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DOCKING AND QUANTUM CHEMICAL INSIGHTS INTO THE ANTICANCER MECHANISMS OF MONOCHLOROACETIC AND DICHLOROACETIC ACIDS DERIVATIVES

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ІНФОРМАЦІЯ

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tumors.

АНОТАЦІЯ

The aim of the work. The present study aims to conduct the comparative quantum chemical analysis of MCA and DCA derivatives, their reactivity in interaction with protein targets, and the determination of the molecular mechanisms underlying their biological activity.

Materials and Methods. The study employed quantum chemical calculations and molecular docking to investigate synthesized compounds' electronic properties and biological interactions. Structures were optimized using DFT (B3LYP/6-311++G(d,p)) in Gaussian 09 with vibrational analyses confirming transition states. Key electronic descriptors were computed to assess reactivity. The results of quantum chemical calculations were visualized using GaussView 5.0.8. Docking simulations involved modeling glutathione-chloroacetamide conjugates at physiological pH, minimizing structures in Avogadro software, and analyzing interactions with GST (PDB ID: 11GS) using the FlexX algorithm in LeadIT. Binding interactions were visualized via BIOVIA Discovery Studio, with docking parameters validated by RMSD comparison to experimental data.

Results and Discussion. Analysis of frontier molecular orbitals and descriptors associated with their energy showed an increase in MCA activity with increasing electrophilicity. However, on individual lines the results ensuing from this dependence may be related to their structure peculiarities. The molecular electrostatic potential analysis showed the steric hindrances' presence due to the generous size of chlorine atoms, which reduce the possibilities for the MCA attack. The change in the Gibbs energy of the substitution reaction also indicates an easier substitution course in MCA. The molecular docking results showed the possibility of effective covalent binding to glutathione S-transferase of both MCA and DCA. However, another reason for the decrease in activity is the possibility of the DCA adduct hydrolysis with glutathione since the studied compounds do not prevent water access when binding in the active center.

Conclusions. The decrease in the DCA reactivity compared to MCA analogs is associated with steric hindrances and the chlorine atom influence in the transition state. In general, DCA's lower biological activity is associated with decreased reactivity and the possibility of joining cysteine residues to their hydrolysis products. The obtained results can become the basis for creating new targeted drugs with increased efficiency and selectivity.

Introduction. The development of innovative approaches to treating diseases with cellular metabolism disorders remains an urgent task in modern medicine. The last decades have become a period of considerable progress in studying the action mechanisms of low molecular weight organic compounds with high therapeutic activity. Among such compounds, monochloroacetic acid (MCA) and dichloroacetic acid (DCA) amides are of special interest. They demonstrate multifunctionality and prospects in pharmacology and attract special attention. These substances can modify metabolic pathways and influence the specific proteins' activity that makes them potential candidates for anticancer therapy.

DCA derivatives show significant potential in oncological diseases' treatment due to their ability to influence the cancer cells' metabolic profile through pyruvate dehydrogenase kinase inhibition. This leads to the activation of the pyruvate dehydrogenase complex, which promotes oxidative phosphorylation in mitochondria and disrupts the tumor cells' glycolytic metabolism, known as the Warburg effect, and affects the tricarboxylic acids (citrate) cycle, that is key to the tumor cell metabolism regulation. These processes increase the cancer cells' apoptosis and reduce their proliferative potential. In addition, in a study of the DCA effect on a lung cancer model, it was found that its use promotes changes in the profile of differentially expressed genes, in particular MIF and CLEC3B, which may be key in the development of genetically targeted treatment strategies [1; 2].

In addition, according to clinical studies, DCA can be used in the therapy of glioblastoma, melanoma, and other cancer types due to its ability to reduce lactate levels and induce apoptosis in tumor cells. However, its therapeutic efficacy requires further detailed studies, especially in the context of molecular targets and possible toxic effects [3].

In turn, MCA derivatives have shown greater activity in inhibiting the growth of certain types of tumors compared to DCA, which requires a detailed analysis of their molecular action mechanisms and effects on different protein targets. One key target is glutathione S-transferase (GST), an enzyme that protects cells from oxidative stress. In particular, studies have shown that chloroacetic acid derivatives can reduce the activity of GST, which reduces the cells' ability to detoxify, enhancing the chemotherapy effects [4].

DCA has also demonstrated the ability to reduce the cancer cells' proliferative potential. They mainly interact with protein sulfhydryl groups, forming covalent bonds. This can affect the regulation of many metabolic pathways and provide new opportunities in the targeted drugs' creation. Recent studies have demonstrated that MCA derivatives are more active in inhibiting the growth of certain types of cancer cells compared to DCA derivatives, raising questions about the molecular mechanisms underlying these differences [5; 6].

It is important to note that molecular docking is a powerful tool for analyzing the molecules' interaction with protein targets. Recently developed docking methods that combine machine learning provide a more efficient exploration of chemical space, allowing for significant reductions in computational cost while maintaining high accuracy of results. This allows identifying potentially active compounds for further study and using them to develop new therapeutic agents. Studies have shown that combined approaches that include docking with active learning can significantly increase the effectiveness of the new biologically active compounds discovery [7].

