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S. Shahab[1, 2], M. Sheikhi[3], H. A. Almodarresiyeh[4], G. K. Mukusheva[5], N. N. Toigambekova[5], E. A. Dikusar[2], E. A. Akishina[2], V. I. Potkin[2], S. R. Albasri[1], M. A. Atroshko[1]

[1]International Sakharov Environmental Institute of Belarusian State University, Minsk, Belarus,
[2]Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, Minsk, Belarus
[3]Young Researchers and Elite Club, Gorgan Branch, Islamic Azad University, Gorgan, Iran
[4]Department of materials Science and Engineering, school of Engineering, Meybod University, Meybod, Yazd, Iran
[5]Karaganda Buketov University, Karaganda, Kazakhstan

DESIGN, DFT, DOCKING AND *IN SILICO* ANALYSIS OF ALKALOIDS ACYL DERIVATIVES AS POTENTIAL INHIBITORS OF SARS-CoV-2 MAIN PROTEASE M^{PRO}

Abstract. In the present work, at first, density functional theory calculations were performed to investigate the molecular structure anabasine, cytisine, quinine alkaloids acyl derivatives by CAM-B3LYP/MidiX level of theory. A detail of quantum molecular descriptors of the title compounds such as Ionization Potential (IP) and Electron Affinities (EA), Hardness (η), Softness (S), Electronegativity (μ), Electrophilic Index (ω), Electron Donating Power (ω^-), Electron Accepting Power (ω^+) and Energy Gap (E_g) have been calculated. Pharmacokinetic properties of the title compounds and their bioactivity were investigated. In the following, a molecular docking study was carried out to screen for effective available compound which may work as a strong inhibitor for the SARS-CoV-2 main protease M^{pro}. The binding energy between SARS-CoV-2 main protease M^{pro} and derivatives of natural alkaloids showed a good binding affinity. Therefore, studied derivatives of natural alkaloids can be used for potential application against the SARS-CoV-2 main protease M^{pro}.

Keywords: SARS-CoV-2 main protease M^{pro}, DFT, molecular docking, derivatives of natural alkaloids, pharmacokinetic properties

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С. Шахаб[1, 2], М. Шейхи[3], Х. А. Альмодарресие[4], Г. К. Мукушева[5], Н. Н. Тойгамбекова[5], Е. А. Дикусар[2], Е. А. Акишина[2], В. И. Поткин[2], С. Р. Альбасри[1], М. А. Атрошко[1]

[1]Международный государственный экологический институт имени А. Д. Сахарова Белорусского государственного университета, Минск, Беларусь
[2]Институт физико-органической химии Национальной академии наук Беларуси, Минск, Беларусь
[3]Клуб молодых исследователей и элиты, Отделение Исламского университета Азад, Горган, Иран
[4]Кафедра материаловедения и инженерии, Университет Мейбод, Мейбод, Йезд, Иран
[5]Карагандинский университет им. Е.А. Букетова, Караганда, Казахстан

ДИЗАЙН, DFT, ДОКИНГ И *IN SILICO* АНАЛИЗ АЦИЛЬНЫХ ПРОИЗВОДНЫХ АЛКАЛОИДОВ КАК ПОТЕНЦИАЛЬНЫХ ИНГИБИТОРОВ ОСНОВНОЙ ПРОТЕАЗЫ SARS-CoV-2 M^{PRO}

Аннотация. Выполнены квантово-химирческие расчеты с применением метода теории функционала плотности (DFT) для исследования молекулярной структуры ацилпроизводных анабазина, цитизина и хининовых алкалоидов с применением уровня теории CAM-B3LYP/MidiX. Были вычислены индексы квантовых молекулярных дескрипторов этих соединений, таких как потенциал ионизации (IP) и сродство к электрону (EA), твердость (η), мягкость (S), электроотрицательность (μ), электрофильный индекс (ω), электронодонорная способность (ω^-), электронопиемная способность (ω^+) и энергетическая щель (E_g). Исследованы фармакокинетические свойства названных со-

единений и их биологическая активность, проведено исследование молекулярного докинга для выявления наиболее эффективного соединения, которое может действовать как сильный ингибитор основной протеазы M^{pro} SARS-CoV-2. Энергия связи между основной протеазой SARS-CoV-2 M^{pro} и производными природных алкалоидов показала хорошее сродство связывания. Таким образом, изученные производные природных алкалоидов могут быть использованы для потенциального применения против основной протеазы M^{pro} SARS-CoV-2.

Ключевые слова: основная протеаза SARS-Cov-2 M^{pro}, DFT, молекулярный докинг, производные природных алкалоидов, фармакокинетические свойства

Для цитирования. Дизайн, DFT, докинг и *in silico* анализ ацильных производных алкалоидов как потенциальных ингибиторов основной протеазы SARS-CoV-2 M^{pro}/ С. Шахаб, М. Шейхи, Х. А. Альмодарресие [и др.] // Весці Нацыянальнай акадэміі навук Беларусі. Серыя хімічных навук. – 2026. – Т. 62, № 1. – С. 45–56. https://doi.org/10.29235/1561-8331-2026-62-1-45-56

Introduction. The appearance of severe acute respiratory syndrome (SARS-CoV-2) created a pandemic in the Wuhan city and more than 212 countries, resulting in the over 27 million infections and about 900,000 deaths worldwide [1–4]. SARS-CoV-2 falls into category of RNA viruses, which causes disorders in hepatic, pulmonary, central nervous and gastrointestinal systems [5, 6]. SARS-CoV-2 has the capability to encode cysteine proteases, including the chymotrypsin-like cysteine ($3CL^{pro}$) or main protease (M^{pro}) and the papain-like cysteine protease (PL^{pro}), which are responsible for catalyzing the proteolysis of polyproteins translated from the genome of virus into nonstructural proteins required for packaging the nascent virion and virus replication [7–10]. Therefore, inhibition of the activity of these proteases would prevent virus replication. M^{pro} hydrolyzes the Gln-Ser peptide bond in the Leu-Gln-Ser-Ala-Gly sequence, which is different from peptide sequence identified by other human cysteine proteases [11]. Therefore, M^{pro} is considered as a promising site for designing the anti-SARS-CoV-2 drugs.

