Supporting Information

Phosphorylation of Covalent Organic Frameworks Nanospheres for Inhibition of Amyloid-β Peptide Fibrillation

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1. Experimental Procedures

1.1 Chemicals and Apparatus.

All reagents and solvents were purchased from commercial sources and used without further purification. 1,3,5-Tris(4-aminophenyl) benzene (TPB) was obtained from Energy Chemical Ailan (Shanghai) Chemical Industry Technology Co., Ltd., and 2,5-dihydroxyterephthaldehyde (DHTP) was obtained from Energy Chemical. Thioflavin T (ThT) was purchased from Sigma. Acetic acid (HAc), tetrahydrofuran (THF), Sodium hydroxide (NaOH), Anhydrous acetonitrile (ACN), methyl alcohol (MeOH) phosphorus oxychloride (POCl₃), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) were obtained from Aladdin Industrial Corporation (Shanghai, China). Beta-Amyloid (1-42) (Aβ₄₂), N to C : DAEFRHDGYEVHHQKLVFFAEDGGSNKGAIIGLMVGGVIA, and FITC-Aβ₄₂ (5-FITC-(Acp)-DAEFRHDGYEVHHQKLVFFAEDGGSNKGAIIGLMVGGVIA) were purchased from Suzhou Qiangyao Biotechnology Co., Ltd. (ChinaPeptides Co., Ltd.). All other chemical reagents were of analytical grade, and millipore ultrapure water with a certain resistivity >18.25 MΩ-cm was used throughout the experiment. The working solution was using a 50 μM phosphate buffer solution (PBS, pH=7.40).

Scanning electron micrographs (SEM) were measured on a LEO1530VP (Zeiss, Germany). Transmission electron microscopy (TEM) was performed using a JEM-200 transmission electron microscope (JEOL, Japan). Dynamic light scattering (DLS) and zeta potential data were recorded on a Zetasizer Nano ZS90 Nanometer particle size potentiometer (Malvern, Britain). Fourier transform infrared (FT-IR) spectra were recorded on a SPECTRUM ONE FTIR Spectrometer (America). The fluorescence spectra were obtained from the RF6000 spectrometer (Shimadzu, Japan). X-ray photoelectron spectroscopy (XPS) measurements were performed on a JSM6510LV instrument (Jeol, Japan). Circular dichroism (CD) spectra were measured on a Chirascan Series Spectrometer (Applied Photophysics, Britain). Isothermal titration
calorimetry (ITC) curves were obtained from TA Instruments-Waters LLC (America). The confocal laser images were performed on HGY08 LSM 900 confocal laser scanning microscopy (CLSM) (Zeiss, Germany).

1.2 Synthetic procedures and methods.

**Synthesis of TD-COFs.** The spherical TD-COFs was synthesized according to the reported method.[1-3] In detail, a centrifuge tube was preloaded with 1,3,5-tris(4-aminophenyl) benzene (TPB, 0.04 mmol) and 2,5-dihydroxyterephthalaldehyde (DHTP, 0.06 mmol). Then 5 mL of ACN was added to the tube and sonicated for 5 min to dissolve the building blocks completely. After that, HAc solution (0.7 mL 12 mol·L⁻¹) was quickly added to the tube and immediately vortexed 1 min. After the solution stood at room temperature for 12 h, yellow precipitates were obtained. The collected yellow precipitates were washed with MeOH 3 times. Finally, the TD-COFs product was dried at 37 °C in a vacuum for 48 h, and then the TD-COFs were obtained.

**Synthesis of SP-COFs.** The spherical SP-COFs was synthesized as follows. The dry TD-COFs powder was sealed with 0.12 mmol POCl₃ in 5 mL anhydrous ACN at room temperature overnight for phosphorylation.[4] Subsequently, the product was alternately centrifuged with ACN 3 times to remove the unreacted POCl₃. After that, the yellow powder was further hydrolyzed with NaOH aqueous solution to obtain the raw SP-COFs. The raw SP-COFs were further rinsed by MeOH which was used to remove the adsorbed solvents and impurities. Finally, the SP-COFs were obtained after activation at 37 °C in a vacuum for 48 h. It is worth noting that methanol activation is crucial to obtaining SP-COFs with high surface areas and reasonable pore size distribution. The activation process is as follows: the products of the room temperature reaction were isolated and collected by atmospheric filtration; the precipitated solids were rinsed with MeOH and then activated in a vacuum.

