IN SILICO PREDICTION AND MOLECULAR DOCKING STUDIES OF BIOLOGICAL ACTIVITY OF HYDROACRIDINE (QUINOLINE) DERIVATIVES

N.V. Smetanin, S.V. Tokarieva, S.A. Varenichenko*, O.K. Farat, V.I. Markov

Ukrainian State University of Chemical Technology, 49005 Dnipropetrovsk, Ukraine
*e-mail: svetlanavarenichenko@gmail.com

To find biological activity among easily available 2-[(4S,4'S/4R,4'R)-2',5'-dioxo-2,3,5,6,7,8-hexahydro-1H-spiro[acridine-4,3'-pyrrolidin]-4'-yl]-N-aryl-acetamide, (4S/4R)-4-[(3R/3S)-1-(2-aryl)-2,5-dioxopyrrolidin-3-yl]-1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile, (3S/4R)-3-[(3R/4S)-9-chloroacridine(quinoline)-4-yl]-1-N-aryl)pyrrolidine-2,5-diones. Methods: Organic synthesis, spectral methods, and molecular docking. We investigated by molecular docking the potential biological activity of previously synthesized compounds containing acridine and pyrrolidine-2,5-diones fragments in their structure, as well as synthesized in this work N’-hydroxy-1,2,3,4,5,6,7,8-octahydroacridine-4-carboximidamide. Based on the literature data, 3 directions of searching for the biological activity of the synthesized compounds have been chosen: cholinesterase inhibitors, anti-inflammatory, and anticonvulsant agents. As inhibitors of acetylcholinesterase and butyrylcholinesterase, substances with good binding free energy and hydrogen bonds with the desired amino acid residues of the Glu-His-Ser triad have been found among the tested compounds. The indicators of synthesized products have exceeded the literature data. The docking data for anti-inflammatory activity has revealed compounds with values above the docking data of the reference drugs - celecoxib and indomethacin. The compounds tested have shown moderate activity as anticonvulsant agents. 3-(7-bromo-9-chloro-1,2,3,4-tetrahydroacridin-4-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione is potentially promising as an acetylcholinesterase inhibitor due to its high binding free energy (-13.7 kcal/mol) and hydrogen bonds with two amino acid residues Ser200, His440. Compound (4S/4R)-4-[(3R/3S)-1-(3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl]-1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile has proved to be the best as an anti-inflammatory agent. The presence of a pyrrolidine-2,5-diones fragment increases the indicators of the biological activity of the synthesized compounds in comparison with just acridine derivatives.

Keywords: 9-chloroacridine(quinoline)-N-aryl)pyrrolidine-2,5-diones, docking studies, cholinesterase inhibitors, anti-inflammatory activity, anticonvulsant activity.
INTRODUCTION. In recent years, more and more information has appeared on the synthesis, structure, pharmacological properties, and use in the medical practice of compounds containing an acridine (quinoline) fragment in their structure [1–2]. Such derivatives have a wide spectrum of therapeutic action causing an increased interest in such structures.

Derivatives of 2,5-pyrrolidin-ones are also known for their biological activity, anti-cancer [3], antinociceptive [4], antibacterial [5], anti-tubercular [6], anti-inflammatory [7], and neuroprotective agents [8]. Pyrrolidine-2,5-dione and its 1,3 substituted derivatives have appeared as the predecessor for pharmacological activity [9]. In this regard, an urgent task in the field of chemistry of heterocyclic compounds is the development of methods for the synthesis of new substances containing the acridine ring and pyrrolidine-2,5-dione in their composition, in order to search for new biologically active substances on their basis.

Previously, we developed a new method for the synthesis of hydroacridine derivatives as a result of rearrangement of geminal azines and oxazines under the action of the Vilsmeier-Haack reagent [10, 11] and studied the reactivity of the rearrangement products [12, 13]. Chloracridines are obtained in one stage with a quantitative yield under the action of a three-fold excess of the formylating agent [11]. To obtain bromderivatives of acridines \(2b,c\), the excess must be doubled. Under the action of an equimolar amount of PBr\(_3\) / DMF complex, acridone derivatives \(3a,b\) (Scheme 1).

