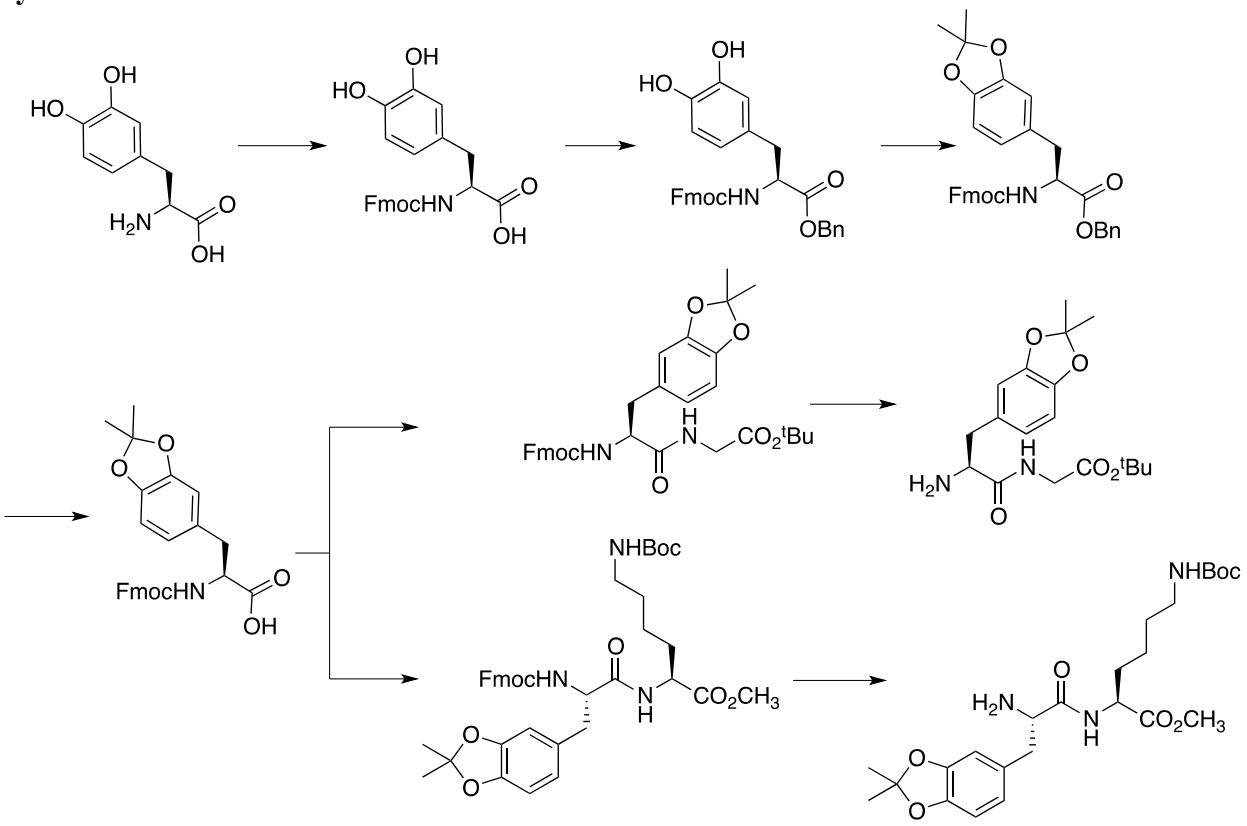
Materials and Methods

Materials

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDC·HCl), N-(9-Fluorenylmethoxycarbonyloxy)succinimide (FmocOSu), 1-Hydroxybenzotriazole (HOBt), HCl·H-Lys(Boc)-OMe, diisopropylamine (DIPEA) were purchased from Aladdin Chemical Co., Ltd. HCl·H-Gly-OtBu was from Adamas Reagent Co., Ltd. Diethylamine was from Energy Chemical. 8ARM-PEG-NHS (the NHS ester of 8ARM PEG, 20k Da) was obtained from JenKem Technology. All solvents and other chemicals were used without further treatment unless otherwise specified.

Synthesis



Scheme S1 The synthetic scheme for H-Dopa(ac)-Gly-OtBu and H-Dopa(ac)-Lys(Boc)-OMe

Fmoc-Dopa-OH [1]

3,4-Dihydroxyphenylalanine (DOPA, 5 g, 25.4 mmol) was dissolved in 20 mL of dioxane and 50 mL of water in an ice-water bath. Sodium carbonate (5 g, 47.2 mmol) was added to the mixture and stirred at 0 °C for 10 min. FmocOSu (8.8 g, 26.1 mmol) in 30 mL of dioxane was added dropwise over 30 min at 0 °C. Then the resulting mixture was allowed to stir at ambient temperature for 12 hours and the reaction was acidified with 6 N HCl to pH ~3. The slurry was extracted with 5×50 mL ethyl acetate. The organic layers were combined, combined, and washed with 50 mL brine. The organic solution was then dried over anhydrous sodium sulfate for 20 min, filtered, and concentrated under vacuum. The residue was subjected to flash chromatography with 10% ethyl acetate in petroleum ether and then 5% methanol in dichloromethane to give pale

white solid as the desired product (8.27 g, Yield: 77.75%.) ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.74 (2 H, *d*, *J*=7.58 Hz), 7.52 (2 H, *m*), 7.38 (2 H, *t*, *J*= 7.09 Hz), 7.28 (2 H, *m*), 6.72 (1 H, *d*, *J*= 7.93 Hz), 6.61 (1 H, *s*), 6.50 (1 H, *d*, *J*=7.97 Hz), 5.38 (1 H, *d*, *J*= 7.97 Hz), 4.58 (1 H, *m*), 4.50 (1 H, *m*), 4.40 (1 H, *m*), 4.17 (1 H, *t*, *J*= 13.37 Hz), 2.98 (2 H, *d*, *J*=4.96 Hz); MS-ESI: m/z (+) calcd for $C_{24}H_{21}NO_6Na^+$: 442.13, found: 442.33, m/z (-) calcd for $C_{24}H_{20}NO_6^-$: 418.13, found: 418.22.

Fmoc-Dopa-OBn [1]

Fmoc-Dopa-OH (2.54 g, 6.05 mmol) in 60 mL of N,N'-dimethyl formamide was suspended with anhydrous potassium carbonate (0.879 g, 6.36 mmol) under an ice-water bath. Benzyl bromide (0.79 mL, 6.66 mmol) was added dropwise to the solution and the mixture was then stirred at ambient temperature overnight. The reaction was then quenched by the addition of 50 mL of 1 N HCl solution and extracted with 3×50 mL ethyl acetate. The organic layers were combined, washed with 50 mL of brine, and dried over anhydrous sodium sulfate. The organic mixture was then filtered and the volatile was removed *in vacuo*. The residue was subjected to flash chromatography with 5% to 20% ethyl acetate in petroleum ether and then 0.5% to 1% methanol in dichloromethane to provide pale brown foam as the desired product (1.43 g, Yield: 46.39%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.76 (2 H, *d*, *J*=10.80 Hz), 7.56 (2 H, *m*), 7.38 (9 H, *m*), 6.82 (1 H, *s*, *br*), 6.75 (1 H, *d*, *J*= 8.03 Hz), 6.57 (1 H, *d*, *J*= 1.41 Hz), 6.43 (1 H, *d*, *J*= 8.01 Hz), 5.34 (1 H, *d*, *J*= 8.26 Hz), 5.16 (2 H, *t*, *J*=11.89 Hz), 4.65 (1 H, *t*, *J*= 6.60 Hz), 4.35 (2 H, *m*), 4.21 (1 H, *t*, *J*= 7.16 Hz), 3.01 (2 H, *d*, *J*= 5.81 Hz); MS-ESI: m/z (+) calcd for $C_{31}H_{27}NO_6Na^+$:532.17, found: 532.33.

Fmoc-Dopa(ac)-OBn [1-2]

Fmoc-Dopa-OBn (309 mg, 0.606 mmol) and $TsOH{\cdot}H_2O$ (12 mg, 0.061 mmol) was suspended in 15 mL of toluene. 2,2-dimethoxypropane (0.86 mL, 7 mmol) was added to the solution in one portion. The resulting mixture was heated to reflux in the presence of a Dean-Stark apparatus overnight. The mixture was concentrated in vacuum and the oily residue was subjected to flash chromatography with 5% to 10% ethyl acetate in petroleum ether to give pale brown oil as the desired product (210 mg, Yield: 63.05%), which solidified upon standing in the refrigerator. ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.78 (2 H, *d*, *J*= 7.53 Hz), 7.59 (2 H, *t*, *J*= 13.4 Hz), 7.42 (2 H, *t*, *J*= 14.86 Hz), 7.37 (2 H, *t*, *J*= 13.70 Hz), 7.33 (4 H, *m*). 6.58 (1 H, *d*, *J*= 7.84 Hz), 6.47 (1 H, *s*), 6.41 (1 H, *d*, *J*= 7.75 Hz), 5.31 (1 H, *m*), 5.18 (2 H, *m*), 4.67 (1 H, *m*), 4.44 (1 H, *m*), 4.36 (1 H, *m*), 4.36 (1 H, *m*), 4.23 (1 H, *t*, *J*= 7.04 Hz), 3.04 (2 H, *d*, *J*= 5.63 Hz), 1.66 (6 H, *s*); MS-ESI: m/z (+) calcd for $C_{34}H_{31}NO_6Na^+$: 572.20, found: 572.33.

Fmoc-Dopa(ac)-OH [1]

Fmoc-Dopa(ac)-OBn (210 mg, 0.328 mmol) and Pd/C (50 mg) was suspended in 20 mL of tetrahydrofuran in the hydrogen atmosphere. The reaction was stirred at ambient temperature overnight. The mixture was then filtered over Celite 545 and the solid was thoroughly washed with tetrahydrofuran. The filtrate solution was concentrated in vacuum and the residue was subjected to flash chromatography with 10% to 50% ethyl acetate in petroleum ether to give white foam as the desired product (140 mg., Yield: 79.76%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.77 (2 H, *d*, *J*= 7.49 Hz), 7.56 (2 H, *t*, *J*= 7.87 Hz), 7.41 (2 H, *t*, *J*= 7.40 Hz), 7.31 (2 H, *m*), 6.66 (1 H, *d*, *J*= 7.72 Hz), 6.56 (2 H, *m*), 4.85 (1 H, *m*), 4.46 (1 H, *m*), 4.38 (1 H, *m*), 4.23 (1 H, *t*, *J*=

6/67 Hz), 3.09 (2 H, *m*), 1.66 (6 H, *s*); MS-ESI: m/z (+) calcd for $C_{27}H_{25}NO_6Na^+$: 482.16, found: 482.33, m/z (-) $C_{27}H_{24}NO_6^-$: 458.16, found: 458.33.

Fmoc-Dopa(ac)-Gly-O^{t}Bu

Fmoc-Dopa(ac)-OH (70 mg, 0.15 mmol), HCl·H-Gly-O^{t}Bu (27 mg, 0.16 mmol), and HOBt (23 mg, 0.17 mmol) in 5 mL of dichloromethane was added with diisopropylethylamine (DIPEA, 0.15 mL, 0.86 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDC·HCl, 35 mg, 0.18 mmol). The mixture was allowed to stir at ambient temperature overnight. The reaction was concentrated in vacuum and the residue was subjected to flash chromatography with 5% to 30% ethyl acetate in petroleum ether to provide white foam as the desired product (59 mg, Yield: 67.78%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.77 (2 H, *d*, *J*= 7.54 Hz), 7.55 (2 H, *dd*, J_1= 11.61 Hz, J_2= 7.47 Hz), 7.41 (2 H, *t*, *J*= 7.43 Hz), 7.33 (2 H, *m*), 6.63 (3 H, *m*), 6.27 (1 H, *s*, *br*), 5.31 (1 H, *s*, *br*), 4.40 (3 H, *m*), 3.90 (2 H, *m*), 3.01 (2 H, *m*), 1.66 (3 H, *s*), 1.65 (3 H, *s*), 1.46 (9 H, *s*); MS-ESI: m/z (+) calcd for $C_{33}H_{36}N_2O_7Na^+$: 595.24, found: 595.44.