In silico and computational approaches are low-cost methods for prediction of pharmacokinetic properties of various natural and artificial compounds before experimental procedures, which give us basic data in the bioinformatics research [12–16]. In this study, computational/in silico methods are utilized to screen the potential inhibitors of derivatives of natural alkaloids for SARS-CoV-2 main protease M^{pro}. ADMET characteristics are evaluated to assess the compatibility of selected inhibitors for human administration, whereas molecular docking and DFT investigations are utilized to analyze their reactivity and binding with SARS-CoV-2 main protease M^{pro}.

Materials and Methods. *ADME analysis.* We used Swiss ADME online software (http://www.swissadme.ch) in our toxicity discovery to predict parameters related to "absorption, distribution, metabolism, and excretion" (ADME) such as medicinal chemistry, druglike nature, friendliness of one or multiple small molecules as well as to compute parameters related to their physicochemistry. Swiss ADME enables assessment of ADME parameters of drug candidates and small molecules, providing information for early risk assessment in the drug development process. Notably, Swiss ADME provides a platform to assess the druglikeness of oral bioavailability through Lipinski's rule of five. Lipinski's Rule of Five was used to investigate derivatives of natural alkaloids that were selected for this study. Filters such as Molecular weight of the ligand (< 500 Da), high lipophilicity (LogP < 5), Number of hydrogen bonds donors (< 5), Number of hydrogen bond acceptors (< 10) and Molar refractivity (40–130) (Ghose Rule) were used to carry out the further selection of the title derivatives of natural alkaloids. Violation of more than 2 of the above stated parameters debarred further analysis of particular molecule. Parameter details were calculated from using Molinspiration Cheminformatics and Swiss ADME online software [17, 18]. This was done by uploading the respective compounds SMILES into the software.

Bioactivity Score. Bioactivity of the investigated acids was predicted by calculating the activity score toward G protein coupled receptors (GPCR ligand), ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor with the help of online software Molinspiration (www.molinspiration.com). These bioactivity scores for organic molecules can be interpreted as active (when the bioactivity score is > 0), moderately active (when the bioactivity score lies between – 5.0 and 0.0) and inactive (when the bioactivity score < –5.0).

Bioavailability radar. A more comprehensible analysis of physiochemical properties was used to continue the filtration of potent ligand molecule. Bioavailability radars of ligands having better results than control compound was obtained using SwissADME web-based tool. A total of 6 parameters were used to scrutinize the compounds: solubility, size, polarity, lipophilicity, flexibility and saturation.

Ligands deviating from the standardized values suggested non oral bioavailability and hence were debarred from further testing.

DFT investigation. A Pentium IV personal computer (CPU at 4.80 GHz) with the Windows 10 operating system was used. The initial geometry optimization of title compounds was performed with HyperChem (Version 8.0 Hypercube, Inc., Alberta, Canada). For all the *ab initio* calculations, Gaussian 16 was employed. The molecular properties of the compounds were calculated by CAM-B3LYP/MidiX level of theory [19, 20]. Lowest energy structures of the species were computed by conformational analysis. Geometry optimization was performed at the CAM-B3LYP level with the same basis set. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are known as the frontier molecular orbitals (FMOs) that participate in electronic properties, optical properties, UV/Vis spectrum and chemical reactions [21]. We used FMO analysis and the electronic properties of the title organic acids by CAM-B3LYP/MidiX level of theory. A detail of quantum molecular descriptors of the title compounds such as Ionization Potential (IP) and Electron Affinities (EA), Hardness (η), Softness (S), Electronegativity (μ), Electrophilic Index (ω), Electron Donating Power (ω^-), Electron Accepting Power (ω^+) and Energy Gap (E_g) have been calculated. The energy of HOMO is directly related to the ionization potential (IP), while the energy of LUMO is related to the electron affinity (EA) [22]. The nucleophilicity of the studied organic acids can be expressed by the ionization potential value, which is calculated as the necessary energy for the abstractions of an electron in the molecule. IP shows the easiness of the electron donating of the title molecules due to electron abstraction is the first antioxidant mechanism. The following formulas were applied to calculate electronic properties of the title molecules [23]:

$$\text{IP} = -E_{\text{HOMO}}, \text{(eV)}, \quad (1)$$

$$\text{EA} = -E_{\text{LUMO}}, \text{(eV)}, \quad (2)$$

$$\eta = (\text{IP} - \text{EA}) / 2, \text{(eV)}, \quad (3)$$

$$\text{S} = 1 / (2\eta), \quad (4)$$

$$\mu = -(\text{IP} + \text{EA}) / 2, \text{(eV)}, \quad (5)$$

$$\omega = \mu^2/2\eta, \text{(eV)}, \quad (6)$$

$$\omega^+ = (\text{IP} + 3\text{EA})^2/16(\text{IP} - \text{EA}), \text{(eV)}, \quad (7)$$

$$\omega^- = (3\text{IP} + \text{EA})^2/16(\text{IP} - \text{EA}), \text{(eV)}, \quad (8)$$

$$E_g = E_{\text{LUMO}} - E_{\text{HOMO}}, \text{(eV)}. \quad (9)$$

The geometry optimization was performed in water environmental. The optimized molecular structures, HOMO and LUMO surfaces were visualized using GaussView 06 program. Marvin version 16.2.29 (ChemAxon, 2016) was applied for pKa prediction of the derivatives of natural alkaloids. Based on empirically determined partial charges, Marvin provides micro- and macro-ionization constants, along with the ionic species distribution diagram. In this investigation, the chemical structure of these compounds was analyzed at room temperature and zero ionic strength. Marvin was run in macro mode, and ACD/Percepta was used in GALAS algorithm mode, which provides more details about macro-ionization compared with the Classic mode.

Molecular docking. Recent developments in drug discovery have led to a renewed interest in the computational study which involves the use of algorithms and programs for predictions of therapeutic interventions in biological processes. Molecular docking is a structure-based drug design approach that predicts binding interactions between ligand and target receptor at the binding site. It is an important virtual screening technique which can screen several thousand ligands against the target, as well as identify potential inhibitors of the target receptor with speed and accuracy.

