Sakarya University Journal of Science

ISSN : 2147-835X
Publisher : Sakarya University

Vol. 28, No. 2, 314-325, 2024
DOI: https://doi.org/10.16984/saufenbilder.1333717

Research Article

DFT Calculations, Molecular Docking, and Pharmacological Properties Investigation for 5-Benzoxazolecarboxylic Acid as a Target Anti-Cancer Agent

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ARTICLE INFO

Keywords:
5-benzoxazolecarboxylic Acid
DFT
Toxicity
ELF
Molecular Docking

Article History:
Received: 27.07.2023
Accepted: 28.12.2023
Online Available: 22.04.2024

ABSTRACT

In this study, the electronic properties of the 5-Benzoxazolecarboxylic acid molecule, a benzoxazole derivative, were calculated at the DFT/B3LYP/6-311++G(d,p) level of theory. Electronic properties and chemical reactivity of the optimized structure, such as Frontier molecular orbital (FMO), global and chemical reactivity descriptors, molecular electrostatic potential (MEP), and charge analyses (APT, Hirshfeld, and NBO), were investigated. Also, electronic properties are supported by electron localization function (ELF) and localized orbital locator (LOL) analyses. Toxicity effects such as mutagenic, tumorigenic, irritant, reproductive effect, and physicochemical properties such as druglikeness and drugscore were investigated. Molecular docking studies were conducted with the vascular endothelial growth factor receptor VEGFR-2 and the PARP-2 inhibitor, which is involved in many critical cellular processes, including DNA single-stranded fracture repair and cell death control, and its effectiveness in cancer treatment was investigated.

1. Introduction

Benzoxazole is an organic heterocyclic molecule formed as a result of the fusion of the oxazole ring along the 4 and 5 positions of the benzene ring. Benzoxazole and its derivatives show a wide range of activities, such as anticancer (multidrug resistance cancer cell activities) [1, 2], antimicrobial [3], antifugal [4], antiviral [5], antiallergic [6], anti-inflammatory [7], anti-Alzheimer [8], and anti-HIV-1 [9]. Also, the benzoxaxazole ring is structurally similar to the adenine and guanine bases in the structure of nucleic acids. For all these reasons, benzoxazole is seen as one of the most important core structures in drug design [10].

With the changing lifestyle, a rapid growth in the diagnosis of cancer has erupted, and cancer affects the lives of millions of people all over the world [11, 12]. The most common types of cancer are lung, mouth, and breast cancers [13]. Chemotherapy is used in almost all stages of cancer treatment. However, the increasing incidence of drug resistance against chemotherapeutic agents causes serious problems in treatments and the death of cancer cells and healthy surrounding tissues [14, 15].

Therefore, there is a great need to research new cancer drugs [16]. In the literature, there are many studies investigating the anticancer activities of benzoxaxazole derivatives. Some examples of these studies could be the following: In one study, benzoxazole-1,3,4 oxadiazole derivatives were synthesized and their anticancer activities were investigated against four human cancer cell lines, including A549 (lung cancer), MCF-7 (breast cancer), A-375 (melanoma cancer), and HT-29 (colon cancer). It has been reported that some of these synthesized compounds give better results against the HT-29 cancer cell line than the standard drug (CA-4) [17]. In another study, benzoxazole fused with

Cite as: C. Küçük (2024). DFT Calculations, Molecular Docking, and Pharmacological Properties Investigation for 5-Benzoxazolecarboxylic Acid as a Target Anti-Cancer Agent, *Sakarya University Journal of Science,* 28(2), 314-325. https://doi.org/10.16984/saufenbilder.1333717

benzofuran and 1,2,4-oxadiazole were synthesized. The cytotoxicity activities of these compounds against human breast cancer (MCF-7), lung (A549), melanoma (A375), and colon (HT-29) cell lines were evaluated. According to the results obtained, some of the synthesized compounds showed stronger activity than the control group [18].

Molecular docking is a computer-aided drug design method that simulates molecular interaction and satisfies the binding mode and affinity between ligands and receptors. Moreover, this method greatly increases the productivity of pharmacological researchers and reduces research costs [19]. There are also many molecular docking studies for cancer research with benzoxazole derivatives in the literature. Carcinogenesis is accompanied by the overactivation of receptor tyrosine kinase (RTK) signaling pathways.

