Electronic Supplementary Information

Palladium and gold catalytic system enables direct access to O- and S-linked non-natural glyco-conjugates

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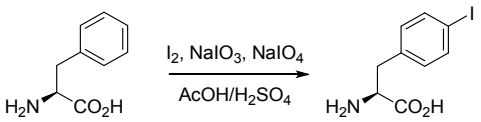
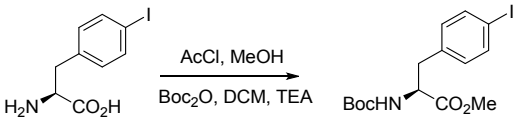
I. Synthesis of Substrates

p-Iodo-L-phenylalanine[1]



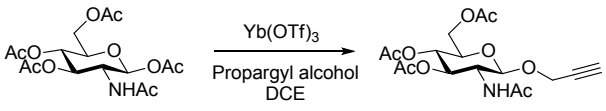
To a suspension of L-phenylalanine (8.52 g, 51.6 mmol) in acetic acid (40 mL), sulfuric acid (8 mL) was added dropwise to make a clear solution. Iodine (5.24 g, 20.7 mmol) and sodium iodate (2.04 g, 10.3 mmol) were then added. The reaction mixture was heated to 70 °C and refluxed while stirring overnight. Sodium periodate (2 × 0.29 g) was added over 5 mins, and the mixture was stirred additionally at 70 °C for 1 h until the mixture turned orange. Acetic acid was removed *in vacuo*. The crude mixture was diluted with water, washed with diethyl ether for 3 times. The aqueous phase was basified until a white precipitate formed. The solid was collected by filtration and dried *in vacuo* to afford *p*-iodo-L-phenylalanine as a white crystal (12.2 g, 81%). ^{1}H NMR (400 MHz, NaOH/D_2O) δ 7.50 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 3.25 (dd, J = 7.2, 5.8 Hz, 1H), 2.70 (dd, J = 13.6, 5.6 Hz, 1H), 2.57 (dd, J = 13.5, 7.3 Hz, 1H).

N-Boc-*p*-iodo-L-phenylalanine methyl ester (**1**)[1]



Acetyl chloride (5 mL) was added dropwise to MeOH (30 mL) at 0 °C. After stirred for 10 min, *p*-iodo-L-phenylalanine (3 g, 10.31 mmol) was added under Ar condition. The reaction was stirred overnight and the reaction mixture was concentrated *in vacuo* to make a white solid. The solid was dissolved in DCM, and triethylamine (4 mL, 28.70 mmol) and di-*tert*-butyl dicarbonate (3.8 g, 17.41 mmol) were added. After stirring overnight, solution was washed with water and extracted with DCM. Organic phase was washed with brine, dried over with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the title product as yellow oil (3.6 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.97 (d, J = 7.3 Hz, 1H), 4.56 (d, J = 7.4 Hz, 1H), 3.71 (s, 3H), 3.07 (dd, J = 13.6, 5.8 Hz, 1H), 2.97 (dd, J = 13.9, 6.1 Hz, 1H), 1.41 (s, 9H).

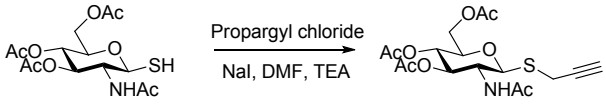
Propargyl 2-*N*-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranose (**5a**)[2]



Propargyl alcohol (29.9 μL, 0.514 mmol) and $Yb(OTf)_3$ (47.8 mg, 0.231 mmol) were added to a solution of 2-*N*-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (100 mg, 0.257 mmol) in dry DCE (6 mL). The solution was stirred for 24 h at 70 °C. The solution was diluted with DCM and washed with water. The organic layer was dried with sodium sulfate and concentrated *in vacuo* to furnish the title compound (86 mg, 87%). ^{1}H

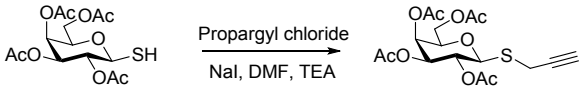
NMR (400 MHz, $CDCl_3$) δ 5.49 (d, J = 8.9 Hz, 1H), 5.27 (t, J = 10.0 Hz, 1H), 5.09 (t, J = 9.6 Hz, 1H), 4.85 (d, J = 8.4 Hz, 1H), 4.38 (s, 2H), 4.27 (dd, J = 12.2, 4.6 Hz, 1H), 4.14 (d, J = 12.2 Hz, 1H), 3.95 (dd, J = 18.5, 9.5 Hz, 1H), 3.72 (d, J = 9.8 Hz, 1H), 2.46 (d, J = 1.3 Hz, 1H), 2.11 – 1.91 (m, 12H).

Propargyl 2-*N*-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-thioglucopyranoside (**5b**)[3]



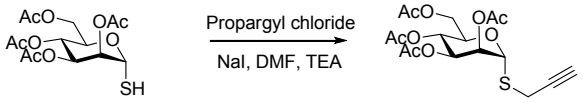
To a solution of 2-*N*-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-thioglucopyranose (200 mg, 0.55 mmol), propargyl chloride (70 µL, 0.968 mmol), and sodium iodide (82.5 mg, 0.55 mmol) in dry DMF (3 mL) was added triethylamine (153.32 µL, 1.1 mmol) and stirred overnight at 50 °C under argon atmosphere. The mixture was diluted with ethyl acetate and the organic layer was washed with 0.5 M $KHSO_4$, H_2O, and then brine. The organic layer was dried over with sodium sulfate and concentrated *in vacuo* to afford the title compound (210 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (d, J = 9.2 Hz, 1H), 5.18 (t, J = 9.7 Hz, 1H), 5.08 (t, J = 9.6 Hz, 1H), 4.81 (d, J = 10.4 Hz, 1H), 4.18 (ddd, J = 27.4, 14.8, 8.4 Hz, 3H), 3.74-3.67 (m, 1H), 3.54 (d, J = 16.6 Hz, 1H), 3.27 (d, J = 16.6 Hz, 1H), 2.26 (s, 1H), 2.11 – 1.97 (m, 9H), 1.94 (s, 3H).

Propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranose (**5c**)[4]



To a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranose (1.882 g, 5.165 mmol), propargyl chloride (577 µL, 7.748 mmol), and sodium iodide (769 mg, 5.165 mmol) in dry DMF (30 mL) was added triethylamine (1.44 mL, 10.330 mmol) and stirred overnight at 50 °C argon atmosphere. The mixture was diluted with EtOAc and the organic layer was washed with 0.5 M $KHSO_4$, H_2O, and then brine. The organic layer was dried over with sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the title product (1.29 g, 89.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (td, J = 3.5, 1.2 Hz, 1H), 5.27-5.21 (m, 1H), 5.10-5.05 (m, 1H), 4.73 (d, J = 10.0 Hz, 1H), 4.18-4.06 (m, 2H), 3.95 (td, J = 6.6, 1.2 Hz, 1H), 3.59-3.52 (m, 1H), 3.32-3.26 (m, 1H), 2.25 (dd, J = 3.3, 2.0 Hz, 1H), 2.15-2.12 (m, 3H), 2.06 (d, J = 2.3 Hz, 3H), 2.03 (d, J = 3.4 Hz, 3H), 1.97 (d, J = 1.7 Hz, 3H).

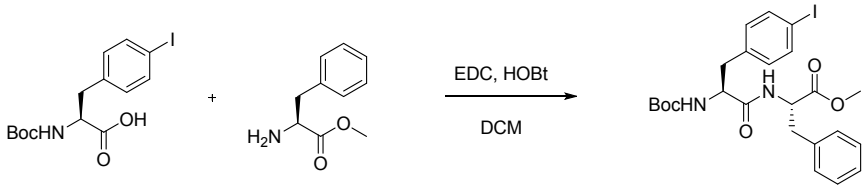
Propargyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose (**5d**)[4]



To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-thiomannopyranose (1 g, 2.744 mmol), propargyl chloride (306 µL, 4.117 mmol), and sodium iodide (411 mg, 2.744 mmol) in dry DMF (30 mL) was added triethylamine (765 µL, 5.489 mmol) and stirred overnight at 50 °C under argon atmosphere. The mixture was diluted with ethyl acetate and the organic layer was washed with 0.5 M $KHSO_4$, H_2O, and then brine. The organic layer was dried over with sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the

title product (944 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 5.39-5.36 (m, 1H), 5.33 (t, J = 9.8 Hz, 1H), 5.22 (ddd, J = 10.0, 3.4, 1.1 Hz, 1H), 4.37-4.29 (m, 2H), 4.10 (dd, J = 10.1, 5.3 Hz, 1H), 3.44-3.36 (m, 1H), 3.27-3.19 (m, 1H), 2.28-2.24 (m, 1H), 2.17 (d, J = 1.1 Hz, 3H), 2.12-2.07 (m, 3H), 2.05 (t, J = 3.1 Hz, 3H), 1.98 (d, J = 1.1 Hz, 3H).

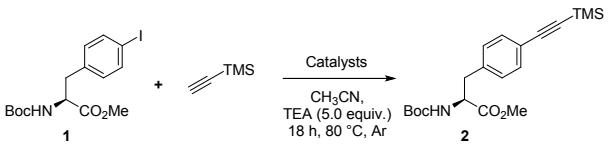
N-Boc-4-iodo-L-phenylalanyl-L-phenylalanine methyl ester (**7**)[5]



To a solution of *N*-Boc-4-iodo-L-phenylalanine (500 mg, 0.511 mmol) dissolved in DCM (20 mL) and DMF (aliquot), HOBT (391 mg, 2.556 mmol) was added and stirred for 5 mins. EDC (338 μL, 1.917 mmol) and L-phenylalanine methyl ester (390 mg, 1.278 mmol) were then added to a mixture and stirred overnight at RT. The mixture was diluted with DCM and washed with water and brine. The combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography to yield the title product (592 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 6.7 Hz, 2H), 7.24 (s, 3H), 6.99 (d, J = 4.9 Hz, 2H), 6.93 (d, J = 7.2 Hz, 2H), 6.22 (s, 1H), 4.91 (s, 1H), 4.77 (d, J = 6.2 Hz, 1H), 4.28 (s, 1H), 3.70 (s, 3H), 3.06 (dq, J = 14.0, 7.3 Hz, 2H), 2.96 (d, J = 5.8 Hz, 2H), 1.41 (s, 9H).

II. Synthesis of Compound 2

N-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**)

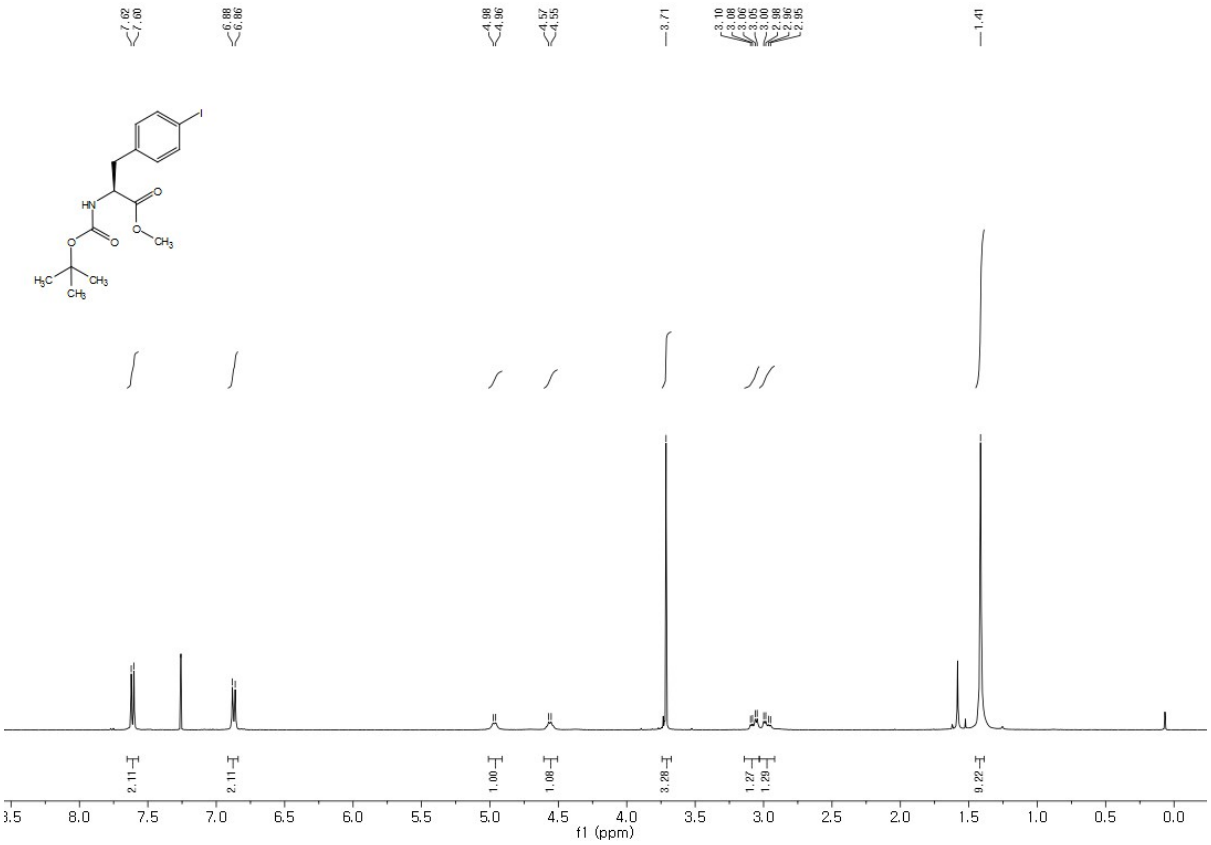


1 (500 mg, 1.234 mmol), $PdCl_2(PPh_3)_2$ (8.66 mg, 0.0123 mmol), and gold iodide (7.99 mg, 0.0247 mmol) were dissolved in acetonitrile and triethylamine (0.860 mL, 6.170 mmol). Ethynyltrimethylsilane (0.209 mL, 1.481 mmol) was added dropwise to the solution and stirred for 18 h at 80 °C under argon atmosphere. The mixture was quenched with water and extracted with diethyl ether for 3 times. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 5.02 (d, J = 7.8 Hz, 1H), 4.57 (q, J = 6.0 Hz, 1H), 3.70 (s, 3H), 3.12 (dd, J = 13.7, 5.8 Hz, 1H), 3.04 (dd, J = 13.7, 5.9 Hz, 1H), 1.43 (s, 9H), 0.25 (s, 9H).

