Journal of Molecular Structure 1199 (2020) 126981

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

A multi-spectroscopic, computational and molecular modeling studies on anti-apoptotic proteins with Boc-D-Lys-OH

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ARTICLE INFO

Article history:
Received 21 March 2019
Received in revised form
22 August 2019
Accepted 22 August 2019
Available online 24 August 2019

Keywords:
Boc-D-Lys-OH (BDLO)
DFT
FT−IR
Molecular docking
Anti-apoptotic

ABSTRACT

Synthesized molecules have attracted much interest due their biological activity. Anti-apoptotic proteins such as BCL-2, BCL-w, MCL-1, AKT1 and BRAF have potential roles in apoptosis mechanism. Suppression of these anti-apoptotic proteins may lead to apoptosis of cancer cells. In this study; spectroscopic, electronic and biological properties of Boc-D-Lys-OH (BDLO) molecule have been examined using quantum chemical calculations. First of all, the molecule was optimized and geometric structure parameters and vibrational wavenumbers were calculated by DFT/B3LYP methods 6-311G++(d,p) basis set. The calculated wavenumbers were then compared with the experimental values of the FT-IR and FT-Raman spectra. Finally, the molecular docking was determined for anti apoptotic proteins with BDLO molecule. The results showed Boc-D-Lys-OH molecule had more binding affinity with AKT1 and concluded this molecule can be used as a potential inhibitor of anti apoptotic proteins and a novel chemotherapy molecule. The electronic properties such as frontier molecular orbital and molecular electrostatic potential (MEP) obtained from these methods at different solvent conditions and gas phase were also studied.

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1. Introduction

Amino acids and their N-protected derivatives, such as Boc and Fmoc amino acids have been used to synthesize various bioactive substances from other molecules and have vital roles in the field of technology and health. It is well known that the chemotherapeutic agents are commonly used in the treatment of cancer. However, the side effects of these drugs on normal cells are a major concern [1,2]. In the study by Saxena et al. [3], Boc-lysinated-betulonic acid molecule was synthesized and used for prostate cancer treatment. Boc-D-Lys-OH and some protected derivatives have been used in the synthesis of cyclic pentapeptide and salts which include LH-RH receptor antigonists. These compounds are effective in preventing and ameliorating prostate, breast and uterine cancer [4]. Also, Boc and its derivatives have been used as preservatives in novel compounds and their salts synthesized by Marlowe et al. to inhibitors of blood coagulation [5,6]. In addition, when the antibacterial properties of some compounds containing D-Lys were examined, it was observed that they retained but did not improve antibacterial activity [7].

As a result of treatment with chemotherapeutic drugs, apoptosis occurs in cells. Cancer cells can also undergo apoptosis by inhibition of anti-apoptotic genes. Apoptosis is generally an action that cells self-destruct, organized by genes, programmed, and preserving homeostasis in the organism. Pro-apoptotic genes have an apoptosis-inducing effect whereas anti-apoptotic genes have apoptosis-suppressing effect. Overexpression of anti-apoptotic members suppresses apoptosis. Bcl-2, an anti-apoptotic regulator, inhibits the cytosolic transition of cytochrome C [8]. Cancer is a disease that manifests itself as an increase in cell proliferation and a decrease in apoptosis [9]. Molecular docking calculations using BDLO molecule showed it as an inhibitor in human anti-apoptotic proteins according to their scoring function.

In this study, BDLO molecule has been studied for the first time since it has an important place in the studies conducted in the field of cancer. Firstly, BDLO molecule was studied and presented by FT-

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https://doi.org/10.1016/j.molstruc.2019.126981
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IR and FT-Raman spectra. Structural optimization by DFT/B3LYP method of BDLO was also performed. Calculated vibrational wavenumber values were compared with experimental results. In order to understand the electronic structure and clarify charge transfer within BDLO molecule; HOMO, LUMO and MEP analysis were also examined. After that, molecular docking was determined for anti-apoptotic proteins with BDLO molecule. As a part of our study we have demonstrated the molecular binding potential of BDLO molecule to human anti-apoptotic proteins.