Therefore, it is very important to identify inhibitors that will inhibit these receptors in cancer treatment. In the study on the Synthesis, Synthesis, Anti-Breast Cancer Activity, and Molecular Modeling of Some Benzothiazole and Benzoxazole Derivatives, molecular docking studies were performed on the RTK receptor, and it was reported that docking with appropriate affinities and modes was determined [20]. In another study, benzoxazole and benzothiazole derivative compounds were synthesized as potential vascular endothelial growth factor receptor-2 (VEGF-2) inhibitors and supported by molecular docking studies for all synthesized compounds to evaluate their affinity towards the active site of VEGFR-2 [21].

In the first stage of this study, conformation analysis was performed using the Spartan software package. And then optimization calculations were carried out for the conformer structure with the highest Boltzman distribution and the lowest value using the Gaussian 09 program. In the second step, DFT calculations were made to determine the electronic properties of the title molecule. The chemical reactivity of the 5-Benzoxazolecarboxylic acid molecule was determined according to the energy of the HOMO-LUMO orbitals. In addition, a molecular electrostatic potential surface (MEP) map was designed to identify negative (electrophilic) and positive (nucleophilic) regions of the title molecule that could react with biological targets and was supported by APT, Hirshfeld, and NBO charge analyses. Finally, electron localization function (ELF) and localized orbital locator (LOL) analysis were performed to determine the reactive sites. In the third and final stage, molecular docking studies on a cancer disease-related protein were performed, along with toxicological and physicochemical property analyses.

2. Computational Details

The conformer structure analysis was performed using MMFF theory by Spartan software [22]. Using the Gaussian 09 and GaussView 5.0 package programs, geometric optimization and electronic properties were calculated at the DFT/B3LYP/6-311++G(d,p) level of theory [23-25]. The Multiwfn program was used for ELF and LOL analyses [26]. Molecular docking studies were performed in the Autodock Vina software. Binding sites of ligand and protein were visualized in Discover Studio software. [27]. Toxicological and physicochemical properties were determined with the Ossiris Property Explorer program [28].

3. Results and Discussion

3.1. Conformational analysis

Before determining the optimized geometric structure of the molecule at the lowest energy (in the most stable state), conformation analysis was performed for the title molecule. Therefore, in the first part of this study, using the Spartan software program [22], two conformational structures (see Figure 1) were determined by the MMMF theory (molecular mechanic) for the 5-Benzoxazolecarboxylic acid molecule according to the Boltzman distribution [29]. Optimization calculations were performed on the Conformer I structure, which has the lowest energy and the highest Boltzmann distribution from these two conformer structures. The optimized geometric structure for 5-Benzoxazolecarboxylic acid molecule, which was calculated at the DFT/B3LYP/ 6-311++G(d,p) level of theory, is presented in Figure 2.

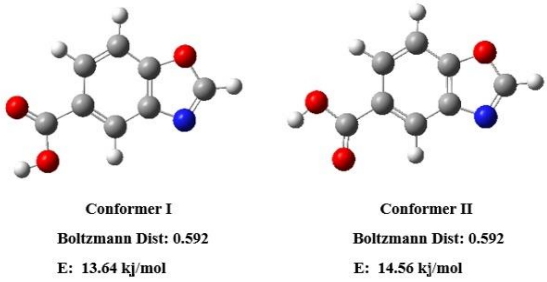


Figure 1. Conformer structures of the 5-Benzoxazolecarboxylic acid molecule obtained in the Spartan 08 package program

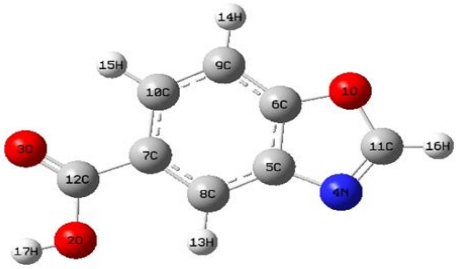


Figure 2. Optimized geometric structure of the 5-Benzoxazolecarboxylic acid molecule

3.2. Frontier molecular orbital analysis

The highest occupied molecular orbital HOMO and the lowest occupied molecular orbital LUMO are related to the ionization potential and electron affinity, and the energy value between these orbitals determines the stability of the molecule [30, 31]. The stability of a molecule is related to its hardness and softness. The lower the energy difference between the HOMO-LUMO orbitals, the more reactive the molecule is and the less energy it needs for excitation.