H-Dopa(ac)-Gly-O^{t}Bu

Fmoc-Dopa(ac)-Gly-O^{t}Bu (59 mg, 0.103 mmol) in 2 mL of DCM was added with diethylamine (2 mL, 19.3 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction was then concentrated in vacuum and the residue was subjected to flash chromatography with 5% to 50% ethyl acetate in petroleum ether to give colorless oily compound as the desired product (25 mg, Yield: 69.25%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.76 (1 H, *t*, *J*=9.72 Hz), 6.66 (1 H, *m*), 6.62 (2 H, *m*), 3.96 (2 H, *dd*, J_1= 10.01 Hz, J_2= 5.43 Hz), 3.59 (1 H, *dd*, J_1= 9.89 Hz, J_2= 3.90 Hz), 3.21 (1 H, *dd*, J_1=13.85 Hz, J_2= 3.88 Hz), 2.57 (1 H, *dd*, J_1= 13.81 Hz, J_2= 9.85 Hz), 1.67 (6 H, *s*), 1.49 (9 H, *s*); MS-ESI: m/z (+) calcd for $C_{18}H_{27}N_2O_5^+$: 351.19, found: 351.33.

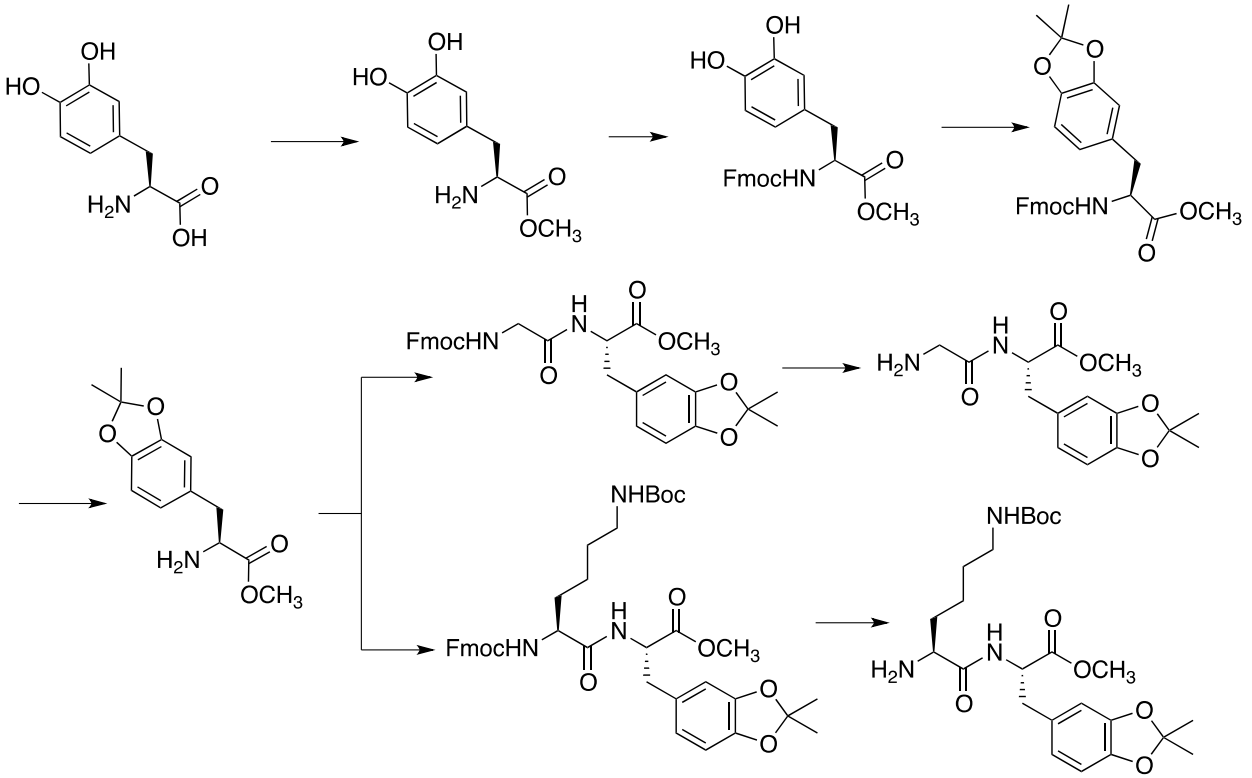
Fmoc-Dopa(ac)-Lys(Boc)-OMe

Fmoc-Dopa(ac)-OH (70 mg, 0.152 mmol), HCl·Lys(Boc)-OMe (48 mg, 0.16 mmol), and HOBt (23 mg, 0.17 mmol) in 5 mL of dichloromethane was added with DIPEA (0.15 mL, 0.86 mmol) and EDC·HCl (35 mg, 0.18 mmol). The reaction was stirred at room temperature overnight. The solution was then concentrated in vacuum and the residue was then subjected to flash chromatography with 5% to 30% ethyl acetate in petroleum ether to give white solid as the desired product (69 mg, Yield: 61.45%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.77 (2 H, *d*, *J*= 7.54 Hz), 7.56 (2 H, *t*, *J*= 8.05 Hz), 7.41 (2 H, *t*, *J*= 7.47 Hz), 7.32 (2 H, *m*), 6.62 (3 H, *m*), 6.35 (1 H, *s*, *br*), 5.43 (1 H, *s*, *br*), 4.65 (1 H, *s*, *br*), 4.53 (1 H, *m*), 4.46 (1 H, *dd*, J_1= 10.58 Hz, J_2= 7.12 Hz), 4.36 (1 H, *m*), 4.22 (1 H, *t*, *J*= 6.96 Hz), 3.90 (1 H, *m*), 3.75 (3 H, *s*), 3.51 (1 H, *m*), 3.06 (3 H, *m*), 2.95 (1 H, *m*), 1.67 (3 H, *s*), 1.65 (3 H, *s*), 1.48 (2 H, *m*), 1.45 (2 H, *m*), 1.43 (9 H, *s*), 1.34 (2 H, *m*); MS-ESI: m/z (+) calcd for $C_{39}H_{47}N_3O_9Na^+$: 724.32, found: 724.44.

H-Dopa(ac)-Lys(Boc)-OMe

Fmoc-Dopa(ac)-Lys(Boc)-OMe (133 mg, 0.190 mmol) in 5 mL of dichloromethane was added with diethylamine (5 mL, 48.36 mmol) and the resulting solution was stirred at room temperature for 1 hour. The reaction was then concentrated in vacuum and the residue was subjected to flash chromatography with 20% ethyl acetate in petroleum ether and then 0.5% to 2% methanol in dichloromethane to give colorless oil as the desired product (68 mg, Yield: 74.83%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.79 (1 H, *d*, *J*=8.41 Hz), 6.67 (1 H, *m*), 6.63 (2 H, *m*), 4.60 (2 H, *m*),

3.75 (3 H, *s*), 3.58 (1 H, *dd*, J_1= 9.28 Hz, J_2= 4.02 Hz), 3.13 (3 H, *m*), 2.62 (1 H, *dd*, J_1= 13.82 Hz, J_2= 9.31 Hz), 1.86 (1 H, *m*), 1.72 (1 H, *m*), 1.68 (6 H, *s*), 1.51 (2 H, *m*), 1.44 (9 H, *s*), 1.34 (2 H, *m*); MS-ESI: m/z (+) calcd for $C_{24}H_{38}N_3O_7^+$: 480.27, found: 480.44.



Scheme S2 The synthetic scheme for H-Lys(Boc)-Dopa(ac)-OMe and H-Gly-Dopa(ac)-OMe

HCl·H-Dopa-OMe [3]

DOPA (5 g, 25.4 mmol) in 100 mL of methanol was added dropwise with thionyl chloride (10 mL, 13.7 mmol) under ice-water bath for 0.5 hour and the mixture was then stirred at room temperature overnight under argon atmosphere. The solution was then concentrated in vacuum to remove all volatile and the residual oil was washed with diethyl ether. The ether was carefully decanted and the residue was dried in vacuum to give white foam as the desired product (6.2 g, Yield: 98.55%). ^{1}H NMR (500 MHz, d_6-DMSO) *δ(ppm)*: 8.95 (1 H, *s*), 8.93 (1 H, *s*), 8,44 (3 H, *s, br*), 6.66 (1 H, *d*, *J*= 8.00 Hz), 6.57 (1 H, *d*, *J*= 1.88 Hz), 6.43 (1 H, *dd*, J_1=8.01 Hz, J_2= 2.08 Hz), 4.15 (1 H, *s*, *br*), 3.69 (3 H, *s*); MS-ESI: m/z (+) calcd for $C_{10}H_{14}NO_4^+$: 212.09, found: 212.22.

Fmoc-Dopa-OMe

FmocOSu (3.88 g, 11.5 mmol) in 20 mL of dioxane was slowly dropwise added to the mixture of HCl·H-Dopa-OMe (2.47 g, 10 mmol) and sodium carbonate in 40 mL of water and 20 mL of dioxane at 0 °C over 30 min. The reaction was stirred at ambient temperature overnight and acidified with 6 N HCl to pH ~ 3. The slurry was extracted with 3×50 mL ethyl acetate and the organic layer was combined and dried over sodium sulfate. The solution was filtered and concentrated in vacuum and the residue was subjected to flash chromatography with 5% to 30% ethyl acetate in petroleum ether to provide pale yellow oil as the desired product (3.1 g, Yield: 71.53%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.77 (2 H, *d*, *J*= 7.51 Hz), 7.56 (2 H, m), 7.41 (2

H, *t J*= 7.42 Hz), 7.32 (2 H, *t*, *J*= 7.43 Hz), 6.76 (1 H, *d*, *J*= 7.99 Hz), 6.60 (1 H, *s*), 6.52 (1 H, *d*, *J*= 7.97 Hz), 5.67 (1 H, *s*), 5.56 (1 H, *s*), 5.32 (1 H, *d*, *J*= 8.18 Hz), 4.62 (1 H, *m*), 4.45 (1 H, *m*), 4.36 (1 H, *m*), 4.21 (1 H, *t*, *J*= 6.80 Hz), 3.73 (3 H, *s*), 3.00 (2 H, *m*); MS-ESI: m/z (+) calcd for $C_{25}H_{23}NO_6Na^+$: 456.14, found: 456.33.

Fmoc-Dopa(ac)-OMe [2]

Fmoc-Dopa-OMe (129 mg, 0.298 mmol), $TsOH{\cdot}H_2O$(5.7 mg, 0.03 mmol), and dimethoxypropane (0.365 mL, 2.98 mmol) was suspended in 10 mL of toluene and refluxed in the presence of a Dean-Stark apparatus overnight. The solution was then concentrated in vacuum and the residue was subjected to flash chromatography with 5% to 10% ethyl acetate in petroleum ether to provide white foam as the desired product (103 mg, Yield: 72.99%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)*7.78 (2 H, *d*, *J*= 7.54 Hz), 7.59 (2 H, t, *J*= 8.19 Hz), 7.42 (2 H, *t*, *J*= 7.42 Hz), 7.32 (2 H, *m*), 6.64 (1 H, *d*, *J*= 7.58 Hz), 6.49 (2 H, *m*), 5.28 (1 H, *d*, *J*= 8.14 Hz), 4.63 (1 H, *m*), 4.45 (1 H, *m*), 4.36 (1 H, *m*), 4.24 (1 H, *t*, *J*= 7.05 Hz), 3.76 (3 H, *s*), 3.02 (2 H, *m*), 1.67 (6 H, *s*); MS-ESI: m/z (+) calcd for $C_{28}H_{27}NO_6Na^+$: 496.17, found: 496.33.

