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Investigation of Anticancer Properties of 2-benzylidene-1-indanone and Its Derivatives by DFT and Molecular Docking

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Abstract: In this study, 2-benzylidene-1-indanone and its derivatives, which is a chalcone compound and contains indanone in its structure, were examined. Quantum chemical parameters for these compounds were calculated with the B3LYP method and the 6-31G(d) basis set and evaluated for their biological activity. The effect of different functional groups (F, Cl, Br, CF3, CH3 and OCH3) attached to the 2-benzylidene-1-indanone compound on biological activity was investigated. Some quantum chemical parameters such as highest energy filled molecule orbital energy (EHOMO), lowest non-bonding empty molecule orbital energy (ELUMO), energy gap (ΔE), hardness (η), softness (σ), global molecular electrophilicity (ω) index, global molecular nucleophilicity (ε) index, electron-accepting (ω+) and electron-donating (ω-) electrophilicity index were calculated for the biological activities of the compounds. Frontier molecular orbitals and molecular electrostatic potential (MEP) maps were interpreted. The biological activities of 2-benzylidine-1-indanone and some of its derivatives bearing the 1-indanone skeleton were evaluated by performing molecular docking studies with the target protein PDB ID = 1HJD corresponding to the melanoma cell line. The activity ranking obtained with quantum chemical parameters was found to be compatible with the binding energies obtained from docking results.

Keywords: Indanone, Quantum chemical parameters, Molecular docking

1. Introduction

A chalcone-like substance with a benzocyclopentanone (1-indanone) skeleton is 2-benzylidene-1-indanone. 1-indanone is a structure created when the benzene and cyclopentanone rings are bonded. The cyclopentanone part's carbonyl group contains α-keto and benzylic hydrogens. Specifically, α,β-unsaturated aromatic ketones include chalcones and 1-indanone (E)-β-phenyl-α,β-unsaturated carbonyl framework derivatives [1]. This structure can therefore display a variety of activities. Because of their α,β-unsaturated groups, they are comparable, and as a result, several studies have considered molecules having a 1-indanone ring to be active. Furthermore, several plants naturally contain 1-indanone, a component that has biological activity and is a molecule of pharmaceutical significance. Upon examining the indanone-derived molecules under study, several notable findings may be found in the literature. It is primarily utilized in the production of compounds with the 1-indanone skeleton for the treatment of cancer [3] and Alzheimer's disease (AD) [2].

The design, synthesis, structure-activity correlations, and anti-inflammatory activity of the 2-benzylidene-1-indanone derivatives have been assessed in the study by Xiao et al. as suitable anti-inflammatory medicines for the treatment of acute lung injury. [4].

In this study, we discussed 2-benzylidine-1-indanone and some of its derivatives. The compounds shown in Figure 1 were synthesized [5], and the effect of different groups (F, Cl, Br, CF_3, CH3 and OCH_3) attached to the 2-benzylidene-1-

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indanone compound was examined. For the biological activities of compounds, quantum chemical parameters such as the highest energy occupy molecule orbital energy (E_{HOMO}), the lowest unoccupied empty molecule orbital energy (ELUMO), energy gap (ΔE), hardness (η), softness (σ), global molecular electrophilicity (ω) index global molecular nucleophilicity (ε) index, electron-accepting (ω+) and electron-donating (ω-) electrophilicity index were examined. Frontier molecular orbitals and molecular electrostatic potential (MEP) maps are interpreted. Chalcones' biological activity have earned them a significant role in pharmaceutical chemistry [6]. Since 2-benzylidene-1-indanone derivatives containing 1-indanone contain a chalcone skeleton, an in-silico study was carried out in skin cancer considering their effectiveness in cancer treatment [7].

2. Computational Method

2-benzylidene-1-indanone (i1) and its derivatives (i1, i2, i3, i4, i5, i6, i7 and i8) GaussView 6.0.16 [8], Gaussian16 IA32W-G16RevB.01, Gaussian09 AS64L-G09RevD.01 [9] were used to calculate Conceptual Density Functional Theory (CDFT) is a concept that provides simple equations for obtaining quantum chemical parameters. Highest occupied molecular orbital energy (E_{HOMO}), lowest empty molecular orbital energy (E_{LUMO}), energy gap (ΔE), hardness (η), softness (σ), electronegativity (χ), chemical potential (μ), spherical molecular Some quantum chemicals Parameters such as electrophilicity (ω) index, global molecular nucleophilicity (ε) index, electron accepting (ω^+) and electron donating (ω^-) forces are used to approximate the biological activities of the studied chemical species [10, 11]. DockingServer was used in docking studies [12]. The equations of the parameters used on the basis of the concept are as follows:

