BINDING INTERACTIONS OF NOVEL PEPTIDOMIMETIC INHIBITORS WITH BUTYRYCHOLINESTERAS

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Cholinesterases are recognized as important biological targets for the regulation of cholinergic transmission, and their inhibitors are currently utilized in the treatment of Alzheimer's disease.[1] Several various strategies were followed to design new cholinesterase inhibitors, including the modification of compounds from a previously developed library, structure-based and fragment-based design, and target-guided synthesis.[2,3] Thus, a diverse collection of drug-like molecules (peptidomimetics) was constructed using an efficient four-component reaction, which was further optimized with innovative mechanochemical and microwave techniques. A novel strategy was employed in which the cholinesterase enzyme itself was used to guide the creation of potential inhibitors. Subsequently, advanced computer modelling and machine learning[4] were employed to correlate a molecule's structure with its inhibitory activity, allowing for the prediction of activity based on its energy profile. Large-scale computer simulations were conducted to explore the binding of these molecules within the enzyme's active site, and the potential for multiligand binding was revealed. Target-guided synthesis facilitated a more effective screening process leading to enhanced affinity of new inhibitors. Furthermore, STD NMR spectroscopy study was utilized for characterizing small molecule interactions with the macromolecule, allowing for the identification of key intermolecular contacts in the bound state.

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