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Research Article

Synthesis, spectral characterization, DFT, and molecular docking studies of 2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol compound

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ABSTRACT

Synthesis of an alkylaminophenol compound used as a drug active material was carried out and the structural analysis of the compound was investigated experimentally and theoretically. For theoretical calculations, DFT / B3LYP method and 6-311 ++ G (d, p) set were used. Many properties of the compound; Spectral data, bond length, bond angle, dihedral angles, thermodynamic parameters, molecular surface, FMO analysis, nonlinear optical (NLO) properties and Natural Bond Orbital analysis were theoretically investigated. Also, a molecular docking study shows that the title compound might exhibit inhibitory activity against 2RAW protein.

Keywords: Alkylaminophenol, DFT, molecular docking, NBO, NLO

2- ((2,3-Dihidrobenzo [b] [1,4] dioksin-6-il) (1H-indol-1-il) metil) fenol bileşiğinin sentez, spektral karakterizasyon, DFT ve moleküler docking çalışmaları

ÖZ

İlaç etken maddesi olarak kullanılan bir alkilaminofenol bileşiğinin sentezi gerçekleştirilmiş ve bileşiğin yapısal analizi deneysel ve teorik olarak incelenmiştir. Teorik hesaplamalar için DFT / B3LYP yöntemi ve 6-311 ++ G (d, p) seti kullanılmıştır. Bileşiğin birçok özelliği; Spektral veriler, bağ uzunluğu, bağ açısı, dihedral açılar, termodinamik parametreler, moleküler yüzey, FMO analizi, doğrusal olmayan optik (NLO) özellikler ve Natural Bond Orbital analizi teorik olarak incelenmiştir. Ayrıca, moleküler doking çalışmaları, başlık bileşiğinin 2RAW proteinine karşı inhibitör aktivite sergilediğini göstermektedir.

Anahtar Kelimeler: Alkilaminofenol, DFT, molekülar docking, NBO, NLO

1. INTRODUCTION

Alkylaminophenols are heterocyclic compounds containing hydroxyl and nitrogen in their structure.[1-4] It is found in the structures of drugs frequently used in cancer treatments. The compounds having antioxidant activity enables them to be used in chemotherapy.[5,6]

Although there are compounds synthesized in this field in recent years, the diversity of cancer types also accelerates the synthesis of new bioactive compounds. In addition, the fact that the radicals formed as a result of cancer cells become neutral and have antioxidant properties increase the importance of this compound class. Although there are many methods in the literature for the synthesis of alkylaminophenols, the method using the petasis reaction was preferred in this study.[7-11] The reaction takes place by the amine and carbonyl compounds forming iminium ion and removing boric acid from the boronate complex formed by the added boronic acid. Studies on theoretical investigations of these compounds with quantum chemical calculations in the literature are quite limited.[12]

In order to ensure the diversity of alkylaminophenol type compounds, a new compound was synthesized in the study and then many properties of this compound were examined theoretically. Gaussian 09W software was

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used for theoretical calculations and DFT/B3LYP/6-311++G(d,p) set was preferred for calculations.[13-15] Also, its biological significance was investigated by examining its effects on 2RAW protein with molecular docking studies.

2. MATERIALS AND METHODS

2.1 Experimental and Calculation methods

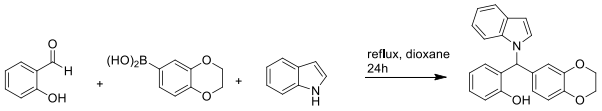

Figure 1. Synthesis of Alkylaminophenol Compound.

Synthesis was carried out according to the procedure in the literatüre (Figure1).[5]

