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SYNTHESIS AND EVALUATION OF β-SECRETASE INHIBITORY ACTIVITY OF NEW GALANTAMINE DERIVATIVES COMPRISING PEPTIDE MOIETY

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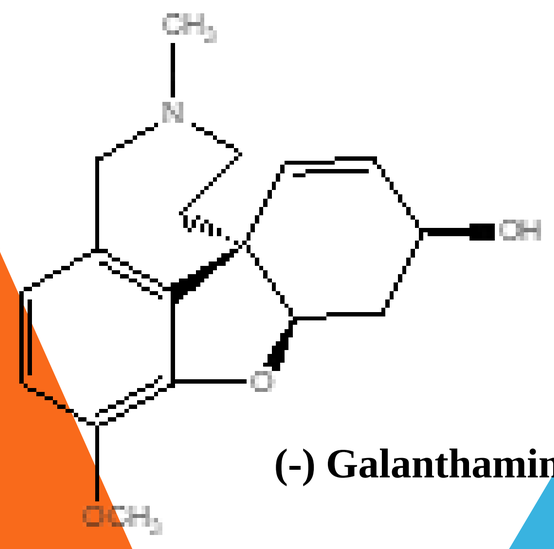
The Alzheimer's disease leads to neurodegenerative processes and affecting negatively million people worldwide. The treatment of the disease is still difficult and incomplete in practice. One of the most useful in a medicine practice cholinesterase inhibitors is Galanthamine (Gal). It inhibit the β-amiloid aggregation and decrease the toxicity of the β-amyloid peptide (Aβ) [1]. The enzyme β-secretase plays an important role in the process of proteolytic cleavage and progression of AD, therefore we directed our research in the search of new potent beta-secretase inhibitors.



(-) Galanthamine structure

Purpose:

The purpose of this work is synthesis of new derivatives of galanthamine comprising peptide moiety as well as study of their β-secretase inhibitory activity.

Methods:

The solid-phase peptide synthesis (SPPS) by Fmoc (9-fluorenylmethoxycarbonyl) chemistry was used to synthesize target compounds.

The peptide purity was monitored on a RP-HPLC. The LC/MC spectra were recorded on a LTQ XL Orbitrap Discovery instrument. The optical rotation was also measured. Analysis of the inhibitory activity of the compounds against β-secretase was performed using the commercial kit (β-secretase activity assay kit (F).

Results:

In our previous studies, we found that incorporation of an anti-aggregating peptide motif at position 6 of Galantamine significantly increased β-secretase inhibitory activity [2].

Compound structure	Concentration [nM]	Inhibition %	IC_{50} [nM]
6-*O*-[Boc-Leu-Val-Phe-Phe-Gly]-Gal	2.1	19.98	5.26
6-*O*-[H-Leu-Nva-Phe-Phe-Gly]-Gal	2.17	51.19	1.95
6-*O*-[Boc-Leu-Nva-Phe-Phe-Gly]-Gal	2.15	27.24	3.95
6-*O*-[H-Leu-Tle-Phe-Phe-Gly]-Gal	2.04	46.03	1.96
6-*O*-[Fmoc-Nle-Val-Phe-Phe-Gly]-Gal	1.86	23.01	4.04

Here we report the synthesis of six novel peptide-galantamine derivatives in which the substitution is at the 11-position of Galantamine in order to establish the influence of the position on biological activity. Inhibitory activity was shown by two of the investigated compounds, which have the following structure:

Table 1 Inhibition of the studied compounds towards BACE-1

Compounds structure	MW	Tested concentration	% inhibition	IC50 calculated
11-N-demethyl-11-N,N-[H-Asp(Lys-Leu-Val-Phe-Phe)]-Gal	1023.35	1 mg/ml	5	5.6 uM
11-N-demethyl-11-N,N-[H-Asp(Tle-Asp-Leu-Ala)]-Gal	801.40	1 mg/ml	8	12.5 uM

Conclusion:

After the studies carried out, we found that the inclusion of peptide moiety at position 11 of galantamine did not result in a significant increase in beta inhibitory activity, unlike that at position 6.

References:

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