The molecular docking studies were performed by using AutoDock/Vina tool (Trott and Olson 2010) [24]. It is a reliable protein-ligand docking tool that uses the Broyden-Goldfarb-Shanno algorithm which significantly improves the average accuracy of the binding mode prediction. The crystal structure of target protein (PDB ID: 7DGG) was downloaded from the Protein Data Bank (http://www.rcsb.org/pdb) in PDB format and were prepared by AutoDock tools. Visualization of the docked pose has been done

by using USCF-Chimera (version 1.13) and Molegro Molecular Viewer 2.5. Water molecules and amino acid that does not belong to the protein were removed by deleting the lines that start with "HETATM" and "CONNECT". The file structure was saved and ready for docking analysis. Manually, initialized the protein molecule by adding hydrogen atoms and Kollman charges using the edit option and saved the protein molecule as write PDB. A grid box of 62.0, 74.0, 39.0 Å centered at 24.1 · 10.6 · 11.4 Å for the SARS-CoV-2 main protease was used in the docking experiments. Biovia Discovery Studio Visualizer v19.1.0.18287 was used to view the docking results and to convert the structures into pdb format. Binding energies (Δ*G*, kcal/mol) of the docked ligands were obtained by Binding energy $\Delta G = RTlnK_i$, where R = Gas constant ($1.987 \cdot 10^{-3}$ kcal/mol); T = 298.15 K; K_i – Inhibition constant. PubChem repository ("PubChem") was used to obtain the structure of the title organic compounds required for the analysis in pdb format.

Results and Discussion. The objects under study were acyl derivatives of anabasine, cytisine and quinine, previously synthesized using the methods described in [25, 26] (Fig. 1).

Pharmacokinetic properties. Drug-likeness evaluated by the Lipinski rule of five that deals four simple physicochemical parameter ranges (MWT ≤ 500, LogP ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status. MiLogP values of **1–3** were observed to be < 5 (from 2.99 to 3.27), indicating their good permeability across the cell membrane. All compounds were observed to have TPSA below 160 Å, molecular weight < 500 (except **5**), number of hydrogen bond donors ≤ 5, number of hydrogen acceptor ≤ 10, *n*violations 0 except **4, 5**, number of rotatable flexible bonds > 5 (except **1–3**). Solubility (LogS) of a drug in aqueous solution affects its absorption and distribution characteristics. The solubility of a compound was predicted using ChemOffice Bio 18 software to identify the low solubility behavior and eliminate from the study based on LogS value. The optimal solubility value is greater than –4. Solubility in water can be considered as the number of hydrogen donors in molecules. Higher amount of hydrogen bond donor translates higher water solubility, which in turn leads to high absorption into the blood and action. Molecular weight of all compounds was found to be less than five hundred, indicating that they are likely to be easily transported, diffused, and absorbed compared to larger molecules. Numbers of rotatable bands are important for conformational changes of the molecules. According to the oral bioavailability criteria, number of rotatable bonds should be less or equal to ten. All studied structures have between 1 and 7 rotatable bonds, indicating large conformational flexibility. Topological polar surface area (TPSA) is correlated with hydrogen bonding of a drug molecule. Topological polar surface area is very good indicator of the bioavailability of the drug molecules. TPSA of the derivatives of natural alkaloids ranged from 42.31 to 77.70 Å (Table 1).

The perfect space of six physicochemical parameters for oral bioavailability – size, polarity, lipophilicity, solubility, saturation and flexibility are located within the pink colored area (Fig. 2).

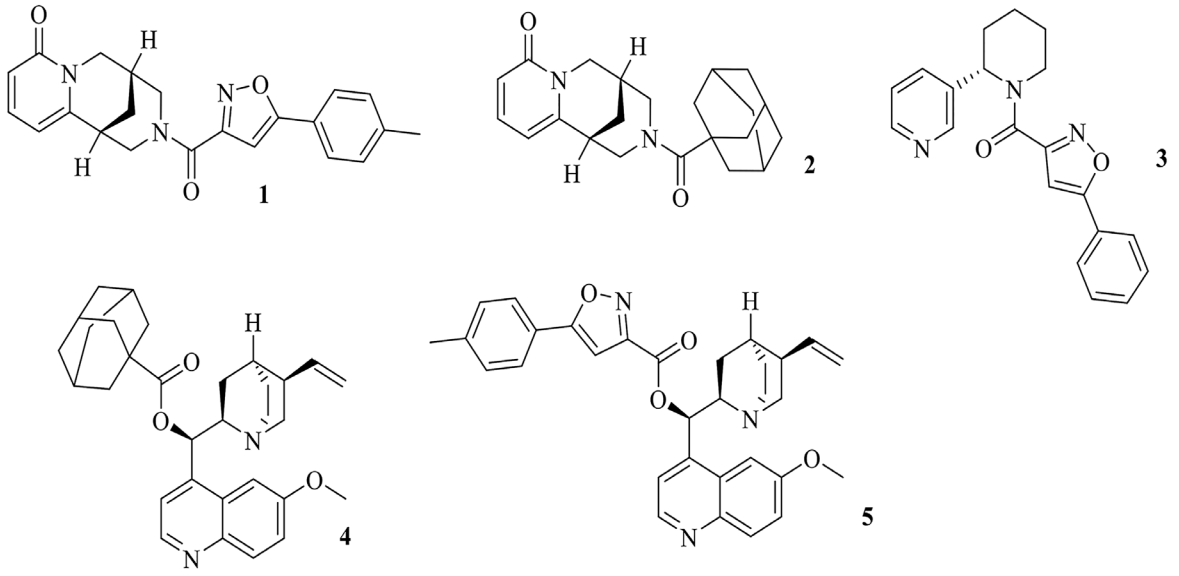


Fig. 1. Structural formulas of the studied compounds **1**–**5**

T a b l e 1. **Pharmacokinetic properties of the title compounds**

Compound	miLogP	TPSA	*n*atoms	MW	*n*HBA	*n*HBD	*n*violations	*n*rotb	LogS
1	2.99	68.35	28	375.43	6	0	0	2	–4.72
2	3.12	42.31	26	352.48	4	0	0	1	–4.15
3	3.27	59.23	25	333.39	5	0	0	3	–4.89
4	6.63	51.67	36	486.66	5	0	1	7	–7.21
5	6.38	77.70	38	509.61	7	0	2	8	–6.43

