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In Silico Molecular Modeling and Prediction of ADMET Properties for Novel Dioxoisoindoline Derivatives as Anticancer Agents

Reem Safi Ali [1], Mohammed Oday Ezzat [2]

[1] *Department of Chemistry, College of Education for Pure Sciences, University of Anbar, Ramadi, Iraq*

[2] *Department of Chemistry, College of Education for Women, University of Anbar, Ramadi, Iraq*

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ABSTRACT

The decreased efficiency of the existing anticancer drugs is an unsolved problem in both basic and advanced medicine. Conducting theoretical chemical studies to identify possible drug candidates using Dioxoisoindoline derivatives is one of the proposed solutions to this problem. This specific study applied molecular docking and ΔG calculations to evaluate the activity of dioxoisoindoline derivatives against cancer-related proteins. The higher the negative ΔG value, the better the match between the compound and protein interactions. According to this study, five compounds (R1_R5) presented significant activity against various proteins. All of them presented high negative values—especially the two compounds R3 and R4, which showed high effectiveness against six cancer-related proteins. The achieved ΔG values for all derivatives were within a suitable range, suggesting their capability as therapeutic agents. According to these results, the Dioxoisoindoline derivatives under observation show the potential to target different cancer-related proteins. A Density Functional Theory study was performed to determine the Lowest Unoccupied Molecular Orbital and Highest Occupied Molecular Orbital for five compounds. It was used to calculate the gap, Electron affinity, Ionization Potential, Electronegativity, Softness and Hardness of the molecules. The online in silico prediction model ADMET lab 3.0 was used to determine ADMET attributes such as Molecular weight, Number of hydrogen bond donors, Number of hydrogen bond acceptors, the logarithm of the n-octanol/water distribution coefficient, topological polar surface area and Boiling point. The physicochemical properties of all five compounds were determined, and they met the Lipinski rule of five (i.e., the drug-like rule). Overall, the study highlights the importance of developing alternative anticancer medications and recommends further research and development of potential anticancer drugs.

Keywords: Anticancer, Molecular modeling, Docking affinity, ADMET, DFT study.

Name: Reem Safi Ali **E-mail:** ree23u4012@uoanbar.edu.iq

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النمذجة الجزيئية الحاسوبية والتنبؤ بخصائص ADMET لمشتقات الديوكسوايزواندولين الجديدة كمضادات للسرطان

ريم صافي علي[1]، محمد عدي عزت [2]

[1]قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة الأنبار، الرمادي، العراق

[2]قسم الكيمياء، كلية التربية للبنات، جامعة الأنبار، الرمادي، العراق

الملخص

انخفاض كفاءة الأدوية المضادة للسرطان الحالية يُعد مشكلة غير محلولة في كل من الطب الأساسي والمتقدم. ومن بين الحلول المقترحة لهذه المشكلة إجراء دراسات كيميائية نظرية لتوضيح إمكانية استخدام مشتقات Dioxoisoindoline كأدوية محتملة. وقد طبقت هذه الدراسة تحديدًا تقنيات الالتحام الجزيئي (molecular docking) وحسابات ΔG لتقييم نشاط مشتقات Dioxoisoindoline ضد البروتينات المرتبطة بالسرطان. وكلما زادت القيمة السالبة لـΔG كان التوافق بين المركب والبروتين أكبر. وبحسب هذه الدراسة، فقد أظهرت خمسة مركبات R1 – R5 نشاطًا ملحوظًا ضد بروتينات مختلفة، حيث اظهرت جميعها قيمًا سالبة عالية. وقد تميز المركبان R3 و R4 بفعالية عالية ضد ستة بروتينات مرتبطة بالسرطان. وكانت قيم ΔG التي تم الحصول عليها لجميع المشتقات ضمن النطاق المناسب، مما يشير إلى قدرتها المحتملة كعوامل علاجية. وقد تم استخدام نظرية الكثافة الوظيفية لتحديد أعلى مستوى طاقة مشغول (HOMO) وأدنى مستوى طاقة غير مشغول (LUMO)للمركبات الخمسة، حيث استُخدمت هذه المعلومات لحساب الفجوة الطاقية، الألفة الإلكترونية، جهد التأين، الكهرسلبية، الليونة والصلابة الجزيئية. كما تم استخدام النموذج الإلكتروني للتنبؤ (ADMET lab 3.0) لتحديد خصائص ADMET مثل الوزن الجزيئي، عدد مستقبلات ومُعطيات روابط الهيدروجين، لوغاريتم معامل توزيع الأوكتانول/الماء، السطح القطبي الطوبولوجي ونقطة الغليان. وقد تم الكشف عن الخصائص الفيزيائية–الكيميائية للمركبات الخمسة جميعها، ولوحظ أنها تفي بمعايير قواعد تشابه الدواء، مثل قاعدة ليبينسكي وبشكل عام، تؤكد الدراسة على أهمية تطوير أدوية بديلة مضادة للسرطان وتوصي بمزيد من البحث والتطوير في هذا المجال.