During the functionalization of tetrahydroacridine by N-arylmaleimides under non-catalytic conditions, succinimides \(1–6\) have been obtained [13] containing acridine and pyrrolidine fragments in their structure. Considering both the practical importance of hydroacridines \(2a-c\) and the new method of direct transformation of the \(s\)\(^p\) \(3\) C–H bond of these compounds, the number of examples of effective functionalization has been expanded, and products \(7–12\) have been synthesized [14] (Scheme 2).

To compare the indicators of biological activity, acridine derivative \(13\) without a pyrrolidine fragment has been also synthesized by the interaction of 1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile with hydroxylamine (Scheme 3).

![Scheme 1](https://ucj.org.ua/)

**Scheme 1:** 1: a – \(R = H\); b – \(R = CH_3\); 2: a – \(R = CH_3\), \(X = Cl\); b – \(R = H\), \(X = Br\), c – \(R = CH_3\), \(X = Br\); 3: a – \(R = H\), b – \(R = CH_3\)
Scheme 2
EXPERIMENT AND DISCUSSION OF THE RESULTS. Molecular Docking Studies Acetylcholinesterase (AChE). For acetylcholinesterase inhibitors, binding to certain amino acids is important. Important amino acid residues in the esterase site are glutamate (Glu), histidine (His), and serine (Ser). According to [15], the aromatic cluster Trp286, Tyr72, Tyr124, Phe338 enhances the binding of ligands to AChE. Phenolic side residues Tyr341, Tyr124, and Tyr337 are directly involved in controlling the movement of substrates and inhibitors to the active site [16]. All the synthesized compounds 1–13 were subjected to docking study. For the receptor-oriented flexible screening, we used the Autodock 4 and the AutoDock Vina software packages [17]. Additionally, molecular modeling studies were performed in order to rationalize the biological activities of the proposed compounds. Test data for compounds 1–13 as acetylcholinesterase inhibitors are shown in Table 1.

Binding to only one of the three required amino acid residues has been found for compounds 4 (His440) and 8 (Ser122). Compounds 5, 7, 10 and 12 have already demonstrated the blocking of two amino acid residues Ser200 (122) and His440. However, compound 10 has a higher binding free energy (-13.7 kcal/mol) (Fig. 1).

### Table 1

| Compound | Binding free energy (kcal/mol) | H-bonds | Amide-Pi Stacked, Pi-Pi Stacked, Pi-Pi T-shaped | Compound | Binding free energy (kcal/mol) | H-bonds | Amide-Pi Stacked, Pi-Pi Stacked, Pi-Pi T-shaped |
|----------|-------------------------------|---------|-----------------------------------------------|----------|-------------------------------|---------|-----------------------------------------------|
| 1        | -12.2                         | -       | Trp84                                        | 8        | -13.1                         | Ser122  | Tyr334, Tyr121                                |
| 2        | -11.8                         | Tyr334  | Trp84, Phe331                                 | 9        | -13.5                         | Tyr121  | Tyr279                                        |
| 3        | -12.9                         | Tyr121, Phe288, Arg289 | Trp84                                        | 10       | -13.7                         | Gly123, Tyr121, His440, Ser200 | Tyr121, Trp279 |
| 4        | -11.2                         | Gly119, His440, Tyr121 | Tyr121, Trp279                               | 11       | -13.4                         | Tyr121  | Tyr121, Tyr334, Trp279                         |

https://ucj.org.ua
Table 1

| Compound | Binding free energy (kcal/mol) | H-bonds | Amide-Pi Stacked, Pi-Pi Stacked, Pi-Pi T-shaped |
|----------|--------------------------------|---------|-----------------------------------------------|
| 5        | -12.4                          | His440, Tyr121, Trp84, Ser200, Trp279 | 12 -12.0 Gly119, Tyr121, His440, Ser200 |
| 6        | -12.4                          | Tyr121, Phe331, Tyr334, Phe330, Tyr121 | 13 -9.7 Asp72, Trp84, Phe330 |
| 7        | -12.8                          | Tyr121, Ser122, His440, Trp84, Tyr334, Gly117 | |

Fig. 1. Binding model of compound 10 for the best docked pose in the active site of AChE (model of the complex obtained by molecular docking, hydrogen bonds are shown in green dashed lines).

