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Theoretical Calculations and Molecular Design of Novel Dioxoisoindoline Derivatives as Anticancer Agents

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ABSTRACT

The decline in the effectiveness of current anticancer drugs is a persisting issue in basic and advanced medicine. One proposed solution is to conduct theoretical chemical studies to identify potential drugs using dioxoisoindoline derivatives. This work utilized molecular docking and ΔG calculations to assess the derivatives' activity against cancer-related proteins. A high negative ΔG value indicates a close match between the chemical and protein interactions. Several compounds, such as S4 ΔG=−8.983, S1 ΔG=−8.498, and S1 ΔG=−9.121, exhibited significant activity against various proteins. The ΔG values obtained for all derivatives were within an acceptable range, suggesting their potential as therapeutic agents. These results indicate that the dioxoisoindoline derivatives under investigation show promise for targeting different cancer-related proteins, underscoring the importance of developing alternative anticancer drugs. This work introduces a chemical study approach using these derivatives. The tested compounds have shown potential activity against specific proteins, positioning them as prospective candidates for further exploration and development as potential anticancer medications.

Introduction

Cancer is a disease in which the control of growth in one or more cells is lost, resulting in either a solid mass of cells known as a tumor or a liquid cancer (i.e., blood or bone marrow-related cancer). It is one of the leading causes of death worldwide, with the primary treatments involving surgery, chemotherapy, and/or radiotherapy. Chemotherapy is the use of low-molecular-weight drugs to selectively destroy tumor cells or at least limit their proliferation. Many cytotoxic agents have drawbacks, such as bone marrow suppression, gastrointestinal tract lesions, hair loss, nausea, and clinical resistance [1][2]. These side effects occur because cytotoxic agents act on tumors and healthy cells. Cancer is a metabolic syndrome that describes the uncontrolled growth of normal cells; it is distinguished by sustained cell proliferation and ability to invade healthy cells (metastasis) and overcome apoptosis [3][4]. Surgical removal and radiation therapy are typically the first steps in the treatment, followed by chemotherapy using various drugs such as cisplatin, doxorubicin, methotrexate, and taxanes [5][6].

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However, chemotherapy has significant drawbacks, including drug resistance, possibility of recurrence, and, most unfortunately, damage to nontargeted cells [7]. Hence, new class of drugs with the same potency but few side effects must be explored. For this goal, we can rely on one of nature's gifts: phytochemicals, which are promising cancer treatment options with low toxicity [8]. To find an effective alternative anticancer drug, this research theoretically evaluated six dioxoisoindoline derivatives, an essential component of numerous substances that have a broad range of medicinal and biological effects. This class of compounds has cytotoxic, antihypertensive, analgesic, antihyperglycemic, antipsychotic, anticancer, and anti-inflammatory properties. We hypothesize that these derivatives have a significant binding affinity (ΔG) with specific proteins within commonly used drugs. As a part of our ongoing research, this study designed and synthesized a series of dioxoisoindoline derivatives with potential anticancer activity.

Materials and Methods

Swiss Dock is a web-based tool provided by the Swiss Institute of Bioinformatics that predicts potential molecular interactions between a target protein and a small molecule. Docking with standard procedure was used to dock the following proteins: 5CT0 (crystal structure of CK2 alpha with 3-(3-chloro-4-(phenyl) benzyl amino) propan-1-ol bound), 1UWJ (the complex of mutant V599E B-RAF and BAY439006), 2IOG human estrogen receptor alpha ligand-binding domain in complex with compound 11F), 2R3J (crystal structure of cyclin-dependent kinase 2 with inhibitor), 1M17 (epidermal growth factor receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib), 5DS3 (crystal structure of constitutively active PARP-1) and 6B8Y(tgf-beta receptor type 1 kinase domain (T204D) in complex with N-(3-fluoropyridin-4-yl)-2-[6-(trifluoromethyl)pyridin-2-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine). Six dioxoisoindolione derivatives were proposed for the protein active site. All chemical structures were created in ChemOffice (Chem Draw 20.0) with the proper 2D orientation. MM2 energy minimization using Chem3D 20.0 calculates steric energy, thermal energy, and other variables and explains how the potential energy surface relates to model conformations. Other factors, such as steric energy and thermal energy, may be used to describe the potential energy surface, the model's conformations [9][10].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, chelation bonding, H-bonding, and Pi-Pi stacking were the SEVEN most common interactions between protein and compounds containing residues. The DFT-optimized structures were fed into Swissdock as input. The Protein Data Bank has the crystal structures of the receptor molecule: 5CT0 (crystal structure of CK2 alpha with 3-(3-chloro-4-(phenyl) benzyl amino) propan-1-ol bound), 1UWJ (the complex of mutant V599E B-RAF and BAY439006), 2IOG (human estrogen receptor alpha ligand-binding domain in complex with compound 11F), 2R3J (crystal structure of cyclin-dependent kinase 2 with inhibitor), 1M17 (epidermal growth factor receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib), 5DS3 (crystal structure of constitutively active PARP-1) and 6B8Y (tgf-beta receptor type 1 kinase domain (T204D) in complex with N-(3-fluoropyridin-4-yl)-2-[6-(trifluoromethyl)pyridin-2-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine).

