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MECHANISTIC EXPLORATION OF UREASE INHIBITION BY ORGANOSULFUR COMPOUNDS VIA GFN2-XTB AND AISS DOCKING SIMULATIONS

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ABSTRACT

MECHANISTIC EXPLORATION OF UREASE INHIBITION BY ORGANOSULFUR COMPOUNDS VIA GFN2-xTB AND aISS DOCKING SIMULATIONS

The increasing environmental and health concerns arising from the excessive use of synthetic urease inhibitors have prompted the exploration of natural alternatives particularly organosulfur compounds (OSCs) derived from garlic such as Diallyl Sulfide, Diallyl Disulfide, Diallyl Trisulfide and Ajoene. This study employed GFN2-xTB semiempirical quantum mechanical calculations in combination with Automated Interaction Site Screening (aISS) to investigate the mechanisms of urease inhibition by OSCs. Geometry optimization and docking simulations were performed on Jack Bean Urease active site by focusing on binding modes, interaction energies and electronic characteristics. The most favourable interaction was observed for (E)-Ajoene at position 2 in Ni116 with an interaction energy of -50.15 kcal/mol that indicating the strongest binding affinity among all inhibitors and configurations. Conversely, the least favourable interaction was also form (E)-Ajoene at position 3 in Ni116 with interaction energy of +111.68 kcal/mol due to poor configuration. Furthermore, (Z)-Ajoene demonstrated consistently strong interactions across all three positions in Ni116, attributed to its compact and planar structure with the most stable at Position 3 which is -43.44 kcal/mol. In contrast, DATS with its elongated sulfur chain showed poor binding due to steric hindrance with some configurations displaying positive interaction energies. Quantum Theory of Atom in Molecules and Electrostatic Potential analysis confirmed the presence of non-covalent interactions and provided insight into the bonding environment and electrostatic changes upon binding. The results highlight the significance of the molecular orientation, sulfur chain length and spatial arrangement in determining the inhibitory efficiency of OSCs. This study supports the use of Ajoene especially (Z)- and (E)-Ajoene as potent natural urease inhibitors and offering an eco-friendly alternative that aligns with sustainable agriculture and SDG goals.

dalam menentukan keberkesanan perencatan OSCs. Kajian ini menyokong penggunaan Ajoene terutamanya (Z)- dan (E)-Ajoene sebagai perencat urease semula jadi yang berpotensi dan menawarkan alternatif mesra alam yang selari dengan pertanian lestari dan matlamat SDG.

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