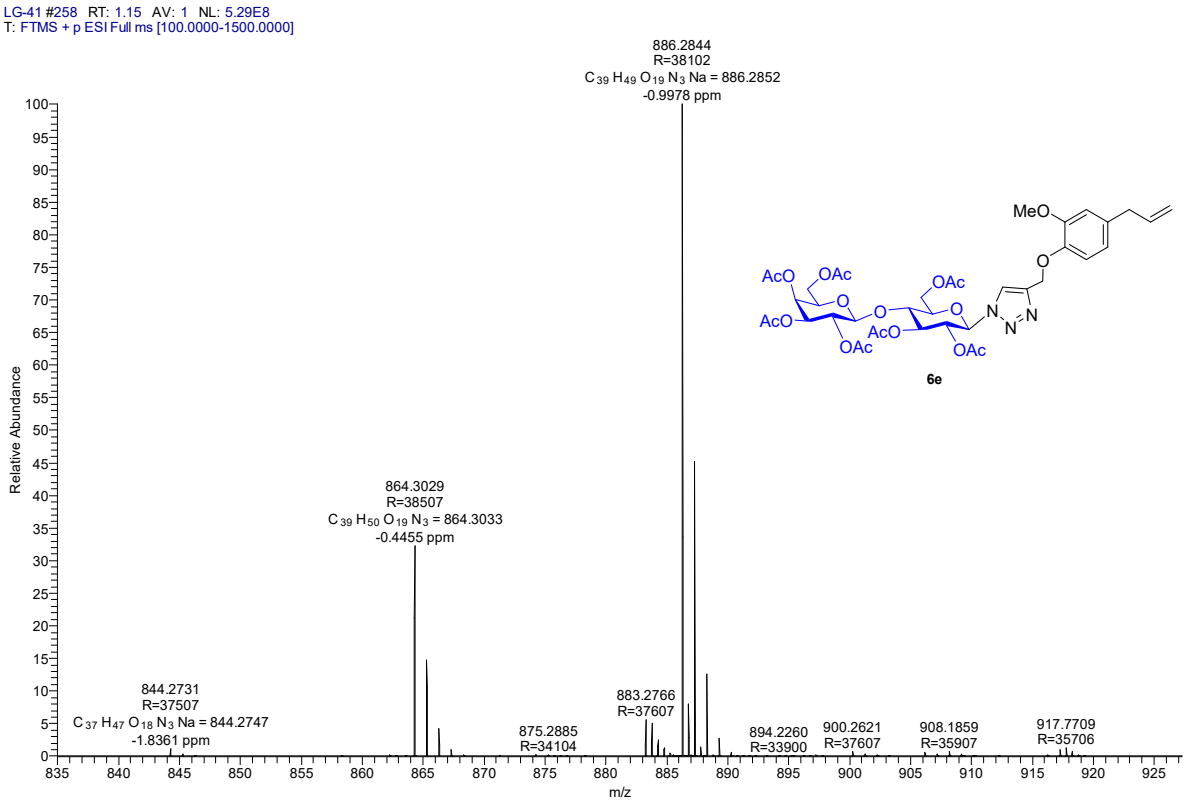
HRMS of **6d**



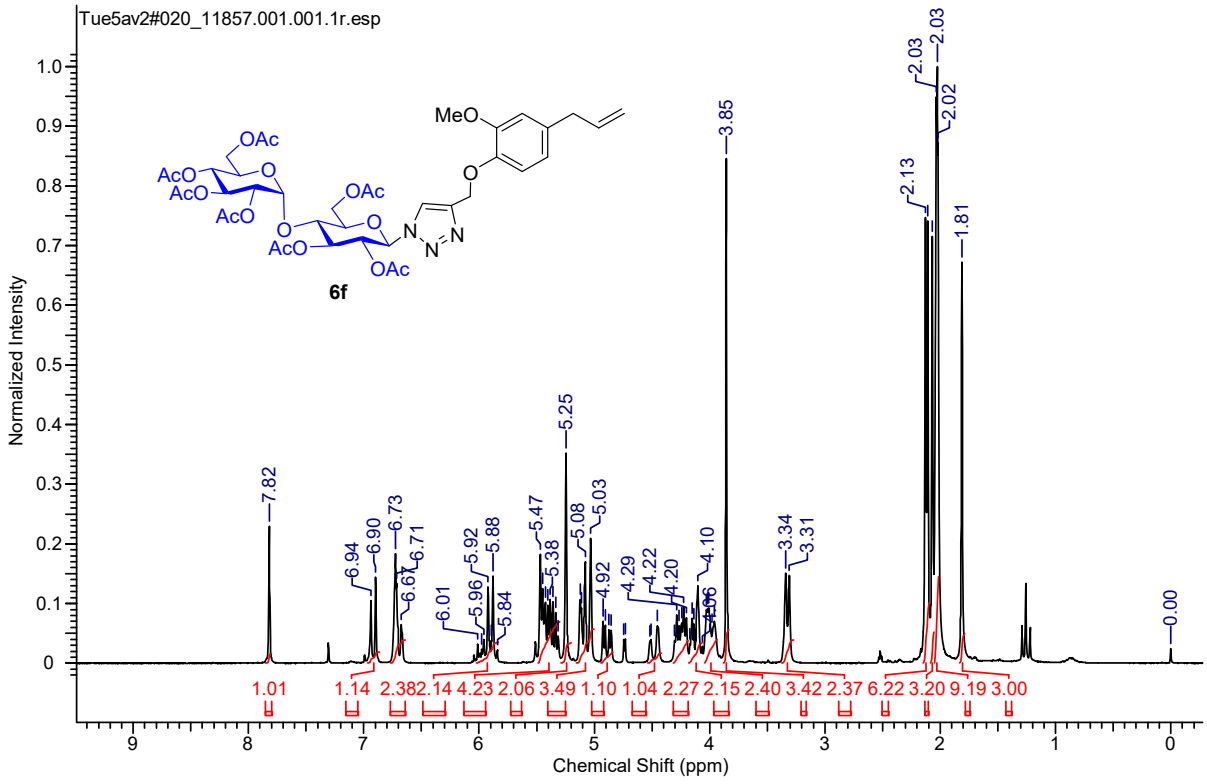
^{1}H NMR ($CDCl_3$, 200 MHz) of **6e**



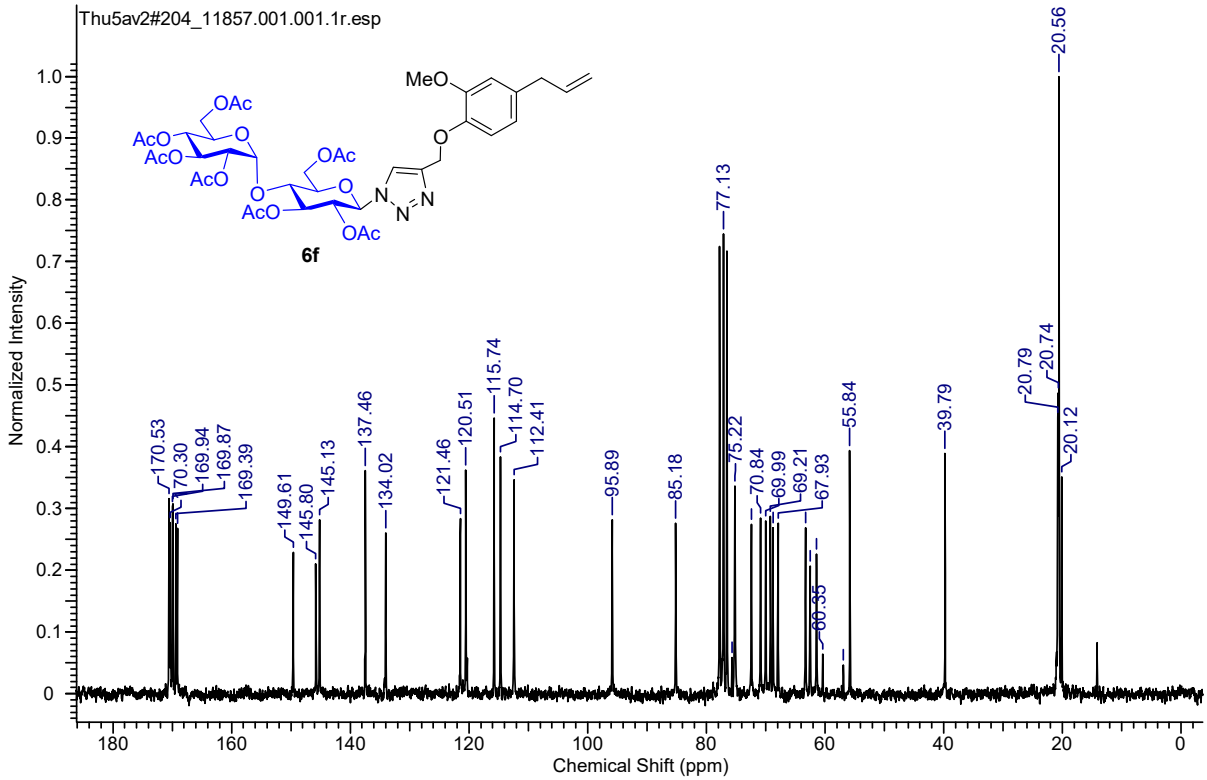
^{13}C NMR ($CDCl_3$, 50 MHz) of **6e**



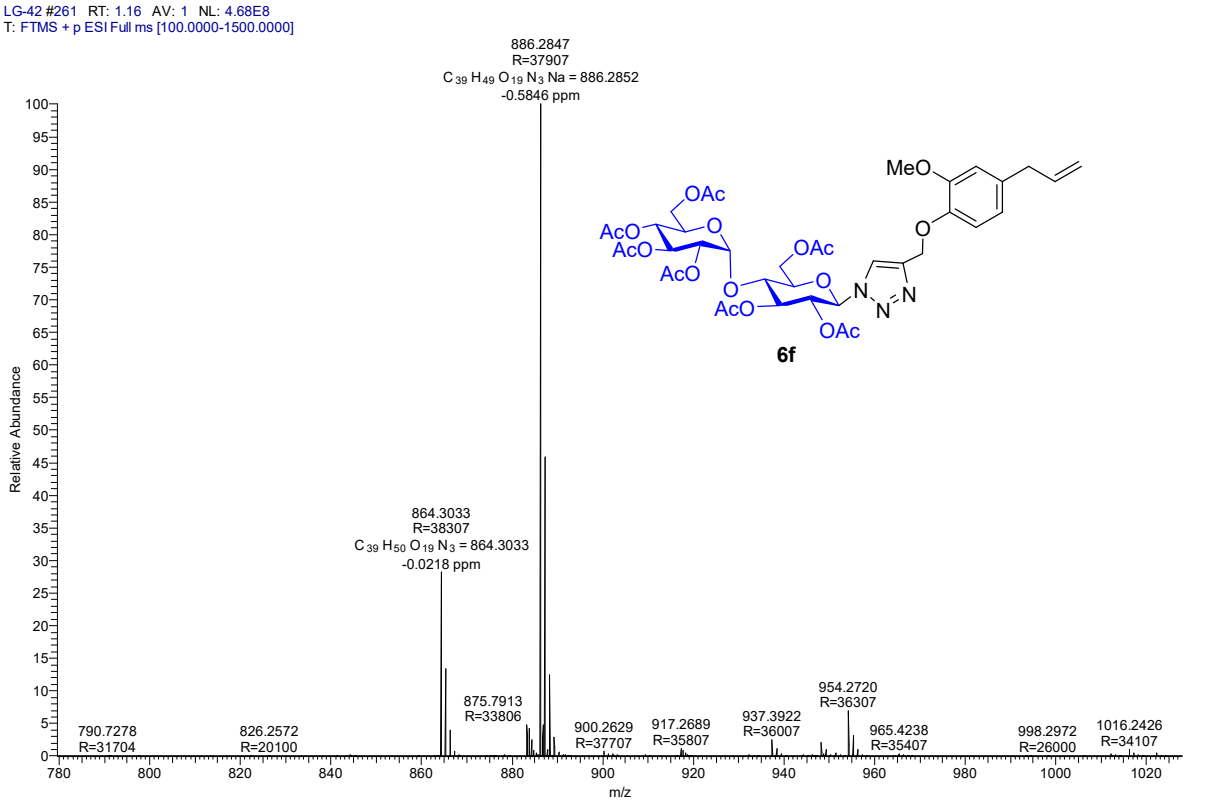
HRMS of **6e**



^{1}H NMR ($CDCl_3$, 200 MHz) of **6f**



^{13}C NMR ($CDCl_3$, 50 MHz) of **6f**



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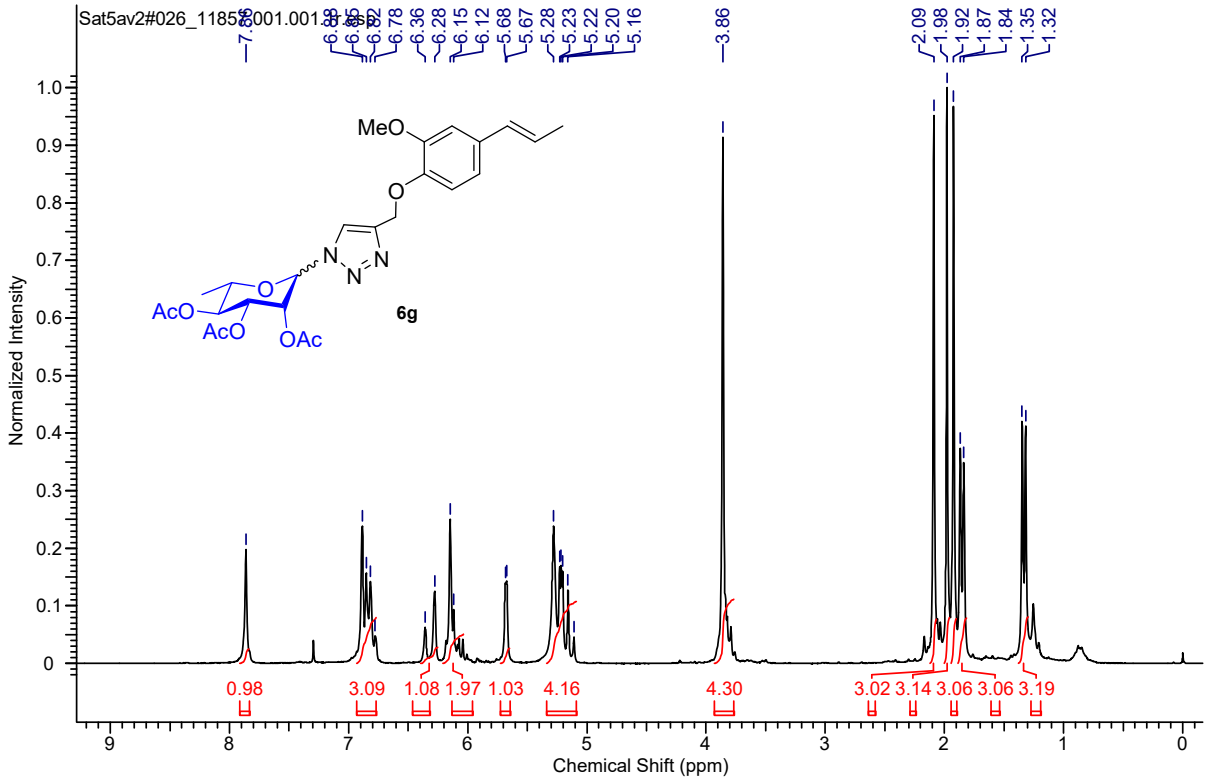
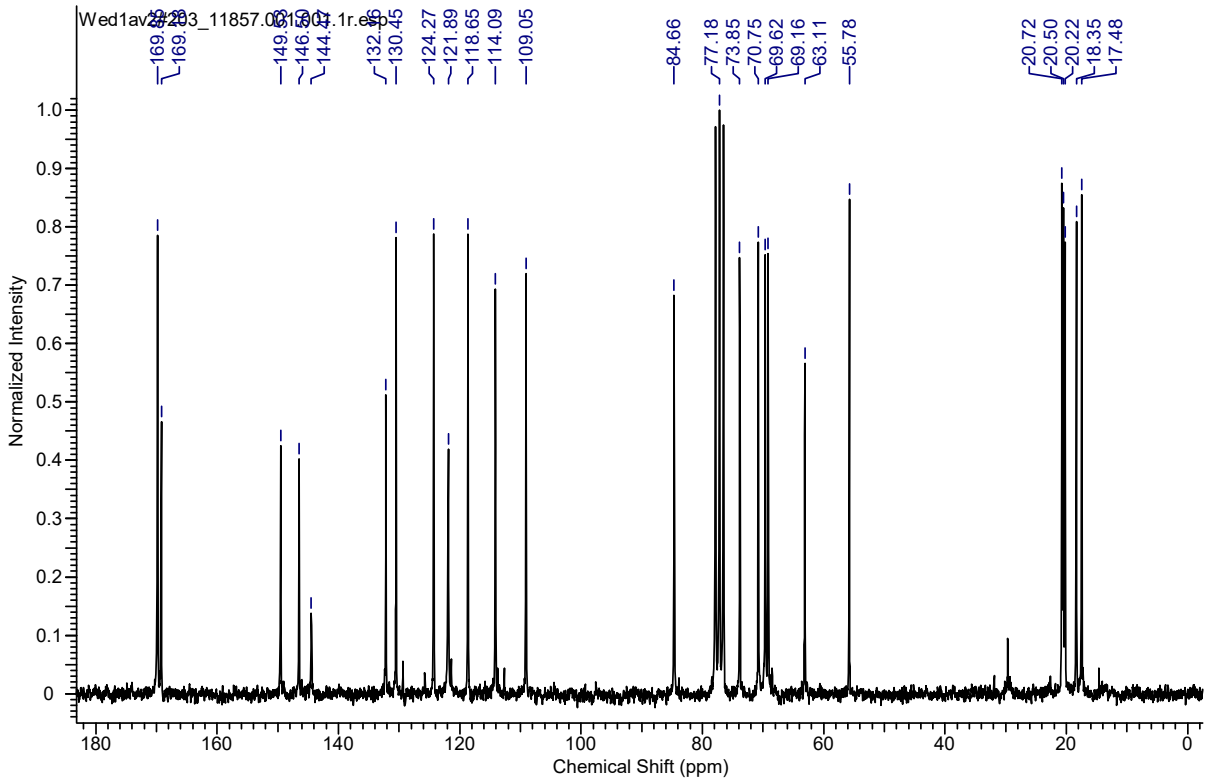
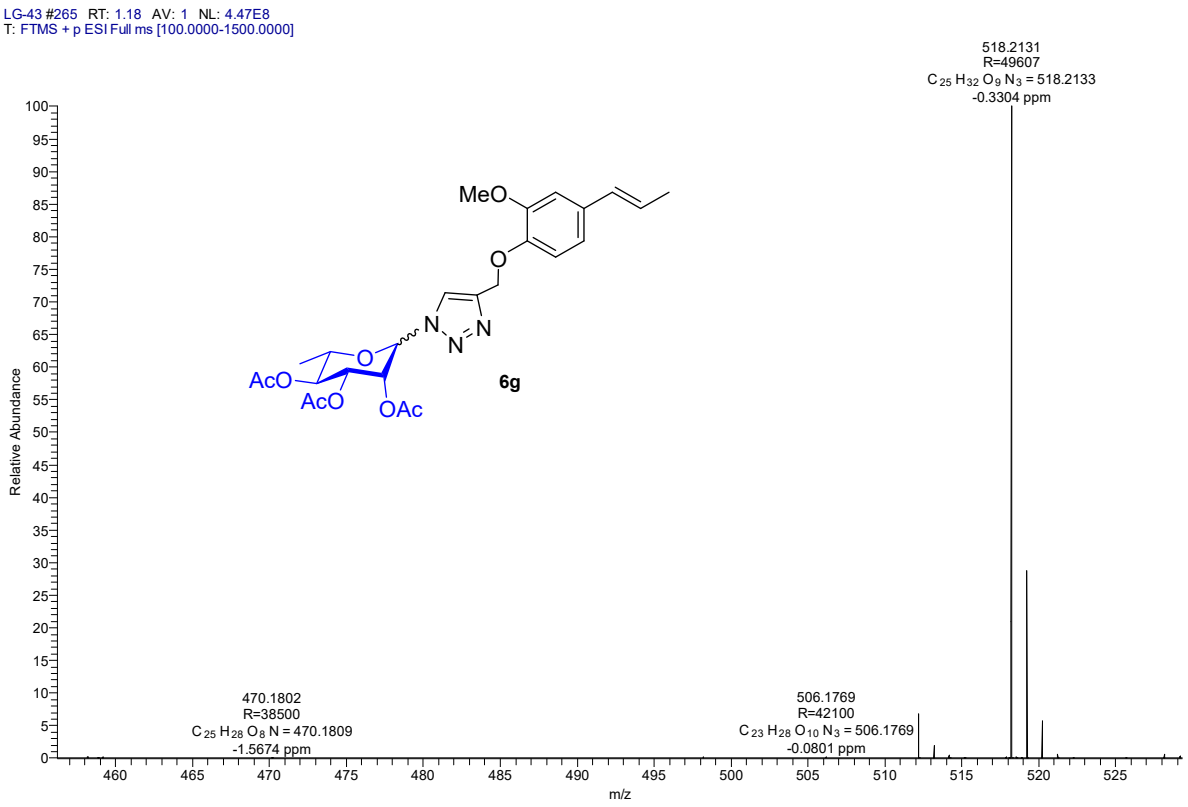


