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Original Research Article

Molecular Docking Studies of Novel Coumarin-Pyrazoline-Sulfonamide Hybrid Derivatives as Potential Antiproliferative Agents: Computer-Aided Design and Pharmacokinetics Studies

Hawazin Aziz Hamim[1]*, Enas Abd Ali Muhsen[2], Hussien Ali Karim[3], Dina Saleem[4]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

***Corresponding Author:** Hawazin Aziz Hamim
Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

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Abstract: Breast cancer is still considered one of the most common malignancies worldwide, requiring the continual development of novel targeted therapeutic agents. This study reports the insilico design, molecular docking, and the ADME analysis of four novel coumarin-pyrazoline-sulfonamide hybrid derivatives (D–G) as potential anti-breast cancer drugs targeting the estrogen receptor alpha (ERα). The four compounds contain different aryl substituents phenyl (D), 4-hydroxyphenyl (E), 4-methoxyphenyl (F), and 4-fluorophenyl (G) at the C-5 position of the pyrazoline ring attached to the coumarin substrate, but the N-1 position carries a 4-aminosulfonylphenyl group. Molecular docking simulations were performed against the ERα ligand-binding domain (PDB: 1ERR) using the Glide Standard Precision procedure within the Schrödinger software suite, with olaparib as the drug of reference. Each of the four designed compounds showed higher binding affinities compared to olaparib (−7.130 kcal/mol). The most favorable Glide score of −7.727 kcal/mol was obtained from the compound E (4-hydroxyphenyl derivative), which was following compounds D (−7.448 kcal/mol), F (−7.257 kcal/mol), and G (−7.192 kcal/mol). Key interactions included hydrogen bonding with Glu353, Asp351, Arg394, Thr347, and His524, in addition to extensive hydrophobic contacts within the ERα bonding pocket. These findings were further corroborated by MM- GBSA calculations, wherein the compound exhibited the highest complex stability with a binding free energy of -65.4 kcal/mol, compared to other derivatives (D, F, and G) and the reference compound (-67.37 kJ/mol). ADME profiling utilizing SwissADME confirmed all compounds comply with Lipinski's Rule of Five with no violations and exhibit favorable pharmacokinetic characteristics. These results demonstrate the promising importance of engineered coumarin derivatives, particularly compound (E), as lead structures for future development as proliferative inhibitors targeting estrogen receptor alpha (ERα).

Keywords: Breast Cancer, Estrogen Receptor-Alpha, Coumarin, Pyrazoline-Sulfonamide.

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies and a leading cause of cancer-related mortality among women worldwide. Despite significant therapeutic advances, the clinical efficacy of conventional chemotherapy is often constrained by severe cytotoxicity, off-target tissue damage, and the emergence of acquired drug resistance [1–4]. Given the disease's genetic heterogeneity and intricate signaling networks, there is an urgent need for molecularly targeted therapies possessing higher selectivity and reduced side effects. Epidemiological and biological studies indicate that the dysregulation or overactivation of estrogen receptor alpha (ERalpha) drives approximately 70% of diagnosed cases [5–6]. Although current endocrine therapies including aromatase inhibitors, selective estrogen receptor modulators (SERMs), and degraders (SERDs)—have shown clinical success, therapeutic relapse due to acquired resistance necessitates the exploration of novel chemical scaffolds with enhanced efficacy [7, 8]. In this framework, heterocyclic frameworks constitute a cornerstone in the discovery of modern molecular inhibitors [9, 10]. Specifically, the coumarin core, a natural benzopyrone scaffold, represents a promising pharmacophore owing to its structural simplicity and functional versatility,

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which underlie its established antitumor, antiangiogenic, anti-inflammatory, and antioxidant properties [11, 12]. In alignment with rational drug design principles, computational chemistry has revolutionized drug discovery by significantly reducing time and financial constraints. Quantitative structure-activity relationship (QSAR) modeling, molecular docking, and molecular dynamics (MD) simulations enable the preliminary evaluation of binding affinity and complex stability prior to in vitro synthesis [13, 14], thereby guiding the design of analogs with optimized physicochemical and pharmacokinetic profiles. Furthermore, early prediction of absorption, distribution, metabolism, and excretion (ADME) parameters is critical for identifying pharmacokinetic liabilities before progressing to costly clinical trials [15, 16], with Lipinski's Rule of Five serving as the benchmark for evaluating oral bioavailability and intestinal absorption [17, 18]. The coumarin core (2H-chromen-2-one) represents a unique heterocyclic scaffold that has drawn substantial research interest. In evaluating its antitumor efficacy, particularly against breast cancer, both natural and synthetic coumarin derivatives have demonstrated significant inhibitory activity against estrogen receptor alpha (ERα) through multifaceted molecular mechanisms [19, 20]. The basic benzopyrone framework of coumarin offers an ideal chemical space for systematic structural modifications aimed at enhancing binding affinity and receptor selectivity [23]. Furthermore, recent studies have validated substituted coumarin analogs as novel aromatase inhibitors, thereby reinforcing their capacity to suppress estrogen biosynthesis [21, 22]. In addition, 3-imidazole-substituted coumarins have exhibited exceptional inhibitory potency alongside superior selectivity profiles over related metabolic enzymes [24]. Mechanistically, this substitution pattern induces programmed cell death (apoptosis) via both caspase-dependent and caspase-independent pathways, while concurrently attenuating tumor angiogenesis and metastatic progression [30, 31]. Furthermore, the strategic hybridization of the pyrazoline pharmacophore with a sulfonamide moiety has yielded a new class of antitumor hybrids. These innovative molecules synergize the therapeutic advantages of both heterocyclic domains, enabling simultaneous targeting of overlapping metabolic and biological cascades in breast cancer [32, 33]. Biological evaluations of these pyrazoline-sulfonamide hybrids revealed dual-action potency in inhibiting ERα signaling and angiogenesis, demonstrating superior efficacy compared to standard reference therapeutics such as tamoxifen and bevacizumab [34, 35]. The three-dimensional spatial features and electronic properties of these hybrid compounds have been improved by adopting structure-based drug design and relying on molecular fusion and computational chemistry techniques [36, 37].

