CHEMISTRY

Synthesis and Characterization of Heterogeneous Substituted Arylamide Backbones

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Traditionally, medicinal chemists have developed small-molecule drugs to target deep hydrophobic pockets within disease-associated proteins. However, a significant portion of the human proteome is considered "undruggable" due to the absence of well-defined binding sites. Protein-protein interactions (PPIs) play a crucial role in disease modulation and present an attractive yet challenging target for therapeutic development. Unlike conventional druggable sites, PPIs span large surface areas and depend on specific amino acid residues or "hot spots" that contribute significantly to binding free energy. Hot spots are dispersed across a large surface area much greater than the size of a small molecule and as a result PPIs aren't effectively disrupted with traditional therapies.

Peptidomimetics are synthetic oligomers (foldamers) that mimic the structure and function of peptides by scaffolding hot spots. Arylamides are a class of foldamers that adopt well-defined conformations in solution. Designing arylamide foldamers with predictable conformations is necessary for projecting functional groups in orientations that are necessary for engaging in surface interactions to disrupt PPIs. In this study, we hypothesize that the conformation of arylamide foldamers composed of 2,6-dialkoxy-meta-aminomethylbenzoic acid (2,6-MAMBA) monomers can be predicted in solution and solid-state based on the alkoxy substitution pattern on the aromatic ring.

Here we describe the design, synthesis and characterization of an arylamide foldamer composed of three MAMBA monomers. The conformation and intramolecular forces that influence the conformation were characterized by variable temperature and 1D and 2D nuclear magnetic resonance (NMR) spectroscopy and single crystal X-ray diffraction.

Our findings suggest that by manipulating key conformational determinants—such as hydrogen bonding and dipolar repulsion, the conformation can of MAMBA-based arylamide foldamers can be predicted. By tuning the oligomer length, shape and functional groups, we aim to design arylamide peptidomimetic foldamers capable of targeting and disrupting a range of undruggable PPIs. This approach expands on the traditional small molecule strategy for modulating diseases that have been incurable with conventional drug therapies.

Chemistry Department Summer Research Fellowship

CHEMISTRY

Exploration of structure-property relationships within a series of low-dimensional hybrid ruthenium (IV) halides

Perovskites are a class of crystals that follow the general structure of ABX3 and have tunable bandgaps and strong light absorption, making them useful for solar cells and scintillators. This study explores a new family of Hybrid Organic-Inorganic Halide perovskites (HOIPs) composed of haloruthenium octahedra (RuX62-, X = Cl, Br) charge balanced with organic halopyridinium cations (XPy, X = H, Cl, Br, I). These compounds were successfully synthesized, and crystalline structures were determined via Single-Crystal X-ray Diffraction (SCXRD), and bulk purity was confirmed via Powder X-ray Diffraction (PXRD). Band gaps of the materials were calculated via the Tauc Plot method using data obtained from Diffuse Reflectance Spectroscopy (DRS) for each material. The determined band gaps of these HOIPs are influenced by the halide composition of the ruthenium octahedra; the RuBr62- containing compounds exhibited a lower bandgap (1.05 eV $\leq$ Egap $\geq$ 1.08 eV) than the RuCl62- containing compounds (1.22 eV $\leq$ Egap $\geq$ 1.43 eV). Structural and electronic properties of the compounds were probed via computational methods, including the Quantum Theory of Atoms in Molecules (QTAIM) analysis, which showed that the electron density and Laplacian values at the bond critical points were generally lower for Ru-Br bonds compared to Ru-Cl bonds, implying weaker bonding in RuBr62- systems. A weaker Ru-Br bond is directly correlated to that compound having a lower band gap and enhanced light absorption. Additionally, Density Functional Theory (DFT)- based Natural Bonding Orbital (NBO) and Second Order Perturbation Theory (SOPT) methods were used to determine the impact second-sphere interactions such as halogen bonding, hydrogen bonding, and halogen-π interactions contribute to the stabilization energy and structure-property relationships. This study highlights the role of second-sphere interactions in tuning the photophysical properties of the material. Understanding the influence of electronic interactions on optical properties can pave the way for informed design of low-dimensional HOIPs with characteristics optimized for the intended application.