The chemicals used for synthesis were used directly without any extra purification. Structure analysis of the synthesized compound has been made by Bruker FT-IR spectrometer and Agilent 600 MHz NMR spectrometers. *2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol:* Verim 0.313 (87%), red brown solid, MP 75-76 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) =2.07(s, 1H, indole), 3.72 (s, 1H, indole),4.15-4.20 (m,4H,dioxin), 5.58 (s, 1H, CH); 5.79 (s, 1H, Ar-OH), 6.63-6.68 (m,3H, Ar-H), 6.76-6.88 (m, 3H, Ar-H), 7.14-7.21 (m, 2H, Ar-H), 7.30 (s, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 8.08 (s, 1H, Ar-H). ^{13}C (CDCl3, 150 MHz): δ = 21.1 (indole); 42.3 (indole); 60.6 (dioxin); 67.6 (chiral carbon), 102.4 (Ar-); 111.1(Ar-), 116.1 (Ar-); 116.9 (Ar-); 117.1 (Ar-); 117.2 (Ar-); 119.5 (Ar-); 119.9 (Ar-); 120.6 (Ar-); 122.3 (Ar-); 123.7 (Ar-); 124.0 (Ar-); 126.8 (Ar-); 130.0 (Ar-); 136.6 (Ar-); 142.1 (Ar-); 143.3 (Ar-); 153.5 (Ar-); 153.8 (C-OH). FT-IR υ (cm^{-1}): 3409, 2978, 2815, 1705,1589, 1501, 1453, 1281, 1254, 1190, 956, 825.

After the experimental characterization of structural, some properties of the compound was calculated with theoretical methods. Calculations include the B3LYP theory and 6-311 ++ G (d,p) set which is composed of Becke's three-parameter energy-functional hybrid approac and Lee-Yang and Parr's correlation function[16] in the Gaussian 09W program. Gauss-View 5.0 program was used for molecular modelling.[17]

3. RESULTS AND DISCUSSION

3.1 Molecular Geometry

The optimization process of the title compound synthesized using the Petasis reaction was carried out using the B3LYP / 6-311 ++ G (d, p) base set. The optimized form of the compound is given in Figure 2.

The bond length, bond angles and dihedral angles of the compound are comparatively given in Table 1.

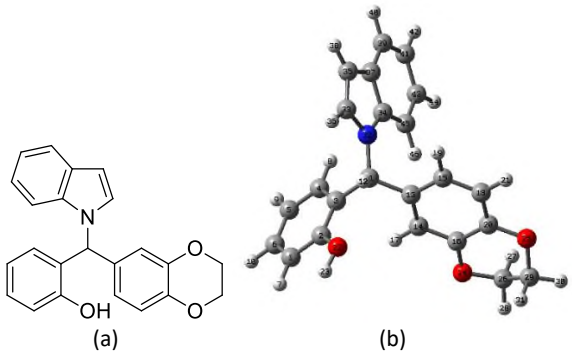

Figure 2. Molecular structure(a) and Optimized form(b) of 2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol compound.

Table 1. Some selected geometric parameters of Alkylaminophenol.

Bond Lenght(A^0)	**B3LYP**	**Bond Angles(^{0})**	**B3LYP**
C1-C2	1.3947	C4-C3-C11	123.1
C2-C3	1.4038	C11-C3-C2	119.0
C3-C4	1.3956	C2-O22-H23	109.8
C4-C5	1.3942	C2-C1-H7	119.7
C5-C6	1.3919	C1-C6-C5	119.9
C4-H8	1.0827	H12-C11-C13	105.6
C1-H7	1.0864	C13-C15-H19	119.9
C2-O22	1.3726	C13-C14-H17	121.4
O22-H23	0.9627	C13-C14-C16	120.8
C3-C11	1.5263	C16-C20-C18	119.3
C11-H12	1.0933	C20-C18-H21	118.4
C11-C13	1.5324	C20-C16-O24	121.8
N32-C33	1.3863	C16-O24-C26	113.8
N32-C34	1.3905	O25-C29-C26	110.2
C34-C37	1.4246	O24-C26-H27	109.5
C33-C35	1.3661	H28-C26-C29	111.3
C11-N32	1.4707	C11-N32-C34	129.7
C37-C39	1.4042	C11-N32-C33	122.2
C34-C45	1.4001	N32-C33-H36	119.6
C45-C43	1.3884	N32-C34-C45	131.3
C39-C41	1.3857	C34-C45-H46	121.6
C33-H36	1.0794	C45-C43-H44	119.1
C45-H46	1.0813	C43-C41-C39	120.7
C13-C14	1.3911	C41-C39-C37	119.2
C13-C15	1.4011	C37-C34-C45	121.3
C15-H19	1.0841	C37-C35-C33	106.8
C14-H17	1.0829	Dihedral Angles	
C20-C16	1.3995	N32-C11-C3-C4	30.6
C16-O24	1.3753	N32-C11-C3-C2	-148.4
C20-O25	1.3739	C11-C3-C2-O22	-0.1
O24-C26	1.4294	H23-O22-C2-C1	0.3
O25-C29	1.4294	N32-C11-C13-C14	79.6
C26-C29	1.5174	N32-C11-C13-C15	55.1
C29-H30	1.0907	C16-O24-C26-C29	45.6
C25-H27	1.0966	H30-C29-O25-C20	165.7