2. Experimental details

1 g of Boc-D-Lys-OH (BDLO) was purchased from Sigma-Aldrich, USA. The infrared spectrum was measured from solid KBr disc/pellets. This spectrum was recorded in the range of 4000–400 cm^{-1} using a Bruker IFS 66/S spectrometer at room temperature, with a scanning speed of 10 cm^{-1} min^{-1} and the spectral resolution of 4.0 cm^{-1}. Thermo Scientific Nicolet 6700 FT-IR/NXR FT-Raman Modul Instrument using 1064 nm excitation from an Nd:YAG laser was used to measure the FT-Raman spectrum in the range of 4000–0 cm^{-1} at room temperature.

3. Computational details

The molecular geometry and vibrational wavenumbers of BDLO were computed using DFT/B3LYP method via 6-311G++(d,p) basis set. Theoretical wavenumbers used were scaled as 0.958 greater and 0.983 smaller than 1700 cm^{-1}, respectively [10,11]. After the optimization of the molecule, the electronic properties such as HOMO-LUMO and MEP analysis were calculated by TD-DFT method [12]. The calculations were carried out using GAUSSIAN09 [13] program. Molecular docking calculations were performed via Lamarckian Generic Algorithm [14] in Autodock Vina [15]. The water molecules and cofactors were removed from the protein to clearly see the ligand-receptor interaction. Binding affinities were defined in Autodock Vina. Furthermore, the structure of anti-apoptotic proteins were freely available from the RCSB Protein Data Bank as a 3D theoretical model (BCL-2 PDB ID: 4MAN, BCL-W PDB ID: 2Y6W, MCl-1 PDB ID: 5FDO; AKT PDB ID: 4gv1, BRAF PDB ID: 5vam). Doxorubicin, anthracycline antibiotic, has effectively antineoplastic activity, was used as control ligand. The 2D structure of molecule was converted to energy minimized 3D-structure and used for in silico docking with protein cavity modeling software by using Autodock Vina.

In this study, the grid size was set to 100 × 108 × 114 points with 1.000 Å spacing centered on MCl-1, 76 × 86 × 126 points with 1.000 Å spacing centered on BRAF, 76 × 78 × 102 points with 1.000 Å spacing centered on BCL-W, 82 × 78 × 78 points with 1.000 Å spacing centered on BCL-2 and 70 × 72 × 108 points with 1.000 Å spacing centered on AKT-1. Lamarckian Genetic Algorithm (LGA) was implemented to analyze protein–ligand interactions.

4. Results and discussion

After the base state energy of the molecule was found, the geometric structure parameters were calculated and the optimized structure of the molecule was given in Table 1. The global minimum energy of the molecule on the basis of optimized structure was −843.12771437 Hartree. When the C=O double bonds in the title molecule were calculated to be ~1.20 Å, theC-O single bond was calculated to be ~1.35 Å. The C–C bonds in the BDLO molecule were generally calculated as 1.53 Å. However, C–C bonds near the nitrogen atom were calculated as 1.54 Å. This extension can be caused by electronegativity of the nitrogen atom. The C4–N18 bond length was calculated to be 1.45 while the C20–N18 bond length was calculated to be 1.37. This may arise from two oxygen atoms bound to the C20 atom (see Fig. 1).

Table 1
Calculated some optimized parameter values of the BDLO [Bond length in (Å). Bond angle in (°)].

Bond Length	BDLO	Bond Angle	BDLO
C1–O2	1.21	O2–C1-03	123.0
C1–O3	1.35	O2–C1–C4	123.9
C1–C4	1.53	C1–C4–N18	114.4
O3–H39	0.97	C12–C15–N36	110.7
C4–H5	1.09	C4–N18–C20	125.6
C4–C6	1.54	N18–C20–O21	123.0
C4–N18	1.45	N18–C20–O22	110.7
C15–N36	1.47	O21–C20–O22	126.3
N18–H19	1.01	C20-022-C23	121.5
N18–C20	1.37	C12–C15–N36	110.7
C20–O21	1.21	C24–C23–C28	110.8
C20–O22	1.35	H34–C32–H35	108.0
O22–C23	1.48	H37–N36–H38	107.1