Therefore, soft molecules tend to react more chemically than hard ones [32]. The energy values of the HOMO-LUMO orbital energies and other quantum chemical properties [33] are presented in Table 1. The energy values of the HOMO and LUMO orbitals of the title molecule are -7.29 and -1.84 eV, respectively. The energy band gap between these two orbitals is 5.44 eV. Chemical hardness and chemical softness energy values were calculated as 2.72 and 0.37 eV.

According to the energy band gap, chemical hardness, and chemical softness values, the 5-Benzoxazolecarboxylic acid molecule is a hard molecule with a low tendency to react chemically. Also, the low chemical potential and high electrophilicity index values calculated for the title molecule are similar to those of bioactive molecules [23, 34, 35].

The electron distributions of the HOMO and LUMO orbitals are presented in Figure 3. When the image of HOMO is examined, electrons are distributed over the entire molecule except for C_{12}, O_2, and H_{17} atoms belonging to the carboxylic group, while for LUMO they are distributed over the entire molecule.

3.3. Molecular electrostatic potential map analysis

The molecular electrostatic potential surface map is used as one of the most important tools to describe the molecular charge distribution on the molecule according to a color scale and to make predictions about the chemical and biochemical reactivity of the molecule. The color scale in this map is given in the following order: red< orange< yellow< green< blue. The red color represents the most negative regions, while the blue color represents the most positive regions. The yellow-colored regions are slightly electron-rich regions [35-39].

The MEP map of the 5-Benzoxazolecarboxylic acid molecule was created for the DFT/B3LYP/6-311++G(d,p) level of theory and is presented in Figure 4. The electronic surface map of the title molecule was found in the region of between -5.816e2 (red) and 5.816e2 (blue). According to the MEP map, the most negative regions of the title molecule (electrophilic) were found as the N_4 atom and the O_3 atom. As a result, we can say that the probability of this molecule entering chemical reactions with these atoms is quite high.

Table 1. The energy values of the global reactvity parameters of the 5-Benzoxazolecarboxylic acid molecule

Parameters	Energy Values (eV)
E_{HOMO}	-7.29
E_{LUMO}	-1.84
Energy band gap ($\Delta E = E_{LUMO} - E_{HOMO}$)	5.44
Iozination potential ($I = -E_{HOMO}$)	7.29
Electron affinity ($A = -E_{LUMO}$)	1.84
Chemical hardness ($\eta = (-E_{HOMO} + E_{LUMO})/2$)	2.72
Chemical softness ($\sigma = 1/2\eta$)	0.37
Electronegativity ($\chi = -\mu_c$)	4.57
Chemical potential ($\mu_c = (E_{HOMO} + E_{LUMO})/2$)	-4.57
Global electrophilicity ($\omega = (\mu_c^{\,2})/2\eta$)	3.83

3.4. ELF and LOL analyses

ELF and LOL maps are important tools to help identify molecular space regions with a high probability of finding an electron pair and to perform covalent bond analysis, and the maps created in both methods depend on the kinetic energy density of the electrons. The ELF map scale is in the range of 0.0–1.0, and delocalized electrons are found in the range below 0.5, whereas bound and unbound localized electrons are over the range of 0.5 [26, 40]. ELF and LOL maps for the 5-Benzoxazolecarboxylic acid molecule were designed using the Multiwfn software program and are presented in Figure 5. According to Figure 5, the red color on the H atoms is indicative of bound and unbound localized electrons. In addition, localized and delocalized electrons are concentrated in the region where the C, N, and O atoms in the benzene and oxazole rings bond with each other. The blue circular regions around the C, N, and O atoms in the structure of the 5-Benzoxazolecarboxylic acid molecule are indicative of a delocalized electron density. On the other hand, LOL has large values in regions where the electron density is dominated by electron localization, and the LOL map presented in Figure 5 gives similar results to the ELF maps.

3.5. Charge analyses

Charge analysis was also performed to obtain information about the binding potential and reactivity of the title molecule [41]. Atomic polar tensor (APT), Hirshfeld, and natural bond orbital (NBO) charge values were calculated using the B3LYP functional with 6-311++G(d,p) basis set in the DFT method and are presented in Table 2. In three different charge analyses, the atom with the most negative (electrophilic) value of the 5-Benzoxazolecarboxylic acid molecule was found to be the O_3 atom. O_2, O_1, and N_4 atoms were found in other highly negative atoms, respectively. Also, the C_7, C_9, and C_{10} atoms of the benzene ring have a negative value. Apart from the atoms discussed above, other atoms in the molecule were found positive in all three charge analysis methods.