Based on the results obtained, the presence of a pyrrolidine-2,5-dione fragment in compounds 1–12 promotes an increase in activity in comparison with acridine derivative 13.

Molecular Docking Studies butyrylcholinesterase (BChE). Butyrylcholinesterase, like other metabolic serine hydrolases, belongs to the family of α/β-hydrolases, and binding to the amino acid residues of the Glu-His-Ser triad is important for their inhibitors. Amino acid residues Asp70, Tyr332, especially Asp70, play an essential role in the binding and transport of substrates and inhibitors to the active site of BChE [18]. Table 2 shows the binding free energy and the presence of hydrogen bonds of compounds 1–13 with the active site of butyrylcholinesterase.
The best binding free energy has been demonstrated by compound 8 as well as the presence of interaction with the amino acid residue His438 (Fig. 2). Compound 3, with lower binding free energy but with the presence of interaction with two amino acid residues Clu197, Ser287, or compound 5, with good binding free energy and the presence of a hydrogen bond with Asp70, may also be promising (Fig. 3).

### Table 2

| Compound | Binding free energy (kcal/mol) | H-bonds | π-anion/π-cation | Compound | Binding free energy (kcal/mol) | H-bonds | π-anion/π-cation |
|----------|-------------------------------|---------|-----------------|----------|-------------------------------|---------|-----------------|
| 1        | -10.7                         | -       |                 | 8        | -12.4                         | His438, Gly116, |
| 2        | -10.9                         | Tyr128, Pro285 | Asp70         | 9        | -10.4                         | His438   |
| 3        | -11.4                         | Glu197, Ser287 | His438, Asp70 | 10       | -11.2                         | Tyr128   |
| 4        | -12.3                         | -       | Asp70           | 11       | -10.6                         | -        | Asp70,His438    |
| 5        | -12.3                         | Asp70   | Glu197,His438   | 12       | -12.6                         | Tyr82,  |
| 6        | -12.6                         | Asp70   |                 | 13       | -8.8                          | -        | Tyr440          |
| 7        | -10.3                         | -       |                 |          |                               |          |

**Fig. 2.** Binding model of compound 8 for the best docked pose in the active site of BChE (model of the complex obtained by molecular docking, hydrogen bonds are shown in green dashed lines).
Our results exceeded the literature data [19], for which the binding free energy was within (-4.43696)--(-6.67689) kcal/mol, and there was an interaction with the side chain and backbone donor of residues Gly118, Ser122.

**Molecular Docking Studies of compounds 1–13 as anti-inflammatory agents.**

Inflammation is a defense mechanism in the body that is triggered by various stimulatory factors including radiation, heat, microbial infections and is often associated with tissue damage. Arachidonic acid metabolism plays a vital role in the mechanism of inflammation. Arachidonic acid is metabolized to thromboxane A2 and prostaglandins by the cyclooxygenase-2 (COX-2) cascade or by the 5-lipoxygenase (5-LOX) pathway with suitable stimulation of the neutrophil. Inhibition of proteases can help fight several diseases, including inflammation. This is more relevant than ever during the fight against COVID-19, since overcoming inflammatory processes plays a key role in its treatment. Some ketoester derivatives of succinimides and acridines [20] exhibit strong anti-inflammatory activity. The good test results for such succinimides have prompted us to test the succinimide derivatives we synthesized for the presence of anti-inflammatory activity. The results of molecular docking of compounds 1–13 as anti-inflammatory agents are presented in Table 3.

