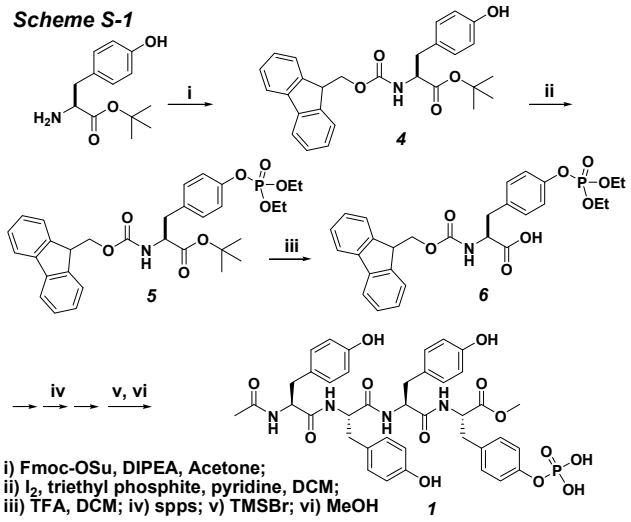
# Supporting Information

## Syntheses and characterizations:

Compound **1** was synthesized according to Scheme S-1.




***Scheme S-1***. Synthetic route for compound **1**

**Preparation of Fmoc-L-Tyr-O$^t$Bu (4)**: L-Tyrosine methyl ester hydrochloride (1.17 g, 5 mmol) and $NaHCO_3$ (840 mg, 10 mmol) were dissolved in 40 mL of water with stirring, the solution of Fmoc-OSu (1.65 g, 4.9 mmol, dissolved in 100 mL of acetone) was added, and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was air-dried, the solid obtained was washed with acid water (pH of 3) (20 ml * 3) and water (20 ml * 2), successively. 1.95 g of ***2*** was collected (93.4%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.03-8.05 (d, 2H), 7.99-8.01 (d, 1H), 7.79-7.82 (t, 1H), 7.55-7.59 (t, 2H), 7.44-7.50 (m, 2H), 7.18-7.20 (d, 2H), 6.80-6.83 (d, 2H), 4.30-4.40 (m, 4H), 3.76 (s, 3H), 3.05-3.10 (m, 1H), 2.90-2.96 (m, 1H). MS: calc. $M^+ = 417.2$, obsvd. $(M+1)^+ = 418.2$.

**Preparation of Fmoc-L-Tyr(PO(OEt)$_2$)-O$^t$Bu (5)**: $I_2$ (5.0 mmol, 1.25 equivalents) was added to a solution of the Triethyl phosphate (5.2 mmol, 1.3 equivalents) in 20 mL of dichloromethane (DCM) at 0 °C. 5 minutes after the addition, the clear,

colorless solution was allowed to warm to room temperature (25°C). Then the solution was added dropwise, over a period of 30 minutes, to a flask containing Fmoc-Tyr-OMe (4.0 mmol, 1.0 equivalent) and pyridine (16.0 mmol, 4.0 equivalents) in 80 mL of DCM at 0°C. After an additional 30 minutes, the reaction mixture was diluted with $Et_2O$ (150 mL). The organic layer was washed with $KHSO_4$ (5 wt%) (30 ml*2), brine (30 ml), dried over anhydrous $MgSO_4$, successively. The residue was purified by flash chromatography on silica gel (eluent: Hexane/Ethyl acetate = 3/2) to afford 1.93 g of title compound (87.2%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.03-8.07 (m, 3H), 7.79-7.82 (m, 2H), 7.55-7.59 (m, 2H), 7.42-7.48 (m, 3H), 7.25-7.27 (d, 2H), 4.35-4.40 (m, 3H), 4.24-4.28 (q, 4H), 3.78 (s, 3H), 3.18-3.22 (m, 1H), 3.00-3.04 (m, 1H), 1.37-1.40 (t, 6H). $^{31}$P NMR (δ -6.36 ppm). MS: calc. $M^+$ = 553.2, obsvd. $(M+1)^+$ = 554.2.

**Preparation of Fmoc-L-Tyr(PO(OEt)$_2$-OH (6):** To a solution of **5** (600 mg, 1.0 mmol) in 5 mL $CH_2Cl_2$, TFA (10 ml) was added at 0 $^0$C. After stirred at room temperature for 4h, the solvent was removed by rotary evaporator. The solid obtained was co-evaporated with toluene twice. 530 mg of title compound was obtained after removing the solvent in vacuum (yield of 98.3%) and it was used directly for solid phase peptide synthesis. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.23-8.25 (d, 2H), 8.01-8.05 (t, 2H), 7.76-7.79 (t, 2H), 7.59-7.62 (m, 4H), 7.47-7.52 (d, 2H), 4.30-4.60 (m, 8H), 3.45-3.48 (m, 1H), 3.21-3.27 (m, 1H), 1.58-1.61 (t, 6H). $^{31}$P NMR (δ -6.348 ppm). MS: calc. $M^+$ = 539.2, obsvd. $(M+H)^+$ = 540.1.