H-Dopa(ac)-OMe

Fmoc-Dopa(ac)-OMe (100 mg, 0.211 mmol) and diethylamine (2 mL, 19.3 mmol) in 2 mL of dichloromethane was stirred at ambient temperature for 1 hour and then concentrated in vacuum. The residue was subjected to flash chromatography to provide colorless oil as the desired product (50 mg, Yield: 94.30%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 6.66 (1 H, *d*, *J*= 8.28 Hz) 6.60 (2 H, *m*), 3.74 (3 H, *s*), 3.69 (1 H, *dd*, J_1= 7.83 Hz, J_2=5.10 Hz), 3.01 (1 H, *dd*, J_1= 13.66 Hz, J_2=5.00 Hz), 2.77 (1 H, *dd*, J_1= 13.66 Hz, J_2=7.93 Hz), 1.675 (3 H, *s*), 1.67 (3 H, *s*); MS-ESI: m/z (+) calcd for $C_{13}H_{18}N_3O_4^+$: 252.12, found: 252.33

Fmoc-Gly-Dopa(ac)-OMe

H-Dopa(ac)-OMe (300 mg, 1.19 mmol), Fmoc-Gly-OH (426 mg, 1.43 mmol), HOBt (200 mg, 1.48 mmol), and DIPEA (1 mL, 5.9 mmol) was dissolved in 15 mL of dichloromethane and EDC·HCl (290 mg, 1.51 mmol) was added in one portion. The resulting mixture was stirred at room temperature overnight and concentrated in vacuum. The residue was subjected to flash chromatography with 5% to 30% ethyl acetate in petroleum ether to provide white foam as the desired product (454 mg, Yield: 71.91%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.78 (2 H, *d*, *J*= 7.55 Hz), 7.61 (2 H, *d*, *J*= 6.60 Hz), 7.42 (2 H, *t*, *J*= 6.72 Hz), 7.33 (2 H, *t*, *J*= 7.46 Hz), 6.61 (1 H, *m*), 6.48 (2 H, *m*), 6.37 (1 H, *d*, *J*= 7.61), 5.43 (1 H, *s)*, 4.84 (1 H, m), 4.42 (2 H, *m*), 4.25 (1 H, *t*, *J*=7.08 Hz), 3.90 (2 H, *m*), 3.75 (3 H, *s*), 3.04 (2 H, *d*, *J*=5.47 Hz), 1.64 (3 H, *s*), 1.63 (3 H, *s*); MS-ESI: m/z (+) calcd for $C_{30}H_{30}N_2O_7Na^+$: 553.20, found: 553.33.

Fmoc-Lys(Boc)-Dopa(ac)-OMe

H-Dopa(ac)-OMe (50 mg, 0.199 mmol), Fmoc-Lys(Boc)-OH (121 mg, 0.26 mmol), HOBt (35 mg, 0.26 mmol), and DIPEA (0.136 mL, 0.776 mmol) was dissolved in 15 mL of dichloromethane and EDC·HCl (50 mg, 0.26 mmol) was added in one portion. The resulting mixture was stirred at room temperature overnight and concentrated in vacuum. The residue was subjected to flash chromatography with 5% to 30% ethyl acetate in petroleum ether to provide white foam as the desired product (107 mg, Yield: 75.97%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.78 (2 H, *d*, *J*=7.52 Hz), 7.61 (2 H, *d*, *J*= 7.26 Hz), 7.41 (2 H, *t*, *J*= 7.46 Hz), 7.33 (2 H, *t*, *J*=

7.44 Hz), 6.61 (1 H, *d, J*= 7.13 Hz), 6.49 (2 H, *m*), 6.36 (1 H, *s*, *br*), 5.44 (1 H, *s*, *br*), 4.79 (1 H, *m*), 4.65 (1 H, *s*, *br*), 4.41 (1 H, *t*, *J*= 7.13 Hz), 4.14 (1 H, *m*), 3.75 (3 H, *s*), 3.11 (2 H, *m*), 3.04 (2 H, *m*), 1.63 (3 H, *s*), 1.63 (3 H, *s*), 1.48 (2 H, *m*), 1.44 (9 H, *s*), 1.40 (4 H, *m*); MS-ESI: m/z (+) calcd for $C_{39}H_{47}N_3O_9Na^+$: 724.32, found: 724.44.

H-Gly-Dopa(ac)-OMe

Fmoc-Gly-Dopa(ac)-OMe (232 mg, 0.437 mmol) in 7 mL of dichloromethane was added with diethylamine (7 mL, 67.7 mmol) and the resulting solution was stirred at room temperature for 1 hour. The reaction was then concentrated in vacuum and the residue was subjected to flash chromatography with 5% to 50% ethyl acetate in petroleum ether and then 1% to 5% methanol in dichloromethane to give colorless oil as the desired product (102 mg, Yield: 75.66%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.61 (1 H, *d*, *J*= 7.63 Hz), 6.63 (1 H, *m*), 6.53 (2 H, *m*), 4.83 (1 H, *m*), 3.74 (3 H, *s*), 3.37 (2 H, *s*), 3.04 (2 H, *dd*, J_1= 5.60 Hz, J_2= 4.69 Hz), 1.67 (6 H, *s*); MS-ESI: m/z (+) calcd for $C_{15}H_{21}N_2O_5^+$: 309.15, found: 309.33.

H-Lys(Boc)-Dopa(ac)-OMe

Fmoc-Lys(Boc)-Dopa(ac)-OMe (270 mg, 0.385 mmol) in 7 mL of dichloromethane was added with diethylamine (7 mL, 67.7 mmol) and the resulting solution was stirred at room temperature for 1 hour. The reaction was then concentrated in vacuum and the residue was subjected to flash chromatography with 20% ethyl acetate in petroleum ether and then 1% methanol in dichloromethane to give colorless oil as the desired product (131 mg, Yield: 70.95%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ(ppm)* 7.68 (1 H, *d*, *J*= 7.63 Hz), 6.63 (1 H, *m*), 6.53 (2 H, *m*), 4.79 (1 H, *m*), 4.59 (1 H, *s*, *br*), 3.74 (3 H, *s*), 3.34 (1 H, *dd*, J_1= 8.03 Hz, J_2= 4.49 Hz), 3.12 (2 H, *m*), 3.02 (2 H, *m*), 1.79 (1 H, *m*), 1.66 (6 H, *s*), 1.50 (4 H, *m*), 1.45 (9 H, *s*), 1.36 (2 H, *m*); MS-ESI: m/z (+) calcd for $C_{24}H_{38}N_3O_7^+$: 480.27, found: 480.44, calcd for $C_{24}H_{37}N_3O_7Na^+$: 502.25, found: 502.44.

8ARM-PEG-Dopa(ac)-Gly-OtBu

8ARM-PEG-NHS (207 mg, ~ 0.01 mmol) and H-Dopa(ac)-Gly-OtBu (86 mg, 0.245 mmol) in 5 mL of anhydrous tetrahydrofuran was stirred at room temperature overnight. EDC·HCl (16 mg, 0.08 mmol) and DIPEA (14 μL, 0.08 mmol) was added in one portion and stirred at room temperature for additional 5 hours. The reaction was then concentrated in vacuum and the residue was used directly without further purification for the following step.

8ARM-PEG-Dopa-Gly

The reaction residue of 8ARM-PEG-20K-Dopa(ac)-Gly-OtBu was added with 5 mL 95% TFA in H_2O for 2 hours at ambient temperature. The mixture was concentrated in vacuum and 5 mL of toluene was added to the residue to assist the removal of the volatile *in vacuo*. The residue was then suspended in 50% aqueous ethanol (~ 10 mL) and transferred to a dialysis bag with a molecular weight cutoff of 3.5k. The solution was dialyzed with argon bubbled water to remove all small molecules. After dialysis, the solution was freeze-dried to provide pale brown solid (226 mg).

8ARM-PEG-Dopa(ac)-Lys(Boc)-OMe

8ARM-PEG-NHS (110 mg, ~ 0.005 mmol) and H-Dopa(ac)-Lys(Boc)-OMe (65 mg, 0.136 mmol) in 3 mL of anhydrous tetrahydrofuran was stirred at room temperature overnight. EDC·HCl (8 mg, 0.04 mmol) and DIPEA (7 μL, 0.04 mmol) was added in one portion and

stirred at room temperature for additional 5 hours. The reaction was then concentrated in vacuum and the residue was used directly without further purification for the following step.

8ARM-PEG-Dopa-Lys
The reaction residue of 8ARM-PEG-20K-Dopa(ac)-Lys(Boc)-OMe was added with 4 mL 95% TFA in H_2O for 2 hours at ambient temperature. The mixture was concentrated in vacuum and 4 mL of toluene was added to the residue to assist the removal of the volatile *in vacuo*. The residue was then suspended in 50% aqueous ethanol (~ 10 mL) and transferred to a dialysis bag with a molecular weight cutoff of 3.5k. The solution was dialyzed with argon bubbled water to remove all small molecules. After dialysis, the solution was freeze-dried to provide whitish solid (96 mg).

8ARM-PEG-Gly-Dopa(ac)-OMe
8ARM-PEG-NHS (207 mg, ~ 0.01 mmol) and H-Gly-Dopa(ac)-OMe (102 mg, 0.334 mmol) in 5 mL of anhydrous tetrahydrofuran was stirred at room temperature overnight. EDC·HCl (16 mg, 0.08 mmol) and DIPEA (14 μL, 0.08 mmol) was added in one portion and stirred at room temperature for additional 5 hours. The reaction was then concentrated in vacuum and the residue was used directly without further purification for the following step.

8ARM-PEG-Gly-Dopa
The reaction residue of 8ARM-PEG-20K-Gly-Dopa(ac)-OMe was added with 5.5 mL 95% TFA in H_2O for 2 hours at ambient temperature. The mixture was concentrated in vacuum and 5 mL of toluene was added to the residue to assist the removal of the volatile *in vacuo*. The residue was then suspended in 50% aqueous ethanol (~ 10 mL) and transferred to a dialysis bag with a molecular weight cutoff of 3.5k. The solution was dialyzed with argon bubbled water to remove all small molecules. After dialysis, the solution was freeze-dried to provide whitish solid (216 mg).

8ARM-PEG-Lys(Boc)-Dopa(ac)-OMe
8ARM-PEG-NHS (200 mg, ~ 0.01 mmol) and H-Lys(Boc)-Dopa(ac)-OMe (131 mg, 0.275 mmol) in 5 mL of anhydrous tetrahydrofuran was stirred at room temperature overnight. EDC·HCl (16 mg, 0.08 mmol) and DIPEA (14 μL, 0.08 mmol) was added in one portion and stirred at room temperature for additional 5 hours. The reaction was then concentrated in vacuum and the residue was used directly without further purification for the following step.

8ARM-PEG-Lys-Dopa
The reaction residue of 8ARM-PEG-20K-Lys(Boc)-Dopa(ac)-OMe was added with 5.5 mL 95% TFA in H_2O for 2 hours at ambient temperature. The mixture was concentrated in vacuum and 5 mL of toluene was added to the residue to assist the removal of the volatile *in vacuo*. The residue was then suspended in 50% aqueous ethanol (~ 10 mL) and transferred to a dialysis bag with a molecular weight cutoff of 3.5k. The solution was dialyzed with argon bubbled water to remove all small molecules. After dialysis, the solution was freeze-dried to provide whitish solid (208 mg).