Based on these data, molecular docking and quantum chemical analysis are effective methods for calculating the molecules' electronic characteristics and their interactions with protein targets. Therefore, this study's purpose is the comparative quantum chemical analysis of MCA and DCA derivatives, their reactivity in interaction with protein targets, and the determination of the molecular mechanisms underlying their biological activity. The obtained results can become the basis for creating new targeted drugs with improved efficiency and selectivity.

To substantiate the different anticancer activity profiles of the MCA and DCA derivatives, we conducted in silico studies of a series of thiazole-bearing amides **1–14** that we had previously synthesized (Fig. 1). It is important to note that according to the anticancer cytotoxicity study of these compounds on the myeloproliferative neoplasms model cell lines Baf3 Wt, Baf3 CARL del52 and Baf3CARL ins5, as well as breast cancer MDA-MB-231 and colon cancer HT-29 cell lines, a clear trend of higher activity profile for MCA derivatives compared to DCA derivatives is observed [5].

Materials and Methods

***Quantum chemical calculation*.** The synthesized compounds' structure was optimized using the Gaussian 09 program, the results were visualized using GaussView 5.0.8 [8; 9]. In all studied structures, geometry was optimized using DFT in the B3LYP approach with the standard set of basic functions 6-311++G(d,p). For each optimized transition state, the frequency analysis showed a single imaginary frequency of oscillation. To confirm the correctness of the found transition states, the corresponding oscillation was visualized.

The theoretical framework of frontier molecular orbitals underpins the calculation of several key indices that describe molecular electronic properties and reactivity. The ionization potential (IP) and electron affinity (EA) are calculated as $IP = -E_{HOMO}$ and $EA = -E_{LUMO}$, respectively, with the HOMO-LUMO gap (HLG) defined as $HLG = IP - EA$.

Further, the electronegativity ($\chi = \frac{IP + EA}{2} = -\mu$) and chemical potential ($\mu = -\frac{IP + EA}{2} = -\chi$) describe a molecule's electron affinity, while global hardness ($\eta = \frac{IP - EA}{2}$) and softness ($S = \frac{1}{2\eta}$) quantify stability and reactivity. Electrophilicity ($\omega = \frac{\mu^2}{2\eta}$) measures the molecule's ability to accept electrons. Advanced descriptors include electrodonating ($\omega^- = \frac{(3IP + EA)^2}{16(IP - EA)}$) and electron-accepting powers ($\omega^+ = \frac{(IP + 3EA)^2}{16(IP - EA)}$) [10; 11].

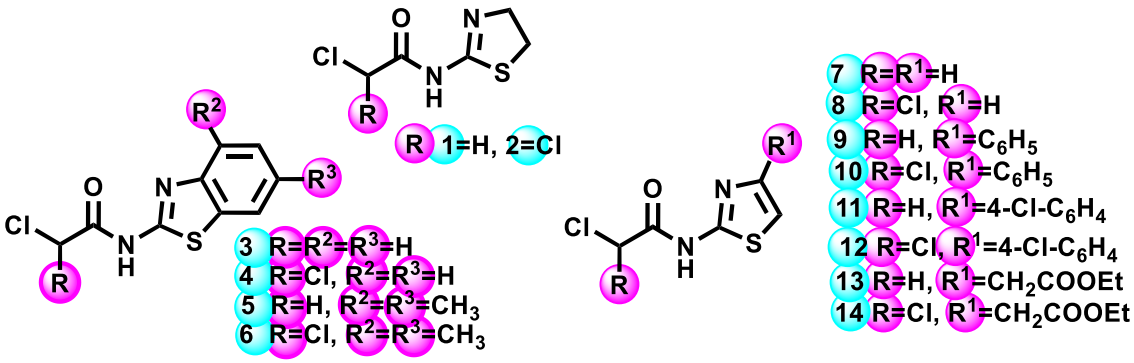

Fig. 1. Structures of studied MCA and DCA derivatives

***Docking simulation*.** Potential glutathione-chloroacetamide (GSH-CA) conjugates were constructed by modifying the glutathione 3D structure with the alkyl groups from the synthesized compounds. The structures' protonation states were adjusted to reflect physiological pH (7.4). These conjugates were subsequently minimized using a molecular mechanics-based optimization approach. The minimization was performed with the MMFF94 [12; 13] force field in Avogadro software, using a maximum of 10,000 steps [14].

The GST crystal structure (PDB ID: 11GS) [15] was retrieved from the Protein Data Bank (PDB) for docking studies. For docking simulations, we employed the FlexX algorithm [16] implemented in LeadIT 2.3.2 due to its capability to accurately predict the glutathione-ethacrynic acid complex binding positions. The algorithm demonstrated sufficient accuracy, with root mean square deviation (RMSD) values of less than 2 Å (observed RMSD: 1.8402 Å), as shown in Fig. 2 [17].