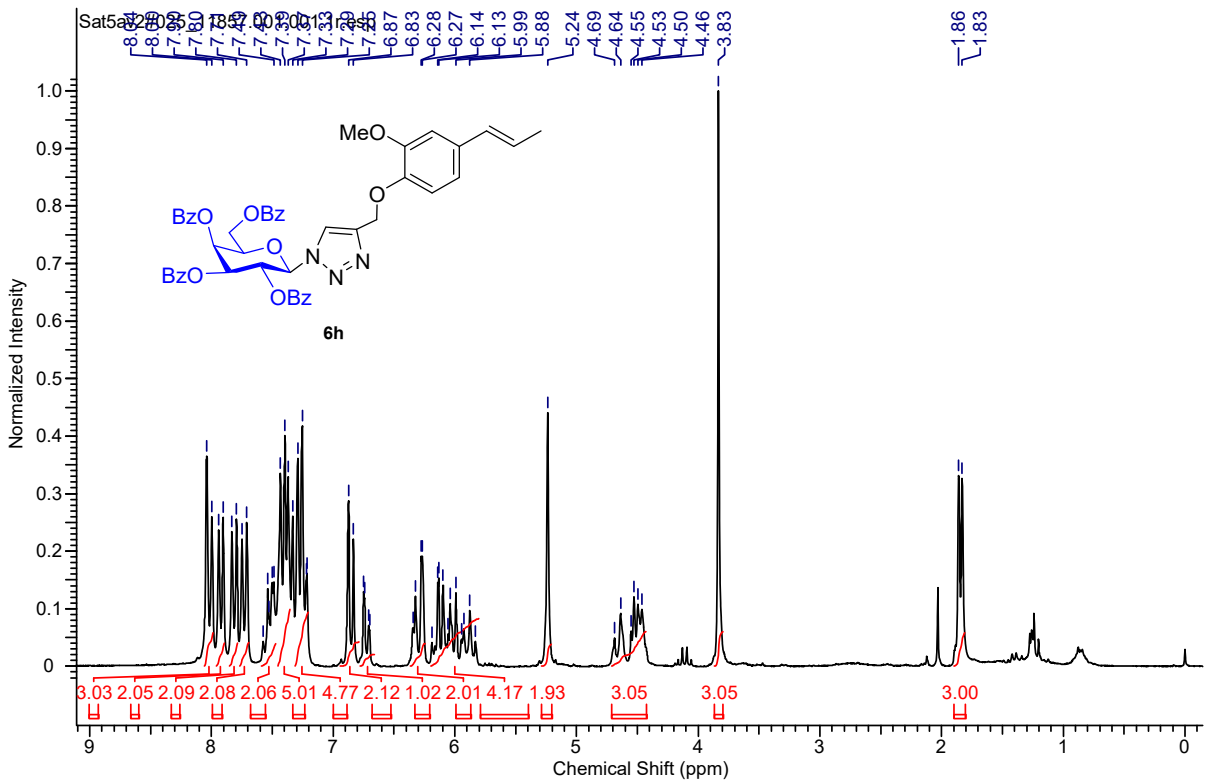
^{1}H NMR ($CDCl_3$, 200 MHz) of **6g**



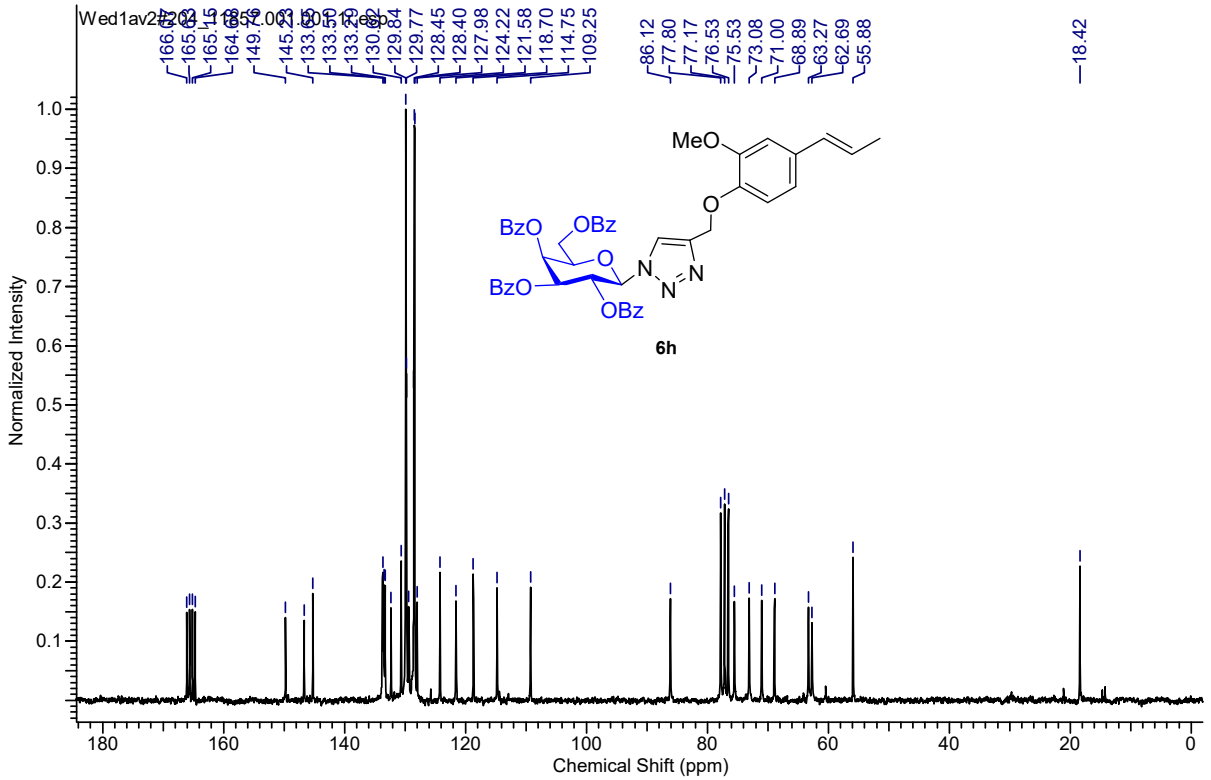
^{13}C NMR ($CDCl_3$, 50 MHz) of **6g**



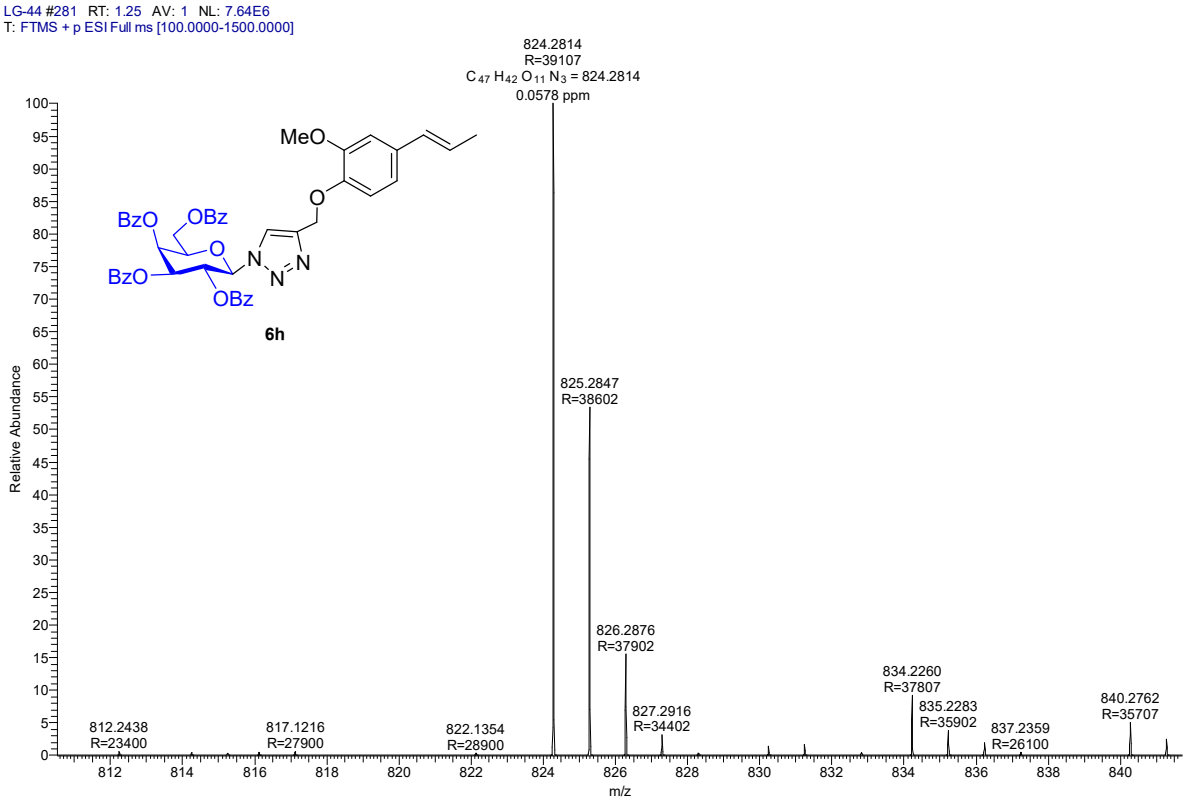
HRMS of **6g**



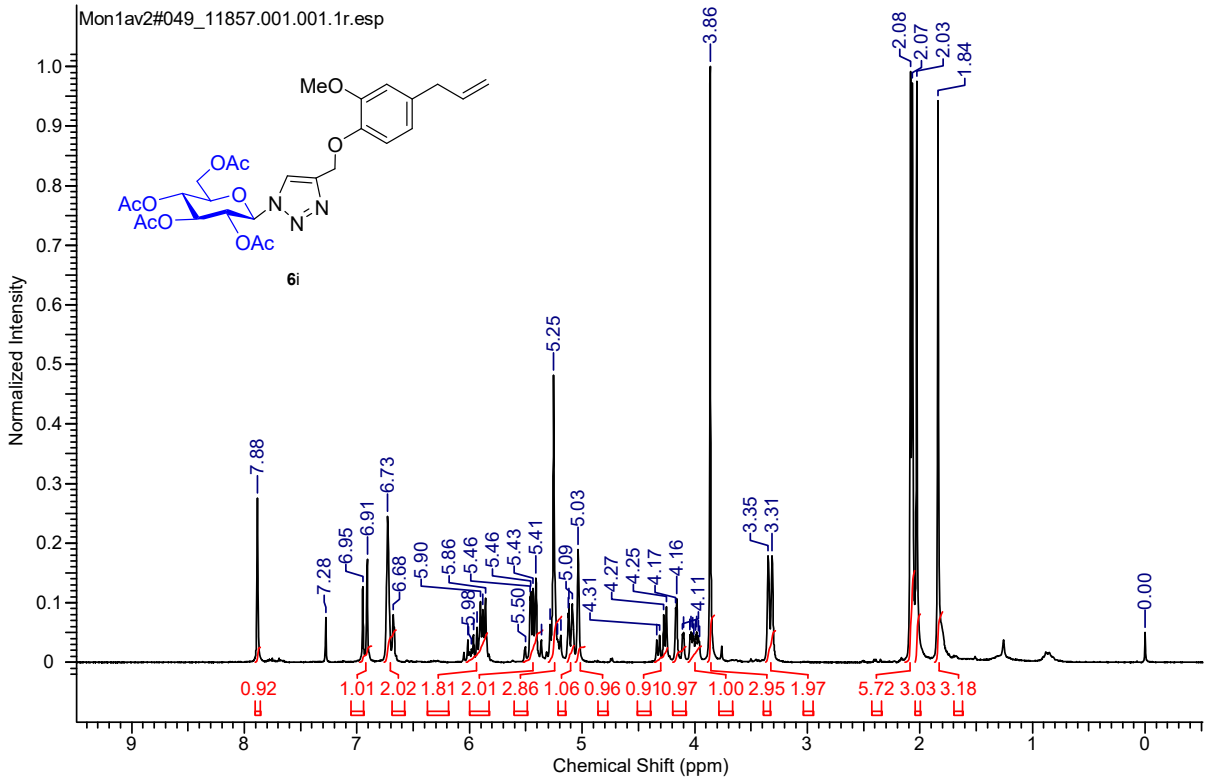
^{1}H NMR ($CDCl_3$, 200 MHz) of **6h**



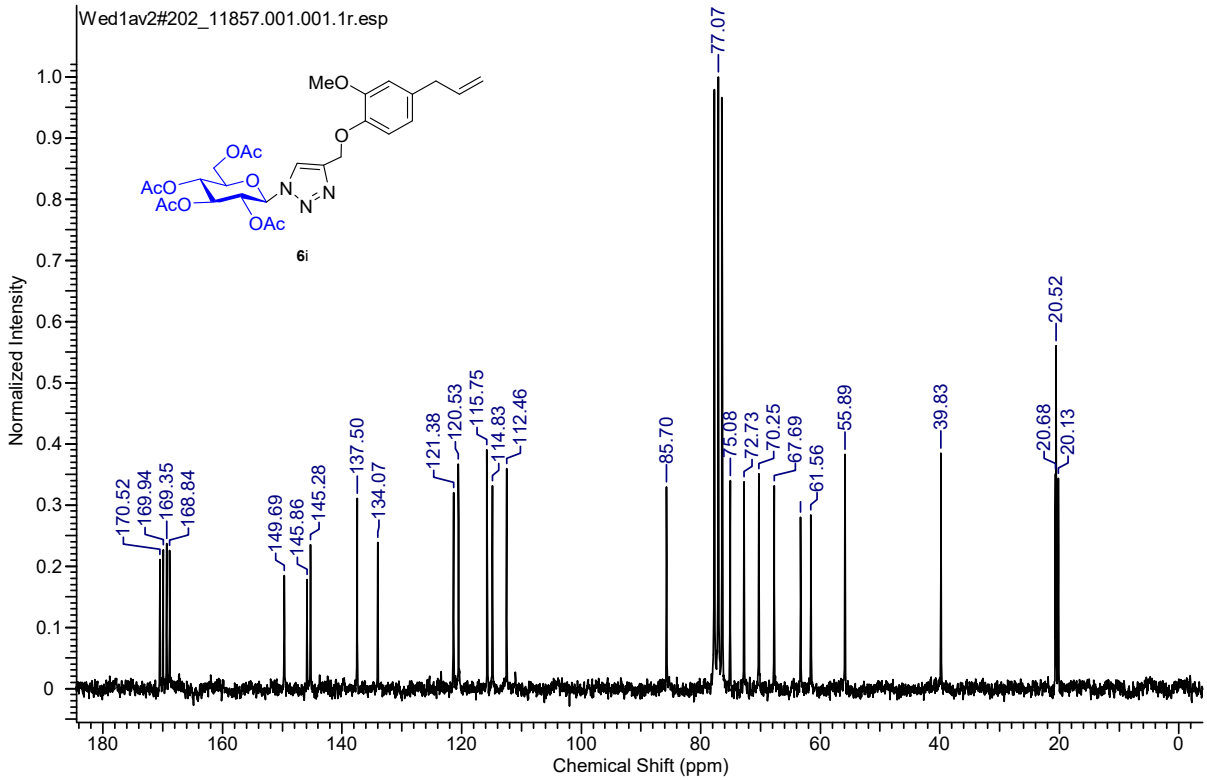
^{13}C NMR ($CDCl_3$, 50 MHz) of **6h**



HRMS of **6h**



^{1}H NMR ($CDCl_3$, 200 MHz) of **6i**



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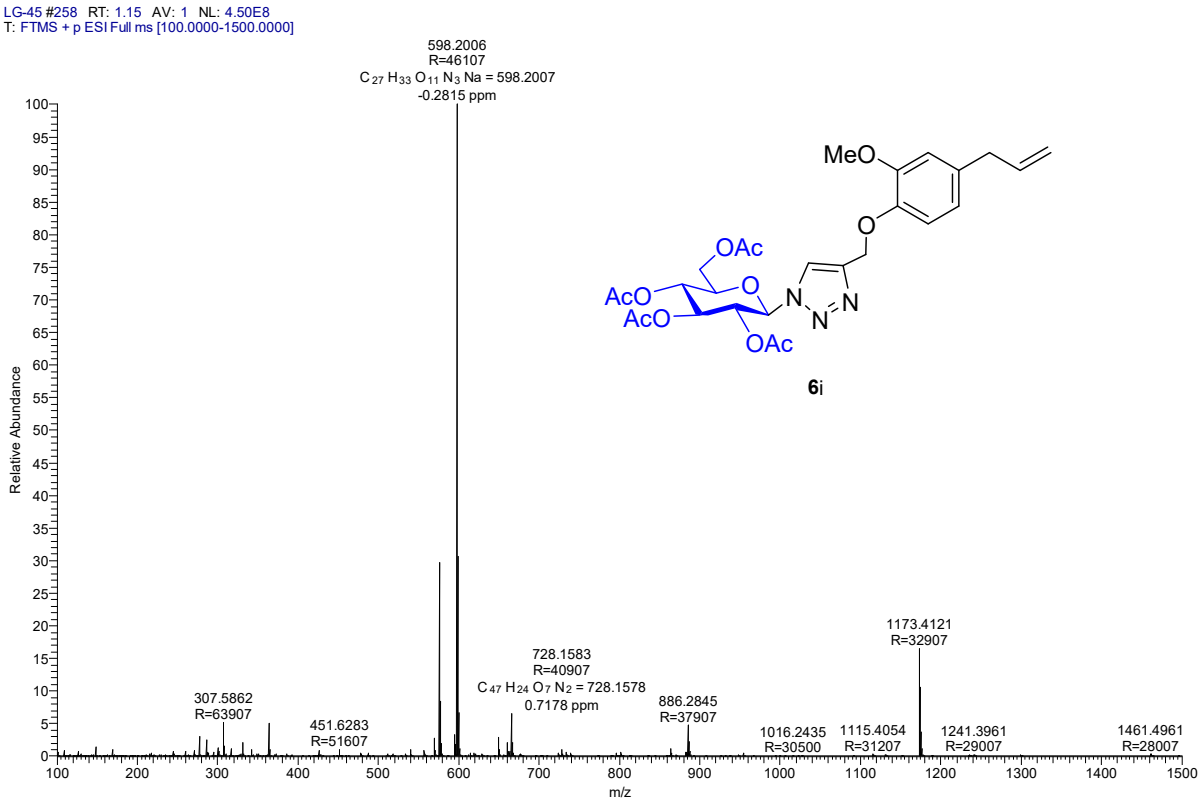
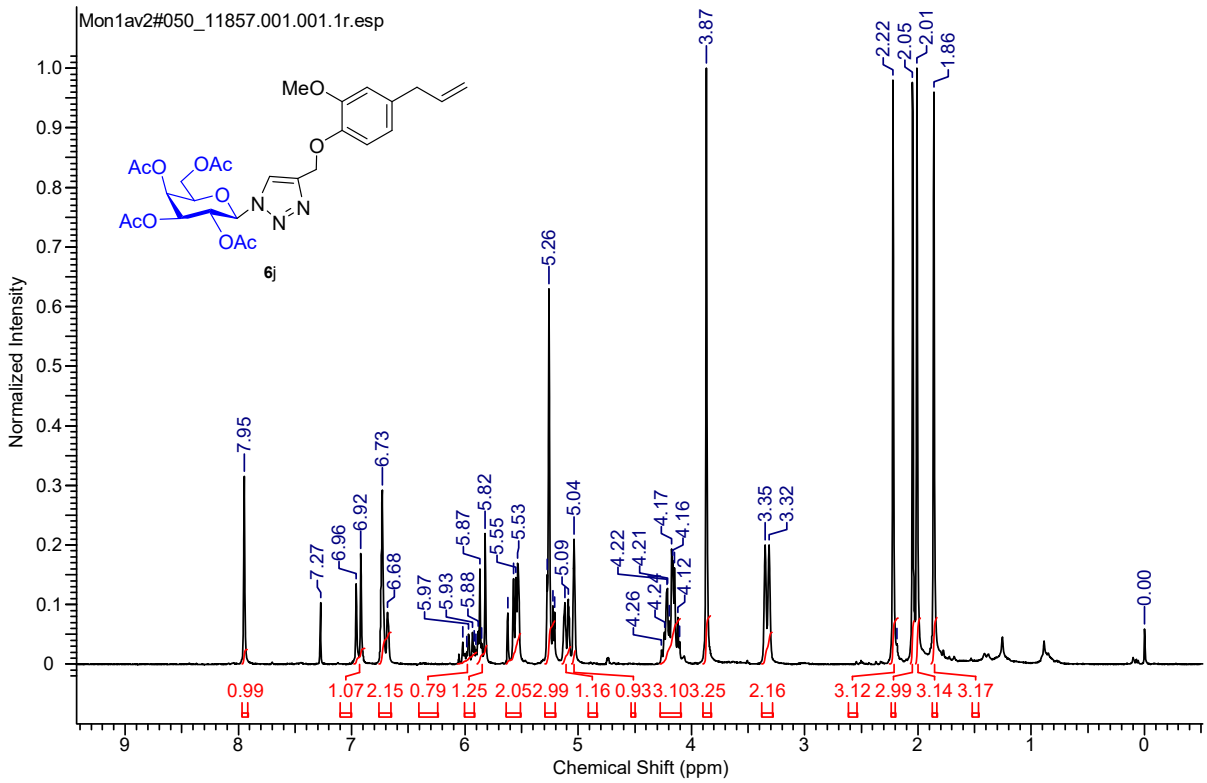
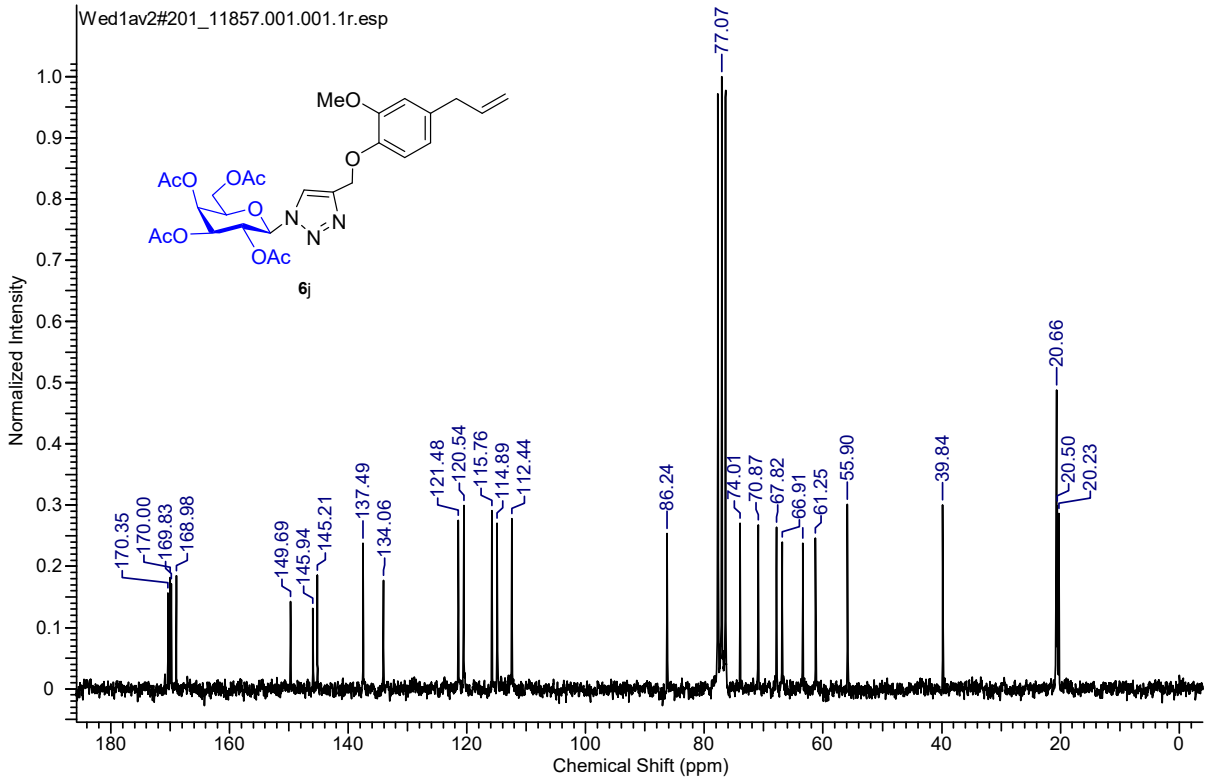