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The O-H bond length was experimentally and theoretically found to be 0.96 Å. While N32-C11 bond length was experimentally 1.47, it was calculated as 1.47 Å with the B3LYP method. In addition, the C = C bond length of 1.37 Å was calculated as 1.40 Å (B3LYP) for C13 = C15 atoms. Besides, the C-O-H bond angle, known to have an angle of 109.5 °, was calculated as 109.8 ° by the B3LYP method for C2-O22-H23. As a result; It can be said that there is a good agreement between the experimental bond length and bond angle values and the calculated values (Table 2).

3.2 NMR Studies

First of all, ^{1}H-NMR and ^{13}C-NMR values of the title compound were calculated with B3LYP / 6-311G ++(d,p). Then chemical shift values in CHCl3 solvent medium and calculated by GIAO-NMR approach and IEFPCM method were compared with experimental values.

Table 2. Experimental and calculated ^{1}H and ^{13}C NMR chemical shifts (ppm).

Atoms	Experimental	B3LYP ($CHCl_3$)
H23	5.79	4.39
H12	5.58	7.16
H27-H28 H30-H31	4.15-4.20	4.19
H36	3.72	7.5
C35	21.1	105.5
C33	42.3	136.5
C26-C29	60.6	67
C13	136.6	140.2
C3	117.2	133.5
C11	67.6	65.0
C2	153.8	159.5

H12 and H23 peaks, which are one of the characteristic peaks of the compound, were experimentally observed at 5.58 ppm and 5.79, respectively, while calculations with the B3LYP method were found to be 7.16 ppm and 4.39 ppm. While our chiral carbon C11 was experimentally seen at 67.4, it was found to be 65.0 in our theoretical calculations.

In addition, the C2 carbon to which the hydroxyl group is attached has experimentally been found to have a value of 153.8 ppm, while theoretically, it has a value of 159.5 ppm. Although there are some deviations due to the presence of the OH group in the structure and intramolecular hydrogen bonds, it can be said that our theoretical data are compatible with the experimental data.

3.3 Mulliken Charge

The most common of the population analysis methods is the mulliken charge distribution. It is often used to make some qualitative estimates of the structure. Analysis; it was carried out with the B3LYP / 6-311G ++ (d, p) method and the results are given in Table 3. Mulliken charges are between-0.710 and 0.710. When we look at the atomic charges of alkylaminophenol, it is seen that the negative charge is around C39, C34, C11, C14, C5, C41 and C6 atoms, and the positive charge is around the N32, C3, C37, C13, H17, H23 atoms.

Tablo 3. Mulliken charges of the studied molecule.

Atoms	Mulliken (B3LYP)	Atoms	Mulliken (B3LYP)
C11	-0.517	C15	-0.138
C3	0.473	O25	-0.135
C2	-0.144	O24	-0.1
O22	-0.194	N32	0.710
H23	0.266	C33	0.051
C1	-0.228	H17	0.269
C5	-0.422	C34	-0.528
C6	-0.320	C37	0.469
C13	0.351	C39	-0.592
C14	-0.424	C41	-0.364

3.4 Frontier Molecular Orbitals (FMO)

FMO tells us about the reactivity of the compound. In order to determine the relevance of the compound to chemical reactions, we need to determine the energy values of the HOMO and LUMO orbitals. The structures showing the energy difference between HOMO and LUMO for our compound are given in Figure 3. HOMO and LUMO energies were calculated as -5.5287 and -0.7252, respectively. In this case, the ΔE energy difference is also calculated as 4.8035 eV. Physicochemical parameters of the compound by using HOMO and LUMO energy values are given in Table 4.

Table 4. HOMO, LUMO, ΔE, electronegativity (χ) chemical hardness (η), softness (S) and electrophilic index (χ) values of 2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol compound.

