Derivatives of Lupinin and Epilupinin as Ligands of Various Cholinesterases

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Abstract—Literature data are summarized on cholinesterases of some mammals and arthropods with a group of isomer derivatives of alkaloid lupinin and its epimer epilupinin. As substrates of cholinesterases of some mammals there are studied 8 acetates containing in their molecule chinolysidin bicycle with different structure of N-alkyl radical, which showed certain elements of action specificity. For 2 isomer esters that are derivatives of protonated base of lupinin and epilupinin, differences are revealed in their substrate characteristics. Polyenzyme analysis of anticholinesterase efficiency is performed for 30 organophosphorus inhibitors that are dialcoxyphosphorus derivatives of lupinin and epilupinin; as a result, we managed to find out quite a few peculiarities of their action depending on structure. Several tested compounds were revealed to be specific inhibitors of cholinesterases of several mammals and arthropods.

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INTRODUCTION

Among the numerous numbers of ligands of cholinesterases (ChE), of great importance are derivatives of nitrogen-containing alkaloids that are substrates, reversible substrates, and irreversible organophosphorus inhibitors (OPI) [1–3]. It is natural that analysis of their interaction with ChE is always performed with taking into account comparison of elements of the molecule effector structure with its activity toward representatives of this voluminous enzyme family. It is to be taken into account that by the mechanism of reaction ability of ligands with respect to ChE, the substrates and OPI in nature are qualitatively related to the covalently bound intermediate complex: in the substrate it is formed due to acylation, while in the case of OPI—due to phosphorylation of the catalytic triad of the ChE active center [2–4]. And, of course, the important block of information provides such variation of the ligand molecule structure, which would not affect their acylating (phosphorylating) activity.

In this connection we paid attention to a group of derivative of lupinin and of its epimer epilupinin [1, 5–7]. Lupinin represents 1-hydroxymethylchinolysidin with axial hydroxymethyl group, whereas epilupinin—a more stable lupinin isomer with the equatorial hydroxymethyl group [6]. Besides, the nitrogen atom of the chinolysidin bicycle was iodoalkylated by radicals of different length and the branching degree [1]. Such structural differences do not affect the reaction ability of the hydroxymethyl group. Based on these alkaloids there were synthesized acyl and phosphoryl derivatives of lupinin and epilupinin that earlier were studied as substrates and inhibitors of various ChE [1–3, 7–14].
The problem of metabolism of the lupinin and epilupinin derivatives in the animal organisms includes many enzymatic processes (alkylation, acylation, hydrolysis, etc.) [1, 5]. From this point of view, study of cholinesterase hydrolysis of the lupinin derivatives is one of stages of their metabolic transformations [1, 8]. This review presents data on study of two rows of acetates based on lupinin (I) and epilupinin (II). Due to that the value of $pK_a$ for lupinin (by analogy with N-methylpiperidin) is equal to 10 [15], the base of lupinin and epilupinin at pH 7.5 (our studies were carried out at pH 7.5) were protonated practically completely. Therefore, all studied compounds are ammonium derivatives. At interaction with ChE of such complex esters with voluminous bicyclic molecules, an important role is played by the process of non-productive substrate binding [2, 3, 16, 17], which is taken into account at analysis of process of enzymatic substrate hydrolysis. Besides, we performed comparison with the row of derivatives of acetylcholine (ACh) [2, 16].

It is well known [2, 3] that phosphorylation of catalytic triad of the ChE active center allows using OPI for estimation of the quantitative measure of reactional ability of various ChE [2–4]. But in the case of lupinin OPI, when variation of the OPI molecule structure does not affect their phosphorylation, it becomes possible to compare directly the structure of inhibitors with their anticholinesterase efficiency. In this review we are presenting data for 4 rows of isomer dialcoxythiolphosphate derivatives of bases of lupinin and epilupinin (as noted above, all studied compounds are ammonium derivatives) as well as of their iodomethylates by ChE inhibition of 4 species of mammals and of 6 species of arthropods. The testing results are analyzed in detail on the effect of OPI structure upon the reaction ability of animals located at different levels of evolutionary development.