* – miLogP: lipophilicity; TPSA: Total Polar Surface Area; MW: Molecular Weight; *n*HBA: number of hydrogen bond acceptors; *n*HBD: number of hydrogen bond donors; *n*violations: number of violated drug–likeness rules; *n*rotb: number of rotating bonds; LogS: solubility

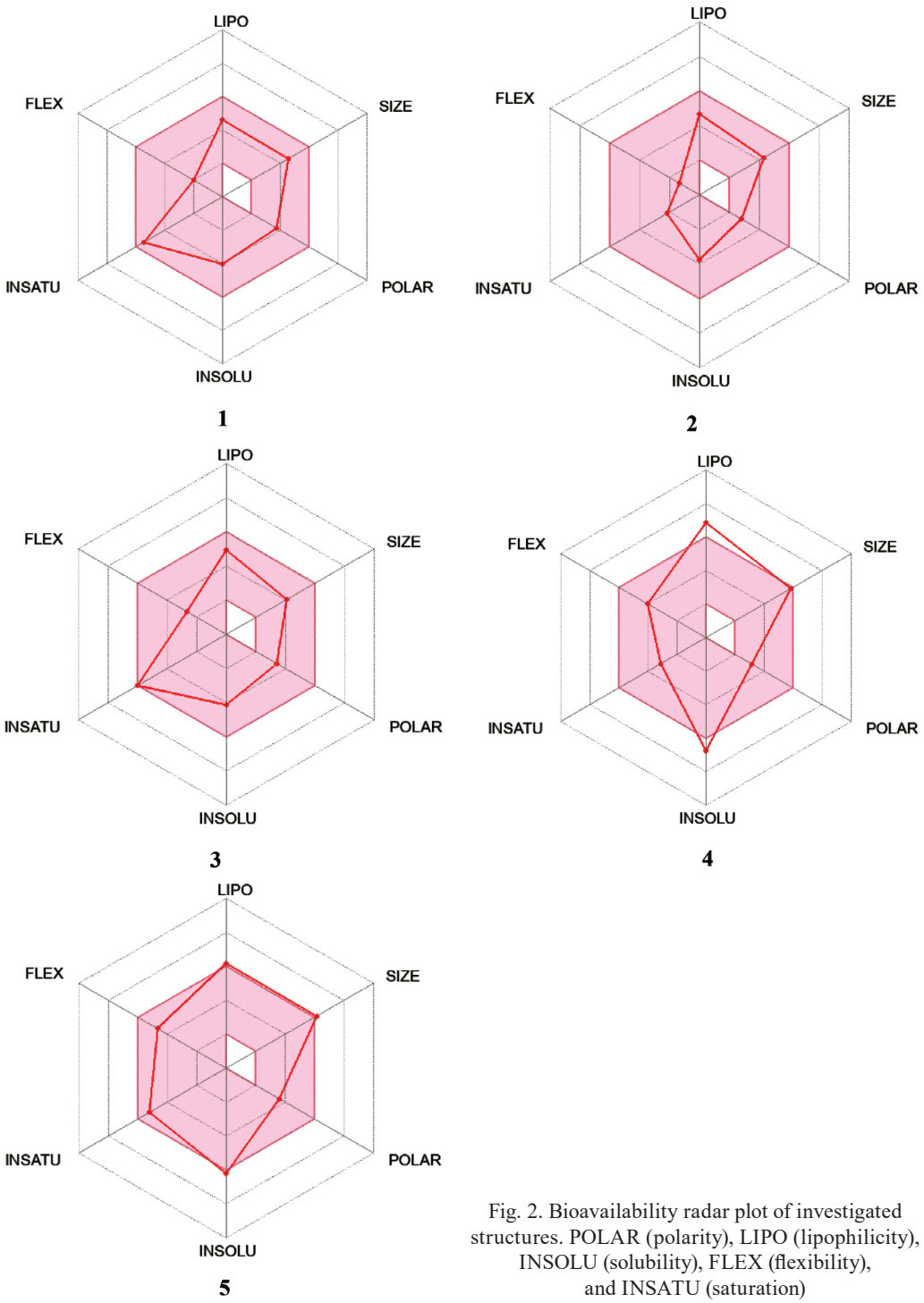


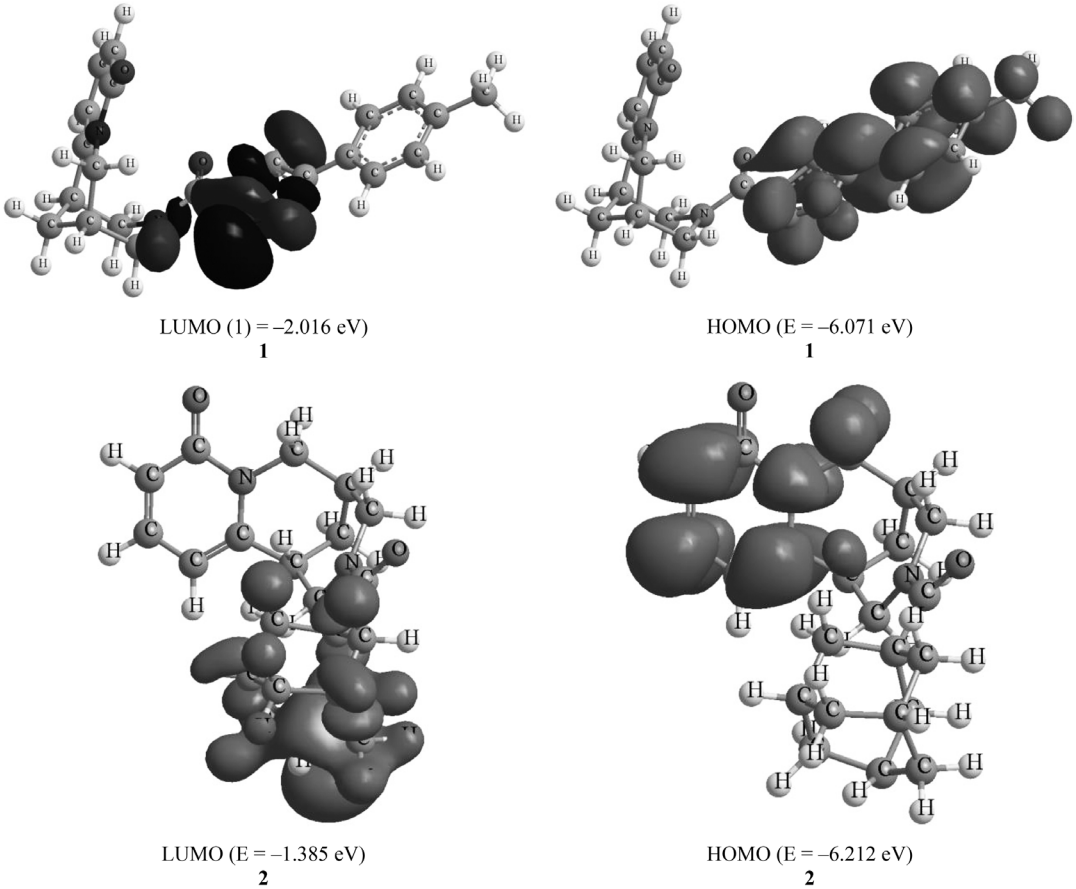
Fig. 2. Bioavailability radar plot of investigated structures. POLAR (polarity), LIPO (lipophilicity), INSOLU (solubility), FLEX (flexibility), and INSATU (saturation)

