



## MOLECULAR DESIGN OF N-ACYL DERIVATIVES OF 2-(2-OXOPYRROLIDIN-1-YL)-ACETAMIDE WITH GABA-ERGIC AND GLUTAMATERGIC ACTIVITIES

I.P. Kodonidi<sup>1</sup>, A.S. Chiriapkin<sup>1</sup>, D.E. Tworowski<sup>2,3</sup>

<sup>1</sup>Pyatigorsk Medical and Pharmaceutical Institute – Branch of Volgograd State Medical University  
11, Kalinin Ave., Pyatigorsk, Russia, 357532

<sup>2</sup>The Weizmann Institute of Science, Department of Structural Biology  
234 Herzl Street, Rehovot, Israel, 7610001

<sup>3</sup>Bar-Ilan University, Cancer Genomics and BioComputing of Complex Diseases Lab  
Azrieli Faculty of Medicine  
8 Henrietta Szold St, Safed, Israel, 1311502

E-mail: alexey.chiriapkin@yandex.ru

Received 20 Nov 2020

Accepted 22 Feb 2021

The first of the most successfully implemented nootropic drugs in medical practice is piracetam, which should be attributed to cyclic derivatives of gamma-aminobutyric acid. The production of new piracetam derivatives with high nootropic activity is a promising direction in the development of new neuroprotective drugs.

**The aim** of the study is to predict GABA-ergic and glutamatergic activities of N-acyl derivatives of 2-(2-oxopyrrolidin-1-yl)-acetamide by a molecular docking method through the energy analysis of interaction of modeled structures with GABA<sub>A</sub> and AMPA receptors with their subsequent targeted synthesis.

**Materials and methods.** The objects of the research are new N-acyl derivatives of 2-oxo-1-pyrrolidineacetamide and a virtual model of the GABA<sub>A</sub> receptor of the *Homo sapiens* organism with the identification code 6D6U and a three-dimensional model of the AMPA-receptor of the *Rattus norvegicus* organism with the identification code 3LSF from the RCSB PDB database. The simulated compounds were designed in the HyperChem 8.0.8 program. This program was also used to optimize geometry using the force field of molecular mechanics MM+. Molecular docking was carried out using the Molegro Virtual Docker 6.0.1 program. The preparation of N-acyl derivatives of 2-(2-oxopyrrolidin-1-yl)-acetamide was carried out by the interaction of 2-(2-oxopyrrolidin-1-yl)-acetamide with an excess of the corresponding anhydride under conditions of acid catalysis.

**Results.** Based on the results of molecular docking, a high affinity of all simulated compounds for the binding site of GABA<sub>A</sub> and AMPA receptors can be estimated. According to the predict, the maximum GABA-ergic activity should be expected for (N-[2-(2-oxopyrrolidin-1-yl)-acetyl]-butyramide. N-acyl derivatives of 2-oxo-1-pyrrolidineacetamide form a more stable complex with amino acid residues Arg207, Phe200, Thr202, Tyr97, Tyr157, Tyr205 and Phe65 of the GABA<sub>A</sub> receptor binding site than the GABA molecule. In terms of the minimum interaction energy, the N-acyl derivatives of 2-(2-oxopyrrolidin-1-yl)-acetamide are superior to a number of known ligands such as GABA, piracetam, anipiracetam, picamilon and pramiracetam. The tested compounds have also shown a high affinity for the binding site of the AMPA receptor. The leader compound is also the compound PirBut, as in the case of the GABA<sub>A</sub> receptor.

**Conclusion.** Molecular modeling of the ligands interaction with the active binding site of gamma-aminobutyric acid of the GABA<sub>A</sub> receptor by molecular docking showed that all virtual N-acyl derivatives of 2-oxo-1-pyrrolidineacetamide can exceed a number of nootropic drugs by activity. In the course of molecular design, a method for predicting a glutamatergic activity for 2-pyrrolidone derivatives has been developed. It suggests a significant nootropic activity for N-[2-(2-oxopyrrolidin-1-yl)-acetamide amides.

**Keywords:** 2-(2-oxopyrrolidin-1-yl)-acetamide; N-acyl derivatives; GABA<sub>A</sub> receptor; AMPA receptor; nootropics; Molecular design; molecular docking; structural pharmacology; QSAR

**Abbreviations:** GABA – gamma-aminobutyric acid; CNS – central nervous system; BAC – biologically active compound; BBB – blood-brain barrier; IC50 – The half maximal inhibitory concentration.

**For citation:** I.P. Kodonidi, A.S. Chiriapkin, D.E. Tworowski. Molecular Design of N-acyl derivatives of 2-(2-oxopyrrolidin-1-yl)-acetamide with GABA-ergic and glutamatergic activities. *Pharmacy & Pharmacology*. 2021;9(1):84-97. DOI: 10.19163/2307-9266-2021-9-1-84-97

© И.П. Кодониди, А.С. Чиряпкин, Д.Е. Творовский, 2021

**Для цитирования:** И.П. Кодониди, А.С. Чиряпкин, Д.Е. Творовский. Молекулярное конструирование N-ацильных производных 2-(2-оксопирролидин-1-ил)-ацетамида, обладающих ГАМК-ергической и глутаматергической активностями. *Фармация и фармакология*. 2021;9(1):84-97. DOI: 10.19163/2307-9266-2021-9-1-84-97

# МОЛЕКУЛЯРНОЕ КОНСТРУИРОВАНИЕ N-АЦИЛЬНЫХ ПРОИЗВОДНЫХ 2-(2-ОКСОПИРОЛИДИН-1-ИЛ)-АЦЕТАМИДА, ОБЛАДАЮЩИХ ГАМК-ЕРГИЧЕСКОЙ И ГЛУТАМАТЕРГИЧЕСКОЙ АКТИВНОСТЯМИ

И.П. Кодониди<sup>1</sup>, А.С. Чиряпкин<sup>1</sup>, Д.Е. Творовский<sup>2,3</sup>

<sup>1</sup> Пятигорский медико-фармацевтический институт – Федеральное государственное бюджетное образовательное учреждение высшего профессионального образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации 357532, Россия, Пятигорск, пр-т Калинина, 11

<sup>2</sup> Научный институт имени Вейцмана, Отдел структурной биологии Израиль, 7610001, Реховот, ул. Герциля, 234

<sup>3</sup> Университет имени Бар-Илана, Лаборатория геномики рака и биокомпьютинга сложных заболеваний медицинского факультета Азриэли Израиль, 1311502, Цфат, ул. Генриетта Шольд, 8

E-mail: alexey.chiriapkin@yandex.ru

Получено 20.11.2020

Принята к печати 22.02.2021

Первым из наиболее успешно внедренных в медицинскую практику ноотропных лекарственных средств является пирацетам, который следует отнести к циклическим производным  $\gamma$ -аминомасляной кислоты. Получение новых производных пирацетама обладающих высокой ноотропной активностью, представляет собой перспективное направление при создании новых нейропротекторных препаратов.

**Цель.** Прогноз ГАМК-ергической и глутаматергической активности N-ацилпроизводных 2-(2-оксопирролидин-1-ил)-ацетамида методом молекулярного докинга посредством анализа энергии взаимодействия моделируемых структур с ГАМК<sub>A</sub>- и AMPA-рецепторами с последующим их целенаправленным синтезом.

**Материалы и методы.** Объектами исследования являются новые N-ацильные производные 2-оксо-1-пирролидина-ацетамида и виртуальная модель ГАМК<sub>A</sub>-рецептора организма *Homo sapiens* с идентификационным кодом 6D6U и трехмерная модель AMPA-рецептора организма *Rattus norvegicus* с идентификационным кодом 3LSF из базы данных RCSB PDB. Моделируемые соединения построены в программе HyperChem 8.0.8. С помощью этой программы также была проведена оптимизация геометрии с использованием силового поля молекулярной механики MM+. Молекулярный докинг осуществлялся посредством программы Molegro Virtual Docker 6.0.1. Получение N-ацильных производных 2-(2-оксопирролидин-1-ил)-ацетамида осуществлялось взаимодействием 2-(2-оксопирролидин-1-ил)-ацетамида с избытком соответствующего ангидрида в условиях кислотного катализа.