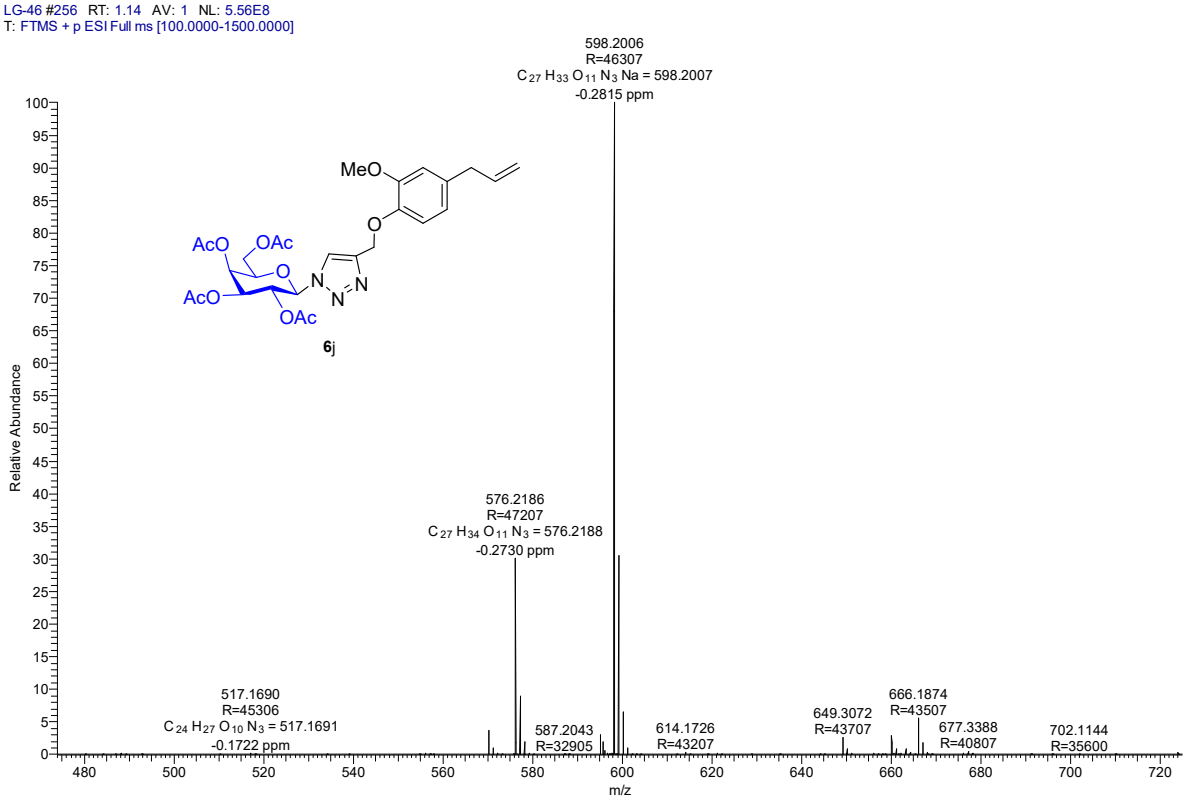
HRMS of **6i**



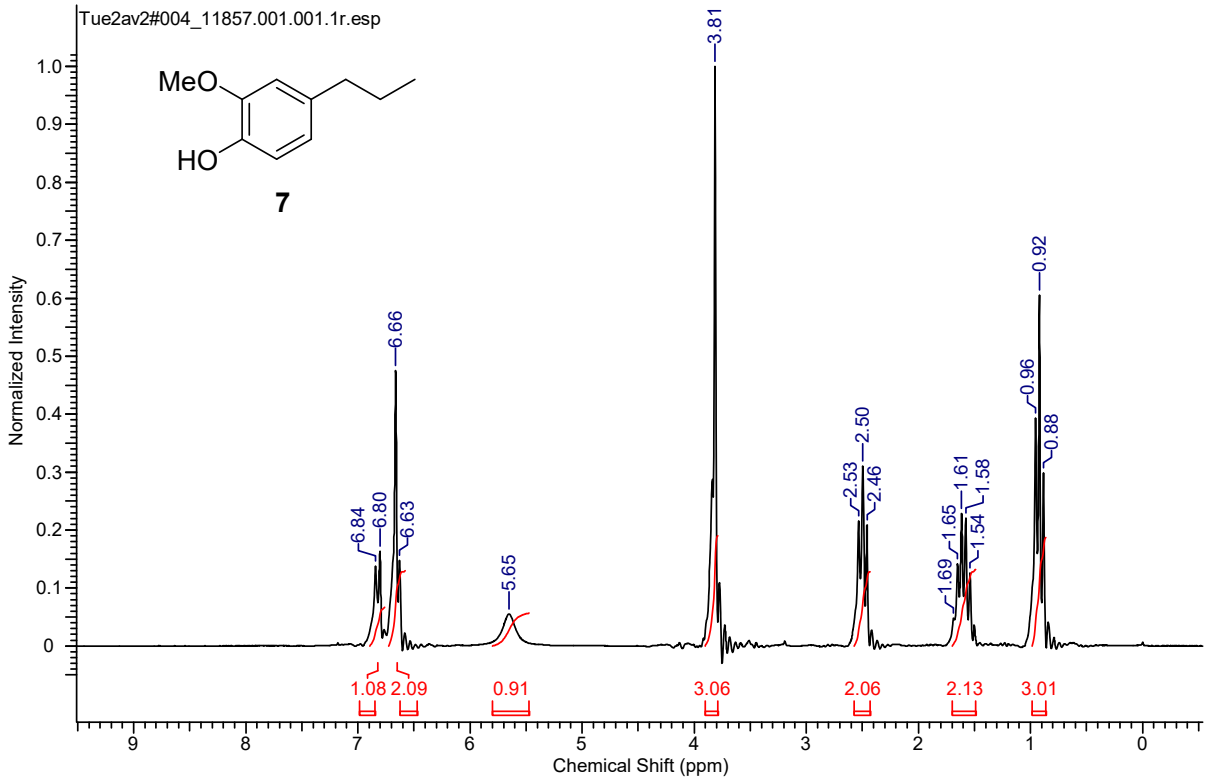
^{1}H NMR ($CDCl_3$, 200 MHz) of **6j**



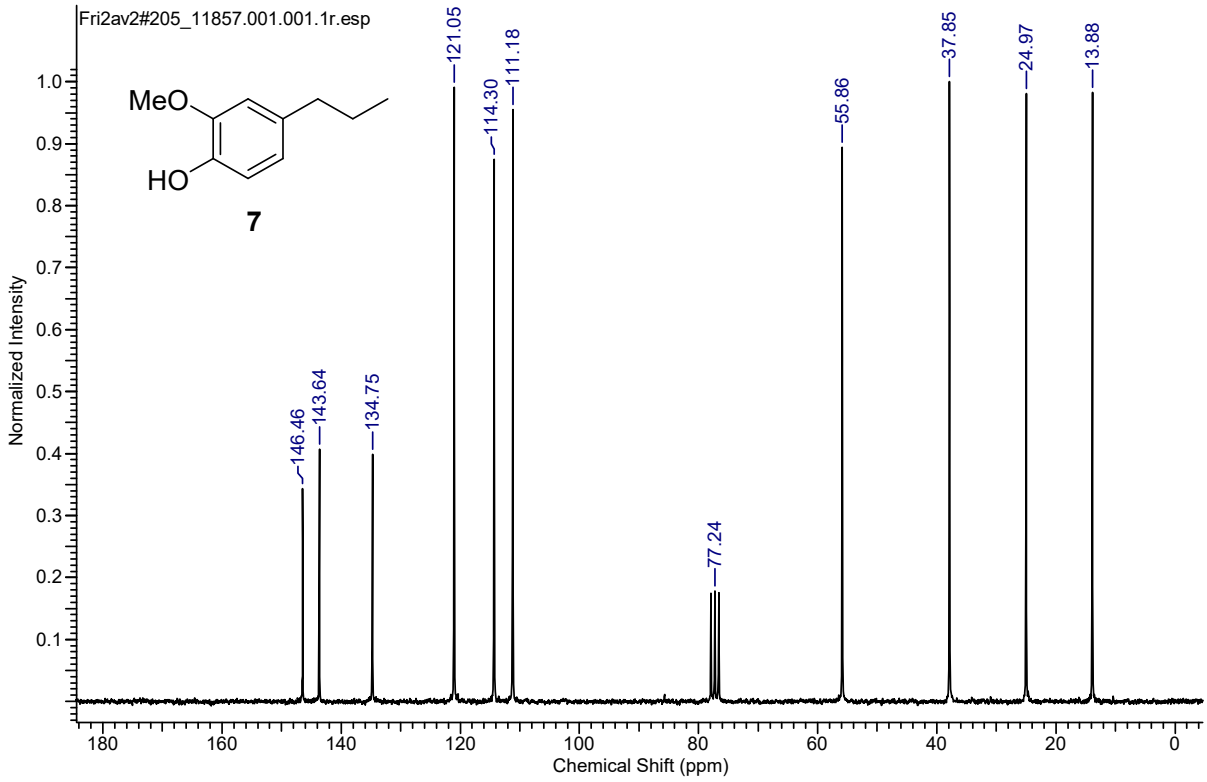
^{13}C NMR ($CDCl_3$, 50 MHz) of **6j**



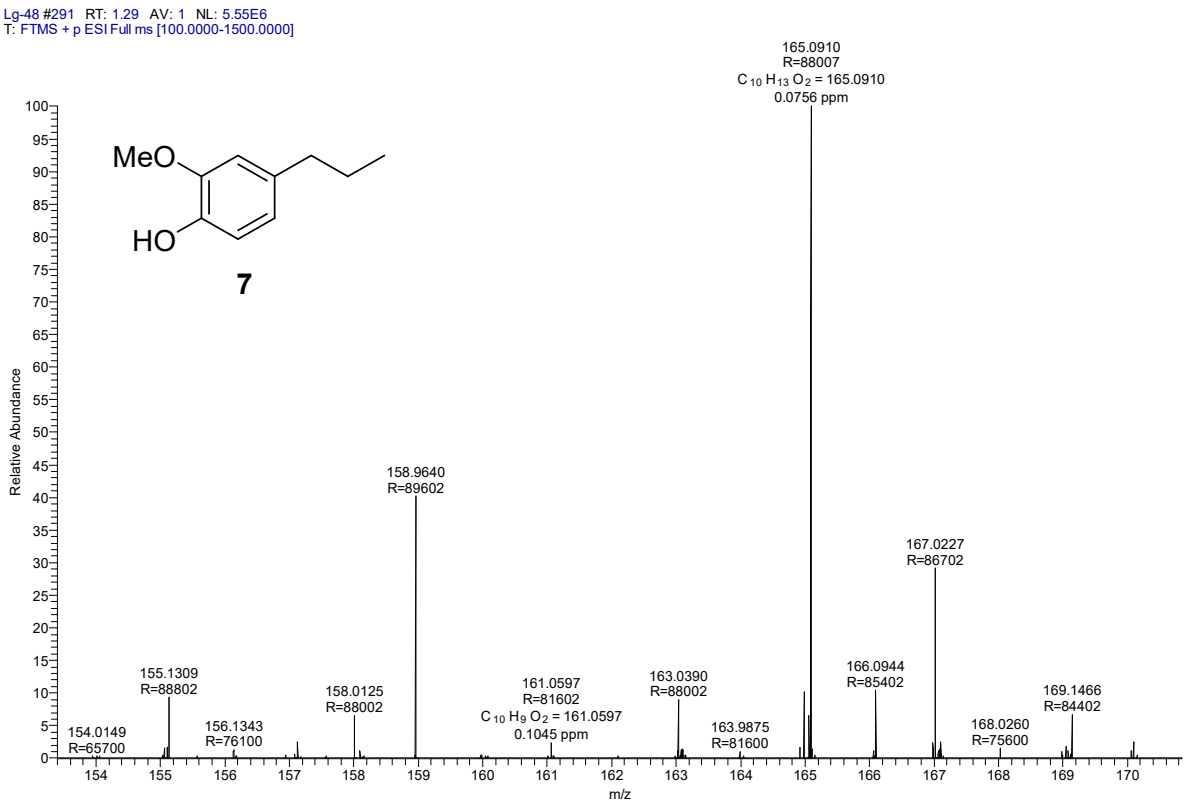
HRMS of **6j**



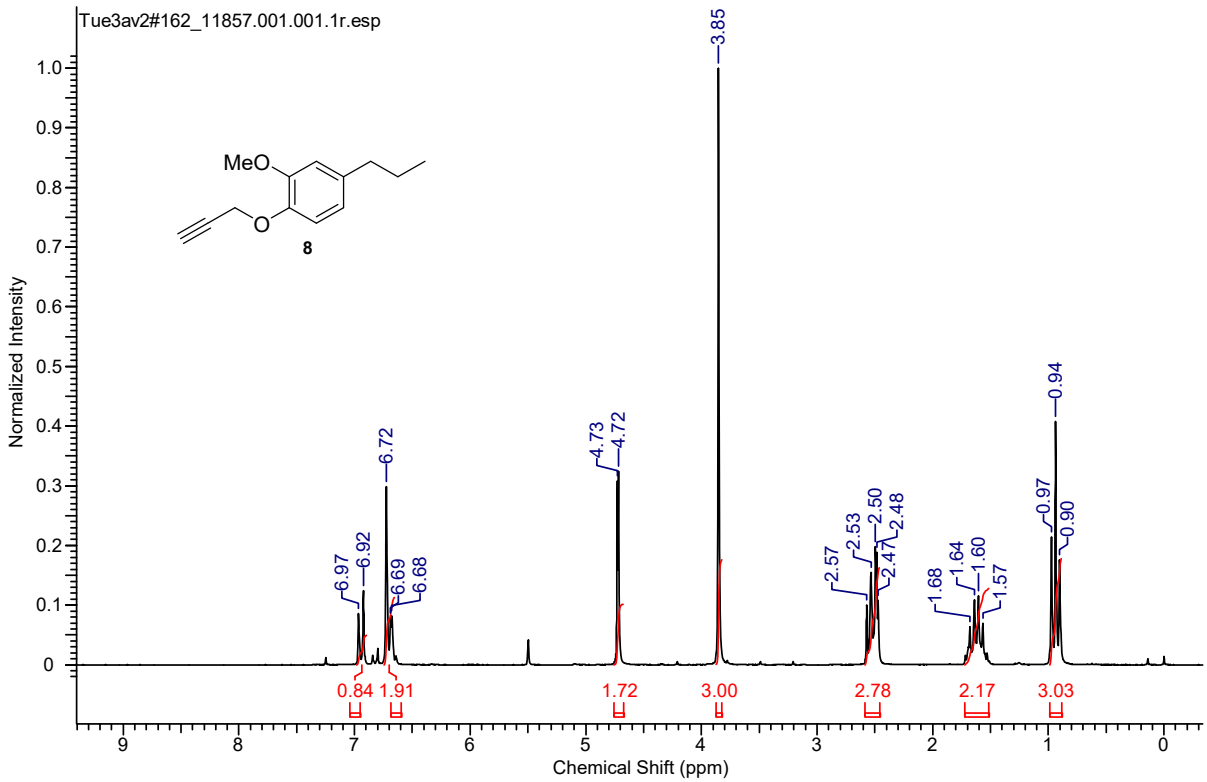
^{1}H NMR ($CDCl_3$, 200 MHz) of **7**



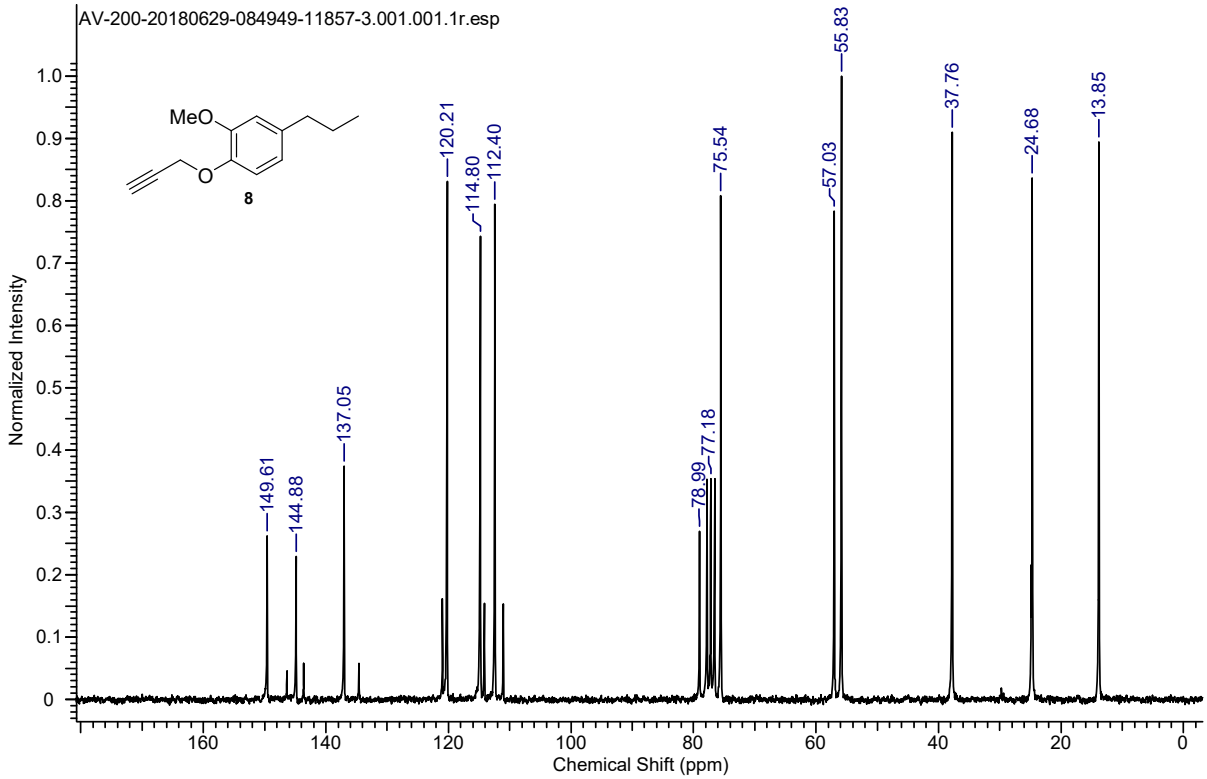
^{13}C NMR ($CDCl_3$, 50 MHz) of **7**



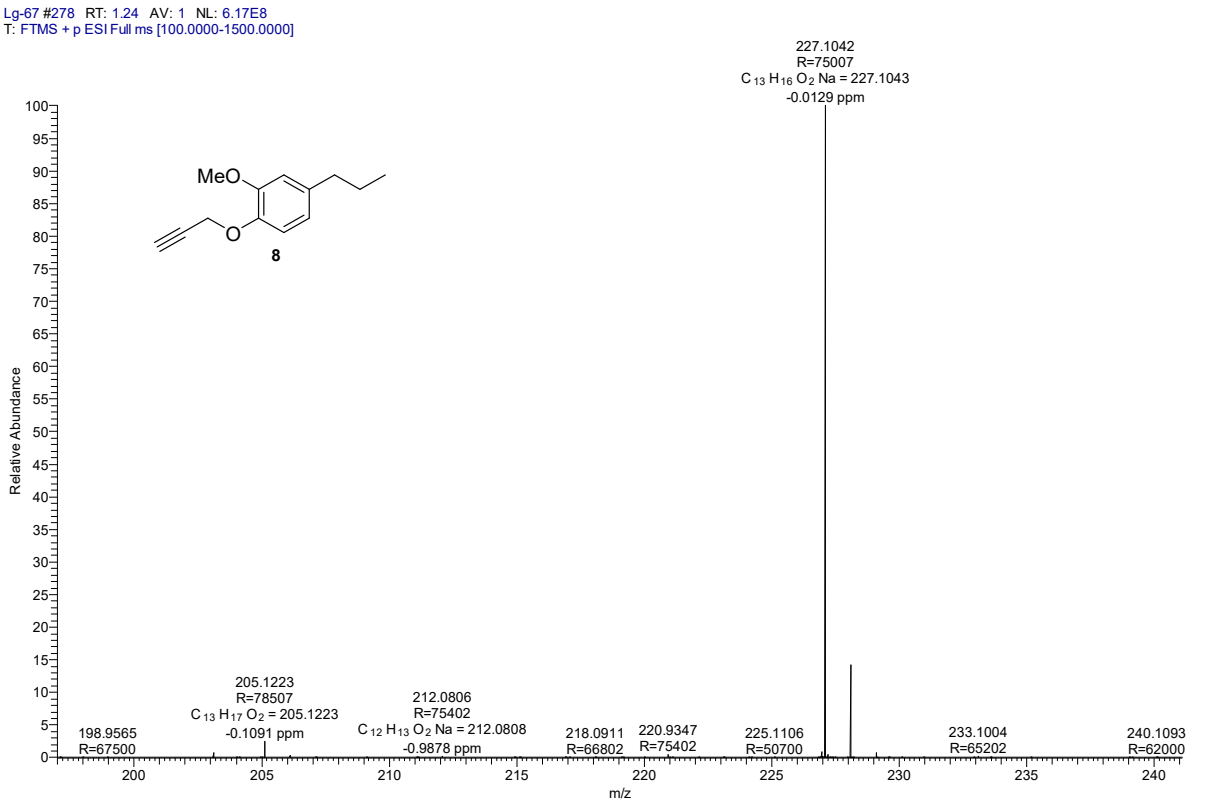
HRMS of **7**



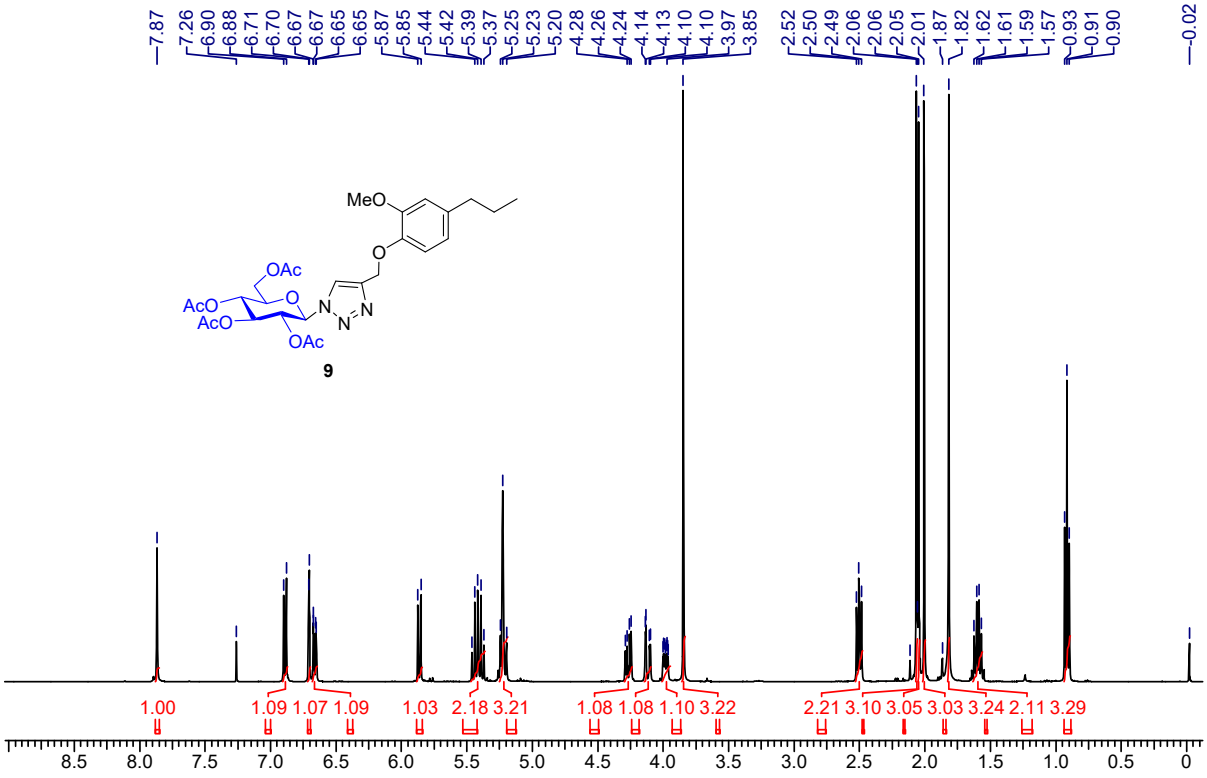
^{1}H NMR ($CDCl_3$, 200 MHz) of **8**



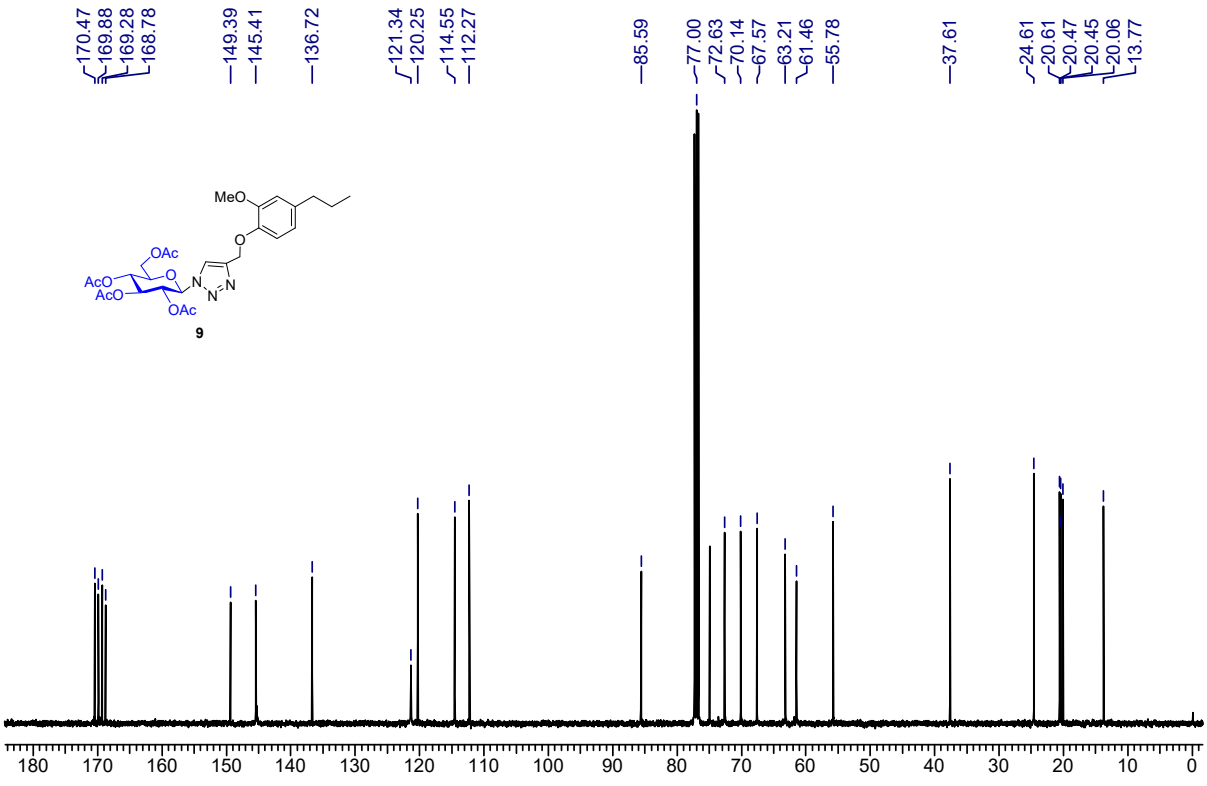
^{13}C NMR ($CDCl_3$, 50 MHz) of **8**