Thereby the subject of study in the present review has become a unique group of cholinesterase ligands whose structures differ both at the level of epimers (the lupinin and epilupinin derivatives) and at the level of isomers (N-alkyl radicals of the normal and isostructure). Here there is presented a rare possibility of the effect of relatively small changes of structure of molecules of substrates and OPI close by structure of detached part upon their ligand properties. Study of anticholinesterase properties of the chinolysidin OPI with respect to the sufficiently large set of different ChE provides important information for the polyenzyme analysis of their reactional ability.

**SUBSTRATES, ORGANOPHOSPHORUS INHIBITORS, ENZYMES**

Studied as substrates were the following derivatives of lupinin (row I) and of epilupinin (row II):

\[
\begin{align*}
&\text{CH}_3\text{C(O)OCH}_2 & &\text{CH}_3\text{C(O)OCH}_2 \\
&\text{I: } R=\text{Me} & &\text{II: } R=\text{H} \\
&\text{R=CH}_3 & &\text{R=CH}_3 \\
&\text{R=C}_2\text{H}_5 & &\text{R=C}_2\text{H}_5 \\
&\text{R=C}_3\text{H}_7 & &\text{R=C}_3\text{H}_7
\end{align*}
\]

as well as derivatives of acetylcholine (ACh)

\[
\begin{align*}
&\text{CH}_3\text{C(O)OC}_2\text{H}_5\text{N}^+\text{R} & &\text{CH}_3\text{C(O)OC}_2\text{H}_5\text{N}^+\text{R} \\
&\text{I: } R=\text{Me} \text{ (ACh)} & &\text{II: } R=\text{H} \\
&\text{R=C}_2\text{H}_5 \text{ (ACh.Et)} & &\text{R=C}_2\text{H}_5 \text{ (ACh.Pr)}
\end{align*}
\]

Used as OPI were the following dialkyl phosphoryl derivatives of lupinin (rows III and V) and of epilupinin (row IV and VI) synthesized by A.A. Abduvakhabov and D.N. Dalimov at Sadykov Institute of Bioorganic Chemistry of the Uzbekistan Academy of Sciences [1]:

**Row III**

\[
\begin{align*}
&\text{R=CH}_3 \text{ (III.6)} & &\text{R=C}_3\text{H}_7 \text{ (III.16)} \\
&\text{R=CH}_2\text{H}(\text{III.9}) & &\text{R=C}_3\text{H}_7 \text{ (III.10)} \\
&\text{R=C}_2\text{H}(\text{III.11}) & &\text{R=C}_3\text{H}_7 \text{ (III.12)} \\
&\text{R=C}_2\text{H}(\text{III.13}) & &\text{R=r-C}_2\text{H}_2 \text{ (III.14)} \\
&\text{R=r-C}_4\text{H}_9 \text{ (III.15)} & &\text{R=r-C}_3\text{H}_11 \text{ (III.16)}
\end{align*}
\]

**Row IV**

\[
\begin{align*}
&\text{R=CH}_2\text{H} \text{ (IV.17)} & &\text{R=C}_3\text{H}_7 \text{ (IV.18)} \\
&\text{R=C}_2\text{H}(\text{IV.19}) & &\text{R=C}_3\text{H}_7 \text{ (IV.20)} \\
&\text{R=C}_2\text{H}(\text{IV.21}) & &\text{R=r-C}_2\text{H}_2 \text{ (IV.22)} \\
&\text{R=r-C}_4\text{H}_9 \text{ (IV.23)} & &\text{R=r-C}_3\text{H}_11 \text{ (IV.24)}
\end{align*}
\]

**Row V**

\[
\begin{align*}
&\text{R=CH}_2\text{H} \text{ (V.25)} & &\text{R=C}_2\text{H}_5 \text{ (V.26)} \\
&\text{R=C}_2\text{H}(\text{V.27}) & &\text{R=C}_3\text{H}_11 \text{ (V.28)} \\
&\text{R=C}_2\text{H}(\text{V.29}) & &\text{R=r-C}_4\text{H}_9 \text{ (V.30)} \\
&\text{R=r-C}_3\text{H}_11 \text{ (V.31)}
\end{align*}
\]