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Computational Insights into Quinazoline-Isatin Conjugates as VEGFR Inhibitors: Anticancer Candidates

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Abstract

Background: As one of the most significant contributors to global mortality, cancer continues to stimulate intensive investigations into the anticancer and free radical-scavenging properties of new conjugates as potential therapeutic agents for advanced cancer treatment strategies.

Method: This study reports the rational design and systematic assessment of four quinazoline-isatin hybrids (HK1-HK4) as potential VEGFR tyrosine kinase inhibitors through molecular docking and dynamic simulations, with binding affinities evaluated based on docking scores and RMSD values.

Results: SwissADME analysis confirmed excellent drug-likeness with complete Lipinski's Rule of Five compliance (MW: 347-401 Da, iLOGP: -0.44 to 1.02). All conjugates showed high GI absorption, no BBB penetration, and 0.55 bioavailability scores. Molecular docking revealed superior VEGFR binding affinities (-7.8 to -9.681 kcal/mol), with HK1 demonstrating optimal binding (-9.681 kcal/mol) through interactions with Lys868, Cys919, and Asp1046.

Conclusion: The quinazoline-isatin hybrids demonstrate excellent drug-likeness with complete Lipinski compliance and superior VEGFR binding. These promising computational results warrant experimental validation through in vitro enzymatic assays and cytotoxicity studies to advance clinical anticancer drug recognition.

رؤى حاسوبية حول مشتقات الكينازولين–إيزاتين كمثبطات لـ VEGFR: مرشّحات مضادة للسرطان

حسين عظيم حسن، سامر علي حسن

الخلاصة

المقدمة: يُعتبر السرطان أحد أهم مسبّبات الوفيات عالميًا، مما يستمر في تحفيز الأبحاث المكثّفة حول الخصائص المضادّة للسرطان وكاسحة الجذور الحرة لمركّبات جديدة يمكن أن تكون مرشّحة كعوامل علاجية لاستراتيجيات علاج السرطان المتقدمة.

المنهجية :يقدّم هذا البحث التصميم العقلاني والتقييم المنهجي لأربعة مشتقات هجينة من الكينازولين–إيزاتين–**(HK1 HK4** كمثبطات محتملة لإنزيم التيروزين كيناز الخاص بمستقبلVEGF ، وذلك من خلال الارتباط الجزيئي والمحاكاة الديناميكية، حيث تم تقييم قوة الارتباط استنادًا إلى قيم الارتباط (Docking Scores) وقيَم الانحراف الجذري.(RMSD)

النتائج :أكّد تحليل SwissADME امتلاك المشتقات خصائص دوائية ممتازة مع الالتزام الكامل بقواعد ليبنسكي (MW: 347–401دا، iLOGP: -0.44 إلى 1.02 .(كما أظهرت جميع المشتقات امتصاصًا عاليًا في الجهاز الهضمي، وعدم القدرة على اختراق الحاجز الدماغي الدموي، وقيمة توافر حيوي تبلغ 0.55. وبيّن الارتباط الجزيئي تآلفات ارتباط عالية مع) VEGFR من 7.8- إلى 9.681- كيلوكال/مول(، حيث أظهر المركب HK1 أفضل ارتباط (9.681-)كيلوكال/مول (عبر تفاعلات مع الأحماض الأمينية Lys868 و Cys919وAsp1046.

الاستنتاج :تُظهر مشتقات الكينازولين–إيزاتين خصائص دوائية ممتازة مع التزام كامل بقواعد ليبنسكي، بالإضافة إلى تآلفات ارتباط عالية مع .VEGFR وتشير هذه النتائج الحاسوبية الواعدة إلى ضرورة إجراء تحقّق تجريبي عبر اختبارات إنزيمية خلوية ودراسات السمية الخلوية لتعزيز فرص اعتمادها كعوامل علاجية مضادّة للسرطان

1. **Introduction** Cancer represents one of the most significant threats to global health, characterized by uncontrolled cellular proliferation, dysregulation of the cell cycle, and accumulation of genetic mutations that collectively drive tumor formation and progression (Glaviano et al., 2025). Cancer is known to be characterized by uncontrolled cell growth, and tumor cells usually have damage to genes that directly govern their cell cycles (Sherr, 1996). Consequently, the development of improved anticancer pharmaceuticals exhibiting robust biological efficacy and enzyme-inhibitory properties, while reducing toxicity to healthy tissues, is crucial for enhancing cancer therapy results (Cerra and Gioiello, 2025). Research focused on enzyme inhibition as a therapeutic target has led to the discovery of novel chemical compounds and innovative approaches for designing safer and more effective anticancer drugs ("Enzyme Inhibition as a Key Target for the Development of Novel Me...: Ingenta Connect," n.d.). Medicinal chemists continue to face ongoing challenges in designing chemotherapeutic agents truly capable of treating malignant conditions effectively while maintaining acceptable safety profiles (Yuriy et al., 2024). Their efforts often focus on understanding and disrupting the complex biochemical pathways that facilitate rapid tumor growth, metastatic dissemination, and resistance to programmed cell death ("Hallmarks of Cancer: The Next Generation: Cell," n.d.). Targeted medicines, including multi-kinase inhibitors, especially tyrosine kinase inhibitors (TKIs), which block important signaling pathways inside tumor cells and assist reduce toxicity and therapeutic resistance, are among the most promising approaches in cancer therapy ("Targeting cancer with small molecule kinase inhibitors | Nature Reviews Cancer," n.d.). The emergence of small molecule kinase inhibitors has revolutionized cancer therapy by offering a targeted and strategic approach that surpasses the efficacy of traditional chemotherapeutic drugs (Kumar et al., 2024). Kinases catalyze the phosphorylation of biomolecules, regulating fundamental processes such as cell motility, proliferation, differentiation, and apoptosis ("Role of protein kinase activity in apoptosis | Cellular and Molecular Life Sciences," n.d.). Targeting these enzymes in cancer cells has become central to multiple modern therapeutic approaches in oncology ("Targeting cancer with small molecule kinase inhibitors | Nature Reviews Cancer," n.d.). Vascular endothelial growth factor (VEGF) is a key angiogenic factor critically involved in tumor development and progression ("Anti-Angiogenics: Current Situation and Future Perspectives | Oncology Research and Treatment | Karger Publishers," n.d.). The main way that VEGFs promote angiogenesis is via attaching to VEGF receptor tyrosine kinases (VEGFR-1, VEGFR-2, and VEGFR-3), which are strongly linked to the development and spread of cancer ("The role of VEGF receptors in angiogenesis; complex partnerships | Cellular and Molecular Life Sciences," n.d.). Although