INTRODUCTION

Cancer is a complex disease with many causes, and multiple factors affect its spread and progression. The combination of environmental and hereditary factors can lead normal cells to transform into tumor cells. Tumor cells can progress to invade adjacent tissues and grow, spreading to other organs [(1)]. In this disease, cells lose the ability to control their growth, leading to the formation of solid cell masses known as tumors, or to liquid cancers (bone marrow cancers and leukemias). It is one of the major causes of death around the world [(2)]. Controlling cancer is achieved by many treatment methods, including radiotherapy, chemotherapy, surgery and immunotherapy, in combination or singly with kinase inhibitors. Most anticancer drugs use the concept of kinase inhibition [(3, 4)]. According to lifestyle and environmental differences, the incidence rate of cancer widely varies across the world. However, the incidence rate is expected to increase in the future. This underscores the importance of developing new and effective medications to mitigate the impact of cancer [(5)]. The discovery silico and computer-aided drug design (CADD) in recent years have assisted scientists in simulating chemical systems, resolving 3D structures, investigating the atomic processes of pharmaceuticals and naturally occurring molecules, and optimizing and developing new chemical compounds. With the new techniques presented, drug discovery and development have become more effective than ever before [(6, 7)]. Dioxoisoindoline derivatives are recognized as a vital component of

several substances that exhibit a broad range of biological and medicinal properties. This class of compounds has analgesic, cytotoxic, antihyperglycemic, antihypertensive, antipsychotic, anti-inflammatory, and anticancer properties. Dioxoisoindoline derivatives are assumed to have a notable binding affinity (ΔG) with certain proteins within these medications. Nowadays, routine calculations of molecular structures, reaction energies, barrier heights, and spectroscopic properties aid many chemical investigations. Density functional theory (DFT) evaluated in atomic-orbital basis sets is used in the majority of these quantum-chemical computations. (DFT) is a quantum-mechanical atomistic modeling method used to determine a wide range of properties for practically any atomic system: surfaces, molecules, and crystals. The DFT method is a useful tool for figuring out how a compound's geometry and electronic characteristics, such as the energy calculation of HOMO and LUMO, are. HOMOs are the highest occupied molecular orbitals, LUMOs are the lowest lying unoccupied molecular orbitals. In the theoretical description of chemical reactivity, HOMO and LUMO are the key concepts. For instance, the localization of the HOMO orbital should be considered rather than the total electron density in a nucleophile since the electrons in this orbital are most able to engage in interactions. Ionization potential is then influenced by the value of HOMO [8]. These features were employed in equations to find many molecular properties, such as ionization potential (IP) and electron affinity EA, softness (S), Hardness (η), Electronegativity (μ) and electrophilicity index (ω).

$$\begin{aligned}
&\text{IP} = -EHOMO \\
&\text{EA} = -ELUMO \\
&\text{S} = -2/(EHOMO - ELUMO) \\
&\eta = -1/2\,(EHOMO - ELUMO) \\
&\mu = -1/2\,(EHOMO + ELUMO) \\
&\omega = \mu^2/2\eta
\end{aligned}$$

In this study, as part of this ongoing research, five dioxoisoindoline derivatives were designed to have potential anticancer activity.

THEORETICAL PROCEDURES

CB-Dock predicts the probable interactions between a small chemical and a target protein. The protein and ligand files are uploaded to the website, and then Run Docking is clicked. The tool automatically identifies binding sites and performs molecular docking. After the calculations are completed, the best binding poses and their binding energies are obtained. Finally, the results are analyzed based on binding energy) since lower binding energy values correspond to more stable, stronger interactions between the ligand and the target protein, and the final files are downloaded for visualization in Schrodinger Maestro. In this study, five dioxoisoindoline compounds (R1_R5) were docked Figure 1. Submitted for the protein active site of the seven proteins: Casein Kinase II (CK2) Alpha Inhibitors (5CT0), Broad-Spectrum Kinase Inhibitor (1UWJ), Human Estrogen Receptor Alpha (2IOG), Cyclin Dependent Kinases (CDK), Epidermal Growth Factor Receptor (1M17), Poly (ADP-Ribose) Polymerase-1 (PARP-1) Inhibitors (5DS3), Transforming Growth Factor Beta (Tgfβ) Receptors (6B8Y). These proteins were retrieved from the Protein Data Bank.[9].

Dioxoisoindolione derivatives have been submitted for the protein active site. Chemical structures were constructed using ChemDraw (version 20.0), part of the Che Office suite. To determine the potential energy surface, MM2 energy minimization was performed for each structure, accounting for thermal degrees of freedom and energies. The models' final conformations were discovered. The energy-minimized ligand molecules were then subjected to quantum mechanics calculations and geometry optimization using the B3LYP/6-31G++ (d, p) level of theory, with Pi-Cation, H-bonding, and Pi-Pi stacking as the most common interactions between proteins and compounds containing residues. The DFT-optimized structures were fed into CB-dock as

input[10]. A total of 5 derivatives were subjected to ADMET analysis using ADMETlab 3.0 to predict their physicochemical properties and drug-likeness [11].