Table 2. Atomic charge values of the 5-Benzoxazolecarboxylic acid molecule

Atoms	APT	Hirshfeld	NBO
O_1	-0.594	-0.104	-0.471
O_2	-0.763	-0.174	-0.689
O_3	-0.847	-0.286	-0.601
N_4	-0.414	-0.187	-0.463
C_5	0.077	0.022	0.070
C_6	0.325	0.067	0.295
C_7	-0.292	-0.025	-0.173
C_8	0.087	-0.022	-0.145
C_9	-0.064	-0.038	-0.236
C_{10}	-0.021	-0.022	-0.146
C_{11}	0.433	0.131	0.390
C_{12}	1.412	0.209	0.790
H_{13}	0.097	0.058	0.240
H_{14}	0.066	0.059	0.226
H_{15}	0.091	0.053	0.234
H_{16}	0.098	0.078	0.192
H_{17}	0.308	0.181	0.486

These results are in good agreement when compared with the MEP, ELF, and LOL maps. We determined that the electrophilic (i.e., the most negative) regions are distributed over the O_3 atom and N_4 atom in the MEP map, and there is a delocalized electron cloud around these atoms in the ELF and LOL maps.

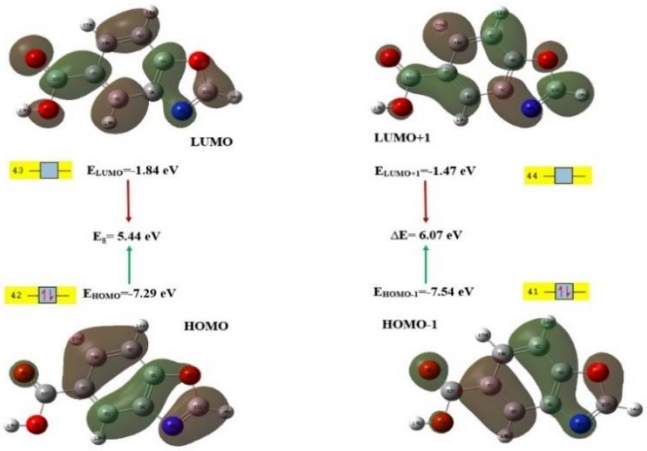


Figure 3. Frontier molecular orbital distribution of the 5-Benzoxazolecarboxylic acid molecule

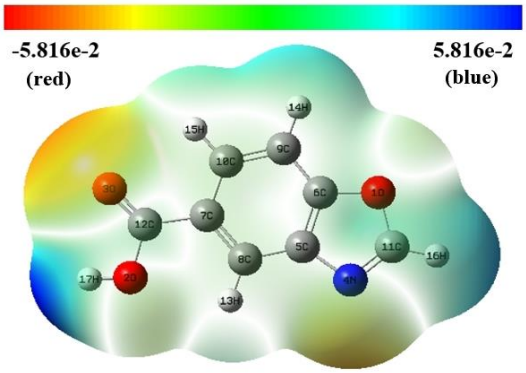
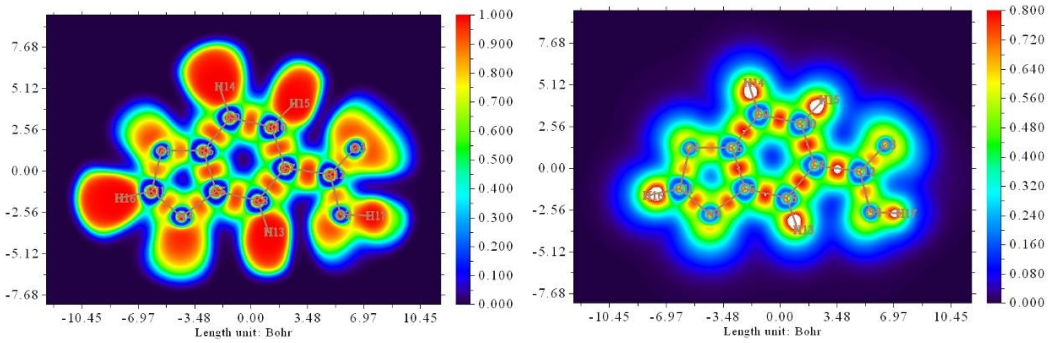