UV measurement
1 mg peptide-derivatized PEG was dissolved in 1 mL of ddH_2O and the UV spectrum from 220-400 nm was recorded in ThermoFischer Nanodrop (the UV absorbance measure with 1 mm wave

path). The calibration curve was measured using dopamine aqueous solution at 280 nm. The concentration of Dopa in the polymer was calculated using equation $C = 10 \times [(A_{sample} - A_{8ARM-PEG-NHS}) - 0.022315]/2.08443$ and the ratio of the peptide and PEG was calculated using equation $ratio = C/(\frac{1000}{MW})$. The molecular weights (MW's) of the peptide-derived PEG's are 21792.72 for 8ARM-PEG-Dopa-Lys and 8ARM-PEG-Lys-Dopa, 21225.44 for 8ARM-PEG-Dopa-Gly, and 21081.20 for 8ARM-PEG-Gly-Dopa.

AFM imaging

The adhesion surface morphology after separation in the lap shear experiments was imaged by AFM (JPK, Nanowizard II) in air using intermittent contact mode. (Imaging conditions: scan rate, 1 Hz; pixel number, 512 × 512). Silicon cantilevers (SSS-SeIHR-50, Nanosensors, Switzerland) with typical tip radii of ~2-10 nm and resonance frequencies of ~96 to 175 kHz were used for imaging. The surface was blow-dried with compressed air prior to the AFM measurement.

Lap joint shear strength test

The test was performed using commercial available glass slide adherends (approximately 76.0 mm × 25.0 mm × 1.4 mm). Prior to use, the glass slides were soaked in freshly prepared chromic acid cleaning solution (20 g $K_2Cr_2O_7$, 40 mL Milli-Q water and 360 mL concentrated H_2SO_4) for 2 h to thoroughly remove any organic contaminants, and then rinsed by a large quantity of Milli-Q water and dried in a heated oven. To prepare the adhesively bonded samples, the lyophilized polymers were first dissolved in 100 mM phosphate buffer (pH=8.0) according to the weight percentage of 10%. Then, 30 μL of the polymer solution was added to one end of the glass slide and another slide was carefully placed over it with an overlapping area of 25 mm × 20 mm. In order to reduce the self-oxidation of DOPA, the polymer solutions were prepared just before use and used immediately once prepared. The samples were fixed by small clips and allowed to cure in an incubator at room temperature and 90% relative humidity for 24 h. Next, the shear strength test was carried out on an Instron universal tensile machine. During experiments, a vertical tensile load was applied to parallelly tear apart the bonded two glass slides at a crosshead speed of 1.0 mm/min. The load—extension force curves were recorded and the adhesion shear strength was calculated by dividing the maximum load (N) with the overlapping area (m^2). For each polymer, at least six independent experiments were conducted. The obtained data was shown as mean ± standard deviation.

Hydrogel preparation

For each peptide-derivatized PEG, 45 mg solid was measured to dissolve thoroughly in 250 μL 500 mM Tris-buffer (pH 7). 50 μL of 327.3 mM $FeCl_3$ in 500 mM Tris-buffer (pH 7) was added to the solution and the obtained mixture was mixed thoroughly with a vortex for 10 seconds. The mixture was then stored still for aging over 24 hours prior to rheological measurements.

Rheological measurement

The hydrogel was carefully transferred to the rheometer plate using a spatulus. The rheology experiments were then carried out with a frequency sweep mode from 0.1 to 100 rad s^{-1} at 10% strain on a Haake RheoStrss 6000 rheometer (geometry: 1^o/20 mm of cone and plate) at 20 ^oC.

Supplementary Figures

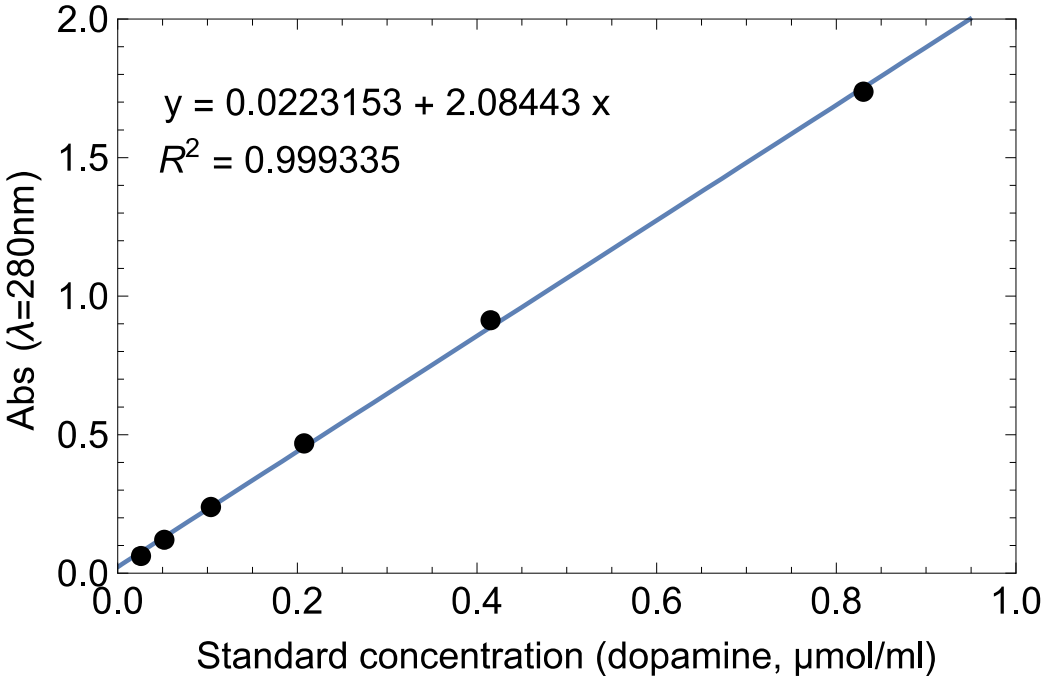


Figure S1 Calibration curve of dopamine at 280 nm

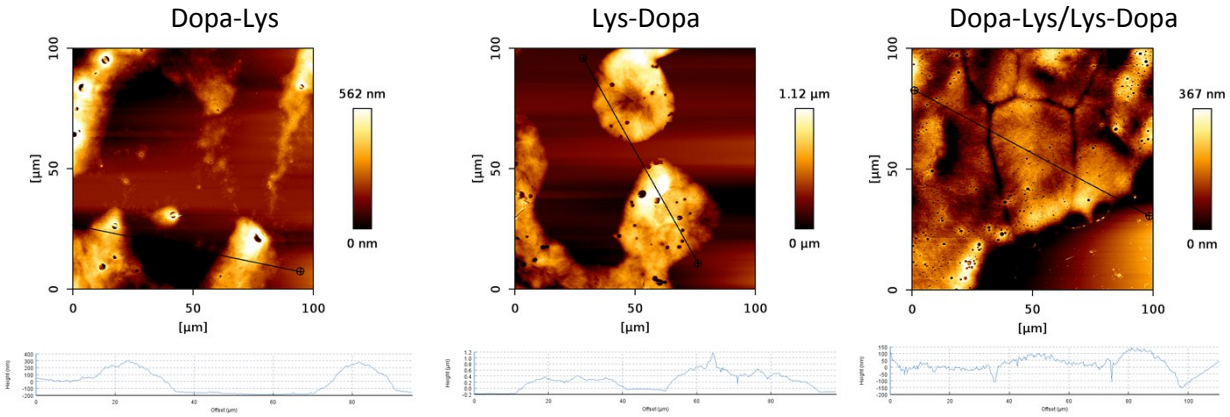


Figure S2 The AFM images of the lap-shear surfaces after failure. Dopa-Lys and Lys-Dopa showed a combined adhesion and cohesion failure with an average thickness of polymers left on the surfaces of ~300-400 nm. On the contrary, the lap-shear surfaces with Dopa-Lys on one side and Lys-Dopa on the other show typical cohesion failure with an average thickness of polymers left on the surfaces of ~ 150-200 nm.

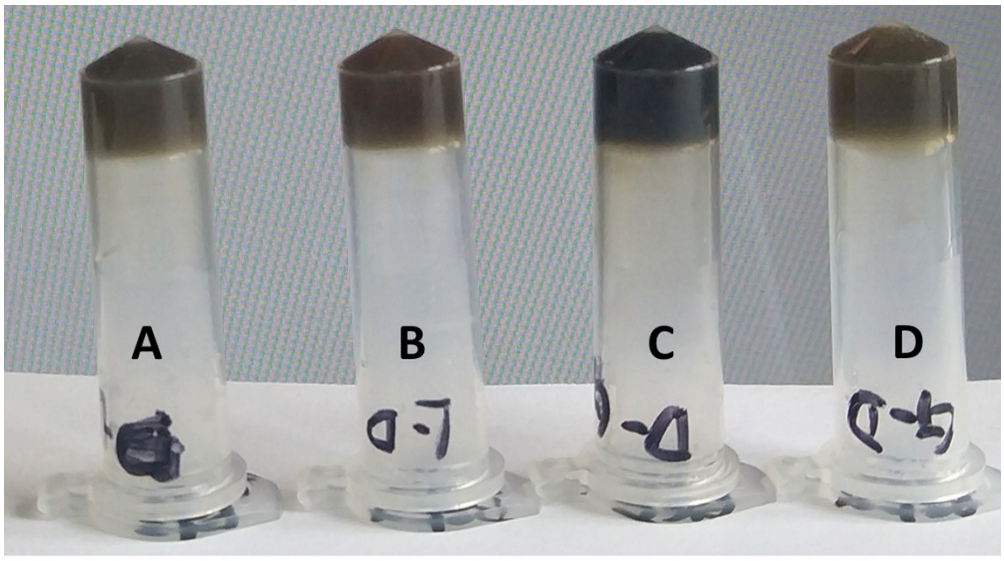


Figure S3 Optical images of peptide-derivatized PEG hydrogels. A) 150 mg mL^{-1} 8ARM-PEG-Dopa-Lys in 500 mM Tris-buffer (pH 7), B) 150 mg mL^{-1} 8ARM-PEG-Lys-Dopa in 500 mM Tris-buffer (pH 7), C) 150 mg mL^{-1} 8ARM-PEG-Dopa-Gly in 500 mM Tris-buffer (pH 7), and D) 150 mg mL^{-1} 8ARM-PEG-Gly-Dopa in 500 mM Tris-buffer (pH 7).

