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A DFT study of the chemical bonding properties, aromaticity indexes and molecular docking study of some phenylureas herbicides

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Abstract: Herbicides have imposed disastrous consequences towards the environment and human health. This practice urges scientists to investigate the physical, chemical and biological properties of these substances to avoid the use of the most harmful pesticides. For this purpose, the molecular structure and chemical bonding properties of phenylurea herbicides namely: fenuron (**L1**), monuron (**L2**), diuron (**L3**) and chlorotoluron (**L4**), were calculated in water, using density functional theory (DFT). The energy decomposition analysis (EDA) and the extended transition state natural orbitals for chemical valence (ETS-NOCV) reveal the dominant ionic character in carbon–nitrogen bond between dimethylurea fragment and benzene ring. Besides, the interaction of these herbicides with the human serum albumin (HSA) was undertaken by molecular modeling. The calculation of *HOMA* and *FLU* indexes indicate that the electronic delocalization is stronger in diuron than the other compounds, mainly caused by the two chloro substituents effects on benzene. Good correlations are found between the calculated parameters such as structural parameters, Mulliken atomic charge, topological and bonding properties and aromaticity indexes. The Vinardo molecular docking results suggest that the binding energies of the complexes formed between HSA target and investigated compounds have the following order: **L3** (–27.57 kJ/mol) < **L2** (–25.56 kJ/mol) < < **L4** (–24.94 kJ/mol) < **L1** (–24.10 kJ/mol), which confirmed that the Fenuron is the less harmful option between the studied herbicides especially against HSA.

Keywords: Mulliken atomic charge; chlorotoluron; HSA; electronic delocalization; dimethylurea.

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INTRODUCTION

Pesticides are substances or mixtures of substances mainly used in agriculture or public health protection programs to protect plants from pests, weeds, or diseases, and humans from vector-borne diseases, such as malaria, dengue fever and schistosomiasis.[1] The application of herbicides on agricultural soils is a well-established and effective practice to control weed growth. They represent about 50 % of the demand for agricultural chemicals; their prolonged use involves the risk of their retention in crops and soils.[2] In genetically engineered plants herbicides metabolism provide efficient and eco-friendly means for enhancement of detoxification of harmful substances.[3] Xenobiotics such as aromatic, pesticides and hydrocarbons are usually synthesized for industrial and agricultural purposes.[4]

Most pesticides are inhibitors of cholinesterases, enzymes, which are critical in neurobiology, toxicology and pharmacology.[5] Recently, phenylurea herbicides have received particular attention because of their high biotoxicity.[6]

Phenylurea herbicides are mostly *N*-dimethyl derivatives bearing various substituents on aromatic ring.[7] The dimethylurea fragment in these molecules is rigid because of the delocalized electrons.[8]

Electronic structure and energetics properties of phenylurea herbicides may become experimentally complicated. Theoretically, phenylurea herbicides have been evaluated in various media by several investigators.[8,10–13] However, to the best of our knowledge, Fenuron, Monuron, Diuron and Chlorotoluron chemical bonding properties and aromaticity indexes have not been analyzed yet.

Understanding the processes of interaction between HSA protein and diuron herbicides is critical for determining the potential risks of these compounds to humans. However, no study detailing the mechanism of interaction of these herbicides with HSA has been published except for diuron.[9] In the first part of our study, the main objective is to reveal the nature of the bond between dimethylurea fragment and the benzene ring of the four phenylurea herbicides using the energy decomposition analysis (EDA) and the extended transition state natural orbitals for chemical valence (ETS-NOCV). QTAIM analysis based on Barder's atoms in the molecule theory is carried out to confirm the presence of the hydrogen bonding between atoms. Also, we have computed the indices of aromaticity based on the measure of electronic delocalization in aromatic molecules. The second part is focused on the molecular docking of the same pesticide molecules with HSA.