Results and Discussion

Docking is a molecular modeling theory utilized to elucidate the binding interactions between proteins and ligands. This theory relies on the calculation of binding free energy (ΔG), where a negative value suggests a strong affinity between the ligand and protein. In this study, six compounds were evaluated for their anticancer potential and drug-likeness using docking simulations.

The results indicated that compound S4 exhibited the most promising activity against cancer due to its interaction with the protein 5CT0 (crystal structure of CK2 alpha with 3-(3-chloro-4-(phenyl) benzyl amino) propan-1-ol bound), with a ΔG value of −8.978. Compound S1 demonstrated significant anticancer activity by interacting with multiple proteins: 1UWJ (mutant V599E B-RAF complexed with BAY439006, ΔG=−8.498), 1M17 (epidermal growth factor receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib, ΔG=−6.901), and 5DS3 (constitutively active PARP-1, ΔG=−9.121). Compound S6 exhibited notable anticancer activity against the protein 2IOG (human estrogen receptor alpha ligand-binding domain in complex with compound 11F, ΔG=−8.608), and compound S2 displayed high activity against 2R3J (crystal Structure of cyclin-dependent Kinase 2 with inhibitor, ΔG=−9.805). In addition, compound S4 showed significant affinity toward the protein 6B8Y (tgf-beta receptor type 1 kinase domain (T204D) in complex with N-(3-fluoropyridin-4-yl)-2-[6-(trifluoromethyl)pyridin-2-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine) with a ΔG value of −8.983.

These findings highlight the potential of these compounds as anticancer agents, indicating their ability to effectively interact with specific protein targets implicated in cancer pathways.

The most effective compound, S4, exhibits a binding free energy (ΔG) of −8.978 when bound to the protein 5CT0 (crystal structure of CK2 alpha with 3-(3-chloro-

