

IN-SILICO STUDY OF MODIFIED SORAFENIB DERIVATIVES AS A POTENTIAL VEGFRS INHIBITORS

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Abstract

The goal of the current investigation was to assess the binding affinity, interaction patterns, and inhibitory applications of modified sorafenib derivatives (S1–S6) with VEGFR-1 and VEGFR-2 by molecular docking study. Inhibitor-protein interaction was study by using auto dock vina, discovery studio, and PyMol, we examined the molecular interactions of six modified compounds against VEGFRs in present work, modified drugs shown an excellent inhibitory potential with targeted VEGFRs (-18.17 to -12.83 kcal/mol). Among the tested derivatives S3 and S2 display a good potential and S2 show least inhibitory activity against targeted VEGFR-1 and VEGFR-2. Further experimental validation will lead to a new therapeutic drug discovery for VEGFRs inhibitors.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most aggressive and commonly diagnosed liver cancers, and cancer is still one of the world's leading causes of death.[1] The incidence of HCC has increased significantly over the past few decades due to factors such as chronic hepatitis infection, alcohol consumption, obesity, and liver cirrhosis. Despite advances in therapeutic strategies, the prognosis of advanced HCC remains poor because of late diagnosis, rapid tumor progression, metastasis, and resistance to conventional chemotherapy.[2, 3]. Angiogenesis, the creation of new blood vessels that provide cancer cells with nutrients and oxygen, is one of the main biological processes involved in tumor growth and metastasis. Since the vascular endothelial growth factor (VEGF) signalling pathway is essential to angiogenesis, it is regarded as a crucial target in cancer

treatment.[4, 5] VEGF exerts its activity mainly through vascular endothelial growth factor receptors, particularly VEGFR-1 and VEGFR-2, which regulate endothelial cell survival, proliferation, migration, and vascular permeability. Abnormal activation of these receptors has been strongly associated with tumor development and progression in hepatocellular carcinoma and several other cancers.[6, 7]

Sorafenib is an orally active multikinase inhibitor that was approved as a first-line treatment for advanced hepatocellular carcinoma due to its ability to inhibit tumor proliferation and angiogenesis through blocking VEGFR-1, VEGFR-2, RAF kinases, and platelet-derived growth factor receptor[8, 9]. Sorafenib dramatically increases survival in patients with advanced HCC, according to clinical research; however, long-term use of the medication is

frequently linked to side effects, poor selectivity, and the development of drug resistance. [10, 11]. These limitations have encouraged researchers to design and develop new sorafenib derivatives with enhanced binding affinity, improved selectivity, and reduced toxicity. In recent years, molecular docking has emerged as an important computational approach in drug discovery and design because it allows the prediction of ligand-receptor interactions, binding conformations, and molecular stability within the active site of target proteins [12, 13]. Molecular docking studies provide detailed insights into hydrogen bonding, hydrophobic interactions, and binding energies, helping researchers identify promising compounds before experimental validation [14-16]. Therefore, the present study focuses on the molecular docking analysis of sorafenib and its derivatives against VEGFR-1 and VEGFR-2 to evaluate their inhibitory potential and interaction behavior. The study aims to identify structurally modified derivatives with stronger receptor binding and improved molecular interactions compared to the parent compound, which may contribute to the future development of more effective anti-angiogenic therapies for hepatocellular carcinoma and related cancers. [17, 18]

The present study focuses on the molecular docking analysis of sorafenib and its derivatives against VEGFR-1 and VEGFR-2 to evaluate their binding affinity, molecular interactions, and inhibitory potential. Comparative docking studies were performed to identify derivatives with stronger receptor interactions and improved binding stability compared to the parent compound [17, 19]. Particular attention was given to the identification of key amino acid residues involved in ligand binding and stabilization within the receptor active sites. The findings of this research may provide useful insights into the rational design of novel VEGFR inhibitors and contribute to the advancement of targeted therapy for hepatocellular carcinoma and other

angiogenesis-dependent cancers.

