Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Electrochemical Chemoselective Hydroxyl Group Transformation: Anthranilic Acyl modification of Tyrosine Bioconjugations

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Supporting Information

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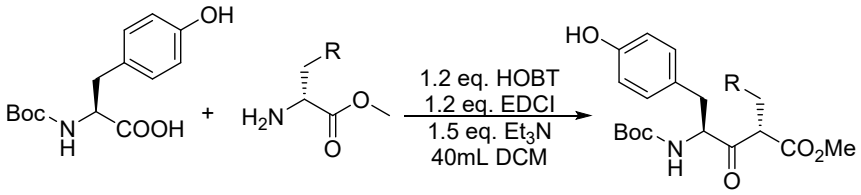
1. General Information

Unless otherwise stated, analytical grade solvents and commercially available reagents were used without further purification. All solvents were analytical reagent or better and were degassed prior to use. The instrument for electrolysis was dual display potentiostat (DJS-292B) (made in China). The anode electrode is platinum plate electrodes (Φ 6mm) and the cathode electrode is lead plate electrodes (15 mm×15 mm×0.3 mm). Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200-300 mesh silica gel in petroleum (boiling point is between 60-90℃). Gradient flash chromatography was conducted eluting with a continuous gradient from DCM to the indicated solvent, and they are listed as volume/volume ratios. High resolution mass spectra (HRMS) for polypeptides were measured with an Agilent 6224 instrument and accurate masses were reported for the molecular ion + Hydrogen (M+H) or molecular ion + Sodium (M+Na). The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Advance III (400 MHz) spectrometers with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. For ^{1}H NMR, chemical shifts (δ) were given in ppm relatives to internal standard (TMS at 0 ppm, $CDCl_3$ at 7.26 ppm, MeOH-d_4 at 3.31 ppm，DMSO-d_6 at 2.50 ppm). For ^{13}C-NMR, chemical shifts (δ) were reported in ppm using solvent as internal standard ($CDCl_3$ at 77.00 ppm, MeOH-d_4 at 49.00 ppm，DMSO-d6 at 39.50 ppm).

2. Synthesis of Starting Materials

2.1 Synthesis of starting materials dipeptides[1][2]

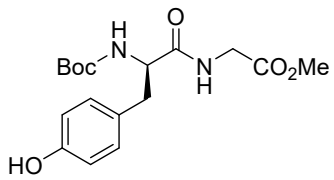


A 2.0 mmol

B 2.0 mmol

Dipeptides **2aa-2ag,2aj,2ak**

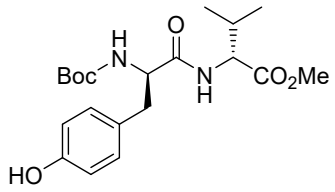
To a solution of Boc-L-tyrosine **A** (410 mg, 2.0 mmol, 1.0 equiv.) in 40 mL CH_2Cl_2 was added HOBT (1-hydroxybenzotriazole) (2.4 mmol), EDCI (1-ethyl-3(3-dimethylpropylamine) carbodiimide) (2.4 mmol) and peptide **B** (2.0 mmol). The mixture was stirred for 10 min at room temperature, and then triethylamine (3.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed 2M hydrochloric acid solution (40 mL x 3) and H_2O (40 mL x 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (DCM/MeOH) to afford corresponding dipeptides **2aa-2ag，2aj，2ak**.



2aa

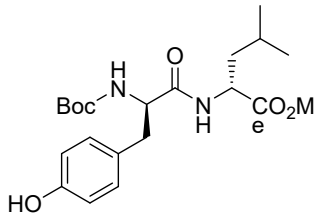
Dipeptide **2aa Boc-Tyr-Gly-OMe**, white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.65 (s, 1H), 7.54 (s, 1H), 6.99 (dt, *J* = 6.1, 0.8 Hz, 2H), 6.68 – 6.63 (m, 2H), 6.44 (d, *J* = 8.2 Hz, 1H), 4.40 (dt, *J* = 8.2, 5.6 Hz, 1H), 3.99 – 3.87 (m, 2H), 3.69 (s, 2H), 3.15 – 3.04 (m, 2H), 1.41 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-d) δ 172.25, 170.46, 156.17, 155.61, 130.62, 129.22, 115.74, 115.73, 79.37, 55.03, 52.28, 41.53, 37.72, 28.30.



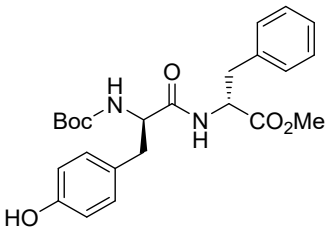
2ab

Dipeptide **2ab Boc-Tyr-Val-OMe**, white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (s, 1H), 7.52 (d, *J* = 9.5 Hz, 1H), 6.99 (dt, *J* = 6.0, 0.9 Hz, 2H), 6.65 (d, *J* = 6.0 Hz, 2H), 6.38 (d, *J* = 8.3 Hz, 1H), 4.49 (d, *J* = 8.4 Hz, 1H), 4.11 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.65 (s, 3H), 3.17 – 2.95 (m, 2H), 2.21 – 2.03 (m, 1H), 1.41 (s, 9H), 1.01 (d, *J* = 5.4 Hz,3H), 0.96 (d, *J* = 5.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.43, 172.16, 156.42, 154.83, 130.64, 130.49, 115.78, 79.34, 57.76, 55.37, 52.40, 37.75, 30.35, 28.29, 19.06，19.03.



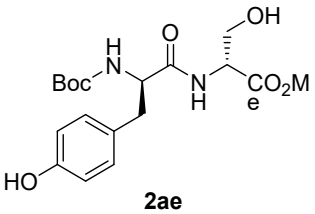
2ac

Dipeptide **2ac Boc-Tyr-Leu-OMe**, white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 (d, *J* = 10.4 Hz, 1H), 7.56 (s, 1H), 6.99 (dt, *J* = 6.0, 0.9 Hz, 2H), 6.68 – 6.62 (m, 2H), 6.38 (d, *J* = 8.3 Hz, 1H), 4.45 – 4.50 (m, 1H), 4.40 – 4.32 (m, 1H), 3.68 (s, 3H), 3.03 (qdt, *J* = 9.9, 5.7, 0.8 Hz, 2H), 1.69 – 1.55 (m, 3H), 1.41 (s, 9H), 0.90 (d, *J* = 5.1 Hz, 3H), 0.85 (d, *J* = 5.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.30, 172.00, 156.09, 154.82, 130.64, 130.49, 115.69, 115.67, 79.35, 55.57, 52.40, 51.33, 40.76, 37.75, 28.29, 24.44, 22.52, 22.46.



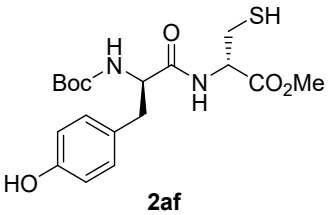
2ad

Dipeptide **2ad Boc-Tyr-Phe-OMe**, white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 (d, *J* = 11.3 Hz, 1H), 7.57 (s, 1H), 7.26 (dd, *J* = 1.7, 0.8 Hz, 2H), 7.25 – 7.22 (m, 3H), 7.02 (dt, J = 6.1, 0.8 Hz, 2H), 6.66 (d, *J* = 6.1 Hz, 2H), 6.34 (d, *J* = 8.2 Hz, 1H), 4.59 (dt, *J* = 9.0, 5.6 Hz, 1H), 4.49 (dt, *J* = 9.0, 5.6 Hz, 1H), 3.69 (s, 3H), 3.09 – 2.92 (m, 4H), 1.41 (s, 9H). ^{13} 13C NMR (101 MHz, Chloroform-d) δ 171.74, 171.32, 156.09, 154.80, 136.71, 130.80, 130.55, 129.27, 129.18, 128.63, 127.01, 115.63, 79.39, 55.59, 53.79, 52.39, 37.76, 37.74, 28.29.



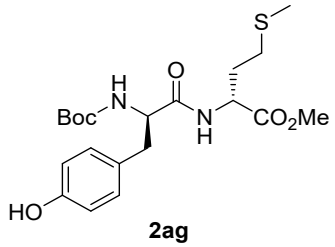
2ae

Dipeptide **2ae Boc-Tyr-Ser-OMe,** white solid, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (s, 1H), 7.51 (d, *J* = 9.6 Hz, 1H), 6.99 (dt, *J* = 6.0, 0.9 Hz, 2H), 6.67 (d, *J* = 6.0 Hz, 2H), 6.42 (d, *J* = 8.2 Hz, 1H), 4.50 (dt, *J* = 8.2, 5.6 Hz, 1H), 4.33 – 4.26 (m, 1H), 4.25 (s, 1H), 3.78 (td, *J* = 5.6, 2.1 Hz, 2H), 3.69 (s, 3H), 3.12 – 3.00 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.28, 170.96, 156.22, 154.83, 130.58, 115.70, 79.34, 64.84, 55.57, 54.42, 52.61, 37.75, 28.28.



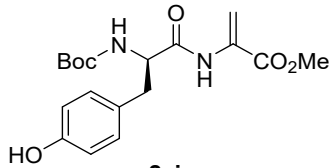
2af

Dipeptide **2af Boc-Tyr-Cys-OMe,** white solid, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 6.99 (dd, *J* = 6.4, 2.2 Hz, 2H), 6.65 (d, *J* = 6.0 Hz, 2H), 6.42 (d, *J* = 8.2 Hz, 1H), 4.52 – 4.44 (m, 2H), 3.72 (s, 3H), 3.15 – 2.99 (m, 2H), 2.89 (s, 1H), 2.84 – 2.68 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.78, 171.95, 156.22, 154.83, 130.86, 130.49, 115.73, 79.32, 55.56, 53.97, 52.37, 37.75, 29.69, 28.29.



2ag

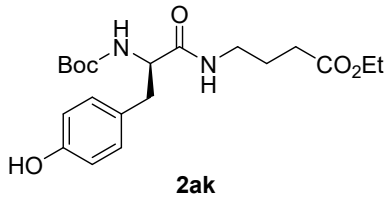
Dipeptide **2ag Boc-Tyr-Met-OMe,** light yellow solid, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.62 (d, *J* = 8.5 Hz, 1H), 7.54 (s, 1H), 6.98 (dd, *J* = 6.0, 2.0 Hz, 2H), 6.66 (d, *J* = 6.0 Hz, 2H), 6.41 (d, *J* = 8.2 Hz, 1H), 4.49 (dt, *J* = 8.2, 5.6 Hz, 1H), 4.26 (dt, *J* = 8.8, 5.6 Hz, 1H), 3.69 (s, 3H), 3.07 – 2.98 (m, 2H), 2.69 – 2.55 (m, 2H), 2.07 (s, 3H), 2.11 – 1.93 (m, 2H), 1.42 (s, 9H).^{13}C NMR (101 MHz, Chloroform-d) δ 173.06, 171.99, 156.08, 154.82, 130.64, 129.95, 115.64, 79.39, 52.47, 51.59, 37.74, 31.04, 30.82, 28.29, 14.78.



2aj

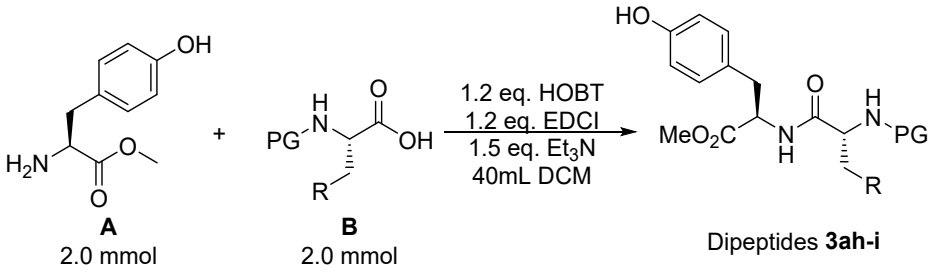
Dipeptide **2aj Methyl (*R*)-2-(2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)acrylate,** white solid, ^{1}H NMR (400 MHz, Chloroform-d) δ 8.99 (s, 1H), 7.55 (s, 1H), 6.99 (dd, *J* = 6.0, 2.0 Hz, 2H), 6.69 (d, *J* = 6.0 Hz, 2H), 6.43 (s, 1H), 5.91 (d, *J* = 2.0 Hz, 1H), 5.32 (d, *J* = 2.0 Hz, 1H), 4.49 (dt, *J* = 8.2, 5.6 Hz, 1H), 3.78 (s, 3H), 3.13 – 3.01 (m, 2H), 1.41 (s, 9H=).

^{13}C NMR (101 MHz, Chloroform-d) δ 170.66, 165.58, 156.37, 155.34, 134.51, 130.72, 129.22, 115.70, 108.56, 79.34, 55.22, 52.34, 37.66, 28.31.



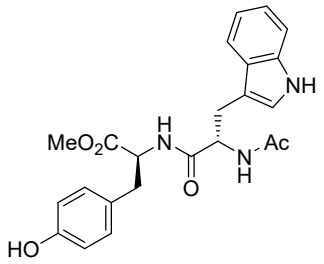
2ak

Dipeptide **2ak Ethyl (*R*)-4-(2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)butanoate,** white solid**,** ^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (s, 1H), 7.42 (s, 1H), 6.99 (dt, *J* = 6, 0.9 Hz, 2H), 6.65 (d, *J* = 6.1 Hz, 2H), 6.26 (d, *J* = 8.2 Hz, 1H), 4.38 (dt, *J* = 8.2, 5.6 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.32 – 3.17 (m, 2H), 3.01 – 2.85 (m, 2H), 2.37 (td, *J* = 5.7, 2.0 Hz, 2H), 1.82 – 1.66 (m, 2H), 1.41 (s, 9H), 1.22 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.13, 172.17, 156.42, 155.62, 130.64, 130.49, 115.77, 79.34, 60.23, 54.94, 39.98, 37.74, 32.23, 28.29, 25.17, 14.19.



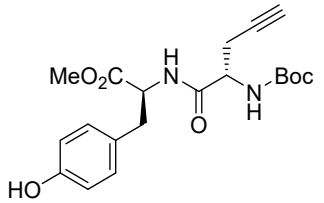
In a round bottomed flask, equipped with a stir bar, peptide **A** (2.0 mmol), HOBT (1-hydroxybenzotriazole) (2.4 mmol), EDCI (1-ethyl-3(3-dimethylpropylamine) carbodiimide) (2.4 mmol) (2.4 mmol), dichloromethane (40 mL) and peptide **B** (2.0 mmol) were combined and added. The mixture was stirred for 10 min at room temperature, and then, triethylamine (3.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed by saturated 2 M hydrochloric acid solution (40 mL x 3) and H_2O (40 mL x 3).

The organic layers were combined, dried over Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (DCM/ MeOH) to afford corresponding dipeptides **2ah-i**.



2ah

Dipeptide **2ah Ac-Trp-Try-OMe,** lignt yellow solid, ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.60 (dd, *J* = 5.8, 1.4 Hz, 1H), 7.55 (s, 1H), 7.34 (dd, *J* = 6.0, 1.3 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.07 (td, *J* = 5.9, 1.3 Hz, 1H), 7.01 (dt, *J* = 6.0, 0.9 Hz, 2H), 6.68 – 6.62 (m, 2H), 4.62 – 4.50 (m, 2H), 3.68 (s, 3H), 3.18 (d, *J* = 5.6 Hz, 2H), 3.01 (qdt, *J* = 9.8, 5.6, 0.7 Hz, 2H), 1.91 (s, 3H).. ^{13}C NMR (101 MHz, Chloroform-d) δ 172.40, 171.97, 171.29, 156.09, 136.71, 131.54, 129.91, 127.73, 123.46, 121.78, 120.03, 118.64, 115.66, 112.31, 110.09, 54.23, 53.68, 52.36, 37.33, 28.33, 22.61.

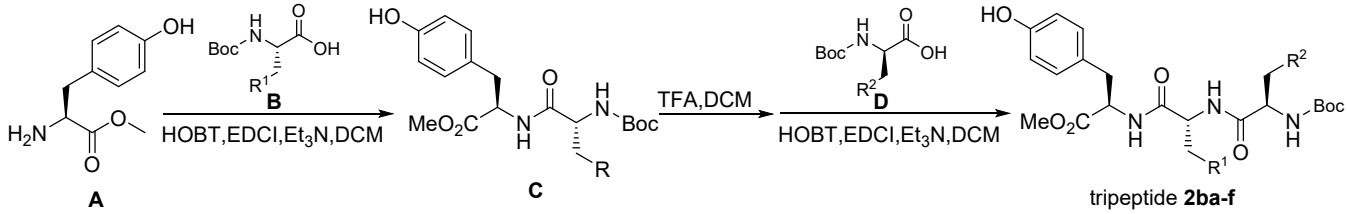


2ai

Dipeptide **2ai Methyl ((*S*)-2-((tert-butoxycarbonyl)amino)pent-4-ynoyl)-L-tyrosinate,** white solid, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.80 (d, J = 9.0 Hz, 1H), 7.55 (s, 1H), 7.01 (dt, J = 6.0, 0.9 Hz, 2H), 6.64 (d, J = 6.0 Hz, 2H), 6.32 (d, J = 7.4 Hz, 1H), 4.56 – 4.50 (m, 1H), 4.47 – 4.39 (m, 1H), 3.67 (s, 3H), 3.02 – 2.99 (m, 2H), 2.74 – 2.61 (m, 3H), 1.41 (s, 9H). ^{13}C NMR (101

MHz, Chloroform-d) δ 171.63, 171.42, 156.42,155.09, 131.39, 129.98, 115.72, 80.61, 79.34, 73.04, 53.67, 53.04, 52.36, 37.3, 28.28, 24.03.

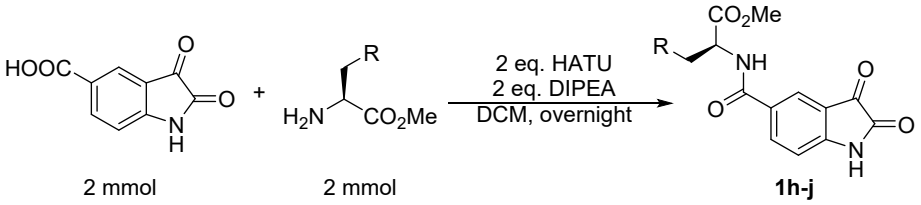
2.2 Synthesis of starting materials tripeptides [3]



In a round bottomed flask, equipped with a stir bar, peptide **A** (2 mmol), HOBT (1-hydroxybenzotriazole) (2.4 mmol), EDCI (1-ethyl-3(3-dimethylpropylamine) carbodiimide) (2.4 mmol) (2.4 mmol), dichloromethane (40 mL) and peptide **B** (2.0 mmol) were combined and added. The mixture was stirred for 10 min at room temperature, and then, triethylamine (3.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed by saturated 2 M hydrochloric acid solution (40 mL x 3) and H_2O (40 mL x 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (DCM/MeOH) to afford corresponding dipeptide **C**. To a solution of dipeptide **C** (2.0 mmol) in dichloromethane (18 mL) at 0 °C was added trifluoroacetic acid (2 mL) to give a 10% solution. The reaction was stirred 6 h at room temperature. After removing the solvent in rotary evaporator, the product was obtained as white solid after freeze drying. Then, to a solution of the product in DCM (30 mL) was added HOBT (1-hydroxybenzotriazole) (2.4 mmol), EDCI (1-ethyl-3(3-dimethylpropylamine) carbodiimide) (2.4 mmol) (2.4 mmol) and peptide **D** (2.0 mmol). After 10 min, triethylamine (3.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed by saturated 2 M hydrochloric acid solution (40 mL x 3) and H_2O (40 mL x 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. The resulting crude

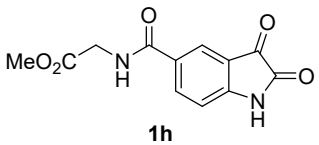
product was purified by flash chromatography (DCM/MeOH) to afford corresponding tripeptide **2ba-f**.

2.3 Synthesis of Isatin derivatives [4]



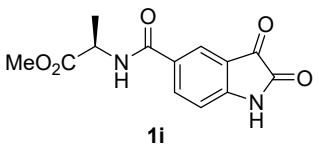
2 mmol 2 mmol **1h-j**

Amino acid (2.0 mmol), HATU (3.0 mmol) and DIPEA (3.0 mmol) were dissolved in DCM (20 mL) and the solution was stirred at 0 °C under an argon atmosphere for 10 min. Then, 2,3-Dioxoindoline-5-carboxylic Acid (2.0 mmol) in DCM (10 mL) was added dropwise, and the reaction mixture was stirred overnight at 0 °C to room temperature. The solvent was removed by reduced pressure, and the crude product was purified by silica gel chromatography with CH_2Cl_2/MeOH to get the product **1h-j**.



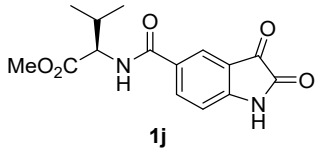
1h

^{1}H NMR (400 MHz, Chloroform-d) δ 8.78 (s, 1H), 8.29 (d, *J* = 6.9 Hz, 1H), 8.13 (d, *J* = 1.3 Hz, 1H), 8.07 (dd, *J* = 6.0, 1.2 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 4.10 – 4.01 (m, 2H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 183.96, 170.65, 167.06, 160.54, 148.87, 130.31, 129.92, 125.37, 121.69, 112.46, 52.36, 41.97.



1i

^{1}H NMR (400 MHz, Methanol-d4) δ 8.10 (d, *J* = 1.2 Hz, 1H), 8.06 (dd, *J* = 6.0, 1.2 Hz, 1H), 7.90 (d, *J* = 6.2 Hz, 1H), 7.62 (d, *J* = 4.8 Hz, 1H), 4.31 (dq, *J* = 7.8, 5.4 Hz, 1H), 3.67 (s, 3H), 1.38 (d, *J* = 5.4 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d4) δ 183.60, 173.02, 166.92, 161.76, 148.92, 130.30, 129.80, 126.13, 121.27, 112.60, 52.58, 48.78, 17.77.



1j

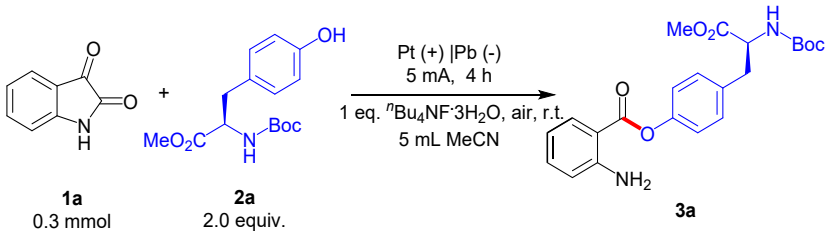
^{1}H NMR (400 MHz, Methanol-d4) δ 8.09 – 8.02 (m, 1H), 7.92 – 7.79 (m, 1H), 6.97 (dd, J = 21.8, 8.2 Hz, 1H), 4.49 – 4.45 (m, 1H), 3.75 (s, 3H), 2.28 – 2.21 (m, 1H), 1.02 (dd, J = 11.5, 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Methanol-d4) δ 183.37, 172.46, 167.37, 160.07, 153.03, 128.82, 123.90, 123.40, 117.69, 111.91, 58.88, 51.27, 30.34, 18.30, 17.88.

3. General Procedure

3.1 Reaction optimization

In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, isatin (0.3 mmol), Tyrosine residue (0.6 mmol) and $^{n}Bu_4NF{\cdot}3H_2O$ (0.3 mmol) were combined and added. Then, solvent (6 mL) were injected into the tubes via syringes. The bottle was equipped with platinum plate (15 mm×15 mm×0.3 mm) as the anode and plumbum plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current under room temperature. When the reaction was finished, the solvent was removed by reduced pressure and the crude product was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate= 5:1). A summary of optimization results is presented in **Table S1** below.

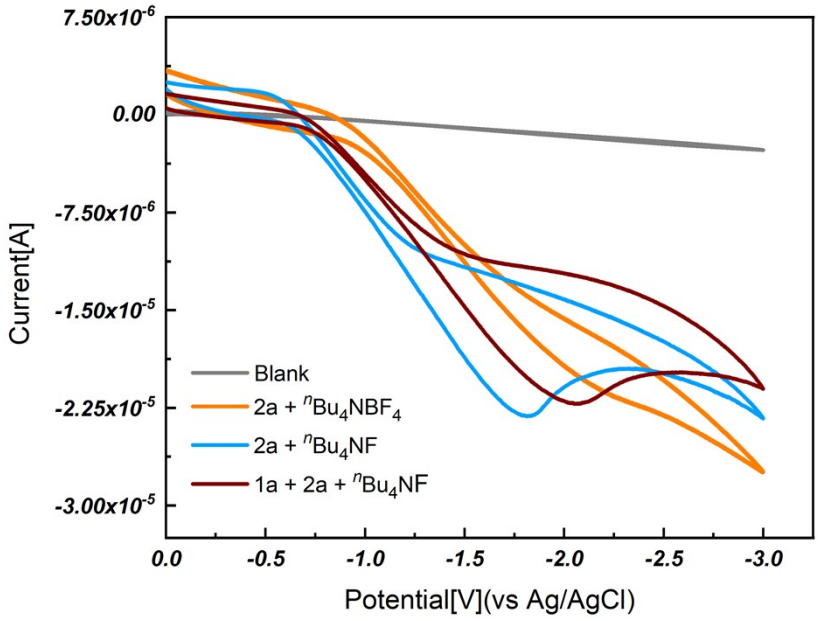
Table S1. Investigation of the reaction conditions



Entry	Variation from Standard Conditions[a]	Yield (%)
1	none	75
2	5 mL CH_3CN, 1 mL PBS was used	67
3	CH_2Cl_2 as the solvent	Trace
4	Acetone as the solvent	45
5	DMF as the solvent	N.D.
6	$^nBu_4NPF_6$ instead of $^nBu_4NF{\cdot}3H_2O$	N.D.
7	$^nBu_4NBr$ instead of $^nBu_4NF{\cdot}3H_2O$	N.D
8	3 mA, 360 min	60
9	10 mA, 120 min	55
10	20 mA, 60 min	47

[a]Reaction conditions: platinum plate anode (15 mm×15 mm×0.3 mm), plumbum plate cathode, (15 mm×15 mm×0.3 mm), constant current = 5 mA, **1a** (0.3 mmol), **2a** (2.0 equiv.), **$^nBu_4NF{\cdot}3H_2O$** (1.0 equiv.), 5 mL MeCN, undivided cell, 4 h. Yields of isolated products are shown. N.D. = Not Detected.

3.2 General procedure for cyclic voltammetry (CV)



Cyclic voltammetry was performed in a three-electrode cell connected to a schlenk line at room temperature. The working electrode was a steady glassy carbon disk electrode, the counter electrode was a platinum wire. The reference was an Ag/AgCl electrode submerged in saturated aqueous KCl solution and separated from a reaction by a salt bridge. The cyclic voltammetry (CV) experiments on 0.015 M $^{n}Bu_4NF$ or $^{n}Bu_4NBF_4$ with 0.003 M **2a, 2af** and **2ac** were performed, respectively. The scan rate is 0.1 V/s. The positive scan range was from 0 V to -3.0 V.

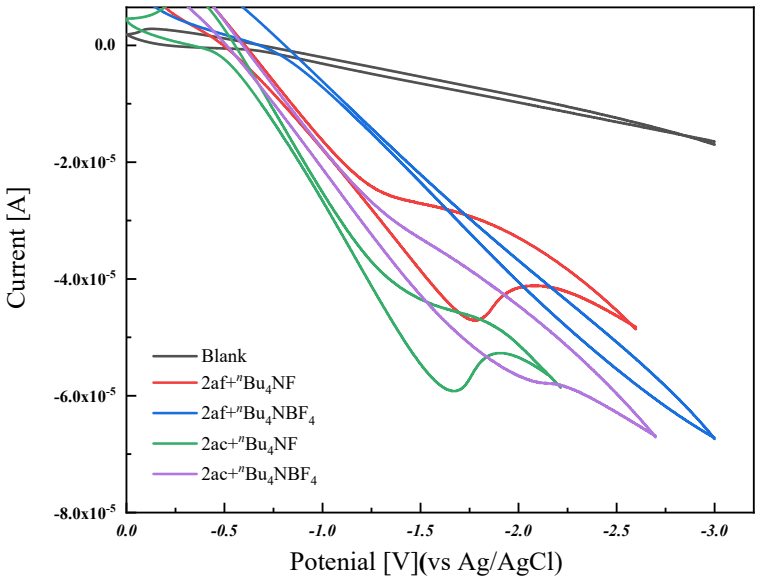
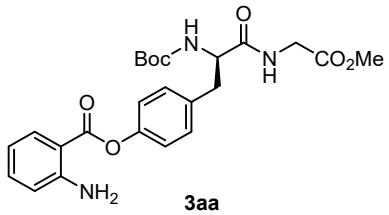


Figure S1. As shown in this graphic, the cyclic voltammograms showed irreversible reduction waves.

3.3 Dipeptides scope and characterization

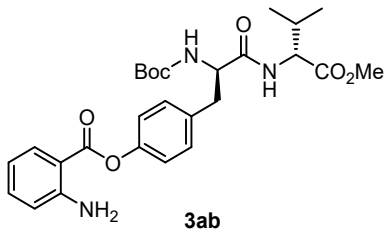
General procedure for product (3aa-k): In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, isatin (0.3 mmol), dipeptide (0.6 mmol) and $^{n}Bu_4NF{\cdot}3H_2O$ (0.3 mmol) were combined and added. Then, CH_3CN (6 mL) were injected into the tubes via syringes. The bottle was equipped with platinum plate (15 mm×15 mm×0.3 mm) as the anode and plumbum plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at a constant current of 5 mA under room temperature for 4 h. After completion of the reaction, as indicated by TLC and LC-MS, the pure product was obtained by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate).

Detailed descriptions for products:



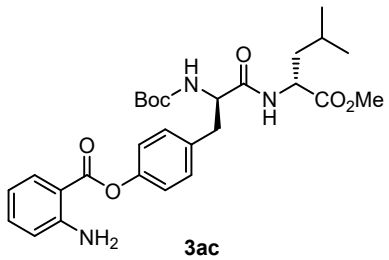
3aa

(*R*)-4-(2-((tert-butoxycarbonyl)amino)-3-((2-methoxy-2-oxoethyl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3aa): light yellow oil (Yield: 60 %, 84.78 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.99 (dd, J = 8.3, 1.3 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.20 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.64 (dd, J = 7.9, 5.6 Hz, 2H), 6.49 (s, 1H), 5.69 (s, 2H), 4.99 (s, 1H), 4.37 (s, 1H), 3.93 (qd, J = 18.3, 5.4 Hz, 2H), 3.67 (s, 3H), 3.05 (d, J = 6.4 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.46, 169.89, 166.78, 155.47, 151.27, 149.79, 134.92, 134.08, 131.58, 130.41, 122.19, 116.80, 116.43, 109.57, 80.47, 55.54, 52.40, 41.22, 37.60, 28.29. HRMS (ESI) cald. for $(M+H)^+$ $C_{24}H_{30}N_3O_7$: 472.2078 found, 472.2075.



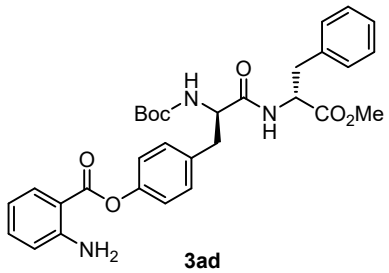
3ab

4-((*R*)-2-((tert-butoxycarbonyl)amino)-3-(((*R*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amin-o)-3-oxopropyl)phenyl 2-aminobenzoate (3ab): light yellow oil (Yield: 63 %, 96.97 mg) , ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 9.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.77 – 6.57 (m, 2H), 6.43 (d, J = 8.1 Hz, 2H), 5.68 (s, 2H), 4.98 (s, 1H), 4.41 (d, J = 13.6 Hz, 1H), 4.30 (d, J = 6.9 Hz, 1H), 3.64 (s, 3H), 3.04 (d, J = 6.7 Hz, 2H), 2.06 (dq, J = 13.5, 6.8 Hz, 1H), 1.37 (s, 9H), 0.81 (dd, J = 11.3, 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.84, 171.08, 166.73, 155.48, 151.28, 149.77, 134.90, 134.13, 131.55, 130.42, 122.15, 116.80, 116.41, 109.58, 80.40, 57.30, 55.80, 52.16, 37.19, 31.29, 28.29, 18.87, 17.79. HRMS (ESI) cald. for (M+H)+ $C_{27}H_{36}N_3O_7$: 514.2548 found, 514.2547.



3ac

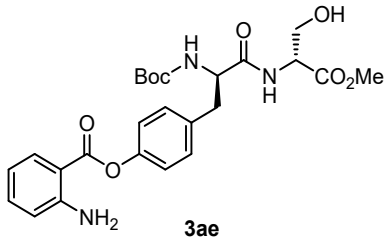
4-((*R*)-2-((tert-butoxycarbonyl)amino)-3-(((*R*)-1-methoxy-4-methyl-1-oxopentan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3ac): light yellow oil (Yield: 65 %, 102.68 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 (d, J = 8.2 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.62 (dd, J = 7.8, 4.5 Hz, 2H), 6.36 (d, J = 7.6 Hz, 1H), 5.67 (s, 2H), 5.02 (d, J = 6.1 Hz, 1H), 4.54 – 4.47 (m, 1H), 4.30 (d, J = 6.1 Hz, 1H), 3.63 (s, 3H), 3.02 (d, J = 6.6 Hz, 2H), 1.56 – 1.40 (m, 3H), 1.36 (s, 9H), 0.84 (t, J = 5.2 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.89, 170.95, 166.72, 155.44, 151.31, 149.77, 134.88, 134.11, 131.54, 130.46, 128.81, 122.11, 116.80, 116.37, 109.54, 80.36, 55.57, 52.29, 50.80, 41.49, 37.32, 28.27, 24.68, 22.77, 21.87.HRMS (ESI) cald. for (M+H)+ $C_{28}H_{38}N_3O_7$: 528.2704 found, 528.2706.



3ad

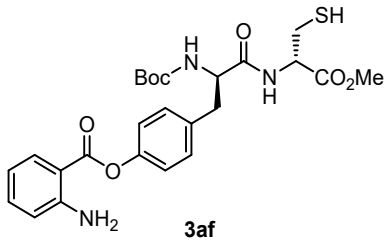
4-((*R*)-2-((tert-butoxycarbonyl)amino)-3-(((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3ad): white oil (Yield: 55 %, 92.67 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (dd, J = 1.4, 8.3 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.20 – 7.15 (m, 5H), 7.03 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 6.3 Hz, 2H), 6.63 (dd, J = 7.8, 6.3 Hz, 2H), 6.31 (d, J = 7.6 Hz, 1H), 5.69 (s, 2H), 4.92 (s, 1H), 4.72 (q, J = 6.2 Hz, 1H), 4.27 (d, J = 5.8 Hz, 1H), 3.62 (s, 3H), 2.99 (tt, J = 13.7, 7.1 Hz, 4H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.44, 170.75, 166.72, 155.32, 151.28, 149.79, 135.66, 134.92, 134.01, 131.55, 130.44, 129.26, 128.63, 127.18, 122.17, 116.81, 116.41, 109.54, 80.35, 55.62, 53.34, 52.38, 37.95, 37.55, 28.28. HRMS

(ESI) cald. for (M+H)+ $C_{31}H_{36}N_3O_7$: 562.2548,found, 562.2545.



3ae

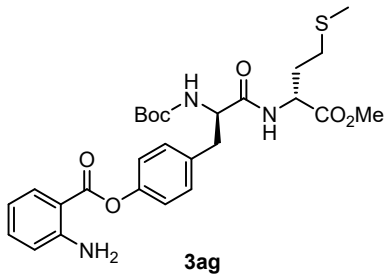
4-((*R*)-2-((tert-butoxycarbonyl)amino)-3-(((*R*)-3-hydroxy-1-methoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3ae): light yellow oil (Yield: 50 %, 75.34 mg), ^{1}H NMR (400 MHz, Methanol-d4) δ 8.00 – 7.95 (m, 1H), 7.36 – 7.27 (m, 3H), 7.11 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.4 Hz, 1H), 6.66 – 6.60 (m, 1H), 4.54 (t, J = 4.2 Hz, 1H), 4.40 (dd, J = 9.0, 5.2 Hz, 1H), 3.91 (dd, J = 11.3, 4.4 Hz, 1H), 3.81 (dd, J = 11.3, 4.1 Hz, 1H), 3.74 (s, 3H), 3.17 (dd, J = 13.9, 5.1 Hz, 1H), 2.89 (dd, J = 13.8, 9.3 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, Methanol-d4) δ 172.94, 170.63, 166.74, 156.33, 152.20, 149.77, 134.70, 134.46, 130.95, 130.07, 121.59, 116.46, 115.26, 108.60, 79.44, 61.47, 55.84, 54.77, 51.50, 37.13, 27.28. HRMS (ESI) cald. for (M+H)+ $C_{25}H_{32}N_3O_8$: 502.2184,found, 502.2188.



3af

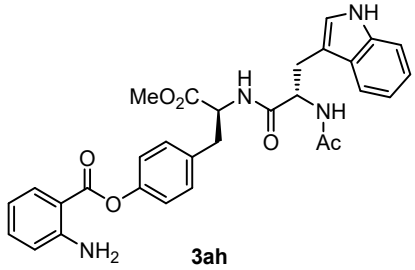
4-((*R*)-2-((tert-butoxycarbonyl)amino)-3-(((*S*)-3-mercapto-1-methoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3af): yellow oil (Yield: 45 %, 69.78 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.72 (dd, J = 8.0, 5.9 Hz, 2H), 6.64 (d, J = 7.1 Hz, 1H), 5.75 (s, 2H), 5.31 (d, J = 8.3 Hz, 1H), 4.81 (q, J = 6.8, 6.4 Hz, 1H), 4.56 (s, 1H), 3.72 (s, 3H), 3.17 (dd, J = 13.9, 4.6 Hz, 1H), 3.07 (d, J = 5.8 Hz, 2H), 3.00 – 2.89 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.17, 170.45, 166.79, 155.38, 151.26, 150.20, 135.12, 134.37, 131.66,

130.48, 122.11, 116.80, 115.69, 109.49, 79.27, 55.68, 55.55, 52.78, 29.71, 28.32. HRMS (ESI) cald. for (M+Na)+ $C_{25}H_{31}N_3O_7SNa$: 540.1775,found, 540.1780.



3ag

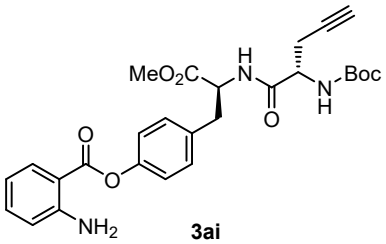
4-((*R*)-2-((tert-butoxycarbonyl)amino)-3-(((*R*)-1-methoxy-4-(methylthio)-1-oxobutan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3ag): light yellow oil (Yield: 55 %, 89.91 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (dd, J = 8.3, 1.3 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.20 (d, J = 6.9 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.67 – 6.58 (m, 3H), 5.70 (s, 2H), 4.98 (d, J = 6.7 Hz, 1H), 4.60 (q, J = 7.3 Hz, 1H), 4.30 (q, J = 5.8 Hz, 1H), 3.67 (s, 3H), 3.02 (dt, J = 13.9, 6.6 Hz, 2H), 2.37 (t, J = 7.1 Hz, 2H), 2.08 (dt, J = 13.4, 6.5 Hz, 1H), 2.00 (s, 3H), 1.89 (dd, J = 14.4, 7.1 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.83, 171.01, 166.76, 155.41, 151.28, 149.82, 134.94, 133.97, 131.56, 130.44, 122.22, 116.80, 116.43, 109.52, 80.50, 55.69, 52.59, 51.60, 37.29, 31.52, 29.74, 28.29, 15.41. HRMS (ESI) cald. for (M+Na)+ $C_{27}H_{35}N_3O_7SNa$: 568.2088,found, 568.2085.



3ah

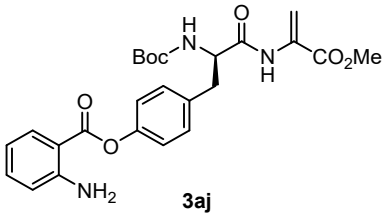
4-((*S*)-2-((*S*)-2-acetamido-3-(1H-indol-3-yl)propanamido)-3-methoxy-3-oxopropyl)phenyl 2-aminobenzoate (3ah): yellow oil (Yield: 70 %, 113.78 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.65 (s, 1H), 8.08 (dd, J = 8.3, 1.5 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.36 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.04 (d, J = 8.5 Hz, 2H), 6.94 – 6.90 (m,

2H), 6.76 – 6.71 (m, 2H), 6.57 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 7.5 Hz, 1H), 6.16 (d, J = 7.5 Hz, 1H), 5.80 (s, 2H), 4.76 (dtd, J = 15.6, 8.4, 7.8, 4.7 Hz, 2H), 3.68 (s, 3H), 3.24 (dd, J = 14.3, 4.4 Hz, 1H), 3.05 (dd, J = 14.3, 9.1 Hz, 1H), 2.95 (dd, J = 14.4, 4.7 Hz, 1H), 2.80 (dd, J = 14.4, 8.1 Hz, 1H), 1.98 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.57, 171.31, 169.98, 167.74, 151.52, 149.80, 136.36, 135.38, 133.13, 131.75, 130.23, 127.06, 123.64, 122.36, 122.16, 119.66, 119.31, 116.97, 116.60, 111.26, 110.37, 109.08, 53.46, 52.84, 52.41, 36.55, 28.89, 23.35. HRMS (ESI) cald. for (M+H)+ $C_{30}H_{31}N_4O_6$: 543.2238,found, 543.2240.



3ai

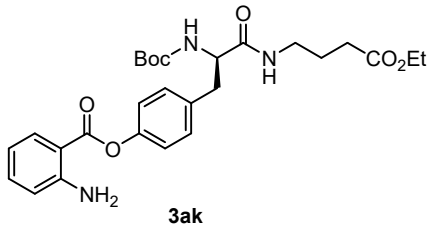
4-((*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)pent-4-ynamido)-3-methoxy-3-oxopropyl)phenyl 2-aminobenzoate (3ai): white oil (Yield: 60 %, 91.75 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.04 (dd, J = 8.3, 1.6 Hz, 1H), 7.32 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.17 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 6.8 Hz, 1H), 6.72 – 6.67 (m, 2H), 5.78 (s, 2H), 5.34 (s, 1H), 4.87 (q, J = 5.8 Hz, 1H), 4.29 (s, 1H), 3.73 (s, 3H), 3.16 (qd, J = 14.0, 5.8 Hz, 2H), 2.78 (d, J = 15.3 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.09 (t, J = 2.6 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.41, 170.05, 166.77, 155.34, 151.33, 149.92, 134.94, 133.28, 131.55, 130.43, 122.18, 116.81, 116.38, 109.45, 80.60, 79.31, 72.09, 53.39, 52.84, 52.48, 37.18, 28.27, 22.26. HRMS (ESI) cald. for (M+H)+ $C_{27}H_{32}N_3O_7$: 510.2235,found, 510.2238.



3aj

(*R*)-4-(2-((tert-butoxycarbonyl)amino)-3-((3-methoxy-3-oxoprop-1-en-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3aj): light yellow oil (Yield: 63 %, 89.30 mg), ^{1}H NMR (400

MHz, Chloroform-d) δ 8.26 (s, 1H), 8.05 (dd, J = 8.3, 1.6 Hz, 1H), 7.33 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.72 – 6.67 (m, 2H), 6.61 (s, 1H), 5.90 (d, J = 1.1, 1H), 5.76 (s, 2H), 5.03 (s, 1H), 4.46 (s, 1H), 3.81 (s, 3H), 3.14 (d, J = 6.2 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.13, 166.72, 164.02, 155.43, 151.29, 149.89, 134.92, 133.77, 131.56, 130.63, 130.30, 122.30, 116.80, 116.42, 109.55, 109.47, 80.71, 56.40, 52.97, 37.37, 28.25.HRMS (ESI) cald. for (M+H)+ $C_{25}H_{30}N_3O_7$: 484.2078,found, 484.2079.



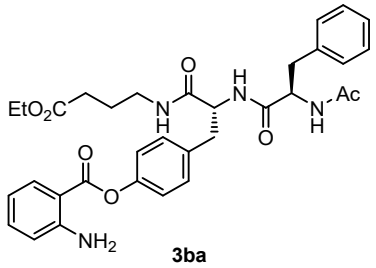
3ak

(*R*)-4-(2-((tert-butoxycarbonyl)amino)-3-((4-ethoxy-4-oxobutyl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3ak): white oil (Yield: 60 %, 92.30 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (dd, J = 8.4, 1.6 Hz, 1H), 7.26 (td, J = 7.7, 7.1, 1.6 Hz, 1H), 7.20 – 7.16 (m, 2H), 7.04 (d, J = 8.5 Hz, 2H), 6.66 – 6.59 (m, 2H), 6.17 (t, J = 5.7 Hz, 1H), 5.72 (s, 2H), 5.11 (d, J = 6.3 Hz, 1H), 4.24 (s, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.73 – 3.63 (m, 2H), 3.15 (q, J = 6.8, 6.3 Hz, 2H), 2.99 (hept, J = 7.8, 7.1 Hz, 2H), 2.18 (t, J = 7.3 Hz, 2H), 1.81 – 1.74 (m, 2H), 1.66 (p, J = 7.0 Hz, 2H), 1.35 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.25, 171.21, 166.76, 155.43, 151.31, 149.75, 134.90, 134.31, 131.55, 130.36, 122.18, 116.35, 109.48, 80.23, 67.97, 60.51, 55.99, 38.86, 38.03, 31.56, 28.31, 25.61, 24.50, 14.21.HRMS (ESI) cald. for (M+H)+ $C_{27}H_{36}N_3O_7$: 514.2547,found, 514.2551.

3.4 Polypeptide scope and characterization

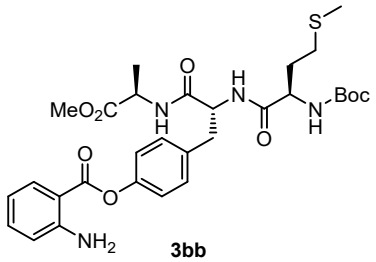
General procedure for product (3ba-f): In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, isatin (0.45 mmol), tripeptide (0.3 mmol) and ^{n}Bu$_4$NF·3H$_2$O (0.3 mmol) were combined and added. Then, CH_3CN (6 mL) were injected into the tubes via syringes. The bottle was equipped with platinum plate (15 mm×15 mm×0.3 mm) as the anode and plumbum

plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at a constant current of 5 mA under room temperature for 4 h. After completion of the reaction, as indicated by TLC and LC-MS, the pure product was obtained by flash column chromatography on silica gel (eluent: DCM/MeOH).