This work is supported by the Department of Energy National Nuclear Security Administration through the Nuclear Science and Security Consortium under award no DE-NA0003996. In addition, this research is made possible by The George Washington University and the High-Performance Computing Cluster at The George Washington University, Research Technology Services.

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CHEMISTRY

Sustainable sequestration of carbon as graphite

Climate change presents an existential threat to global society's health and safety. To combat climate change, utilization of bioenergy and "green" carbon negative or neutral processes will be required. Decarbonization of transportation represents a critical step towards reducing fossil fuel combustion emissions, reducing as much as 28% of all US CO2 emissions. Large scale adoption of electric vehicles (EVs) is an effective solution, however, EVs are reliant upon expensive lithium-ion batteries, which can total upwards of ~1/3 of the cost of an EV.

The anode of a lithium-ion battery is predominantly graphite. A single EV battery pack contains 70-90 kg of high-grade graphite and current graphite production methods are predicted to be quickly outpaced. Highly crystalline, highly pure, battery-grade graphite is only produced through either highly wasteful and polluting mining practices, or energy intensive and highly emissive fossil fuel-based synthetic methods. Increasing production to meet skyrocketing demand will only exacerbate the environmental impacts of such methods and will overwhelm existing supply chains.

We developed a novel carbon negative process to convert previously non-graphitizable carbons such as biochar or lignite into graphite. Biochar is the waste product of biomass pyrolysis, valorization of which could provide new sustainable uses for a low value material. However, geologically preprocessed biomass such as coal is an advantageous starting material due to its low cost, valuable chemical and metal byproducts, and the preservation of biomass resources. The supply chain for coal is already well established with minimal need for raw material transport and associated emissions and our process is entirely emission free.

Current work is focused on understanding the variables involved in our process, increasing the versatility and adaptability of our process to different starting materials, and improving the quality of graphite produced. We will present our work on the synthesis of graphite from both biomass and coal, as well as the optimizations to the overall process.

This material is based upon work supported by a grant from the town of Estevan, Canada.

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CHEMISTRY

Designing and Synthesizing Peptide Probes for the N-terminus of the Alpha 4 Protein

Traditionally druggable proteins require a deep, hydrophobic pocket that can be targeted with a small molecule. The ability to target protein-protein interactions (PPI) as well as flatter and more extensive surfaces is imperative to expanding the druggable proteome. New modalities, such as cyclic peptides, are being explored as PPI interrupters and protein surface binders, and concurrently, probes that can interrogate their binding to a specific protein surface must be developed. We present the synthesis of four different amino acid probes that mimic the catalytic subunit of PP2A, which interacts closely with the Alpha4N Protein. This PPI is important to study because (PP2A) regulates many biological functions through phosphorylation and thus plays parts in both cancer suppression and proliferation. Understanding how to modulate PP2A, and create good quality probe molecules, is therefore an important step in order to clarify its role in cancer and potentially offer a path to novel treatments. To determine the sequence of each probe, computational alanine scanning mutagenesis was done to determine hotspot residues in the co-crystal structure PDB: 4 IYP (PP2AC and Alpha 4N complex) protein-protein interaction. Mutations were then made to improve helix stability, solubility and ease of synthesis. Each probe was synthesized via solid phase synthesis, labelled with a fluorescein isothiocyanate (FITC) tag, purified on high-performance liquid chromatography (HPLC) and characterized using mass spectrometry. The FITC tag allows for two types of fluorescence polarization spectroscopy: direct binding assays and displacement assays. While the characterization of the peptide probes are still in progress, we anticipate that they will be an important step towards testing the binding affinity of compounds designed to target the PPI interphase between PP2A and Alpha4N.

Supported by the Madeleine Reines Jacobs Summer Scholarship and the George Washington University Department of Chemistry.