$$I = -E_{HOMO}$$

$$A = -E_{LUMO}$$

$$\eta = \frac{1}{2}\left[\frac{\partial^2 E}{\partial^2 N}\right]_{v(r)} = \frac{I-A}{2}$$

$$\langle\alpha\rangle = \frac{1}{3}\left[\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right] \sigma = \frac{1}{\eta}$$

$$\mu = -\chi = \left[\frac{\partial E}{\partial N}\right]_{v(r)} = -\left(\frac{I+A}{2}\right)$$

$$\omega = \frac{\chi^2}{2\eta}$$

$$\varepsilon = \frac{1}{\omega}$$

$$\omega^+ = \frac{(I+3A)^2}{16(I-A)}$$

$$\omega^- = \frac{(3I+A)^2}{16(I-A)}$$

Docking Server was used for molecular docking studies [13]. Optimization was made in DockingServer with MMFF94 method. Load calculations were performed using the Gasteiger method. The media pH was taken as 7.0. Grid maps for ligand and protein 90 × 90 × 90 Å (x, y and z) and Lamarckian genetic algorithm (LGA) and Solis & amp; wet local search method was used [14]. The population size was set to 150 while docking was occurring. A translation step of 0.2 Å and a 5 Å quaternion and torsion steps were applied during the search for the appropriate region of the target protein of the molecules studied.

3. Result and Discussion

3.1. Optimized Structure

2-benzylidene-1-indanone (i1) and its derivatives (i2, i3, i4, i5, i6, i7, and i8) molecular structure was drawn using GaussView 6.0.16 [15]. The corresponding calculations obtained using B3LYP/6-31G(d) level were made in Gaussian16 IA32W-G16RevB.01, Gaussian09 AS64L-G09RevD.01 [16]. The optimized structures of i1-i8 complexes are shown in Figure 1.

3.2. Molecular Reactivity

For the purpose of examining the potential biological activity of i-derived molecules, quantum chemical characteristics were examined. Table 1 displays the results of the calculation of the quantum chemical parameters and B3LYP/6-31G(d) level for the structures of 2-benzylidene-1-indanone (i1) and its derivatives (i2-i8).

The chemical reactivity parameters computed at the B3LYP/6-31G(d) level in the gas phase are displayed in Table 1. Based on quantum chemical characteristics, theoretical predictions were generated regarding the substances under

investigation's biological anticancer properties. The energy of the HOMO is the first and most significant parameter in quantum chemical parameters. Because HOMO has a high energy, its electrons can move about more freely. The molecules' activity efficiency increases with electron freedom [17]. The second parameter is the energy of LUMO, and these energy values define its electron-receiving capability. Activity is high when LUMO energy is low [18,19]. The energy differential between LUMO and HOMO is a key metric used to measure the biological activity feature. [20]. Energy differential between LUMO and HOMO is a key metric used to measure the biological activity characteristic. Electron freedom has a significant role in identifying the activity pattern in this parameter. When the energy gap (ΔE) narrows, anticancer activity rises [21]. Additional factors, namely chemical hardness (η) and softness (σ), indicate the compound's polarization and interaction value with respect to the suitable structure. Chemical species with low hardness values and high softness values are excellent for biological activity. The activity qualities of the compounds can also be effectively determined by the index parameters, ω and ε. The electrophilicity index and nucleophilicity index are in a comparable position. An advantage is a declining nucleophilicity index value and an increasing electrophilicity index value [22]. Electrodonation power and electroacceptance power metrics quantify a molecule's capacity to give and receive electrons. The chemical species under investigation are supposed to easily give way to biological macromolecules. It is possible to ascertain the substances' functional group action based on the generalizations of these characteristics. The biological actions of substances i1 through i8 can be enumerated as follows.

i5 > i3 > i8 > i2 > i4 > i6 > i7 > i1

3.4. Frontier molecular orbitals

The lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) are known as frontier molecular orbitals. These frontier molecular orbitals' contour maps can be useful in locating atomic surfaces that actively participate in electron acquisition and transport [18]. It also clarifies how to ascertain a compound's electrical characteristics. The border molecular orbitals of i1 and its derivatives, computed at the B3LYP/6-31G(d) level, are displayed in Figure 2.