**Peptide Synthesis**: The peptide derivative was prepared by solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride resin and the corresponding N-Fmoc protected amino acids with side chains properly protected by a tert-butyl group. The first amino acid was loaded on the resin at the C-terminal with the loading efficiency about 0.6 mmol/g. 20% piperidine in anhydrous N,N'-dimethylformamide (DMF) was used during deprotection of Fmoc group. Then the next Fmoc-protected amino acid was coupled to the free amino group using

O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU) as the coupling reagent. The growth of the peptide chain was according to the established Fmoc SPPS protocol. At the final step, the N-terminus of the peptides was coupled with Acetic Anhydride to attach the acetic group on the tetrapeptides. After the last coupling step, excessive reagents were removed by a single DMF wash for 5 minutes (5 ml per gram of resin), followed by five steps of washing using DCM for 2 min (5 ml per gram of resin). The peptide derivative was cleaved using 1% of trifluoroacetic acid in DCM for ten times (one minute for each time, 5 ml per gram). All the solutions were combined and concentrated, and then 20 mL of ice-cold diethylether was added. The resulting precipitate was centrifuged for 10 min at 2 $^{0}$C at 10,000 rpm. Afterward the supernatant was decanted and the resulting solid was dissolved in DMSO for HPLC separation.

**Synthesis and Characterization of Ac-YYYpY-OMe.** The compound obtained by general solid phase peptide synthesis (spps) was treated with 20 equiv. of TMSBr in 10 ml of dry DCM for 24 hours. The solvent was removed and then 10 mL of methanol was added, the mixture was stirred at room temperature for another 2 hours. The solid obtained after evaporating the solvents was purified by HPLC to afford title compound **1** in a yield of about 45%. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.99-8.02 (t, J=7.82Hz, 2H), 7.92-7.94 (d, J=7.99Hz, 1H), 6.97-7.19 (m, 11H), 6.61-6.67 (m, 6H), 4.44-4.52 (m, 3H), 4.37-4.39 (m, 3H), 3.58 (s, 3H), 2.61-3.03 (m, 9H) 1.73 (s, 3H). $^{31}$P NMR (δ -6.21 ppm). MS: calc. $M^{+}$ = 806.9, obsvd. $(M+H)^{+}$ = 806.8. HR-MS: 807.2645.

