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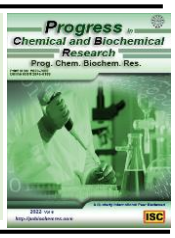

Original Research Article

Molecular Docking Studies of some Coumarin Derivatives as Anti-Breast Cancer agents: Computer-Aided Design and Pharmacokinetics Studies

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ABSTRACT

In spite of the modern analytic and therapeutic progressions, breast cancer is still one of the leading fatality-causing diseases and the second most common cancer found in women's populace globally. In this work, more potent and safer coumarin derivatives as anti-breast cancer agents were designed via molecular docking studies and structural modification of the design template. The results of docking studies performed between 26 coumarin derivatives and the predicted VEGFR-2 active site leads to the adoption of compound 7 (docking score = -149.893 cal/mol) which is greater than that of Sorafenib (docking score = -144.289 cal/mol) as the design template. Five novel coumarin derivatives with improved binding affinities ranging from -156.185 to -171.985 cal/mol were designed by adding electron-releasing $-NH_2$ and –OH groups which push electrons into the pyridine ring system via +I inductive effect, thereby increasing the basic character of the designed compounds and their binding affinities. Therefore, they bind more effectively with the target compared to Sorafenib. The designed derivatives demonstrate drug-likeliness and encouraging ADMET profiles as evidenced by the findings of pharmacological studies. Consequently, the outcomes of this inquiry could lead to the discovery of new and upgraded anti-breast tumor drugs.

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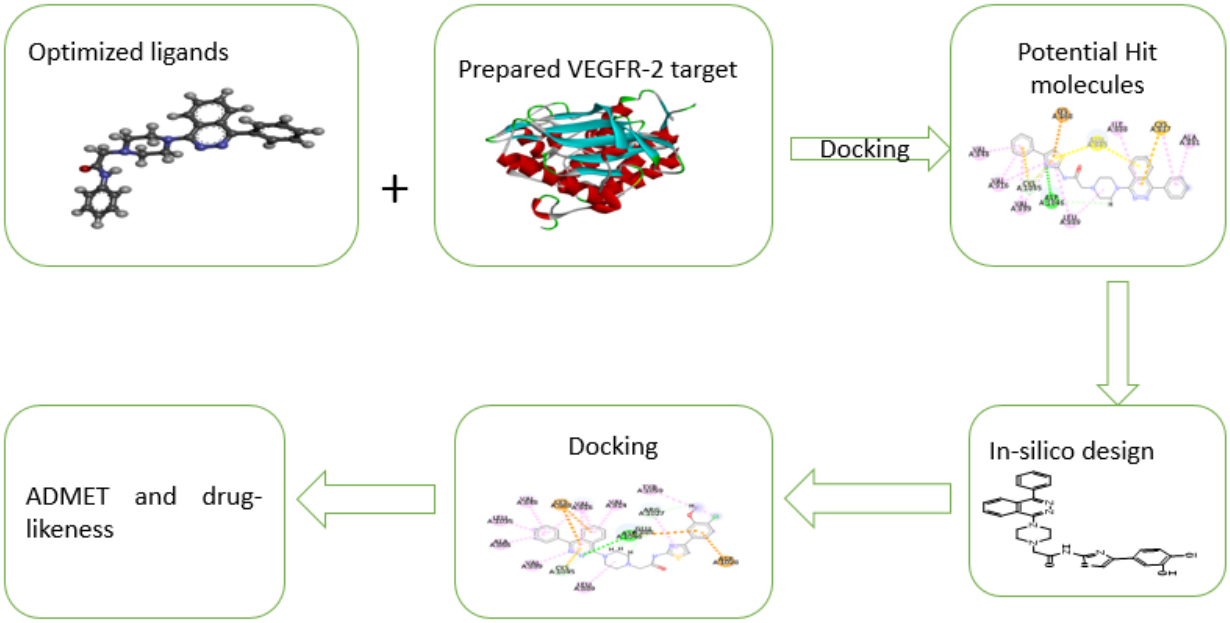
GRAPHICAL ABSTRACT



