LITHUANIAN UNIVERSITY OF HEALTH SCIENCES
FACULTY OF PHARMACY

ABSTRACT BOOK

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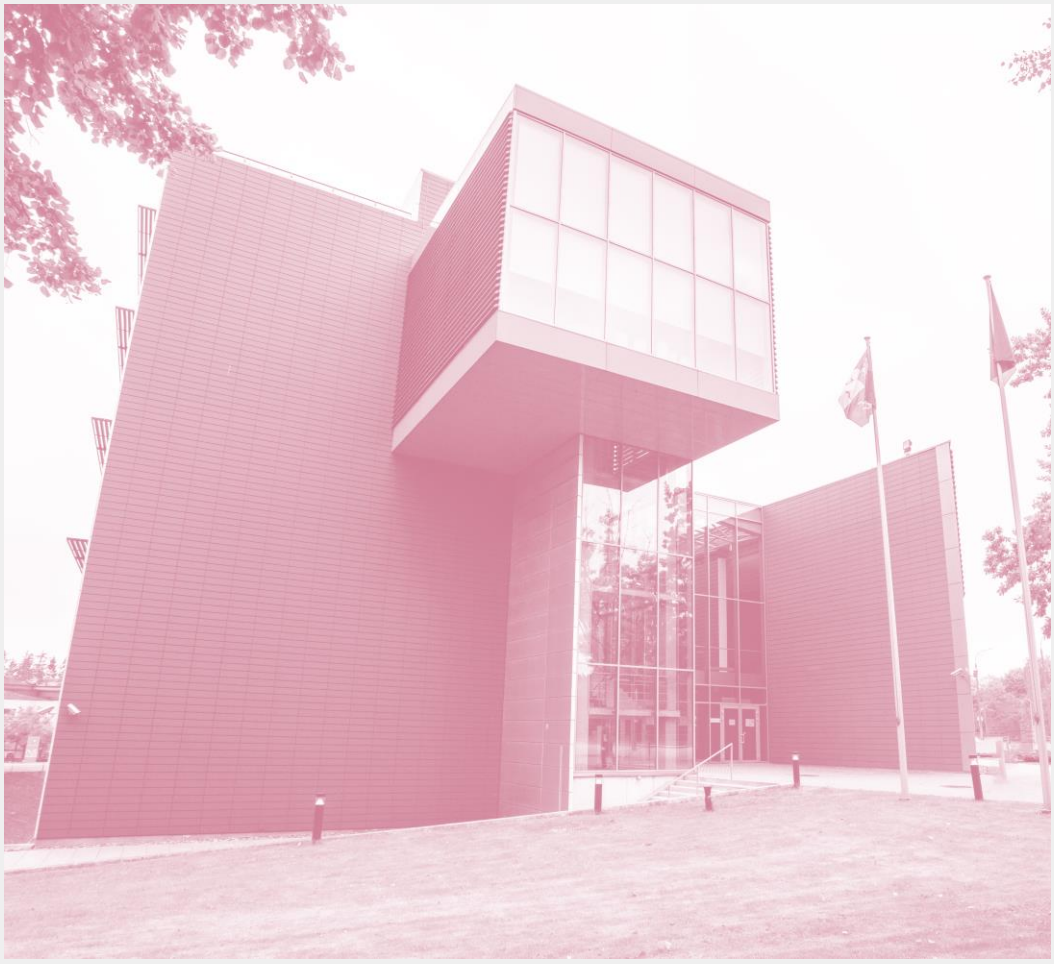

Contemporary Pharmacy: Issues, Challenges and Expectations 2024

March 22
Lithuania, Kaunas

In Silico Study of the Metabolic Pathways of a New Promising Anticonvulsant Epimidine

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Background: Epilepsy remains one of the most common neurological diseases in the world – according to the WHO [1]. Despite a relatively wide range of antiepileptic drugs only 65-70% of patients achieve satisfactory seizure control [2]. Scientists at the National University of Pharmacy have developed a new effective anticonvulsant agent – Epimidine, with a powerful spectrum of activity, as well as a favourable profile of concomitant pharmacological properties and low toxicity [3]. In order to reduce the risk of withdrawal of a drug candidate compound at the clinical trial stage due to unfavourable metabolic characteristics, it is possible to predict the directions of biotransformation of a molecule using *in silico* methods. The aim of the presented research is in silico prediction of possible biotransformation pathways of Epimidin – 1-(4-methoxyphenyl)-5-(2-[4-(4-methoxyphenyl)piperazin-1-yl]-2-oxoethyl)-pyrazolo[3,4-d]pyrimidin-4-one.