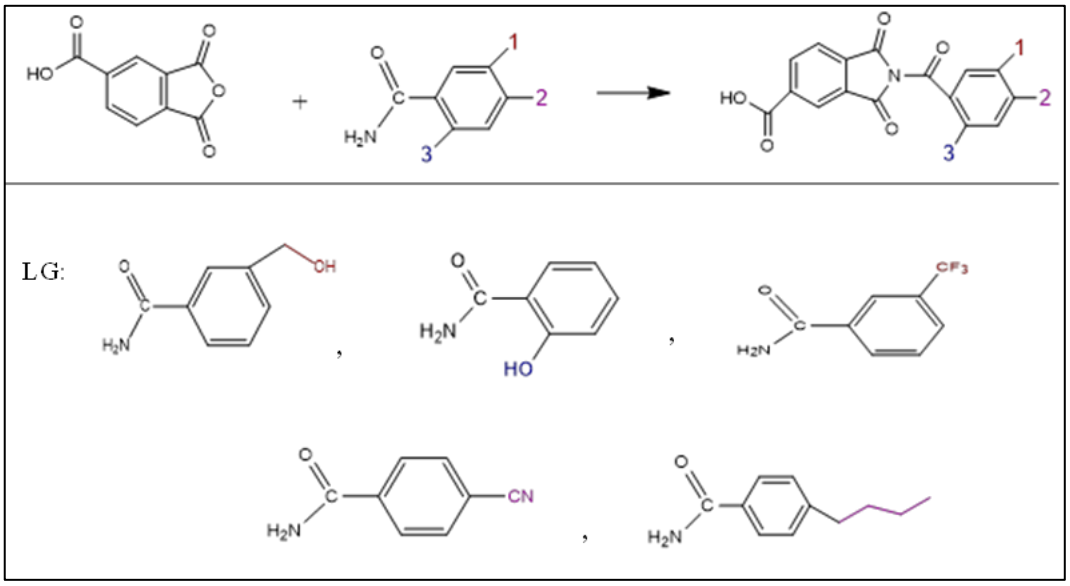

Fig. 1 shows the chemical structure of the five compounds (R1_R5).

ADMET PREDICTION

By using the ADMETlab 3.0 site, a total of five derivatives were subjected to the ADMET study. The ADMETlab 3.0 site is an integrated online platform for comprehensive, accurate predictions of ADMET properties. It is the second updated version of the web server, providing an efficient and comprehensive platform for evaluating ADMET-related parameters, as well as medicinal chemistry, physicochemical properties and characteristics involved in the drug discovery process [11]. The structures of the suggested compounds are converted to Simplified Molecular-Input Line-Entry System (SMILES). Then, the chemical compounds were submitted to the same site for in silico pharmacokinetic prediction, including molecular weight (MW). It is used to determine the size of the molecule and how easily it is absorbed and distributed within the body, i.e., the number of hydrogen bond donors (nHD). Hydrogen bonds are essential for molecular stability and interaction with biological receptors in drug design. Molecules with a high number of donors may be more reactive. Several hydrogen bond acceptors (nHA) help determine how the molecule interacts with receptors and stabilize the interaction with biological targets. The logarithm of the n-octanol/water distribution coefficients (logP) reflects the solubility in fats versus solubility in water. It helps determine the compound's biological stability, membrane permeability, and metabolism. High logP values indicate fat solubility, which can enhance absorption and passage through biological barriers. The logarithm of aqueous solubility value (logS) reflects the compound's solubility in water. Water solubility is an important indicator in drug design because poorly soluble molecules may have difficulty with absorption and distribution within the body [12]. And the logarithm of the n-octanol/water distribution coefficient at pH=7.4 (logD), as well as other properties such as Topological Polar Surface Area (TPSA) and Boiling Point (BP), have been predicted. The physicochemical properties of all five compounds were detected. It was observed that they meet the criteria of the drug-like rule, i.e., Lipinski rule of five, which includes the Molecular weight should be less than 500 Daltons, the compound should have less than 5 hydrogen bond donors (e.g., -OH or -NH groups), and it should have less than 10 hydrogen bond acceptors (e.g., nitrogen or oxygen atoms). The logP (a measure of lipophilicity or how fat-

soluble the compound is) should be less than 5. If a compound violates more than one of these rules, it is probable to have poor absorption or permeation in the human body. However, it is important to note that the rule does not guarantee a drug's efficacy or safety, but it serves as a useful guideline for early drug discovery [13].

RESULTS AND DISCUSSION

Molecular docking: "Docking" is a molecular modeling technique. Explains the fit between two or more proteins and ligands, which is dictated by "ΔG." Better matching between the chemical molecule and the protein, which is indicated by a larger negative ΔG value. This procedure makes the discovery and development OF DRUGS much easier, as it helps to predict the molecular mechanisms of protein-ligand interactions. Amino acid interactions within a protein's active site are critical to the protein's function. Different amino acids have different docking affinities because of the properties and functional groups they bring to the active site. [14]. In this study, quantum-mechanical computations and molecular-level theory are used to examine how different compounds interact with anticancer-active proteins. All five compounds (R1_R5) interact with anticancer-active proteins and show a large negative "ΔG" value. When comparing the results with the Doxorubicin anticancer drug ("ΔG = -9.7 kJ/mol ", we found that compound (R3, R4) interacted with the protein 5CT0, which has a large negative "ΔG" value (-9.9, -10 kJ/mol) .All Compounds (R1, R2, R3, R4, R5) exhibited a high affinity for the protein 1UWJ with a ΔG value (-10, -9.9, -10.6, -10.1, 9.8) kJ/mol, sequentially, which is higher than the ΔG value of the Doxorubicin drug with the protein, which is equal to -9.2 kJ/mol.