Accordingly, this research focuses on design. Computing and comprehensive evaluation of newly synthesized coumarin derivatives as promising anti-breast cancer agents targeting alpha-type estrogen receptors (ER alpha). This study integrates computational methodologies, including molecular ligand binding with ligand-binding domains (LBD) and ADME property prediction based on well-established pharmacokinetic models, to identify high-potential therapeutic precursors. The proposed derivatives include various heterocyclic components, such as pyrazoline and sulfonamide groups, which are specifically designed to increase binding affinity and selectivity and improve pharmacokinetic properties compared to currently approved treatments.

2. COMPUTATIONAL METHOD

2.1. Computer System and Software

All computational docking and modeling protocols were performed using the Swiss ADMET online program, the ChemDraw expert software program V.22.0, and Schrodinger software V.22.0.

2.2. Drug-Likeness Profile

The assessment of pharmacokinetic and ADME properties of the investigated compounds were conducted using the SwissADME online program (www.swissadme.ch) [38]. The boiled egg server was used to predict the lipophilicity and extremities of these molecules.

2.3. Protein Preparation and Grid Generation

The crystal structure of the target protein was retrieved from the Protein Data Bank (PDB code: ERα (1ERR) with 253 amino acids at a resolution of 2.6 A was selected. Chain A of the enzyme was selected for docking. The application was processed using the protein structure preparation wizard in Schrodinger, New York, 2022. The center of the docking box was selected based on the X (67.97), Y (34.84), and Z (74.42). The docking process was done using the Ligand Docking module. In the docking procedure, the ligand was considered a flexible molecule for rotating all rotatable ligand bonds to obtain the best optimal ligand conformer within the active sites of the receptor. started by excluding the water molecules and adding hydrogen in protein residues. The hydrogen bonds were optimized by the OLPS-2005 (Optimized Potentials for Liquid Simulations) force field. The receptor grid was prepared using the co-crystallized ligand as the center for the boundary box when the prepared ligands docked on the binding site of the protein. The dimension of the boundary box used was 12 ºA. Finally, docking results were saved using the XP GlideScore scoring function.

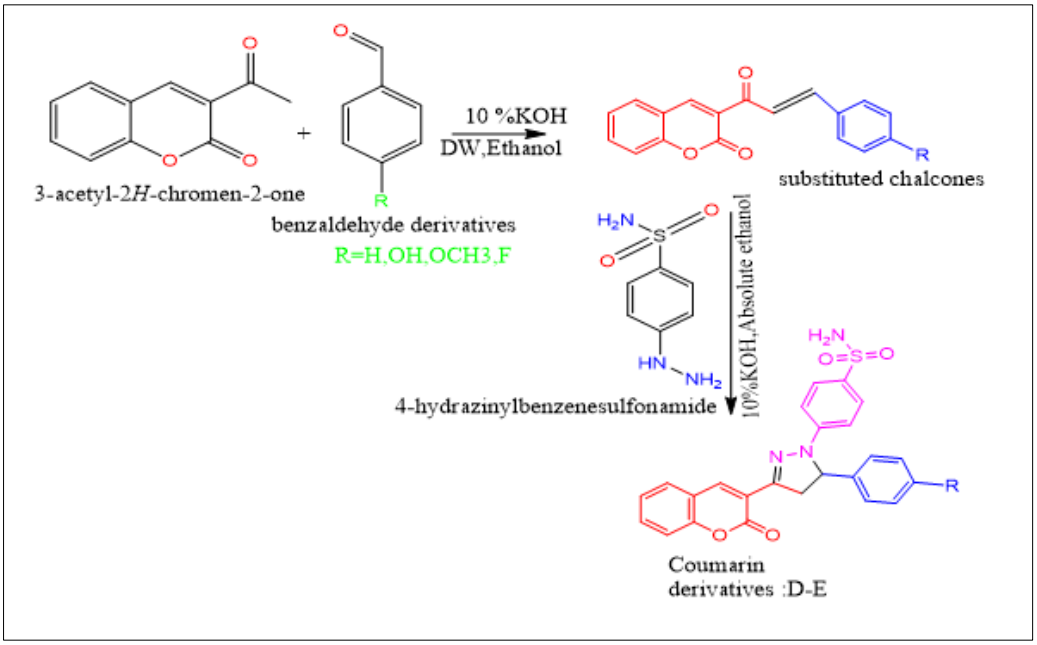
2.4. Ligand Preparation

The chemical structures of the newly designed ligands were drawn using ChemAxon (MarvinSketch), and their SMILES strings were used as input for the ligand preparation workflow. The 2D structure of the designed ligands (Table 1) was plotted and optimized using the Ligprep module in the Schrodinger suite 2022. In this part, the ionization state was

considered for each input compound at the physiological pH (7.4 ± 0.5). Finally, ligand optimization was performed using the OPLS-AA_2005 force field to obtain the best conformer for each ligands.

Free Binding Energy (MM-GBSA)

Free binding energy (ΔG bind) is considered a more accurate and reliable criterion for classifying ligands and assessing binding affinities compared to the approximate XP GlideScore. The free binding energy between a ligand and an acceptor is composed of the sum of the molecular mechanical energy and the effects of both polar and nonpolar solvents. In this study, the free binding energy was calculated using the generalized molecular mechanics/Born surface area (MM-GBSA) technique via the Prime module of the Schrödinger software package (version 2022). The best three-dimensional configuration of the ligand-protein complex was selected for energy calculation using the OPLS-2005 force field and the GBSA model.



