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YOUTH PHARMACY SCIENCE

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Table 1. Prediction of the druglikeness of 5-methoxy pyridine derivatives

Compound	Lipinski	Ghose	Veber	Egan	Muegge
1	Yes	No	Yes	Yes	No
2	Yes	No	Yes	Yes	No
3	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes

According to this study, compounds (3) and (4) fully comply with the above 5 filters. All pyrimidine derivatives (1-4) comply with the Lipinski, Veber and Egan rules. They do not comply with the Ghose rule (1-2), since the molecular weight is less than 160, the number of atoms is less than 20 and the molecular weight according to the Muegge rule must be more than 200.

Conclusions. The analysis of 4 pyrimidine derivatives was carried out using *in silico* methods. According to the results of online prediction of pharmacokinetic parameters, the compounds are orally bioavailable, meet the parameters of druglikeness and are low-toxic. This study proves the feasibility of synthesizing 5-methoxy-2-methylpyrimidine (1), 2-cyclopropyl-5-methoxypyrimidine (2), *tert*-butyl (2-(5-methoxypyrimidin-2-yl)ethyl)carbamate (3) and *tert*-butyl ((5-methoxypyrimidin-2-yl)methyl)carbamate (4) as biologically active compounds and have prospects for further research.

RATIONAL DESIGN OF HYBRID THIENOPYRIMIDINE DERIVATIVES AS POTENTIAL MODULATORS OF NEURODEGENERATION

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Introduction. Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and other forms of cognitive decline represent one of the most significant medical and social challenges of modern healthcare. Their pathogenesis is multifactorial, involving disturbances in cholinergic and glutamatergic neurotransmission, oxidative stress, neuroinflammation, imbalance of neurotransmitter systems, and the accumulation of pathological protein aggregates. This complexity of biological mechanisms makes it impossible to effectively modify the course of neurodegeneration using drugs with narrowly targeted mechanisms of action.

Current therapeutic approaches provide only symptomatic relief and do not influence the key pathways driving disease progression. This underscores the need to develop new chemical platforms and molecular architectures capable of simultaneously modulating several pathogenetically relevant targets. In this context, multitarget hybrid molecules that combine pharmacophoric elements of different origins are considered a promising direction in medicinal chemistry.

The integration of biogenic fragments and synthetic structural modules within a single chemical scaffold enables the reproduction of biologically relevant interaction patterns while providing optimal pharmacokinetic and pharmacodynamic characteristics. Particular attention has been directed toward heterocyclic systems, including thienopyrimidines, which have demonstrated

strong potential as versatile platforms for creating multimodal agents active toward enzymes, receptors, and signaling pathways implicated in neurodegeneration.

Aim. To perform rational design of biogenic–thienopyrimidine hybrid molecules targeted to acetylcholinesterase as a key enzyme involved in neurodegenerative processes, followed by in silico selection of the most promising structural candidates for experimental evaluation of their potential to modulate cognitive and anxiety-related impairments.

Materials and methods. PubChem (NIH) was used to analyze the structures, physicochemical properties, and bioactivity profiles of chemical compounds. DrugBank provided information on pharmacological targets, mechanisms of action, and structural features of approved drugs. Three-dimensional structures of protein targets, including acetylcholinesterase (PDB ID: 5NAU), were obtained from the Protein Data Bank (PDB). SwissADME was employed to predict pharmacokinetic parameters and toxicity-related characteristics of the potential ligands. BIOVIA Draw and BIOVIA Discovery Studio Visualizer were used to construct two-dimensional structures of the designed molecules and to prepare initial ligand geometries. Ligand and protein preparation for docking was carried out using AutoDockTools 1.5.6, and molecular docking simulations were performed with AutoDock Vina.

Research results. The development of new molecular structures was based on the principles of rational design of hybrid compounds aimed at modulating neurodegenerative processes. The thieno[2,3-d]pyrimidine system, functionalized at position 3 with a glycine linker, was selected as the core scaffold, providing a versatile platform for the integration of various biogenic and synthetic fragments. This approach enables the creation of multitarget molecules capable of interacting simultaneously with several central neurotransmitter and neuroprotective mechanisms.

To broaden the pharmacological spectrum, the designed hybrids incorporated: biogenic substrates relevant to inhibitory and excitatory amino acid systems (tert-butyl esters of glycine, β-alanine, and γ-aminobutyric acid; glutamic acid imides); tryptamine as a modulator of serotonergic and dopaminergic pathways; synthetic amines and CNS-pharmacophoric elements such as 2-(piperazin-1-yl)ethanamine and the 6-fluoro-3-(piperidin-4-yl)-1,2-benzoxazole fragment. The selected fragments enabled targeted interactions with receptor and enzymatic systems involved in cognitive deficits, emotional responses, and neuroinflammation.

A pharmacophore-based analysis was conducted to define key structural features required for binding to acetylcholinesterase and other relevant targets. Essential pharmacophoric elements included hydrogen-bond donors and acceptors, hydrophobic pockets, aromatic surfaces enabling π–π and π–cation interactions, and flexible linkers capable of adapting to the spatial architecture of the binding site. This pharmacophore template was applied to all designed structures, enabling the selection of molecules with optimal spatial and electronic characteristics.

Given the established role of cholinergic dysfunction in cognitive decline and neurodegeneration, acetylcholinesterase (AChE) was chosen as a principal molecular target. AChE regulates synaptic acetylcholine levels and is critically involved in memory, learning, and neuroplasticity. Moreover, AChE participates in pathological processes, including acceleration of Aβ aggregation and formation of neurotoxic complexes. Therefore, AChE in its conformation complexed with donepezil was selected as the primary target for predicting the activity of the designed molecules, enabling evaluation of their potential to counteract cholinergic deficit and modulate pathways relevant to neurodegenerative disease progression.

Docking simulations demonstrated that the majority of the constructed hybrids fit stably within the catalytic gorge of AChE, forming interactions characteristic of donepezil: π–π stacking with Trp84 and Phe330, hydrogen bonds with His440, Gly118, and Ser200, and hydrophobic filling

of the peripheral anionic site. The highest predicted affinity was observed for hybrid molecules combining the thienopyrimidine scaffold with biogenic and synthetic fragments, demonstrating binding energies around -12.5 kcal/mol and optimal occupation of both catalytic and peripheral sites. Molecules containing γ-aminobutyric acid fragments formed pronounced hydrophobic contacts in the peripheral site and aligned well along the acetylcholine channel, producing the highest docking scores.

Structures featuring β-alanine linkers formed extended hydrogen-bonding networks with key residues of the catalytic domain, contributing to enhanced stabilization within the active site. Hybrids containing tert-butyl glycine esters exhibited balanced lipophilicity and polar interaction points, enabling efficient occupation of the peripheral subsite and additional stabilization of the ligand–enzyme complex.

Validation of the docking protocol was confirmed by redocking of donepezil, which resulted in RMSD < 0.1 Å, indicating high reproducibility of the native binding pose and reliability of the model for predicting ligand affinity.

Conclusions. The performed pharmacophore and molecular docking studies demonstrated that combining the thieno[2,3-*d*]pyrimidine scaffold with biogenic fragments, particularly derivatives of γ-aminobutyric acid, β-alanine, and tert-butylglycine, provides optimal interactions within the active site of acetylcholinesterase and yields the most favorable predicted affinity profile. These findings indicate that such structural combinations represent the most promising candidates for further experimental validation and may serve as a foundation for the development of new multitarget neuroprotective agents.