1. INTRODUCTION

In spite of the modern analytic and therapeutic developments, breast cancer is still one of the leading fatalities causing disease among female globally, and the second most common cancer found in women populace [1]. Currently, more appraisal of breast cancer biology channeled the progression of drugs precisely targeting tumorigenesis-associated molecular paths [2, 3]. Angiogenesis, which is the evolution of new blood vessels, is regarded as one of the tumor marks and breast vasculature has been conveyed to have a decisive part in breast tumor regulation [4, 5]. Therefore, various anti-angiogenic medications were assessed in breast cancer sufferers, comprising of the oral vascular endothelial growth factor-receptor (VEGFR-2) tyrosine kinase inhibitor, Sunitinib, which was recognized by the Food and Drug Administration for the treatment of varied cancer types [6,7]. Ideal anti-cancer agents exterminate cancer cells without causing unfavorable effects on common tissues [8]. Regrettably, the currently approved drugs do not comply with these principles because they displayed several unwanted effects and some patients are resilient to these drugs during the early treatment period. Consequently, the design of novel anti-cancer agents with improved activities and being orally safe is necessary [9]. The diverse medicinal properties of coumarin frame are principally based on the chemical structure and physicochemical character of its heterocyclic ring, which enables easy linkage to various target enzymes. The aromaticity, planarity, and lipophilicity of 2H-chromen-2-one ring enable its interaction with diverse biological targets, and the presence of lactone group pave the way for the coumarin molecules to make strong polar bonds such as hydrogen bonds [10]. Computational approaches were recently utilized to boost the efficiency of novel drug innovation, facilitating the inspection of numerous molecular entities in a lesser time, and disclosing their mode of linkages with targets of pharmacological attentiveness prior to production. Moreover, the process enables the simulation and prediction of several crucial parameters which include: toxicity, activity, bioavailability, and efficacy, before *in vitro* evaluation, thus enabling suitable preparation and direction of the researchers [11]. Among the computational methods, molecular docking is remarkably becoming a reliable approach in

isolating a lead molecule, and also in the screening of large molecular databases for pharmacologically effective molecules [12]. Docking approach entails ligand conformation (poses) prediction and the calculation of the pose's binding energy by employing a scoring function derived from a knowledge-based potential. In this work, we intend to utilize the molecular docking computational approach to design more potent coumarin derivatives as anti-breast cancer agents. The ADMET and drug-likeness properties of the newly designed compounds were predicted to avoid failure after development or advance discovery state and adverse effect.

2. EXPERIMENTAL

2.1. Materials and Methods

2.1.1 Data Set Retrieval and 2D Structural Drawing

26 compounds comprising of coumarin derivatives were obtained from Ahmed *et al.* [13]. 2-dimensional structures of the compounds were sketched with care by using the Perkin Elmer ChemDraw software using ACS 1996 document, and then saved in cdx format, as presented in Table 1.

2.1.2 Ligand Preparation

The sketched 2D structures in cdx format were converted to 3-dimensional layout by means of Graphical user interface Spartan v14.0 software which was further utilized for the molecular optimization via the density functional theory calculations (DFT) and B3LYP/631-G* basis set chosen for the accomplishment of accurate results. The optimized molecular structures were kept in the recommended format PDB [14].

2.1.3 Target Receptor Retrieval and Preparation

The crystal structure of the VEGFR-2 target protein in complex with Sorafenib (pdb code: 4ASD) was downloaded from the protein data bank online site [15].

BIOVIA discovery studio visualizer was employed for the protein preparation by the elimination of all kind of solvent molecules and the co-crystallized Sorafenib followed by optimization of hydrogen ions and finally saved in pdb format [16].

2.1.4. Docking Simulation

Due to its ability to produce more reliable results compared to other docking softwares, Molegro Virtual docker (MVD) was utilized for the docking simulation in this work. Before the commencement of the process, the prepared VEGFR-2 protein was taken to the Software's work space for the electrostatic surface creation and binding cavity detection. The predicted binding cavity was inserted into constrained sphere having X, Y, and Z coordinates of -27.60, -8.97, and -6.00Å. The optimized ligand were imported one after another for the docking process performed using 0.30Å GRID resolution, 2.0Å root mean square deviation (RMSD) for collection of poses with 100.00 energy penalty scores. Furthermore, the docking algorithm was set for a maximum of 1500 rounds with overall populace of 50. The docking simulation was run for at least 50 times for the 5 poses, and the determination of the best poses was based on the MolDock scoring functions [17]. Discovery studio 3.5 software was used in the visualization and interpretation of the ligand-protein interactions.

2.1.5. In silico Drug Design

To affirm the reliability of the docking algorithm utilized in this research, Sorafenib was redocked with the primary binding cavity of the target receptor. The initial pose was then superimposed with the redocked pose using PyMol software and RMSD value was calculated [18].

In addition, the docking score of Sorafenib was used as a benchmark for the identification of design template which was structurally modified

by introduction and substitution of various fragments to design more potent therapeutic agents [19].

2.1.6. Pharmacological Profile Prediction

The assessment of medicinal and principal ADMET properties of a molecule is necessary at the primary phase of drug exploration as they enable the assessment of the undesirable properties of the molecules. The medicinal properties assessment was performed via the renowned Lipinski standards by means of SwissADME online web whereas pkCSM web was utilized for the ADMET profiling [20, 21].