Methods: BioviaDraw 2021; XenoSite was used for prediction of the of metabolism [4].

Results. According to the results of the prediction, the following transformations are most likely to occur in the first phase of metabolism: unstable oxygenation of methoxy groups at the 4-position of phenyl radicals by O-dealkylation reaction with formation of O-dealkylated derivative – 1-(4-hydroxyphenyl)-5-[2-[4-(4-hydroxyphenyl)piperazin-1-yl]-2-oxo-ethyl]pyrazolo[3,4-d]pyrimidin-4-one; high probability of formation of stable oxidation - aliphatic hydroxylation at CH_2 by groups of the piperazine cycle, with a higher probability of formation of 3- or 5-hydroxy-4-(4-methoxyphenyl)piperazin-1-yl]-2-oxo-ethyl]-1-(4-methoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-one; high probability of hydrolysis of the cycloamide group with the formation of two products - 2-[1-(4-methoxyphenyl)-4-oxo-pyrazolo[3,4-d]pyrimidin-5-yl]acetic acid and 1-(4-methoxyphenyl)piperazine; it is also possible to form glucuronide at position 1 of the pyrimidine cycle with the participation of Uridine diphosphate glucuronosyltransferases (UGTs) as a catalyst. The low probability of formation of epoxides, which are common reactive metabolites and often cause drug toxicity, was determined.

Conclusions: The probability of Epimidine metabolism by O-dealkylation, hydrolysis and oxidative hydroxylation, as well as the low probability of toxic metabolites formation were determined.

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Determination of the Prospects of New 8-thia/oxa-1,3-diazaspiro[4.5]decane-2,4-dione Derivatives as Acetylcholinesterase Inhibitors

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Background: The spectrum of cognitive impairment is very wide and ranges from normal cognitive decline with age to diseases of the central nervous system, including Alzheimer's disease, Parkinson's disease and others [1]. The most important trajectory of cognitive impairment is the cholinergic hypothesis, which postulates that cognitive deterioration is associated with a decrease in the amount of the neurotransmitter acetylcholine [2]. Today the cholinesterase inhibitors (AChEIs) donepezil, galantamine and rivastigmine are prescribed for the treatment of cognitive disorders, in particular, Alzheimer's disease [3]. The search for new AChEIs benefits from well-established knowledge of the molecular interactions of selective AChEIs, such as donepezil and related dual binding site inhibitors [4]. The high level of diseases with neurological deficits requires the search for effective treatment strategies and the development of new drugs to correct these conditions. The aim of the study was to predict the acetylcholinesterase inhibitory activity of new 1-aryl/heteryl-substituted derivatives of 3-(5-oxopyrrolidin-3-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione.

Methods: The following programs were used BioviaDraw 2017R2, Discovery studio Visualizer 2021, VMD1.9.3, AutoDock Tool and Autodock Vina. Crystallographic data for AChE (PDB ID 5NAU) were obtained from the Protein Data Bank (http://www.rcsb.org/pdb).

Results: Based on the hydride-pharmacophore concept, 3-aryl/heteryl-substituted derivatives of (5-oxopyrrolidin-3-yl)methyl-8-thia/oxa-1,3-diazaspiro[4.5]decane-2,4-dione were designed as possible agents for the correction of cognitive impairment. To evaluate the prospects of studying experimental ligands for acetylcholinesterase inhibitory activity, molecular docking into the active site of inhibitor of the AChE isolated from *Tetronarce californica* was performed. Donepezil was used as a reference ligand, and the docking methodology was validated using the native ligand (2E)-2-[(1-benzyl-4-piperidyl)methylene]-5-methoxy-indan-1-one as a promising simplified Donepezil analogue. According to the results obtained high affinity was predicted for the studied ligands: the binding energy ranged from -9.2 to -10.8 kcal/mol, compared to 11.0 kcal/mol for Donepezil.

