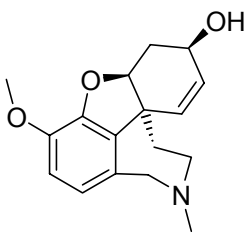
Galanthamine as lead structure – Advancements of drugs against Alzheimer's disease

In the present work contributions were made for the improvement of drugs against Alzheimer's disease (AD) through syntheses, biochemical procedures and theoretical investigations. The studies are based on the *amaryllidaceen alkaloid* (–)-galanthamine as lead structure.



(-)-Galanthamine

(–)-Galanthamine is a selective inhibitor of the enzyme acetylcholinesterase (AChE). AChE is responsible for the termination of the chemical transmission in cholinergic synapses through cleavage of the neurotransmitter acetylcholine (ACh). The reduced cholinergic activity in AD can be improved by the reversible inhibition of AChE. (–)-Galanthamine is the only approved AChE inhibitor, which in addition to esterase inhibition also acts as allosterically potenting ligand (APL) on the nicotinic acetylcholinereceptor (nAChR) and therefore shows a dual effect on the cholinergic system.

In the context of this work photoaffinity labelling experiments with the nicotinic acetylcholinereceptor and (–)-galanthamine were performed. For these experiments tritium labelled (–)-galanthamine was needed which is not commercially available. Therefore, three routes were investigated for the synthesis of specifically labelled (–)-galanthamine of high specific radioactivity. For the final preparation stereospecific reduction of the carbonyl group of the (–)-galanthamine precursor (–)-narwedine with tritiated L-Selectrid® was employed. Using this labelled compound in photoaffinity labelling experiments it was shown that the binding site of (–)-galanthamine is located on the α-subunit of the receptor.

Potential (–)-galanthamine-based AChE inhibitors were examined by docking studies in order to extended the interaction of this ligand and the enzyme. To this extend six classes of compounds were docked, which may interact with both known binding sites of AchE, the ester cleavage site and the peripheral binding site, respectively. For two of these evaluated classes syntheses were developed. In the further course of the project these compounds shall be evaluated in a biological assay in order to prove the results of the theoretical investigations.