Physicochemical parameters	B3LYP/6-311++G(d,p)
E(HOMO, eV)	-5.5287
E(LUMO, eV)	-0.7252
ΔE(eV)	4.8035
χ	3.1270
η	2.4018
s	1.2009
ω	4.0711

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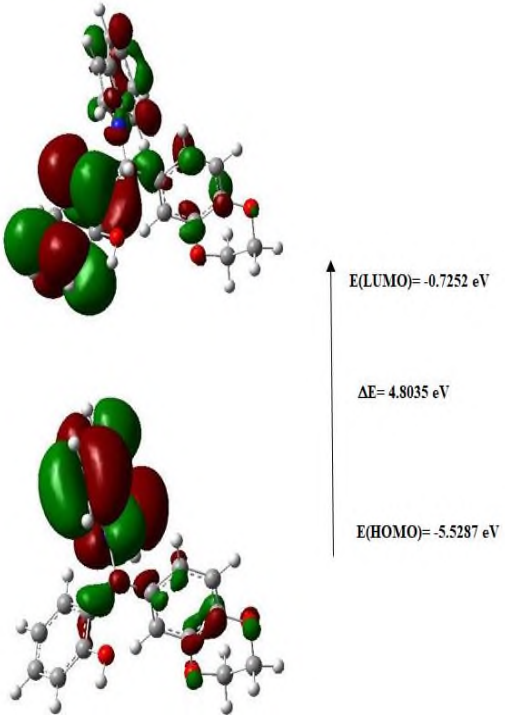

Figure 3. Frontier molecular orbitals, HOMO-LUMO energies.

3.5 Molecular Electrostatic Potential (MEP)

When looking at the three-dimensional molecular electrostatic potential surface of the compound (Figure 4), the energy scale is +6.476 e-2 a.u. and between -6.476 e-2 a.u. These values are; gives information about the chemical behaviour of the molecule. Looking at the structure, it is seen that the negative charge is concentrated around the hydroxyl group and the positive part is concentrated on the nitrogen and phenyl protons. Determination of MEP surfaces; It is important in terms of providing information about intermolecular interactions and biological properties.

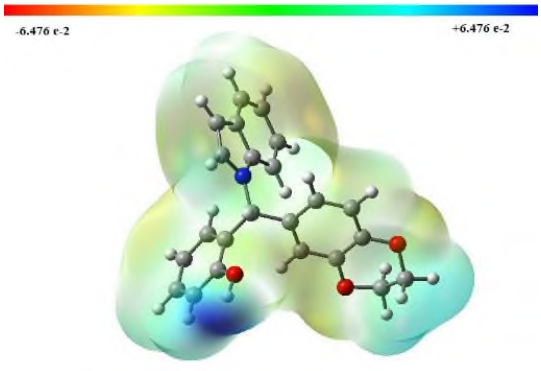

Figure 4. Molecular electrostatic potential surface and total electron density of 2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol.

3.6 Natural Bond Orbital (NBO) Analysis

NBO analysis is used to determine the electron density in all orbitals of the molecule.[18,19] A quadratic Fock matrix is used to evaluate the resulting donor-acceptor interactions. When each donor is defined as (i) and the recipient (j), delocalization is associated with i→j, and the stability energy (E2) is expressed by the equation we define below.[20]

$$E(2)=\Delta E_{i,j}= q_i[F_{(i,j)}^2]/[E_i-E_j]$$

Table 5. NBO analysis using a quadratic Fock matrix for selected chemical bonds.

NBO(i) Donor	NBO(j) Acceptor	E(2) Kcal/mol	E(j)-E(i) a.u	F(i,j) a.u.	NBO(i) Donor	NBO(j) Acceptor	E(2) Kcal/mol	E(j)-E(i) a.u	F(i,j) a.u.
σ(C2-O22)	σ*(C1-C2	0.81	1.47	0.031	π(C1-C2)	π*(C1-C2)	0.53	0.28	0.011
	σ*(C1-C6)	1.18	1.48	0.037		π*(C3-C4)	27.61	0.20	0.067
	σ*(C2-C3)	0.80	1.48	0.031		σ*(C5-C6)	21.81	0.29	0.072
	σ*(C4-C8)	5.10	0.29	0.035	π(C33-C35)	σ*(C11-H12)	2.65	0.33	0.027
	σ*(C16-C20)	15.59	0.06	0.032		σ*(C34-C45)	1.57	0.49	0.026
	σ*(C29-H31)	1.43	0.98	0.034		σ*(C33-C37)	0.51	2.30	0.012

