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In silico investigation of novel sorafenib analogues as potential inhibitors of VEGFR kinase and c-RAF kinase

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ABSTRACT: Cancer is the second most prevalent reason for mortality. Researching new drugs to fight cancer is a priority for many research teams due to the lack of specificity in present therapies. Developing target-specific anti-cancer drugs improves therapeutic potency and safety. Also, Computational chemistry play an important role in the research of new possible medicines. Thus, the goal of present research, was to determine *in silico* studies using the molecular docking and ADME profiling on three newly designed Sorafenib analogues against tyrosine kinase and c-Raf kinase inhibitor enzymes. Molecular docking studies were conducted using PDB ids 2XIR and 3OMV. The Autodock-4 software was utilised for this purpose. Additionally, software tools such as SwissADME and Pro-TOX were employed to perform physiochemical studies and predict toxicity. Molecular docking results showed that compounds (1-3) had strong binding energies of -10.23, -10.24, and -11.39 kcal/mol with VEGFR (PDB Id: 2XIR), while Sorafenib had -11.49; and the energies for c-Raf (PDB Id: 2OMV) were -9.41, -9.48, and -10.89, respectively with reference standard to Sorafenib was -10.39 kcal/mol. It was concluded that compound 3 showed the similar affinity to inhibit VEGFR and c-Raf kinase. It proved by both docking study, molecular dynamic simulation, ADME and tox properties evaluation.

KEYWORDS: Sorafenib; anticancer; c-Raf kinase; *in silico*; ADMET; molecular dynamic simulation

1. INTRODUCTION

Cancer is regarded as the second largest cause of mortality globally, behind cardiovascular disorders. The World Health Organization (WHO) estimates that over 13 million cancer deaths will occur globally by 2030 [1] Sorafenib, an established multiple-targeted drug, inhibits multiple kinases, including, VEGFR, Raf, KIT and PDGFR which are involved in tumor proliferation and angiogenesis, making it useful for advanced primary liver cancer and renal cell carcinoma. In recent years, it has been considered a lead chemical for optimization [2]. Sorafenib interferes with cancer cell proliferation in three ways: phosphorylating B-Raf and Raf 1/c-Raf kinase, blocking VEGFR, PDGFR-β, and c-kit, and inducing tumor cell apoptosis by reducing elF4E phosphorylation and Mcl-1, respectively [3]. Sorafenib is a member of the VEGFR-2 super family of protein tyrosine kinase receptors, controls angiogenesis, and cancer metastasis and is connected to solid tumor formation. Signaling pathways are complicated circuit networks, not linear procedures. When a pathway is handled alone, adjacent pathways compensate because of redundancy and interaction. Thus, multi kinase inhibition of B-Raf, B-RafV600E, and VEGFR-2 may be a synergistic cancer treatment [4].

Many years have been spent on sorafenib modifications to enhance the drug's kinase and cell growth inhibitory properties [5]. Organic and medicinal chemists are actively seeking derivatives similar to Sorafenib to potentially decrease cancer progression. Sorafenib structural modification can be categorized into three classes (Figure 1) first by adding halogen atoms like fluorine chlorine and bromine to the benzene ring such analogs were effective against c-MET, VEGFR1, VEGFR2, VEGFR3, and PDGFRβ pathways. Second was Picolinamide replaced with trifluoromethyl (CF_3) imidazole, indazole ring, thieno [3, 2-d] pyrimidinine, and 1, 2, 4-triazole [6-11] compared to Sorafenib, they reduced MDA-MB-231, HT-29, H460, and SMMC-7721. Third class was by replacing aryl urido or thiourido with pyrazole [12], 4, 5-dihydro-1H-pyrazole [13] and chalcone [14]. After thorough review of the literature and using molecular designing strategy (Drug mapping), design three novel compounds of sorafenib analogues bearing benzimidazole unit

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and naphthalene. For this Optimization, the activity of sorafenib by structural alteration has recently been our emphasis. As an important pharmacophore, the aryl urea group was preserved. The primary components of sorafenib that were changed to the left-most pyridyl group and the intermediate linker. The target molecules were modified to improve interaction with receptors by adding a 4-benzimidazole and naphthalene group. The phenoxyl group's linker moiety remained unchanged, but a 3-aminobenzyl group was substituted for it in the second molecule, while a benzimidazole or naphthalene group replaced the pyridyl moiety of sorafenib. Organic assembly of the benzimidazole and urea groups, which are important pharmacophores, was achieved via the middle linker, which is 3-aminobenzyl or the same as the phenoxyl group referring to Figure 1. The structures of designed compounds and Sorafenib are depicted in (Figure 2A, 2B, 2C and 2D).