The binding site for docking was defined as the amino acid residues surrounding the binding GST region. To ensure comprehensive coverage of potential interactions, the docking site radius was expanded from the default 6.5 Å to 8.5 Å. The glutathione-ethacrynic acid conjugate from the available X-ray crystal structure was used to validate the docking parameters and to benchmark docking scores against those of the predicted complexes.

The docking results visualization and analysis were performed using BIOVIA Discovery Studio and the built-in PoseView module from LeadIT.

Results and Discussion. The chloroacetamides biological activity is usually associated with their ability to covalently bind to protein molecules. Covalent bond formation is possible due to the chlorine atom substitution for a cysteine residue. Such a substitution reaction is possible in both MCA and DCA. In practice, a significant difference in the biological activity of MCA and DCA analogs has been recorded [5]. To explain this difference, a quantum chemical study of their electronic structure and their interaction mechanism was carried out.

The studied compounds' reactivity is directly influenced by their electronic structure. When calculating their reactivity parameters, their frontier orbitals' location has a decisive influence. When comparing the

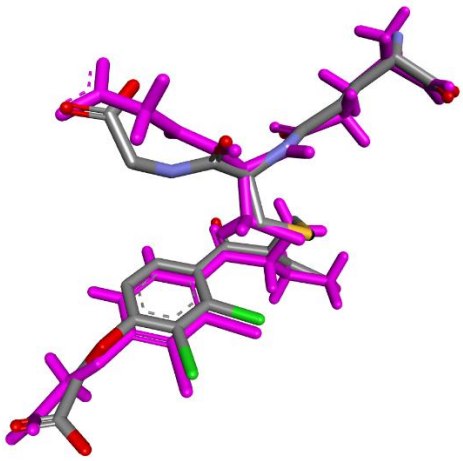

Fig. 2. The real (grey-colored) and predicted positions of the glutathione-etacrynic acid complex inside GST (PDB 11GS) are shown, with an RMSD of 1.8402 Å

energy levels' location, it should be noted both the chlorine atoms influence and the heterocycle's nature and substituents (Fig. 3). In general, the DCA energy levels are shifted down due to the additional chlorine atom acceptor effect. The HOMO location is less affected by an additional chlorine atom since the conjugated system atoms are mainly involved in its formation. Accordingly, the HOMO energy increases with the donor substituents appearance in the thiazole ring. Comparing the heterocycle nature, it should be noted that it has less effect on the HOMO energy, which slightly decreases in the following row: dihydrothiazole, thiazole, and benzothiazole. The two chlorine atoms presence in the molecule has a much greater effect on lowering the LUMO energy. On the one hand, this is due to the greater electron-accepting influence of two chlorine atoms, and on the other hand, the chlorine atoms' spatial arrangement. When optimizing the geometry, one MCA chlorine atom is located in the opposite position relative to oxygen, and two DCA chlorine atoms occupy a partially eclipsed position in which their orbitals can partially interact with the conjugated system orbitals. As a result of such an interaction, the LUMO also covers two chlorine atoms in DCA, which helps to reduce their energy. Unlike in MCA, chlorine orbitals do not participate in LUMO formation.