2. Methodology

VEGFR-1 and VEGFR-2 were chosen for the title study because it is believed that they are essential for angiogenesis in HCC, according to the literature review. The new modified sorafenib derivatives (S1-S6) are shown in Figure 1. These compounds were selected due to their capacity to block the specified enzymes, specifically VEGFR-1 and VEGFR-2. Additionally, tests were conducted. The newly designed sorafenib derivatives were assessed for their effects of the conventional medications sorafenib, against the target enzymes. The computational, modelling, and simulation tools required for molecular docking in the recent work are Chem Draw, Chem3D, Open Babel, Auto Dock tools, PyMol, and Discovery Studio Visualization. These applications enable ligand optimization and docking with particular targeted enzymes. [20, 21]. The mechanism of binding contact of the produced urea derivatives was, examined for both competitive and non-competitive inhibition of VEGFR-1 and VEGFR-2, the HCC mark enzymes, using the molecular docking procedure (shown in Figure 1). The three-dimensional crystal VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1) structures proteins were obtained from the Protein Databank. [22]. In order to facilitate calculations, Following the theoretical creation of the title proteins utilizing Auto Dock MGL tools, inhibitors, co-factors, heteroatoms, and all water molecules were eliminated for optimization. The docking conformer with the lowest binding energy and the highest stability was selected for further investigation. All of the selected drugs Sorafenib derivatives S1-S6 were optimized using 6-31g basis sets based on DFT, B3LYP theory, Gaussian 09 software, and Avogadro. To prepare the targeted title proteins, The co-factors, heteroatom, and water molecule were removed. The protein targets are changed by adding polar hydrogen and charges to Auto Dock vina. [23]

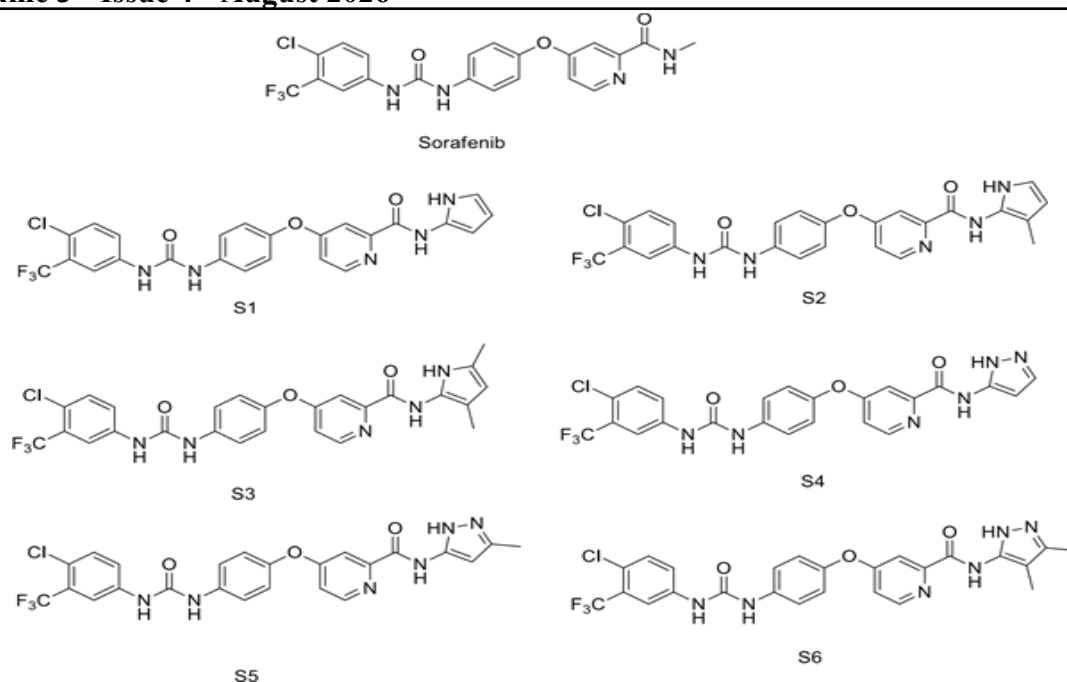


Figure 1. Structural formula of phenyl pyridine derivatives Sorafenib (standard) and its derivatives (S1-S6).

3. Result and Discussion

Molecular docking modelling was utilized in order to examine the binding mechanism of Sorafenib and its modified derivatives with VEGFR-1 and VEGFR-2.