**Aβ₄₂ Pretreatment.** HFIP-pretreated peptides were used to obtain a homogeneous, aggregate-free preparation.[5] This step is necessary because pre-formed aggregates
induce rapid aggregation of amyloidogenic Aβ42, which results in poor reproducibility among experiments. To treat the peptides with HFIP, pre-chill the HFIP container on ice inside a fume hood wearing adequate protection (HFIP is volatile and toxic). Add HFIP to pre-chilled tubes containing peptide lyophilizes to obtain a nominal peptide concentration of 0.5 mM. Sonicate the peptide solutions in a water-bath sonicator for 5 mins at room temperature. Vortex gently and incubate the tubes for 30 mins at room temperature. Remove HFIP by freeze-drying. The final product will be a peptide film at the bottom of the microfuge tubes. Dry peptide films were kept at -20 °C until use.

Fibrillation Assay and ThT Fluorescence Monitoring. The HFIP-pretreated monomers of Aβ42 (50 μM) were dissolved in 50 μM PBS buffer containing 0.02% NaN₃ (accelerated aggregation) and incubated in a water bath at a constant temperature of 37 °C for fibrillation kinetics assays in the presence or absence of TD-COFs and SP-COFs (60 μg·mL⁻¹).[^6] ThT fluorescence was used to monitor the kinetics of Aβ42 fibrillation. At different time intervals, aliquots of the aggregating solutions were taken out for ThT fluorescence measurements. 30 μL of the aggregating solutions were mixed with 240 μL of 10 μM ThT in 50 μM PBS, pH 7.40, at different time points. The fluorescence was measured at λ_ex = 437 nm and λ_em = 485 nm. The data are presented as mean (3 independent experiments).

The binding specificity of SP-COFs. 50 μM amino acid (13 amino acids. hydrophobicity: Ala, Phe, Met; hydrophilicity: Asn, Tyr, Gly, Ser, Thr, acidity: Asp, Glu, alkalinity: Lys, His, Arg) was added to the SP-COFs&Aβ42 co-incubation system respectively. The fibrillation kinetics curve was monitored with ThT in a water bath at a constant temperature of 37 °C. ThT was cultured in the polymerization solution for 12h, and the fluorescence value at 485nm was plotted for binding specificity assay. Similarly, in the co-incubation system without SP-COFs&Aβ42, 13 amino acids were cultured and their ThT fluorescence kinetics curves were also measured.

TEM and DLS measurements. The TEM and DLS experiments were performed with
another aggregating solution (5 μM Aβ42 with 60 μg·mL⁻¹ SP-COFs). In detail, 3 μL aliquots from the aggregation reactions in the absence or presence of SP-COFs were diluted 10 times and spotted on carbon-coated Formvar grids to obtain TEM images at different time intervals. At the same time, the size distribution of scattering particles was recorded using a 2 mL aggregating solution. The control experiments were performed with Aβ42 alone.

**SP-COFs Inhibit Toxicity of Aβ42 in Cell Culture.** PC12 cells cultured in 1240 medium (5% CO₂, 37 °C) were used to study the toxicity induced by Aβ42. We tested whether SP-COFs protected cultured cells against toxicity induced by Aβ42. We used the MTT (2 mg·mL⁻¹) reduction assay for the measurement of cell viability.⁷ Before initiating inhibition experiments, we tested whether SP-COFs were toxic to the cells (SP-COFs with varying concentrations: 5-60 μg·mL⁻¹). By comparison, remarkable cytotoxicity was observed when Aβ42 (0-20 μM) was incubated with the PC12 cells alone. (The co-culture time of the above three experiments with cells was 48 h)

