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# Biocompatible Heterogeneous MOF-Cu Catalyst Used for *In Vivo* Drug Synthesis at Targeted Subcellular Organelles

Faming Wang, Yan Zhang, Zhengwei Liu, Zhi Du, Lu Zhang, Jinsong Ren and Xiaogang Qu*

**Abstract:** As a typical bioorthogonal reaction, copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has been used for drug design and synthesis. However, for localized drug synthesis, it is still an urgent conundrum for artificially determining the location where CuAAC reaction occurred in living cells. Herein, we constructed a heterogeneous copper catalyst on metal-organic frameworks, which could preferentially accumulate in mitochondria of living cells with high catalytic activity and have been successfully demonstrated by *in vivo* tumor therapy. Our system could realize localized drug synthesis via site-specific CuAAC reaction in mitochondria and had a wide applicability for synthesizing multiple drugs with good biocompatibility. Importantly, the subcellular catalytic process for localized drug synthesis avoided the problems of delivery and distribution of toxic molecules. *In vivo* tumor therapy experiments indicated that the localized synthesized resveratrol derived drug showed better antitumor efficacy, and could enhance the expected functions and minimize the side effects of target drugs. This is crucial for decreasing multiple side effects occurred in drug delivery and distribution.

Bioorthogonal chemistry has emerged as a powerful toolbox for manipulating biological processes in the native environment.[1] A series of chemical reactions, which are orthogonal to most functional groups in biological systems, have shown great potential to selectively modulate specific events.[2] Among them, owing to the high selectivity and efficiency, click chemistry has demonstrated satisfactory adaptability in chemical and biological fields.[3] Typically, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has become one of the most powerful tools in chemical biology.[4] So far, the CuAAC reactions and the derived reactions have been successfully applied for labeling protein, glycans, lipids, and nucleic acids in vitro.[5] Besides, another important contribution of click reaction is present in pharmaceutical science. Click chemistry has an advantage in drug synthesis, which can accelerate drug discovery process.[6] However, most of the drug synthesis through click chemistry by now are carried out under a "two-step" model. In this strategy, the active drug is pre-synthesized *in vitro* and then delivered to the organism.[7] Therefore, the problems about toxicity, delivery and localization of the synthesized active drug molecules are emergent and inevitable.[8] For living system, not only the misplaced biomolecules would cause severe diseases but also the misplaced drugs would cause serious side effects.[9] Actually, the active drugs may have totally different properties at different sites in living cells. For example, mitochondria have been important targets of many drugs as their critical roles in maintaining cellular survival and function.[10] So, localized synthesis of drugs at corresponding drug target sites has become a more attractive mode for drug intake, which can maximize the expected functions and minimize the side effects of the same drugs.[11] To solve the relative problems, the concept of "click to release" for drug synthesis and delivery has been put forward.[12] Although it is good at releasing active drugs after click reactions occurring, the complex pre-modification of each desire drug results in huge difficulties in application. In contrast, through CuAAC reaction, the simplest terminal alkyne and azide could achieve a desired compound or drug avoiding complex pre-synthesis. This "Bottom-up" model for drug synthesis is more suitable for a variety of desire drugs. However, site-specific CuAAC reaction for localized drug synthesis in living cells is still in infant stage.[13] Bradley *et al*. designed a heterogeneous copper catalyst to synthesize an anticancer agent. However, the size of their resin beads catalyst was around 150 μm, which was much larger than cells. Thus, the catalyst could not be endocytosed by living cells and the reactions were carried out in extracellular matrix. They further developed dual drug synthesis by using cancer-targeting palladium catalysts.[13b]

As a typical catalyst for CuAAC reaction, $Cu^{I}$ ion has drawbacks in producing reactive oxygen species and causing severe cytotoxicity in living cells.[14] Besides, homogeneous Cu-organic ligands catalysts are still challenging in the issues of water solubility, stability and biocompatibility.[15] Though copper-free strain-promoted azide-alkyne cyclo-addition (SPAAC) reaction could avoid toxic copper ion, the reaction substrates of SPAAC reaction are limited to strained alkynes and the strained alkynes may react with intracellular nucleophiles.[16] Recently, non-toxic, heterogeneous metal catalysts are used successfully in multiple bioorthogonal reactions.[17] Regretfully, so far, few heterogeneous catalysts of CuAAC reaction could meet the requirements of localized drug synthesis under subcellular organelles.

