Delving into the Intricacies of CHARMM Force Field Parameterization for Flupyradifurone Pesticide: A Thorough Optimization Journey !

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Résumé

As the world population is projected to reach 9 billion by November 2037(1), there is an increasing need for food supply. One critical aspect of modern sustainable agriculture is the development of potent, effective, and safe pesticides to protect crops from pests. These pesticides should be highly selective for insects over mammals and pollinators. One approach to address this selectivity is targeting the nicotinic acetylcholine receptors (nAChRs) of insects. The neonicotinoid family of insecticides has gained interest for years as a solution for crop protection and animal health(2).

Flupyradifurone (FLU) also known by its trademark name Sivanto is the last member of nAChR competitive modulators designed by Bayer CropScience (3,4) and the most recent member of the neonicotinoid class of insecticides to reach market with an innovative pharmacophore including a butenolide moiety. Mainly claimed as harmless for non-targeted organisms such as pollinators (e.g. honey bees) and mammals, concerns about FLU resistance and toxicity for mammalian and the environment have been raised. However, these effects and the corresponding mechanisms are still debated and poorly described. Indeed, if the mechanism of ac ion of FLU appears admitted, the information related to its interactions at the atomic level at the targeted insect nAChRs is limited.

Molecular modeling methodologies (e.g. molecular docking, molecular dynamics (MD)) are imperative tools in the absence of experimental information. However the question of results reliability is strongly correlated to force field parameters quality. Indeed, if force field parameters for biopolymers are readily available and widely used in MD simulations, this not the always the case for small ligands. Furthermore, knowing the bias of such fields toward pharmaceutical applications, the availability of force field parameters is even scarcer for pesticides related compounds like FLU.

In the present talk, we will discuss the workflow used for the development and optimization of CGenFF force field compatible parameters for FLU in order to be used in molecular dynamic and/or molecular docking. A set of initial parameters were used as a starting point and were derived from CHARMM General Force Field database (CGenFF) using CGenFF program (5,6). Then the non-bonded and bonded terms were optimized using Force Field

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Tool Kit (FFTK) software to reproduce MP2/6-31G* quantum calculations accuracy. The relevance of the obtained parameters was validated by comparing physical properties such as IR-spectra, Normal Modes Analysis (NMA) and water-octanol partition coefficient (logKow) to their experimental values. MD simulations of FLU/AChBP complexes were carried out to evaluatethe ability of the optimized parameters n reproducing recently observed crystallographic trends.

References

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