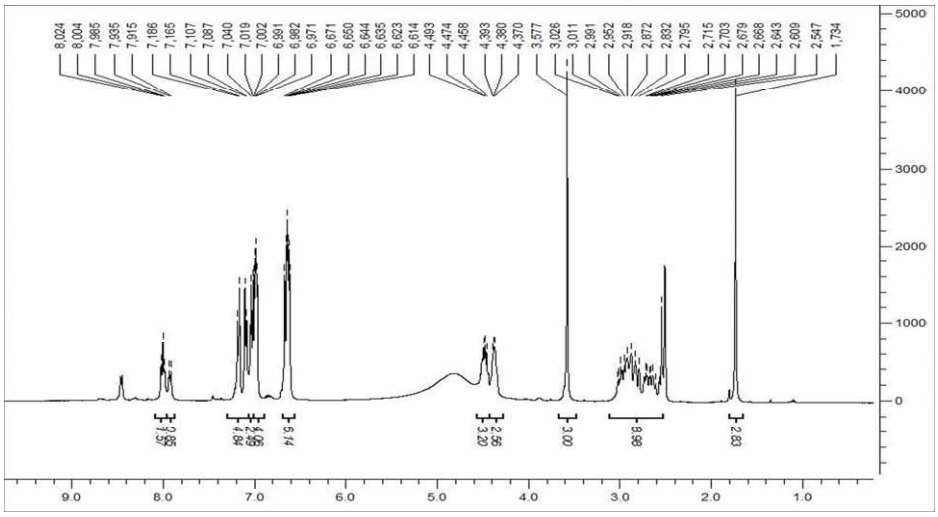


***Fig. S-1.*** **$^{1}$H NMR of Ac-YYYpY-OMe**

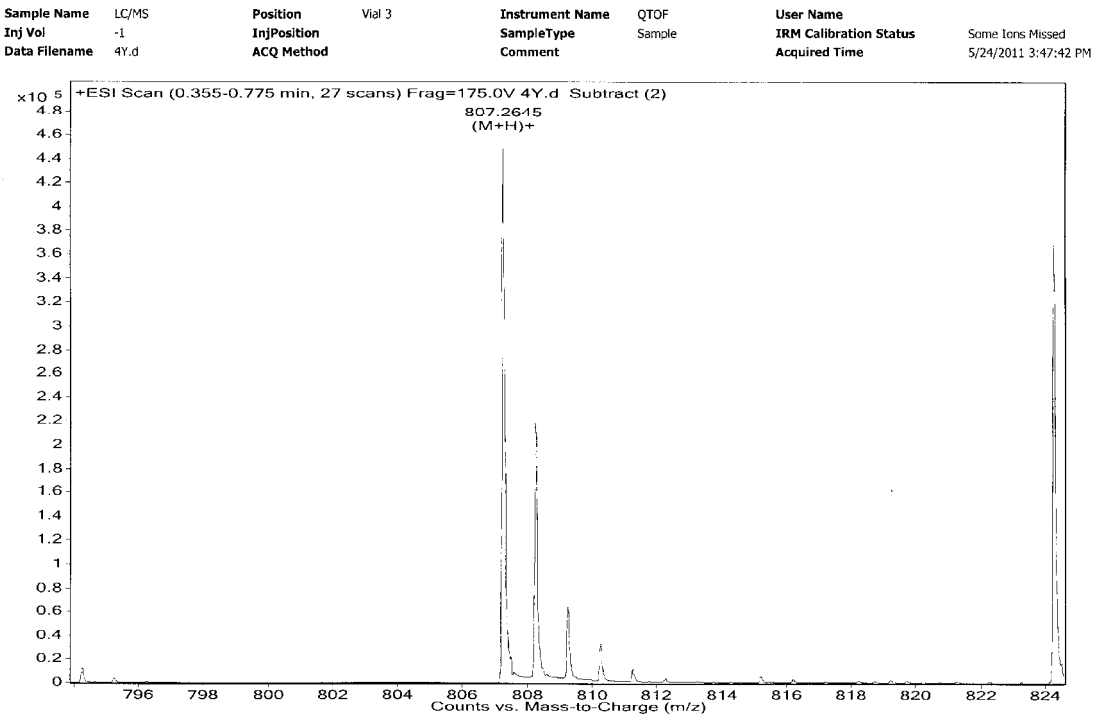



***Fig. S-2.*** HR-MS of Ac-YYYpY-OMe

**The same procedure was used to synthesize Ac-FYYpY-OMe, Ac-FFYpY-OMe, and Ac-FFFpY-OMe.**

**Ac-FYYpY-OMe:** $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.01-8.06 (m, 2H); 7.93 (d, J=8.21 Hz, 1H); 7.15-7.21 (m, 6H); 6.95-7.08 (m, 5H); 6.61 (dd, J1=8.28 Hz,

J2=16.51 Hz, 3H); 4.38-4.46 (m, 4H); 3.57 (s, 3H); 2.83-3.01 (m, 5H); 2.61-2.71 (m, 3H); 1.70 (s, 3H). $^{31}$P NMR (δ -6.24 ppm). MS: calc. $M^+$ = 790.3, obsvd. $(M+H)^+$ = 791.3. HR-MS: 791.2692.