dysregulated angiogenesis can directly contribute to the development of cancer, inflammation, and autoimmune illnesses, angiogenesis is necessary for cells to achieve their nutritional and oxygen needs ("Anti-Angiogenics: Current Situation and Future Perspectives | Oncology Research and Treatment | Karger Publishers," n.d.). Thus, anti-angiogenic therapy offers a strategic avenue in cancer treatment, now supported by several FDA-approved small molecule inhibitors, including sunitinib and sorafenib ("Sorafenib in Advanced Hepatocellular Carcinoma | New England Journal of Medicine," n.d.).

Because of their adaptable chemical structures and capacity to target important molecular pathways linked to tumor development and survival, quinazoline and its derivatives have become a very promising family of anticancer medicines (Barbosa et al., 2014). Quinazolines are preferred scaffolds in medicinal chemistry because they inhibit a number of targets, such as checkpoint kinases, DNA repair enzymes, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR), which prevents angiogenesis, tumor growth, and cell proliferation (Barbosa et al., 2014). Four essential pharmacophoric characteristics are shared by VEGFR-2 inhibitors, according to recent research: an aromatic heterocycle for hinge-region interaction, a spacer group for active site orientation, a pharmacophore for attachment to amino acid residues at the DFG motif, and a hydrophobic element in the allosteric binding site (El Kerdawy et al., 2019). Recent studies have demonstrated that new synthetic quinazoline conjugates possess potent cytotoxic activity against a broad array of cancer cell lines, often outperforming clinically established drugs in vitro by targeting EGFR, VEGFR-2, and other kinases vital in cancer cell signaling (Barbosa et al., 2014). Isatin, which is present in many anticancer medications, particularly VEGFR-2 inhibitors, is a scaffold of particular importance. One clinically licensed medication with an isatin heteroaromatic system is sunitinib, which has been extensively researched for its strong multi-targeted receptor tyrosine kinase inhibitory action. The growing interest in isatin as a novel class of antineoplastic medicines is highlighted by the FDA's recent approval of sunitinib as a kinase inhibitor for the treatment of gastrointestinal stromal tumors and advanced renal carcinoma (Ferraz De Paiva et al., 2021).

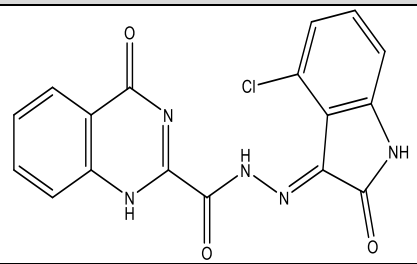
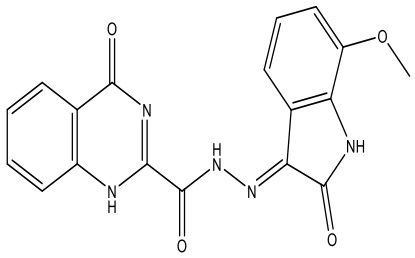
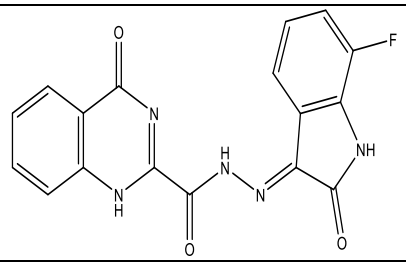
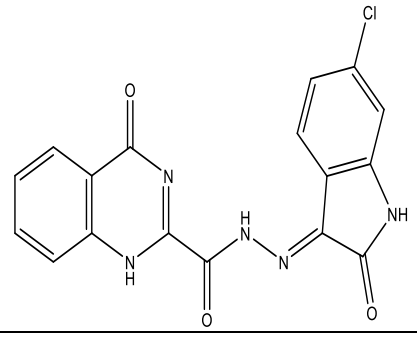
2. Methods

2.1. ADME Properties Analysis

The SwissADME computational platform serves as a predictive tool for evaluating the pharmacokinetic characteristics of drug candidates, specifically their absorption, distribution, metabolism, and excretion (ADME) profiles. This web-based tool also assesses critical pharmacological parameters, including the capacity of compound to penetrate the blood-brain barrier (BBB), its interaction potential with P-glycoprotein (P-gp) efflux transporters, and overall bioavailability. The primary application of SwissADME lies in identifying the most viable and safest therapeutic candidates during early drug development, while

simultaneously filtering out compounds with unfavorable ADME properties that increase the likelihood of failure in subsequent preclinical and clinical phases (Alhawarri et al., 2024), Table1.