In addition, five compounds (R1_R5) interacted with protein 2IOG and showed a higher negative "ΔG" value compared with Doxorubicin with protein, which is equal to -6.9 kJ/mol .At the same time, the values of ΔG for the compounds are equal to (-9.1, -9.1, -10, -9.3, -8.8) kJ/mol, sequentially . Compounds (R3, R4) interacted with protein 2R3J and showed a higher negative "ΔG" value compared with Doxorubicin with protein, which is equal to -9 kJ/mol. At the same time, the values of ΔG for the compounds are equal to (-9.7, -9.3) kJ/mol, sequentially .The binding with the protein 1M17 showed that all five compounds had large ΔG values, but they were lower than the "ΔG" value of the drug, which is -8.9 kJ/mol. At the same time, the values of ΔG for compounds are equal to (-8.6, -8.4, -8.6, -8.2, -8) kJ/mol, sequentially .Binding of compounds with protein 5DS3, the results showed that only compound R3 had a higher ΔG" value which is equal to –9.9 kJ/mol and the other compounds had a slightly lower ΔG" value which is equal to (-9.1,-8.9, -9.2, -8.9) kJ/mol than the Doxorubicin drug with protein, which is equal to –9.7 kJ/mol . All five compounds (R1_R5) interacted with protein 6B8Y and showed high negative "ΔG" values, which are equal to (-9.4, -8.9, -9.5, -9.3, -----9.3) kJ/mol, sequentially. All binding affinity values, surrounding residues, and hydrogen-bonding interactions for the investigated compounds against the target proteins are listed in Table 3. While the values of ΔG for drug Doxorubicin are equal to -7.2 kJ/mol. Compounds that showed more negative values than the Doxorubicin drug have the potential to be effective anticancer medications. Based on these results, it is clear that compounds R3 and R4 have the most negative ΔG values when interacting with all seven proteins, indicating greater activity and potential as anticancer drugs. Figure 2 shows the 2D and 3D drawings of the association of Compound R3 with the protein 1UWJ. In addition, for the five compounds, the chemical and physical characteristics were predicted using the ADMETlab 3.0 website, and each was found to comply with Lipinski's rule of five and meet the criteria of the drug-like rule .Compound R1 has a molecular weight of 325.06 g/mol, with 7.0 hydrogen bond acceptors and 2.0 hydrogen bond donors. The logarithm of aqueous solubility is -3.249, and the logarithm of the n-octanol/water distribution coefficients is 0.736. Furthermore, the n-

octanol/water distribution coefficient is 0.984. Refer to Table 1 to continue the values for the other compounds. The energy of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for each of the five compounds was determined using Density functional theory (DFT) [8]. Knowing the values of HOMO and LUMO helps determine the reactivity of the molecule and its ability to interact with biological receptors. Molecules with a small HOMO-LUMO gap are more reactive and thus more pharmacologically effective. Additionally, the ionization potential, gap, EA, Electronegativity, softness (S) and Hardness (η) finding equations were computed. Knowing the ionization potential helps determine a molecule's stability and its tendency to lose electrons. Molecules with low ionization energy may be more reactive with protein receptors, which affects their ability to bind and interact. Electronegativity affects a molecule's polarity and its interactions with proteins. Molecules with high electronegativity tend to attract electrons, making them more reactive in interactions with protein receptors, thereby improving the drug's efficacy. Soft molecules are often more reactive and more likely to interact with biological targets, such as proteins. They may form stable complexes with receptors or other macromolecules. Hard molecules tend to be more stable and less reactive, which may make them suitable for designing drugs with low toxicity or prolonged action. The electrophilicity index can be useful for predicting how a drug molecule will interact with biological nucleophiles, such as amino acids in proteins. Molecules with higher ω values may form covalent bonds with their targets, which could be beneficial for drugs designed to inhibit a protein (15) irreversibly. Table (2) is a List of quantum chemical parameters, and Figure (3) shows HOMO, LUMO and Gap for R3 and R4.

Table 1: ADMET Predictions of studied compounds.

Physicochemical Property					
qualities	R1	R2	R3	R4	R5
MW g/mol	325.06	311.04	363.04	320.04	351.11
nHA	7.0	7.0	6.0	7.0	6.0
nHD	2.0	2.0	1.0	1.0	1.0
TPSA	111.98	111.98	91.75	115.54	91.75
logS	-3.249	-2.927	-4.262	-3.368	-4.287
logP	0.736	1.834	2.544	0.839	3.675
logD7.4	0.981	1.693	2.167	0.907	2.677

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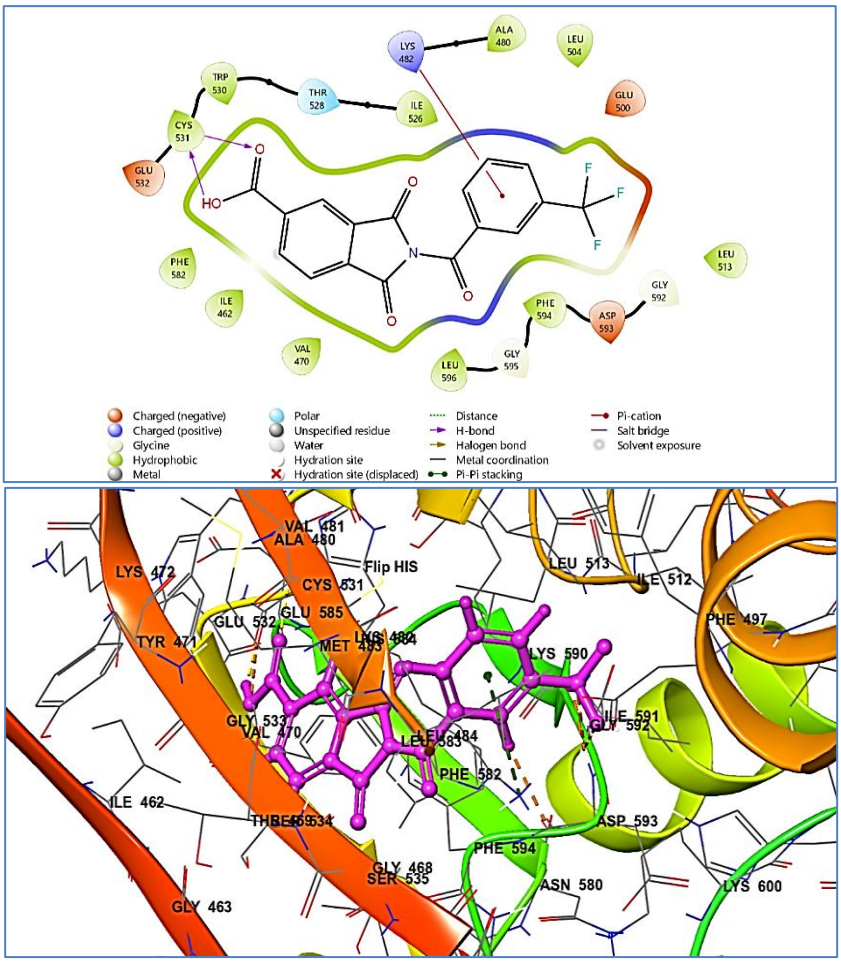

Fig. 2 shows the 2D and 3D drawings of the association of Compound R3 with the protein1UWJ (The complex of mutant V599E B-RAF and BAY439006).