EXPERIMENTAL

DFT calculations

All the geometries optimizations were performed using density functional theory (DFT) and quantum calculation program Gaussian09[14] employing B3LYP/6-31G++(d,p) basis set[15-17] in water. The bonding interactions have been analyzed by means of Morokuma-type energy

decomposition analysis (decomposition of the bonding energy into the Pauli exchange repulsion, total steric interaction and orbital interaction terms)[18] developed by Ziegler and Rauk for DFT methods; incorporated in ADF.[19] ETS-NOCV[20] analyses were performed using the ADF program package. EDA-NOCV calculations were carried out at the GGA-PBE/TZP level. QTAIM analysis was carried out by employing the DGrid/Basin program[21] and Chemcraft 1.4 program[22] was used for the representation of critical points. For these compounds, we compute the indices of aromaticity, the harmonic oscillator model of aromaticity (*HOMA*) index[23,24] and the aromatic fluctuation index (*FLU*).[25]

Molecular docking study

To study how the selected herbicides interact with HSA,[9] the related protein was taken from the Protein Data bank (http://www.rcsb.org/pdb): HSA complexed with myristic acid and the R-(+) enantiomer of warfarin (PDB ID: 1H9Z).[26] The crystal structure of HSA has three homologous α-helix domains: I (residues 1–195), II (residues 196–383), and III (residues 384–585). Within these domains, there is a further subdivision into A and B subdomains. Notably, domains IIA and IIIA stand out as they possess distinct molecular binding sites, often referred to as active binding site I and active binding site II, respectively. These active binding sites (Sudlow's sites) are characterized by hydrophobic cavities and play a pivotal role in HSA's ability to interact with various molecules, making it a crucial protein in the bloodstream for transporting drugs and other ligands throughout the body. [27]

The protein was freed from ligands (myristic acid and the R-(+) enantiomer of warfarin) by Discovery Studio 3.5 Visualizer.[28] Then polar hydrogen atoms and Kollman charges were added to the protein using the AutoDockTools4.[29] The molecular docking of each studied structure was performed by Vinardo[30] as implemented in GNINA 1.0 code[31] in the following Box Center (BC) and the box dimension (BD): (PDB: 1H9Z; BC: $X = 22.97$, $Y = 8.71$, $Z = 12.87$; BD: $X = 10$, $Y = 10$, $Z = 10$) this box is related to the active Sudlow's sites of interaction.[26] Vinardo was chosen as a scoring function because it has more power of ranking than AutoDock Vina scoring.[30,32] The GNINA code is based on smina[33] and AutoDock Vina.[34]

RESULTS AND DISCUSSION

DFT study

Four models of phenylurea herbicides, namely fenuron (**L1**), monuron (**L2**), diuron (**L3**) and chlorotoluron (**L4**), were optimized in water and in the ground state (Fig. 1).

Mulliken atomic charges analysis

Mulliken atomic charge results are crucial in quantum chemical calculations, as atomic charges affect molecular polarizability, dipole moment, and electronic structural features of molecular systems.[35]

The existence of positive charges on the carbon (C_3) atom of the ring in all systems and negative charges on nitrogen N(–H) atoms indicate the existence of a carbon–nitrogen ionic bond. In compound **L3**, it is observed that the positive charge of the carbon (C_3) atom (+0.168 e) of the ring is higher than in other compounds. We can also see that the charge of the nitrogen atom N(–H) of this compound is more negative (–0.630 e) compared to other compounds (see Table

I). This finding leads to the conclusion that the ionic bond is stronger in **L3** than in the other compounds, caused by substituents effects of the electron density of dichlorobenzene.

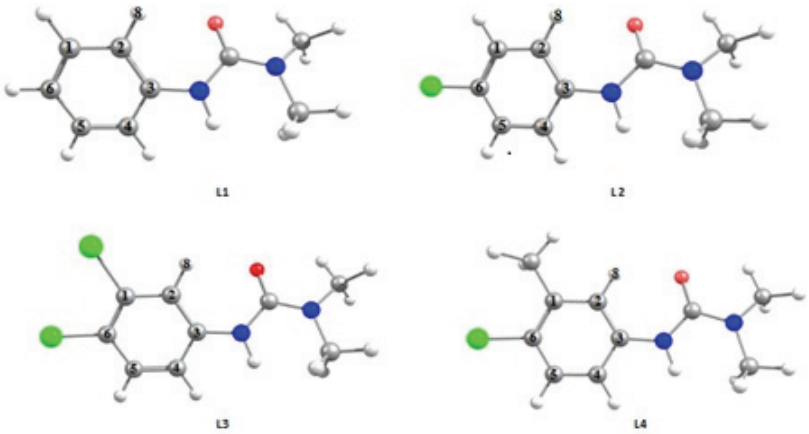


Fig. 1. Molecular structures of four phenylureas herbicides.