The results obtained agree with the literature data of similar compounds, which were tested in vitro showing binding free energy of -6.60--(-6.95) kcal/mol [9]. All synthesized compounds are docked in the COX-2 binding pockets. In COX-2, an additional secondary side pocket contains an Arg120/Tyr355 residue. This additional pocket is bordered by a small Val523 residue. In addition, COX-2 also contains the conservative Arg513. Other residues important for COX-2 selectivity are His90, Gln192, Leu352, and Ser353. The docking data have been compared with the docking data of the reference drugs – celecoxib and indomethacin. Interaction analysis of celecoxib, a COX-2 selective inhibitor, has shown that it interacts with amino acid residues (His90, Leu352, Ser353, and Arg513) present in the COX-2 additional pocket. Likewise, indomethacin interacts with Ser353 and Tyr355.
Table 3

Binding free energy calculation results for synthesized compounds 1–13 bound with 1CX2

| Compound | Binding free energy (kcal/mol) | H-bonds | Amide-Pi Stacked | Compound | Binding free energy (kcal/mol) | H-bonds | Amide-Pi Stacked |
|----------|--------------------------------|---------|------------------|----------|--------------------------------|---------|------------------|
| 1        | -7.6                           | Asn581  | -                | 8        | -9.0                           | Gln192, Asp515 | Gln350          |
| 2        | -7.8                           | -       | Asp515           | 9        | -8.4                           | -       | -                |
| 3        | -7.9                           | His351, Gln192 | -   | 10        | -9.5                           | Gln192, Asp515 | Gln350          |
| 4        | -9.0                           | Asn581  | -                | 11        | -9.0                           | Gln192  | Asp515           |
| 5        | -9.7                           | Gln192  | -                | 12        | -8.1                           | Tyr355, Asn581 | -               |
| 6        | -8.5                           | Gln192  | -                | 13        | -7.5                           | Met522  | -                |
| 7        | -8.3                           | Gln192, Asn581 | - |            |                                  |         |                  |

Compounds 3, 5, 6, 7, 8, 10–12 have exhibited binding free energy in the range of -7.9 to -9.7 kcal/mol; and they bind to the amino acid residue Gln192. The energy index is better for compound 5, and it has a hydrogen bond with the amino acid Gln192 as well (Fig. 4). Compound 10 with good binding free energy and a hydrogen bond with the amino acid residue Gln192 is also promising (Fig. 5).

Fig. 4. Binding model of the most active compound 5 with 1CX2 (model of the complex obtained by molecular docking, hydrogen bonds are shown in green dashed lines).
**Molecular Docking Studies of compounds 1–13 as anticonvulsant agents.**

Many succinimide derivatives exhibit high anticonvulsant activity [21]. Phenytoin, which forms hydrogen bonds with amino acid residues Asp415 and Ser403, has been chosen as a reference drug for testing antiepileptic activity. Of the nine compounds tested, six have formed a hydrogen bond with the Ser403 amino acid residue of the active site 1OHY (Table 4). However, according to the binding free energy, compound 3 will be the most promising for further testing (Fig. 6).

**Table 4**

| Compound | 1  | 2  | 3  | 7  | 8  | 9  | 10 | 11 | 12 |
|----------|----|----|----|----|----|----|----|----|----|
| Binding free energy (kcal/mol) | -5.2 | -4.0 | -5.9 | -3.4 | -4.5 | -4.6 | -2.4 | -5.5 | -2.8 |
| H-bonds | Ser403 | Arg404 | Pro399, Ser403 | Arg222, Ser403 | Lys442, Arg404 | Ser403 | Lys442, Ser403 | Arg404, Ser403 | - |

**Fig. 5.** Binding model of compound 10 for the best docked pose in the active site of 1CX2 (model of the complex obtained by molecular docking, hydrogen bonds are shown in green dashed lines).
**Ligand and Receptor Structure Preparation.**
Ligand structures were prepared using MGL Tools 1.5.6 software (MGL Tools 1.5.6 (Scrips Research Institute) http://mgltools.scripps.edu/) and Vega ZZ [22]. Receptor-based virtual screening was used to analyze the binding of the compound collection. Docking was performed at ATP-binding sites of protein database AChE (database code PDB: 1acl – 2.80Å), BChE (database code PDB: 1p0p – 2.30Å), COX-2 (database code PDB: 1CX2 – 3.00Å), anticonvulsant activity (database code PDB: 1OHY – 2.80Å), using Autodock 4.2.6. The structures taken for docking were kinase domains in an active state. Water molecules, ions and ligands were removed from the PDB file. The receptor structures were prepared using MGL Tools and AutoGrid. Hydrogen atoms were removed from nonpolar atoms. The incoming formats of receptor and ligands data were converted into PDBQT-format with Vega ZZ in AUTODOCK force field.

