MULTITARGET AGENTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE BASED ON CHOLINESTERASE INHIBITORS

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The current strategy for increasing the effectiveness of therapy for complex multifactorial diseases, which includes Alzheimer's disease (AD), consists in the development of multitarget agents that interact with several targets responsible for pathogenesis. One of the approaches is based on the development of hybrid structures – conjugates containing two different pharmacophores connected by a spacer. In this case, one of the pharmacophores is a molecule of a well-known anticholinesterase drug, and as the second, fragments are introduced that impart neuroprotective and disease-modifying properties to the conjugates. Using the concept of esterase profile, supplemented by an assessment of the potential ability of compounds to block AChE-induced aggregation of β -amyloid and their antioxidant activity, and with extensive use of computer molecular modeling methods, we have found new multitarget compounds based on conjugates of 4-amino-2,3-polymethylenequinolines with derivatives of 1,2,4-thiadiazole, salicylic acid, p-tolylsulfonamide, BHT, vanillin. The conjugates have good intestinal absorption and high permeability across the blood-brain barrier and should not cause unwanted drug-drug interactions due to the very weak CES inhibition. The pharmacological profile of conjugates is largely determined by the structure of the spacer. Within the framework of this concept, a number of derivatives of the domestic anticholinesterase preparation amiridine were also investigated. Methods of computer molecular modeling have shown ways to increase their anticholinesterase and antiaggregatory activity.

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