TABLE I. Mulliken atomic charges

Position	L1	L2	L3	L4
C_3(Ring)	0.161	0.158	0.168	0.155
C_2(Ring)	–0.102	–0.085	–0.080	–0.089
C(CO)	0.544	0.544	0.546	0.544
N(–H)	–0.637	–0.634	–0.630	–0.636
H_8	0.146	0.162	0.170	0.157
H(–N)	0.343	0.347	0.350	0.346
O	–0.426	–0.423	–0.421	–0.424
Cl	–	0.087	0.259	0.106

The intramolecular hydrogen bonds (IHB) are also analyzed, with positives charges on the hydrogens atoms, negatives charges on the nitrogen (N) atom, on the oxygen (O) atom and on the carbon (C_2) atom of ring in all systems studied. Thus, the third compound presents higher positive charges on the hydrogen atoms (0.170 and 0.350 e, respectively), higher negatives charges on the carbon (C_2) atom, on the nitrogen atom and on the oxygen atom (–0.080, –0.630 and –0.421 e, respectively). These results could facilitate the charge transfer over the formation of intramolecular hydrogens bonds (C-H...O and N-H…O).[35]

Energy decomposition analysis

The binding interactions were investigated using a Morokuma-type energy decomposition described by Ziegler and Rauk. The advantage of this approach is

to estimate the interaction energy between two fragments. The total bond energy E_{int} is the sum of three terms:

$$E_{int} = E_{orb} + E_{elec} + E_{Pauli} = E_{orb+Pauli} + E_{elec} \quad (1)$$

Where E_{elec} is the electrostatic stabilization energy between the two organic fragments. The Pauli repulsion E_{Pauli} comprises the destabilizing interactions between occupied orbitals, the orbital interaction E_{orb} is the interaction energy of the occupied orbitals on one fragment and unoccupied orbitals on another.[36] The binding decomposition energy EDA of carbon–nitrogen was obtained between the dimethylurea fragment and the benzene ring of the four phenylurea herbicides (see Fig. 2) using the ADF code with GGA-PBE/TZP and the ZORA approximation.

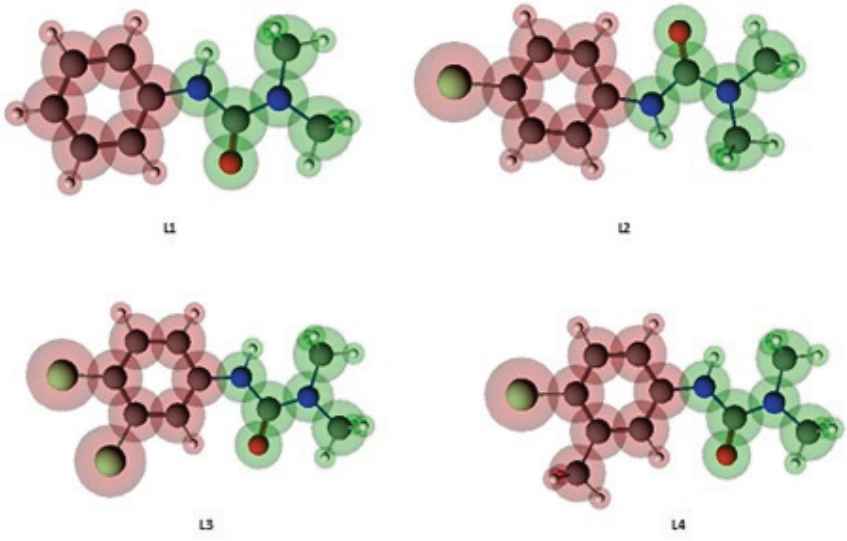


Fig. 2. Energy decomposition fragments related to the four molecules.

As shown in Table II, the total bond energy (E_{int}) between dimethylurea fragment and the benzene ring is in the range of ≈ –1180.01 to ≈ –1225.33 kJ mol^{-1}. The electrostatic interaction (E_{elec}) makes major contributions of compounds, while E_{pauli} + E_{orb} are the smallest component of the interaction energy. These results confirm the existence of a carbon–nitrogen ionic bond between the two fragments and it is relatively stronger in **L3**. Good correlations are found between the nature of this bond and Mulliken atomic charges (Table I).

ETS-NOCV analysis

We have employed extended transition state natural orbitals for chemical valence (ETS-NOCV) to study the nature of the bonds of compounds **L1**−**L4**.