Figure 4. Molecular electrostatic potential surface map of the 5-Benzoxazolecarboxylic acid molecule



(a) (b)

Figure 5. Color-filled ELF (a) and LOL (b) map of the 5-Benzoxazolecarboxylic acid molecule

3.6. Pharmacological property analysis

The toxic risk assessment and psychochemical properties of the title molecule were evaluated using the Ossiris Property Explorer program and the results are listed in Table 3. After a drug is taken orally, it first passes through the intestinal lining and enters the aqueous blood. It then passes through the lipid-based cell membrane to reach the cell. Therefore, the water solubility of a molecule that is thought to be used as a potential drug is very important. The cLogP value is used to estimate the water solubility, and if this value is below 5.00, it is interpreted that the molecule is well soluble in water. In addition, the solubility of the molecule in water significantly affects its absorption and distribution properties. Good solubility results in good absorption, and the aim is to avoid the use of poorly soluble compounds [42].

The logS value is another measure of water solubility, and the larger this value, the better the solubility. For more than 80% of drugs on the

market, the logS value is greater than -4 [43]. The TPSA value is related to the passage of the structure through the cell membrane and should be less than 140A2. Molecules with a TPSA value higher than this value make passing through the cell membrane more difficult [44, 45]. In addition, if the molecular weight of a molecule is above 450, intestinal absorption begins to be restricted, and absorption from the cell membrane becomes difficult [46]. If the drug score of a molecule is close to 1, it is concluded that that molecule can be used as a drug, and if it is close to 0, its use as a drug carries a great risk [47]. When the results obtained are evaluated, the 5-Benzoxazolecarboxylic acid molecule does not carry a toxic risk. In addition, the values obtained for the psychochemical properties are within the limits of the above-mentioned values, and this molecule has the potential to be used as a drug.

3.7. Molecular docking

In this study, molecular docking studies were carried out for the vascular endothelial growth factor receptor VEGFR-2 (PDB ID: 4ASD) [48], which plays a key role in tumor angiogenesis and the formation of new blood vessel networks necessary to provide nutrition and oxygen for tumor growth, and PARP-2 inhibitor (PDB ID: 4TVJ) [48] involved in many critical cellular processes, including DNA single-strand break repair and cell death control, using the Autodock Vina program [49].

Table 3. Toxicological and physicochemical properties of the 5-Benzoxazolecarboxylic acid molecule

Toxicity risks	Mutagenic Tumorigenic Irritant Reproductive effect	- - - -
Physicochemical properties	ClogP Solubility MW TPSA Druglikeness Drugscore	1.16 -2.47 163.13 63.33 0.48 0.76

The resulting binding modes and affinity values are listed in Tables 4-5, while the molecular docking between ligand and protein is presented in Figures 6-7. The energy value of the minimum binding affinity of the 5-Benzoxazolecarboxylic acid molecule with 4ASD and 4TJV proteins was -6.60 kcal/mol and 7.2 kcal/mol for mode 1, which contains a pose with optimal binding on the basis of RMSD~0.00 Å. As a result of the ligand interaction of the 4ASD protein, it was determined that the O_2 atom of the title molecule is located at a distance of 2.31 Å from the H atom of CYS919. Also, the O atom of GLU917 was found at a distance of 2.09 Å from the H_{17} atom of the ligand. In the ligand interaction of the 4TVJ protein, it was found that the O_3 atom of the title molecule is located at a distance of 2.11 Å from the H atom of GLY429. Also, the O atoms of SER 470 and TRP427 were found at a distance of 2.06 and 2.84 Å from the H_{17} atom of the ligand. The general assumption in the literature is that for good docking, the distance between the ligand and the receptor should be close to 2.00 Å [50]. The results obtained from molecular docking studies provide information that the 5-Benzoxazolecarboxylic acid molecule can exhibit biological activity for the treatment of cancer disease, and this molecule can be used in the synthesis of new drugs.

