

PLENARY PRESENTATIONS

CHEMICAL MODIFICATIONS OF PLANT ALKALOIDS AS A RELIABLE STRATEGY FOR DESIGNING AND RECOGNIZING OF NEW GROUPS OF ACETYLCHOLINESTERASE INHIBITORS

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Alkaloids represent a promising source for the discovery of new therapeutic agents due to the diversity of their chemical structures and pharmacological activities. The neuroprotective properties of alkaloids in Alzheimer's disease are attributed to their ability to regulate processes such as beta-amyloid aggregation, oxidative stress, synaptic dysfunction, tau protein hyperphosphorylation, neuroinflammation and also cholinesterase inhibition.

To develop novel acetylcholinesterase inhibitors, we propose the use of a dual-scaffold approach, where one scaffold is an alkaloid structure, connected by a rigid aminopropynyl spacer.

Natural methylxanthines – caffeine, theobromine, and theophylline – are widely used in medicinal chemistry for the development of potent bioactive agents. A copper-catalyzed one-pot three-component reaction (A^3 -coupling) of 8-ethynylcaffeine with secondary amines and formaldehyde was employed as the primary method for the synthesis of substituted 8-aminopropynylcaffeinines (yield 65–79%). The A^3 -coupling reaction of 3,7-dimethyl-1-propynylxanthine or 1,3-dimethyl-7-propynylxanthine with secondary amines and formaldehyde was used for the synthesis of N-substituted 1-aminobutynyl- or 7-aminobutynyldimethylxanthines (yield 52–68%)

Isatin (1*H*-indole-2,3-dione) is widely distributed in nature and serves as the monomeric structure of the natural antitumor drug indirubin. We have proposed efficient methods for the modification of isatin derivatives at the C-5 position. The proposed approaches for the synthesis of 5-(3-X-prop-1-yn-1-yl)-substituted isatin derivatives are based on a A^3 -coupling reaction of 3-(1,3-dioxolane)-5-ethynylisatins with formaldehyde and secondary amines. The second approach involved the Sonogashira coupling of C-3 protected iodoisatins with fluoro-N-(prop-2-ynyl)benzamide or prop-2-ynyl 4-fluorobenzoate. Deprotection of the dioxolane ketal was successfully achieved by treatment with HCl in MeOH (1:9 v/v) (yield 53–87%).

The biological activity of all new compounds was evaluated using the Ellman method. The results showed that most of the synthesized substances exhibit moderate to high inhibitory activity against acetylcholinesterase *in vitro*. Compounds demonstrating significant inhibitory activity against acetylcholinesterase were identified, with IC_{50} values in the range of 0.068–3.19 μ M. The obtained biological data are in agreement with the results of molecular docking, which showed strong binding energies of the investigated compounds under study with biological targets – Tyr72, Trp86, Tyr124, Tyr133, and others, including Ser203 and His447 residues of the AChE catalytic triad.

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