3ba

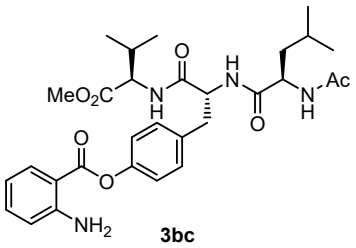
4-((*R*)-2-((*R*)-2-acetamido-3-phenylpropanamido)-3-((4-ethoxy-4-oxobutyl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3ba): light yellow oil (Yield: 68 %, 123.02 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.24 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.91 (dt, J = 15.4, 6.4 Hz, 2H), 7.34 – 7.15 (m, 8H), 7.10 (t, J = 7.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.59 (t, J = 7.5 Hz, 1H), 4.53 – 4.40 (m, 2H), 4.03 (q, J = 7.0 Hz, 2H), 3.09 – 2.59 (m, 6H), 2.25 (q, J = 7.8 Hz, 2H), 1.75 (s, 3H), 1.62 (dq, J = 14.0, 7.0 Hz, 2H), 1.16 (d, J = 18.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 173.12, 171.64, 171.01, 169.81, 166.44, 152.60, 149.54, 138.43, 135.56, 135.26, 131.43, 130.62, 129.59, 128.44, 126.64, 122.16, 117.13, 115.40, 108.07, 60.21, 54.64, 54.50, 38.29, 37.77, 37.51, 31.28, 24.81, 22.90, 14.56. HRMS (ESI) cald. for (M+H)+ $C_{33}H_{39}N_4O_7$: 603.2774,found, 603.2769



3bb

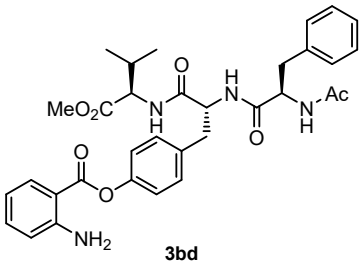
Methyl(6*R*,9*R*,12*R*)-9-(4-((2-aminobenzoyl)oxy)benzyl)-2,2,12-trime-thyl-6-(2-(methylthio)ethyl)-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (3bb): yellow oil (Yield: 63 %, 115.72 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 9.73 (d, J = 8.3 Hz, 1H), 8.80 (d, J = 6.3 Hz, 1H),

7.90 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.65 (d, J = 7.4 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.66 – 4.60 (m, 1H), 4.54 – 4.49 (m, 1H), 4.35 – 4.30 (m, 1H), 3.64 (s, 3H), 3.16 (d, J = 13.5 Hz, 1H), 2.96 (dt, J = 22.7, 9.5 Hz, 2H), 2.84 – 2.75 (m, 1H), 2.11 (s, 3H), 2.00 (dq, J = 20.2, 11.5, 11.0 Hz, 2H), 1.44 (s, 9H), 1.34 (d, J = 7.3 Hz, 3H).^{13}C NMR (101 MHz, DMSO-d6) δ 172.86, 169.75, 165.98, 156.45, 152.16, 152.07, 149.21, 134.83, 134.80, 131.01, 130.07, 121.82, 116.67, 114.93, 107.58, 79.81, 54.45, 51.97, 47.84, 44.19, 39.93, 35.97, 31.29, 29.04, 27.79, 16.77, 14.79. HRMS (ESI) cald. for (M+Na)+ $C_{30}H_{40}N_4O_8SNa$: 639.2459,found, 639.2463.



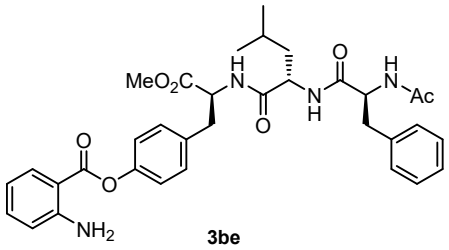
3bc

4-((*R*)-2-((*R*)-2-acetamido-4-methylpentanamido)-3-(((*R*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate: yellow oil (Yield: 55%, 93.82 mg), ^{1}H NMR (400 MHz, Methanol-d4) δ 7.97 (dd, J = 8.2, 1.5 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.25 – 7.23 (m, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.79 (dd, J = 0.8, 8.4 Hz, 1H), 6.63 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 4.70 – 4.62 (m, 2H), 3.69 (s, 3H), 3.18 (dd, J = 13.9, 5.6 Hz, 1H), 3.11 – 2.99 (m, 2H), 2.82 (dd, J = 13.9, 9.1 Hz, 1H), 2.23 – 2.11 (m, 2H), 2.06 – 2.01 (m, 1H), 1.88 (s, 3H), 1.00 (d, J = 4.0 Hz, 3H), 0.92 – 0.91 (m, 3H), 0.83 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d4) δ 172.12, 171.66, 171.57, 171.54, 166.69, 152.23, 149.90, 134.09, 130.90, 130.04, 128.87, 121.69, 116.45, 115.23, 108.52, 57.35, 54.45, 53.67, 53.53, 41.13, 37.37, 29.97, 22.93, 22.34, 20.98.HRMS (ESI) cald. for (M+H)+ $C_{30}H_{41}N_4O_7$: 569.2931,found, 569.2933.



3bd

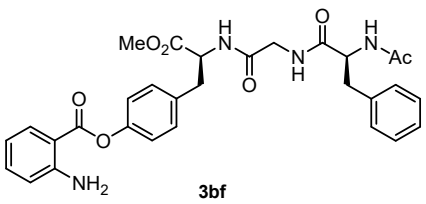
4-((*R*)-2-((*R*)-2-acetamido-3-phenylpropanamido)-3-(((*R*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-oxopropyl)phenyl 2-aminobenzoate (3bd): yellow liquid (Yield: 60 %, 108.52 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 (d, J = 7.2 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.23 (dd, J = 16.5, 7.4 Hz, 5H), 7.10 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.60 (t, J = 7.4 Hz, 1H), 4.49 (d, J = 6.9 Hz, 1H), 4.40 (d, J = 7.7 Hz, 1H), 4.18 (t, J = 8.9 Hz, 1H), 3.57 (s, 3H), 3.00 (dp, J = 22.2, 7.9, 6.9 Hz, 3H), 2.78 – 2.69 (m, 1H), 1.61 (dd, J = 12.6, 6.3 Hz, 1H), 1.31 (s, 3H), 0.87 (dd, J = 6.2, 16.0 Hz, 6H).^{13}C NMR (101 MHz, DMSO-d6) δ 172.54, 172.22, 171.79, 166.51, 155.77, 152.60, 149.45, 137.53, 136.11, 135.25, 131.44, 130.61, 129.47, 128.70, 126.98, 122.07, 117.15, 115.42, 108.12, 56.13, 53.95, 52.25, 51.14, 37.61, 36.96, 24.40, 23.48, 22.21. HRMS (ESI) cald. for (M+H)+ $C_{33}H_{39}N_4O_7$: 603.2774,found, 603.2771.



3be

4-((*S*)-2-((*S*)-2-((*S*)-2-acetamido-3-phenylpropanamido)-4-methylpentanamido)-3-methoxy-3-oxopropyl)phenyl 2-aminobenzoate (3be): yellow oil (Yield: 71 %, 129.32 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 (d, J = 7.2 Hz, 1H), 7.92 (dd, J = 16.9, 8.2 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.23 (dd, J = 16.5, 7.4 Hz, 5H), 7.10 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.60 (t, J = 7.4 Hz, 1H), 4.49 (q, J = 7.3, 6.7 Hz, 1H), 4.40 (q, J = 7.5 Hz, 1H), 4.18 (t, J = 9.0 Hz, 1H), 3.57 (s, 3H), 2.99 (dtd, J = 20.6, 15.1, 14.5, 6.5 Hz, 3H), 2.80 –

2.69 (m, 1H), 1.62 (dt, J = 12.6, 6.5 Hz, 1H), 1.31 (s, 3H), 1.29 – 1.21 (m, 2H), 0.87 (dd, J = 15.8, 6.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d6) δ 172.54, 172.22, 171.79, 166.51, 155.77, 152.60, 149.45, 137.53, 136.11, 135.25, 131.44, 130.61, 129.47, 128.70, 126.98, 122.07, 117.15, 115.42, 108.12, 56.13, 53.95, 52.25, 51.14, 41.73, 37.61, 36.96, 24.40, 23.48, 22.21. HRMS (ESI) cald. for (M+H)+ $C_{34}H_{41}N_4O_7$: 617.2931,found, 617.2926.



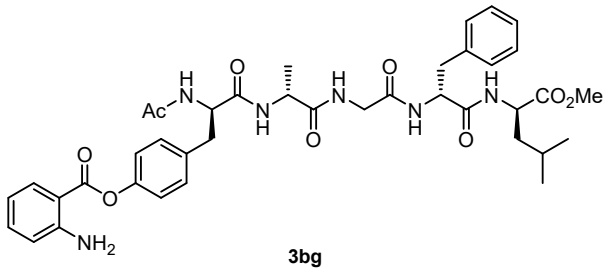
3bf

4-((S)-2-(2-((S)-2-acetamido-3-phenylpropanamido)acetamido)-3-methoxy-3-oxopropyl)phenyl 2-aminobenzoate (3bf): yellow oil (Yield: 67%, 93.82 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.34 (p, J = 7.3, 6.3 Hz, 2H), 8.20 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.28 – 7.24 (m, 5H), 7.20 – 7.16 (m, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.3 Hz, 1H), 6.74 (s, 2H), 6.60 (t, J = 7.5 Hz, 1H), 4.49 (dp, J = 9.9, 6.3, 4.3 Hz, 2H), 3.74 (ddd, J = 35.5, 16.9, 5.8 Hz, 2H), 3.62 (s, 3H), 3.08 – 2.92 (m, 3H), 2.78 – 2.69 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 172.76, 172.63, 171.11, 168.00, 166.29, 156.48, 156.10, 135.31, 133.16, 131.92, 130.67, 130.38, 127.87, 127.64, 122.97, 115.51, 111.58, 108.33, 107.27, 54.37, 52.13, 49.05, 36.48, 32.94, 28.66. HRMS (ESI) cald. for (M+H)+ $C_{30}H_{33}N_4O_7$: 561.2306,found, 561.2310.

General procedure for bioconjugation of polypeptides (3bg-j): In an oven-dried undivided three-necked bottle (15 mL) equipped with a stir bar, polypeptides (5 mg), isatin (10 mg), ^{n}Bu$_4$NF 3H$_2$O(10 mg),CH$_3$CN (0.75 mL) and phosphate buffer solution (0.75 mL, pH= 7.4) were combined and added. The bottle was equipped platinum plate (10 mm×10 mm×0.1 mm) as the anode and plumbum plate (10 mm×10 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 5 mA under room temperature for 30 min. After completion of the reaction, the solution was analyzed by LC-MS spectroscopy. The reaction was

analyzed by reverse phase HPLC using a gradient of 60% to 50% buffer B over 20 minutes on an Agilent Zorbax SB-Aq 5μm column of 250 mm length. HPLC analysis used buffers A (water) and B (acetonitrile + 0.1% TFA). Conversion reported as a % conversion as determined.

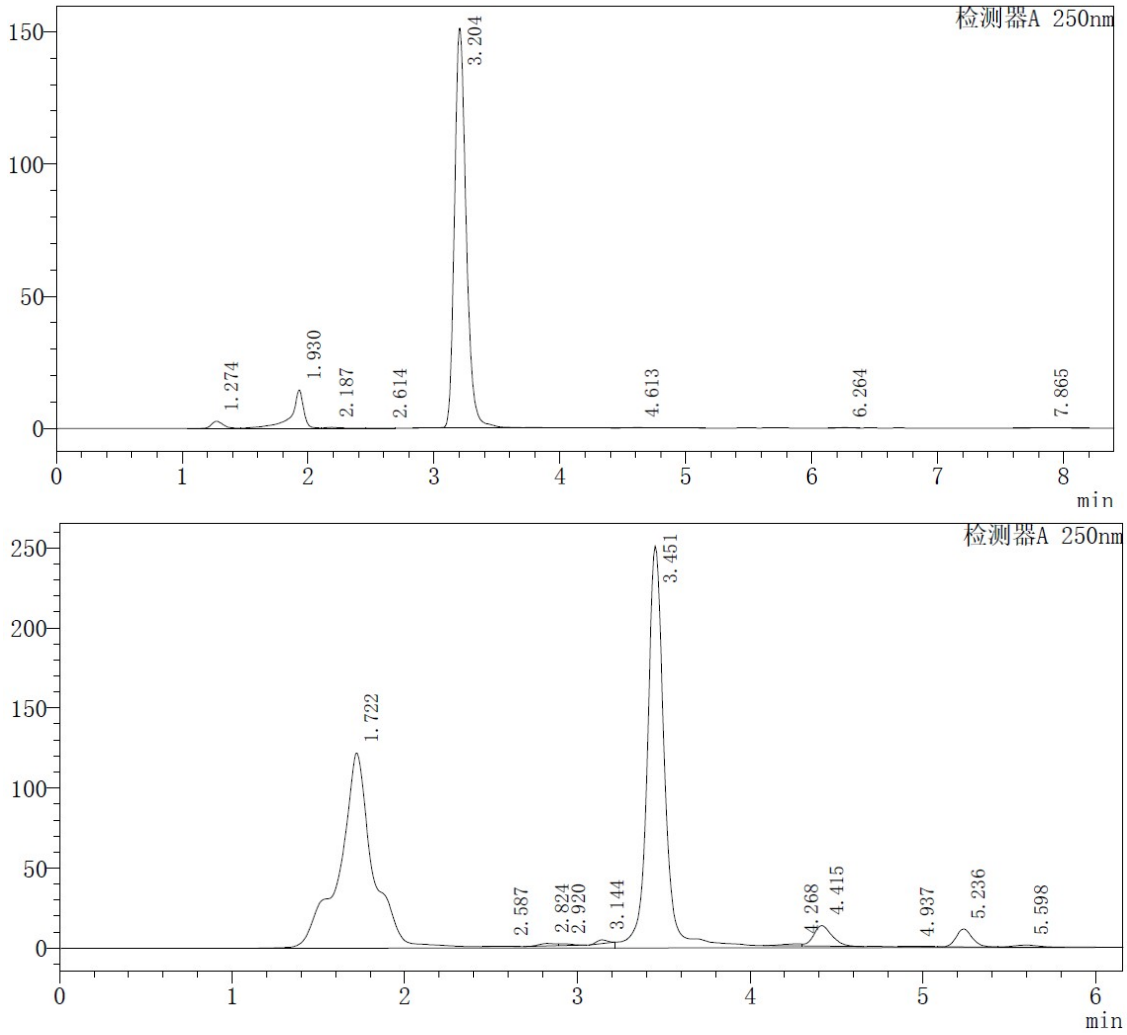
bioconjugated product 3bg :



3bg

HPLC: >99% conversion.

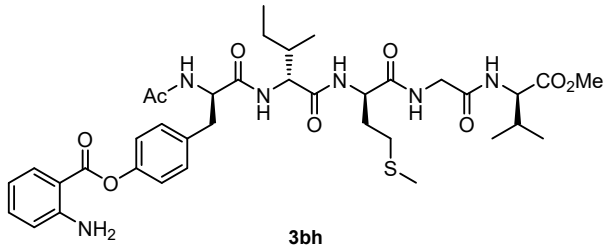
After the reaction finished, there are four peaks that elute at 50% buffer B (acetonitrile + 0.1% TFA) with retention times of 1.722 min , 3.415 min, 4.415 min and 5.236 min. Polypeptide **2g** is a peak that elutes at 50% buffer B (acetonitrile + 0.1% TFA) with a retention time of 3.204 min.



HPLC Spectra:

HRMS (ESI-TOF) calcd for $C_{39}H_{48}N_6O_9$, [M+Na]+, 767.3375, found 767.3371.

bioconjugated product 3bh :

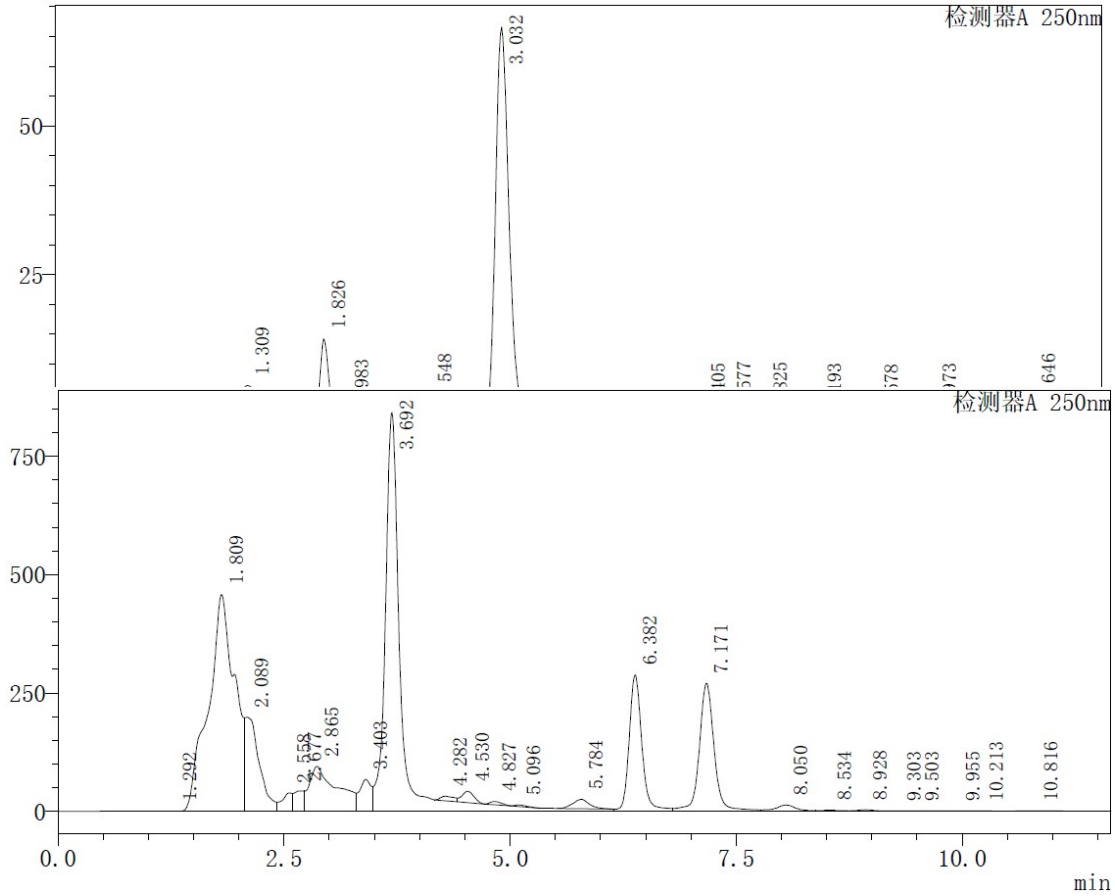


3bh

HPLC: >99% conversion.

After the reaction finished, there are four peaks that elute at 50% buffer B (acetonitrile + 0.1% TFA) with retention times of 1.809 min , 3.629 min, 6.382 min and 7.171 min. Polypeptide

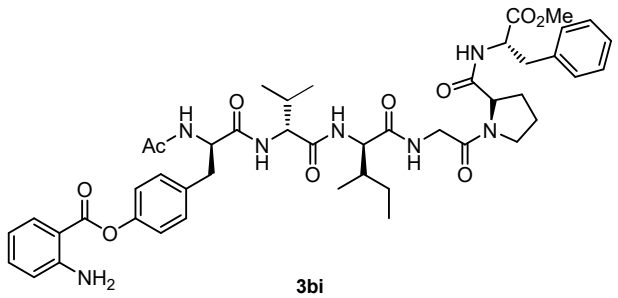
2h is a peak that elutes at 50% buffer B (acetonitrile + 0.1% TFA) with a retention time of 3.032 min.



HPLC Spectra:

HRMS (ESI-TOF) calcd for C37H52N6O9S, [M+K]+, 795.3348, found 795.3345.

bioconjugated product 3bi :

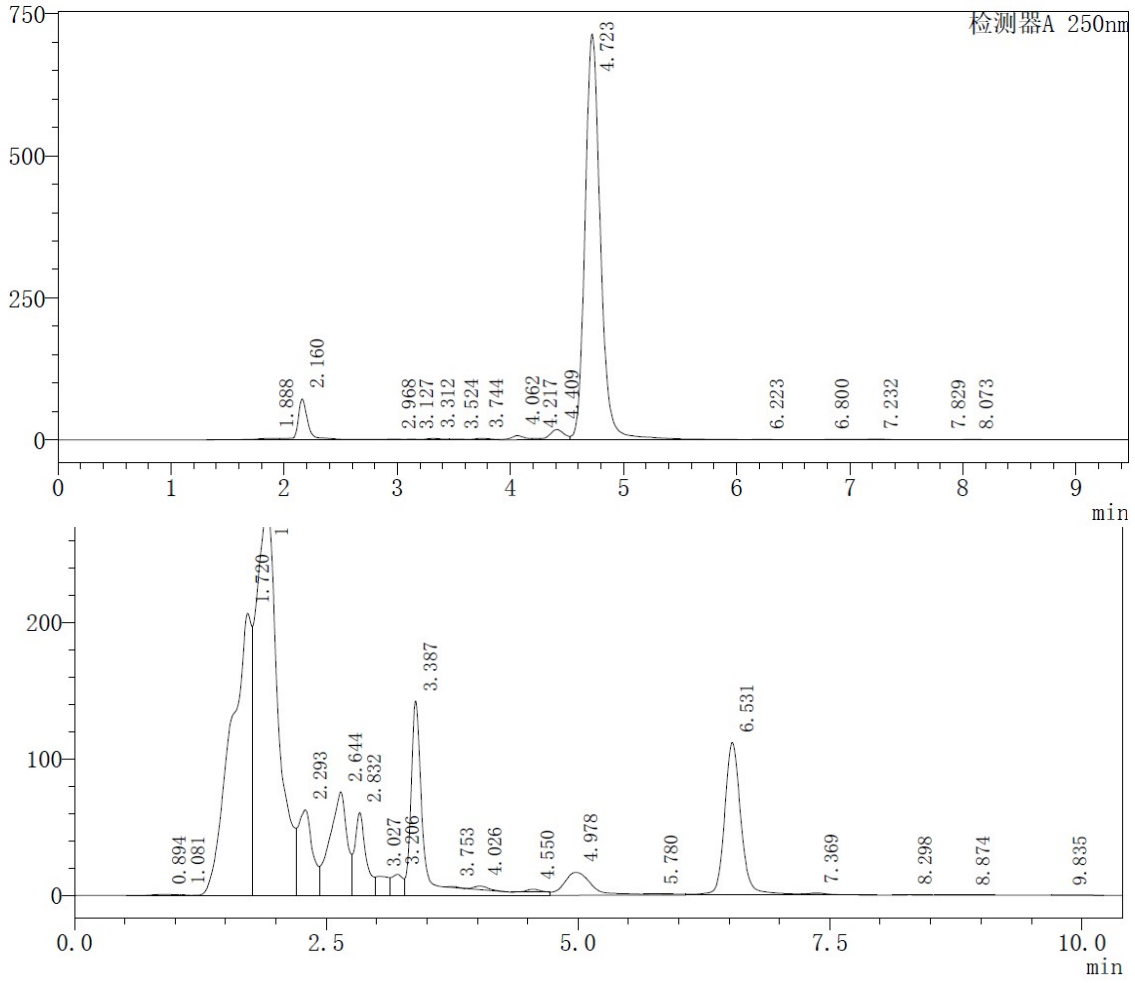


3bi

HPLC: >99% conversion.

After the reaction finished, there are four peaks that elute at 50% buffer B (acetonitrile + 0.1% TFA) with retention times of 1.720 min , 1.911 min, 3.387 min and 6.531 min. Polypeptide

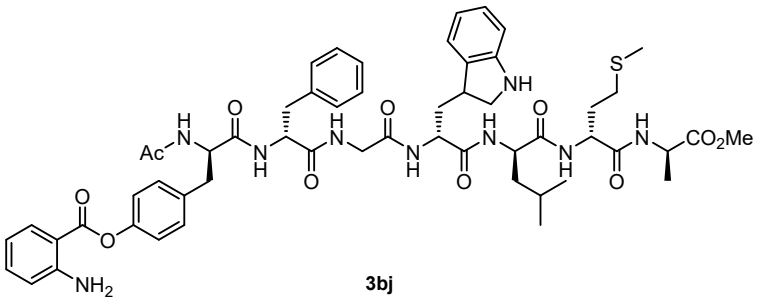
2i is a peak that elutes at 50% buffer B (acetonitrile + 0.1% TFA) with a retention time of 4.723 min.



HPLC Spectra:

HRMS (ESI-TOF) calcd for $C_{46}H_{59}N_7O_{10}$, [M+H]+, 892.4255, found 892.4257.

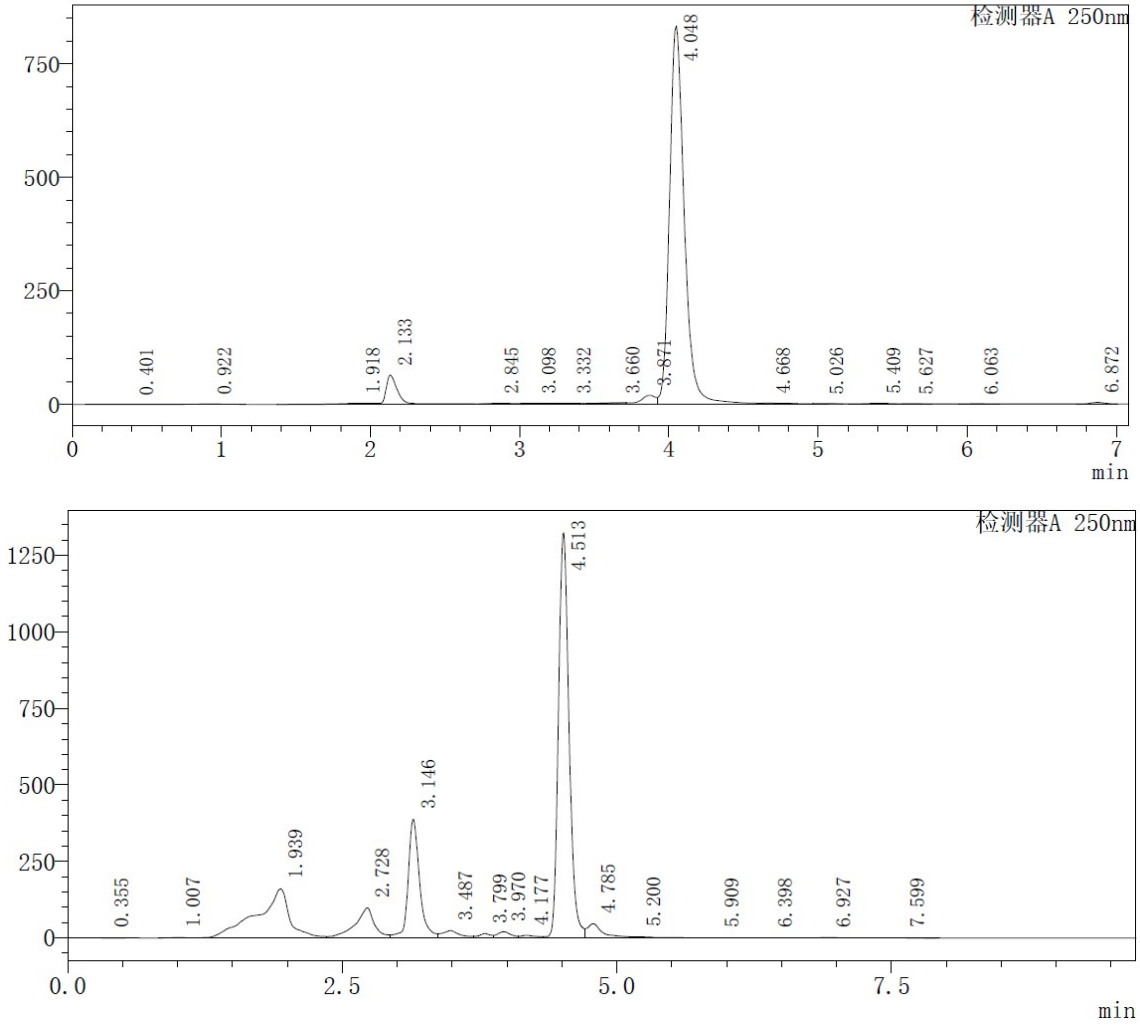
bioconjugated product 3bj:



3bj

HPLC: >99% conversion.

After the reaction finished, there are four peaks that elute at 50% buffer B (acetonitrile + 0.1% TFA) with retention times of 1.939 min , 2.728 min, 3.146 min and 4.513 min. Polypeptide **2j** is a peak that elutes at 50% buffer B (acetonitrile + 0.1% TFA) with a retention time of 4.048 min.

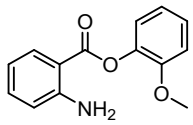


HPLC Spectra:

HRMS (ESI-TOF) calcd for $C_{55}H_{69}N_9O_{11}S$, [M+H]+, 1086.4735, found 1086.4731

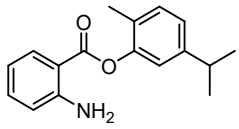
3.5 Drug molecules and Natural products scope and characterization

Detailed descriptions for products:



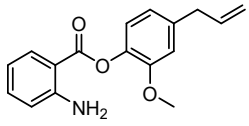
3ca

2-methoxyphenyl 2-aminobenzoate (3ca): yellow oil (Yield: 78%, 57.10 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.12 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.16 – 7.12 (m, 1H), 7.03 – 6.97 (m, 2H), 6.72 (t, J = 8.6 Hz, 2H), 5.74 (s, 2H), 3.82 (s, 3H). ^{13}13C NMR (101 MHz, Chloroform-d) δ 166.39, 151.53, 151.13, 139.79, 134.75, 131.91, 126.87, 123.26, 120.85, 116.71, 116.42, 112.51, 109.74, 55.95. HRMS (ESI) cald. for (M+H)+ $C_{14}H_{14}NO_3$: 244.0968,found, 244.0966.



3cb

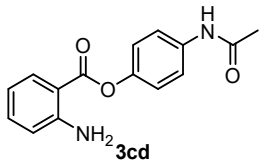
5-isopropyl-2-methylphenyl 2-aminobenzoate (3cb): yellow oil (Yield: 73%, 58.91 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.12 (dd, J = 8.4, 1.4 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.05 (dd, J = 7.8, 1.4 Hz, 1H), 6.97 (d, J = 1.3 Hz, 1H), 6.76 – 6.69 (m, 2H), 5.78 (s, 2H), 2.89 (dd, J = 11.4, 4.2 Hz, 1H), 2.19 (s, 3H), 1.25 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 166.59, 151.23, 149.29, 148.13, 134.78, 131.62, 130.91, 127.65, 124.10, 120.15, 116.79, 116.43, 109.76, 33.61, 23.96, 15.90. HRMS (ESI) cald. for (M+H)+ $C_{17}H_{20}NO_2$:270.1488,found, 270.1490.



3cc

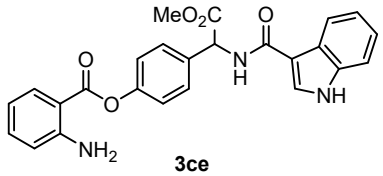
4-allyl-2-methoxyphenyl 2-aminobenzoate (3cc): light yellow oil (Yield: 75%, 63.67 mg), ^{1} 1H NMR (400 MHz, Chloroform-d) δ 8.12 (dd, J = 8.0, 1.3 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 9.8 Hz, 2H), 6.74 – 6.68 (m, 2H), 5.99 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H), 5.75 (s, 2H), 5.17 – 5.09 (m, 2H), 3.81 (s, 3H), 3.41 (d, J = 6.7 Hz, 2H). ^{13}C NMR (101 MHz,

Chloroform-d) δ 166.52, 151.28, 151.11, 138.97, 137.99, 137.18, 134.72, 131.90, 122.96, 120.79, 116.70, 116.40, 116.16, 112.85, 109.79, 55.93, 40.17. HRMS (ESI) cald. for (M+H)+ $C_{17}H_{18}NO_3$: 284.1281,found, 284.1278.



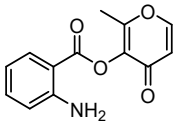
3cd

4-acetamidophenyl 2-aminobenzoate (3cd): light yellow solid (Yield: 74%, 59.94 mg), ^{1}H NMR (400 MHz, Methanol-d4) δ 7.97 (dd, J = 8.1, 1.4 Hz, 1H), 7.60 (d, J = 8.9 Hz, 2H), 7.29 (ddd, J = 8.5, 7.1, 1.5 Hz, 1H), 7.12 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.4 Hz, 1H), 6.66 – 6.59 (m, 1H), 2.13 (s, 3H). [13] 13C NMR (101 MHz, Methanol-d4) δ 170.23, 166.83, 152.19, 146.97, 136.11, 134.49, 130.96, 121.93, 120.69, 116.48, 115.29, 108.56, 22.42. HRMS (ESI) cald. for (M+H)+ $C_{15}H_{15}N_2O_3$: 271.1077,found, 271.1081.



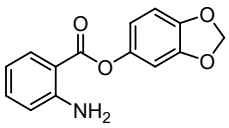
3ce

4-(1-(1*H*-indole-3-carboxamido)-2-methoxy-2-oxoethyl)phenyl 2-aminobenzoate (3ce): yellow oil (Yield: 74%, 98.55 mg), ^{1}H NMR (400 MHz, Methanol-d4) δ 8.05 (d, J = 8.1 Hz, 1H), 7.99 (dd, J = 8.8, 1.3 Hz, 2H), 7.49 – 7.46 (m, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.20 (dt, J = 19.4, 7.4 Hz, 4H), 6.82 (d, J = 8.4 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 4.90 (dd, J = 9.1, 5.6 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d4) δ 172.77, 166.63, 166.33, 152.30, 149.88, 136.62, 135.11, 134.70, 131.14, 130.15, 128.33, 125.96, 122.35, 121.98, 120.88, 120.71, 116.56, 115.27, 111.75, 110.02, 108.42, 53.96, 51.57. HRMS (ESI) cald. for (M+H)+ $C_{25}H_{22}N_3O_5$: 444.1554,found, 444.1551.



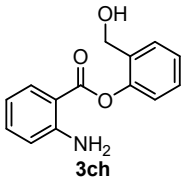
3cf

2-methyl-4-oxo-4*H*-pyran-3-yl 2-aminobenzoate (3cf): light yellow solid (Yield: 67%, 49.25 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.04 (dd, J = 8.5, 1.5 Hz, 1H), 7.71 (d, J = 5.7 Hz, 1H), 7.32 (td, J = 7.7, 7.3, 1.5 Hz, 1H), 6.70 – 6.65 (m, 2H), 6.45 (d, J = 5.7 Hz, 1H), 5.74 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.42, 164.78, 159.53, 154.19, 151.51, 138.66, 135.22, 131.90, 116.92, 116.44, 108.59, 15.12. HRMS (ESI) cald. for (M+H)+ $C_{13}H_{12}NO_4$: 246.0761,found, 246.0759.



3cg

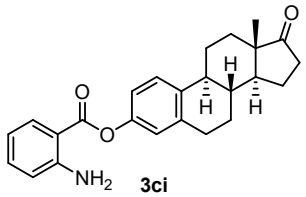
benzo[*d*][1,3]dioxol-5-yl 2-aminobenzoate (3cg): yellow oil (Yield: 72%, 55.52 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.05 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.74 – 6.66 (m, 3H), 6.63 (dd, J = 8.3, 2.0 Hz, 1H), 6.00 (s, 2H), 5.76 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 167.10, 151.25, 148.09, 145.38, 145.09, 135.90, 131.56, 116.79, 116.42, 114.35, 109.55, 108.06, 104.16, 101.72. HRMS (ESI) cald. for (M+H)+ $C_{14}H_{12}NO_4$: 258.0761,found, 258.0766.



3ch

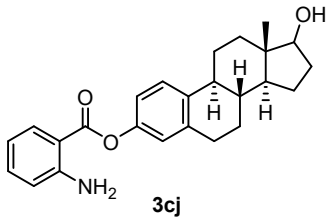
2-(hydroxymethyl)phenyl 2-aminobenzoate (3ch): yellow oil (Yield: 70%, 51.05 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.96 (d, J = 5.3 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.04 (s, 1H), 6.97 (s, 1H), 6.90 – 6.80 (m, 2H), 6.75 – 6.63 (m, 2H), 5.75 (s, 2H), 4.82 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.90, 155.99, 150.51, 134.16, 129.46, 129.25, 128.04, 124.91, 120.06, 116.89, 116.46, 116.17, 113.12, 64.30. HRMS (ESI) cald. for (M+H)+

$C_{14}H_{14}NO_3$: 244.0968,found, 244.0967.



3ci

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl) 2,3-dimethyl 6-iodoquinoline-2,3,4-tricarboxylate (3ci): light yellow oil (Yield: 60%, 70.03 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.07 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 6.99 – 6.90 (m, 2H), 6.71 (t, J = 7.1 Hz, 2H), 5.77 (s, 2H), 2.98 – 2.90 (m, 2H), 2.57 – 2.40 (m, 2H), 2.32 (t, J = 8.7 Hz, 1H), 2.21 – 1.94 (m, 4H), 1.56 (ddq, J = 43.2, 20.1, 11.2, 10.4 Hz, 6H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 220.88, 167.14, 151.22, 148.68, 138.08, 137.36, 134.82, 131.60, 126.47, 122.00, 119.21, 116.78, 116.40, 109.76, 50.47, 47.99, 44.21, 38.06, 35.89, 31.59, 29.45, 26.39, 25.80, 21.62, 13.86. HRMS (ESI) cald. for (M+H)+ $C_{25}H_{28}NO_3$: 390.2064,found, 390.2065.



3cj

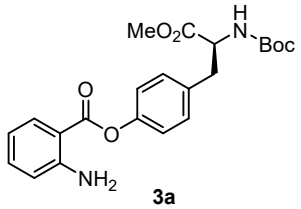
(8*R*,9*S*,13*S*,14*S*)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-3-yl 2-aminobenzoate (3cj): white oil (Yield: 57%, 66.85 mg), ^{1} 1H NMR (400 MHz, Chloroform-d) δ 8.07 (dd, J = 8.5, 1.6 Hz, 1H), 7.36 – 7.29 (m, 2H), 6.94 (dd, J = 8.4, 2.5 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.74 – 6.68 (m, 2H), 5.77 (s, 2H), 3.74 (t, J = 8.5 Hz, 1H), 3.64 (s, 1H), 2.93 – 2.84 (m, 2H), 2.39 – 2.21 (m, 2H), 2.16 – 2.08 (m, 1H), 2.01 – 1.94 (m, 1H), 1.90 (ddt, J = 11.3, 5.6, 3.0 Hz, 1H), 1.71 (dddt, J = 13.1, 10.3, 6.4, 3.0 Hz, 1H), 1.61 – 1.15 (m, 7H), 0.79 (s, 3H). ^{13} 13C NMR (101 MHz, Chloroform-d) δ 167.18, 151.20, 148.50, 138.33, 137.97, 134.78, 131.62, 126.47, 121.91, 119.01, 116.77, 116.40, 109.83, 81.92, 50.09, 44.19, 43.24, 38.52, 36.70, 30.60, 29.59, 27.08, 26.20, 23.15, 11.07. HRMS (ESI) cald. for (M+H)+

$C_{25}H_{30}NO_3$: 392.2220,found, 392.2217.

3.6 Other substrates expansion

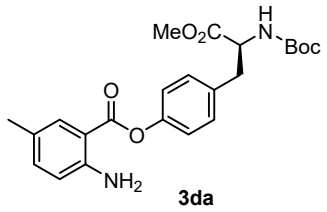
General procedure for product (3da-dl): In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, isatin derivatives (0.3 mmol), Tyrosine residue (0.6 mmol) and $^{n}Bu_4NF{\cdot}3H_2O$ (0.3 mmol) were combined and added. Then, solvent (6 mL) were injected into the tubes via syringes. The bottle was equipped with platinum plate (15 mm×15 mm×0.3 mm) as the anode and plumbum plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at a constant current of 5 mA under room temperature for 4 h. After completion of the reaction, as indicated by TLC and LC-MS, the pure product was obtained by flash column chromatography on silica gel.

Detailed descriptions for products:



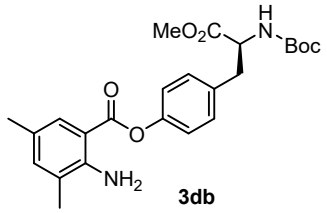
3a

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-aminobenzoate (3a): light yellow oil (Yield: 75%, 93.15 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 (dd, J = 8.3, 1.5 Hz, 1H), 7.33 (ddd, J = 8.5, 7.2, 1.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.73 – 6.68 (m, 2H), 5.79 (s, 2H), 5.04 (d, J = 8.1 Hz, 1H), 4.64 – 4.55 (m, 1H), 3.73 (s, 3H), 3.11 (qd, J = 13.9, 6.0 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.28, 166.76, 155.15, 151.32, 149.84, 134.92, 133.59, 131.58, 130.34, 122.10, 116.81, 116.39, 109.52, 80.06, 54.42, 52.33, 37.70, 28.33. HRMS (ESI) cald. for (M+H)+ $C_{22}H_{27}N_2O_6$: 415.1864,found, 415.1867.



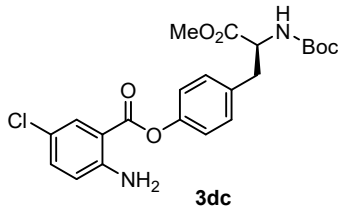
3da

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-amino-5-methylbenzo-ate (3da): light yellow oil (Yield: 67%, 86.03 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.86 (d, J = 1.1 Hz, 1H), 7.20 – 7.15 (m, 3H), 7.11 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 8.4 Hz, 1H), 5.63 (s, 2H), 5.02 (d, J = 8.0 Hz, 1H), 4.60 (q, J = 6.1 Hz, 1H), 3.73 (s, 3H), 3.11 (qd, J = 13.9, 5.9 Hz, 2H), 2.27 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.23, 165.72, 154.08, 148.83, 148.14, 135.09, 132.49, 130.02, 129.29, 124.52, 121.06, 115.90, 108.37, 79.01, 53.35, 51.28, 36.66, 27.28, 19.28. HRMS (ESI) cald. for (M+H)+ $C_{23}H_{29}N_2O_6$: 429.2020,found, 429.2018.



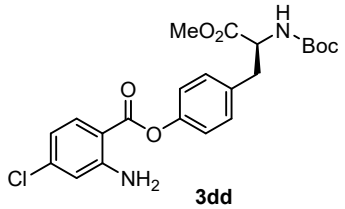
3db

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-amino-3,5-dimeth-ylbe-nzoate (3db): light yellow oil (Yield: 67%, 83.53 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.78 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.12 (dd, J = 5.5, 2.9 Hz, 3H), 5.72 (s, 2H), 5.02 (d, J = 8.0 Hz, 1H), 4.60 (q, J = 6.0 Hz, 1H), 3.73 (s, 3H), 3.11 (qd, J = 14.0, 6.0 Hz, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.28, 167.24, 155.13, 149.95, 147.76, 137.02, 133.48, 130.33, 128.94, 124.81, 123.29, 122.14, 108.90, 80.06, 54.40, 52.34, 37.69, 28.33, 20.34, 17.45. HRMS (ESI) cald. for (M+H)+ $C_{24}H_{31}N_2O_6$: 443.2177,found, 443.2176.



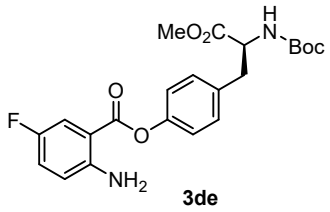
3dc

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-amino-5-chlorobenzo-ate (3dc): light yellow solid (Yield: 73%, 98.31 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (d, J = 8.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 1.9 Hz, 1H), 6.67 (dd, J = 8.6, 2.0 Hz, 1H), 5.86 (s, 2H), 5.02 (d, J = 8.1 Hz, 1H), 4.60 (q, J = 6.1 Hz, 1H), 3.73 (s, 3H), 3.11 (qd, J = 13.9, 5.9 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.26, 166.20, 155.13, 151.92, 149.62, 140.96, 133.76, 132.97, 130.39, 122.00, 116.94, 116.05, 108.11, 54.39, 52.36, 37.72, 28.33. HRMS (ESI) cald. for (M+H)+ $C_{22}H_{26}ClN_2O_6$: 449.1474,found, 449.1476.



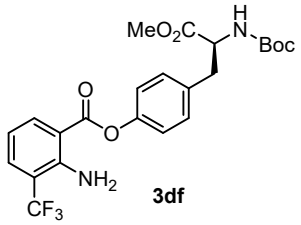
3dd

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-amino-4-chlorobenzo-ate (3dd): light yellow solid (Yield: 78%, 104.81 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (d, J = 8.6 Hz, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 1.8 Hz, 1H), 6.67 (dd, J = 8.6, 1.9 Hz, 1H), 5.88 (s, 2H), 5.04 (d, J = 8.1 Hz, 1H), 4.60 (q, J = 6.1 Hz, 1H), 3.73 (s, 3H), 3.11 (qd, J = 13.9, 5.9 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.26, 166.20, 155.14, 151.96, 149.63, 140.94, 133.76, 132.96, 130.38, 122.00, 116.89, 116.06, 108.08, 80.09, 54.40, 52.35, 37.72, 28.33. HRMS (ESI) cald. for (M+H)+ $C_{22}H_{26}ClN_2O_6$: 449.1474,found, 449.1476.



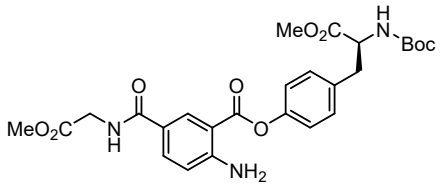
3de

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-amino-5-fluroben-zo-ate (3de): light yellow oil (Yield: 60%, 79.81 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 7.72 (dd, J = 9.0, 3.6 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.1 Hz, 2H), 5.73 (s, 2H), 5.15 (d, J = 8.2 Hz, 1H), 4.52 (q, J = 6.1 Hz, 1H), 3.68 (s, 3H), 2.99 (tt, J = 14.2, 6.7 Hz, 2H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-d) δ -128.04. ^{13}C NMR (101 MHz, Chloroform-d) δ 172.83, 166.03, 155.53 (d, J = 8.9 Hz), 152.59, 149.58, 148.07, 130.29, 126.91 (d, J = 14.5 Hz), 123.12 (d, J = 23.4 Hz), 122.00, 118.18 (d, J = 7.1 Hz), 116.16 (d, J = 23.2 Hz), 109.14, 80.37, 54.72, 52.34, 37.39, 28.30. HRMS (ESI) cald. for (M+H)+ $C_{22}H_{26}FN_2O_6$: 433.1769,found, 433.1771.



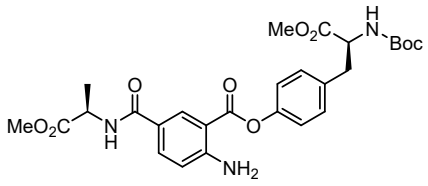
3df

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 2-amino-3-(trifluoro-me-thyl)benzoate (3df): light yellow solid (Yield: 50%, 72.31 mg), ^{1}H NMR (400 MHz, Chloroform-d) δ 8.29 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.76 (t, J = 7.9 Hz, 1H), 6.49 (s, 2H), 5.03 (d, J = 8.0 Hz, 1H), 4.60 (d, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.11 (qd, J = 13.9, 6.0 Hz, 2H), 1.43 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-d) δ -63.44. ^{13}C NMR (101 MHz, Chloroform-d) δ 171.19, 165.27, 154.08, 148.48, 147.72, 134.87, 132.96, 131.67 (q, J = 5.0 Hz), 120.89, 113.88, 110.12, 79.08, 53.37, 51.30, 36.74, 28.68, 27.28. HRMS (ESI) cald. for (M+H)+ $C_{23}H_{26}F_3N_2O_6$: 483.1737,found, 483.1734.



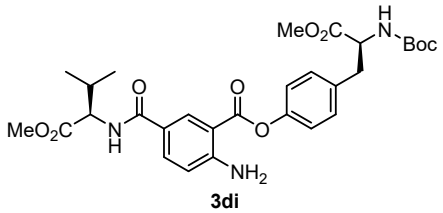
3dg

(*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 5-((acetoxymethyl)carbamoyl)-2-aminobenzoate (3dg): light yellow oil (Yield: 65%, 103.16 mg), ^{1}H NMR (400 MHz, Methanol-d4) δ 8.58 (d, J = 2.1 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.78 (d, J = 8.8 Hz, 1H), 4.35 (dd, J = 8.9, 5.6 Hz, 1H), 4.04 (s, 2H), 3.67 (d, J = 11.9 Hz, 6H), 3.08 (dd, J = 13.8, 5.4 Hz, 1H), 2.90 (dd, J = 13.7, 9.1 Hz, 1H), 1.36 (s, 9H). ^{13}13C NMR (101 MHz, Methanol-d4) δ 172.77, 170.91, 168.18, 166.22, 156.44, 154.73, 149.66, 134.72, 133.09, 131.60, 129.95, 121.66, 119.89, 116.15, 107.58, 79.33, 55.14, 51.33, 51.29, 40.99, 36.64, 27.33. HRMS (ESI) cald. for (M+H)+ $C_{26}H_{32}N_3O_9$: 530.2133,found, 530.2131.