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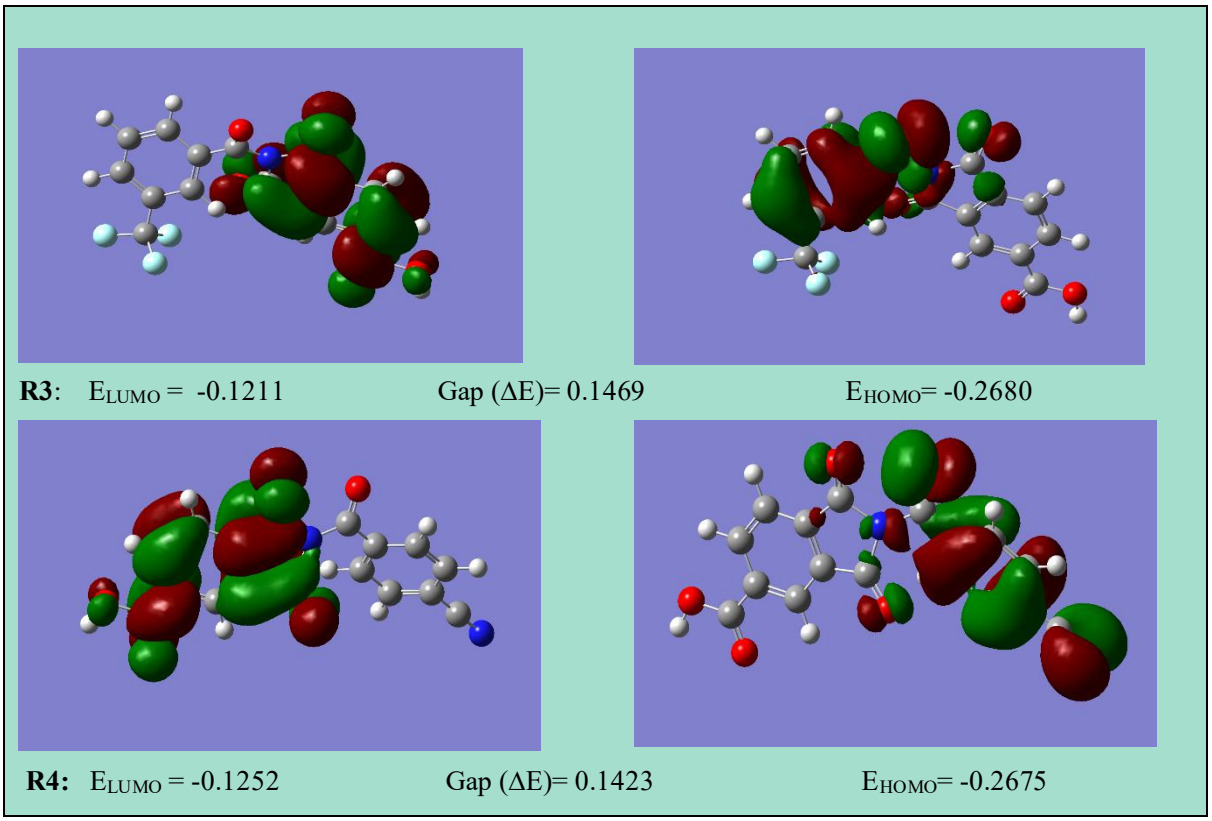


Figure 3: The figure shows HOMO, LUMO and Gap for R3 and R4

Table 2: List of quantum chemical parameters

Comp	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{gap} (eV)	IP	EA	η(eV)	s (eV^{-1})	μ (eV)	ω (eV)
R1	-0.2459	-0.1221	0.1238	0.2459	0.1221	0.0619	16.1446	0.1840	0.2734
R2	-0.2320	-0.1106	0.1214	0.2320	0.1106	0.0607	16.4676	0.1713	0.2417
R3	-0.2680	-0.1211	0.1469	0.2680	0.1211	0.0734	13.6128	0.1946	0.2577
R4	-0.2675	-0.1252	0.1423	0.2675	0.1252	0.0711	14.0508	0.1964	0.02709
R5	-0.2424	-0.1147	0.1276	0.2424	0.1147	0.0638	15.6629	0.1785	0.2497

Table 3: The results ΔG from docking of compounds and proteins.