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Table 5. Continued

σ(C3-C11)	σ*(N32-C33)	1.09	1.08	0.031	σ(C33-C35)	σ*(C4-C8)	212.67	0.07	0.109
	σ*(C4-H8)	5900.53	0.01	0.226		σ*(C11-N32)	16.76	0.43	0.076
	σ*(C26-H27)	25.83	0.65	0.116		σ*(C29-H31)	9.99	0.75	0.077
	σ*(C29-H31)	51.55	0.69	0.169		σ*(C26-H27)	5.03	0.71	0.033
	σ*(C34-C5)	3.15	0.82	0.048		σ*(C39-C41)	8.18	0.06	0.021
	σ*(C34-C45)	7.45	0.87	0.072		σ*(C45-H46)	14.90	0.24	0.031
	σ*(C43-C45)	11.04	0.22	0.048	LP(1) O22	σ*(C1-C2)	6.09	1.16	0.075
	σ*(C45-H46)	5.90	0.18	0.03		π*(C43-C45)	6.45	0.20	0.035
σ(C11-C13)	σ*(C45-H46)	9.62	0.66	0.071		σ*(C45-H46)	6.90	0.17	0.030
	σ*(C45-H46)	3.14	1.05	0.051	LP(2) O22	π*(C1-C2)	26.28	0.35	0.093
	σ*(C45-H46)	2.05	0.84	0.037		π*(C3-C4)	0.50	0.27	0.011
	σ*(C45-H46)	51.05	0.19	0.095		σ*(C11-N32)	3.68	0.07	0.014
	σ*(C45-H46)	100.07	0.15	0.111	LP(1) O24	σ*(C16-C20)	4.50	1.09	0.063
σ(C11-N32)	σ*(C4-C5)	5.88	0.90	0.025		σ*(C29-H31)	10.25	0.62	0.072
	σ*(C4-H8)	646.14	0.11	0.237		π*(C43-C45)	1.69	0.15	0.015
	σ*(C11-H12)	6.48	0.81	0.065	LP(2) O24	σ*(C45-H46)	10683.23	0.04	0.569
	σ*(C26-H27)	23.54	0.75	0.119		π*(C43-C45)	5180.26	0.07	0.572

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Table 5. Continued

	σ*(C29-H31)	34.51	0.79	0.148		σ*(C35-C37)	68.94	2.53	0.384
	σ*(C43-C45)	8.71	0.32	0.05		σ*(C34-C45)	119.08	0.73	0.270
LP(1) O25	σ*(C43-C45)	19797.48	2.17	5.885	LP(2) O25	σ*(N32-C34)	14853.90	2.28	5.201
	π*(C43-C45)	1916.29	6.09	3.300		σ*(O24-C26)	1437.84	4.73	2.227
	σ*(C43-H46)	2203.48	6.05	3.276		σ*(C13-C14)	2840.76	5.12	3.418
	σ*(C34-C37)	49110.31	0.93	6.049		π*(C13-C14)	32.19	6.54	0.448

When NBO analysis results are examined, it is seen that the atoms with the highest E (2) value are O22, O24, O25 atoms. It has been demonstrated by the data that these atoms (Table 5) are in strong interaction with phenyl rings. It can also be said that the chiral C11 atom is in strong interaction with the indole ring and phenyl rings to which it is attached with the N32 atom.

3.7 Nonlinear Optical Properties (NLO)

The NLO properties of the compound are due to its electrons. The presence of conjugation or donor groups in the structure changes many properties of the compound. Theoretical calculations made for this purpose give information about the electronic properties of the compound. Calculations were made by selecting the *p*-nitroaniline compound used as a reference in the study. Isotropic linear polarization $\langle\alpha\rangle$, anisotropic linear polarization $\Delta\alpha$, first-order hyperpolarization $\langle\beta\rangle$ and total dipole moment (μ) values were calculated using the B3LYP method using the equations below.[21]

$$\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2} \quad (1)$$

$$<\alpha> = 1/3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (2)$$

$$\Delta\alpha = [1/2((\alpha_{xx}-\alpha_{yy})^2+(\alpha_{yy}-\alpha_{zz})^2+(\alpha_{zz}-\alpha_{xx})^2)]^{1/2} \quad (3)$$

$$<\beta> = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2+(\beta_{yyy} + \beta_{xxy} + \beta_{yzz})^2+(\beta_{zzz} + \beta_{xxz} + \beta_{yyz})^2]^{1/2} \quad (4)$$

Table 6. NLO Analysis Results.