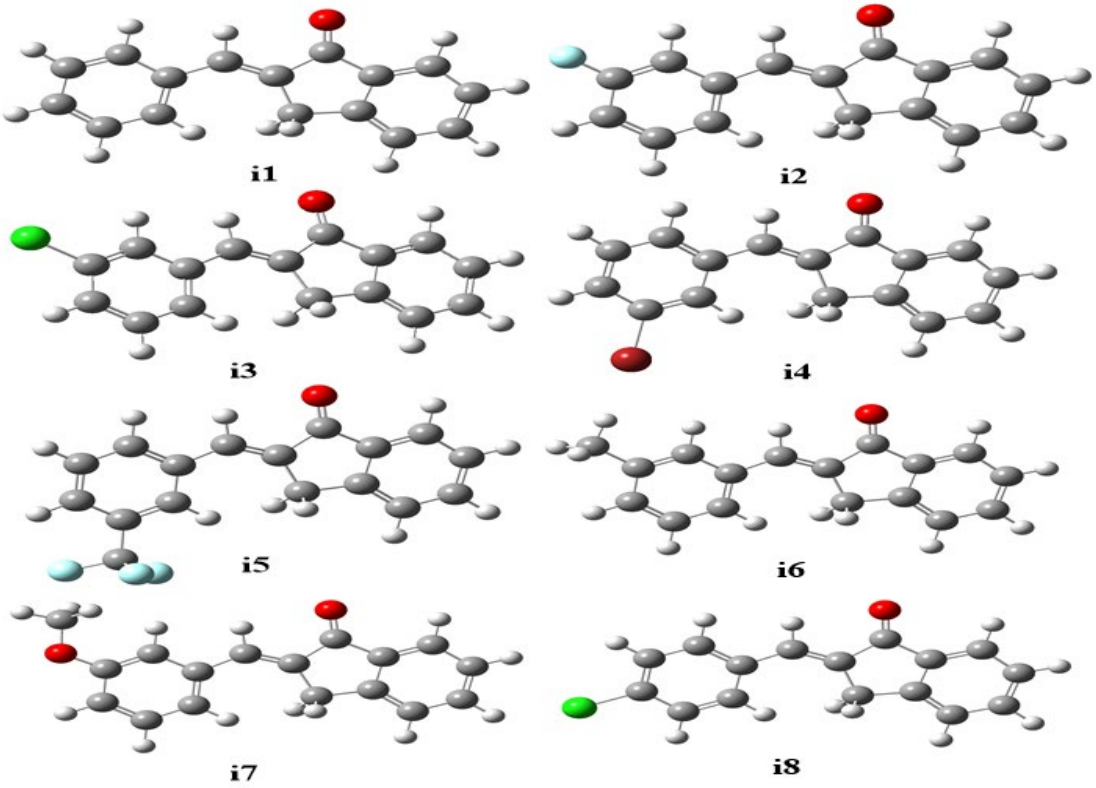

Figure 1. Calculated optimized structures of studied 2-benzylidene-1-indanone and its derivatives at the B3LYP/6-31G(d) level.

