

## Theoretical studies of PP5-Mg<sup>2+</sup> with potential inhibitors and H304A mutation

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**Abstract:** Serine/threonine protein phosphatase 5 (PP5) is a promising target for anticancer therapies and neurodegenerative diseases[1,2]. This enzyme is a member of the gene family of PPP phosphatases, which catalyze dephosphorylation reactions, a regulatory process in the signal transduction pathways that control various biological processes [2,3]. A strong inhibitor of PPP phosphatases is Cantharidin. This natural toxin acts on several cellular processes, such as DNA damage, cell cycle arrest and apoptosis [2,4]. However, the clinical application of this toxin is limited due to severe side effects in the gastrointestinal tract, kidney and ureter [4]. In this context, it is necessary to search for less toxic compounds than cantharidin, in order to aid in the future development of new compounds with important pharmacological properties for the PP5 inhibition. This work aims to study how the inhibition takes place between human PP5 and its inhibitors derived from cantharidin. Molecular dynamics techniques were employed in order to investigate the key interactions that occur in the active site and analyze the interference of the H304A mutation on the inhibition activity of ten compounds (Fig.1). The results obtained indicate that the inhibition activity of the cantharidin analogs takes place openly in the catalytic site and the most important residues, i.e., that contribute favorably to the interaction of the ligand within PP5, are Arg400, His304, Arg275, His244, Phe446 and Val429. In turn, the Asp271 and Asp274 residues disfavor such interactions. In addition, through the mutation, it was possible to evaluate the importance of the His304 residue interfering with the activity of these toxins, suggesting that the inhibitory potency of these compounds may be related to the



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coordination mode with the metal and not only with the interaction in the PP5 active site.

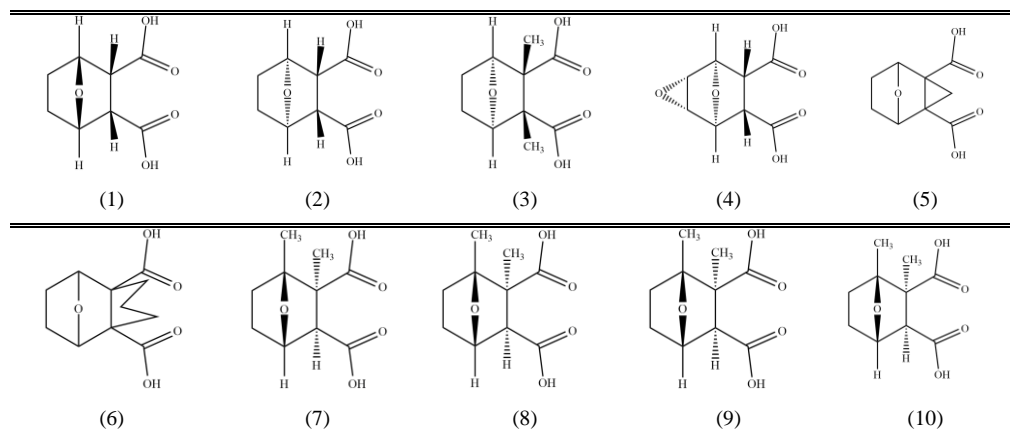


Figure 1: Chemical structures of the 10 analogous compounds of cantharidin.

**Key-words:** Serine/Threonine phosphatase 5, Cantharidin, Molecular Dynamics, H304A mutation

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