Conclusions: The docking studies for the readily synthetically available 3-aryl/heteryl substituted derivatives (5-oxopyrrolidin-3-yl)methyl-8-thia/oxa-1,3-diazaspiro[4.5]decane-2,4-dione showed the expediency of their study as the novel class of potent AChEIs. The 7 designed compounds with the lowest binding energy values and fixation in the active site by amino acid residues of the active site (Tyr121, Tyr334, Trp84, Trp279) were selected for further in vitro and in vivo studies.

Funding: The research was funded by the Ministry of Health Care of Ukraine at the expense of the State Budget on the topic “Research of original substances for the correction of neurological deficits symptoms, prediction and assessment of factors affecting the mechanisms of action”, 2023-2025; №: 0123U101751.

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Glutamate Receptors for In Silico Evaluation of Antiparkinsonian Activity of New Compounds

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Background: Neurodegenerative diseases are debilitating conditions that lead to progressive deterioration or death of nerve cells [1], causing cognitive dysfunction, dementia, and slow down motor function in various parts of the brain [2]. It is now evident glutamatergic signalling in brain plays the central role in its functioning, as well as in the modulation of neurodegenerative pathologies, including Parkinson's disease [3]. Modulation of glutamate receptors (GluRs) has been shown to improve the motor symptoms of Parkinson's disease, increase the effectiveness of antiparkinsonian dopaminergic agents and protect substantia nigra neurons. The search for new ligands-modulators of glutamate receptors is a priority for the development of new drugs.

Aim: The aim of the study is to review the available crystallised glutamate receptors in conformation with promising antiparkinsonian ligands and validate docking methodologies for their further use for *in silico* studies.

Methods: The following programs were used Discovery studio Visualizer 2021, AutoDock Tool1.5.6rc3, Autodock Vina. Crystallographic data for all glutamate receptors were obtained from the Protein Data Bank.

Results: The results of the study are presented below:

Receptor	PDBID/ Expression System	Native ligand / Finding an active site	Binding energy kkal/mol	Amino acid residues of the active site GluR
NMDA	3QEL/ Trichoplusia ni	Ifenprodil –NAM, ATD	-11.2	Glu236, Leu135, Phe114, Phe176,Ala107, Leu135, Pro78, Ile111, Pro177
	5UOW/ Homo sapiens	Dizocilpine – NAM, TMD	-8.0	Leu630, Leu649,Leu636, Ala643, Ala 631
AMPA	6FQH/ Escherichia coli	NBQX – NAM, LBD	-8.2	Tyr61, Tyr220, Thr91, Thr 174, Glu193, Pro89, Arg96
	5L1G/ Homo sapiens	Talampanel, LBD	-10.2	Asn791, Ser615, Ser790, Asp519, Phe623, Leu620, Leu624, Leu787, Pro520
mGluR1/ 5	4OO9/ Homo sapiens	Mavoglurant, NAM, TMD	-9.0	Asn747, Ser805, Ser809, Val740, Ser654, Pro65, Ala813, Ile625, Ile651, Val740, Pro743, Leu744, Tyr659, Trp785, Phe788, Pro655, Ala810
	6FFH/ Homo sapiens	Fenobam –NAM, TMD	-8.7	Trp785, Val806, Ser809 Ser658, Gly624, Tyr659, Ala810
mGlu 2/3	4XAQ/ Homo sapiens	LY379268 – agonist, ATD	-7.9	Ala166, Asp295, Thr168, Ser145, Lys377, Arg61, Ser143, Tyr 216, Tyr 144, Glu273
mGluR4, 6,7,8	8JD5/ Homo sapiens	ADX88178 – PAM mGluR4	-11.2	Leu774, Ala775, Ala800, Ile804, Leu777, Pro778, Leu828, Pro778, Val824, Leu590, Pro591, Val824

NAM – negative allosteric modulator; PAM – positive allosteric modulator; ATD – amino-terminal domain; TMD – ransmembrane domain, LBD – ligand-binding domain.

Conclusions: The available crystallographic structures of glutamate receptors in conformations with NAM and PAM, which are promising as antiparkinsonian agents, were selected; docking methodologies for native ligands were validated, and parameters for future in silico studies of the glutamatergic effect of new ligands were determined.

Funding: The research was funded by the Ministry of Health Care of Ukraine at the expense of the State Budget on the topic “Molecular modeling and synthesis of innovative pyrimidine derivatives as promising agents for the treatment of neurodegenerative diseases”, 2024-2026.

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