Supporting Information

DNA-Mimicking Metal-Organic Frameworks with Accessible Adenine Faces for Complementary Base Pairing

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Experimental Section

**Materials.** All reagents and solvents were purchased from commercial sources and used without further purification. Linker L has been synthesized from previously reported procedure.¹

**Physical Measurements.** The Fourier transform infrared (FTIR) spectra were recorded using a Thermo Scientific spectrometer (Nicolet iS10). PXRD patterns were recorded using Cu-Kα radiation (1.5418 Å) on a Bruker D8 Advance diffractometer. Thermogravimetric analysis (TGA) measurements were carried out on a Q5000 (TA Instruments) and the samples were heated from room temperature to 600 °C at a rate of 5 °C min⁻¹ under N₂ atmosphere. Low-pressure gas adsorption measurements were performed using a Microactive 4.0 ASAP 2020 instrument. To remove all guest solvents in the framework, the fresh samples were first solvent-exchanged with dry acetone at least 10 times within 2 days and degassed at 343 K for 12 h. The sorption measurement was maintained at 77 K under liquid nitrogen. Room temperature CO₂ Gas sorption experiments were performed using a Micromeritics ASAP 2020 instrument. Solid state NMR spectra were acquired on an Avance III 600 WB spectrometer equipped with a 3.2 mm low-temperature CPMAS probe capable of spinning speed up to 24 kHz. Transmission electron microscopy (TEM) was conducted on FEI Titan-ST electron microscope. Dynamic light scattering (DLS) and zeta potential analysis were performed using a Malvern Nano ZS instrument at 25 °C.

**Single Crystal X-ray Diffraction.** The crystal and refinement data for KBM-1 and 2 were collected in Table S1 and Table S2. In this case, a crystal of suitable size was selected from the mother liquor and immersed in paratone oil and then it was mounted on the tip of glass fiber and cemented using epoxy resin. Single crystal X-ray data were collected at 120 K on a Bruker SMART APEX II CCD diffractometer using graphite-monochromated Mo-Kα radiation (0.71073 Å). The linear absorption coefficients, scattering factors for the atoms and the anomalous dispersion corrections were taken from International Tables for X-ray Crystallography. The data integration and reduction were processed with SAINT
software. An empirical absorption correction was applied to the collected reflections with SADABS using XPREP. The structure was solved by the direct method using SHELXTL and was refined on $F^2$ by a full-matrix least-squares technique using the SHELXL-2014 program package. For all the cases, non-hydrogen atoms were refined anisotropically. Attempts to identify the highly disordered solvent molecules were failed. Instead, a new set of $F^2$ (hkl) values with the contribution from the solvent molecules withdrawn were obtained by the SQUEEZE procedure implemented in PLATON. The cationic guests $\text{Me}_2\text{NH}_2^+$ could be located in the channels from Difference Fourier Map for KBM-1.

**Computational Details:** The initial structure of the KBM-1 and KBM-2 are prepared using the experimentally obtained crystal structures. non-coordinating solvent DMF molecules are removed from the KBM-1 model, whereas DMF and H$_2$O molecules coordinating to Zn were left in the KBM-2 model. The geometries of KBM-1 and KBM-2 were optimized using self-consistent-charge density-functional tight-binding (DFTB) method with the third-order expansion as implemented in the DFTB+ package version 18.2. The 3ob parameter set with Hubbard parameters, -0.1492 for C, -0.1857 for H, -0.1575 for O, -0.03 for Zn and -0.1535 for N were used, and Grimme’s D3 type dispersion was included. Since the MOF is an infinite system, periodic boundary condition was applied for the both frameworks, and the cell parameters were fixed to the experimental values during the optimizations. After two Thy are introduced into the pore channels of KBM-1 and KBM-2, we again optimized Thy@KBM-1 and Thy@KBM-2 with the fixed cell parameter as well.

