Biodegradable Covalent Organic Frameworks Achieving Tumor Micro-Environment Responsive Drug Release and Antitumor Treatment

Tong Li\textsuperscript{a,b,d}, Dianwei Wang\textsuperscript{a,b,d}, Zhaopei Guo\textsuperscript{a,d}, Lin Lin\textsuperscript{a,d}, Meng Meng\textsuperscript{a,b,d}, Cong Liu\textsuperscript{c}, Kai Hao\textsuperscript{c*}, Xuan Pang\textsuperscript{a,b,d}, Huayu Tian\textsuperscript{a,b,c,d,e*}, Xuesi Chen\textsuperscript{a,b,d}

\textsuperscript{a} Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China

\textsuperscript{b} School of Applied Chemistry and Engineering, University of Science and Technology of China, Hefei 230026, China

\textsuperscript{c} State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

\textsuperscript{d} Jilin Biomedical Polymers Engineering Laboratory, Changchun 130022, China

\textsuperscript{e} Innovation Laboratory for Sciences and Technologies of Energy Materials of Fujian Province (IKKEM), Xiamen 361005, China

Prof. Huayu Tian, Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022; School of Applied Chemistry and Engineering, University of Science and Technology of China, Hefei 230026, China; State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China; Jilin Biomedical Polymers Engineering Laboratory, Changchun 130022, China;
Innovation Laboratory for Sciences and Technologies of Energy Materials of Fujian Province (IKKEM), Xiamen 361005, China, E-mail: thy@xmu.edu.cn.

Dr. Kai Hao, State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China, E-mail: kaihao@xmu.edu.cn.

Table S1. Different conditions for the exploration of synthetic COF-TpAzo NPs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Volume of TFA (µL)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Precipitate solvent</th>
<th>Wash solvent</th>
<th>SEM</th>
<th>XRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>20</td>
<td>70</td>
<td>15</td>
<td>ether</td>
<td>DMF</td>
<td>S1a</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>20</td>
<td>70</td>
<td>15</td>
<td>ether</td>
<td>DCM</td>
<td>S1b</td>
<td>S2a</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>20</td>
<td>120</td>
<td>15</td>
<td>ether and n-hexane</td>
<td>-</td>
<td>S1c</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>20</td>
<td>70</td>
<td>15</td>
<td>n-hexane</td>
<td>-</td>
<td>S1d</td>
<td>S2b</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>20</td>
<td>35</td>
<td>24</td>
<td>n-hexane</td>
<td>DMAc</td>
<td>S1e</td>
<td>S2c</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>20</td>
<td>70</td>
<td>24</td>
<td>n-hexane</td>
<td>DMAc</td>
<td>S1f</td>
<td>S2d</td>
</tr>
<tr>
<td>7</td>
<td>DCM</td>
<td>20</td>
<td>70</td>
<td>72</td>
<td>n-hexane</td>
<td>DMAc</td>
<td>S1g</td>
<td>S2e</td>
</tr>
<tr>
<td>8</td>
<td>Dry DCM</td>
<td>20</td>
<td>70</td>
<td>72</td>
<td>n-hexane</td>
<td>DMAc</td>
<td>S1h</td>
<td>S2f</td>
</tr>
<tr>
<td>9</td>
<td>DCM</td>
<td>10</td>
<td>70</td>
<td>72</td>
<td>n-hexane</td>
<td>DMAc</td>
<td>-</td>
<td>S2g</td>
</tr>
</tbody>
</table>

Figure S1. SEM images of the nanoparticles obtained by the corresponding synthesis method in Table S1.
Figure S2. XRD spectrums of the nanoparticles obtained by the corresponding synthesis method in Table S1.

Figure S3. Larger magnification SEM image of the COF-TpAzo NPs. Scale bar: 200 nm.

Figure S4. $^{13}$C CP-MAS NMR spectra of the COF-TpAzo NPs.
Figure S5. XPS spectra of Fe-COF.

Figure S6. Thermogravimetric analyses of COF-TpAzo and Fe-COF under N$_2$ atmosphere.

Figure S7. The synthesis route of the model compound.
Figure S8. (A) UV-vis spectra of DOX·HCl of different concentrations in DMSO. (B) Standard curve of DOX·HCl in DMSO.

Figure S9. UV-vis spectra of DOX soaked from 1 mg DOX@COF NPs and 1 mg DOX@Fe-COF NPs in DMSO.

Figure S10. DOX release profiles from NPs in PB solution of different pH (A) pH = 5.5. (B) pH = 7.4.
Figure S11. Calculation of IC50 of DOX@Fe-COF with and without H2O2. IC50 of DOX@Fe-COF without H2O2 was 15.28 μg/mL; IC50 of DOX@Fe-COF with H2O2 was 6.43 μg/mL.

Figure S12. FT-IR spectrum of Fe-COF/HA, Fe-COF, and HA. The peak at 1036 cm⁻¹ was attributed to the C-O-C stretching of HA.
Figure S13. Hydrodynamic size and zeta potential of Fe-COF, DOX@Fe-COF, DOX@Fe-COF/HA. Fe-COF: 333.6 nm ± 6.6 nm; DOX@Fe-COF: 602.5 nm ± 7.6 nm; DOX@Fe-COF/HA: 295.7 nm ± 3.2 nm.

Figure S14. Flow cytometry of cellular uptake of DOX@Fe-COF and DOX@Fe-COF/HA.
Figure S15. The quantification of the normalized fluorescence signal of the organs and tumors of each group.