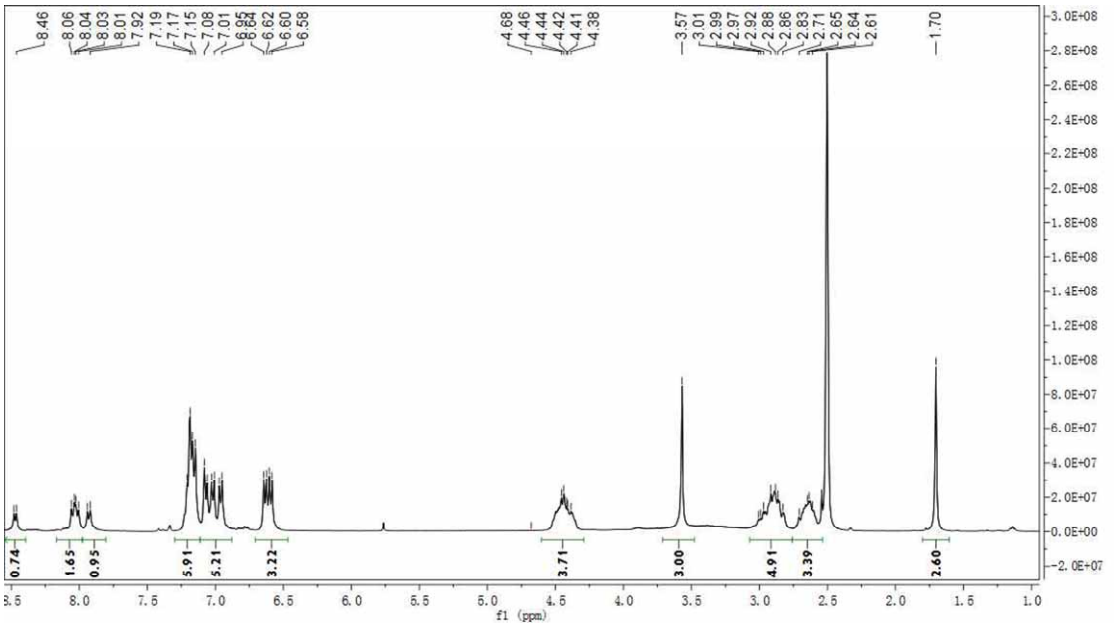



***Fig. S-3.*** **$^1$H NMR of Ac-FYYpY-OMe**

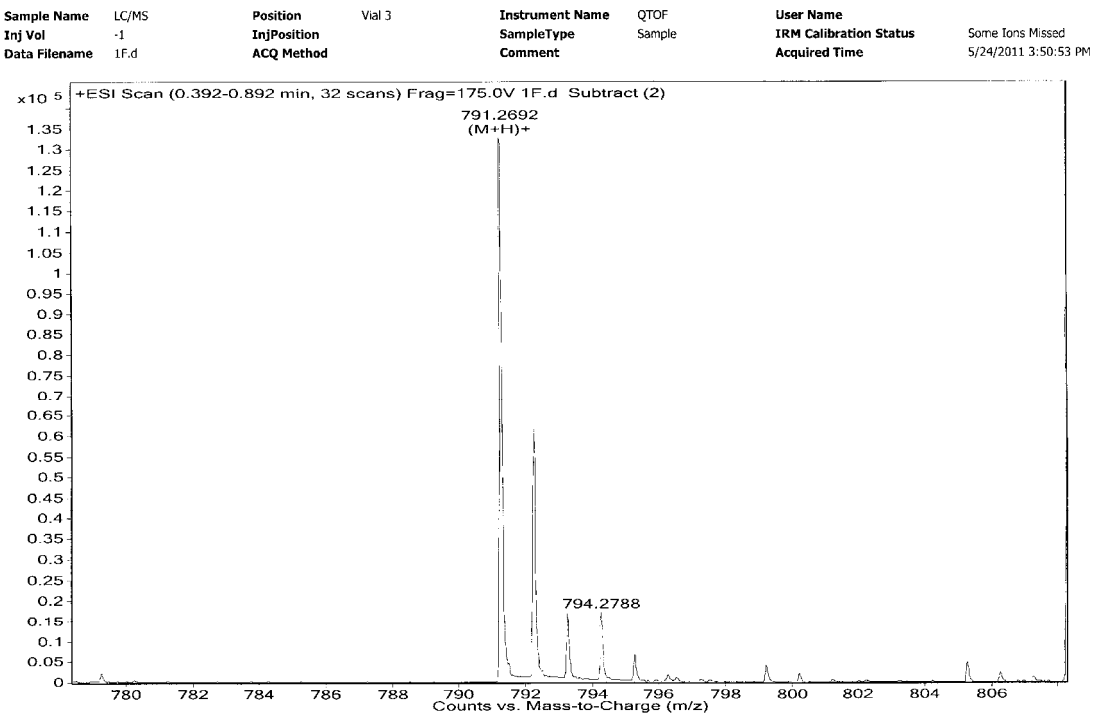



***Fig. S-4.*** HR-MS of Ac-FYYpY-OMe

**Ac-FFYpY-OMe:** $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.02-8.08 (m, 3H); 7.15-7.19 (m, 10H); 7.05 (dd, J1=8.09 Hz, J2=16.81 4H); 6.64 (d, 2H); 6.61 (dd, $J_1$=8.28 Hz, $J_2$=16.51 Hz, 3H); 4.44-4.50 (m, 4H); 3.57 (s, 3H); 2.88-2.97 (m, 5H); 2.60-2.76 (m, 3H); 1.70 (s, 3H). $^{31}$P NMR (δ -6.24 ppm). MS: calc. $M^+$ = 774.3, obsvd. $(M+H)^+$ = 775.3. HR-MS: 775.2743.