To shed light on the noncovalent interactions (NCI) between the Thy and KBM frameworks of Thy@KBM-1 and Thy@KBM-2, NCIPlot software was used. The relation between the electron density ($\rho$) and its reduced density gradient ($s$) is as follows,

$$s = \frac{1}{2(3\pi^2)^{1/6}} \left| \nabla \rho \right| \frac{\rho^{1/6}}{\rho^{1/6}},$$

where $\nabla \rho$ is the gradient of $\rho$. The promolecular approach has been considered for the computations in this work. The sign($\lambda_2$)$\rho$ as the reduced density gradient ($s$) is plotted using VMD visualization package.
**MTT assay for cytotoxicity evaluation:** HeLa and HDF cells were seeded in a 96-well plate at 1X10^4 cells/well. Cells were incubated at 37 °C, 5% CO₂ for 24 hours, then different concentrations of KBM-1, KBM-2, BioMOF-1, and ZIF-8 were added to cells. Cells in media containing MOFs were incubated for 24 hours. Then, the MTT assay was performed following manufacturer protocol (BioVision #K299-1000). Three biological replicates were analyzed using Bio-Rad XMark microplate spectrophotometer. Same procedure was used to evaluate control ssDNA, anti-PCNA aptamer, KBM-2, ssDNA KBM-2, control ssDNA@KBM-2 and Anti-PCNA@KBM-2. The optimal concentration of free ssDNA control and Anti-PCNA was calculated based on KBM-2 ssDNA loading efficiency (~41%) as follows:

Amount of DNA to be added to cell (μg) = (DNA in loading reaction in μg x 0.41) / (5000 / corresponding KBM-2 in μg)

**KBM ssDNA loading:** 5mg of KBM-1, Thy@KBM-1, KBM-2, Thy@KBM-2 or BioMOF-1 were prepared in 250 μl of 20mM Tris-HCl pH 7 and 10 μM of DNA, were mixed. The mixture was incubated for 4 hours at 25 °C, 900 RPM. Then BioMOFs were centrifuged at 3000 RPM For 10 mins. Supernatants were collected for analysis of unloaded DNA. KBMs were washed twice with the same buffer and vacuum dried. KBMs were resuspended in 250 μl of 20 mM Tris-HCl pH 7 buffer and boiled at 95 °C for 5 mins. DNA retention of KBMs was analyzed by loading 20μl of Boiled KBMs and 5μl of input (10μM DNA in 250μl 20mM Tris-HCl pH 7) to 2% agarose gel electrophoresis. Agarose gel was subjected to electrophoresis at 80 V for 90 mins. In addition, we analyze the percentage of unloaded DNA in supernatant of loading reaction using ssDNA and dsDNA quantitative assays (Thermofisher scientific # O11492 and Q33120) following the manufacturer protocol. Percentage of Loaded DNA was calculated as following 100-% unloaded= % loaded DNA.

Loaded oligonucleotides
*Control ssDNA and DsDNA (5'-
ATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATC-3')
* Poly CT (5’-CTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCT-3’).
* Poly CA (5’-CACACACACACACACACACACACACACACACACACACACACACACACACACACACACACACACAC-3’).
* Anti-PCNA Aptamer (5’-CATGCTTCCCCAGGGAGATGCCTATGGTCCCCGCGTAGGGTCGAGCTCA-3’)19

**ssDNA release analysis.** KBMs loaded with ssDNA labeled with Fluorescein amidite (FAM) were redispersed in 250μl of 20 mM Tris-HCl at either pH-7 or pH-5.5 incubated at 25 °C, 900 rpm. Release profiles were analyzed by quantifying the FAM signal in the release buffer over 24 hours. We quantify FAM from release buffer collected at time points (0.5, 1, 2, 4, 6, 12, 24 hours) using Tecan plate reader. Intensity of time point were the divided by 41% of input intensity in case of **KBM-2** and 13% for **KBM-1**.

