THE INNOVATIVE TETRAHYDROACRIDINE'S HYBRIDS WITH ANTI-INFLAMMATORY COMPONENT

The aim of the study has been synthesized new series of compounds (hybrids), showing an inhibition activity against to acetyl- and butyrylcholinesterase, with an additional anti-inflammatory and antioxidant activity. The new series of eight compounds - 9-amino-1,2,3,4-tetrahydroacridine and indomethacin derivatives, linked by an alkyldiamine chain of various length - from 2 to 9 carbon atoms in the chain - was designed and synthesized. Inhibitory potency against AChE and BuChE was studied. All of tested compounds were showed a high inhibitory activity against cholinesterases with the IC50 values between 10nM and 7μM, higher than the well-known inhibitors of AChE and BuChE - tacrine and donepezil. Compounds **3h** showed the highest inhibitory potency and was selected to the study of reaction kinetics on AChE and BuChE – mixed type of enzyme inhibition has been specified. The cytotoxicity against HepG2 and EA.hy96 cells, using the MTT and MTS tests, for obtained compounds were studied and showed similar low cytotoxicity at the micromolar concentrations. The inhibitory activity against cholinesterase at the nanomolar level suggests that the obtained compounds may have a high therapeutic index as potential drugs. The antioxidant properties for all obtained compounds were studied and compared with known strong antioxidant – Trolox, and compounds without antioxidant activity – tacrine and indomethacin. The compounds with longer alkyldiamine linker showed much higher antioxidant activity, while the compound 3h was the strongest. Molecular modeling confirmed the possibility of binding between tested compounds with a longer linker and significant fragments of the AChE and BuChE enzyme molecules. Multidirect activity of 3h compounds confirmed by research (high inhibitory potency against cholinesterases, antioxidant activity) and low cytotoxicity, makes of it a promising potential drug in the treatment of Alzheimer's disease.