**Результаты.** По результатам молекулярного докинга можно судить о высоком сродстве всех моделируемых соединений к сайту связывания ГАМК<sub>A</sub>- и AMPA-рецепторов. Согласно прогнозу, максимальную ГАМК-ергическую активность следует ожидать у (N-[2-(2-оксопирролидин-1-ил)-ацетил]-бутирамида. N-ацильные производные 2-оксо-1-пирролидина-ацетамида образуют более устойчивый комплекс с аминокислотными остатками Arg207, Phe200, Thr202, Tyr97, Tyr157, Tyr205 и Phe65 сайта связывания ГАМК ГАМК<sub>A</sub>-рецептора, чем молекула ГАМК. По величине минимальной энергии взаимодействия N-ацильные производные 2-(2-оксопирролидин-1-ил)-ацетамида превосходят целый ряд известных лигандов, таких, как ГАМК, пирацетам, анипирацетам, пикамилон и прамирацетам. Также исследуемые соединения показали высокое сродство к сайту связывания AMPA-рецептора. Соединением-лидером также является соединение PirBut, как и в случае с ГАМК<sub>A</sub>-рецептором.

**Заключение.** Молекулярное моделирование взаимодействия лигандов с активным сайтом связывания гамма-аминомасляной кислоты ГАМК<sub>A</sub>-рецептора методом молекулярного докинга показало, что все виртуальные N-ацильные производные 2-оксо-1-пирролидина-ацетамида по активности могут превышать целый ряд ноотропных лекарственных препаратов. В ходе молекулярного конструирования разработана методика прогнозирования глутаматергической активности для производных 2-пирролидона. Она позволяет предположить значительную ноотропную активность для амидов N-[2-(2-оксопирролидин-1-ил)-ацетамида.

**Ключевые слова:** 2-(2-оксопирролидин-1-ил)-ацетамид; N-ацильные производные; ГАМК<sub>A</sub>-рецептор; AMPA-рецептор; ноотропы; молекулярное конструирование; молекулярный докинг; структурная фармакология, QSAR

**Список сокращений:** ГАМК – гамма-аминомасляная кислота; ЦНС – центральная нервная система; БАС – биологически активные соединения; ГЭБ – гематоэнцефалический барьер; IC50 – концентрация полумаксимального ингибирования

## INTRODUCTION

In recent years, the requirement of a systematic search for efficient therapeutic substances targeting the human CNS diseases associated with emotional disorders has been recognized. Among the drugs currently used in

clinical practice are those with neuroprotective effects on the brain function integrity, and beneficial for the resistance of neurons to aggressive endogenous and exogenous factors. Specifically, an interesting group of substances identified as “nootropics” have been

proposed to improve mental performance, memory, and other cognitive CNS processes. Nootropic drugs are shown to enhance the resistance of nerve cells to the effects of hypoxia, intoxication, and post-traumatic brain injury [1].

An important advantage of nootropic drugs is their low toxicity and compatibility with CNS drugs from other pharmacological groups that affect the central nervous system, and almost a complete absence of undesirable side effects [2].

Nootropics are involved in the enhancement of neuronal processes, the exchange of nucleic acids and proteins in cells, the adenosine triphosphate production, glucose transport across the blood-brain barrier (BBB) and its further utilization in brain tissues [3].

To search for new biologically active compounds (BACs) that affect the GABA-ergic and/or glutamatergic systems, it is advisable to combine various methods of molecular modeling. For example, the combination of molecular logical descriptors and a structure-based analysis of molecular databases comprising ligands with known activities enables identification of common structural fragments/motifs ("pharmacophores") responsible for a certain type of activity. The combination of conformational analysis and molecular docking methods makes it possible to identify the preferable ligand positions at protein binding sites and to find correlations with the strength of the pharmacological effect of interest.

**THE AIM** of the study is to predict a GABA-ergic and glutamatergic activities of N-acyl derivatives of 2-(2-oxopyrrolidin-1-yl)-acetamide by a molecular docking method through the energy analysis of interaction of modeled structures with GABA<sub>A</sub> and AMPA receptors with their subsequent targeted synthesis.

### MATERIALS AND METHODS

The geometry optimization was carried out by using the MM+ molecular mechanics method as implemented in the HyperChem 8.0.8 program [4]. The ligand-receptor interactions at the gamma-aminobutyric acid binding site of the GABA<sub>A</sub> receptor and at the active site of the AMPA receptor were calculated using MolDockScore algorithm implemented in the Molegro Virtual Docker 6.0.1 program [5]. In the molecular docking protocol used in this study, 300 most stable conformations of N-acyl derivatives of 2-(2-oxopyrrolidine-1-yl)-acetamide were docked into the 12-nm binding area of the GABA<sub>A</sub> and the AMPA receptors. The initial 3D structures of the GABA<sub>A</sub> and the AMPA receptors were taken from the Protein Data Bank, with the PDB codes 6D6U [6] and 3LSF [7], respectively.

#### Molecular docking to the GABA<sub>A</sub> receptor-binding site

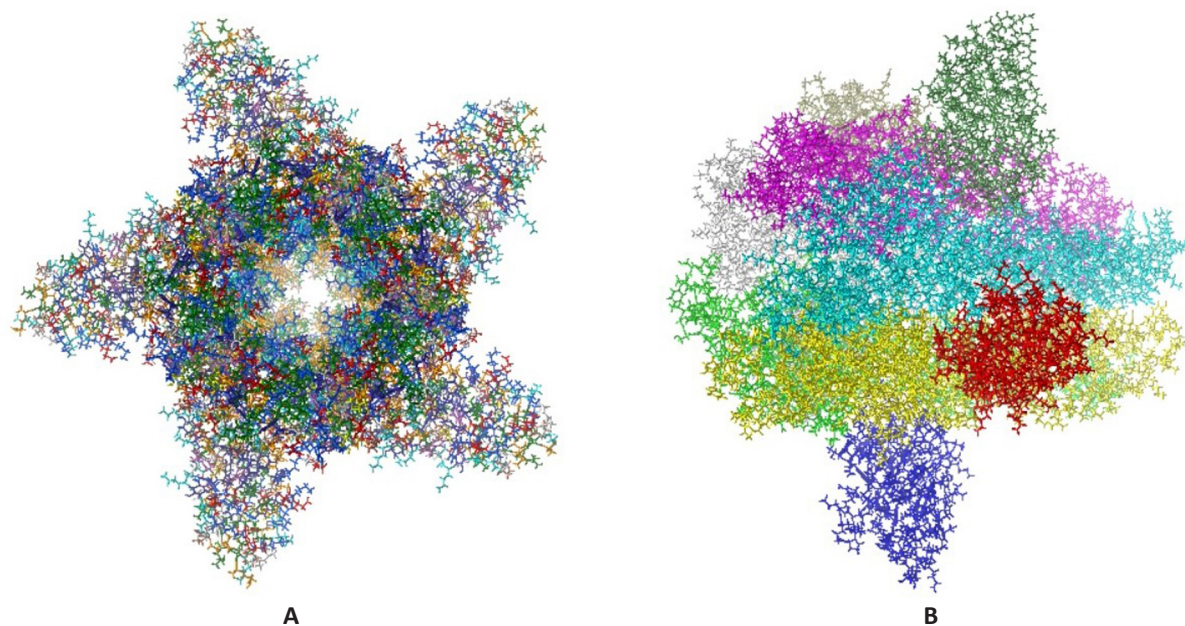
The biological target of docking is the GABA<sub>A</sub> receptor, which is one of the family of Cys-loop receptors containing

disulfide bonds between two cysteine residues. All the described GABA receptors are polymorphic protein formations; its structure largely depends on their localization in the tissues of the body. According to the modern classification, GABA receptors are divided into two groups – ionotropic receptors of the GABA<sub>A</sub>/GABA<sub>C</sub> type and metabotropic GABA<sub>B</sub> receptors [8].