**The Confocal Laser Scanning Microscopy Images.** The images during the co-incubation of PC12 cells with SP-COFs and Aβ42 were investigated by confocal laser scanning microscopy (CLSM). We introduced a NIR fluorescent dye (stilbazolium derivative, 4-N, N-dimethylamino-4'-N-methyl-1,3-butadienyl|pyridinium dimer, synthesized by our lab) into SP-COFs to enable cell imaging through host-guest recognition.⁸ The fresh SP-COFs (2 mg) were soaked in stilbazolium dye/ACN (10 μM) for 24 h, and then the product was alternately centrifuged with MeOH 3 times to remove the residual dye. After that, the yellow powder was further rinsed by MeOH which was used to remove the adsorbed solvents until the filtrate is colorless. Finally, the SP-COFs were obtained after activation at 37 °C in a vacuum for 48 h. The confocal laser images during the co-incubation of PC12 cells with SP-COFs were measured under the excitation of a 488 nm laser. SP-COFs were co-incubated with PC12 cells in the absence or presence of Aβ42 (5 μM) for 4 h.
**Molecular dynamics simulation.** Molecular dynamics simulation was done with Amber14 software. Molecular dynamics time: > 20 ns; Molecular dynamics requirements: $\text{A}\beta_{42}$ peptide was completely stretched from one side of the pore of SP-COF to the other side in aqueous solution, and time nodes-structure phase of $\text{A}\beta_{42}$ peptide across the single pore of SP-COFs in molecular dynamics process. The whole peptide system adopts gaff and ff14SB force fields, taking the $\text{A}\beta_{42}$ peptide as the center, adding 10 Å cubic water box, and adding Na$^+$ to make the system electrically neutral. The topology and coordinate structure were saved and then carried out the simulation.
2. Figures and Tables

Figure S1. (A) TEM image and (B) particle size distribution of TD-COFs.
Figure S2. Energy-dispersive X-ray (EDX) spectroscopy of C, N, P, and O in SP-COFs.
**Figure S3.** The amino acid sequence and molecular structure of $\alpha\beta_{32}$ peptide.
| Time Interval | Image 1 | Image 2 | Image 3 | Image 4 |
|--------------|---------|---------|---------|---------|
| 0-1 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| 1-2 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| 2-3 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| 3-4 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| 4-5 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| 5-6 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| 6-7 ns       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
Figure S4. Time nodes-structure phase of Aβ42 peptide across SP-COF (the single pore of SP-COFs) in molecular dynamics process.

Noted: The preformation of Aβ42 peptide going through SP-COF is a holistic process, so the binding state between the two in real-time was monitored and nine structures were selected to display.

(1) 0-1 ns: Aβ42 has not yet had any contact with the SP-COF;
(2) 1-2 ns: The head of Aβ42 began to insert into the SP-COF and formed a polar interaction with SP-COF. Subsequently, a strong salt bridge between the lysine (K28) and phosphate group was formed. This action pulled Aβ42 close to the SP-COF;
(3) 2-3 ns: With Aβ42 keeping entering the SP-COF, two hydrogen bonds were formed between asparagine (N27) and serine (S26) on the Aβ42 chain and two phosphate groups on the inner pore of SP-COF, which maintained the contact between Aβ42 and SP-COF;
(4) 3-4 ns: When half of the body position of Aβ42 (1/2 of the length) has entered the inner pore of SP-COF, histidine (H14) and glutamine (Q15) sites on the Aβ42 chain formed three hydrogen bonds with phosphate groups on SP-COF;
(5) 4-5 ns: Notably, nearly 3/4 of the body position of Aβ42 (3/4 of the length) has passed through the inner pore of the channel of SP-COF, and a salt bridge was
formed among histidine (H₁₃) and lysine (K₁₆) sites and phosphate groups. This is conducive to the stable binding between Aβ₄₂ and the inner pore of SP-COF;

(6) 5-6 ns: Aβ₄₂ has almost completely passed through the SP-COF. At this time, both salt bridge and hydrogen bond were formed between the histidine (H₆), serine (S₈) at the end of the Aβ₄₂ chain, and the phosphate group on SP-COF;

(7) 6-7 ns: The Aβ₄₂ peptide has gradually passed through the SP-COF. Aspartic acid (D₁) on the tail of Aβ₄₂ formed a hydrogen bond with the phosphate group. Besides, histidine (H₆), arginine (R₅), and a phosphate group formed two salt bridges. These polarity effects made it difficult to dissociate Aβ₄₂ from SP-COF;