4-(phenyl) benzyl amino) propan-1-ol). Similarly, the most effective ligand, 54P (Piyalepaşa Mahallesi-Taksim), displays a binding free energy of −9.33. With regard to the ΔG values, the ligand 54P demonstrates a stronger binding affinity to the protein compared with compound S4. This result suggests that the ligand 54P may have a wide range of potential compounds for drug development due to its high ΔG value. When interacting with the protein 1UWJ (the complex of mutant V599E B-RAF and BAY439006), compound S1 yields a ΔG of −8.498. Meanwhile, the most effective ligand, BAX (apoptosis regulator), exhibits a significantly low ΔG of −11.574. This finding indicates that treatments involving BAX may have broader applicability in drug design due to its stronger binding affinity to the protein compared with compound S1. In conjunction with the protein 2IOG (human estrogen receptor alpha ligand-binding domain in complex with compound 11F), compound S6 displays a ΔG of −8.608. The most effective ligand, raloxifene, demonstrates a ΔG of −9.483. This result implies that raloxifene's higher ΔG value suggests it may be more versatile in binding to a wider range of compounds for potential drug development compared with compound S6. Compound S2, shows a ΔG of −9.805 when binding to the protein 2R3J (crystal structure of cyclin-dependent Kinase 2 with inhibitor). Meanwhile, the most effective ligand, SCJ (SC Johnson), presents a ΔG of −9.916. This finding indicates that treatments involving SCJ may have broader potential in drug design due to its stronger binding affinity to the protein compared with those involving compound S2. When interacting with the protein 1M17 (epidermal growth factor receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib), compound S1 exhibits a ΔG of −6.901, and the most effective ligand, gefitinib, displays a ΔG of −8.382. The higher ΔG value of gefitinib suggests it may have a broader range of compounds for drug development compared with compound S1. When bound to the protein 5DS3 (crystal structure of constitutively active PARP-1), compound S1 shows a ΔG of −9.121. Meanwhile, the most effective ligand, olaparib, demonstrates a significantly low ΔG of −13.474. This result indicates that treatments involving olaparib may have a wider range of potential compounds for drug development due to its stronger binding affinity to the protein compared with compound S1. When interacting with the protein 6B8Y (tgf-beta receptor type 1 kinase domain (T204D) in complex with N-(3-fluoropyridin-4-yl)-2-[6-(trifluoromethyl)pyridin-2-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine), compound S4 displays a ΔG of −8.983. By contrast, the most effective ligand (tgf-beta receptor type 1 kinase domain) exhibits a ΔG of −11.971. This finding suggests that because of its higher ΔG value, the ligand has broader applicability in binding to a wider range of compounds for drug development compared with compound S4. Overall, olaparib emerges as the most promising candidate among the ligands, exhibiting the highest ΔG value of −13.474. This high ΔG value implies a strong binding affinity, potentially offering broad prospects in drug design and development.

TABLE LEGENDS

Table 1. Binding affinity (ΔG) and 5CT0, 1UWJ, 2IOG, 2R3J, 1M17, 5DS3 and 6B8Y protein residues surrounding the assessed compounds. Amino-acid abbreviations used: ALA, alanine; ARG, arginine; ASN, asparagine; ASP, aspartic acid; CYS, cysteine; GLU, glutamic acid; GLN, glutamine; GLY, glycine; HIE, histidine with hydrogen on the epsilon nitrogen; HIS, histidine; ILE, isoleucine; LEU, leucine; LYS, lysine; MET, methionine; PHE, phenylalanine; PRO, proline; SER, serine; THR, threonine; TRP, tryptophan; TYR, tyrosine; VAL, valine.