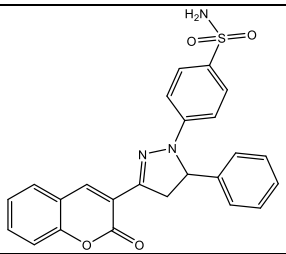
Scheme 1: Design of Coumarin derivatives (compounds D–G)

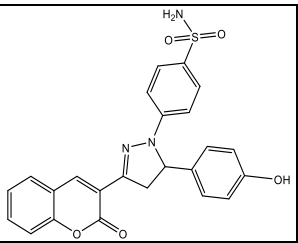
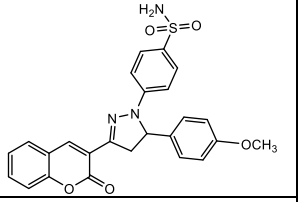
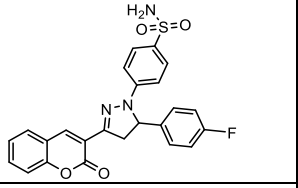
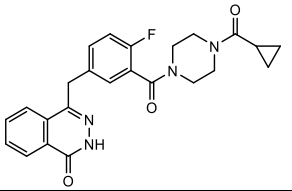
3. RESULT AND DISCUSSION

3.1 Chemistry: Design of Target Compounds

Guided by structure-activity relationship (SAR) insights and a comprehensive literature survey, four novel coumarin derivatives (compounds D–G) bearing the pyrazoline-sulfonamide pharmacophore were rationally designed as candidate ERalpha inhibitors. The synthetic design strategy involves two consecutive steps: the reaction of 3-acetyl-2H-chromen-2-one with C4-substituted benzaldehyde derivatives (phenyl for D, 4-hydroxyphenyl for E, 4-methoxyphenyl for F, and 4-fluorophenyl for G) to yield the corresponding substituted chalcones. The subsequent cyclocondensation of these chalcone intermediates with 4-hydrazinylbenzenesulfonamide to construct the novel coumarin-pyrazoline hybrids (D–G). These chemical modifications were aimed at increasing the lipophilicity of the pyrazoline-based derivatives (PBDs), thereby improving their gastrointestinal absorption and enhancing their anticancer potency. Consequently, all four designed candidates were subjected to in silico virtual screening against ERalpha. This molecular combination was tailored to optimize binding affinity, target selectivity, and drug-like properties in comparison with the reference drug olaparib. The chemical structures and IUPAC nomenclature for all synthesized compounds are illustrated in Table 1.

Table 1: Structures, IUPAC names, and SMILES notations of the designed coumarin derivatives (D–G) and reference drug olaparib

comp	Structure	Name	Smiles
D		4-(3-(2-oxo-2H-chromen-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide	O=C1OC2=CC=CC=C2C=C1C3=NN(C4=CC=C(S(N)(=O)=O)C=C4)C(C5=CC=CC=C5)C3

E		4-(5-(4-hydroxyphenyl)-3-(2-oxo-2H-chromen-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide	O=C1OC2=CC=CC=C2C=C1C3=NN(C4=CC=C(S(N)(=O)=O)C=C4)C(C5=CC=C(O)C=C5)C3
F		4-(5-(4-methoxyphenyl)-3-(2-oxo-2H-chromen-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide	O=C1OC2=CC=CC=C2C=C1C3=NN(C4=CC=C(S(N)(=O)=O)C=C4)C(C5=CC=C(OC)C=C5)C3
G		4-(5-(4-fluorophenyl)-3-(2-oxo-2H-chromen-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide	O=C1OC2=CC=CC=C2C=C1C3=NN(C4=CC=C(S(N)(=O)=O)C=C4)C(C5=CC=C(F)C=C5)C3
olaparib		4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2H-phthalazin-1-one	O=C1NN=C(CC2=CC=C(F)C(C(N3CCN(C(C4CC4)=O)CC3)=O)=C2)C5=C1C=CC=C5

3.2 ADME Studies (Drug-Likeness Evaluation)

In this study, the pharmacokinetic properties of the four designed compounds (D–G) were evaluated in comparison with the reference drug (olaparib) using the free electronic server website (SwissADME), which predicts absorption, distribution, metabolism, and excretion (ADME) based on the Lipinski rule. The pentad and related drug similarity criteria.. Key parameters including hydrogen bond acceptors and donors, molecular weight (MWT), topological polar surface area (TPSA), gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, oral bioavailability score, and Lipinski rule violations were calculated As shown in Table 2, all four designed compounds and the reference drug olaparib comply with Lipinski's Rule of Five with zero violations, confirming their drug-like character and predicted oral bioavailability. Compound D (MWT = 445.49 g/mol, TPSA = 114.35 Å²) and compound G (MWT = 463.48 g/mol, TPSA = 114.35 Å²) both exhibit high gastrointestinal absorption. Compound (F) ((MWT = 475.52 g/mol, topographic polar surface area) TPSA = 123.58 Å²) also showed high absorption in the digestive system despite having the highest molecular weight within this series. In contrast, compound (E) (molecular weight = 461.49 g/mol, TPSA = 134.58 Å²) showed low absorption in the digestive system; This is attributed to the relatively high topographic polar surface area resulting from the (4-hydroxyphenyl) group in its chemical structure, which adds an extra hydrogen bond donor (the number of hydrogen bond donors is two for compound E compared to one for compounds D, F, and G).

On the other hand, none of our four designed compounds crossed the blood-brain barrier, which is desirable according to the targeted application in breast cancer treatment. All of them achieved a bioavailability coefficient of 0.55, a value that matches that of (Olaparib), indicating acceptable oral bioavailability characteristics. The TPSA values for compounds (D) and (G) (114.35 Å²) fall within the acceptable range (where it is preferable that they be less than or equal to 140 Å²to ensure good absorption in the digestive system, while compounds that exceed this limit show bioavailability). (weakly orally). In general, the results of the Pharmacokinetic Prediction (ADME) confirm that all the developed compounds have suitable.

