MMSL
Military Medical Science Letters
Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2022, 91 (supplementum 1)
ISSN 0372-7025 (Print)
ISSN 2571-113X (Online)

27th Interdisciplinary Toxicology Conference; https://toxcon2022.bpp.cz/
29.8. - 1.9.2022, University of Hradec Kralove, Hradec Kralove, Czech Republic

## MEETING ABSTRACTS

# TARGETING TACRINE HEPATOTOXICITY ASSOCIATED WITH THE CYP BIOTRANSFORMATION

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Current symptomatic pharmacotherapy for Alzheimer's disease is primarily focused on acetylcholinesterase inhibitors and blocking of the NMDA receptor (N-methyl-D-aspartate). Tacrine, a molecule with both of the mechanisms of action, was withdrawn from the market in 2013 after 20 years of use due to the hepatotoxicity probably caused by its 7-hydroxytacrine metabolite. A rationale substitution of the tacrine molecule can potentially hinder the formation of a toxic species. The introduction of the methoxy or phenoxy group to position 7 led to 7-phenoxytacrine (7-PhO-THA) which we hypothesize to bypass the toxic metabolization via 7-OH tacrine and quinon methid. Furthermore, 7-PhO-THA was confirmed being of dual potency, i.e. potent and balanced inhibition of both AChE and NMDARs. We discovered that it selectively inhibits the GluN1/GluN2B subtype of NMDARs via an ifenprodil-binding site, in addition to its voltage-dependent inhibitory effect at both GluN1/GluN2A and GluN1/GluN2B subtypes of NMDARs. Furthermore, whereas NMDA-induced lesion of the dorsal hippocampus confirmed potent anti-excitotoxic and neuroprotective efficacy, behavioral observations showed that 7-PhO-THA manages to avoid side effects, symptoms of schizophrenia typical for NMDA antagonists.

The work was supported by the Ministry of Education, Youth and Sports of Czech Republic (project ERDF no. CZ.02.1.01/0.0/0.0/18_069/0010054

*Keywords: tacrine; hepatotoxicity; CYP450; biotransformation; quinon methid*