Can noncovalent interactions be visualized and interpreted using the random phase approximation?

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Introduction

Natural products have served as models for designing new anticancer drugs over the past several decades.[1,2] One example is the chlorolissoclimide (CL) extracted from the ascidian *Lissoclinum voeltzkowi* which inhibits cell growth by binding to eukaryotic ribosomes and preventing translation.[3] The X-ray co-crystal structure of CL with the eukaryotic 80S ribosome revealed a novel halogen–π interaction between the ligand's alkyl chloride and two guanine nucleotides.[4,5] However, the specificity of the halogen–π interactions is not well understood. In this project, I will address the problem by developing a computational tool based on electronic structure theory to characterize and visualize noncovalent interactions (NIs). This can then be used to guide the design and synthesis of lissoclimide analogues for new cancer therapeutics.

To achieve the project's goal, the correct computational and theoretical understanding of dispersion interactions is key to designing new therapeutics. Dispersion interactions are viewed as long-range electronic interactions that are non-trivial to compute and difficult to characterize. In a recent publication, I demonstrated that nonperturbative methods such as the random phase approximation (RPA) provides the correct description of dispersion interactions compared to the many-body perturbation theory (MBPT) for NIs.[6] RPA is an unprecedented theory that achieves this accuracy without any additional empirical parameters while remaining computationally efficient.[7] Based on this study, I propose using RPA to develop a tool for characterizing dispersion interactions and verifying the tool in collaboration with the Vanderwal Group by contributing to the synthesis of novel lissoclimide analogues for drug binding.

Research Plan

The halogen-π interactions between the CL and ribosome were studied based on a simplified model by Könst *et al.*[5] I have performed preliminary work by improving upon this model and varied the functional group, see Fig. 1, that showed binding energies increasing going down the halogen group. In addition, the methylissoclimide surprisingly yielded a binding energy within 1 kcal/mol compared to iodolissoclimide. Dispersion interactions are expected but, these remain to be intuitively understood. Hence, I will be spending time with Prof. Filipp Furche attempting to capture and visualize the spontaneously induced electronic attractions through analyzing the corresponding eigenvectors of the RPA correlation energy. Lastly, I will work with Prof. Christopher Vanderwal and graduate student Bonnie Pak to refine and confirm the computational tool through the synthesis of the substituted lissoclimide along with testing the drug's potency through *in vitro* studies.

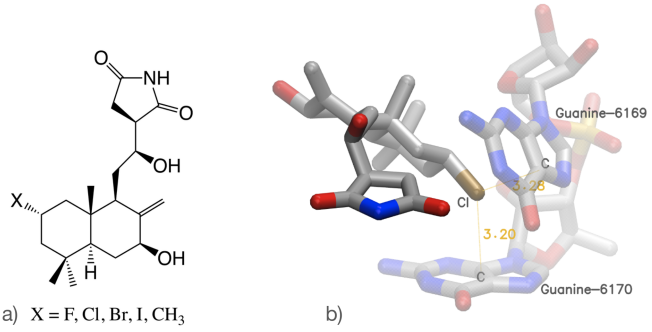

Figure 1: a) A series of substituted lissoclimides of different functional groups. b) Geometry optimized model of CL and guanine nucleotides using the hybrid density functional TPSSh-D3.[8,9] Bond lengths are in Angstroms. Hydrogens were removed for clarity. Color codes for atoms are Cl = brown, N = blue, C = gray, O = red, and P = orange.

Contribution to Academic Career

The proposal will help contribute to my dedication for mentoring, teaching, and research. This year, I am mentoring a high school student who is working alongside me to understand NIs. Furthremore, the proposal will contribute to the doctoral dissertation by guiding the development of the theory and methods for characterizing NIs. The extensive skills from organic synthesis and theoretical chemistry will further develop my ability to work across disciplines that address the challenges of NIs.

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