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MEETING ABSTRACTS

CASE STUDIES FOR SUCCESSFUL COMBINATION OF ChE INHIBITORS AND GPCR LIGANDS (CANNABINOID 2 AND HISTAMINE 3 RECEPTORS)

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The combination of cholinesterase inhibitors with GPCR ligands in hybrid molecules seems highly promising for Alzheimer's disease (AD) therapy, since two very different molecular targets can be addressed at the same time. Nevertheless, significant challenges come with this rationale: a) hybrids might possess too high molecular weights to be orally bioavailable and/or pass the blood-brain-barrier, b) the compounds might act in different concentration ranges, c) and selectivity and affinity has to be optimized for several very distinct targets.

We have designed – applying computational methods - and synthesized dual-acting ChE-inhibitors that act with high potency and selectivity also at the histamine 3 receptor (hH$_3$R) [1], and the same could be achieved for cannabinoid 2 receptors (hCB$_2$R) [2, 3], both GPCRs represent important AD targets. Regarding dual-acting ChE inhibitors and hCB$_2$R agonists both covalently connected hybrids using the unselective ChE inhibitor tacrine as well as merged small molecules with high butyrylcholinesterase (BChE) selectivity have been obtained and pharmacologically characterized *in vitro*. Representative examples from all sets of compounds have been investigated *in vivo* in different AD mice models [3].

The case studies demonstrate that it is possible to obtain dual-acting compounds that a) act highly selectively and with high affinity at the respective targets, b) work in the same concentration range ("balanced affinity"), c) exhibit pronounced *in vivo* activity.

Keywords: GPCR; cannabinoid; histamine; merged ligands; hybrid molecules

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