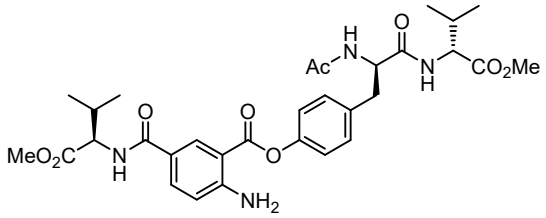
3dh

4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 5-(((*S*)-1-acetoxyethyl)carbamoyl)-2-aminobenzoate (3dh): light yellow oil (Yield: 55%, 89.61 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.63 (d, J = 6.9 Hz, 1H), 8.53 (d, J = 7.6 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 8.8, 2.2 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 2.4 Hz, 2H), 7.19 (s, 2H), 6.86 (d, J = 8.8 Hz, 1H), 4.59 – 4.43 (m, 2H), 3.63 (s, 3H), 3.60 (s, 3H), 2.97 (dt, J = 13.9, 3.9 Hz, 2H), 1.73 (s, 9H), 1.38 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d4) δ 173.56, 173.32, 168.75, 166.78, 156.95, 155.20, 150.19, 135.23, 133.77, 132.38, 130.47, 122.20, 120.64, 116.54, 108.06, 79.83, 59.32, 55.65, 51.66, 37.15, 30.79, 27.84, 18.84. HRMS (ESI) cald. for (M+H)+ $C_{27}H_{34}N_3O_9$: 544.2295,found, 544.2290.



3di

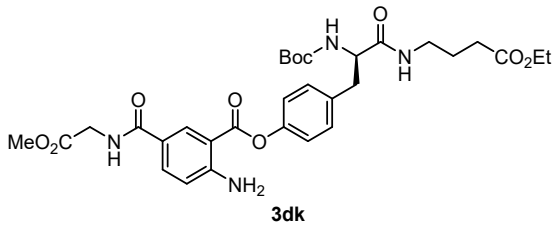
4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl 5-(((*S*)-1-acetoxy-2-methylpropyl)carbamoyl)-2-aminobenzoate (3di): yellow oil (Yield: 55%, 97.64 mg), ^{1}H NMR (400 MHz, Methanol-d4) δ 8.62 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 8.8, 2.1 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.8 Hz, 1H), 4.46 (d, J = 7.1 Hz, 1H), 4.39 (dd, J = 8.8, 5.6 Hz, 1H), 3.72 (d, J = 9.0 Hz, 6H), 3.14 (dd, J = 13.8, 5.5 Hz, 1H), 2.95 (dd, J = 13.7, 9.1 Hz, 1H), 2.24 (dq, J = 13.7, 6.8 Hz, 1H), 1.40 (s, 9H), 1.01 (dd, J = 11.1, 6.8 Hz, 6H). ^{13}13C NMR (101 MHz, Methanol-d4) δ 172.74, 168.28, 166.27, 156.46, 154.72, 149.70, 134.73, 133.24, 131.86, 129.94, 121.66, 120.15, 115.99, 107.56, 79.29, 58.81, 55.13, 51.29, 51.09, 36.64, 30.27, 27.30, 18.29, 17.95. HRMS (ESI) cald. for (M+H)+ $C_{29}H_{39}N_3O_9$: 572.2608,found, 572.2605.



3dj

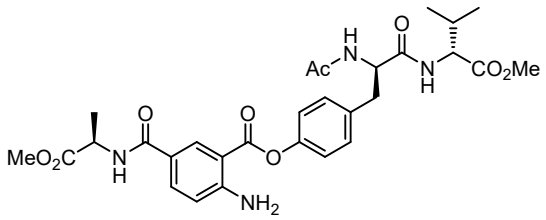
4-((*R*)-2-acetamido-3-(((*R*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-oxopropyl)phenyl 2-amino-5-(((*R*)-1-methoxy-3-methyl-1-oxobutan-2-yl)carbamoyl)benzoate (3dj): light yellow oil (Yield: 56%, 102.82 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.57 – 8.50 (m, 2H), 8.45 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.90 (dd, J = 8.8, 2.1 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.18 (s, 2H), 6.87 (d, J = 8.8 Hz, 1H), 4.54 (dq, J = 14.4, 7.7, 6.5 Hz, 2H), 4.26 (t, J = 7.8 Hz, 1H), 3.62 (d, J = 13.8 Hz, 6H), 3.13 – 2.92 (m, 2H), 2.70 (dd, J = 13.8, 10.0 Hz, 1H), 2.16 (dq, J = 13.7, 6.8 Hz, 1H), 1.74 (s, 3H), 1.06 (dd, J = 10.7, 4.7 Hz, 6H), 0.94 (dd, J = 19.4, 6.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d6) δ 172.57, 171.70, 171.65, 169.07, 165.99, 165.82, 154.12, 149.19, 134.67, 133.83, 131.90, 130.18, 129.15, 128.01, 120.15, 116.01,

58.67, 53.61, 53.57, 51.91, 51.56, 37.51, 35.93, 29.47, 22.43, 19.30, 19.22. HRMS (ESI) cald. for (M+H)+ $C_{31}H_{41}N_4O_9$: 613.2829,found, 613.2833.



3dk

(*R*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-((4-ethoxy-4-oxobutyl)amino)-3-oxopropyl)phenyl 2-amino-5-((2-methoxy-2-oxoethyl)carbamoyl)benzoate (3dk): light yellow oil (Yield: 60%, 113.19 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.58 (d, J = 6.3 Hz, 1H), 8.25 (d, J = 7.4 Hz, 1H), 7.87 (d, J = 11.7 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 6.99 (d, J = 7.8 Hz, 2H), 6.74 (s, 2H), 6.67 (d, J = 7.9 Hz, 2H), 6.20 (d, J = 18.2 Hz, 1H), 4.39 (q, J = 8.0, 7.5 Hz, 1H), 4.04 – 3.93 (m, 4H), 3.58 (s, 3H), 2.93 – 2.84 (m, 3H), 2.82 – 2.74 (m, 1H), 2.07 (t, J = 5.5 Hz, 2H), 1.59 – 1.50 (m, 2H), 1.37 (s, 9H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 172.76, 172.61, 171.10, 166.28, 166.21, 156.50, 156.09, 154.64, 135.31, 131.92, 130.38, 127.63, 120.38, 115.51, 110.64, 107.25, 77.95, 54.37, 52.12, 49.05, 36.47, 32.94, 28.66, 26.23. HRMS (ESI) cald. for (M+H)+ $C_{31}H_{41}N_4O_{10}$: 629.2778,found, 629.2780.



3dl

4-((R)-2-acetamido-3-(((R)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-oxopropyl)phenyl 2-amino-5-(((R)-1-methoxy-1-oxopropan-2-yl)carbamoyl)benzoate (3dl): yellow oil (Yield: 60%, 105.13 mg), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.64 (d, J = 6.9 Hz, 1H), 8.58 – 8.52 (m, 2H), 8.10 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 8.8, 2.2 Hz, 1H), 7.32 (s, 2H), 7.27 – 7.24 (m, 2H), 7.20 (s, 2H), 6.87 (d, J = 8.8 Hz, 1H), 4.54 (dt, J = 15.3, 6.2 Hz, 2H), 4.48 – 4.41 (m, 1H), 3.62 (d, J = 10.4 Hz, 6H), 3.08 – 2.95 (m, 2H), 2.73 – 2.67 (m, 1H), 1.74 (s, 3H), 1.38 (d, J = 7.3 Hz, 3H),

0.99 (dd, J = 8.3, 4.3 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d6) δ 173.94, 172.15, 172.11, 169.52, 166.26, 165.81, 154.59, 149.64, 132.04, 130.63, 130.47, 129.60, 128.46, 120.43, 115.53, 54.41, 54.01, 52.36, 52.27, 48.67, 37.97, 36.39, 22.88, 19.10, 17.26. HRMS (ESI) cald. for (M+H)+ $C_{29}H_{37}N_4O_9$: 585.2482,found, 585.2484.

3.7 Additional application of electrochemical bioconjugation

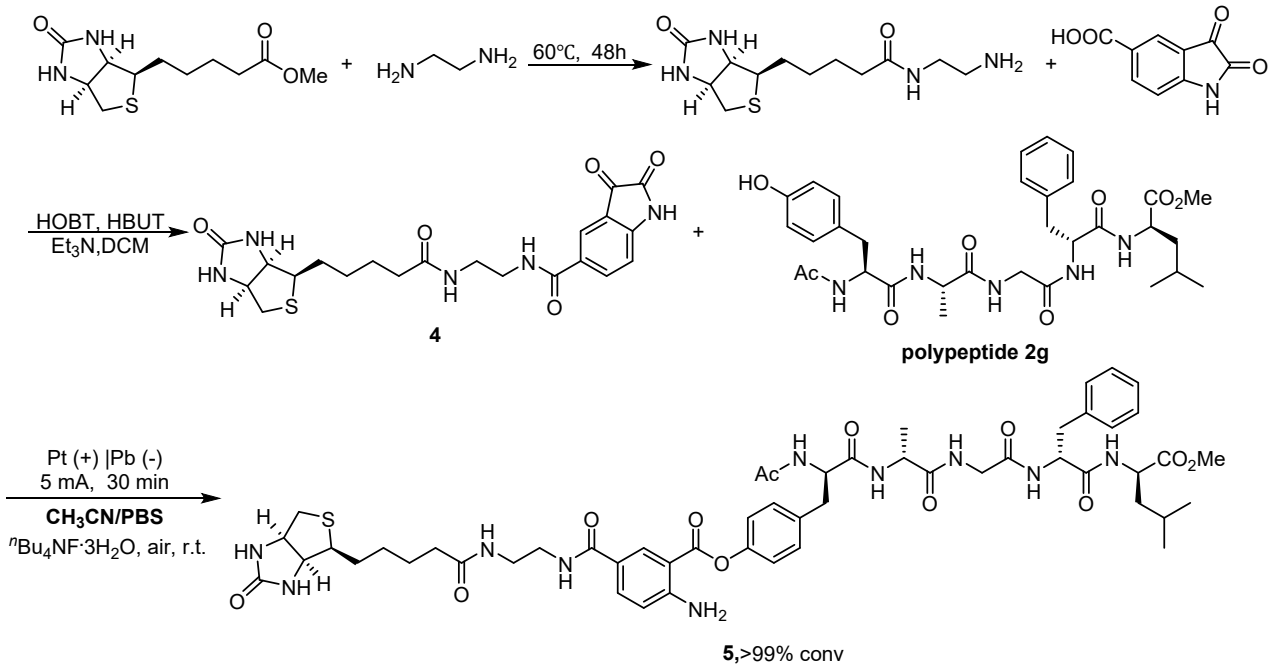
3.7.1 Bioconjugation of Biotin[5]

Synthesis of compound 5: In a round bottomed flask, add an excess of ethylene diamine (10 mL) to a solution of methyl biotinate (2.5 mmol) in methanol (10 mL). Keep the solution at 60 °C for 48 hours, and then, remove the excess ethylene diamine and methanol under reduced pressure. Obtain the product as light yellow solid biotin (2-amino-ethyl)-amide) and use directly for the next experiment. [5]

In a round bottomed flask, equipped with a stir bar, Dioxoindoline-5-carboxylic Acid (2.0 mmol), HOBT (3.0 mmol), HBTU (3.0 mmol), dichloromethane (40 mL) and triethylamine (2.4 mmol) were combined and added. The mixture was stirred for 30 min at room temperature. And then, biotin (2-amino-ethyl)-amide) (2.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed with saturated $NaHCO_3$ solution (40 mL x 3), 2M hydrochloric acid solution (40 mL x 3) and H_2O (40 mL x 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. Evaporation of the solvent that was dissolved in DMSO. Then a crude product recrystallize by methanol.

In an oven-dried undivided three-necked bottle (15 mL) equipped with a stir bar, polypeptides **2g** (5 mg), compound **4** (20 mg), $^{n}Bu_4NF{\cdot}3H_2O$ (10 mg), CH_3CN (1.0 mL) and phosphate buffer solution (0.75 mL, pH= 7.4) were combined and added. The bottle was equipped platinum plate (10 mm×10 mm×0.1 mm) as the anode and plumbum plate (10 mm×10 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 5 mA under room

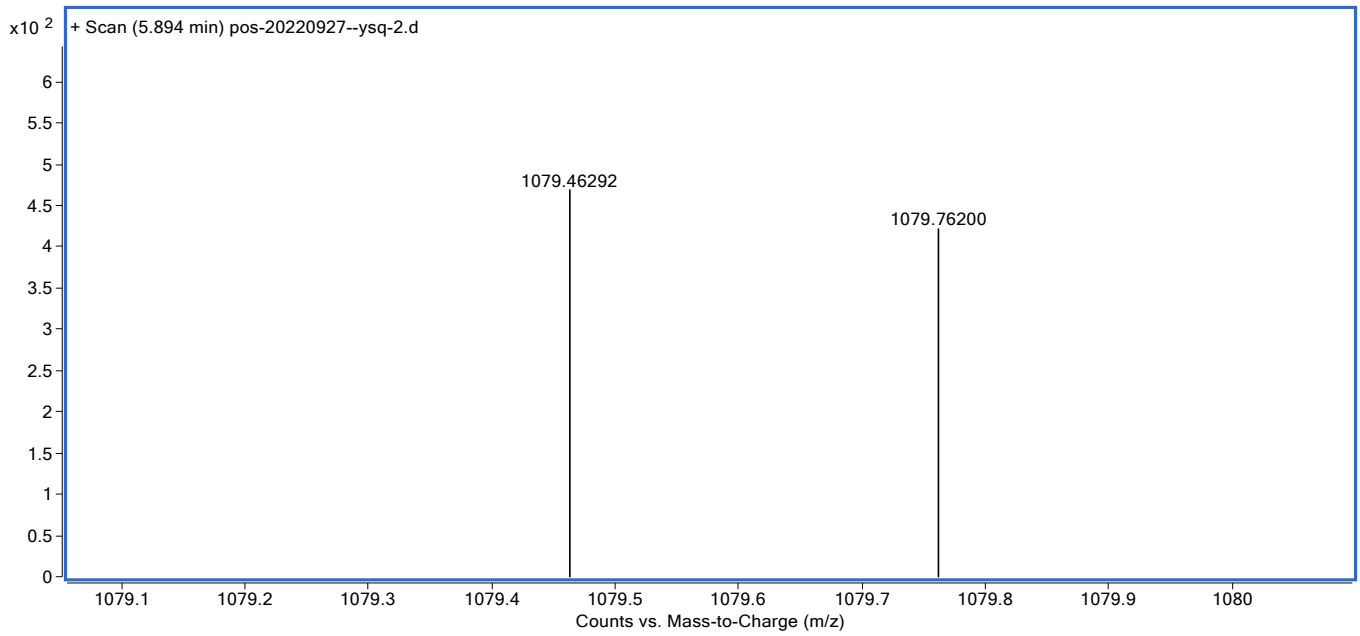
temperature for 30 min. After completion of the reaction, the solution was analyzed by LC-MS spectroscopy. The reaction was analyzed by reverse phase HPLC using a gradient of 60% to 50% buffer B over 20 minutes on an Agilent Zorbax SB-Aq 5µm column of 250 mm length. HPLC analysis used buffers A (water) and B (acetonitrile + 0.1% TFA). Conversion reported as a % conversion as determined.



Detailed descriptions for products 5:

HPLC: >99% conversion.

After the reaction finished, there are four peaks that elute at 50% buffer B (acetonitrile + 0.1% TFA) with retention times of 1.828 min , 2.541 min, 3.077 min and 4.055 min. Polypeptide

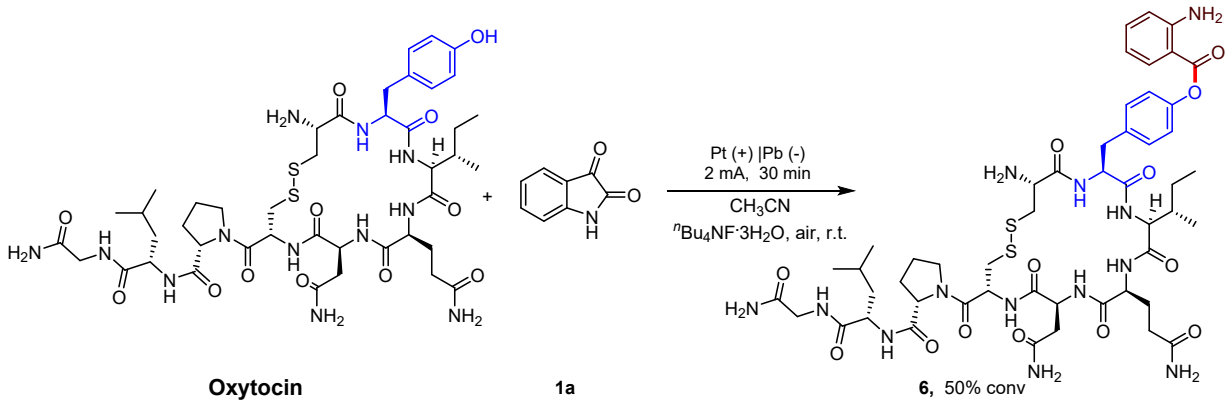


2g is a peak that elutes at 50% buffer B (acetonitrile + 0.1% TFA) with a retention time of 3.204 min.

HRMS (ESI-TOF) calcd for $C_{52}H_{68}N_{10}O_{12}SNa$, [M+Na]+, 1079.4631, found 1079.4629

3.7.2 Bioconjugation of Oxytocin

Synthesis of compound 6: In an oven-dried undivided three-necked bottle (15 mL) equipped with a stir bar, Oxytocin (10 mg), **1a** (15 mg), $^{n}Bu_4NF{\cdot}3H_2O$ (10 mg), CH_3CN (2.0 mL) were combined and added. The bottle was equipped platinum plate (10 mm×10 mm×0.1 mm) as the anode and plumbum plate (10 mm×10 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 2 mA under room temperature for 30 min. After completion of the reaction, the solution was analyzed by LC-MS spectroscopy. The reaction was analyzed by reverse phase HPLC using a gradient of 60% to 50% buffer B over 20 minutes on an Agilent Zorbax SB-Aq 5μm column of 250 mm length. HPLC analysis used buffers A (water) and B (acetonitrile + 0.1% TFA). Conversion reported as a % conversion as determined.

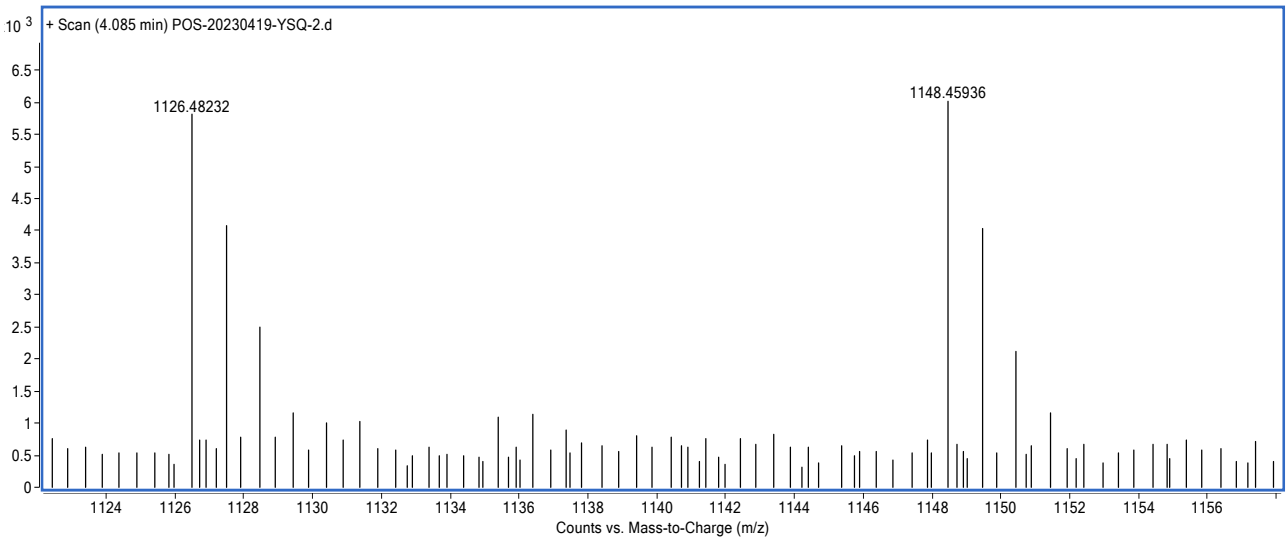


Oxytocin **1a** **6,** 50% conv

Detailed descriptions for products 6:

HPLC: 50% conversion.

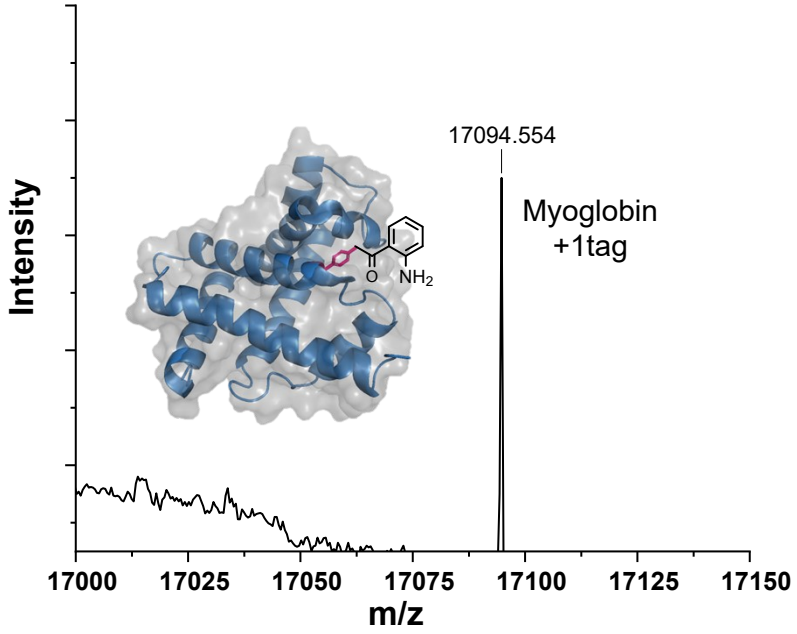
After the reaction finished, there are three peaks that elute at 50% buffer B (acetonitrile + 0.1% TFA) with retention times of 2.028 min , 4.543 min, 5.09 min. Oxytocin is a peak that elutes at 50% buffer B with a retention time of 3.98 min.



HRMS (ESI-TOF) calcd for $C_{50}H_{72}N_{13}O_{13}S_2$, [M+H]+, 1126.4814, found 1126.4823.

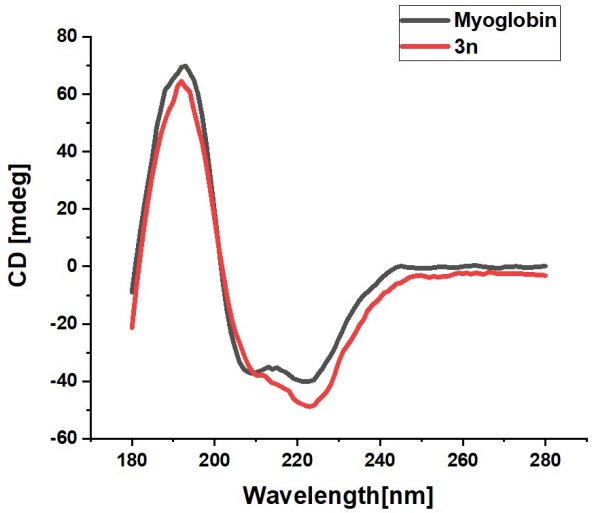
3.7.3 Bioconjugation of Protein

Synthesis of 3n: In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, Myoglobin (5 mg), **1a** (10 mg), $^{n}Bu_4NF{\cdot}3H_2O$ (10 mg), CH_3CN (1.0 mL) and phosphate buffer solution (0.75 mL, pH= 7.4) were combined and added. The bottle was equipped platinum plate (10 mm×10 mm×0.1 mm) as the anode and plumbum plate (10 mm×10 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 2 mA under -20℃ for 10 min. After completion of the reaction, the solution was analyzed by Maldi-Tof MS.

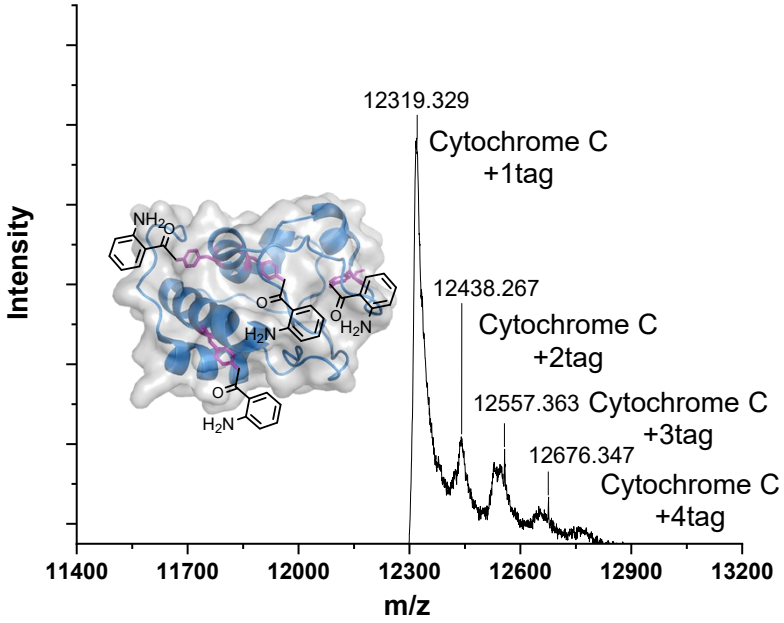


Effect of anthranilic acyl modification on structure of Myoglobin

Comparison of CD spectra between Myoglobin and **3n** sample (100μg/mL in PBS buffer).

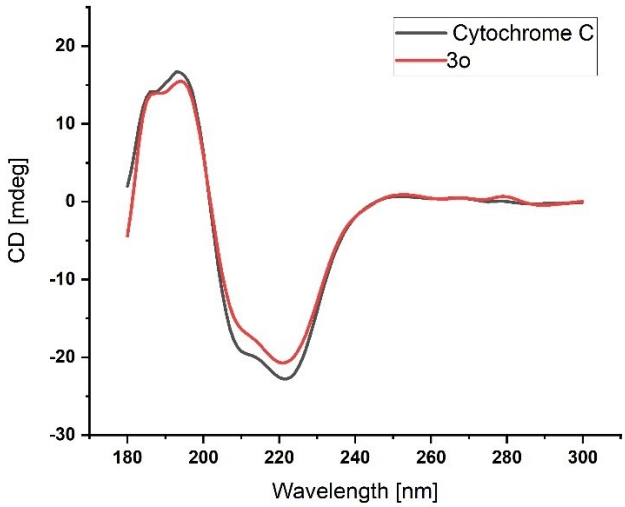


Synthesis of 3o : In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, Cytochrome C (5 mg), **1a** (7 mg), $^{n}Bu_4NF{\cdot}3H_2O$ (5 mg), CH_3CN (1.0 mL) and phosphate buffer solution (0.75 mL, pH= 7.4) were combined and added. The bottle was equipped platinum plate (10 mm×10 mm×0.1 mm) as the anode and plumbum plate (10 mm×10 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 2 mA under -10℃ for 15 min. After completion of the reaction, the solution was analyzed by Maldi-Tof MS.

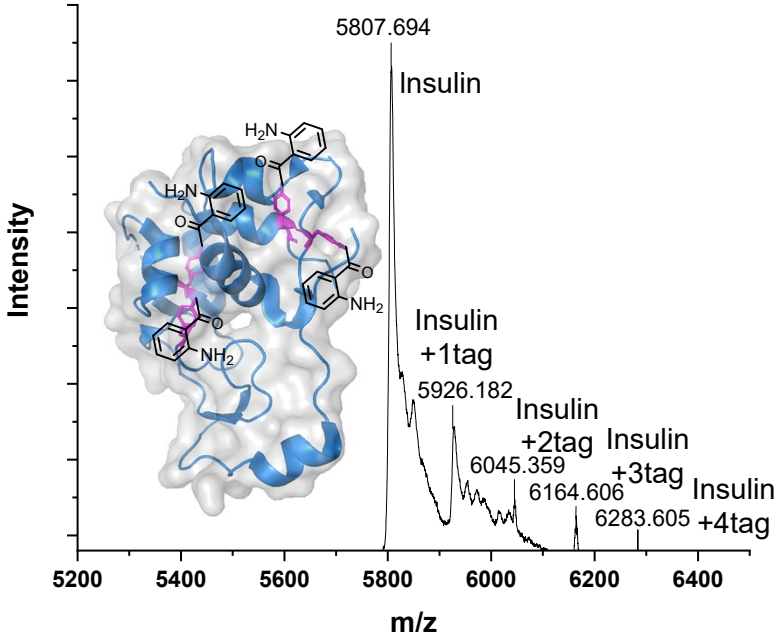


Effect of anthranilic acyl modification on structure of Cytochrome C

Comparison of CD spectra between Cytochrome C and **3o** sample (100μg/mL in PBS buffer).

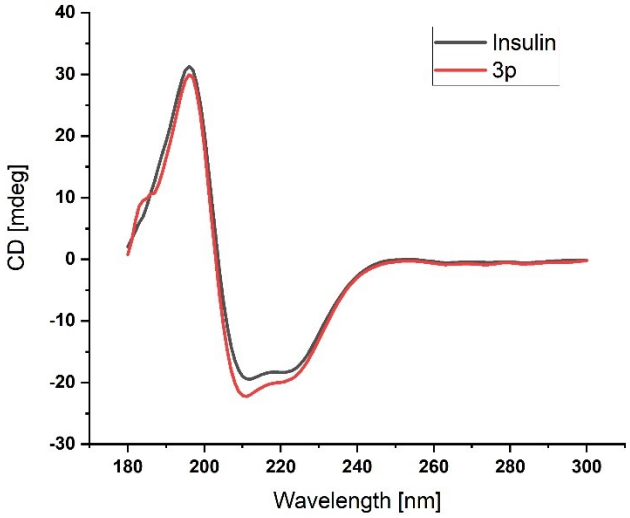


Synthesis of 3p : In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, insulin (10 mg), **1a** (15 mg), $^{n}Bu_4NF{\cdot}3H_2O$ (15 mg), CH_3CN (1.0 mL) and phosphate buffer solution (0.75 mL, pH= 7.4) were combined and added. The bottle was equipped platinum plate (10 mm×10 mm×0.1 mm) as the anode and plumbum plate (10 mm×10 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 2 mA under -15°C for 20 min. After completion of the reaction, the solution was analyzed by Maldi-Tof MS.



Effect of anthranilic acyl modification on structure of insulin

Comparison of CD spectra between insulin and **3p** sample (100μg/mL in PBS buffer).



4. References

[1] R. A. Serwa, J.-M. Swiecicki, D. Homann, C. P. R. Hackenberger, Phosphoramidate-peptide synthesis by solution- and solid-phase Staudinger-phosphite reactions. *J. Pept. Sci.* **2010**, *16*, 563–567.

[2] Alam J, Keller T H, Loh T P. Functionalization of peptides and proteins by Mukaiyama aldol reaction. *J. Am. Chem. Soc.* **2010**, *132*, 9546-9548.

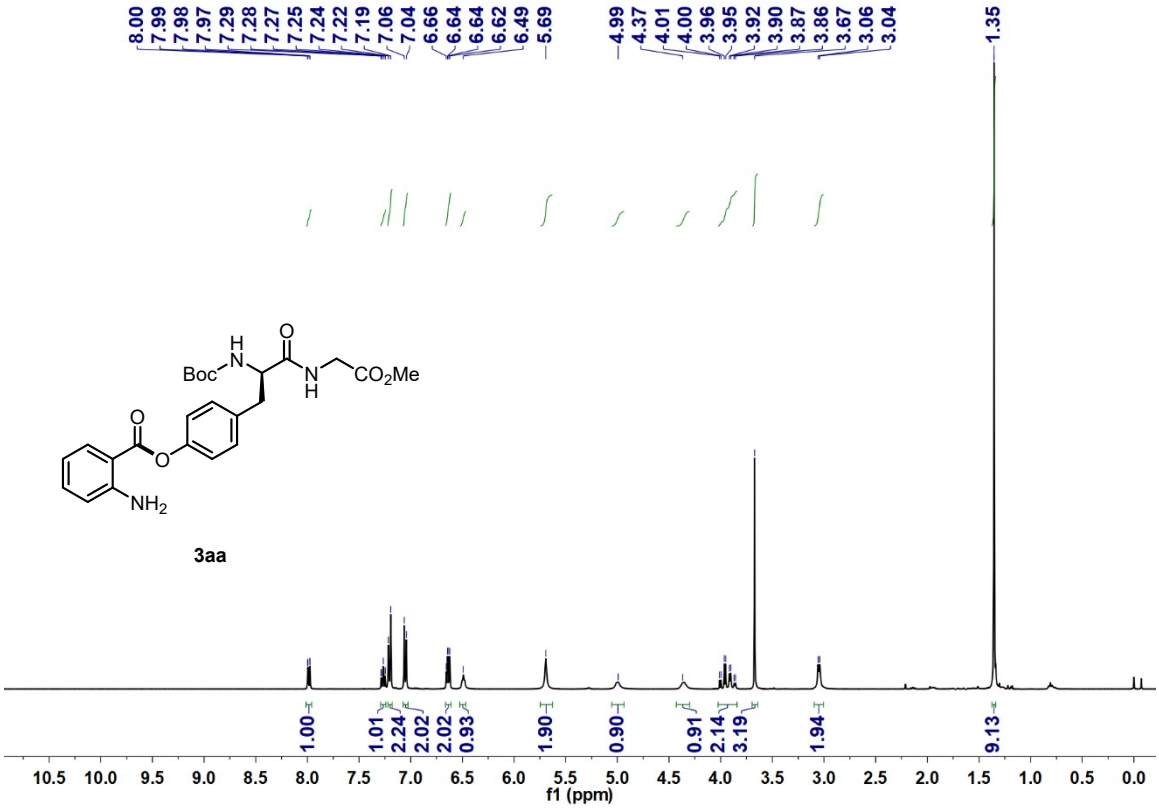
[3] Gu, K., Liu, Y., Guo, Z., Lian, C., Yan, C., Shi, P., Zhu, W. H. In situ ratiometric quantitative tracing of intracellular leucine aminopeptidase activity via an activatable near-infrared fluorescent probe. *ACS Appl. Mater. Inter.* **2016**, *8*, 26622-26629.

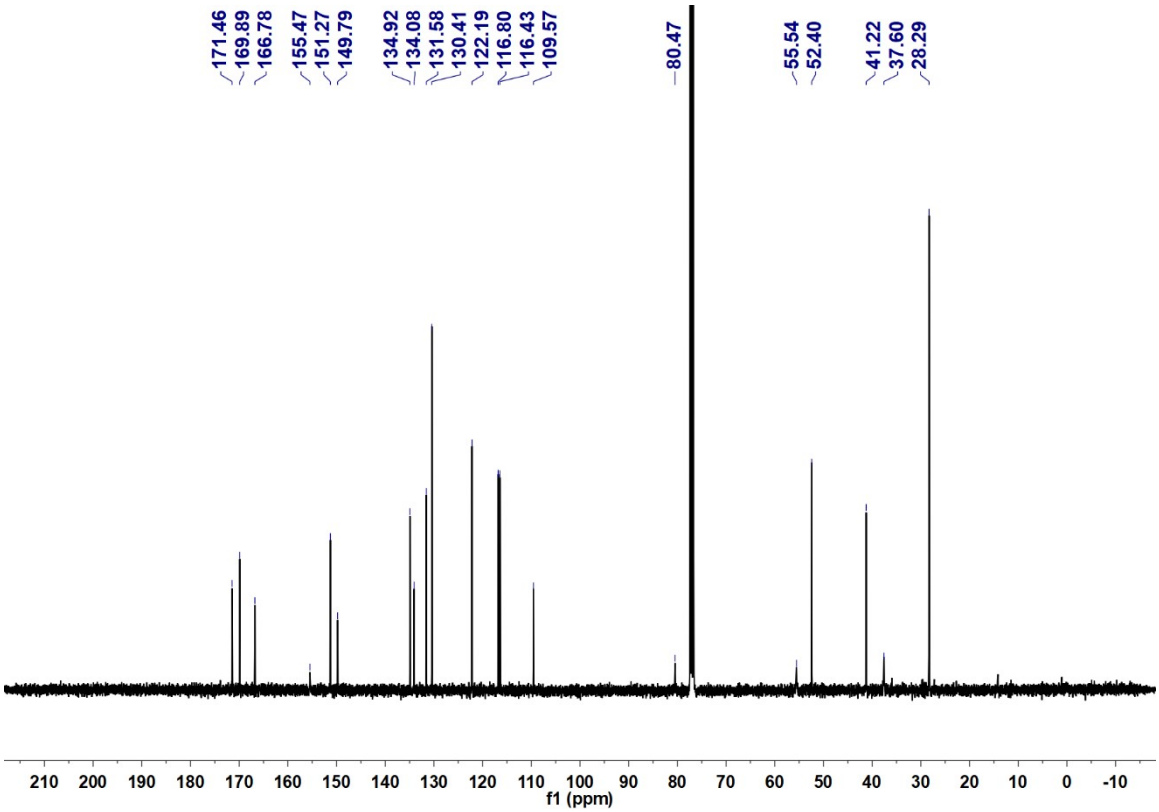
[4] Bravo, F., McDonald, F. E., Neiwert, W. A., & Hardcastle, K. I. Alkene Substituents for Selective Activation of *Endo*-Regioselective Polyepoxide Oxacyclizations. *Org. Lett.* **2004**, *6*, 4487-4489.

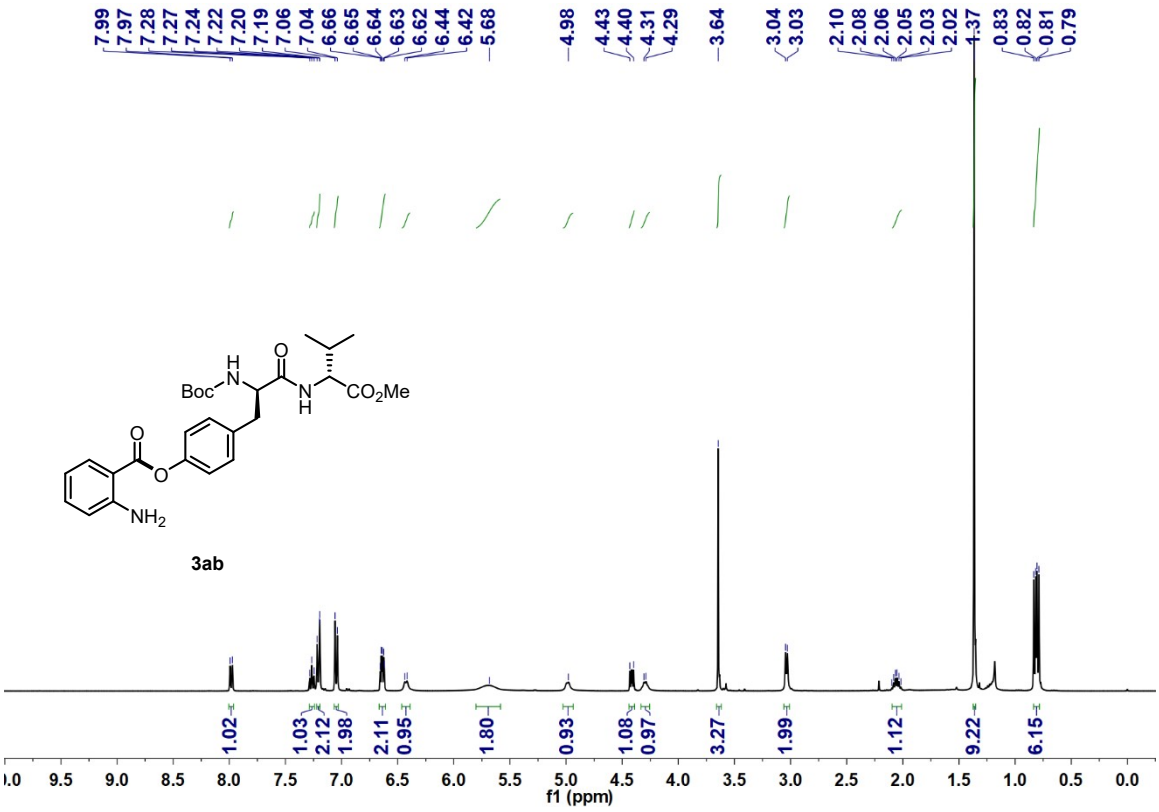
[5] I. A. Inverarity, R. F. H. Viguier, P. Cohen, A. N. Hulme, Biotinylated Anisomycin, A Comparison of Classical and “Click” Chemistry Approaches. *Bioconj. Chem.* **2007**, 18, 1593–1603.

5. Spectra

5.1 NMR Spectra of Products






7.99
7.97
7.28
7.27
7.24
7.22
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7.19
7.06
7.04
6.66
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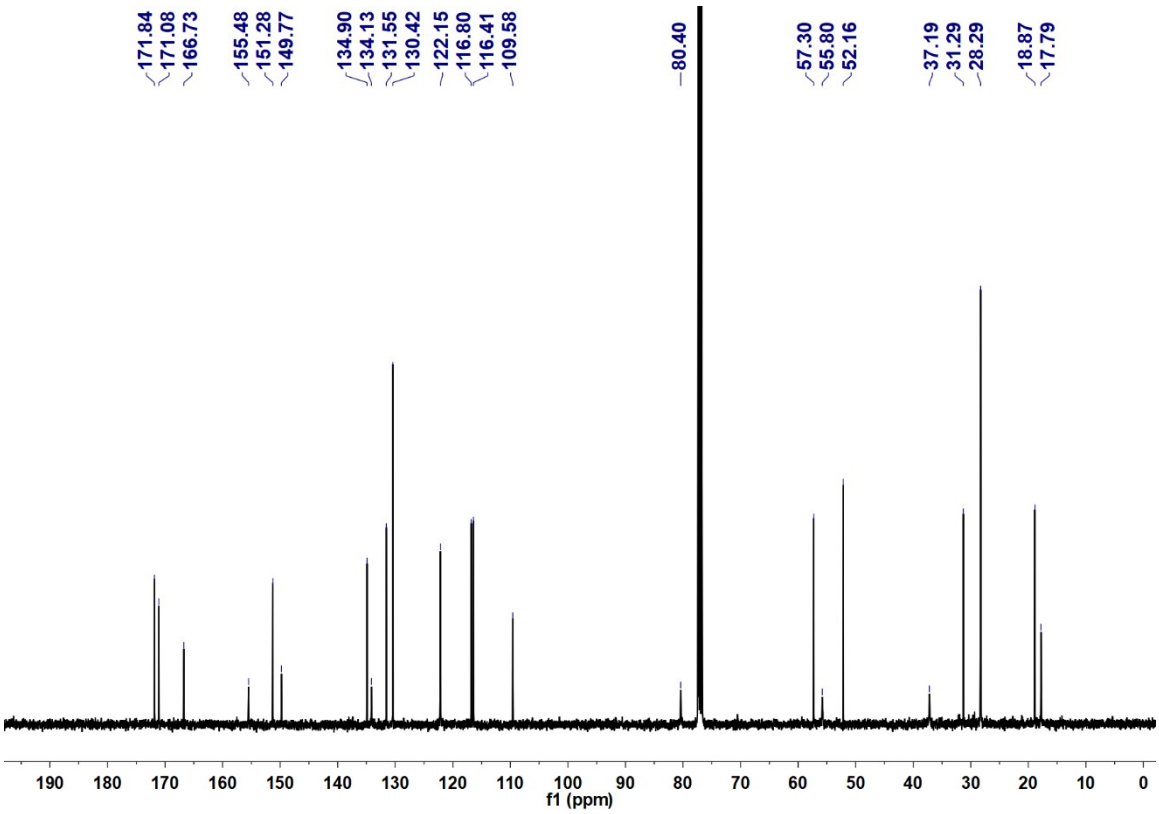
6.64
6.63
6.62
6.44
6.42
5.68
4.98
4.43
4.40
4.31
4.29
3.64
3.04
3.03
2.10
2.08
2.06
2.05
2.03
2.02
1.37
0.83
0.82
0.81
0.79
Boc
H
N
O
N
H
CO2Me
O
O
NH2
3ab
1.02
1.03
2.12
1.98
2.11
0.95
1.80
0.93
1.08
0.97
3.27
1.99
1.12
9.22
6.15
f1 (ppm)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134.90
134.13
131.55
130.42
122.15
116.80
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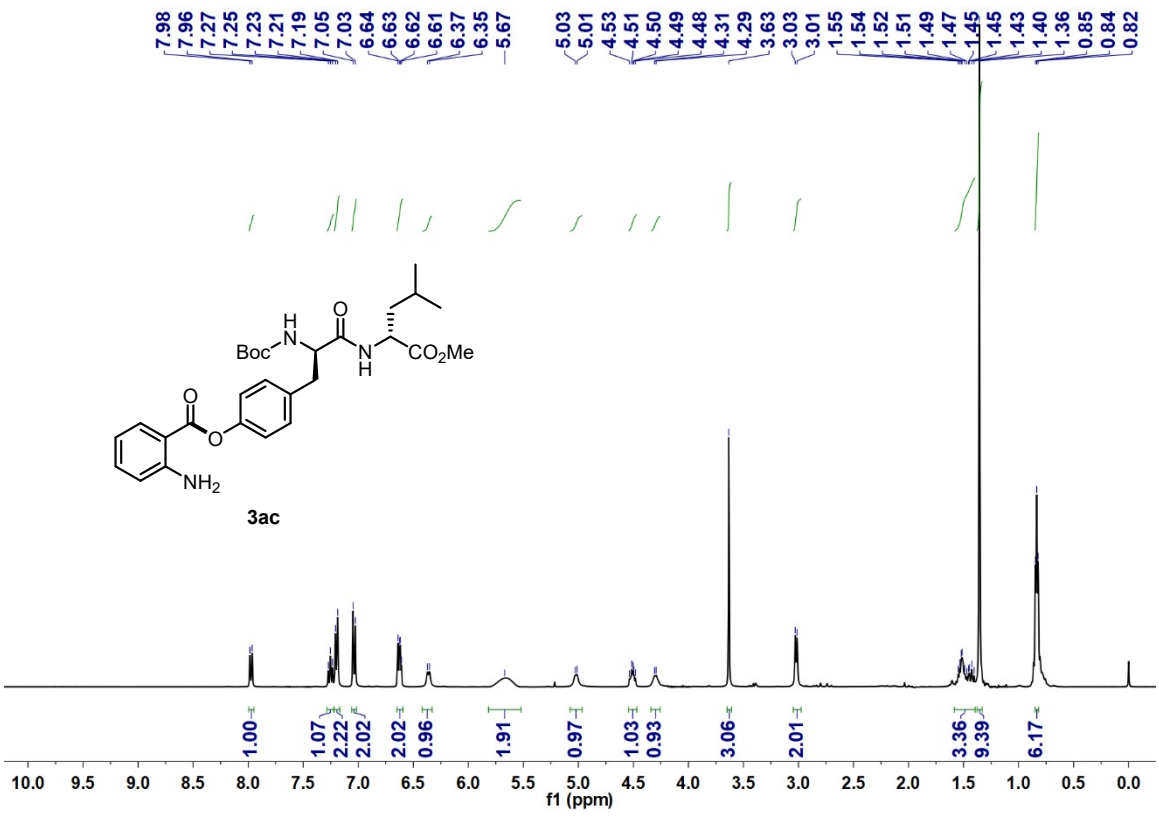
37.19
31.29
28.29
18.87
17.79
f1 (ppm)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7.23
7.21
7.19
7.05
7.03
6.64
6.63
6.62
6.61
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5.67
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3.01
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1.54
1.52
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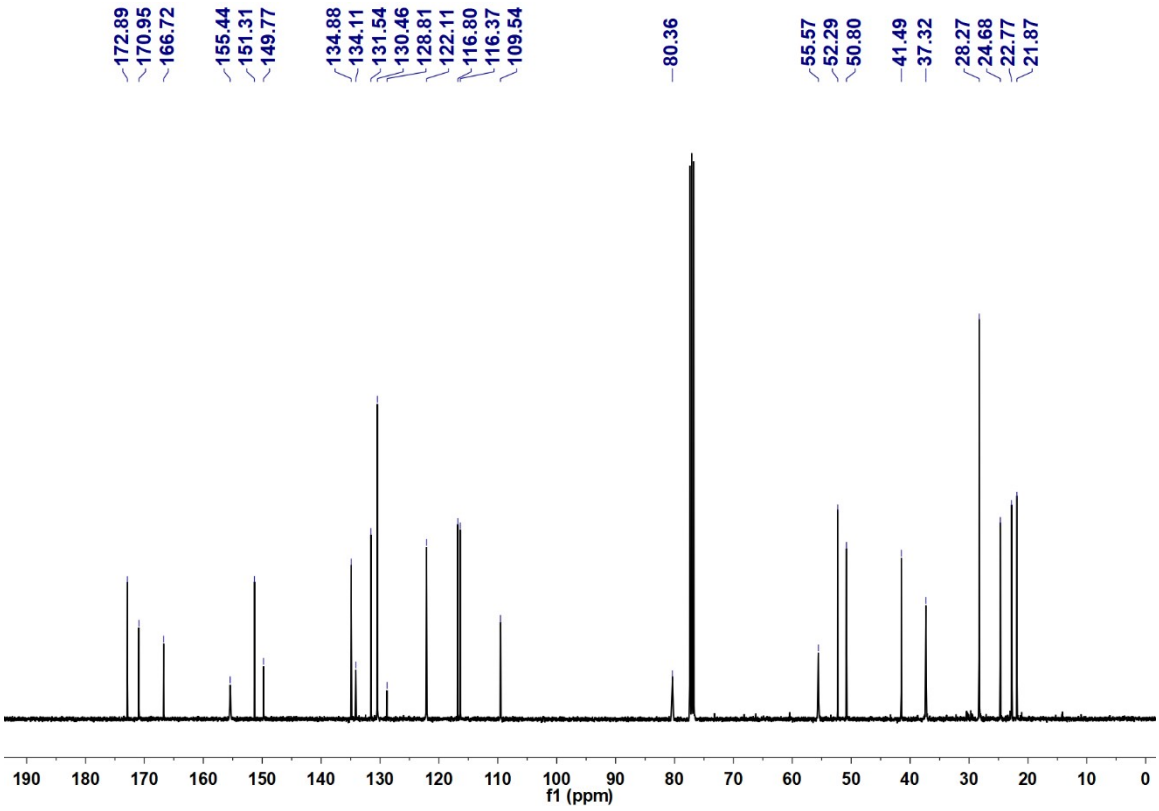
1.47
1.45
1.45
1.43
1.40
1.36
0.85
0.84
0.82
Boc
N
H
O
N
H
CO2Me
O
O
NH2
3ac
1.00
1.07
2.22
2.02
2.02
0.96
1.91
0.97
1.03
0.93
3.06
2.01
3.36
9.39
6.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


