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

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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-arylpyrrolidine-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 anti-convulsant agents. As inhibitors of acetylcholinesterase and butylcholinesterase, 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-arylpyrrolidine-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 reac-

tivity 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 sp^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: **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

Scheme 3

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

Binding free energy calculation results for synthesized compounds 1-13 bound with 1acI

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

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
5	-12.4	His440, Tyr121, Ser200	Trp84, 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). Butylcholinesterase, 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 butylcholinesterase.

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 pre-

sence 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

Binding free energy calculation results for synthesized compounds 1-13 bound with 1p0p

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, Tyr440	
6	-12.6	-	Asp70	13	-8.8	-	
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*).

Fig. 3. Binding model of compound **5** 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 succinim-

ides 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*).

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).

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 ac-

tivity. 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

Binding free energy calculation results for synthesized compounds 1–3, 7–12 bound with 1OHY

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. 6. Binding model of compound 3 for the best docked pose in the active site 1OHY (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 (Scripps 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 data-bank 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.

^1H and ^{13}C NMR spectrum was recorded on a Bruker Avance II 400 spectrometer (400 MHz,) in $\text{DMSO}-d_6$ 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(1*H*)-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-*d*₆), δ, ppm: 7.46 (1H, s, NH), 7.29-7.37 (2H, m, H-Ar), 6.70-6.73 (2H, m, H-Ar), 2.13-2.16 (1H, m, CH₂), 2.04-2.06 (1H, m, CH₂), 1.64-1.66 (1H, m, CH), 1.47-1.54 (4H, m, 2CH₂), 1.24-1.27 (2H, m, CH₂), 0.90 (3H, m, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆), δ, ppm: 162.5, 147.1, 135.4, 129.1, 128.2, 117.7, 115.1, 89.0, 34.6, 30.8, 29.5, 21.6. MS (EI), *m/z* (*I*_{OTH}, %): 231 [M]⁺ (16). Anal. calcd. for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.83; H, 7.65; N, 6.26.

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-*d*₆), 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, CH₂+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-*d*₆), δ, ppm: 158.9, 146.0, 139.7,

129.4, 128.4, 128.1, 126.8, 124.3, 123.0, 35.2, 33.0, 29.9, 28.1, 21.4. MS (EI), *m/z* (*I*_{OTH}, %): 233 [M(³⁷Cl)+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.

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-*d*₆), 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*_{OTH}, %): 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-Bromo-2-methyl-1,2,3,4-tetrahydroacridine (2c): The synthesis procedure from compound 1b is similar to the preparation of 2b. Yield: 58 %. M. p.: 65–67 °C. ¹H NMR (400 MHz, DMSO-*d*₆), δ, ppm: 8.10-8.07 (1H, d, *J*=8.3 Hz, H-Ar), 7.92-7.90 (1H, d, *J*=8.3, H-Ar), 7.71-7.75 (1H, t, *J*=7.3 Hz, H-Ar), 7.61-7.65 (1H, t, *J*=7.3 Hz, H-Ar), 3.07-3.10 (2H, m, CH₂), 2.41-2.45 (2H, m, CH₂), 1.93-1.96 (2H, m, CH₂), 1.46-1.51 (1H, m, CH), 1.11-1.13 (3H, d, *J*=6.6 Hz, CH₃). MS (FAB), *m/z* (*I*_{OTH}, %): 275 [M+H (⁸¹Br)]⁺ (90), 277 [M+H (⁷⁹Br)]⁺ (100). Anal. calcd. for C₁₄H₁₄BrN: C, 60.89; H, 5.11; N, 5.07. Found: C, 60.67; H, 5.25; N, 5.26.

1,3,4,10-Tetrahydroacridin-9(2*H*)-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 3a, as colorless crystals, mp 358–360 °C (Ref. [24]: mp 355–358 °C). Spectral data for 3a (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- d_6), δ , ppm: 11.24 (1H, 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, CH_2+CH), 1.85–1.89 (2H, m, CH_2), 1.70–1.73 (1H, m, CH_2), 1.34–1.37 (1H, m, CH), 1.04–1.06 (3H, d, $J=6.4$ Hz, CH_3). ^{13}C NMR (100 MHz, DMSO- d_6), 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 (I_{OTH} , %): 213 [M] $^+$ (35). Anal. calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.58; H, 6.35; N, 7.26.