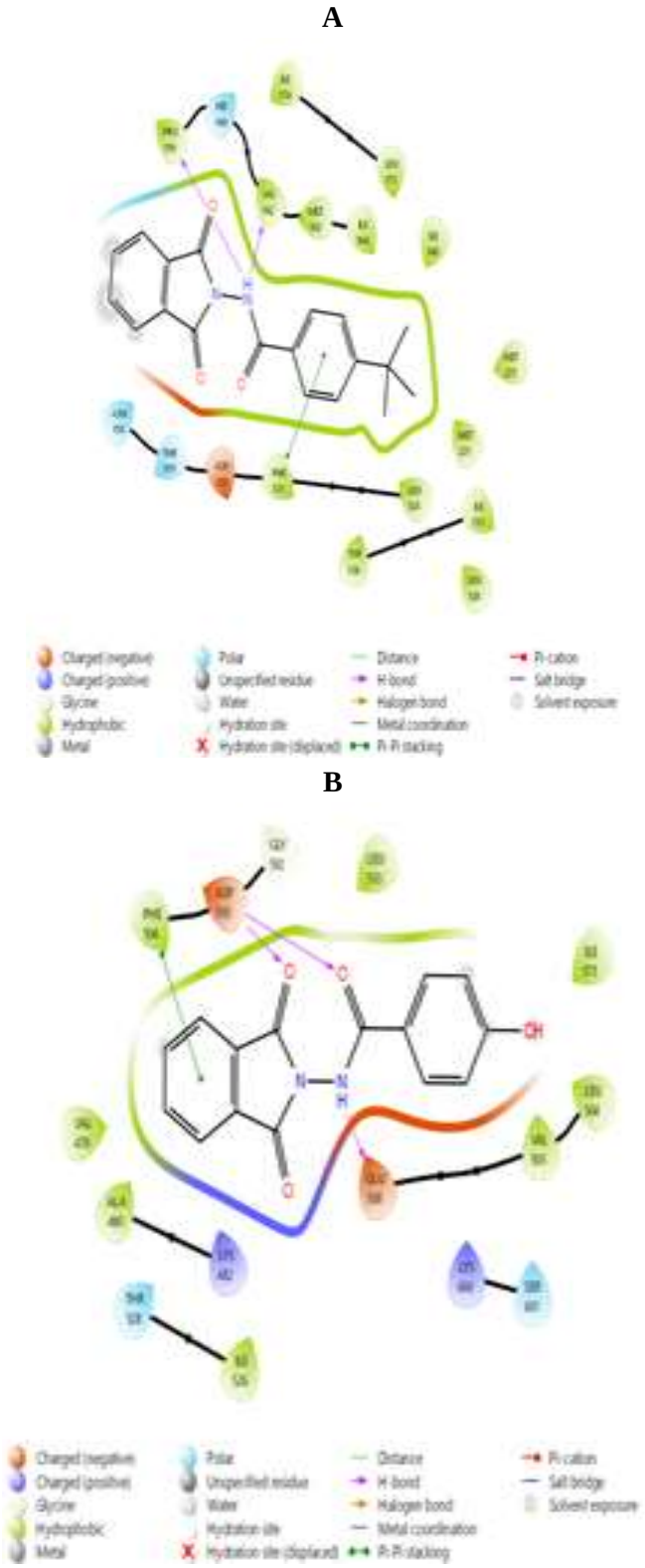

Figure 1:(A) Protein 5CT0 interactions with compound S4 (B) Protein 1UWJ interactions with compound S

Table: ΔG and protein Residues relevant

Compound	ΔG	Residues Surrounding the compounds	Residues with interferences
S6	-8.608	$LEU_{384,387,391,428,349,346,525}$& $MET_{388,421,528}$&ARG_{394}& $PHE_{404,425}$&ILE_{424}&GLU_{53}&VAL_{418}&&CYS_{530}& HIS_{524}	PHE_{404}(pi-pistacking) GLU_{353} (H-bonding)
S1	-8.259	ARG_{394}&$LEU_{391,387,384,525,346,349,428}$&$MET_{388,343,528}$&$TRP_{83}$&$PHE_{404}$&$ILE_{424}$&$THR_{347}$&$ALA_{350}$&$GLU_{353}$&$CYS_{530}$&$HIS_{524}$&$GLY_{521}$	LEU_{387}&ARG_{394} (H-bonding) PHE_{404}(pi-pi stacking)
S4	-7.995	ARG_{394}&$LEU_{391,387,384,525,346,349,428}$&$MET_{388,343,528,421}$ &TRP_{383}&PHE_{404}&ILE_{424} &ALA_{350}&GLU_{353}&CYS_{530}&HIS_{524}&GLY_{521}	PHE_{404} (pi-pi stacking)
S3	-7.538	$LEU_{525,391,387,346,384,354,428}$&$THR_{347}$&$ALA_{350}$& ASP_{351}&LYS_{531}&CYS_{530}&$ILE424$&MET_{388} &TRP_{383}&PHE_{404}	LEU_{346} (H-bonding)
S2	-6.922	VAL_{418}&$GLU_{419,353}$&$MET_{421,528,388,343}$&ILE_{424} &GLY_{521}&HIS_{524}&$LEU_{525,391,387,384,428}$&$PHE_{404}$&$ALA_{350}$	