III. NMR Spectra and HRMS

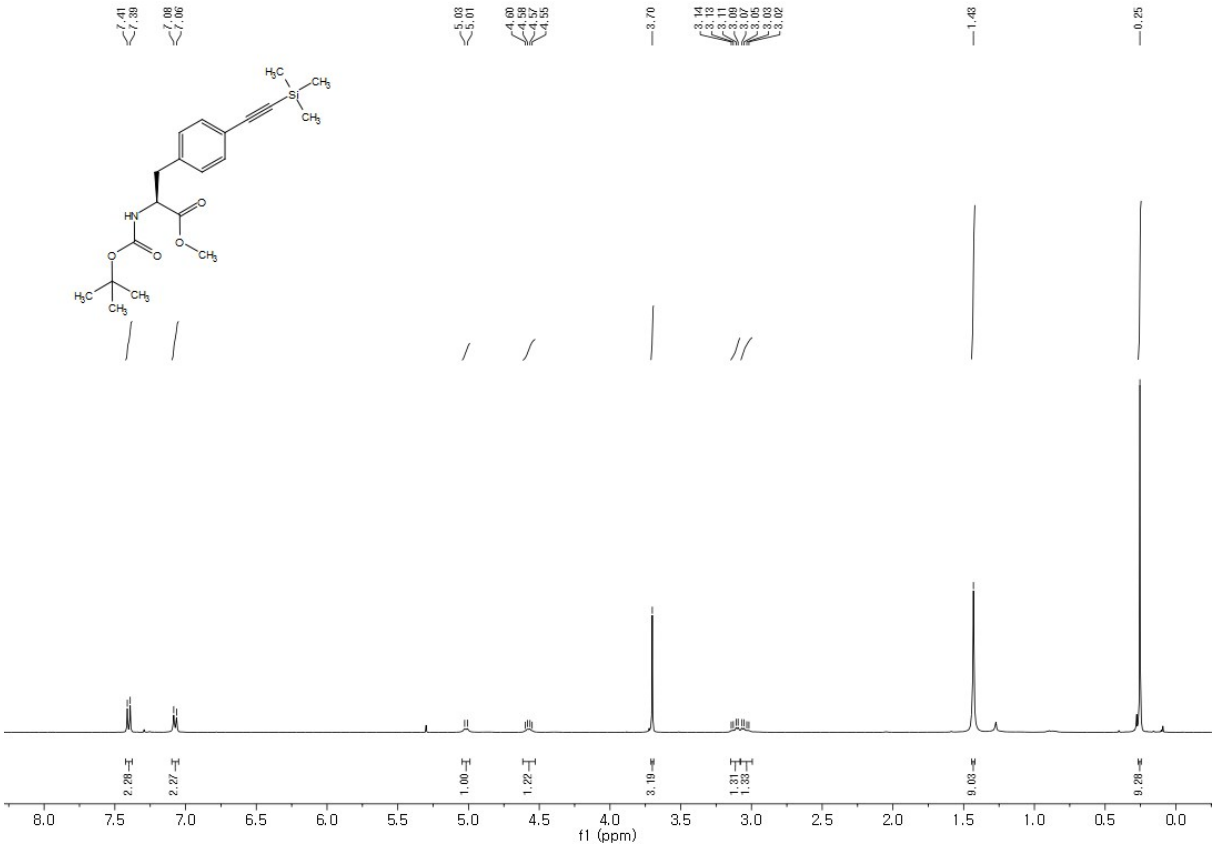
Compound **1**

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



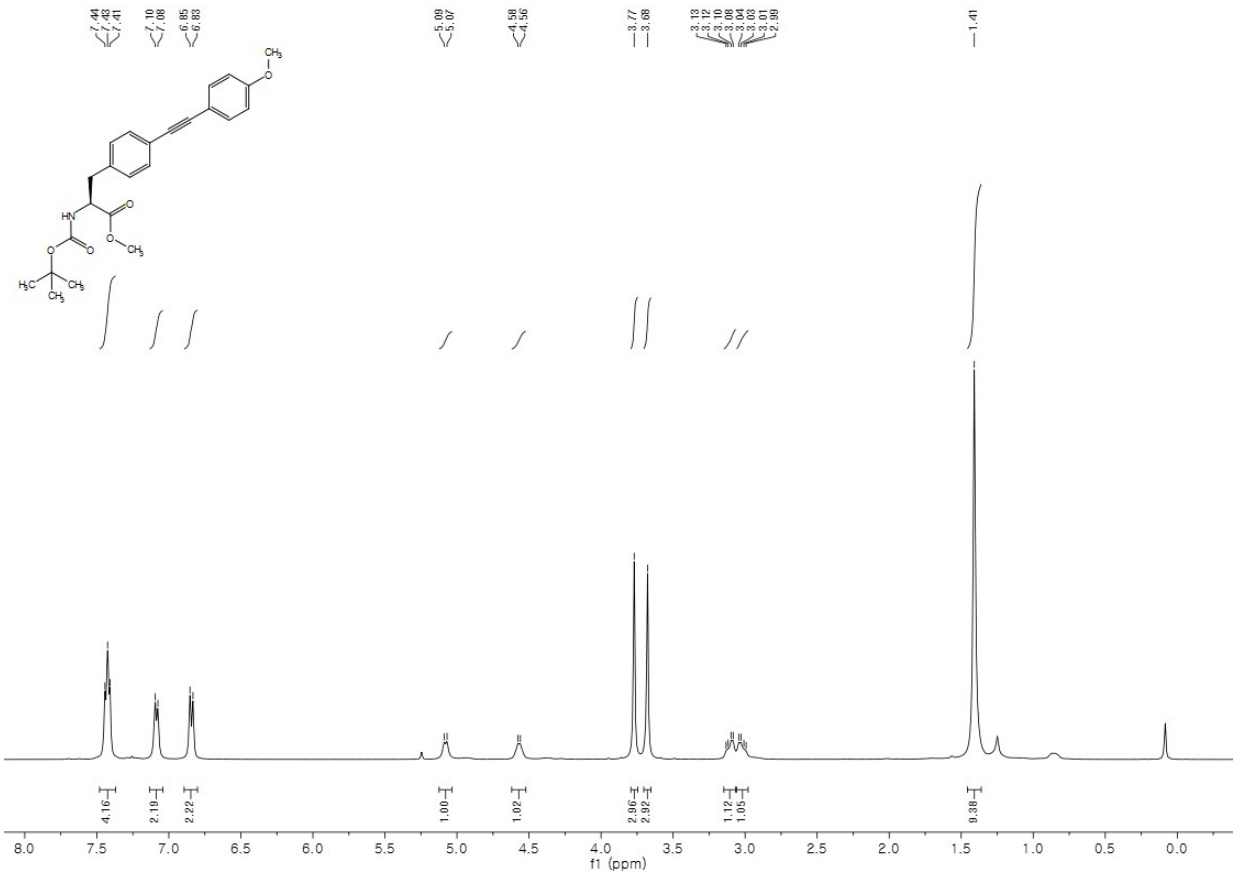
Compound **2**

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



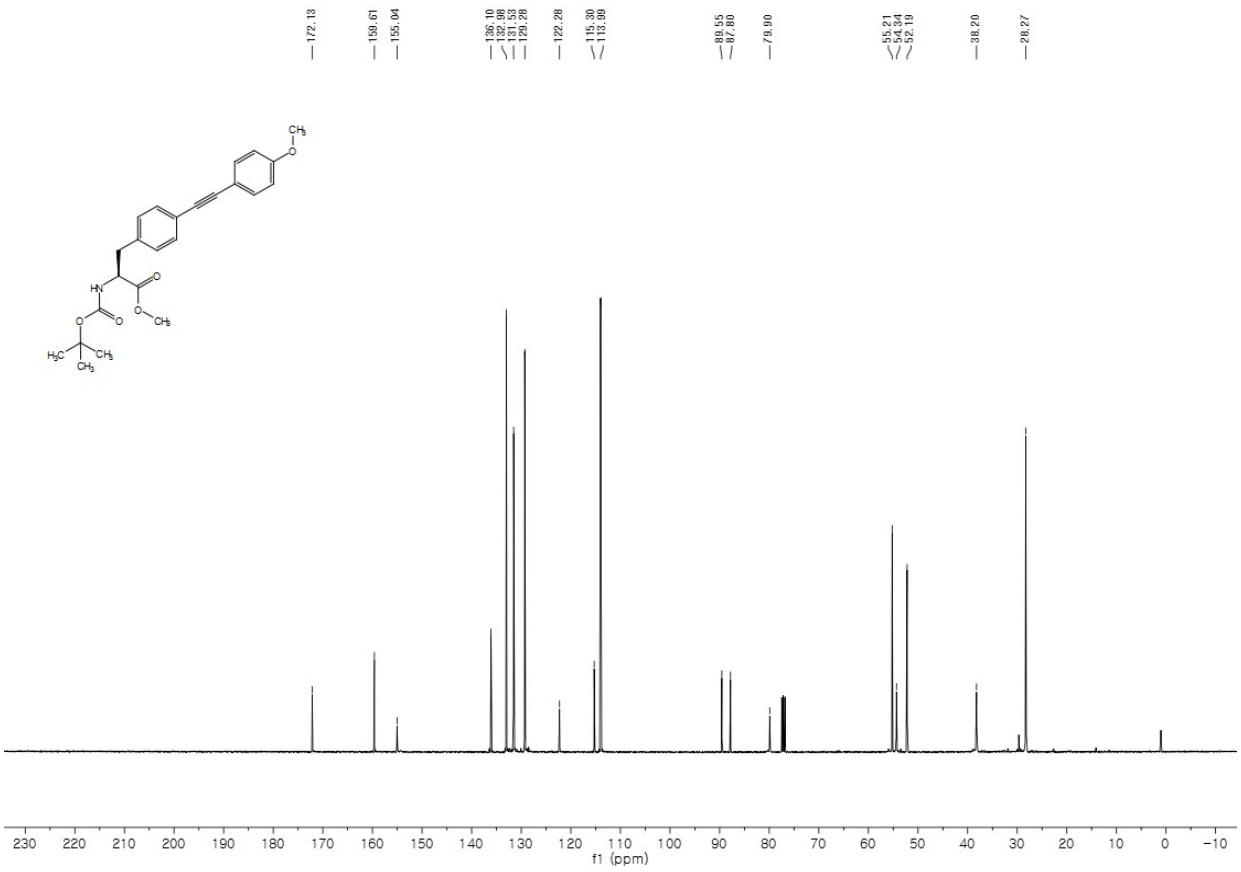
Compound **4a**

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



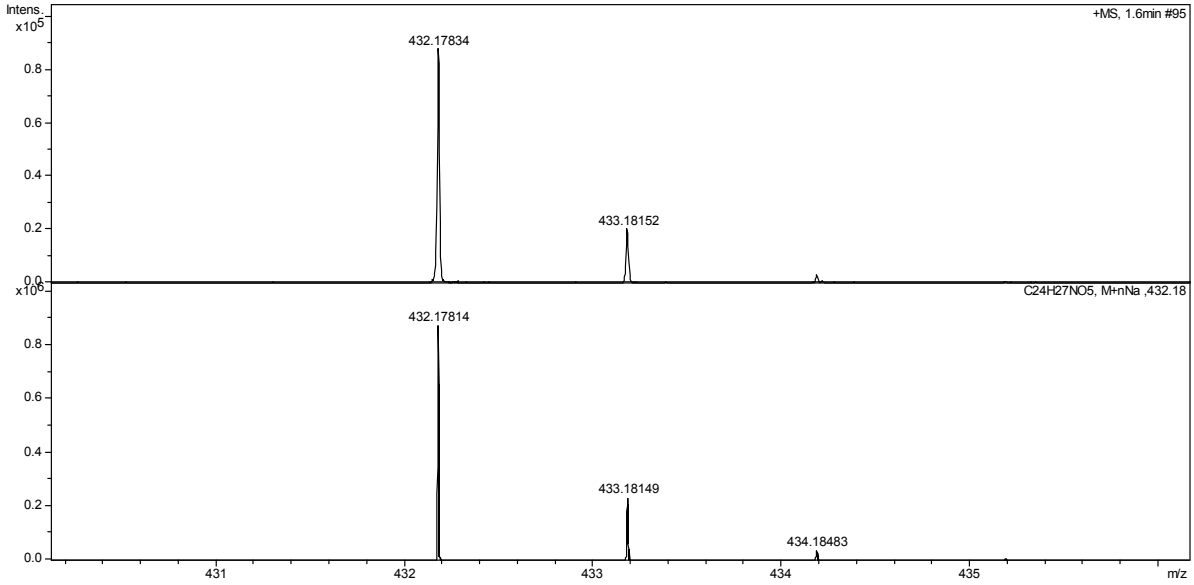
Compound **4a**

^{13}C NMR (101 MHz, $CDCl_3$)



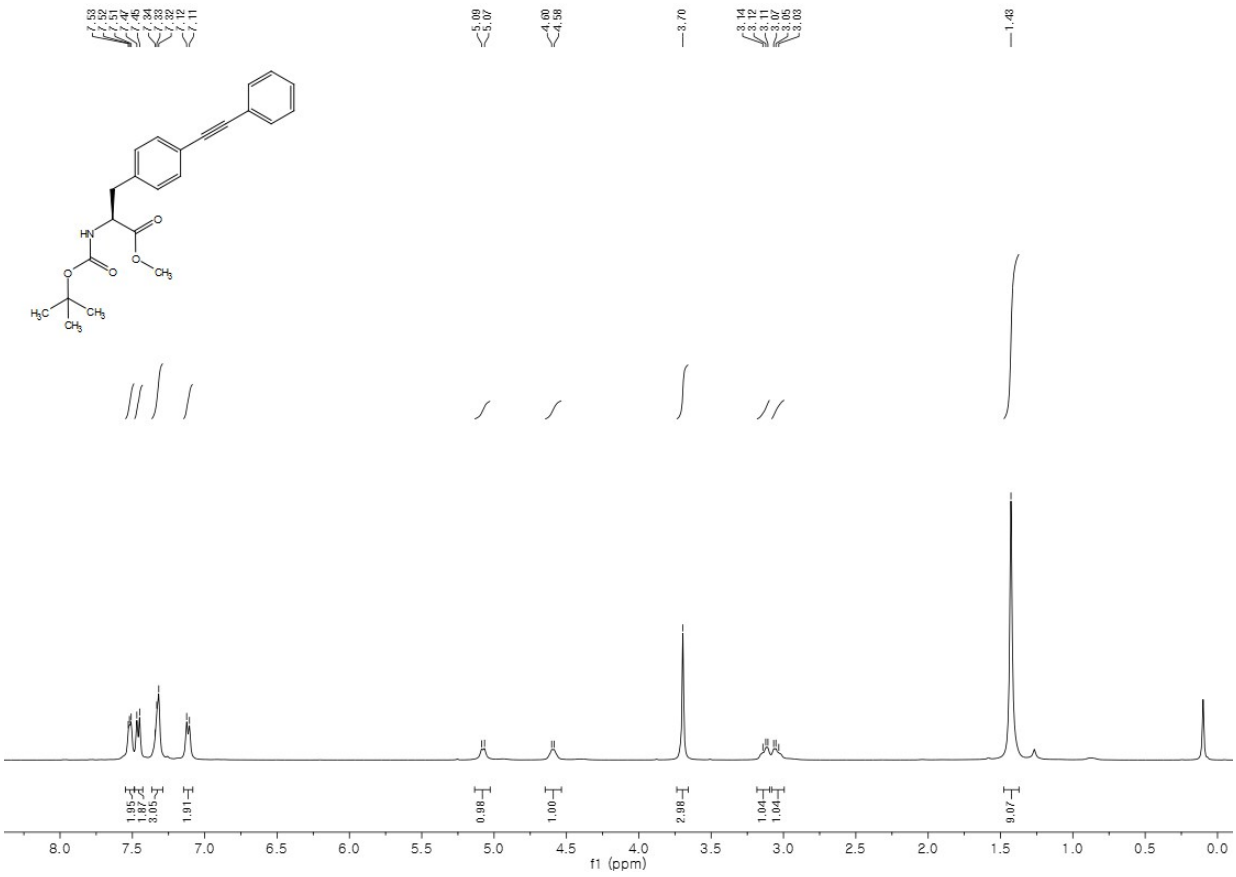
Compound **4a**

HRMS



Compound **4b**

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



Compound **4b**

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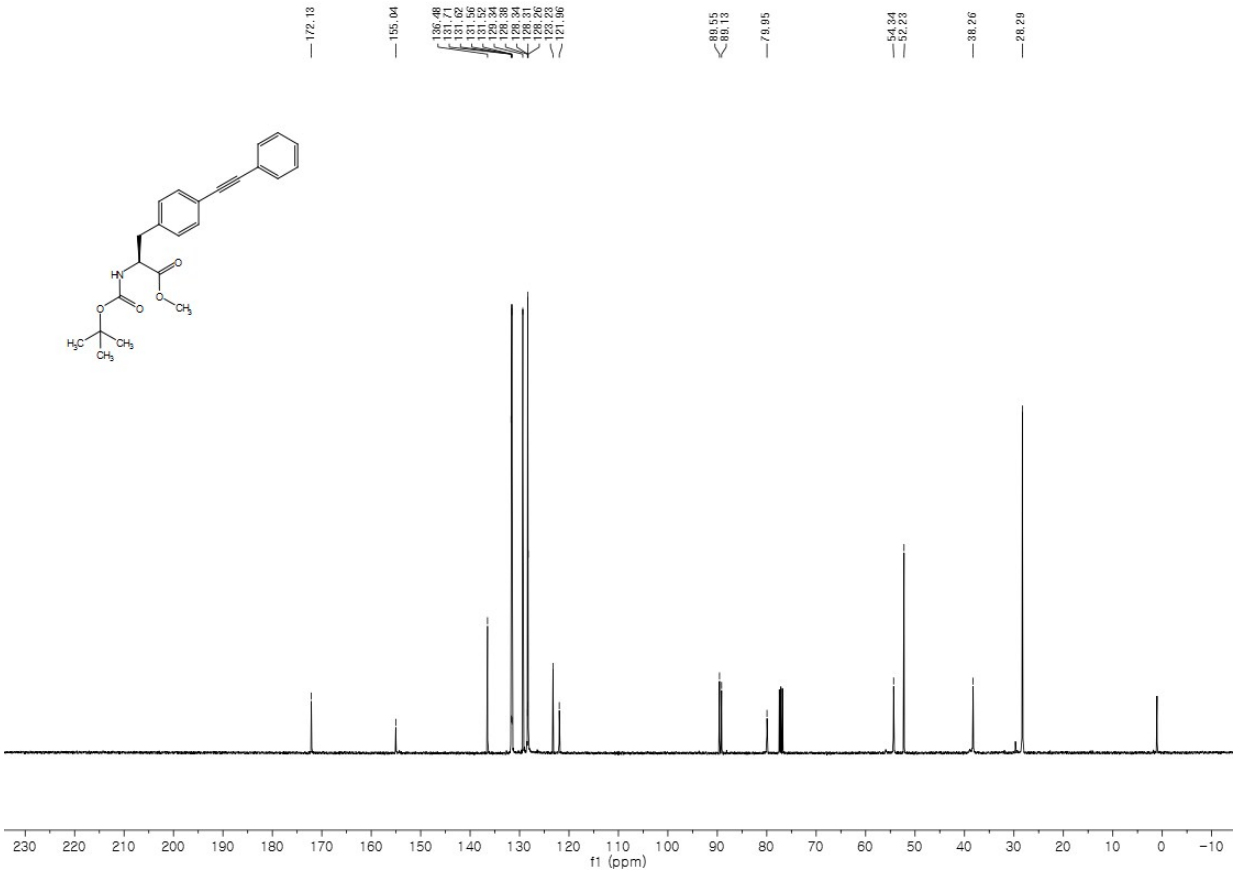