The theoretical IR and Raman spectra of BDLO were computed using DFT method of theory via 6-311++G(d,p) basis set as shown in Fig. 2 with experimental FT-IR and FT-Raman spectra. The BDLO molecule has 39 atoms and 111 vibrational modes. Some of the calculated wavelengths for the BDLO molecule were shown in Table 2 in order to compare with the experimental wavelengths. The vibration assignments corresponding to these wave numbers were given in the same table as the potential energy distribution PED calculated using the Veda 4 program [16]. N–H stretching vibration, one of the important vibrations in the molecule occurred in the range of 3500–3000 cm^{-1} in heterocyclic compounds [17]. The N–H vibration band were calculated in range of 3459 and 3426 cm^{-1} and asymmetric 3350 cm^{-1} was defined symmetrically from these bands. This band was observed at 3398 cm^{-1} in FT-IR and FT-Raman. C–H stretching vibrations generally occurred in the range of 3000–3100 cm^{-1} in hetero aromatic rings [17–20]. The C–H stretching vibrations were computed in the region between 3010 and 2917 cm^{-1} by DFT/B3LYP/6–311G++(d,p) method and this band definition was called as asymmetric vibration bands. The asymmetric vibration bands were observed at 2937 and 2983 cm^{-1} in FT–Raman and at 2970 cm^{-1} in FT–IR. The symmetrical vibration bands of 2906–2914 cm^{-1} were assigned. The carbon and oxygen double bond was formed by π-π bond. Electronegativities of two atoms were not equal so that stretching frequencies were observed as a higher C-band from its bond. C=O stretching band was unaffected by other vibrations appeared

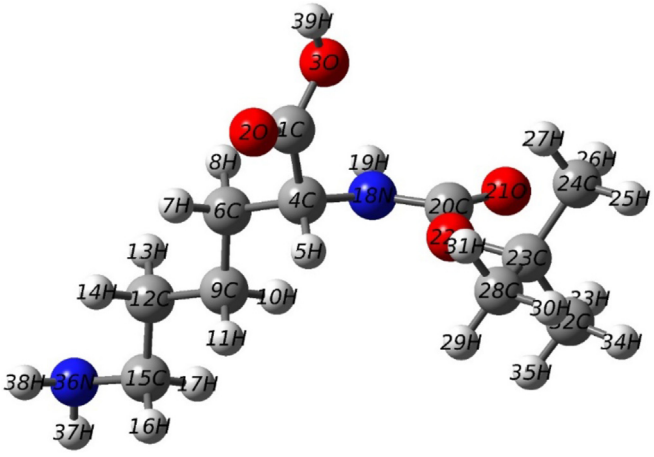

Fig. 1. Theoretical optimized geometric structure of the BDLO.

