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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.202010714

Link to VoR: https://doi.org/10.1002/anie.202010714
Ligand-dependent activity engineering of glutathione peroxidase-mimicking MIL-47(V) metal–organic framework nanzyme for therapy

Jiangjixing Wu,[a]† Yijun Yu,[b]† Yuan Cheng,[a]† Chaoqun Cheng,[a] Yihong Zhang,[a] Bo Jiang,[c]† Xiaozhi Zhao,[c]† Leiyang Miao,[b]† and Hui Wei*[a,d]

Abstract: Glutathione peroxidase (GPx) plays an important role in maintaining the reactive oxygen metabolic balance, yet limited GPx-mimicking nanzymes are currently available for in vivo therapy. Herein, a ligand engineering strategy is developed to modulate the GPx-mimicking activity of a metal–organic framework (MOF) nanzyme. With different substituted ligands, the GPx-mimicking activities of MIL-47(V)-X (X = F, Br, NH2, CH2, OH, and H) MOFs are rationally regulated. With the best one as an example, both in vitro and in vivo experiments reveal the excellent antioxidant ability of MIL-47(V)-NH2, which alleviates inflammatory response effectively for both ear injury and colitis, better than less-active MIL-47(V). This study proves that high-performance GPx-mimicking nanzymes can be rationally designed by a ligand engineering strategy, and that structure-activity relationships can direct the in vivo therapy. Therefore, it not only enriches the research of nanzymes, but also expands the range of the biomimetic MOFs and knowledge-enabled nanomedicine.

Introduction

Reactive oxygen species (ROS), such as superoxide and hydrogen peroxide (H2O2), are well-known to contribute to various intracellular functions. Therefore, any cellular redox imbalance with elevated levels of ROS would cause oxidative damage to the living cells and lead to various disorders in the long term.[1] Among cellular ROS, H2O2 plays a crucial role. H2O2 is not only longer lived as compared to superoxide, it can also easily diffuse or transfer across lipid membranes and is a precursor to the highly damaging hydroxyl radical.[1,2] Consequently, modulating intracellular ROS levels, especially H2O2 level, below the toxic threshold is important for protecting the cells from oxidative damage. In biological systems, several antioxidant enzymes, including glutathione peroxidase (GPx) and catalase, are capable of converting H2O2 to benign H2O to limit the harmful effects. Of these, GPx has received a lot of attentions, leading to its investigation in many disease therapies, such as cancer, inflammation, and cardiovascular disease.[3]

Although GPx plays a critical role in maintaining intracellular redox balance, it suffers from some limitations common to most natural enzymes, namely low stability and poor availability, which have limited its practical biomedical applications. To overcome these limitations, considerable effort has been devoted to developing GPx mimics.[4] Of these mimics, nanzymes, nanomaterials with enzyme-mimicking activities, have attracted much attention in recent years due to their exceptional advantages, such as low cost, large surface area, and robustness under extreme conditions.[5] In fact, several types of nanzymes, including peroxidase-, oxidase-, and catalase-mimicking nanzymes, have been developed and applied in bioanalysis and diagnosis, as well as numerous disease therapies.[6] However, few applications of GPx-mimicking nanzymes in therapy have been reported despite the critical role GPx plays in maintaining the reactive oxygen metabolic balance and protecting against injury by removing the excess H2O2. The reason for this relative dearth of applications is that limited types of nanzymes (only vanadium, manganese and selenium-containing nanzymes listed in Table S1 in the Supporting Information) were reported to exhibit GPx-mimicking activities.[7] And the moderate activities required them to couple with other antioxidants to maintain the reactive oxygen metabolic balance in vivo.[8] The discovery of highly efficient GPx-mimicking V2O5 nanozymes was a breakthrough,[7a,8] though the exploration of high-performance GPx-mimicking nanozymes is...
still in an early stage and application of high-performance GPx-mimicking nanozymes alone for in vivo therapy has not yet been accomplished.