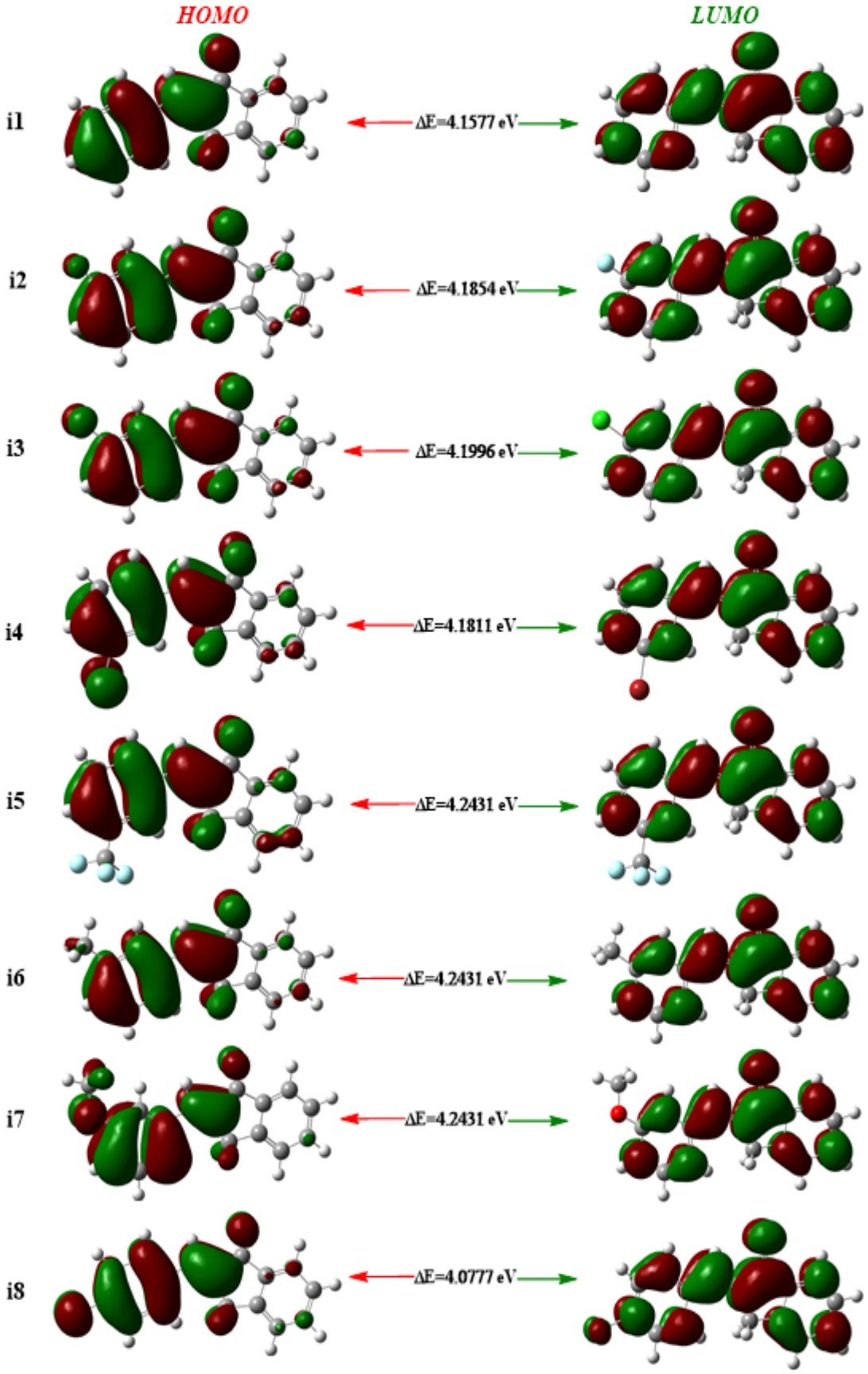

Figure 2. Frontier molecular orbitals of studied molecules.

Table 1. Quantum chemical parameters of investigated 2-benzylidene-1-indanone and its derivatives.

	E_{HOMO}*	E_{LUMO}*	ΔE*	η*	σ**	ω	ε	ω^+	ω^-
i1	-6,7564	-2,0001	4,7563	2,3782	0,4205	4,0302	0,2481	1,9446	6,517
i2	-6,4921	-1,9557	4,5364	2,2682	0,4409	3,9329	0,2543	2,0801	6,328
i3	-5,9117	-2,5285	3,3832	1,6916	0,5912	5,2640	0,1900	1,9260	7,586
i4	-6,1553	-2,3552	3,8001	1,9000	0,5263	4,7648	0,2099	1,7748	7,130
i5	-5,9389	-2,5666	3,3723	1,6862	0,5931	5,3631	0,1865	1,9576	7,700
i6	-6,4043	-2,1764	4,2279	2,1139	0,4731	4,3537	0,2297	1,6324	6,763
i7	-6,4301	-2,0335	4,3966	2,1983	0,4549	4,0732	0,2455	1,5262	6,464
i8	-5,9294	-2,5018	3,4276	1,7138	0,5835	5,1849	0,1929	1,9026	7,507

