MMSL
Military Medical
Science Letters
Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2018, 87(supplementum 1)
ISSN 2571-113X (Online)

MEETING ABSTRACTS

BIOLOGICAL EVALUATION OF CYSTEINE TARGETED INSECTICIDES

Hrabinova M. [1,2], **Schmidt M.** [1,3], **Gorecki L.** [1,2], **Kucera T.** [1,2], **Psotka M.**, **Svobodova B.** [1,2], **Hrabcova V.** [1,3], **Hepnarova V.** [1,2], **Jun D.** [1,2], **Kuca K.** [1,3], **Musilek K.** [1,3], **Korabecny J.** [1,2]
Presenting authors: Martina Hrabinova, Monika Schmidt

[1] University Hospital Hradec Kralove, Biomedical Research Centre, Sokolska 581, 500 05 Hradec Kralove, Czech Republic
[2] University of Defense, Faculty of Military Health Sciences, Department of Toxicology and Military Pharmacy, Trebeska 1575, 500 01Hradec Kralove, Czech Republic
[3] University of Hradec Kralove, Faculty of Science, Department of Chemistry, Rokitanskeho 62, 500 03 Hradec Kralove, Czech Republic

According to the World Malaria Report, there were 216 million cases of malaria with 445000 causalties in 2016. Current anticholinesterase insecticides, such as carbamates and organophosphates, act via covalent modification of serine at the bottom of the active site. Traditional chemical insecticides are highly toxic to insect but similarly to mammals. The cysteine-targeting concept of new insecticides is focused on cysteine 447 located in the peripheral site of mosquito acetylcholinesterase. In mammalian enzyme, the cysteine residue is replaced by phenylalanine, whereas honeybees or bumble-bees have this cysteine residue protected. This approach has been proposed to overcome insecticide resistance and to develop promising environmental-friendly insecticides.

The eight cysteine-targeted insecticides (succimides or maleinimides) were prepared via optimised synthetic route. The inhibitory activity of novel compounds and standards (paraoxon, bendiocarb and carbofuran) towards human acetylcholinesterase, human butyrylcholinesterase and mosquito acetylcholinesterase from *Anopheles gambiae* were determined using the modified spectrophotometric Ellman's method. The potentiometric titration using acetylcholine as a substrate was used for validation of Ellman's method. All data showed that the IC_{50} values obtained from both methods were almost similar. Human butyrylcholinesterase was used as common off-target for acetylcholinesterase inhibitors, and no inhibitory effect was determined. The binding mode of the inhibitors was determined using the rapid dilution assay.

Pyridinium maleimides were found with excellent efficacy towards mosquito acetylcholinesterase in contrast to the human enzyme and with significantly improved selectivity index compared to paraoxon. Despite some limitations, we believe that specific optimisation of the structure of molecule connected to maleimide moiety may lead to the development of novel promising insecticides.

Keywords: malaria; acetylcholinesterase; insecticide; cholinesterase inhibitor; cysteine

Acknowledgement

This work was supported by Ministry of Health of the Czech Republic (no. 16-34390A) and University of Defense (Long-term organization development plan Medical Aspect of Weapons of Mass Destruction).