3. RESULTS and DISCUSSION

3.1. Docking Studies

The results of docking studies performed between the optimized structures of the coumarin derivatives and the predicted binding site of the VEGFR-2 target receptor are presented in Table 1. Moreover, Sorafenib was also re-docked into the initial binding site and the result of superimposition of the initial and the re-docked poses of Sorafenib reliably validated the docking protocol of the algorithm utilized in this research with RMSD value of 1.63Å, as displayed in Fig 1. Docking score of Sorafenib (MolDock score = -144.289 cal/mol) was utilized as a benchmark for the identification of design template. Compound 7 with MolDock score of -149.893 cal/mol was identified as the template, being the only compound in the series with better docking score compared to Sorafenib.

3.2. In silico Design

For the design purpose, the template was structurally modified by the addition of amino (-NH_2) and hydroxyl (-OH) groups onto the various positions of the pyridine groups of the compound. These groups are electron-rich and tend to push electrons into the pyridine ring system via +I inductive effect thereby increasing the basic character of the designed compounds and their binding affinities. Five compounds with binding affinities ranging from -156.185 to -171.985 cal/mol were designed, their 2D structures and MolDock scores are presented in Table 2, while various intermolecular interactions of the VEGFR-2 docked complexes of the designed compounds, the template and Sorafenib are listed in Table 3. The modes of interactions of designed compounds 3 and 4 (having the highest binding affinities) were discussed and compared with that of Sorafenib.