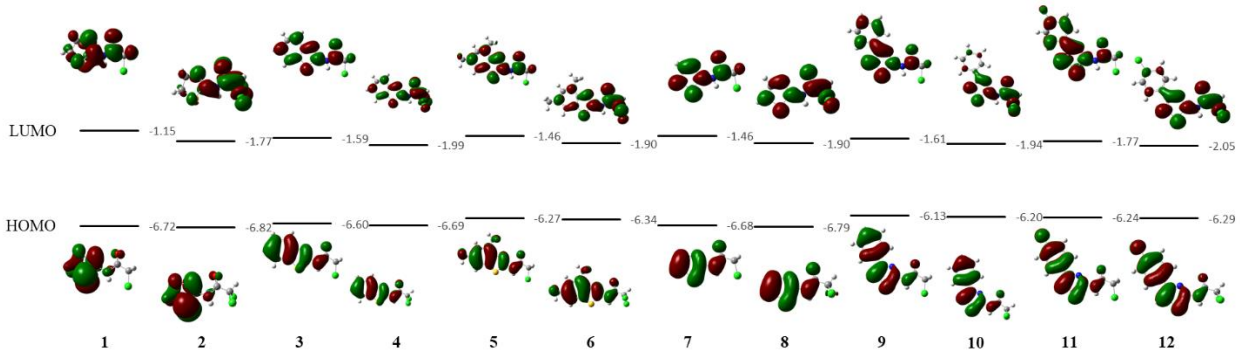

Fig. 3. The location and shape of the studied compounds' frontier orbitals

Table 1
The MCA and DCA calculated reactivity parameters

	1	2	3	4	5	6	7	8	9	10	11	12
LUMO, eV	-1.15	-1.77	-1.59	-1.99	-1.46	-1.90	-1.46	-1.90	-1.61	-1.94	-1.77	-2.05
HOMO, eV	-6.72	-6.82	-6.60	-6.69	-6.27	-6.34	-6.68	-6.79	-6.13	-6.20	-6.24	-6.29
EA	1.15	1.77	1.59	1.99	1.46	1.90	1.46	1.90	1.61	1.94	1.77	2.05
IP	6.72	6.82	6.60	6.69	6.27	6.34	6.68	6.79	6.13	6.20	6.24	6.29
HLG	5.57	5.06	5.01	4.69	4.81	4.45	5.22	4.89	4.52	4.27	4.46	4.24
χ	3.94	4.29	4.09	4.34	3.86	4.12	4.07	4.34	3.87	4.07	4.00	4.17
μ	-3.94	-4.29	-4.09	-4.34	-3.86	-4.12	-4.07	-4.34	-3.87	-4.07	-4.00	-4.17
η	2.78	2.53	2.50	2.35	2.40	2.22	2.61	2.45	2.26	2.13	2.23	2.12
S	0.18	0.20	0.20	0.21	0.21	0.22	0.19	0.20	0.22	0.23	0.22	0.24
ω	2.78	3.65	3.34	4.01	3.10	3.82	3.17	3.85	3.31	3.88	3.59	4.10
ω−	5.10	6.11	5.70	6.47	5.34	6.16	5.53	6.33	5.52	6.18	5.87	6.45
ω+	1.16	1.82	1.61	2.13	1.47	2.03	1.46	1.99	1.66	2.11	1.87	2.28

Such an arrangement is not fundamental, and its influence only shows a partial case, since there are no significant spatial difficulties and at room temperature a complete rotation around the terminal C–C bond is possible, although most of the time the molecule will still be in the most favorable conformation, which is modeled as a result of corresponding compounds geometry optimization.

Different arrangements of energy levels will contribute to their different reactivity. The calculated parameters (Table 1), which result from the frontier molecular orbitals analysis, show their reactivity dependence on the structure. The energy gap characterizing the ability to transition to an excited state is generally lower in DCA. The studied compounds act as electrophiles in substitution reactions with cysteine anion. Therefore, their reactivity in such reactions should be determined by their electrophilicity (ω). According to the calculations, it is possible to unequivocally assert the higher electrophilicity and, accordingly, the reactivity of DCA. However, in practice, they are less effective on different cancer cell lines [5, 6]. The most electrophilic DCA **12** showed little activity on some lines, while others showed almost no activity. If we compare the activity of MCA, in general, their activity increases with increasing electrophilicity, except compounds **3** and **11** (although on some lines they worked better than others), which should be associated not only with their reactivity but also with their spatial structure. Another descriptor that measures the system's ability to accept a charge fractional amount is the electron-donating ability (ω^+). Its values are roughly correlated with electrophilicity, so it can also be used to predict reactivity.

Geometry optimization and molecular electrostatic potential (MESP) calculation allow us to estimate how prone the attack site is to electrophilic or nucleophilic attack [18; 19]. Possible nucleophilic attack places are marked on MESP in blue, and electrophilic in red. In the studied compounds, three regions can generally be distinguished: the nucleophilic center near the carbonyl group and the thiazole ring nitrogen atom, the electrophilic center near the amide group, and the less positively charged electrophilic center near the carbon atom bound to chlorine (Fig. 4). The latter is a reaction center in the substitution reaction and the charge on it will affect the cysteine anion electrophilic attack. In general, the conjugated system type, the donor or acceptor substituents presence have negligible effect on the electrostatic potential near the reaction center. If we compare MCA and DCA MESP, we should note a much larger difference in the electrostatic potential distribution near the terminal carbon atom through which the attack on the sulfur atom of the cysteine residue is carried out. As is well known, in nucleophilic substitution (S_N2) the attack