Table 2: ADME Results for Designed Compounds (D–G) and Reference Drug Olaparib

Comp.	H-bond acceptor	H-bond donor	MWT (g/mol)	TPSA (Å²)	GI Abs	BBB permeant	Bioavailability Score	Lipinski violation
D	6	1	445.49	114.35	High	No	0.55	0 violation
E	7	2	461.49	134.58	Low	No	0.55	0 violation
F	7	1	475.52	123.58	High	No	0.55	0 violation
G	7	1	463.48	114.35	High	No	0.55	0 violation
Olaparib	5	1	434.46	86.37	High	No	0.55	0 violation

3.3 Molecular Docking Studies Against ERα (PDB: 1ERR)

Molecular docking simulations were performed using the Glide module of the Schrödinger software suite in Standard Precision (SP) mode against the crystal structure of estrogen receptor-alpha (ERα) co-crystallized with a potent ligand (PDB: 1ERR). The ERα ligand-binding domain contains a well-defined hydrophobic pocket lined by key amino acid residues including Glu353, Arg394, His524, Asp351, Thr347, Phe404, and several leucine/methionine residues. All four designed compounds were docked into this binding pocket, with olaparib serving as the reference drug. The resulting XP GScore (kcal/mol) (binding energies), hydrogen bond interactions, hydrophobic contacts and MM/GBSA are compiled in Table 3, ordered by decreasing binding affinity.

Table 3: Binding Energies and Interaction Details for Designed Compounds (D–G) and Olaparib Docked against ERα (PDB: 1ERR)

Comp.	XP GScore (kcal/mol)	H bonds and other interactions with A.A residue	Other bonds hydrophobic interaction with A.A residue	MM/GBSA
E	**−7.727**	**GLU353, ASP351, ARG394, THR347, HIS524**	LEU349, ALA350, LEU354, LEU391, MET388, LEU387, LEU384, TRP383, LEU346, LEU428, MET343, PHE404, MET421, LEU525, GLY521	**-65.4**
D	−7.448	ASP351, THR347, ARG394, ALA350	TRP383, LEU384, LEU387, MET388, PHE404, LEU354, LEU391, LEU349, LEU346, LEU428, MET343, PHE425, ILE424, GLY521, LEU525, MET421, HIS524	-55.91
F	−7.257	GLU353, ASP351, ARG394, HIS524	LEU349, ALA350, THR347, MET343, LEU346, LEU428, PHE425, ILE424, GLY521, TRP383, LEU387, LEU384, MET388, PHE404, LEU536	-52.66
G	−7.192	ASP351, GLU353, ARG394, THR347, HIS524	LEU349, LEU354, PHE404, ALA350, LEU391, MET388, LEU387, LEU384, TRP383, LEU346, LEU428, MET343, PHE425, ILE424, GLY521, LEU525, MET421	-57.15
Olaparib	−7.130	THR347, LEU346, MET343	LEU349, ALA350, ASP351, GLU353, LEU354, LEU387, MET388, TRP383, LEU384, PHE404, GLY521, LEU525, TYR526, MET528, PRO535, LEU536, LEU539	-67.34

Our research results showed that the molecular docking listed in Table 3 demonstrated that all four designed compounds exhibited superior binding affinity to ER alpha-type estrogen receptors compared to the reference drug olaparib (Olaparib: -7.130 kcal/mol), thus confirming the efficacy and validity of the strategy. Rational Drug Design. Compound (E) recorded the highest binding energy according to the Glide Score, reaching (-7.727 kcal/mol), thus surpassing the rest of the designed compounds and the reference drug. This remarkable superiority in the stability of the complex is attributed to the presence of a 4-hydroxyphenyl group at position (C-5), which contributed to the formation of an additional hydrogen bond with the acidic amine glutamic acid (Glu353). via its hydroxyl group, thus enhancing the existing interactions between the two groups. Carbonyl and sulfonamide are present in the coumarin nucleus. This finding is consistent with the well-established role of both Glu353 and Arg394 as major hydrogen bond donors and receptors within the bond-binding pocket of the alpha-type estrogen receptor (ERα LBD).

The carbonyl and sulfonamide are present in the coumarin nucleus. In contrast, compound (D) (-7.448 kcal/mol) formed axial hydrogen bonds with (Asp351), (Thr347), (Arg394), and (Ala350), while extensive hydrophobic interactions with (Trp383), (Leu384), and (Phe404), in addition to adjacent leucine residues, contributed significantly. It is large in raising its binding energy. As for compound (F) (-7.257 kcal/mol), which carries a group (4-methoxyphenyl), it has formed four hydrogen bonds with the amino acids (Glu353), (Asp351), (Arg394), and (His524); the methoxy group modifies the electron density of the aromatic ring without introducing new polar bonds. On the other hand, compound (G) (-7.192 kcal/mol) replaced by the electron-withdrawing (4-fluorophenyl) group showed five hydrogen bonds that included the amino acids (Asp351), (Glu353), (Arg394), (Thr347), and (His524), along with a wide network of hydrophobic interactions. Despite the high electronegativity of the fluorine atom, it does not participate in forming strong hydrogen bonds; rather, its role is limited to influencing the distribution of electron clouds within the aromatic system. The reference drug “Olaparib” (Olaparib: -7.130 kcal/mol) showed less intense polar effects, as they were limited to the amino acid residues (Thr347), (Leu346), and (Met343). However, it compensated for this deficiency in polar bonds by forming strong hydrophobic interactions that extend over a wider bonding radius inside the target pocket. Figures (1) to (5) illustrate the interaction diagrams for all the compounds and the reference drug, which display two-dimensional (2D) interaction maps between the protein and the ligand, extracted by the Schrödinger software package.