Bioactivity. These bioactivity scores for organic molecules can be interpreted as *active* (when the bioactivity score is > 0), *moderately active* (when the bioactivity score lies between − 5.0 and 0.0) and *inactive* (when the bioactivity score < −5.0). That means that **1** can be considered a moderately active as a GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor. The **3** can be considered a bioactive as a GPCR ligand and moderately active as an Ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor. The **4** can be considered a bioactive as a GPCR ligand, Ion channel modulator, nuclear receptor ligand, protease inhibitor, enzyme inhibitor and moderately active as a kinase inhibitor. **2** can be considered a bioactive as a GPCR ligand and Ion channel modulator and moderately active as a kinase inhibitor, protease inhibitor, nuclear receptor ligand and Enzyme inhibitor. **5** can be considered a bioactive as a GPCR ligand, protease inhibitor and Enzyme inhibitor and moderately active as an Ion channel modulator, kinase inhibitor and nuclear receptor ligand (Table 2).

T a b l e 2. **Bioactivity scores against different drug targets of the title compounds**

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	–0.11	–0.02	–0.27	–0.52	–0.27	–0.39
2	0.05	0.01	–0.37	–0.49	–0.08	–0.24
3	0.09	–0.02	–0.28	–0.30	–0.18	–0.10
4	0.25	0.11	–0.07	0.13	0.17	0.19
5	0.09	–0.10	–0.17	–0.14	0.08	0.00

DFT calculations. The structures with low IP values can undergo oxidation more easily (**4** with IP = 3.880 eV). The Electron Affinity (EA) of the **4** is the lowest (1.165 eV). The global hardness (η) corresponds to the energy gap between the LUMO and HOMO (Fig. 3). A molecule with a small energy gap has high chemical reactivity, low kinetic stability and is a soft molecule, while a hard molecule has a large energy



LUMO (1) = –2.016 eV) **1** HOMO (E = –6.071 eV) **1**

LUMO (E = –1.385 eV) **2** HOMO (E = –6.212 eV) **2**

Fig. 3. Calculated frontier molecule orbitals (FMOs) of the title compounds by CAM-B3LYP/MidiX level of theory

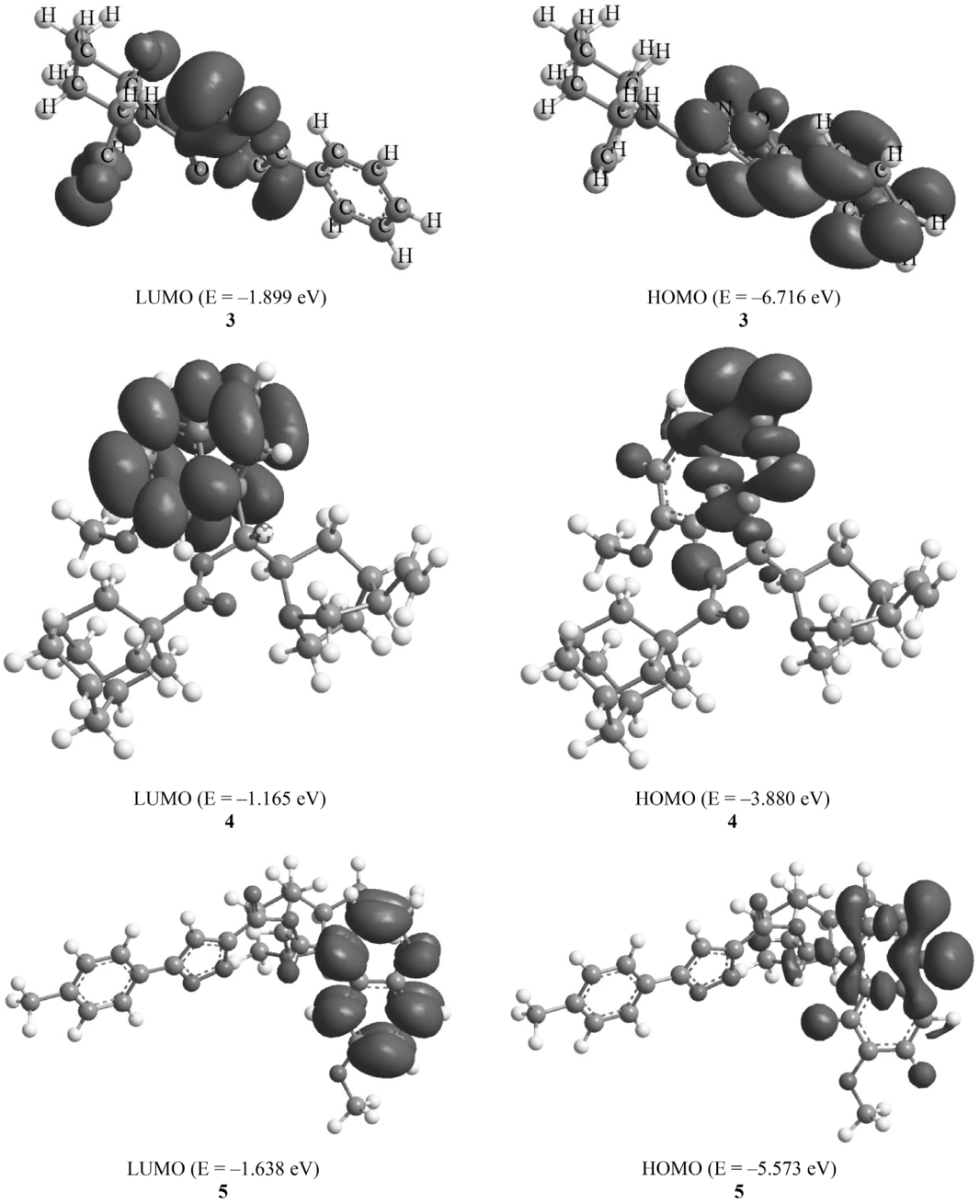


Fig. 3. Calculated frontier molecule orbitals (FMOs) of the title compounds by CAM-B3LYP/MidiX level of theory

