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MEETING ABSTRACTS

OXIMES WITH ORTHO-POSITIONED CHLORINE MOIETY EXHIBIT IMPROVED PHYSICAL-CHEMICAL PROPERTIES, EFFICIENT REACTIVATION OF INHIBITED HUMAN ACETYLCHOLINESTERASE AND REDUCED *IN VIVO* TOXICITY

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The series of bisquaternary oximes with ortho-positioned chlorine moiety was designed, prepared and evaluated. The novel compounds exhibited valuable pK_a properties [1] with improved *in vitro* reactivation ability of sarin, cyclosarin, VX, paraoxon- and dichlorvos-inhibited human AChE exceeding the standard monoquaternary or bisquaternary reactivators (pralidoxime, methoxime, trimedoxime, obidoxime and asoxime syn. HI-6). Additionally, some chlorinated compounds presented *in vitro* reactivation ability of tabun-inhibited human AChE similar to the efficiency of trimedoxime. The *in vitro* results were further explained by molecular docking study. The *in vitro* non-cytotoxic properties of novel compounds were determined with miscellaneous results. However, assessment of maximum tolerated dose highlighted that the selected chlorinated reactivator is well tolerated by mice on the level similar to the clinically or experimentally used oxime reactivators [2]. The *in vivo* reactivation study is in progress.

Keywords: organophosphate; antidote; oxime; chlorinated oxime; pK_a

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References

1. Musil, K. et al. J. Pharm. Biomed. Anal. 2016, 117, 240-246.
2. Musilek, K. and Zorbaz, T. et al. in progress.