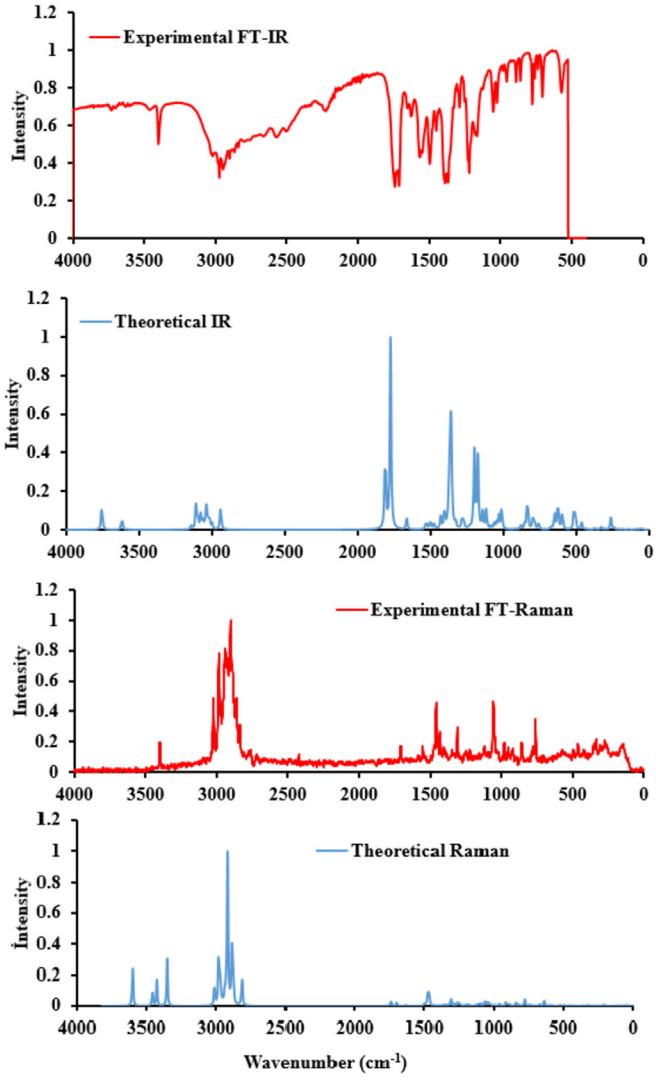

Fig. 2. The experimental and calculated (with the scale factor) FT-IR and FT-Raman spectra of the BDLO.

remarkably in the region of 1700–1800 cm^{-1}. The stretching vibrations for BDLO molecule were observed as 1736 cm^{-1} in FT-IR spectrum and was calculated as 1742 cm^{-1} via B3LYP/6-311++G(d,p) methods. In addition, C–O stretching band was observed at 858 and 888 cm^{-1} in FT-IR and at 856 cm^{-1} in FT-Raman that calculated in between of 885–836 cm^{-1}. The assignment of the O–H stretching vibrations was pure and apprehensible. In this study, the O–H stretching modes of BDLO molecule were calculated at 3596 cm^{-1}.

4.1. Frontier molecular orbitals

The frontier molecular orbitals play an important role in the electrical and optical properties [21]. The energy values HOMO and LUMO orbitals for BDLO were presented by TD-DFT method and given in Fig. 3 for gas phase. HOMO and LUMO energy values calculated by using TD–DFT/B3LYP/6–311++G(d,p) were presented in Table 2. The HOMO was localized in the NH2 (N36, H37 and H38) groups and LUMO was localized in the carboxyl (O3, O2, C1 and H39) groups. The energy difference between HOMO and LUMO is a critical parameter in determining molecular electrical transport properties [22]. The energy gap of HOMO and LUMO was found to be 6.22 eV (in DMSO) for BDLO. The values of chemical harness, chemical potential, electronegativity and electrophilicity index for BDLO were also calculated and given Table 3. Chemical hardness is a measure of inhibition of charge transfer within the molecule. A hard molecule has a large HOMO–LUMO gap and a soft molecule has a small HOMO–LUMO gap [23]. Molecules with high chemical hardness values have little or no intramolecular charge transfer [24]. In the literature review of the recent molecular docking studies, the chemical hardness value was in the range of 0–4 eV [25–28]. The chemical hardness, chemical potential, electronegativity and electrophilicity values calculated for the BDLO molecule is considered to be suitable for interactions in the molecule.

4.2. Molecular electrostatic potential surface

Molecular electrostatic potential (MEP) mapping is very useful in the investigation of the molecular structure with its physiochemical property relationships [29–32]. 2D contour map provides predicting different interactions [33–39]. The contour map of electrostatic potential and molecular electrostatic potential surface of BDLO were shown in Fig. 4. The red color indicated the lowest electrostatic potential energy, and blue indicated the highest electrostatic potential energy. The color code maps for the title compound were predicted in the range between −0.06037 (dark red) and 0.06037 a.u. (dark blue). Fig. 4 showed that the region around the oxygen atoms (O21) linked with carbon through the double bond was the most negative potential region (red) and the hydrogen atom linked with oxygen (O3) was the most bang of positive region (blue).

4.3. Molecular docking

Docking results were obtained from two different programs; Autodock Vina and VMD (Version 1.9.3) [15,40]. The binding strength was defined by use of scoring function based on the Lamarckian Generic Algorithm. The binding free energy may include electrostatic, hydrogen bonding, and van der Waals interactions. The highest binding score represents tight binding between the protein and ligand. In our study the highest binding score were obtained between BDLO molecule and antiapoptotic protein AKT 1. The docking results calculated by the Vina for BDLO-BRAF, BDLO-BCL-2, BDLO-BCL-w, BDLO-MCL-1 and BDLO-AKT1 complexes were −7.3 kcal/mol, −6.4 kcal/mol, −6.9 kcal/mol, −6.8 kcal/mol and −7.4 kcal/mol, respectively (Table 4).