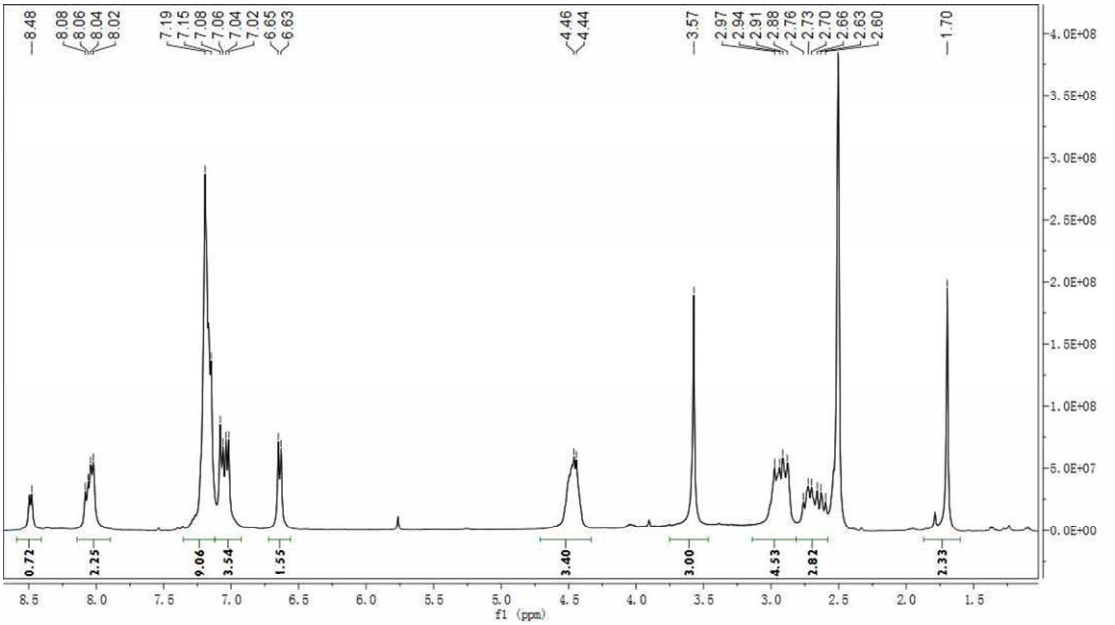



***Fig. S-5.*** **$^{1}$H NMR of Ac-FFYpY-OMe**

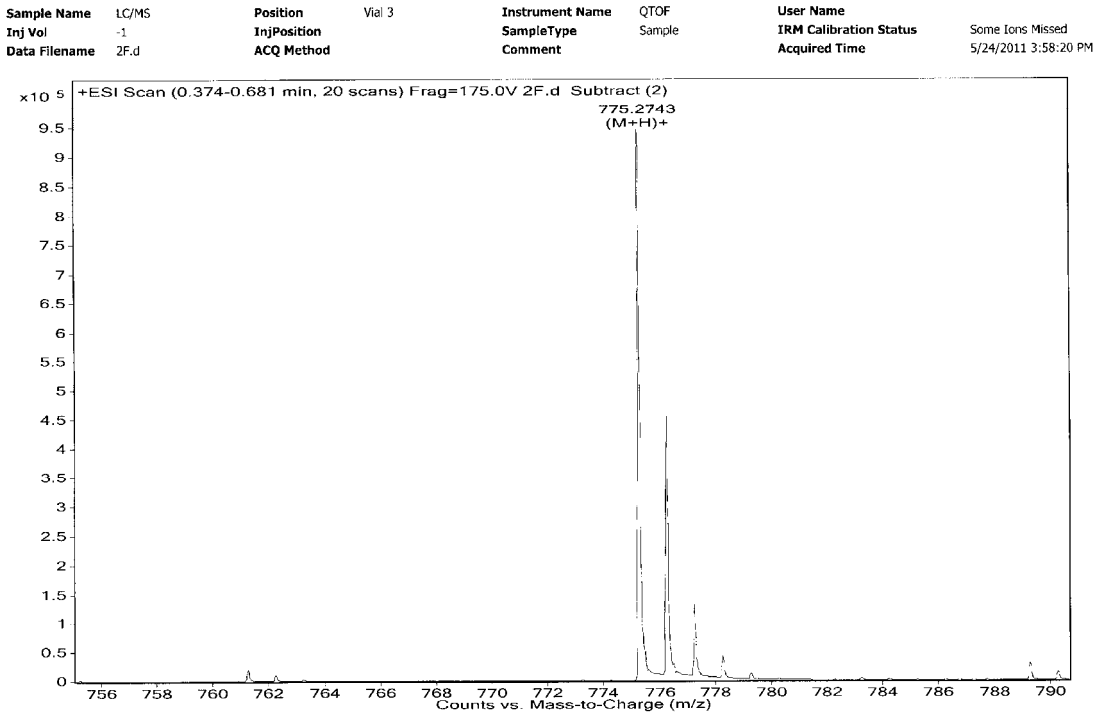



***Fig. S-6.*** HR-MS of Ac-FFYpY-OMe

**Ac-FFFpY-OMe:** $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.15 (d, J=8.06 Hz, 1H); 8.01 (t, J=7.53 Hz, 3H); 7.18-7.26 (m, 14H); 7.08 (d, J=8.18 Hz, 2H); 4.46-4.62 (m, 4H); 3.58 (s, 3H); 2.58-3.02 (m, 7H); 1.69 (s, 3H). $^{31}$P NMR (δ -6.23 ppm). MS: calc. $M^+$ = 758.3, obsvd. $(M+H)^+$ = 759.3. HR-MS: 759.2787.