Compound **4b**

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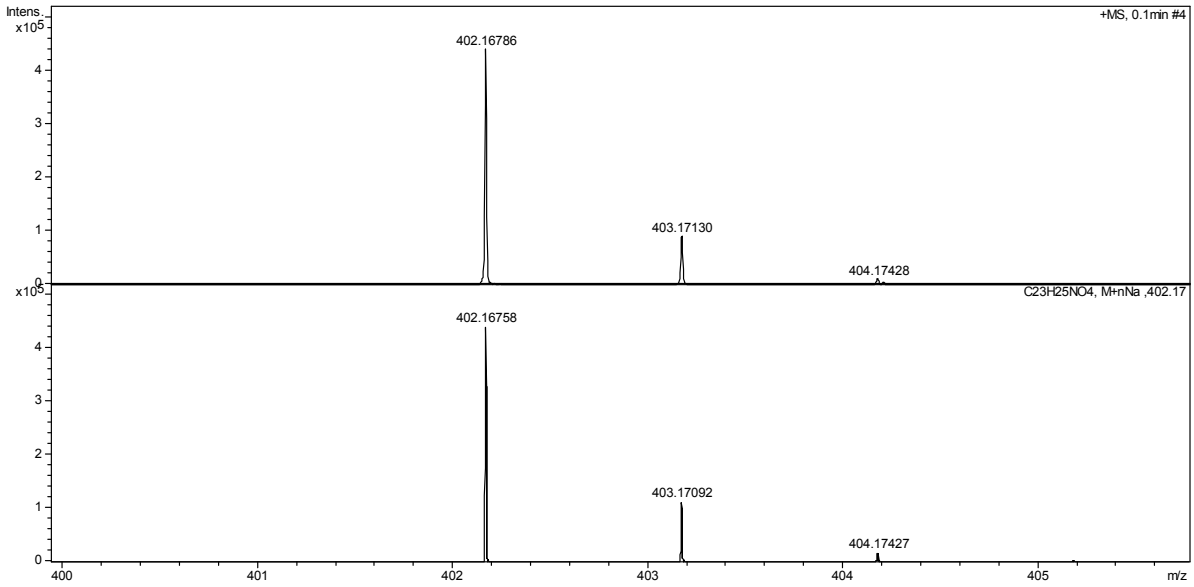

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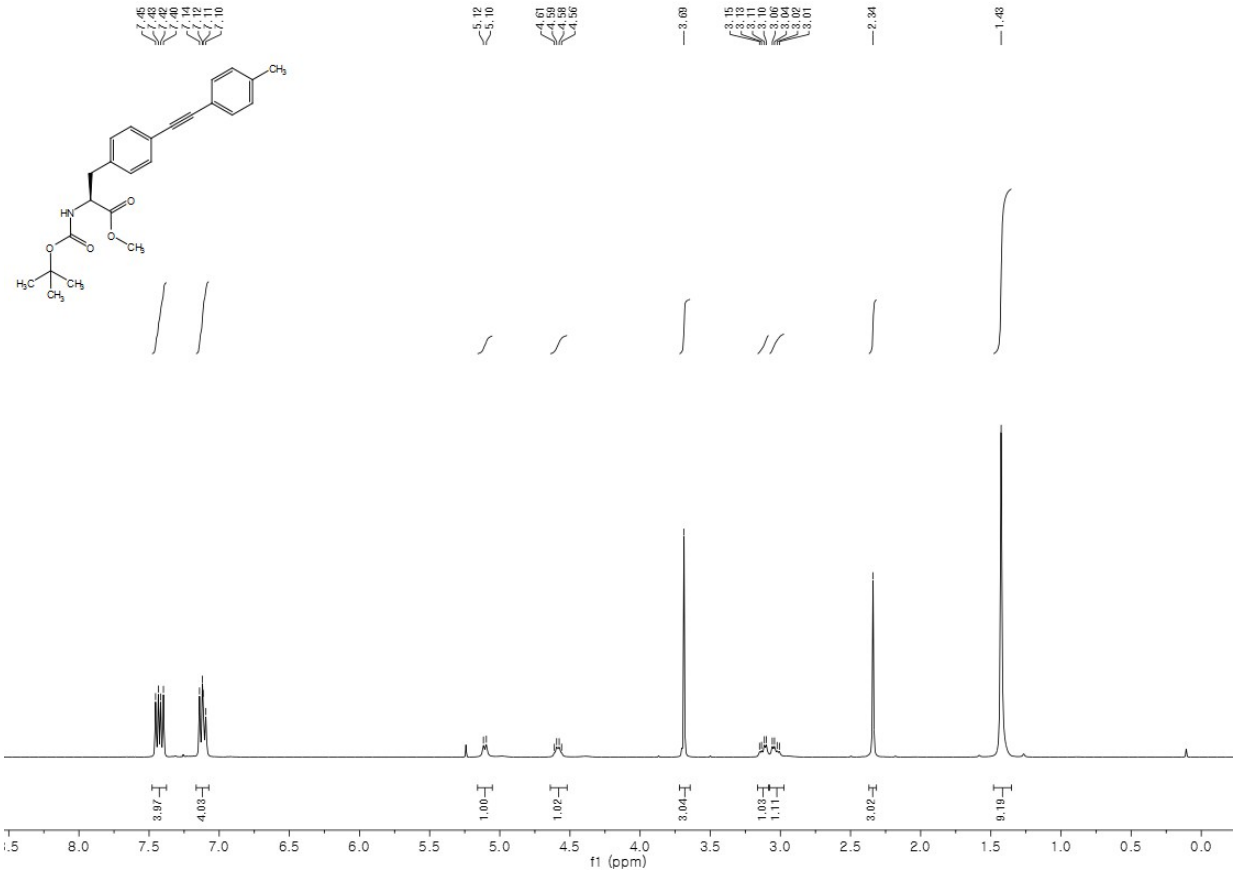

Compound **4c**

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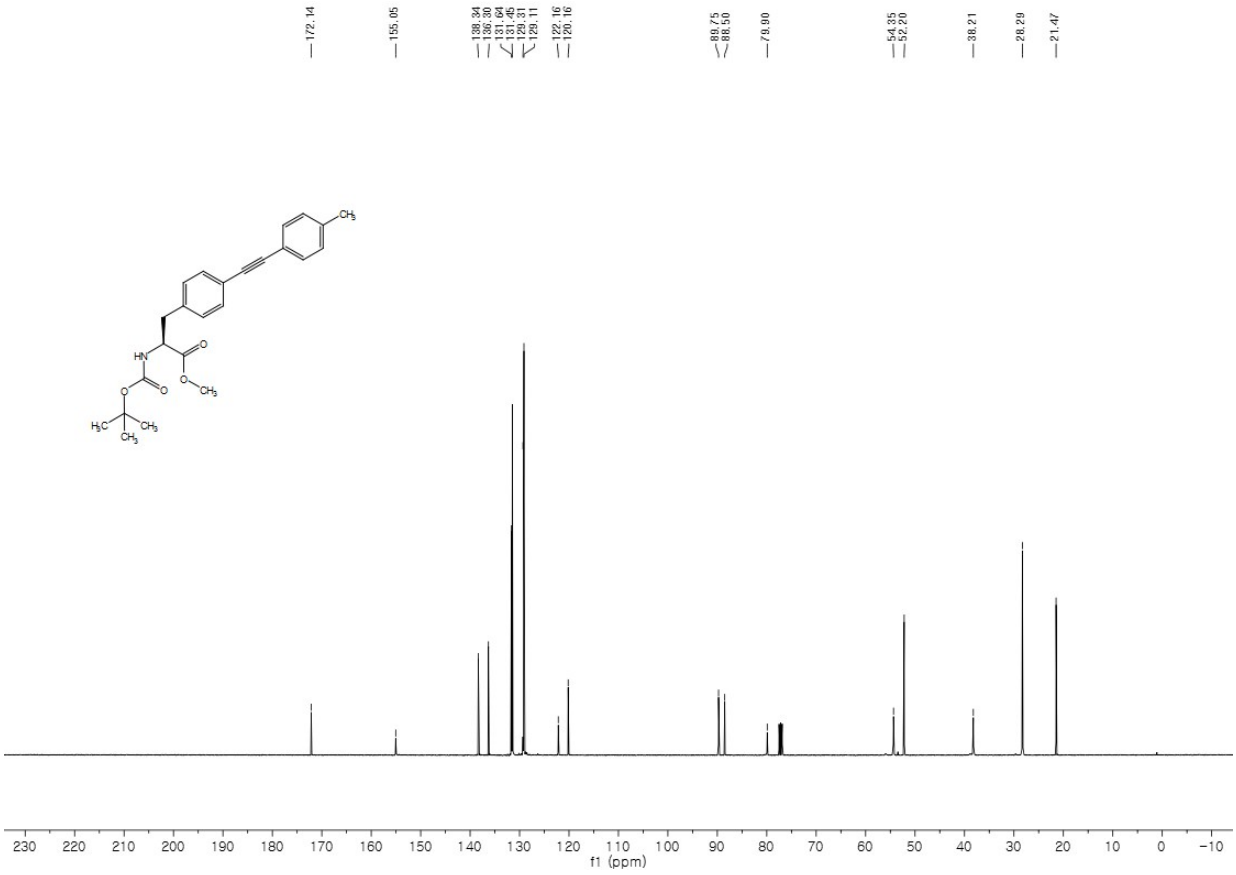

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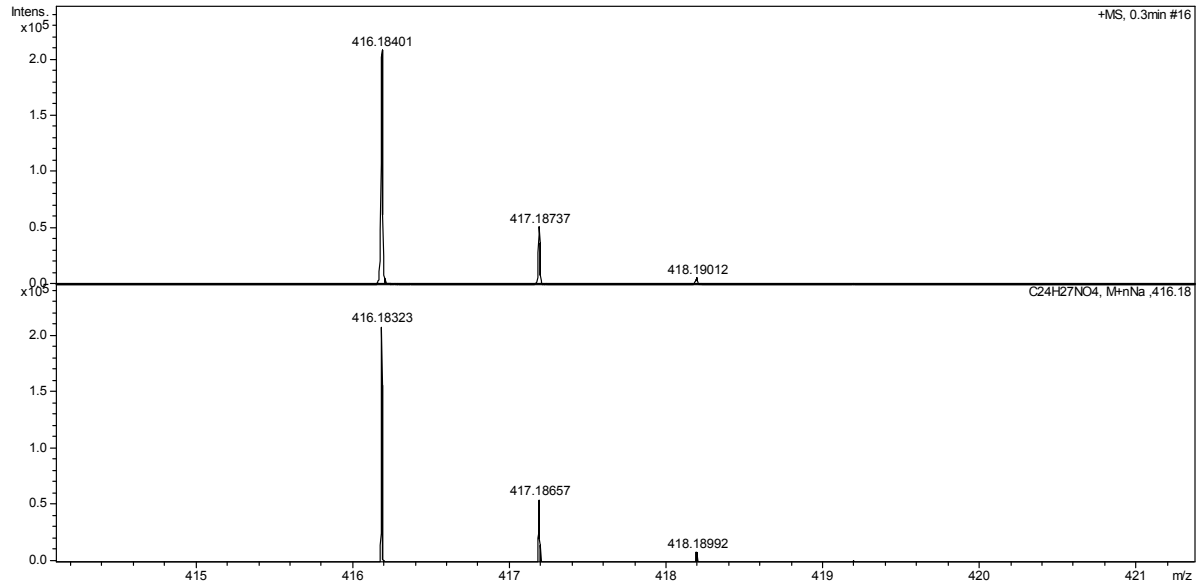

Compound **4d**

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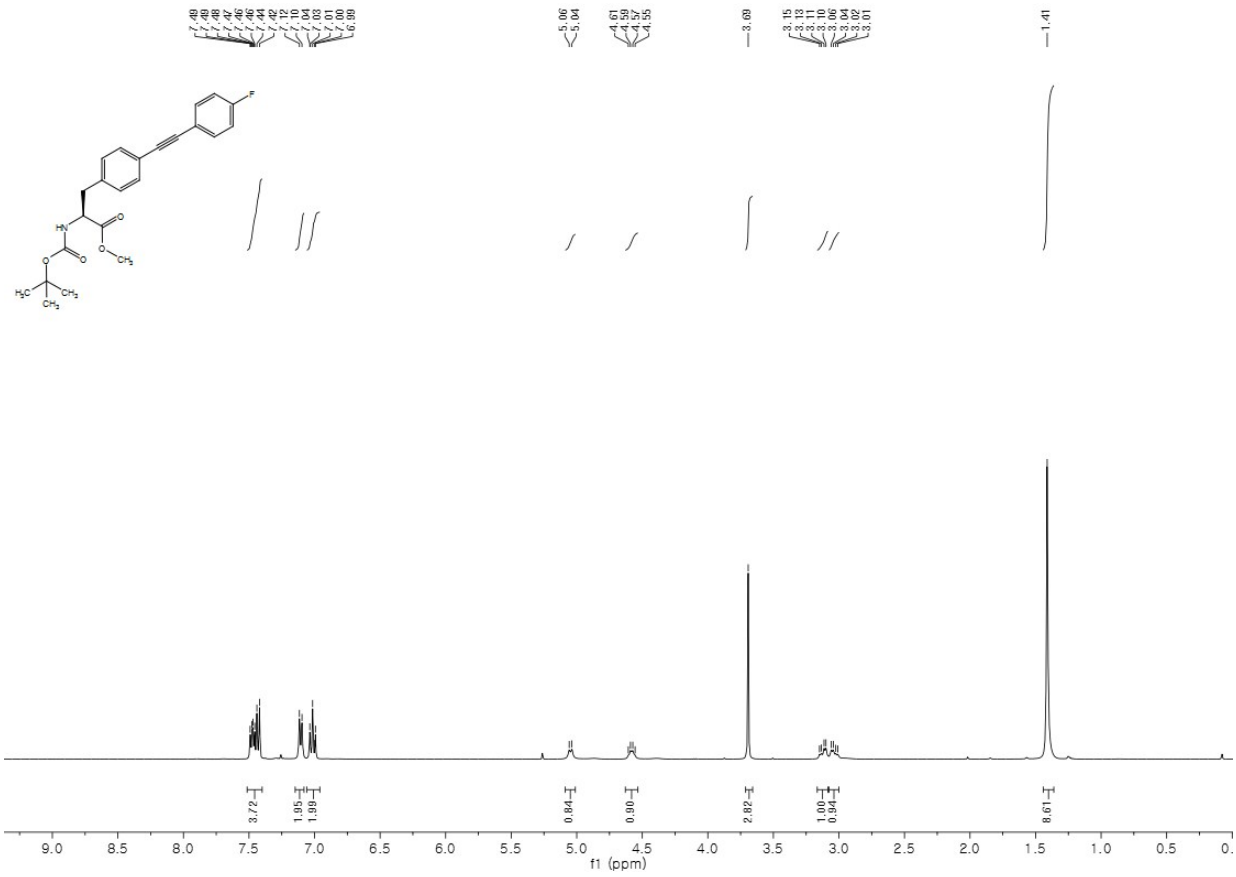