gap [27–29]. The **2** has higher global hardness and is a hard molecule (2.414 eV). Electronegativity (μ) is a measure of the power of an atom or a group of atoms to attract electrons, and the chemical softness (S). It describes the capacity of an atom or a group of atoms to receive electrons. The Electrophilic Index (ω) represents the stabilization energy of the systems when it becomes saturated with electrons. The results show that **4** has the lowest value ω = 2.345 eV and is nucleophilic in nature, whereas the **1** has the highest value ω = 4.033 eV and is strongly electrophilic in nature. In addition, among the set of compounds, the **1** has the highest Electron Accepting Power (ω^+) and Electron Donating Power (ω^-) values (2.264 and 6.307 eV, respectively). As can be seen from Table 3, the E_g value for the **4** (2.715 eV) is the lowest. Thus, this structure can act better as an antioxidant.

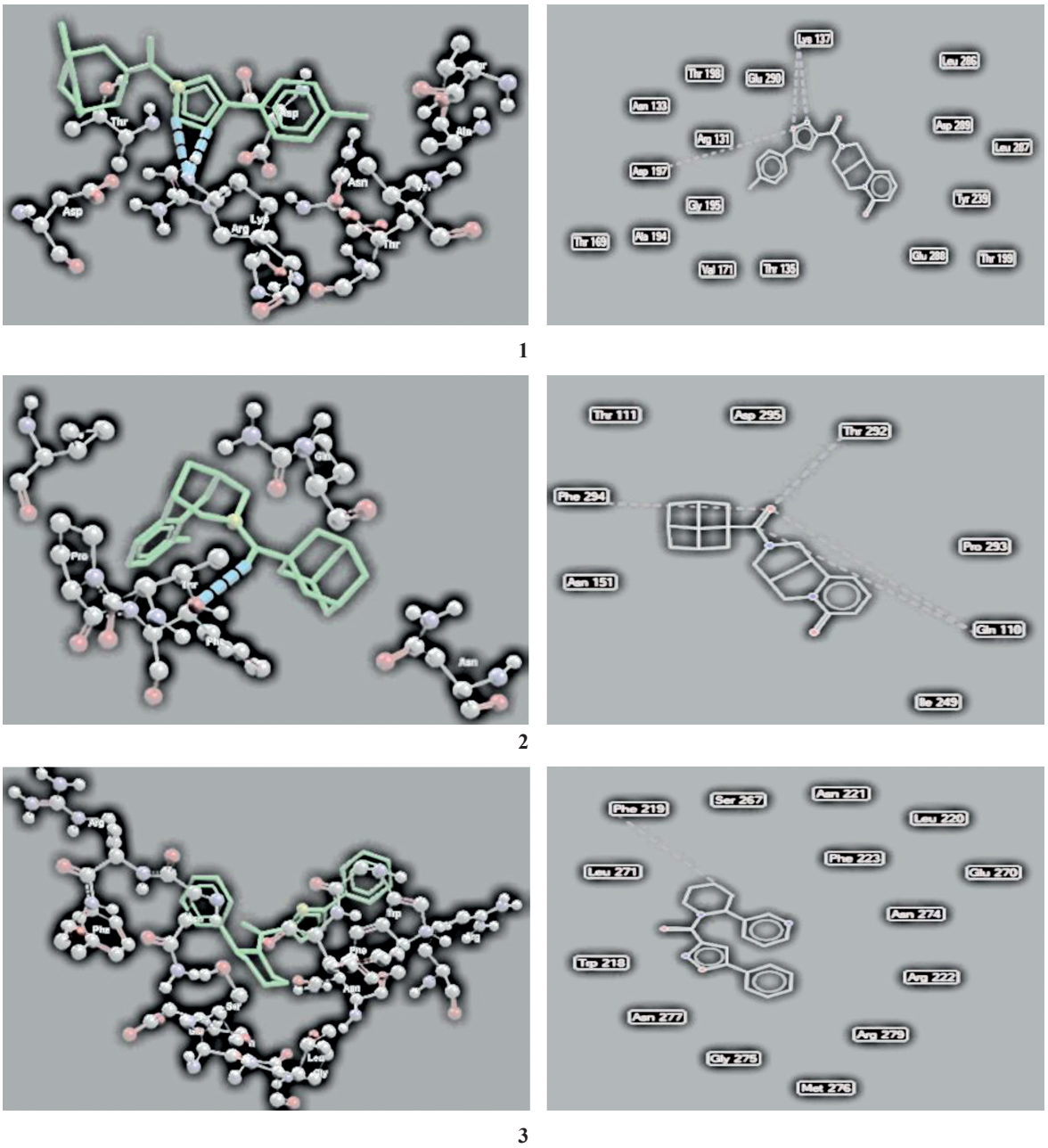
Molecular docking analysis. In order to study potential inhibitor of SARS-CoV-2 M^{pro}, AutoDock/Vina (MGL tools – 1.5.6), CHIMERA (www.cgl.ucsf.edu/chimera), Molegro Molecular Viewer 2.5, and Biovia Discovery Studio 4.5 were applied. The ligands were docked to the active site of the receptor protein molecule (Fig. 4). The docking and glide scores of the title compounds are presented in Table 4,

T a b l e 3. **The calculated electronic properties in eV of the title compounds**

Structure	IP	EA	η	S	μ	ω	ω^+	ω^-	E_g
1	6.071	2.016	2.028	0.247	–4.044	4.033	2,264	6,307	4.055
2	6.212	1.385	2.414	0.207	–3.799	2.990	1,392	5,190	4.827
3	6.716	1.899	2.409	0.208	–4.308	3.853	1,999	6,307	4.817
4	3.880	1.165	1.358	0.368	–2.523	2.345	1,252	3,775	2.715
5	5.573	1.638	1.968	0.254	–3.606	3.305	1,747	5,352	3.935

which has binding energy, glide score, number of hydrogen bonds and steric interactions formed. The maximum number of hydrogen bonds and steric interactions validates the strong binding energy.