Table1: IUPAC Name, SMILES, And Chemical Structure Of Designed Quinazoline-Isatin Hybrids

Comp.	IUPAC name	Smiles	Molecular structure
HK1	(E)-N'-(7-chloro-2-oxoindolin-3-ylidene)-4-oxo-1,4-dihydroquinazoline-2-carbohydrazide	O=C(N/N=C1C(NC2=C/1C(Cl)=CC=C2)=O)C(NC3=C4C=CC=C3)=NC4=O	
HK2	(E)-N'-(7-methoxy-2-oxoindolin-3-ylidene)-4-oxo-1,4-dihydroquinazoline-2-carbohydrazide	O=C(C(NC1=C2C=CC=C1)=NC2=O)N/N=C3C(NC4=C/3C=CC=C4OC)=O	
HK3	(E)-N'-(7-fluoro-2-oxoindolin-3-ylidene)-4-oxo-1,4-dihydroquinazoline-2-carbohydrazide	O=C(C(NC1=C2C=CC=C1)=NC2=O)N/N=C3C(NC4=C/3C=CC=C4F)=O	
HK4	(E)-N'-(6-chloro-2-oxoindolin-3-ylidene)-4-oxo-1,4-dihydroquinazoline-2-carbohydrazide	O=C(C(NC1=C2C=CC=C1)=NC2=O)N/N=C3C(NC4=C/3C=CC(Cl)=C4)=O	

2.2. Molecular Docking

Molecular docking simulations represent a fundamental computational approach for elucidating the probable binding poses and conformational preferences of ligand molecules within receptor binding domains. In the present investigation, comprehensive molecular docking studies were conducted to accomplish the following objectives: (A) to characterize the molecular interactions between the examined ligand compounds and the amino acid residues comprising the active site of the selected protein target; (B) to perform comparative analysis of binding free energies and root-mean-square deviation (RMSD) values across all investigated ligands, the co-crystallized reference ligand, and positive control compounds; and (C) to identify the most favorable binding conformers on the basis of superior binding affinity scores. All molecular docking calculations were performed utilizing the Schrödinger Suite 2025 computational platform (Schrödinger, Inc., New York, NY, USA), which integrates advanced algorithms for ligand-receptor binding prediction and conformational sampling.

Ligand preparation: Quinazoline-isatin hybrids (**HK1-HK4**), as shown in **Table2,** constructed using PerkinElmer ChemDraw Professional 20.0 (PerkinElmer, Massachusetts, USA), underwent energy minimization and conformational analysis using Schrodinger Suite by means of the Molecular Mechanics Force Field (OPLS4).

Protein preparation : The crystallographic structure of VEGFR-2 in complex with the PF-00337210 inhibitor (PDB ID: 2XIR), as shown in **Fig.1**, obtained from the RCSB database("RCSB PDB: Homepage," n.d.), underwent systematic preparation through the following sequential procedures:

Prior to computational docking studies, the three-dimensional protein structure was systematically prepared through a multi-step procedure. Initially, only the polypeptide chains directly involved in the catalytic mechanism were retained, while non-essential structural components, including exogenous ligands, crystallographic water molecules, and heteroatoms, were removed to minimize computational complexity and potential artifacts. Subsequently, polar hydrogen atoms were appended to the protein structure, and the force field parameters were assigned to all protein atoms using the OPLS3 force field. The active site residues were subsequently identified and defined based on the three-dimensional coordinates of the reference ligand within the binding cavity. All prepared ligand molecules, previously optimized and saved in the designated database format, were systematically imported into the Schrödinger computational suite. Molecular docking calculations were executed using the Schrödinger suite with the co-crystallized ligand serving as the positive control reference for validation of the computational methodology. The predicted binding poses for each ligand were ranked according to their docking scores (ΔG values), with conformers exhibiting superior binding affinities—characterized by more favorable (lower) docking energies—being selected for subsequent structural analysis and interpretation, Fig.2.

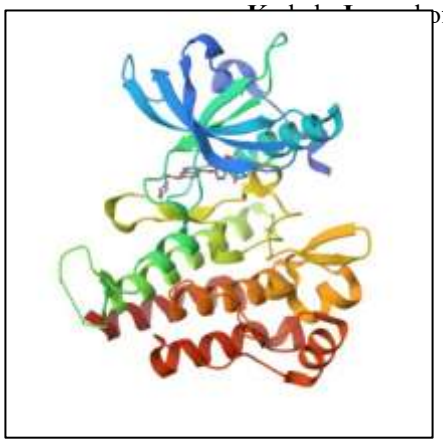


Figure1: The crystal structure of VEGFR-2 with bound inhibitor PF-00337210

Table2: Information Details Related to The Protein 2XIR

protein	Method	Resolution (Å)	Amino acid number	Atom Count	Total Structure Weight	Organism	Co-crystalized ligand (LBE)	Docking Score (kcal/mol)	RMSD (Å)
2XIR	X-ray diffraction	1.5	1166	2,709	36.66 kDa	Homo sapiens	(N,2-dimethyl-6-(7-(2-morpholinoethoxy) quinolin-4-yloxy) benzofuran-3-carboxamide)	-12.51	0.5831

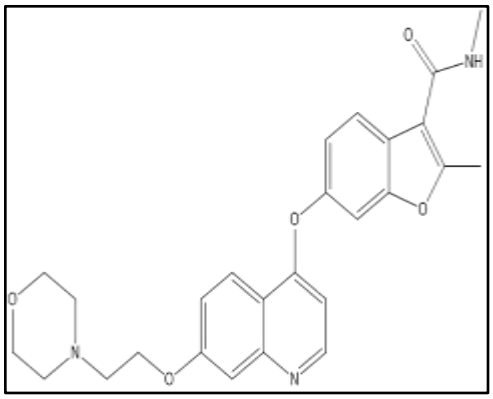


Figure2: The molecular structure of the co-crystalline ligand **(LBE)**.