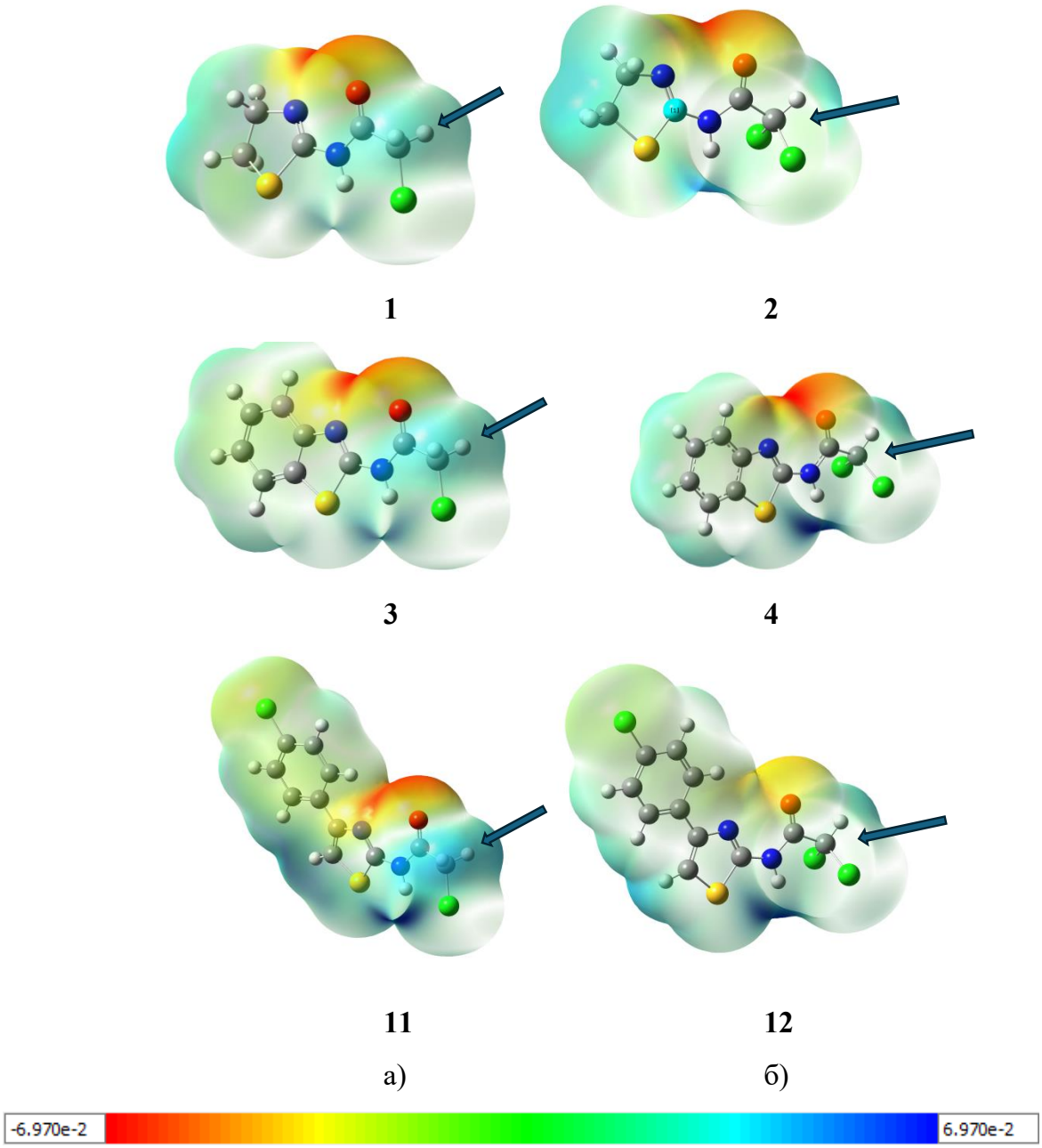

Fig. 4. The MCA **1, 3, 11** (a) and DCA **2, 4, 12** (б) synthesized thiazoles MESP with the direction indication of attack by the cysteine residue. (For comparison, the color scale for all molecules was set from red at -0.0697 a. u. (-43.7 kcal/mol) to blue at +0.0697 a. u. (+43.7 kcal/mol))

occurs from the chlorine atom's opposite side (as indicated by the arrows in Fig. 4), and at these locations the difference in MESP distribution between MCA and DCA is visible. At the attack site, MCA has a larger positively charged region, which may facilitate easier nucleophilic attack, while DCA attack sites are less positively charged due to the generous size of the two chlorine atoms, which are slightly negatively charged. Therefore, one of the factors in reducing the DCA activity will be steric hindrance during the substitution reaction.

In the substitution reaction, the transition state occurs due to a change in the carbon atom hybridization from sp^3 to sp^2 (Fig. 5). Accordingly, in the transition state, the lone pair of the p-orbital of the second chlorine atom, which is not substituted in DCA, is conjugated with the carbon atom on which the attack occurs and the rest of the conjugated system of these compounds and, due to the donor M+ effect, will reduce the electron density on the carbon atom, which will reduce its ability to interact. The Gibbs energies of all reactants, the transition state, and the products of the model reaction with the cysteine anion under standard conditions were calculated. For comparison, the total Gibbs energy of MCA **7** and the cysteine anion and DCA **8** and the same cysteine anion