**Flexible docking.** Autodock 4.2.6 programs package was used for the receptor-based flexible docking [17].

**Visual analysis.**
A visual analysis of the molecular docking results (interaction of compounds with the amino acid residues of AChE, BChE, COX-2 and GABA transaminase active-binding site) was carried out using Discovery Studio Visualizer 4.0 (http://accelrys.com/).

**Chemical synthesis.**
$^1$H and $^{13}$C NMR spectrum was recorded on a Bruker Avance II 400 spectrometer (400 MHz,) in DMSO-$d_6$ using TMS as an internal standard. Mass spectra (EI ionization, 70 eV) was recorded on a MX1321 apparatus with direct sample injection at 200 °C ionization chamber temperature. Elemental analysis was performed on a LECO CHN-900 Elemental analyzer. Melting points were determined on an Electrothermal 9100 Digital apparatus. The reaction progress and purity of
compounds were monitored by TLC on Silicagel gel 60 F254 (Merck) plates, eluent CHCl3 - i-PrOH (10:1), visualization in the iodine chamber. Compound 1a was obtained according to the literature method [23].

4’-Methylspiro[3,1-benzoxazine-2,1’-cyclohexan]-4(1H)-one (1b): The compound is obtained by literary methods [23]. The 1H and 13C NMR spectra for compound are presented for the predominant isomer. Yield: 70 %. M. p.: 150–152 °C. 1H NMR (400 MHz, DMSO-d6), δ, ppm: 7.46 (1H, s, NH), 7.29-7.37 (2H, m, H-Ar), 7.57-7.61 (1H, t, J=7.3 Hz, H-Ar), 2.13-2.16 (1H, m, 2CH2), 1.47-1.54 (4H, m, 2CH2), 1.06-1.27 (2H, m, CH2). 13C NMR (100 MHz, DMSO-d6), δ, ppm: 158.9, 146.0, 139.7, 135.5, 21.6. MS (EI), m/z (I rel %): 231 [M(35Cl)+H]+ (32), 231 [M(35Cl)+H]+ (100). Anal. calcd. for C14H14ClN: C, 72.48; H, 7.65; N, 6.04. Found: C, 72.39; H, 6.15; N, 6.26.

9-Bromo-1,2,3,4-tetrahydroacridine (2b): The Vilsmeier reagent was prepared from PBr3 (5.7 mL, 0.06 mol) and DMF (4.6 mL, 0.06 mol) with ice cooling. Chloroform in a volume of 15 mL is used as a solvent. Compound 1a (2.17 g, 0.01 mol) was added to the Vilsmeier reagent. After 2 h, the reaction mixture was poured on ice and treated with aq ammonia, the obtained solid was filtered off and dried to give acridine 2b. Yield: 60 %. M. p.: 62–64 °C. 1H NMR (400 MHz, DMSO-d6), δ, ppm: 8.11-8.08 (1H, d, J=8.3 Hz, H-Ar), 7.90-7.92 (1H, d, J=8.3, H-Ar), 7.75-7.77 (1H, t, J=7.3 Hz, H-Ar), 7.59-7.61 (1H, t, J=7.3 Hz, H-Ar), 3.10-3.12 (2H, m, CH2), 2.39-2.41 (2H, m, CH2), 1.89-1.96 (4H, m, 2CH2). MS (FAB), m/z (I rel %): 262 [M+H(81Br)]+ (90), 264 [M+H(79Br)]+ (100). Anal. calcd. for C13H12BrN: C, 59.56; H, 4.61; N, 5.34. Found: C, 59.69; H, 4.55; N, 5.46.