172.89
170.95
166.72
155.44
151.31
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134.88
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131.54
130.46
128.81
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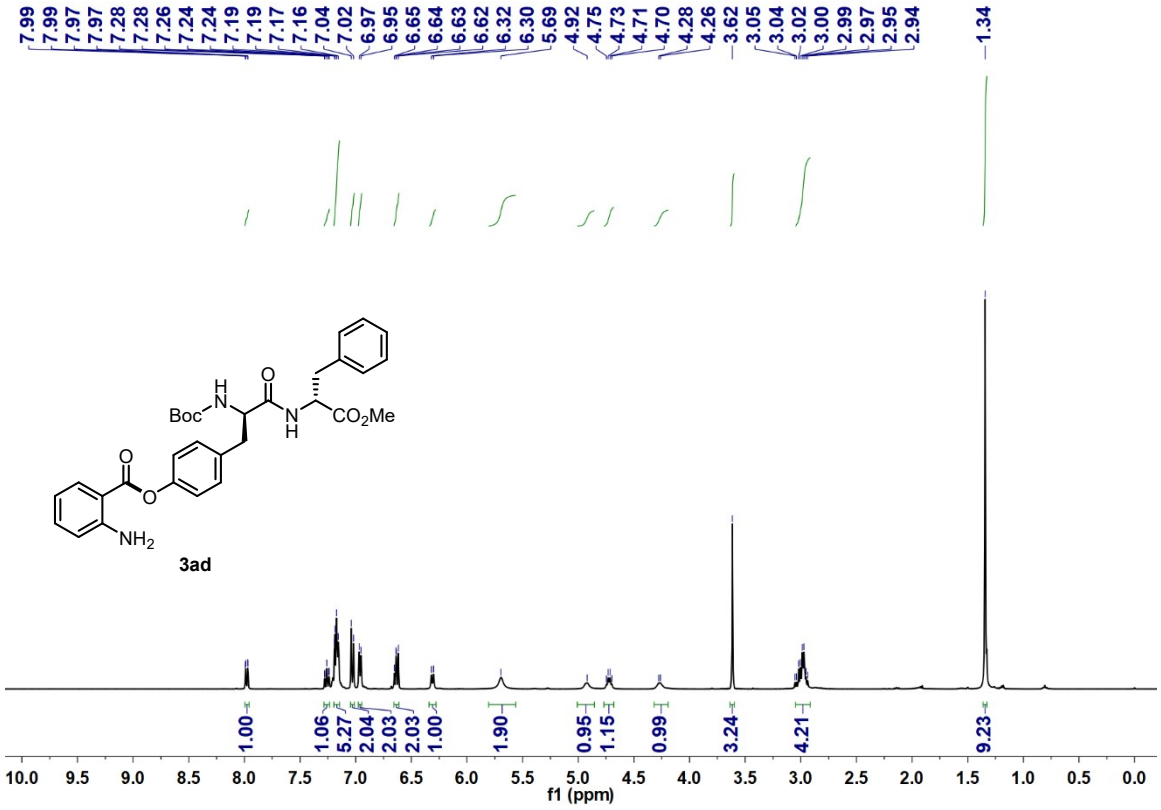
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3.05
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3.02
3.00
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2.97
2.95
2.94
1.34
Boc
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H
O
N
H
CO2Me
O
O
NH2
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5.27
2.04
2.03
2.03
1.00
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0.95
1.15
0.99
3.24
4.21
9.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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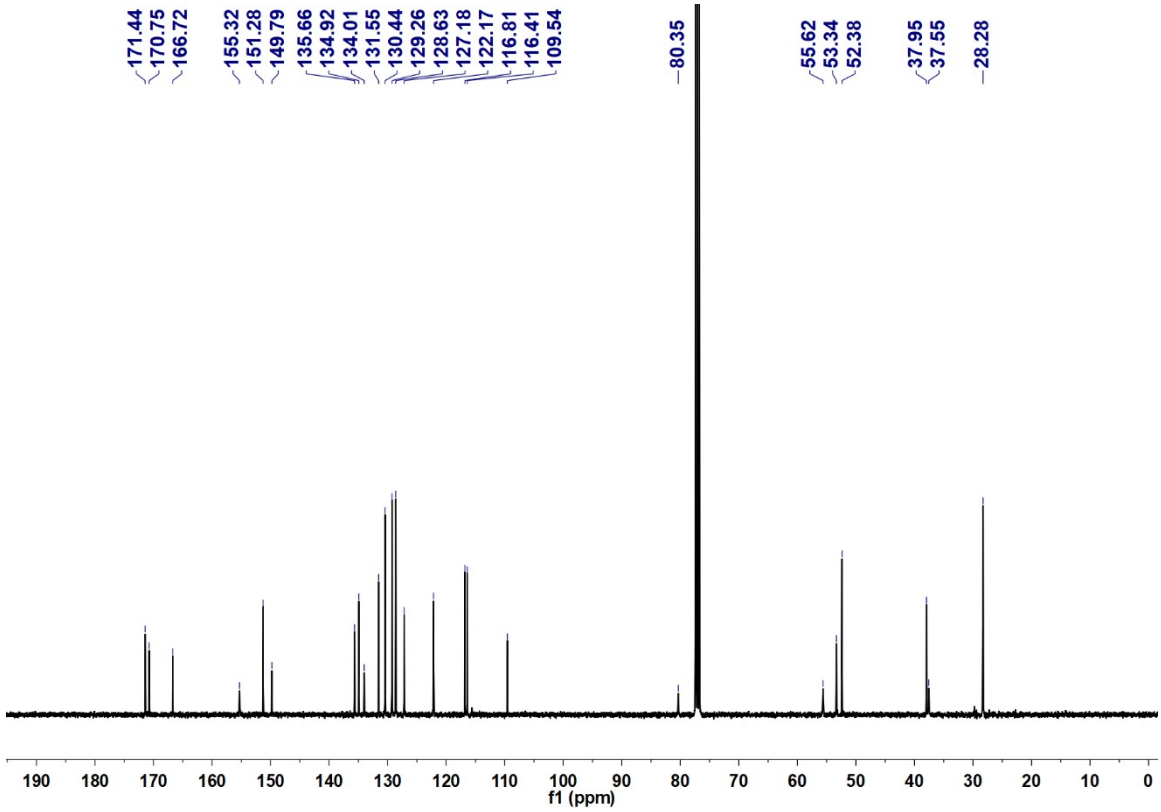
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109.54
80.35
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37.95
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28.28
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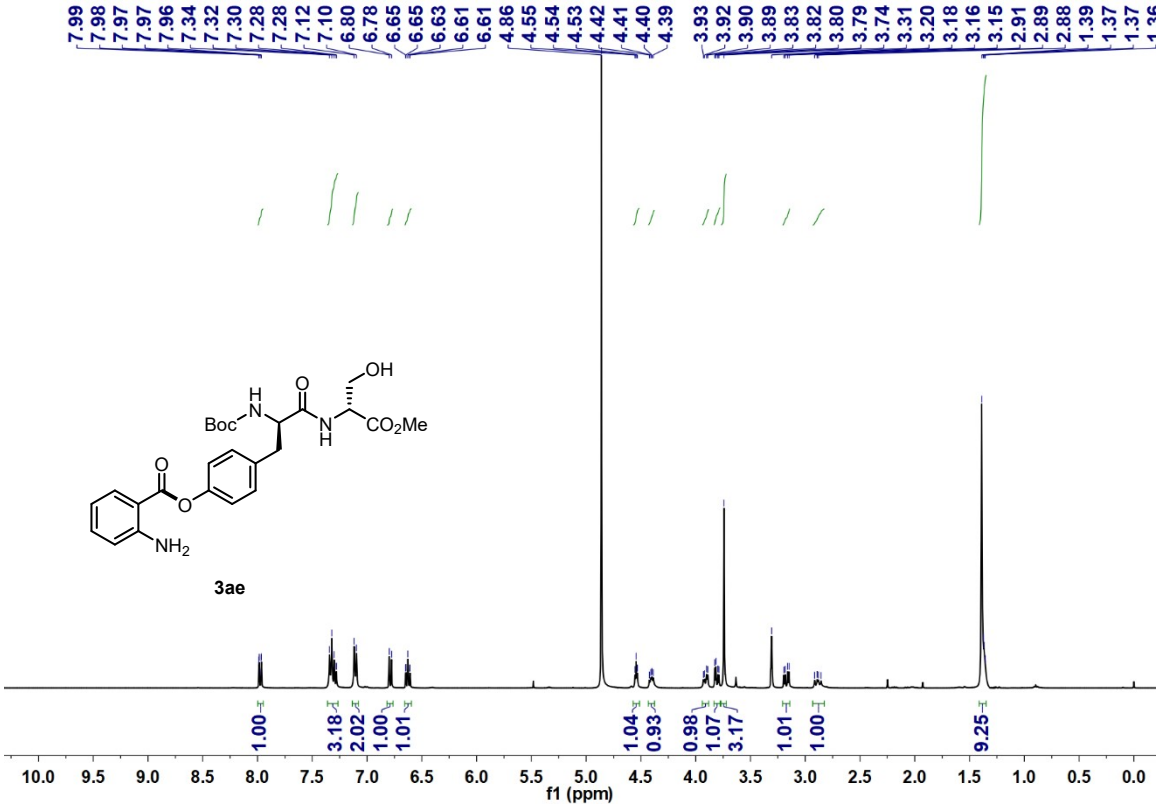
f1 (ppm)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6.65
6.65
6.63
6.61
6.61
4.86
4.55
4.54
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4.40
4.39
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3.92
3.90
3.89
3.83
3.82
3.80
3.79
3.74
3.31
3.20
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3.16
3.15
2.91
2.89
2.88
1.39
1.37
1.37
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Boc
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H
O
N
H
CO2Me
O
O
NH2
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3.18
2.02
1.00
1.01
1.04
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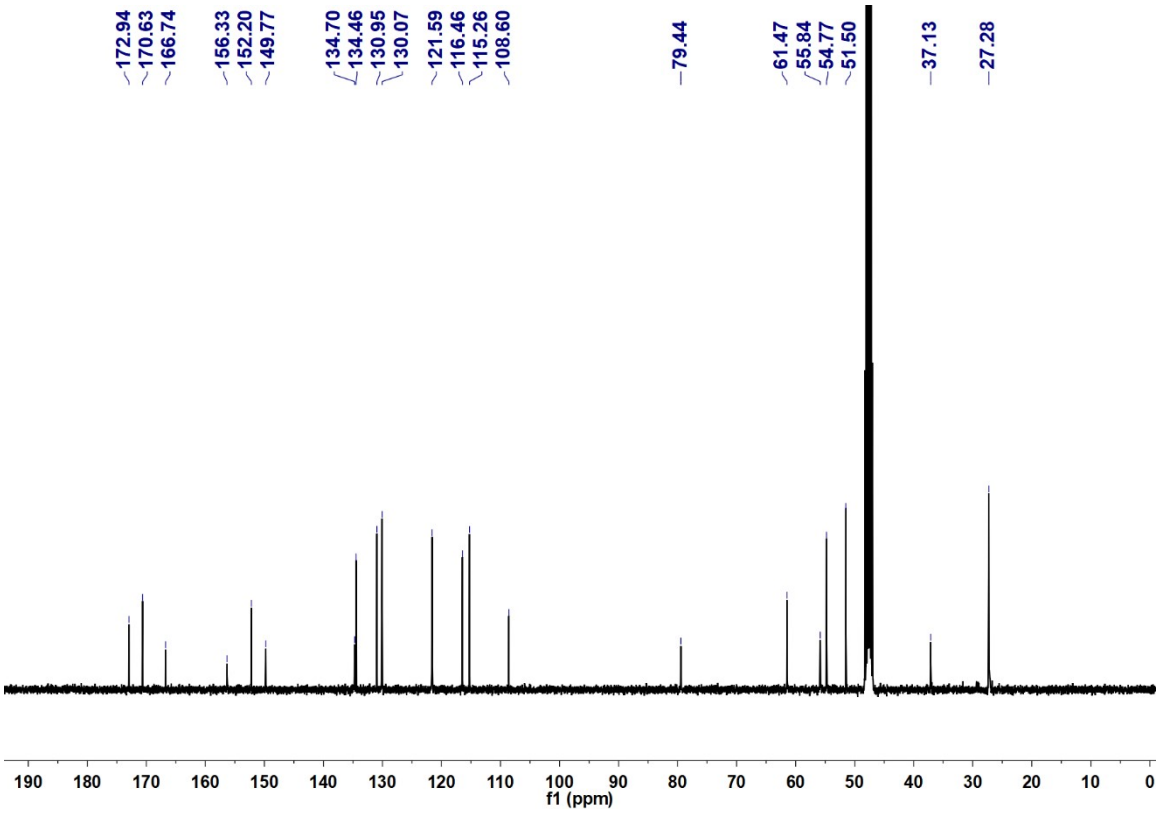
0.98
1.07
3.17
1.01
1.00
9.25
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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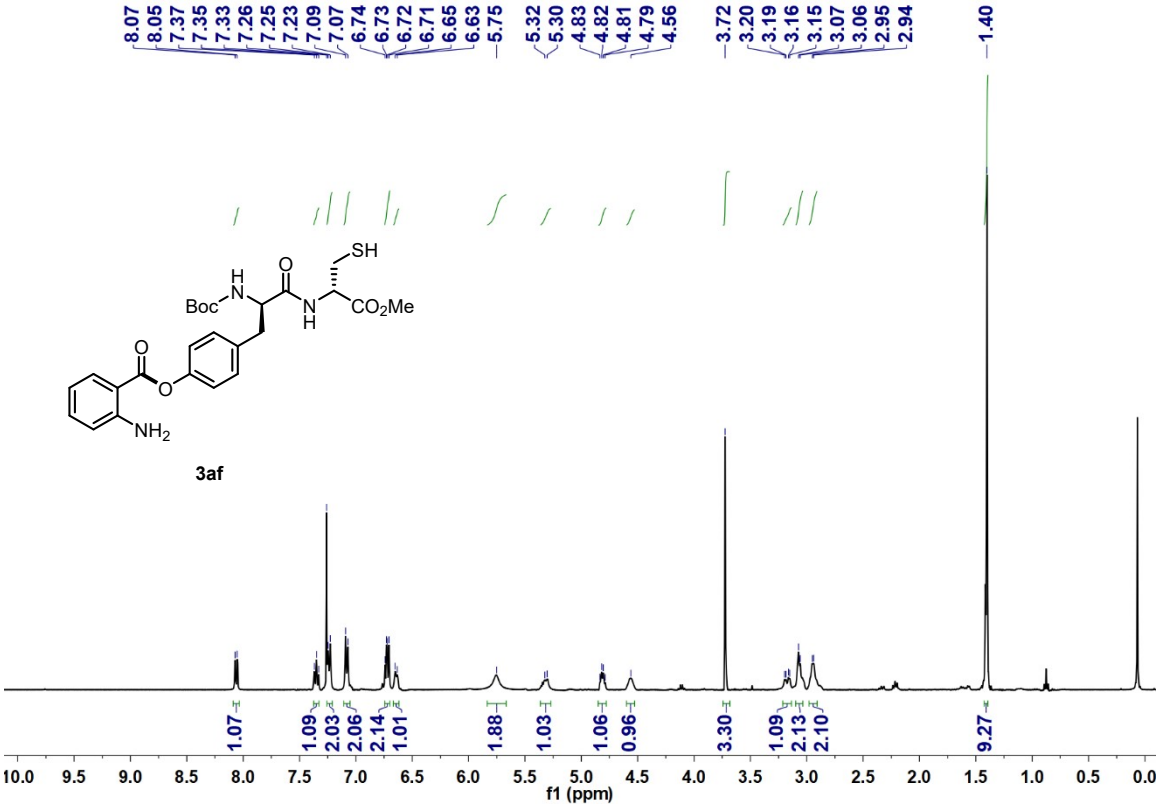
f1 (ppm)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6.71
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6.63
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5.32
5.30
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3.72
3.20
3.19
3.16
3.15
3.07
3.06
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Boc
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H
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NH2
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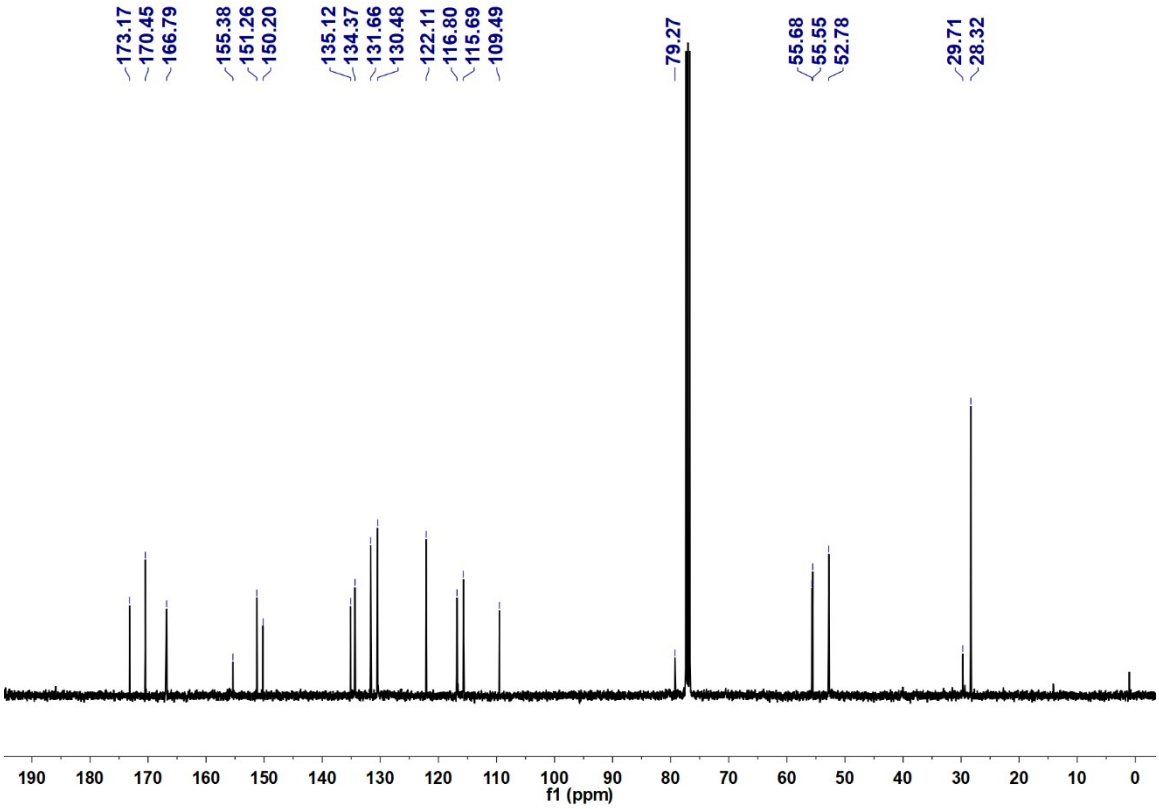
2.06
2.14
1.01
1.88
1.03
1.06
0.96
3.30
1.09
2.13
2.10
9.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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115.69
109.49
79.27
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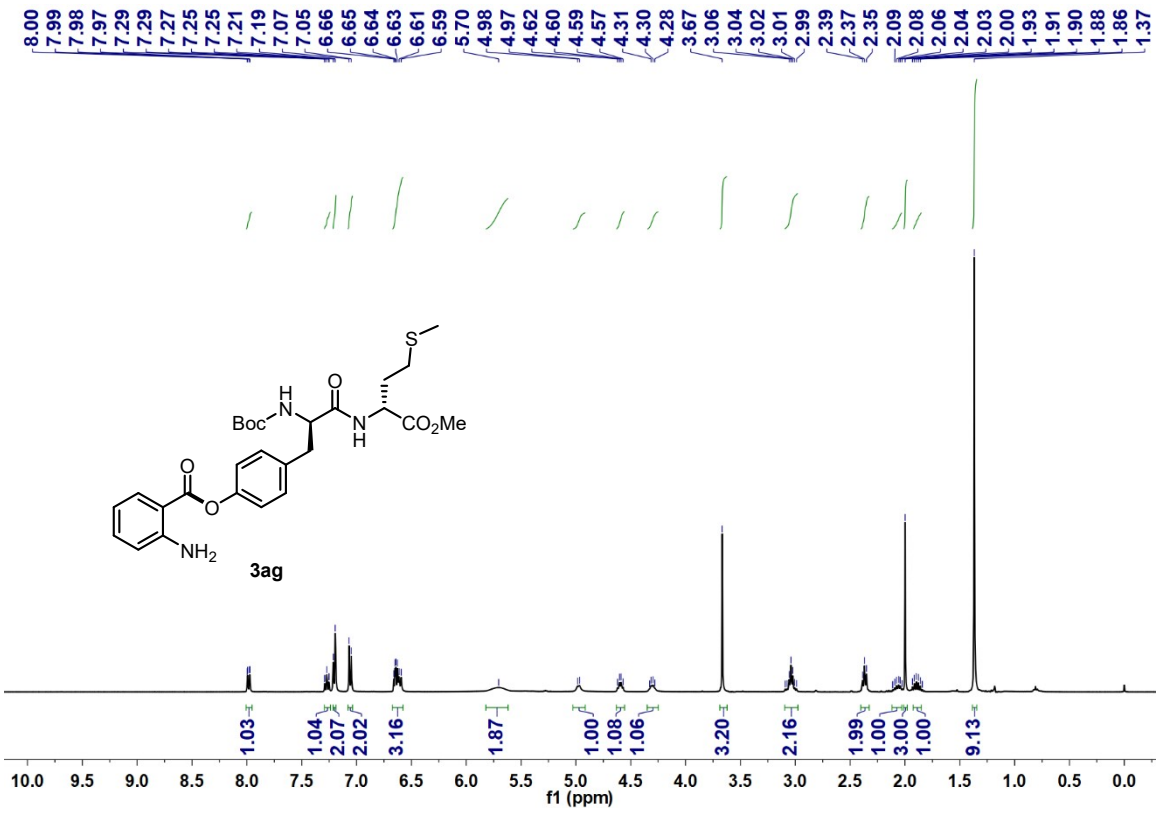
55.55
52.78
29.71
28.32
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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Boc
CO2Me
NH2
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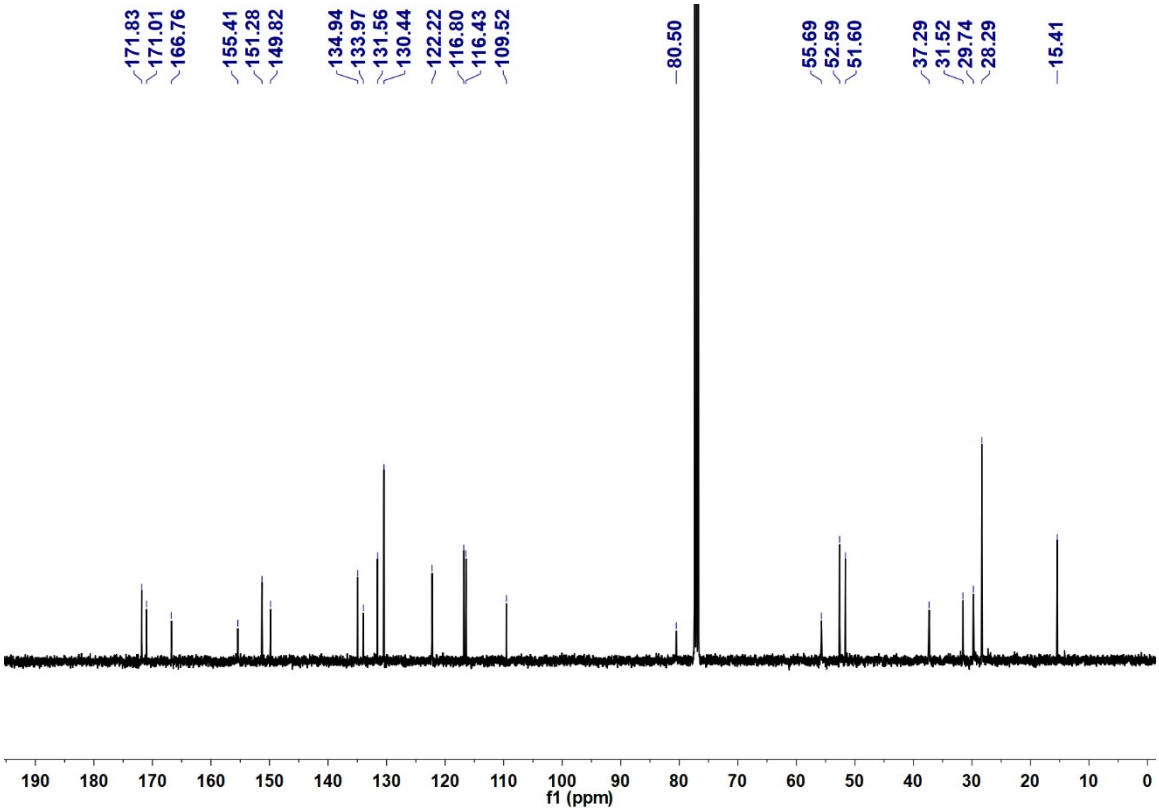
1.03 1.04 2.07 2.02 3.16 1.87 1.00 1.08 1.06 3.20 2.16 1.99 1.00 3.00 1.00 9.13
f1 (ppm)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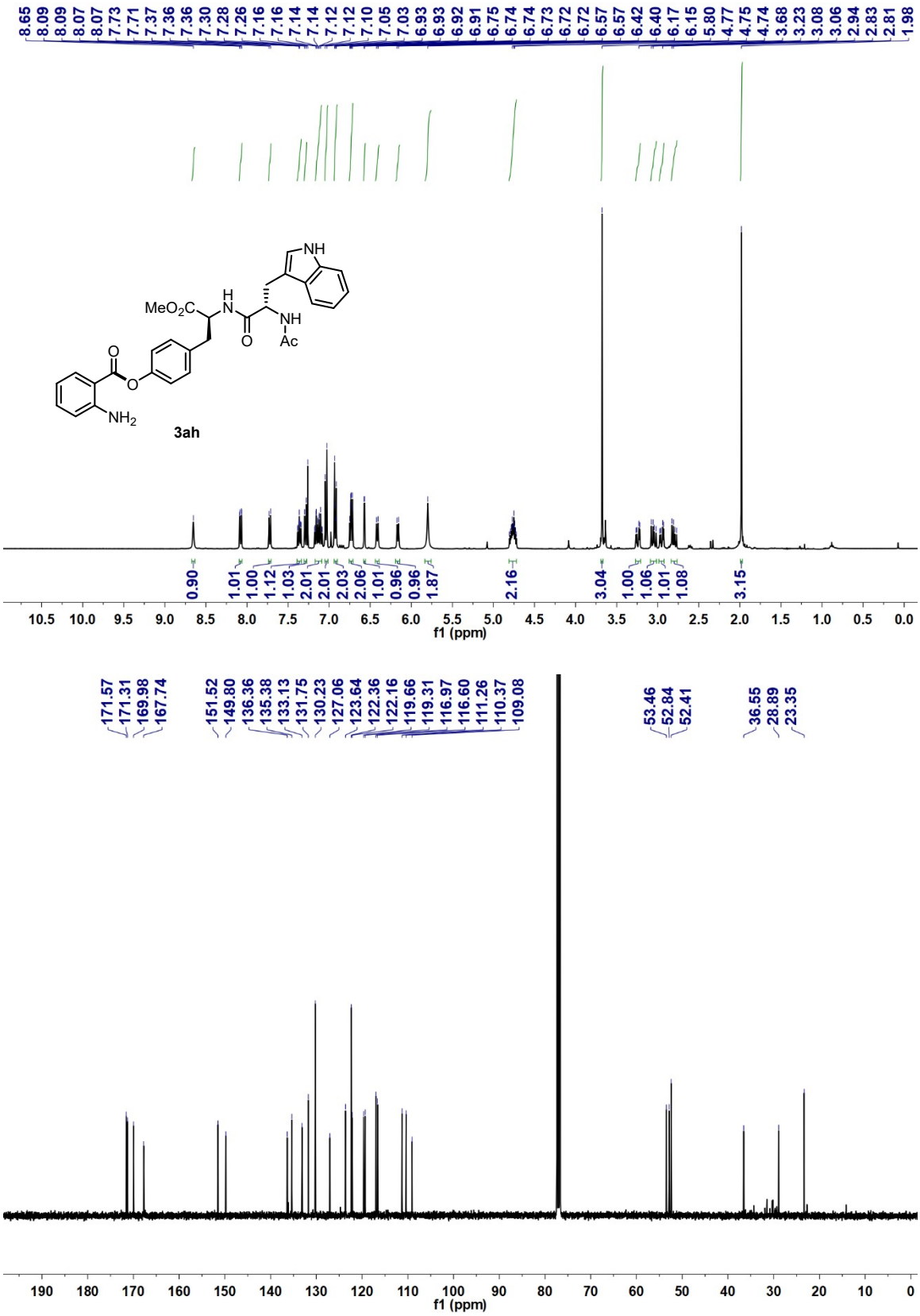
f1 (ppm)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NH
MeO2C
H
N
O
NH
Ac
O
O
NH2
3ah
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f1 (ppm)
171.57 171.31 169.98 167.74 151.52 149.80 136.36 135.38 133.13 131.75 130.23 127.06 123.64 122.36 122.16 119.66 119.31 116.97 116.60 111.26 110.37 109.08 53.46 52.84 52.41 36.55 28.89 23.35
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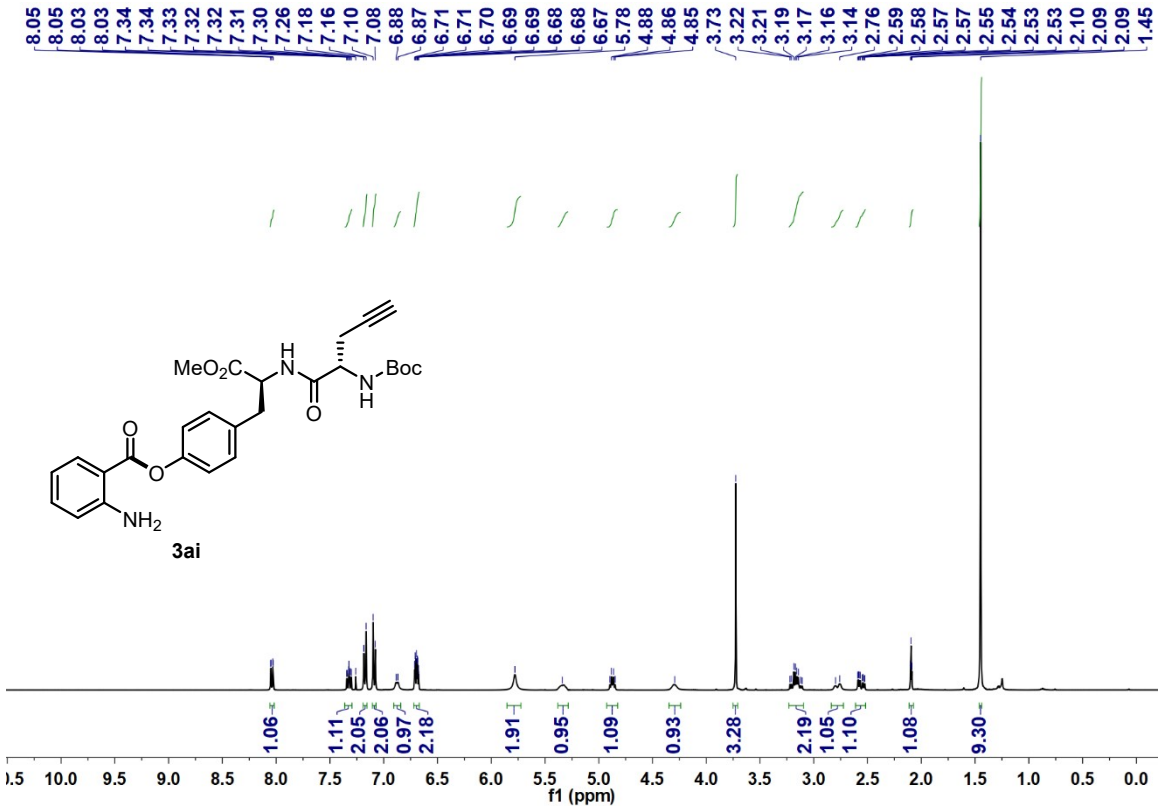
f1 (ppm)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MeO2C
H
N
O
N
H
Boc
O
O
O
NH2
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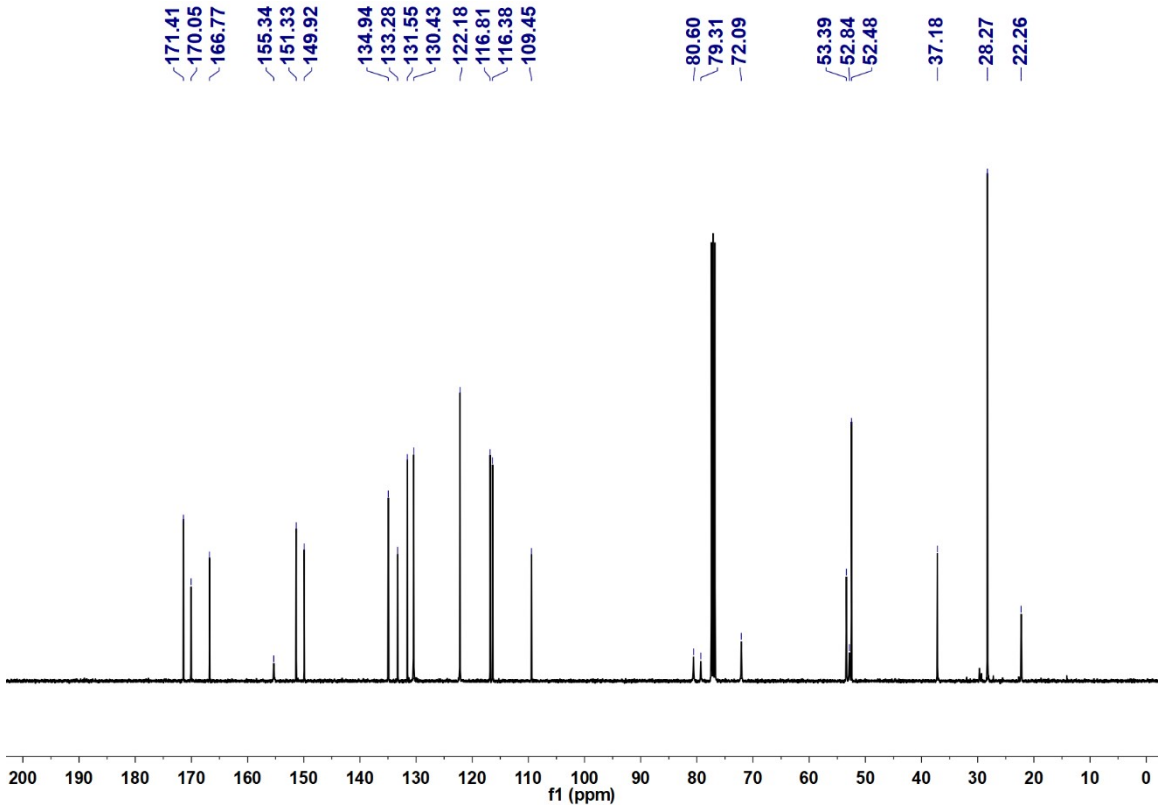
f1 (ppm)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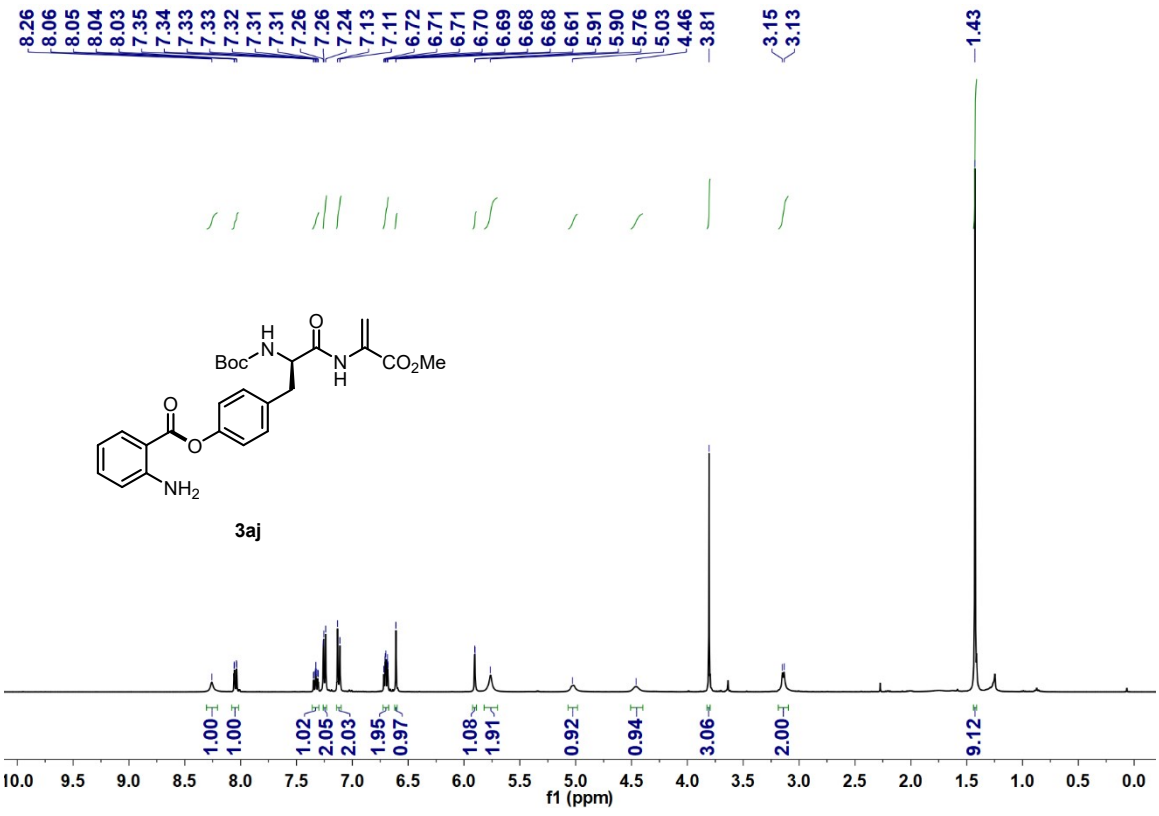
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N
H
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O
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NH2
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2.03
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1.08
1.91
0.92
0.94
3.06
2.00
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9.0
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7.0
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5.5
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2.0
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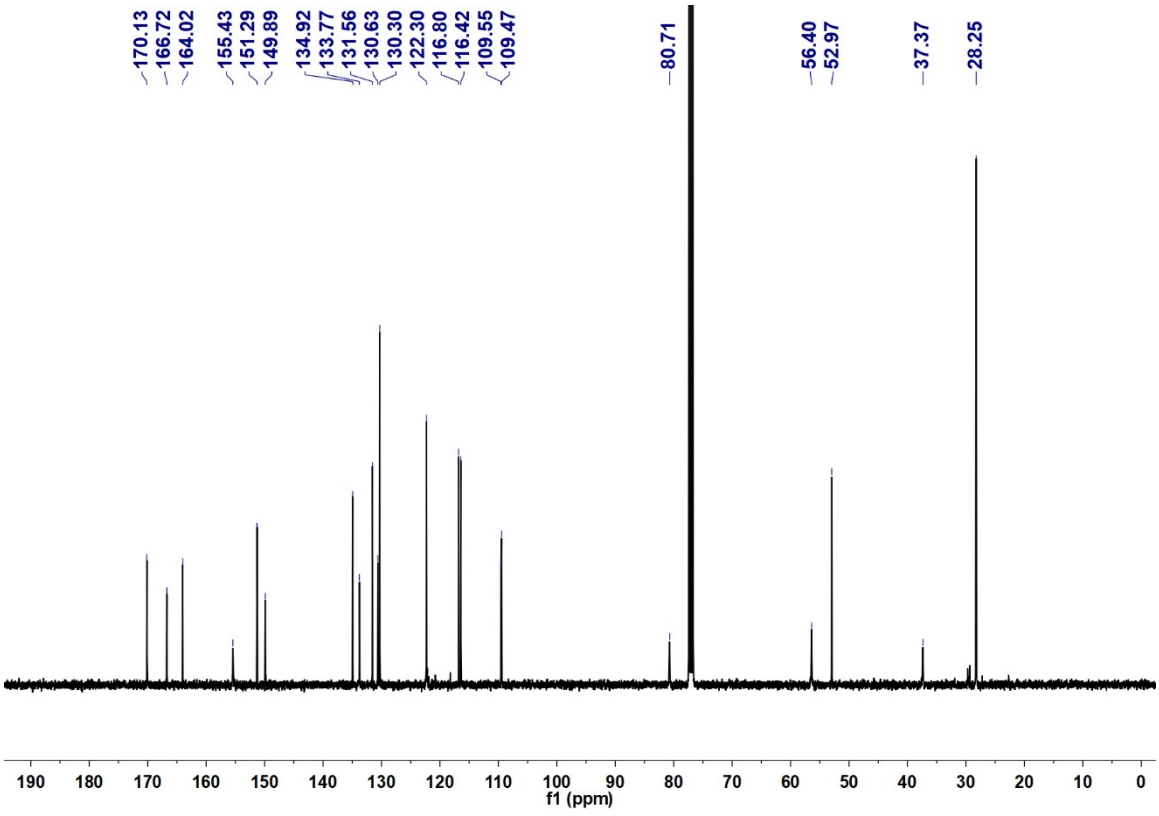
f1 (ppm)