Metal–organic framework (MOF) is a class of porous materials hybridized by metal nodes and multidentate organic linkers. MOFs possess large surface areas and highly modular structure making them widely useful in gas adsorption, chemical sensing, heterogeneous catalysis and so on. Recently, biomimetic MOFs have attracted great attention and have been actively explored in mimicking hydrolase, peroxidase, and so on. However, no MOFs have been reported to specifically mimic GPx nor applied alone as antioxidation defense against inflammation in vivo. Herein, inspired by protein engineering, we reason that the shared metal–ligand coordination of natural metalloenzymes and MOFs will enable us to rationally modulate the enzyme-mimicking activity of MOFs via a ligand engineering strategy. Specifically, we intentionally modulated the GPx-mimicking activities of MIL-47(V)-X (MIL stands for Materials of Institute Lavoisier) MOFs by varying the substitution of H in 1,4-benzenedicarboxylic acid (BDC) ligand with F, Br, NH₂, CH₃, and OH. The corresponding isostuctural MOFs are named as MIL-47(V)-H, MIL-47(V)-F, MIL-47(V)-Br, MIL-47(V)-NH₂, MIL-47(V)-CH₃, and MIL-47(V)-OH, respectively (Figure 1). The substitution tunes the electronic properties of the BDC ligand and thus fine-tunes the enzymatic activities. Among these isostuctural MOFs of MIL-47(V)-X, MIL-47(V)-NH₂ exhibits the highest GPx-mimicking activity. Further, its excellent in vitro antioxidation ability in reducing ROS level and in vivo protection from ear-inflammation and colitis are also demonstrated.

Results and Discussion

MIL-47(V)-X (X = F, Br, NH₂, CH₃, OH, and H) is assembled by vanadium metal nodes and terephthalate linkers (substituted terephthalate linkers, Figure 1), forming 1-D cavities in the final framework. The synthesis of MIL-47(V)-X MOFs was carried out by a microwave method as previously reported. Then various characterizations were performed for MIL-47(V)-X MOFs. As shown in Figure 2A, the powder X-ray diffraction (PXRD) patterns of MIL-47(V)-X MOFs were in accordance with literature results, conforming the successful preparation of the MIL-47(V)-X MOFs. The thermogravimetric analysis (TGA) in Figure S1A in the Supporting Information indicated that the stability of all the MIL-47(V)-X MOFs could be guaranteed to at least 300 °C, with little difference between the substituted linkers. Moreover, the ultraviolet–visible (UV-vis) absorption spectra of MIL-47(V)-X MOFs were also recorded and depicted in Figure S1B. The specific peak-maxima around ~350 nm and 400 nm for the MIL-47(V)-NH₂ and MIL-47(V)-OH are induced by the introduction of the amino and hydroxyl groups on the BDC linker, respectively, in accordance with previous studies. The X-ray photoelectron spectroscopy (XPS) analysis confirmed the presence of elements V, C, and O in all of the MOFs and N, F, and Br in the NH₂-, F-, and Br-substituted MOFs (Figure S1C). Their morphologies were determined by using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis. As shown in Figure S2 with different magnifications, the synthesized MOF particles are discrete with different sizes of ~ 20–100 nm.
Figure 1. Schematic illustration of the synthesis of rationally designed GPx-mimicking MIL-47(V)-X MOF nanozymes for anti-inflammation therapy. Substituted terephthalate linkers (X = F, Br, NH$_2$, CH$_3$, OH, and H) were used to coordinate with vanadium metal ions to form isostructural MIL-47(V)-X MOFs with modulated GPx-mimicking activities. Among them, MIL-47(V)-NH$_2$ had the highest GPx-mimicking activity and was selected for further investigation in anti-inflammation therapy. Its excellent antioxidation ability can effectively attenuate inflammation in both ear-inflammation and colitis models.
After the successful fabrication of MIL-47(V)-X MOFs, their GPx-mimicking catalytic activities were investigated through monitoring the absorbance change at 340 nm of nicotinamide adenine dinucleotide phosphate (NADPH). In this assay, MIL-47(V)-X catalytically couples the reduction of H$_2$O$_2$ to the oxidation of glutathione (GSH) to glutathione disulfide (GSSG). Glutathione reductase (GR) then consumes NADPH to catalyze the reduction of GSSG back to GSH, leading to the observed decrease in the characteristic absorption peak of NADPH (Figure 2B). As shown in Figure 2C and 2D, each of the MIL-47(V)-X MOFs exhibited GPx-mimicking activities, with MIL-47(V)-NH$_2$, MIL-47(V)-F, and MIL-47(V)-Br having the highest activities among these isostructural MOFs. Of these, MIL-47(V)-NH$_2$ showed a slightly higher activity than the other two. The superoxide dismutase (SOD)-mimicking and hydroxyl radical scavenging activities of these isostructural MIL-47(V)-X MOFs were also systematically evaluated. Under the same concentration of MIL-47(V)-X MOFs as GPx-mimicking activity test, very low SOD-mimicking activities and negligible hydroxyl radical scavenging activities were observed (Figure S3A and B). These results suggest that MIL-47(V)-X MOFs could effectively eliminate H$_2$O$_2$ selectively over superoxide or hydroxyl radicals.