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S3	S6	S1	S2	Compound	S5
-8.776	-9.052	-9.598	-9.805	ΔG	-6.606
$ASP_{86,145}$&HIE_{84}&$LEU_{83,134}$&$PHE_{82,80}$&$GLU_{81,8}$&$VAL_{64,18}$&$ALA_{31,144}$&$LYS_{33,20}$&ILE_{10}	ASP_{145}&$LEU_{83,134}$&$PHE_{82,80}$&$GLU_{81,12,162}$&$VAL_{64,18,164}$&$ALA_{31,144}$&LYS_{129}&ILE_{10}&$GLY_{11,13}$&$THR_{14,165}$&ASN_{132}&GLN_{131}	$ASP_{86,145}$&HIE_{84}&$LEU_{83,134}$&$PHE_{82,80}$&$GLU_{81,8}$&$VAL_{64,18}$&$ALA_{31,144}$&$LYS_{33,20}$&ILE_{10}	$ASP_{86,145}$&HIE_{84}&$LEU_{83,134}$&$PHE_{82,80}$&$GLU_{81,8}$&$VAL_{64,18}$&$ALA_{31,144}$&$LYS_{33,20}$&ILE_{10}	Residues Surrounding the compounds	$LEU_{384,387,391,428,349,346}$&$MET_{388,343,528}$&$ARG_{394}$&$PHE_{404,425}$&$ILE_{424}$&$GLU_{419,353}$&$VAL_{418}$&$ALA_{350}$&$CYS_{530}$&$HIS_{524}$
LEU_{83}(H-bonding)	GLN_{131}&LYS_{129}(H-bonding)	LEU_{83}&GLU_{8}(H-bonding)	LEU_{83}&GLU_{8}(H-bonding)	Residues with interferences	PHE_{404}(pi-pi stacking)

S5	S6	S3	S1	Compound	S4	S5
-6.355	-6.574	-6.882	-6.901	ΔG	-5.457	-6.358
$LEU_{694\&820,768,764}$&LYS_{721}&GLY_{772}&PRO_{770}&$MET_{769,742}$&PHE_{832}&$THR_{766,830}$&ALA_{719}&VAL_{702}&ASP_{831}&GLU_{738}	$LEU_{694\&820,768,764}$&GLY_{772}&PRO_{770}&$MET_{769,742}$&$THR_{766,830}$&ALA_{719}&LYS_{721}&VAL_{702}&ASP_{831}&GLU_{738}	$LEU_{694\&820,768,753,764}$&$GLY_{772}$&$PRO_{770}$&$MET_{769,742}$&$THR_{766,830}$&$ALA_{719}$&$LYS_{721}$&$VAL_{702}$&$ASP_{831}$&$GLU_{738}$	$LEU_{694\&820,768}$&CYS_{773}&&GLY_{772}&$PRO770$&MET_{769}&$THR_{766,830}$&ALA_{719}&LYS_{721}&VAL_{702}&ASP_{831}&GLU_{738}	Residues Surrounding the compounds	$ASP_{86,145}$&$LEU_{83,134}$&$PHE_{82,80}$&$GLU_{81,12,162}$ $VAL_{64,18,164}$&$ALA_{31,144}$&LYS_{129}&ILE_{10}&$GLY_{11,13}$&$THR_{14,165}$&ASN_{132}&GLN_{131}	ASP_{145}&$LEU_{83,134}$&$PHE_{82,80}$&$GLU_{81,12,162}$&$VAL_{64,18,164}$&$ALA_{31,144}$&LYS_{129}&ILE_{10}&$GLY_{11,13}$&$THR_{14,165}$&ASN_{132}&GLN_{131}
MET_{769}(H-bonding)	MET_{769}&GLU_{738}(H-bonding)	MET_{769} (H-bonding)	MET_{769}(H-bonding)	Residues with interferences	GLN_{131}(H-bonding)	GLN_{131}&LYS_{129}(H-bonding)

S1	S4	Compound	S2	S6
-8.945	-4.9	ΔG	-7.174	-7.196
$ILE_{164,174,140,133}$&$MET_{163,221,225,137}$&VAL_{162}&HIS_{160}&PRO_{159}&$LEU_{171,124,128}$&PHE_{121}&TYR_{136}&ASP_{120}&THR_{119}&ASN_{118}&R_{136}	SER_{904}&$GLY_{863,888}$&$HIS_{862,937}$&TRP_{861}&MET_{890}&$TYR_{907,989,896}$&LYS_{903}&$ALA_{898,935}$&GLU_{988}&PHE_{897}&$1PE_{1101}$	Residues Surrounding the compounds	$ASN_{868,987}$&$SER_{864,904}$&GLY_{863}&HIS_{862}&TRP_{861}&ILE_{872}&$LYS903$&$ALA898$&$TYR_{907,989,896}$&GLU_{988}&PHE_{897}&$1PE_{1101}$	$ASN_{868,987}$&ARG_{878}&$SER_{864,904}$&GLY_{863}&HIS_{862}&TRP_{861}&ILE_{872}&LEU_{877}&LYS_{903}&$TYR_{907,989,896}$&GLU_{988}&PHE_{897}&$1PE_{1101}$&ALA_{898}
ASN_{118}(H-bonding)	TYR_{907}(pi-pi stacking)	Residues with interferences	SER_{904}&GLY_{863}(H-bonding)	SER_{904}&GLY_{863}(H-bonding)HIS_{862}(pi-pi stacking)