Table 4. The binding afnity values of different poses of 4ASD protein interaction with the 5-Benzoxazolecarboxylic acid molecule

Mode	Affinity (kcal/mol)	Distance from best mode	
		RMSD l.b.	RMSD u.b.
1	-6.6	0.000	0.000
2	-6.6	1.800	4.357
3	-6.4	2.171	4.917
4	-6.2	1.483	2.349
5	-5.9	8.692	10.233
6	-5.9	12.546	14.792
7	-5.7	1.854	4.750
8	-5.7	18.170	19.529
9	-5.6	13.337	15.238

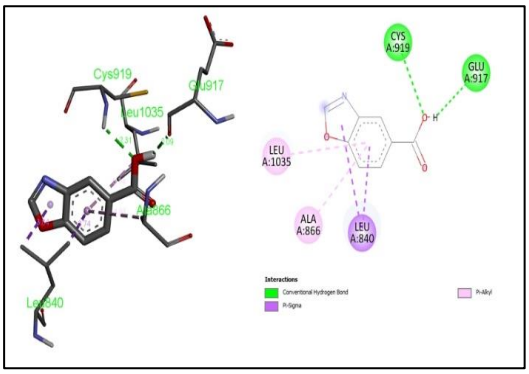


Figure 6. 3D bonding and 2D interaction between the 5-Benzoxazolecarboxylic acid molecule and 4ASD protein

Table 5. The binding afnity values of different poses of 4TVJ protein interaction with the 5-Benzoxazolecarboxylic acid molecule

Mode	Affinity (kcal/mol)	Distance from best mode	
		RMSD l.b.	RMSD u.b.
1	-7.2	0.000	0.000
2	-7.0	1.194	2.072
3	-6.9	1.754	4.368
4	-6.7	2.181	3.136
5	-6.2	11.762	13.248
6	-6.1	9.623	10.682
7	-6.1	8.217	9.200
8	-5.9	2.781	3.973
9	-5.9	10.928	12.046

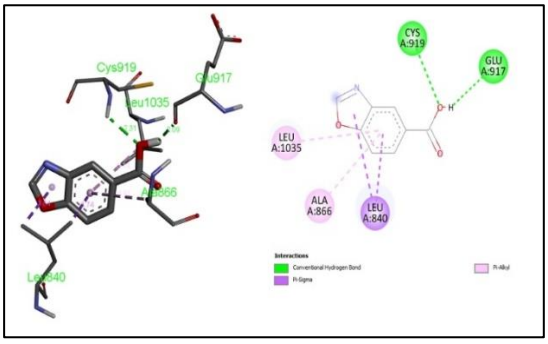


Figure 7. 3D bonding and 2D interaction between the 5-Benzoxazolecarboxylic acid molecule and 4TVJ protein

4. Conclusion

In this study, conformation analysis, electronic, toxicity, and pharmacological properties of the 5-Benzoxazolecarboxylic acid molecule were investigated. Two stable conformer structures were obtained for the title molecule. The conformer structure with the lowest energy and the highest Boltzman distribution was selected, and all other calculations were performed for this structure. The energy values of the HOMO-LUMO orbitals were calculated to determine and interpret various global reactivity parameters.

The energy gap, global hardness, and global softness values of the 5-Benzoxazolecarboxylic acid molecule between the HOMO and LUMO orbitals are 5.44, 2.77, and 0.37 eV, respectively. The MEP map shows that the O_3 atom of the carboxyl group is dark red, and the N_4 atom in the oxazole ring has the most negative value. In addition, ELF and LOL maps were also used to determine the density of localized and delocalized electrons and gave results consistent with the MEP map. APT, Hirshfeld, and NBO charge analyses of the 5-benzoxazolecarboxylic acid molecule were performed. O_3, O_2, O_1, and N_4 atoms were found to have the most negative values in the calculations for the three charge analyses.

It was determined that the 5-Benzoxazolecarboxylic acid molecule, whose toxicity and pharmacological properties were investigated, did not have any mutagenic, tumorigenic, irritant, or reproductive effects and had a very good drug score. Molecular docking studies were performed with the vascular endothelial growth factor receptor VEGFR-2 and the PARP-2 inhibitor, which is involved in many critical cellular processes, including DNA single-stranded fracture repair and cell death control. The conventional hydrogen bonding of the title molecule with these protein structures, which have important roles in cancer, gives the idea that this molecule can be evaluated as an anti-cancer drug.

Article Information Form

Acknowledgments
The authors would like to thank Prof. Dr. Şenay YURDAKUL for her contributions.

Funding
The author (s) has no received any financial support for the research, authorship or publication of this study.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the authors.

The Declaration of Ethics Committee Approval

This study does not require ethics committee permission or any special permission.

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