Sonigashira Coupled Ligand for Improved Functionalization of Metal-Organic Framework Drug Delivery System

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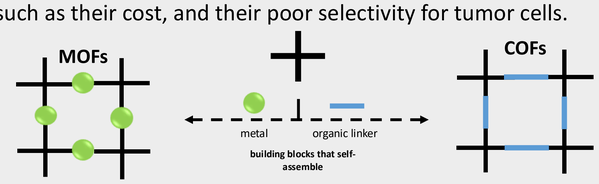
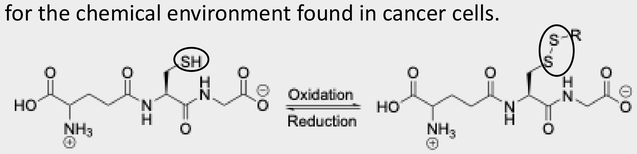
Introduction

Cancer remains one of the leading causes of death worldwide, with an estimated 2 million new cases expected in the United States this year alone. Cancer involves the unchecked and rapid process of cell division, which can lead to the formation of a tumor. Treatment options for cancer include chemotherapy, radiation, hormonal therapy, and surgery. While these treatments can be effective, they each come with limitations, such as their cost, and their poor selectivity for tumor cells.



Metal and Covalent-Organic Frameworks (MOFs/COFs) both show promising potential for drug delivery applications. Along with their ability to self assemble, these complex crystalline nanocarriers made up of organic building blocks can be highly functionalized to respond to stimuli. This high tunability can be utilized for design of a drug delivery system with a selectivity for the chemical environment found in cancer cells.



Glutathione (GSH) | **Glutathione Disulfide (GSSR)**

A tripeptide known as glutathione (GSH) can be exploited in tumor cells as a drug releasing agent. This is possible thanks to the cysteine residue on the peptide and its ability to cleave disulfide bonds. A unique property of tumor cells when compared to their healthy counterparts is that their glutathione concentrations is factorially greater. These characteristics influenced our schematic design of a chemotherapeutic prodrug tethered via a disulfide bond to a highly rigid MOF.

Our objective is to deliver chemotherapeutics with disulfide tethered Metal-Organic Frameworks to induce apoptosis in cancer cells.

Experimental Methods

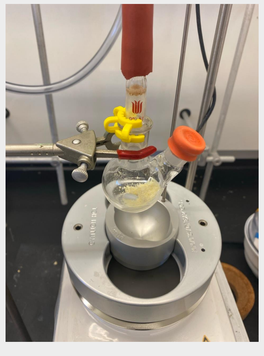


Figure 1: *Images showcasing the air free process of the Sonigashira Cross Coupling reaction.*

Molecular Design

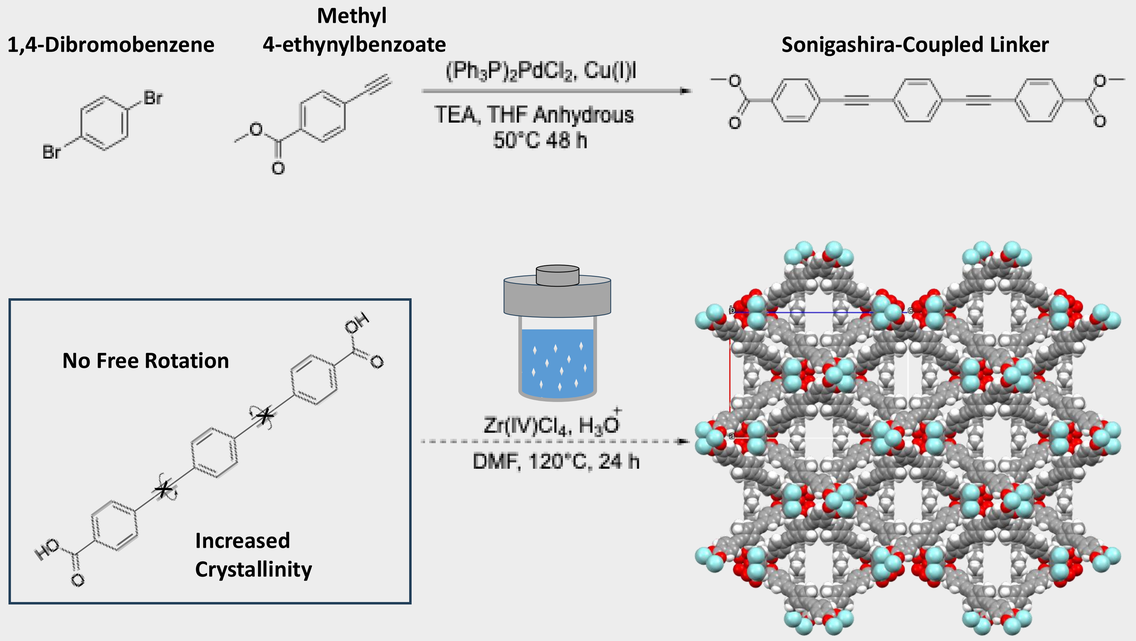
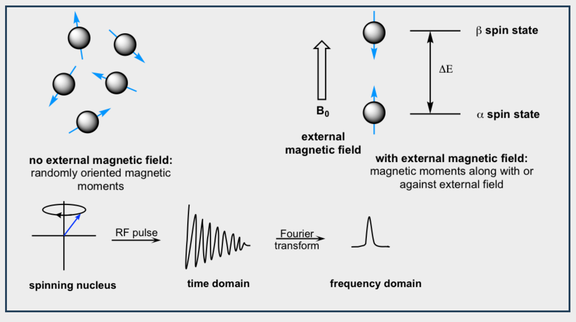