The designed compounds will undergo molecular docking to elucidate their binding affinity and interaction with the VGFR and c-Raf kinase inhibitors enzyme. The effect of specific groups present in compounds on their binding affinity with proteins will also be examined. In addition, an assessment of the drug-likeness of the chosen compounds will be conducted to make predictions about their absorption, distribution, metabolism, and excretion (ADME) features. Particularly in view of the development of sorafenib analogues, this study may contribute to the advancement of anticancer drug development.

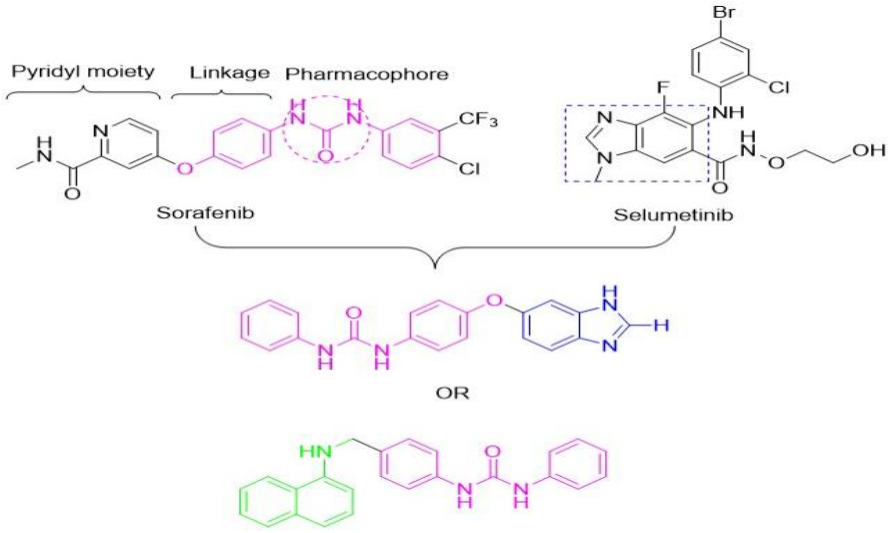

Figure 1. Designing of Compounds

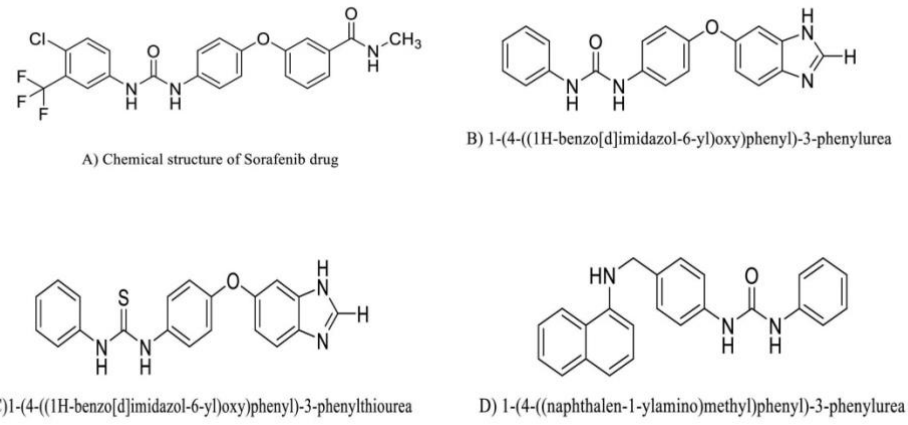

Figure 2. A) Chemical structure of Sorafenib B) Structure of compound 1 C) Structure of compound 2 D) Structure of compound 3

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2. RESULT AND DISCUSSION

2.1 Molecular docking analysis of designed compounds

Molecular docking studies was performed on the active site of proteins (PDB Id: 2XIR, 3OMV) with the designed ligands (compounds 1-3) in order to determine the possible binding interactions of highly potent molecules