Compound **4d**

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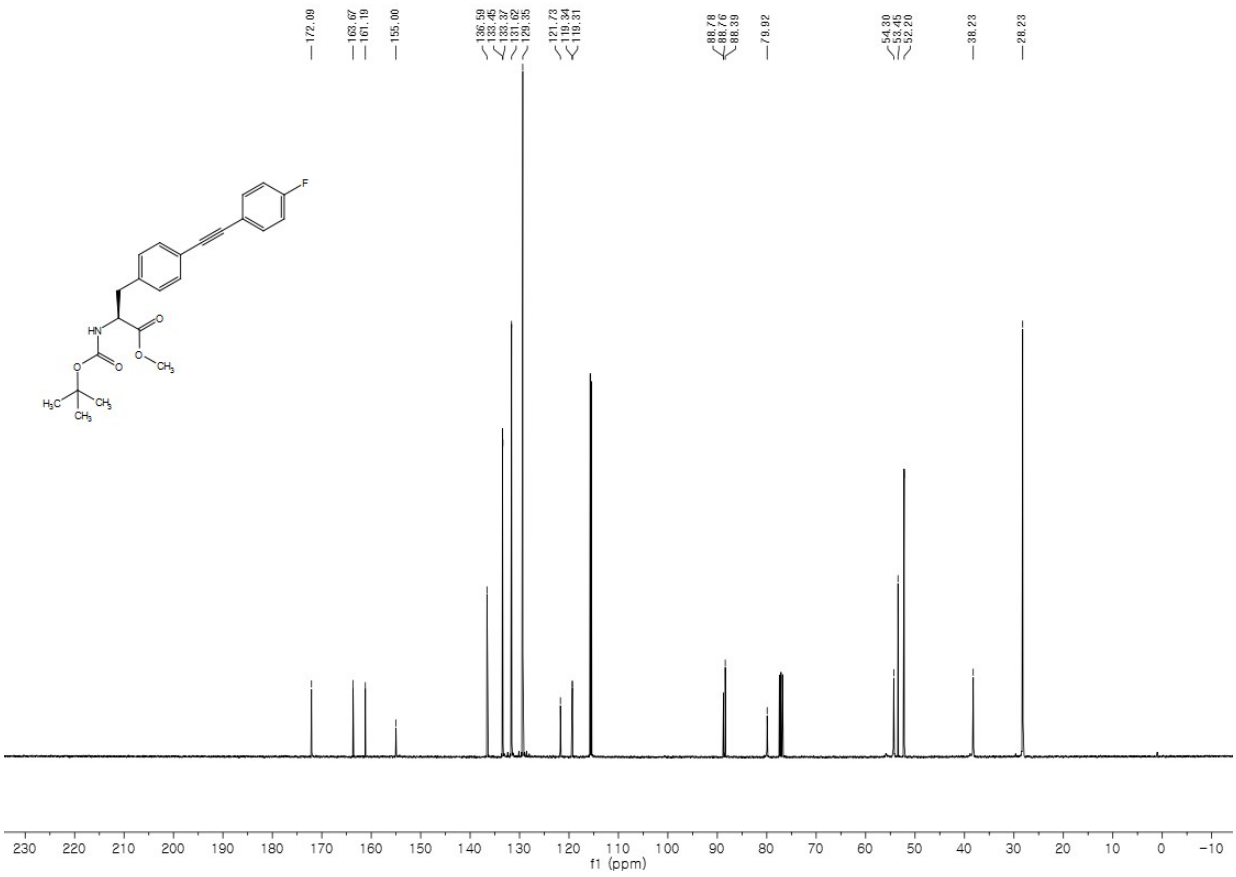
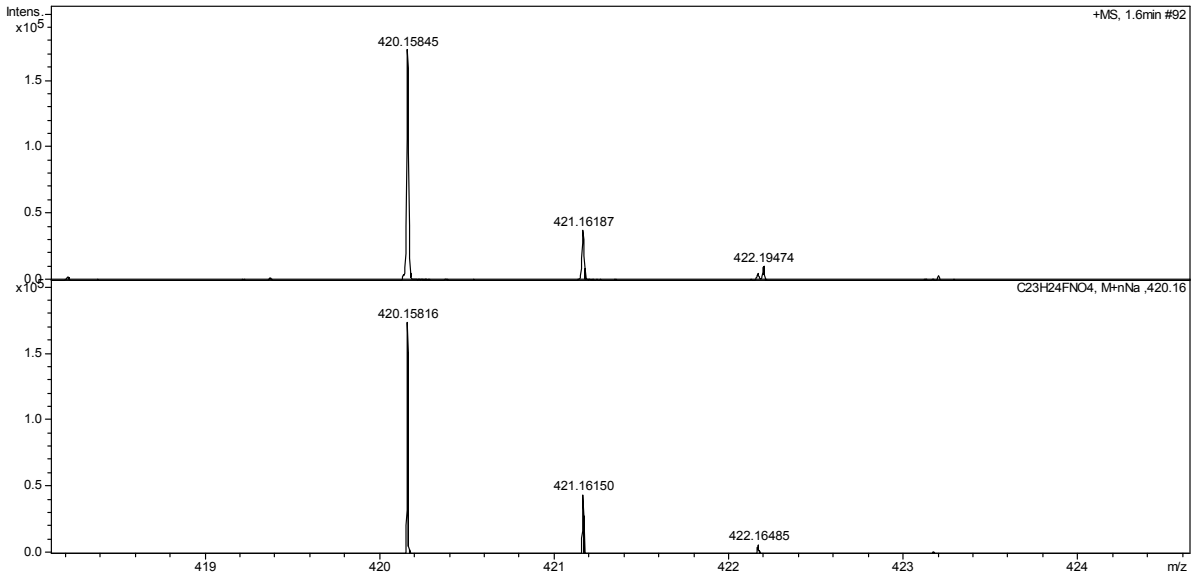


Compound **4d**

HRMS



Compound **4e**

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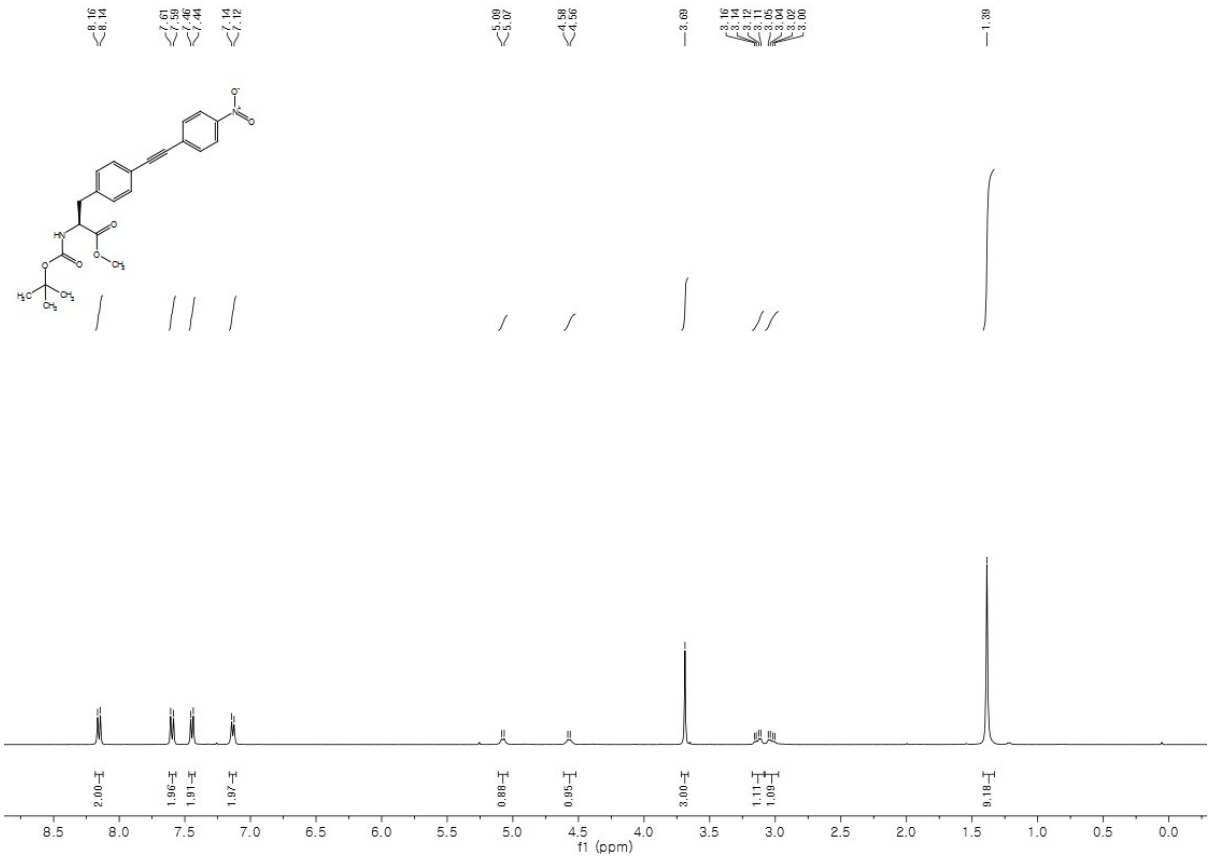

Compound **4e**

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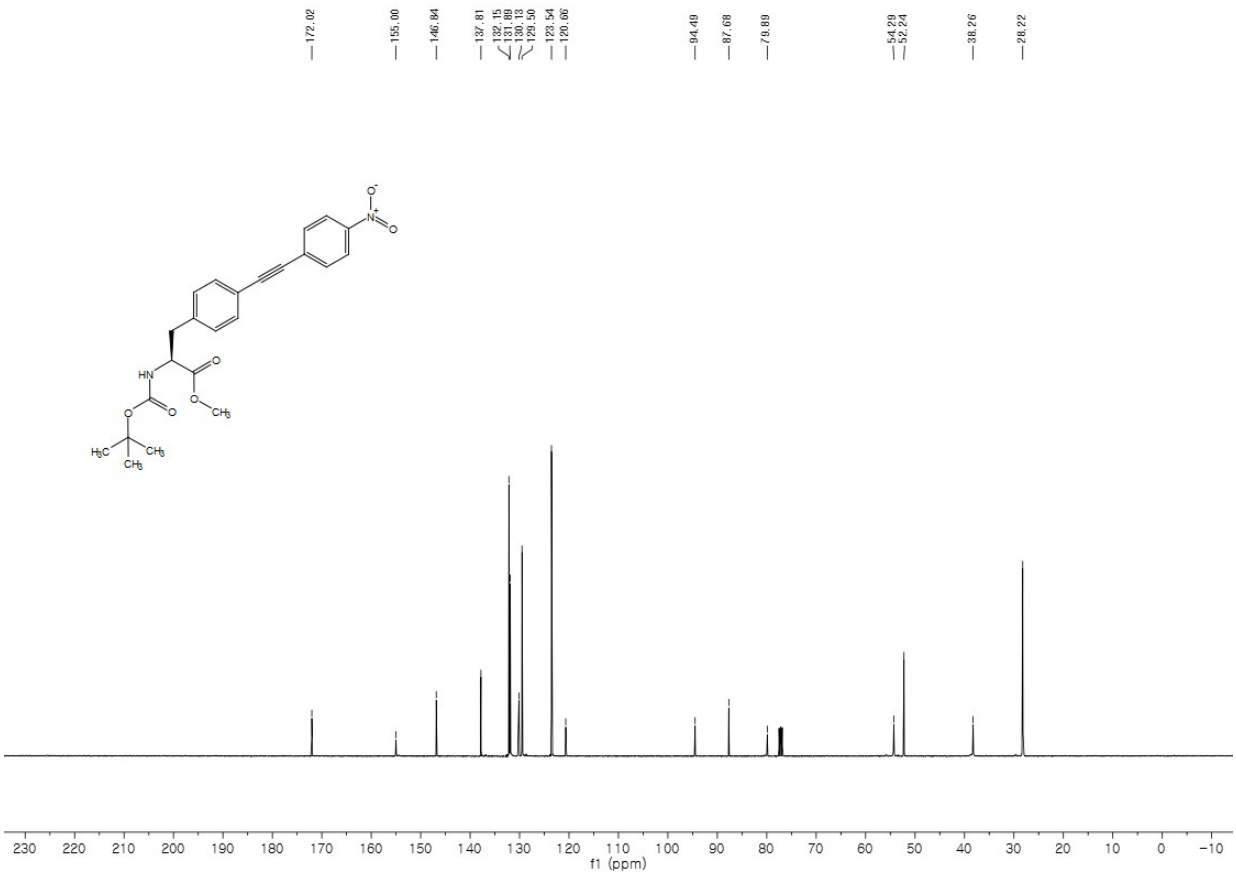
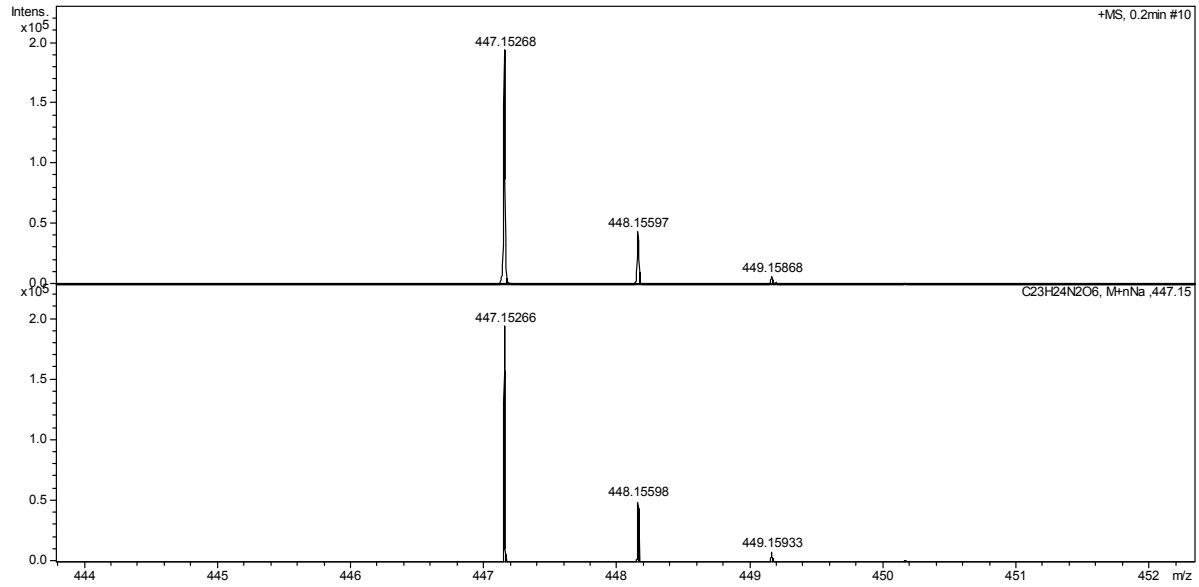


Compound **4e**

HRMS



Compound **4f**

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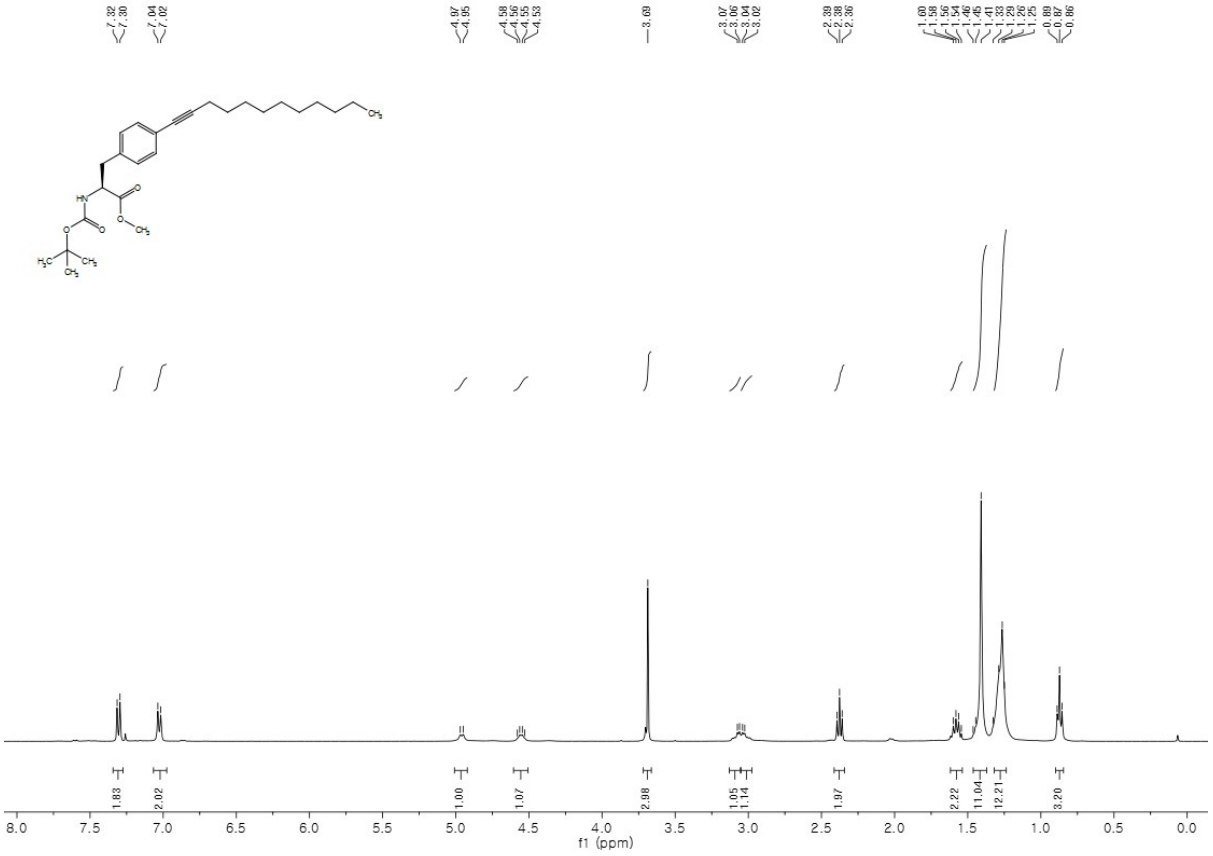