S5	S3	Compound	S1	S2
-7.415	-7.423	ΔG	-9.121	-5.386
$ASN_{868,987}$&$SER_{864,904}$&GLY_{863}&HIS_{862}&ILE_{82}&LEU_{877}&LYS_{903}&$TYR_{907,989,896,8}$&GLU_{98}&PHE_{897}&$1PE_{1101}$&ALA_{898}	$ASN_{868,987}$&$ARG_{865,878}$&$SER_{864,904}$&GLY_{863}&HIS_{862}&TRP_{861}&ILE_{872}&LEU_{877}&LYS_{903}&$TYR_{907,989,896,9}$&GLU_{988}&PHE_{897}&$1PE_{1101}$&ALA_{898}	Residues Surrounding the compounds	$ASN_{868,987}$&ARG_{865}&$SER_{864,904}$&GLY_{863}&$HIS8662$&TRP_{861}&ILE_{872}&LEU_{877}&LYS_{903}&$TYR_{907,989,896}$&GLU_{988}&PHE_{897}&$1PE_{1101}$	LEU_{694}&$_{820,768}$&GLY_{772}&PRO_{770}&$MET_{769,742}$&$THR_{766,830}$&ALA_{719}&LYS_{721}&VAL_{702}&ASP_{831}&GLU_{738}
SER904&GLY 863(H-bonding)	SER_{904}&GLY_{863}(H-bonding) HIS_{862}(pi-pi stacking)	Residues with interferences	SER_{904}&GLY_{863}(H-bonding)HIS_{862}(pi-pi stacking)	MET_{769}(H-bonding)

S4	Compound	S1	S2
-4.332	ΔG	-9.121	-5.386
LEU_{694}&$_{820,768}$&CYS_{773}&GLY_{772}&PRO_{770}&$MET_{769,742}$&$THR_{766,830}$&ALA_{719}&LYS_{721}&VAL_{702}&ASP_{831}&GLU_{738}&GLN_{767}	Residues Surrounding the compounds	$ASN_{868,987}$&ARG_{865}&$SER_{864,904}$&GLY_{863}&$HIS8662$&TRP_{861}&ILE_{872}&LEU_{877}&LYS_{903}&$TYR_{907,989,896}$&GLU_{988}&PHE_{897}&$1PE_{1101}$	LEU_{694}&$_{820,768}$&GLY_{772}&PRO_{770}&MET_{769}&CYS_{773}&$THR_{766,830}$&ALA_{719}&LYS_{721}&VAL_{702}&ASP_{831}&GLU_{738}
	Residues with interferences	SER_{904}&GLY_{863}(H-bonding)HIS_{862}(pi-pi stacking)	MET_{769}(H-bonding)