9-Chloro-2-methyl-1,2,3,4-tetrahydroacridine (2a): Compound 1b (2.17 g, 0.01 mol) was added to DMF (1 mL). The suspension formed was treated with the ice-cold Vilsmeier reagent obtained from DMF (6 mL) and POCl3 (2.75 mL, 0.03 mol) under ice-cooling. A yellow solid precipitated abundantly within 10-15 min. After 0.5 h, the reaction mixture was poured on ice and treated with aq ammonia, the obtained solid was filtered off and dried to give acridine 2a. Yield: 75 %. M. p.: 58–60 °C. 1H NMR (400 MHz, DMSO-d6), δ, ppm: 8.07-8.05 (1H, d, J=8.3 Hz, H-Ar), 7.89-7.91 (1H, d, J=8.3 Hz, H-Ar), 7.69-7.73 (1H, t, J=7.3 Hz, H-Ar), 7.57-7.61 (1H, t, J=7.3 Hz, H-Ar), 2.99-3.07 (3H, m, CH3+CH), 2.32-2.39 (1H, m, CH2), 1.89-1.92 (2H, m, CH2), 1.42-1.46 (1H, m, CH), 1.06-1.08 (3H, d, J=6.4 Hz, CH3). 13C NMR (100 MHz, DMSO-d6), δ, ppm: 158.9, 146.0, 139.7, 129.4, 128.4, 128.1, 126.8, 124.3, 123.0, 35.2, 33.0, 29.0, 28.1, 21.4. MS (EI), m/z (I rel %): 233 [M(35Cl)+H]+ (32), 231 [M(35Cl)+H]+ (100). Anal. calcd. for C14H14ClN: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.39; H, 6.15; N, 6.26.

1,3,4,10-Tetrahydroacridin-9(2H)-one (3a): The Vilsmeier reagent was prepared from PBr3.
(2.9 mL, 0.03 mol) and DMF (4.6 mL, 0.06 mol) with ice cooling. Chloroform in a volume of 15 ml is used as a solvent. Compound 1a (2.17 g, 0.01 mol) was added to the Vilsmeier reagent. After 2 h, the reaction mixture was poured on ice and treated with aq ammonia, the obtained solid was filtered off and dried to give acridine 3а, as colorless crystals, mp 358–360 °C (Ref. [24]: mp 355–358 °C). Spectral data for 3а (FTIR, NMR) were identical to the reported data [25].

2-Methyl-1,3,4,10-tetrahydroacridin-9(2H)-one (3b): The synthesis procedure from compound 1b is similar to the preparation of 3a. Yield: 64 %. M. p.: 352–354 °C. 1H NMR (400 MHz, DMSO-d6), δ, ppm: 11.24 (1Н, s, NH), 8.05-8.03 (1H, d, J=7.8 Hz, H-Ar), 7.52-7.56 (1H, t, J=7.8, H-Ar), 7.43-7.45 (1H, t, J=8.3 Hz, H-Ar), 7.18-7.22 (1H, t, J=7.3 Hz, CH-Ar), 2.69-2.73 (3H, m, CH2+CH), 1.85-1.89 (2H, m, CH2), 1.70-1.73 (1H, m, CH2), 1.34-1.37 (1H, m, CH), 1.04-1.06 (3H, d, J=6.4 Hz, CH3). 13C NMR (100 MHz, DMSO-d6), δ, ppm: 175.9, 146.5, 139.2, 130.9, 124.8, 123.2, 121.9, 117.3, 115.1, 30.2, 29.5, 28.0, 27.1 21.6. MS (EI), m/z (Iорн, %): 213 [M]+ (35). Anal. calcd. for C14H19N3O: C, 68.54; H, 7.81; N, 17.26. Found: C, 68.29; H, 7.65; N, 17.26.

CONCLUSIONS.

Using molecular docking of the synthesized compounds, products with high performance have been found during the study. 3-(7-Bromo-9-chloro-1,2,3,4-tetrahydroacridin-4-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (10) is potentially promising as an acetylcholinesterase inhibitor due to its high binding free energy (-13.7 kcal/mol) and hydrogen bonds with two amino acid residues Ser200, His440. Compound (4S/4R)-4-[(3R/3S)-1-(3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl]-1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile (5) has proved to be the best as an anti-inflammatory agent. This allows them to be recommended for further research as potential acetylcholinesterase inhibitors and anti-inflammatory agents. N’-Hydroxy-1,2,3,4,5,6,7,8-octahydroacridine-4-carboximidamide do not form hydrogen bonds with amino acid residues while revealing moderate binding energies. Compound 13 differs from compounds 1–12 in that it does not contain a pyrrolidine-2,5-dione heterocycle and a nitrobenzene nucleus, which are involved in the formation of additional hydrogen bonds with fragments of the corresponding enzymes, as proved by molecular docking. The data obtained lead us to the conclusion that the presence of the pyrrolidine-2,5-diones fragment enhances the biological activity of acridine derivatives.
The authors are grateful to the grant for Young Scientists of Dnepropetrovsk region 2020.
REFERENCES