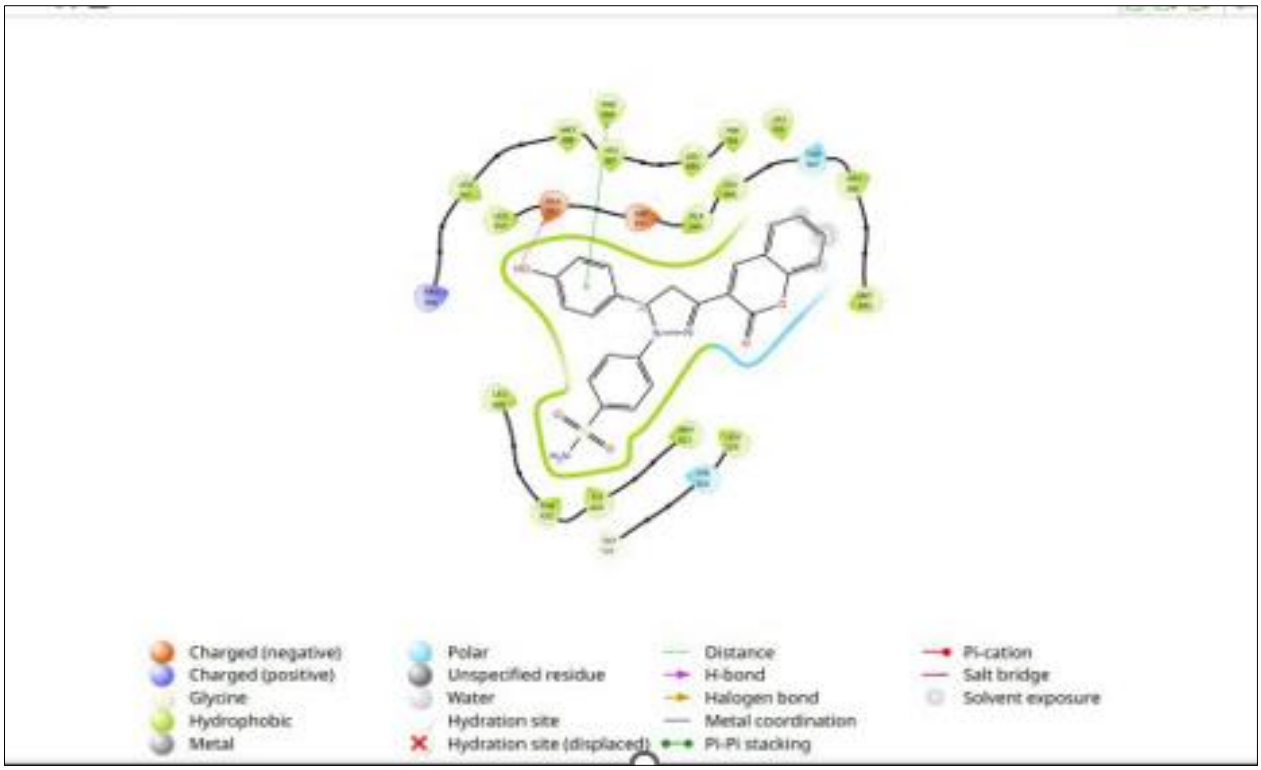


Figure 1: Ligand interaction diagram of compound E docked into ERα (PDB: 1ERR). Glide score: −7.727 kcal/mol