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S4	S1	Compound	S3	S2	S5	S6
-7.849	-8.498	ΔG	-7.251	-7.386	-8.298	-8.794
HIE_{573}&$ILE_{572,571,591,512,526}$&$LEU_{566,504,513}$&$GLY_{592}$&$ASP_{593}$&$PHE_{594}$&$VAL_{470,481,503}$&$ALA_{480}$&$LYS_{482,600}$&$GLU_{500}$&$THR_{528}$&$SER_{601}$	$LYS_{600,482}$&SER_{601}&GLU_{500}&$VAL_{503,470}$&$LEU_{504,513}$&$ILE_{571,526}$&GLY_{592}&ASP_{563}&PHE_{594}&ALA_{470}&THR_{528}	Residues Surrounding the compounds	ASN_{118}&THR_{119}&$ASP_{120,132}$&PHE_{121}&$LEU_{124,128,222}$&$ILE_{140,133,164}$&$MET_{137,225,221,163}$&TYR_{136}&PRO_{159}&HIS_{160}&VAL_{162}	$ILE_{164,140,133}$&$MET_{163,137,221,225}$&VAL_{162}&HIS_{160}&PRO_{159}&ASN_{118}&THR_{119}&PHE_{121}&$LEU_{124,128,222}$&TYR_{136}&SER_{224}	$MET_{221,225,137,163}$&$LEU_{222,128,124}$&TYR_{136}&$ILE_{133,164}$&PHE_{121}&THR_{119}&ASN_{118}&VAL_{162}&HIS_{160}&PRO_{159}	$ILE_{164,133,140}$&$MET_{163,137,225,221}$&VAL_{162}&HIS_{160}&PRO_{159}&ASN_{118}&THR_{119}&PHE_{121}&$LEU_{124,128,218,222}$
	ASP_{593}&GLU_{500} (H-bonding) PHE_{594}(pi-pi stacking)	Residues with interferences			ASN_{118} (H-bonding)	ASN_{118}(H-bonding)

S1	S4	Compound	S5	S3	S2	S6
-8.666	-8.983	ΔG	-7.099	-7.264	-7.479	-7.757
$LEU_{340,352,260,278}$&ASN_{338}&SER_{287280}&$LYS_{337,213,232}$&GLY_{214}&ASP_{351}&$ALA_{350,230}$&TYR_{249}&GLU_{245}&$VAL_{279,231,219}$&PHE_{262}	$LEU_{340,278,260}$&$SER_{287,280}$&ILE_{211}&$LYS_{337,232,213}$&$GLY_{212,214}$&$ASP_{351,290}$&$ALA_{350,230}$&TYR_{249}&GLU_{245}&$VAL_{279,231,219}$&PHE_{262}	Residues Surrounding the compounds	$ILE_{526,462}$&THR_{528}&GLN_{529}&TRP_{530}&CYS_{531}&$GLY_{533,592}$&$PHE_{582,594}$&ALA_{480}&$LYS_{482,600}$&VAL_{470}&$LEU_{504,513}$&GLU_{500}&ASP_{593}	$LEU_{566,513,504}$&HIE_{573}&$ILE_{571,526}$&$VAL_{503,481,470}$&GLU_{500}&$LYS_{600,482}$&SER_{601}&THR_{528}&ALA_{480}&PHE_{594}&ASP_{593}&GLY_{592}	CYS_{531}&TRP_{530}&GLN_{529}&THR_{528}&$ILE_{526,462}$&$LEU_{513,504}$&PHE_{594}&ASP_{593}&GLY_{592}&GLU_{500}&LYS_{482}&ALA_{480}&VAL_{470}	$ILE_{526,462}$&THR_{528}&GLN_{529}&TRP_{530}&CYS_{531}&$GLU_{532,500}$&$GLY_{533,592}$&$PHE_{582,594}$&VAL_{470}&ALA_{480}&LYS_{482}&$LEU_{504,513}$&ASP_{593}
TYR_{249}&ASP_{351}(H-bonding)	TYR_{249}&ASP_{351}&LYS_{232}(H-bonding)	Residues with interferences	ASP_{593}&CYS_{531}(H-bonding) PHE_{594}(pi-pi stacking)	GLU_{500}&ASP_{593} (H-bonding)	LYS_{482} (Pi-cation)	LYS_{482}(Pi-cation) GLU_{500}(H-bonding)