The molecular docking analysis demonstrated that compound 1,2 and 3 had strong binding energies -10.23kcal/mol, -10.24 and -11.39 respectively with tyrosine kinase receptor VEGFR (PDB Id: 2XIR) where the reference standard Sorafenib showed the binding energy of -11.49 kcal/mol(table 1). Moreover, compound 1 arbitrated one hydrogen bonds interaction with the residues of Ile1044 (2.3 Å) as well as one pi-cation with Lys868, one pi-sigma with Leu889, one pi-sulfur with Cys1044, one pi-pi Phe918 and six pi- alkyl interactions with Leu840, Val916, Val899, Cys919, Leu1035, Ala866 residues (Figure 3A). Compound 2 mediated three hydrogen bonds interaction with the residues of Cys919 (2.2 Å) and Asp1046(2.4 Å) also one pi-cation with Glu885, one pi-sulfur with Lys860, one pi-pi stacked Phe918 and six pi- alkyl interactions with Leu889, Cys1045, Val848, Leu1035, Leu840, Ala866 residues (Figure 3B). Compound 3 mediated one hydrogen bonds interaction with the residues of Cys919 (2.9 Å), and also two pi-cation with Phe918, Lys868, one pi-pi T shaped Phe1047 and five pi- alkyl interactions with Leu1035, Cys1045, Val848, Ala866, Val916 residues (Figure 3C). Where the reference compound Sorafenib showed three hydrogen bonds with the residues of Cys919, Glu885, Asp946 as well as two carbon-H bonds with Cys1045, His1026, one halogen(fluorine) bond with Ile1044, one unfavourable donor-donor bond with Lys868 and one pi- sulphur interactions with Cys919 residues (Figure 3D). Docking scores of compounds 1 and 2 were found to be lower than that of the reference standard. However, the docking score of compounds 3 exhibited some similarity and demonstrated a same potency comparable to the reference standard.

Compounds 2, 3, and Sorafenib were docked in association with VEGFR kinase in the same docking manner and showed similar hydrogen bond interactions with amino acid residues Cys919 and Asp1046, which are the same interactions seen in Sorafenib. The addition of the naphthalene moiety may improve the binding force of the previously mentioned target compounds with VEGFR.

Table 1. Docking results of the selected ligands and the reference ligand (CID: 216239) with tyrosine kinase (PDB Id: 2XIR)

Compound	PDB ID	Docking Score (kcal/mol)	H bond interaction	Other interactions
1.	2XIR	-10.23	Ile1044	Lys868(pi-cation), Leu889(pi-sigma), Cys1044(pi-sulfur), Phe918(pi-pi), Leu840, Val916, Val899, Cys919, Leu1035, Ala866(pi-alkyl)
2.	2XIR	-10.24	Cys919, Asp1046,	Lys860 (pi-sulfur), Phe1047, Phe918(pi-pi stacked), Leu889, Cys1045, Val848, Leu1035, Leu840, Ala866 (pi-alkyl)
3.	2XIR	-11.39	Cys919	Phe918, Lys868(pi-cation), Phe1047(pi-pi T-shaped), Leu1035, Cys1045, Val848, Ala866, Val916 (pi-alkyl)
Sorafenib	2XIR	-11.49	Cys919, Glu885, Asp1046	Cys1045, His1026(carbon-H bond), Ile1044 (HalogenFluorine), Lys868 (unfavourable donor-donor), Cys919(pi-sulfur), Leu1035, Ala866, Val848, Val916, Leu1019, Leu889, Ile892 (pi-alkyl), Asn923, Phe918, Gly922, Phe921, Lys920, Leu840, Glu917, Phe1047, Ile888, Val898 (vander waals)

The docking analysis of c-Raf kinase receptor (PDB Id: 3OMV) with compound 1,2 and 3 had strong binding energies -9.41kcal/mol, -9.48 and -10.89 respectively where the reference Sorafenib binding energy of -10.39 kcal/mol (Table 2). Moreover, compound 1 arbitrated three hydrogen bonds interaction with the residues of Gly87, Cys85, Ile80 as well as two pi-pi stacked with Phe136, Trp84 and three pi- alkyl interactions with Val24, Ala34, Lys36 residues (Figure 4A). Compound 2 mediated three hydrogen bonds interaction with the residues of Cys85, Gly87, Leu137and also three pi-cation with Trp84, Phe136, Lys36 and four pi- alkyl interactions with Ile16, Ile80, Ala34, Val24 residues (Figure 4B). Compound 3 mediated one hydrogen bonds interaction with the residues of Asp147 and also one pi-sigma with Val24, one pi-sulfur with Cys85, two pi-

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pi stacked with Phe136, Trp84, two pi-alkyl with Ala34, Ile80 residues (Figure 4C). Where the reference compound Sorafenib showed two hydrogen bonds with the residues of Lys92, Cys85 as well as one carbon-H bonds with Glu54, two pi-pi stacked with Phe136, Trp84, three pi-alkyl interaction with Lys36, Val24, Ala34 residues (Figure 4D). Compounds 1 and 2 show lower docking scores than the reference standard where Compound 3 docking score was slightly similar and showed same potency comparable to the reference standard.