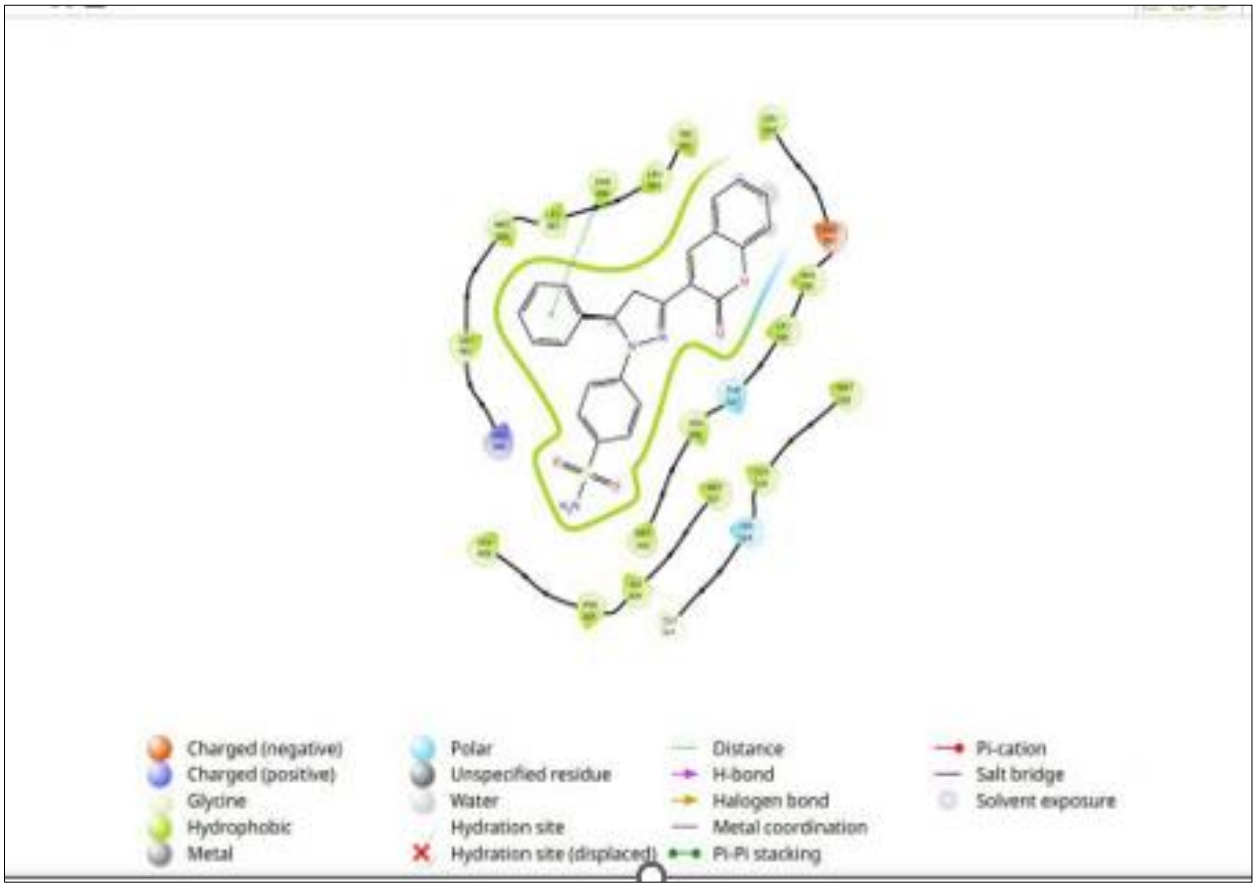


Figure 2: Ligand interaction diagram of compound D docked into ERα (PDB: 1ERR). Glide score: −7.448 kcal/mol

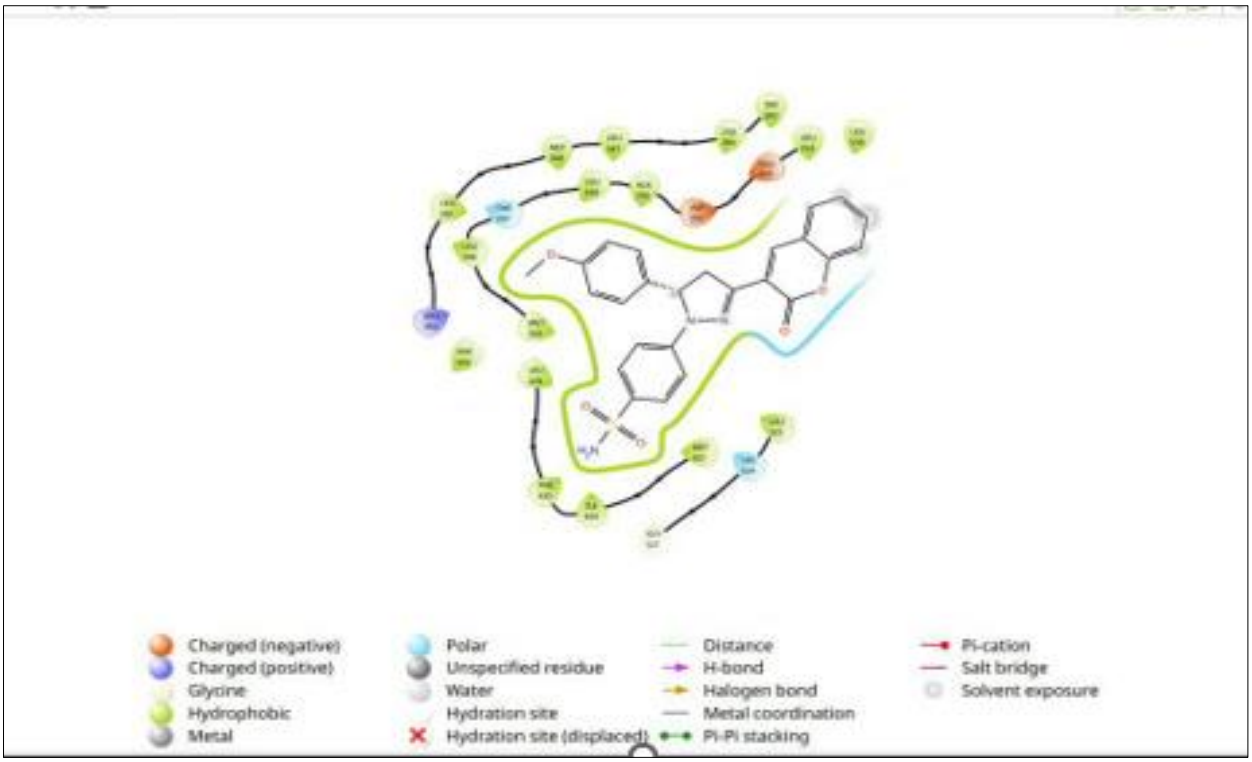


Figure 3: Ligand interaction diagram of compound F docked into ERα (PDB: 1ERR). Glide score: −7.257 kcal/mol

