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MECHANISTIC INSIGHTS INTO ORGANOSULFUR COMPOUND-UREASE INTERACTIONS: A COMPUTATIONAL CHEMISTRY ANALYSIS USING aISS DOCKING SUBMODULE AND GFN2-xTB SEMIEMPIRICAL METHOD

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This Final Year Project Report entitled "**Mechanistic Insights Into Organosulfur Compound-Urease Interactions: A Computational Chemistry Analysis Using aISS Docking Submodule and GFN2-xTB Semiempirical Method**" was submitted by Raja Nur Shafiqa binti Raja Alias in partial fulfilment of the requirements for the Degree of Bachelor of Science (Hons.) Applied Chemistry, in the Faculty of Applied Sciences, and was approved by

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ABSTRACT

MECHANISTIC INSIGHTS INTO ORGANOSULFUR COMPOUND-UREASE INTERACTIONS: A COMPUTATIONAL CHEMISTRY ANALYSIS USING AISS DOCKING SUBMODULE AND GFN2-XTB SEMIEMPIRICAL METHOD

Urease is a dinuclear nickel-dependent metalloenzyme that catalyzes the hydrolysis of urea to ammonia and carbon dioxide, thus contributing to nitrogen loss and reduced fertilizer efficiency in agricultural system. Despite the documented reports of natural organosulfur compounds as potential urease inhibitors, the detailed of their molecular binding mechanisms and electronic interaction patterns remain to be fully elucidated. The objective of this study is to elucidate the binding modes, interaction energies, and electronic characteristics of selected organosulfur compounds, allicin, diallyl disulfide (DADS), and diallyl sulfide (DAS) toward the urease active site using integrated computational approach, so the limitation of quantitative analysis of urease-inhibitor compound can be overcome. The automated interaction site screening (aISS) docking methodology was employed to generate binding orientations, followed by geometry refinement and interaction energy evaluation using semi-empirical GFN2-xTB method. The results demonstrated that allicin exhibit the strongest interaction energy by -61.68 kcal mol^{-1} followed by DADS and DAS where its interaction energy both -51.74 $kcalmol^{-1}$ and -43.04 kcal mol^{-1} respectively. Allicin formed multiple stabilising interactions in the proximity of the dinuclear Ni^{2+} centre, including agnostic Ni –H contacts (2.0 –2.6 Å) and strong hydrogen bonds (1.8 –2.1 Å). Molecular electrostatic potential mapping revealed higher polarity mapping revealed higher polarity in allicin due to its sulfinyl group, while Quantum Theory of Atoms in Molecules (QTAIM) analysis confirmed stronger electron density accumulation at key bond critical points. The findings demonstrate distinct interaction patterns among the inhibitors, thus highlighting allicin as the most stable binder and supporting organosulfur compounds as promising environmentally sustainable urease inhibitor candidates.

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