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POTENT AND SELECTIVE MOLECULES TARGETING VECTOR-BORNE INFECTIOUS DISEASES

Vector Control, and Steps Towards Drug Target Identification

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Akademisk avhandling

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Abstract
This thesis encompasses two projects aimed at combating vector-borne infectious diseases. The first project focuses on developing public health insecticides against diseases transmitting mosquitoes. One of the most critical approaches in controlling mosquito-borne infections is vector control through insecticides. However, the effectiveness of current insecticides is increasingly challenged by the rise of insecticide resistance in mosquitoes, lack of target selectivity, and off-target toxicity. Consequently, there is an urgent need for new, mosquito-selective insecticides with different mechanisms of action that can overcome mosquito resistance and acute toxicity. To address these issues, this project explores the potential of vector control by investigating two classes of non-covalent inhibitors target disease transmitting mosquitoes. The first class of inhibitors is based on an indole scaffold, which targets acetylcholinesterase (AChE) in the species *Anopheles gambiae* (*Ag*AChE1), and *Aedes aegypti* (*Aa*AChE1). AChE is an essential cholinergic enzyme presents in insects and mammals. The concept of pro-insecticides was introduced to address the issues related to in vivo inefficiency of insecticides, and applied on this indole class. Furthermore, we investigated the mechanisms of inhibition for a newly developed class of thiazolidinone scaffold based compounds against both mosquito and human AChEs (mosquito AChE1, and *h*AChE). We also identified key functional, and structural differences between mosquito AChE1 and AChE2 in honey bees (*Am*AChE2). These differences were proved significant in the molecular recognition of *Am*AChE2 by exploration with non-covalent inhibitors from different classes, demonstrating that different AChEs exhibit distinct molecular recognition profiles. The second project focuses on improving drug therapy for treatment of trypanosomiasis, caused by Trypanosoma parasites, and spread between mammals through the bite of tsetse flies. Current therapeutics suffer from problem such as resistance development, and adverse side effects due to the lack of well-identified targets in protozoan. Therefore, identification of a potential protozoan-specific target is strongly needed. By taking a medicinal chemistry approach and utilizing target-based high throughput screening (HTS) this project focuses on the identification of new chemical compounds that regulates the activity of an enzyme in the protozoa Trypanosoma brucei (*Tb*MCA-Ib). This is a cysteine protease that belong to a family of metacaspases (MCAs), which are present in all form of life except mammals. A number of selected modulator were identified as potential inhibitors, and activators for *Tb*MCA-Ib, suggesting its potential as therapeutic target against trypanosomiasis.

Keywords
Vector-borne diseases, Vector control, Acetylcholineasterase, Insecticides, Pro-insecticides, Non-covalent inhibitors, Disease-transmitting mosquitoes, Off-target toxicity, Structure activity relationship, Selectivity, Mammals, Mechanism of inhibition, Honey bee, Recombinant enzyme, Structural analysis, Kinetics, Inhibition kinetics, Insecticidal efficiency, High throughput screening, Hit compounds, Metacaspase, Target identification, Modulators, Activators.

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