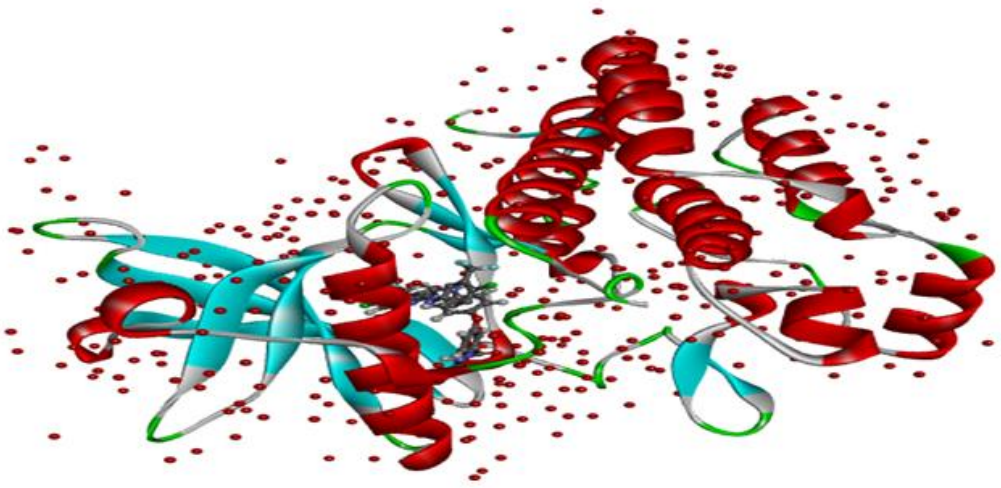
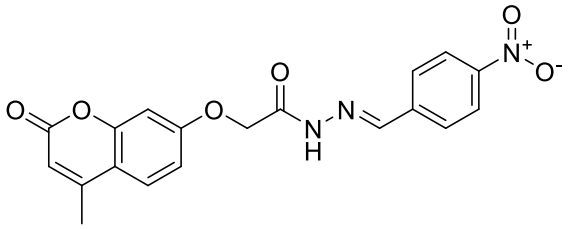
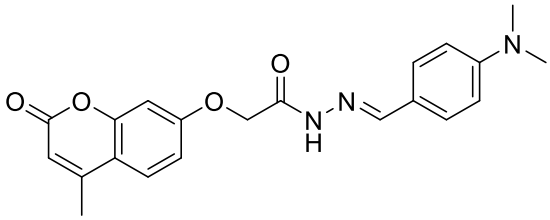
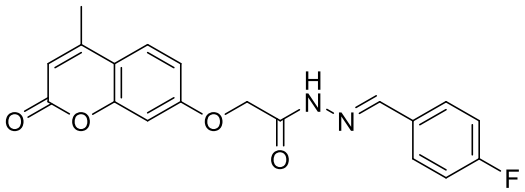
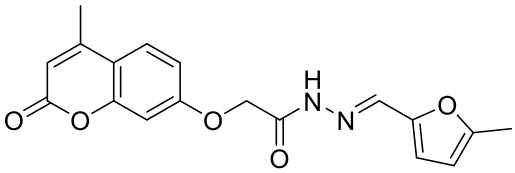
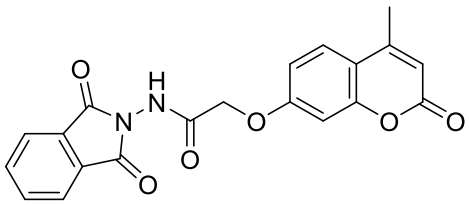
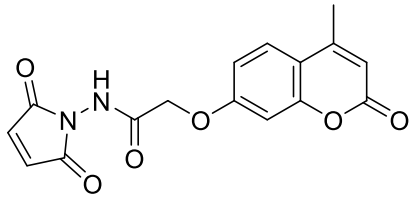
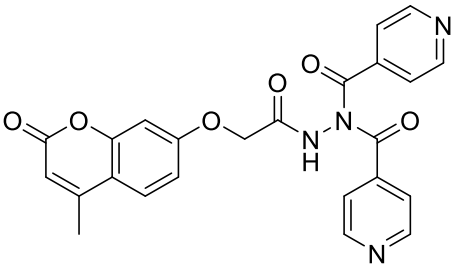
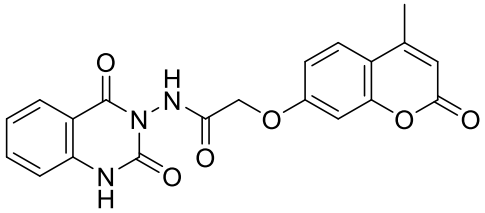
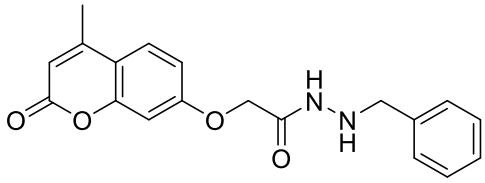
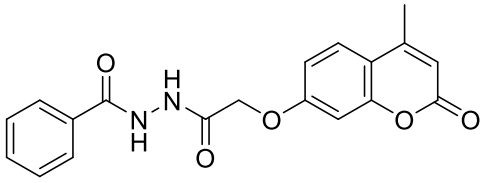
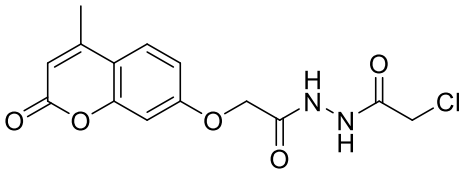
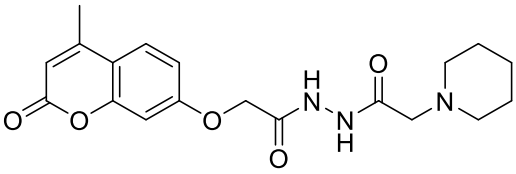
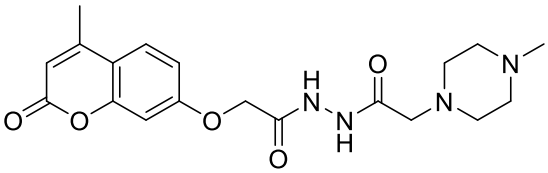
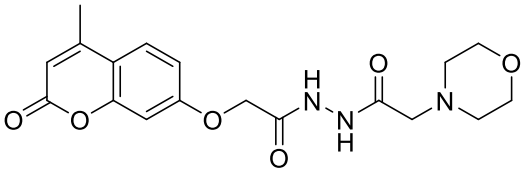
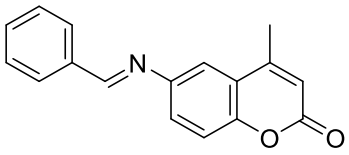
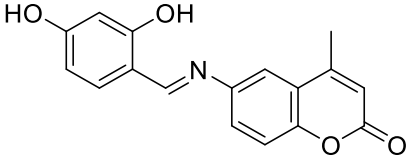


Fig 1.3D superimposed structure of the initial and redocked poses of Sorafenib

Table 1.2D structures of the coumarin derivatives and their corresponding docking scores

Complex	IUPAC name	MolDock score (cal/mol)
1		-125.683
2		-136.276
3		-135.38
4		-133.482
5		-130.848
6		-130.139
7		-149.893

8		-121.555
9		-124.273
10		-123.401
11		-105.443
12		-126.571
13		-142.5
14		-131.382
15		-118.865
16		-126.562

