ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové

Training Workplace	Department of Biochemical Sciences
Doctoral Degree Program	Xenobiochemistry and Pathobiochemistry
Candidate	Mgr. Thuy Linh Nguyen
Supervisor	Prof. RNDr. Lenka Skálová, Ph.D.
Advisor	Assoc. Prof. Ing. Petra Matoušková, Ph.D.
Title of Doctoral Thesis	Advances in the discovery and testing of anthelmintics

The parasitic nematodes cause a considerable problem in human and animal health worldwide. The group of gastrointestinal nematodes is responsible for economic losses in livestock production. The treatment relies on the use of a limited number of anthelmintics, but their efficacy is hampered due to widespread drug resistance. Given the need for new drugs, the present thesis focuses on discovering novel compounds with potential anthelmintic effects and on the development of testing methods.

Based on the literature search, we presented the possible approaches in the current development of new anthelmintics and evaluated their advantages and disadvantages in a review article. For the experiments, we used a model organism Haemonchus contortus, which is one of the most important gastrointestinal pathogens of small ruminants. The primary phenotypic screening of a small compound library against larvae identified two 'hit' compounds BLK127 and HBK4. Based on further studies of efficacy against the adult stage and toxicity in sheep, we selected BLK127 for biotransformation studies in H. contortus and ovine liver. The promising results may advance this molecule for further drug development. Additionally, we provided a study on the efficacy, biotransformation and toxicity of sertraline in H. contortus, which represents the repurposing strategy for the development of novel anthelmintics.

Moreover, the thesis presents an optimised viability assay for testing in adults of H. contortus based on bioluminescence determination of adenosine triphosphate concentration. This assay might serve for the detection of drug-resistant isolates. Furthermore, we took advantage of a deep learning algorithm dealing with image recognition tasks, Mask R-CNN. Progress on this front improved the power of automated classification of the nematode including motile/non-motile phenotype.