Within the random phase approximation, can noncovalent interactions be visualized and interpreted?

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Natural products have been an important source for designing new cancer drugs over the past several decades.[1,2] For example, the chlorolissoclimide (CL) extracted from the ascidian *Lissoclinum voeltzkowi* is a powerful cytotoxic bicyclic diterpene alkaloid that inhibits eukaryotic translation elongation.[3] This inhibition leads to ribosome accumulation and eventual cell death. 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] This type of interaction has been noted to be dispersion dominant.[6–8] In this research project, I will combine both experimental and theoretical methods to tune dispersion interactions for designing and synthesizing analogues of lissoclimide for new cancer therapeutics.

To achieve the project's goal, the correct computational and theoretical understanding of dispersion interactions are key to designing new therapeutics. Dispersion is not only non-trivial to predict computationally but also, it is even harder to characterize and interpret. In a recent publication, we demonstrated that the random phase approximation (RPA) provides the correct description of dispersion interactions compared to the many-body perturbation theory (MBPT) for noncovalent interactions (NIs).[9] The accuracy of RPA is achieved without any additional empirical parameters and at an efficient computational cost. Based on this study, I propose using RPA to develop a visualization tool for characterizing dispersion interactions that can then be applied to a simplified model of the intermolecular interactions between the CL and eukaryotic 80S ribosome, see Fig. 1.

I will be coordinating with my primary advisor Filipp Furche in theoretical chemistry and my secondary advisor Chris Vanderwal in organic chemistry to elucidate the behaviors of NIs and then apply these predictions to design better cancer therapeutics. The research plan consists of three parts where the first two parts are done in the Furche Group while the third part is performed in the Vanderwal Group.

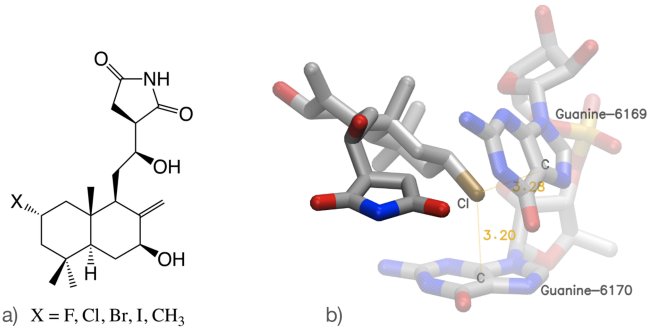

Figure 1: a) A series of substituted lissoclimides of different halogens. b) Geometry optimized model of CL and guanine nucleotides using the hybrid density functional TPSSh-D3.[10,11] Bond lengths are in Angstroms. Hydrogens were removed for clarity. Color codes for atoms are Cl = brown, N = blue, C = gray, O = red, and P = orange.

First, I will conduct a comprehensive computational study on the nature and magnitude of the intermolecular interaction by varying the halogen moiety (X = F, Cl, Br, I, CH_3) as an extension to the work by Könst *et al.*,[5] see Fig. 1. My preliminary gas phase binding energies for the lissoclimide family were shown to increase going down the halogen group. However, the question of why this trend is observed remains. To explain this observation, I will develop a visualization tool for dispersion interactions by interpreting the corresponding eigenvectors of the RPA correlation energies as plasmonic modes describing collective excitations of the electrons. Lastly, the third part is the confirmation of the computational results by synthesis of the substituted lissoclimide along with testing the drug's potency through *in vitro* studies.

For my doctoral studies, I have envisioned my dissertation to be focused on developing state-of-the-art approaches that accurately describe NIs. We have concluded from our recent landmark publication that RPA with its superior accuracy for NIs may safely replace MBPT for predictions of NIs in most systems of chemical interest.[9] With this research project, I will be able to apply diverse skills from organic synthesis and theoretical chemistry to develop RPA based methods that interpret NIs relevant for drug design.

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