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MEETING ABSTRACTS

FROM DUAL BINDING SITE AChE INHIBITORS TO CHAMELEON MOLECULES: DISCOVERY OF POTENT BuChE INHIBITORS

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Current pharmacotherapy for Alzheimer's disease (AD) involves compounds aimed at increasing the levels of acetylcholine in the brain through inhibition of AChE. These drugs, known as acetylcholinesterase inhibitors, have been shown to improve cognition and global functions but have little impact on improving the eventual progression of the disease. However, there are evidences that other cholinesterases such as butyrylcholinesterase (BuChE) can play an important role in cholinergic function in the brain, and the long-suspected non-cholinergic actions of acetylcholinesterase, mainly the interference with the beta-amyloid protein cascade, have recently driven a profound revolution in cholinesterase drug research [1-2].

We will present our journey from dual binding site AChE inhibitors as potent beta-amyloid modulators to the more recent serie of indolylpiperidines hybrids with an unexpected and very potent *h*BuChE inhibition. Experimental and computational studies have revealed the chameleon behavior of these molecules able to change their bioactive conformation depending on the cholinesterase binding site. Based on the potent activity of these compounds targeting BuChE, the low cellular toxicity and the *in vivo* target engagement, we can propose these indolylpiperidine derivatives as valuable tools for the study of the role of BuChE in AD and probably as potential drugs candidates for its future pharmacotherapy.

References

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