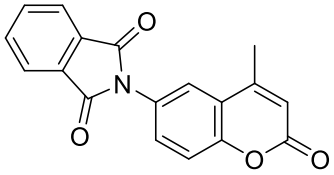
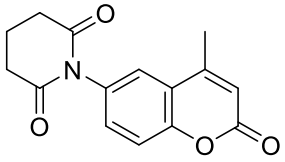
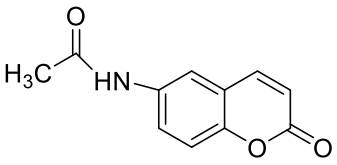
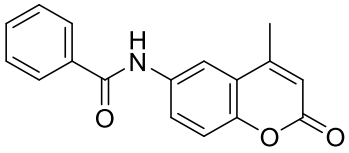
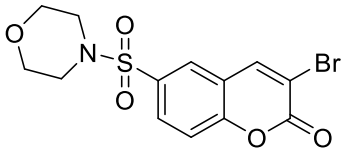
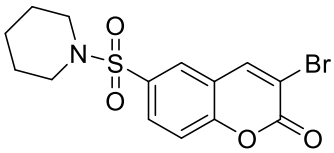
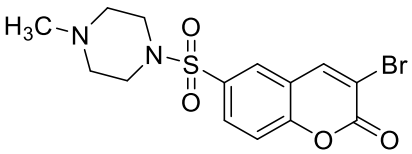
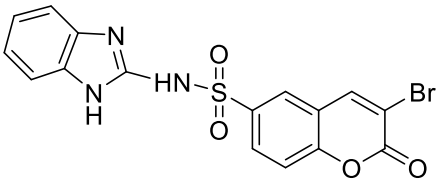
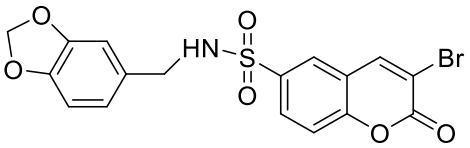
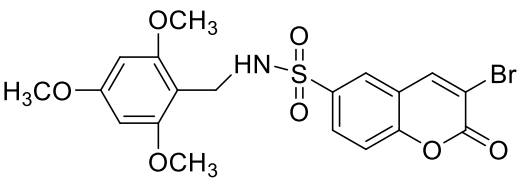
17		-128.389
18		-85.6353
19		-86.6107
20		-112.713
21		-88.5752
22		-93.3607
23		-93.5715
24		-109.6
25		-132.911
26		-126.575
Sorafenib		-144.289

Table 2.2D structures of the designed compounds and their MolDock score

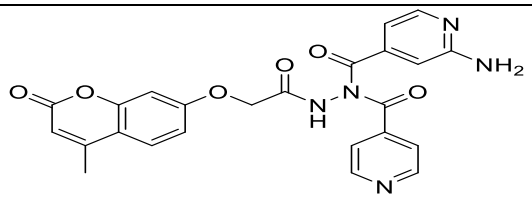
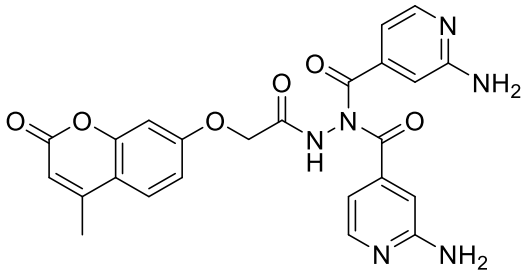
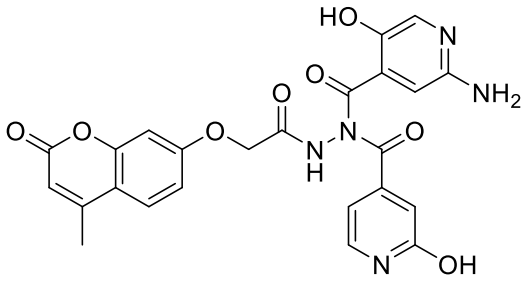
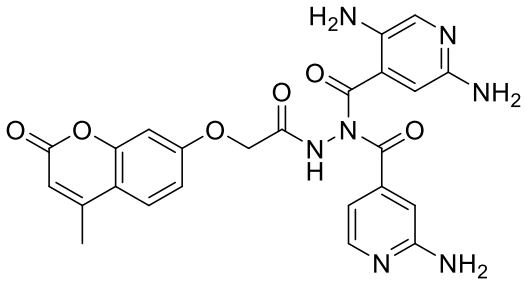
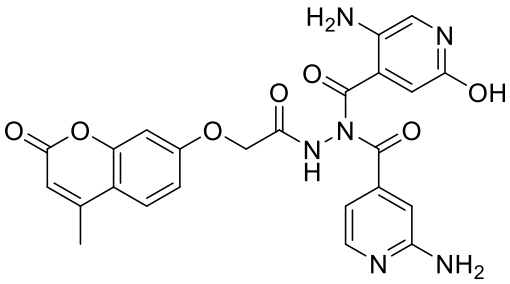
S/No.	2D structure	MolDock score
1		-158.599
2		-161.956
3		-171.985
4		-166.795
5		-156.185