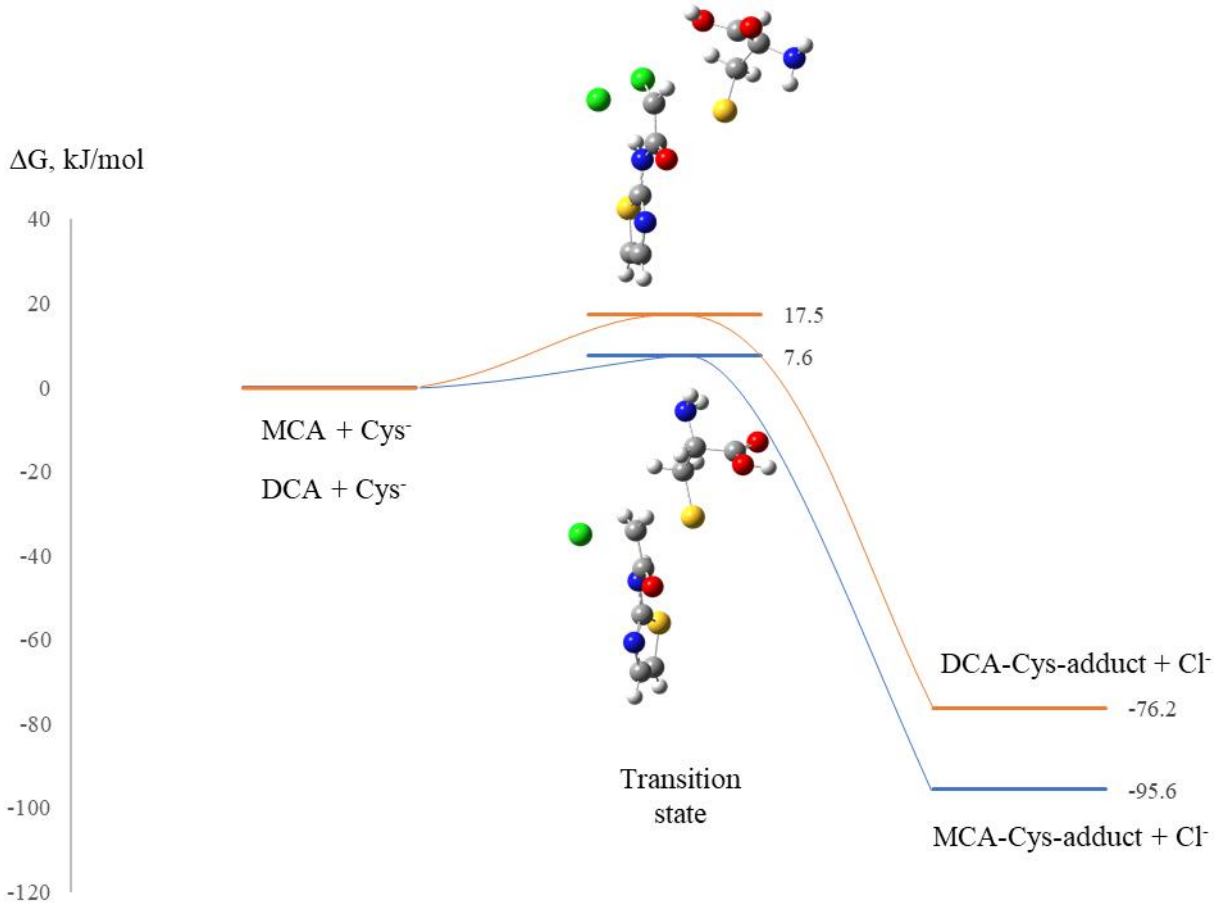

Fig. 5. Change in the reaction Gibbs energy during the chlorine atom replacement by the cysteine anion in MSA **7** (orange) and DCA **8** (blue)

were taken as 0. The correctness of the transition state modeling was confirmed by the presence of one imaginary (negative) oscillation frequency and visualization of the corresponding oscillation for both transition states. This reaction activation energy is insignificant, which indicates the ease of the studied substances' interaction with the cysteine anion, however, the transition state in the DCA reaction has a 10 kJ/mol higher energy than with MCA, due to the reasons discussed above. The MCA adduct higher thermodynamic stability should also be noted. Accordingly, the DCA adduct is less stable and subsequently more capable of further transformations.

If we assume that the nucleophilic substitution occurs by the S_N1 mechanism, the key role will be played by the chlorine atom bond dissociation energy (BDE). Which can be calculated as $BDE = E_{cation} + E_{Cl-} - E_{neutral}$. The chlorine atom calculated BDE in MCA **3** is 747.5 kJ/mol, and in DCA **4** is 694.6 kJ/mol. Given the generous size of the chlorine atoms, which create steric hindrance, and the lower BDE for DCA, the S_N1 mechanism is more likely. However, during the formation of a carbocation from DCA, the remaining chlorine atom, with its lone pair, enters into conjugation with the rest conjugated system and acts as a donor, because the carbon transforms into sp^2-hybridization like in a transition state (Fig. 5). Therefore, due to the donor effect of chlorine, the course of the S_N1 reaction by the DCA mechanism will be more complicated.

Based on the electronic structure of the investigated MCA and DCA, it can be argued that the second chlorine atom, which exhibits an electron-accepting effect, should contribute to an easier passage of the substitution reaction. However, the observed lower rate of the DCA substitution reaction [20] can be explained, on the one hand, by the steric hindrance of two chlorine atoms, which is clearly visible from the MESP analysis, as well as by the structure of the transition state in which the chlorine atom begins to act as a donor, reducing their ability to further attack. The DCA low biological activity can be explained not only due to a decrease in reactivity but also because the formed adduct can split off a chlorine atom in an aqueous environment with subsequent interaction with water and transformation into an aldehyde incapable of further interaction with cysteine. MCA does not have a chlorine atom that can be split off, so such a transformation under the water action is not possible and it can be bound to the target protein for a longer time. DCAs could be excellent inhibitors only if the adduct formed in the active site of the protein molecule due to a certain location would prevent the water access to the binding site, which would not allow it to further interact with water.