(8) 7-8 ns: The Aβ₄₂ sequence completely passes through the inner pore of SP-COF. The salt bridge between arginine (R₅) on the tail of Aβ₄₂ and the phosphate group of SP-COF made Aβ₄₂ and SP-COF suspended at the last moment, and maintained the final contact between them;

(9) 8-9 ns: The Aβ₄₂ sequence was completely passed through the SP-COF.
Table S1. Binding free energy of SP-COFs and Aβ_{42} complex (kcal/mol) and important polar residues.

| Time note | Hydrophobic items | H-bonds items | Desolve energy items | Electrostatic items | Total energy | Interaction sites |
|-----------|-------------------|---------------|----------------------|---------------------|--------------|-------------------|
| 0-1 ns    | -1.03             | -1.07         | -1.12                | -1.04               | -4.26        | -                 |
| 1-2 ns    | -0.69             | -1.83         | -1.11                | -1.72               | -5.35        | K_{28}            |
| 2-3 ns    | -0.39             | -1.94         | -1.31                | -1.89               | -5.53        | N_{27}, S_{26}    |
| 3-4 ns    | -0.28             | -1.95         | -1.28                | -1.9                | -5.41        | Q_{15}, H_{14}    |
| 4-5 ns    | -0.34             | -2.34         | -1.26                | -1.98               | -5.92        | K_{16}, H_{13}    |
| 5-6 ns    | -0.43             | -1.91         | -1.21                | -1.92               | -5.47        | S_{8}, H_{6}      |
| 6-7 ns    | -0.29             | -2.48         | -1.24                | -2.32               | -6.33        | H_{6}, R_{5}, D_{1}|
| 7-8 ns    | -0.86             | -1.6          | -0.89                | -1.34               | -4.69        | R_{5}             |
| 8-9 ns    | -1.35             | -0.76         | -1.11                | -1.02               | -4.24        | -                 |
**Figure S5.** Steered molecular dynamics of the most stable phase (4-5 ns) of Aβ_{42} and single pore structure in SP-COFs during Aβ_{42} peptides pass through SP-COFs.
**Figure S6.** TEM images and DLS measurements of fibrillation time courses of $\text{A}\beta_{42}$ (5 μM). $\text{A}\beta_{42}$ monomers were incubated at 37 °C for 0 h (A), 24 h (B), and 96 h (C) in the absence of SP-COF nanospheres; (D) $\text{A}\beta_{42}$ monomers were incubated at 37 °C for 96 h in the presence (D) of SP-COFs (60 μg·mL$^{-1}$). Buffer: 50 μM PBS, pH = 7.40.
Figure S7. Zeta potential of $\alpha\beta_{42}$ alone and co-incubation with SP-COFs.
Figure S8. Fluorescence spectra of SP-COFs, ThT, and their mixture in PBS buffer solution.
Figure S9. (A) The UV-Vis spectra of Aβ<sub>42</sub> (5 μM) before and after co-incubation (10 h) with SP-COF (60 μg·mL<sup>-1</sup>); (B) The change of peptide concentration before and after mixing of Aβ<sub>42</sub> (5 μM) and the SP-COFs (60 μg·mL<sup>-1</sup>).

**Note:**

We used UV-Vis absorption spectroscopy to explore the concentration changes of Aβ<sub>42</sub> before and after mixing with SP-COFs. According to the analysis of absorbance change, ca. 16.0 % of the protein was adsorbed by SP-COFs when they were mixed.
**Figure S10.** ThT fluorescence assay (co-incubate for 12 h) of Aβ_{42} or single amino acid (50 μM, 10 times of Aβ_{42}).