In this study, the grid size were set to 74 × 78 × 72 points with 1.0 Å spacing centered on AKT1, 82 × 78 × 78 points with 1.0 Å spacing centered on Bcl-2, 76 × 78 × 102 points with 1.0 Å spacing centered on Bcl-w, 76 × 86 × 126 points with 1.0 Å spacing centered on BRAF and 100 × 108 × 114 points with 1.0 Å spacing centered on MCL-1. Lamarckian Genetic Algorithm (LGA) was implemented to analyze protein–ligand interactions. The default settings were applied for other parameters. AutoDock tools was used to produce the grid and docking parameter files [41].

BDLO molecule was found to be docked at all tested antiapoptotic proteins, particularly for AKT1 and BRAF genes. So, this molecule could play an active role in the inhibition of these proteins. AKT 1, Bcl-2 and BDLO molecule interactions can be observed in Fig. 5 and Fig. 6. Interactions of hydrogen bonds of Gly 162 with oxygen atom of the ester and Thr 195 residues were identified. van der Waals interactions with amino acid residues His 194, Glu 191, Gly 294, Lys 163, Lys 158, Gly 159 and Phe 161 were also determined. According to the docking results of BCL2 and BDLO molecule, amino acids Gly 142, Ala 97, Leu 134 and Arg 143 performed van der Waals interactions with the molecule. Carbon–Hydrogen

Table 2
Comparison of some the calculated and experimental vibrational spectra and proposal assignments of BDLO molecule.

No	Experimental wavenumber		Theoretical wavenumber			PED (≥10%)
	FT-IR	FT-Raman	Scaled Freq.	I_{IR}	S_{Ra}	Assignments
1			9	0.18	0.71	τCCCN(92)
27		459	451	5.30	0.51	νCC(10)+δCCC(32)+τCCCO(31)
30	569		580	78.43	1.24	τCCOH(24)+τCONH(25)
36		762	768	24.30	1.80	τCOON(75)
37	775		771	8.72	10.19	νCC(39) +τCOON(15)
40	858	856	836	14.70	8.24	νCO (22)+ νCC (22)
41	889		885	4.79	5.02	νOC(12)+νCC (42)+δCCN(12)
45	953		954	0.10	0.01	δCHH(45)+τCCCH(47)
49	1022		1027	7.35	3.10	νCC(42)+νCN(14)+ δCCC(12)
52	1049		1043	12.38	2.38	νCC(35) +τCCCH(60)
53		1059	1065	9.86	14.11	νCN (57)+ νCC (26)
57	1161		1175	247.68	3.06	δCHH(10)+δCCC(12)+τCCCH(26)
59	1217		1208	5.63	1.35	δCNH(12) +τCCCH(37) +τCCOH(49)
64	1286		1282	4.74	4.27	δCNH(15)+ δCOH(26) δCCH(11)
65		1307	1307	7.08	15.08	δCCH(37)+ δCNH(15)+τ CCCH(12)
70	1365		1361	17.42	2.15	τCCCH(27)+τCCOH(33)
76	1448		1446	0.17	0.73	δCHH(61)+τCCCH(11)
77		1458	1455	13.10	9.72	δCNH(38)+ δCHH(55)
85	1493		1494	3.62	3.50	δCHH(85)
87	1622		1632	34.14	2.93	δCNHH(75)+τCCNH(22)
89	1736		1742	347.20	13.47	νOC (86)
99		2937	2932	22.73	62.68	νCH (89)
100			2948	52.96	11.17	νCH (92)
103	2970		2976	31.93	60.49	νCH (91)
105		2983	2980	5.48	39.17	νCH (99)
108	3398	3398	3350	0.55	170.46	νNH (99)
109			3426	1.06	90.47	νNH (99)
110			3459	38.41	63.02	νNH (100)
111			3596	73.02	166.12	νOH (100)