To confirm that the GPx-mimicking activity was from the metal nodes of MOFs rather than the substituted ligands, control experiments with only the ligands were performed under the same condition. As shown in Figure S4, the ligands possess no innate catalytic activity. It is apparent that all the metal nodes in MIL-47(V)-X MOFs rather than the corresponding substituted ligands contributed to the catalytic activities, and large channels present in MIL-47(V) made the metal nodes accessible to the substrates. Thus, the observed catalytic activity difference of MIL-47(V)-X MOFs was inferred to be due to the substitution-induced electronic effect on the metal nodes. XPS analysis in Figure S1D and Table S2 revealed that though V oxidation state in all MIL-47(V)-X MOFs was V(III), the -NH$_2$-, -F, and -Br substitution made the V less oxidized than that in -OH, -CH$_3$, and -H. According to the previous studies, interaction with H$_2$O$_2$ to form the vanadium peroxido intermediate was the first and key step for the catalytic reaction. Thus, compared with MIL-47(V)-OH, MIL-47(V)-CH$_3$, and MIL-47(V)-H, the less oxidized V in MIL-47(V)-NH$_2$, MIL-47(V)-F, and MIL-47(V)-Br is more capable of reacting with H$_2$O$_2$. 

![Figure 2](https://example.com/figure2.png)
leading to an enhanced catalytic activity. To conclude this part, MIL-47(V)-X MOFs were first reported to behave as GPx-mimicking nanozymes, and high-performance MIL-47(V)-NH₂ was selected for further biological study.

Prior to employing MIL-47(V)-NH₂ in biological experiments, we investigated the effects of substrate and catalyst concentration on the reaction kinetics. As shown in Figure S5, the GPx-mimicking activity increases gradually with increasing concentration of GSH (0–2 mM), H₂O₂ (0–400 µM), and MIL-47(V)-NH₂ (0–80 µg mL⁻¹). The apparent steady-state kinetic parameters (Table S1), the Michaelis constant Kₘ, and the maximal reaction velocity vₘₐₓ, for GSH and H₂O₂ are ~2.85 mM and ~0.0035 mM s⁻¹, ~0.003 mM and ~0.0019 mM s⁻¹, respectively. Based on these results, the 20, 50, and 80 µg mL⁻¹ concentrations of MIL-47(V)-NH₂ were selected for the further in vitro and in vivo studies.

![Figure 3](image-url)

**Figure 3.** (A) Schematic illustration of cytoprotection. (B) Cell viability under different concentrations of MIL-47(V)-NH₂ MOF. Data are expressed as mean ± standard error of 3 experiments. **** means P < 0.0001 vs. no MIL-47(V)-NH₂ MOF-treated group. (C) The cytoprotection ability of MIL-47(V)-NH₂ MOF. Data are expressed as mean ± standard error of 3 experiments. *** means P < 0.001 vs. control group. ** means P < 0.01 vs. H₂O₂ group. (D) Fluorescence microscopy images of cells under different treatments.