The supramolecular structure of the GABA<sub>A</sub> receptor is a heteropentameric glycoprotein complex. The structure of the ionotropic receptor can include 7 types of subunits:  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\pi$  and  $\theta$ . In turn, the  $\alpha$  subunit is represented by 6 isoforms,  $\beta$  and  $\gamma$  include 3 isoforms each, and the other types of subunits in the GABA<sub>A</sub> receptor have 1 isoform each. In the mammalian brain, the GABA<sub>A</sub> receptor is a pentamer formed by two  $\alpha$ - and  $\beta$ -subunits and one  $\gamma$ -subunit (Fig. 1) [9]. Each subunit of the ionotropic channel has a tertiary structure, which is represented by the order of 400 amino acid residues. The subunit includes an N-terminal extracellular domain and 4 transmembrane domains – M1, M2, M3 and M4, which have a structural organization in the form of  $\alpha$ -helices. It is the N-terminal domain that has numerous sites for binding various ligands, which can be represented by gamma-aminobutyric acid, benzodiazepines, barbiturates, and neuronal hormones [10]. It is assumed that the transmembrane domains M2 and M3 are involved in ligand binding and ion channel modulation [11].

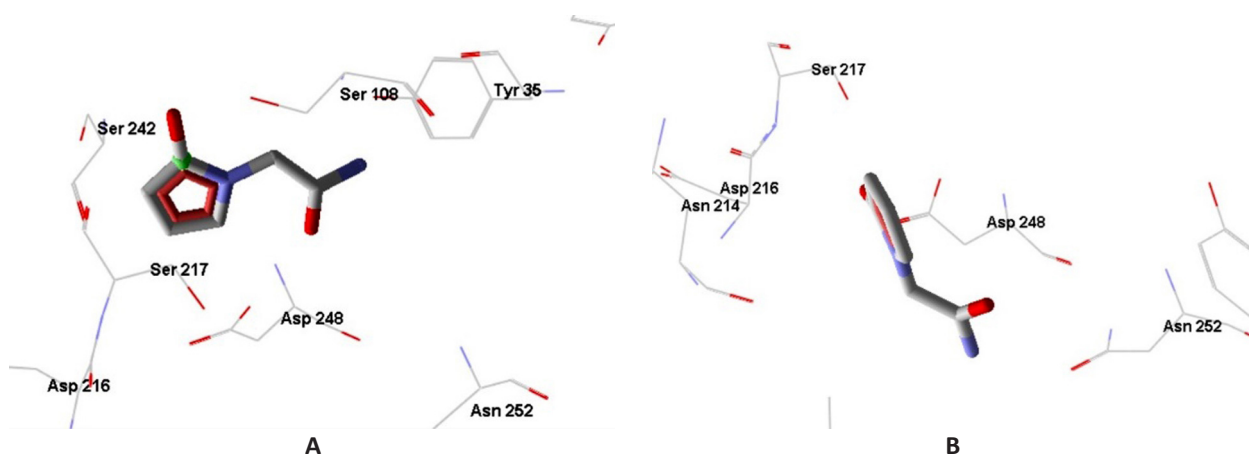
#### Molecular docking to the AMPA receptor binding site

Previously, researchers found that amino acids P494, S497, S754, S729, D760, Y424 and N764 are responsible for the process of positive allosteric modulation of the AMPA receptor. In this case, the piracetam molecule can occupy three pharmacologically active locations at the binding site of the AMPA receptor. These spatial arrangements of piracetam molecules are located in close proximity to each other. In the first case, the piracetam molecule forms bonds with amino acids P494, S497 and S754; in the second case, it mainly interacts with amino acids D760 and Y424, but also binds to amino acid S729. Herewith, the first and second locations of the piracetam molecule are mutually exclusive. In the third case, the piracetam molecule interacts with amino acids S729, D760 and N764 [7]. Thus, only two piracetam molecules can simultaneously occupy pharmacologically active locations at the binding site of the AMPA receptor. In the study, the second location of piracetam was selected at the binding site of the AMPA receptor, and amino acids S729, D760, Y424 and N764 were designated as Ser 217, Asp 248, Tyr 35 and Asn 252, respectively. Two possible simultaneous variants of the location of the piracetam molecule at the binding site of the AMPA receptor in the 3LSF protein-ligand complex are shown in Fig. 2.



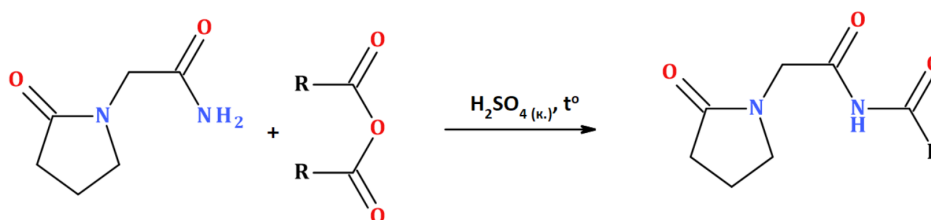
**Figure 1 – Molecular structure of the GABA<sub>A</sub> receptor**

Note: A is a horizontal position of the GABA<sub>A</sub> receptor in the plane; B is a vertical one



**Figure 2 – Location of the piracetam molecule at the binding site of the AMPA receptor in the 3LSF protein-ligand complex**

Note: A – the second location option. B – the third location option



R = CH<sub>3</sub> (PirAc); C<sub>2</sub>H<sub>5</sub> (PirPr); C<sub>3</sub>H<sub>7</sub> (PirBut)

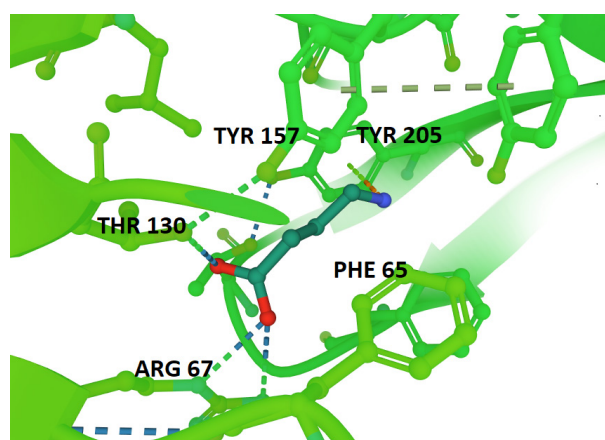
**Figure 3 – Synthesis of N-acyl derivatives of 2-oxo-1-pyrrolidinacetamide**

**Table 1 – Structural formulas of ligands from the Binding DB with corresponding  $K_i$  indices**

| Ligand code, structural formula, $K_i$ nM | Ligand code, structural formula, $K_i$ nM | Ligand code, structural formula, $K_i$ nM | Ligand code, structural formula, $K_i$ nM |
|---|---|---|---|
| BDBM50128264, <u>370</u><br>              | BDBM50107595, <u>218</u><br>              | BDBM50126764, <u>175</u><br>              | BDBM50252922, <u>112</u><br>              |
| BDBM50060627, <u>105</u><br>              | BDBM50252920, <u>80</u><br>               | BDBM50252873, <u>61</u><br>               | BDBM50060632, <u>45</u><br>               |
| BDBM50060635, <u>4</u><br>                | BDBM50166287, <u>2.9</u><br>              |   |   |

**Table 2 – The minimum value of the ligand-receptor interaction of the predicted ligands in the active center of the GABA<sub>A</sub> receptor**

| Ligand       | Minimum energy of ligand-receptor complex formation, kcal/mol |
|--------------|---|
| GABA         | -71.708   |
| Piracetam    | -86.509   |
| PirAc        | -88.691   |
| PirPr        | -95.354   |
| PirBut       | -95.507   |
| Aniracetam   | -81.509   |
| Fonturacetam | -97.105   |
| Phenibut     | -94.692   |
| Picamilonum  | -78.629   |
| Pramiracetam | -76.046   |