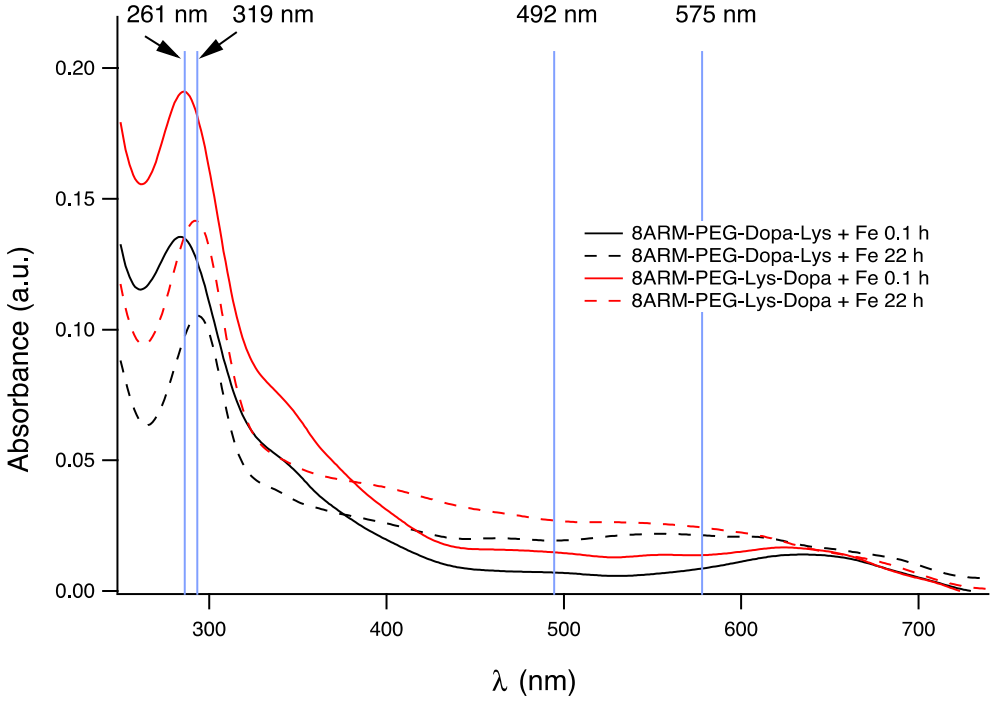


Figure S4 UV spectra for the incubation of 8ARM-PEG-Lys-Dopa and 8ARM-PEG-Lys-Dopa with $FeCl_3$ in Tris-HCl buffer (pH 7.0). The incubation condition: PEG-dipeptide is 10 mg mL^{-1}, and Fe^{3+} is 3.63 mM in 500 mM Tris-HCl. The mixture was diluted 10 times with Tris-HCl (pH 7.0) for UV spectra recording. After incubation, the oxidative products were significantly increased, as the major absorption peak shifted from ~261 nm for catechol to ~319

nm for o-quinone in both 8ARM-PEG-Dopa-Lys and 8ARM-PEG-Lys-Dopa samples. The dominant coordination species is the bis-complex, with an absorption peak at ~575 nm and there are also considerable number of tris-complexes (at ~492 nm), especially in the Lys-Dopa sample. Note that, based on the UV-Vis spectra, the absorption at ~ 400 nm was also increased for both samples after incubation, suggesting that high degree oxidation species may also exist.

References for supporting materials

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[2] P. B. Mesersmith, B.-h. Hu, Z. Liu*, Vol. US20100087622 A1*, Northwestern University, United States, **2009**, p. 123.

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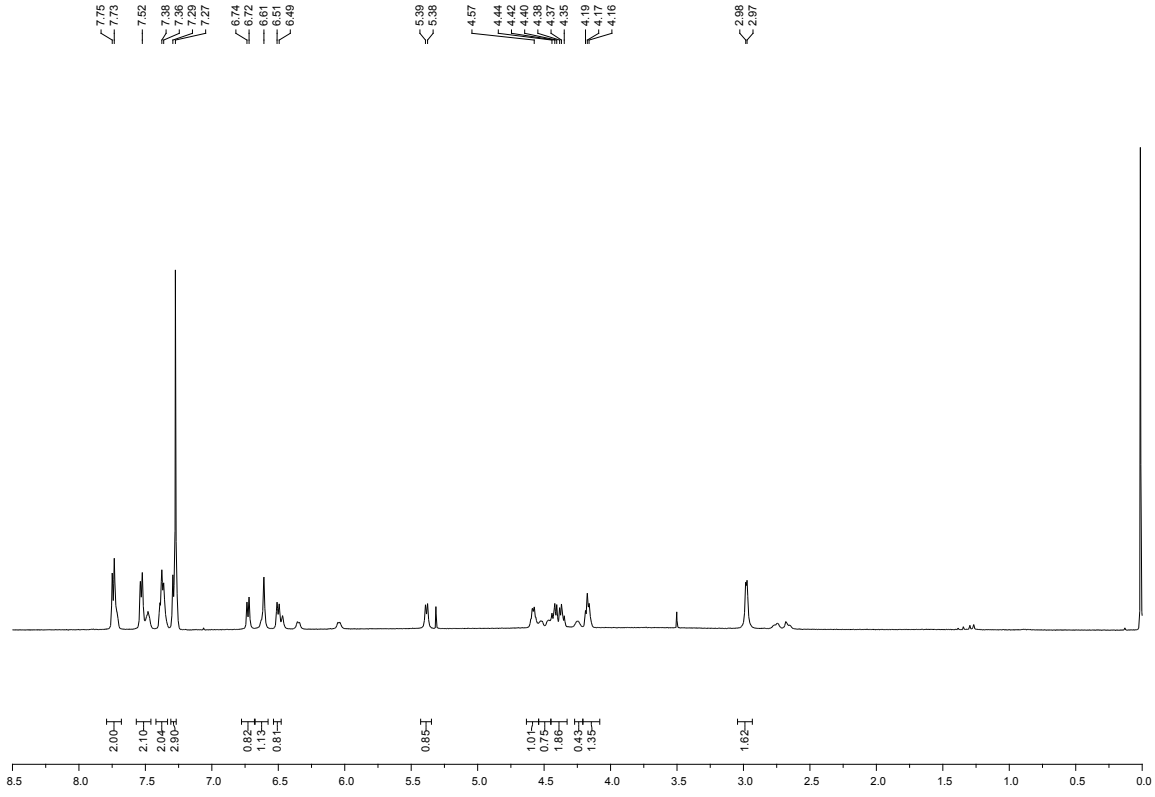
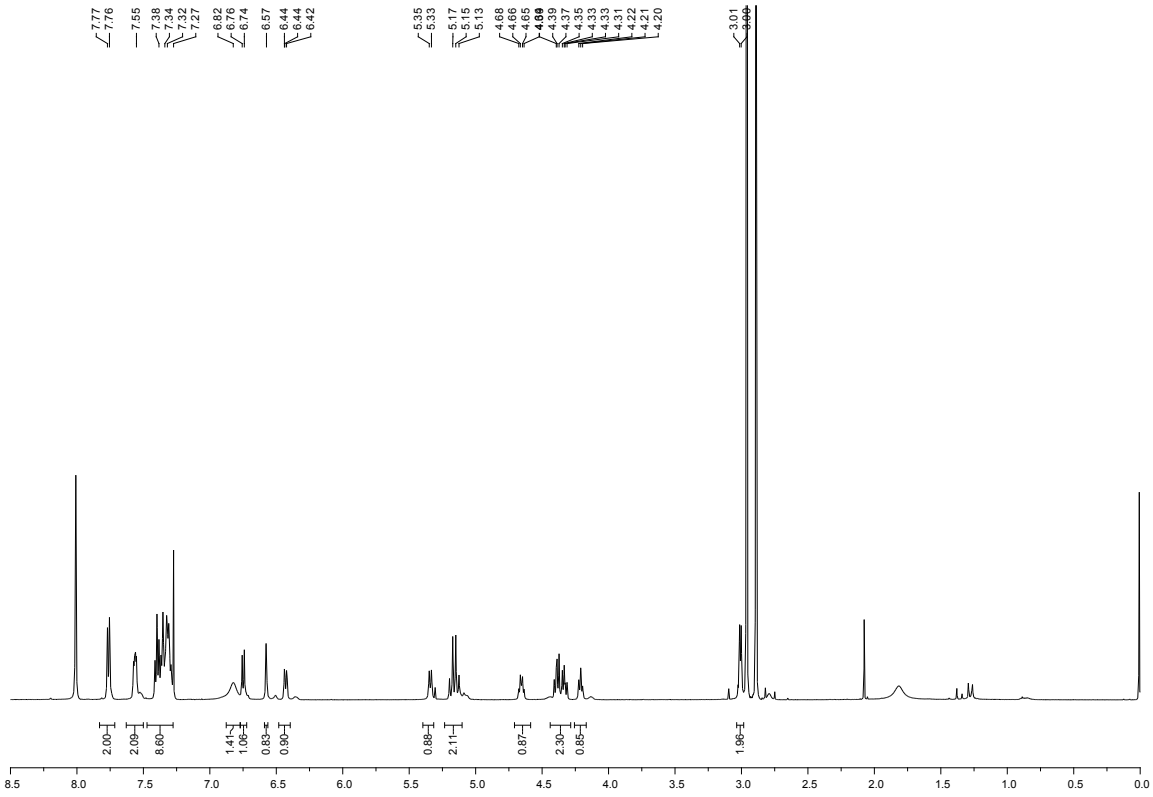
NMR spectra

Fmoc-Dopa-OH



Fmoc-Dopa-OBn



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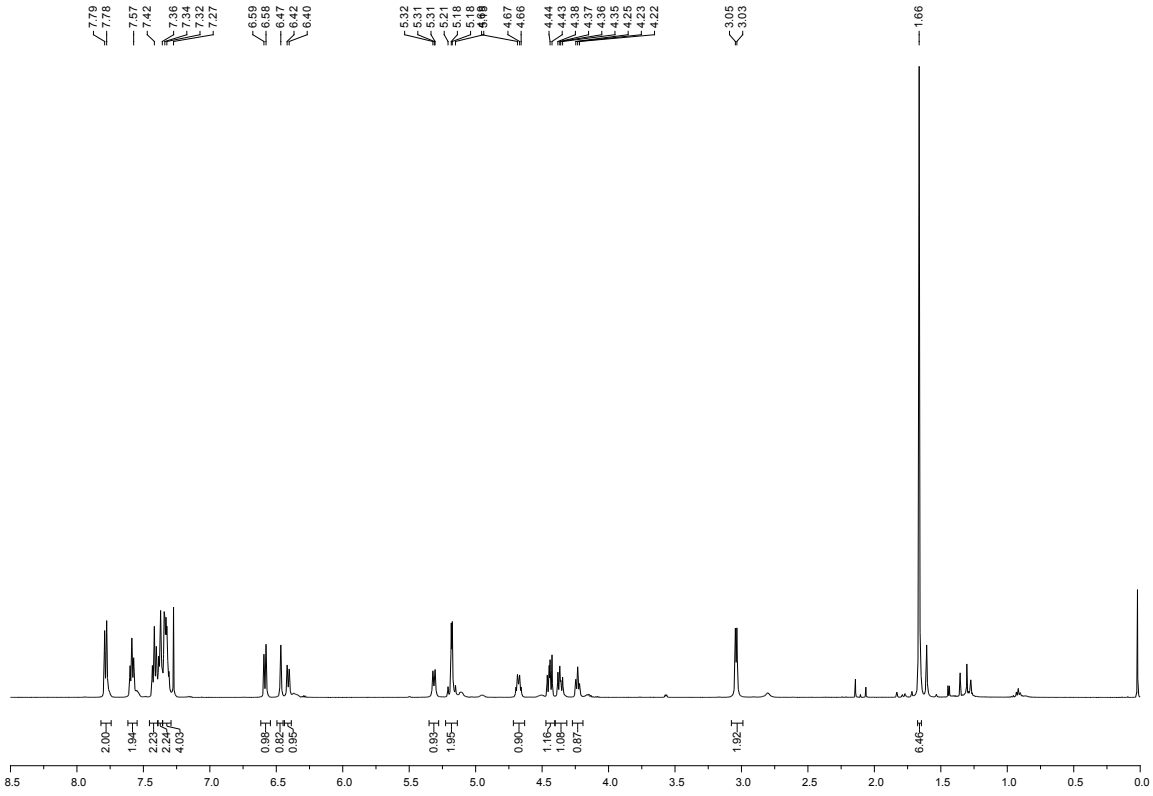

