Towards Mosquitocides for Prevention of Vector-Borne Infectious Diseases

Discovery and Development of Acetylcholinesterase 1 Inhibitors

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Akademisk avhandling

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Abstract
Diseases such as malaria and dengue impose great economic burdens and are a serious threat to public health, with young children being among the worst affected. These diseases are transmitted by mosquitoes, also called disease vectors, which are able to transmit both parasitic and viral infections. One of the most important strategies in the battle against mosquito-borne diseases is vector control by insecticides and the goal is to prevent people from being bitten by mosquitoes. Today's vector control methods are seriously threatened by the development and spread of insecticide-resistant mosquitos warranting the search for new insecticides. This thesis has investigated the possibilities of vector control using non-covalent inhibitors targeting acetylcholinesterase (AChE); an essential enzyme present in mosquitoes as well as in humans and other mammals. A key requirement for such compounds to be considered safe and suitable for development into new public health insecticides is selectivity towards the mosquito enzyme AChE1. The work presented here is focused on AChE1 from the disease transmitting mosquitoes *Anopheles gambiae* (*Ag*AChE1) and *Aedes aegypti* (*Aa*AChE1), and their human (*h*AChE) and mouse (*m*AChE) counterparts. By taking a medicinal chemistry approach and utilizing high throughput screening (HTS), new chemical starting points have been identified. Analysis of the combined results of three different HTS campaigns targeting *Ag*AChE1, *Aa*AChE1, and *h*AChE allowed the identification of several mosquito-selective inhibitors and a number of compound classes were selected for further development. These compounds are non-covalent inhibitors of AChE1 and thereby work via a different mechanism compared to current anti-cholinergic insecticides, whose activity is the result of a covalent modification of the enzyme. The potency and selectivity of two compound classes have been explored in depth using a combination of different tools including design, organic synthesis, biochemical assays, protein X-ray crystallography and homology modeling. Several potent inhibitors with promising selectivity for the mosquito enzymes have been identified and the insecticidal activity of one new compound has been confirmed by *in vivo* experiments on mosquitoes. The results presented here contribute to the field of public health insecticide discovery by demonstrating the potential of selectively targeting mosquito AChE1 using non-covalent inhibitors. Further, the presented compounds can be used as tools to study mechanisms important in insecticide development, such as exoskeleton penetration and other ADME processes in mosquitoes.

Keywords
Mosquito, vector-borne diseases, vector control, insecticide, acetylcholinesterase, medicinal chemistry, high-throughput screening, organic synthesis, homology modeling, structure activity relationship, structure selectivity relationship

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