Before investigating the potential biological applications of the MIL-47(V)-NH₂ MOF nanozyme, its excellent GPx-mimicking activity encouraged us to assess the cytoprotection effect and in vitro ROS scavenging ability (Figure 3A). First, cytotoxicity...
experiments were performed to assess the biocompatibility of MIL-47(V)-NH₂ MOF nanozyme. As shown in Figure 3B, after 24 h incubation with 0–100 μg mL⁻¹ of MIL-47(V)-NH₂ MOF, the cell viability could still remain 90%, demonstrating that the MIL-47(V)-NH₂ MOF within 100 μg mL⁻¹ exhibited negligible cytotoxicity. Then, the cell protective ability of MIL-47(V)-NH₂ MOF nanozyme against oxidative stress induced by H₂O₂ was studied. As seen in Figure 3C, H₂O₂ treatment caused cell death while MIL-47(V)-NH₂ MOF alleviated the oxidative stress-induced cell death gradually with the increase of MIL-47(V)-NH₂ MOF with 80 μg mL⁻¹ cells having viability nearly equal to the control. The intracellular ROS scavenging ability of MIL-47(V)-NH₂ MOF was monitored with 2',7'-dichlorofluorescein diacetate (DCFH-DA) as an intracellular ROS fluorescent probe. ROS were generated by lipopolysaccharide (LPS), as indicated by the remarkable fluorescent signal as compared to controls (Figures 3D and S6). The fluorescent intensity of DCFH-DA then significantly decreased by 36% with 20 μg mL⁻¹ MIL-47(V)-NH₂ MOF treatment. And the more GPx-mimicking MIL-47(V)-NH₂ MOF nanozyme was added, the more fluorescent intensity of DCFH-DA decreased. Together, these results show MIL-47(V)-NH₂ MOF to not only possess good biocompatibility, but also to be an effective ROS scavenger, protecting cells from oxidative damage.

We also evaluated the effect of MIL-47(V)-NH₂ MOF on the polarization of macrophages from the M1 to M2 phenotype. Macrophages play a prominent part in innate immunity as the first line of host immune system. Macrophages typically exist in a dormant state, M0, and switch to the activated M1 state, releasing inflammatory factors such as IL-1β, iNOS, and TNF-α, when facing bacterial infection or other stimulations. Macrophages can also adopt the activated M2 phenotype to promote tissue repair and wound healing by releasing anti-inflammatory cytokines such as IL-10, IL-4, and Arg-1. The qPCR analysis showed about five hundred times increase of IL-1β mRNA expression (Figure 4A), four hundred times increase of iNOS (Figure 4B), and forty times increase of TNF-α (Figure 4C) when treated with LPS. These elevated markers demonstrated the inflammatory conditions and M1 polarization of macrophages induced by LPS, as previously reported. When subsequently treated with MIL-47(V)-NH₂ MOF, mRNA expression levels of pro-inflammatory M1 markers notably decreased (Figure 4A-C) while expression levels of anti-inflammatory M2 markers (IL-10, IL-4, and Arg-1) were notably enhanced in a dose-dependent manner (Figure 4D-E). Therefore, MIL-47(V)-NH₂ MOF was verified to successfully induce the M1 to M2 phenotypic polarization of macrophages and displayed satisfactory in vitro anti-inflammation activity.

**Figure 4.** mRNA expression levels of M1 and M2 markers in the LPS-induced macrophages receiving different concentrations of MIL-47(V)-NH₂ nanozyme. (A) IL-1β, (B) iNOS, (C) TNF-α, (D) IL-10, (E) IL-4, and (F) Arg-1 levels under different treatments. Data are expressed as mean ± standard error of 3 experiments.