Herein, a new strategy regarding site-specific CuAAC reaction for localized drug synthesis in mitochondria has been presented. We constructed a functionalized heterogeneous copper catalyst on metal-organic frameworks (MOFs) with excellent catalytic activity (Scheme 1). As porous inorganic-organic hybrid materials, MOFs have attracted increasing attention in gas separation, gas storage, drug delivery and heterogeneous catalysis.[18] In this work, MOFs were used as scaffolds to stabilize and protect ultra-small copper nanoparticles. Further,

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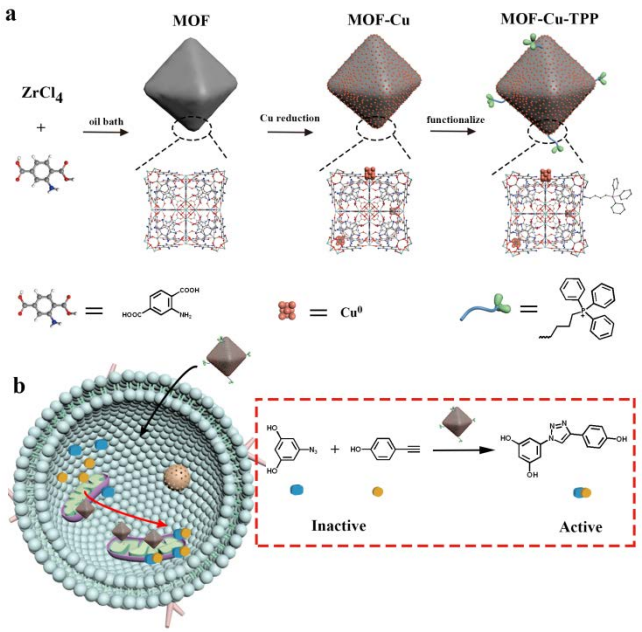
by decorating a triphenylphosphonium (TPP) vector, the catalyst could accumulate in the mitochondria of living cells. Importantly, the localized drug synthesis could maximize the expected functions of drugs, which had been proved in live cells and *in vivo* tumor therapy. This new strategy provides a more biocompatible and effective way for localized drug synthesis under subcellular organelles.




**Scheme 1.** Illustration of constructing of mitochondria-targeted CuAAC reaction catalysts and the in-situ drug synthesis under subcellular organelle. (a) Zr metal-organic frameworks (MOF), Cu-combined MOF materials (MOF-Cu) and TPP modified catalyst (MOF-Cu-TPP) used in the study. (b) Intracellular bioorthogonal reaction for in-situ drug synthesis under mitochondria catalyzed by MOF-Cu-TPP.

The heterogeneous MOF-Cu catalysts were synthesized in three steps (Scheme 1a).[19] Construction of MOF scaffold, Cu reduction and functionalization were carried out successively.[20] The average diameter of MOF was 120 nm (Figure S1). Next, ultrafine copper nanoparticles were synthesized and distributed throughout MOF (MOF-Cu), which was clearly shown in the TEM images (Figure S2) and distribution analysis (Figure S4). For the ability of targeting mitochondria, MOF-Cu was further modified by 3-Carboxypropyltriphenylphosphonium bromide (TPP) (MOF-Cu-TPP). The powder X-ray diffraction (XRD) analysis indicated that TPP modification did not destroy the structure of MOF (Figure S5). The P elemental mapping (Figure S3), Fourier transformation infrared spectroscopy (FT-IR) spectrum (Figure S6) and X-ray photoelectron spectroscopy (XPS) analysis (Figure S7) demonstrated the successful modification of TPP. The quantity of TPP modified on MOF-Cu was estimated about 5% wt through the thermogravimetric analysis (TGA) curves (Figure S8).