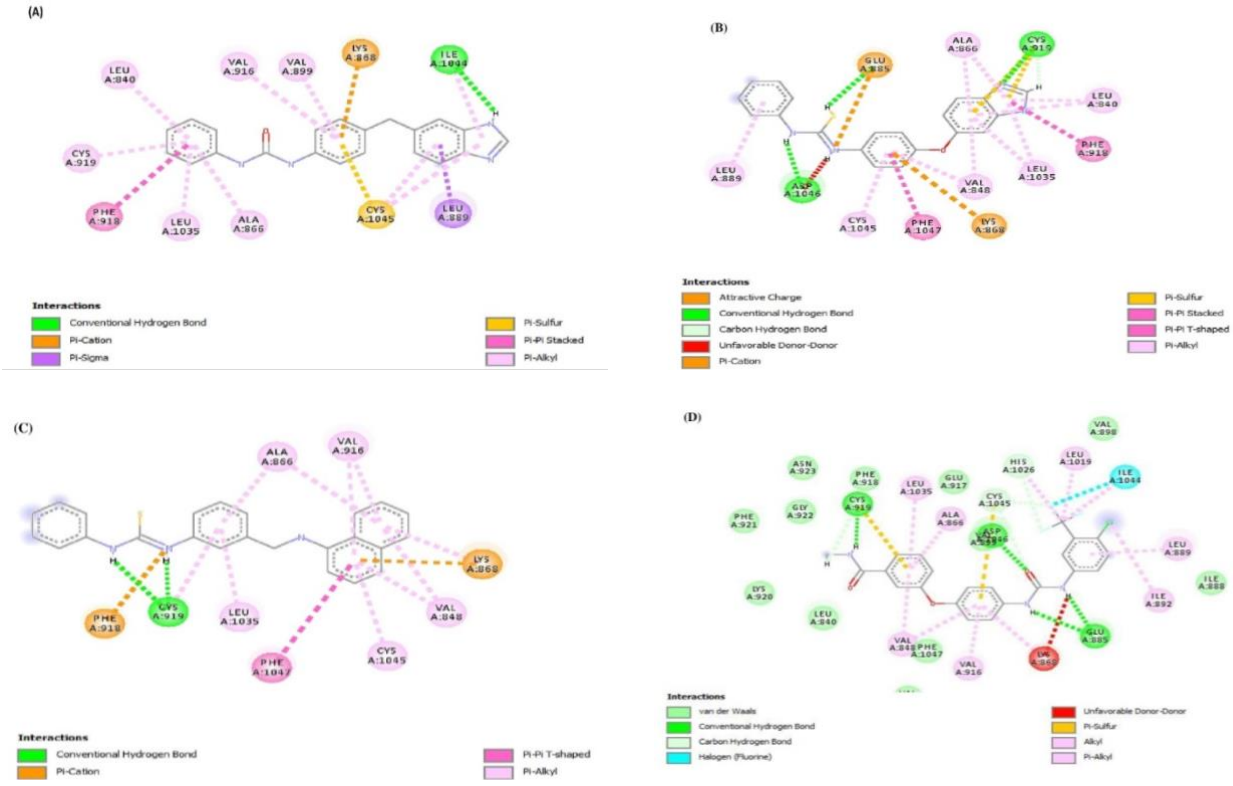

Figure 3. 2D interaction of compounds with PDB ID- 2XIR; A) Compound 1 - 2XIR B) Compound 2 - 2XIR, C) Compound 3 - 2XIR, D) Sorafenib - 2XIR

Compounds 1, 2, and Sorafenib were docked in combination with c-raf kinase using the same docking technique. Both compounds have a hydrogen bond interaction with the amino acid residue cys85 that is comparable to the interactions that are seen in Sorafenib. The framework of designed compounds 1 and 2 is similar, but the linkage was differed urido and thiourido, respectively. In Compound 3 benzimidazole ring was replaced by naphthalene ring with methylene amine linkage

Table 2. Docking results of the selected ligands and the reference ligand (CID: 216239) with c-Raf kinase inhibitors (PDB Id: 3OMV)