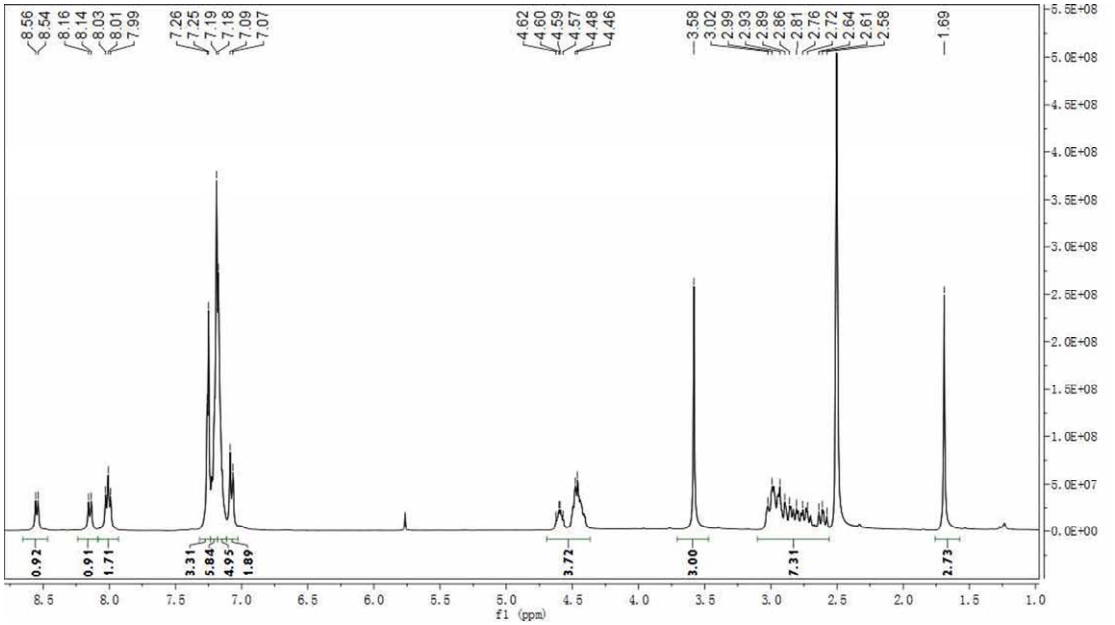



***Fig. S-7.*** **$^{1}$H NMR of Ac-FFFpY-OMe**

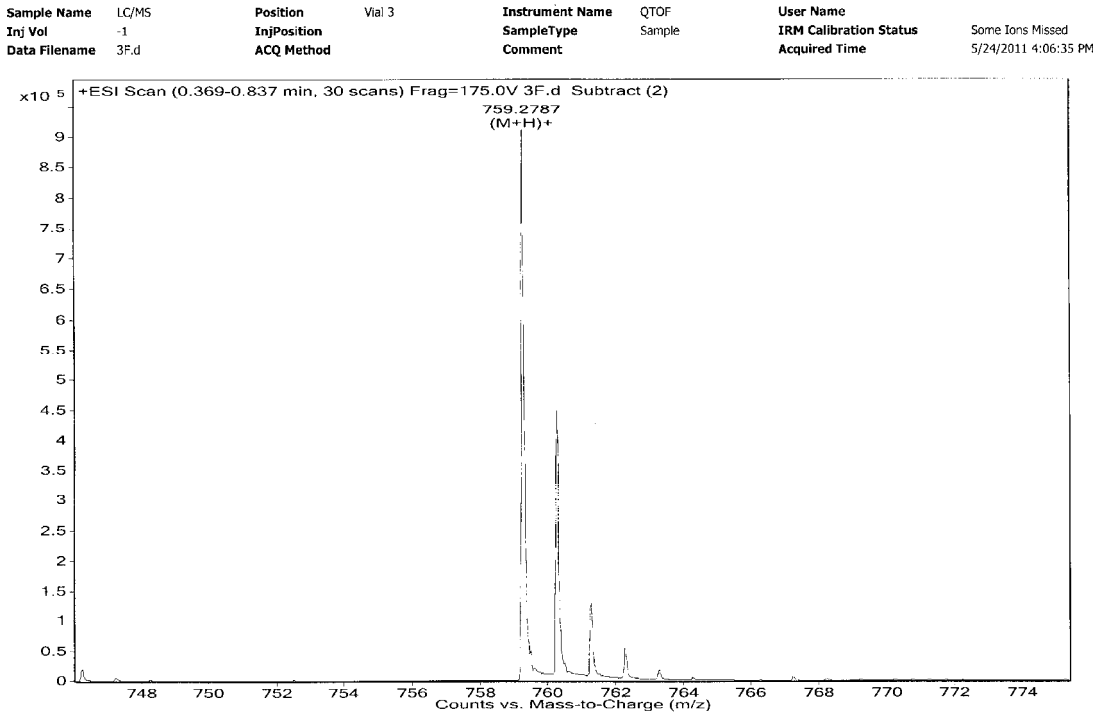



***Fig. S-8.*** HR-MS of Ac-FFFpY-OMe

**Alkaline Phosphatase (30 U/μL)**: 1 U corresponds to the amount of enzyme which hydrolyzes *p*-nitrophenyl phosphate to form 1 μmol of *p*-nitrophenol at pH 8.0 and 37 $^{o}$C.

**Tyrosinase (25 U/μL)**: 1 U will cause an increase in A280 nm of 0.001 per minute at pH 6.5 at 25°C in a 3 mL reaction mixture containing L-tyrosine.

**Determination of the minimum gelation concentration (MGC)**: The PBS solution (pH = 7.4) with different concentrations of the compounds were treated with the alkali phosphatase (final concentration of the enzyme = 60 U/mL). The formation of the hydrogels was determined by the invert-tube method after being incubated at room temperature (22-25 ℃) overnight. The MGC value was the lowest concentration of the precursors in the solutions that could form hydrogels post the treatment of the enzyme. The MGC values of Ac-FFFpY-OMe, Ac-FFYpY-OMe, Ac-FYYpY-OMe, and Ac-YYYpY-OMe are the same, all are 0.5 wt%.

**Determination of percentage of gelators in the gel at different time scales:** At each point of time, 50 μL of gel was taken from the same hydrogel containing 1.0 wt% of the precursor and 60 U/mL of the enzyme (final concentration) and dissolved in 450 μL of DMSO. Precursors and gelators in DMSO were separated by HPLC, and the percentage of them was determined by calculating the peak area of each part on the chromatographic curve.