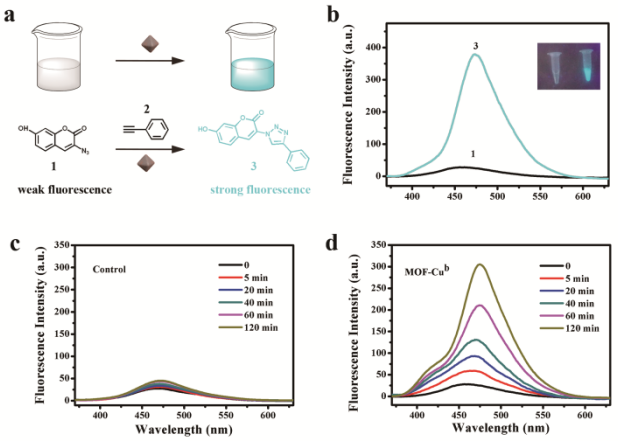



**Figure 1.** Catalytic reaction of MOF-Cu nanoparticles in vial. (a) The schematic diagram of MOF-Cu catalyzed Huisen 1,3-dipolar cycloaddition reaction between azides, **1**, and terminal alkynes, **2**, to produce the fluorescent molecule, **3**, in vial. (b) The fluorescent spectra of the click reaction without (black line) and with (red line) MOF-Cu catalyst, corresponding fluorescent photos of the experiment (insert photos). (c) The changes of fluorescence spectra under different time of the reaction without catalyst (from 0 to 120 min). (d) The changes of fluorescence spectra under different time of the reaction with MOF-Cu catalyst (from 0 to 120 min). The obvious increase of the fluorescence intensity showed the good catalytic activity of MOF-Cu. Data were presented as mean ± s.d. (n = 3).

As a prerequisite, we investigated whether the MOF-Cu catalysts possessed catalytic activity for CuAAC reaction (Figure 1a). The formation of triazole, **3**, between "pro-fluorophore" **1** and **2** would cause an obvious change of fluorescence intensity (Figure 1b, Figure S12).[21] In order to study the role of Cu in the catalytic process, we synthesized MOF-Cu with different Cu doping levels as the controls, which were termed as MOF-Cu$^a$ (3.6 wt%), MOF-Cu$^b$ (10.6 wt%) and MOF-Cu$^c$ (29.8 wt%), respectively (Figure S9-S11). The content of Cu in MOF-Cu complexes was determined by inductively coupled plasma mass spectrometry (Table S1). MOF-Cu$^a$, MOF-Cu$^b$ and MOF-Cu$^c$ were incubated with precursor molecules in vial, respectively. After 12 h, the tubes showed obvious cyan-blue fluorescence, indicating the superior catalytic activity of the catalyst (Figure S13-S14). Furthermore, the fluorescence spectra were also monitored (Figure S15). All three MOF-Cu catalysts could induce gradual increase in fluorescence intensity. As shown in conversion curve, MOF-Cu$^b$ and MOF-Cu$^c$ exhibited obviously higher catalytic activity than MOF-Cu$^a$ owing to more catalytic centers. Though MOF-Cu$^c$ possessed slightly higher catalytic efficiency than MOF-Cu$^b$, the excessive copper content induced the presence of free Cu nanoparticles, which could destroy the stability and uniformity of MOF-Cu (Figure S10). So, we chose MOF-Cu$^b$ as model catalyst in following experiments. To further study the kinetic process and catalytic efficiency, we followed fluorescence change from 0 to 120 min of MOF-Cu$^b$ (Figure 1c,d). Remarkable increase of fluorescence intensity in 5 min showed the excellent catalytic activity (Figure S16). The data of high-performance liquid chromatography (HPLC) indicated that the conversion of the catalytic process was above 80% at 8 h (Figure S17). The related statistics of translation ratio and

concentration was consisted with the fluorescence results (Figure S18). To evaluate the tolerance of different reaction conditions, we carried out the reactions under $H_2O$, phosphate buffered saline (PBS) and cell culture medium with or without serum, respectively (Figure S19-S20). Three groups all showed the increase of fluorescence, indicating the applicability of the designed catalyst. Furthermore, the reusability of MOF-Cu was also studied. The catalysts were washed with water and collected by centrifugation for next turn (Figure S21). The relative activity and SEM of the cycled catalysts indicated that our catalysts exhibited good reusability and stability under the experimental conditions (Figure S22). In addition, the supernatant of the catalysts after a 72 h treatment in $H_2O$ showed no catalytic ability, further confirming the stability of MOF-Cu.

Next we explored their intracellular performance in human breast adenocarcinoma cells (MCF-7 cells) (Figure 2a). Firstly, the cellular uptake was quantified via analyzing [$^{63.5}$Cu] by ICP-MS. Both MOF-Cu and MOF-Cu-TPP could be endocytosed effectively (Figure S23-S24). In addition, the cytotoxicity of the catalysts was detailed studied by MTT method. From 0 to 100 μg mL$^{-1}$, MOF-Cu (Figure S25) and MOF-Cu-TPP (Figure S26) were observed negligible cytotoxicity. After that, click reaction was carried out in situ in MCF-7 cells. Compared to the controls, the cells treated with MOF-Cu showed significant increase of fluorescence by flow cytometry analysis (Figure 2b). Meanwhile, the live-cell fluorescence microscopy experiments also indicated similar results (Figure 2c).