**Figure 4 – Location of the gamma-aminobutyric acid molecule in the active center of the GABA<sub>A</sub> receptor**

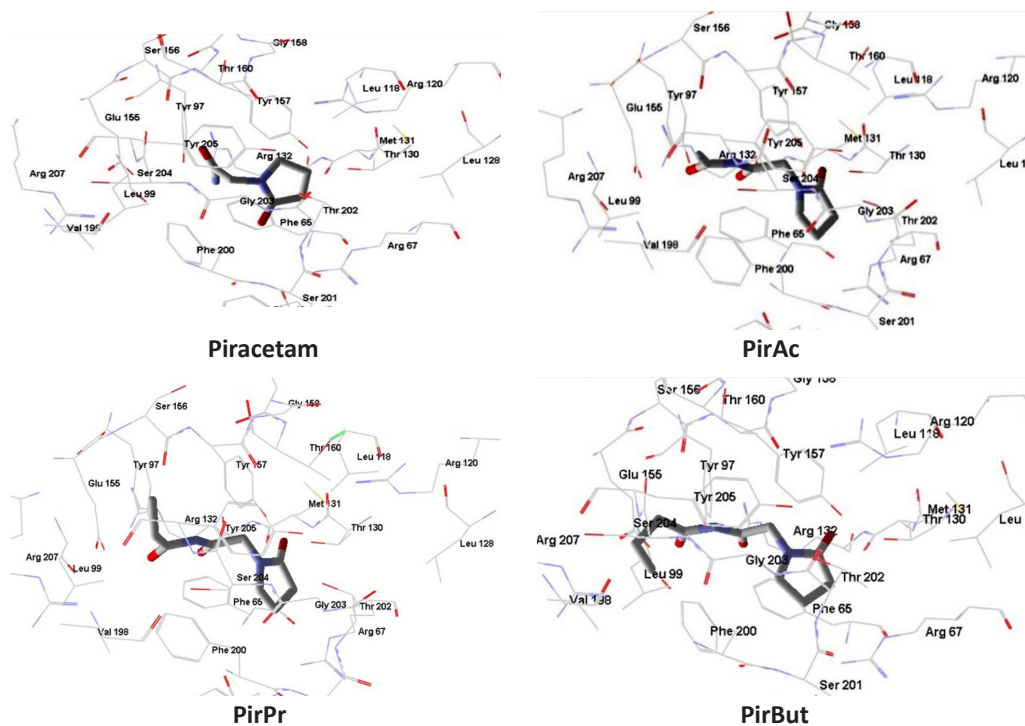


Figure 5 – Location of piracetam and its N-acyl derivatives in the active center of the GABA<sub>A</sub> receptor according to the results of molecular docking

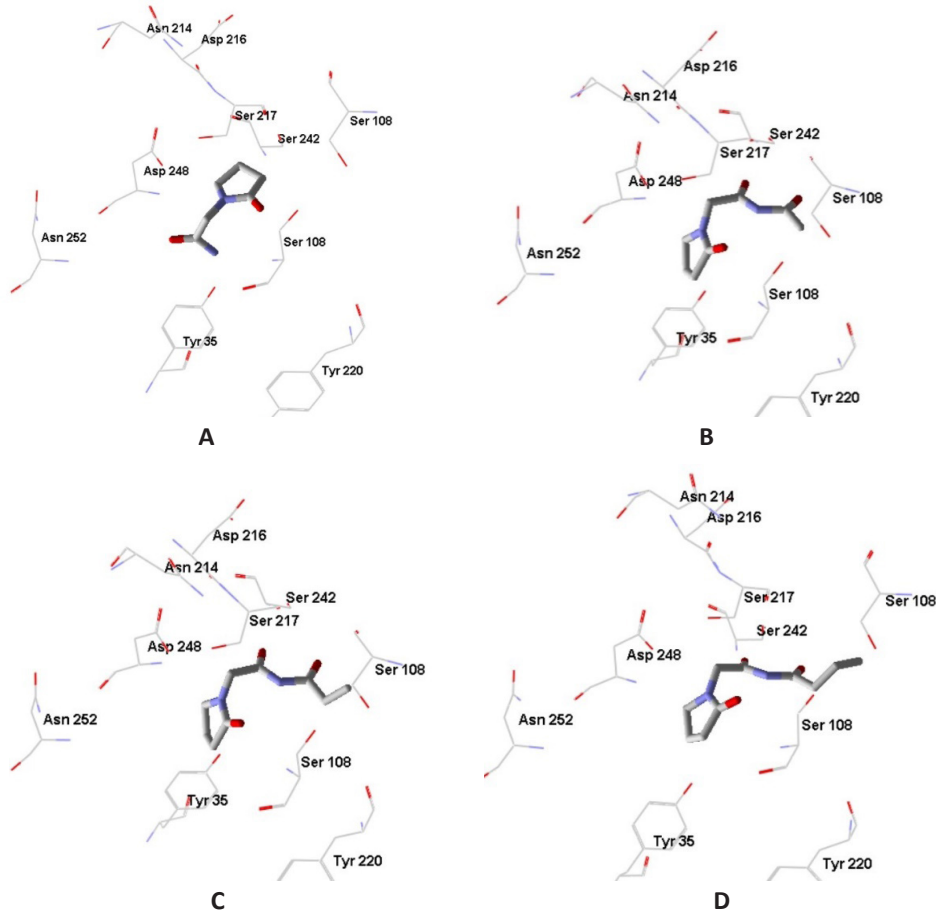


Figure 6 – The location of ligands at the binding site of the AMPA receptor according to the results of molecular docking

Note: A – piracetam; B-PirAc; C – PirPr; D – PirButt

**Table 3 – The formation energy of ligand bonds with amino acids Thr 130, Arg 67, Tyr 205, Tyr 157 and Phe65, kcal/mol**

| Ligand       | Amino acid |         | Sum     | Amino acid |         |         | Sum     |
|--------------|------------|---------|---------|------------|---------|---------|---------|
|              | Thr 130    | Arg 67  |         | Tyr 205    | Tyr 157 | Phe 65  |         |
| GABA         | -3.402     | -11.652 | -15.054 | -6.693     | -8.628  | -8.315  | -23.635 |
| Piracetam    | -3.295     | -3.771  | -7.066  | -15.209    | -17.001 | -8.056  | -40.266 |
| PirAc        | -3.126     | -7.932  | -11.058 | -18.353    | -10.854 | -12.668 | -41.875 |
| PirPr        | -3.387     | -7.281  | -10.669 | -16.311    | -12.056 | -12.136 | -40.504 |
| PirBut       | -3.045     | -7.515  | -10.559 | -10.936    | -15.734 | -10.192 | -36.862 |
| Aniracetam   | -2.707     | -6.371  | -9.077  | -17.433    | -16.844 | -9.811  | -44.089 |
| Fonturacetam | -0.501     | -12.521 | -13.022 | -23.481    | -16.458 | -14.223 | -54.162 |
| Phenibut     | -1.416     | -9.197  | -10.614 | -26.125    | -12.417 | -11.563 | -50.105 |
| Picamilon    | -7.555     | -3.325  | -10.880 | -25.993    | -10.147 | -13.068 | -49.207 |
| Pramiracetam | -2.281     | -7.117  | -9.399  | -17.954    | -14.522 | -10.145 | -42.620 |

**Table 4 – Calculated interaction energies of the studied compounds with residues of amino acids Thr 130, Arg 67, Tyr 205, Tyr 157, Arg 207, Glu 155, Phe 200, Thr 202, Tyr 97, Asp 44 и Leu 118, kcal/mol**

| Amino acid | GABA     | Piracetam | PirAc    | PirPr    | PirBut  |
|------------|----------|-----------|----------|----------|---------|
| Arg 207    | 0.561    | -         | -0.590   | -2.436   | -3.291  |
| Glu 155    | -1.881   | -1.524    | -2.67262 | -0.83446 | -0.998  |
| Phe200     | -5.189   | -13.994   | -11.515  | -10.532  | -16.502 |
| Thr 202    | -4.137   | -5.205    | -8.562   | -7.454   | -8.294  |
| Tyr 97     | -1.231   | -7.239    | -4.117   | -5.967   | -4.487  |
| Tyr 157    | -8.628   | -17.001   | -10.854  | -12.056  | -15.734 |
| Tyr 205    | -6.693   | -15.209   | -18.353  | -16.311  | -10.936 |
| Arg 67     | -11.652  | -3.771    | -7.933   | -7.281   | -7.515  |
| Asp 44     | 0.718    | -         | -        | -        | -       |
| Leu 118    | -1.989   | -1.795    | -1.951   | -1.887   | -1.954  |
| Thr 130    | -3.40186 | -3.295    | -3.125   | -3.387   | -3.045  |

**Table 5 – The minimum value of the interaction energy of ligands with the binding site of the AMPA receptor**

| Ligand    | Minimum energy of ligand-receptor interaction, kcal/mol |
|-----------|---|
| Piracetam | -80.3646  |
| PirAc     | -94.9684  |
| PirPr     | -101.0150   |
| PirBut    | -107.0790   |