2.3. Molecular Dynamics Simulation

The **HK1-2XIR** protein-ligand complex was systematically prepared for molecular dynamics (MD) simulations utilizing the Schrödinger Suite 2025 computational platform. The protein structure underwent comprehensive preprocessing through the Protein Preparation Wizard module, which involved (A) assignment of correct bond orders and connectivity, (B) addition of polar hydrogen atoms, and (C) optimization of ionizable residue protonation states to reflect physiological conditions (pH 7.0 ± 2.0). The ligand molecule was parameterized using the OPLS4 force field to ensure consistent treatment of intra- and intermolecular interactions. The solvated system was constructed by immersing the protein-ligand complex within an orthorhombic periodic boundary box containing TIP3P water molecules, with a minimum solvent shell extending at least 10 Å beyond the van der Waals surface of the solute. To reproduce physiological ionic conditions and maintain electrostatic neutrality, monovalent counter ions (Na^+ and Cl^-) were added at a concentration approximating 150 mM ionic strength. Prior to production dynamics simulations, the entire solvated system underwent a restrained minimization procedure in which heavy atoms of the protein and ligand were harmonically constrained while allowing solvent relaxation, thereby eliminating residual steric incompatibilities and establishing a stable initial configuration.

3. Results and Discussion

3.1. ADME Study of The HK1-HK4 Result

All four conjugates (**HK1**-**HK4**) demonstrated excellent drug-likeness, fully complying with Lipinski's rule of five with molecular weights ranging from 351.29 to 367.75 g/mol. Each conjugate possessed low rotatable bond counts (3-4) and optimal hydrogen bonding capacity (5-6 acceptors, 3 donors), favorable for receptor binding, as showing in **Table 3**. The series exhibited consistent high gastrointestinal absorption potential, indicating favorable oral bioavailability. Topological polar surface area values (116.31-125.54 Ų) and lipophilicity indices (iLOGP: 0.71-1.02) remained within optimal ranges for effective membrane permeability. Significantly, all conjugates were classified as blood-brain barrier non-permeant and non-P-glycoprotein substrates, minimizing central nervous system penetration and efflux transporter-mediated clearance. **HK3** demonstrated the lowest molecular weight and most favorable lipophilicity, suggesting enhanced bioavailability. **HK2** exhibited the highest polar surface area yet maintained high GI absorption**.** **HK4** showed the highest lipophilicity while preserving drug-like properties. The uniform bioavailability scores across the series indicate comparable pharmacokinetic behavior, enabling reliable optimization of binding affinity and selectivity. These conjugates represent well-optimized pharmaceutical candidates meeting rigorous development criteria. The structural diversity provides opportunities for fine-tuning potency while maintaining favorable ADME characteristics. Future experimental validation through metabolic

stability and in vivo pharmacokinetic studies would confirm predictions and identify the optimal clinical candidate.

Table 3: The ADME Output For The Designed Drug-Likeness Derivatives (HK1-HK4) Using The Swissadme Platform

Parameters Comp.	MW (g/mol)	nRB	nHBA	nHBD	MR (m^3/mol)	TPSA (Å^2)	iLOGP	GI absorption	BBB permeant	P-gp	BS	Ro5
HK1	367.75	3	5	3	98.87	116.31	0.83	High	No	No	0.55	Yes
HK2	363.33	4	6	3	100.35	125.54	0.89	High	No	No	0.55	Yes
HK3	351.29	3	6	3	93.82	116.31	0.71	High	No	No	0.55	Yes
HK4	367.75	3	5	3	98.87	116.31	1.02	High	No	No	0.55	Yes