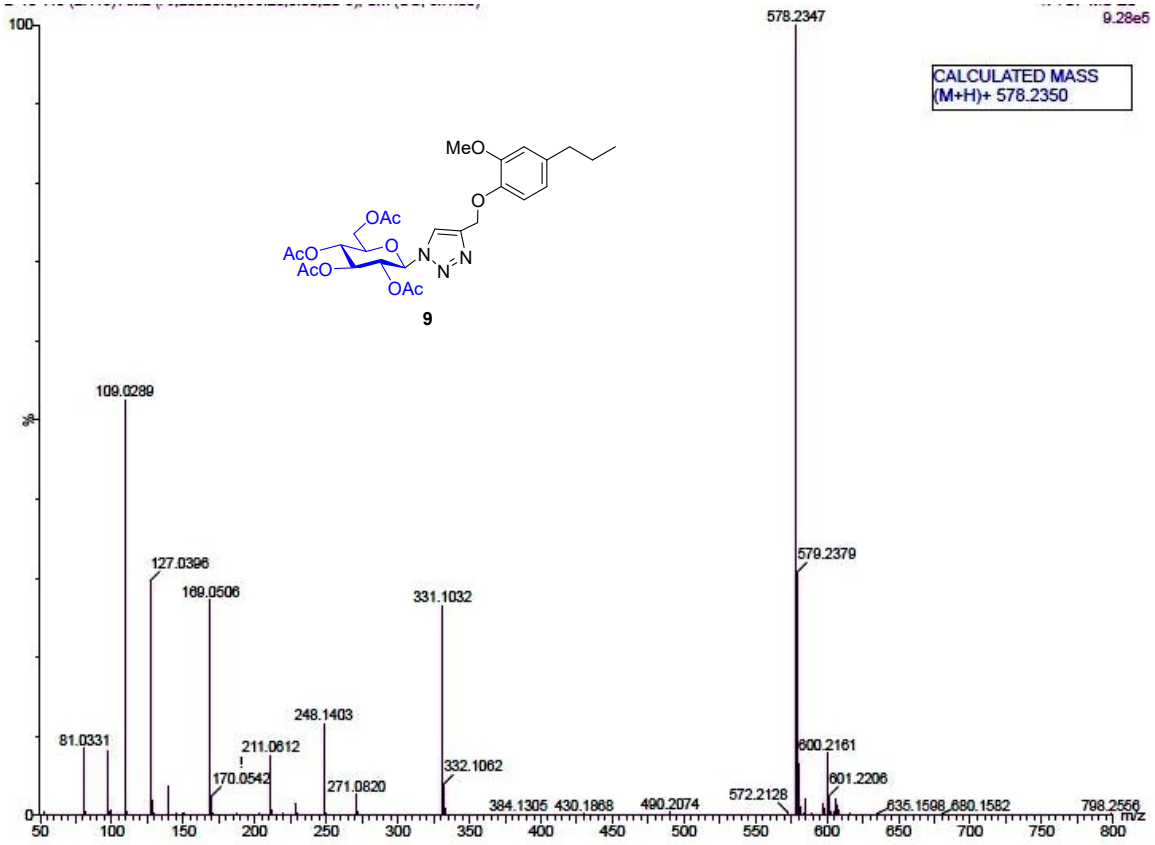
HRMS of **8**



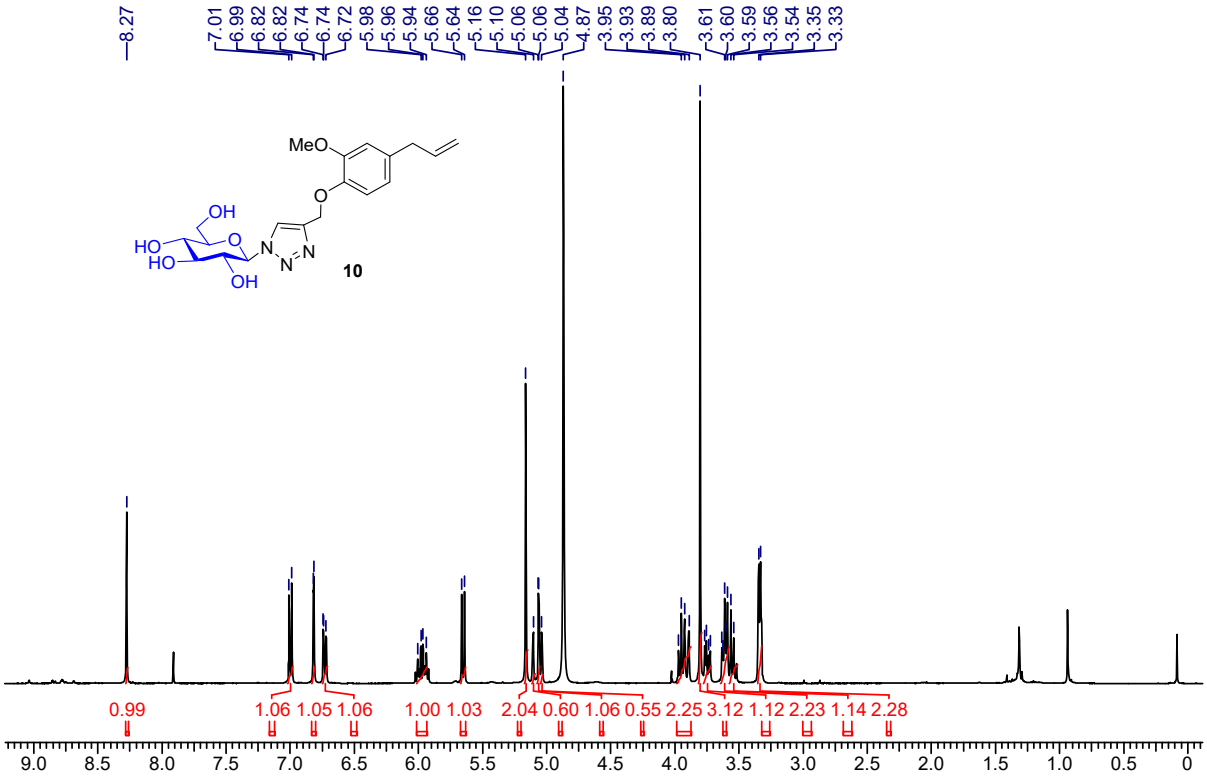
^{1}H NMR ($CDCl_3$, 400 MHz) of **9**



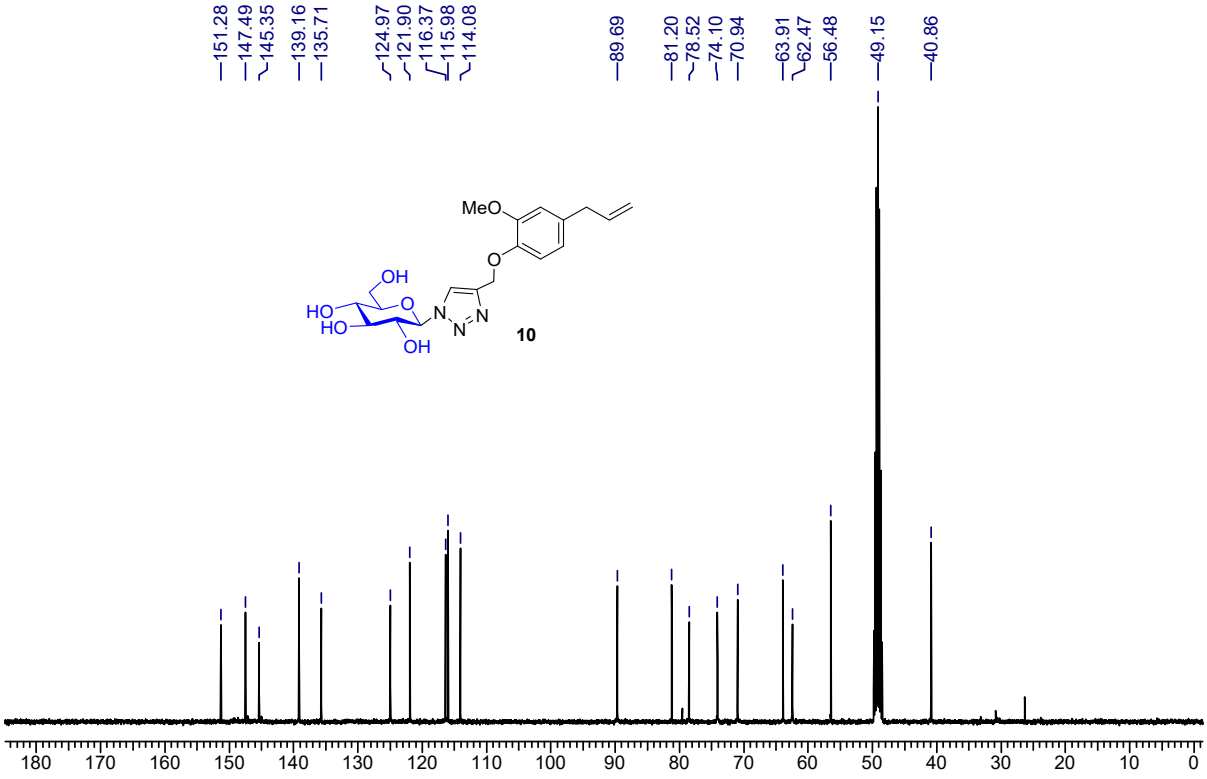
^{13}C NMR ($CDCl_3$, 100 MHz) of **9**


578.2347
9.28e5
CALCULATED MASS
(M+H)+ 578.2350
MeO
OAc
AcO
AcO
OAc
9
109.0289
127.0396
169.0506
331.1032
579.2379
248.1403
81.0331
211.0612
170.0542
271.0820
332.1062
600.2161
601.2206
384.1305
430.1868
490.2074
572.2128
635.1598
680.1582
798.2556
%
m/z

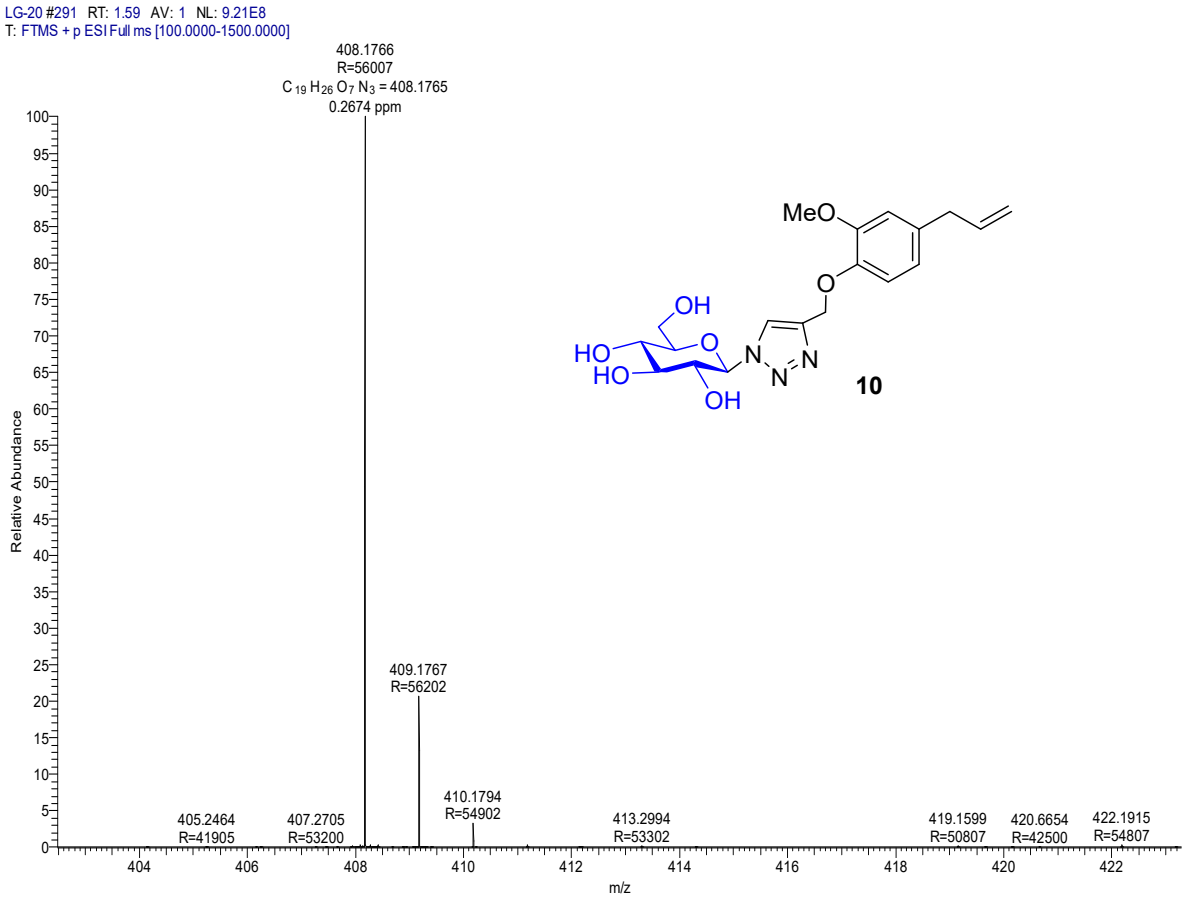
HRMS of **9**



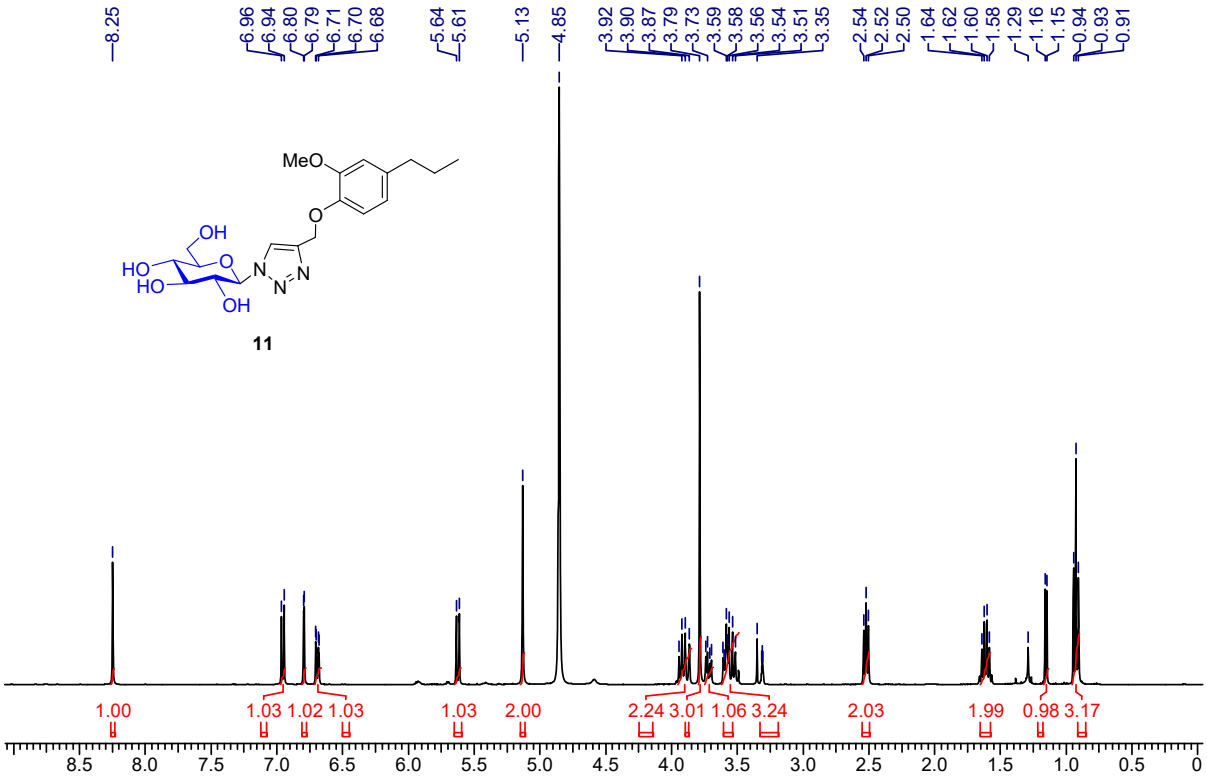
^{1}H NMR ($CDCl_3$, 400 MHz) of **10**



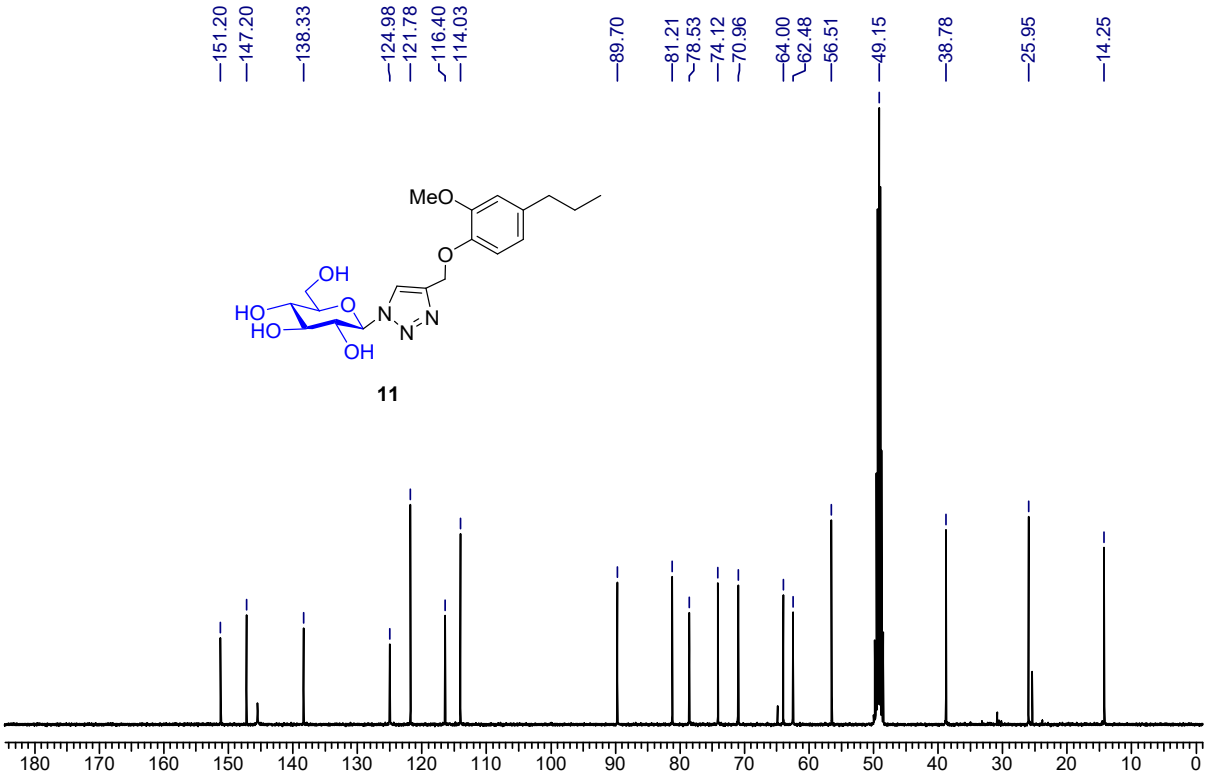
^{13}C NMR ((MeOH-d_4, 100 MHz) of **10**