**Table 6 – Interaction energies of the studied compounds with amino acids of the AMPA receptor binding site, kcal/mol**

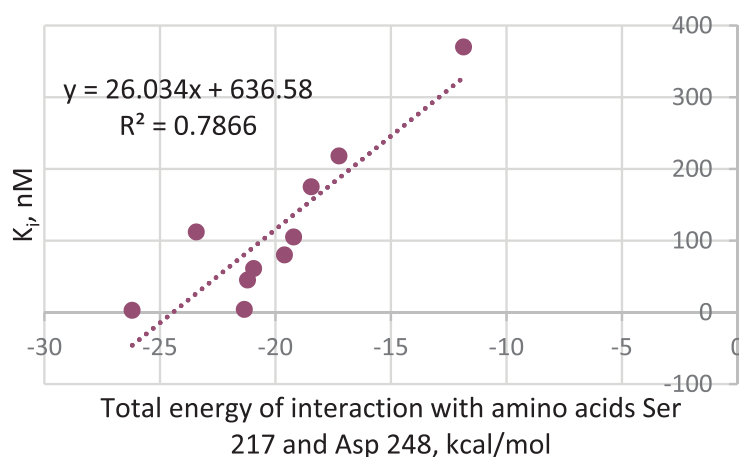
| Amino acids | Piracetam | PirAc    | PirPr    | PirBut   |
|-------------|-----------|----------|----------|----------|
| Asp 248     | -8.6384   | -7.0767  | -7.2909  | -7.1325  |
| Leu 247     | -17.2258  | -10.5279 | -10.946  | -10.5261 |
| Lys 251     | -3.2265   | -3.7261  | -4.2831  | -3.9035  |
| Met 107     | -7.8311   | -14.4516 | -15.6796 | -14.981  |
| Phe 106     | -2.7516   | -11.6726 | -12.144  | -11.9543 |
| Pro 105     | -0.9851   | -7.7395  | -10.1021 | -12.8108 |
| Ser 108     | -0.6031   | -9.5983  | -10.9815 | -11.098  |
| Ser 242     | -4.3652   | -6.5524  | -6.1867  | -6.4454  |
| Tyr 35      | -3.6829   | -1.7938  | -2.3966  | -1.9694  |
| Asp 216     | -0.3789   | -        | -        | -        |
| Lys 218     | -1.24     | -2.8374  | -3.687   | -6.3321  |
| Ser 217     | -7.1949   | -11.9722 | -11.3445 | -12.6389 |
| Sum         | -58.124   | -87.9485 | -95.042  | -99.792  |

**Table 7 – The interaction energy value of ligands from the database bindingdb.org with amino acids Ser 217 and Asp 248 of the binding site of the AMPA receptor**

| Ligand code according to the database bindingdb.org | $K_i$ , nM | Interaction energy with Ser 217, kcal/mol | Interaction energy with Asp 248, kcal/mol | Total interaction energy, kcal/mol |
|---|------------|---|---|------------------------------------|
| BDBM50128264  | 370        | -10.4842                                  | -1.3701                                   | -11.8543                           |
| BDBM50107595  | 218        | -15.0233                                  | -2.2196                                   | -17.2429                           |
| BDBM50126764  | 175        | -13.3183                                  | -5.1289                                   | -18.4472                           |
| BDBM50252922  | 112        | -18.9924                                  | -4.4265                                   | -23.4189                           |
| BDBM50060627  | 105        | -14.7070                                  | -4.4979                                   | -19.2049                           |
| BDBM50252920  | 80         | -17.1936                                  | -2.4128                                   | -19.6064                           |
| BDBM50252873  | 61         | -15.8562                                  | -5.0815                                   | -20.9377                           |
| BDBM50060632  | 45         | -14.1395                                  | -7.0648                                   | -21.2043                           |
| BDBM50060635  | 4          | -14.2827                                  | -7.0615                                   | -21.3442                           |
| BDBM50166287  | 2.9        | -20.0334                                  | -6.1673                                   | -26.2007                           |

**Table 8 – The predicted value of the biological activity of N-acyl derivatives of 2-oxo-1-pyrrolidine acetamide**

| Ligand    | Interaction energy with Ser 217, kcal/mol | Interaction energy with Asp 248, kcal/mol | Total interaction energy, kcal/mol | $K_i$ predicted, nM |
|-----------|---|---|------------------------------------|---------------------|
| Piracetam | -7.1949                                   | -8.6384                                   | -15.8333                           | 224.3759            |
| PirAc     | -11.9722                                  | -7.0767                                   | -19.0489                           | 140.6609            |
| PirPr     | -11.3445                                  | -7.2909                                   | -18.6354                           | 151.4260            |
| PirBut    | -12.6389                                  | -7.1325                                   | -19.7714                           | 121.8514            |



**Figure 7 – Precise diagram of the linear relationship between the value of the inhibition constant and the total interaction energy of ligands with amino acids Ser 217 and Asp 248 of the AMPA-receptor binding site**

The index of the inhibition constant ( $K_i$ ) can be used to assess the affinity of low-molecular compounds to the binding site of the protein target. In order to develop a methodology for predicting the biological activity of the studied compounds in relation to the AMPA receptor, 10 structural formulas and their corresponding  $K_i$  values for the *Rattus norvegicus* organism were used, they had been given in the Binding Database (<https://www.bindingdb.org/bind/index.jsp>) (Table 1).

#### Objects of molecular design

N-acyl-substituted 2-(2-oxopyrrolidine-1-yl)-acetamide (piracetam) were selected as ligands for the molecular design of GABA-ergic and glutamatergic BACs and the subsequent synthesis. They are: N-[2-(2-oxopyrrolidine-1-yl)-acetyl]-acetamide (PirAc), N-[2-(2-oxopyrrolidine-1-yl)-acetyl]-propionamide (PirPr) and N-[2-(2-oxopyrrolidine-1-yl)-acetyl]-butyramide (PirBut).

The synthesis of N-acyl derivatives of 2-(2-oxopyrrolidine-1-yl)-acetamide was carried out by dissolving



a suspension (0.01 mol) of 2-(2-oxopyrrolidine-1-yl) acetamide in the excess of the corresponding anhydride at the temperature of 70–80°C during the stirring. Then 0.1 ml of concentrated sulfuric acid was added. The acylation reaction was monitored by thin-layer chromatography. The target product was isolated from the cooled reaction medium with diethyl ether. Recrystallization of the substance was performed from ethyl or isopropyl alcohol (Fig. 3) [12].

## RESULTS AND DISCUSSION

### Molecular docking to the GABA<sub>A</sub> receptor binding site

The study of the ligand-receptor complex of gamma-aminobutyric acid 6D6U revealed that ligand forms two hydrogen bonds with amino acids Thr 130 and Arg 67, and enters into hydrophobic interactions with Tyr 205, Tyr 157 and Phe 65 in the active center of the GABA<sub>A</sub> receptor (Fig. 4).

The results of molecular docking (Table 2) show that all N-acyl derivatives of 2-(2-oxopyrrolidine-1-yl) acetamide exceed a number of the known ligands by the value of the minimum interaction energy, such as GABA, piracetam, anipiracetam, picamilonum and pramiracetam. The calculated energies are also comparable to the interaction energy of phenibut, but are inferior to phenylpiracetam (fonturacetam). From the values of the average energy of interaction with the active site of the GABA receptor it follows that PirAc, PirPr and PirBut have the greatest affinity for the GABA receptor among the studied structures.

The further study of the ligand-receptor interaction consisted in comparing the energies of hydrogen bonds and hydrophobic interactions. The energies of hydrogen bonds with amino acids Thr 130 and Arg 67 show that the ligands under study form a more stable hydrogen bond with Arg 67 residue. GABA and phenylpiracetam can form the strongest hydrogen bonds. In terms of the total energy of hydrogen bonds, they are inferior to PirAc, PirPr and PirBut, but all these ligands are superior in energy values to the modified drug – piracetam (Table 3). In other compounds, this energy is comparable to similar energies of N-acyl derivatives of 2-oxo-1-pyrrolidine acetamide. The calculated energies of hydrophobic interactions with amino acid residues Tyr 205, Tyr 157 and Phe 65 show that the simulated structures are characterized by higher interaction energies compared to GABA. However, these values are comparable to those of piracetam, aniracetam and pramipiracetam, but are inferior to fonturacetam, phenibut and picamilon. These results can be explained by the structural feature of phenylpiracetam, phenibut and picamilon, i.e. the presence of volumetric aromatic fragments in their struc-

ture. The molecules of phenylpiracetam and phenibut contain a benzoin ring, and picamilonum contains a pyrrolidine heterocyclic system.