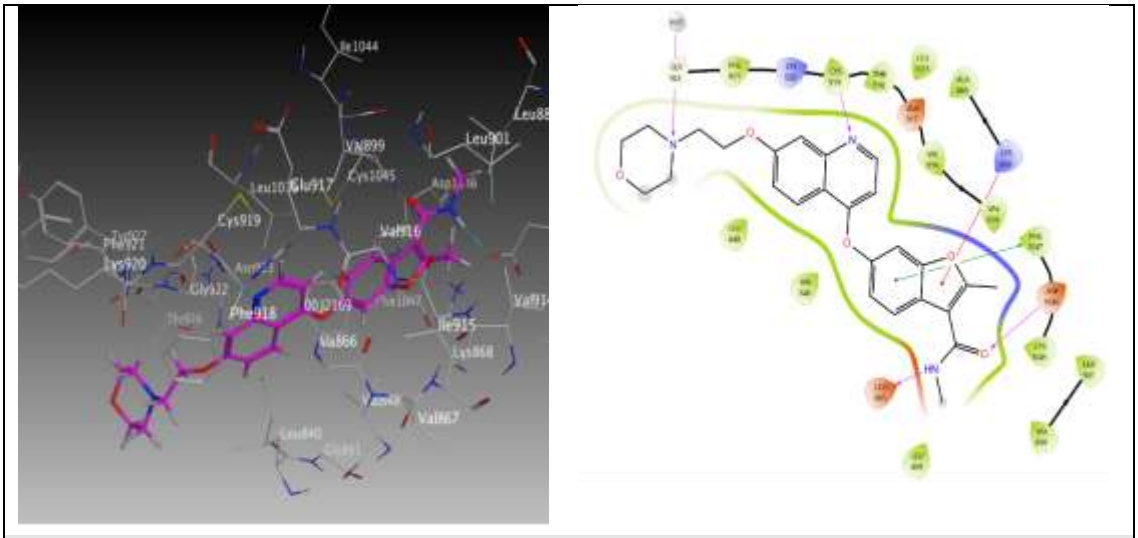
3.2. Molecular Docking Results

Comprehensive molecular docking studies were conducted using the Schrödinger Suite 2025 to evaluate the binding interactions of four conjugates (**HK1**-**HK4**) with the target protein active site, validated against the co-crystallized reference ligand, Table4. The co-crystallized ligand achieved a docking score of -12.51 kcal/mol, RMSD: 0.5831, with a Glide g score of -14.267 and interaction energy of -128.957 kcal/mol, establishing the benchmark for comparison. This compound engaged six amino acid residues through multiple hydrogen bonds, pi-pi and pi-cation interactions, demonstrating comprehensive binding site occupancy. Among the investigated conjugates, **HK1** exhibited the strongest binding affinity with a docking score of -9.681 kcal/mol (Glide gscore: -10.28, RMSD: 0.6801, interaction energy: -76.73 kcal/mol), representing approximately 77% of the reference ligand's binding energy. **HK1** demonstrated productive interactions with key residues, including critical hydrogen bonding between the ether oxygen on the benzimidazole ring and CYS919, and between the isatin carbonyl and ASP1046. The remaining conjugates (**HK2**-**HK4**) exhibited progressively lower binding scores (ranging from -7.8 to -8.323 kcal/mol), indicating reduced binding affinity compared to **HK1**. **HK2** demonstrated the lowest affinity (-7.8 kcal/mol) despite engaging the most amino acid residues, suggesting that increased binding site contacts do not necessarily correlate with enhanced binding strength. Conversely, **HK3** displayed competitive interactions with ASP1046 through dual hydrogen bonds from both indole and pyrazine nitrogen atoms, compensating for fewer total residue contacts (12 residues). **HK4** showed intermediate binding characteristics with favorable interactions involving the fluorinated benzoxazole ring and extensive hydrophobic contacts, positioning it as a viable alternative candidate. All compounds engaged critical residues, including CYS919, ARG1051, LYS866, ASP1046, and GLU885, highlighting conserved interaction patterns across the series. The

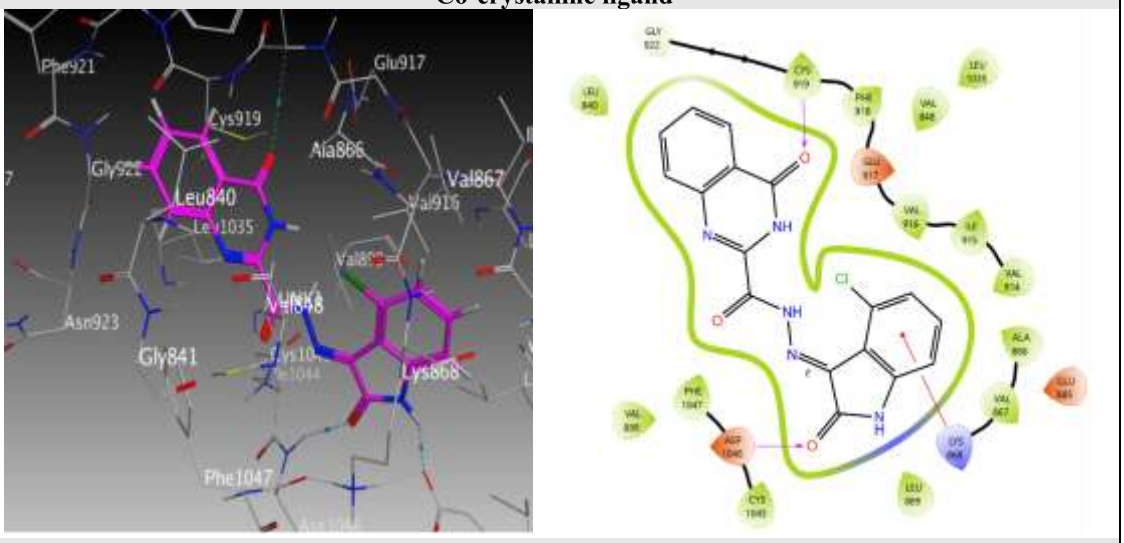
consistent utilization of these anchor residues suggests robust structure-binding relationships. **HK1**'s superior performance reflects the optimal balance between hydrogen bonding capacity, lipophilicity, and conformational geometry, establishing it as the lead candidate for advancement to biological validation studies, Fig.3.