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Motivated by the above in vitro results, the in vivo anti-inflammation activity of MIL-47(V)-NH₂ MOF nanozyme was assessed with a murine ear inflammation model. First, phorbol 12-myristate 13-ace-tate (PMA) was applied to the right ear of a mouse to induce ear inflammation (Figure 5A). As shown in Figure S7, right ear was visibly red and swollen for the pre-treated mouse, indicating that the ear inflammation was successfully established. The ear inflammation also led to hyperthermia, as evidenced by −3 °C increase of right ear temperature in the PMA group as compared to the control group (Figure S8). Varying concentrations of MIL-47(V)-NH₂ MOF were then subcutaneously injected in the inflamed ear for treatment. The in vivo ROS scavenging activity of MIL-47(V)-NH₂ MOF nanozyme are shown in Figures 5B and S9, based on the fluorescent intensity of the ROS probe DCFH-DA. The reduction in DCFH-DA fluorescence was observed to be dose-dependent and corresponding ear tissue sections stained with hematoxylin and eosin (H&E) also demonstrated a dose-dependent antioxidant effect of MIL-47(V)-NH₂ MOF with the inflammatory response effectively alleviated at the highest dose (Figure 5C). And the relieved inflammation made the right ear temperature decreased by ~2 °C as well (Figure S8). When comparing with MIL-47(V)-H MOF nanozyme (Figures S9-10), the MIL-47(V)-NH₂ MOF with a better GPx-mimicking activity exhibited greater anti-inflammation capability, especially at low dosage. These results suggested that the rationally designed MIL-47(V)-NH₂ MOF nanozyme had elevated ROS scavenging capacity and enhanced the in vivo anti-inflammation efficacy. Moreover, a commercial anti-inflammation drug dexamethasone (Dex) was applied in the in vivo anti-inflammation model as well. Both reduced (around ~98%) in vivo DCFH-DA fluorescent intensity and corresponding ear tissue section stained with H&E indicated that the therapeutic efficacy of Dex was comparable to that of MIL-47(V)-NH₂ under the same dosage (Figures S11). After the treatment, no obvious histological changes or inflammatory damage of major organs including liver, spleen and kidney of mice were observed (Figure S12), indicating good in vivo biocompatibility of our MOF nanozymes. These results together show GPx-mimicking MIL-47(V)-NH₂ MOF nanozyme to possess excellent in vivo anti-inflammatory activity and to protect effectively against oxidative stress damage.

Figure 5. (A) Schematic illustration of ear inflammation model. (B) In vivo fluorescence imaging of mice with PMA-induced ear inflammation after different treatments. (C) H&E stained images of ear tissue after different treatments.

To further evaluate the in vivo anti-inflammation effect of MIL-47(V)-NH₂ beyond treatment of superficially inflamed ears, we also established an acute dextran sulfate sodium (DSS)-induced colitis model, as a typical refractory chronic inflammatory bowel disease associated with overproduced ROS.18 As shown in Figure 6A, DSS was administrated by feeding over six days, followed by intraperitoneal administration of MIL-47(V)-NH₂ MOF nanozyme once per day for three consecutive days. Then, the colon was collected to evaluate the therapeutic efficacy on the tenth day. The body weight of each mouse was recorded daily during this process with the body weights of all DSS induced groups decreasing, indicating the successful establishment of colitis model, as shown in Figure 6B. Upon the treatment with MIL-47(V)-NH₂ nanozyme, the body weights of the mice gradually recovered, suggesting anti-inflammatory effect of MIL-47(V)-NH₂ to extend to colitis treatment. Colon length (Figures 6C and S13)
and corresponding colon sections stained with H&E (Figure 6D) also suggested that the inflammatory response was effectively alleviated after the administration of MIL-47(V)-NH$_2$ nanozyme as compared with the shortened colon length and inflamed colon tissue in the DSS group. Further, the significant down-regulated levels (around −60%) of inflammatory cytokines IL-1β (Figure 6E) and TNF-α (Figure 6F) in MIL-47(V)-NH$_2$ nanozyme treated group were observed, which were just a little higher than the control group, consistent with the phenomena of the in vitro study (Figure 4). These results strongly suggest that the MIL-47(V)-NH$_2$ nanozyme significantly down-regulated the levels of inflammatory cytokines IL-1β and TNF-α, and thus effectively mitigated colonic inflammation.