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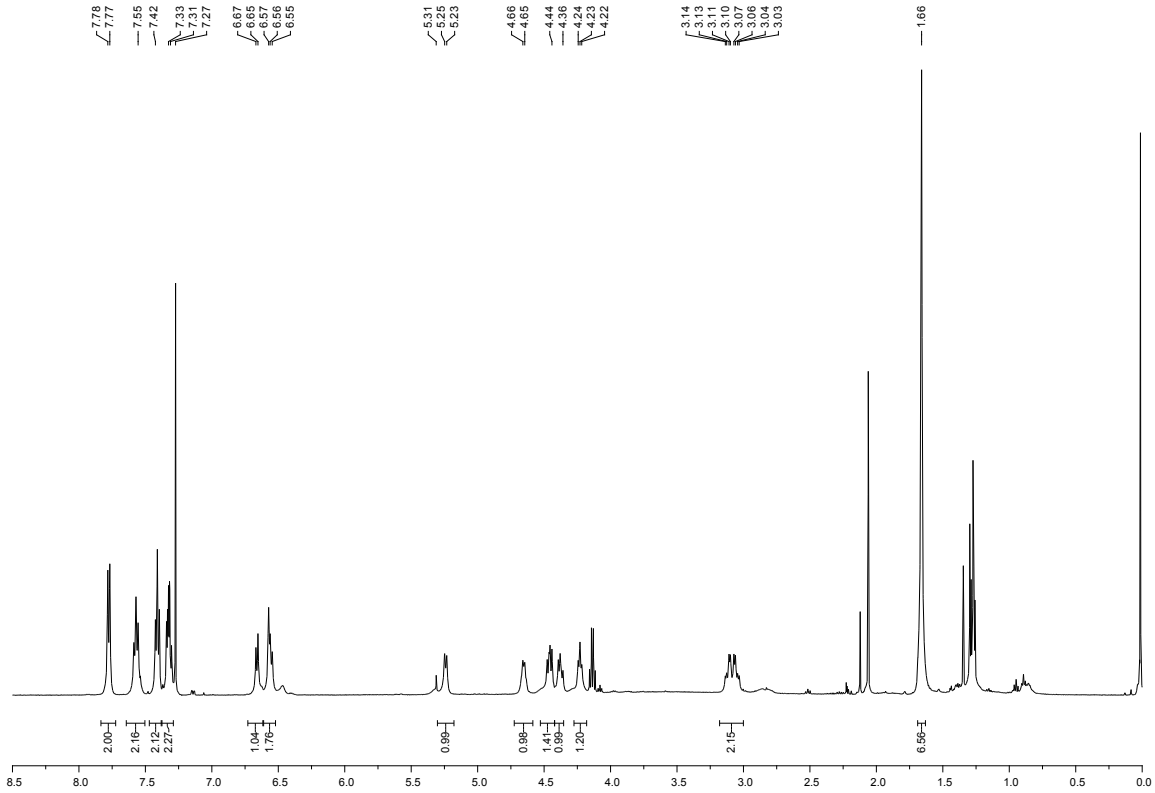
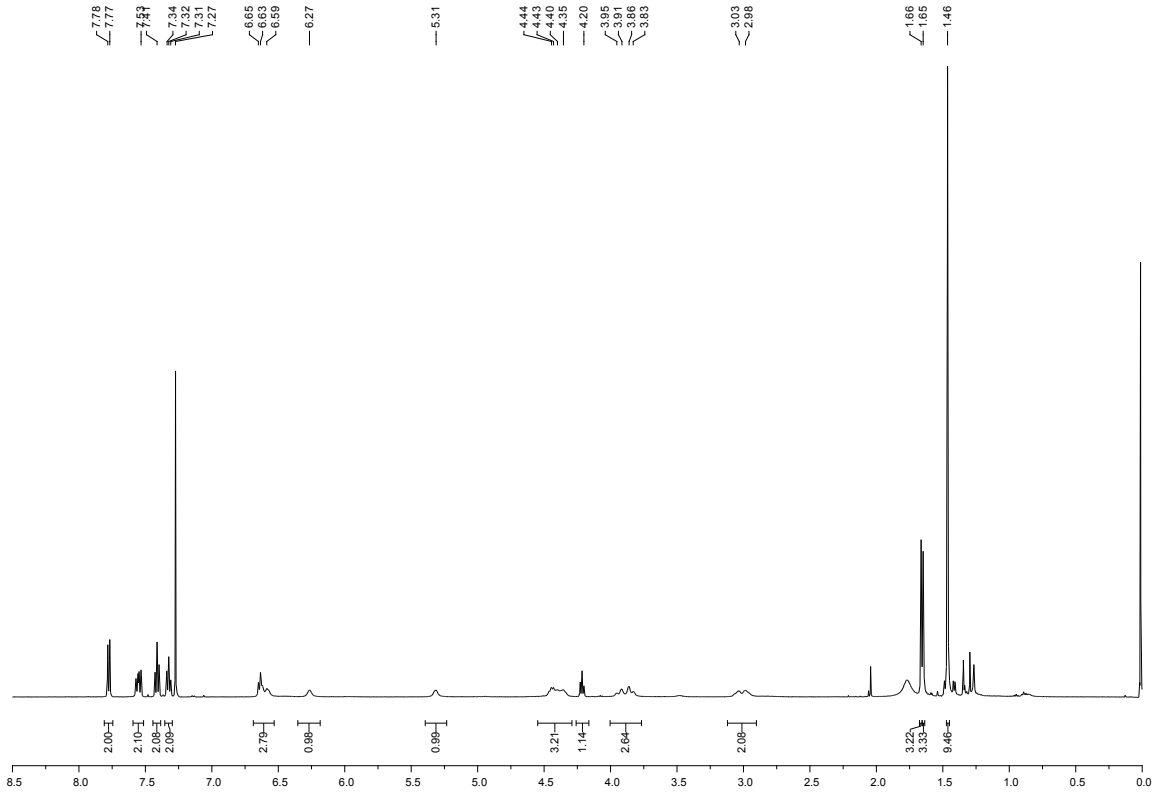


Fmoc-Dopa-Gly-OtBu



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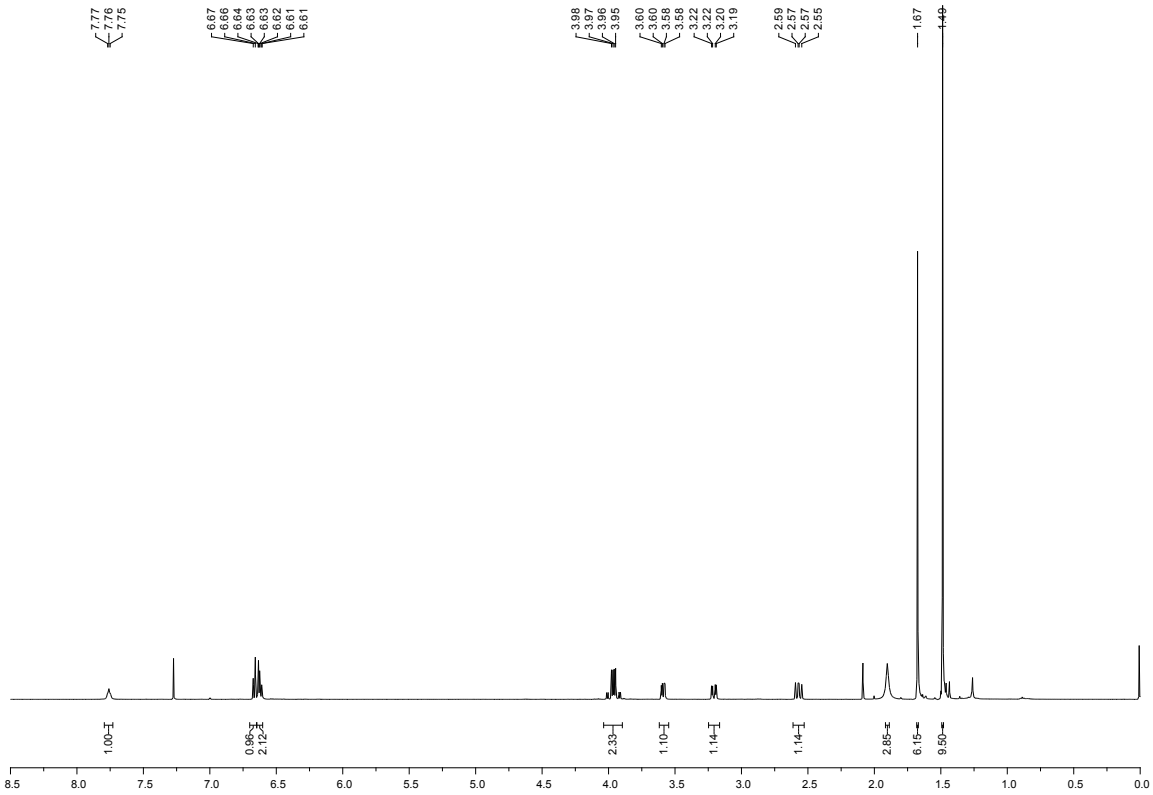

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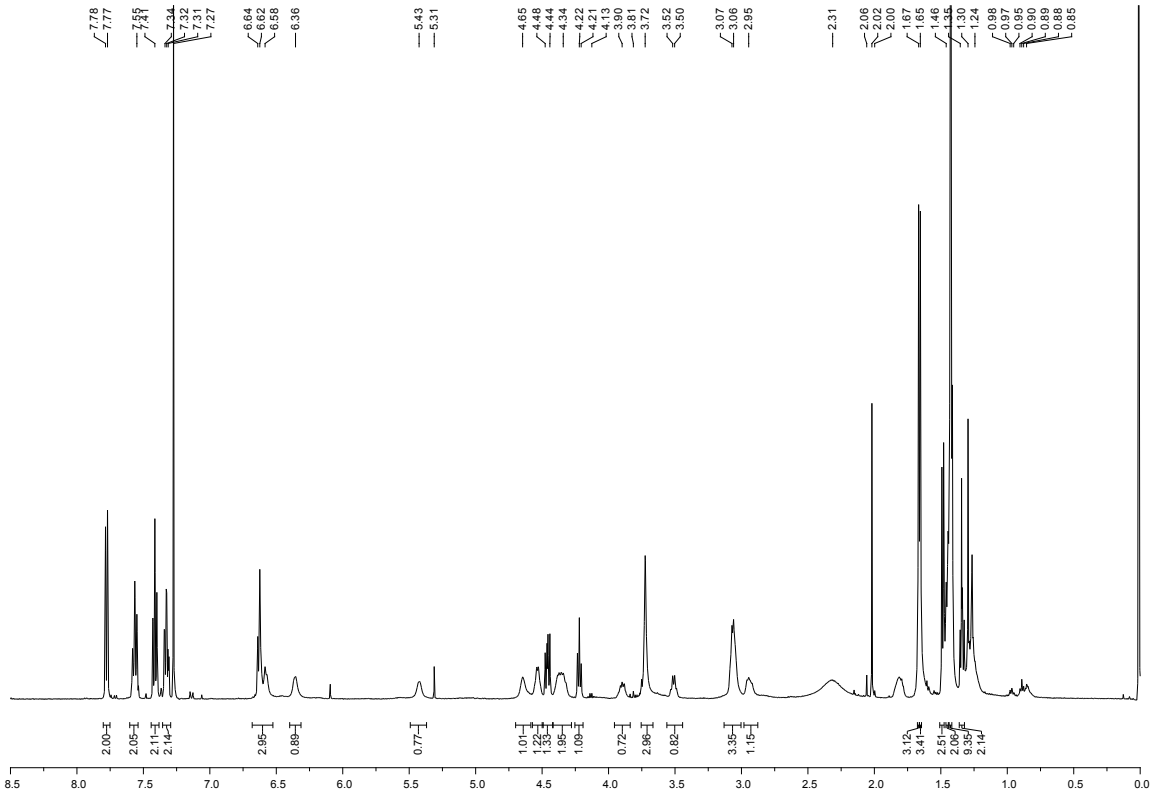