*,**; eV^-

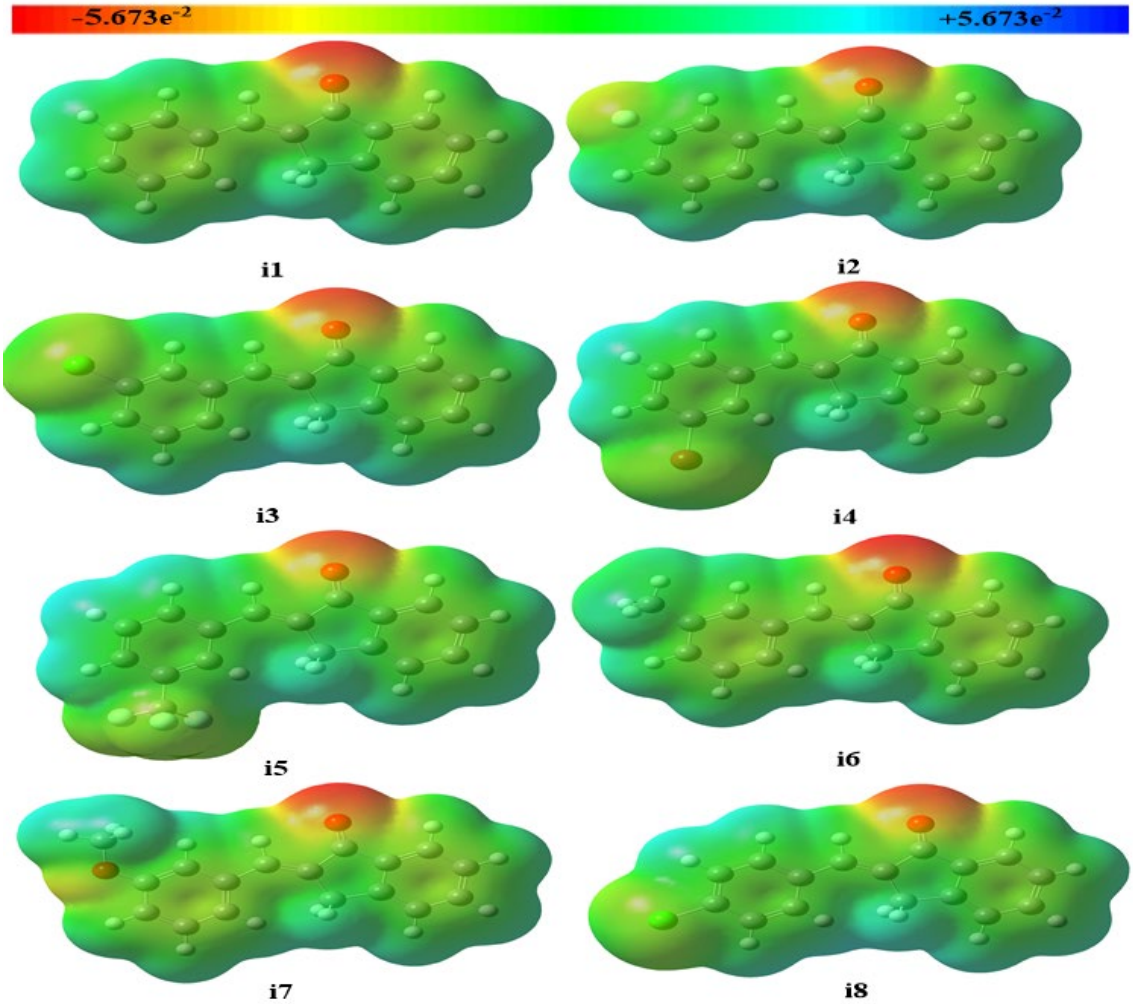

Figure 3. 2-benzylidene-1-indanone (i1) and its derivatives (i2- i8) MEP maps.

Table 2. The calculated energy of binding between the target proteins and the investigated chemicals

	BE	Ki	SE	IE	IS
i1	-5.30 kcal/mol	130.16 µM	-5.62 kcal/mol	-5.60 kcal/mol	482.171
i2	-5.74 kcal/mol	62.52 µM	-6.03 kcal/mol	-6.03 kcal/mol	481.814
i3	-6.22 kcal/mol	27.80 µM	-6.48 kcal/mol	-6.51 kcal/mol	524.936
i4	-5.68 kcal/mol	69.20 µM	-5.94 kcal/mol	-5.97 kcal/mol	492.003
i5	-7.49 kcal/mol	3.21 µM	-7.85 kcal/mol	-7.91 kcal/mol	518.866
i6	-5.49 kcal/mol	95.34 µM	-5.73 kcal/mol	-5.78 kcal/mol	518.317
i7	-5.32 kcal/mol	126.84 µM	-5.88 kcal/mol	-5.93 kcal/mol	540.847
i8	-5.80 kcal/mol	56.17 µM	-6.11 kcal/mol	-6.10 kcal/mol	497.766

Upon examining the contour diagrams of the compounds, it becomes evident that the electron donor orbitals do not contain the benzene ring located in the indole portion of the complex. It's also important to notice that the trifluoromethyl moiety does not donate electrons. Nonetheless, it demonstrates that when it comes to electron acquisition, the orbitals throughout the entire molecule might be actively involved [23].