3aj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37.37
28.25
190
180
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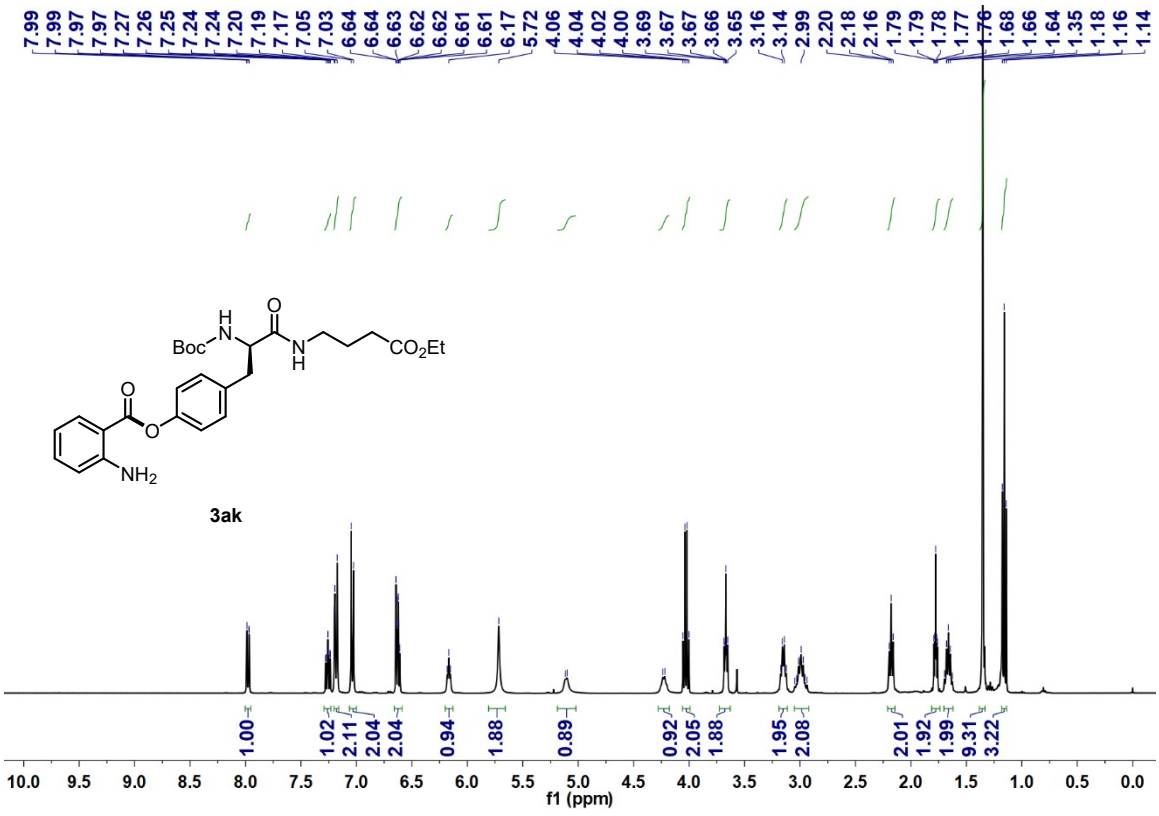
f1 (ppm)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1.77
1.76
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1.64
1.35
1.18
1.16
1.14
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O
N
H
CO2Et
O
O
NH2
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2.04
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0.92
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1.88
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2.08
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1.92
1.99
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6.0
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2.0
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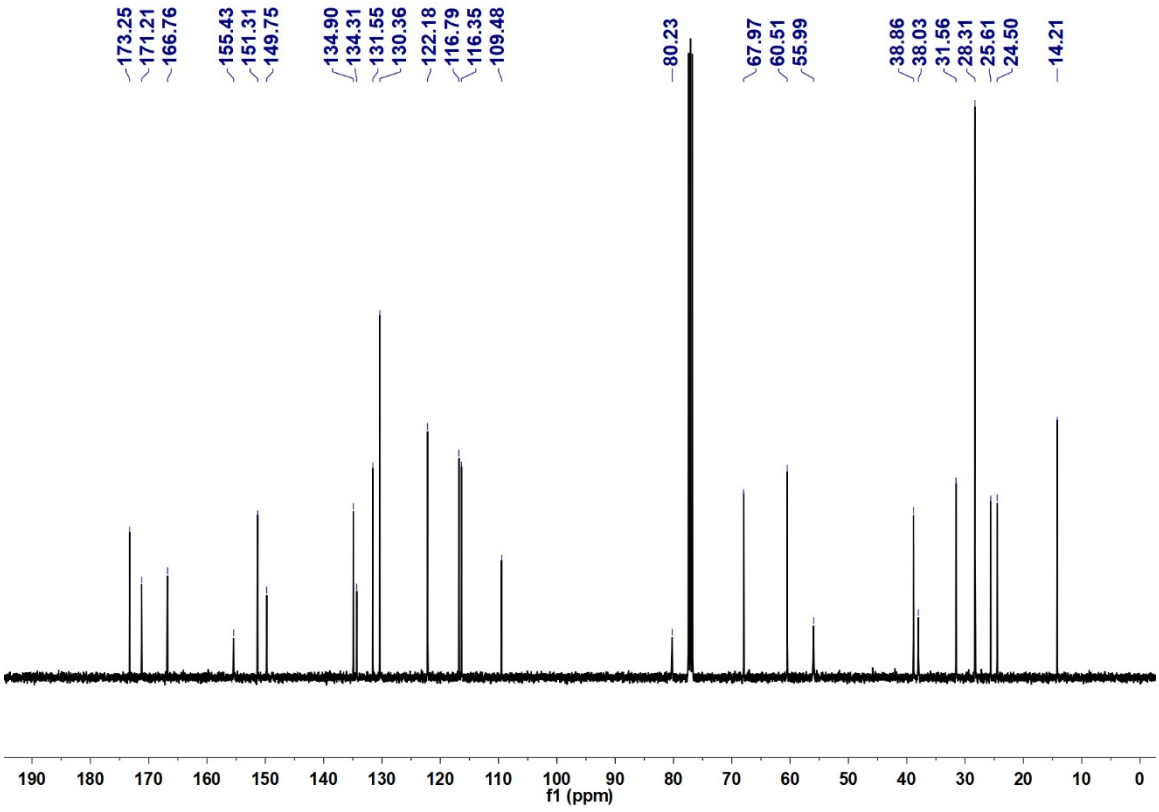
1.0
0.5
0.0
f1 (ppm)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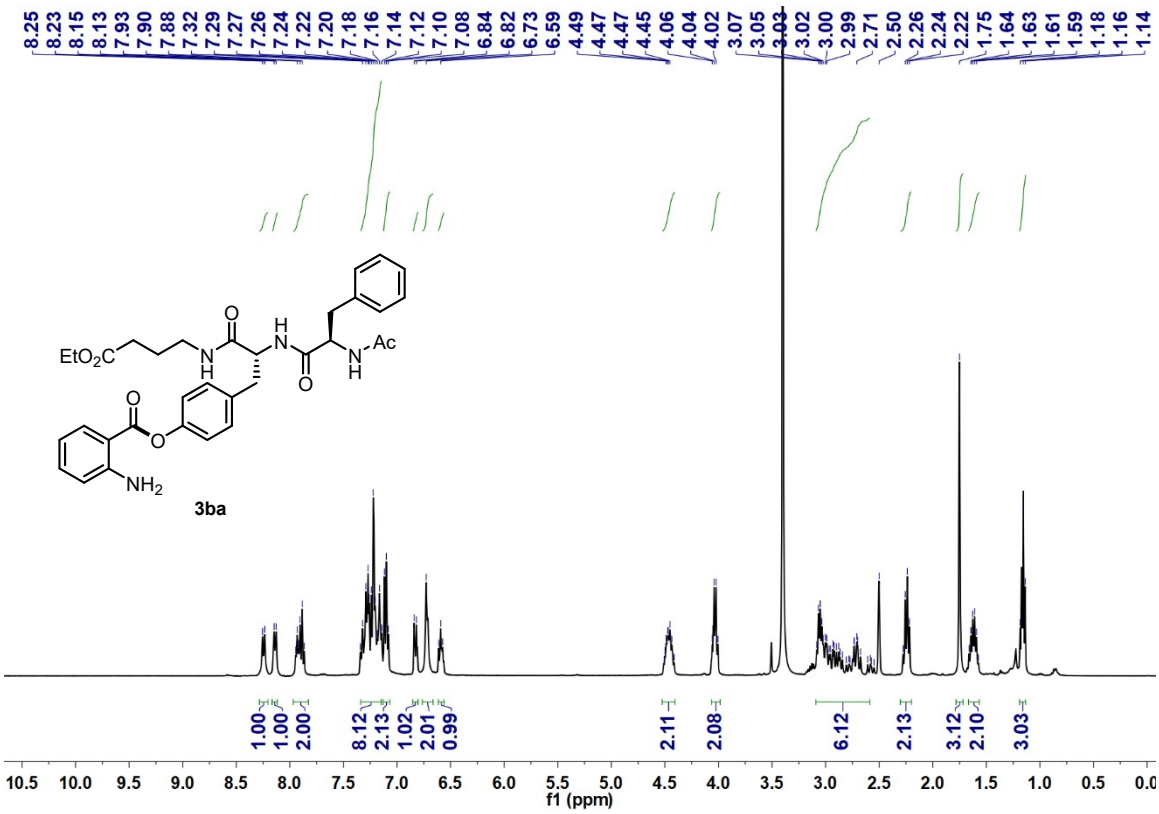
f1 (ppm)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EtO2C
O
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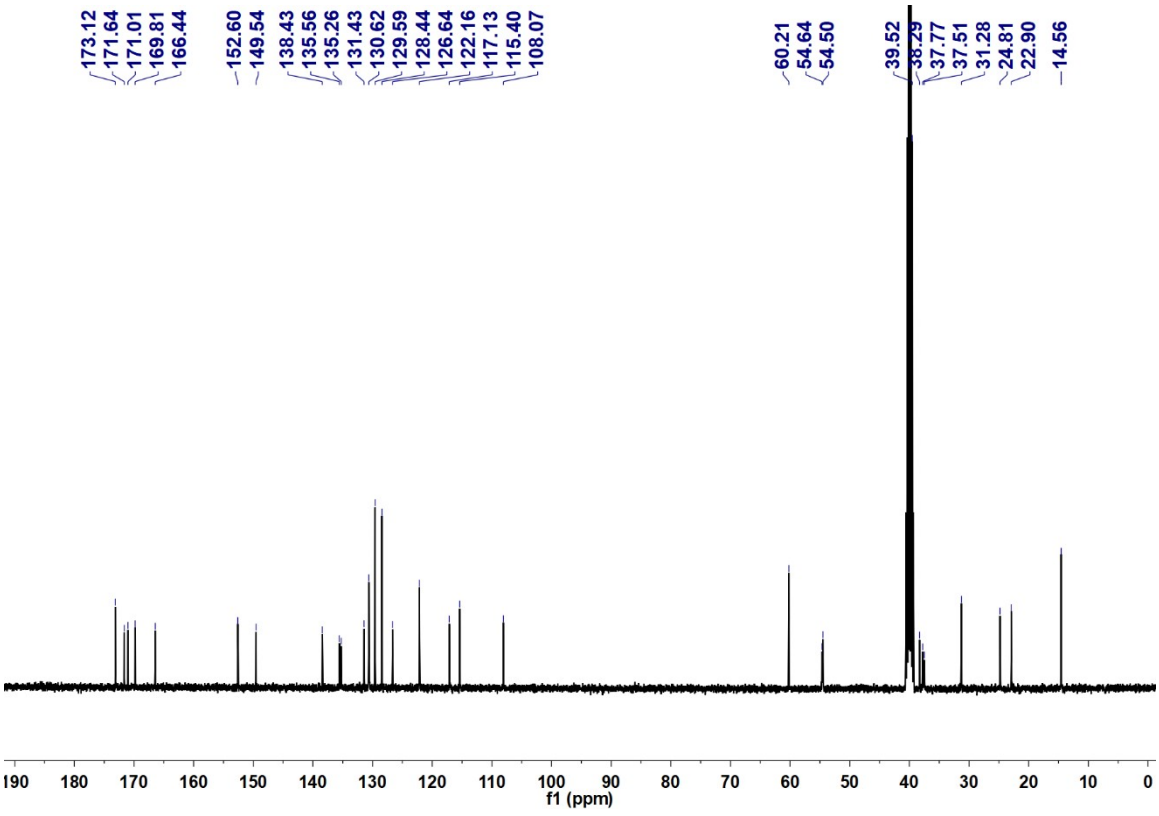
H
H
N
O
N
H
Ac
O
O
O
NH2
3ba
1.00 1.00 2.00 8.12 2.13 1.02 2.01 0.99 2.11 2.08 6.12 2.13 3.12 2.10 3.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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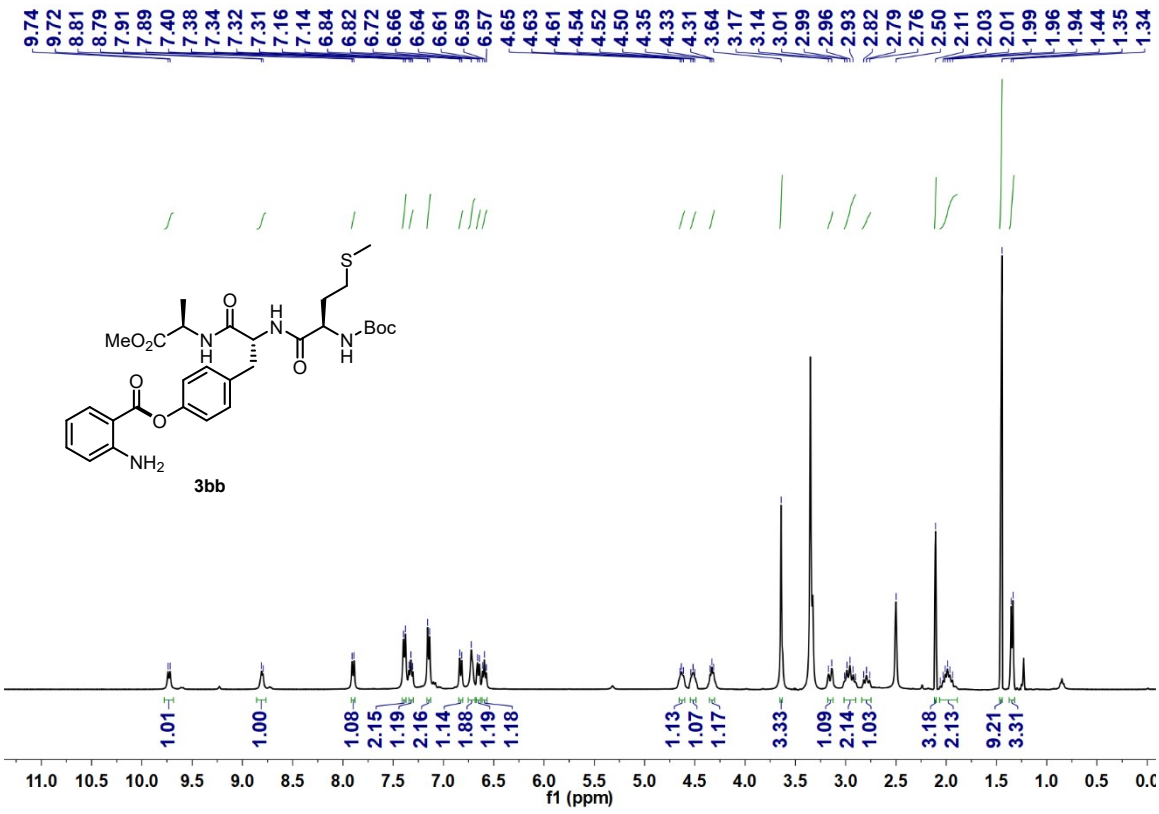
f1 (ppm)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MeO2C
Boc
NH2
3bb
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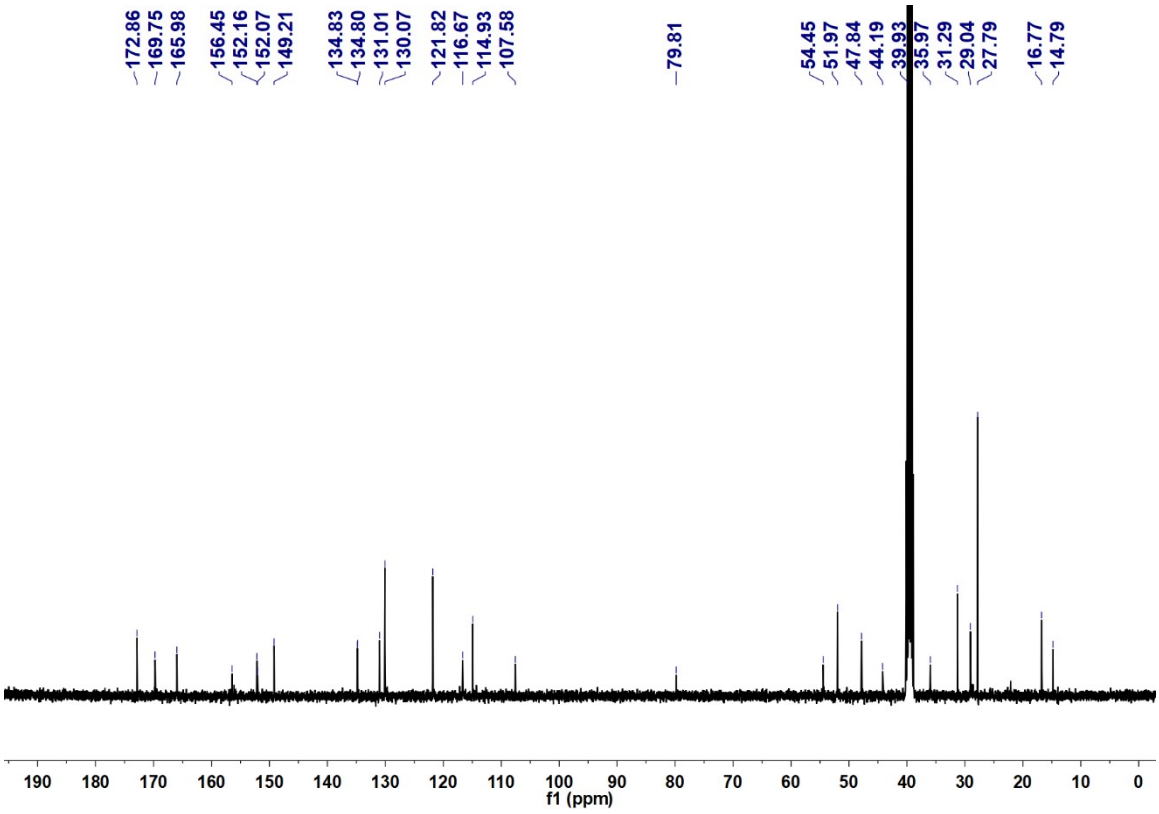
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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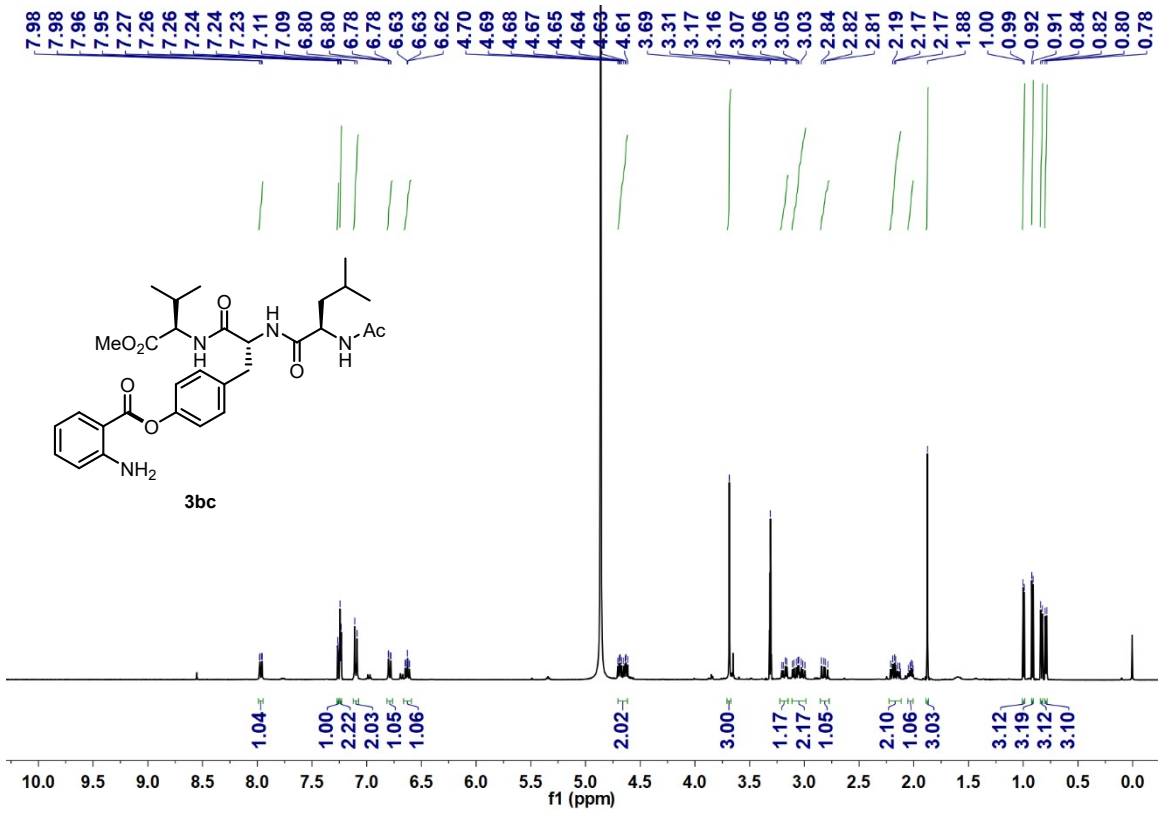
f1 (ppm)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0.80
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MeO2C
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H
O
H
N
N
H
Ac
O
O
O
NH2
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9.0
8.5
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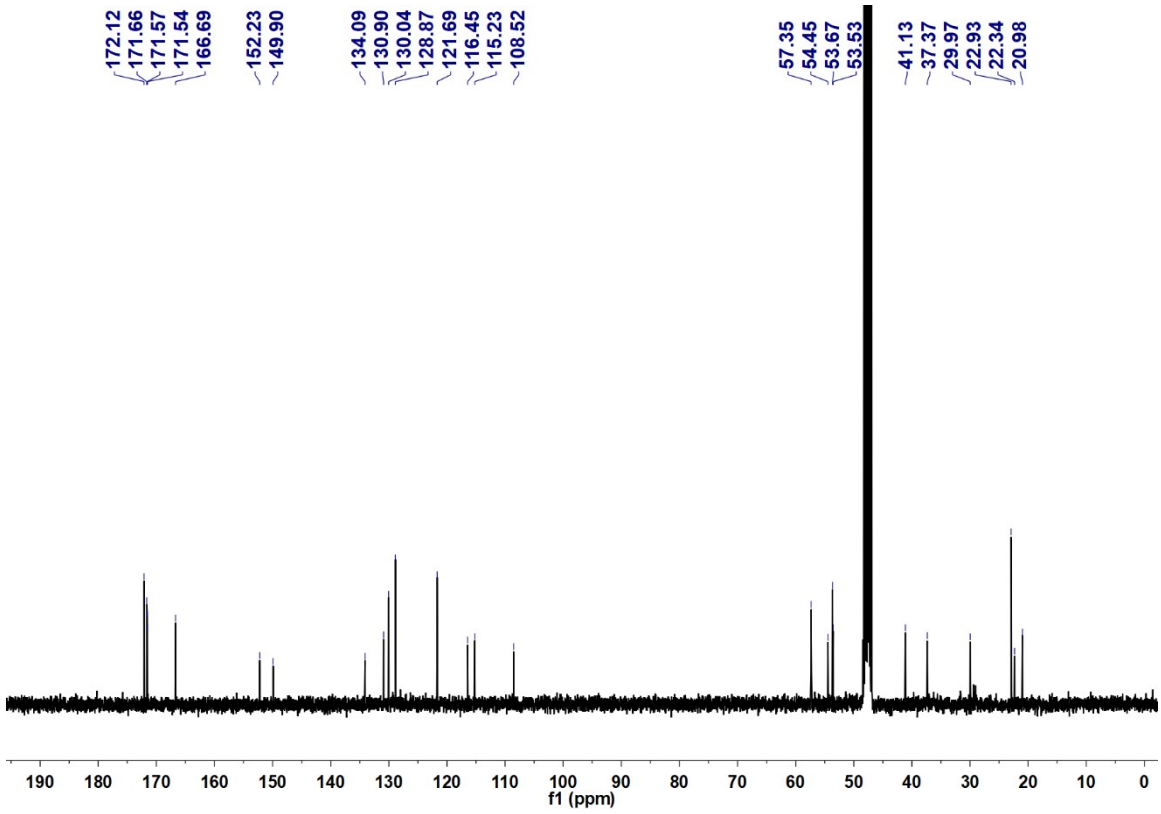
f1 (ppm)

3bc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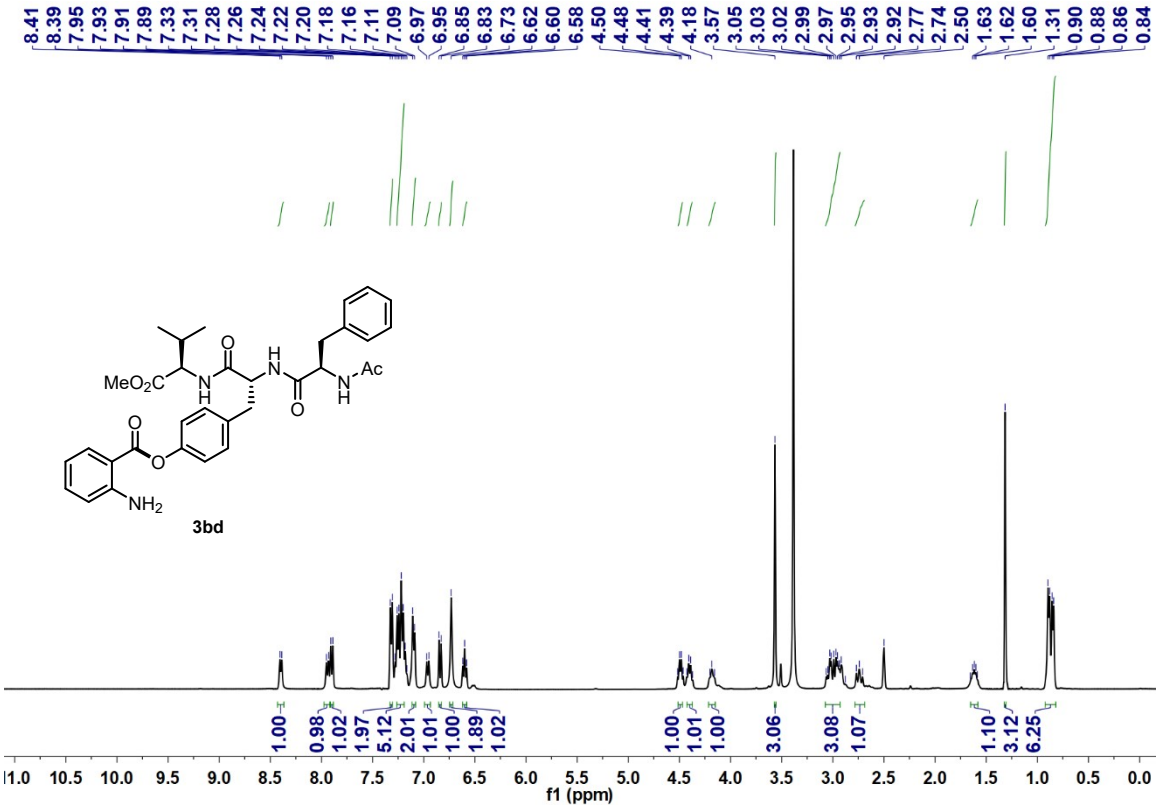
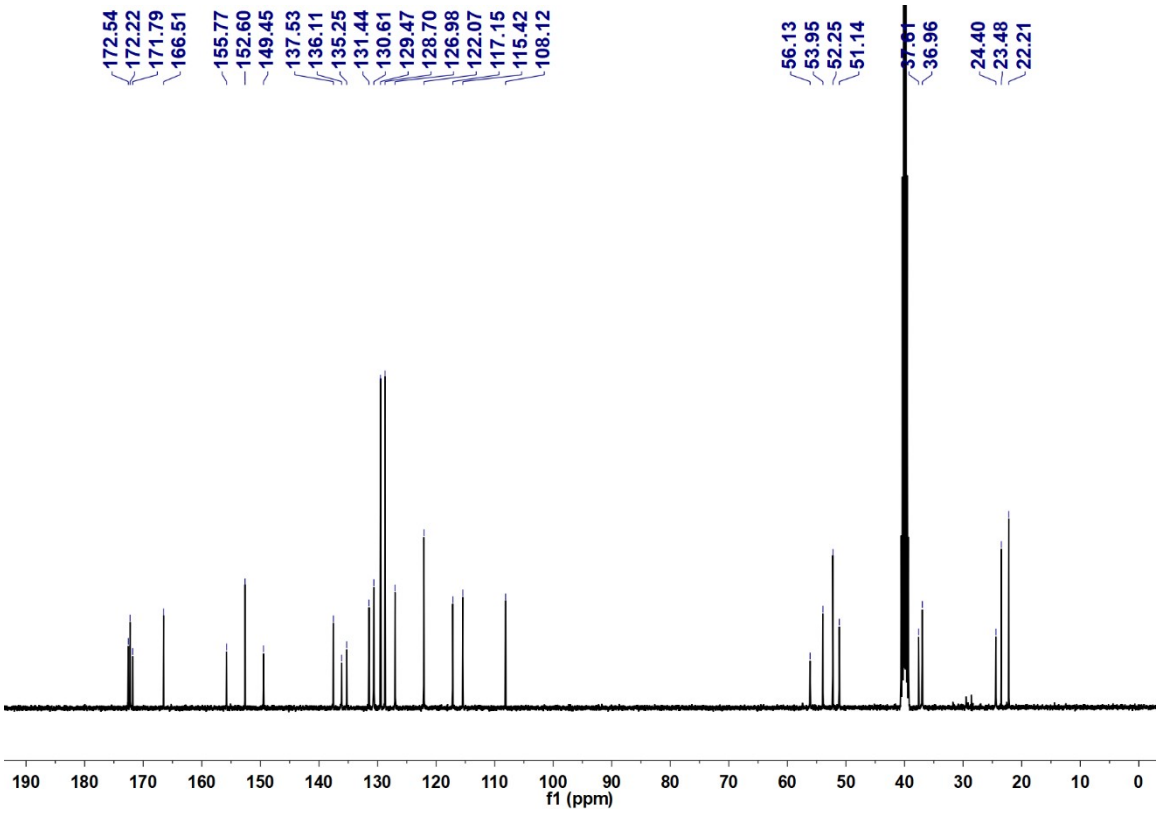
166.69
152.23
149.90
134.09
130.90
130.04
128.87
121.69
116.45
115.23
108.52
57.35
54.45
53.67
53.53
41.13
37.37
29.97
22.93
22.34
20.98
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.41 8.39 7.95 7.93 7.91 7.89 7.33 7.31 7.28 7.26 7.24 7.22 7.20 7.18 7.16 7.11 7.09 6.97 6.95 6.85 6.83 6.73 6.62 6.60 6.58 4.50 4.48 4.41 4.39 4.18 3.57 3.05 3.03 3.02 2.99 2.97 2.95 2.93 2.92 2.77 2.74 2.50 1.63 1.62 1.60 1.31 0.90 0.88 0.86 0.84
MeO2C
Ac
NH2
3bd
1.00 0.98 1.02 1.97 5.12 2.01 1.01 1.00 1.89 1.02 1.00 1.01 1.00 3.06 3.08 1.07 1.10 3.12 6.25
f1 (ppm)


172.54 172.22 171.79 166.51 155.77 152.60 149.45 137.53 136.11 135.25 131.44 130.61 129.47 128.70 126.98 122.07 117.15 115.42 108.12
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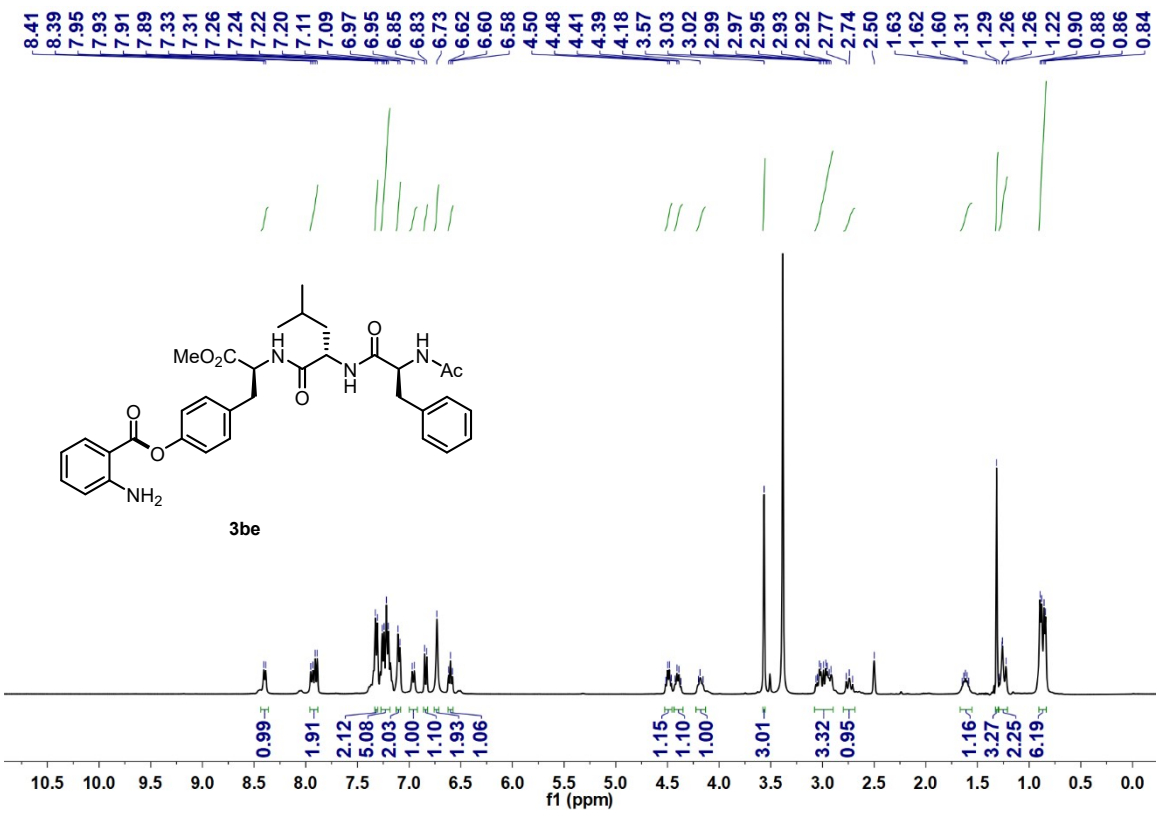
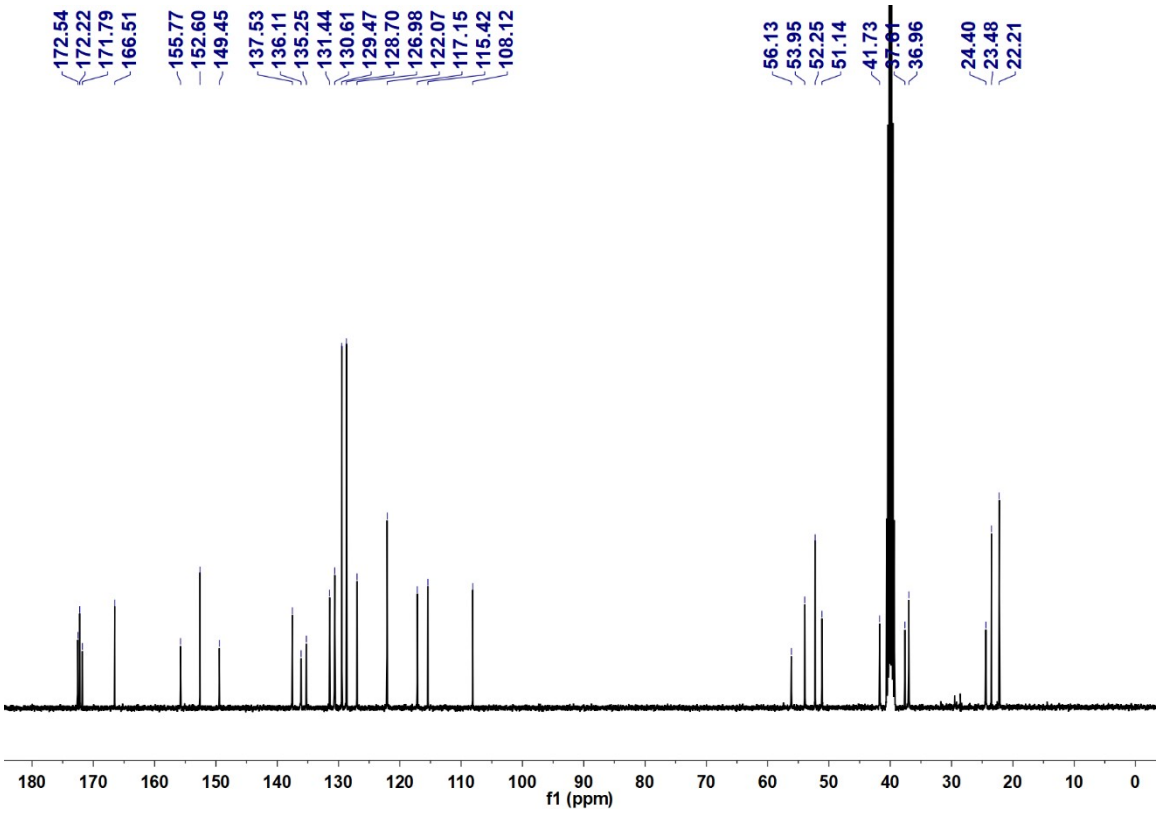
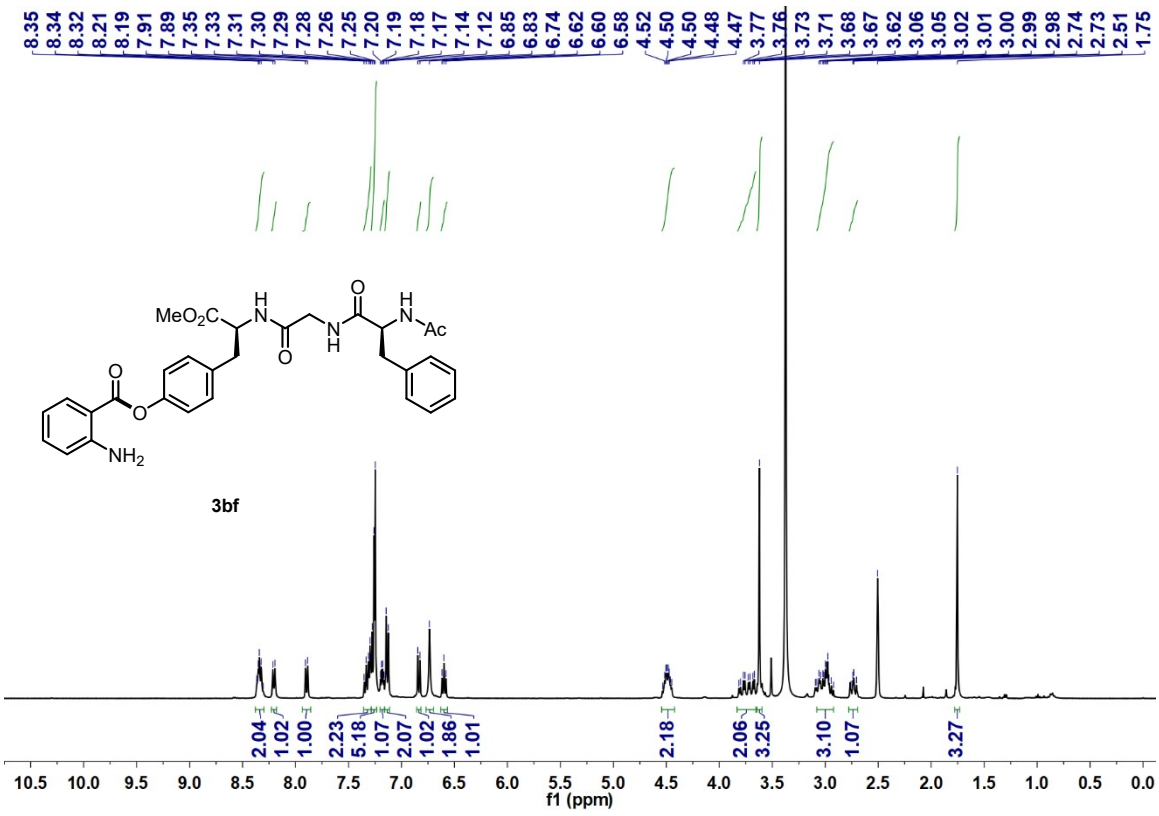
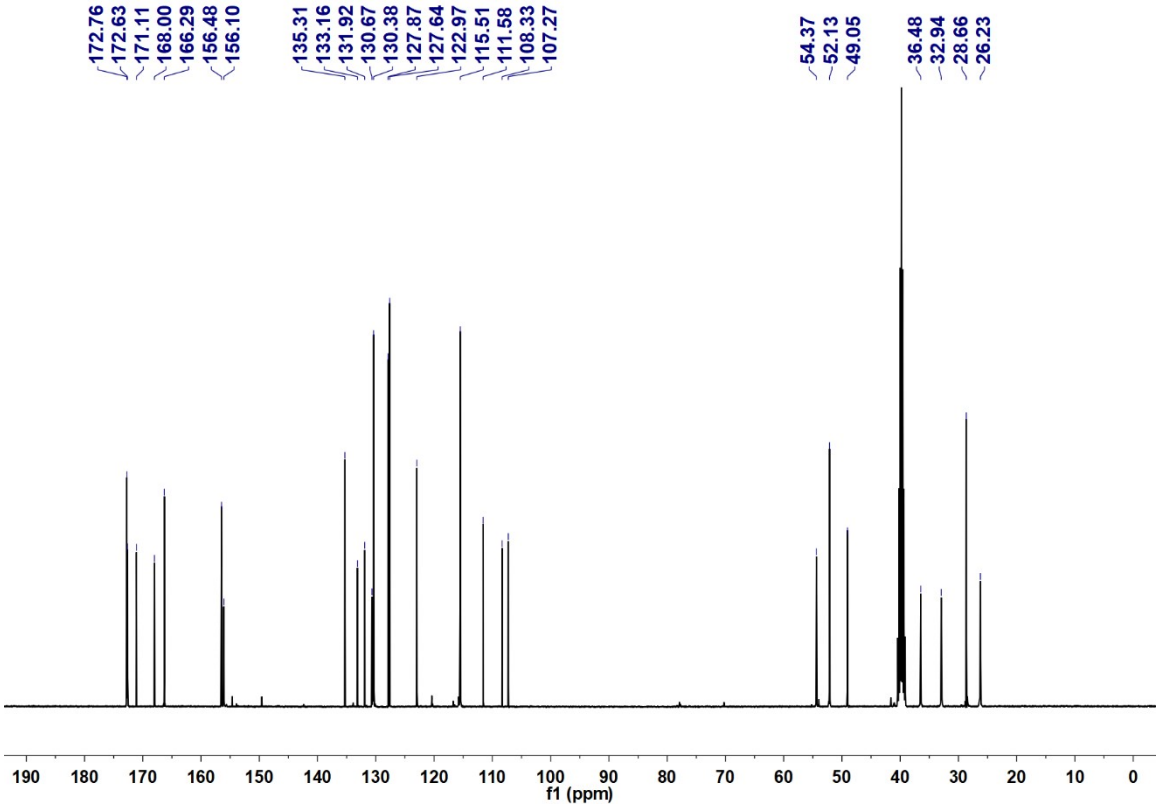
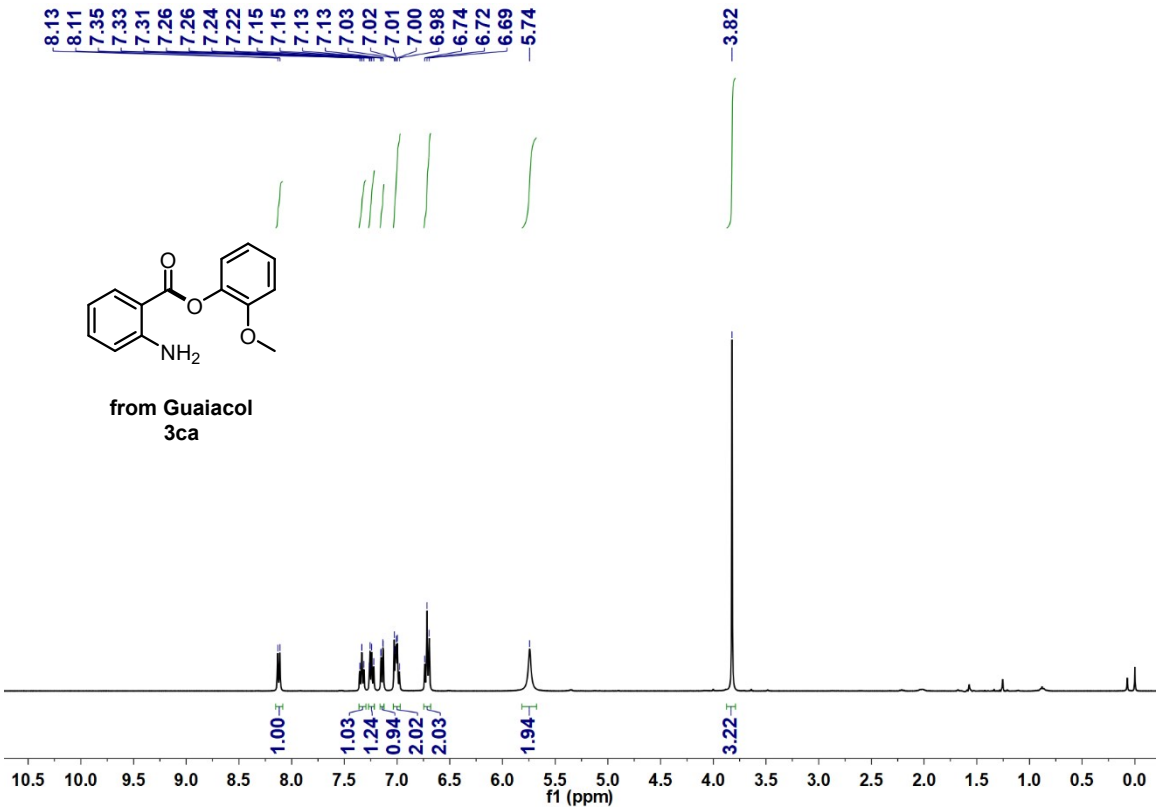
f1 (ppm)


8.41
8.39
7.95
7.93
7.91
7.89
7.33
7.31
7.26
7.24
7.22
7.20
7.11
7.09
6.97
6.95
6.85
6.83
6.73
6.62
6.60
6.58
4.50
4.48
4.41
4.39
4.18
3.57
3.03
3.02
2.99
2.97
2.95
2.93
2.92
2.77
2.74
2.50
1.63
1.62
1.60
1.31
1.29
1.26
1.26
1.22
0.90
0.88
0.86
0.84
MeO2C
H
N
O
N
H
O
H
N
Ac
O
O
NH2
3be
0.99
1.91
2.12
5.08
2.03
1.00
1.10
1.93
1.06
1.15
1.10
1.00
3.01
3.32
0.95
1.16
3.27
2.25
6.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

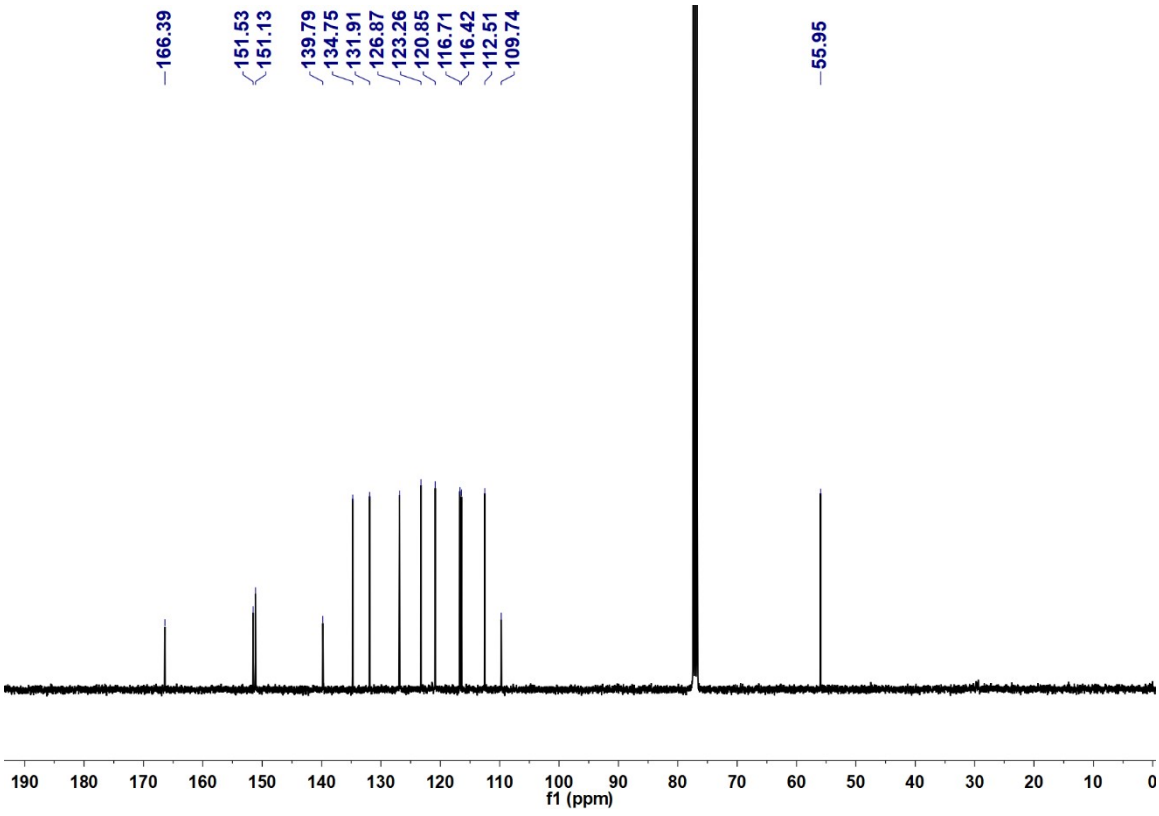

172.54
172.22
171.79
166.51
155.77
152.60
149.45
137.53
136.11
135.25
131.44
130.61
129.47
128.70
126.98
122.07
117.15
115.42
108.12
56.13
53.95
52.25
51.14
41.73
37.61
36.96
24.40
23.48
22.21
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