***Table S-1.*** Percentage of gelators in the gels at different time scales (determined by HPLC).

| Time (minute) | Gelling-point (≤2.5) | 30 | 60 |
|---|---|---|---|
| Percentage of 4Y Gelator (%) | 47.9±1.4 | 89.9±1.0 | 96.0±0.6 |
| Percentage of 1F Gelator (%) | 51.7±1.2 | 92.1±0.8 | 97.2±0.7 |
| Percentage of 2F Gelator (%) | 56.2±0.6 | 91.3±1.0 | 95.8±1.1 |
| Percentage of 3F Gelator (%) | 59.7±0.9 | 93.9±0.8 | 97.8±0.5 |

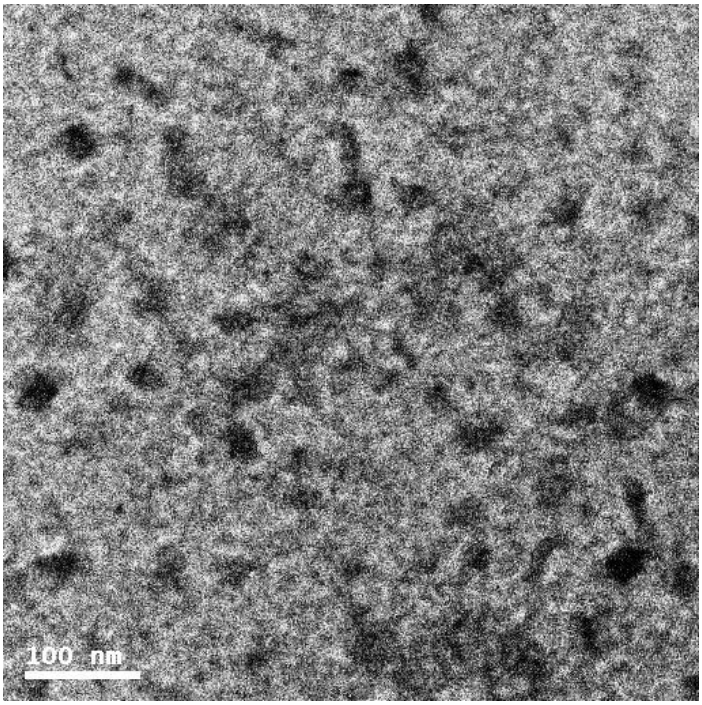



***Fig. S-9.*** TEM image of sol II in Fig. 1

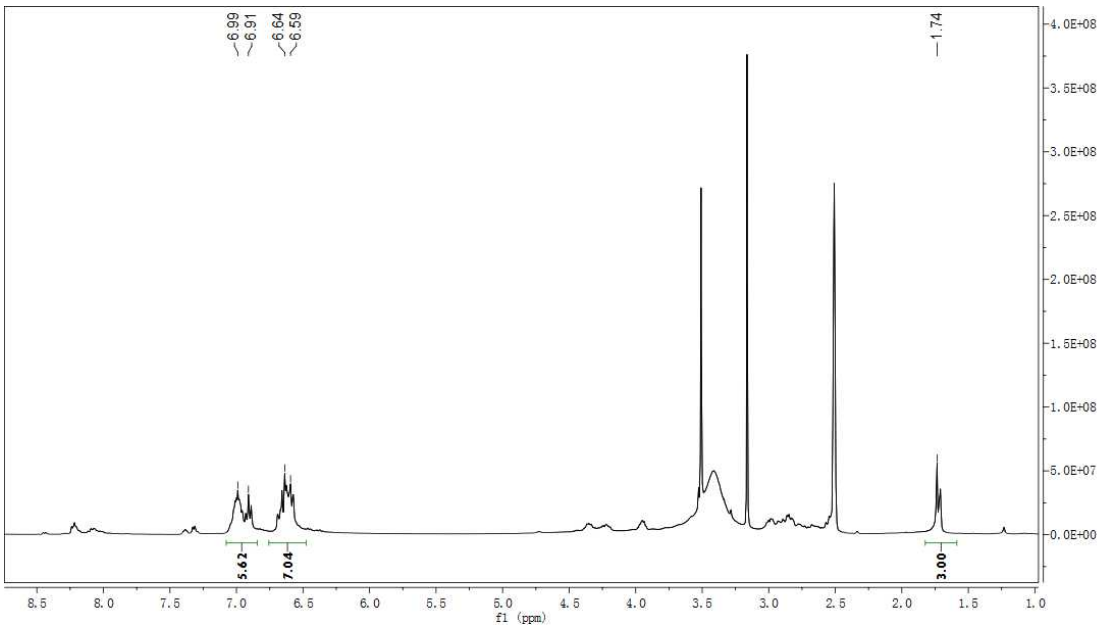



***Fig. S-10.*** $^{1}$H NMR of freeze-dried sol II in Fig. 1B-III (compared to $^{1}$H NMR of Ac-YYYpY-OMe and based on integrations of peaks in 6.5-7.2 Hz, 83.5% of phenol rings on Ac-YYYY-OMe were oxidized to quinol or quinone by tyrosinase)

