Supporting Information

Double-Shelled, Rattle-Architecture Covalent Organic Framework: Harnessing Morphological Manipulation for Enhanced Synergistic Multi-Drug Chemo-Photothermal Cancer Therapy

Nafiseh Rahmani Khalili [a], Alireza Badiei[*, a], Zanyar Pirkani [b], Ghodsi Mohammadi Ziarani [c], Hossein Vojoudi [d], Amir Golmohamadi [d], Rajender S. Varma [e]

[a] *School of Chemistry, College of Science, University of Tehran, Tehran, Iran*

[b] *Department of Animal Internal Medicine, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran*

[c] *Department of Chemistry, Alzahra University, Vanak Square, Tehran, Iran*

[d] *College of Health Sciences, West Chester University of Pennsylvania, PA, USA*

[e] *Centre of Excellence for Research in Sustainable Chemistry, Department of Chemistry, Federal University of São Carlos, 13565-905 São Carlos – SP, Brazil.*

[*] *E-mail address:* abadiei@ut.ac.ir

Materials

All the chemical reagents in this experiment were purchased from the Sigma-Aldrich and Merck companies and were used as received without any further purification. Water is purified with a Milli-Q system. (≥ 18 MU.cm).

Characterizations

Fourier transform infrared (FTIR) spectra were recorded using Perkin–Elmer Spectrum RXI FT-IR spectrometer by using KBr pellets technique. Field emission scanning electron

microscopy (FE-SEM), TESCAN MIRA III instrument, Transmission electron microscopy (TEM) and element mapping analysis (Philips TECNAI G2 electron microscope operating at 200 kV) was used to study the morphology of all samples. N_2 adsorption-desorption isotherms and corresponding pore-size distribution were characterized by a Micromeritics TriStar II plusat 77 K. The specific surface area was calculated by the Brunauer-Emmett-Teller (BET) method. To investigate the crystallinity of the samples, powder X-ray diffraction (PXRD) measurement was operated on a Bruker D5000 diffractometer with Cu Ka (λ=0.154 nm) radiation. X-ray photoelectron spectroscopy (XPS) analysis was conducted on a Thermo Scientific K-Alpha XPS system (Thermo Fisher Scientific, UK) equipped with a microfocused, monochromatic Al Kα X-ray source. AvaSpec-2048 TEC spectrometer was used to measure UV-vis spectra. Dynamic light scattering (DLS) measurements were performed on a Horiba SZ-100 to obtain the size and ζ-potential of the nanoparticles. To record the CLSM images, confocal laser scanning microscopy (CLSM; Nikon Eclipse Ti, Japan) was utilized. Infrared thermal imaging camera (PLIR A325SC camera, USA) was used to record the temperature changes at tumor region.

Table S1. Fractional atomic coordinates for the unit cell:

Hexagonal P6/m α = β = 90°, γ=120°			
N1	*0.63438*	*0.29755*	*-0.50000*
C2	*0.67073*	*0.30004*	*-0.50000*
O3	*0.59286*	*0.32525*	*-0.50000*
C4	*0.58545*	*0.35677*	*-0.50000*
C5	*0.80280*	*0.45443*	*-0.50000*
C6	*0.84210*	*0.46416*	*-0.50000*
C7	*0.85194*	*0.43540*	*-0.50000*
C8	*0.82228*	*0.39712*	*-0.50000*
C9	*0.78301*	*0.38756*	*-0.50000*
C10	*0.89285*	*0.44464*	*-0.50000*
N11	*0.92142*	*0.47987*	*-0.50000*
C12	*0.96171*	*0.49001*	*-0.50000*
C13	*0.99052*	*0.52903*	*-0.50000*
C14	*1.03010*	*0.53982*	*-0.50000*
H15	*-0.20646*	*0.47870*	*0.50000*
H16	*-0.13520*	*0.49627*	*0.50000*
H17	*-0.17194*	*0.37247*	*0.50000*
H18	*-0.24268*	*0.35547*	*0.50000*
H19	*-0.10201*	*0.41952*	*0.50000*
H20	*-0.01955*	*0.55273*	*0.50000*
H21	*0.05211*	*0.57215*	*0.50000*