(A): The results ΔG from docking of compounds and 5CT0			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-9	LYS_{122}, LYS_{158}, PHE_{121}, ASP_{120}, ASP_{175}, ASN_{118}, ASN_{161}, MET_{163}, $VAL_{162,53}$,HIS_{160},PRO_{159},SER_{51},$GLY_{48,46}$, ARG_{47},LEU_{45}	LYS_{158}, ASP_{175}, ASP_{120} (H-bond)
R2	-9.4	ASN_{118},THR_{119},ASP_{120},PHE_{121},LEU_{124}, LEU_{128}, LEU_{218}, LEU_{222}, TYR_{136}, MET_{137}, MET_{221}, MET_{225}, MET_{163}, ILE_{140}, ILE, ILE_{164}, SER_{224}, PRO_{159}, HIS_{160}, VAL_{162}	ASN_{118}, VAL_{162} (H-bond)
R3	-9.9	MET_{163}, HIS_{160}, HIS_{115}, LYS_{158}, $VAL_{53,116}$, SER_{51}, ASP_{175}, $GLY_{48,46}$, LEU_{45}, ARG_{43}, ASN_{118}	
R4	-10	$LEU_{124,45}$, LYS_{122},PHE_{121},ASP_{120},THR_{119},ASN_{118}, ILE_{164}, MET_{163},VAL_{162}, HIS_{160}, PRO_{159}, GLY_{46}, ARG_{47}	VAL_{162}, PHE_{121}, LYS_{122}, ARG_{47} (H-bond); HIS_{160} (Pi – Pi stacking)
R5	-9.5	GLY_{46}, GLY_{48}, ARG_{47}, SER_{51}, VAL_{53}, VAL_{162}, ILE_{174}, PRO_{159}, HIS_{160}, MET_{163}, LEU_{124}, ILE_{164}, LYS_{122}, PHE_{121}, ASP_{120}, THR_{119}, ASN_{118}	H_2O(H-bond)

(B): The results ΔG from docking of compounds and 1UWJ			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-10	PHE_{582}, PHE_{594}, ILE_{462}, ILE_{526}, VAL_{470}, LEU_{596}, LEU_{513}, LEU_{504}, ASP_{593}, GLY_{592}, LYS_{600}, LYS_{482}, GLU_{500}, GLU_{532}, THR_{528} , GLN_{529}, TRP_{530}, CYS_{531}, ALA_{480}	CYS_{531}, ASP_{593} (H-bond); LYS_{482} (Pi-cation)
R2	-9.9	GLY_{533}, GLY_{592}, GLU_{532} , GLU_{500}, CYS_{531}, TRP_{530}, GLN_{529}, THR_{528}, ILE_{526}, ILE_{462}, LEU_{513}, ALA_{480}, LYS_{482}, ASP_{593}, PHE_{594}, $_{582}$, VAL_{470}	CYS_{531}, THR_{528} (H-bond); PHE_{594} (Pi – Pi stacking)
R3	-10.6	GLU_{523}, GLU_{500}, CYS_{531}, TRP_{530}, THR_{528}, ILE_{526}, ILE_{462}, LYS_{482}, ALA_{480}, LEU_{504}, LEU_{513}, LEU_{596}, GLY_{592}, GLY_{595} ASP_{593}, PHE_{594}, PHE_{582}, VAL_{470}	CYS_{531}(H-bond); LYS_{482}(Pi-cation)
R4	-10.1	GLU523, 500, CYS531, TRP530, GLN529, THR528, ILE526, 462, ALA480, LYS482, LEU504, 513,596, GLY592, ASP593 , PHE594, 582, VAL470	CYS_{531}(H-bond); PHE_{594} (Pi – Pi stacking)
R5	-9.8	ILE_{462}, ILE_{526}, PHE_{582}, PHE_{594}, CYS_{531}, TRP_{530}, GLN_{529}, THR_{528}, ILU_{526}, ILU_{462}, LEU_{504}, LEU_{513}, ALA_{480}, LYS_{482}, GLU_{500}, VAL_{470}	CYS_{531}(H-bond); PHE_{594} (Pi – Pi stacking)
(C): The results ΔG from docking of compounds and 2IOG			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-9.1	CYS_{530}, LYS_{531}, LEU_{346}, LEU_{525}, LEU_{349}, LEU_{384}, LEU_{387}, LEU_{391}, LEU_{428}, TRH_{347}, ALA_{350}, ASP_{351}, GLU_{353}, ARG_{394}, MET_{388}, PHE_{404}, TRP_{383}	LYS_{531}, ASP_{351}, GLU_{353} (H-bond); PHE_{404} (Pi – Pi stacking)
R2	-9.1	ARG_{394}, LEU_{391}, LEU_{349}, LEU_{387}, LEU_{346}, LEU_{384}, LEU_{428}, LEU_{525}, MET_{388}, GLY_{521}, $MET_{522,343,528,421}$, HIS_{524}, PHE_{425}, VAL_{418}, PHE_{404}, ALA_{350}, GLU_{353}	GLY_{521}, GLU_{353}, ARG_{394}, LEU_{387}, H_2O (H-bond); PHE_{404} (Pi – Pi stacking)
R3	-10	ARG_{394}, LEU_{391}, LEU_{349}, LEU_{387}, LEU_{346}, LEU_{384}, LEU_{428}, LEU_{384}, LEU_{525}, MET_{388}, MET_{343}, MET_{528}, MET_{421}, ILE_{424}, VAL_{418}, CYS_{530}, PHE_{404}, ALA_{350}, GLU_{353}	GLU_{353}, ARG_{394}, LEU_{387}, H_2O (H-bond);PHE_{404} (Pi – Pi stacking
R4	-9.3	ARG_{394}, LEU_{391}, LEU_{349}, LEU_{387}, LEU_{428}, LEU_{346}, LEU_{348}, LEU_{525} , MET_{388}, MET_{528}, MET_{421}, GLU_{353} , GLU_{419}, ALA_{350}, PHE_{404}, ILE_{424}, $GLY_{420,\ 521}$, VAL_{418}, HIS_{524}	ARG_{394}, GLU_{353}, LEU_{387}, H_2O (H-bond);PHE_{404} (Pi – Pi stacking)
R5	-8.7	GLU_{353}, GLU_{419}, ALA_{350}, ARG_{394}, LEU_{391}, LEU_{349}, LEU_{428}, LEU_{387}, LEU_{384}, LEU_{346}, LEU_{525}, MET_{388}, MET_{421}, MET_{528}, MET_{343}, PHE_{425}, PHE_{404}, ILE_{424}, $GLY_{420,521}$, VAL_{418}, HIS_{524}	GLU_{353}, LEU_{387}, ARG_{394}, H_2O (H-bond);PHE_{404} (Pi – Pi stacking
(D): The results ΔG from docking of compounds and 2R3J			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-8.9	ASP_{145}, ASP_{127}, ALA_{144}, ALA_{31}, LEU_{134}, LEU_{83}, ASN_{132}, GLN_{131}, LYS_{129}, LYS_{33}, TRH_{14}, GLY_{13}, GLY_{11}, GLU_{12}, GLU_{81}, ILE_{10}, VAL_{18}, VAL_{64}, PHE_{82}, PHE_{80}	ASP145, ASN132 (H-bond)
R2	-8.9	LUE_{134}, LUE_{83}, LUE_{148}, ASN_{132}, GLN_{131}, GLN_{85} LYS_{33}, ALA_{31}, ALA_{144}, ASP_{145}, ASP_{86}, PHE_{80}, PHE_{82}, HIE_{84}, ILE_{10}, GLU_{8}, VAL_{18}, VAL_{64}	ASP145, LUE83 (H-bond)
R3	-9.7	LYS_{129}, GLN_{131}, GLN_{85}, ASN_{132}, LEU_{134}, LEU_{83}, ALA_{31}, ALA ALA_{144}, PHE_{82}, HIE_{84}, ASP_{86}, ASP_{145}, ILE_{10}, VAL_{18}, GLY_{11}, GLY_{13}, GLU_{12}, THR_{14}	GLU12, LYS129 (H-bond)