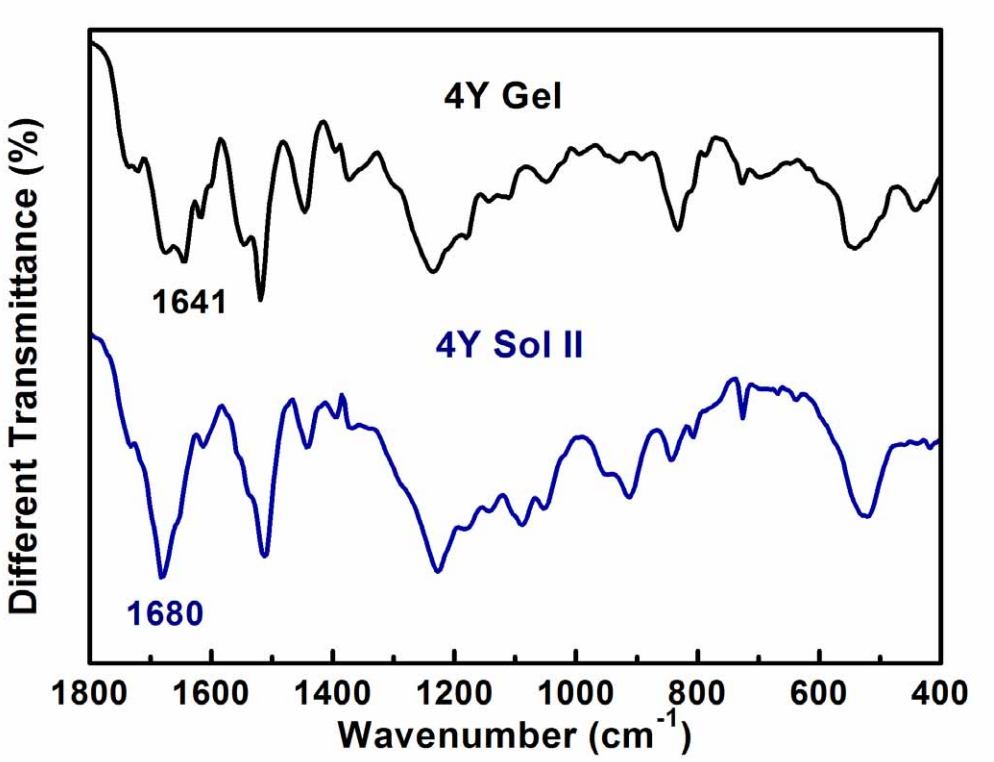



***Fig. S-11.*** FT-IR spectra of freeze-dried gel of Ac-YYYY-OMe and sol II in Fig. 1B-III (the peak at 1680 $cm^{-1}$ indicated the formation of quinone)

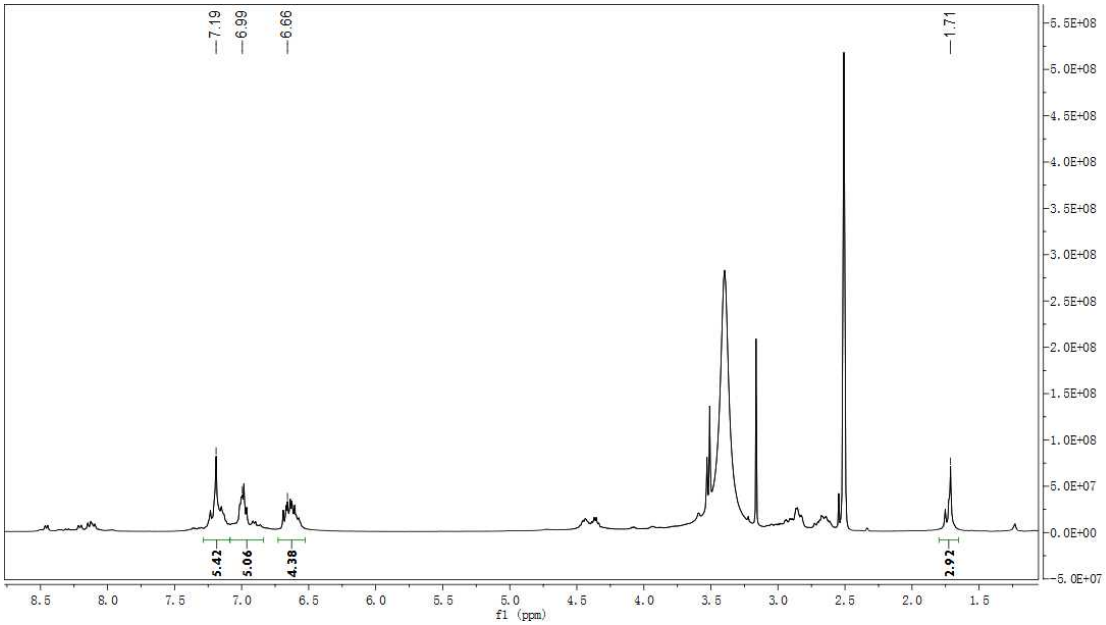



***Fig. S-12.*** $^{1}$H NMR of freeze-dried gel of Ac-FYYY-OMe treated by tyrosinase for 24 hours (compared to $^{1}$H NMR of Ac-FYYpY-OMe and based on integrations of peaks in 6.5-7.2 Hz, 71.3% of phenol rings on Ac-FYYY-OMe were oxidized to quinol or quinone by tyrosinase)