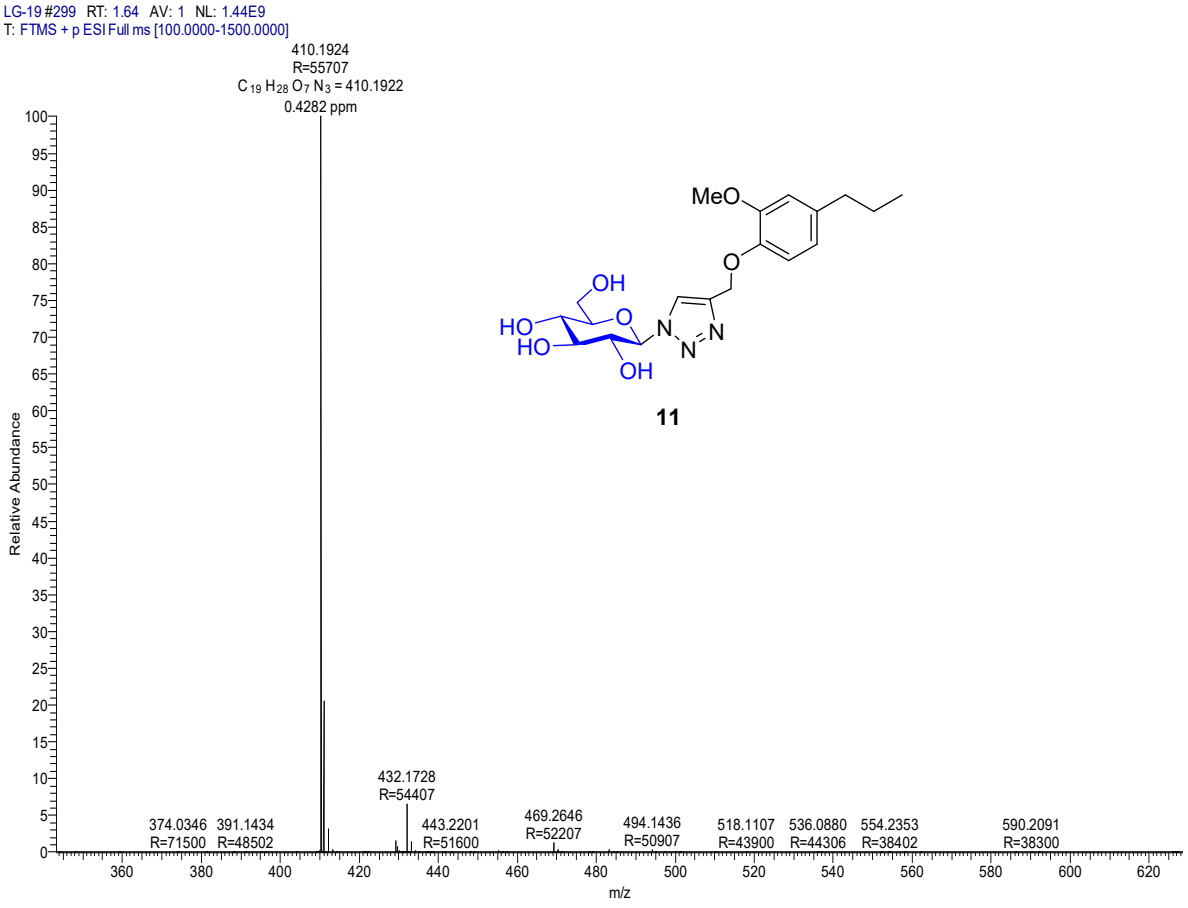
HRMS of **10**



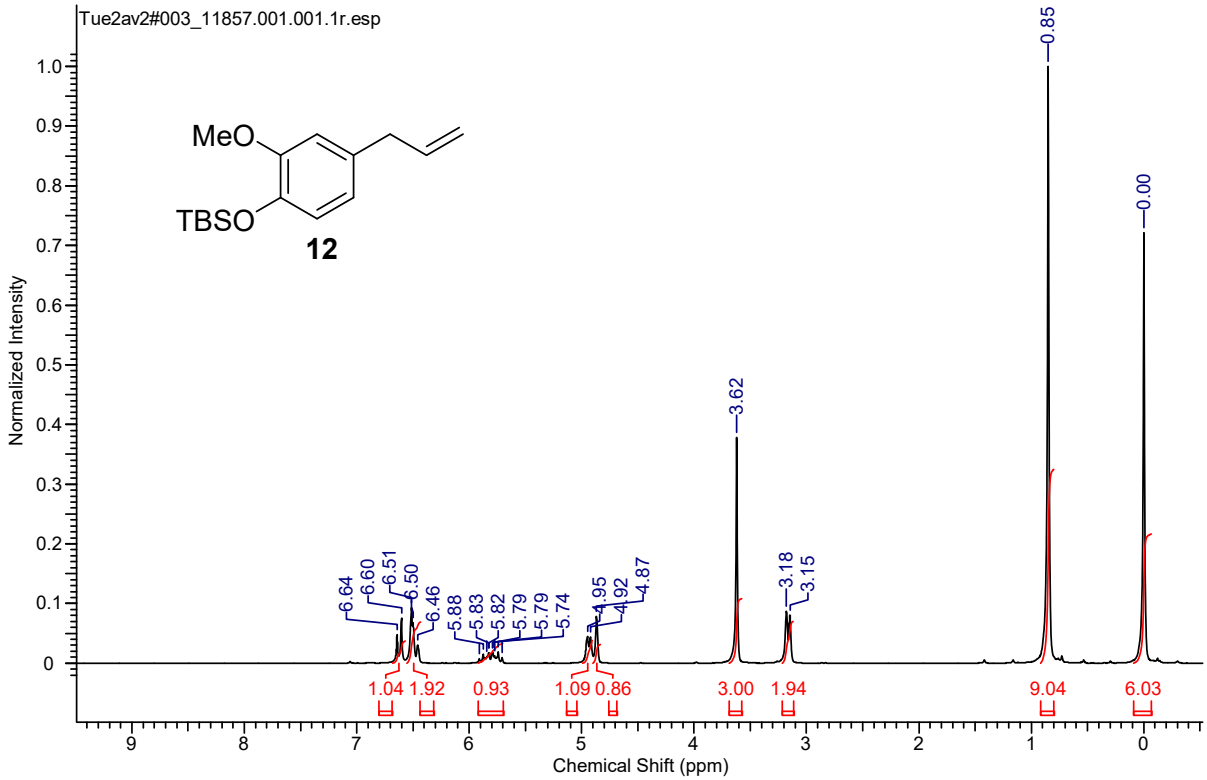
^{1}H NMR (MeOH-d_4, 400 MHz) of **11**



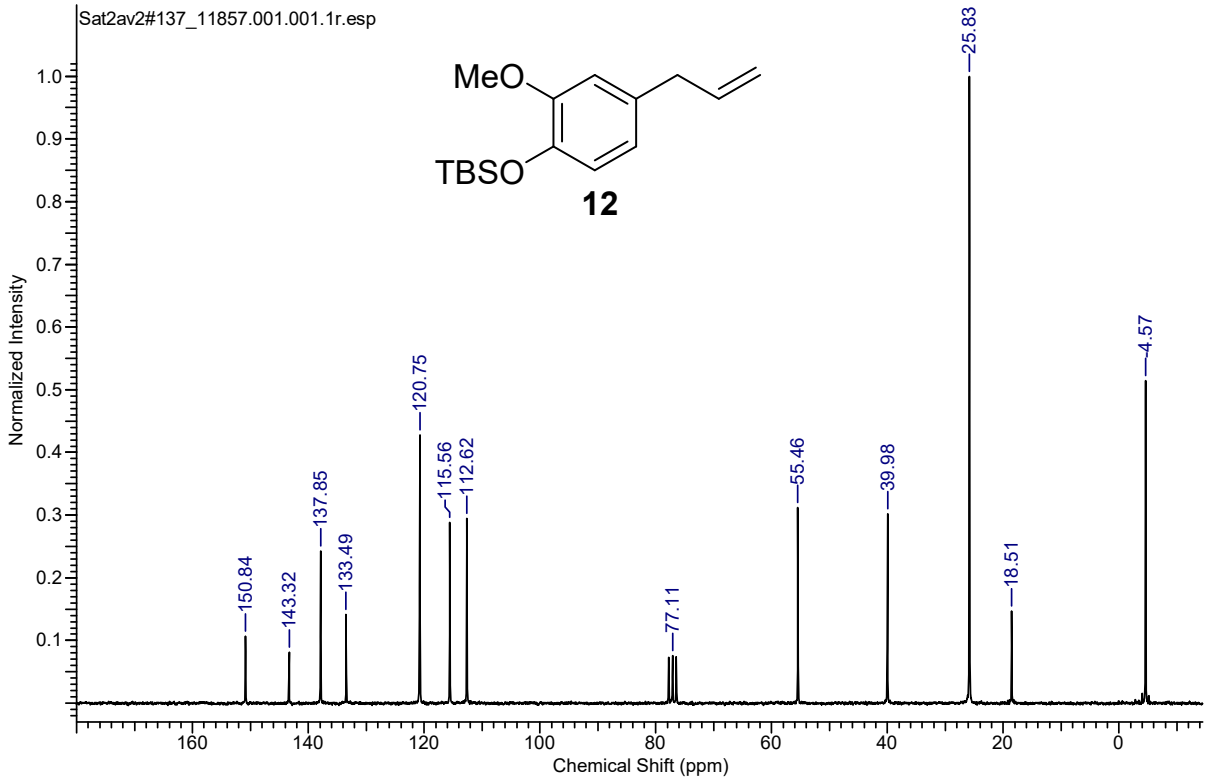
^{13}C NMR ((MeOH-d_4, 100 MHz) of **11**