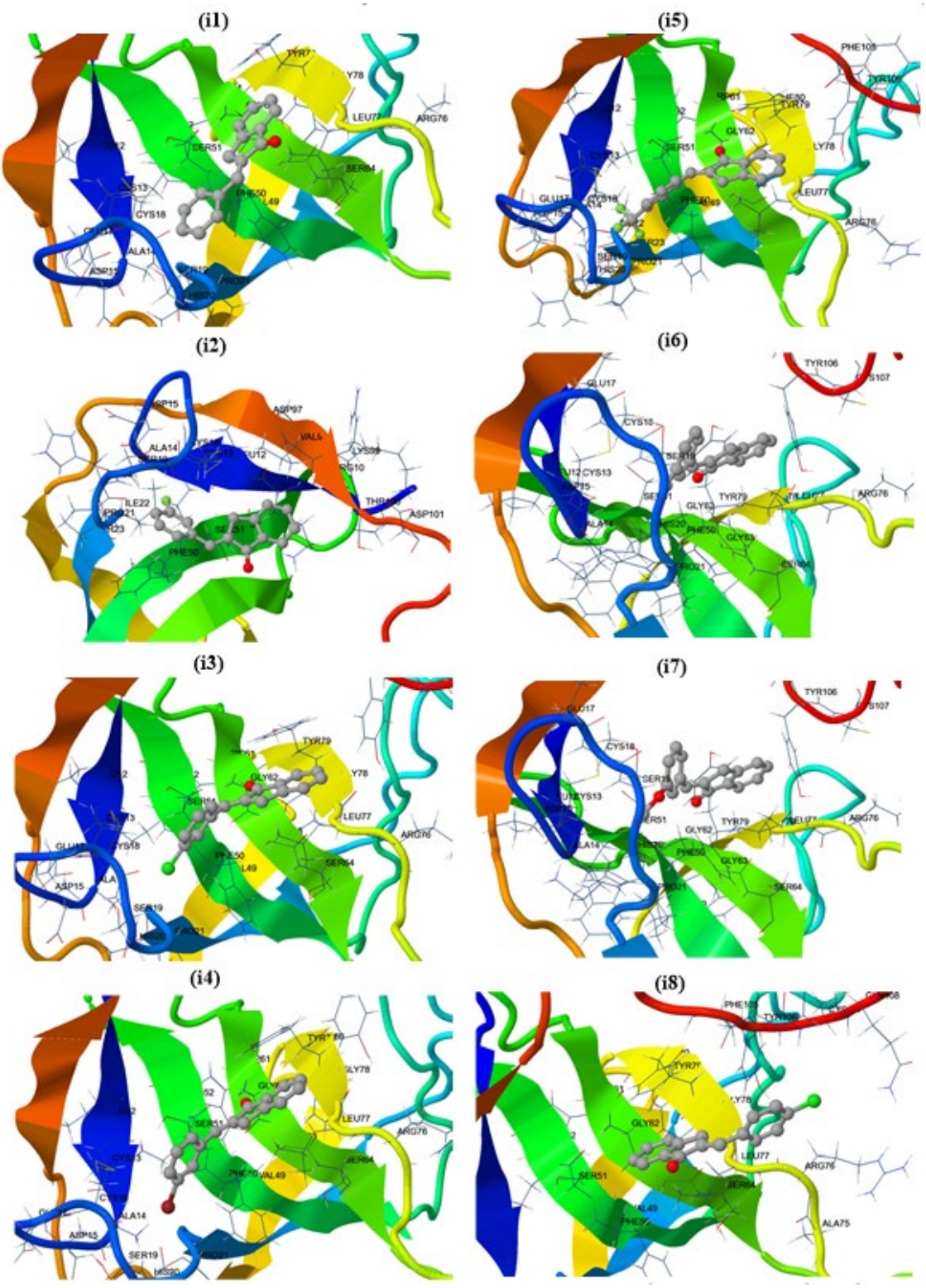

Figure 4. Docking poses of 1HJD and i1-i8 compounds.