1. Chen R., Huo L., Jaiswal Y., Huang J., Zhong Zh., Zhong J., Williams L., Xia X., Liang Y., Yan Zh. Design, Synthesis, Antimicrobial, and Anticancer Activities of Acridine Thiosemicarbazides Derivatives. *Molecules*. 2019. 24(11): 2065.

2. Rupar J.S., Dobričić V.D., Aleksić M.M., Brborić J.S., Čudina O.A. A review of published data on acridine derivatives with different biological activities. *Kragujevac Journal of Science*. 2018. 40: 83–101.

3. Ali I., Lone M.N., Alothman Z.A., Alwarthan A. Insights into the pharmacology of new heterocycles embedded with oxopyrrolidine rings DNA binding, molecular docking, and anticancer studies. *Journal of Molecular Liquids*. 2017. 234: 391–402.

4. Obniska J., Salat K., Librowski T., Kamiński K., Lipkowska A., Wiklik B., Rybka S., Rapacz A. Antinociceptive properties of N-Mannich bases derived from 3-substituted pyrrolidine-2,5-dione in the formalin model of persistent pain in mice. *Pharmacological Reports*. 2015. 67(1): 63–68.

5. Pardeshi S.D., Sonar J.P., Dokhe S.A., Zine A.M., Thore S.N. Synthesis and anti-microbial activity of novel pyrrolidine containing chalcones and pyrazolines. *IJCPS*. 2016. 5: 34–40.

6. Abass S.J.: Synthesis and characterization of some new pyrrolidine-2,5-dione derivatives using anthranilic acid. *Journal of Kerbala University*. 2015. 13(2): 236–42.

7. Tsai Y.F., Yang S.C., Hwang T.L. Formyl peptide receptor modulators: a patent review and potential applications for inflammatory diseases. *Expert Opinion on Therapeutic Patents*. 2016. 26(10): 1139–56.

8. Socała K., Mogilski S., Pieryg M., Nieczym D., Abram M., Szulczyk B., Lubelska A., Latacz G., Doboszewska U., Wla P. and Kamiński K. KA-11, a novel pyrrolidine-2, 5-dione derived broad-spectrum anticonvulsant: its antiepileptogenic, antinociceptive properties and in-vitro characterization. *ACS chemical neuroscience*. 2018. 10(1): 636–48.

9. Jan M.S., Ahmad S., Hussain F., Ahmad A., Mahood F., Rashid U., Abid O-U-R, Ullah F., Ayaz M., Sadiq A. Design, synthesis, in-vitro, in-vivo and in-silico studies of pyrrolidine-2, 5-dione derivatives as multi-target anti-inflammatory agents. *Eur J Med Chem*. 2020. 186: 111–863.

10. Markov V.I., Farat O.K., Varenichenko S.A., Velikaya E.V. Rearrangement of 5',6',7',8'-tetrahydro-1'H-spiro(cyclohexane-1,2'-quinazolin)-4'(3'H)-one during Vilsmeier reaction. *Mendeleev Commun*. 2012. 22: 101–102.

11. Farat O.K., Markov V.I., Varenichenko S.A., Dotsenko V.V., Mazepa A.V. The Vilsmeier-Haack formylation of 2,3-dihydro-4H-1,3-benzoxazin-4-ones and isomeric 1,2-dihydro-4H-3,1-benzoxazin-4-ones: an effective approach to functionalized 2H-/4H-Chromenes and Tetrahydroacridines. *Tetrahedron*. 2015. 71: 5554.