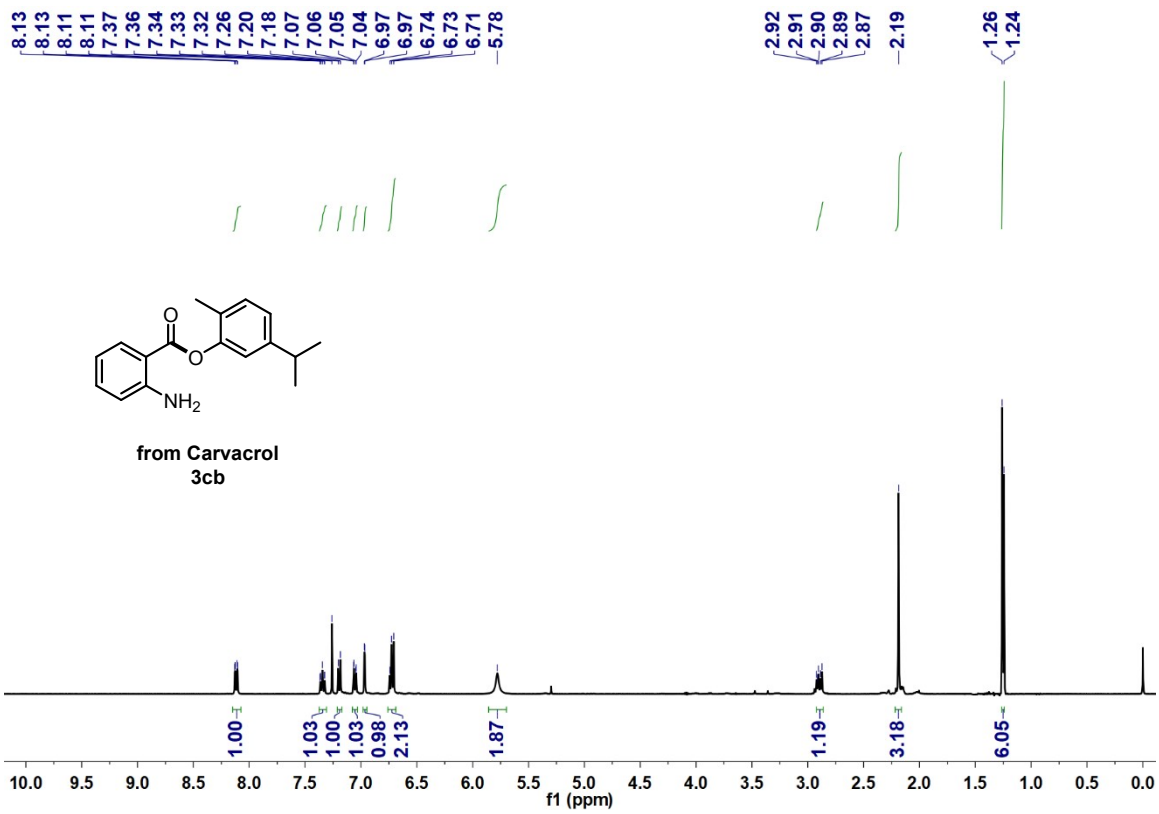

8.35 8.34 8.32 8.21 8.19 7.91 7.89 7.35 7.33 7.31 7.30 7.29 7.28 7.26 7.25 7.20 7.19 7.18 7.17 7.14 7.12 6.85 6.83 6.74 6.62 6.60 6.58 4.52 4.50 4.50 4.48 4.47 3.77 3.76 3.73 3.71 3.68 3.67 3.62 3.06 3.05 3.02 3.01 3.00 2.99 2.98 2.74 2.73 2.51 1.75
MeO2C
H N
O
N H
O
H N
Ac
O
O
NH2
3bf
2.04 1.02 1.00 2.23 5.18 1.07 2.07 1.02 1.86 1.01 2.18 2.06 3.25 3.10 1.07 3.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

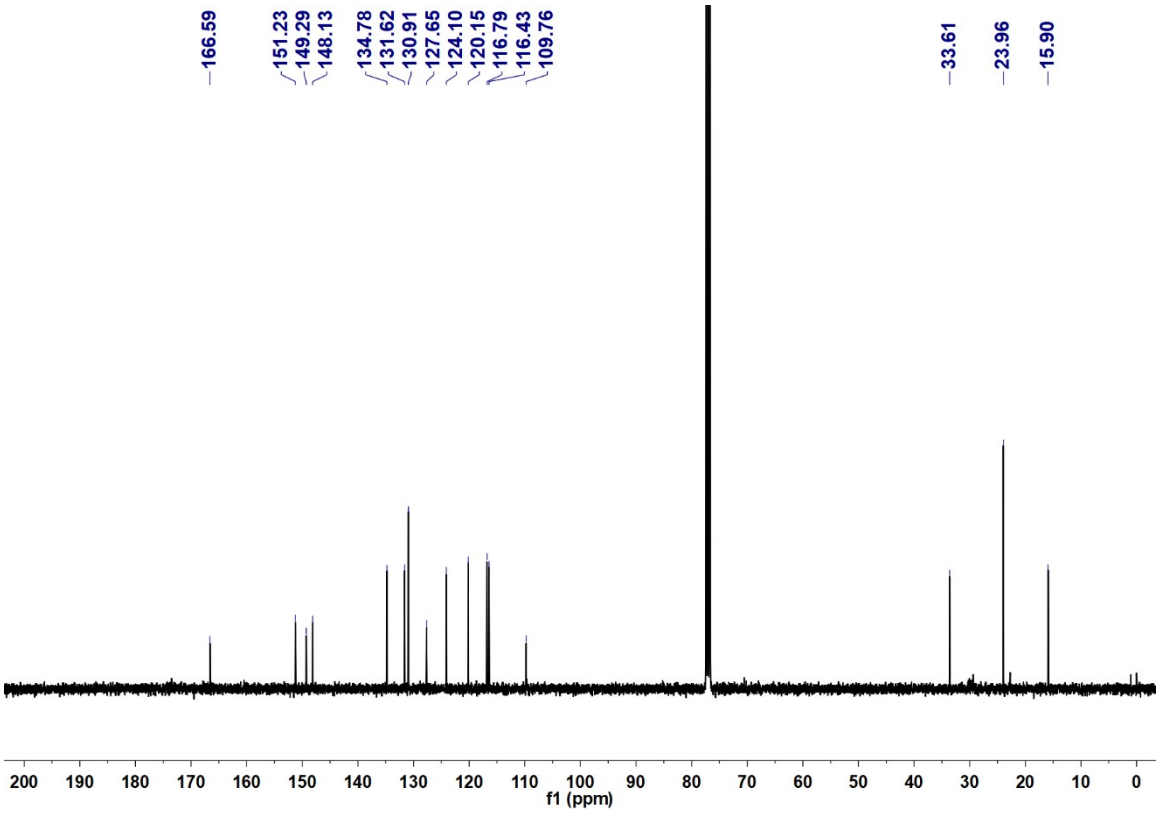

172.76 172.63 171.11 168.00 166.29 156.48 156.10 135.31 133.16 131.92 130.67 130.38 127.87 127.64 122.97 115.51 111.58 108.33 107.27 54.37 52.13 49.05 36.48 32.94 28.66 26.23
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

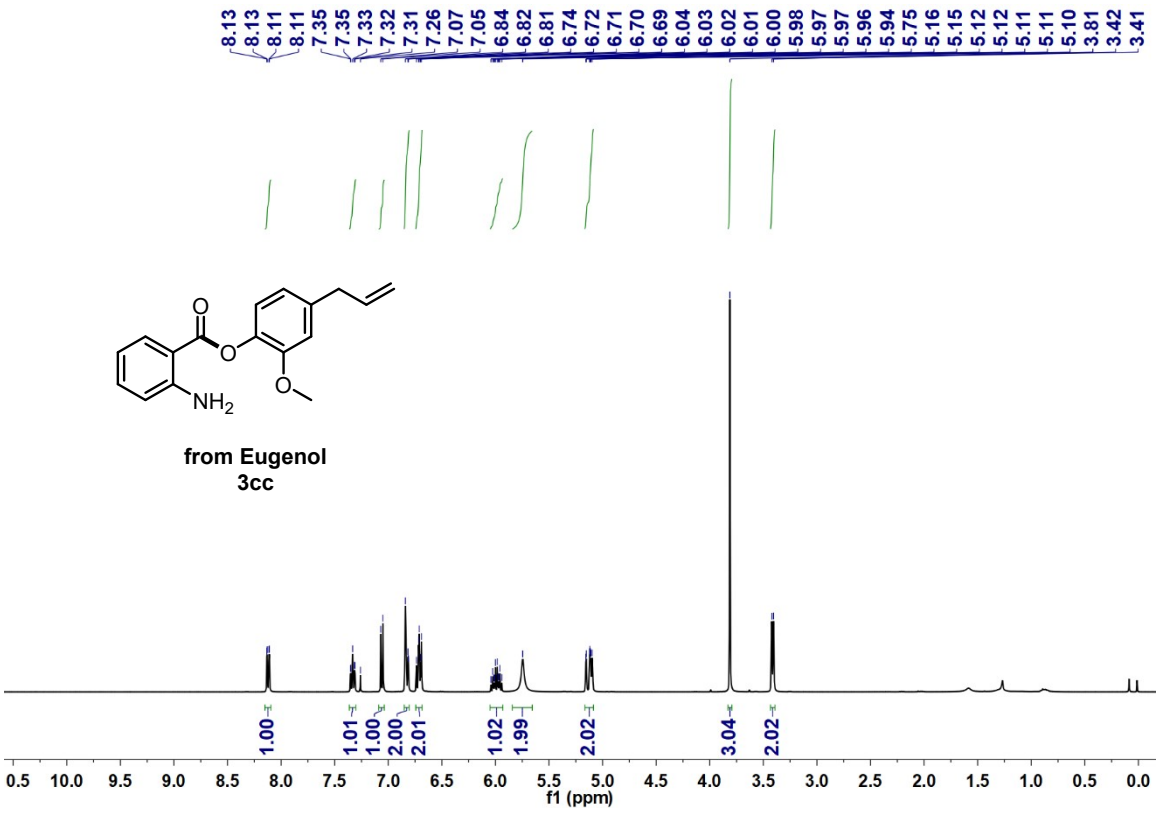


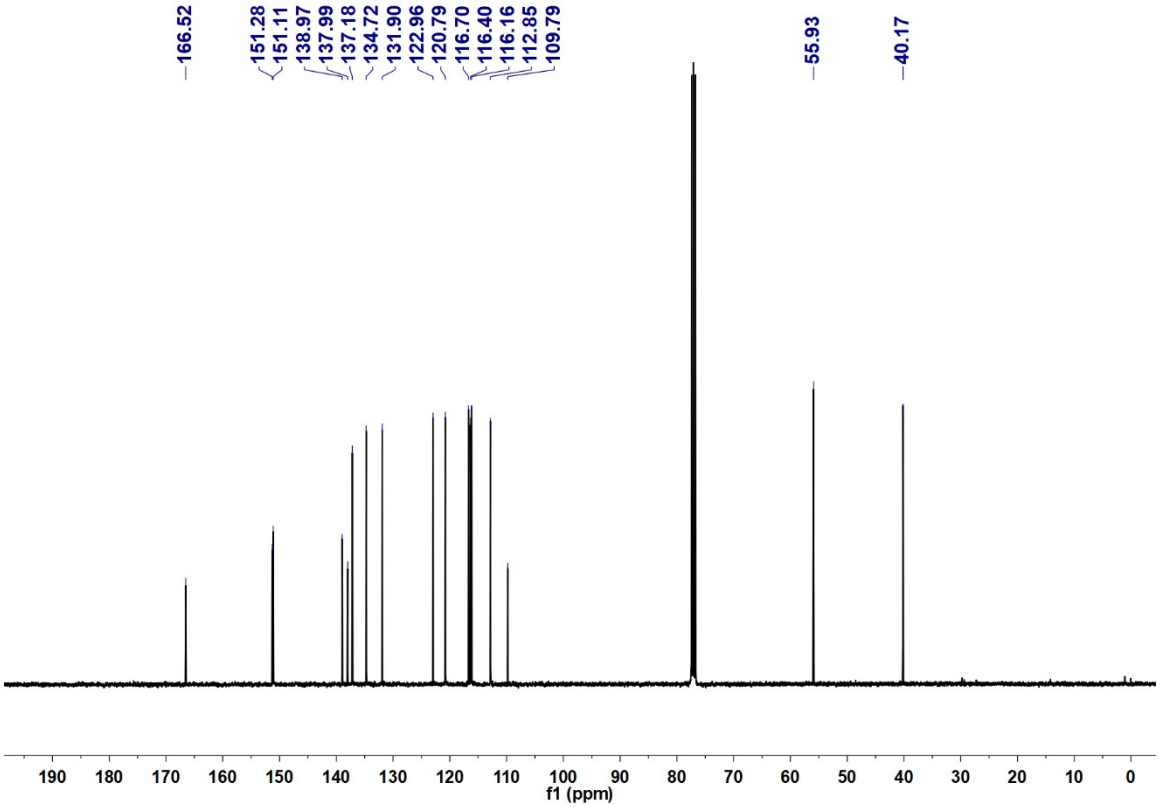
from Guaiacol
3ca

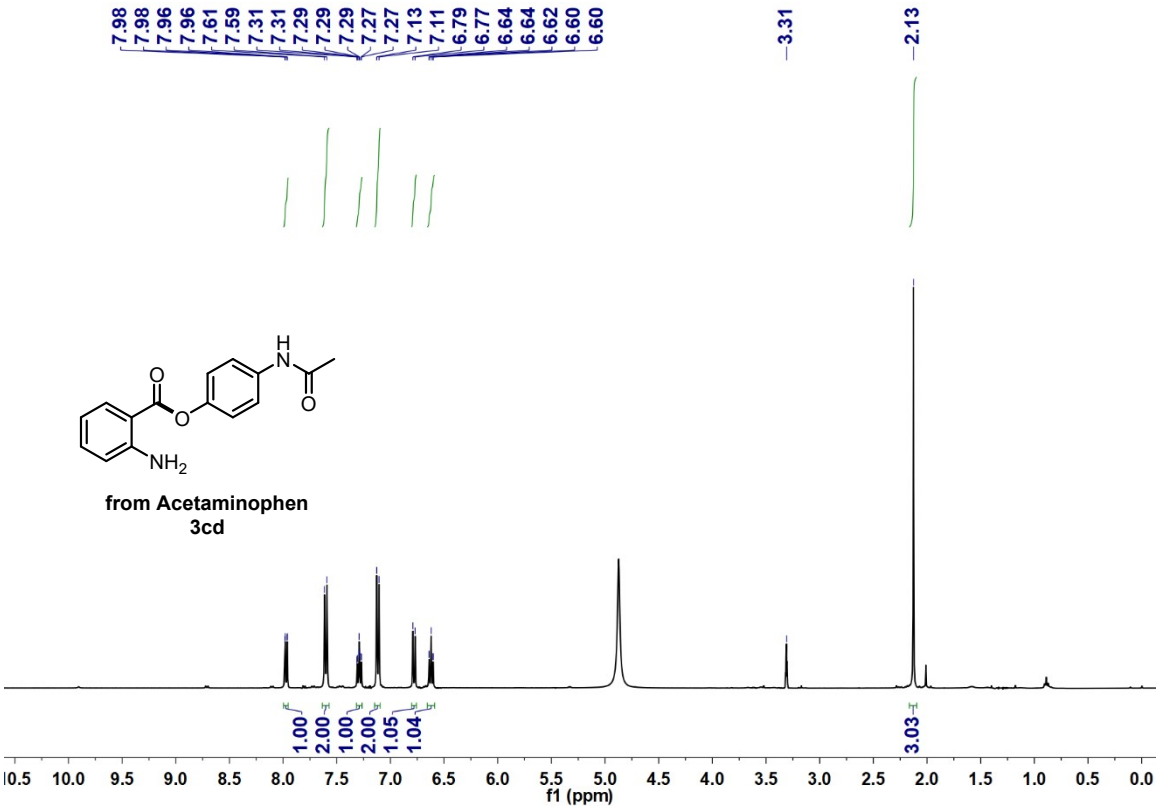


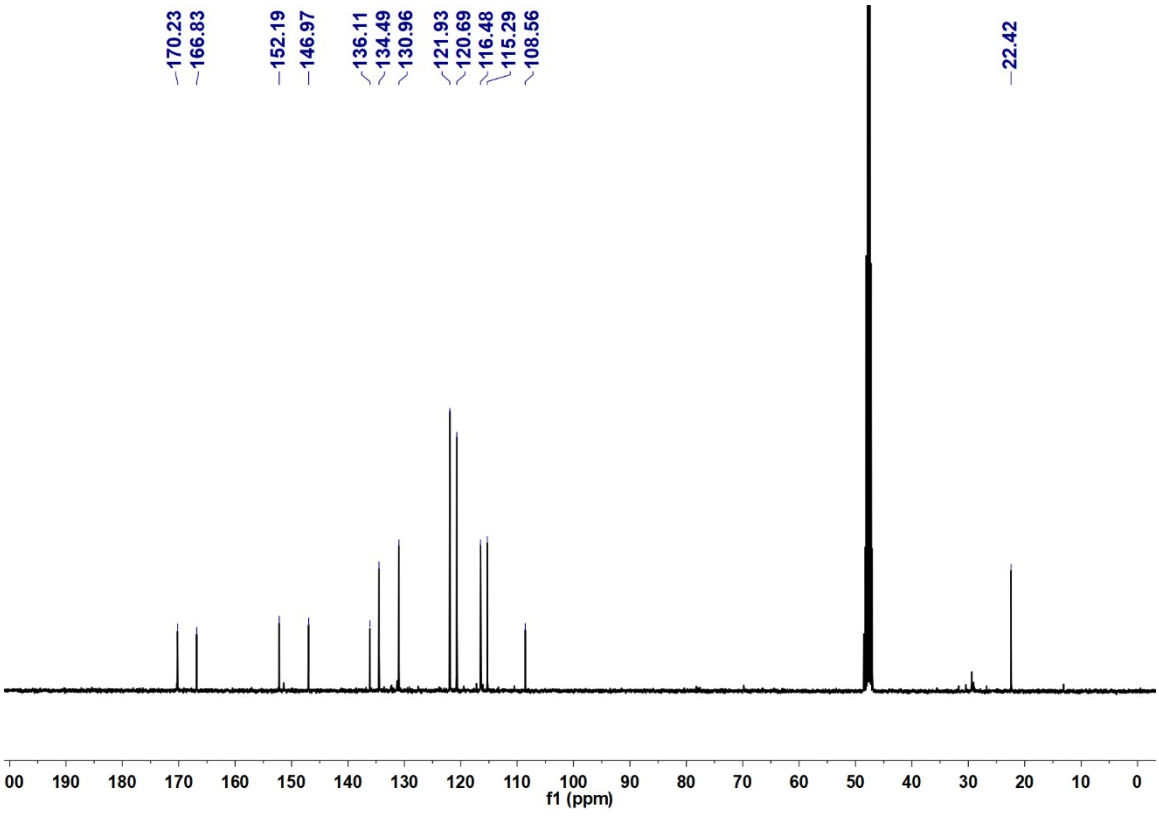

8.13
8.13
8.11
8.11
7.37
7.36
7.34
7.33
7.32
7.26
7.20
7.18
7.07
7.06
7.05
7.04
6.97
6.97
6.74
6.73
6.71
5.78
2.92
2.91
2.90
2.89
2.87
2.19
1.26
1.24
O
O
NH2
from Carvacrol
3cb
1.00
1.03
1.00
1.03
0.98
2.13
1.87
1.19
3.18
6.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

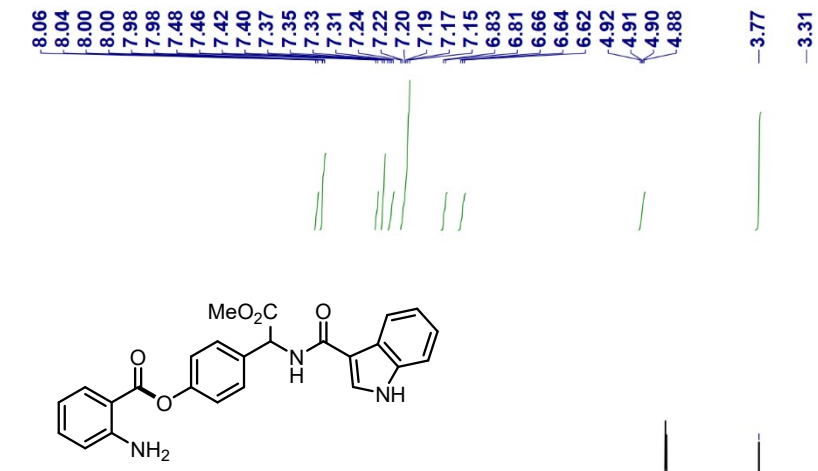

166.59
151.23
149.29
148.13
134.78
131.62
130.91
127.65
124.10
120.15
116.79
116.43
109.76
33.61
23.96
15.90
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.13
8.13
8.11
8.11
7.35
7.35
7.33
7.32
7.31
7.26
7.07
7.05
6.84
6.82
6.81
6.74
6.72
6.71
6.70
6.69
6.04
6.03
6.02
6.01
6.00
5.98
5.97
5.97
5.96
5.94
5.75
5.16
5.15
5.12
5.12
5.11
5.11
5.10
3.81
3.42
3.41
O
O
O
NH2
from Eugenol
3cc
1.00
1.01
1.00
2.00
2.01
1.02
1.99
2.02
3.04
2.02
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

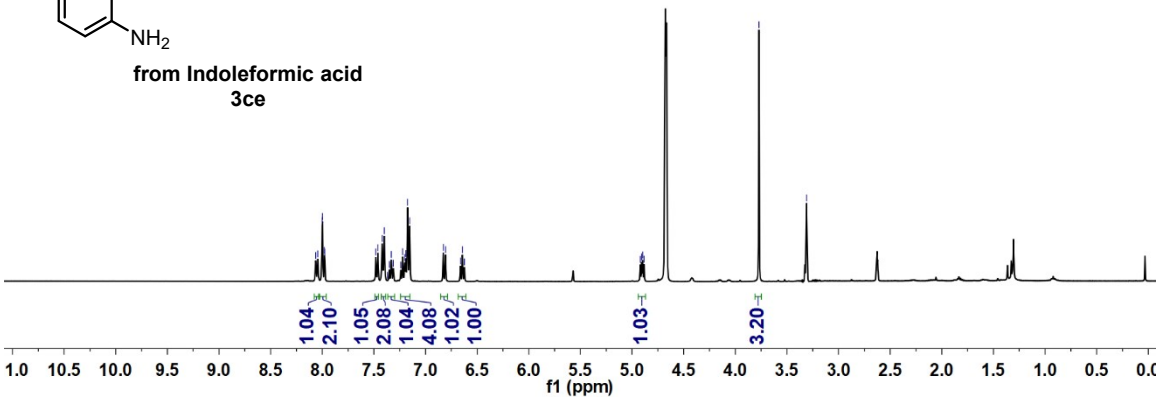

166.52
151.28
151.11
138.97
137.99
137.18
134.72
131.90
122.96
120.79
116.70
116.40
116.16
112.85
109.79
55.93
40.17
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

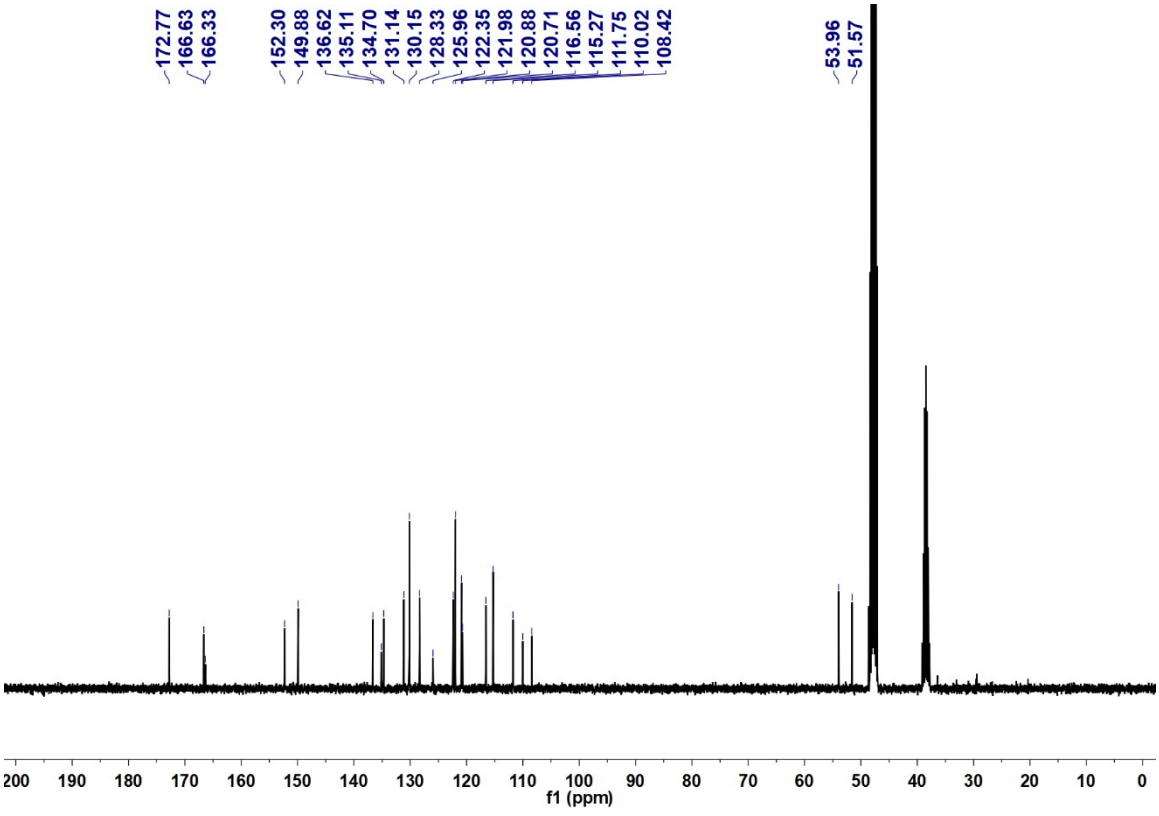

7.98
7.98
7.96
7.96
7.61
7.59
7.31
7.31
7.29
7.29
7.29
7.27
7.27
7.13
7.11
6.79
6.77
6.64
6.64
6.62
6.60
6.60
3.31
2.13
H
N
O
O
O
NH2
from Acetaminophen
3cd
1.00
2.00
1.00
2.00
1.05
1.04
3.03
f1 (ppm)

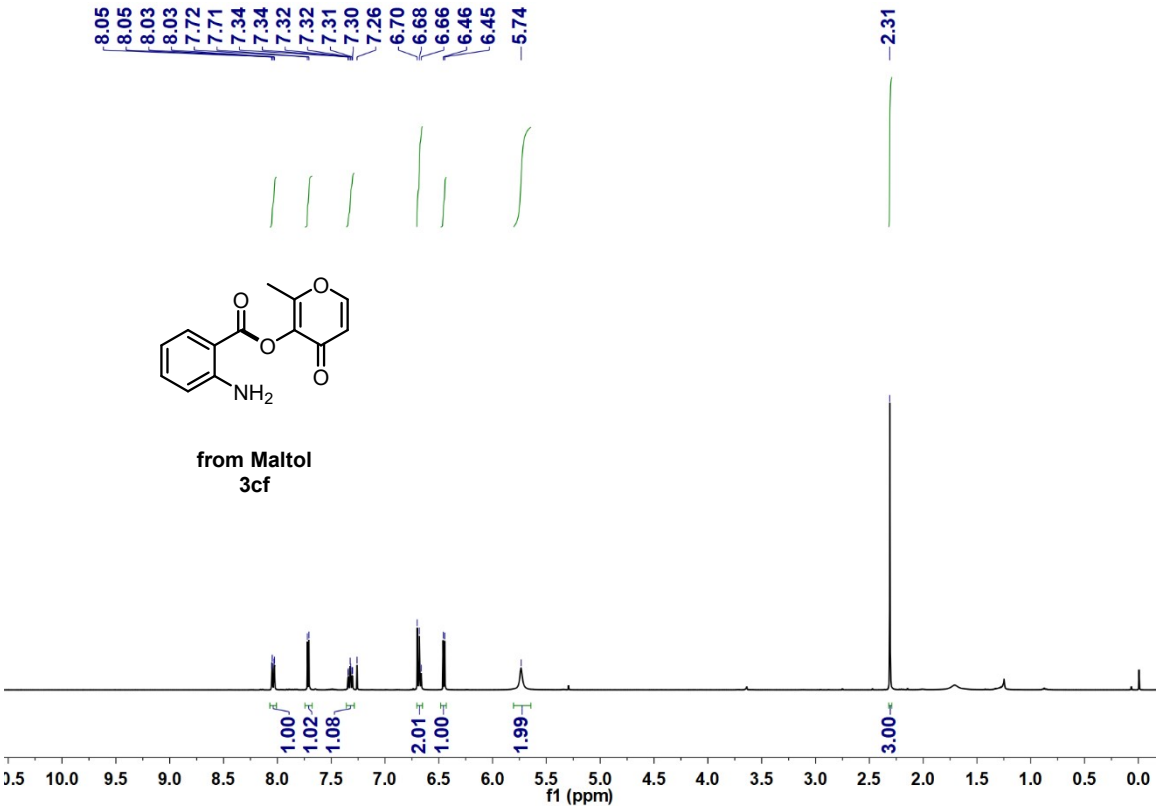

170.23
166.83
152.19
146.97
136.11
134.49
130.96
121.93
120.69
116.48
115.29
108.56
22.42
f1 (ppm)



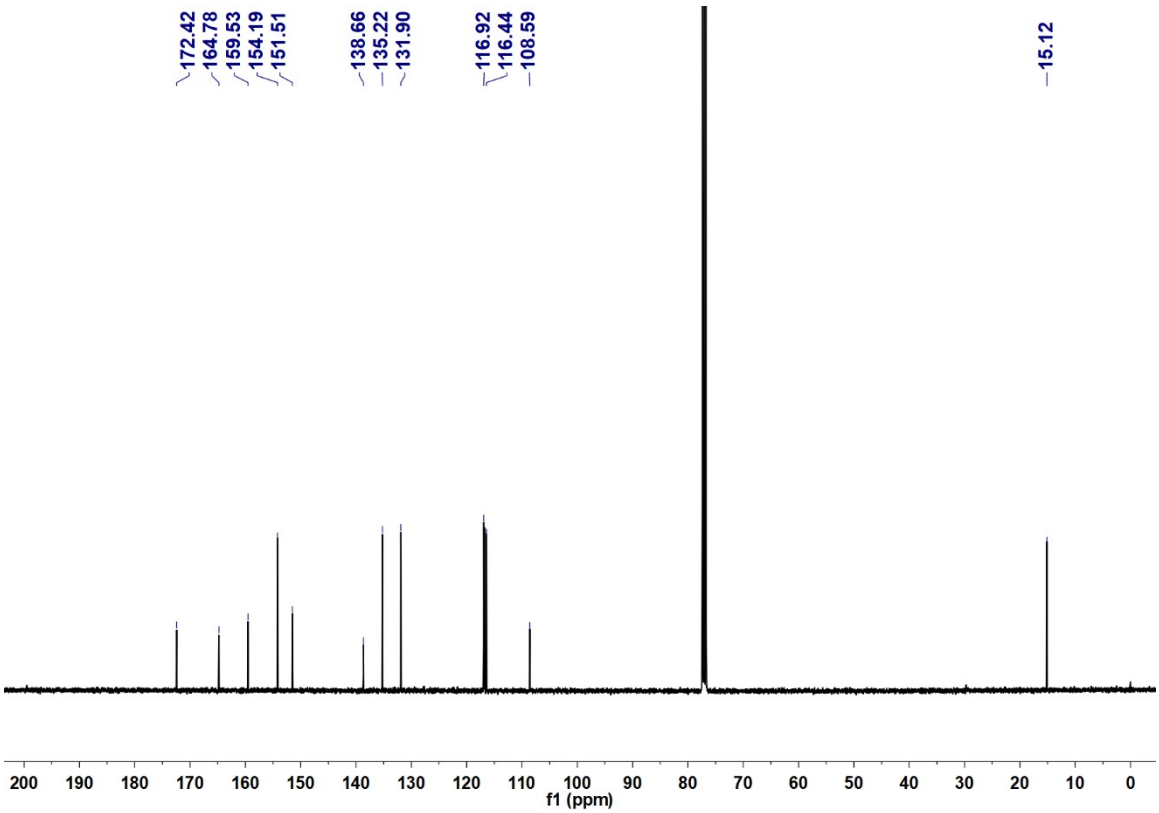
from Indoleformic acid
3ce

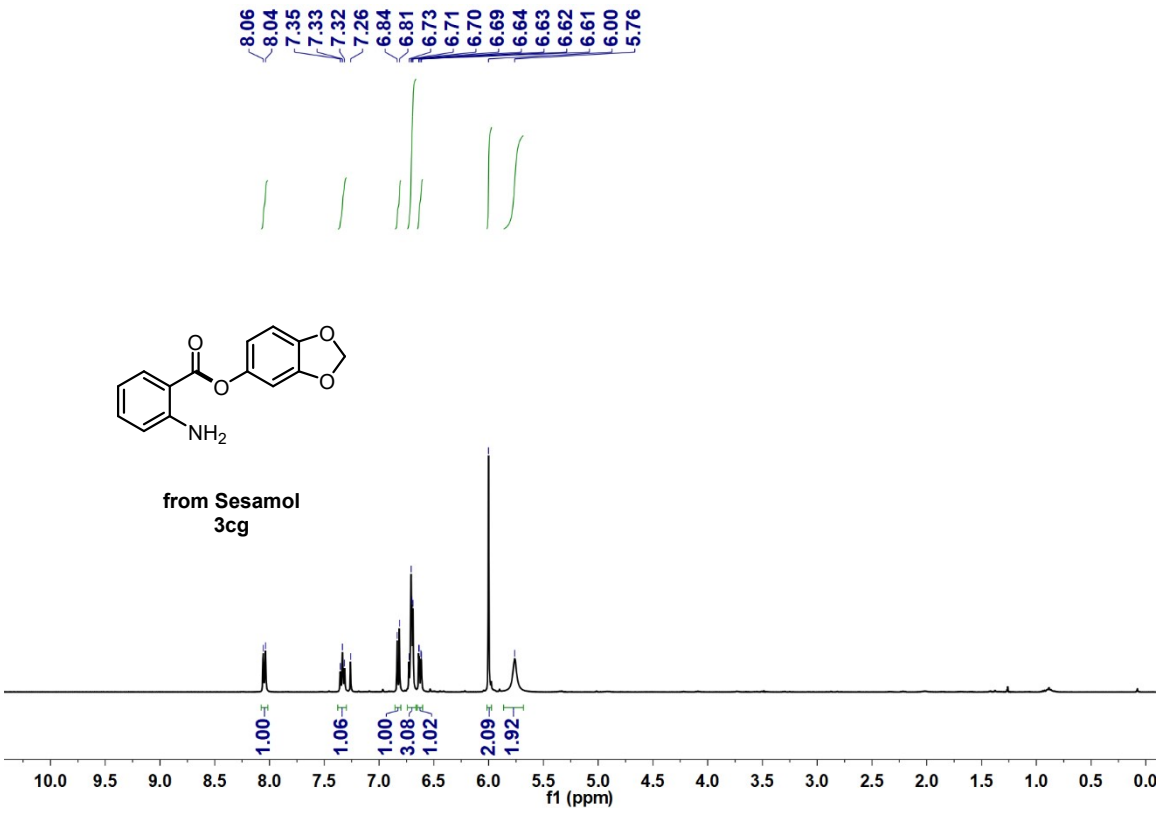


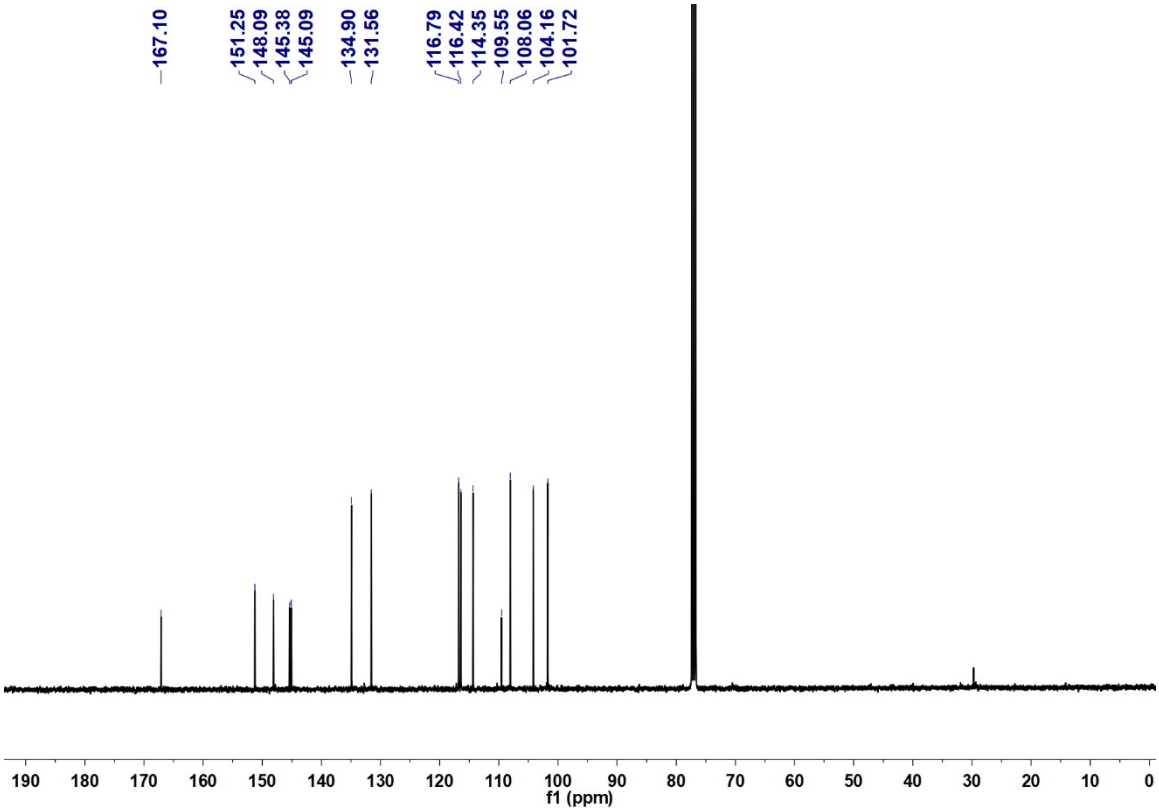


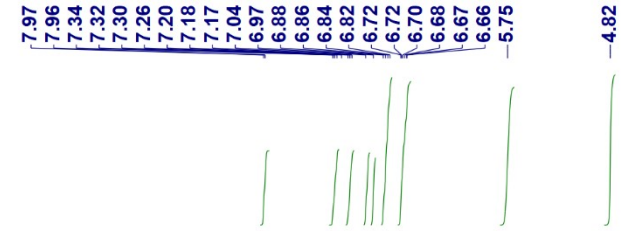


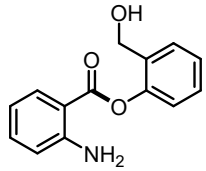
from Maltol
3cf



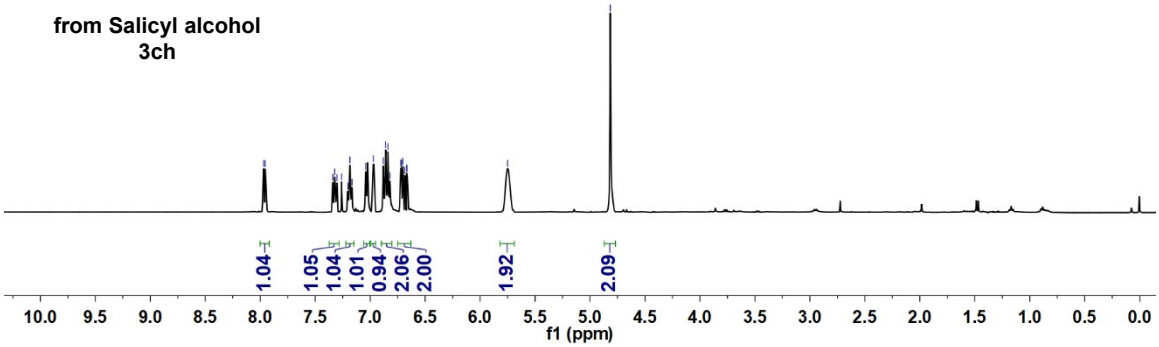

8.06
8.04
7.35
7.33
7.32
7.26
6.84
6.81
6.73
6.71
6.70
6.69
6.64
6.63
6.62
6.61
6.00
5.76
O
O
O
NH2
from Sesamol
3cg
1.00
1.06
1.00
3.08
1.02
2.09
1.92
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

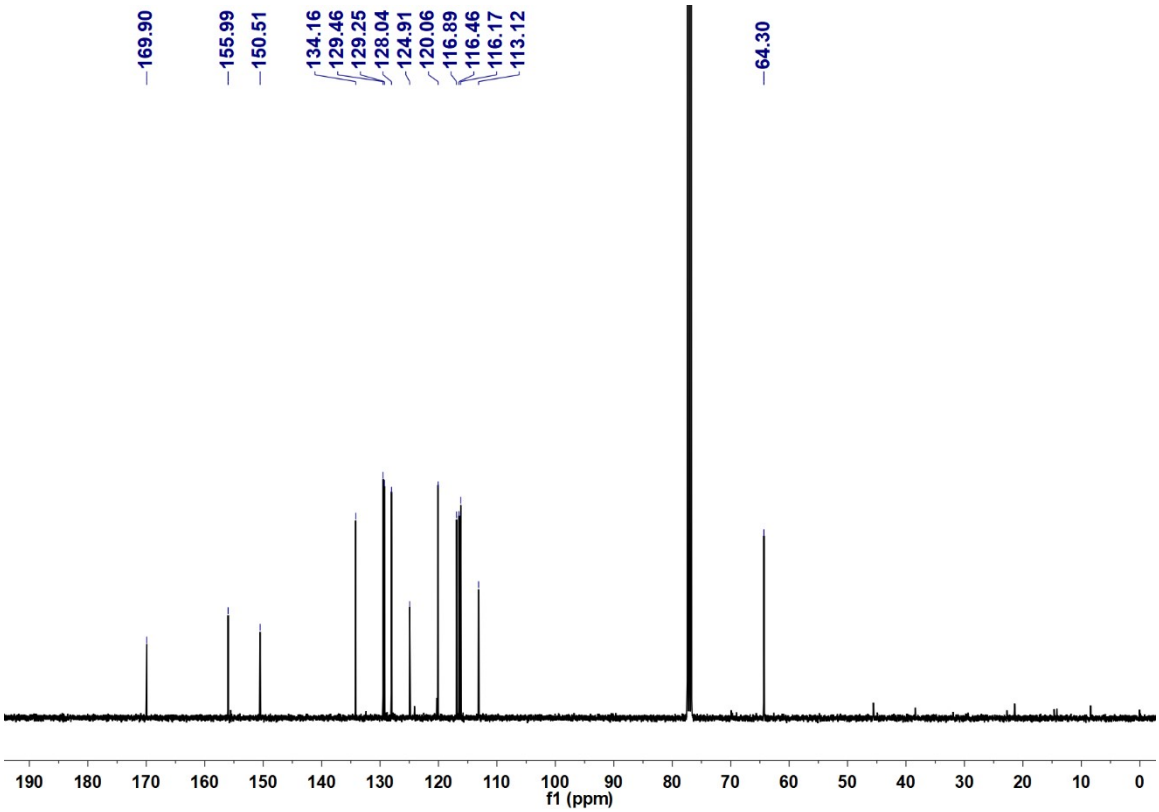

167.10
151.25
148.09
145.38
145.09
134.90
131.56
116.79
116.42
114.35
109.55
108.06
104.16
101.72
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