Table 3.VEGFR-2 docked complex interactions of the designed compounds, the template, and Sorafenib

Complex	H-Bond interactions and distance (Å)	Hydrophobic interactions	Electrostatic and other interactions
1	ASP1046 [1.905] CYS1045 [2.626]	PHE1047, VAL848 (2), LYS868 (3), VAL916 (3), ALA866, VAL899 (2), and ILE888	LYS868, CYS817, CYS1024, and CYS1045 (2)
2	LYS868 [2.576, 2.529] CYS1045 [1.704]	LYS868, VAL899, VAL916, LEU1019, and LEU889	LYS868, GLU885, and CYS1045
3	VAL899 [2.191] ARG1027 [2.289] ASP1046 [2.234] LEU813 [2.176] ILE1044 [1.991] VAL898 [3.029] HIS1026 [2.772] GLU885 [2.509] ASP1046 [2.270]	ALA866 (2), VAL848 (2), LYS868 (2), VAL916 (3), ILE888, VAL899 (2), LEU889, ILE892, VAL898, and LEU1019	LYS868, ASP814, CYS1024, and CYS1045 (2)
4	GLN847 [2.873] ALA1050 [2.771] ASP1046 [2.028] ASP814 [2.073] GLY846 [2.491] ASP1046 [1.769] GLU885 [3.098]	LYS868, LEU882, CYS1045, ASP1046, LEU870, LEU882 (2), LEU1049 (2), ILE888, LEU1049, and ALA881	GLU885, CYS1024, and CYS1024
5	ARG1027 [2.381] ARG1051 [2.181] ASP1046 [2.503] LEU813 [2.892] SER884 [2.108] GLY1048 [2.296]	SER884, GLU885 ARG1027, ASP1028, ILE1053 (2), PRO1068 TYR1059, and ILE888 (2)	ASP814, ASP1028 (2), CYS817, and CYS1024
Template	ARG1027 [1.913] CYS1045 [2.544] ILE1025 [2.924]	PHE1047 (2), ASP1046 VAL914, ARG1027, VAL848, LYS868 (2) LEU889, VAL899 (2), and VAL916 (3)	LYS868 (2), ASP814, GLU885 (2) CYS817, and CYS1045 (2)
Sorafenib	CYS1045 [2.756] ASP1046 [2.119] ALA881 [2.701] GLU885 [2.835] SER884 [2.321] GLU885 [2.739]	SER884, GLU885, ALA866, VAL848, VAL916 (3), LEU1035, VAL848 LYS868, PHE1047 LYS868, and VAL899 (2)	LYS868 (2), ASP814, ASP1046 CYS817, and CYS1045

Interactions of designed compound 3 with the VEGFR-2 binding pocket were through conventional and carbon-hydrogen bonds with these group of amino acid residues and their respective distances in Å: VAL899 [2.191], ARG1027 [2.289], ASP1046 [2.234], LEU813

[2.176], ILE1044 [1.991], VAL898 [3.029], HIS1026 [2.772], GLU885 [2.509], and ASP1046 [2.270]. Hydrophobic interactions formed with these amino acid residues: ALA866 (2), VAL848 (2), LYS868 (2), VAL916 (3), ILE888, VAL899 (2), LEU889, ILE892, VAL898, and LEU1019. Electrostatic and other interactions with these amino acid residues: LYS868, ASP814, CYS1024, and CYS1045 (2), as shown in Fig 1(a). Similarly, the interactions of designed compound 4 with the VEGFR-2 binding pocket were through conventional and carbon-hydrogen bonds with these group of amino acid residues and their respective distances in Å: GLN847[2.873], ALA1050 [2.771], ASP1046 [2.028], ASP814 [2.073], GLY846 [2.491], ASP1046 [1.769], and GLU885 [3.098]. Hydrophobic interactions formed with these amino acid residues: LYS868, LEU882, CYS1045, ASP1046, LEU870, LEU882 (2), LEU1049 (2), ILE888, LEU1049, and ALA881. Electrostatic and other interactions are also produced with GLU885, CYS1024, and CYS1024 residues, as depicted in Fig 1(b).