To verify the location of our compounds in the active center of the target protein, computer docking was performed. Previous research on chloroacetamide derivatives suggests that potential targets could include Fibroblast Growth Factor Receptors (FGFR 1-4) [21] and the Epidermal Growth Factor Receptor (EGFR) [22]. However, irreversible inhibitors of these receptors are typically large molecules, as they must mimic ATP to bind effectively to the kinase domain [23].

In our case, the synthesized derivatives are significantly smaller, which raises doubts about their ability to inhibit these kinases effectively.

Given the alkylating properties of CA, Glutathione S-transferase (GST) is considered a likely target for the tested compounds. There is a substantial body of literature indicating that CA derivatives, including herbicides, can interact with glutathione [24]. This interaction is suggested to contribute to both their primary mode of action and their associated toxic side effects. However, some compounds, such as etacrynic acid, which can covalently bind to glutathione, have been shown to act as ligands that block GST activity [25]. This inhibition of GST may enhance the efficacy of chemotherapy regimens by increasing the levels of reactive oxygen species (ROS), thereby promoting cellular damage [26]. If these conjugates exhibit strong affinity for GST, they could also function as GST inhibitors. This approach may be useful for anticancer therapy or as an adjunct to existing treatments, to reduce resistance or enhance the efficacy of the selected chemotherapy regimen [27].

Therefore, we aimed to evaluate the affinity of potential glutathione-MCA conjugates as GST inhibitors. The obtained FlexX docking scores are presented in Table 2.

The FlexX docking scores for DCA derivatives are predominantly higher compared to those of CA analogs. However, as previously noted in the literature [20], such derivatives are often unstable, leading to rapid inactivation, and are therefore unlikely to inhibit GST activity effectively. Most conjugates exhibit improved binding affinity compared to the native glutathione-etacrynic acid complex. The **glutathione-9 complex** achieved the best docking score among the CA derivatives. As shown in Fig. 6, the 4-phenylthiazol-2-yl motif fits well into the hydrophobic pocket formed by several lipophilic amino acids, including Ile104, Tyr108, Val10, Tyr7, and Phe8.

Table 2
The FlexX docking scores of the predicted glutathione-MCAs conjugates and complex with the etacrynic acid

Compounds	GST (PDB 11GS) FlexX docking score	Compounds	GST (PDB 11GS) FlexX docking score
GSH-EAA complex	-29.2766		
MCA		DCA	
1 Gor-20097	-26.5358	**2 Gor-20098**	-33.2352
3 Gor-20105	-33.2909	**4 Gor-20106**	-36.2589
5 Gor-20107	-31.4291	**6 Gor-20108**	-28.1277
7 Gor-18913	-28.9050	**8 Gor-20096**	-30.4950
9 Gor-20099	-34.4758	**10 Gor-20100**	-31.3164
11 Gor-20101	-33.0665	**12 Gor-20102**	-37.0972
13 Gor-20260	-29.8119	**14 Gor20261**	-24.4709

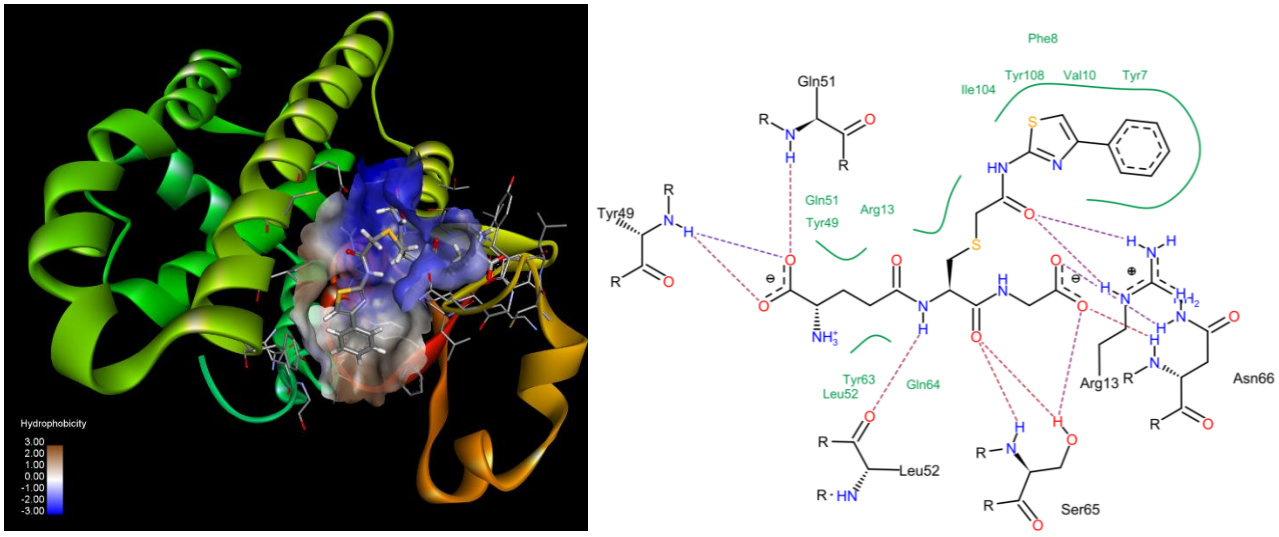

Fig. 6. The 3D and 2D interaction diagrams of the **glutathione-9** conjugate with GST (PDB code 11GS). Pink indicates hydrogen bonds, while green represents lipophilic interactions

Other chloroacetamides interact similarly; however, in the case of compound **3c**, the presence of a phenyl substituent increases the number of amino acids involved in lipophilic interactions.