The experimental data of the X-ray diffraction analysis of the GABA<sub>A</sub>-receptor complex with a gamma-aminobutyric acid molecule [6] made it possible to increase the number of amino acid residues involved in the formation of the ligand–receptor complex. Fragments of Arg 207, Glu 155, Phe 200, Thr 202, Tyr 97, Asp 44 and Leu 118 should be added to the previously considered amino acid residues. A comparative analysis of the calculated energy characteristics of binding GABA, piracetam and its modified derivatives (Table 4) suggested that the N-acyl derivatives of 2-oxo-1-pyrrolidineacetamide form a more stable complex with amino acid residues Arg 207, Phe 200, Thr 202, Tyr 97, Tyr 157, Tyr 205 and Phe 65 than the GABA molecule. The interaction energy of the designed structures with the Arg 67 residue is lower compared to GABA, and the results for amino acids Leu 118 and Thr130 are comparable. PirAc has a stronger interaction with the Glu 155 residue than PirPr and PirBut. The amino acid of the active center of the GABA<sub>A</sub> receptor Asp 44 does not participate in the interaction with piracetam and its modifications, however, it should be noted that the GABA molecule also forms a weak interaction with it. Thus, PirAc, PirPr and PirBut have a greater affinity for the active center of the GABA receptor compared to the GABA molecule and the drug piracetam.

### Molecular docking to the AMPA receptor binding site

According to the results of molecular docking in the Molegro Virtual Docker 6.0.1 program, the most energetically favorable locations of N-acyl derivatives of 2-oxo-1-pyrrolidine acetamide at the binding site of the AMPA receptor were established. Fig. 6 shows examples of the location of the studied compounds with the minimum energy in the interaction with the amino acids of the AMPA-receptor binding site. This figure shows the main amino acids that are involved in the implementation of the activating effect on the receptor: Ser 217, Asp248, Tyr 35 and Asn 252.

The minimum value of the interaction energy of ligands with the binding site of the AMPA receptor is shown in Table 5. These results show that all three N-acyl derivatives of 2-oxo-1-pyrrolidine acetamide have a greater affinity for the binding site of the ionotropic glutamate receptor than the piracetam molecule. At the same time, the most energetically favorable location is occupied by PirBut. Then PirPr and PirAc molecules follow, according to the interaction energy with the binding site of the AMPA receptor.

Using the 3LSF protein-ligand complex, it was found out that the piracetam molecule, in addition to Ser 217, Asp248, Tyr 35 and Asn 252, also interacts with the following amino acids of the active center of the AMPA receptor: Leu 247, Lys 251, Met 107, Phe 106, Pro 105, Ser 108, Ser 242, Asp 216 and Lys 218. The interaction energies of the piracetam molecule with the amino acids of the AMPA receptor binding site were obtained from the ligand complex 3LSF according to the already established X-ray diffraction analysis of the pharmacologically active location of this substance. In this case, the second location of the piracetam molecule was used, where the formation of bonds with Asn 252 does not occur (Fig. 2A). The interaction energies of PirAc, PirPr and PirBut with the amino acid environment of the AMPA-receptor binding site were obtained using a molecular complex with a minimum energy of the ligand-receptor interaction. The results of the study in Table 6 show, that the N-acyl derivatives of 2-oxo-1-pyrrolidinacetamide exceed the piracetam molecule in terms of the interaction energy with amino acids Met 107, Phe 106, Pro 105, Ser 108, Ser 242, Lys 218 and Ser 217. According to amino acids Asp 248, Lys 251 and Tyr 35, the studied substances have a small difference in the interaction energy compared to the piracetam molecule (the maximum difference in PirAc and Tyr 35, is 1.8891 kcal/mol), and there is a decrease in the interaction energy with the amino acid Leu 247. PirAc, PirPr, PirBut do not interact with the amino acid Asp 216, but the piracetam molecule forms a very weak bond with this amino acid (–0.3789 kcal/mol).

The method for calculating nootropic biological activity by molecular docking using the Molegro Virtual Docker 6.0.1 program, has been developed to predict the biological activity of N-acyl derivatives of 2-oxo-1-pyrrolidinacetamide. Based on the results of molecular docking of ligands given in the database bindingdb.org, the ligand-receptor complex with the lowest MolDock Score interaction energy was selected for each ligand with the AMPA receptor binding site. The energy of bond formation with amino acids Ser 217 and Asp 248 of the binding site of the AMPA receptor responsible for the implementation of the pharmacological action, was studied for the selected locations of low-molecular compounds. The results of the study are shown in Table 7.

In order to determine the relationship between the total interaction energy of ligands with amino acids Ser 217 and Asp 248 of the AMPA-receptor binding site and the corresponding values of the inhibition constant, a dot diagram was constructed. As a result, a linear mathematical relationship between the value of the inhibition constant and the total interaction

energy of the selected ligands with the amino acids Ser 217 and Asp 248 of the AMPA receptor binding site was obtained:  $Y=26,034x+636,58$ . In this mathematical dependence, the value at Y corresponds to the value of the inhibition constant, and the value of X corresponds to the total interaction energy of the ligands with amino acids Ser 217 and Asp 248 of the AMPA receptor binding site.

To assess the reliability of the obtained mathematical dependence between the value of the inhibition constant and the total interaction energy of the selected ligands with amino acids Ser 217 and Asp 248 of the AMPA-receptor binding site, the approximation reliability factor and the root mean square deviation were calculated. The accuracy coefficient of the approximation was obtained using the Microsoft Excel program, and it is 0.7866. The root mean square deviation was calculated using the formula:

$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^N \Delta K_i^2},$$

where: RMSD is a root mean square deviation; N is the number of ligands; the difference between  $K_i$  calculated from the derived linear mathematical dependence and  $K_i$  – taken from the database bindingdb.org.

The root mean square deviation is 49.15237. Thus, based on the obtained values of the approximation reliability coefficient and the standard deviation, it is possible to talk about an acceptable accuracy of calculating the linear dependence of the inhibition constant on the total energy of the interaction of ligands with amino acids Ser 217 and Asp 248 of the AMPA-receptor binding site.

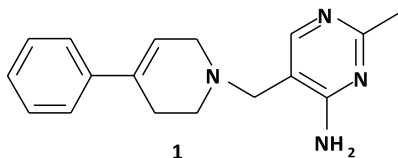
According to the developed methods, the prediction of the biological activity of N-acetyl-2-(2-oxocyclopentyl acetamide)acetamide (PirAc), N-propanoyl-2-(2-oxocyclopentyl)-acetamide (PirPr) and N-butanoyl-2-(2-oxocyclopentyl)-acetamide (PirBut) regarding the AMPA receptor, were calculated (Table 8).

## DISCUSSION

The pharmacological effect of nootropic drugs is associated with their effect on the work of GABA-ergic, monoaminergic, cholinergic and glutamatergic neurotransmitter systems of the brain [13].

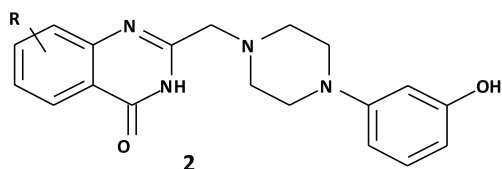
In addition to the involvement of GABA receptors and metabotropic glutamate receptors (mGluRs) in the nootropic activity, the effect on other G-protein coupled receptors (GPCRs) is also conjugated with the nootropic effect [14]. In particular, the pyrimidine derivative Ro10-5824 (1) shows a pronounced nootropic effect as the agonist of dopamine D4 receptors. The activation of this type of receptors

is associated with an increase in cognitive functions of the brain, such as a learning ability, a cognitive activity, etc. [15].



The antioxidant effect of some nootropics is explained by the fact that their molecules are able to inhibit the formation of free radicals and the processes of lipid peroxidation [16].

In [17], using the example of (3H)-quinazolin-4-one derivatives, the possibility of a directed combination of various pharmacophores in one molecule was shown in order to enhance the target pharmacological activity.