3.1. Interaction of Sorafenib with VEGFR-1 and VEGFR-2: To understand inhibitory mechanism, we docked sorafenib with the VEGFR-1 and VEGFR-2 enzymes. The best result examined with VEGFR-1, **table-1** indicate

strong binding evidence by a docking energy of -13.65 kcal/mol and an inhibition constant of 97.97 pM. The mode confirms that sorafenib fits deeply into the VEGFR-1 binding pocket, where it forms essential bonds with specific amino acids Asp-1040 effectively inhibit its activity forming hydrogen bond ($O \cdots HN$, 2.1Å)[24], as shown in **table-2**. The said compound also forms a weak interaction due to Leu-833, Gly-915, Cys-912) and Vander Waal interactions with Asn-916, Glu-910, Val-909). Given in Figure-2.

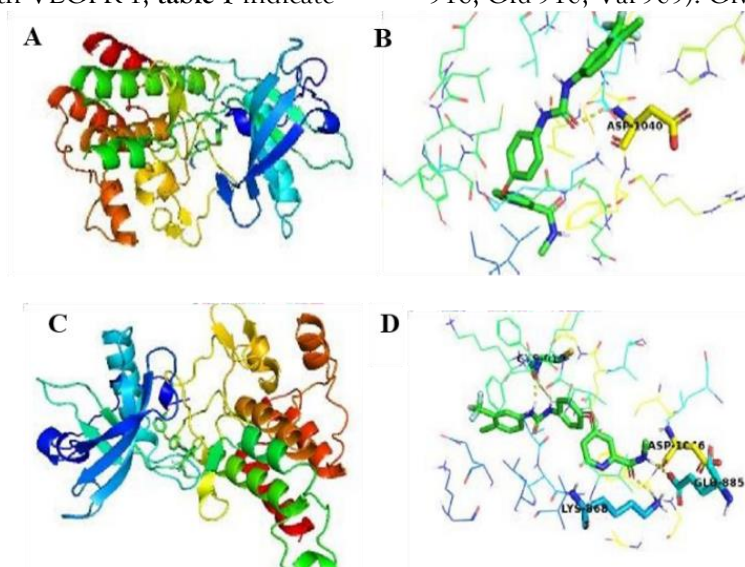


Figure 2. Binding pose of sorafenib with VEGFR-1, (A & B) and VEGFR-2 (C & D)

3.2. Interaction of S1 with VEGFR-1 and VEGFR-2: To explore new ways to inhibit VEGFR-1 and VEGFR-2, we choose to study a compound called S1. The initial results are promising with VEGFR-2, its binding potential is -17.46kcal/mol and it has an exceptionally high potency with an inhibition constant of just 158.06 fM. The mentioned compound S1 forms

a strong and reliable interaction with active site of amino acid through Glu-885 (NH...O, 2.3Å), (NH...S, 1.9Å), Asp-1046 (O...HN, 1.8Å) Glu-917 (N...O, 3.5Å), Cys-919 (HN...O, 2.8Å), (O...HN, 1.7Å), as shown in **table-2**. It also show a weak interaction like pi-anion Cys-1045, Vander Waal interactions with, Val-898, Asn-923, Glu-917, His-1026. Given in Figure-3

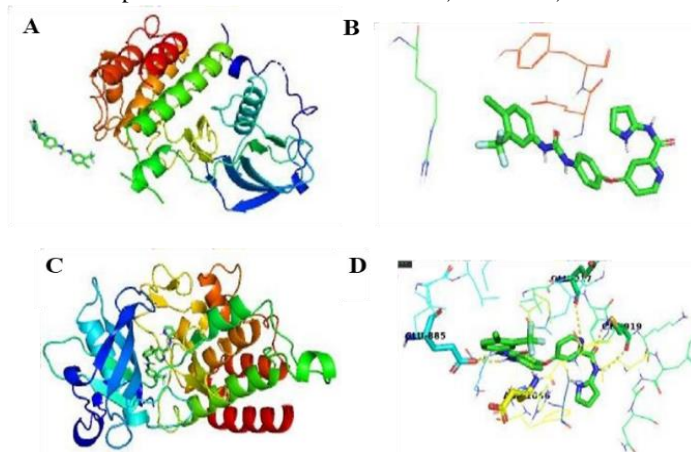


Figure 3. Binding pose of S1 with VEGFR-1, (A &B) and VEGFR-2 (C & D)