TABLE II. Energies (in kJ mol^{-1}) of decomposition bonding in the four molecules

Parameter	**L1**	**L2**	**L3**	**L4**
$E_{\text{pauli+orb}}$	44.39	9.62	28.95	27.95
E_{Elec}	–1251.39	–1223.40	–1254.20	–1216.96
E_{Int}	–1180.01	–1213.78	–1223.40	–1188.67
% Covalent	0	0	0	0
% Ionic	100	100	100	100

The ETS-NOCV results are summarized in Table III. The major contribution to the bonding is through the electrostatic interaction between the two fragments. Consequently, the ETS-NOCV approach produces decomposition energies that increase in the same way as the Energy decomposition analysis of Ziegler–Rauk.

TABLE III. The results of ETS-NOCV analysis of **L1**–**L4** in kJ mol^{-1}

Energy	**L1**	**L2**	**L3**	**L4**
E_{Pauli}	3570.66	3614.56	3565.19	3582.34
E_{orb}	–3110.39	–3154.74	–3098.25	–3119.17
E_{elec}	–1012.11	–1019.22	–1020.90	–1012.11
E_{int}	–619.23	–623.42	–615.47	–612.96

QTAIM analysis

In recent years, the quantum theory of atoms in molecules (QTAIM) has been extensively used for study of the hydrogen bond (HB).[37,38] Popelier[39,40] proposed the following criteria for strength of HB:

For weak HB, $\nabla^2\rho(r) > 0$ and $H(r) > 0$, for HB of medium strength, $\nabla^2\rho(r) > 0$ and $H(r) < 0$, and for strong HB, $\nabla^2\rho(r) < 0$ and $H(r) < 0$.

According to this analysis, we found one critical point of the oxygen–hydrogen bond between hydrogen atom (H_8) of the ring and oxygen atom (O) of dimethylurea fragment in all systems analyzed (see Table IV and Fig. 3). This result confirms the existence of an intramolecular hydrogen bond (C–H···O). It can be observed also that the N–H···O hydrogen bond is not to be considered in this analysis. This is verified by the values of Mulliken atomic charges, when the carbon atoms (C_2) of a ring have higher negative charges than the nitrogen (N) atom (see Table I).

It can be seen also from Table IV that the maximum total electronic density $\rho(r)$ and its corresponding Laplacian $\nabla^2\rho(r)$ at bond critical point of intramolecular hydrogen bond are positives in all compounds, and the values of $-G/V$ are greater than unit of covalent nature ($\nabla^2\rho(r) < 0$) of IHB ($0.5 < -G/V < 1$).[41] These results show that the IHB (C–H···O) has noncovalent nature ($\nabla^2\rho(r) > 0$) and it is higher in **L3** than those of **L1**, **L2** and **L4**. The latter of which correlated to the electronegativity of the dichloro-atom substituted in **L3**.

The strength of the hydrogen bond is described by geometrical parameters (HB lengths and angle).[42]

TABLE IV. Structural parameters (HB lengths in Å and angle in °) and topological properties (a.u) of bond critical point (BCP) of intramolecular H-bonds of **L1**–**L4** at DFT levels

Parameter	**L1**	**L2**	**L3**	**L4**
$d_{C\text{-}H}$	1.079	1.079	1.078	1.078
$d_{H\cdots O}$	2.173	2.154	2.147	2.162
∠C–H···O	120.7	120.7	120.5	120.2
$\rho_{BCP}(r)$	0.014	0.016	0.018	0.011
$\nabla^2\rho_{BCP}(r)$	0.055	0.063	0.070	0.042
$H_{BCP}(r)$	0.002	0.002	0.002	0.0017
$-G/V_{BCP}$	1.197	1.163	1.141	1.234

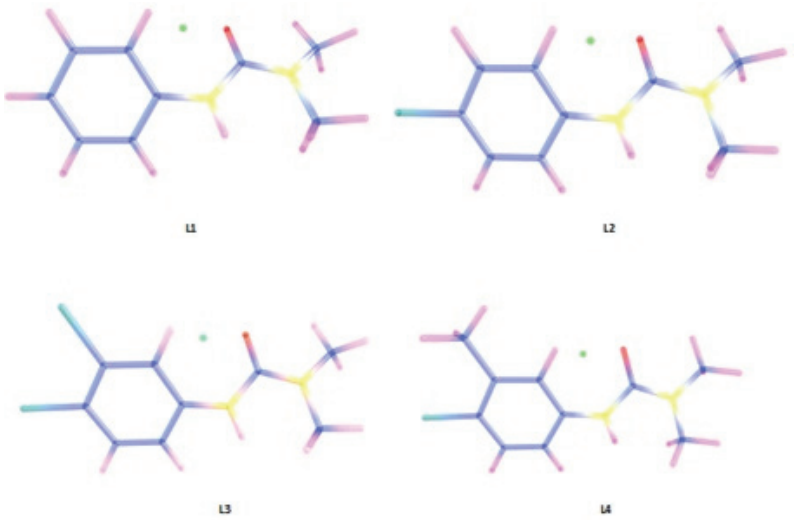


Fig. 3. Molecule graph of **L1**–**L4**.