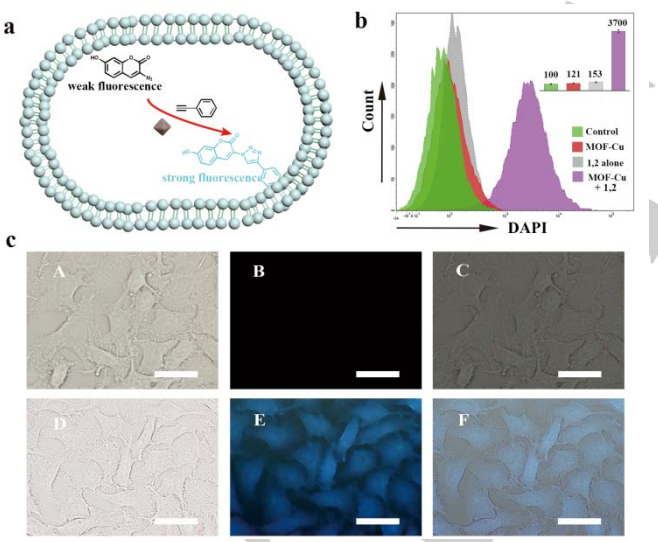



**Figure 2.** Click reaction in living cells catalyzed by the catalysts. **(**a) The schematic diagram of MOF-Cu catalyzed click reaction between azides and terminal alkynes in living cells. (b) The flow cytometry analysis of fluorescence changes, control (cells alone), MOF-Cu alone, precursor **1** with **2** and MOF-Cu with precursors, respectively. (c) Fluorescence images of MCF-7 cells treated without (A-C) and with (D-F) MOF-Cu catalyst. (A) bright field image of cells, (B) emission of the product **3** (blue channel), (C) merging with A and B, (D) bright field image of cells, (E) emission of the product **3** (blue channel), (F) merging with D and E. An obvious fluorescence was shown in the cells treated with MOF-Cu catalyst (E) (Scale bar = 10 μm). Data were presented as mean ± s.d. (n = 3).

To achieve our vision about localized drug synthesis in subcellular organelles, we modified MOF-Cu with TPP moiety, which is a well-established mitochondria-targeting group (MOF-Cu-TPP). To monitor the ability of targeting mitochondria, we incubated MOF-Cu-TPP with FITC as a fluorescence marker (f-MOF-Cu-TPP). f-MOF-Cu-TPP showed an obvious fluorescence emission at 512 nm (Figure S27). After incubating with f-MOF-Cu-TPP, MCF-7 cells were labeled by a commercial mitochondrial red dye (MitoTracker Red CMXRos) and nuclear dye (Hoechest 33258). As shown in fluorescence images, f-MOF-Cu-TPP gave remarkable fluorescence signal co-localized with MitoTracker (Figure S28), confirming that MOF-Cu-TPP could effectively target mitochondria. In addition, as indicated by click reaction experiments, MOF-Cu-TPP still retained the catalytic activity (Figure S29).