Figure 2: *A chemical synthetic scheme showing the Sonigashira coupling of our two aromatic precursors as well as the solvothermal formation of a Zirconium coordinated MOF with the activated rigid linker.*

Nuclear Magnetic Resonance (NMR)



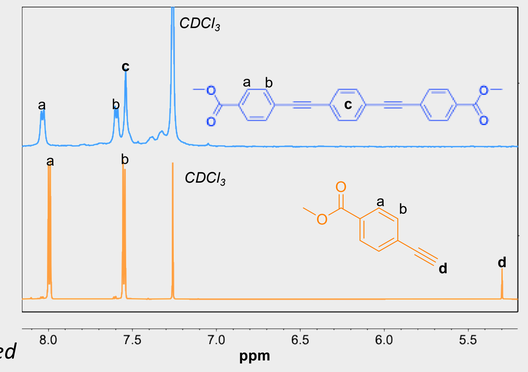
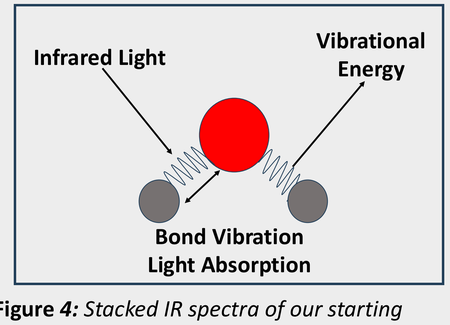


Figure 3: *Stacked ^1H NMR Spectra of both the synthesized organic linker, and the alkyne starting material. 500 Hz*

Infrared Spectroscopy (IR)



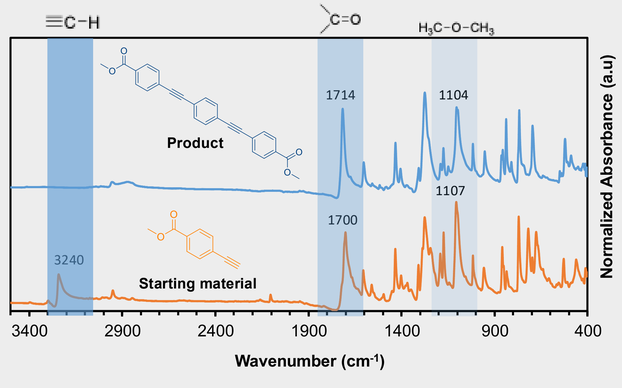


Figure 4: *Stacked IR spectra of our starting material and product measuring absorbance*

Future Work

After Successfully synthesizing our rigid organic ligand, the next step is to coordinate it to Zirconium metal. MOF formation relies on the high reversibility of bonds to crystalize from a single nucleation point. In order to increase the reversibility of our solvothermal reaction, an acidic modulator must be added to slow down the coordination.

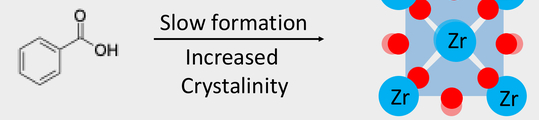


Figure 5: *A schematic showing the importance of an acidic modulator in improving MOF formation.*

Once the zirconium network is formed, it can be characterized using powder X-Ray Diffraction (pXRD). Once this step is successful, we will begin to functionalize our linker with a free thiol group. This will allow for desirable drug tethering to our network and target the reductive properties of GSH to use as an effective chemotherapeutic delivery system. The purpose of the tethering is to navigate the difficulties of accessing the MOFs porous structure, and to provide a more effective payload release. An effective formation of our tethered MOF will allow us to begin preliminary cellular studies with both cancer and non cancer cells to quantify our delivery system.

Drug Tethering Studies

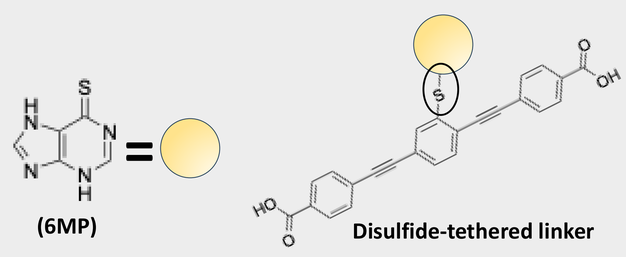


Figure 6: *Chemical Structure of 6-Mercaptopurine (6MP). A common and inexpensive chemotherapeutic compatible with disulfide tethering.*

Acknowledgements

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