Compound	PDB ID	Docking Score (kcal/mol)	H bond interaction	Other interactions
1	3OMV	-9.41	Gly87, Cys85, Ile80	Phe136, Trp84(pi-pi stacked), Val24, Ala34, Lys36 (pi-alkyl)
2	3OMV	-9.82	Cys85, Gly87, Leu137	Trp84, Phe136, Lys36(pi-cation), Ile16, Ile80, Ala34, Val24 (pi-alkyl)
3	3OMV	-10.89	Asp147	Val24(pi-sigma),Cys85(pi-sulfur), Phe136, Trp84(pi-pi stacked), Ala34, Ile80 (pi-alkyl)
Sorafenib	3OMV	-10.39	Lys92, Cys85	Glu54(carbon-H bond) Phe136, Trp84(pi-pi stacked), Lys36, Val24, Ala34(pi- alkyl)

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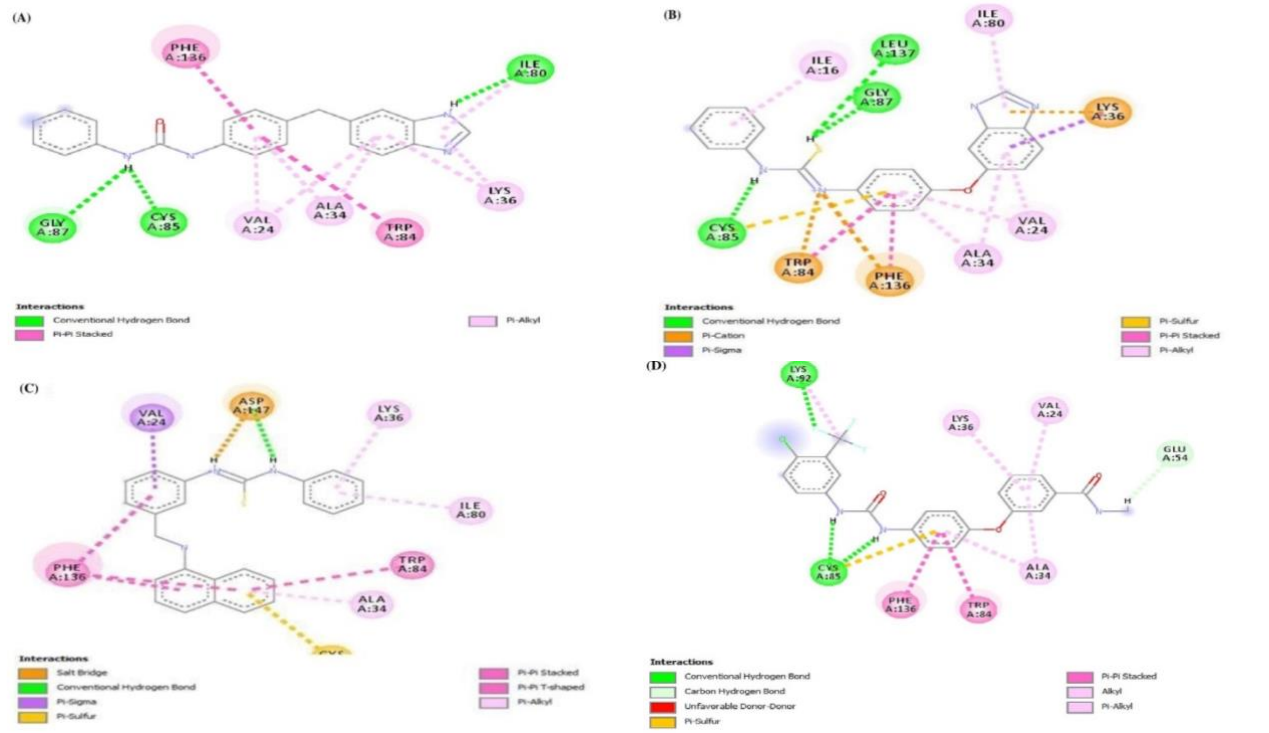

Figure 4. 2D interaction of compounds with PDB ID - 3OMV; A) Compound 1 - 3OMV B) Compound 2 - 3OMV, C) Compound 3 - 3OMV, D) Sorafenib - 3OMV

2.2 Molecular Dynamics Simulation

MD modelling helps to examine structural stability and molecular interactions. MD analyses were used to study target protein-ligand complex binding and stability over time. The dynamic behaviour of the simulated system was studied using quantitative measures such RMSD, RMSF and protein-ligand H bond interactions (Table 3) [15].

Table 3. The studied complexes' minimum, maximum, and average characteristics, including RMSD, RMSF, RGyr, and hydrogen bonding.