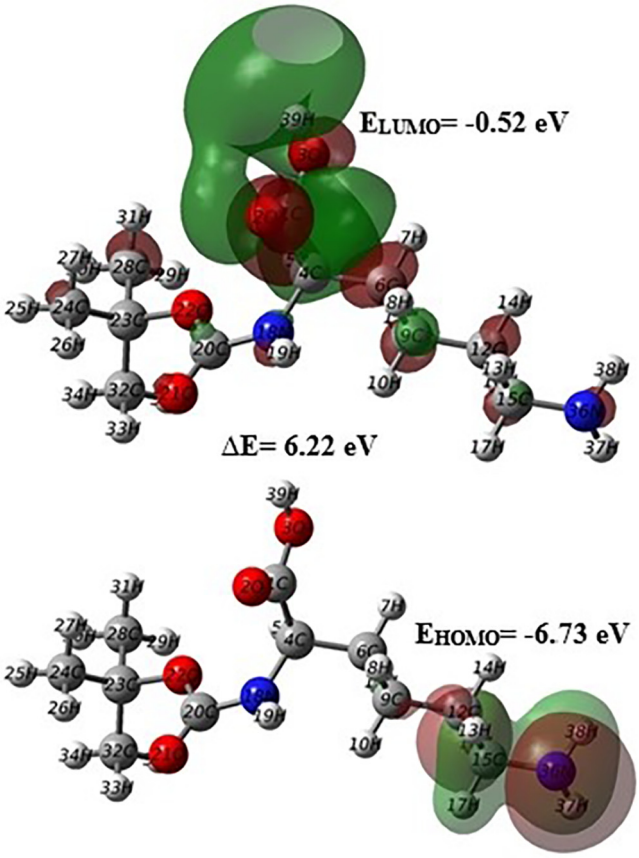

Fig. 3. The frontier molecular orbitals of the BDLO for gas phase.

bond formed between molecule and protein with Phe 101 residue.

The interaction of BCL W and BDLO molecules was represented in Fig. 7. Interactions of hydrogen bonds of Ala 98 with oxygen atom of the ester and Val 82 residues were defined. Van der waals interactions with amino acid residues Glu 85, Phe 57, Ala 105, Val 101, Phe 53 and Thr 60 were also determined. BRAF protein and BDLO molecule interaction of hydrogen bond with Glu 501 was identified (Fig. 8). Van der waals interactions with amino acid residues; Val 471, Leu 505, Ile 527, Lys 483, Thr 529, Cys 532, Trp 531 and Ile 463 were also defined. MCL 1 and BDLO molecule interaction was shown in Fig. 9. van der Waals interactions with amino acid residues; His 224, Phe 228, Thr 266, Leu 267 and Val 249 were identified. Interactions of hydrogen bonds with Leu 246 residue were also defined.

5. Conclusion

The molecular structure parameters and vibrational wavenumbers of BDLO molecule were analyzed. The vibrational FT-IR and FT-Raman spectra of molecule were compared with the theoretical data which showed good agreement. MEPs contour/surface and HOMO-LUMO graphics were drawn to understand the properties and dynamics of the molecule. When examined the electronic properties of BDLO molecule, it was observed that HOMO and LUMO orbitalswere localized around the most electronegative atoms in the molecule. This was also confirmed by FMO and MEP analysis. The possible docking alternatives were studied in Autodock Vina between BDLO molecule as an inhibitor and human anti apoptotic proteins; BCL-2, BCL-w, MCL-1, AKT1 and BRAF. Inhibition ability of this molecule on these proteins was evaluated and potential inhibition of BDLO molecule was tested in silico. The most promising result was obtained from interaction between BDLO molecule and AKT1. In this interaction, more stable conformation with lower energy in ligand-protein complex was analyzed. Hence,

Table 3
The calculated energies values of BDLO.

5Br1HB	Gas	DMSO	Chloroform	Ethanol
E_{total} (Hartree)	−843.12851465	−843.14536117	−843.14043594	−843.14480838
E_{LUMO+1} (eV)	−0.45	−0.32	−0.35	−0.32
E_{LUMO} (eV)	−0.52	−0.54	−0.52	−0.54
E_{HOMO} (eV)	−6.73	−6.76	−6.73	−6.76
E_{HOMO-1} (eV)	−7.29	−7.46	−7.40	−7.45
$E_{HOMO-1-LUMO+1\ gap}$ (eV)	**−6.84**	**−7.14**	**−7.05**	**−7.13**
$E_{HOMO-LUMO\ gap}$ (eV)	**−6.22**	**−6.22**	**−6.21**	**−6.22**
Chemical hardness (h)	−3.11	−3.11	−3.11	−3.11
Electronegativity (χ)	3.62	3.65	3.63	3.65
Chemical potential (μ)	−3.62	−3.65	−3.63	−3.65
Electrophilicity index(ω)	−2.11	−2.14	−2.12	−2.14

