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In Silico Study of the Computationally Designed Novel Vinca Alkaloid Derivatives VADRPA01 and VADRPH01 Effects on Calmodulin and Calmodulin Dependent Ca^{2+} Transport ATPase

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Abstract

Vinblastine was the first Vinca Alkaloid (VA) with antiproliferative properties discovered in plant *C. roseus*. The ability of VA drugs to bind with the Calmodulin (CaM) and Calmodulin-dependent Ca $^{2+}$ transport ATPase (CaM-dep-Ca^{2+} TATPase) causes neurotoxic side effects due to antagonist the activity of the enzyme. The optimized derivative forms of the natural VAs are playing an important role in clinical practice to reduce the side effect of the Vinca Drugs. This in-silico study was conducted to evaluate the CaM binding characteristics of the novel VAs derivatives VADRPA01 and VADRPH01 and their effect on CaM-dep-Ca^{2+} TATPase compared to the marketed Vinca drug. VADRPA01 demonstrates the highest water solubility at 7.4 pH, LogS=-0.91. Klaus Gietzen *et al* confirmed that VAs have two binding sites at the Calmodulin molecule with high and low affinity by in vitro analysis. The CHARMM36 updated force field was used to calculate binding energy and identified two binding sites (A and B) on the CaM molecule. The binding affinity of VAs varies between 1.9% to 8.1% related to Vinflunine (-6.2 kcal/mol). In silico results compared with Klaus Gietzen *et al* in-vitro analysis data show the antagonist activity of Vinca drugs on the CaM-dep-Ca^{2+} TATPase enzyme depends on the strength of the complex formed with CaM. The conducted gmxMMPBSA analysis shows that the binding energy is not the only factor influencing the antagonist activity of Vinca alkaloids. The conducted Vinca-free and Vinca-bound CaM|CaM-dep-Ca^{2+} TATPase binding behaviour analysis confirmed that the binding position geometry of the Vinca molecule with CaM plays an essential role in their antagonist activity on the CaM-dep-Ca^{2+} TATPase. The present study found that VADRPA01 lowered CaM binding affinity with CaM-dep-Ca^{2+} TATPase by 81.8% compared to Vinblastine.

Keywords: *VA, Molecular docking, Molecular dynamics, Anticancer, Calmodulin*