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CHEMISTRY

Characterization of the Microbial PPCS Binding Pocket via P-Pan-CMP Analogs

While many drugs have been effective in treating infectious diseases such as tuberculosis and malaria, their extensive use over the past few decades has led to drug-resistant strains of their respective pathogens. Because of this, novel therapeutics are needed to treat drug-resistant infections. Coenzyme A (CoA) is a ubiquitous cofactor and acyl carrier that aids in the citric acid cycle and fatty acid synthesis. All organisms synthesize CoA in a five-step process starting from pantothenate; however, distinct differences in the enzymes that catalyze this pathway in humans and microbes make the CoA biosynthetic pathway a promising drug target. Specifically, many pathogens possess CoaBC, a fused, bifunctional protein that has two enzymatic domains, unlike eukaryotes, which have distinct enzymes. The CoaB domain contains the PPCS functionality which couples PPan and cysteine over two steps, forming P-PanCys. In the first step, human PPCS recruits ATP, resulting in the transient intermediate P-Pan-AMP, while bacterial enzymes use CTP, forming the intermediate P-PanCMP. Due to this difference, it is believed that P-Pan-CMP mimetics will competitively inhibit PPCS and kill bacteria by preventing CoA biosynthesis. To mimic the natural substrate P-Pan-CMP, a series of compounds consisting of pantothenate linked by a triazole to varying aromatic groups has been proposed as inhibitors. From this series, an SAR can be explored, giving insight into the PPCS binding pocket. Of these compounds, seven have shown modest inhibitory activity against Pf. parasites, with IC50 values ranging from 13 to 89 µM. These compounds have also been phosphorylated and tested against isolated Mtb PPCS, showing binding to the target enzyme. Further analogs must be made to explore the PPCS binding pocket and design inhibitors that are potent and selective.

This work was supported by NIH grant R01AI36836 awarded to Dr. Erick Strauss.

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CHEMISTRY

Investigating Neuronal Protein Degradation Pathways using Mass Spectrometry techniques

Protein homeostasis is critical for neuronal function, with disruptions closely linked to neurodegenerative diseases. Neurons rely on the lysosome and proteasome to break down and recycle proteins. Dynamic Stable Isotope Labeling by Amino acids in Cell culture (dynamic SILAC) enables precise measurement of protein turnover. We previously developed a SILAC-compatible cell culture medium that supports healthier, functionally mature neurons compared to traditional media. Here, we apply this system to examine the effects of lysosomal and proteasomal inhibition on neuronal protein turnover. Neurons were cultured in our custom SILAC medium and treated with Bafilomycin A1, a lysosomal inhibitor, and Epoxomicin, a proteasomal inhibitor. Using dynamic SILAC and mass spectrometry-based proteomics, we quantified protein turnover across conditions, revealing distinct alterations in protein turnover. Proteasome inhibition with Epoxomicin led to increased overall protein turnover, accelerating degradation of lysosome-associated and phosphorylation-regulated proteins while slowing turnover of proteasome targets such as ribosomal and RNA-regulatory proteins. Lysosomal inhibition with Bafilomycin A1 reduced overall protein turnover, particularly affecting lysosomal, mitochondrial, and neurotransmission-associated proteins, while increasing turnover of proteasome-related proteins. These findings suggest compensatory crosstalk between the proteasome and lysosome, where inhibition of one system increases reliance on the other, showing their distinct yet interconnected roles in neuronal proteostasis.

This work was supported by a Luther Rice Fellowship.

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CHEMISTRY

CoA Biosynthesis in Mycobacterium tuberculosis: Developing PPCS Inhibitors

Antibiotic resistance is a burgeoning public health threat as pathogens evolve to evade existing therapeutics. Mycobacterium tuberculosis (Mtb), Plasmodium falciparum (Pf), and the ESKAPE pathogens are at the forefront of this global issue. Mtb causes tuberculosis, the leading cause of death from a single infective agent. The malaria parasite Pf is responsible for over 600,000 deaths annually. The six ESKAPE pathogens are the primary cause of nosocomial infections. A novel anti-infective agent that exploits interspecies similarities may provide a singular solution to this broad issue. In recent years, the coenzyme A (CoA) pathway emerged as a target for drug discovery. CoA is an essential cofactor for various biochemical processes, from cellular energy production to cell structure development. A universal CoA biosynthetic pathway exists in all prokaryotic and eukaryotic species, but key differences between the bacterial and human pathways prompt the investigation of a selective inhibitor. Distinctive features of the binding pocket of the PPCS enzyme of the CoA pathway provide a unique opportunity to design tight binding inhibitors that preferentially inhibit CoA biosynthesis in prokaryotic species, initiating a bactericidal effect. We have synthesized several inhibitors to probe the PPCS binding pocket, focusing on how the linker length and electronic properties of the inhibitors affect the enzymatic activity and whole-cell survivability.

This work was supported by a Luther Rice Fellowship.

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