It is seen from Table 4 that the binding energies of the **1–5** with SARS-CoV-2 main protease M^{pro} are –8.8, –8.1, –8.4, –10.2, and –9.6 kcal/mol with inhibition constants of 0.36, 1.16, 0.71, 0.03, and 0.09 μM, respectively. It is observed that the studied compounds are taken for the investigations exhibit better



1

2

3

Fig. 4. **1–5** binding interactions with SARS-CoV-2 main protease M^{pro}

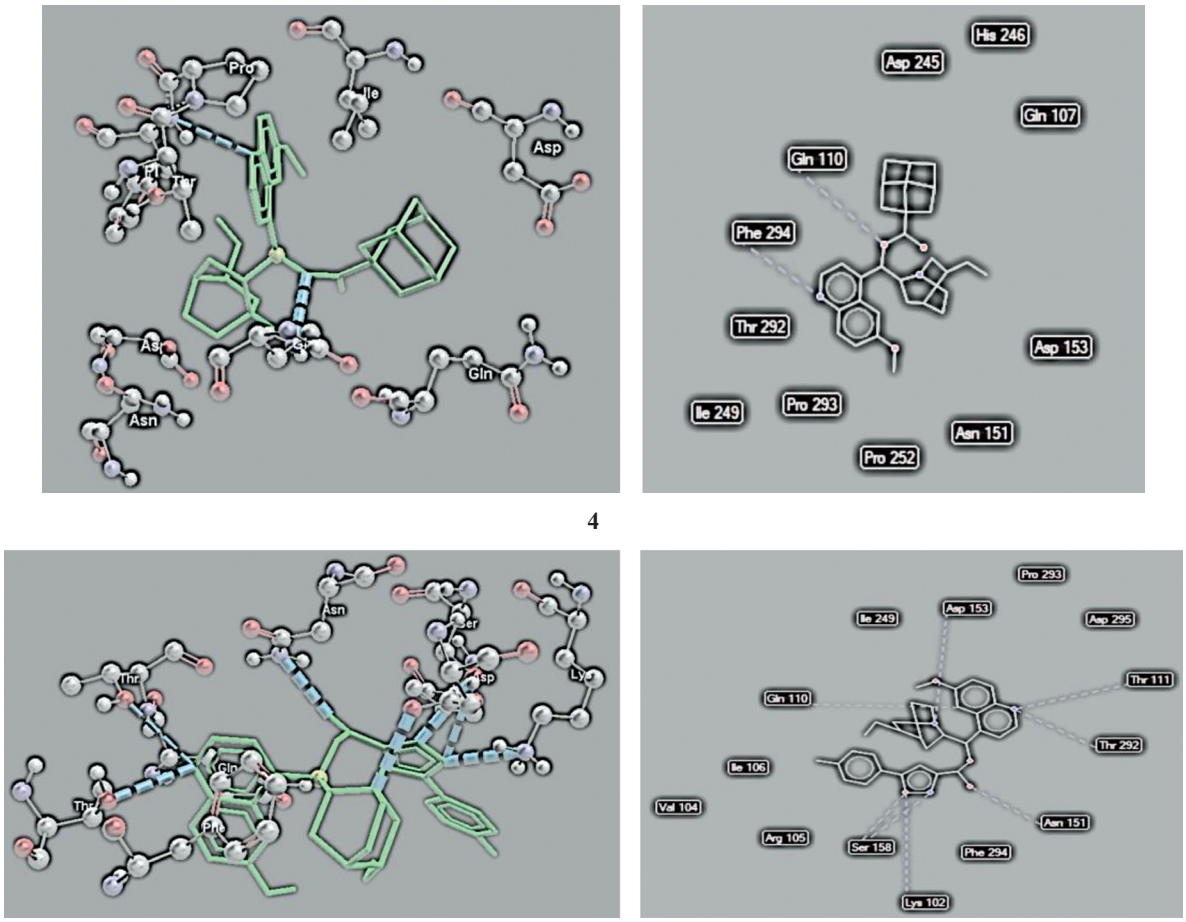


Fig. 4. **1–5** binding interactions with SARS-CoV-2 main protease M^{pro}

T a b l e 4. **Molecular docking analysis of the 1-5 with SARS- CoV-2 main protease M^{pro}**

Ligands	Binding Energy, kcal/mol	Inhibition constant (K_i), μM	Glide Score, kcal/mol	Number of H-bonds	Number of Steric Interactions
1	–8.8	0.36	–92.423	2	6
2	–8.1	1.16	–88.304	1	6
3	–8.4	0.71	–83.957	0	5
4	–10.2	0.03	–86.903	2	8
5	–9.6	0.09	–136.080	7	14

binding energy and various interactions involving hydrogen bonds and steric interactions with the SARS-CoV-2 main protease M^{pro}. The scoring function is a mathematical method predicting the strength of binding affinity between protein and ligand complex.