**DNase I digestion Reaction:** To normalize ssDNA input, we added amounts of **KBM-1** and **KBM-2** that load the same amount of DNA as we have in the free DNA control. 1μM of free ssDNA, 3.8mg of ssDNA@**KBM-1** (5mg loads 10 μM X 13% = 1.3 μM) and 1.2 mg ssDNA@**KBM-2** (5 mg loads 10 μM X 41% = 4.1 μM) were resuspended in 100 ul of DNase I buffer (10 mM Tris-HCl 2.5 mM MgCl2 0.5 mM CaCl2 pH 7 @37 °C) and divided into two tubes. One tube was kept as a control for DNase I independent degradation and 1 μl of 1U/μl DNase I (Thermo scientific # K0441). Digestion reaction was performed for 30 mins and then enzyme was deactivated by heating at 70 °C for 5 mins. 20 μl of the reaction was analyzed on 2% Agarose gel.

**Cellular uptake of KMB-2 and ssDNA KBM-2**

5X10^4 HeLa cells were seeded in 4-well slide. Cells were left to grow for overnight. Cells were treated with PBS (control), Rhodamine B **KBM-2** (100μg/ml) and FAM-ssDNA@Rhodamine B **KBM-2** (100μg/ml), free FAM labelled anti-PCNA (0.319 μg). Cell were washed and fix with 4% PFA after 4 hours. Cells were then stained with DAPI and imaged using Leica TCS LSI confocal microscope at KAUST core lab.
### Table S1. Crystal Data and structure refinements for *KBM-1*

| Property                        | Value                          |
|---------------------------------|--------------------------------|
| **Empirical formula**           | C$_{37}$ H$_{38}$ N$_{24}$ O$_{7}$ Zn$_{3}$ |
| **Formula weight**              | 1127.02                        |
| **Temperature (K)**             | 120(1)                         |
| **Radiation**                   | Mo-Kα                          |
| **Wavelength (Å)**              | 0.71069 Å                      |
| **Crystal system**              | orthorhombic                   |
| **Space group**                 | Pbcn                           |
| **a [Å]**                       | 29.0608(7)                     |
| **b [Å]**                       | 14.9493(3)                     |
| **c [Å]**                       | 23.5731(5)                     |
| **α[°]=β[°]=γ[°]**              | 90.00                          |
| **Volume [Å$^3$]**              | 10241.1(4)                     |
| **Z**                           | 8                              |
| **Density (calculated) [Mg/m$^3$]** | 1.462                       |
| **Absorption coefficient [mm$^{-1}$]** | 1.463                   |
| **F(000)**                      | 4592                           |
| **Ref. used [I > 2σ(I)]**       | 11119                          |
| **Independent reflections**     | 15644                          |
| **R$_{int}$**                   | 0.1066                         |
| **Refinement method**           | full-matrix least squares on F$^2$ |
| **GOF**                         | 1.069                          |
| **Final R indices [I > 2σ(I)]** | $R_1$=0.0499; $wR_2$=0.1484   |
| **R indices (all data)**        | $R_1$=0.0746; $wR_2$=0.1591   |
Figure S1. Comparison in the coordination environment between KBM-1 (a) and ZIF-8 (b) (Color code; Carbon: gray, hydrogen: white, oxygen: red, nitrogen: blue, zinc: dark yellow).

Figure S2. Representation of the packing diagram of KBM-1 having the solvent accessible volume around 39% of the total volume. The cations and guest solvent molecules are omitted for clarity.
Figure S3. Two types of binding environment in the crystal structure of KBM-1.

Figure S4. Due to having the unique coordination environment between Zn and Adenine unit, the H-bonding interaction resemblance the Watson-Crick model in DNA molecule.

Figure S5. FT-IR spectra of the as synthesized KBM-1.
Figure S6. Comparison of the PXRD pattern of KBM-1 as synthesized (black) with simulated version (pink) and its air stability for 1 month (blue).

Figure S7. PXRD patterns of KBM-1: experimental and after immersion in water for one month.
Figure S8. PXRD patterns of KBM-1: chemical stability test towards acidic and basic conditions for 24 hours. PBS concentration = 10mM, pH adjusted with HCl.