R4	-9.3	LEU_{148}, LEU_{134}, LEU_{83}, VAL_{18}, VAL_{64}, ASP_{145}, ASP_{86}, ALA_{144}, ALA_{31}, PHE_{80}, PHE_{82} , HIE_{84}, GLN_{85}, GLU_{8}, GLU_{81}, ILE_{10}, LYS_{33}	ASP145, LUE83 (H-bond)
R5	-8.8	ALA_{144}, ALA_{31}, ASP_{145}, ASP_{86}, VAL_{64}, VAL_{18}, PHE_{80}, PHE_{82}, LEU_{83}, LEU_{134}, HIE_{84}, GLN_{85}, GLN_{131}, LYS_{89}, LYS_{20}, LYS_{33}, GLU_{8}, ILE_{10}	ASP145, LUE83 (H-bond)
(E): The results ΔG from docking of compounds and 1M17			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-8.6	GLY_{695}, GLY_{772}, LEU_{694}, LEU_{768}, LEU_{764}, LEU_{820}, MET_{769}, GLN_{767}, THR_{766}, THR_{830}, GLU_{738}, ASP_{831}, LYS_{721}, ALA_{719}, VAL_{702}	ASP_{831}, MET_{769}, LEU_{694} (H-bond)
R2	-8.4	GLY_{772}, PHE_{771}, PRO_{770}, MET_{769}, LEU_{768}, LEU_{820}, LEU_{764}, LEU LEU_{694}, GLN_{767}, THR_{766}, THR_{830}, ALA_{719}, LYS_{721}, GLU_{738}, ASP_{831}, VAL_{702}	PRO_{770}, MET_{769}, THR_{766} (H-bond)
R3	-8.6	GLY_{772}, PHE_{771}, PHE_{832}, PRO_{770}, MET_{769}, MET_{742}, LEU_{768}, LEU LEU_{820}, LEU_{764}, LEU_{694}, GLN_{767}, THR_{766}, THR_{830}, ASP_{831}, GLU_{738}, LYS_{721}, ILE_{720}, ALA_{719}, VAL_{702}	PRO_{770}, MET_{769} (H-bond)
R4	-8.2	GLY_{772}, PHE_{771}, PRO_{770}, MET_{769}, MET_{742}, LEU_{768}, LEU_{820}, LEU_{764}, LEU_{753}, LEU_{694}, GLN_{767}, THR_{766}, THR_{830}, GLU_{738}, ALA_{719}, LYS_{721}, ASP_{831}, VAL_{702}	PRO_{770} (H-bond) LYS_{721} (Pi-cation)
R5	-8	CYS_{773}, CYS_{751}, GLY_{772}, PRO_{770}, MET_{769}, MET_{742}, LEU_{768}, LEU_{820}, LEU_{764}, LEU $_{753}$, LEU $_{694}$, GLN_{767}, THR_{766}, THR_{830}, ILE_{765}, ILE_{720}, LYS_{721}, ALA_{719}, $GLU7_{38}$, ASP_{831}, VAL_{702}	MET_{769} (H-bond)
(F): The results ΔG from docking of compounds and 5DS3			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-9.1	GLY_{863}, GLY_{888}, HIS_{862}, TRP_{861}, LYS_{903}, SER_{904}, TYR_{907}, TYR_{896}, TYR_{889}, ALA_{898}, PHE_{897}, GLU_{988}, MET_{890}, $1PE_{1101}$	GLY_{863}, TRP_{861} TYR_{889}, H_2O(H-bond); TYR_{907}(Pi – Pi stacking
R2	-8.9	LUE_{984}, GLU_{988}, TYR_{896}, TYR_{907}, TYR_{889}, PHE_{897}, PHE_{891}, ALA_{989}, TRP_{861}, HIS_{862}, GLY_{863}, GLY_{888}, SER_{904}, LYS_{903}, MET_{890},$1PE_{1101}$	GLY_{863}, GLU_{988}, SER_{904} (H-bond) TYR_{907} (Pi – Pi stacking)LYS_{903} (Pi-cation)
R3	-9.9	GLY_{863}, GLY_{888}, HIS_{862}, TRP_{861}, LYS_{903}, SER_{904}, TYR_{907}, TYR_{896}, TYR_{889}, PHE_{897}, ALA_{898}, GLU_{988}, MET_{890}, $1PE_{1101}$	GLY_{863} (H-bond) TYR_{907}, TYR_{889} (Pi – Pi stacking)
R4	-9.2	GLY_{863}, GLY_{888}, HIS_{862}, TRP_{861}, LYS_{903}, SER_{904}, TYR_{907} , TYR_{896}, TYR_{889}, PHE_{897}, ALA_{898}, $1PE_{1101}$	GLY_{863}, TRP_{861} (H-bond); TYR_{907}, TYR_{889} (Pi – Pi stacking)
R5	-8.9	LEU_{984}, GLU_{988}, LYS_{903}, SER_{904}, ASN_{906}, TYR_{907}, TYR_{896}, TYR_{889}, PHE_{897}, ALA_{898}, GLY_{863}, GLY_{888}, HIS_{862}, TRP_{861}, $1PE_{1101}$, MET_{890}	LYS_{903}, MET_{890} SER_{904}, GLY_{863} (H-bond); TYR_{907} (Pi – Pi stacking)
(g): The results ΔG from docking of compounds and 6B8Y			
Comp	binding affinity ΔG kJ/mol	Residues surrounding the compounds	Residues with interferences
R1	-9.4	SER_{287}, SER_{280}, GLY_{286}, GLU_{284}, GLU_{245}, HIS_{283}, TYR_{282}, TYR_{249},VAL_{279}, VAL_{231}, VAL_{219}, LEU_{278}, LEU_{260}, LEU_{340}, PHE_{262}, ALA_{230}, ALA_{250}, LYS_{232}, ASP_{351}, ILE_{211}	HIS_{283}, LYS_{232} (H-bond)
R2	-8.9	ASP_{290}, ASP_{351}, SER_{287}, SER_{280}, GLY_{286}, ILE_{211}, LEU_{340}, LEU_{260}, LEU_{278} , LEU_{325} , PHE_{262}, VAL_{279}, VAL_{231}, VAL_{219}, SER_{280}, ALA_{230}, ALA_{350} , LYS_{232}, TYR_{249}, GLU_{245}	GLU_{245}, TYR_{249}, ASP_{351}, ASP_{290}, LYS_{232} (H-bond)