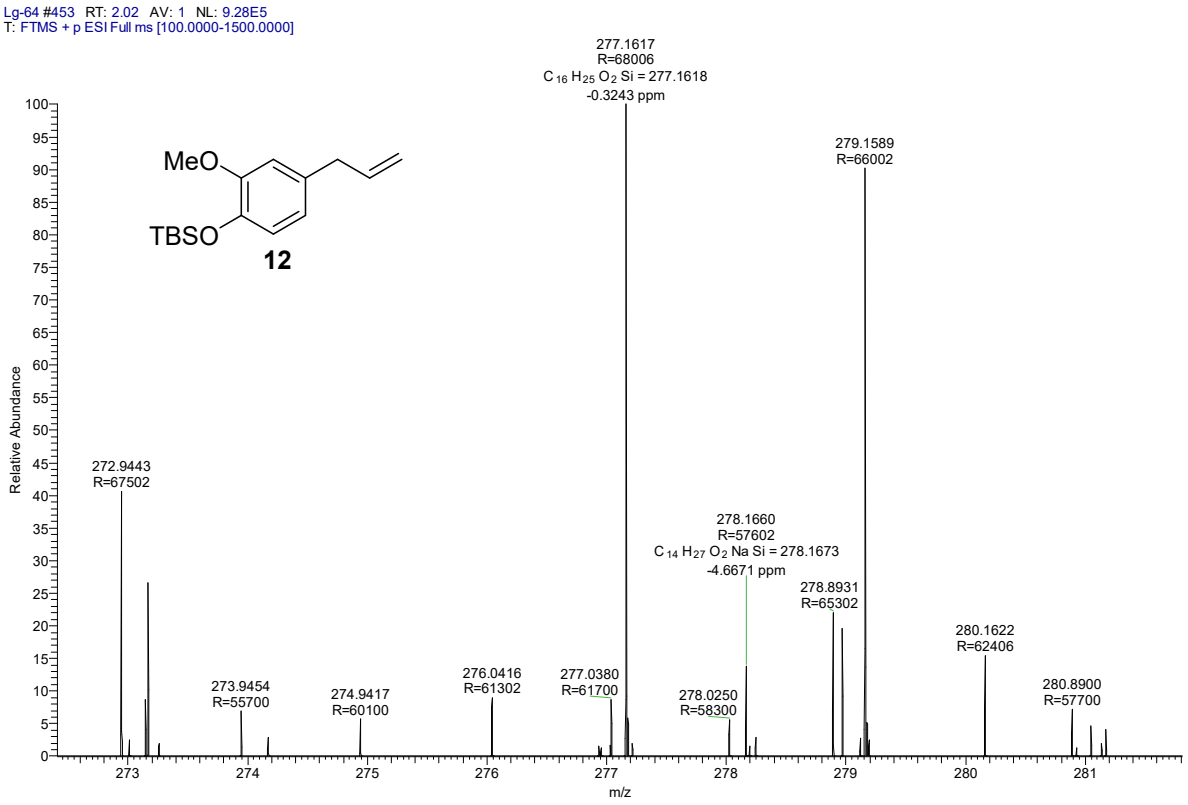
HRMS of **11**



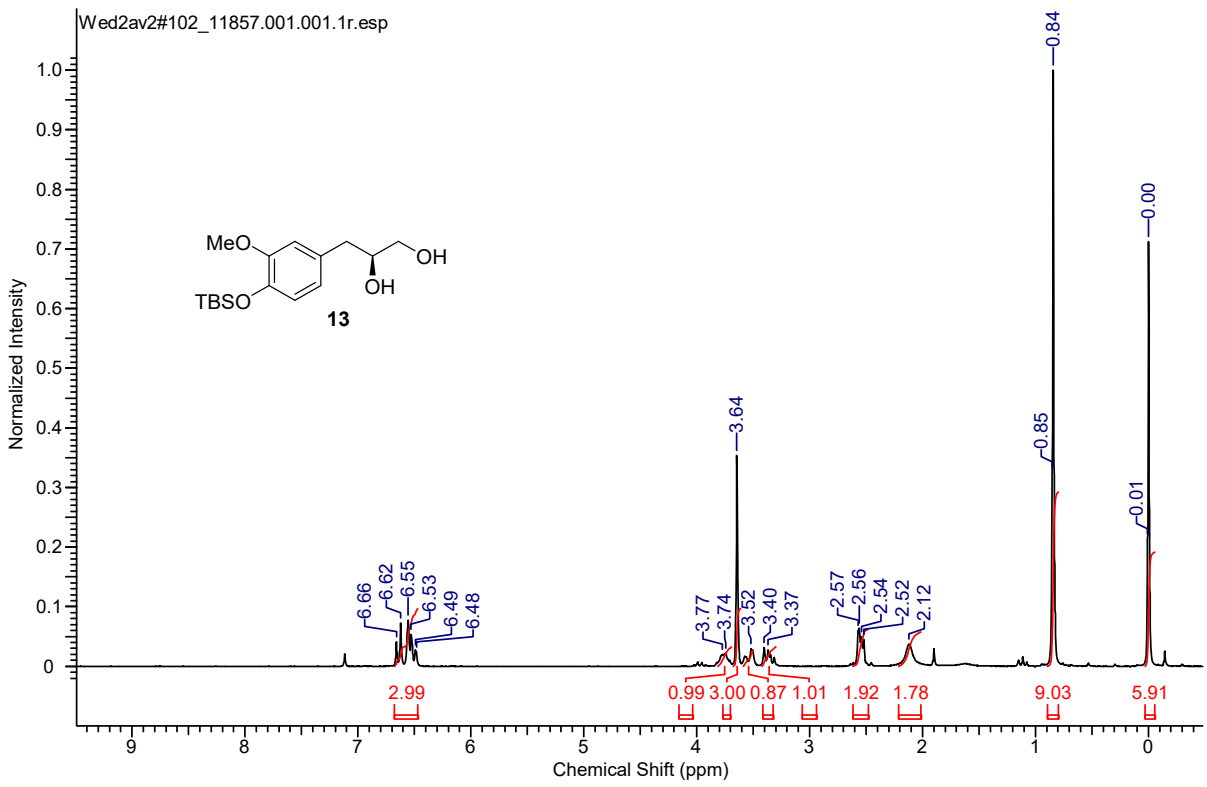
^{1}H NMR ($CDCl_3$, 200 MHz) of **12**



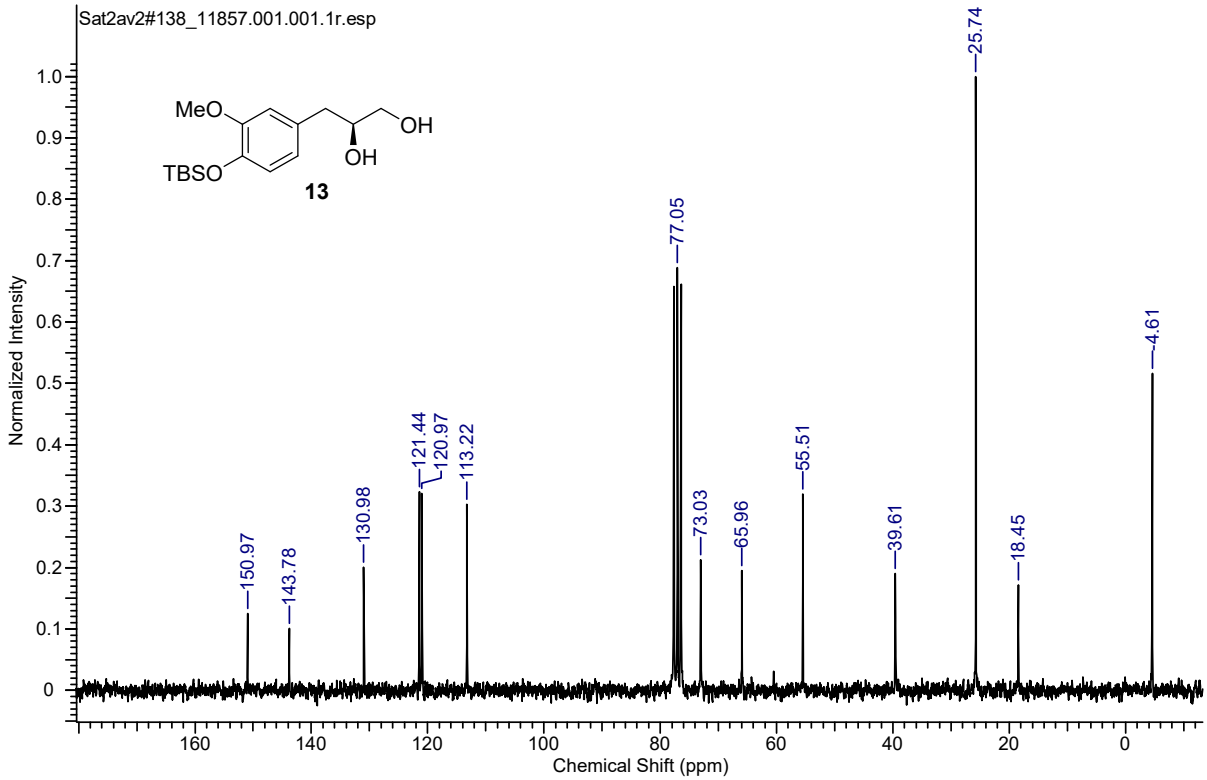
^{13}C NMR ($CDCl_3$, 50 MHz) of **12**



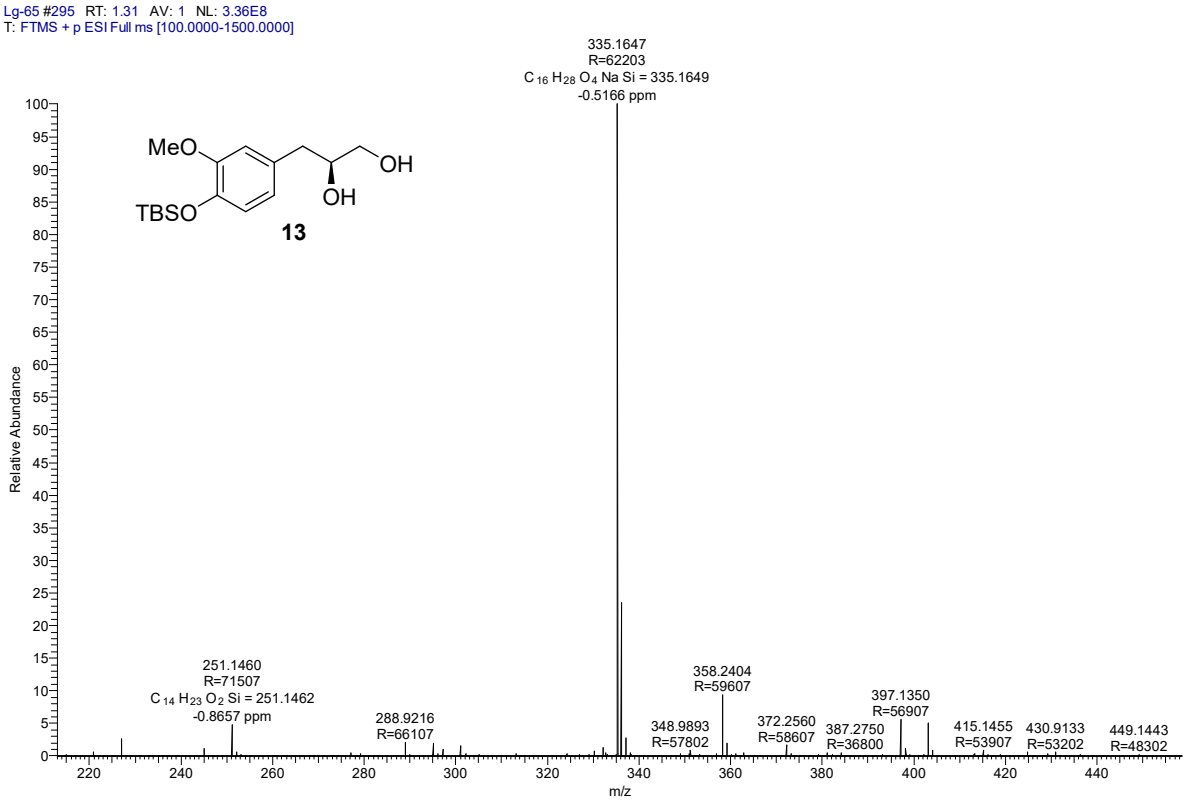
HRMS of **12**



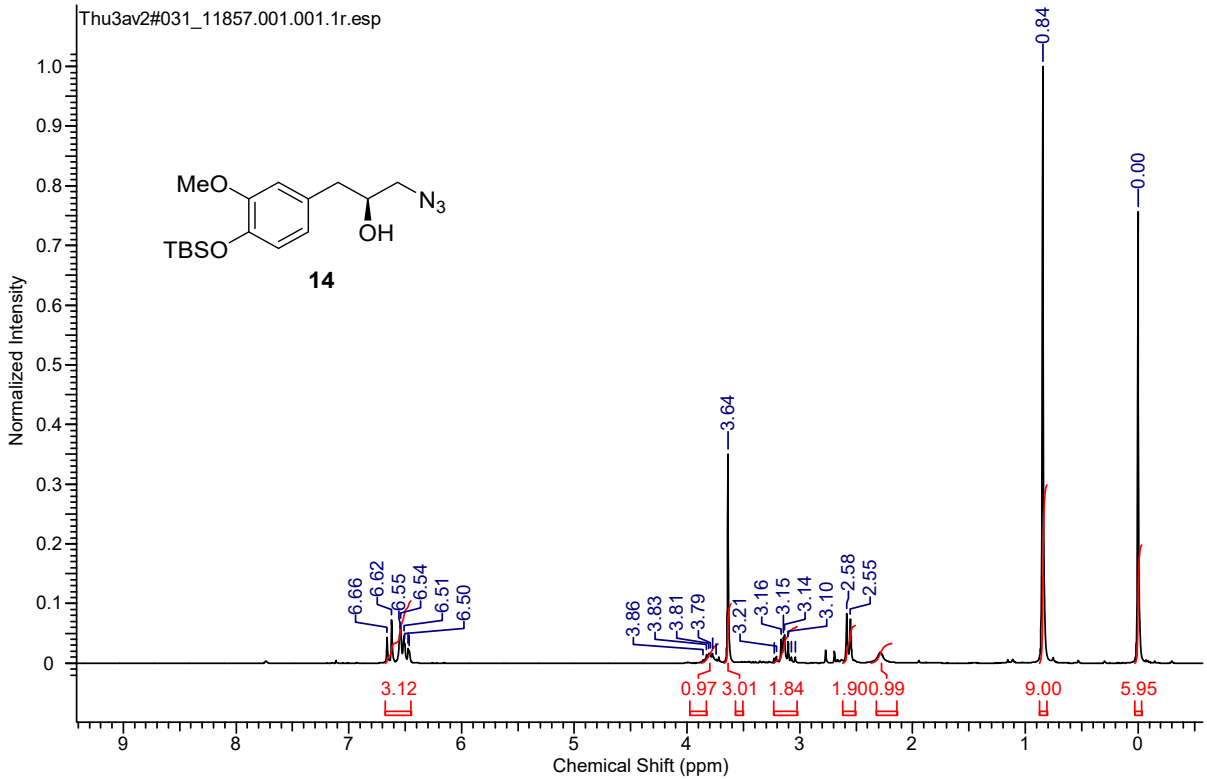
^{1}H NMR ($CDCl_3$, 200 MHz) of **13**



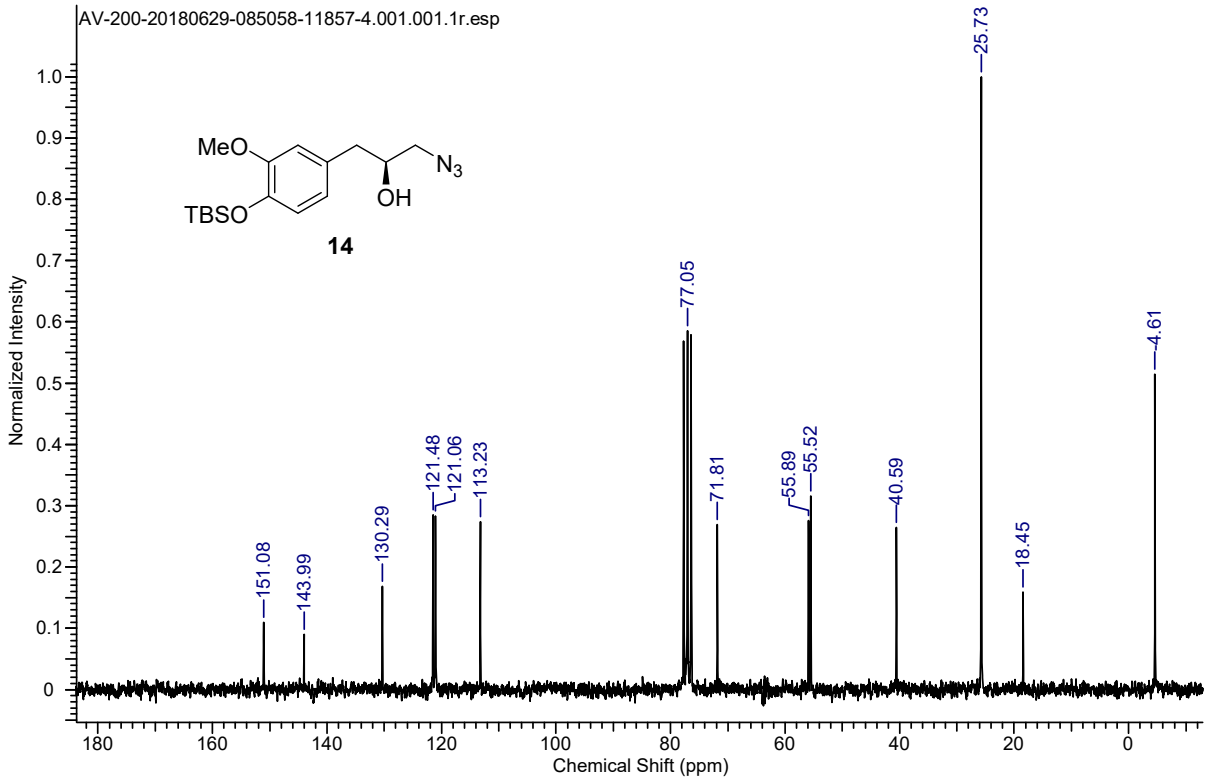
^{13}C NMR ($CDCl_3$, 50 MHz) of **13**



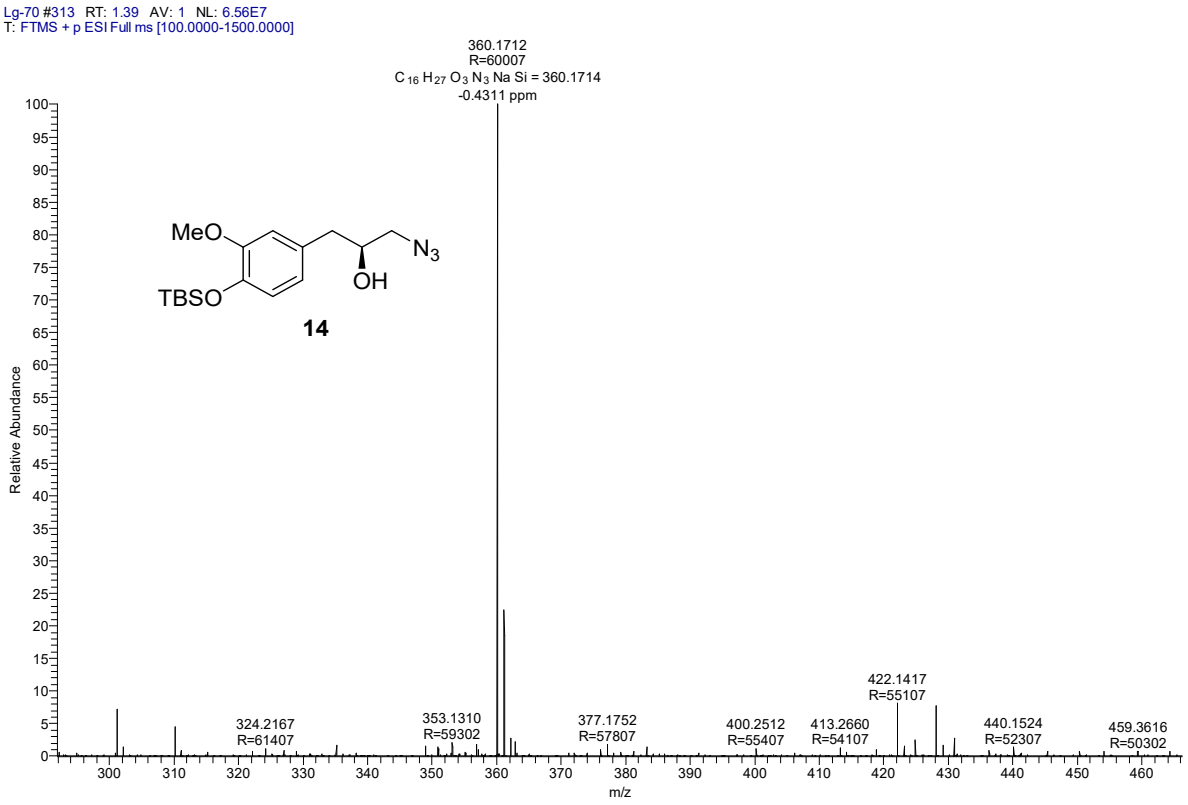
HRMS of **13**