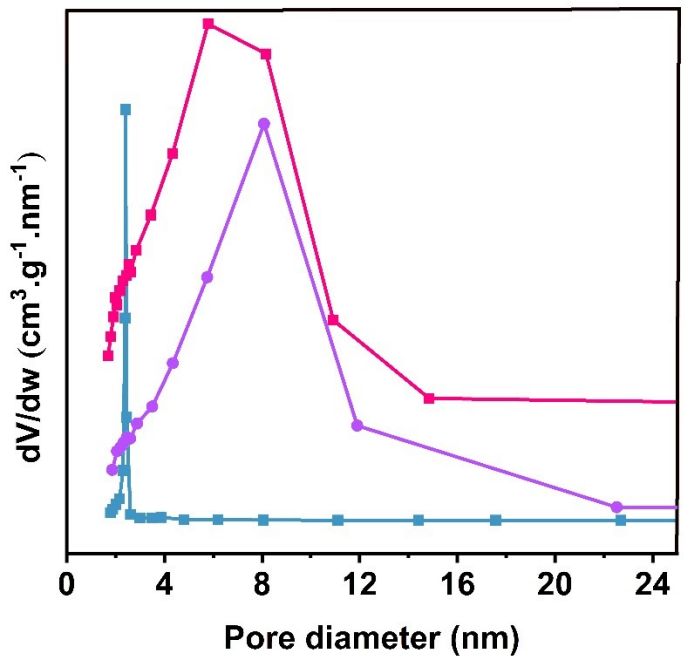


Figure S1. BJH plots of rattle-structured Au@RCOF nanospheres (blue), DOX@RCOF (purple), and DOX@RCOF@PDA (pink).

Table S2. Specific surface area, pore volume and pore diameter of prepared materials.

Samples	S_{BET} (m^2g^{-1})	V (cm^3g^{-1})	D_{BJH} (nm)
RCOF	*1883*	*1.171*	*2.4*
DOX@RCOF	*273*	*0.162*	*2.3*
DOX@RCOF@PDA	*105*	*0.293*	*11*

