

// CHOLINERGIC ACTIVITY ENHANCERS (CAES)

Ref-Nr: TA-5831

HINTERGRUND

Acetylcholine (ACh) is an essential neurotransmitter with a major function in the central and peripheral nervous system. Furthermore, ACh plays a crucial role in the autonomic nervous system stimulating preganglionic parasympathetic and sympathetic nerve fibres and postganglionic parasympathetic neurons. In certain pathophysiological conditions ACh concentrations can be reduced, leading to a huge variety of clinical symptoms. The ACh depletion may originate from reduced ACh synthesis, an alteration of the receptor response, an increased acetylcholin-esterase (AChE) activity and a degeneration of cholinergic neurons in the central nervous system. CAEs represent naturally occurring alkaloids, which indirectly stimulate muscarinic and nicotinic receptors by increasing ACh concentrations by an AChE inhibition.

LÖSUNG

Since the important role of these receptors in the central nervous system on cognitive function is well known, the AChE is a target of neuroenhancement and for treating diseases with cognitive dysfunction (e.g. Alzheimer's disease). For instance, galanthamine, donepezil and rivastigmine, which are potent inhibitors of the AChE, are first-line drugs for treating dementia. The pharmacological data of the novel alkaloids was collected using isolated organs of mice within ex vivo experiments and enzyme assays. AChE inhibition was dose-dependent and potentiated smooth muscle contraction similar to galanthamin, that was used for comparison.

Besides the pharmacodynamics, pharmacokinetic properties are of major interest. The glucose moiety of the alkaloids leads to a good solubility in water and might enhance the absorption of the compounds in the gastrointestinal tract. In addition, acetylated derivatives with increased lipo-philicity for better barrier penetration are available, which may serve as prodrugs.

A great advantage is that the alkaloids can be regarded as non-toxic. Based on a toxicological in vitro assessment including different cell lines (human liver cells, human keratinocytes, epithelial intestinal cells) the compounds do not influence proliferation over a wide concentration range (1 to 100 μ M). This is of high significance, since hepatotoxicity can be a limiting factor for AChE inhibitors, as it is for tacrine, the prototype of AChE inhibitors. Due to the AChE inhibition an



PROvendis GmbH

Dr. Constanze Vogel
+49.208 94105-41
cv@provendis.info
www.provendis.info

ENTWICKLUNGSSTAND

Labormuster

PATENTSITUATION

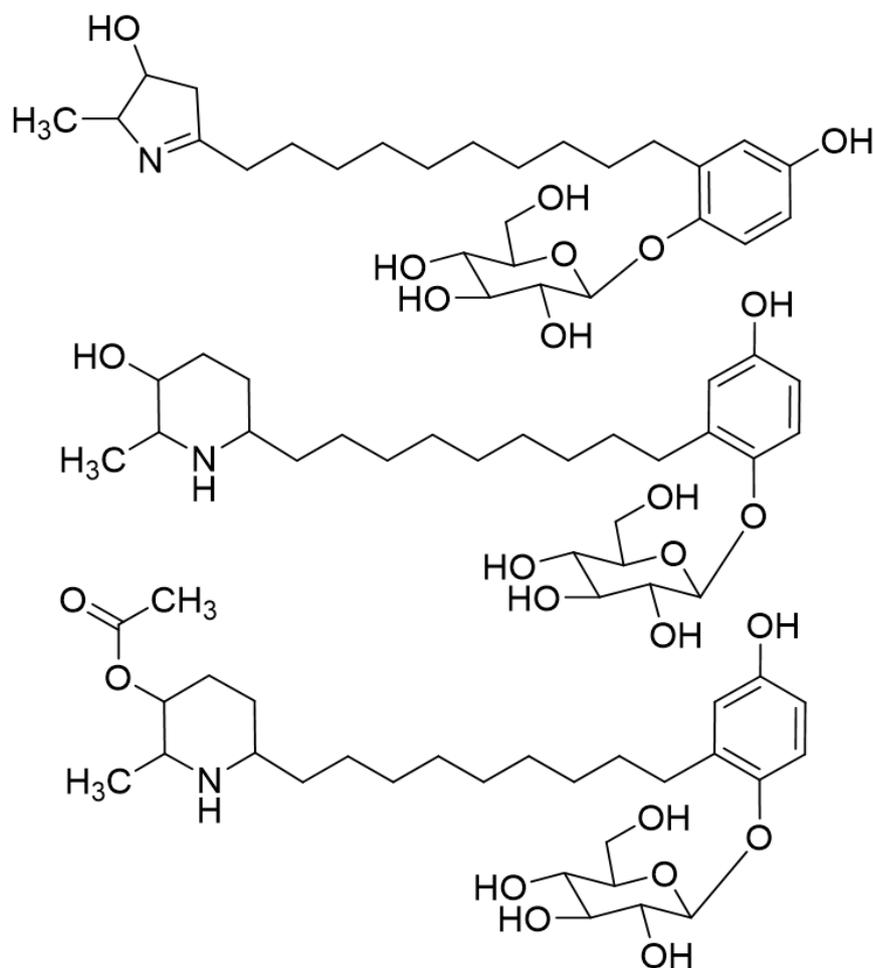
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CATEGORIES

//Medizin und Pharma //Therapie
und Wirkstoffe

administration of the innovative alkaloids might have beneficial effects on Alzheimer´s disease or function as neuroenhancers in states of cognitive dysfunction. Besides, there are further promising indication areas for the novel alkaloids. Peripheral cholinergic effects on muscle cells could be advantageous for treating Myasthenia gravis or hypotonic bladder.

The piperidine- and dihydropyrrole-alkaloids can be synthesized or isolated from plant material. In addition, it is possible to administrate the alkaloids as plant extracts with enriched and standardized amounts of the alkaloids, which could be an optimal alternative for patients with a high demand for natural and sustainable products.



Structures of cholinergic activity enhancing alkaloids

VORTEILE

- Bioactive alkaloids
 - Neuroenhancement
 - Inhibition of AChE
 - Natural products from plants
 - Novel synthesizable compounds
 - Useable also as standardized plant extract
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ANWENDUNGSBEREICHE

On behalf of the University of Münster, PROvendis is offering this opportunity for licensing or co-development to interested companies.

SERVICE

For the innovative alkaloids in vitro and ex vivo data are available. In case of interest, we are pleased to inform you about the patent status.