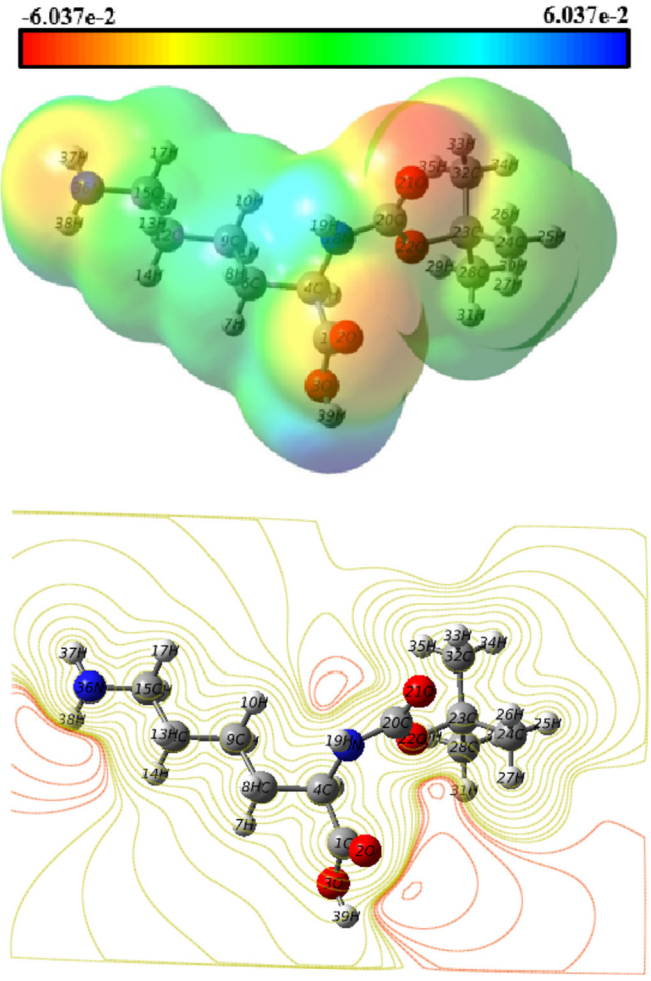

Fig. 4. Molecular electrostatic potential (MEPs) 3D and 2D contour map for BDLO.

Table 4
Docking binding energy results of novel BDLO molecule and Doxorubicin(Control) as inhibitor with anti apoptotic proteins.

BDLO molecule	**Binding Energy (K.Cal/mol)**
BRAF	−7.3
BCL-2	−6.4
BCL-w	−6.9
mcl-1	−6.8
AKT1	−7.4
Doxorubicin (Control)	**Binding Energy (K.Cal/mol)**
BRAF	−9.7
BCL-2	−9.0
BCL-w	−9.0
mcl-1	−9.1
AKT1	−11.2

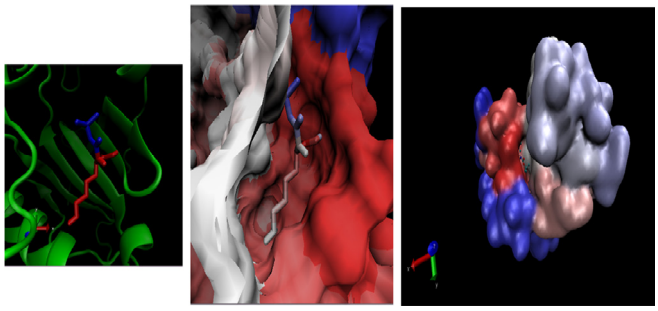

Fig. 5. Representation of BDLO molecule at the active site of AKT 1 gene in molecular docking.