Conclusion. Density functional theory calculations were performed to investigate the molecular structure of the alkaloids anabasine, cytisine and quinine acyl derivatives **1–5** by CAM-B3LYP/MidiX level of theory. Ionization Potential (IP) of the **4** is 3.880 eV and this structure can act as an antioxidant. The **2** has higher global hardness and it is a hard molecule (2.414 eV). The results show that **4** has the lowest value ω = 2.345 eV and is nucleophilic in nature, whereas the **1** has the highest value ω = 4.033 eV and is strongly electrophilic in nature. In addition, among the set of compounds, the **1** has the highest Electron Accepting Power (ω^+) and Electron Donating Power (ω^-) values (2.264 and 6.307 eV, respectively). In addition, the value of E_g for the **4** (2.715 eV) is the lowest. Thus, this structure can act better as an antioxidant. miLogP values of **1–3** were observed to be < 5 (from 2.99 to 3.27), demonstrating their good permeability across the cell membrane. All compounds were observed to have TPSA below 160 Å, molecular weight < 500 except **5**, number of hydrogen bond donors ≤ 5, number of hydrogen acceptor ≤ 10, *n*violations 0 ex-

cept **4, 5**, number of rotatable flexible bonds > 5 except **1–3**. The **3** can be considered a bioactive as a GPCR ligand and moderately active as an Ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor. The **4** can be considered a bioactive as a GPCR ligand, Ion channel modulator, nuclear receptor ligand, protease inhibitor, enzyme inhibitor and moderately active as a kinase inhibitor **2** can be considered a bioactive as a GPCR ligand and Ion channel modulator and moderately active as a kinase inhibitor, protease inhibitor, nuclear receptor ligand and enzyme inhibitor **5** can be considered a bioactive as a GPCR ligand, protease inhibitor and enzyme inhibitor and moderately active as an Ion channel modulator, kinase inhibitor and nuclear receptor ligand. It was found that the investigated ligands show good affinity towards of the SARS-CoV-2 main protease M^{pro}. The binding energies for SARS-CoV-2 main protease M^{pro} and the **1–5** are –8.8, –8.1, –8.4, –10.2, and –9.6 kcal/mol with inhibition constant 0.36, 1.16, 0.71, 0.03, and 0.09 μM, respectively in which show good binding affinity between them and SARS-CoV-2 main protease M^{pro}.

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Информация об авторах

Шахаб Сиямак – доктор химических наук, доцент, заведующий кафедрой. МГЭИ им. А. Д. Сахарова БГУ (ул. Долгобродская, 23/1, 220070, Минск, Республика Беларусь). E-mail: siyamakshahab@mail.ru

Шейхи Масоме – кандидат химических наук. Клуб молодых исследователей и элиты, Отделение Исламского университета Азад (Горган, Иран). E-mail: m.sheikhi2@gmail.com

Алмодарресие Хора Алхоссейни – кандидат химических наук. Университет Мейбод (89616-99557, Мейбод, Йезд, Иран). E-mail: h_al1994@yahoo.com

Мукушева Гулим Кенесбековна – доктор химических наук, профессор, заведующий кафедрой. Карагандинский университет им. Е. А. Букетова (ул. Университетская, 28, 100024, Караганда, Казахстан). E-mail: mukusheva1977@mail.ru

Information about the authors

Shahab Siyamak – Dr. Sci. (Chemistry), Associate Professor, Head of the Department. Belarusian State University, ISEI BSU (23/1, Dolgobrodskaya Str., 220070, Minsk, Republic of Belarus). E-mail: siyamakshahab@mail.ru

Sheikhi Masoome – Ph. D. (Chemistry). Young Researchers and Elite Club, Gorgan Branch, Islamic Azad University (Gorgan, Iran). E-mail: m.sheikhi2@gmail.com

Almodarresiyeh Hora Alhosseini – Ph. D. (Chemistry). Meybod University (8961699557, Meybod, Yazd, Iran). E-mail: h_al1994@yahoo.com

Mukusheva Gulim K. – Dr. Sci. (Chemistry), Professor, Head of the Department. Karaganda Buketov University (28, Universitetskaya Str., 100024, Karaganda, Kazakhstan). E-mail: mukusheva1977@mail.ru

Toigambekova Nurizat N. – Ph. D. (Chemistry), Karaganda Buketov University (28, Universitetskaya Str., 100024, Karaganda, Kazakhstan). E-mail: nukonti92@mail.ru

Тойгамбекова Нуризат Нуржановна – кандидат химических наук. Карагандинский университет им. Е. А. Букетова (ул. Университетская, 28, 100024, Караганда, Казахстан). E-mail: nukonti92@mail.ru

Дикусар Евгений Анатольевич – кандидат химических наук, старший научный сотрудник. Институт физико-органической химии НАН Беларуси (ул. Сурганова, 13, 220072, Минск, Республика Беларусь). E-mail: evgen_58@mail.ru

Акишина Екатерина Александровна – научный сотрудник. Институт физико-органической химии НАН Беларуси (ул. Сурганова, 13, 220072, Минск, Республика Беларусь). E-mail: che.semenovaea@mail.ru

Поткин Владимир Иванович – академик, доктор химических наук, профессор, заведующий лабораторией. Институт физико-органической химии НАН Беларуси (ул. Сурганова, 13, 220072, Минск, Беларусь). E-mail: potkin@ifoch.bas-net.by

Альбасри Саджад Рад – аспирант. МГЭИ им. А. Д. Сахарова Белорусского государственного университета (ул. Долгобродская, 23/1, 220070, Минск, Республика Беларусь). E-mail: yuridragonv@gmail.com

Атрошко Михаил Александрович – преподаватель. МГЭИ им. А. Д. Сахарова Белорусского государственного университета (ул. Долгобродская, 23/1, 220070, Минск, Республика Беларусь). E-mail: atroshkomikhail@gmail.com

Dikusar Evgenij A. – Ph. D. (Chemistry), Senior Researcher. Institute of Physical Organic Chemistry of the National Academy of Sciences of Belarus (13, Surganov Str., 220072, Minsk, Republic of Belarus). E-mail: evgen_58@mail.ru

Akishina Ekaterina A. – Researcher. Institute of Physical Organic Chemistry of the National Academy of Sciences of Belarus (13, Surganov Str., 220072, Minsk, Republic of Belarus). E-mail: che.semenovaea@mail.ru

Potkin Vladimir I. – Academician, Dr. Sci. (Chemistry), Professor, Head of the Laboratory. Institute of Physical Organic Chemistry of the National Academy of Sciences of Belarus (13, Surganov Str., 220072, Minsk, Republic of Belarus). E-mail: potkin@ifoch.bas-net.by

Albasri Sajjad Raad – Postgraduate Student. Belarusian State University, ISEI BSU (23/1, Dolgobrodskaya Str., 220070, Minsk, Republic of Belarus). E-mail: yuridragonv@gmail.com

Atroshko Mikhail A. – Teache. Belarusian State University, ISEI BSU (23/1, Dolgobrodskaya Str., 220070, Minsk, Republic of Belarus). E-mail: atroshkomikhail@gmail.com