SYNTHESIS OF NEW ACETYLCHOLINESTERASE REACTIVATORS STRUCTURAL FRAGMENTS AND IN VITRO EVALUATION OF THEIR BIOLOGICAL POTENCY

M. Paar\textsuperscript{a}, K. Kuča\textsuperscript{b}, D. Jun\textsuperscript{b}, M. Hrabinová\textsuperscript{b}, V. Opletalová\textsuperscript{a}

\textsuperscript{a}Department of Pharmaceutical Chemistry and Drug Control, Charles University in Prague, Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, CZ-500 05 Hradec Králové, Czech Republic

\textsuperscript{b}Department of Toxicology, University of Defence in Brno, Faculty of Military Health Sciences in Hradec Králové, Třebešská 1575, CZ-500 01, Hradec Králové, Czech Republic

Nerve agents (NA), such as sarin, cyclosarin, tabun or agent VX, are potent inhibitors of enzyme acetylcholinesterase (AChE; EC 3.1.1.7). Its inhibition leads to the cholinergic crisis in the body due to acetylcholine excess which can cause death of the intoxicated organism. In the treatment of NA intoxications, AChE reactivators are applied as causal antidotes. These compounds are able to renew AChE functionality by the release of NA fragment bonded to the enzyme active site by the mechanism of a nucleophilic attack. Tabun is probably one of the most dangerous compounds among the warfare nerve agents. The lone electron pair located on the amidic group makes the nucleophilic attack almost impossible, and deleterious effects of tabun are extraordinarily difficult to counteract. Commonly used reactivators of phosphorylated acetylcholinesterase (e.g. obidoxime, methoxime and HI-6) exhibit low reactivating efficacy and are not able to neutralize the toxic effects of tabun. Two years before, we have developed two new promising AChE reactivators (K027 and K048) with a satisfactory efficacy to reactivate AChE inhibited with tabun.

\[\text{tabun} \quad \begin{array}{c}
O \text{NC} \text{N} \\
\text{CH3} \text{H3C} \text{CH3}
\end{array} \]

\[\begin{array}{c}
O \text{NH2} \\
\text{CH2 -(CH2)n-CH2}
\end{array} \quad \begin{array}{c}
\text{NOH} \\
\text{2 Br}
\end{array} \]

\[\text{K027 (n = 1); K048 (n = 2)}\]

In this work, we were interested in the contribution of several structural fragments of these reactivators to their reactivation potency. We have synthesized all their possible quaternary pyridinium sub-structures involved in their molecules and tested their biological potencies.

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