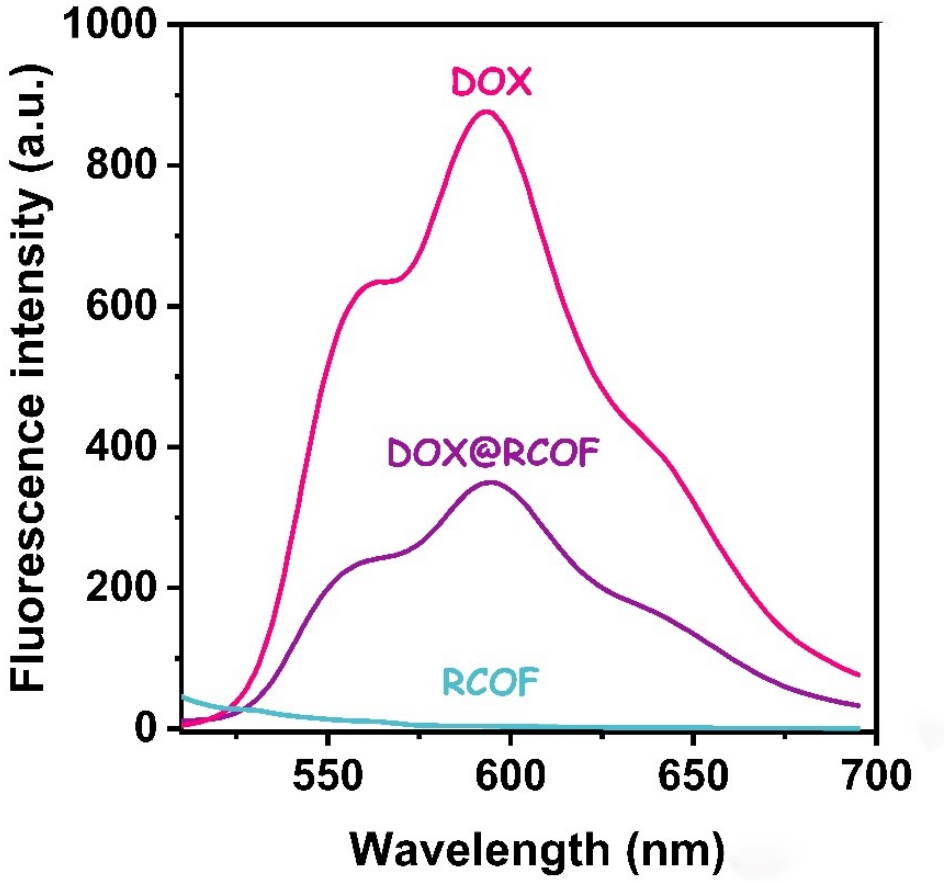
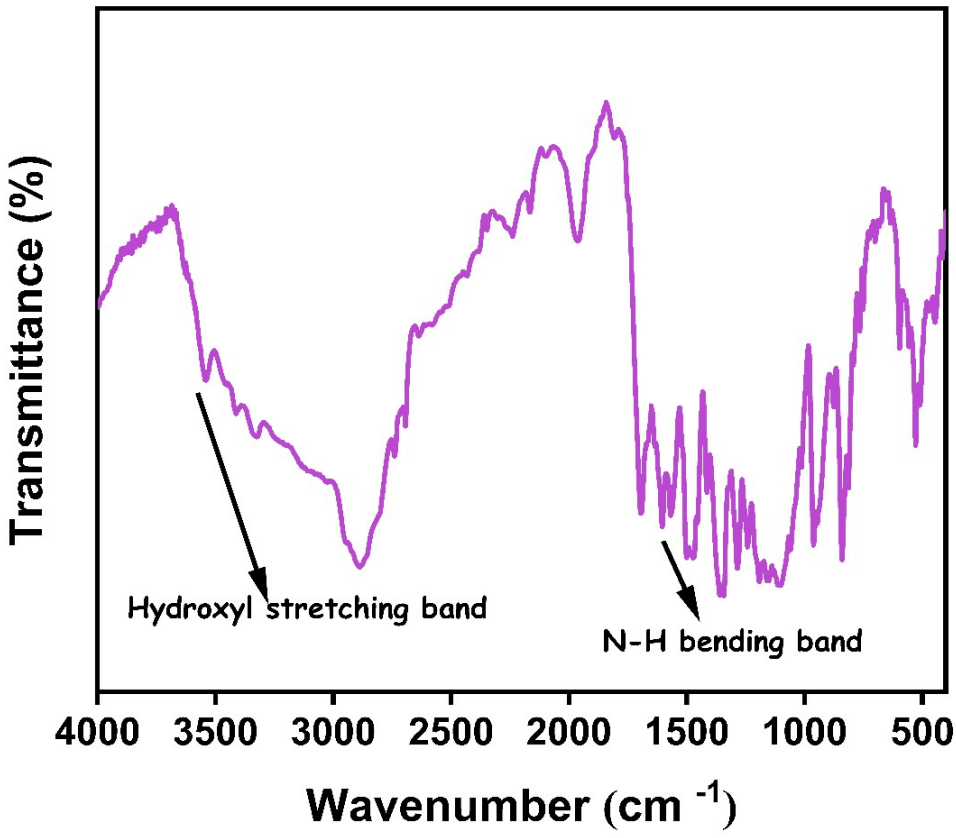
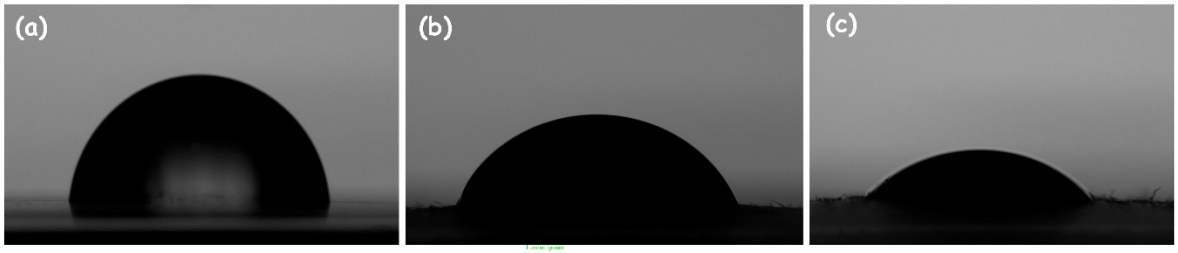


Figure S2. Fluorescence emission spectrum of free DOX (pink), RCOF (blue), and DOX@RCOF (purple). (λ_{ex}= 488 nm, H_2O, pH 7.4).



57

58 **Figure S3.** FT-IR spectra of RCOF@PDA-PEG-FA.



59

60 **Figure S4.** Water contact angle of (a) RCOF, (b) RCOF @PDA, and (c) RCOF @PDA-PEG-FA.

61

62

63

Table S3. Drug loading comparison of Au@RCOF@PDA with previously reported COFs for drug delivery.

Entry	COF Based system	Drug	Drug loading (%)	Morphology	Surface Area $m^2 . g^{-1}$	Ref.
1	PI-3-COF & PI-2-COF	5-Fluorouracil	30	Bulk	1000-1700	[1]
2	Tp-ASH	5-Fluorouracil	12.0	Nanosheet	500	[2]
3	PEG-CCM@APTESCOF-1	Doxorubicin	9.7	Bulk	442	[3]
4	TABP-DMTP	Doxorubicin	32.1	Spherical	1000	[4]
5	BTA-DHDS	Doxorubicin	18	Irregular slice	328	[5]
6	HAPTP	Ibuprofen	20.0	Hollow sphere	955	[6]
7	PDA-TPB	Doxorubicin	17.8	Hollow sphere	1204	[7]
8	DHPA-TAPP	Doxorubicin	10.2	Hollow	246	[8]
9	TAP-DFB	Doxorubicin	14.3	Sea urchin	510	[9]
10	TAPB-DMTP	Rose Bengal	20.6	Nanobowl	---	[10]
11	Tp-Azo	Doxorubicin	20	-----	503	[11]
12	DiSe-Por	Doxorubicin	35.12	Sheet-like	73.5	[12]
13	TAPB-DMTP	Doxorubicin	4.35	Sphere-shaped	198.6	[13]
14	PDA-TFPTA	Doxorubicin & Docetaxel	83.7	Rattle-structure	1883	This work