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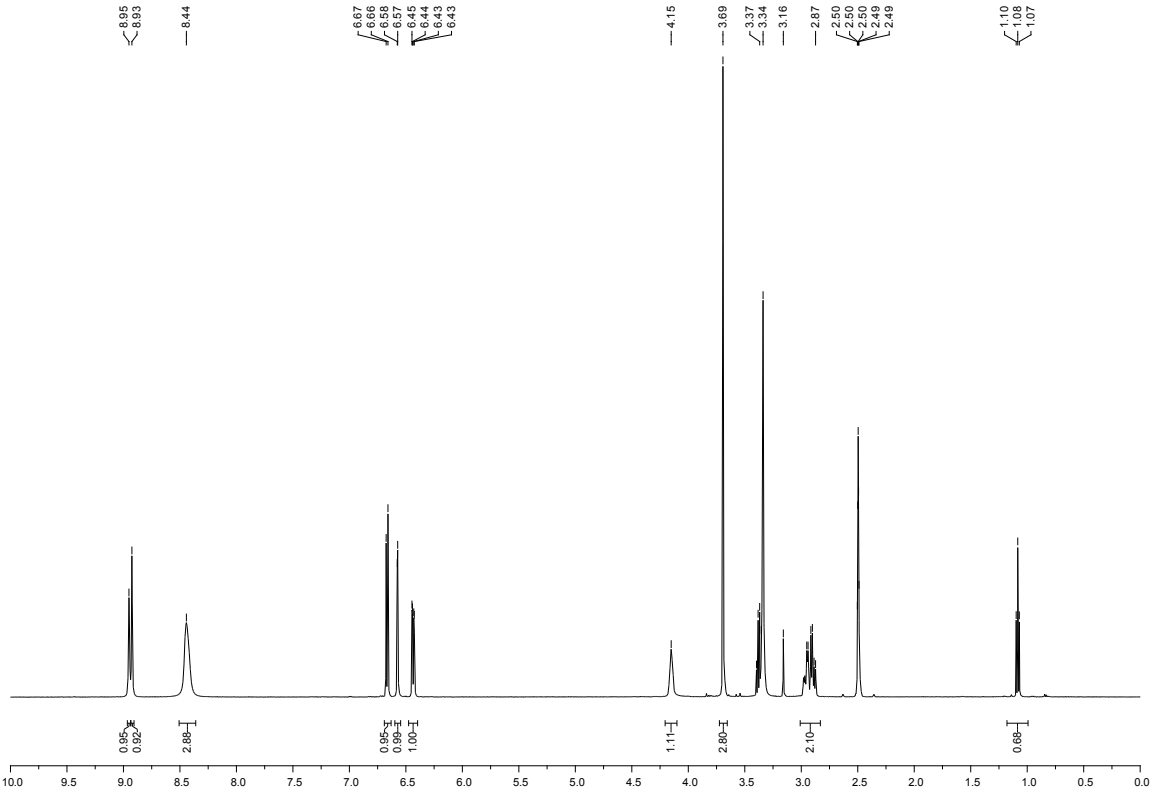

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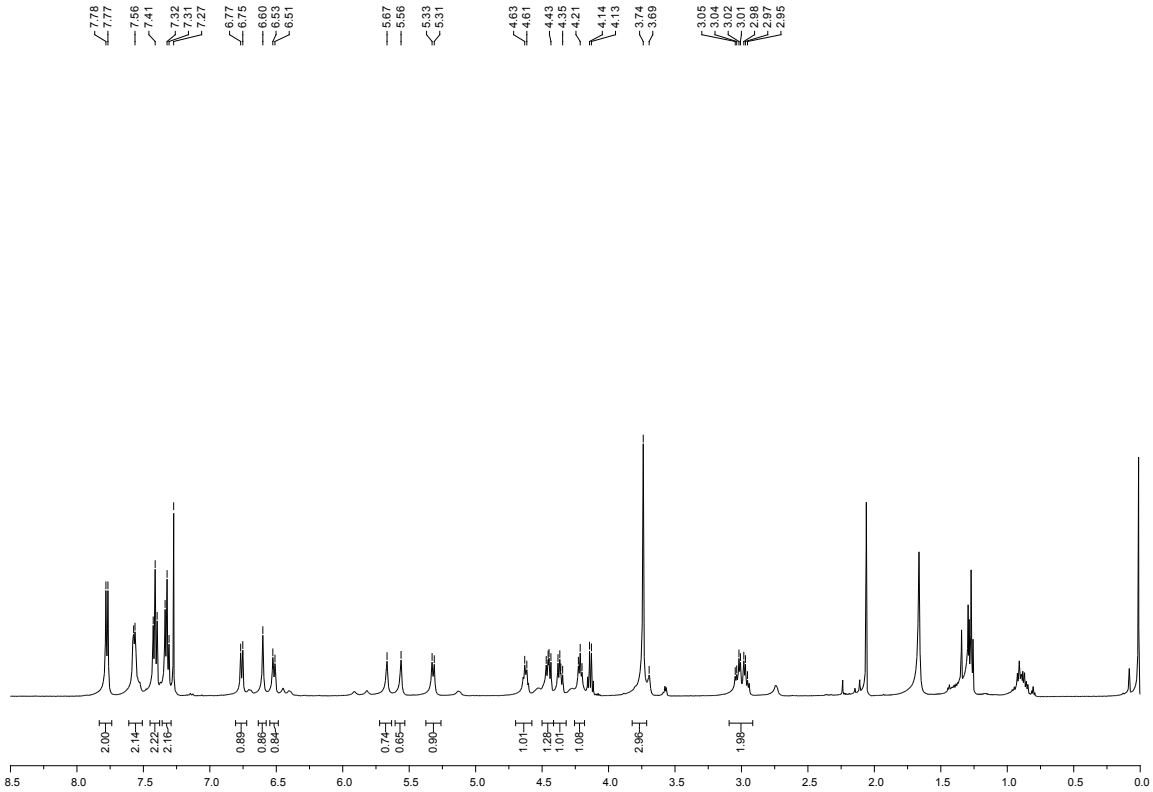

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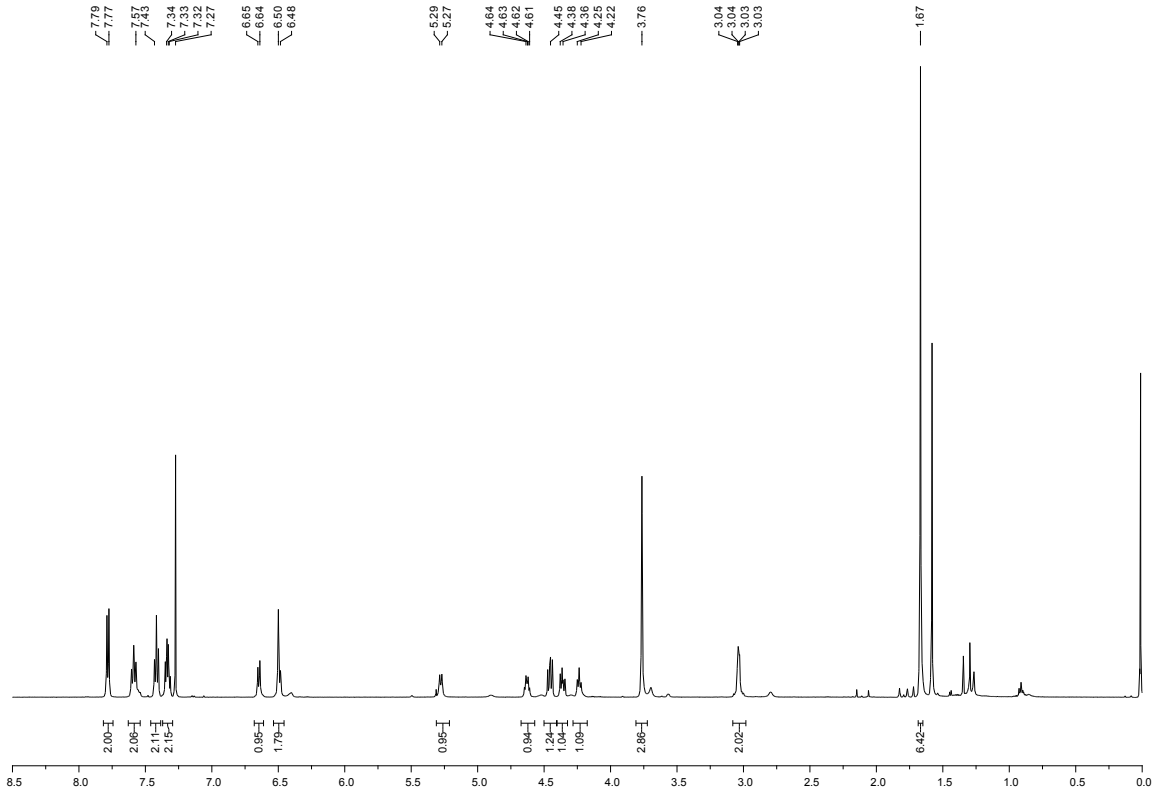

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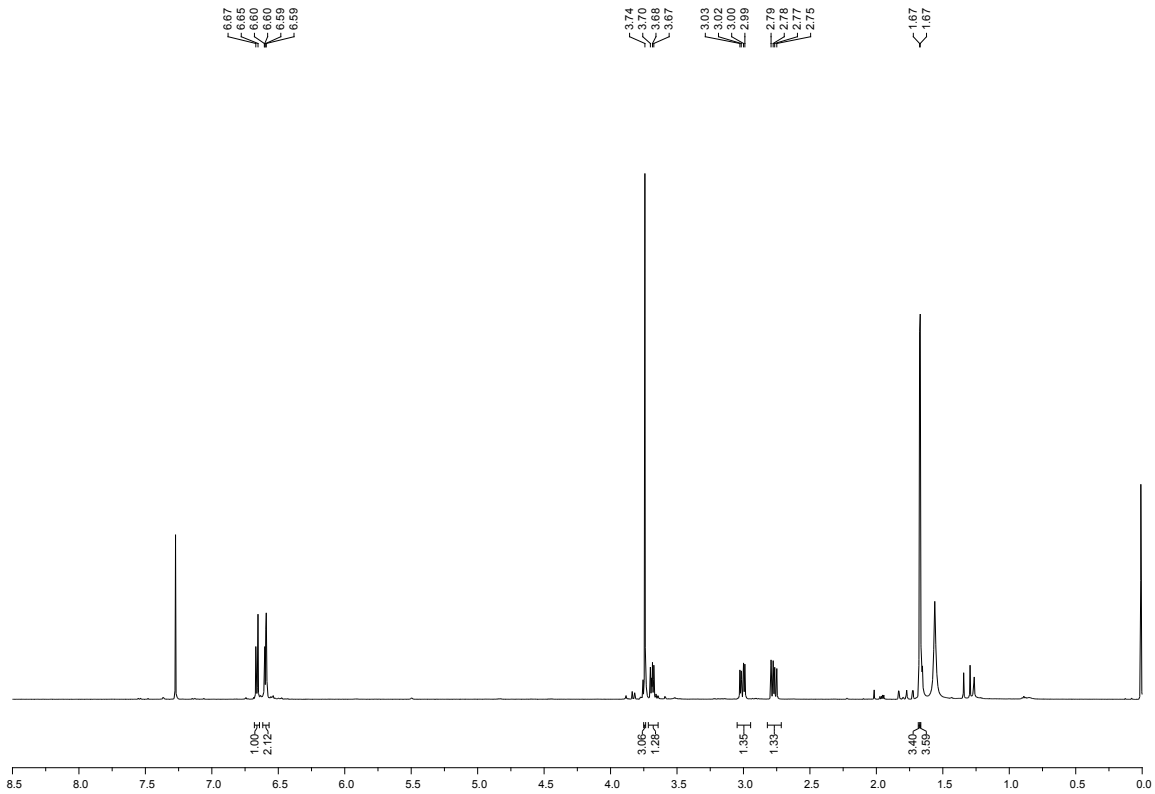