For example, quinazolinone derivatives (2) were synthesized. Their ability to activate brain dopamine D4 receptors is combined with an antioxidant effect due to the presence of a phenolic hydroxyl (a hydroxyphenyl fragment). It was shown [17] that one of the most useful manifestations of such a combination is an increase in the blood flow in the microcirculatory bed and, as a result, an improvement in peripheral blood circulation.

Thus, having the possibility of simultaneous effects on various pharmacological mechanisms, nootropic drugs are an indispensable group in the modern arsenal of drugs used in the treatment of disorders of functioning of the higher nervous system in humans.

A design of novel therapeutics is based on the structural modifications of the approved drugs, or chemical substances with known activities, including endogenous biologically active compounds. In this regard, close attention is attracted by neuroactive amino acids: GABA, glutamic acid, taurine, etc., which are found to influence a variety of neuronal processes in the brain [18].

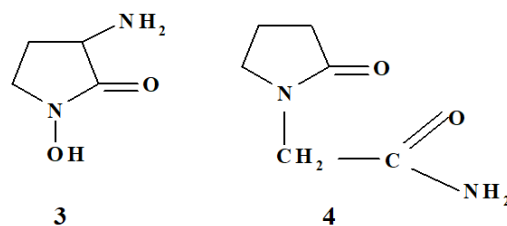
A significant role of GABA as an inhibitory neurotransmitter in the relationship between various functions of the central nervous system and the effect on hormonal homeostasis and the activity of the cardiovascular system is shown [19]. It has been proved that the first metabolites of GABA affect the passage

of the ketoglutarate dehydrogenase stage of the Krebs cycle.

Accordingly, the GABA-ergic system makes it possible to protect the body in cases of extreme conditions associated with various types of hypoxia by participating in metabolic processes. The influence of GABA on the course of oxidative phosphorylation, the participation in glucose metabolism and, as a result, in the regulation of osmotic processes, and this leads to the manifestation of antihypoxic and antioxidant effects has been confirmed [20].

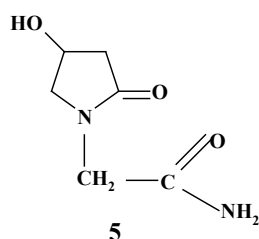
In the process of searching for biologically active compounds with a nootropic effect, the interaction of the simulated compounds with GABA and NMDA receptors, which are largely responsible for the processes of inhibition and excitation of the central nervous system, is predicted [21]. The optimal relationship between the inhibitory and excitatory neurotransmission systems of the central nervous system ensures the normal activity of the brain, autonomic functions and metabolic processes in the body, and a violation of the balance between these systems leads to various pathological conditions of the body [22]. These facts allow assessing the relevance of the molecular design and targeted synthesis of modified structures of GABA-ergic drugs with cerebroprotective, antihypoxic and nootropic properties.

Cyclic forms of GABA – derivatives of  $\alpha$ -pyrrolidone – penetrate through the BBB easier and show an anticonvulsant activity in high doses. The compound 3-amino-1-hydroxypyrrolidinone-2 (3) has a potential for the treatment of the diseases associated with extrapyramidal disorders.



One of the most successful derivatives of N-substituted lactams synthesized in the laboratory of UCB (Belgium) is 2-(2-oxopyrrolidin-1-yl)acetamide (4). The drug piracetam (4) has a higher lipophilicity than GABA, passes through the BBB easier and affects the cortical, subcortical and transallosal reactions of the central nervous system [23].

2-(4-hydroxy-2-oxopyrrolidin-1-yl) was synthesized as a structural analog of piracetam-acetamide (5), which is a lactam of 4-amino-3-hydroxybutyric acid (the drug gamibetal).



This drug and its compounds similar in structure are able to normalize memory processes and improve the cognitive properties of the brain [24].

Based on these studies, a new direction has been formed in the field of creating neuropharmacological drugs – a targeted search for gabaergic compounds. At the initial stage, this direction was a set of empirical methods or, at best, it was based on a logical-structural approach. The results of modern studies of X-ray diffraction and radioligand analysis of ligand-receptor complexes sufficiently reliably describe the molecular mechanisms of synaptic processes, which opens up additional opportunities for the molecular construction of GABA-ergic substances *in silico*, through the use of computer modeling methods [25].

One of the protein targets through which the pharmacological effect of nootropic drugs is realized is the AMPA receptor. This receptor received its name in honor of its selective agonist- $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). The AMPA receptor is a subtype of ionotropic glutamate receptors that are able to pass positive charged ions through the cell membrane of neurocytes and thus participate in the transmission of rapid excitatory signals in intraneuronal synapses [13].

In these works, special attention of researchers is drawn to the problem of selective interaction of molecules of natural neurotransmitters and ligands with receptors. The emergence of new three-dimensional

structures of protein receptors in the Protein Data Bank ([www.wwpdb.org](http://www.wwpdb.org)) [26], combined with the intensive development of computer methods for analyzing intra- and intermolecular interactions, contribute to the creation of more accurate models in ligand-receptor systems.

The highest GABA-ergic activity can be expected in the molecule N-[2-(2-oxo-pyrrolidine-1-yl)-acetyl]-propanamide. The results of the conducted prognostic study indicate that all N-acyl derivatives of 2-(2-oxopyrrolidin-1-yl)-acetamide may be superior in GABA-ergic activity to a modified drug – piracetam, as well as an endogenous inhibitory neurotransmitter –  $\gamma$ -aminobutyric acid.

The analysis of the  $K_i$  values obtained *in silico* for N-acyl derivatives of 2-oxo-1-pyrrolidinacetamide shows that their hypothetical nootropic pharmacological activity significantly exceeds piracetam as a result of their allosteric modulation of the AMPA receptor. In this case, the leader compound is N-butanoyl-2-(2-oxocyclopentyl)-acetamide. Thus, PirAc, PirPr and PirBut are promising compounds with a higher predicted nootropic pharmacological activity than the piracetam molecule.

The conducted pharmacological studies confirm the pronounced nootropic properties of the synthesized N-acyl derivatives of 2-(2-oxopyrrolidine-1-yl)acetamide [27, 28].

### CONCLUSION

It was found out that all N-acyl derivatives of 2-oxo-1-pyrrolidinacetamide can surpass gamma-aminobutyric acid and piracetam in a nootropic activity by molecular modeling of the ligands interaction with the active binding site of gamma-aminobutyric acid of the GABA receptor by molecular docking. These compounds have also a great affinity for the binding site of the AMPA receptor. In the course of the conducted studies, a method for predicting glutamatergic activity was proposed.

### FUNDING

The reported study was funded by RFBR, project number 20-315-90060.

### CONFLICT OF INTEREST

Authors declare no conflict of interest.

### AUTHORS' CONTRIBUTION

- I.P. Kodonidi – research design, determination of the structure of the obtained compounds and interpretation of the results of the computational experiment;
- A.S. Chiriapkin – synthesis, determination of the structure of the obtained compounds, molecular modeling, analysis of the data of the computational experiment.
- D.E. Tworowski – interpretation of the results of the computational experiment. All the authors participated in the discussion of the results and the writing of the article.

## ACKNOWLEDGMENTS

The authors of the article express their gratitude to Eduard T. Oganessian – Doctor of Sciences (Pharmacy), Professor, the Head of the Department of Organic Chemistry of Pyatigorsk Medical and Pharmaceutical Institute – Branch of Volgograd State Medical University), Glushko A. Alexander Candidate of Sciences (Pharmacy), Associate Professor of the Department of Inorganic, Physical and Colloidal Chemistry of Pyatigorsk Medical and Pharmaceutical Institute – Branch of Volgograd State Medical University), for the advisory assistance provided in writing the article.