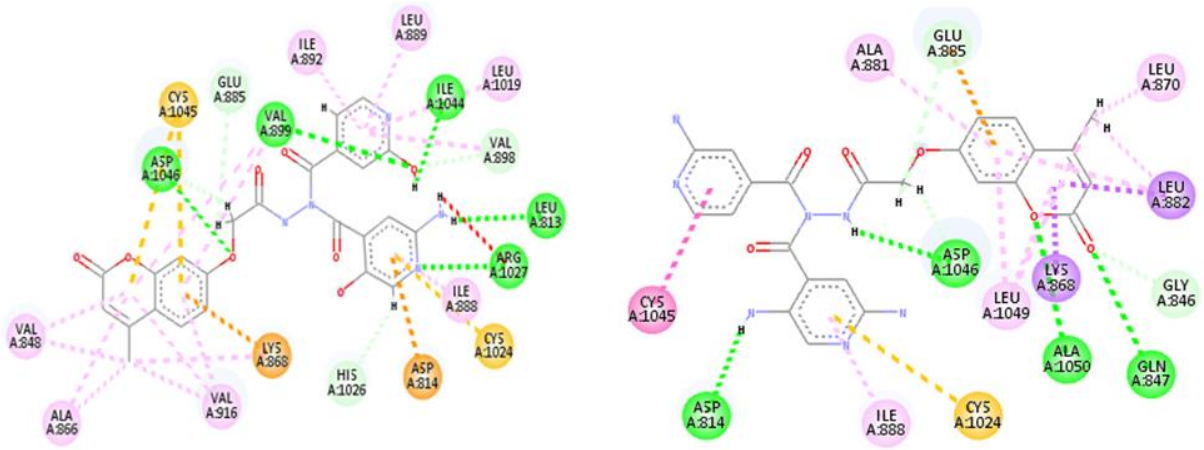


Fig2. (A) 2D representation of VEGFR-2 docked (B) 2D representation of VEGFR-2 docked complex of designed compound 3 complex of designed compound 4

The modes of interactions of Sorafenib with the VEGFR-2 target protein is through conventional and carbon-hydrogen bonds with the following amino acid residues and their respective distances in Å: CYS1045 [2.756], ASP1046 [2.119], ALA881 [2.701], GLU885 [2.835], SER884 [2.321], and GLU885 [2.739]. Hydrophobic interactions with: SER884, GLU885, ALA866, VAL848, VAL916 (3), LEU1035, VAL848, LYS868, PHE1047, and LYS868, VAL899 (2) residues. Electrostatic and other interactions with LYS868 (2), ASP814, ASP1046, CYS817, and CYS1045 residues are displayed in Fig 2.

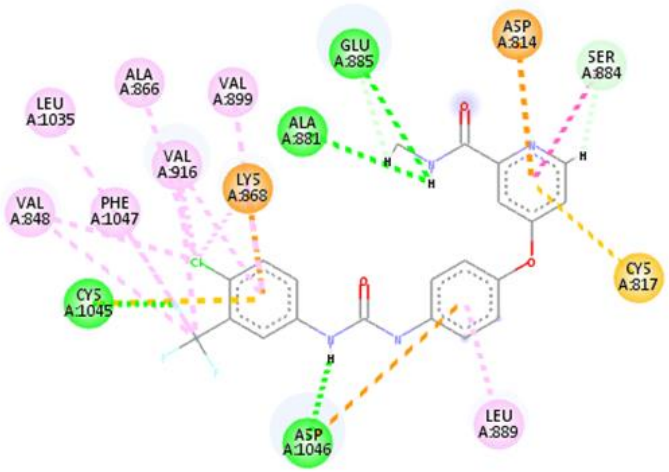


Fig3. 2D representation of VEGFR-2 docked complex of Sorafenib

Hydrogen bond is the ultimate driving force that regulates the existing interactions between the designed coumarin derivatives and the VEGFR binding site residues [8]. Designed compound 3 and 4 interacted with the VEGFR active site residues through 9 and 7 conventional and carbon-hydrogen bonds (Fig 1 (a and b)), while Sorafenib interacted with the VEGFR active site residues through fewer conventional and carbon-hydrogen bonds (Fig 2). This difference in the number of hydrogen bonds might be the reason for the better docking scores of the compounds compared to Sorafenib and hence they binds more effectively with the target.