3.3. Interaction of S2 with VEGFR-1 and VEGFR-2: S2 inhibition VEGFR-1 and VEGFR-2, it shows great promise with VEGFR-1 a potential of -18.17kcal/mol and a potent inhibition constant of 48.17 fM. It demonstrated important interaction with key amino acid through hydrogen bonds, Glu-878

(NH...O, 1.7Å), (NH...O, 2.2Å) Cys-912, (NH...O, 2.1Å), Asp-1040 (O...HN, 1.9Å), Shown In **Table-2**. It can also contribute a weak interaction like pi-pi (π - π) Ala-859, Val-909, Tyr-911, and Vander Waal interaction with Tyr-914, Gly-915, Lys-913). Given in Figure-4

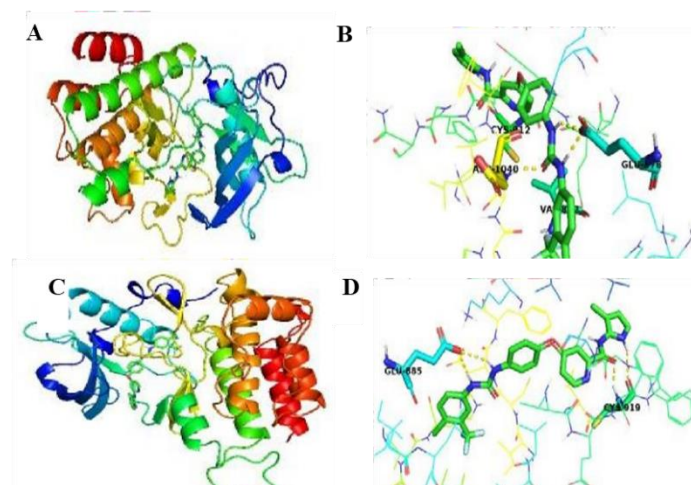


Figure 4. Binding pose of S2 with VEGFR-1, (A &B) and VEGFR-2 (C & D)

3.4. Interaction of S3 with VEGFR-1 and VEGFR-2: Our docking results indicated that compound S3 effectively inhibit the VEGFR-2 enzyme with a binding affinity of -13.14kcal/mol

and an inhibition constant of 233.35 pM. S3 showed promising activity and formed an interaction with critical residues necessary for the enzyme's inhibition, Asp-1056, form one

hydrogen bond (NH...S, 2.1Å), shown in table-2. S3 also form weak interaction π - π (Phe-1047), Vander Waal (Asp-1062, Asn-923) and a

Halogen interaction (Flourine) with (Val-914, Val-867). Given in Figure-5

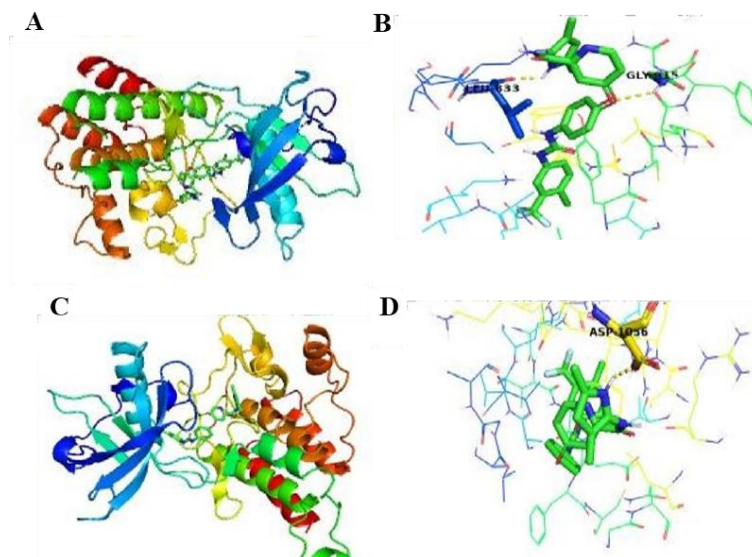


Figure 5. Binding pose of S3 with VEGFR-1, (A &B) and VEGFR-2 (C & D)