Figure S9. Thermo gravimetric analysis (TGA) data of the as synthesized KBM-1.
Figure S10. PXRD patterns of KBM-1 (a) and KBM-2 (b) after solvent exchange and degassing.

Figure S11. N₂ sorption at 77 K/1 bar of KBM-1.

Figure S12. The CO$_2$ sorption isotherm of KBM-1 and KBM-2 at 298 K.

Figure S13. (a) Pore dimensions of KBM-1 after considering VDW interactions. (b) Packing diagram showing DMF solvent molecules (CPK model) inside the pore. (c) Dimethyl ammonium cations sitting inside the interlayer space of the framework.
Figure S14. SEM (top) and TEM (bottom) images for KBM-1 particles.

Figure S15. Particle size statistics analysis of KBM-1.
Figure S16. SEM images of KBM-1 particles after incubation (16 hr) in (a) water, (b) media, (c) at pH 7 and (d) at pH 8.

Table S2. Crystal data and structure refinements for KBM-2.

| Identification code | KBM-2 |
|---------------------|-------|
| Empirical formula   | 'C_{82} H_{69} N_{26} O_{37} Zn_{8}' |
| Formula weight      | 2533.78 |
| Temperature (K)     | 150(2) |
| Radiation           | Mo-Kα |
| Wavelength (λ)      | 0.71073 |
| Crystal system      | Triclinic |
| Space group         | P-1 |
| a [Å]               | 17.716(9) |
| b [Å]               | 23.726(13) |
| c [Å]               | 25.856(15) |
| α [°]               | 115.39(2) |
| Parameter                        | Value             |
|---------------------------------|-------------------|
| $\beta$ [°]                    | 92.62(4)          |
| $\gamma$ [°]                   | 90.210(17)        |
| Volume [Å$^3$]                 | 9805(9)           |
| $Z$                             | 2                 |
| Density (calculated) [Mg m$^{-3}$] | 0.8581           |
| Absorption coefficient [mm$^{-1}$] | 1.012            |
| $F$(000)                       | 2564              |
| Refl. used [$I > 2\sigma(I)$]  | 9640              |
| Independent reflections        | 31589             |
| $R_{\text{int}}$               | 0.1611            |
| Refinement method              | full-matrix least squares on $F^2$ |
| GOF                            | 0.9050            |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0864; \, wR_2 = 0.1916$ |
| $R$ indices (all data)         | $R_1 = 0.2017; \, wR_2 = 0.3004$ |

**Figure S17.** Coordinated Solvent molecules which are making open metal Zn(II) sites upon activation for KBM-2.
Figure S18. Pore dimensions of KBM-2 after considering VDW interactions.

Figure S19. N₂ sorption at 77 K of KBM-2.
**Figure S20.** Thermo gravimetric analysis (TGA) data of the as synthesized **KBM-2**.

**Figure S21.** Comparison of the PXRD pattern of **KBM-2** as synthesized (black) with its water stability for 24 hours (red).
Figure S22. PXRD patterns of **KBM-2**: chemical stability test towards acidic and basic conditions for 24 hours. PBS concentration = 10mM, pH adjusted with HCl.

Figure S23. FTIR spectra of **KBM-2** and **Thy@KBM-2**.
Figure S24. SEM (left) and TEM (right) images for KBM-2.

Figure S25. Particle size statistics analysis of KBM-2.
Figure S26. SEM images of KBM-2 particles after incubation (16 hr) in (a) water, (b) media, in PBS (c) pH 7 and (d) in pH 8.

Figure S27. PXRD patterns of (a) KBM-1 and (b) KBM-2 after Thy loading experiments.
Figure S28. Plots of the NCI surfaces of Thy@KBM-1. Blue, green, and red regions indicate strong attractive interaction, weak interaction, repulsive interactions, respectively. The plotted range is -0.05 < sign(\(\lambda_2\)) < 0.05, and the plotted isosurface of reduced density gradient is 0.5. The gray, white, red, blue, and silver of atoms indicate C, H, O, N, and Zn, respectively.