Compound **4f**

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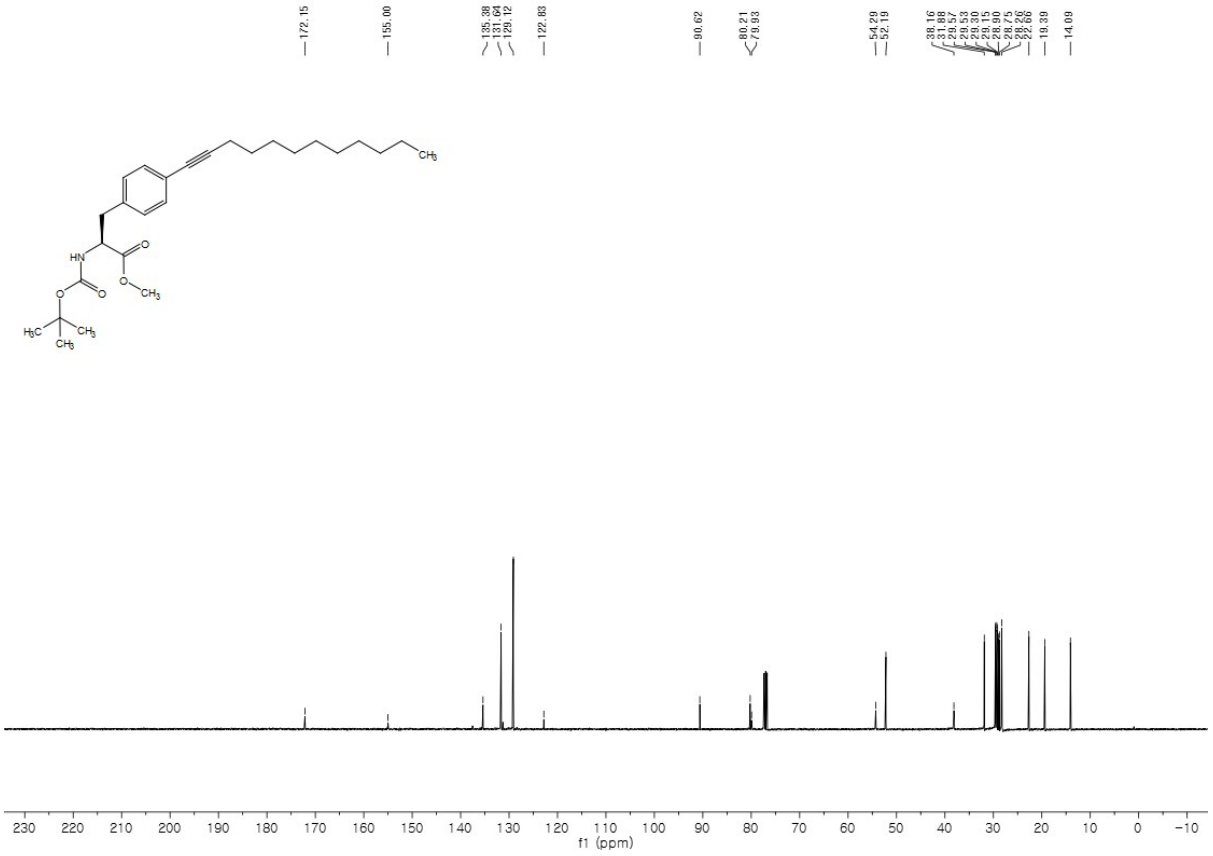
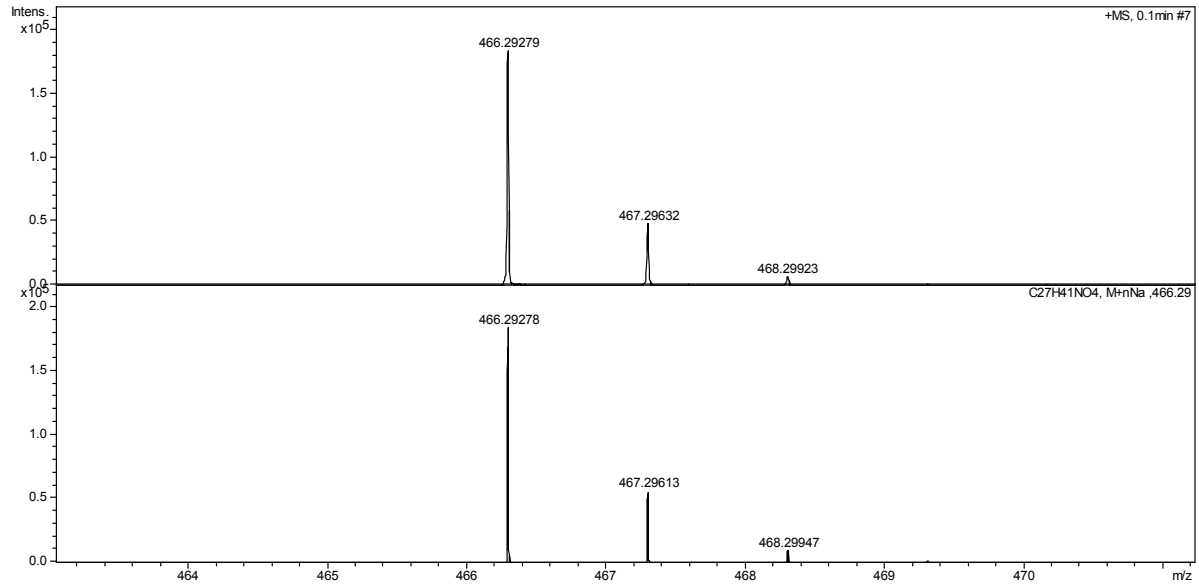


Compound **4f**
HRMS



Compound **4g**

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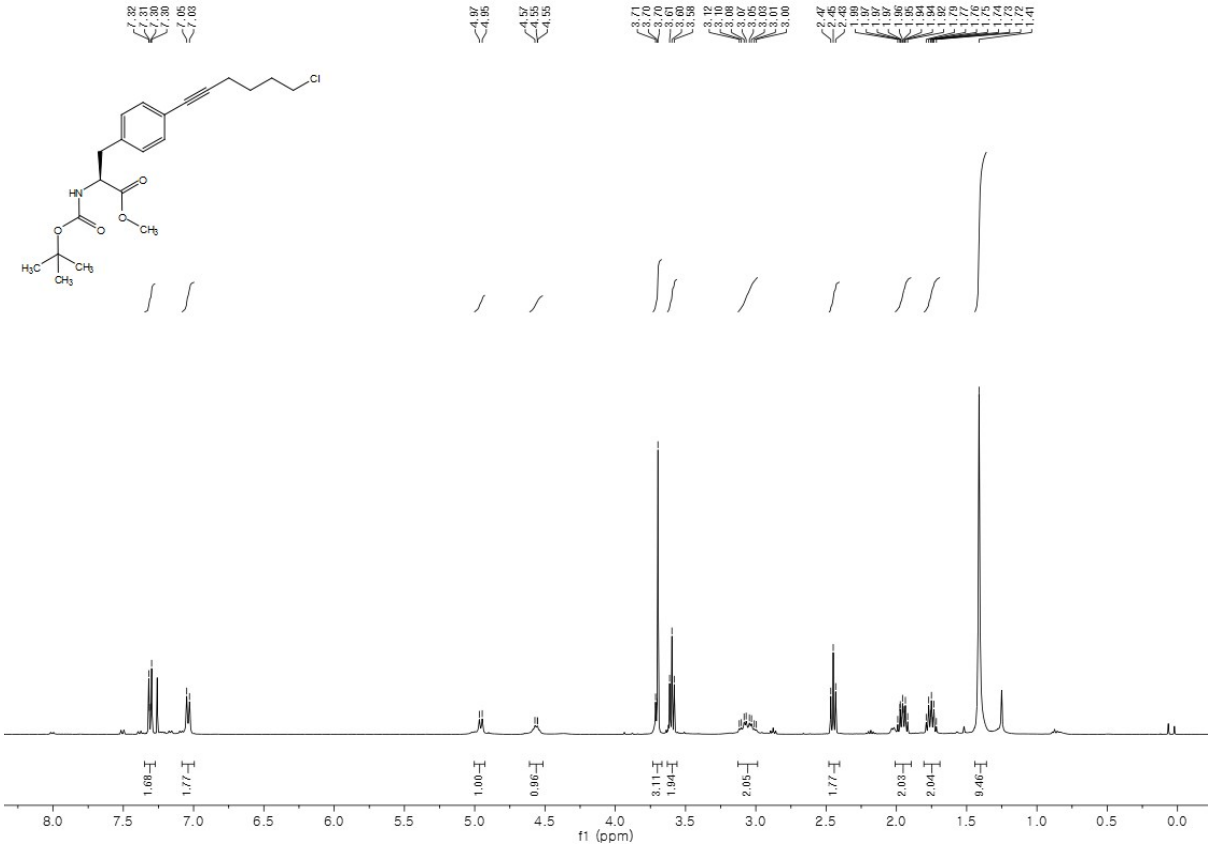

Compound **4g**

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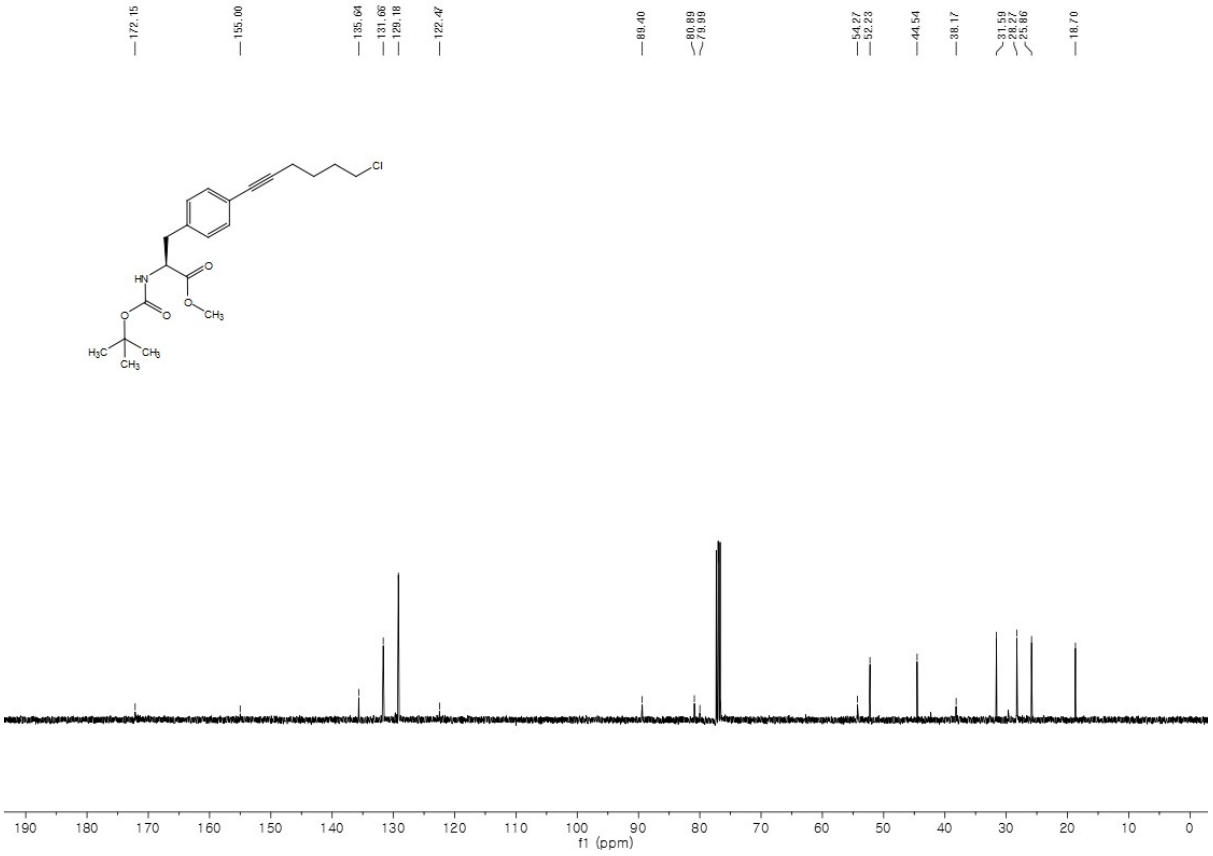
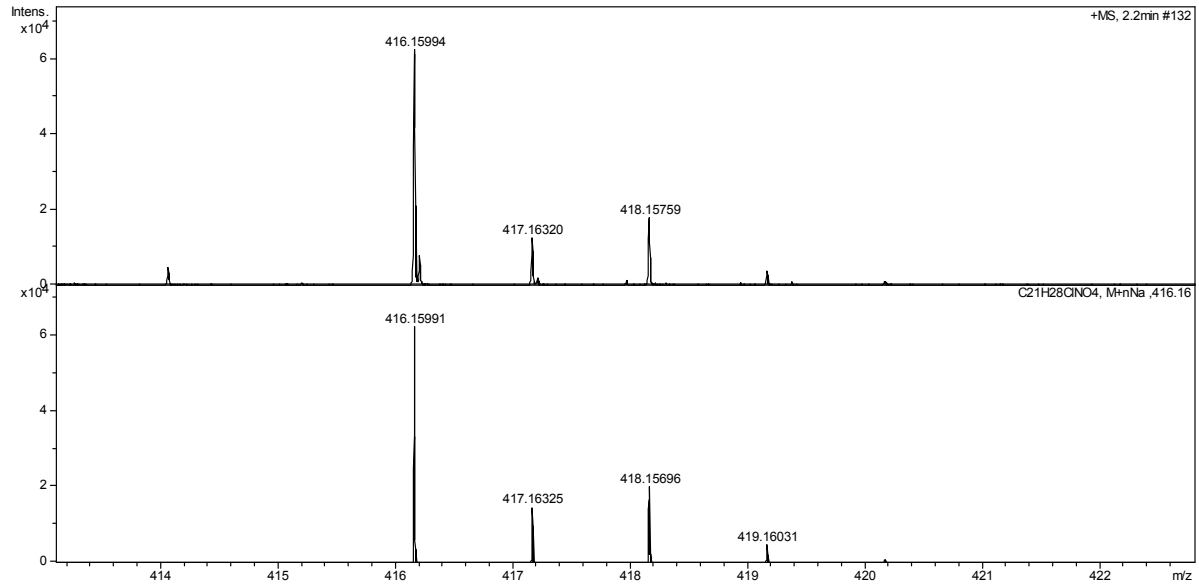