S2	**-8.452**	**$LEU_{340,278,260,278}$&ASN_{338}&$SER_{287,280}$&$LYS_{337,232}$&ILE_{211}&ASP_{351}&$ALA_{350,230}$&TYR_{249}&GLU_{245}&$VAL_{279,231,219}$&PHE$_{262}$**	**TYR_{249}&ASP_{351}(H-bonding) TYR_{249}(pi-pi stacking)**
S6	**-8.433**	**$LEU_{340,278,260}$&$SER_{287,280}$&ILE_{211}&$LYS_{337,232}$&GLY_{286}&$ASP_{351,290}$&$ALA_{350,230}$&TYR_{249}&GLU_{245}&$VAL_{279,231,219}$&PHE$_{262}$&ASN_{338}**	**TYR_{249}&ASP_{351}(H-bonding) TYR_{249}(pi-pi stacking)**
S3	**-8.169**	**$LEU_{340,278,260}$&$SER_{287,280}$&ILE_{211}&$LYS_{337,232}$&$GLY_{212,286}$&$ASP_{351,290}$&$ALA_{350,230}$&TYR_{249}&GLU_{245}&$VAL_{279,231,219}$&PHE$_{262}$**	**TYR_{249}&ASP_{351}&LYS_{232}(H-bonding)TYR_{249}(pi-pi stacking)**
S5	**-8.028**	**$LEU_{340,278,260}$&$SER_{287,280}$&ILE_{211}&LYS_{232}&GLY_{286}&$ASP_{351,281}$&$ALA_{350,230}$&$TYR_{249,282}$&$GLU_{245,284}$&$VAL_{279,231,219}$&PHE$_{262}$&HIS$_{283}$**	**TYR_{249} (pi-pi stacking)**

Conclusions

A molecular modeling theory called docking was used to clarify the binding interactions between ligands and proteins. The basis of this idea is the computation of binding free energy (ΔG), which indicates the affinity between the ligand and protein. A large negative value is favorable. Docking simulations were used to assess the anticancer potential and drug-likeness of six substances. With the correct 2D orientation, all chemical structures were built using ChemOffice (Chem Draw 20.0). Steric energy, thermal energy, and other variables were calculated via (MM2) energy minimization, which also elucidates the relationship between the estimated model conformations and the potential energy surface. MM2 uses Chem3D 20.0. The potential energy surface and the conformations of the model may be described by other variables, such as steric and thermal energy. The tested compounds displayed anticancer activity in the scPTZ screen, with olaparib (ΔG=−13.474) being the most effective treatment against cancer. The effectiveness of the treatment was determined from the association of each protein with the compound and the resulting ΔG values. The proteins 6B8Y, 5DS3, and 1UWJ were associated with compounds S4, S1, and S1 respectively, and all demonstrated higher ΔG values than the rest of the proteins. Therefore, treatments with these compounds could be potentially utilized for anticancer therapy.

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الحسابات النظرية والتصميم الجزيئي لمشتقات الديوكسوايزويندولين الجديدة كعوامل مضادة للسرطان

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الخلاصة:

يعد الانخفاض في فعالية الأدوية المضادة للسرطان الحالية مشكلة مستمرة في كل من الطب الأساسي والمتقدم. أحد الحلول المقترحة هو إجراء دراسات كيميائية نظرية لتحديد الأدوية المحتملة باستخدام مشتقات الديوكسوايزويندولين. استخدمت هذه الدراسة بالذات الالتحام الجزيئي وحسابات ΔG لتقييم نشاط المشتقات ضد البروتينات المرتبطة بالسرطان. تشير قيمة ΔG السالبة الأعلى إلى تطابق أوثق بين التفاعلات الكيميائية والبروتينية. أظهرت العديد من المركبات، مثل ΔG=-8.983 S4، وΔG=-8.498 S1، وΔG=-9.121 S1، نشاطًا كبيرًا ضد البروتينات المختلفة. كانت قيم ΔG التي تم الحصول عليها لجميع المشتقات ضمن نطاق مقبول، مما يشير إلى إمكاناتها كعوامل علاجية. تشير هذه النتائج إلى أن مشتقات الديوكسوايزويندولين قيد البحث تظهر نتائج واعدة لاستهداف البروتينات المختلفة المرتبطة بالسرطان. يؤكد على أهمية تطوير أدوية بديلة مضادة للسرطان ويقدم منهجًا للدراسة الكيميائية باستخدام هذه المشتقات. أظهرت المركبات التي تم اختبارها نشاطًا محتملاً ضد بروتينات معينة، مما يجعلها مرشحة محتملة لمزيد من الاستكشاف والتطوير كأدوية محتملة مضادة للسرطان.

الكلمات المفتاحية: مشتقات الديوكسوايزويندولين، المضادة للسرطان، النمذجة الجزيئية، بروتين تقارب الإرساء.