3.3. ADMET and Drug-Likeness Studies

To ensure that the designed coumarin analogs are the possible drug candidates, their ADMET, and pharmacological profiles were predicted, and presented in Table 4 and 5. The designed compounds complies with the Lipinski's rule as compounds 1, 2, 4, and 5 has only one violation (MW >500) while 3 has two violations (MW >500 and NHA=10). Consequently, they are deemed to be viable drug candidates. Their bioavailability scores were 0.55 except designed compound 3 whose value is 0.17, thus illustrating an excellent form of permeability and bioavailability [20]. They exhibit low synthetic accessibility values below 5, asserting their easy synthesis when referred to a scale between 1 (easily synthesized) and 10 (tedious to synthesize). In addition, they exhibit high intestinal (human) absorption, ranging from 63.287% to 84.545%. This implies that they are well absorbed by the human intestine because poorly soaked molecules displays absorbance below 30% [22]. BBB and CNS penetration ratings were utilized to establish permeability status of a molecule through the blood-brain barrier and the central nervous system. A log BB > 0.3 recommends easy BBB permeate property while log BB < -1 suggests poor BBB dispersal. Furthermore, log PS > -2 illustrates easy CNS dispersal while log PS < -3 suggests poor dispersal [23]. Predicted log BB of the designed entities indicated the non-potentiality of crossing the blood-brain barrier, while predicted logPS scores revealed that only compound 5 possess the CNS permeant. Cytochrome P450 (CYP450) are category of super enzymes enabling the drug's metabolism as it is the prime liver protein system responsible for oxidation (phase-1 metabolism), as in the case of this research. Furthermore, cytochrome CYP3A4 inhibition is an essential phenomenon in this study [23]. This research revealed that

designed compounds 5, 16, and 13 exhibit CYP3A4 inhibitive properties. Clearance describes the drug level in the system in relation to its period of excretion. Low clearance score predicted a renowned resolution of the drugs in a human system, and all the designed compounds exhibits clearance score below 1 which suggest good resolution in the body for the drug [24]. Moreover, probing the extent of toxicity is ultimate as it plays a significant role in evading drug failure. The designed compounds do not possess AMES toxicity status, thus affirming them as orally safe without any serious toxicity threat [25].

Table 4. Drug-likeliness profiles of the coumarin derivatives

ID	Molecular weight	Number of H-bond acceptors	Number of H-bond donors	MLOGP	Bioavailability score	Synthetic accessibility
1	473.44	8	2	0.96	0.55	3.54
2	488.45	8	3	0.61	0.55	3.62
3	505.44	10	4	0.13	0.17	3.73
4	503.47	8	4	0.13	0.55	3.75
5	504.45	9	4	0.13	0.55	3.78
RO5	<500	<10	<5	<5		

Table 5.ADMET profiles of the coumarin derivatives

S/No.	Absorption	Distribution		Metabolism							Excretion	Toxicity
	Intestinal Absorption (Human)			Substrate				inhibitors			Tolerance clearance	AMES Toxicity
				CYP								
		BBB Permeability	CSN Permeability	2D6	3A4	1A2	2C19	2C9	2D6	3A4		
1	82.195	-1.408	-3.231	NO	YES	NO	NO	YES	NO	YES	0.826	NO
2	73.225	-1.353	-4.071	NO	YES	NO	NO	NO	NO	YES	0.76	NO
3	64.451	-1.913	-4.370	NO	NO	NO	NO	NO	NO	NO	0.808	NO
4	63.287	-1.722	-4.298	NO	YES	NO	NO	NO	NO	NO	0.575	NO
5	84.545	-1.605	-2.401	YES	NO	NO	YES	NO	NO	YES	0.728	NO

4. Conclusion

Molecular docking technique was executed using 26 coumarin derivatives as VEGFR-2 inhibitors for the design of more effective and safer derivatives based on the docking scores and pharmacological profile evaluation. VEGFR-2 target protein co-crystallized with Sorafenib (pdb id = 4ASD) was obtained from the protein data bank and prepared with aid of BIOVIA discovery studio visualizer by eliminating all kinds of solvent molecules and the co-crystallized Sorafenib followed by optimizing hydrogen ions and later saved in pdb format. The positive control (Sorafenib) was further re-docked into the initial VEGFR-2 binding pocket of the receptor and the result of superimposition of the initial and the re-docked pose of Sorafenib reliably validated the docking protocol of the algorithm utilized in this research with RMSD value of 1.63Å. Compound 7 (MolDock score = -149.893 cal/mol) was identified as the template, being the only compound in the series with better docking score compared to Sorafenib

(MolDock score = -144.289 cal/mol). Consequently, the template was structurally modified via the addition of electron releasing –NH_2 and –OH groups for the design of five novel derivatives with better docking scores ranging from -156.185 to -171.985 cal/mol. The designed derivatives exhibit drug-likeliness and encouraging ADMET profiles as evident from the findings of pharmacological studies. Consequently, the outcomes of this enquiry could lead to the discovery of new and upgraded anti-breast tumor drugs.

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