Compound **4g**
HRMS



Compound **6a**

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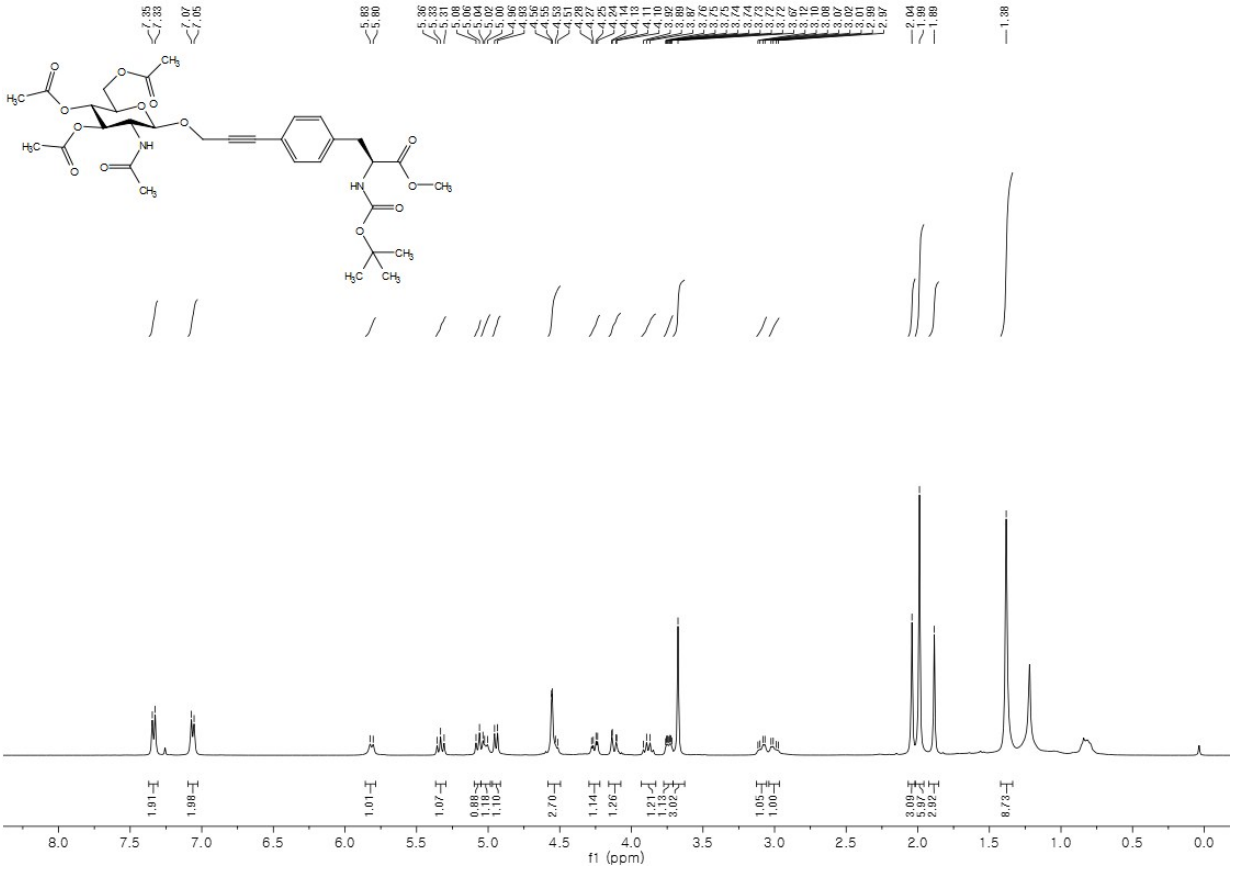
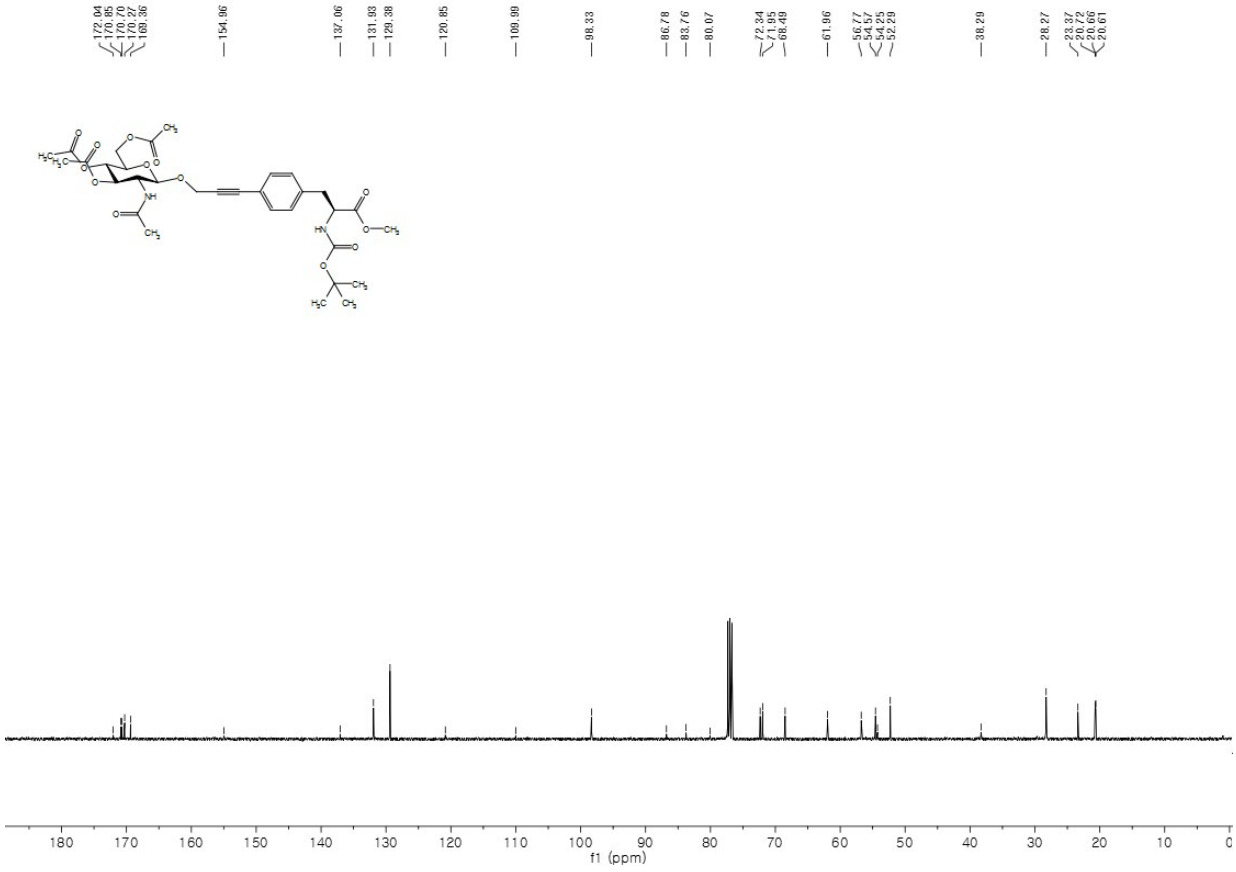


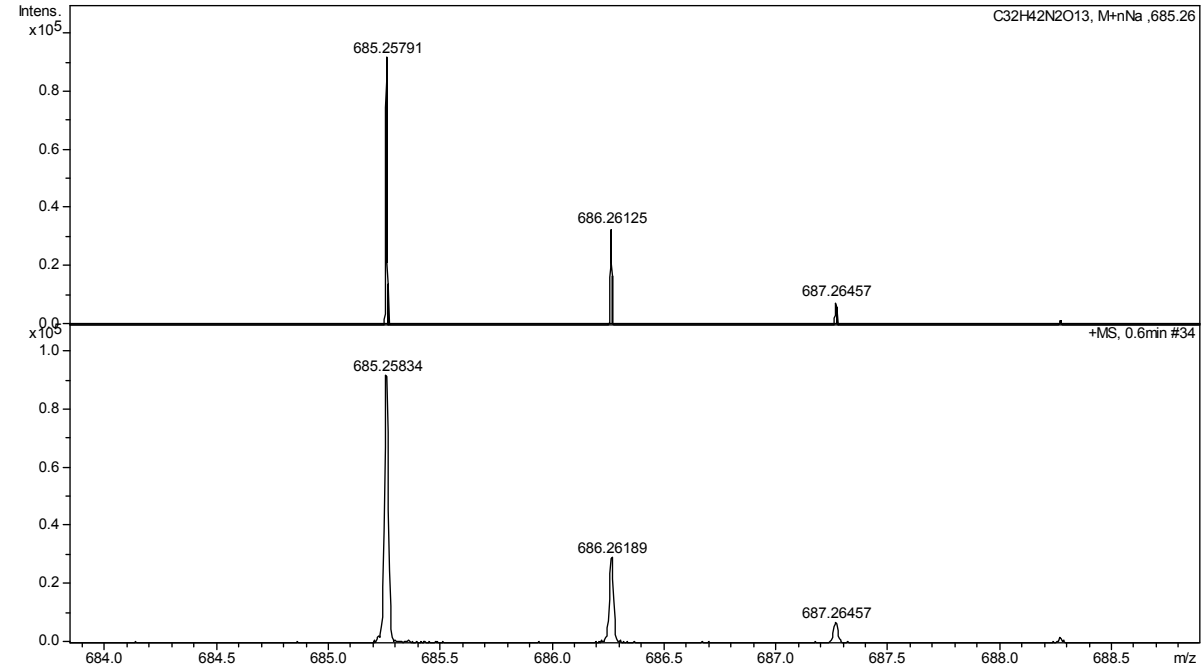
Compound **6a**

^{13}C NMR (101 MHz, $CDCl_3$)



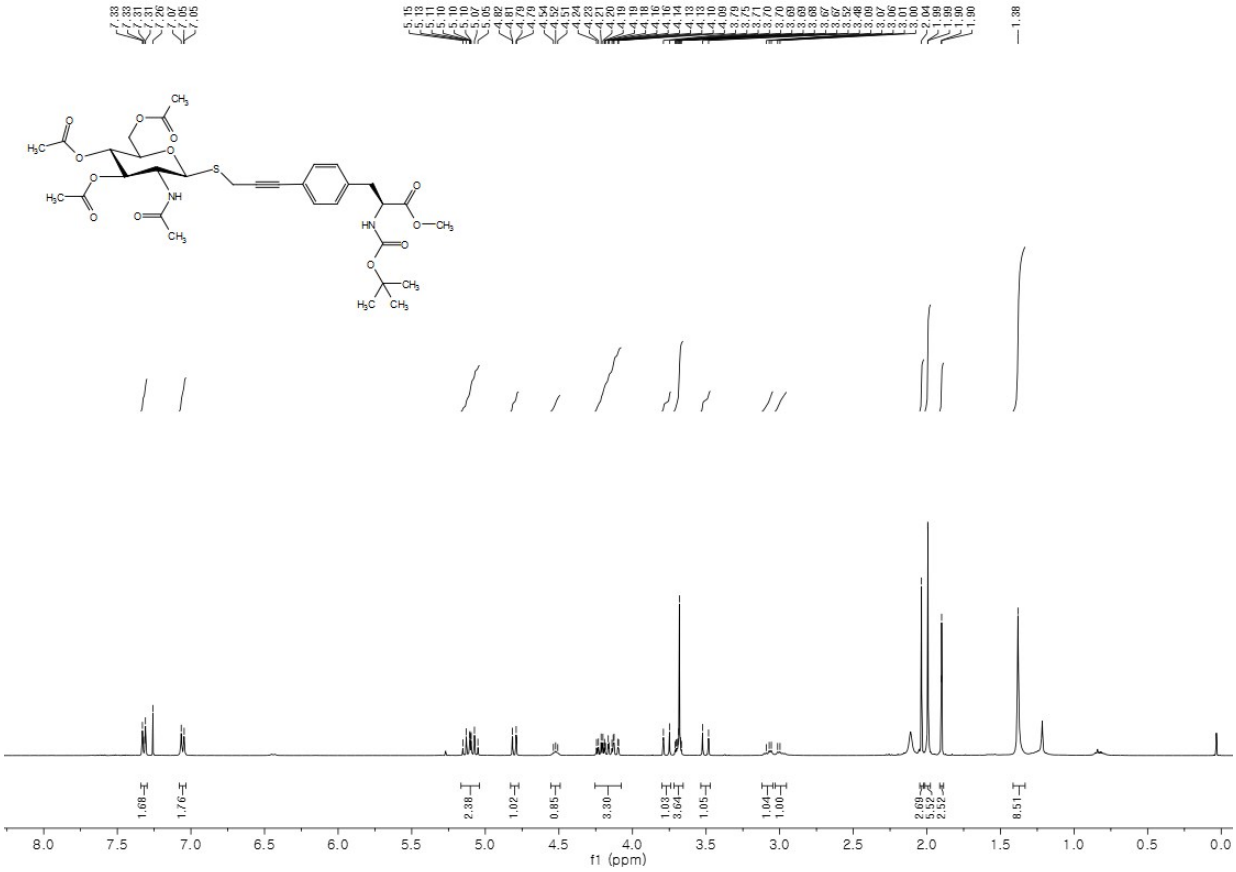
Compound **6a**

HRMS



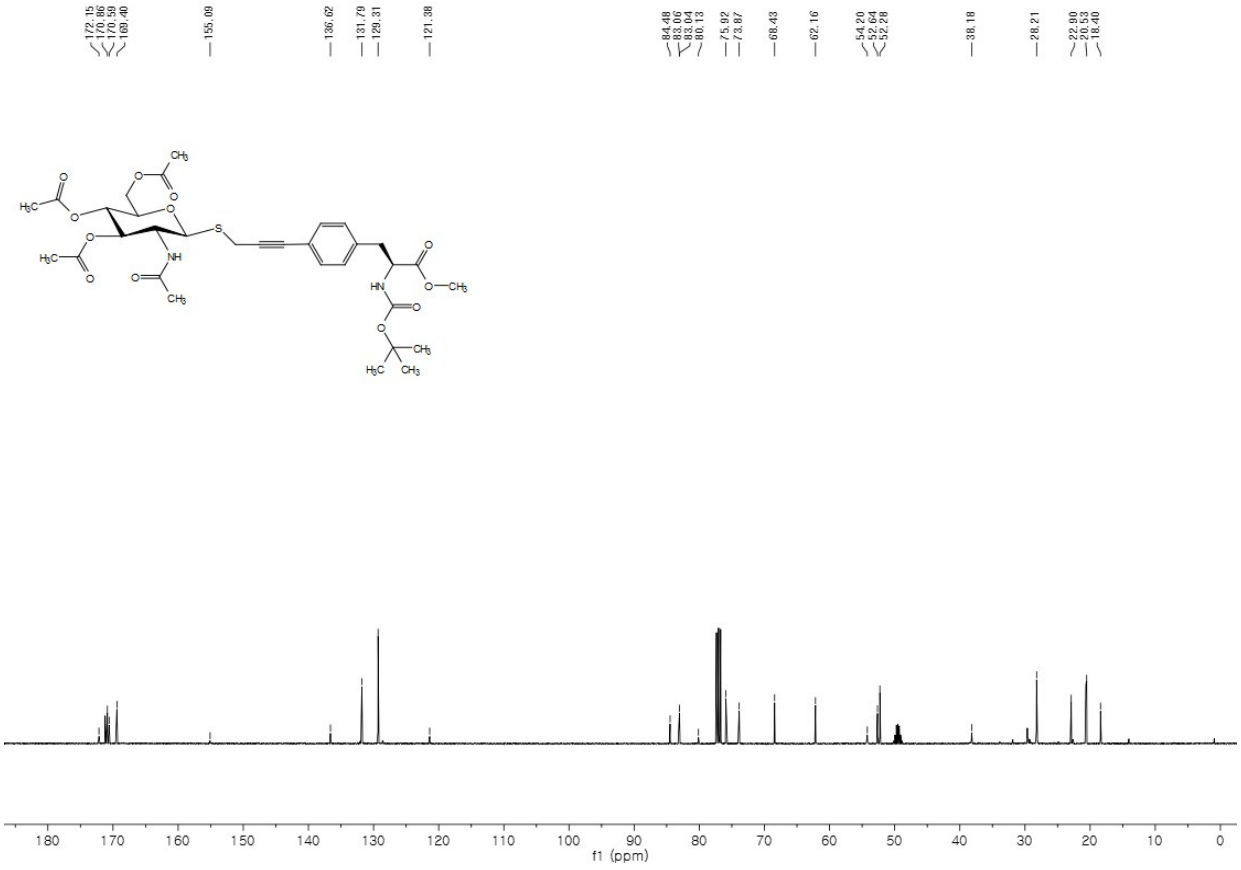
Compound **6b**

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

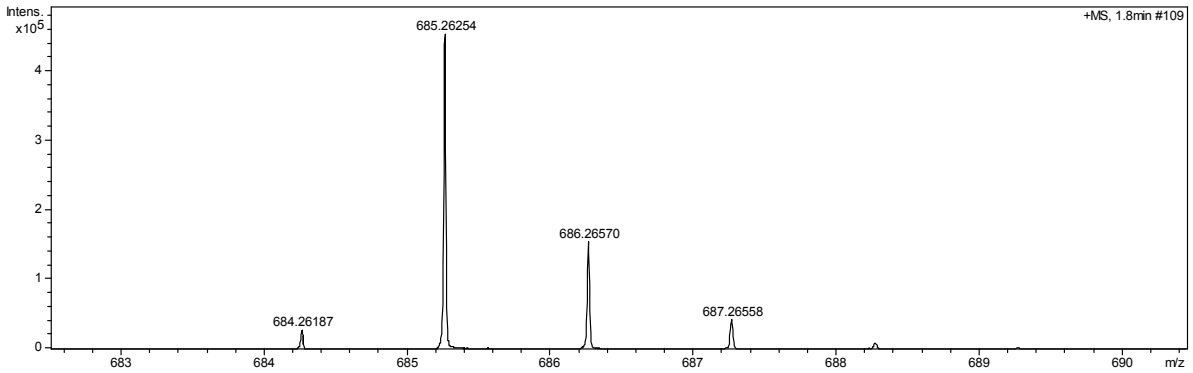


Compound **6b**

^{13}C NMR (101 MHz, $CDCl_3$)