Name	Root-mean-square deviation (RMSD) A°		
	Min	Max	Avg
2XIR	1.1	2.8	1.95
Compound- 3	0.6	2.2	1.4

Min- Minimum, Max- Maximum, Avg- Average

Root-mean-square deviation (RMSD) analysis of protein alpha carbon atoms across simulation time revealed structural changes and conformational stability of each molecule. The MD simulation modified the protein's atom structure, as shown by the RMSD. Simulation results show that low RMSD indicates system stability. The RMSD values of the ligand 3 complexes were stable and the tyrosine kinase protein showed minimal fluctuations with an RMSD deviation of 2.8 Å. This shows minimal structural changes and variations in the protein during simulations without compound 3 shown in Figure 5A.

The RMSF value of protein 0.97 A° a rigid behavior with minimal variations (RMSF < 1.5 Å) was observed in MD simulation experiments. These residues low flexibility supports stable interactions with prospective compounds 3, compared to other residues in the tyrosine kinase protein binding site (Figure 5B).

Figure 5C shows an extensive MD analysis that found the interactions between simulated ligands and amino acid residues and Figure 5D shows stacked bar histograms of protein residues interactions with ligands, including hydrogen bonds, hydrophobic interactions, and water-bridged hydrogen bonds. In compound 3, a hydrogen bond formed and the simulation time with particular contact was maintained with GLN-885 (96% and 86%) and ASP-10

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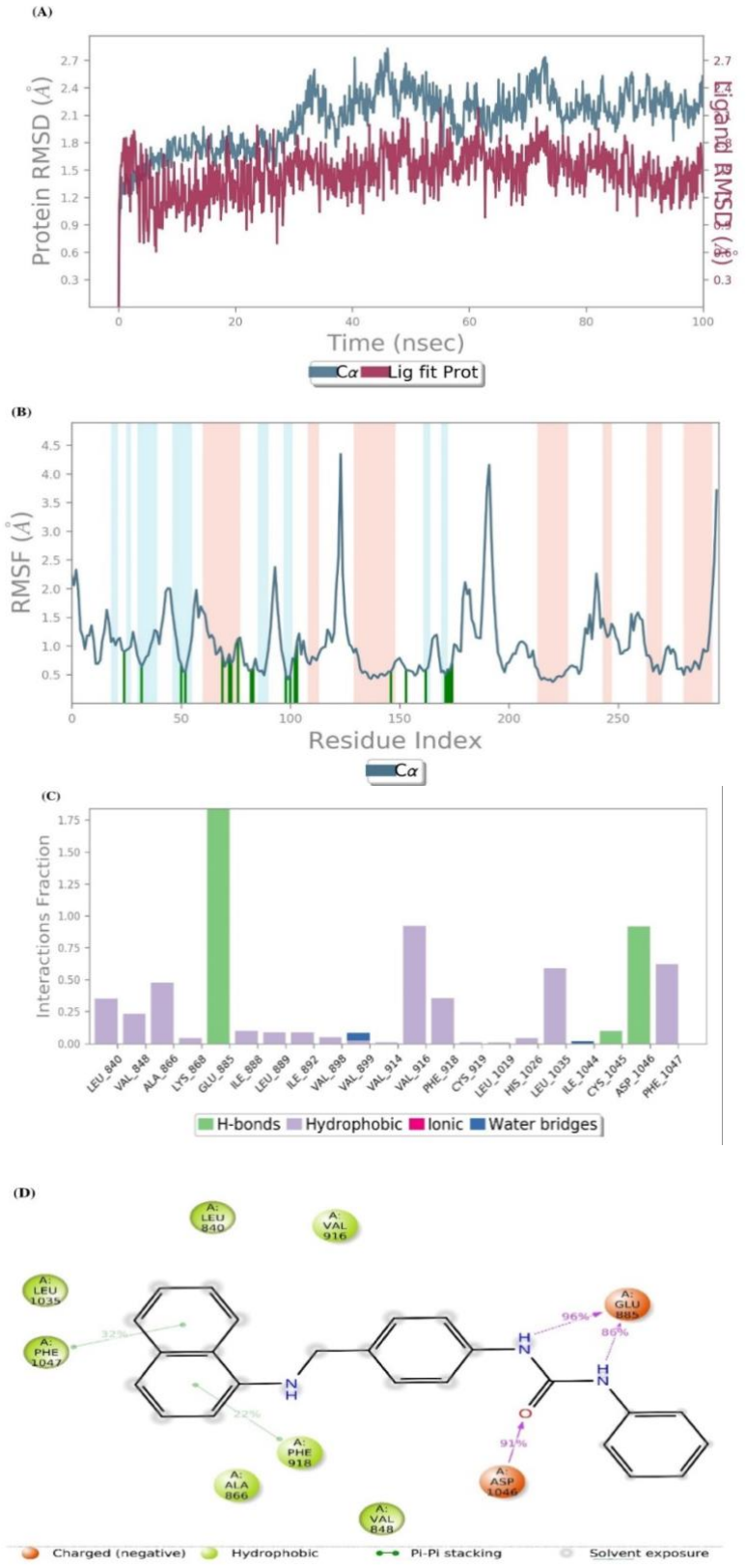

Figure 5. A) Protein and ligand RMSD values generated by a 100ns MD simulation B) Protein RMSF values generated by a 100ns MD simulation C) The protein–ligand interactions of the ligands with 2XIR during 100 ns MD. D) A 2D diagram to demonstrate protein residue-ligand atom interactions.

