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MEETING ABSTRACTS

PHOTO-INDUCED RELEASE OF AN ACETYLCHOLINESTERASE INHIBITOR

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Light–induced isomerization of enzyme ligands allows controlling specific biological processes in time and space. Photoisomerisable azobenzene-based inhibitors allow photo-control of acetylcholine (ACh) signalling by regulating acetylcholinesterase (AChE), the enzyme that catalyses ACh hydrolysis in the central and peripheral nervous system. By regulating AChE, this family of inhibitors would allow spatial and temporal regulation of ACh levels in the synaptic cleft. Adequate regulation of ACh levels is an essential part of Alzheimer's disease (AD) treatment and other common pathologies. Win this work we present the crystal structures of AChE in complex with three different azobenzene derived inhibitors, we confirmed AzoTHA-1 as the only photoactive compound and we determined its structure in its *cis*- and *trans*- isomeric forms bound to AChE. Three-dimensional structures, supported by online UV-Vis spectroscopy and kinetic data, explain why only AzoTHA-1 is an effective photoactive AChE inhibitor and suggest possible ways to improve photoactive drugs. We utilised S/WAXS to follow photo-isomerisation induced-changes in the wide-angle scattering region to demonstrate that photoisomerisation of the inhibitor induces its release from AChE's active site.

Keywords: Photopharmacology; Alzheimer disease; acetylcholinesterase dynamics