Figure S29. Plots of the NCI surfaces of Thy@KBM-2. Blue, green, and red regions indicate strong attractive interaction, weak interaction, repulsive interactions, respectively. The plotted range is -0.05 < sign (\(\lambda_2\)) < 0.05, and the plotted isosurface of reduced density gradient is 0.5. The gray, white, red, blue, and silver of atoms indicate C, H, O, N, and Zn, respectively.
**Figure S30.** Comparison of N$_2$ sorption isotherm of KBM-1 and Thy loaded KBM-1.

**Figure S31.** Comparison of the FT-IR spectra of KBM-1 and Thy@KBM-1.
Figure S32. Solid state $^{13}$C NMR spectra (CP-MAS) of KBM-1.

Figure S33. Solid state $^{13}$C NMR spectra (CP-MAS) of Thy@KBM-1.
Figure S34. Solid state $^{13}$C NMR spectra (CP-MAS) of KBM-2.

Figure S35. Solid state $^1$H NMR spectra (CP-MAS) of KBM-1.
Figure S36. Solid state $^1$H NMR spectra (CP-MAS) of Thy@KBM-1.

Figure S37. Solid state $^1$H NMR spectra (CP-MAS) of KBM-2.
Figure S38. Solid state $^1$H NMR spectra (CP-MAS) of Thy@KBM-2.

Figure S39. Analysis of KBM-2 and ZIF-8 loading efficiency of Anti-PCNA aptamer.
**Figure S40.** Cytotoxicity analysis of **KBM-1** and **KBM-2** to HeLa and HDF cells using MTT assay ($n = 3$).

**Table S3.** Zeta potential analysis of **KBM-1**, **KBM-2** and ssDNA **KBM-2**.

| KBM           | Zeta potential |
|---------------|----------------|
| KBM-1         | -6.8           |
| KBM-2         | 0.47           |
| ssDNA@KBM-2   | -11.34         |
Figure S41. Gel agarose analysis of DNase I digestion reaction of ssDNA loaded to KBM-1 and KBM-2.

Figure S42. ssDNA release from KBM-1 and KBM-2 over 24 hours incubation in Tris-HCl buffer at pH 7 and pH 5.5.
Figure S43. PXRD patterns of **KBM-1** (a) and **KBM-2** (b) chemical stability test towards different acidic media conditions for 24 hours. PBS concentration = 10mM, pH adjusted with HCl.

Figure S44. Dynamic light scattering (DLS) study of **KBM-1** and **KBM-2** in aqueous media (16 hr).
Figure S45. Analysis of KBM-2 cellular uptake and ssDNA delivery using confocal microscopy.

Figure S46. Analysis of FAM labelled Anti-PCNA cellular uptake using confocal microscopy.
Figure S47. Cytotoxicity evaluation of KBM-2, cDNA@KBM-2 and Anti-PCNA@KBM-2 using MTT assay ($n = 3$).

Figure S48. Cytotoxicity analysis of control ssDNA and Anti-PCNA to HeLa MTT assay ($n = 3$).
Table S4. Selected bond distances and angle observed in KBM-1

| Bond | Zn1 – O1  | Zn2 – N2  | Zn2 – N9  | Zn3 – O5  | Zn3 – N11 | Zn3 – N17 |
|------|-----------|-----------|-----------|-----------|-----------|-----------|
|      | 1.943(2)  | 2.009(2)  | 2.023(2)  | 1.947(2)  | 1.977(2)  | 1.991(2)  |
| Zn1 – N1 | 1.977(2)  |           |           |           |           |           |
| Zn1 – N6 | 1.997(2)  |           |           |           |           |           |
| Zn1 – N12 | 2.009(2)  |           |           |           |           |           |
| Zn2 – O4 | 1.9350(19)|           |           |           |           |           |
| Zn2 – N16 | 1.974(2)  |           |           |           |           |           |