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2.3 *In silico* ADME-tox Predications

In the initial screening phase of designed compounds, *in-silico* ADME assessment is used to predict pharmacological properties before more arduous and expensive *in vitro* and *in vivo* studies. The anticipated physicochemical parameters of compounds 1 to 3 were calculated using Swiss ADME (http://www.swissadme.ch/).
The Lipinski Rule of 5 (Ro5) is a commonly recognized approach to evaluating ADME properties. Originally, the Lipinski rule of five contributed to the development of orally bioavailable medicines. [16]. The features of absorption were associated with drugs taken orally. These properties can be influenced by a number of factors, including the coefficient partition (ClogP) and polar surface area (PSA). The ClogP is crucial for assessing drug candidate absorption and permeability. The acceptable log p range was -2 to 5. Log P increases absorption % within the permitted range. Drug with ClogP having moderate bioavailability and it ranges with 0-3 . The ClogP shows molecular lipophilicity. High log P reduces drug water solubility, while low log P prevents lipid bilayer passage. [17].

The LogP values of every selected compound were less than 5. Furthermore, it was noted that for these compounds, MW< 500g/mol, the number of hydrogen donors≤3 and acceptors≤3 was both present. This led to the conclusion that compounds 1-3 do not break any of the laws established by Lipinski and Veber [18]. Besides pharmacokinetic characteristics, toxicity profiling is important in drug development because toxicology and lipophilicity are related each other. Toxicity affects drug attrition during discovery and development; thus, it must be assessed. The lethal dose was calculated using the Pro-Tox II web tool to evaluate acute toxicity in rats (Table 4) According to that, the designed ligand showed fairly low acute toxicity, as indicated by a high value for the lethal dose. Levels 4 and 5 represent the unconcerned acute toxicity classification for the majority of ligands.

All the developed ligands conform to the Lipinski and Veber rule, in comparison with the standard drug Sorafenib. In the case of toxicity resulting from designed ligands, two compounds exhibit a toxicity level of 4, comparable to that of the standard drug Sorafenib.

Table 4. Predicted ADME properties, bioavailability and toxicity of designed compounds

Ligand	ADME properties					Lipinski Rule Nviol*	Veber's Rule Nviol*	Bio-availability	LD (mg/kg) **
	H don[a]	H Acc [b]	clogP	MW (g/mol)	TPSA				
1	3	3	3.36	344.37	79.04	0	0	0.55	1000[d]
2	3	2	3.87	360.43	94.06	0	0	0.55	2400[e]
3	3	1	3.98	367.44	53.16	0	0	0.55	1500[d]
Sorafenib	3	4	5.54	464.83	92.35	0	0	0.60	800[d]

a- Hydrogen bond donor,
b- Hydrogen bond acceptor
* Lipinski rule of five H donor<5, H acceptor<10, MW<500mg/ml, ClogP 2<5, TPSA<140 A°
** Lethal dose (LD) represent the acute toxicity (d) toxicity level 4, (e) toxicity level 5

3. CONCLUSION

This study shows safer and selective VEGFR and c-Raf kinase inhibitors and evaluates there *in silico* enzyme inhibition potentials and ADMET profiles. Autodock-4 was used to examine the affinities of 3 new drugs against VEGFR and c-Raf kinases. Finally, an assessment was conducted to determine the drug-like characteristics of the selected compounds 1 to 3, revealing their adherence to the Lipinski and Veber guidelines. Future studies may focus on the production of substances as identified through *in silico* investigations, as well as the investigation of their in vitro effects.

4. MATERIALS AND METHODS

4.1 Molecular docking studies

Autodock-4 software [19] developed by Scripps Research Institute's was used to carried out molecular docking studies for designed compounds with tyrosine kinase receptor VEGFR (PDB Id-2XIR) [20] and c-Raf kinase receptor (PDB Id- 3OMV) [21].