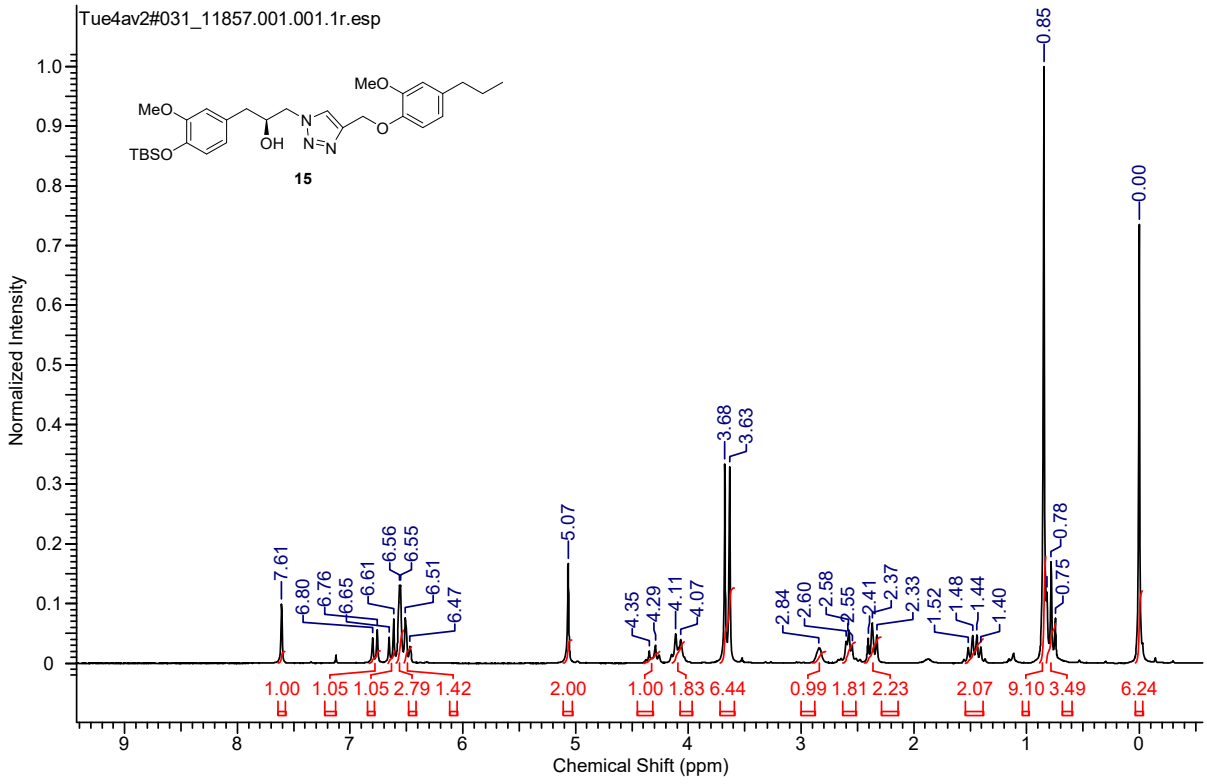
^{1}H NMR ($CDCl_3$, 200 MHz) of **14**



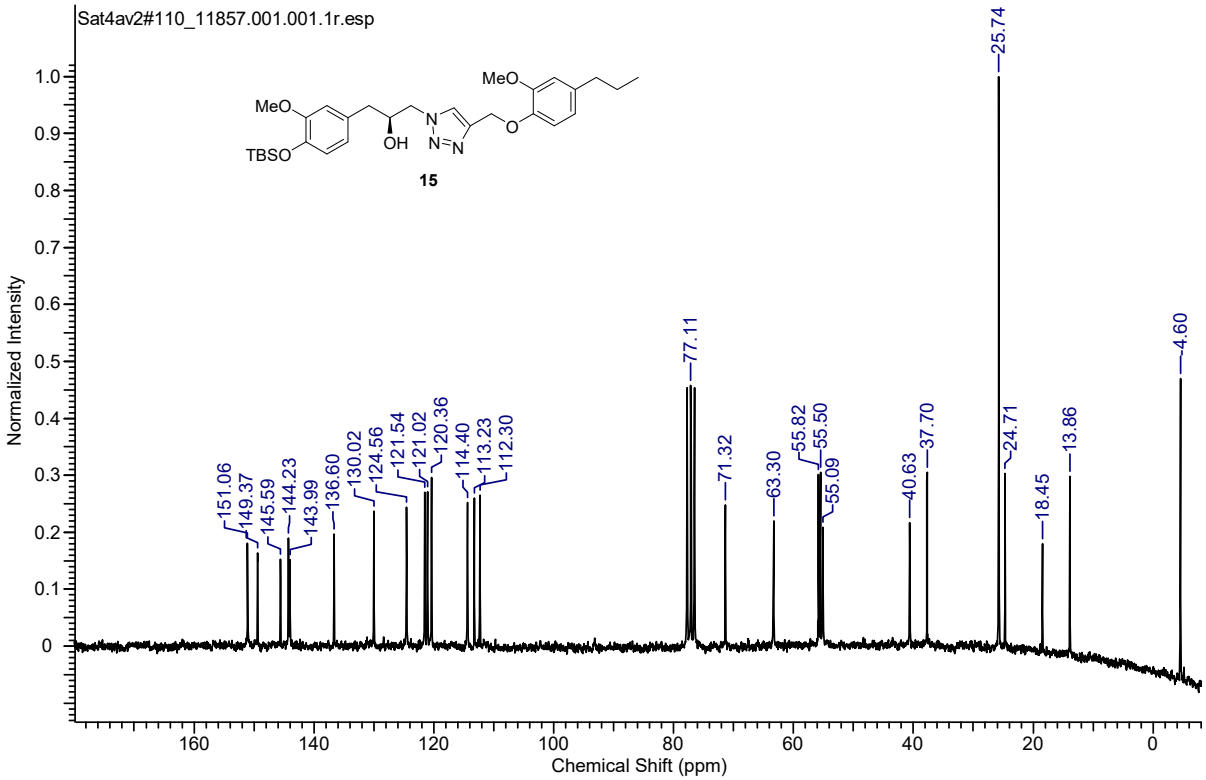
^{13}C NMR ($CDCl_3$, 50 MHz) of **14**



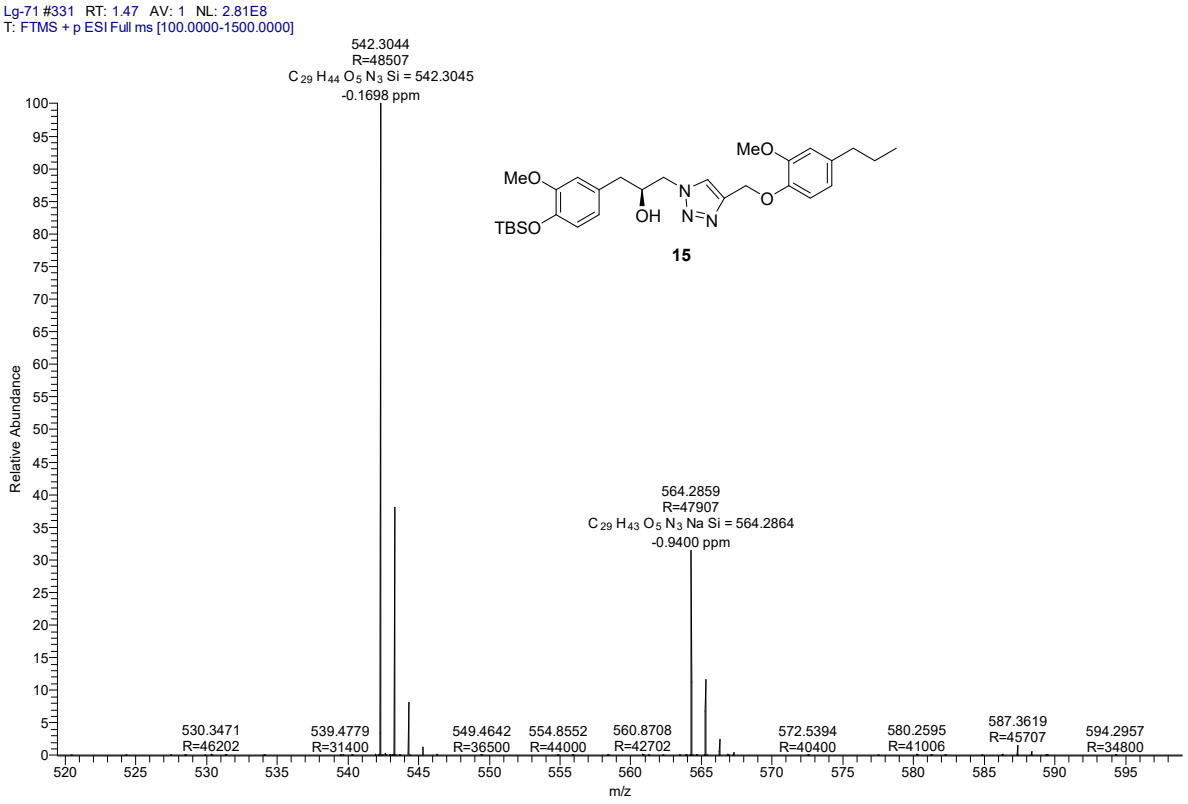
HRMS of **14**



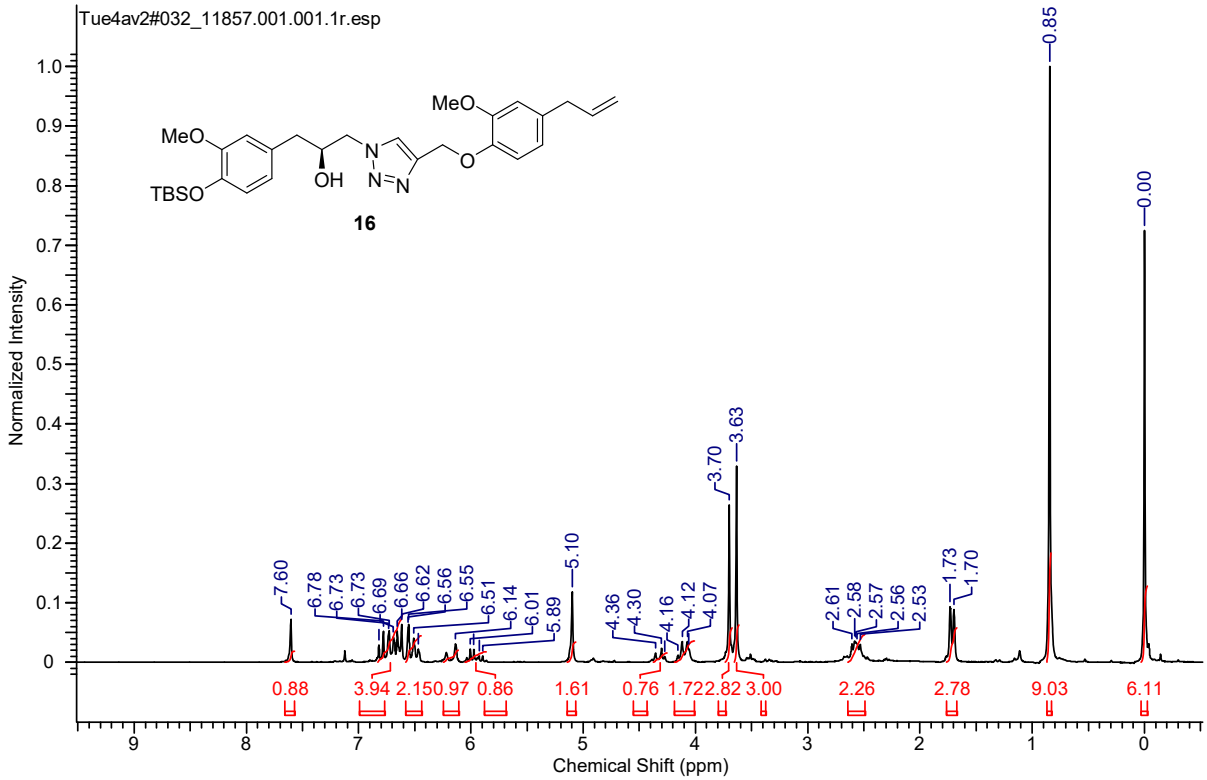
^{1}H NMR ($CDCl_3$, 200 MHz) of **15**



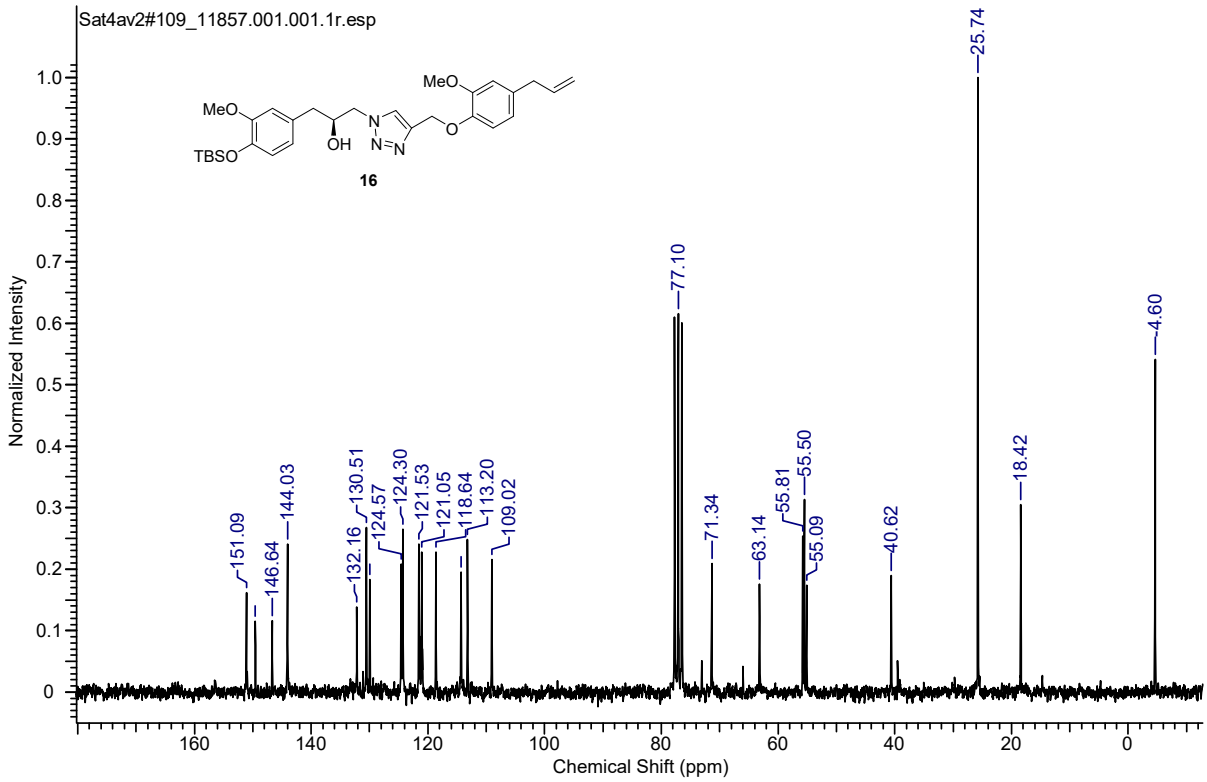
^{13}C NMR ($CDCl_3$, 50 MHz) of **15**



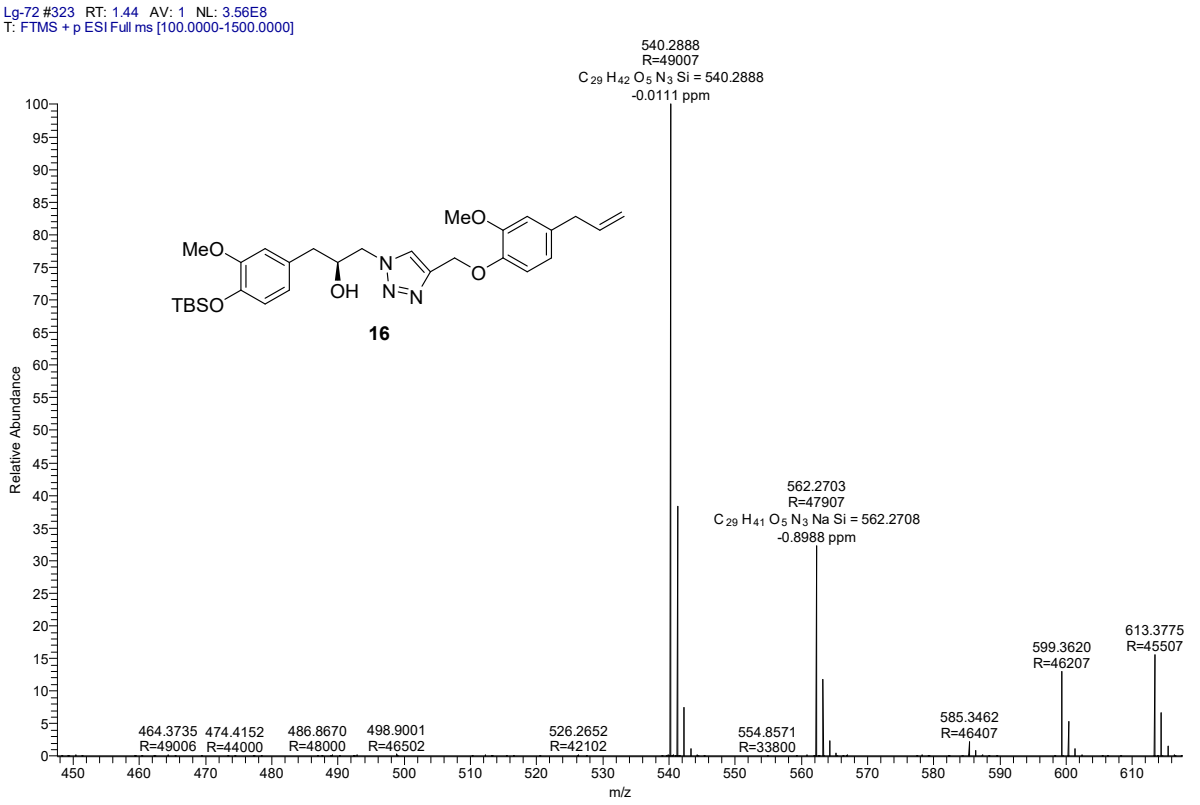
HRMS of **15**



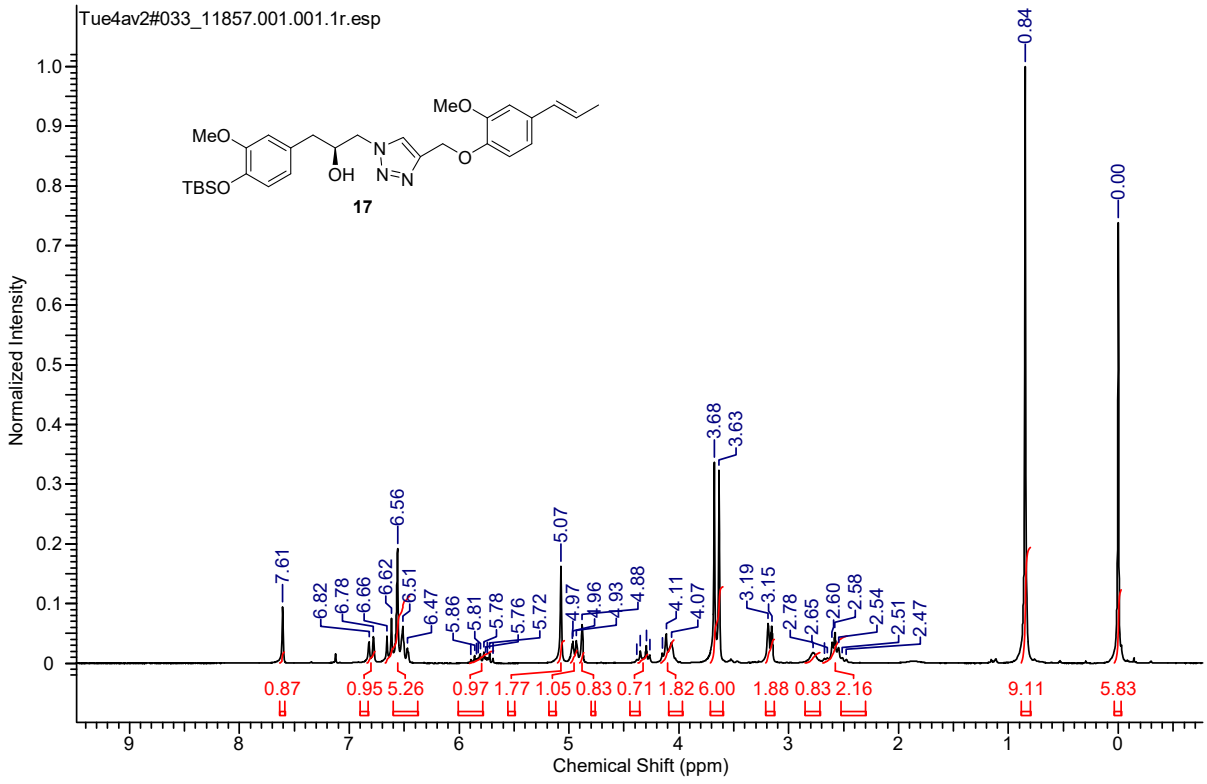
^{1}H NMR ($CDCl_3$, 200 MHz) of **16**