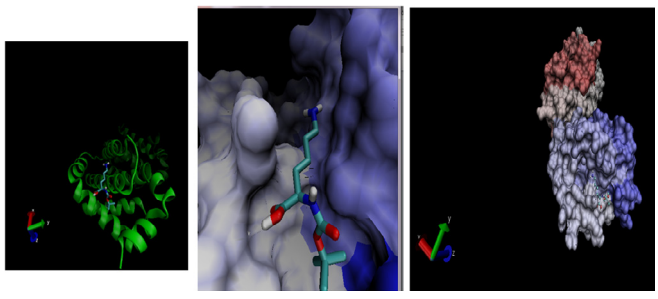

Fig. 6. Representation of BDLO molecule at the active site of BCL 2 gene in molecular docking.

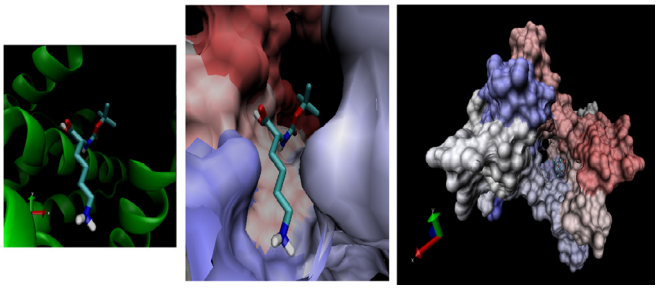

Fig. 7. Representation of BDLO molecule at the active site of BCL W gene in molecular docking.

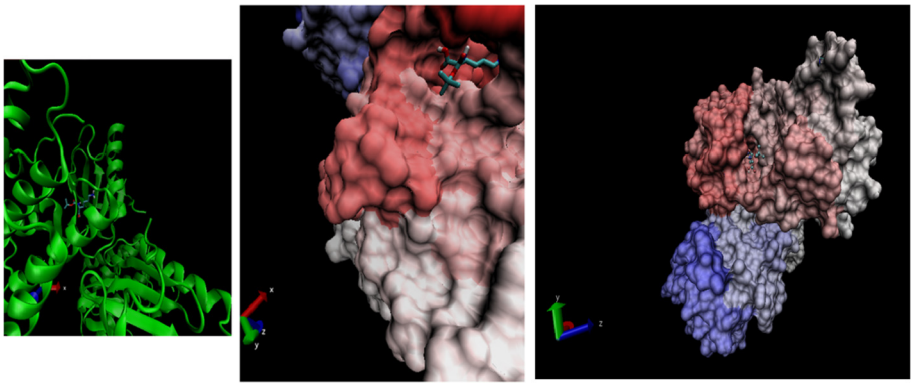

Fig. 8. Representation of BDLO molecule at the active site of BRAF gene in molecular docking.

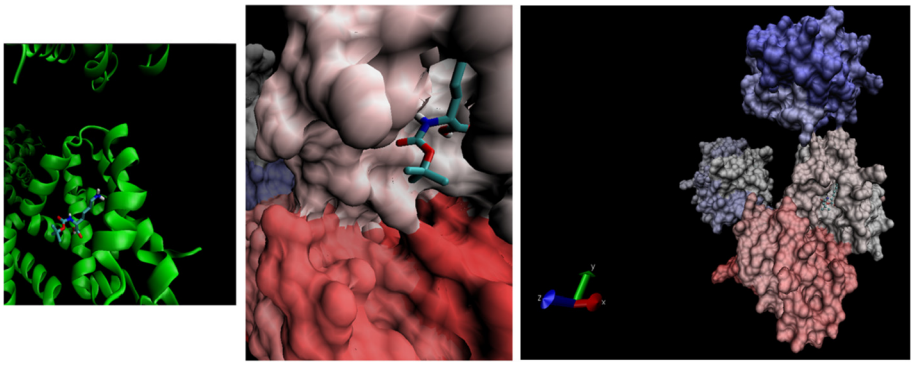

Fig. 9. Representation of BDLO molecule at the active site of MCL1 gene in molecular docking.

binding studies was shown to be a useful tool that revealed electronic affinity and can help to understand ligand-protein interactions.

Acknowledgements

This work was supported by Kirsehir Ahi Evran University Scientific Project Unit (BAP), Project No: TBY.A3.17.004.

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