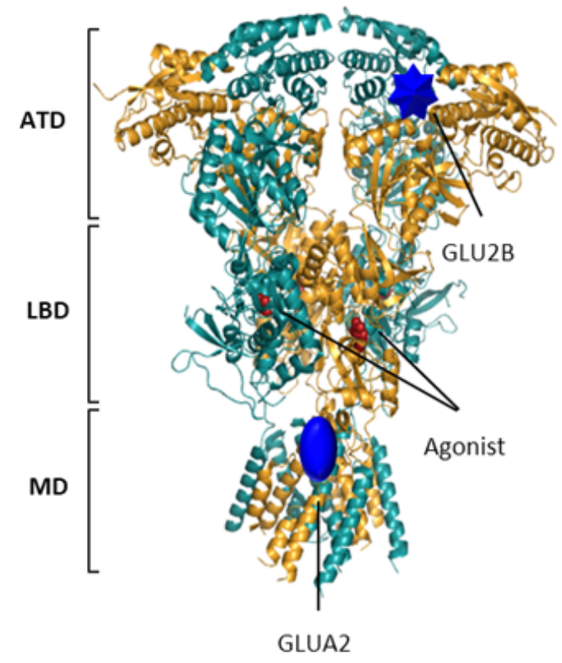
# DUALLY ACTING DERIVATIVES IN DISEASE

# TACRINE ALZHEIMER'S TREATMENT





## TECHNOLOGY OWNER

University Hospital Hradec Králové
Institute of Physiology CAS
National Institute of Mental Health
Institute of Experimental Medicine CAS

## INVENTORS

Ondřej Soukup, Martin Horák, Anna Misiachna, Jan Korábečný, Karel Valeš, Ladislav Vyklický


## IPR STATUS

Czech patent applications
PV 2021-34 & PV 2021-35
(priority date 26. 1. 2021)
PCT/CZ2022/050004

## STAGE OF DEVELOPMENT

In vivo validation

Pharmaco - kinetics in rats

Leading compound in vivo

Structure-activity relationships


LUCIE BARTOŠOVÁ
LUCIE.BARTOSOVA@FNHK.CZ
+420 727 802 314


## Background

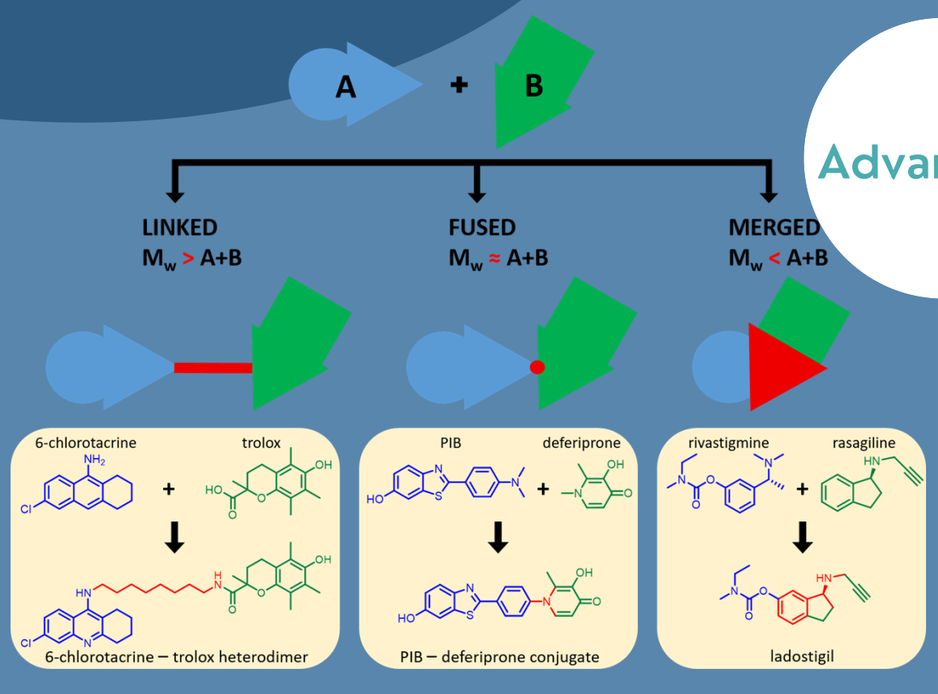
The so-called **multitarget-directed ligand paradigm** has been widely applied in the last decade to find novel drug candidates against Alzheimer's disease (AD). However, this approach seems to be limited by oversimplified design of novel drug candidates combining pharmacophores with incompatible mechanisms of action, or by reason of irrelevance in the context of disease progression in time. Another limitation is associated with the fact that simple linking of the two pharmacophores usually leads to lower drug-likeness, and hence fused or merged strategies are more preferred. Since AD is currently treated by **acetylcholinesterase inhibitors** (AChEI) and memantine, an **antagonist of N-methyl-D-aspartate receptors** (NMDAR), a combination of such drugs makes sense, given the fact that impairment of both cholinergic and glutamatergic neurotransmission occurs simultaneously, i.e. in the latter stage of the disease.

## Description

We developed novel tacrine derivatives with dual effect on cholinesterases and NMDAR, specifically with preference towards **GluN1/GluN2A** and/or **GluN1/GluN2B** receptors. Specifically, we synthesized a series of 30 tacrine derivatives and investigated their inhibitory potency towards human recombinant AChE (hAChE) and human plasmatic butyrylcholinesterase (hBChE), and their ability to block GluN1/GluN2A and GluN1/GluN2B receptors at negative and positive membrane potentials. These experiments were followed by analyses of quantitative structure-activity relationships (QSAR). In addition, to follow the potential clinical application of such dually-acting compounds, we have selected the **six most promising candidates** with more or less balanced activities and characterized them for their ability to **cross the blood-brain barrier** and for their **safety in vivo**, since a major concern for NMDAR ligands is their psychotomimetic side effects. From the (pre-) clinical point of view, we observed in rats that the tested novel compounds did not induce hyperlocomotion, neither impaired the prepulse inhibition of startle response. Thus despite of proved CNS availability of this class of compounds **absence of side-effects** typical for blockers of NMDA receptors was observed. Thus, the data have indicated that tacrine derivatives are promising dual-acting compounds, which in addition to their anti-ChE effects, act as centrally available subtype-specific inhibitors of the NMDARs without negative behavioral side effects.

## Advantages

AD is a multifactorial pathology and thus it requires a multi-faceted approach to therapy. Our dual concept applying inhibition of both AChE and NMDAR even in one molecule corresponds to these efforts. It was proved that AChE and NMDAR inhibitors' combination benefits patients with usually additive effects, without any increase in adverse effects. While tacrine (approved for AD treatment in 1993) was withdrawn from the market due to its hepatotoxicity and other side effects in 2013, our compounds were prepared to **avoid this hepatotoxic effect**, that is now being proved. Additionally, since these compounds have also been found acting as GluN2B selective NMDAR antagonists, they are therefore believed to hold strong therapeutic potential in the treatment of other disorders – e.g. ischemic damage, chronic pain and depression.




WWW.CTBT.CZ

CTBT
Centrum transferu biomedicínských technologií