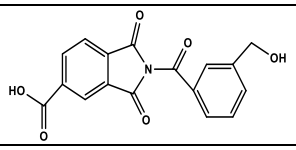
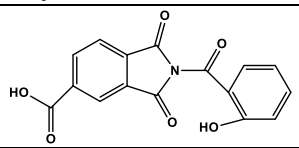
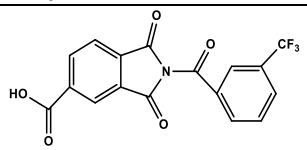
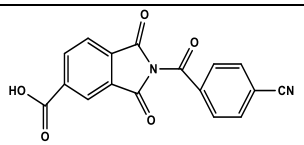
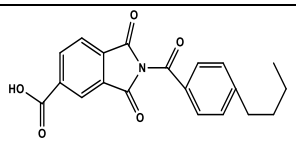
R3	-9.5	SER287,280&GLY286&HIS283&TYR282,249&VAL279,231, 219&LEU278,260,340&PHE262&GLU245,284&ALA230,350 LYS232&ASP351&ILE211	LYS_{232}, HIS_{283} (H-bond)
R4	-9.3	ASP290,351&SER287,280&GLY286&ILE211&LEU340,278 ,352,260&VAL279,219&TYR249&PHE262&ALA350, 230&LYS232&GLU245	LYS_{232}, ASP_{290} (H-bond)
R5	-9.3	SER280,287&ASP281,351,290&TYR282&HIS283&GLU284& GLY286,212,214&PHE289&LYS335,337,213,232&ASN338 &LEU340,260&ILE211&VAL219&ALA350,230	LYS_{232}, HIS_{283} (H-bond)

CONCLUSION

The results revealed that the five compounds exhibited anticancer activity; all of them have a high "ΔG" negative value when interacting with the seven proteins, especially the R3 and R4 compounds ,which have higher negative values when interacting with six out of seven proteins. As for the other compounds, they showed "ΔG" values that were either higher or slightly lower than those of Doxorubicin. It means that the compounds, which showed more negative values than the drug, have the potential to be effective anticancer medications, indicating that they are more active and could be used as possible anticancer drugs. In addition, the physicochemical properties of all five compounds were determined, and they met the criteria of the drug-like rule, i.e., the Lipinski rule of five, increasing the likelihood that they will be used as effective cancer drugs.

Conflict of interest: The authors state they have none.

Appendices: Structural Formula and Name of Compounds of the five studied dioxoisoindoline derivatives.

comp	Structural Formula	Name of Compounds	M.wt g/mol
R1		2-(3-(hydroxymethyl)benzoyl)-1,3-dioxoisoindoline-5-carboxylic acid	325.28
R2		2-(2-hydroxybenzoyl)-1,3-dioxoisoindoline-5-carboxylic acid	311.25
R3		1,3-dioxo-2-(3-(trifluoromethyl) benzoyl)isoindoline-5-carboxylic acid	363.25
R4		2-(4-cyanobenzoyl)-1,3-dioxoisoindoline-5-carboxylic acid	320.26
R5		2-(4-butylbenzoyl)-1,3-dioxoisoindoline-5-carboxylic acid	351.36

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