## REFERENCES

- Sahjesh S, Rashmi S, Ayush B. Smart Drugs: A Review. *International Journal for Innovation Education and Research*. 2020 Nov;8(11):1–13.
- Malykh AG., Sadaie MR. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. *Drugs*. 2012 Sep 17;70(3):287–312. DOI: 10.2165/11319230-000000000-00000.
- Perfilova VN, Sadikova NV., Prokof'ev II, Inozemtsev OV, Tyurenkov IN. Comparative study of the heart functional reserve under stress-induced blockade of no-ergic system and GABA<sub>A</sub> receptors in rats. *Eksp Klin Farmakol*. 2016 Aug;79(5):10–14. DOI: 10.30906/0869-2092-2016-79-5-10-14. Russian
- Teppen B.J. HyperChem, release 2: molecular modeling for the personal computer. *J. Chem. Inf. Comput. Sci*. 1992; 32:757–759.
- Thomsen R, Christensen MH. MolDock: A new technique for high-accuracy molecular docking. *J Med Chem*. 2006 Jun 1;49(11):3315–21. DOI: 10.1021/jm051197e.
- Zhu S, Noviello CM, Teng J, Walsh RM, Kim JJ, Hibbs RE. Structure of a human synaptic GABAA receptor. *Nature*. 2018 Jul;559(7712):67–72. DOI: 10.1038/s41586-018-0255-3.
- Ahmed A, Oswald R. Piracetam defines a new binding Site for allosteric modulators of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. *J Med Chem*. 2010 Mar 11;53(5):2197–203. DOI: 10.1021/jm901905j.
- Semyanov AV. GABA-ergic inhibition in the CNS: types of GABA receptors and mechanisms of tonic GABA-mediated inhibitory action. *Neurophysiology*. 2002 Jun;34(1):71–80. DOI: 10.1023/A:1020274226515. Russian
- Sieghart W, Sperk G. Subunit composition, distribution, and function of GABA(A) receptor subtypes. *Curr Top Med Chem*. 2002 Aug;2(8):795–816. DOI: 10.2174/1568026023393507.
- Sigel E, Luscher BP. A closer look at the high affinity benzodiazepine binding site on GABAA receptors. *Curr Top Med Chem*. 2011;11(2):241–6. DOI: 10.2174/156802611794863562.
- Masiulis S, Desai, Uchanski T, Martin IS, Laverty D, Karia D, Malinauskas T, Zivanov J., Pardon E., Kotecha A., Steyaert J., Miller K.W., Aricescu A.R. GABA A receptor signalling mechanisms revealed by structural pharmacology. *Nature*. 2019 Jan;565(7740):454–459. DOI: 10.1038/s41586-018-0832-5.
- Kodonidi IP, Chiriapkin AS, Morozov AV, Smirnova LP, Ivchenko AV, Zhilina OM. Synthesis and thermochemical modeling of reaction mechanism for producing N-acyl derivatives of 2-(2-oxo-1-pyrrolidine-1-yl)-acetamide. *J. Chem. & Chem. Tech*. 2020;63(2):38–44. DOI: 10.6060/ivkkt.20206302.6080. Russian
- Suliman NA, Mat Taib CN, Mohd Moklas MA, Hidayat Baharuldin MT, Basir R, Adenan MI. Establishing Natural Nootropics: Recent Molecular Enhancement Influenced by Natural Nootropic. *Evidence-Based Complementary and Alternative Medicine*. 2016;2016(4391375). DOI: 10.1155/2016/4391375.
- Terunuma M. Diversity of structure and function of GABA-B receptors: a complexity of GABA-B-mediated signaling. *Proc Jpn Acad Ser B Phys Biol Sci*. 2018;94(10):39. DOI: 10.2183/pjab.94.026
- Newman-Tancredi A, Heusler P, Martel J.C, Ormière A.M, Leduc N, Cussac D. Agonist and antagonist properties of antipsychotics at human dopamine D4.4 receptors: G-protein activation and K<sup>+</sup> channel modulation in transfected cells. *The International Journal of Neuropsychopharmacology*. 2008 May;11(3):293–307. DOI: 10.1017/S1461145707008061.
- Volkovoy VA, Sevrakov OV, Kolisnyk SV, Derkach NV, Kryzhna SI, Ostapets MO. The experimental study of the antihypoxic and antioxidant activity of 5,7-dihydro-1H-pyrrolo-[2,3-d]pyrimidine derivatives. *News of Pharmacy*. 2017;3(91):61–65. DOI: 10.24959/nphj.17.2173. Russian
- Patent US 8349850 B2 / 08-01-2013. Heterocyclic compounds and uses thereof in the treatment of sexual disorders. 2007, WO 2007110868. Tworowski D, Matsievitch R. Kogan V.
- Jakaria M, Azam S, Haque ME, Jo SH, Uddin MS, Kim IS, Choi DK. Taurine and its analogs in neurological disorders: Focus on therapeutic potential and molecular mechanisms. *Redox Biol*. 2019 Jun;24(101223). DOI: 10.1016/j.redox.2019.101223.
- Vargas RA. The GABAergic System: An Overview of Physiology, Physiopathology and Therapeutics. *Int J Clin Pharmacol Pharmacother* 2018 Dec;3(3:JICPP-142). DOI: 10.15344/2456-3501/2018/142
- Kovalev GV, Tyurenkov IN. The search for substances that activate the GABA-ergic system, a new direction in the creation of antihypertensive drugs. *Pharmacology and toxicology*. 1989; 1: 5–11. Russian
- Nuss Ph. Anxiety disorders and GABA neurotransmission: a disturbance of modulation // *Neuropsychiatr. Dis. Treat.* – 2015. – V. 11. – P. 165–175. DOI: 10.2147/NDT.S58841
- Srinivas N, Maffuid K, Kashuba ADM. Clinical Pharmacokinetics and Pharmacodynamics of Drugs in the Central Nervous System. *Clin Pharmacokinet*. 2018 Sep;57(9):1059–1074. DOI: 10.1007/s40262-018-0632-y.
- Giurgea G, Salama H. Nootropic drugs. *Progr. Neuro-Psychopharmacol*. 1977;1:235–247. DOI: 10.1016/0364-7722(77)90046-7
- Li W, Liu H, Jiang H, Wang C, Guo Y, Sun Y, Zhao X, Xiong X, Zhang K, Nie Z, Pu X. (S)-Oxiracetam is the Active Ingredient in Oxiracetam that Alleviates the Cognitive Impairment Induced by Chronic Cerebral Hypoperfusion in Rats.

- Sci Rep. 2017 Aug 30;7(1):10052. DOI: 10.1038/s41598-017-10283-4.
25. Kodonidi IP, Oganessian ET, Glushko AA, Zolotykh DS, Pogrebnyak AV, Turenkov IN, Bagmetova VV, Zolotykh DS, Pogrebnyak AV. Molecular design and targeted synthesis of N-substituted 4-oxo-1,4-dihydropyrimidine derivatives on the basis of inhibitory neurotransmitters. *Pharmaceutical Chemistry Journal*. 2009;43(10):32–39. Russian
26. Berman H, Westbrook J, Feng Z, Gilliland G, Bhat T, Weissig H, Shingyalov IN, Bourne PE. The Protein Data Bank. *Nucleic Acids Res*. 2000;28(1):235–242. DOI: 10.1093/nar/28.1.235.
27. Voronkov AV, Pozdnyakov DI, Sosnovskaya AV, Chiryapkin AS, Kolonidi IP, Mamleev AV. Influence of new 2-pyrrolidone derivatives to change vasodilative function of vascular endothelium in experimental cerebral ischemia. *EruditioJuvenium*. 2020;8(1):53–62. DOI:10.23888/HMJ20208153-62. DOI: 10.23888/HMJ20208153-62. Russian
28. Pozdnyakov DI, Voronkov AV, Kodonidi IP, Chiryapkin AS, Anenko DS. Neuroprotective effect of organic acids diamides. focus on changing mitochondrial function. *PharmacologyOnline*. 2020;1:237–247.

## AUTHORS

**Ivan P. Kodonidi** – Doctor of Sciences (Pharmacy), Professor of the Department of Organic Chemistry, Pyatigorsk Medical Pharmaceutical Institute – a branch of Volgograd Medical State University. ORCID ID: 0000-0003-1333-3472. E-mail: kodonidiip@mail.ru.

**Alexey S. Chiriapkin** – Postgraduate student of the Department of Organic Chemistry Pyatigorsk Medical Pharmaceutical Institute – a branch of Volgograd Med-

ical State University. ORCID ID: 0000-0001-8207-2953. E-mail: alexey.chiriapkin@yandex.ru.

**Dmitry E. Tworowski** – Candidate of Sciences (Pharmacy), Structural Biology, Weizmann Institute of Science Genomics and BioComputing of Complex Diseases, Bar-Ilan University (BIU), The Azrieli Faculty of Medicine. ORCID ID: 0000-0002-9414-9951. E-mail: dmitwor@gmail.com.