Table 4: The Results obtained from docking of the quinazoline-isatin hybrids with the active site of 2xir

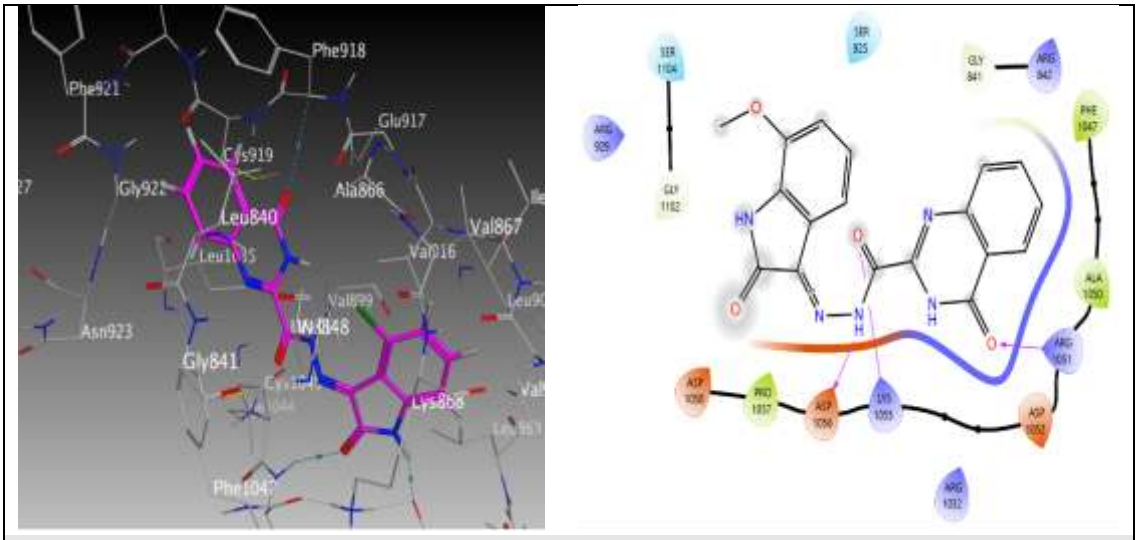
Compound	Docking score	Glide Gscore	Glide energy	RMSD (Å)	amino acid involves in interaction	Type of interactions
Co-crystalized ligand (LEB)	-12.51	-14.267	-128.957	0.5831	LYS 868	Pi-cat
					GLU 885	H-bond
					CYS 919	H-bond
					GLY 922	H-bond
					ASP 1046	H-bond
					PHE 1047	Pi-pi
HK1	-9.681	-10.28	-76.73	0.6801	LYS 868	H-bond
					CYS 919	Pi-cat
					ASP 1046	H-Bond
HK2	-7.8	-9.64	-43.648	0.6770	ARG 1051	H-Bond
					LYS 1055	H-Bond
					ASP 1056	H-Bond
HK3	-8.098	-9.402	-62.036	1.4191	LYS 866	Pi-cat
					ASP 1046	H-Bond
HK4	-8.323	-9.403	-62.036	1.4196	LYS 868	Salt bridge
					PHE 1047	Pi-pi



Co-crystalline ligand



HK1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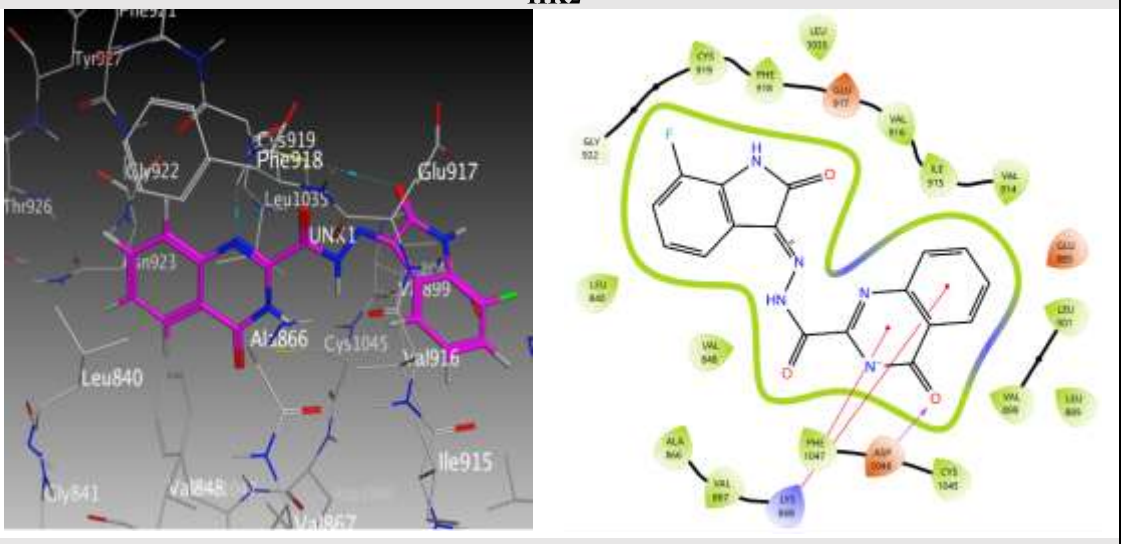
HK2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HK3

