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ABSTRACT BOOK

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Novel thieno[2,3-d]pyrimidine hybrids incorporating biogenic fragments: synthesis and molecular docking studies

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Background: Neurodegenerative disorders such as Alzheimer's disease are characterized by progressive cognitive decline and disturbances in emotional regulation. Inhibition of acetylcholinesterase (AChE) remains a key pharmacological strategy for improving cholinergic neurotransmission and alleviating cognitive symptoms. Hybrid molecule design combining heterocyclic scaffolds with biologically relevant fragments has emerged as an effective approach for developing multitarget neuroactive agents. Thieno[2,3-d]pyrimidine derivatives are promising scaffolds due to their structural versatility and reported activity against neurodegeneration-associated targets. Biogenic fragments, including amino acids and tryptamine derivatives, may further enhance biological compatibility and interactions with neuronal systems (1–3).
Aim: The aim of this study was the rational design, synthesis, and computational evaluation of novel thieno[2,3-d]pyrimidine hybrids as potential acetylcholinesterase-targeted compounds for the development of neuroactive agents.
Methods:The structures of the synthesized compounds were confirmed by ^1H and ^13C NMR spectroscopy and LC–MS. Molecular modeling was performed using BioviaDraw 2021, Discovery Studio Visualizer 2021, VMD 1.9.3, AutoDockTools, and AutoDock Vina. The crystal structure of AChE (PDB ID 7E3H) was obtained from the Protein Data Bank.
Results: A series of hybrid thieno[2,3-d]pyrimidine derivatives incorporating amino acid and biogenic fragments was synthesized using a stepwise strategy involving N-alkylation of 5-methylthieno[2,3-d]pyrimidin-4(3H)-one, hydrolysis to the corresponding acetic acid intermediate, and subsequent amide coupling with selected amines. The structures of the obtained derivatives were confirmed by ^{1}H and ^{13}C NMR spectroscopy and LC–MS analysis. Molecular docking studies revealed strong predicted binding affinities of the synthesized compounds toward the AChE active site, with calculated binding energies ranging from –8.4 to –12.5 kcal/mol, comparable to or exceeding that of the reference inhibitor donepezil. Three hit compounds demonstrated particularly favorable docking profiles and stable accommodation within the catalytic gorge of AChE. Notably, the compound 3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]-2-oxoethyl}-5-methylthieno[2,3-d]pyrimidin-4(3H)-one exhibited the strongest predicted binding affinity (–12.5 kcal/mol) and formed an extended interaction network involving hydrogen bonding, π–π stacking, and halogen interactions within the aromatic gorge of AChE.
Conclusions: The results demonstrate that hybrid thieno[2,3-d]pyrimidine derivatives are promising scaffolds for the development of new acetylcholinesterase-targeted compounds. The identified hit structures showed strong predicted affinity toward AChE and are recommended for further investigation in a scopolamine-induced amnesia model in rats.

References

1. Kassab A.E., Gedawy E.M., Sayed A.S. Fused thiophene as a privileged scaffold: a review on anti-Alzheimer's disease potentials via targeting cholinesterases, monoamine oxidases, glycogen synthase kinase-3, and Aβ aggregation. *International Journal of Biological Macromolecules*. 2024;265:131018.
2. Eissa K.I. et al. Design, synthesis and biological evaluation of thienopyrimidine derivatives as multifunctional agents against Alzheimer's disease. *Drug Development Research*. 2023;84:937–961.
3. Singh Y.P., Kumar H. Tryptamine: a privileged scaffold for the management of Alzheimer's disease. *Drug Development Research*. 2023;84:1578–1594.