References

[1] L. Bai, S.Z.F. Phua, W.Q. Lim, A. Jana, Z. Luo, H.P. Tham, L. Zhao, Q. Gao, Y. Zhao, Nanoscale covalent organic frameworks as smart carriers for drug delivery, Chemical communications 52(22) (2016) 4128-4131.
[2] S. Mitra, H.S. Sasmal, T. Kundu, S. Kandambeth, K. Illath, D. Diaz Diaz, R. Banerjee, Targeted drug delivery in covalent organic nanosheets (CONs) via sequential postsynthetic modification, Journal of the American Chemical Society 139(12) (2017) 4513-4520.
[3] G. Zhang, X. Li, Q. Liao, Y. Liu, K. Xi, W. Huang, X. Jia, Water-dispersible PEG-curcumin/amine-functionalized covalent organic framework nanocomposites as smart carriers for in vivo drug delivery, Nature Communications 9(1) (2018) 2785.
[4] S. Liu, C. Hu, Y. Liu, X. Zhao, M. Pang, J. Lin, One-pot synthesis of DOX@ covalent organic framework with enhanced chemotherapeutic efficacy, Chemistry–A European Journal 25(17) (2019) 4315-4319.
[5] C. Wang, H. Liu, S. Liu, Z. Wang, J. Zhang, pH and Redox dual-sensitive covalent organic framework nanocarriers to resolve the dilemma between extracellular drug loading and intracellular drug release, Frontiers in Chemistry 8 (2020) 488.
[6] C. Du, W. Na, M. Shao, S. Shang, Y. Liu, J. Chen, Self-templated synthesis of triphenylene-based uniform hollow spherical two-dimensional covalent organic frameworks for drug delivery, Chemistry of Materials 35(3) (2023) 1395-1403.
[7] T. Huo, Y. Yang, M. Qian, H. Jiang, Y. Du, X. Zhang, Y. Xie, R. Huang, Versatile hollow COF nanospheres via manipulating transferrin corona for precise glioma-targeted drug delivery, Biomaterials 260 (2020) 120305.
[8] S. Yao, M. Zheng, S. Wang, T. Huang, Z. Wang, Y. Zhao, W. Yuan, Z. Li, Z.L. Wang, L. Li, Self-driven electrical stimulation promotes cancer catalytic therapy based on fully conjugated covalent organic framework nanocages, Advanced Functional Materials 32(47) (2022) 2209142.
[9] F. Benyettou, G. Das, A.R. Nair, T. Prakasam, D.B. Shinde, S.K. Sharma, J. Whelan, Y. Lalatonne, H. Traboulsi, R. Pasricha, Covalent organic framework embedded with magnetic nanoparticles for MRI and chemo-thermotherapy, Journal of the American Chemical Society 142(44) (2020) 18782-18794.
[10] S. Zhang, S. Xia, L. Chen, Y. Chen, J. Zhou, Covalent Organic Framework Nanobowls as Activatable Nanosensitizers for Tumor-Specific and Ferroptosis-Augmented Sonodynamic Therapy, Advanced Science 10(6) (2023) 2206009.
[11] T. Li, D. Wang, Z. Guo, L. Lin, M. Meng, C. Liu, K. Hao, X. Pang, H. Tian, X. Chen, Biodegradable covalent organic frameworks achieving tumor micro-environment responsive drug release and antitumor treatment, Biomaterials Science 11(19) (2023) 6524-6536.
[12] H. Lou, L. Chu, W. Zhou, J. Dou, X. Teng, W. Tan, B. Zhou, A diselenium-bridged covalent organic framework with pH/GSH/photo-triple-responsiveness for highly controlled drug release toward joint chemo/photothermal/chemodynamic cancer therapy, Journal of Materials Chemistry B 10(39) (2022) 7955-7966.
[13] S. Wang, Y. Pang, S. Hu, J. Lv, Y. Lin, M. Li, Copper sulfide engineered covalent organic frameworks for pH-responsive chemo/photothermal/chemodynamic synergistic therapy against cancer, Chemical Engineering Journal 451 (2023) 138864.