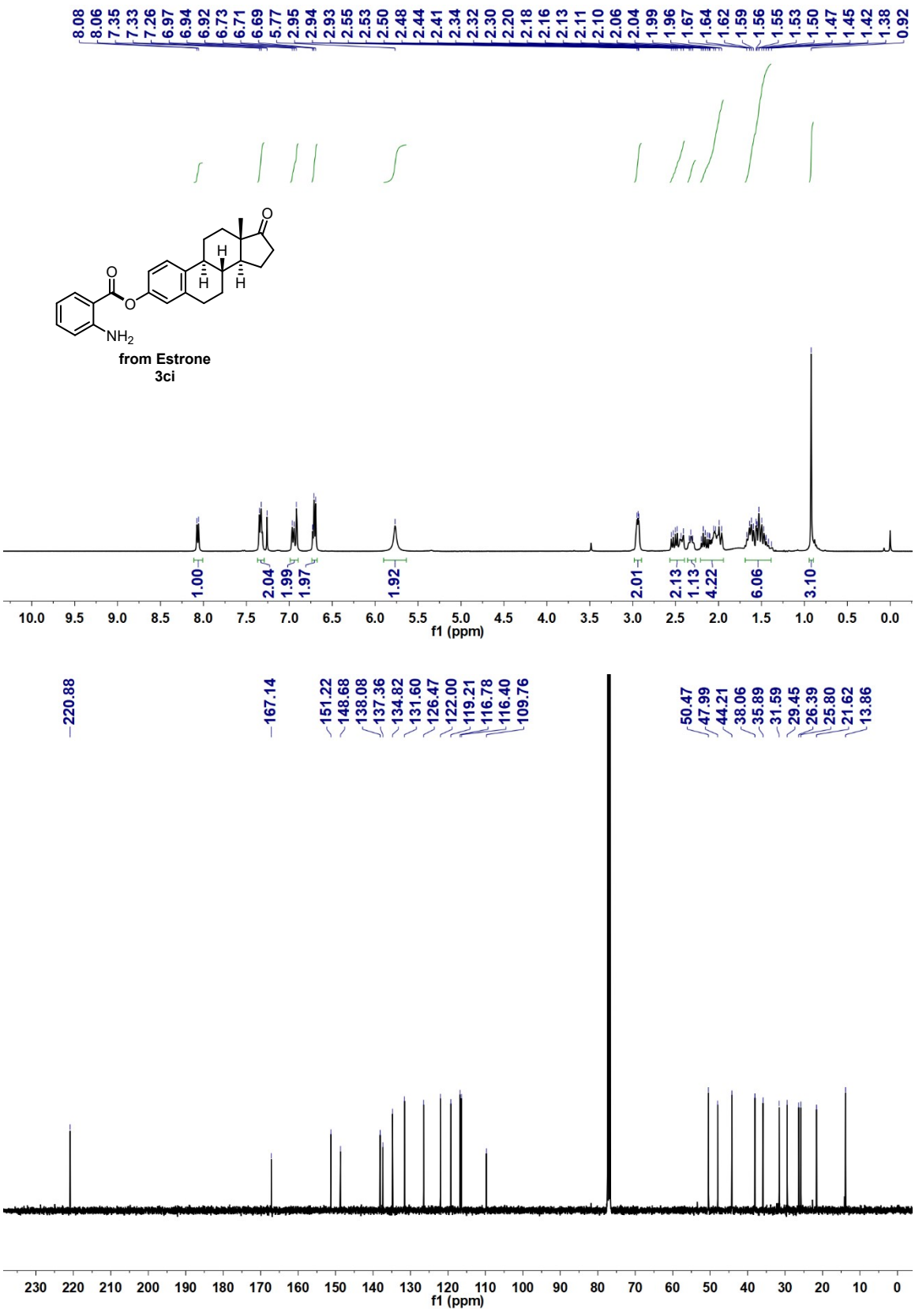


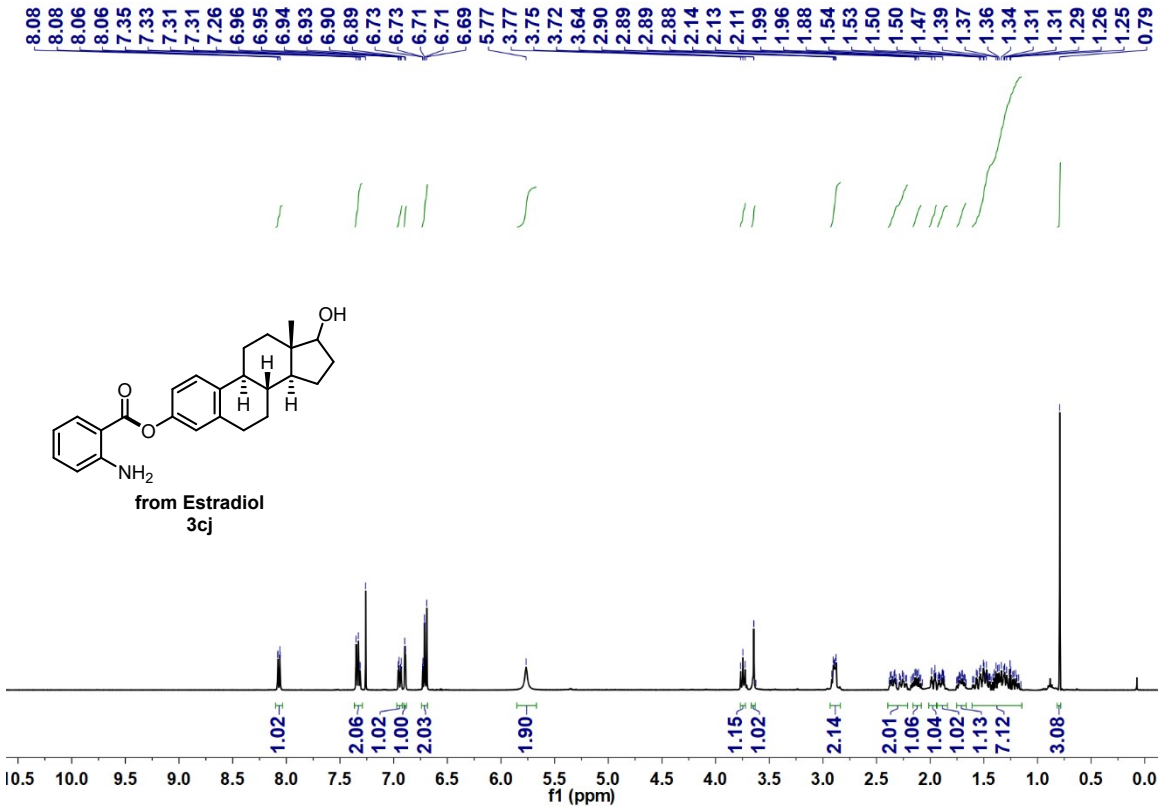


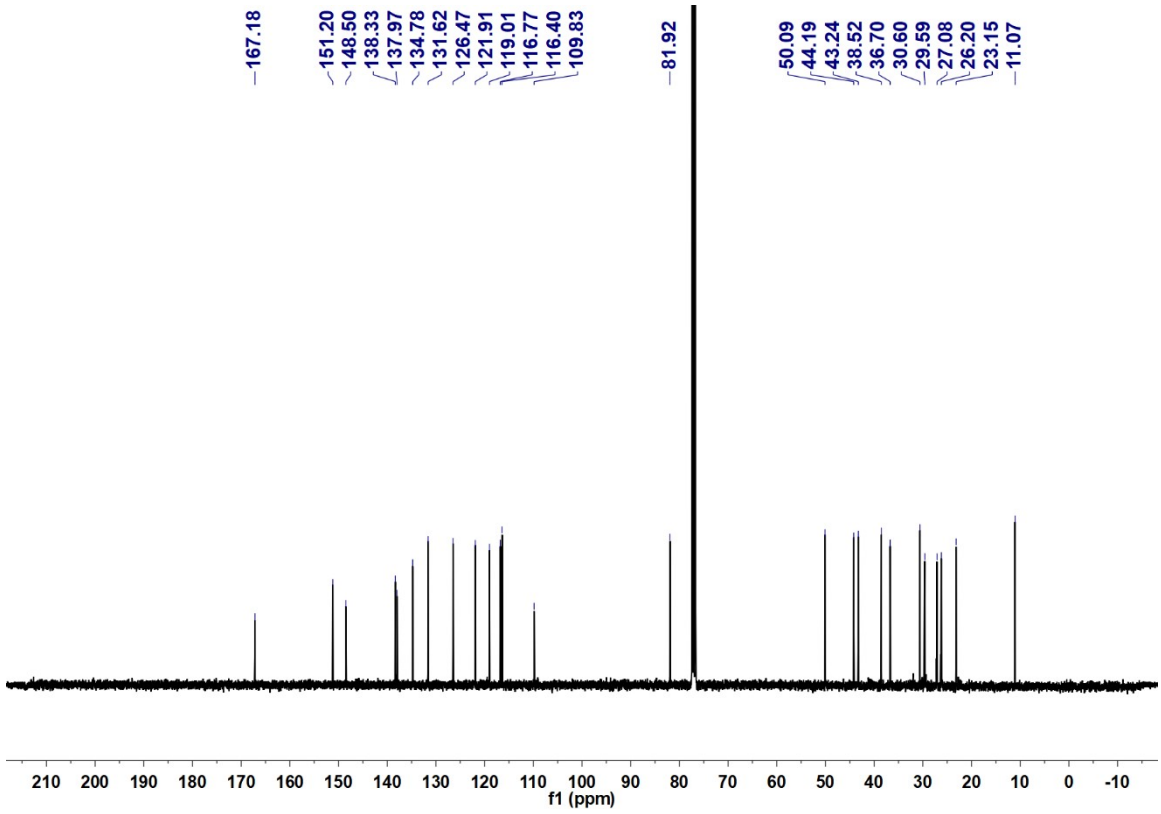
from Salicyl alcohol
3ch

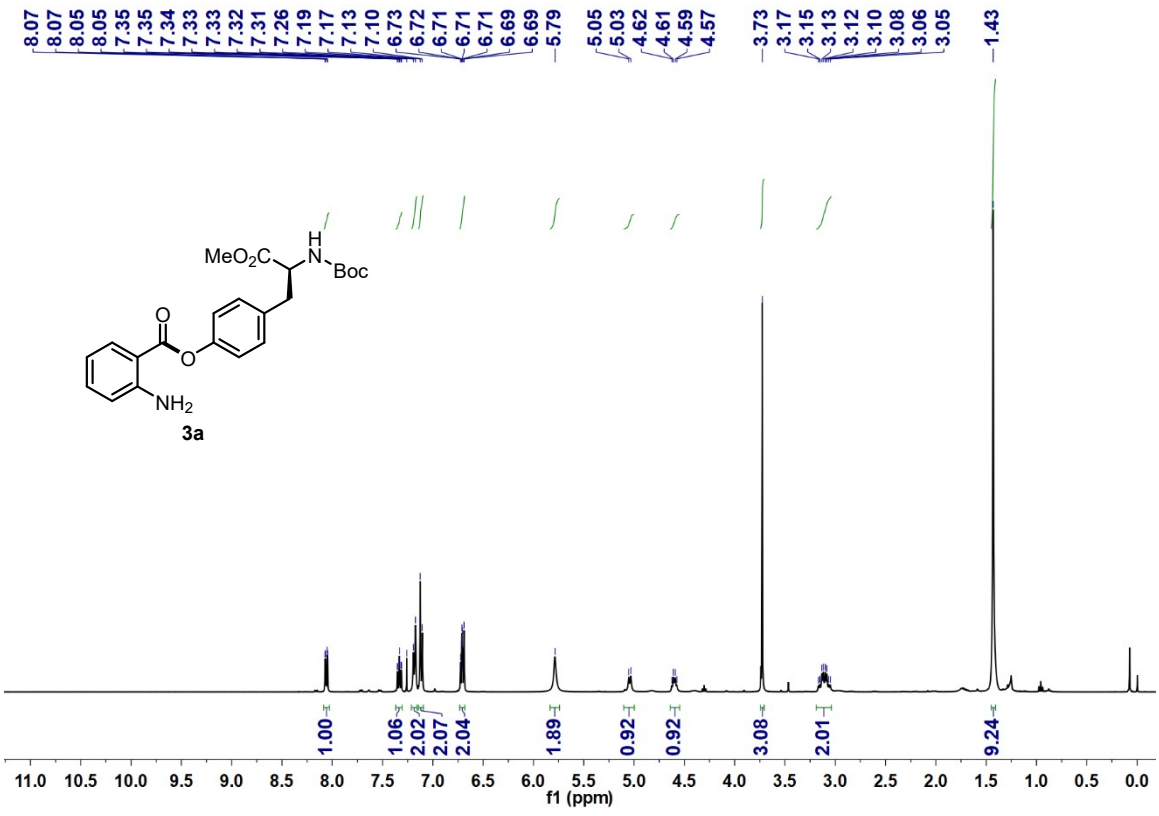


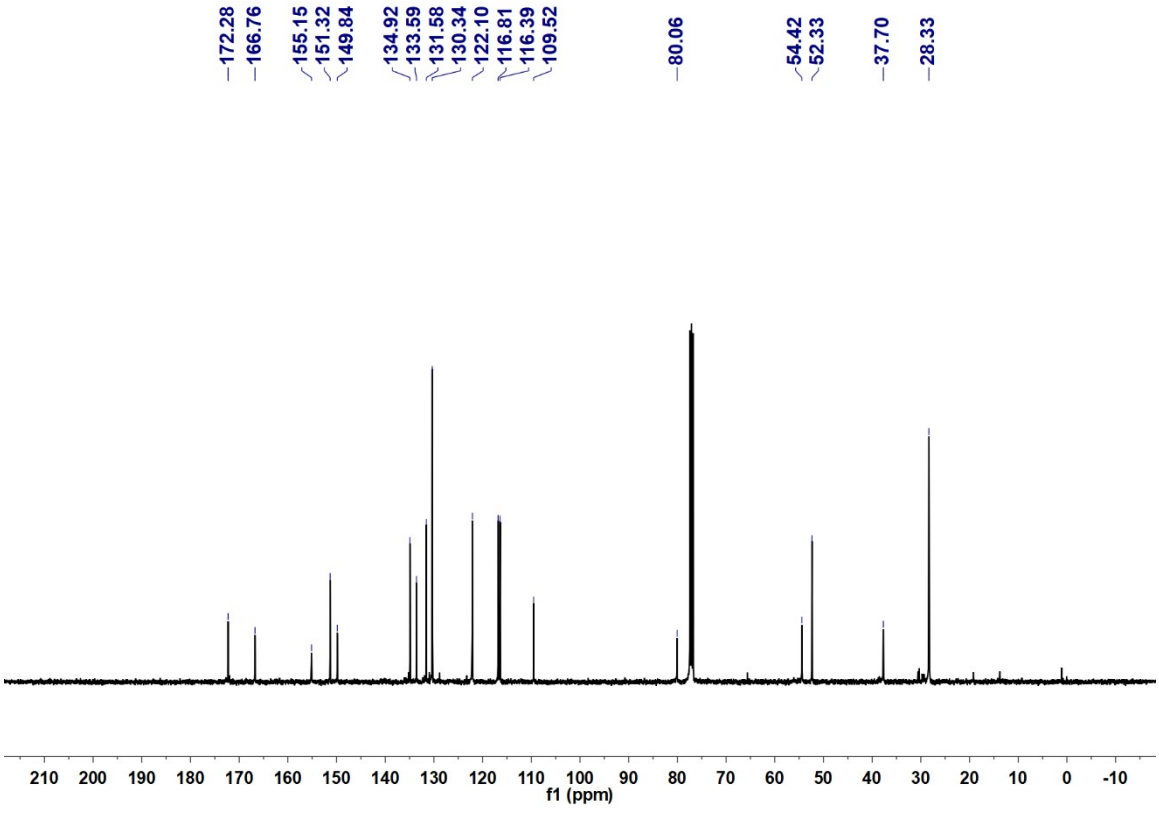



8.08 8.06 7.35 7.33 7.26 6.97 6.94 6.92 6.73 6.71 6.69 5.77 2.95 2.94 2.93 2.55 2.53 2.50 2.48 2.44 2.41 2.34 2.32 2.30 2.20 2.18 2.16 2.13 2.11 2.10 2.06 2.04 1.99 1.96 1.67 1.64 1.62 1.59 1.56 1.55 1.53 1.50 1.47 1.45 1.42 1.38 0.92
O
H
H
H
O
O
NH2
from Estrone
3ci
1.00 2.04 1.99 1.97 1.92 2.01 2.13 1.13 4.22 6.06 3.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
220.88 167.14 151.22 148.68 138.08 137.36 134.82 131.60 126.47 122.00 119.21 116.78 116.40 109.76 50.47 47.99 44.21 38.06 35.89 31.59 29.45 26.39 25.80 21.62 13.86
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.08 8.08 8.06 8.06 7.35 7.33 7.31 7.31 7.26 6.96 6.95 6.94 6.93 6.90 6.89 6.73 6.73 6.71 6.71 6.69 5.77 3.77 3.75 3.72 3.64 2.90 2.89 2.89 2.88 2.14 2.13 2.11 1.99 1.96 1.88 1.54 1.53 1.50 1.50 1.47 1.39 1.37 1.36 1.34 1.31 1.31 1.29 1.26 1.25 0.79
OH
H
O
H
H
O
NH2
from Estradiol
3cj
1.02 2.06 1.02 1.00 2.03 1.90 1.15 1.02 2.14 2.01 1.06 1.04 1.02 1.13 7.12 3.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


167.18
151.20 148.50 138.33 137.97 134.78 131.62 126.47 121.91 119.01 116.77 116.40 109.83
81.92
50.09 44.19 43.24 38.52 36.70 30.60 29.59 27.08 26.20 23.15 11.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.07
8.07
8.05
8.05
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.26
7.19
7.17
7.13
7.10
6.73
6.72
6.71
6.71
6.71
6.69
6.69
5.79
5.05
5.03
4.62
4.61
4.59
4.57
3.73
3.17
3.15
3.13
3.12
3.10
3.08
3.06
3.05
1.43
MeO2C
H
N
Boc
O
O
NH2
3a
1.00
1.06
2.02
2.07
2.04
1.89
0.92
0.92
3.08
2.01
9.24
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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116.39
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37.70
28.33
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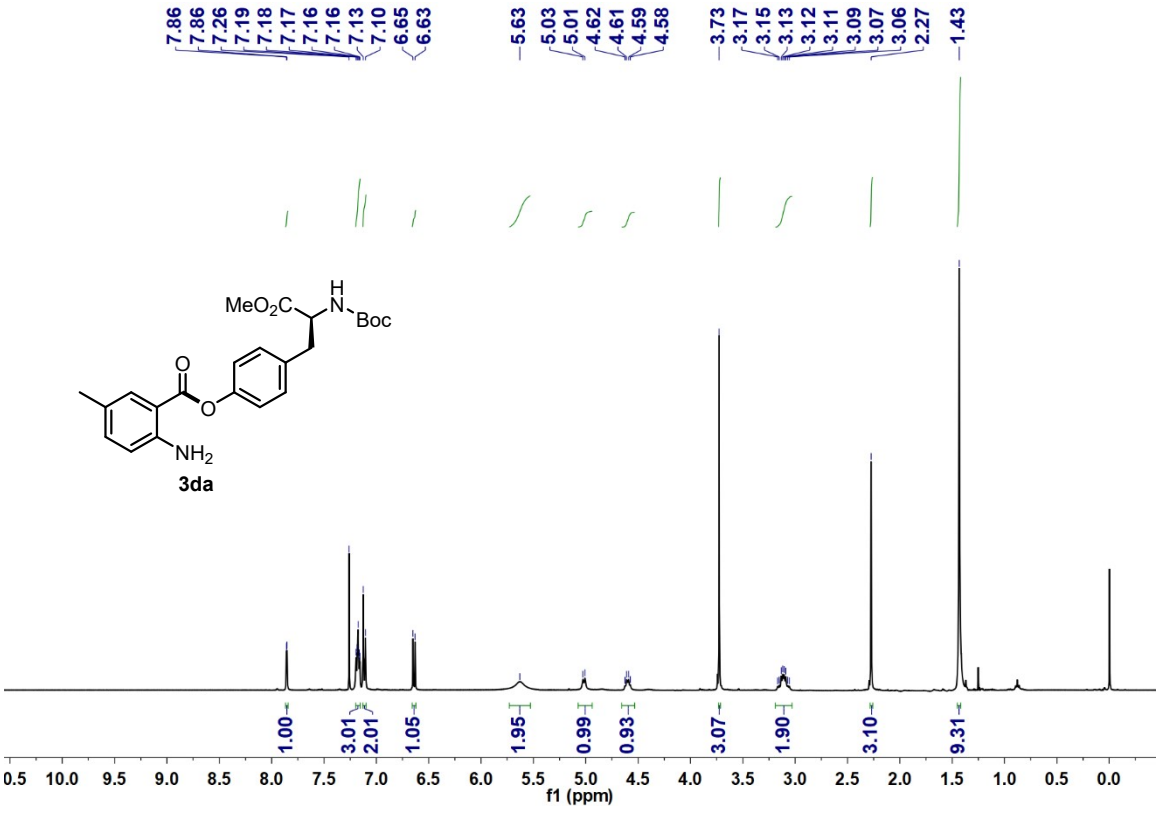
f1 (ppm)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6.63
5.63
5.03
5.01
4.62
4.61
4.59
4.58
3.73
3.17
3.15
3.13
3.12
3.11
3.09
3.07
3.06
2.27
1.43
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H
N
Boc
O
O
NH2
3da
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1.05
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0.93
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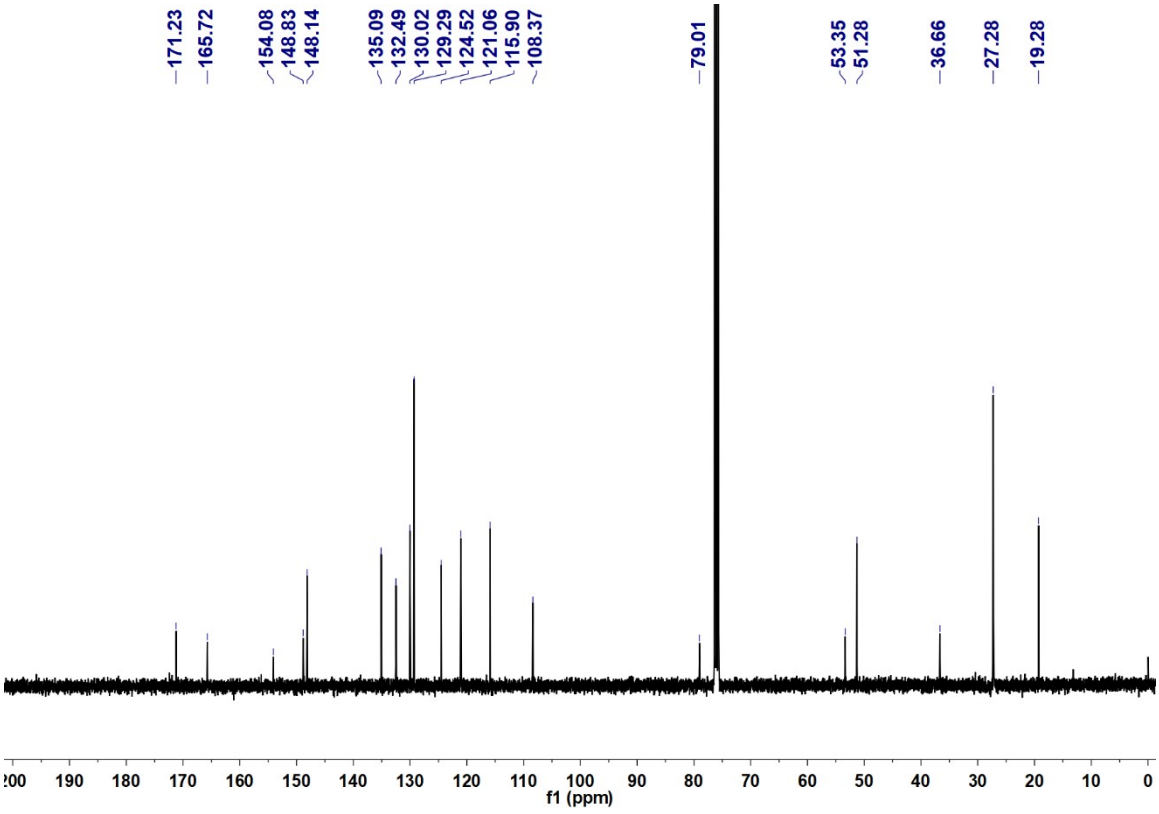
1.90
3.10
9.31
f1 (ppm)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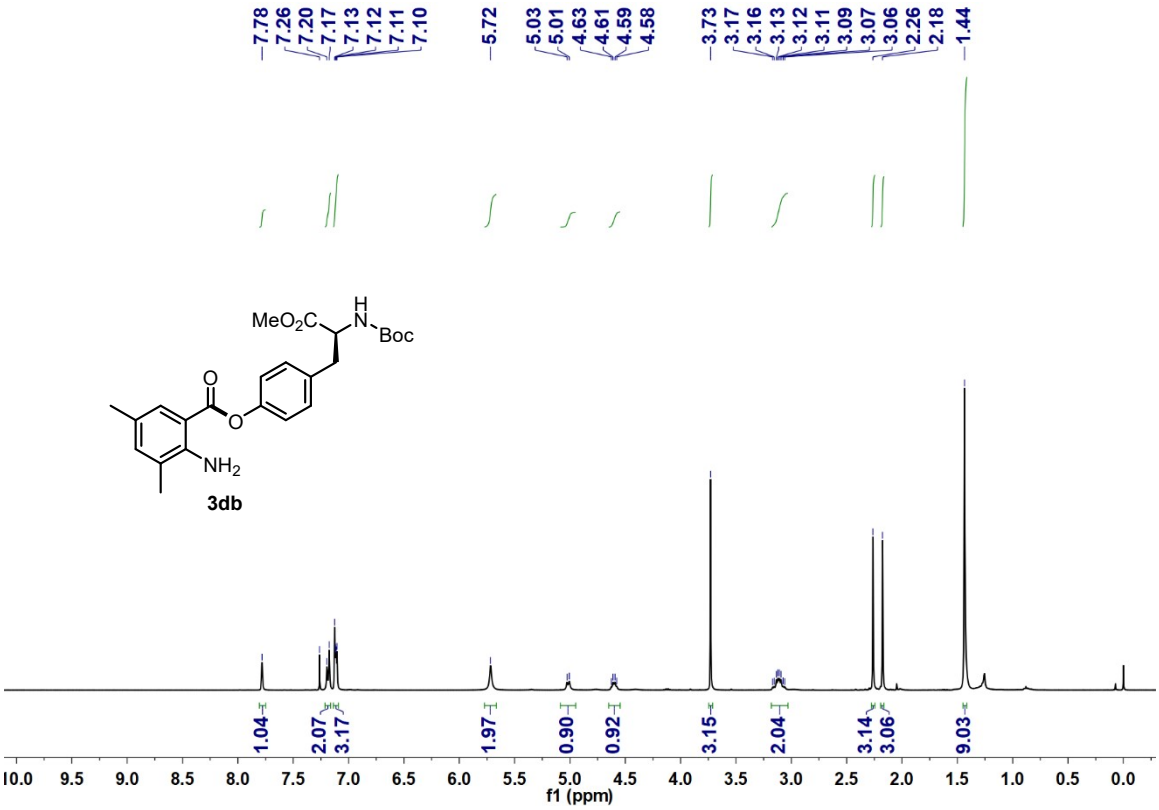
19.28
f1 (ppm)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3.13
3.12
3.11
3.09
3.07
3.06
2.26
2.18
1.44
MeO2C
H
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Boc
O
O
NH2
3db
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3.14
3.06
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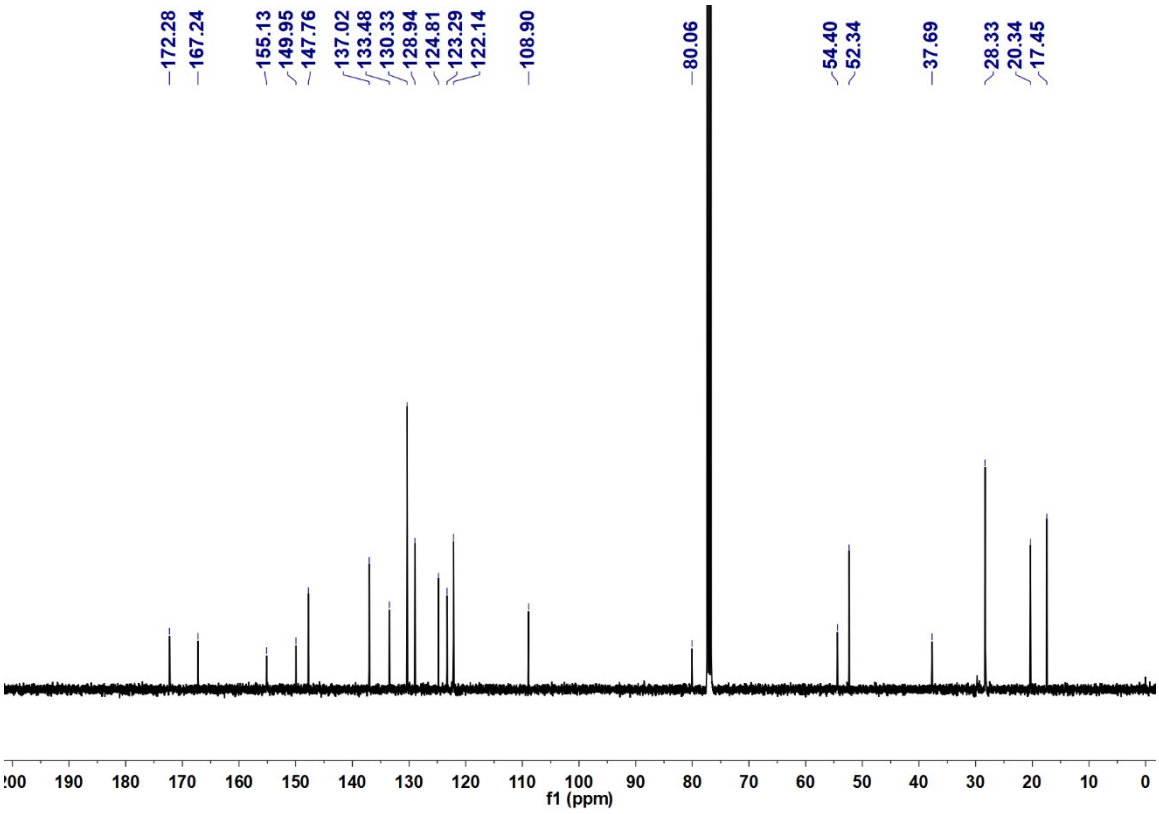
f1 (ppm)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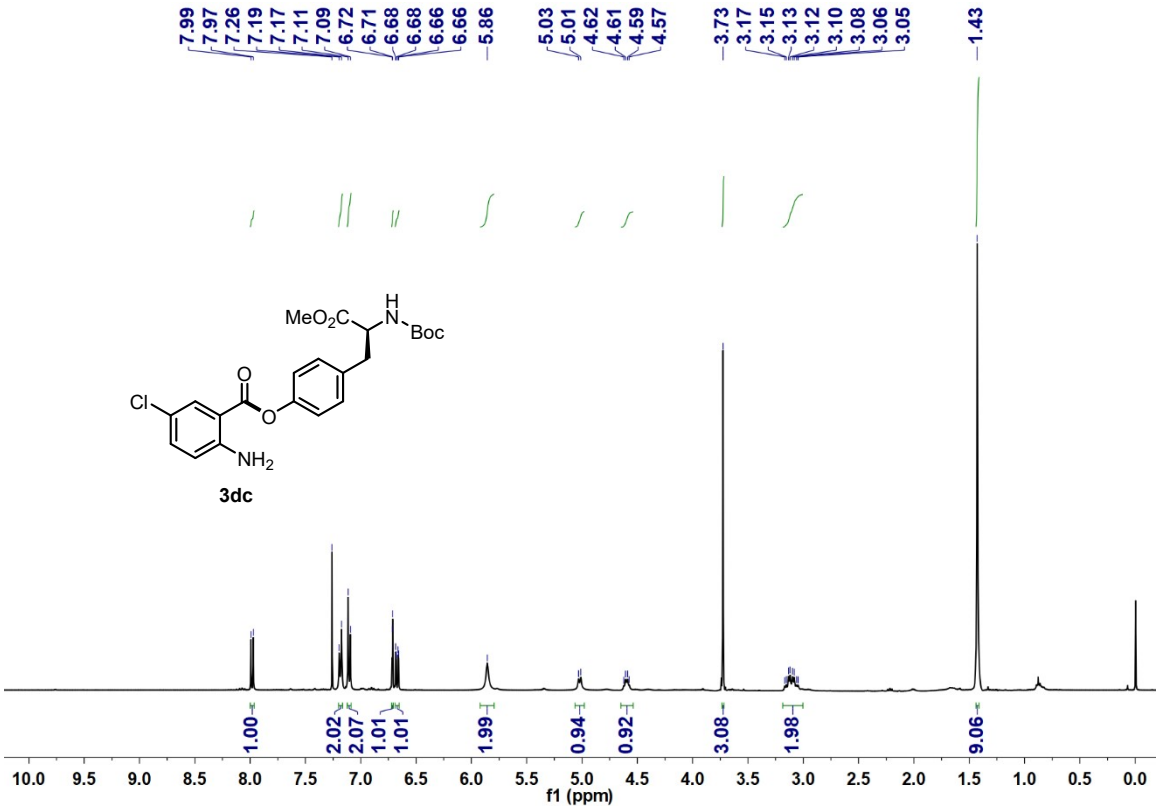
17.45
f1 (ppm)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3.17
3.15
3.13
3.12
3.10
3.08
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3.05
1.43
MeO2C
H
N
Boc
O
Cl
O
NH2
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3.08
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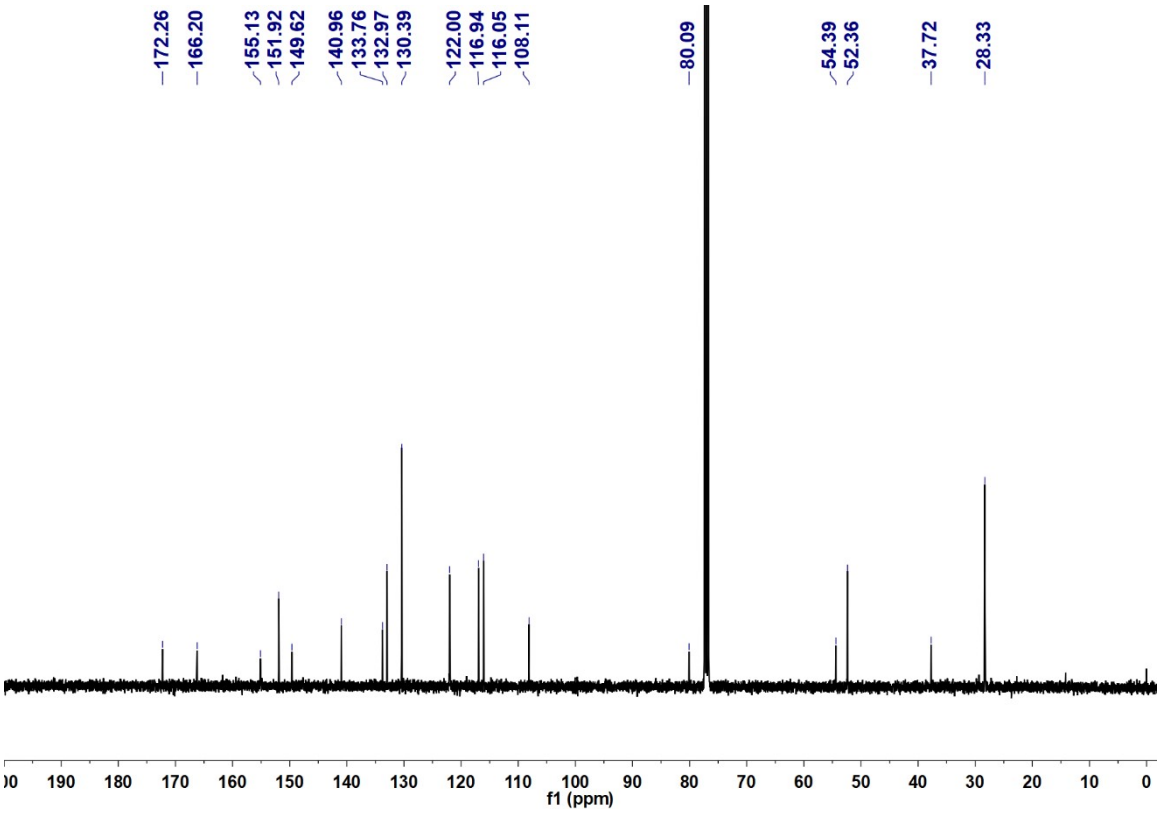
9.06
f1 (ppm)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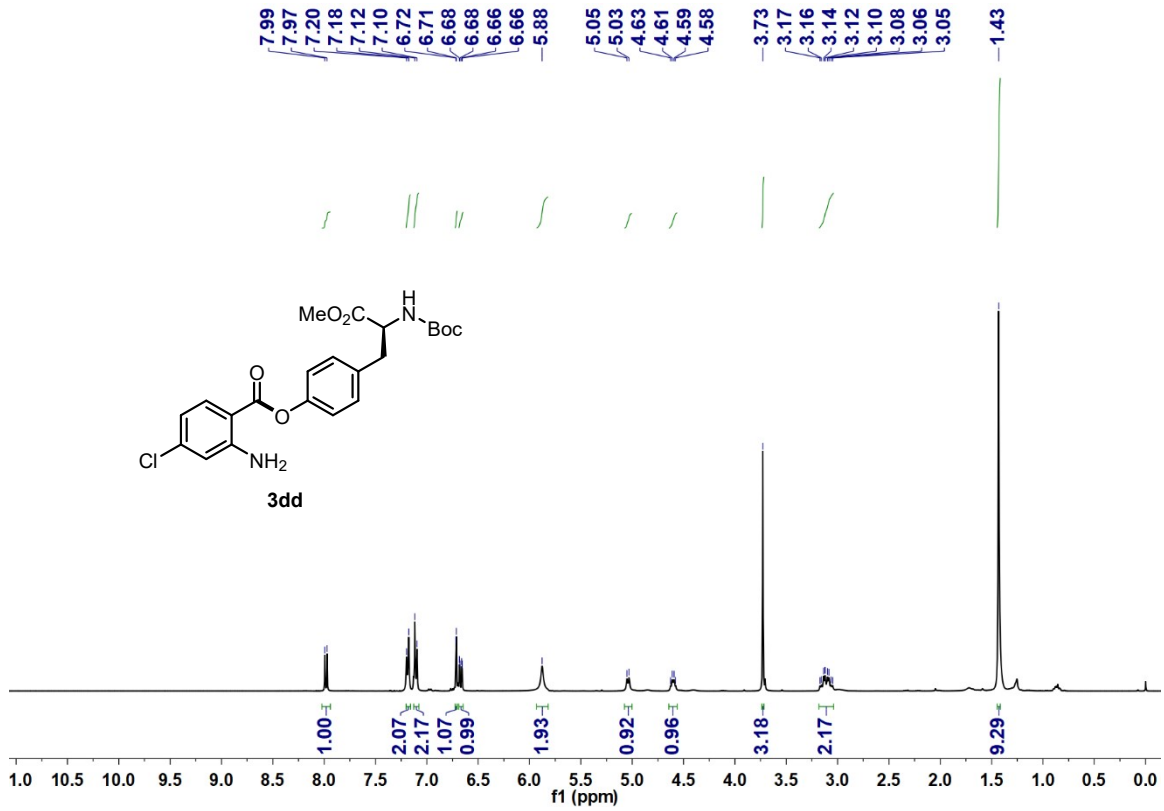
52.36
37.72
28.33
f1 (ppm)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5.88
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5.03
4.63
4.61
4.59
4.58
3.73
3.17
3.16
3.14
3.12
3.10
3.08
3.06
3.05
1.43
MeO2C
H
N
Boc
O
O
Cl
NH2
3dd
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1.07
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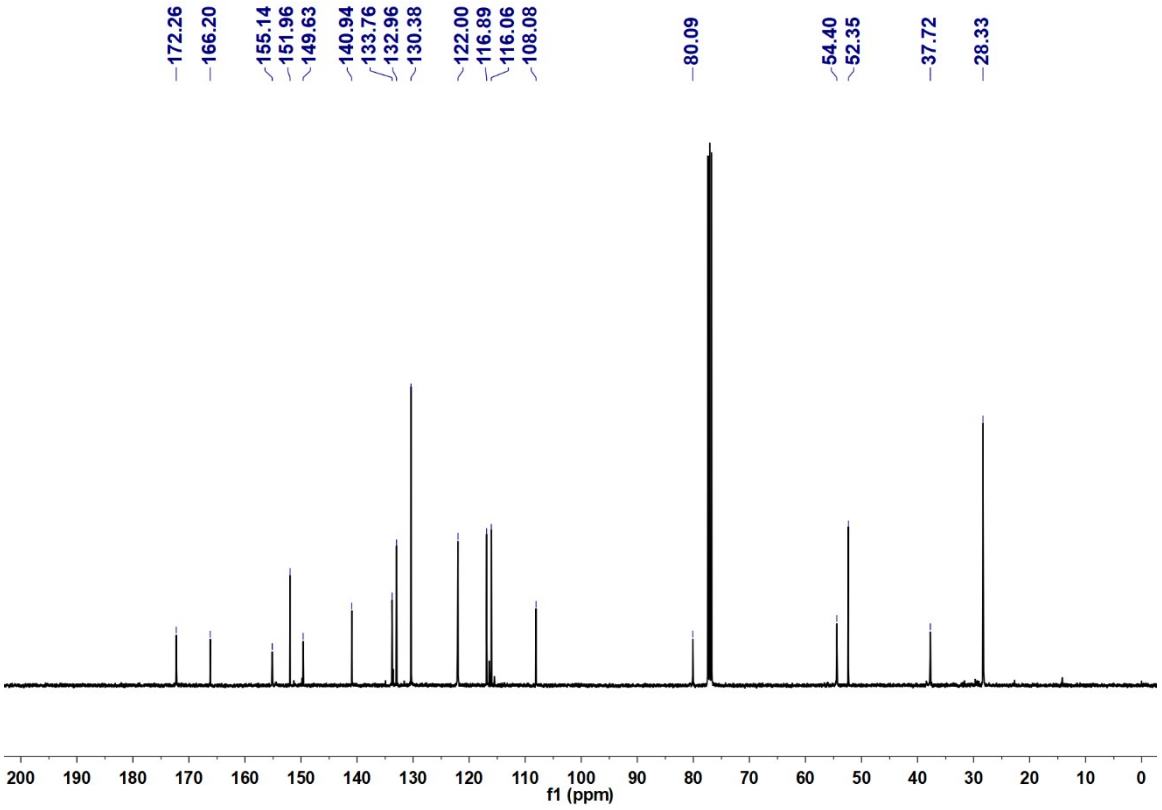
1.93
0.92
0.96
3.18
2.17
9.29
f1 (ppm)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133.76
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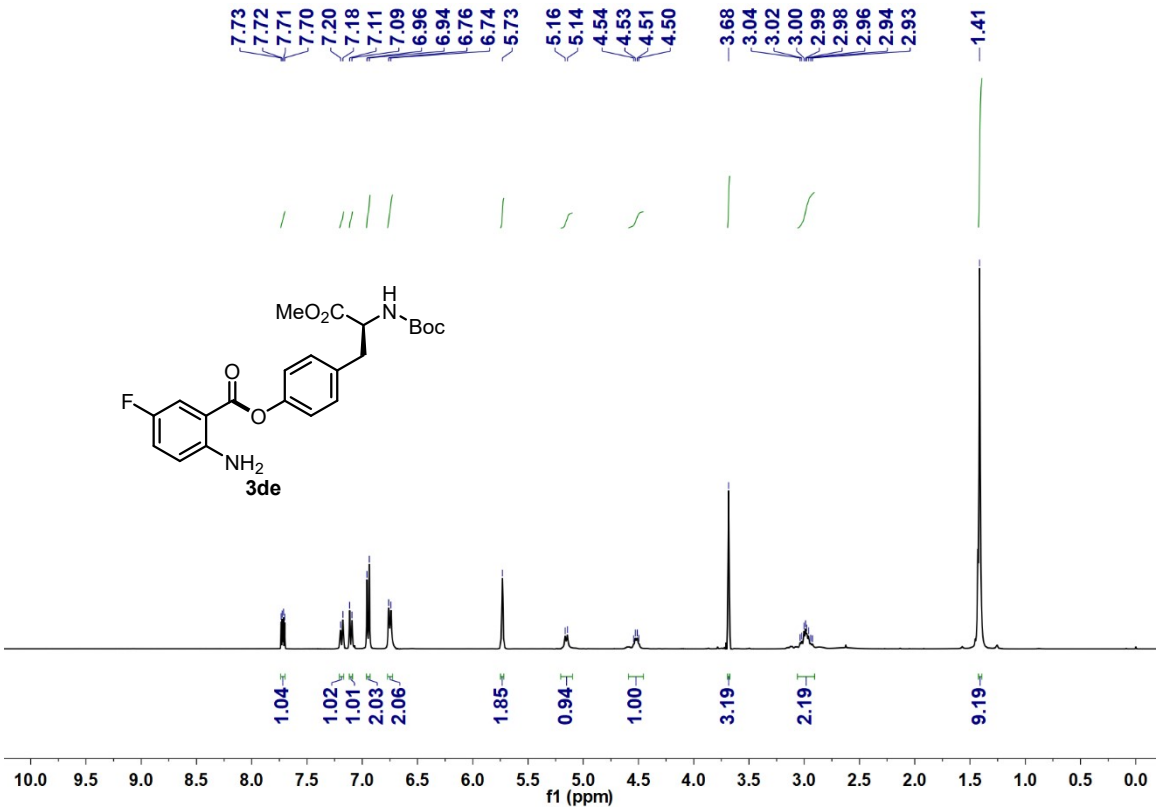
116.06
108.08
80.09
54.40
52.35
37.72
28.33
f1 (ppm)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6.94
6.76
6.74
5.73
5.16
5.14
4.54
4.53
4.51
4.50
3.68
3.04
3.02
3.00
2.99
2.98
2.96
2.94
2.93
1.41
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H
N
Boc
O
F
O
NH2
3de
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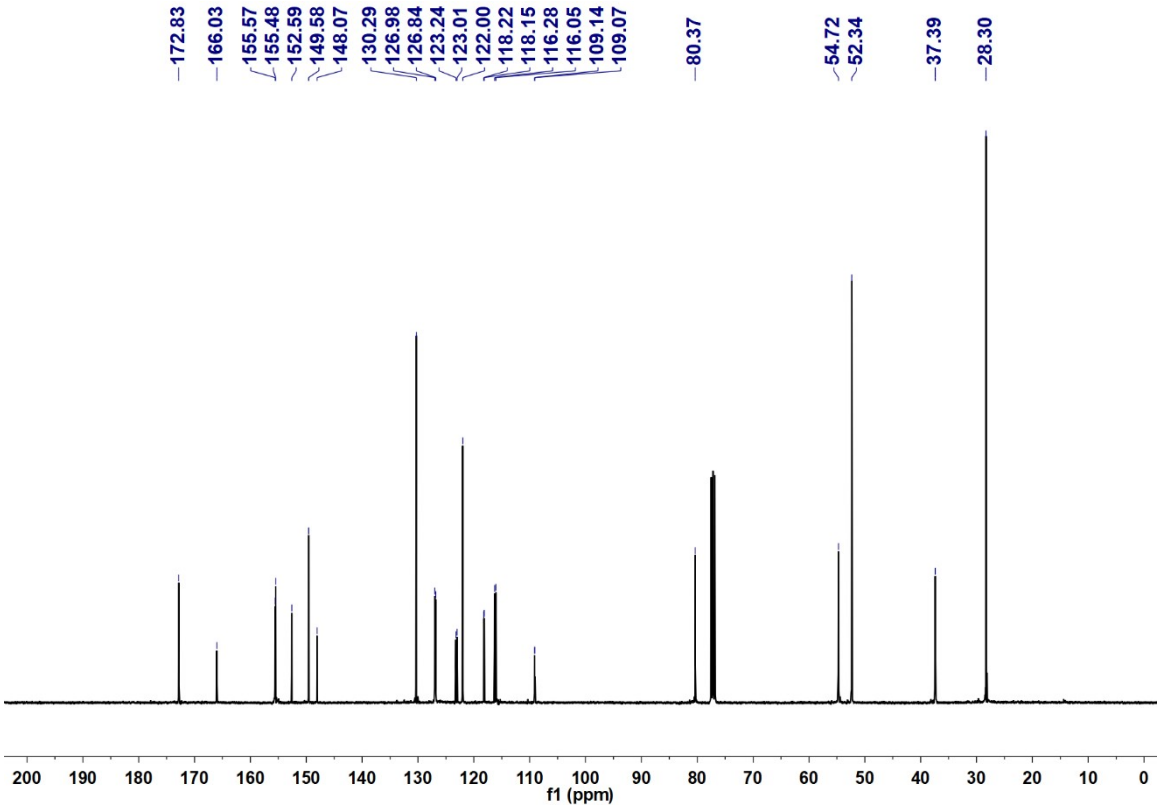
1.02
1.01
2.03
2.06
1.85
0.94
1.00
3.19
2.19
9.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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118.15
116.28
116.05
109.14
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54.72
52.34
37.39
28.30
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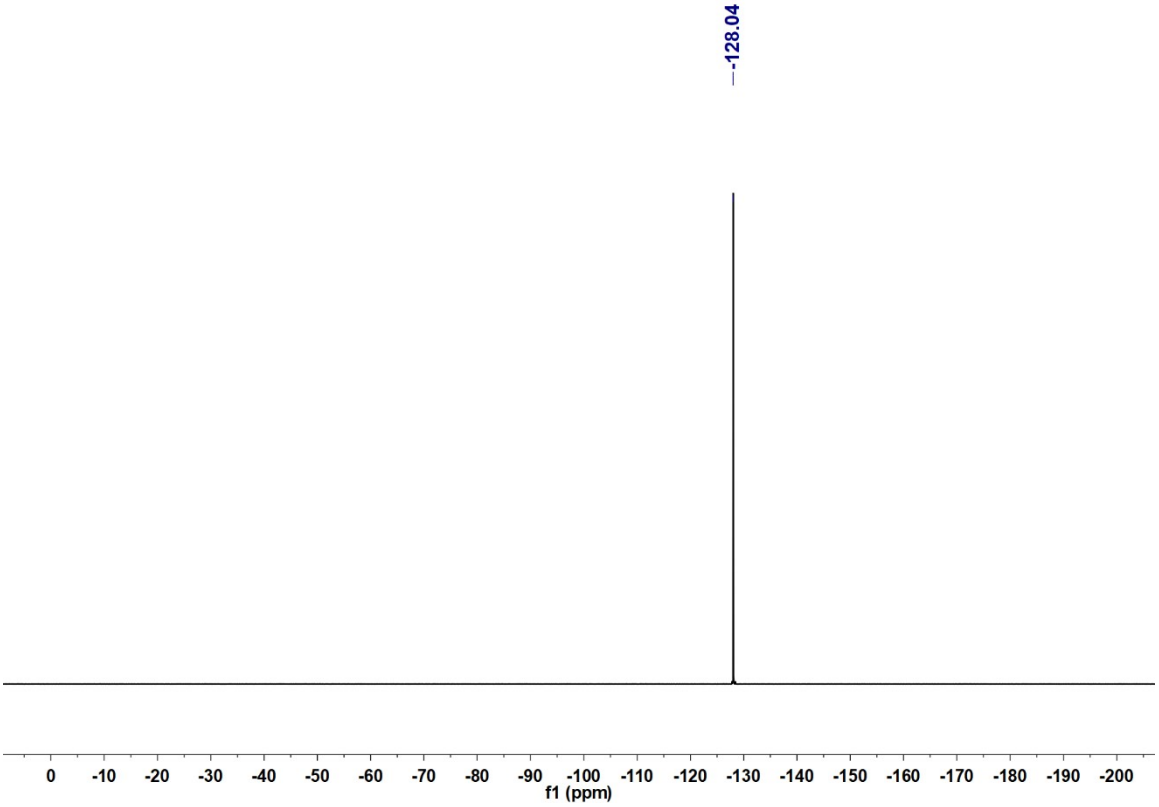
f1 (ppm)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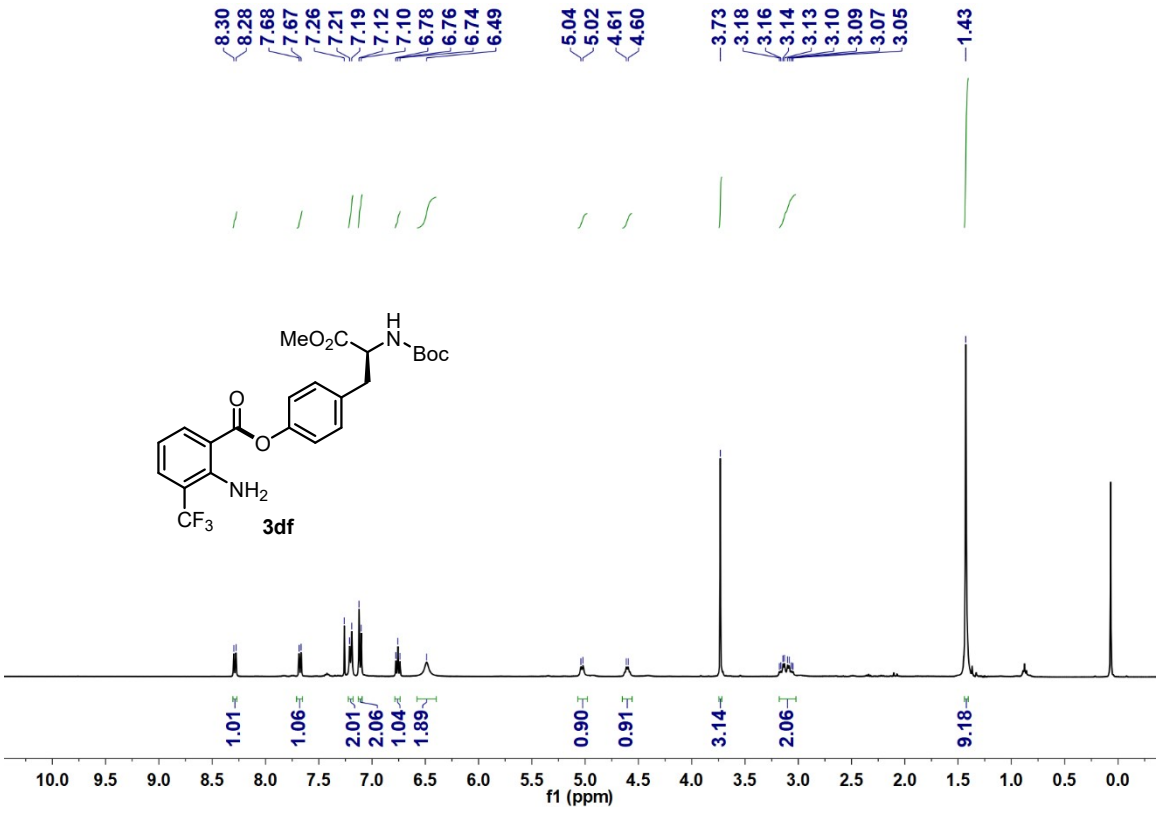
f1 (ppm)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5.02
4.61
4.60
3.73
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3.16
3.14
3.13
3.10
3.09
3.07
3.05
1.43
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H
N
Boc
O
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NH2
CF3
3df
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1.06
2.01
2.06
1.04
1.89
0.90
0.91
3.14
2.06
9.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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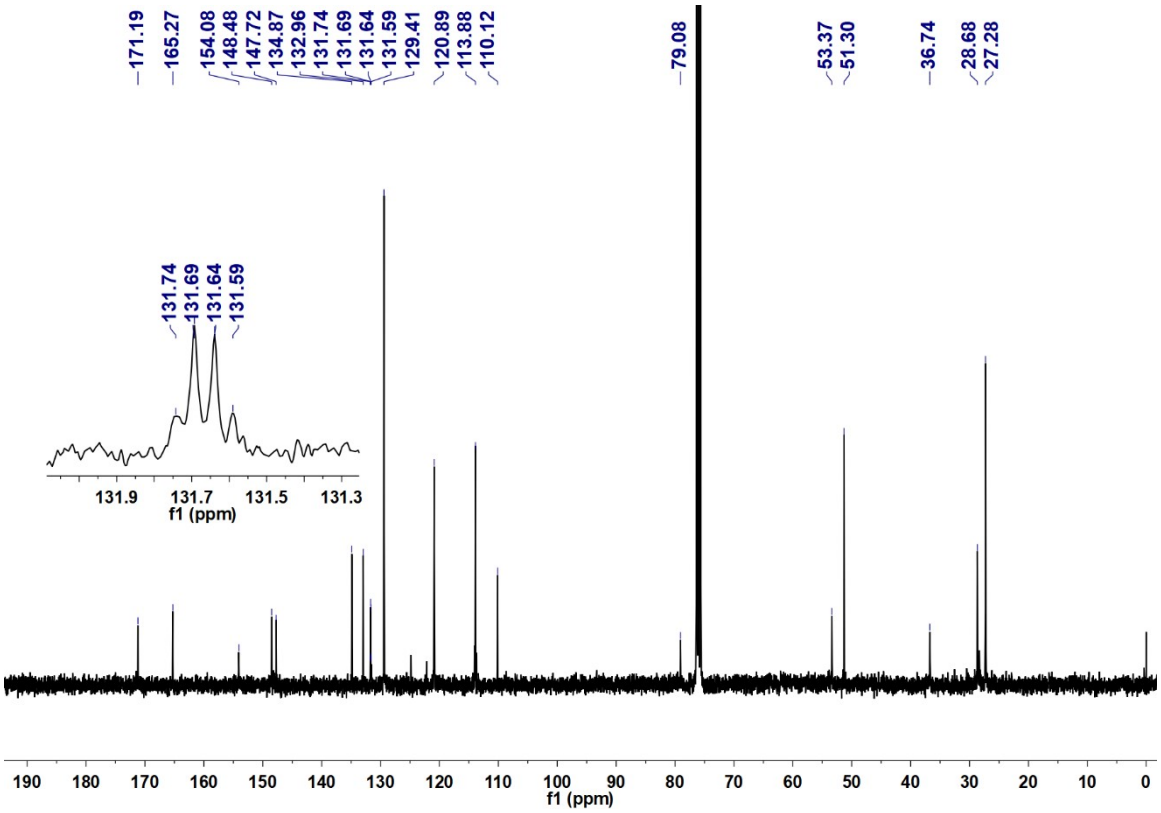
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36.74
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27.28
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131.69
131.64
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131.5
131.3
f1 (ppm)
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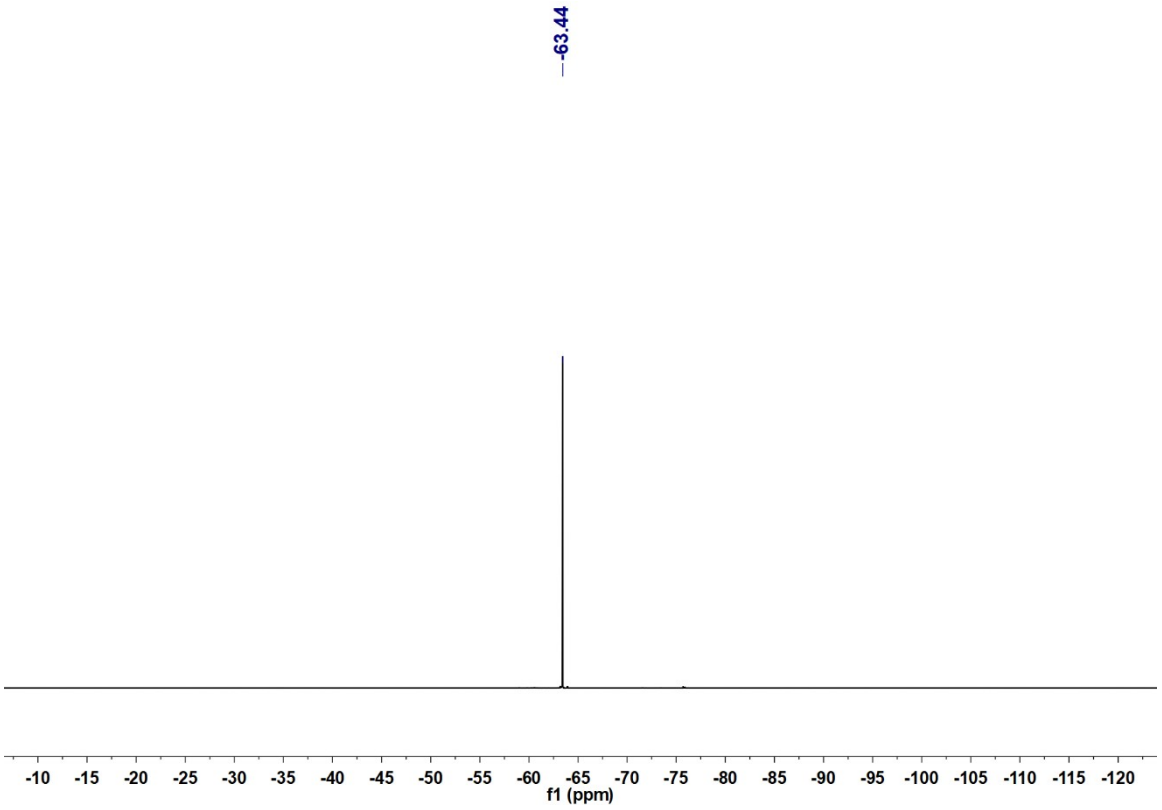
f1 (ppm)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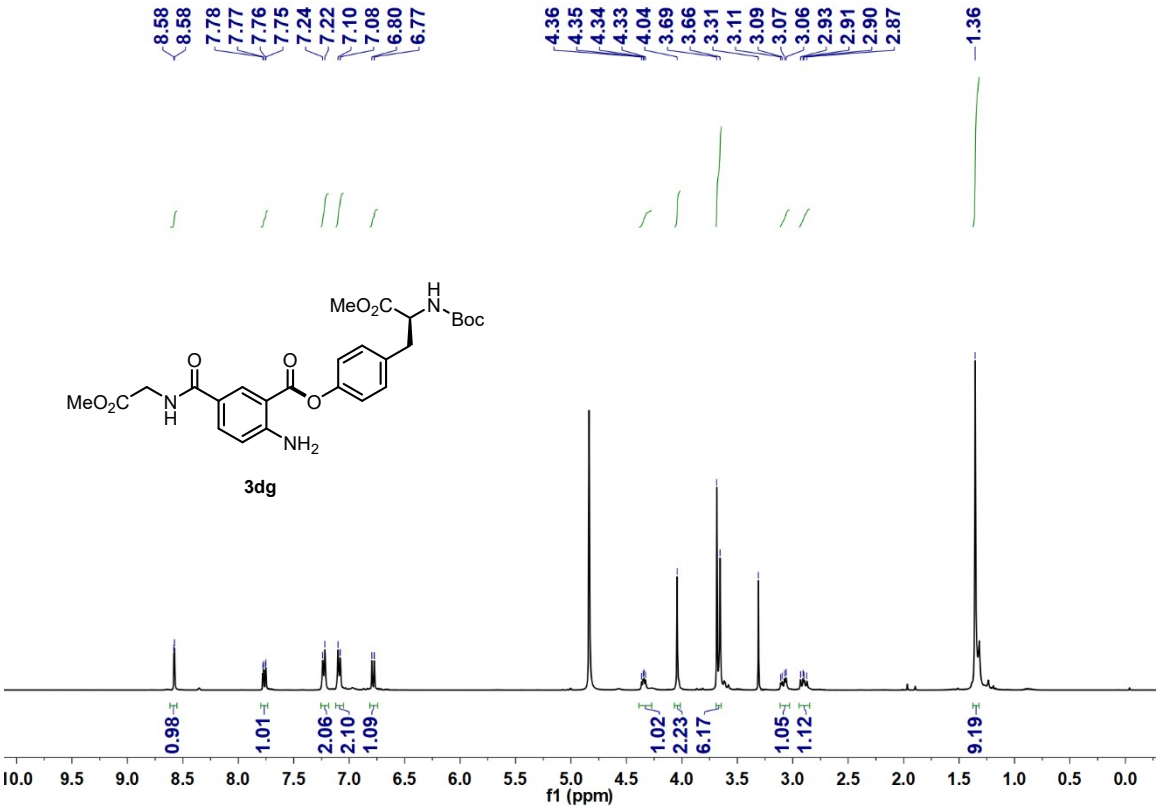
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4.34
4.33
4.04
3.69
3.66
3.31
3.11
3.09
3.07
3.06
2.93
2.91
2.90
2.87
1.36
MeO2C
H
N
Boc
O
O
MeO2C
N
H
O
NH2
0.98
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1.02
2.23
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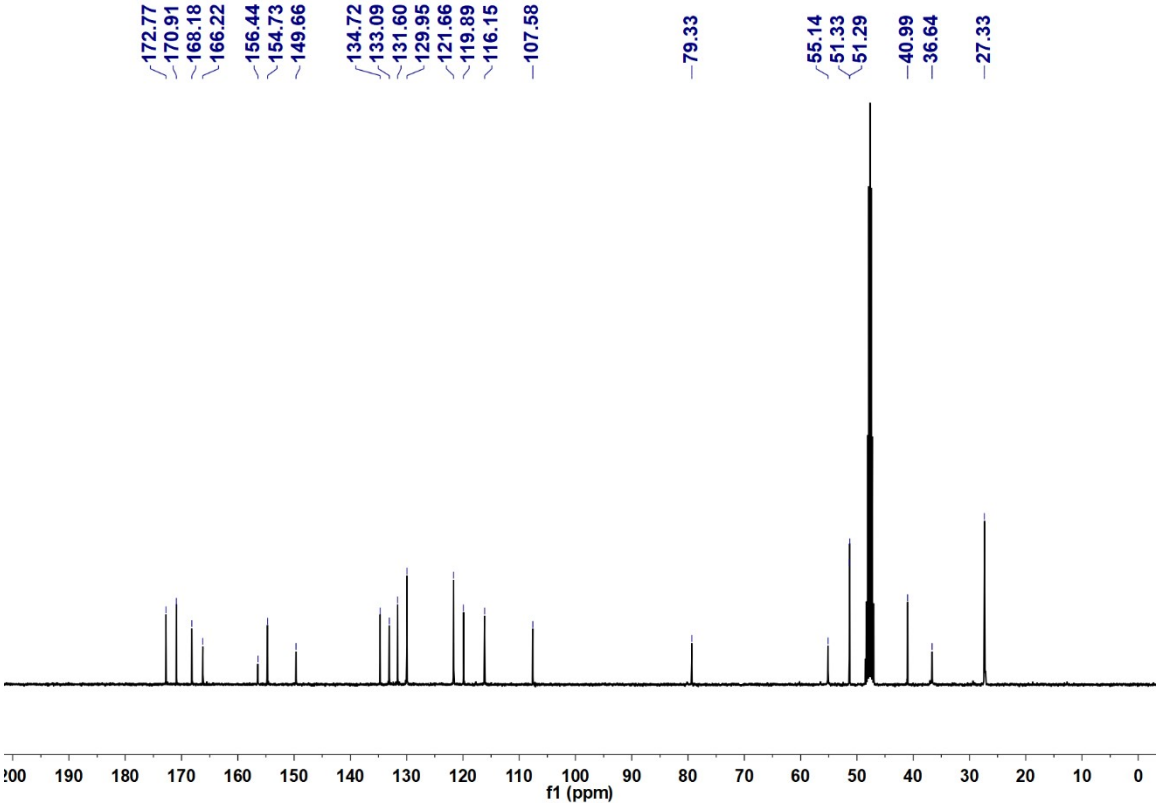
9.19
f1 (ppm)