3.4. Molecular electrostatic potential (MEP) maps

Different colors appear on molecules in molecular electrostatic potential maps. Any molecule's reactivity as well as its size, shape, and electrostatic potential values can be discussed because of these maps [24]. The molecule's electrophilic and nucleophilic reactive components are also identified using the MEP map. The electrostatic potentials on the surface range in value from red to blue. The most electronegative region is represented by red, and the most electropositive region is represented by blue. MEP maps come in a variety of colors besides red and blue. The potentials for these colors are arranged as follows: red, orange, yellow, green and blue [25, 26]. Figure 3 shows the MEP maps of the chemicals that were studied.

According to MEP maps, the oxygen atom in 2-benzylidene-1-indanone compounds is the dense electron donor. The electron-accepting potentials of the various additional substituents are also highlighted.

3.5. Molecular docking

Molecular docking computations have emerged as one of the most important components of in silico research in recent years. Biological activation investigations are potentially possible because of docking. Molecular biology can be used to study interactions between chemical species and biological macromolecules. New concepts for an experimental investigation can be proposed in this manner [27]. In order to achieve this, we used molecular docking to match our indanone-derived molecules to the target protein PDB ID: 1HJD [28], which stands for the melanoma cancer cell line. Table 2 lists the docking findings.

Estimated Free Energy of Binding (BE), Estimated Inhibition Constant (Ki), vdW + Hbond + desolved Energy (SE), Total Intermolecular Energy (IE), and Interaction Surface (IS) are among the data derived from docking parameters. The interactions between drugs and pertinent target proteins are predicted using these factors. Compounds' ability to inhibit cancer is predicted by their binding energy on target proteins. An indicator of a compound's potency on target proteins is its inhibition constant. specifies the chemicals' effective concentrations. It demonstrates how secondary chemical reactions actively participate in the protein-ligand interaction. In actuality, binding energy is analogous to total intermolecular energy. The area of the protein surface where the ligand binds is known as the interaction surface [29]. Upon examining the docking characteristics of the chemicals listed in Table 2, it is evident that i5 possesses the greatest anti-cancer activity. Indeed, a comparable scenario agrees pretty well with the information derived from quantum chemical characteristics. 1HJD and i5 have a binding energy of -7.49 kcal/mol. Following i5, it goes on to the highly biologically active i3, i8, and i2. The trifluoromethyl (-CF3) group is one of the strongest electron-withdrawing groups structurally, which could be the cause of this. For the electron-withdrawing group chlorine (Cl), the same holds. Structures comprising fluorine and chlorine can be considered to have anticancer properties due to the nature of these chemicals. In fact, the anticancer activity was enhanced by the presence of electron donor groups when the molecules as a whole were studied. It is important to consider the bonded group effect in compounds with chalcone structures. Figure 4 shows the chemicals' positions about the target protein. The substances were discovered to interact with a large number of the protein's amino acid residues. Hydrogen bonds are the most efficient form of interaction between molecules and the 1HJD target protein. The target protein's amino acid residues TYR79, SER51, and LYS11 were joined by compounds i5 and i3 to create h-bonds. H-bonds were formed by compounds i8 and i2 with the amino acid residues of LYS11. Compounds i4, i6 and i7 formed H-bonds with amino acid residues TYR79 and SER51.

4. Conclusions

The structure of 2-benzylidene-1-indanone (i1) was modified by the addition of various donor and electron-withdrawing groups. Using computational chemistry, the effects of these chemicals on biological activity were investigated and comparisons were performed. It is based on the widely used density functional theory (DFT), a computational chemistry technique that links molecules' biological functions. Using quantum chemical parameters and molecular docking investigations, it was found that the CF3 electron-withdrawing group's anticancer activity was enhanced by the molecular size change. Molecular

electrostatic potential maps (MEP) and contour diagrams of 2-benzylidene-1-indanone and its derivatives were displayed. It was found that the 1-indanone portion of 2-benzylidene-1-indanone and the compounds derived from it include oxygen atoms that remove electrons. Results from molecular docking and biological activities revealed comparable patterns in terms of quantum chemical parameters.

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