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MEETING ABSTRACTS

FROM ACETYLCHOLINESTERASE INHIBITORS TO MULTI-TARGET-DIRECTED LIGANDS (MTDLs): A STEP FORWARD IN ALZHEIMER'S DISEASE DRUG DISCOVERY

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Notwithstanding clinical effectiveness evidences continue to suggest benefit from the acetylcholinesterase inhibitors (AChEIs) in alleviating Alzheimer's disease (AD) symptoms, these drugs do not appear to delay or prevent the underlying neurodegeneration. In this context, novel prospects are offered by the strategy of developing single chemical entities able to modulate multiple targets, i.e. the multi-target-directed ligands (MTDLs). On this basis, several multifunctional AChEIs have been rationally designed with the deliberate aim of enlarging their biological profiles, beyond the ability to inhibit cholinesterases. This is because it has been recognized that a balanced simultaneous modulation of multiple targets critically intertwined in AD pathological cascade can provide a superior therapeutic and toxicological profile compared to the action of a selective AChEI.[1]

Building on this founding principle, we and others have developed several series of anti-AD MTDL compounds that combine cholinesterase inhibition with anti-aggregating, anti-oxidant, and anti-neuroinflammatory properties.[2] As a further step, to explore the possibility to discover new MTDLs based on inexpensive resources, we have developed a series of MTDLs obtained by properly modifying constituents from the cashew nut shell liquid (CNSL), a waste from cashew nut processing factories.[3] Such hybrid compounds, obtained from renewable and inexpensive material, might be promising bio-based, sustainable MTDLs for AD drug discovery.

Working in the field for almost 20 years, we should draw lessons from the past and try our best to chart innovative directions and hopefully address the scientific and societal challenges of neurodegenerative diseases.

Keywords: Alzheimer's disease; amyloid; acetylcholinesterase; multitarget compounds; neuroinflammation

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