

## // BETTER TOGETHER – NOVEL DUAL-ACTING AND DISEASE-MODIFYING APPROACH TO COMBAT ALZHEIMER'S

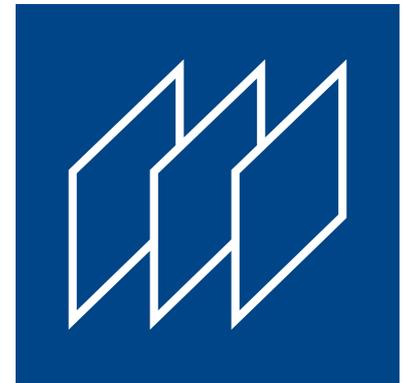
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### HINTERGRUND

Alzheimer's disease (AD) is a neurodegenerative disorder with cognitive, functional, and behavioral alterations. AD is progressive and memory loss and personality changes pose a great burden for the more than 25 million patients and their families worldwide. Despite all efforts to identify the cause and halt the fast progression, only 5 drugs are currently approved in the US for treating the cognitive decline with no new therapies in over a decade. The cholinesterase (ChE) inhibitor tacrine raises levels of the neurotransmitter acetylcholine (ACh). However, the compound exhibits dose-dependent hepatotoxicity and acts only symptomatically, like all approved drugs. Due to the complex pathophysiology of AD, multi-target strategies may be the way forward<sup>1</sup>. Here, tacrine can pose a promising start for developing a multitarget drug. The last years have yielded evidence that activating the human cannabinoid receptor subtype 2 receptor reduces overall AD-like pathology by attenuating associated neuroinflammation and improving cognitive impairment in animal models<sup>2</sup>.

### LÖSUNG

Here, we present hybrids of tacrine and an hCB2R agonist connected by different linkers. All synthesized hybrids showed pronounced inhibition of human ChEs compared to tacrine alone and interfered with overall  $\beta$ -amyloid aggregation. The most promising hybrids showed pronounced anti-neuroinflammatory effects in vitro on microglia cells and neuroprotection in vivo as evidenced by attenuation of short- and long-term memory in a murine Alzheimer's model<sup>3</sup>. Importantly, even high doses of hybrid compounds (3mg/kg) lacked hepatotoxicity seen with tacrine alone.



Bayerische Patentallianz GmbH

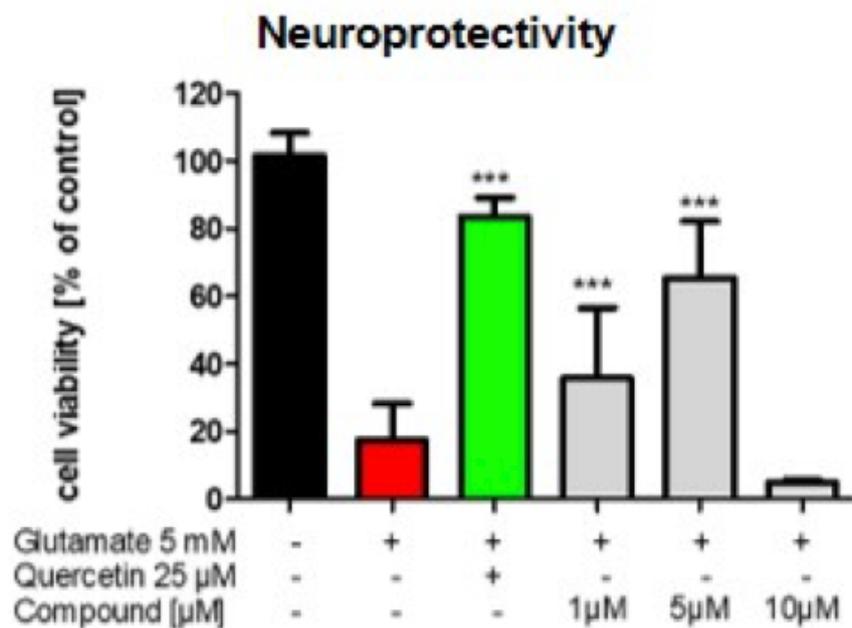
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### ENTWICKLUNGSSTAND

Machbarkeit

### CATEGORIES

//Life Sciences



Glutamate-induced oxidative stress test in a neuronal cell line confirms hybrids to have a pronounced neuroprotective effect comparable to positive control quercetin but already at much lower concentration.

#### VORTEILE

- Stronger inhibition of ChEs compared to tacrine alone
- Efficient crossing of blood-brain barrier despite high molar mass
- High in vivo efficacy even at low dosages (0.1 mg/kg) and no liver toxicity