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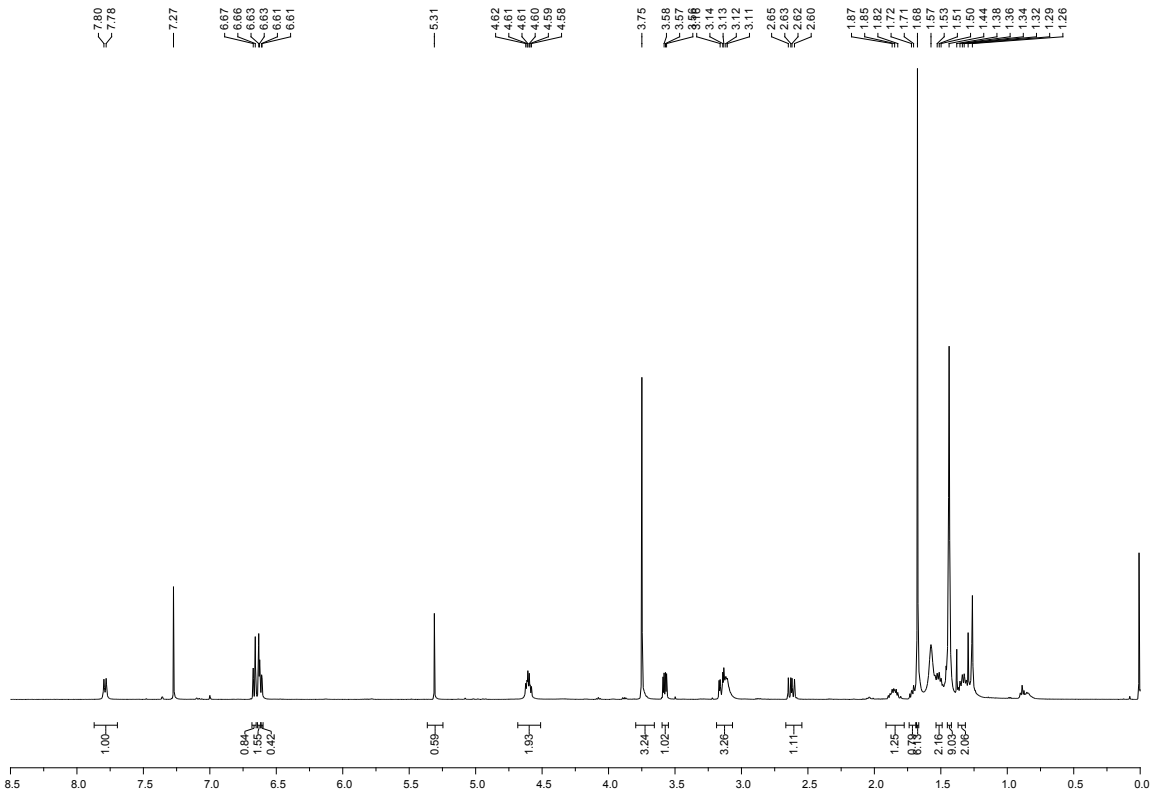

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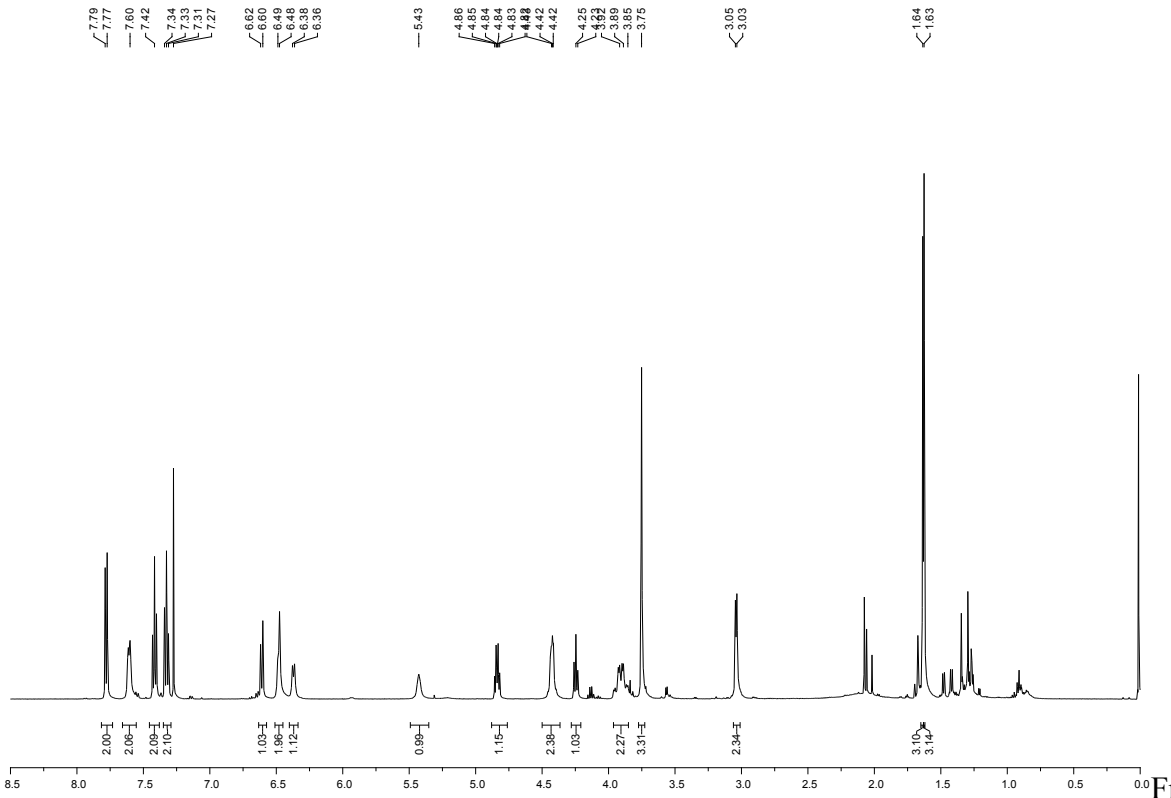

Fmoc-

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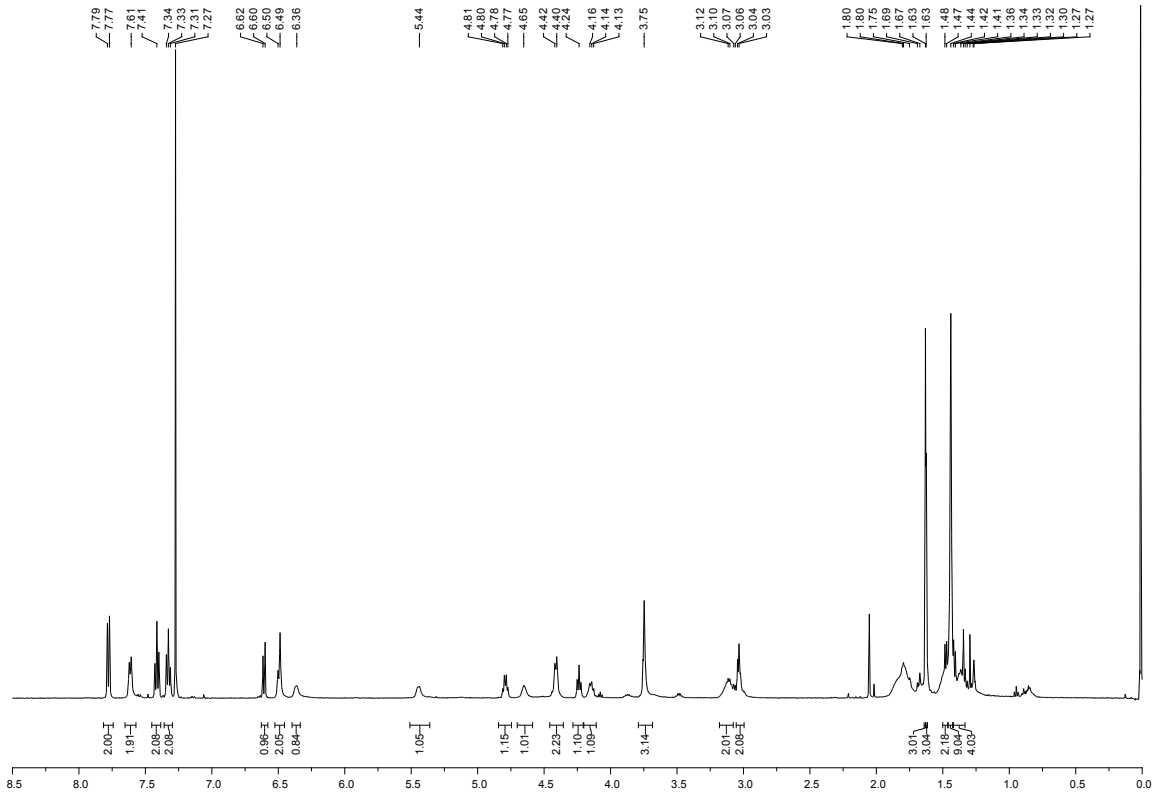

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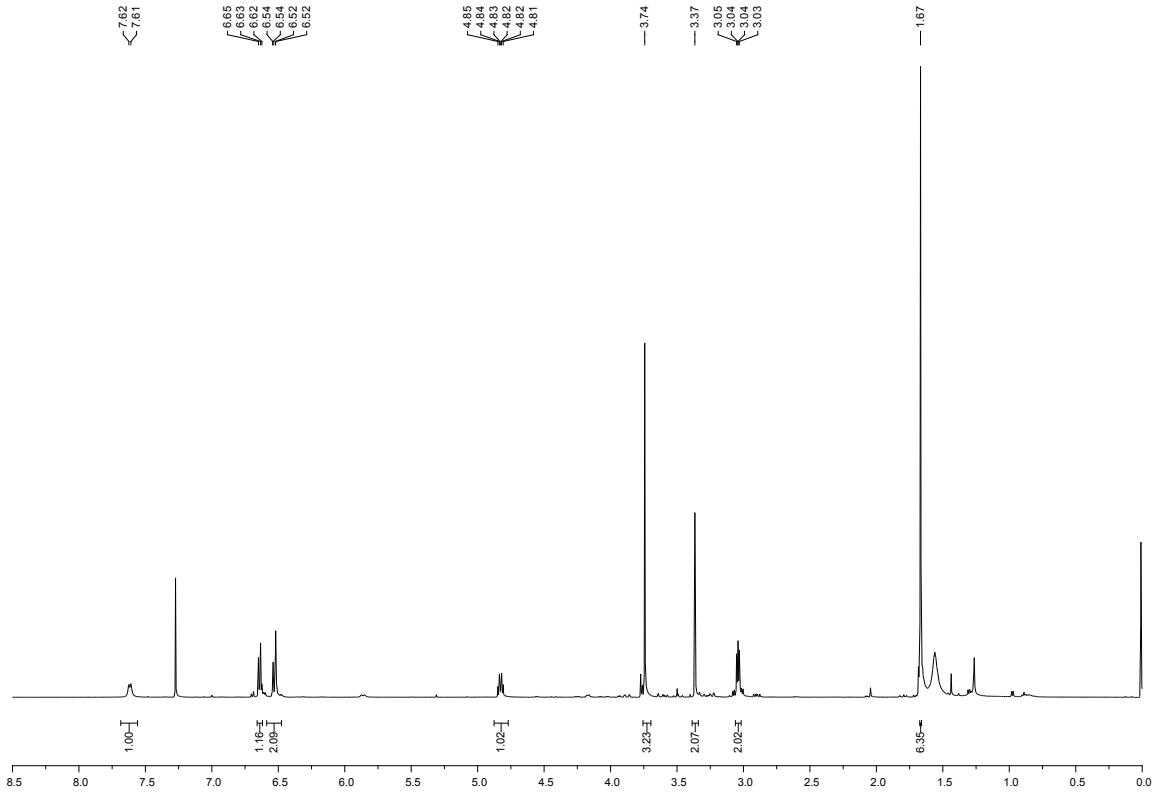

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