Characterizing the Pharmacophoric Features of Bufadienolides from *Drimia* species as Na^+/K^+ ATPase Inhibitors: Advancing Cancer Therapeutics through Molecular Dynamic Simulations

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The Na^+/K^+-ATPase, or the Na^+ pump, is a transmembrane protein that maintains the electrochemical gradient across the plasma membrane, which is crucial for ion homeostasis and apoptosis. Recent studies have also identified the Na^+/K^+-ATPase as a potential biological marker and target in cancer. Bufadienolide compounds have been widely studied as Na^+/K^+-ATPase inhibitors in chemotherapeutic research. By binding to and inhibiting the alpha-subunit of the Na^+/K^+-ATPase, these compounds inhibit cell proliferation and migration, as well as induce apoptosis. The *Drimia* genus of bulbous plants are widely used in sub-Saharan Africa as medicinal plants. These plants abundantly express various bufadienolides and have been evidenced to demonstrate anticancer properties. This study aimed to identify and evaluate, using computational techniques, the structural mechanisms of inhibition of *Drimia* bufadienolides on the Na^+/K^+-ATPase. A pharmacophoric scaffold, based on the most optimal complexes was then designed to demonstrate the vital molecular groups required for chemotherapeutic activity. A total of 53 compounds were identified from literature. These compounds were structurally optimized and docked to the Na^+/K^+-ATPase. Complexes demonstrating optimal docking scores were subjected to molecular dynamic simulations and free-binding energy calculations. Four complexes (binding scores of -59.96 kcal/mol, -61.79 kcal/mol, -50.08 kcal/mol, and -52.86 kcal/mol) were used to generate a pharmacophoric scaffold. Pharmacokinetic profiling also showed that all compounds demonstrated favorable ADME properties and indicated efficient synthetic characteristics. This pharmacophoric approach serves as a foundation for the design of effective synthetic Na^+/K^+-ATPase inhibitors, with decreased toxicity and enhanced patient adherence.