AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

Ai Can Be Used For Identification Of Modified Oxime Nucleophiles With Enhanced Cholinesterase Reactivation

Kamil Musilek University of Hradec Kralove **David Malinak** University of Hradec Kralove, Faculty of Science, Department of Chemistry, Hradec Kralove, Czech Republic **Rudolf Andrys** University of Hradec Kralove, Faculty of Science, Department of Chemistry, Hradec Kralove, Czech Republic **Tamara Zorbaz** Institute for Medical Research and Occupational Health, Zagreb, Croatia **Zrinka Kovarik** Institute for Medical Research and Occupational Health, Zagreb, Croatia **Marek Bajda** Jagiellonian University Medical College, Faculty of Pharmacy, Krakow, Poland **Young-Sik Jung** Korea Research Institute of Chemical Technology, Daejeon, Republic of Korea **Kamil Kuca** University of Hradec Kralove, Faculty of Science, Department of Chemistry, Hradec Kralove, Czech Republic

The cholinesterase reactivators (so called “oximes”) are used as causal antidotes in case of organophosphorus intoxications. The effectiveness of the reactivator is strongly dependent on the formation of active nucleophile, the oximate anion. Its formation can be supported by optimizing the physical-chemical properties (i.e. pKa) of the oxime and the decreased pKa should lead to enhanced reactivation of phosphylated cholinesterases.

For this reason, the charged chlorinated oximes were introduced and proved to highly effective in vitro for reactivation of acetylcholinesterase and butyrylcholinesterase inhibited by multiple organophosphorus agents [1]. More recently, the charged fluorinated oximes were prepared and thoroughly evaluated with promising reactivation results against multiple organophosphorus (OP) agents, although their particular lower stability was found [2].

In the recent work, we have used artificial intelligence (AI) techniques to identify further molecular scaffolds of oxime nucleophiles that could modify oxime properties and enhance OP reactivation. The original ligands were obtained from Zinc database [3] and selected on the basis of particular physical-chemical properties. The oxime moiety was attached to selected molecular scaffolds and the molecular docking with OP-inhibited cholinesterases was performed. Over 250 modified oxime nucleophiles were selected with some valuable binding mode. After manual inspection, over 10 modified oxime nucleophiles were chosen for chemical synthesis. The stability and efficiency of oxime anion formation (pKa) was determined for all prepared molecules. Some modified nucleophiles were proved to be in vitro effective and excellent for reactivation of nerve agent surrogates, i.e., NEMP, NIMP or NEDPA-inhibited AChE [4]. In addition, such oxime nucleophiles can be encapsulated to ferritin nanovehicles for enhanced CNS delivery.

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