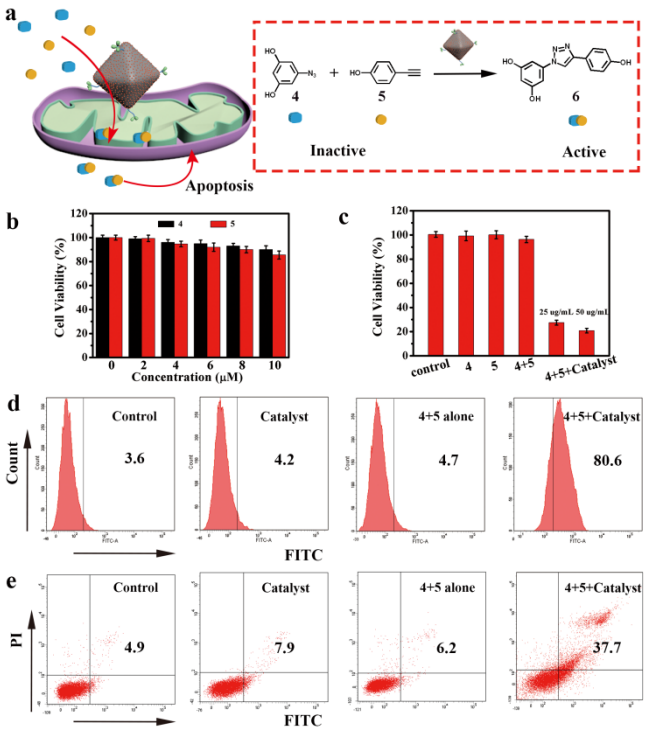



**Figure 3.** In-situ resveratrol analogue synthesis in mitochondria by the designed mitochondria-targeted catalysts**. (**a) The schematic diagram of in-situ resveratrol analogue synthesis in mitochondria. (b) The MTT of compound, **4**, and compound, **5**, under low concentration on MCF-7 cells (from 0 to 10 μM). (c) The MTT of compound, **6**, in situ synthesized in mitochondria with MOF-Cu-TPP catalyst (10 μM, **4**; 10 μM, **5**). (d) The flow cytometry analysis via DCFH-DA probe about the accumulation of oxidative stress in cells when the reaction occurred (10 μM, **4**; 10 μM, **5**). (e) The apoptosis experiment of MCF-7 cells analyzed by double staining with Annexin V-FITC and propidium iodide via flow cytometry analysis. Data were presented as mean ± s.d. (n = 3).

For finding suitable catalytic product, we put our sights in resveratrol (Rsv). Previous research has indicated that Rsv and its derivates may act as an anti-oxidant, reduce cardiovascular disease, increase lifespan, and also be used as a cancer chemopreventive agent.[22] However, the molecular mechanisms

of Rsv and its derivates are complicated because they have many biological targets and play different roles under different conditions.[23] Previous studies indicate that Rsv and its derivates can effectively induce cell apoptosis by causing mitochondrial damage (Figure 3a).[24] Therefore, in situ synthesis of Rsv analogues in mitochondria can improve its antitumor efficacy and minimize the side effects. So, we synthesized precursor molecule, **4** and **5**. The cytotoxicity of precursors **4** and **5** was also evaluated. As shown in Figure 3b and Figure S30, precursors **4** and **5** both have negligible cytotoxicity up to 25 μM in MCF-7 cells.

Then, in situ synthesis of **6** in mitochondria was studied.[25] As shown in Figure 3c, an obvious decrease in cell viability was observed. Meanwhile, induced the apoptosis of MCF-7 cells owing to the synthesized active agent **6** was also proved by double staining with Annexin V-FITC and propidium iodide (Figure 3e). Furthermore, to verify the interaction between the synthesized drug agent and mitochondria, the changes of mitochondria at different time were monitored. Mitochondrial damage would cause a decrease of membrane potential and fail to sequester MitoTracker Red CMXRos dye, causing a much less defined and decreased intensity of red staining. As shown in Figure S31, after 6h, the contour and intensity of fluorescence image became blurred and decreased gradually. There was an obvious decrease in red fluorescence at 24 h, indicating the mitochondrial damage. Interestingly, the accumulation of oxidative stress and release of cytochrome c along with the mitochondrial damage were also observed by flow cytometry (Figure 3d) and western blot, respectively (Figure S32). Furthermore, the LC-MS of the final product, **6**, (269.10) confirmed that the CuAAC reaction catalyzed by MOF-Cu-TPP was carried out smoothly (Figure S33). As a control, we added resveratrol and **6** in MCF-7 cells directly. The survival rate of cells was above 80 % even at the high tested (50 μM) concentration (Figure S34).[26] The accumulation of oxidative stress experiment also indicated that the direct incubation of Rsv analogue **6** did not increase oxidative stress under our experimental concentration (Figure S35). This could be due to the drug agent with different distribution and multiple cellular targets.[23a] The localized drug synthesis in targeted subcellular organelles showed its unique advantage to improve efficacy and avoid side effects.