The correlation between these parameters and ρ(r) are inverse to each other, *i.e.*, decrease in H···O distance corresponds to increase in the electron density. Thus, the short value of O···H distance in **L3** is (2.147 Å) shows strong HB and is observed for C–H···O interaction with high stability. For angles, if HB is stronger, thus the X–H···Y angle is closer to 180°, it was stated that for very strong HBs, the X–H···Y angle range is 175–180°, for strong it is 130–180°, while for weak it is 90–180°.[43] In our analysis, we have found a weak HB in four compounds with small C–H···O angle range (120.2–120.7°).

Measures of aromaticity indexes

In this part, we have analyzed the variation of aromaticity in the studied molecules. The concept of aromaticity is of central importance for the interpret-

ation of molecular structure, stability, reactivity and magnetic properties of many compounds, and remains still unquestionable.[44,45] The origin of the aromatic properties is the cyclic delocalized distribution of π-electrons, for this reason recently many new ways to quantify the aromaticity based on the measure of electron delocalization in aromatic molecules have been devised.[46] Among the most common structure-based indices of aromaticity are the harmonic oscillator model of aromaticity (*HOMA*)[23, 24] index and the electron *FLU*ctuation index (*FLU*).[25]

The values of the *HOMA* and *FLU* aromaticity indexes of the four molecules are shown in Table V. The values of the *HOMA* aromaticity index indicate that **L3** has the highest value. This result showed that the electronic delocalization is stronger in **L3**, compared to other compounds, caused by substituents effects of dichlorobenzene.

Aromaticity indexes analyses are in a good agreement with structural parameters, topological and bonding properties, which confirm that the electronic delocalization is strong in **L3**.

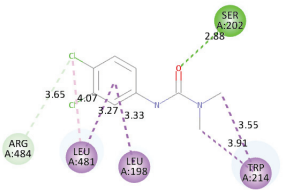
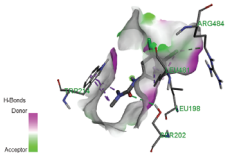
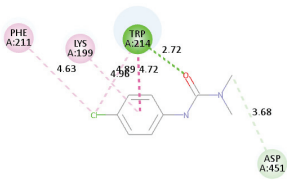
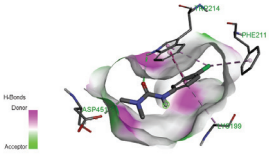
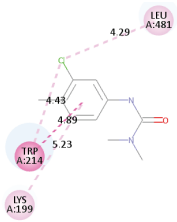
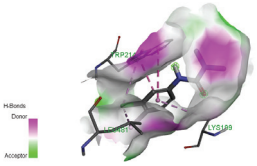
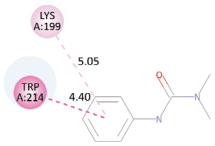
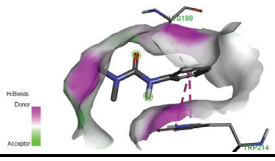
TABLE V. Aromaticity indices of the ring for the four molecules

Index	**L1**	**L2**	**L3**	**L4**
HOMA	0.956	0.950	0.957	0.946
FLU	1.007	1.013	1.011	1.013

Molecular docking simulation

HSA is the most abundant protein component in human plasma,[47] it is the primary transporter that in*FLU*ences *in vivo* molecules absorption, metabolism, excretion and particularly distribution.[48] The distribution of a pesticide *in vivo* could have dangerous toxic[9] consequences, hence this molecular docking study searches for the less harmful pesticide among fenuron (**L1**), monuron (**L2**), diuron (**L3**) and chlorotoluron (**L4**). The four studied molecular structures were docked to HSA (PDB ID:1H9Z) using GNINA 1.0 and the best Vinardo scores were obtained. The best poses associated to the lowest binding energies were selected as the binding mode (Table VI). The Vinardo binding energies of the generated complexes pursue the following trend HSA-**L3** (–27.57 kJ/mol) < < HSA-**L2** (–25.56 kJ/mol) < HSA-**L4** (–24.94 kJ/mol) < HSA-**L1** (–24.10 kJ/mol). These results suggested that the studied pesticides could interact with HSA using hydrogen, hydrophobic and van der Waals interactions. Diuron interacts by hydrogen bonding with the residue Ser-202 (2.88 Å).[49] Monuron establishes one hydrogen bond with the residue Trp-214 (2.72 Å).[47,49,50] Finally, chlorotoluron and fenuron form no hydrogen bond. These findings suggest that the use of fenuron is the less harmful option between the studied pesticides especially against HSA. Diuron is the least stable and the most harmful among the studied compounds.