3.5. Interaction of S4 with VEGFR-1 and VEGFR-2: We conducted a molecular docking study to visualize how compound S4 interact with and inhibit VEGFR-1 and VEGFR-2 enzyme. The simulation demonstrated that S4 binds tightly to the VEGFR-2 enzymes active region achieving an impressive affinity score of -17.41kcal/mol. For comparison the enzymes natural ligand has an inhibition constant of 173.27 fM. The analysis showed that S4 fits

strongly into the active site effectively burying itself within the groove and physically obstructing the enzymes normal activity through a hydrogen interaction, Cys-919 (O...HN, 1.9Å), Asp-1046 (O...HN, 2.0Å, Glu-885 (NH...S, 2.4Å), (NH...S, 2.0Å), as shown in table-2. S4 form weak interactions are π - π (Phe-1047) halogen interaction (Flourine) (Ile-1044, Cys-1045) and Vander Waal interaction (Val-898, Ile-888). Given in figure-6

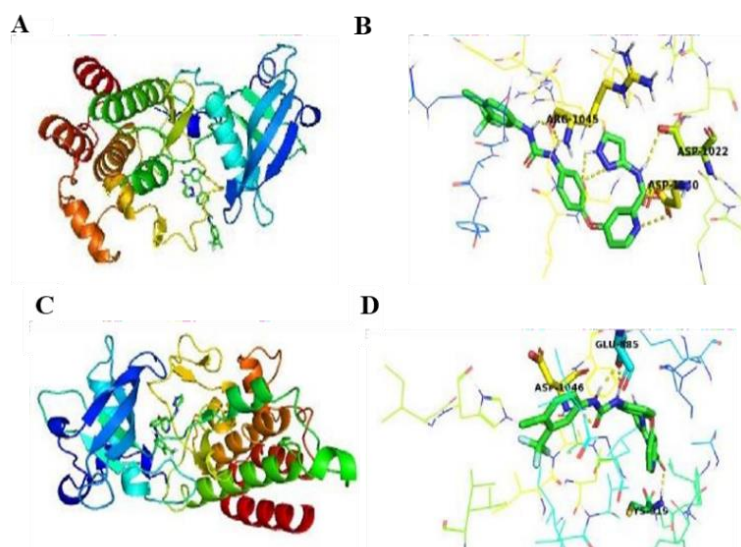


Figure 6. Binding pose of S4 with VEGFR-1, (A &B) and VEGFR-2 (C & D)

3.6. Interaction of S5 with VEGFR-1 and VEGFR-2: Our molecular docking analysis showed that compound **S5** effectively inhibits VEGFR-2. This is supported by its high binding affinity -17.88kcal/mol and remarkable low inhibition constant of 77.79 fM as detailed in the table. The said compound **S5** was docked against the VEGFR-2 and it was effectively by

binding the active sites of enzymes VEGFR-2 through hydrogen bonding of Glu-885 (NH...S, 2.0Å, 2.3Å) and three π - π interactions of Asp-1046 (O...HN, 1.9Å), Glu-917 (N...O, 3.5Å), Cys-919 (O...N, 1.8Å), shown in **table-2**. It can also make a weak interaction such as Vander Waal forces (Ile-888, Val-898), Halogen (Ile-1044, Cys-1045). Given in Figure-7