12. Zaliznaya E.V., Smetanin N.V., Varenichenko S.A., Mazepa A.V., Farat O.K., Markov V.I. Synthesis of new hexahydro-5H-indolo[3,2-c]acridines and indolybutanoic acids by Fischer cyclization of arylhydrazones. *Chemistry of Heterocyclic Compounds*. 2018. 2: 138–145.

13. Zaliznaya E.V., Farat O.K., Varenichenko S.A., Mazepa A.V., Markov V.I. Functionalization of tetra- and octahydroacridine
derivatives through Michael addition. *Tetrahedron Lett.* 2016. 57 (31): 3485–3487.

14. Smetanin N.V., Varenichenko S.A., Zaliznaya E.V., Mazepa A.V., Farat O.K., Markov V.I. Functionalization of N-arylmaleimides by sp³ C-H bonds of hydroacridines(qinolines). *Voprosy Khimii i Khimicheskoi Tekhnologii.* 2020. 6: 165–170.

15. Sussman J.L., Harel M., Frolow F., Oefner C., Goldman A., Toker L., Silman I. Atomic structure of acetylcholinesterase from Torpedo californica: a prototypic acetylcholine-binding protein. *Science.* 1991. 253(5022): 872–879.

16. Kharlamova A.D., Lushchekina S.V., Petrov K.A., Kots E.D., Nachon F., Villard-Wandhammer M., Zueva I.V., Krejci E., Reznik V.S., Zobov V.V., Nikolsky E.E., Masson P. Slow-binding inhibition of acetylcholinesterase by an alkylammonium derivative of 6-methyluracil: mechanism and possible advantages for myasthenia gravis treatment. *Biochem. J.* 2016. 473(9): 1225.

17. Morris G.M., Huey R., Lindstrom W., Sanner M.F., Belew R.K., Goodsell D.S., Olson A.J. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J. Comput. Chem.* 2009. 30 (16): 2785–91.

18. Makhacheva G.F., Rudakova E.V., Kovaleva N.V., Lushchekina S.V., Boltneva N.P., Proshin A.N., Shchegolkov E.V., Burgart J.V., Saloutin V.I. Cholinesterase and carboxylesterase inhibitors as pharmacological agents. *Izvestiya Akademii nauk. Seriya khimicheskaya.* 2019. 5: 967–984 [In Russian].

19. Ahmad A., Ullah F., Sadiq A., Ayaz M., Jan M.S, Shahid M., Wadood A., Mahmood F., Rashid U., Ullah R., Sahibzada M-U-K, Alqahtani A.S., Mahmoud H.M. Comparative Cholinesterase, α-Glucosidase Inhibitory, Antioxidant, Molecular Docking, and Kinetic Studies on Potent Succinimide Derivatives. *Drug Design, Development and Therapy.* 2020. 14: 2165–2178.

20. Muhammad S.J., Sajjad A., Fida H., Ashfaq A., Fawad M., Umer R., Obaid-ur-Rahman A., Farhat U., Muhammad A., Abdul S. Design, synthesis, in-vitro, in-vivo and in-silico studies of pyrroldidine-2,5-dione derivatives as multitarget anti-inflammatory agents. *European Journal of Medicinal Chemistry.* 2019. 45: 555–563.

21. Maru A. Molecular docking study of new-Mannich bases derived from pyrrolidine-2,5-dione as anticonvulsant agents. *International Journal of Pharmaceutical Sciences and Research.* 2020. 11(3): 1243–1248.

22. Pedretti A., Villa L., Vistoli G. VEGA – An open platform to develop chemobioinformatics applications, using plugin architecture and script programming. *J.C.A.M.D.* 2004. 18: 167–173.

23. Hu M.-K., Lu C.-F. A facile synthesis of bis-tacrine isosteres. *Tetrahedron Lett.* 2000. 41 (11): 1815–1818.

24. Zigeuner G., Gübitz G. Über das tetrahydro[spirocyclohexan-1,2(1H)-chinazolin]-4-(3H)-on. *Monatshefte Chem.* 1970. 101: 1547–1558.

25. Son J. K., Kim S. III, Jang Y. A modified Niementowski reaction for the synthesis of 4-hydroxyquinoline and its related compounds. *Heterocycles.* 2001. 55 (10): 1981–1986.

Стаття надійшла 30.06.2021.