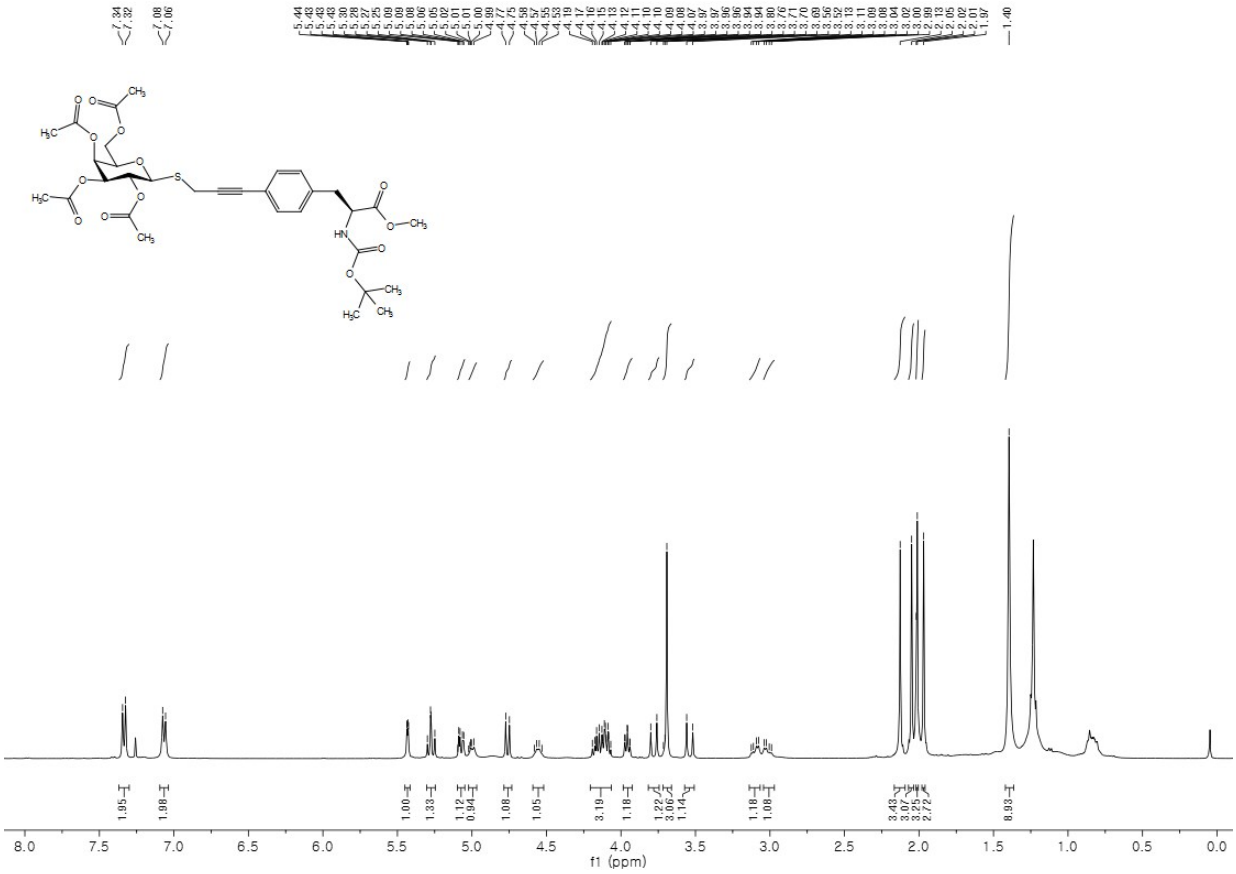


Compound **6b**
HRMS



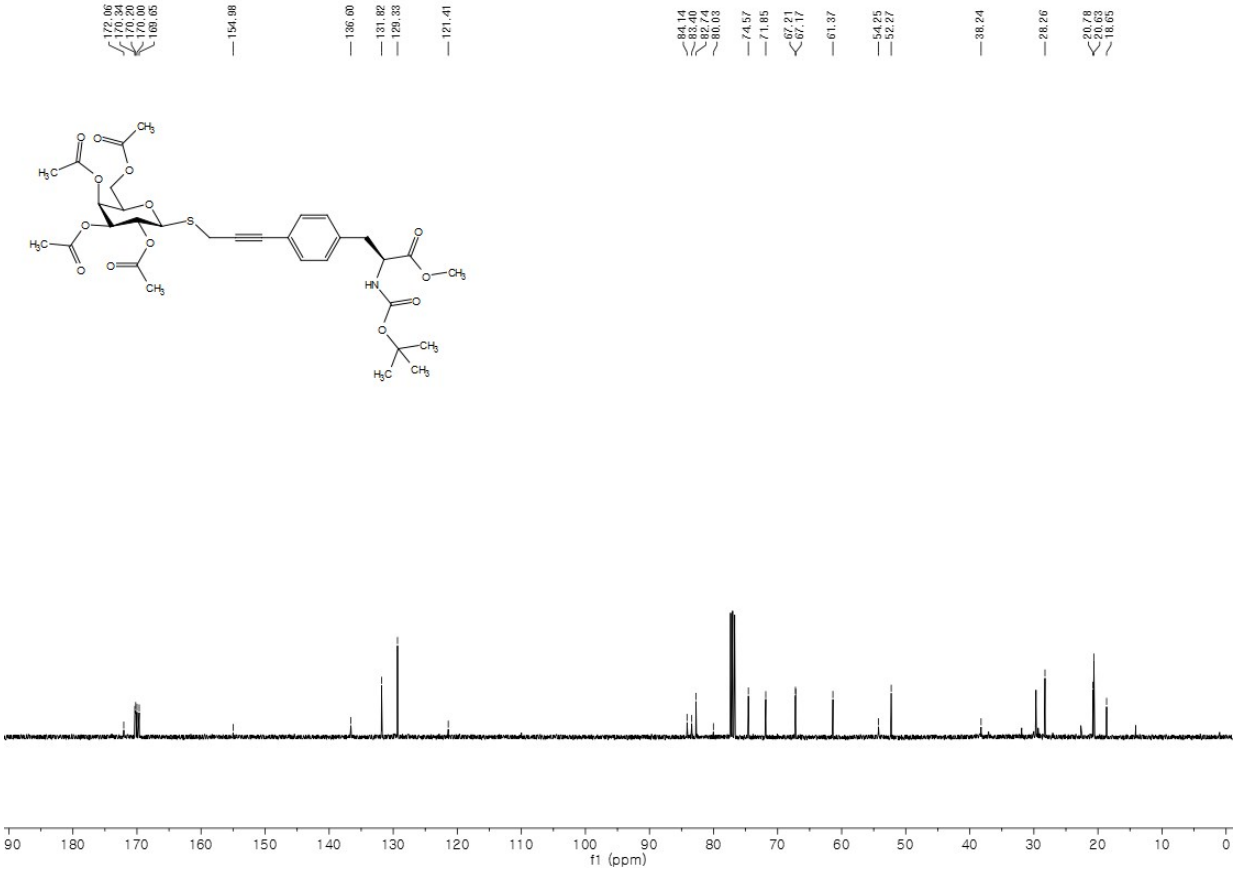
Compound **6c**

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



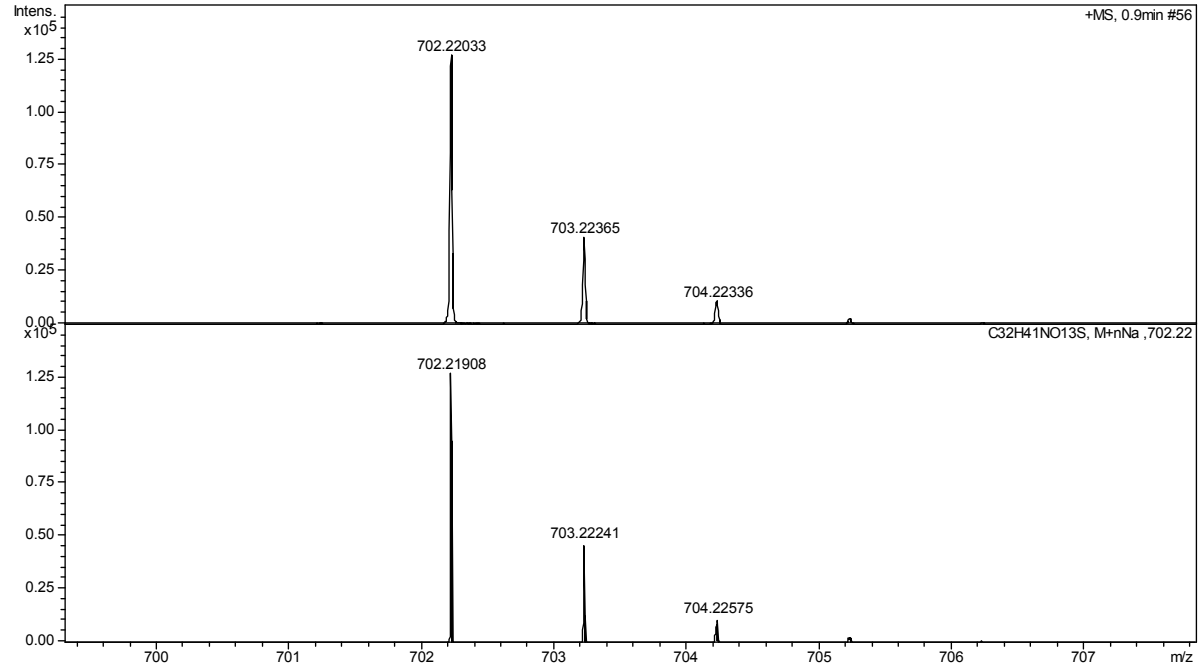
Compound **6c**

^{13}C NMR (101 MHz, $CDCl_3$)



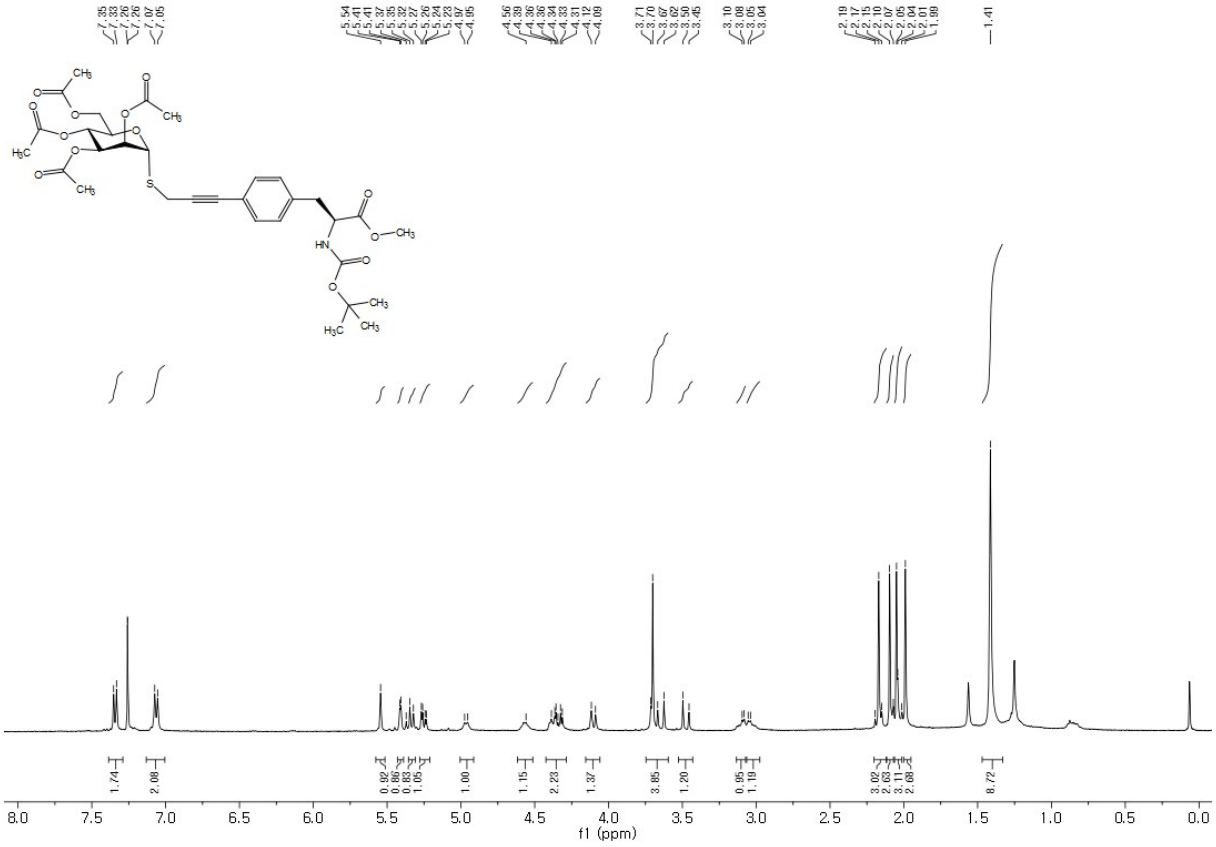
Compound **6c**

HRMS



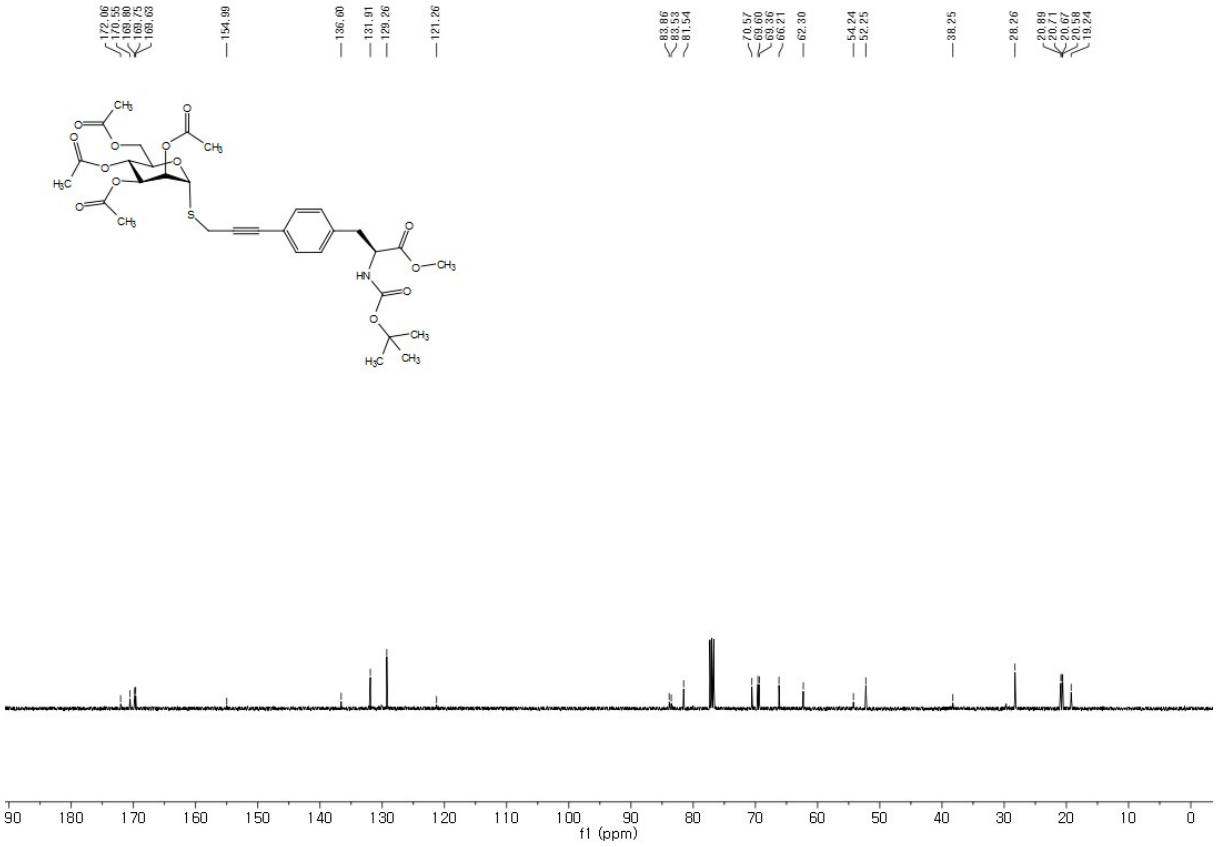
Compound **6d**

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



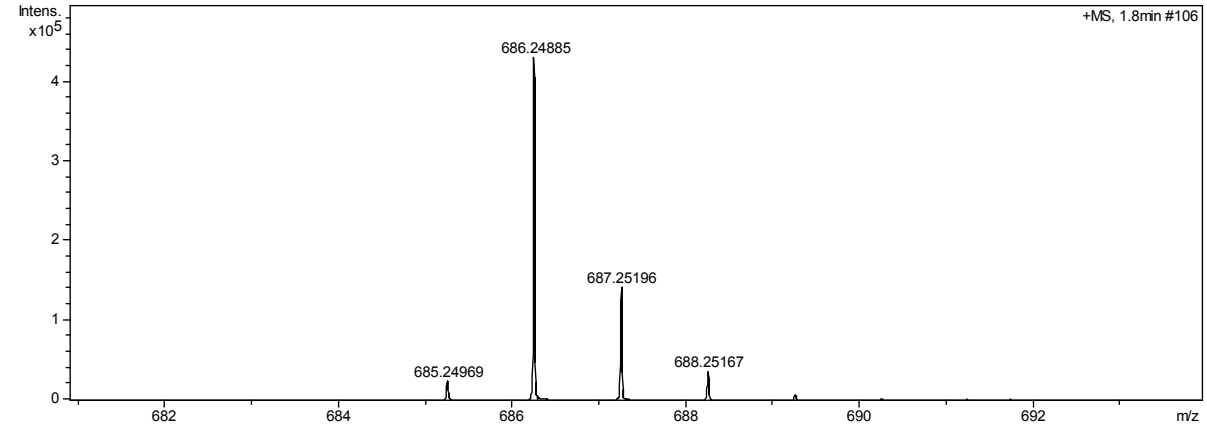
Compound **6d**

^{13}C NMR (101 MHz, $CDCl_3$)