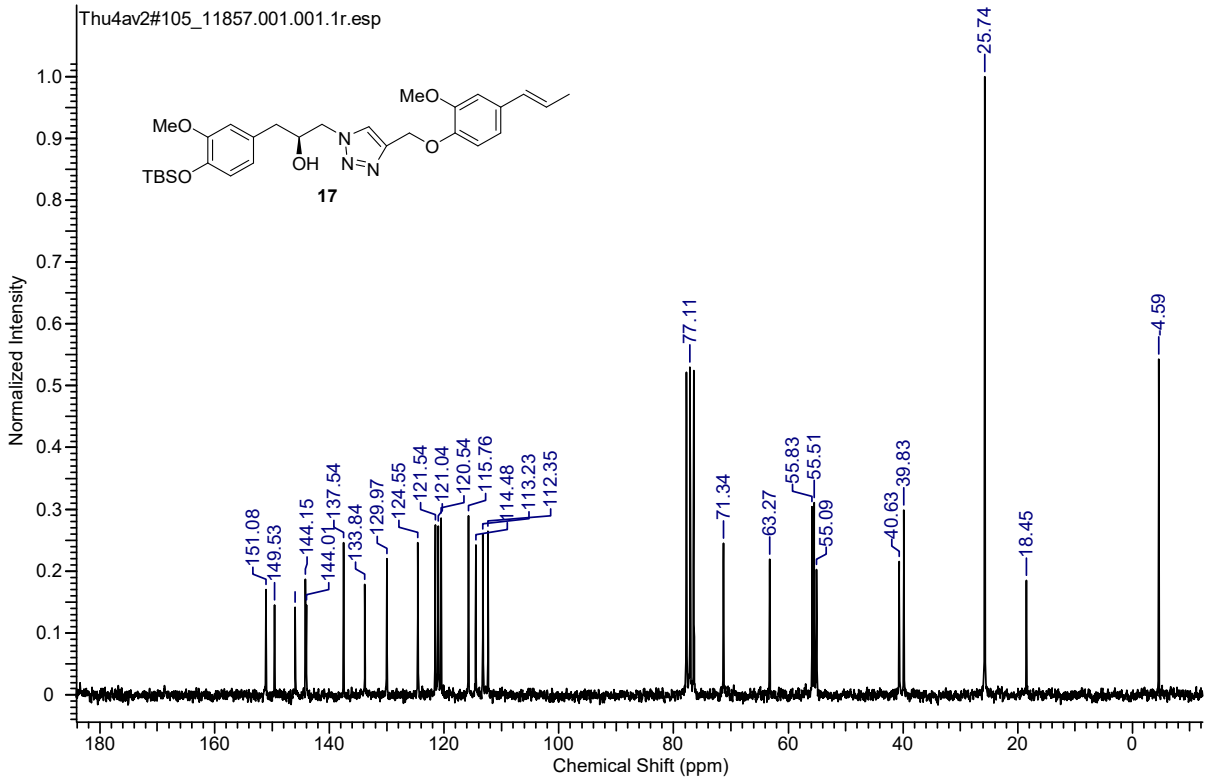
^{13}C NMR ($CDCl_3$, 50 MHz) of **16**



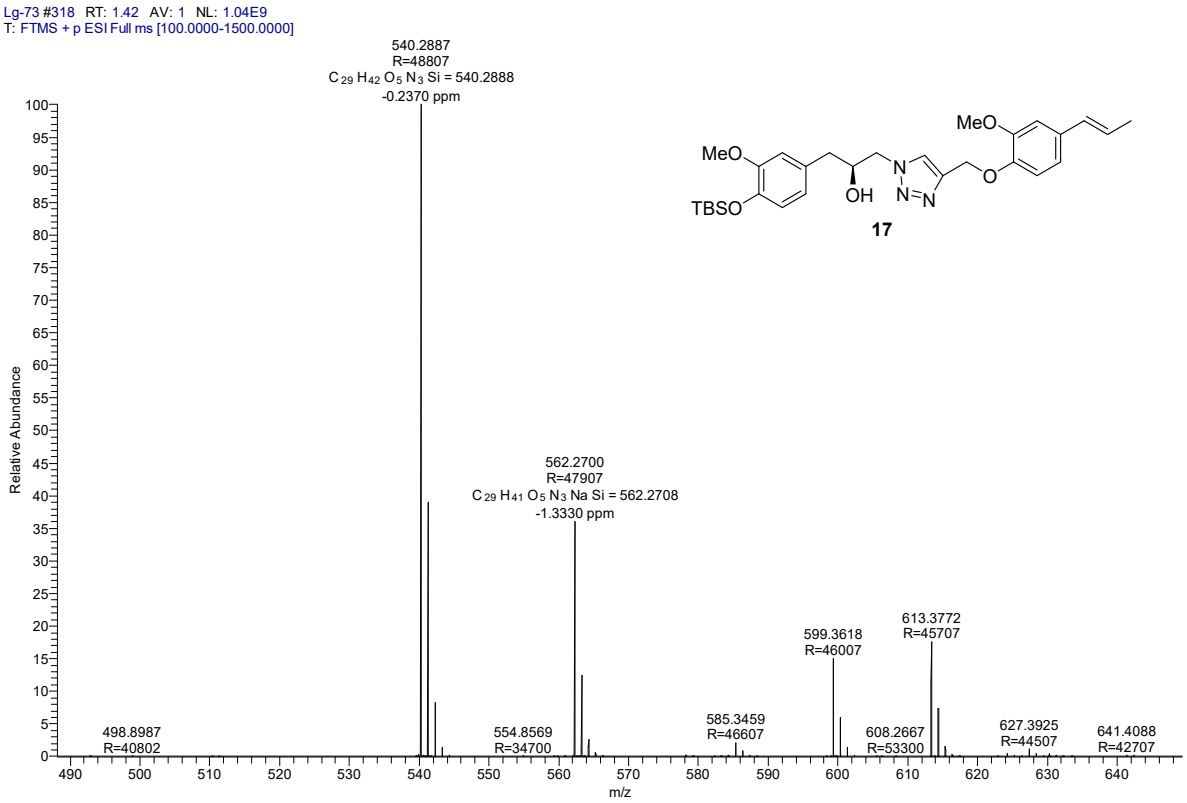
HRMS of **16**



^{1}H NMR ($CDCl_3$, 200 MHz) of **17**



^{13}C NMR ($CDCl_3$, 50 MHz) of **17**



HRMS of **17**

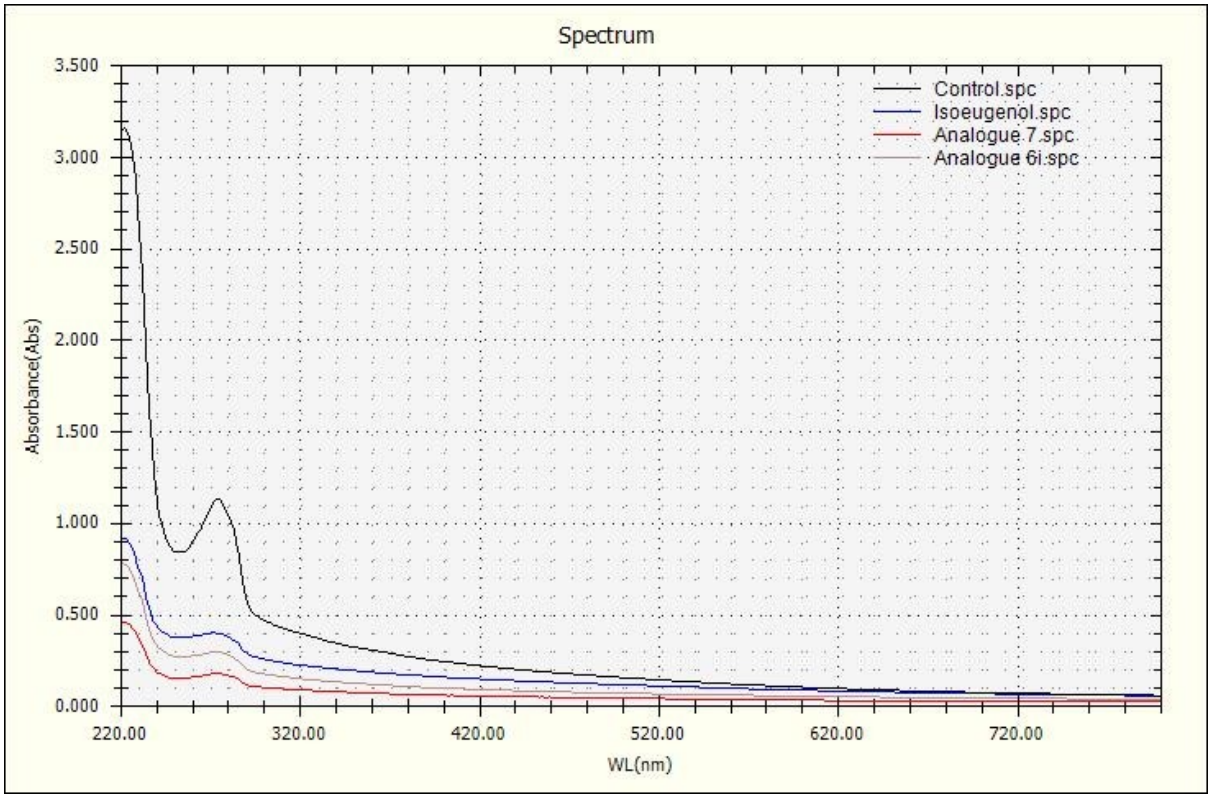


Fig S1 UV-visible spectrum of melanin isolated from eugenol and its analogues (**6i** and **7**) treated *A. fumigatus* conidia, which showed a characteristic peak at UV region (265-290 nm) with gradual decrease in absorption towards visible range.