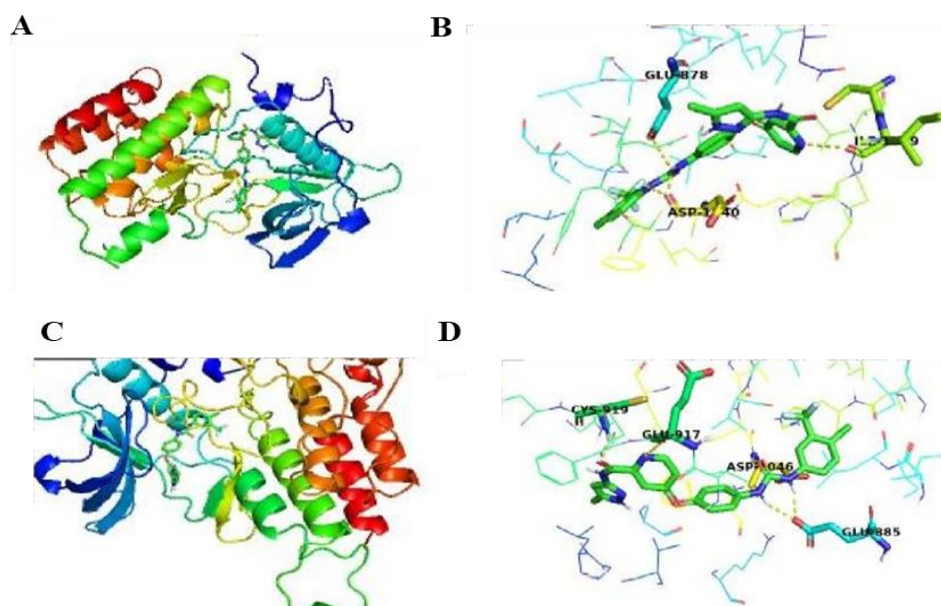


Figure 7. Binding pose of S5 with VEGFR-1, (A &B) and VEGFR-2 (C & D)

3.7. Interaction of S6 with VEGFR-1 and VEGFR-2: The docking results revealed that compound **S6** is a potent inhibitor of VEGFR-1 with a strong binding affinity of -17.47kcal/mol and an inhibition constant of 158.97 fM. The analysis showed that compound **S6** successfully access the enzymes binding pocket and form a critical interaction, through π - π interactions of

Cys-912, (N...O, 3.2Å) and hydrogen bond of Glu-878 (NH...O, 2.1Å), Asp-1040 (NH...O, 2.3Å), (NH...O, 2.5Å), Lue-833 (NH...O, 1.9Å), as shown in **table-2**. **S6** also contributes in weak interactions like π - π (Phe-1041), Vander Waal (Lue-1030, Asn- 916) and π -sulphur (Cys-1039). Given in Figure-7

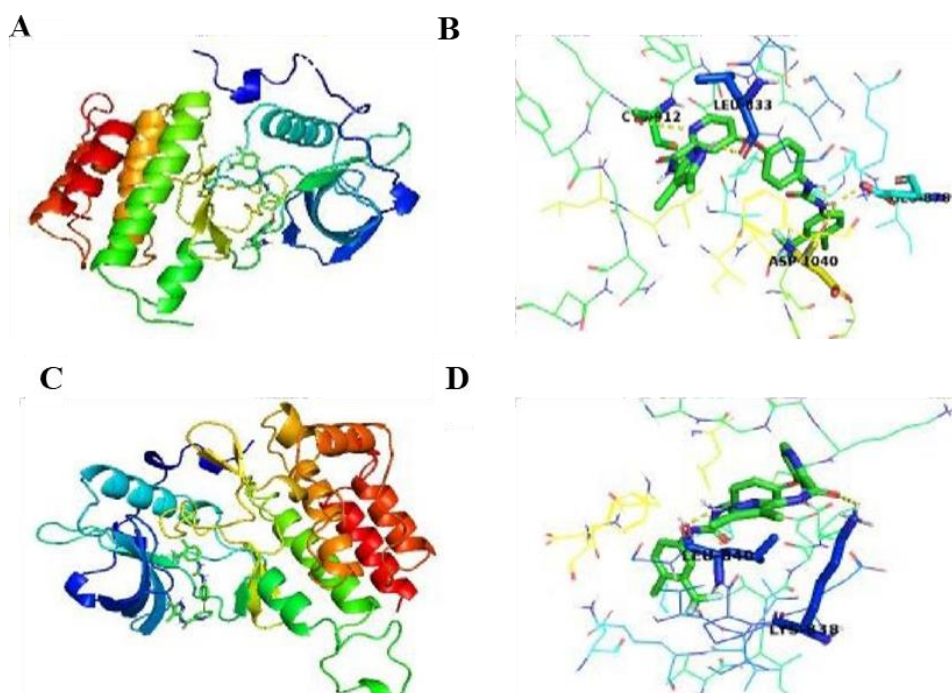


Figure 8. Binding pose of S6 with VEGFR-1, (A & B) and VEGFR-2 (C & D)

Table 1. Binding energies and Inhibition constant of Sorafenib and their derivatives (S1-S6) with VEGFRs