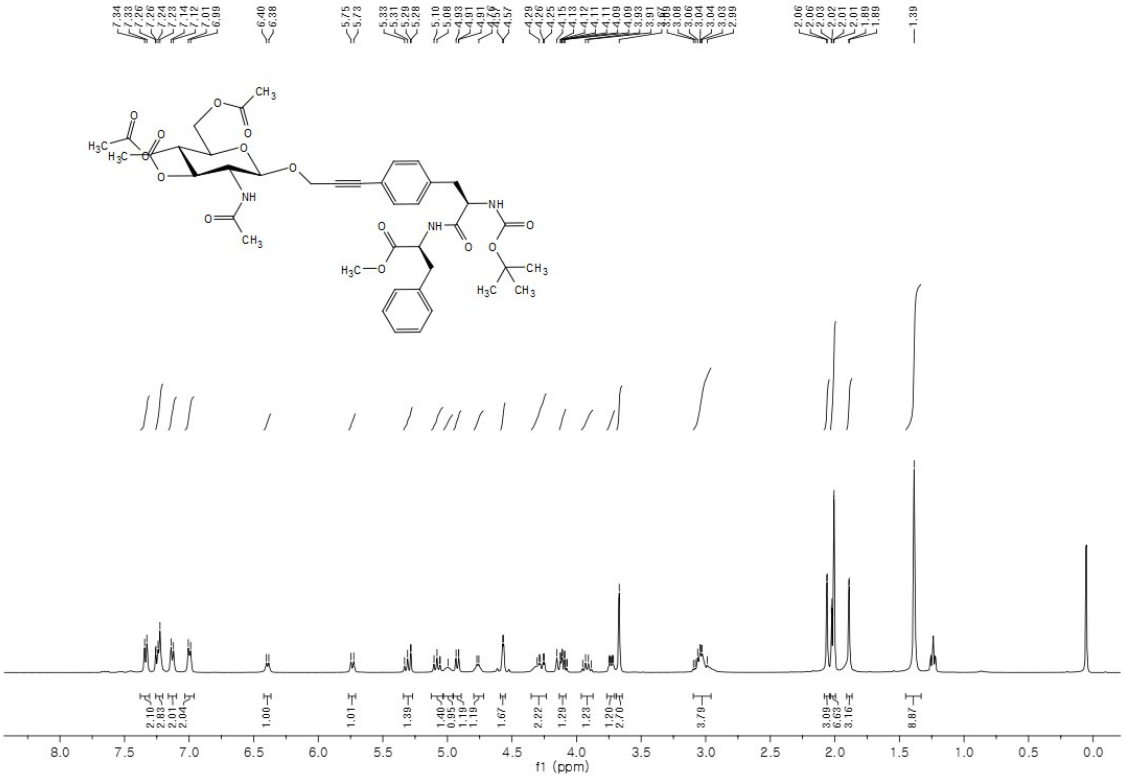


Compound **6d**

HRMS

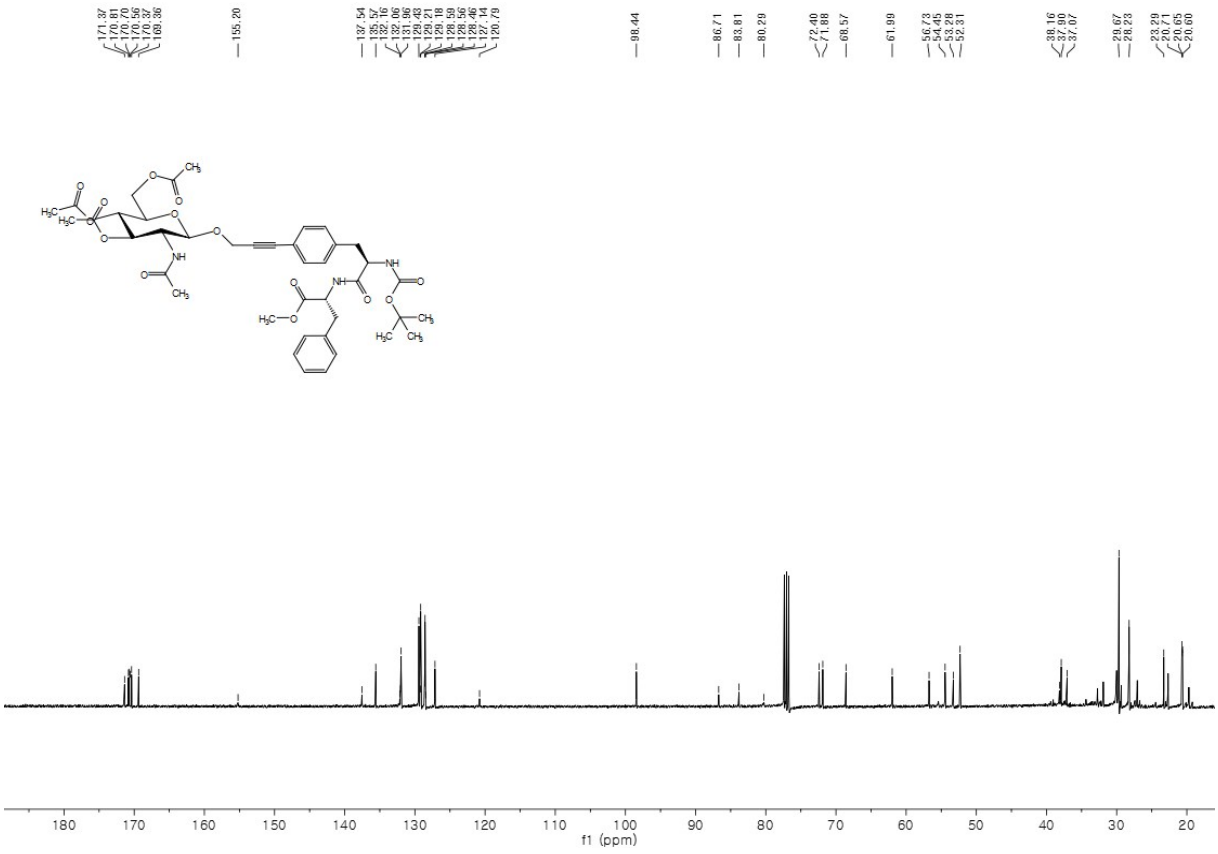


Compound **8a**
^{1}H NMR (400 MHz, $CDCl_3$)

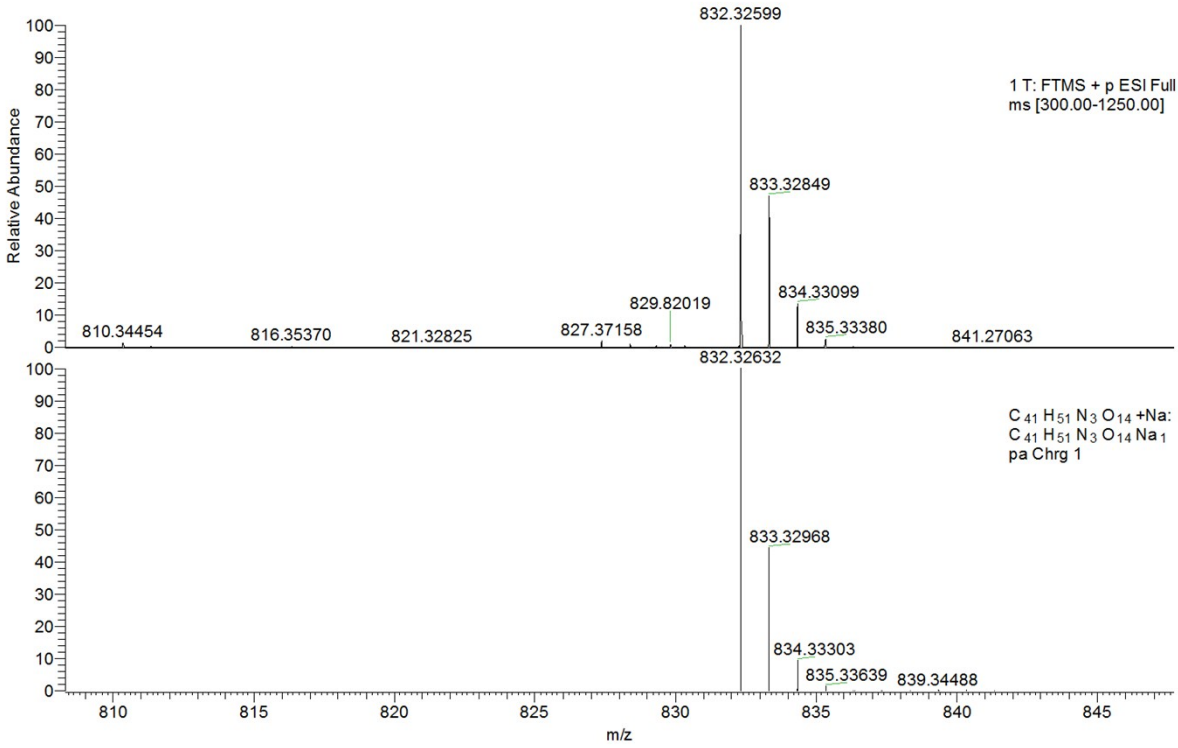


Compound **8a**

^{13}C NMR (101 MHz, $CDCl_3$)

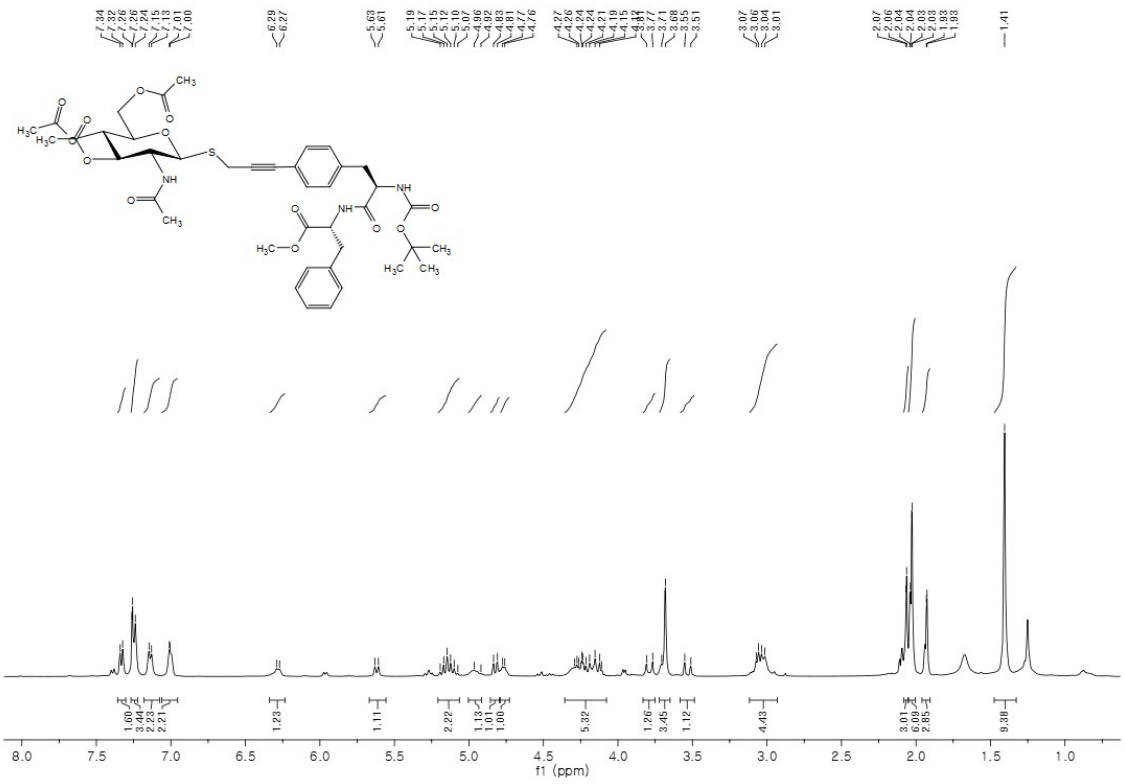


Compound **8a**
HRMS



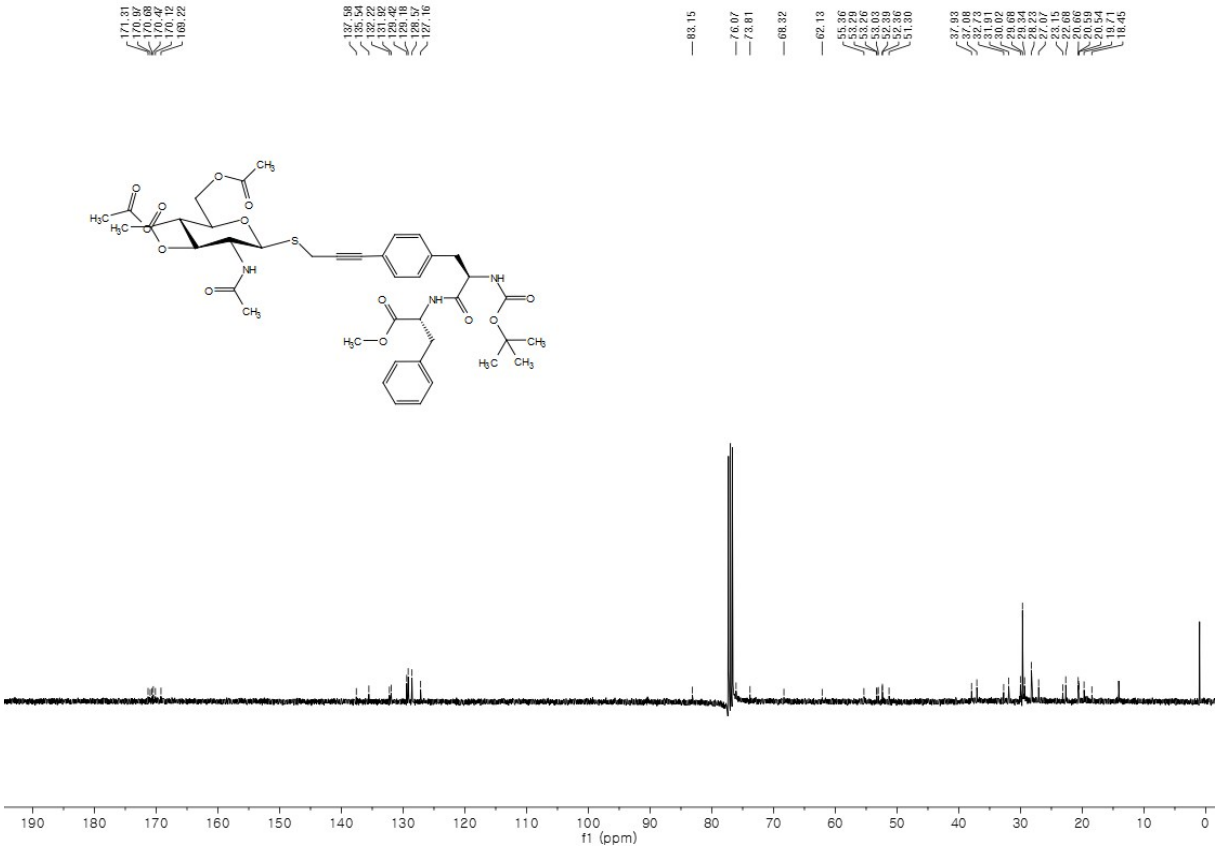
Compound **8b**

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

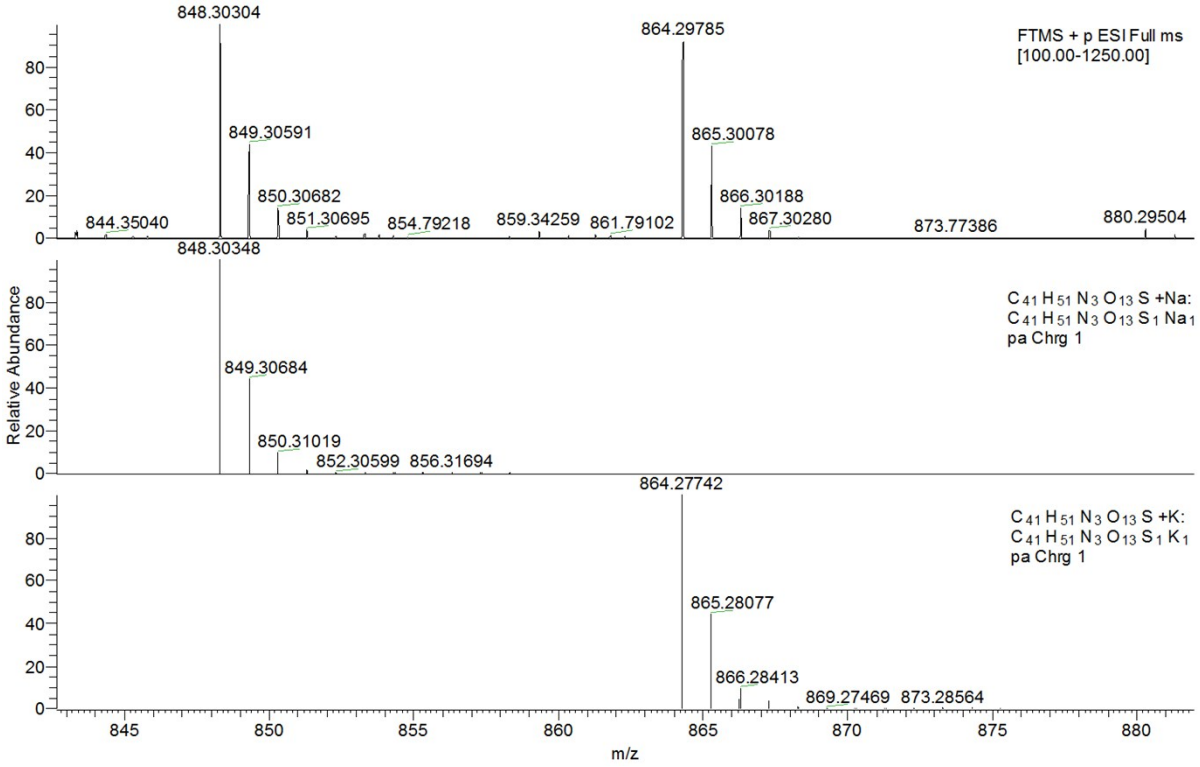


Compound **8b**

^{13}C NMR (101 MHz, $CDCl_3$)



Compound **8b**
HRMS



IV. References

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