N'-Hydroxy-1,2,3,4,5,6,7,8-octahydroacridine-4-carboximidamide (13): A portion of 1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile [10] (1 g, 4.7 mmol) and hydroxylamine гидрохлорид (0.66 g, 10.2 mmol) was dissolved in 5 ml of DMSO. An equimolar amount of alcoholic solution of sodium methylate relative to hydroxylamine hydrochloride is then added to the solution as a catalyst. The reaction mixture was heated at 130 °C for 5 hours. Then the solution is poured into 20 ml of water. The precipitate formed is filtered off and purified by

crystallization from isopropyl alcohol. Yield: 64 %. M. p.: 162–164 °C. ^1H NMR (400 MHz, DMSO- d_6), δ , ppm: 8.89 (1H, s, OH), 7.08 (1H, s, H-Ar), 5.27 (2H, s, NH_2), 3.48 (1H, t, $J=4.9$ Hz, CH), 2.69–2.63 (6H, m, 3CH_2), 1.77–1.70 (8H, m, 4CH_2). MS (EI), m/z (I_{OTH} , %): 245 [M] $^+$ (100). Anal. calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}$: C, 68.54; H, 7.81; N, 17.13. 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.

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ПРОГНОЗУВАННЯ *IN SILICO* БІОЛОГІЧНОЇ АКТИВНОСТІ ТА МОЛЕКУЛЯРНИЙ ДОКІНГ ПОХІДНИХ ГІДРОАКРИДИНІВ (ХІНОЛІНІВ)

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Мета: Знайти біологічну активність серед легкодоступних 2-[(4S,4'S/4R,4'R)-2',5'-діоксо-2,3,5,6,7,8-гексагідро-1H-спіро[акридин-4,3'-пірролідін]-4'-іл]-N-арил-ацетамідів, (4S/4R)-4-[(3R/3S)-1-(2-арил)-2,5-діоксопірролідін-3-іл]-1,2,3,4,5,6,7,8-октагідроакридин-4-карбонітрилів, (3S/4R)-3-[(3R/4S)-9-хлоракридин(хінолін)-4-іл]-1N-арил)пірролідін-2,5-діонів. **Методи:** Органічний синтез, спектральні методи та молекулярний докінг. **Результати:** За допомогою молекулярного докінгу ми дослідили потенційну біологічну активність раніше синтезованих сполук, що містять у своїй структурі акридиновий та пірролідін-2,5-діоновий фрагменти, та синтезованого у цій роботі N'-гідрокси-1,2,3,4,5,6,7,8-октагідроакридин-4-карбоксаміду. На основі літера-

турних даних обрано 3 напрямки пошуку біологічної активності серед синтезованих сполук: інгібітори холінестераз, протизапальні та протисудомні засоби. Як інгібітори ацетилхолінестерази та бутилхолінестерази серед досліджуваних сполук були знайдені речовини з хорошими показниками енергії зв'язування та водневих зв'язків із бажаними амінокислотними залишками тріади Glu-His-Ser. Показники синтезованих продуктів перевищили літературні дані. Дані докінгу протизапальної активності виявили сполуки, показники яких перевищували дані докінгу референтних препаратів – цефекоксибу та індометацину. Випробувані сполуки показали помірну активність як протисудомні засоби. 3-(7-бром-9-хлор-1,2,3,4-тетрагідроакридин-4-іл)-1-(3-нітрофеніл)пірролідін-2,5-діон потенційно перспективний як інгібітор ацетилхолінестерази завдяки його показникам енергії зв'язування (-13,7 ккал/моль) та водневим зв'язкам із двома залишками амінокислот Ser200, His440. Сполука (4S/4R)-4-[(3R/3S)-1-(3-нітрофеніл)-2,5-діоксопірролідін-3-іл]-1,2,3,4,5,6,7,8-октагідроакридин-4-карбонітрил виявилася кращою у ролі протизапального засобу. Отримані дані підводять нас до висновку, що присутність пірролідін-2,5-діонового фрагменту посилює біологічну активність похідних акридину.

Ключові слова: 9-хлоракридин(хінолін)-N-арил)пірролідін-2,5-діони, дослідження стикування, інгібітори холінестерази, протизапальна активність, протисудомна активність.

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