Property	***p-NA***	*Alkylaminophenol*	*Property*	***p-NA***	*Alkylaminophenol*
μ_x	-7.4519	3.0798	β_{xxx}	-99.4560	178.3004
μ_y	-0.001	3.0908	β_{xyy}	16.7004	9.9421
μ_z	0.6869	0.1066	β_{xzz}	12.9992	10.6264
μ	7.48 Debye	4.36 Debye	β_{yyy}	-0.0012	118.0253
α_{xx}	-58.7480	-142.3714	β_{xxy}	-0.0004	-20.6859
α_{yy}	-53.2767	-146.1486	β_{yzz}	0.0001	7.9136
α_{zz}	-60.6128	-152.3852	β_{zzz}	0.4969	-5.5628
$<\alpha>$	-8.52×10^{-24} esu	-2.18×10^{-23} esu	β_{xxz}	12.9100	23.8653
$\Delta\alpha$	9.79×10^{-25} esu	1.3×10^{-24} esu	β_{yyz}	0.4172	-5.5387
			$<\beta>$	8.99×10^{-31} esu	1.95×10^{-30} esu

Looking at the NLO data (Table6); it is seen that the dipole moment value of our alkylaminophenol compound is lower than p-NA. However, it is seen that the value of isotropic linear polarization, anisotropic linear polarization and first-order hyperpolarization is two times greater than p-NA. Based on these data, the compound of 2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol has very high NLO properties in optoelectronics, laser technology, optical It appears to be a new compound that will contribute to many areas such as data storage.

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3.8 Molecular Docking

Molecular docking studies were performed using Autodock Vina program.[22] The binding sites were centred on the Protein (PDB ID: 2RAW). Molecular docking techniques demonstrated that alkylaminophenol compound is Centromere-associated protein inhibitör. When looking at the 2D diagram (Figure 5), it was seen that there were alkyl-pi alkyl interactions and hydrogen bonds between the ligand and the protein. It was determined that there were interactions at a distance of 4.37 and 4.58 Å between alkyl and pi-alkyl. Hydrogen bond lengths were calculated to be 1.11, 1.86, 1.93 and 2.03 Å, respectively. The settlement score of the compound was determined to be-6.6 kcal/mol. This value clearly indicates that the alkylaminophenol compound has good biological activity (Table 7).

Table 7. Molecular Docking Results for Alkylaminophenol compound.

Protein ID	Binding Energy (Kcal/mol)	RMSD (Å)	Interactions	Distance (Å)
2RAW	-6.6	2.0	ABN A:118	1.11
				1.86
				1.93
				2.05
			LYS A:121	4.37
				4.58

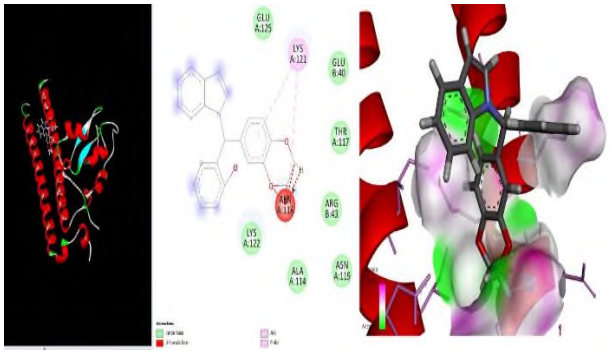

Figure 5. Docking analysis for the title compound.

4. CONCLUSION

In this study, the new alkylaminophenol type 2 - ((2,3-Dihydrobenzo [b] [1,4] dioxin-6-yl) (1H-indol-1-yl) methyl) phenol compound was synthesized with high yield for the first time. Structural analyzes of the compound were carried out experimentally and theoretically. Theoretical calculations were made by considering the DFT / B3LYP method and the 6-311 ++ G (d, p) base set. Many electronic properties of the compound (bond length, bond angle, dihedral angles) and the distribution of these electrons in orbitals (NBO) and chemical reactions have been calculated. Biological efficacy was predicted by molecular docking studies. In addition, it has been determined that NLO analysis can be effective in optoelectronics other than medical applications.

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Conflict of interests

Author declare that there is no a conflict of interest with any person, institute, company, etc.

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