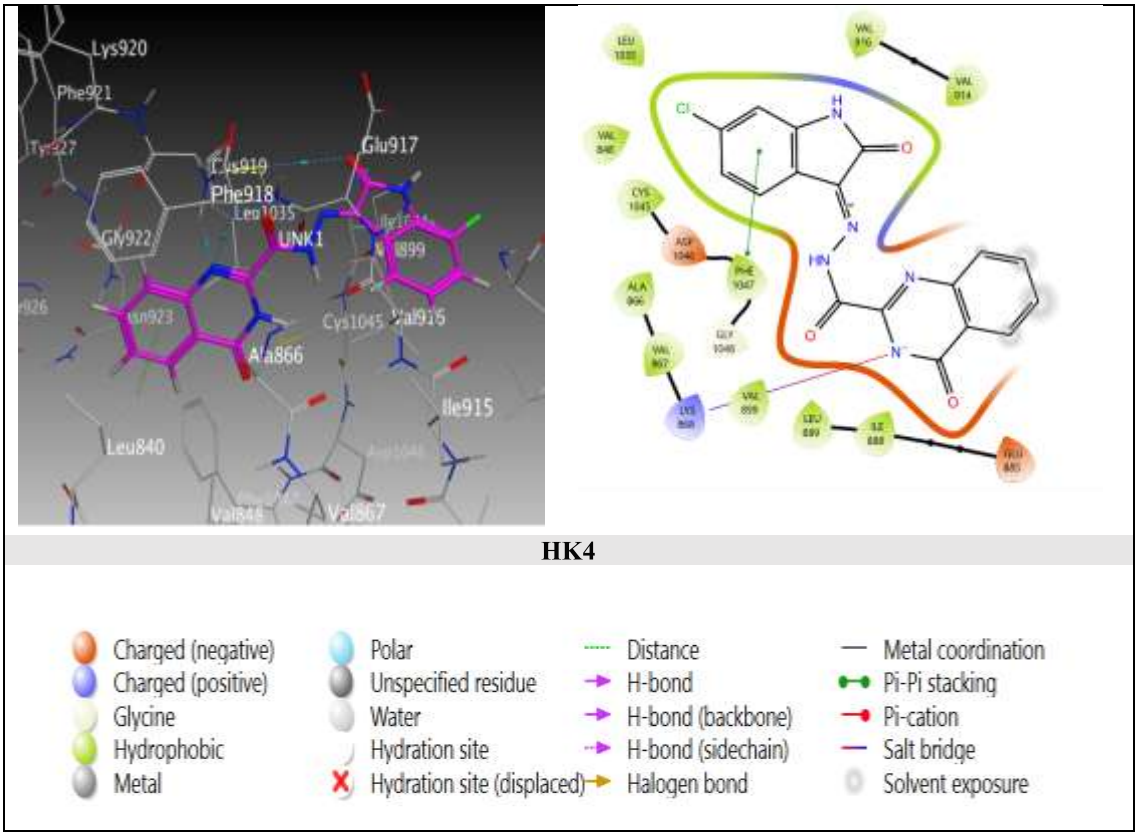

Figure3: 2d and 3d Ligands' Interaction with The Active Site Of 2xir Protein.

3.3. Molecular Dynamic Simulation Results

A comprehensive 50-nanosecond molecular dynamics simulation was conducted using the Desmond package to evaluate the stability and dynamic behavior of the HK1-protein complex under physiological conditions (300 K, NPT ensemble). The system comprised 37,208 atoms, including 10,726 water molecules solvated with physiological ionic strength (approximately 150 mM NaCl), providing a realistic representation of biological conditions. The protein backbone RMSD converged to approximately 2.0-2.5 Å after initial equilibration and remained stable throughout the 50 ns trajectory, indicating successful equilibration and structural stability within acceptable ranges for globular proteins. Notably, the ligand RMSD values remained consistently below 1.0 Å when fitted to the protein reference frame, demonstrating exceptional binding pocket stability and minimal conformational drift from the initial docked pose. This low ligand RMSD confirms that **HK1** maintains stable interactions within the active site without diffusing from its binding location, validating the docking predictions and supporting the compound's potential as a viable inhibitor.

Protein Flexibility and Secondary Structure Maintenance: Root mean square fluctuation (RMSF) analysis revealed that the protein maintained its secondary structure composition throughout the simulation,

with 30.85% helical content and 14.39% beta-strand content (45.24% total secondary structure elements). Residue-specific RMSF values indicated expected fluctuation patterns, with terminal regions and loop domains exhibiting higher mobility (3-4 Å) while structured regions remained rigid (0.5-1.5 Å). Importantly, residues forming the ligand binding pocket, including VAL867, LYS868, GLU885, ASP1046, and CYS1045, demonstrated low fluctuations, confirming binding site rigidity essential for stable ligand recognition. The ligand RMSF analysis showed minimal atomic fluctuations across the molecule, with the chlorinated indole ring system and benzimidazole core exhibiting particularly low mobility, suggesting strong anchoring interactions with the protein. Slightly elevated fluctuations were observed at the peripheral atoms, consistent with solvent-exposed regions experiencing greater conformational freedom.

Protein-Ligand Interaction Profile: The interaction timeline analysis revealed persistent contacts with 24 key residues, including VAL848, ALA866, VAL867, LYS868, GLU885, ILE888, LEU889, VAL899, VAL914, VAL916, GLU917, CYS1045, and ASP1046. Critically, ASP1046 maintained hydrogen bonding interactions for 76% of the simulation time, while VAL914 engaged in hydrophobic contacts for 90% of the trajectory, demonstrating the most stable and consistent interactions. LYS868 exhibited persistent hydrophobic and potential ionic **interactions** with the ligand scaffold, contributing to binding stabilization. The predominance of hydrophobic interactions throughout the simulation underscores the importance of the chlorinated aromatic systems in **HK1**'s binding mechanism. Water-mediated interactions were observed intermittently, suggesting dynamic solvent participation in ligand stabilization. The sustained interaction profile confirms that the binding mode predicted by molecular docking remains stable under dynamic conditions, providing strong computational evidence for **HK1**'s therapeutic potential, as shown in Fig.4.

