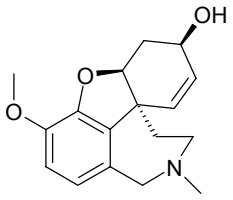
Galanthamin als AChE-Inhibitor – Beiträge zum rationalen Wirkstoffdesign

by Christian Pilger

Alzheimer's dementia (AD) is characterized by a progressive memory loss, that leads to profound emotional disturbances in later stages. The disease is accompanied by dysfunctions within the system of cholinergic neurotransmission in the central nervous system. The nerve impuls in cholinergic synapses is terminated by the enzyme acetylcholinesterase (AChE), which cleaves the neurotransmitter acetylcholine. Reversible inhibition of this enzyme leads to an increase of the neurotransmitter concentration within the synaptic cleft, which positively affects patients suffering from AD. Based on the *cholinergic hypothesis*, this treatment solely has lead to drugs for the symptomatic treatment of AD.



(–)-galanthamine

Being a potent inhibitor of AChE with an acceptable pharmacological and toxicological profile, the *amaryllidaceae* alkaloid (–)-galanthamine is a promising lead structure for the development of the next generation AD drugs.

In the course of this dissertation a new synthetic strategy for galanthamine was developed, which is based on a stereoselective Heck reaction as the key step. The approach lead to the tetracyclic framework of the galanthamine moiety. The new pathway was found to be a versatile tool for the synthesis of derivatives of the lead structure galanthamine.

In accompanying Molecular Modelling studies the interactions between the enzyme and each member of a database of known galanthamine derivatives was investigated by automated docking. The employed techniques allowed for the correct prediction of the structure of the galanthamine/AChE complex (species: *Torpedo californica*). Based on the docking results a 3D-QSAR model was developed and successfully validated by different statistical methods. This model is a useful tool to estimate the biological activities of new galanthamine deivatives.