3dg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107.58
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55.14
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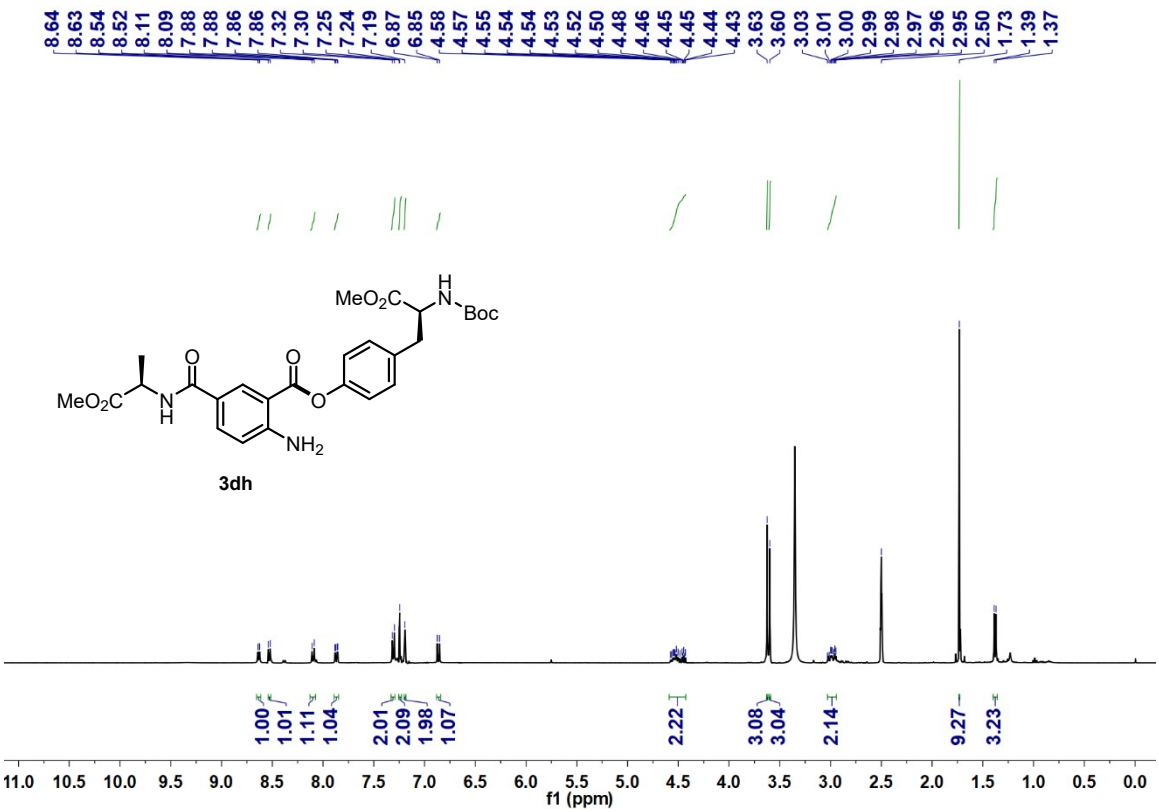
51.29
40.99
36.64
27.33
f1 (ppm)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4.43
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3.60
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3.01
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2.98
2.97
2.96
2.95
2.50
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1.39
1.37
MeO2C
N
H
Boc
MeO2C
N
H
O
O
O
NH2
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1.01
1.11
1.04
2.01
2.09
1.98
1.07
2.22
3.08
3.04
2.14
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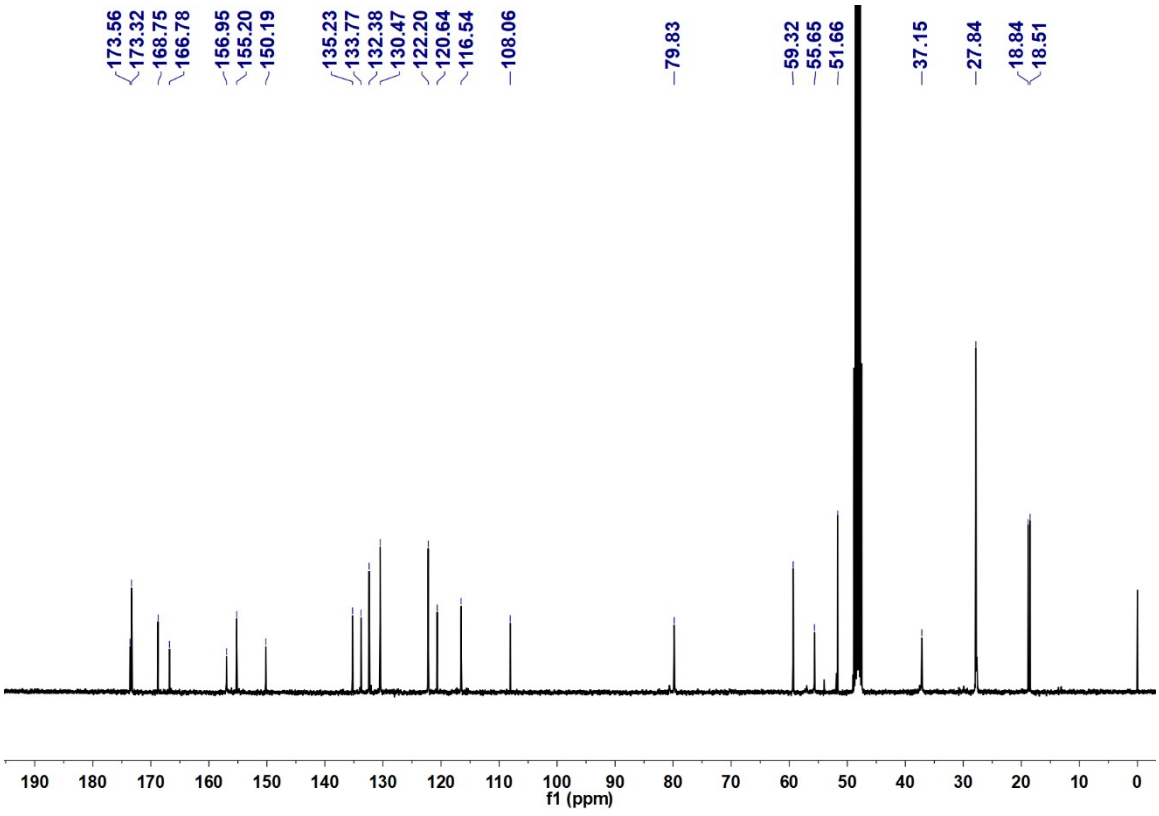
f1 (ppm)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108.06
79.83
59.32
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37.15
27.84
18.84
18.51
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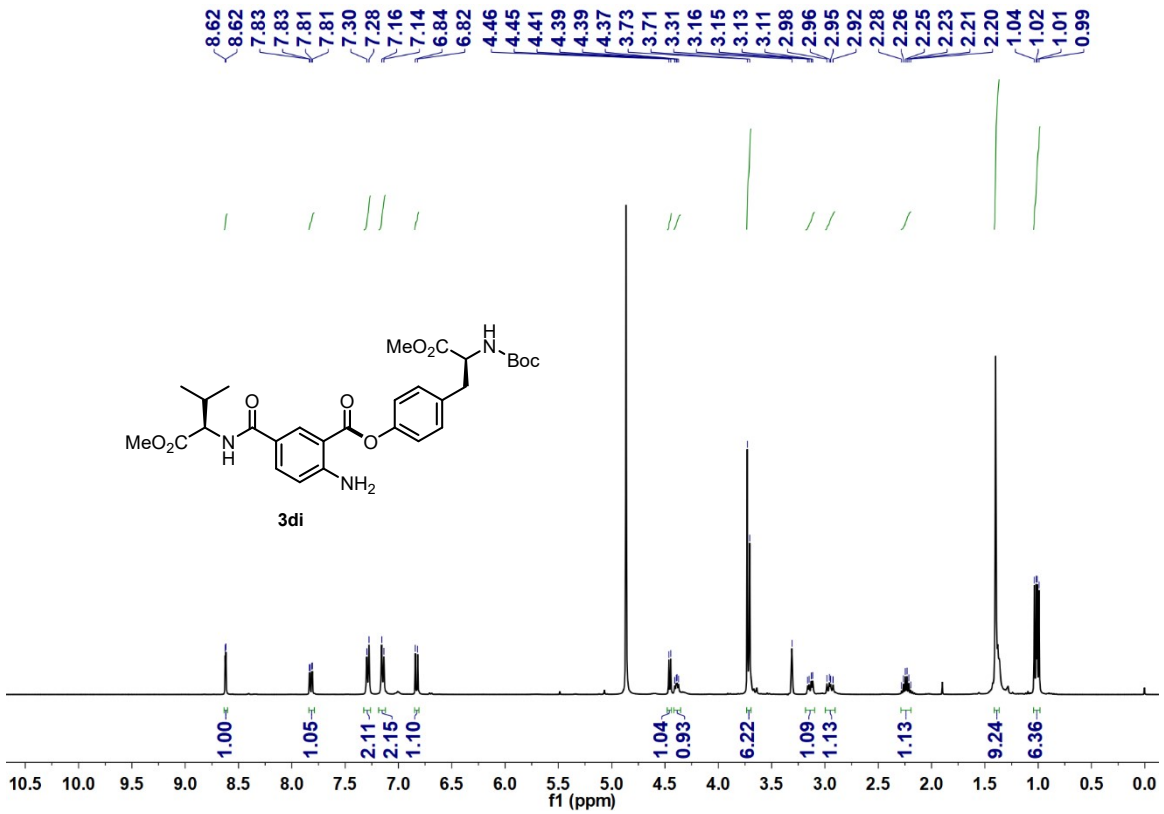
f1 (ppm)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2.96
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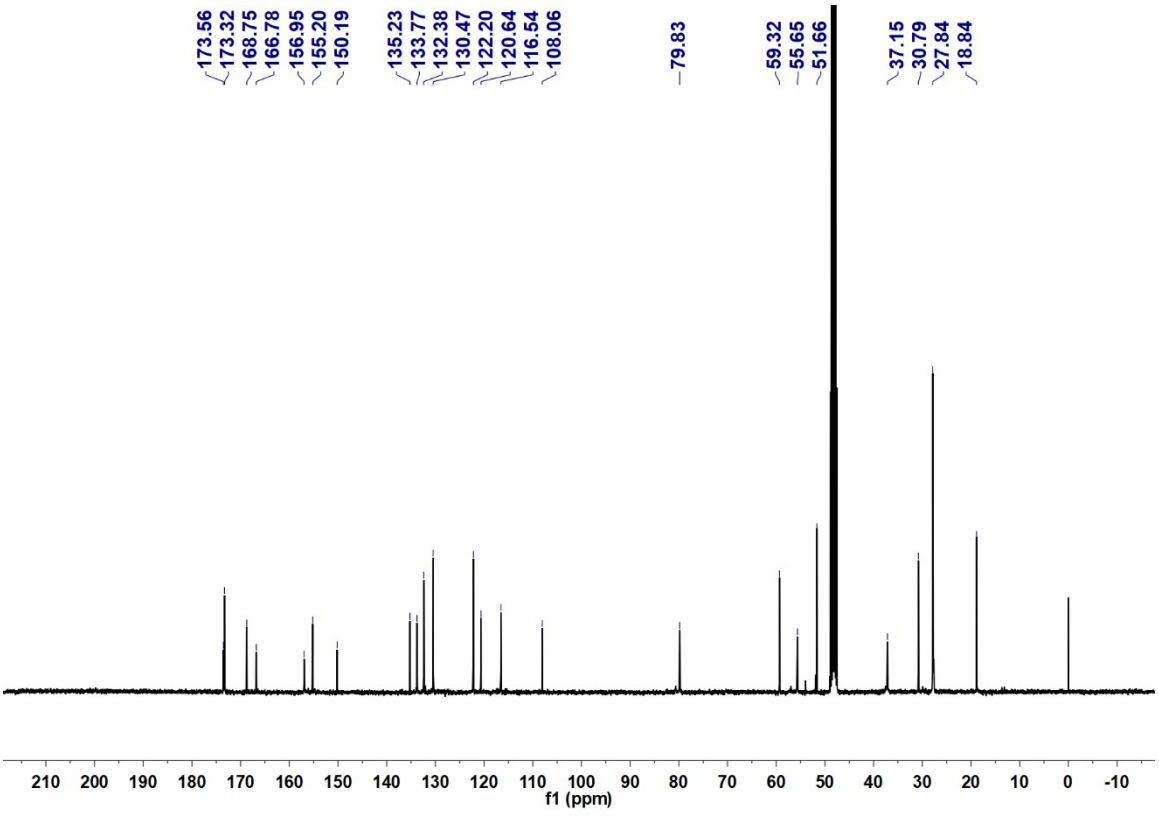
2.23
2.21
2.20
1.04
1.02
1.01
0.99
MeO2C
H
N
Boc
MeO2C
N
H
O
O
O
NH2
3di
1.00
1.05
2.11
2.15
1.10
1.04
0.93
6.22
1.09
1.13
1.13
9.24
6.36
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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108.06
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59.32
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18.84
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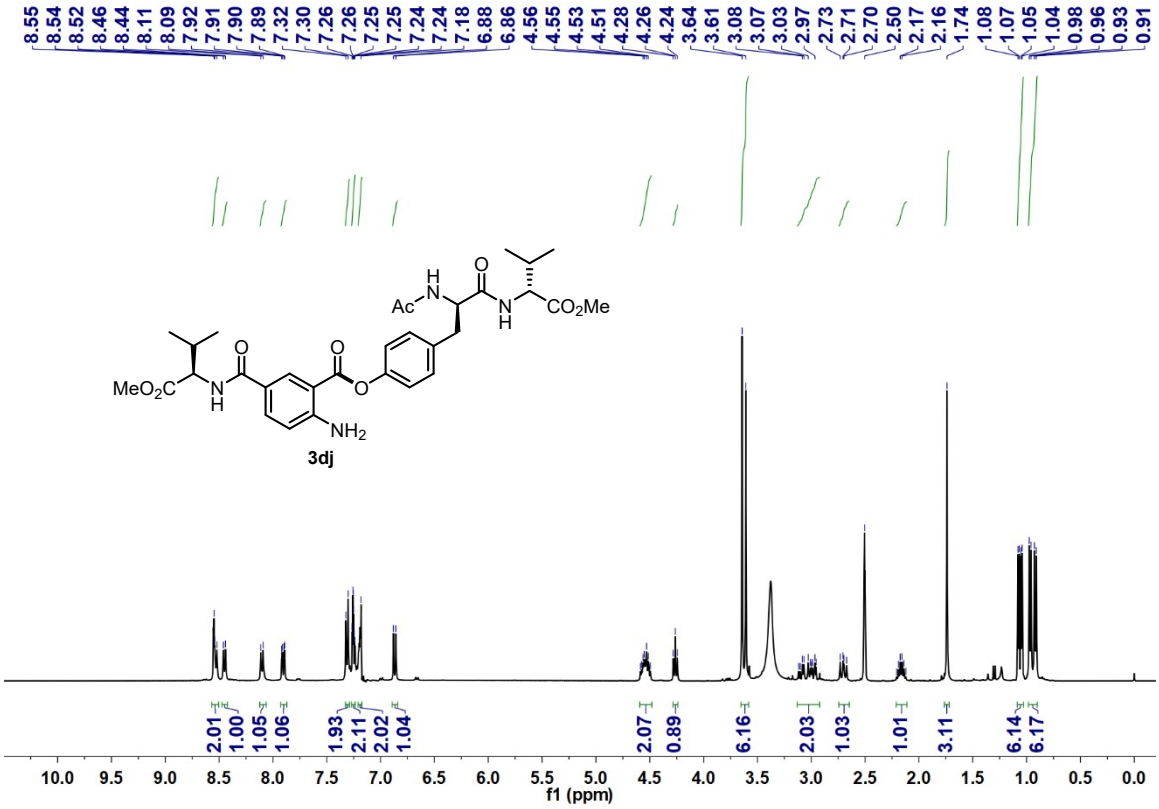
f1 (ppm)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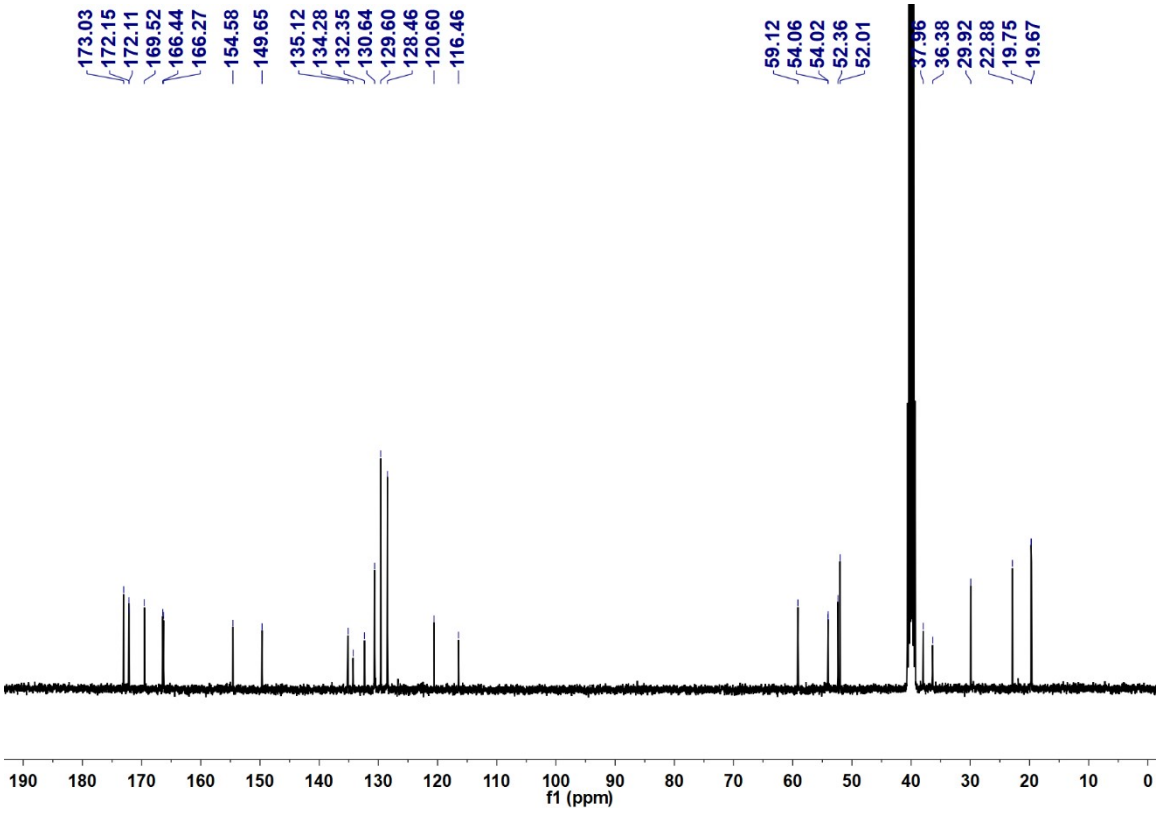
Ac
CO2Me
MeO2C
NH2
3dj
2.01 1.00 1.05 1.06 1.93 2.11 2.02 1.04 2.07 0.89 6.16 2.03 1.03 1.01 3.11 6.14 6.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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59.12 54.06 54.02 52.36 52.01 37.96 36.38 29.92 22.88 19.75 19.67
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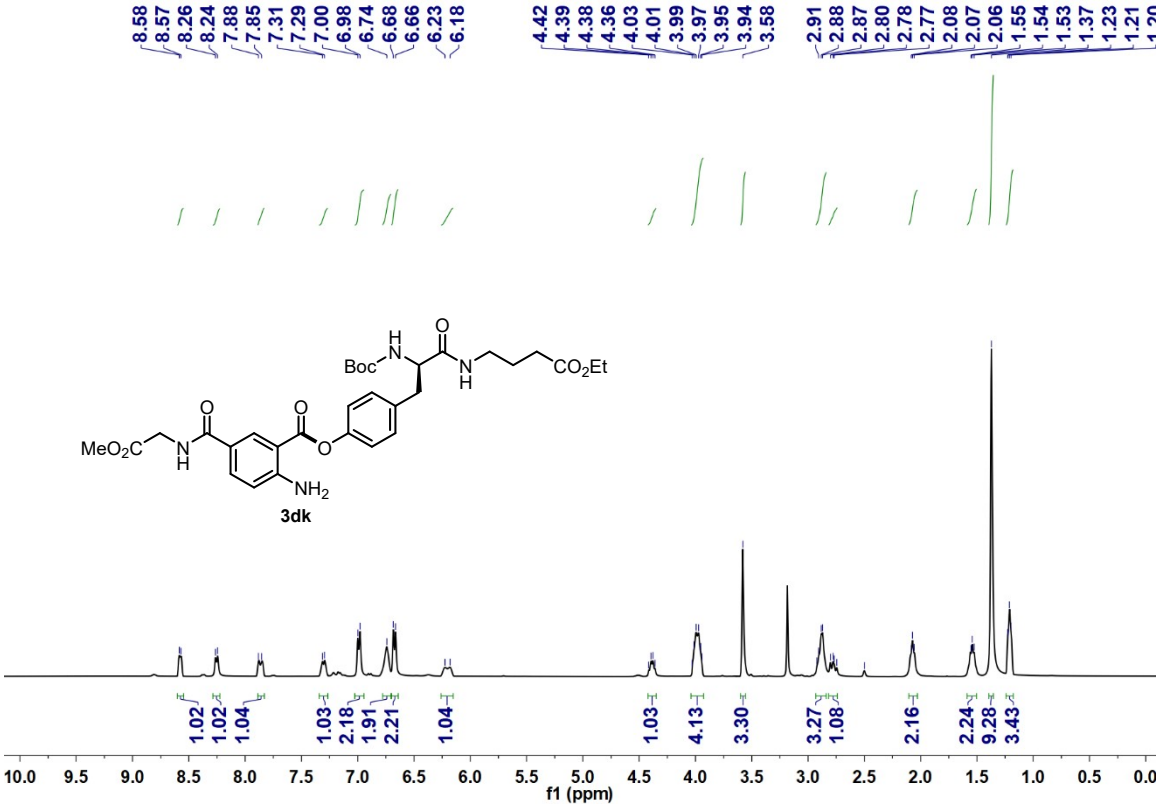
f1 (ppm)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1.23
1.21
Boc
CO2Et
MeO2C
NH2
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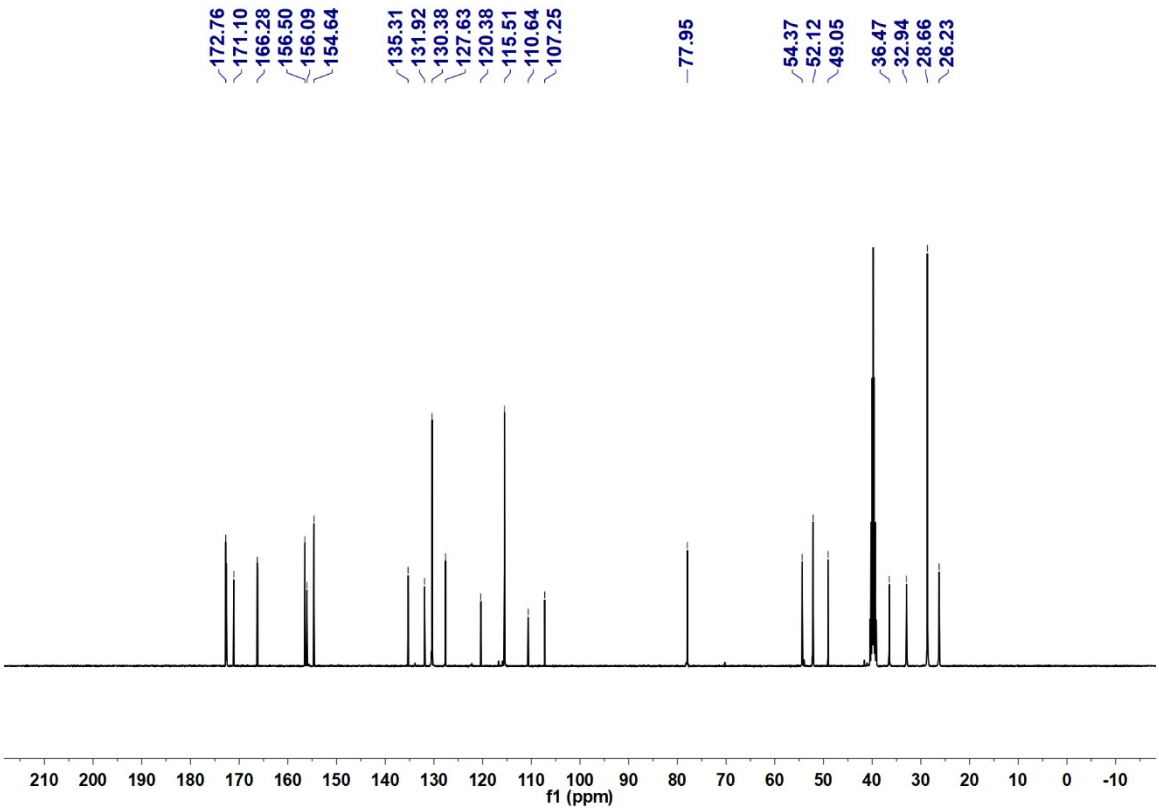
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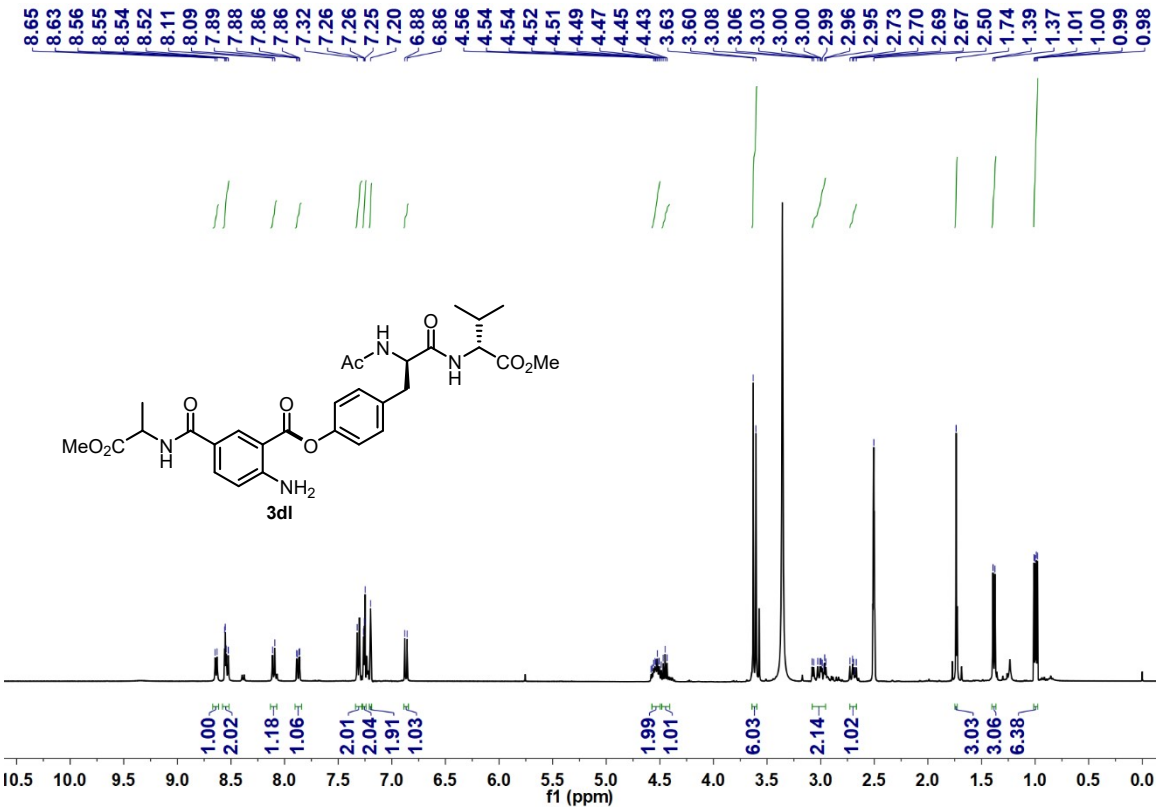
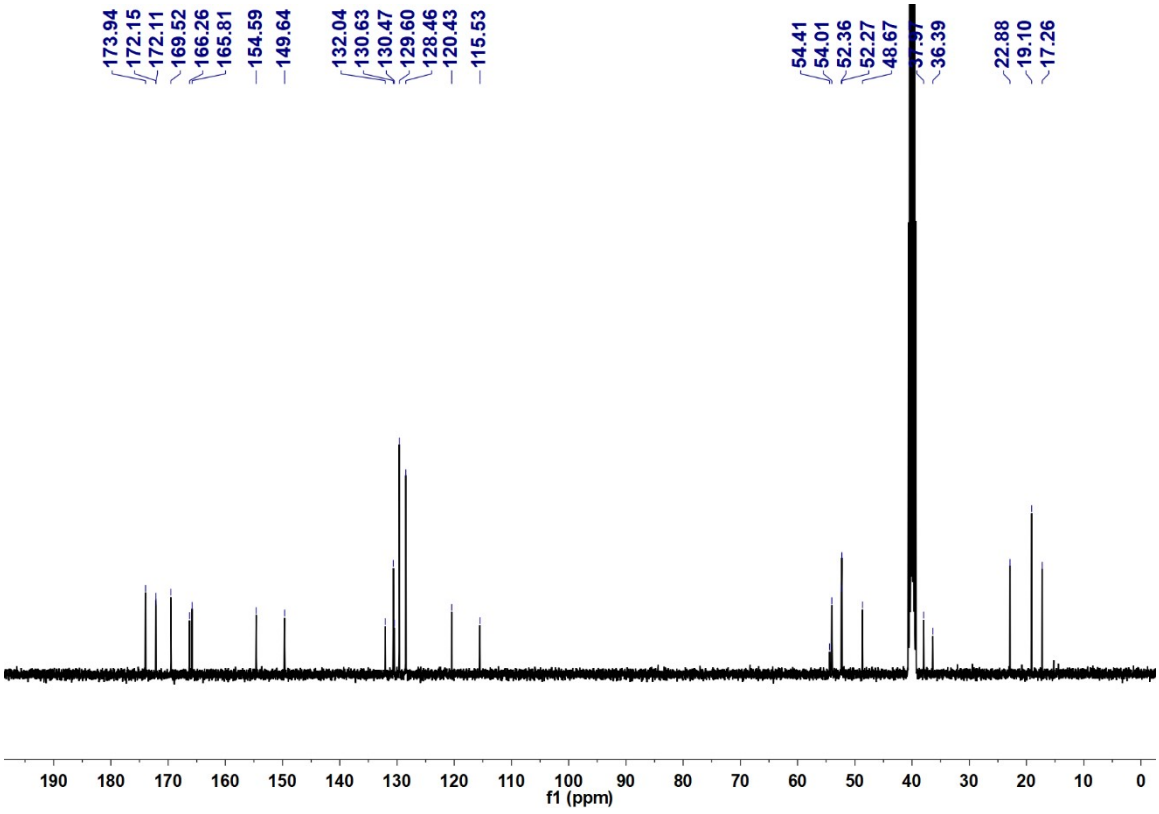
107.25
77.95
54.37
52.12
49.05
36.47
32.94
28.66
26.23
f1 (ppm)


8.65 8.63 8.56 8.55 8.54 8.52 8.11 8.09 7.89 7.88 7.86 7.86 7.32 7.26 7.26 7.25 7.20 6.88 6.86 4.56 4.54 4.54 4.52 4.51 4.49 4.47 4.45 4.43 3.63 3.60 3.08 3.06 3.03 3.00 3.00 2.99 2.96 2.95 2.73 2.70 2.69 2.67 2.50 1.74 1.39 1.37 1.01 1.00 0.99 0.98
Ac
CO2Me
MeO2C
NH2
3dl
1.00 2.02 1.18 1.06 2.01 2.04 1.91 1.03 1.99 1.01 6.03 2.14 1.02 3.03 3.06 6.38
f1 (ppm)


173.94 172.15 172.11 169.52 166.26 165.81 154.59 149.64 132.04 130.63 130.47 129.60 128.46 120.43 115.53
54.41 54.01 52.36 52.27 48.67 36.39 22.88 19.10 17.26
f1 (ppm)

5.2 ^{1}H NMR spectroscopic investigation

The concentration dependence of isochroman of the chemical shift of 2-H of Boc-Tyr-OMe

Entry	Isochroman (eq.)	Average chemical shift of 2-H of Boc-Tyr-OMe
1	0	6.731 ppm
2	0.05	6.732 ppm
3	0.1	6.734 ppm
4	0.2	6.765 ppm
5	0.4	6.809 ppm
6	0.8	6.834 ppm
7	1.0	6.836 ppm

Stacked ^{1}H NMR spectrum of 2-H of Boc-Tyr-OMe