| Angle | O1– Zn1– N1 | N16 — Zn2 — N9 | O1 ─ Zn1 ─ N6 | N2 ─ Zn2 ─ N9 | O4 ─ Zn2 ─ N9 | N1 ─ Zn1 ─ N12 | O5— Zn3 ─ N11 | N2 ─ Zn2 ─ N9 | O4 ─ Zn2 ─ N2 | N11 ─ Zn3 ─ N17 | O5 ─ Zn3 ─ N17 | N7─ Zn3 ─ N17 | N16 — Zn2 — N2 | N7— Zn3 — N17 |
|-------|-------------|----------------|--------------|--------------|--------------|----------------|---------------|--------------|---------------|----------------|----------------|--------------|----------------|---------------|
|       | 108.17(9)   | 112.78(9)     | 114.56(10)   | 107.27(9)    | 114.27(10)   | 111.03(9)     | 107.69(10)    | 110.92(10)   | 113.23(9)    | 114.05(10)     | 114.05(10)     | 114.05(10)   | 114.05(10)     |

References:

1) Lü, J.; Perez-Krap, C.; Suyetin, M.; Alsmail, N. H.; Yan, Y.; Yang, S.; Lewis, W.; Bichoutskaiia, E.; Tang, C. C.; Blake, A. J.; Cao, R.; Schröder, M. J. Am. Chem. Soc. 2014, 136, 12828.
2) SAINT. Bruker AXS. Inc, Madison, Wisconsin, USA, 2014.
3) SADABS. G. M. Sheldrick. University of Gottingen, Germany, 2008.
4) XPREP, 5.1 ed. Siemens Industrial Automation Inc., Madison, WI, 1995.
5) Sheldrick, G. M. SHELXTL ™Reference Manual: version 5.1, Bruker AXS, Madison, WI, 1997.
6) Sheldrick, G. M. Crystal Structure Refinement with SHELXL. Acta Cryst C, 2015, 71, 3–8.
7) WinGX. L. J. Farrugia, J. Appl. Cryst. 2012, 45, 849-854.
8) Spek, A. L. Single-crystal Structure Validation with the Program PLATON. J. Appl. Crystallogr. 2003, 36, 7–13.
9) M. Elstner, D. Porezag, G. Jungnickel, J. Elsner, M. Haugk, Th. Frauenheim, S. Suhai, and G. Seifert, Phys. Rev. B, 1998, 58, 7260–7268.
10) Y. Yang, H. Yu, D. York, Q. Cui, M. Elstner, J. Phys. Chem. A 2007, 111, 10861–10873.
11) B. Aradi, B. Hourahine, and Th. Frauenheim, J. Phys. Chem. A, 2007, 111, 5678–5684.
12) M. Gaus, A. Goez, M. Elstner, J. Chem. Theory Comput., 2013, 9, 338–354.
13) S. Grimmea, J. Antony, S. Ehrlich, H. Krieg, J. Chem. Phys., 2010, 132, 154104.
14) E. R. Johnson, S. Keinan, P. M-Sanchez, J. Contreras-García, A. J. Cohen, W. Yang, J. Am. Chem. Soc. 2010, 132, 6498–6506.
15) J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, W. Yang, J. Chem. Theo. Comput. 2011, 7, 625–632.
16) W. Humphrey, A. Dalke, K. Schulten, J. Mol. Graphics. 1996, 14, 33–38.
17) An, J.; Geib, S. J.; Rosi, N. L. J. Am. Chem. Soc. 2009, 131, 8376.
18) Banerjee, R.; Phan, A.; Wang, B.; Knobler, C.; Furukawa, H.; O'Keeffe, M.; Yaghi, O. M. Science 2008, 319, 939–943.
19) E. Kowalska, F. Bartnicki, R. Fujisawa, P. Bonarek, P. Hermanowicz, T. Tsurimoto, K. Muszynska, W. Strzalka, Nucleic Acids Res. 2018, 46, 25–41.