The *in-silico* simulation data generally support a correlation between the FlexX docking scores of the conjugates and the observed cytotoxicity of the tested compounds. However, as previously noted, chloroacetamides may target other enzymes with thiol groups within their active or allosteric sites. Thus, the overall cytotoxic effect of the tested chloroacetamide derivatives may involve more complex mechanisms.

Conclusions. Our quantum chemical studies show that there is a certain dependence between electrophilicity and biological activity of the studied compounds only in MCA. It is not possible to compare the activity between MCA and DCA using electrophilicity. Since MCA and DCA, which have generally the same structure, react with cysteine at different rates. Mainly due to steric hindrance caused by the presence of two chlorine atoms, which have a significant size and a small negative charge, as well as the transition state in which the chlorine atom enters into conjugation with the rest of the conjugated system and reduces the intermediate compounds' activity. The MCA and DCA biological effects differ greatly, although docking studies show no significant difference in active site binding, also due to protein binding strength. Since DCA-adducts are capable of splitting off chlorine with further interaction with water, their non-selective biological activity will be much lower than MCA.

Conflict of interest. The authors declare that they have no conflict of interest concerning this study, including financial, personal, authorship, or any other, that could affect the study, and its results presented in this article.

Конфлікт інтересів. Автори заявляють, що у них немає конфлікту інтересів щодо цього дослідження, включаючи фінансовий, особистий, авторський чи будь-який інший, який міг би вплинути на дослідження та його результати, представлені в цій статті.

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Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

ДОКІНГ ТА КВАНТОВО-ХІМІЧНІ ДОСЛІДЖЕННЯ ПРОТИПУХЛИННИХ МЕХАНІЗМІВ ПОХІДНИХ МОНОХЛОРООЦТОВОЇ ТА ДИХЛОРООЦТОВОЇ КИСЛОТ

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Мета. Це дослідження спрямоване на проведення порівняльного квантово-хімічного аналізу похідних монохлорооцтової (МХК) та дихлорооцтової (ДХК) кислот, їх реакційної здатності у взаємодії з білковими мішенями та визначення молекулярних механізмів, що лежать в основі їх біологічної активності.

Матеріали та методи. Під час дослідження використовувалися квантово-хімічні розрахунки та молекулярний докінг для дослідження електронних властивостей і біологічних взаємодій синтезованих сполук. Усі структури були оптимізовані за допомогою DFT (B3LYP/6-311++G(d,p)) у Gaussian 09. Результати квантово-хімічних розрахунків були візуалізовані за допомогою GaussView 5.0.8. Молекулярний докінг передбачав моделювання кон'югатів глутатіон-хлороацетамід при фізіологічному pH, мінімізацію структур у програмному забезпеченні Avogadro та аналіз взаємодії з GST (PDB ID: 11GS) за допомогою алгоритму FlexX у LeadIT. Взаємодії прив'язування візуалізувалися за допомогою BIOVIA Discovery Studio з параметрами стикування, перевіреними за допомогою порівняння RMSD з експериментальними даними.

Результати і обговорення. Аналіз граничних молекулярних орбіталей та дескрипторів, пов'язаних з їх енергією, показав збільшення активності МХК зі збільшенням їх електрофільності. Хоча на окремих лініях результати, що випадали з такої залежності, можуть бути пов'язані з особливостями їхньої структури. Аналіз молекулярного електростатичного потенціалу показав наявність стеричних перешкод, зумовлених великими розмірами атомів хлору, які зменшують можливості для атаки МХК. Зміна енергії Гіббса реакції заміщення теж вказує на легший перебіг заміщення в МХК. Результати молекулярного докінгу показали можливість ефективного ковалентного зв'язування з глутатіон S-трансферазою як МХК, так і ДХК. Проте ще однією причиною зменшення активності є можливість гідролізу ДХК-аддукту з глутатіоном, оскільки досліджені сполуки не перешкоджають доступу води у разі зв'язування в активному центрі.

Висновки. Зменшення реакційної здатності ДХА порівняно з аналогами МХА пов'язане зі стеричними утрудненнями та впливом атома хлору в перехідному стані. Загалом нижча біологічна активність ДХА пов'язана як зі зменшенням їх реакційної здатності, так і з можливістю до гідролізу їхніх продуктів приєднання до залишків цистеїну. Отримані результати можуть стати основою для створення нових таргетних препаратів з підвищеною ефективністю та селективністю.

Ключові слова: дихлороацетат, дихлорооцтова кислота, дихлороацетамід, монохлороацетат, монохлорооцтова кислота, монохлороацетамід, квантово-хімічні розрахунки, молекулярний докінг, протипухлинна активність, пухлини.

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