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4.2 Preparation of ligands 3D structures of compounds 1-3 and Sorafenib

Building the ligands, was accomplished through the use of the software Chembiodraw Ultra 14.0. Conformation was chosen, and the structures of those compounds were saved in PDB format after being transformed to 3D structure. The compounds that were used for docking given in a 3D representation. Compounds 1 through 3 were subsequently converted to pdbqt file format using the Autodock tools application. The Sorafenib was chosen from the PubChem database, specifically identified by its PubChem ID (CID: 216239). The reference standard was chosen on the basis of its broad anticancer efficacy against tyrosine and c-Raf kinase inhibitors [22-24].

4.3 Preparation of Protein 3D structure of the c-Raf kinase enzyme and VEGFR kinase enzyme

The protein structure c-Raf kinase (PDB Id- 3OMV, resolution: 4.0 Å) and VEGFR kinase structure (PDB Id- 2XIR, resolution: 1.50 Å) were obtained from the Protein Data Bank (https://www.rcsb.org/pdb/home/home.do). C-Raf kinase PDB consist of the original ligand was SM5 (CA name: (1E)-5-(1-piperidin-4-yl-3-pyridin-4- yl-H-pyrazol-4-yl)-2, 3-dihydro-1H- inden-1-one oxime) and missing residues of 3OMV (from 493 to 504) was modelled using Modeller [25]. The VEGFR kinase consist of co-crystallized inhibitors PF-00337210. Both these co-crystals and water molecules were removed from native protein by using the Discovery Studio Visualizer 2021 software.

Following this, polar hydrogens were optimized, hydrogen atoms were added, and Kollman charges were assigned utilizing the MGL Autodock Tools 1.5.6 software. To mark the active site of kinase inhibitors, grid boxes measuring 50×50×50 were employed. Subsequently, the protein structure that went processing was archived in PDBQT format in consideration of the docking program.

4.4 Molecular docking studies and analysis of results

In this study, used local docking approach similar to previous study [26]. A grid box of 50 x 50 x 50 grid points was constructed around the active location of VEGFR and c-Raf, with a grid spacing of 0.375. During docking, we kept the receptor rigid and the ligand flexible. The Lamarckian Genetic Algorithm was used to create the ligand output conformations. The docked conformations were then grouped further using an all-atom RMSD cut-off of 4. The clusters were further examined in terms of binding energy, ligand efficiency, inhibitor constant, intermolecular energy, van der Waals, electrostatic energies, and so on. The interaction study was performed using PyMol [27] and Discovery Studio Visualize [28] using the lowest binding energy conformation of the ligand.

4.5 Molecular dynamic simulation studies

MD simulations were performed on the complexes generated between the compound having more docking score and the VEGFR2 kinase receptor using the Desmond Schrodinger program [29]. The systems were solvated utilizing a simple point charge (SPC) water model, and a neutral environment was established by employing an appropriate pairing of ions such as sodium and chloride. The Desmond System Builder panel was utilized to assign a 0.15 M NaCl salt concentration that corresponded to the physiological system. To eliminate steric conflicts, this solvated and neutral system underwent unconstrained energy minimization using the steepest descent criterion and a fixed parameter of the OPLS3e force field. A brief 100 ns isothermal-isobaric or NPT ensemble equilibrium condition was present in the resultant system at constant temperature and pressure. NPT equilibration was conducted with the temperature maintained at 300 K for 100 ns via a "Nose-Hoover chain thermostat." The Martyna-Tobias-Klein barostat was employed to regulate the pressure throughout the NPT equilibration process at 1.0315 bar. At intervals of 100 ns, trajectory samples were captured during the 100 ns that the simulation ran. Desmond's Simulation Interaction Diagram (SID) was employed to ascertain the stability and binding orientation of the ligand by analysing 1000 MD trajectories. Desmond was executed on a Linux platform: NVIDIA RTX A4000, Ubuntu 22.04.2 LTS 64-bit, Intel Xeon W-2245 3.90 GHz, 8-Core, CUDA 12.

4.6 Drug likeness study of designed ligands

The Swiss ADME web-based tool [30] was employed to assess the solubility characteristics and structural descriptors of the selected ligands. In order to determine the compliance of the target compounds to the Lipinski rule, their Log P values, molecular weights, and the count of hydrogen bond acceptors/donors. Additionally, their compliance with Veber's rule by calculating the topological polar

surface areas of compounds 1-3. Using the open-source web tool ProTox (http://tox.charite.de/protox_II) the toxicity profiles of designed compounds were computed by calculating their fatal dose (LD50).

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Conflict of interest statement: The authors declared no conflict of interest.

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