Furthermore, we carried out this reaction in animal model (Figure 4a). The C. elegans was chosen as a model first.[27] The N2 wild-type strain worms were incubated with the designed catalyst. Complete paralysis occurred around 15 days for both control and experiment groups proving the biocompatibility of catalyst (Figure 4b). Then, the click reaction in C. elegans was studied through compounds **1** and **2**. The group fed with catalyst and precursors (C, F) showed an obvious fluorescence signal proving the catalytic process (Figure 4c). In addition, no signs of toxicity, and morphology alteration was emerged in C. elegans (Figure S36). For observing the vitality of nematode directly, the simple movie about movement of C. elegans indicated they maintained energetic activity after reactions occurred (Movie S1). Next, the biocompatibility of catalysts in mice model was tested (Figure S37-S40).[28] All the results demonstrated the good biocompatibility of the catalyst for possible in vivo therapeutic applications and ineffectiveness of prodrugs without catalysts. Besides, the therapy efficiency of in-suit drug synthesis by the designed catalyst was evaluated by mice tumor model (Fig S41-S44). Taking together, all the experimental results proved the good tumor therapy efficiency of in-suit drug synthesis.

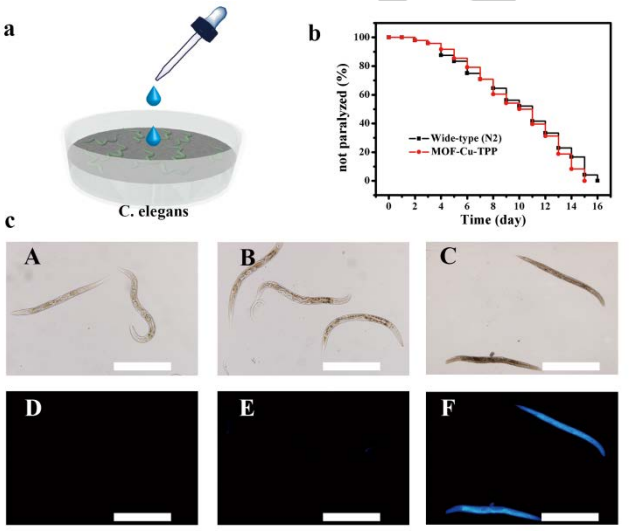



**Figure 4.** Click reactions occurred in C. elegans model. (a) The schematic diagram of click reactions catalyzed by designed catalyst in C. elegans. (b) Kaplan-Meier survival curves of the N2 wild-type strain worm fed with or without catalyst. (Scale bar = 10 μm). (c) The fluorescence images of C. elegans in blue channel. The bright field images (A-C) and fluorescence images (D-F). Control (A, D), catalyst alone (B, E), catalyst with fluorescent precursor molecules (C, F). Plots are representative of three independent experiments. Data were presented as mean ± s.d. (n = 3).

In summary, for the first time, we have successfully constructed a mitochondria-targeted heterogeneous catalyst and demonstrated their application in tumor therapy. The designed catalyst possesses high catalytic activity and stability, which could be reused conveniently. The catalyst can be used to activate the profluorophore and to perform the localized drug synthesis in mitochondria. The in-situ generation of an active drug from inert prodrugs in subcellular organelles has unparalleled advantages in minimizing the toxic side effects of cytotoxic drugs and maximizing their efficacy. The C. elegans experiments proved the biocompatibility of the designed catalyst and *in vivo* tumor therapy indicated that the localized synthesized resveratrol derived drug showed better antitumor efficacy. Our work provides new insights into decreasing multiple side effects occurred in drug delivery and distribution.

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**Keywords:** Heterogeneous catalyst, bioorthogonal chemistry, click reaction, drug synthesis, subcellular organelles

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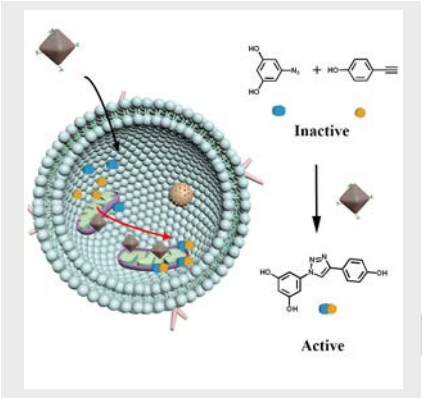
# COMMUNICATION

The complex MOF-Cu-TPP catalysts realize localized drug synthesis via site-specific CuAAC reaction in mitochondria. This system has a wide applicability for synthesizing multiple drugs with good biocompatibility and plays its unique advantage to improve efficacy of active drugs avoid reduce side effects.

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**Biocompatible heterogeneous MOF-Cu catalyst used for in vivo drug synthesis at targeted subcellular organelles**