Figure 6. (A) Schematic illustration of the establishment and treatment procedure of colitis model. (B) Daily body weight record under different treatments. (C) Images of the colons taken on day 10. (D) H&E stained images of colons under different treatments. (E) IL-1β and (F) TNF-α levels in colon homogenates under different treatments. Data are expressed as mean ± standard error of 5 experiments. **** means P< 0.0001 vs. control group. ** means P< 0.01 vs. DSS group. *** means P< 0.001 vs. DSS group. **** means P< 0.0001 vs. DSS group.
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Similar to the findings in ear-inflammation model, the MIL-47(V)-NH$_2$ MOF demonstrated greater anti-inflammatory activity than the less active MIL-47(V)-H nanozyme (Figures S13-14). Notably, for MIL-47(V)-NH$_2$ nanozyme, the therapeutic efficacy under three different concentrations was similar, suggesting that the treatment of MIL-47(V)-NH$_2$ at 0.4 mg kg$^{-1}$ was effective enough for therapy. For the less active MIL-47(V)-H nanozyme, a positive correlation between the therapeutic efficacy and the treated concentrations was revealed, and only at the highest dose of 1.6 mg kg$^{-1}$ was the therapeutic efficacy comparable to that of MIL-47(V)-NH$_2$ nanozyme. The above results not only confirmed that a high-performance GPx-mimicking nanozyme alone could be applied in anti-inflammation therapy, but also advanced nanozyme-based therapy studies that the structure-activity regulation of nanozyme could be explored to guide in vivo therapy. Moreover, a clinical small-molecule drug 5-aminosalicylic acid (5-ASA) was applied in our model as well. The slight down-regulated levels (around ~20%) of inflammatory cytokines (Figure S13C-D) and corresponding colon tissue section stained with H&E (Figure S14) indicated that the therapeutic efficacy of 5-ASA was weaker than that of both MIL-47(V)-NH$_2$ and MIL-47(V)-H nanozymes under the same dosage of 1.0 mg kg$^{-1}$. No distinguishable tissue damage or inflammatory lesions of other organs including heart, lung, liver, spleen and kidney in mice were observed in either nanozyme therapy (Figure S15), further supporting the good in vivo biocompatibility of our MOFs. Therefore, these results demonstrate that the high-performance MIL-47(V)-NH$_2$ nanozyme could relieve the inflammatory bowel disease state, indicating a promising potential of MIL-47(V)-NH$_2$ as an efficient nanomedicine for anti-inflammation therapy.

Conclusion

In summary, we have successfully synthesized MOF nanozymes with GPx-mimicking activities, which to our knowledge is the first report of GPx-mimicking MOF nanozymes. Even though both nanozymes and biomimetic MOFs have been widely studied for more than 20 years, few studies have reported GPx-mimicking nanozymes, especially GPx-mimicking MOF nanozymes. By using vanadium metal nodes and (substituted) terephthalate linkers, MIL-47(V)-X (X = F, Br, NH$_2$, CH$_3$OH, and H) MOFs were successfully fabricated with rationally regulated GPx-mimicking activities. With the best performance one as an example, we demonstrated the use of MIL-47(V)-NH$_2$ to scavenge ROS in vitro and protect cells from oxidative damage. This result was extended to in vivo anti-inflammation, demonstrating a broad-spectrum anti-inflammatory effect toward both ear-inflammation and colitis. Moreover, the therapeutic efficacy of the high-active MIL-47(V)-NH$_2$ was superior to that of the less-active MIL-47(V)-H. These results not only verify that a GPx-mimicking nanozyme alone can be applied in anti-inflammation therapy, but also demonstrate that traditional concepts of structure-activity relationships can be applied in the design of nanozyme-based therapies. Thus, the study of GPx-mimicking MOF nanozymes has the potential to greatly expand the range of biomimetic MOFs, allowing this class of antioxidant nanozymes to enrich the current nanozyme research.

Acknowledgements

The authors acknowledge Prof. Liming Zheng and Mr. Mingfeng Qin for providing the microwave reactor and helping with MOF synthesis. The authors thank Christopher J. Butch for valuable comments and proofreading of the manuscript. This work was supported by National Natural Science Foundation of China (21722503 and 21874067), the National Key R&D Program of China (2019YFA0709200), PAPD program, Open Funds of the State Key Laboratory of Coordination Chemistry (SKLCC1819), and Fundamental Research Funds for the Central Universities (14801145).

Keywords: glutathione peroxidase mimicking • metal–organic framework nanozyme • ligand engineering strategy • activity modulation • anti-inflammation therapy

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The first glutathione peroxidase (GPx)-mimicking metal–organic framework nanozymes are reported and optimized to high performance through a ligand engineering strategy analogous to strategies employed in protein engineering. In vivo therapy for both ear injury and colitis demonstrate the anti-inflammation effect of these nanozymes to have broad applicability and show the established in vitro structure-activity relationship to be meaningful in vivo.