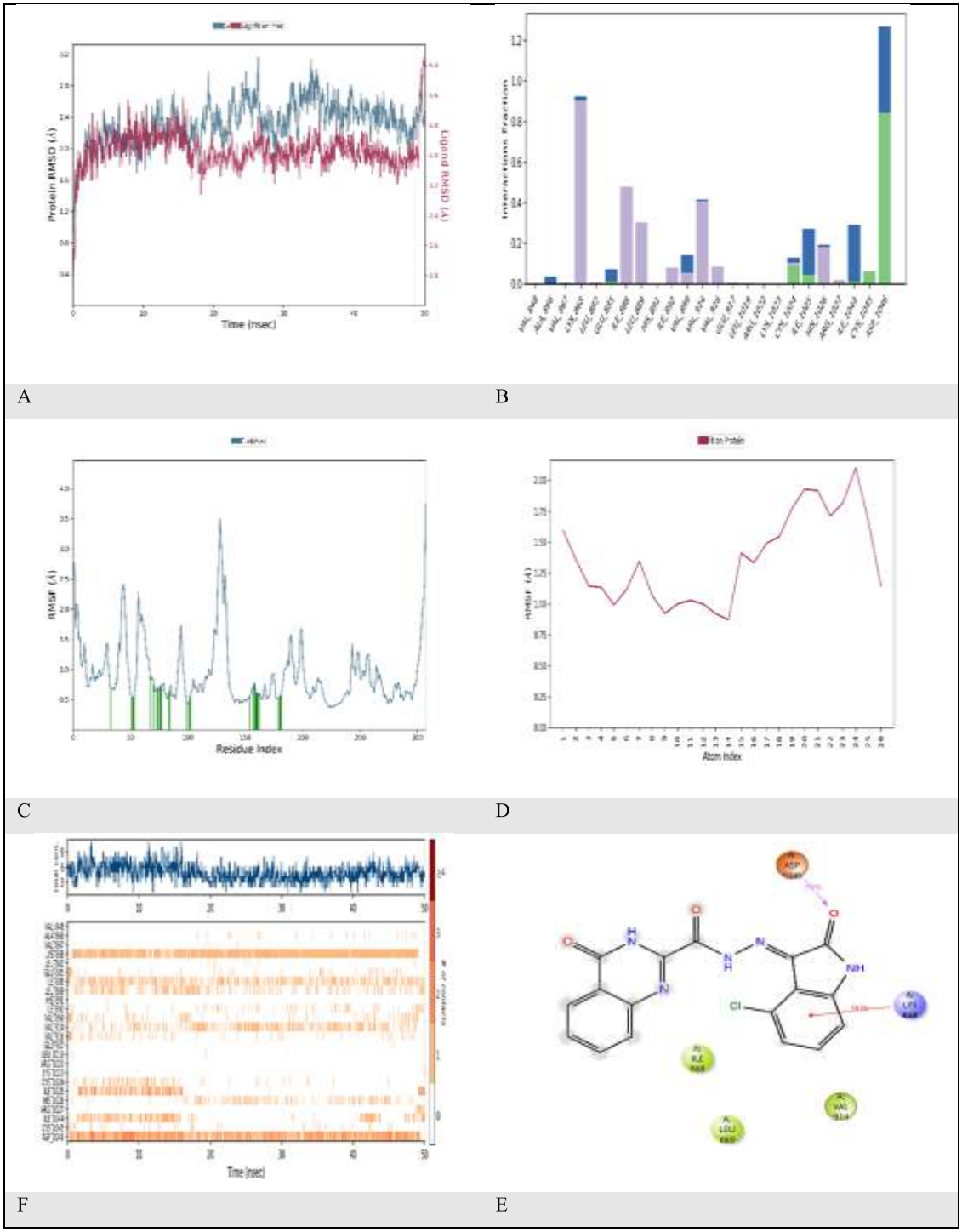

Figure4: Molecular Dynamic Analysis of HK1 Interaction With 2XIR. (A) Protein-Ligand RMSD; (B) Histogram of Protein-Ligand Contact Frequencies; (C) Protein RMSF; (D) Ligand RMSF; (E) Protein-Ligand Contacts; (F) Ligand-Protein Contact.

4. Conclusion

The study concludes that the quinazoline–isatin hybrids (**HK1–HK4**) are well-positioned as theoretical VEGFR-2 inhibitors with potential anti-angiogenic and anticancer activity. Their favorable docking energies, consistent binding modes, and interaction with key catalytic residues support their classification as next-generation kinase-targeting scaffolds. The quinazoline–isatin hybrid compounds **HK1–HK4** exhibit strong theoretical potential as VEGFR-2 inhibitors, with docking S-scores ranging from −9.64 to −7.8 kcal/mol, outperforming. Among them, **HK1** (R4 = Cl) shows the highest binding affinity (−9.64 kcal/mol) with a stable fit (RMSD 0.6801 Å), underscoring the beneficial role of halogen substitution on interaction strength.

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