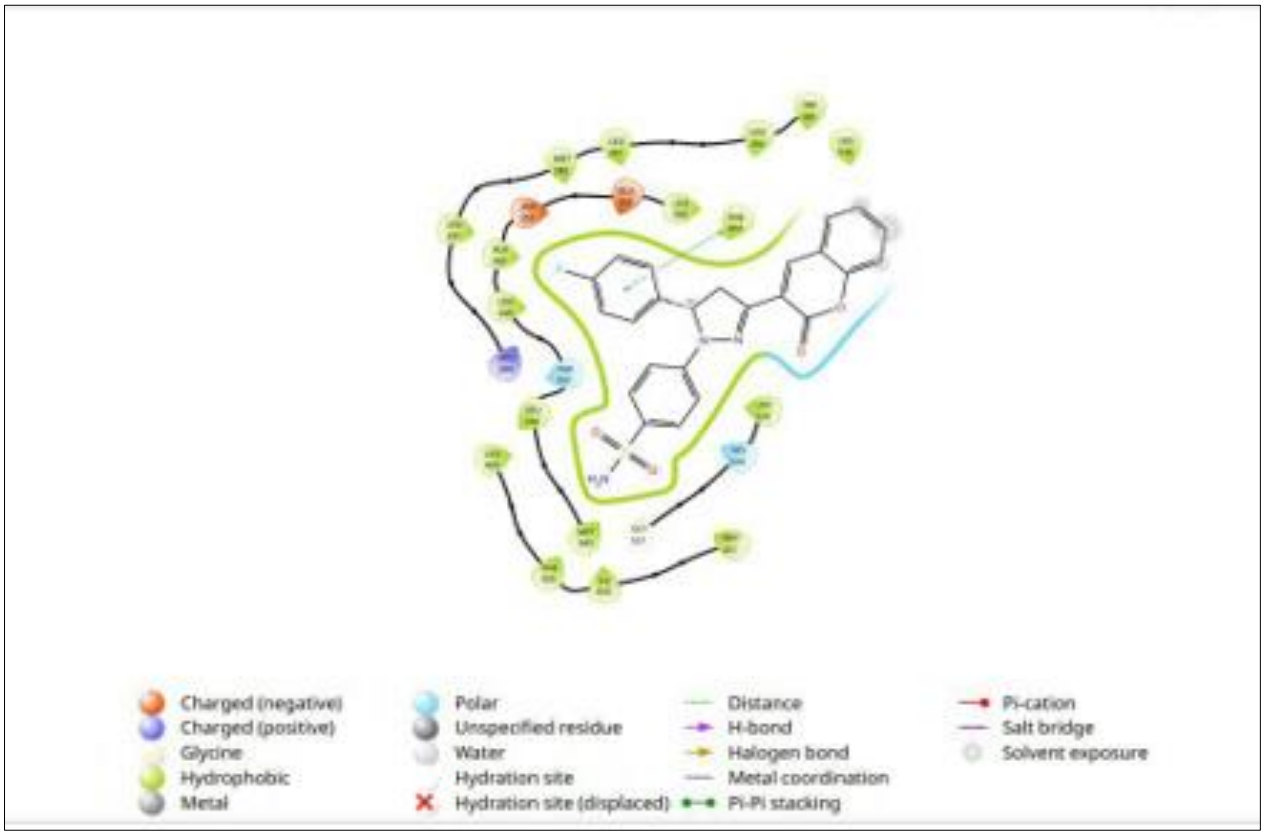


Figure 4: Ligand interaction diagram of compound G docked into ERα (PDB: 1ERR). Glide score: −7.192 kcal/mol

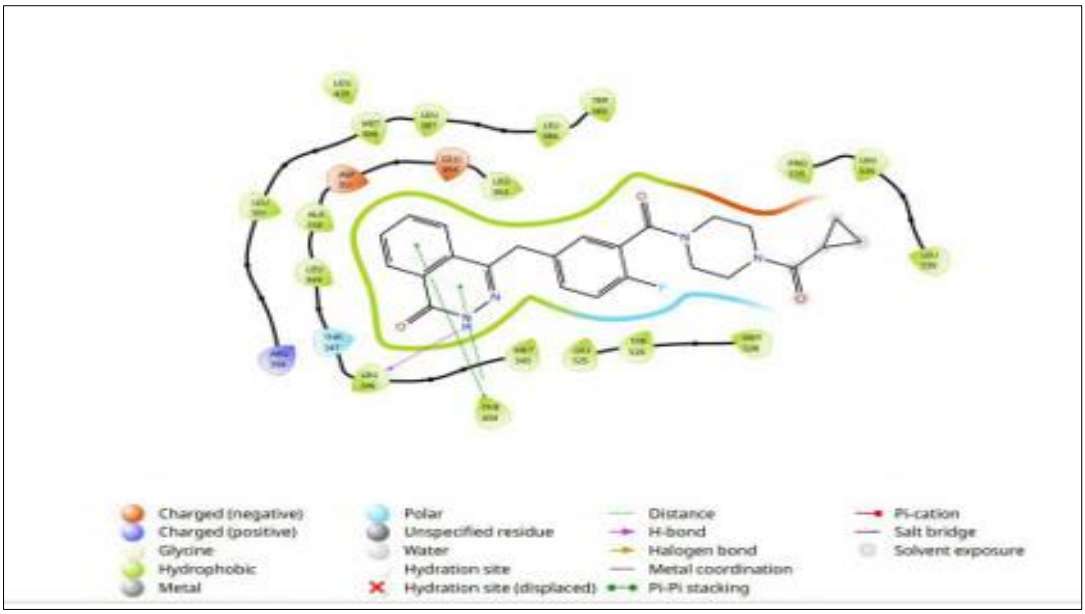


Figure 5: Ligand interaction diagram of olaparib docked into ERα (PDB: 1ERR). Glide score: −7.130 kcal/mol

To validate the docking process and investigate the main interactions between the crystallographic ligand-binding domain (LBD) and ER alpha(1ERR) a molecular docking study was performed. According to the findings, the catalytic GLU 353 and LEU 387 residues and PHE 404 amino acids are known as the main residues in the bottom and the edges pocket of ER alpha, respectively. The docking study analysis showed that all reported residues have formed hydrogen bonds with ligand (LBD) such as GLU 353 and ARG 394. Also, pi-pi stacking between the aromatic rings of the ligand core and the phenyl ring of phenylalanine 404 (PHE 404) and the main hydrophobic amino acids located around ligand (LBD) such as: Leu 346, Leu 349, Ala 350, Leu 354, Met 388, Leu 391, Phe 425, Leu 525, Leu 536, Leu 53. The results of our study are consistent with a previous study, Molecular basis of agonism and antagonism in the oestrogen receptor, that included the presence of the same interactions, most notably the GLU 353 hydrogen bond [39], as confirmed by another recent study [34] that showed the same associations with amino acids; the most critical residues identified include Glu353 and Arg394 [40], as shown in Figure 6.