**Note:**

The aggregation kinetic curves of the independent Aβ_{42} with amino acids were also adopted as control experiments to investigate the effect of surface properties on the Aβ_{42} fibrillation. Notably, the fluorescence intensity of ThT in the SP-COFs-free systems was no discernible difference by adding acidic amino acids, basic amino acids, and hydrophobic amino acids, as shown in Figure S10.
Table S2. The secondary structure content of Aβ42 according to the CD spectra.

| Content (%) | Aβ42/0 h | Aβ42/24 h | Aβ42/96 h | Aβ42&SP-COF/96 h |
|-------------|----------|-----------|-----------|-----------------|
| Helix       | 19.9     | 1.3       | 8.1       | 4.3             |
| Antiparallel| 1.8      | 15.8      | 16.7      | 16.2            |
| Parallel    | 5.9      | 4.1       | 12        | 4.6             |
| Turn        | 25.4     | 21.2      | 16.3      | 21.9            |
| Others      | 47.0     | 57.6      | 46.9      | 53.0            |

Note:

As shown in Table S2, the secondary structure contents of Aβ42 species including monomers (incubation for 0 h at 37 °C), oligomers (incubation for 24 h at 37 °C), and fibrils (incubation for 96 h at 37 °C), as well as the SP-COFs@Aβ42 co-culture system (co-incubation for 96 h at 37 °C) were quantitatively analyzed by BeStSel webserver. In the oligomerization process in 0 to 24 hours, the main change in the secondary structure of Aβ42 is that the helical structure is significantly reduced (19.9 % to 1.3 %), the antiparallel structure is significantly increased (1.8 % to 15.8 %), the configurations of parallel and turn are not significantly changed, and the "other" is significantly increased (47.0 % to 57.6 %). In contrast, from 24 hours to 96 hours, it is a fibrotic process, which is mainly characterized by the increase of parallel configurations (4.1 % to 12 %). The antiparallel configuration remained unchanged, and the turn decreased (21.2 % to 16.3 %), so the increase of helix was transformed from "others". Comparing the CD data of Aβ42 incubation for 96 hours in the presence and absence of SP-COFs, it can be found that the parallel configuration of Aβ42 in the presence of SP-COFs is significantly reduced (12.0 % to 4.6 %). The CD results strongly suggested that the SP-COFs could hinder the conformation transition of Aβ42 from α-helical to β-sheet, confirming the interactions between Aβ42 and SP-COFs, which supports the conclusion that SP-COFs are process-specific inhibitors.
of aberrant Aβ_{42} fibrillation.

**Figure S11.** TEM images of SP-COFs after co-incubation with Aβ_{42} monomers at 37 °C for 0 h (A), 24 h (B), 72 h (C), and 96 h (D).
Figure S12. PXRD of SP-COFs after co-incubated with Aβ42 monomers in PBS buffer at 37 °C at different intervals (0 h, 24 h, 72 h, 96 h).
Figure S13. TEM images of SP-COFs were co-incubated in cell sap for 0 h (A) and 96 h (B).
Figure S14. (A) Molecular structure, (B) UV-Vis and photoluminescence spectra, (C) mass spectrum (D) and $^1$H NMR (400 MHz, DMSO-$d_6$) of the stilbazolium dye (4-N, N-dimethylamino-4'-N-methyl-1, 3- butadienyl] pyridinium dimer, DMBPD).
Figure S15. The CLSM images with excitation light of 488 nm of 60 μg·mL⁻¹ DMBPD&SP-COFs. Darkfield (left), bright field (center), and superposition field (right).
Figure S16. The CLSM images with excitation light of 488 nm of 60 μg·mL⁻¹ DMBPD&SP-COFs and 5 μM Aβ₄₂ (without labeling). Darkfield (left), bright field (center), and superposition field (right).
Figure S17. The CLSM images with excitation light of 488 nm of 5 μM FITC-Aβ42. Darkfield (left), bright field (center), and superposition field (right).
Figure S18. The CLSM images of 60 μg·mL⁻¹ DMBPD&SP-COFs and 5 μM FITC-Aβ₄₂ co-culture system with excitation light of 488 nm. Darkfield (two of left), bright field (center), and superposition field (right).

Note:

The cytotoxicity experiments of other three kinds of cells including Hela, HUVECs, and A549 cells were added to evaluate the effect of SP-COFs on cell viability and Aβ-induced cytotoxicity
Figure S19. The cell viability was measured by a standard MTT assay. The viability of cells without any treatment for 48 h was specified as 100%. The PC12 (A), Hela (B), HUVECs (C), and A549 (D) cells were preincubated with SP-COFs (0 – 60 μg mL⁻¹) and Aβ42 (5 μM).
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