TABLE VI. Molecular Docking Results: Vinardo Scores, 2D interaction residues and the hydrogen bonding surface

Target/top compound (Vinardo binding energy)	2D interaction residues	Hydrogen bonding surface
1H9Z/L3 (–27.57 kJ mol^{-1})		
1H9Z/L2 (–25.56 kJ mol^{-1})		
1H9Z/L4 (–24.94 kJ mol^{-1})		
1H9Z/L1 (–24.10 kJ mol^{-1})		

CONCLUSION

The DFT study of the energy decomposition analysis (EDA) and the extended transition state natural orbitals for chemical valence (ETS-NOCV) reveal a strong ionic bonding of carbon–nitrogen in all compounds.

The quantum theory of atoms in molecules confirms the existence of intramolecular hydrogen bonds (C–H···O) in all compounds. This result is verified by the values of Mulliken atomic charges and of the geometrical parameters (HB lengths and angle, respectively), ($d_{C–H}$ between 1.078 and 1.079 Å, $d_{H···O}$ between 2,147 and 2,173 Å and ∠C-H···O between 120.2 and 120.7°).

The dichlorobenzene ligand in **L3** increases electron delocalization, this is shown by the *HOMA* and *FLU* values of this compound (*HOMA* = 0.957 and *FLU* = 1.011).

The molecular docking results suggest that the compound **L3** is the most stable and the most harmful compound among the studied pesticides. In contrast,

L1 is the least harmful compound. Thus, the Vinardo binding energies follow the trend: **L3** (–27.57 kJ/mol) < **L2** (–25.56 kJ/mol) < **L4** (–24.94 kJ/mol) < **L1** (–24.10 kJ/mol). The use of fenuron is the less harmful option between the studied pesticides especially against HSA.

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И З В О Д

DFT СТУДИЈА ОСОБИНА ХЕМИЈСКОГ ВЕЗИВАЊА, ИНДЕКСА АРОМАТИЧНОСТИ И СТУДИЈА МОЛЕКУЛСКОГ ДОКОВАЊА НЕКИХ ХЕРБИЦИДА НА БАЗИ ФЕНИЛУРЕА

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Хербициди узрокују катастрофалне последице за животну околину и здравље људи. То подстиче научнике да истраже физичке, хемијске и биолошке особине ових супстанци, како би се избегла употреба најштетнијих пестицида. У ту сврху су молекулске структуре и особине хемијског везивања фенилуреанских хербицида, наиме фенурона (**Л1**), монурона (**Л2**), диурона (**Л3**) и хлоротолурона (**Л4**), израчунате за водени раствор, користећи теорију функционала густине (DFT). Анализа разлагања енергије (EDA) и природних орбитала за проширено прелазно стање за хемијске валенце (ETS-NOCV) показују доминантно јонски карактер у вези угљеник–азот између диметилуреинског фрагмента и бензеновог прстена. Поред тога, молекулским моделовањем је испитана интеракција ових хербицида са албумином хуманог серума (HSA). Израчунавање *HOMA* и *FLU* индекса указује да је делокализација електрона јача у диурону него у другим једињењима, што је углавном узроковано ефектом два хлоро супституента на бензену. Нађена је добра корелација међу израчунатим параметрима као што су структурни параметри, Маликенова наелектрисања атома, тополошке и везивне особине и индекси ароматичности. Винардови резултати молекулског доковања сугеришу да енергије везивања у комплексима између HSA мете и испитиваних једињења има следећи редослед: **Л3** (–27,57 kJ/mol) < **Л2** (–25,56 kJ/mol) < **Л4** (–24,94 kJ/mol) < **Л1** (–24,10 kJ/mol), што потврђује да је фенурон мање штетна опција међу испитиваним хербицидима, посебно према HSA.

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