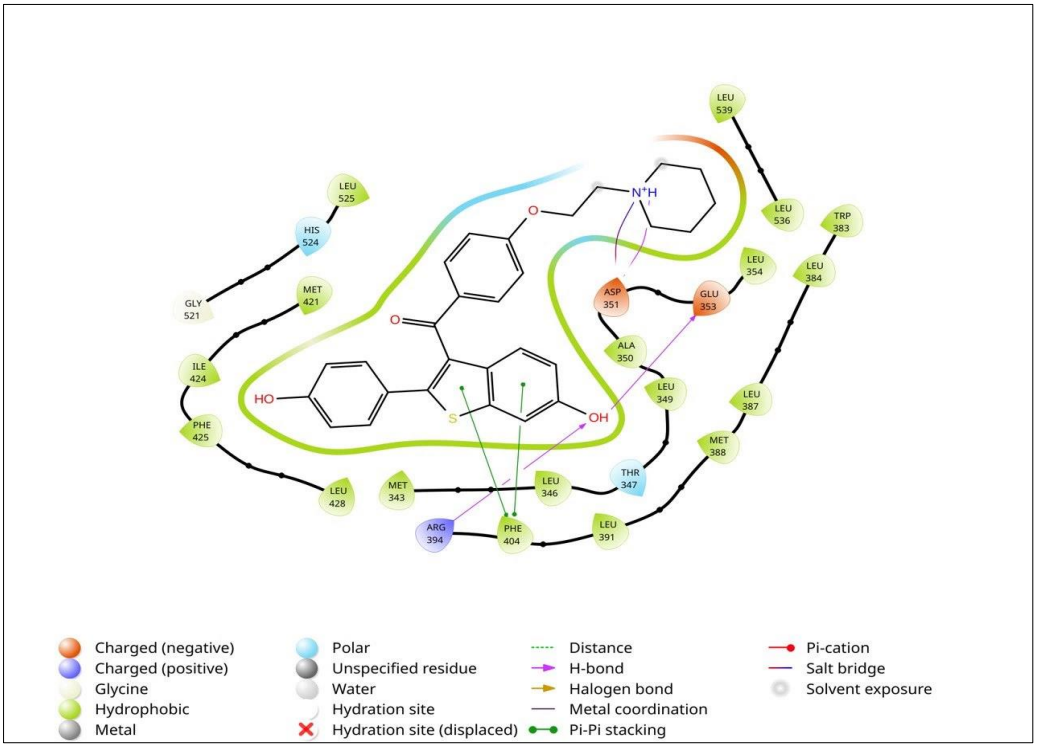


Figure 6: The interaction of compound LBD with Erα

4. CONCLUSION

This study presents the computational design and molecular simulation, as well as the evaluation of the absorption, distribution, metabolism, and excretion (ADME) characteristics of four newly designed (coumarin-pyrazolene-sulfonamide) (D–G) hybrid derivatives, and compares them to the reference drug, as potential estrogen receptor alpha (ERα) inhibitors for breast cancer treatment. The rational design strategy combined structural insights derived from the binding pocket properties of the estrogen receptor alpha with the known pharmacokinetic properties of pyrazolene, sulfonamides, and coumarin structures, resulting in a series of heterogeneous hybrid compounds with multiple functions and a suitable bonding architecture.

Molecular docking simulations of the estrogen receptor alpha crystal structure (PDB:1ERR) – using standard Glide SP processes – showed that all four of our designed compounds exhibited superior binding affinity compared to the reference drug olaparib (7,130 kJ/kg). (kcal/mol) Among them, compound (E), which carries a 4-hydroxyphenyl group, emerged as the most promising candidate, registering the highest binding energy (-7.727 kcal/mol). The high binding affinity of compound (E) is attributed to the formation of an additional hydrogen bond between its hydroxyl group and the basic amino acid residue (Glu353) in the receptor binding pocket, complementing the conserved interactions with (Asp351), (Arg394), (Thr347), and (His524). Compound (D) (-7.448 kcal/mol) came in second, indicating that the unsubstituted vinyl analog also exhibits strong interactions with the receptor, while compounds (F) and (G) (-7.257 and -7.192 kcal/mol, respectively) showed good binding properties with multiple interactions. Polarity and hydrophobicity were evaluated.

As confirmed by the Absorption, Distribution, Metabolism, and Excretion (ADME) analysis using the SwissADME pharmacokinetic platform for all the developed compounds, the four derivatives met the Lipinski quintuple rule without any violations and showed no penetration across the blood-brain barrier (making them suitable for peripheral organ antitumor applications), achieving an oral bioavailability coefficient of 0.55. Compounds (D), (F), and (G) exhibited high gastrointestinal absorption, while compound (E) showed lower absorption due to its high topographic polarity surface area (134.58 Å²), attributed to the additional hydroxyl group. These pharmacokinetic properties are remarkably similar to the pharmacokinetic profile of olaparib, thus enhancing the potential clinical significance of these compounds.

Accordingly, computational evidence confirms that compound (E) deserves to be considered a "lead compound" among all the designed compounds. Compared to the reference drug, it combines the highest affinity for alpha-type estrogen receptors (ER alpha) with an acceptable pharmacokinetic profile. This hybrid scaffold of "(pyrazoline-sulfonamide-coumarin)" shows promising potential as a structural scaffold for developing novel agents against breast cancer. Therefore, future studies should prioritize the chemical synthesis and in vitro biological evaluation (In vitro) of compound (E) against estrogen receptor-positive breast cancer cell lines (e.g., MCF-7 and T47D), followed by molecular dynamics simulations to evaluate Molecular complex stability over time. In conclusion, improving the structure-activity relationship (SAR) through systematic substitution at the (C-5) site of the pyrazoline ring may contribute to increasing binding affinity, selectivity, and pharmacokinetic performance; this will result in the emergence of a new generation of highly effective therapeutic candidates.

5. Financial Support

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6. Conflict of Interest'

The authors acknowledge that there are no known conflicts of interest or personal relationships that could influence the research published in this paper.

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