Compounds	Binding Energy (kcal/mol)		Inhibition Constant	
	VEGFR-1	VEGFR-2	VEGFR-1	VEGFR-2
Sorafenib	-13.65	-13.50	97.97pM	126.95pM
S1	-13.59	-17.46	109.30pM	158.06fM
S2	-18.17	-17.64	48.17fM	117.25fM
S3	-12.83	-13.14	395.62pM	233.35pM
S4	-11.48	-17.41	3.83nM	173.27fM
S5	-15.99	-17.88	1.92pM	77.79fM
S6	-17.46	-13.85	158.97fM	70.07pM

Table 2. Residues involved in interactions and their distances of selected compounds with VEGFRs

Compounds	Enzymes	Interacting amino acids	Interactions	Types of interactions	Distances(Å)
Sorafenib	VEGFR-1	Asp-1040	O...HN	H-Bonding,	2.1
	VEGFR-2	Lys-868, Glu-885, Asp-1046, Cys-919	O...HN	H-Bonding	2.1, 2.5, 2.0, 2.3, 2.0
S1	VEGFR-1	~	~	~	~
	VEGFR-2	Glu-885, Asp-1046, Glu-917, Cys-919	NH...S, NH...S, O...HN, N...O, NH...O	π - π interaction, H-Bonding	2.3, 1.9, 1.8, 3.5, 1.7
S2	VEGFR-1	Glu-878, Cys-912, Asp-1040	O...HN	H-Bonding	1.7, 2.2, 2.1, 1.2

	VEGFR-2	Glu-885, Cys-919	NH...S, N...O, O...HN	H-Bonding, π - π interaction	2.6, 2.2, 2.2, 1.9
S3	VEGFR-1	Leu-833, Gly-915	O...HN	H-Bonding	2.1, 2.3
	VEGFR-2	Asp-1056	S...HN	H-Bonding	2.1
S4	VEGFR-1	Asp-1040, Asp-1022, Arg-1045, Gly-1042	N...O, NH...O, NH...O, NH...O, N...O, NH...O	H-Bonding, π - π interaction	2.9, 2.4, 2.3, 2.2, 2.3, 2.2
	VEGFR-2	Cys-919, Asp-1046, Glu-885	O...HN, O...HN, NH...S, NH...S	H-Bonding	1.9, 2.0, 2.4, 2.0
S5	VEGFR-1	Ile-1019, Asp-1040, Glu-878	N...O, O...HN	π - π interaction, H-Bonds	3.1, 2.1, 2.3, 2.7
	VEGFR-2	Glu- 85, Asp-1046, Glu-917, Cys-919	NH...S, NH...S, O...HN, N...O, O...N	H-Bonding, π - π interaction	2.0, 2.3, 1.3, 3.5, 1.8
S6	VEGFR-1	Glu-878, Asp-1040, Cys-912, Leu-833	NH...O, NH...O, NH...O, N...O, NH...O	H-Bonding, π - π interaction,	2.0, 2.1, 2.3, 2.5, 3.2, 1.9
	VEGFR-2	Leu-833, Lys-840	O...HN, O...N	H-Bonding, π - π interaction	2.3, 1.8

4. Conclusion

The inhibitory ability of six modified sorafenib derivatives (S1–S6) against VEGFR-1 and VEGFR-2 was examined in the current investigation using molecular docking. Several of the developed derivatives showed stronger projected binding affinities than the parent sorafenib, according to the computational results, suggesting that structural alteration of the sorafenib scaffold can positively affect ligand–receptor interactions. With a binding energy of -18.17 kcal/mol and an inhibition constant of 48.17 fM, S2 exhibited the strongest predicted binding toward VEGFR-1, while S5 showed the most favourable binding toward VEGFR-2, with a binding energy of -17.88 kcal/mol and an inhibition constant of 77.79 fM. S1 and S4 also showed strong predicted interactions with VEGFR-2, while S6 showed significant affinity for VEGFR-1. The derivatives within the VEGFR binding pockets were stabilized by hydrogen bonding, π - π interactions, halogen interactions, and van der

Waals contacts, according to an analysis of the binding modes. Residues like Asp-1040, Glu-878, Glu-885, Asp-1046, Cys-919, and related active-site residues, in particular, were often implicated in interactions with the proposed compounds, supporting their favorable docking profiles.

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