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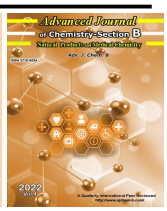

Original Research Article

In-Silico Design of Phthalazine Derivatives as VEGFR-2 Inhibitors: Molecular Docking and Pharmacological Profile Studies

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ABSTRACT

According to the world health organization (WHO) reports, cancer is thought to be the condition that causes the most fatalities after coronary disease, and by 2030, thirteen million deaths are anticipated to be recorded. In this research, molecular docking approach was utilized in designing more potent phthalazine derivatives as VEGFR-2 inhibitors. The pharmacological properties of the designed compounds were predicted to avoid drug failure after production. Before the start of the process, the docking protocol of the algorithm utilized in this work was validated by redocking the co-crystallized ligand (Sorafenib) with the initial VEGFR-2 binding site. The root mean square deviation (RMSD) score computed between the superimposed complexes of initial and redocked poses of Sorafenib was found to be 1.03Å. Moreover, the binding affinities of Sorafenib (MolDock score = -144.289 Kcal/mol, Re-rank score = -113.368 Kcal/mol) were utilized as a yardstick for the adoption of lead molecules among which compounds 21 and 22 with binding affinities of -146.77, and -151.651 Kcal/mol MolDock scores and -115.096, and -115.757 Kcal/mol Re-rank scores exceeding that of Sorafenib were explored. Compound 22 was utilized as a design template from which five hypothetical compounds with binding affinities ranging from -159.014 to -169.245 Kcal/mol MolDock scores and -121.591 to -134.697 Kcal/mol Re-rank scores were designed via the introduction of electron releasing groups to the ortho- and meta-positions of the p-chlorophenyl group. Pharmacological profiling leads to the affirmation of the designed inhibitors as potential drug candidates with welcoming ADMET properties with no serious toxicity challenges.

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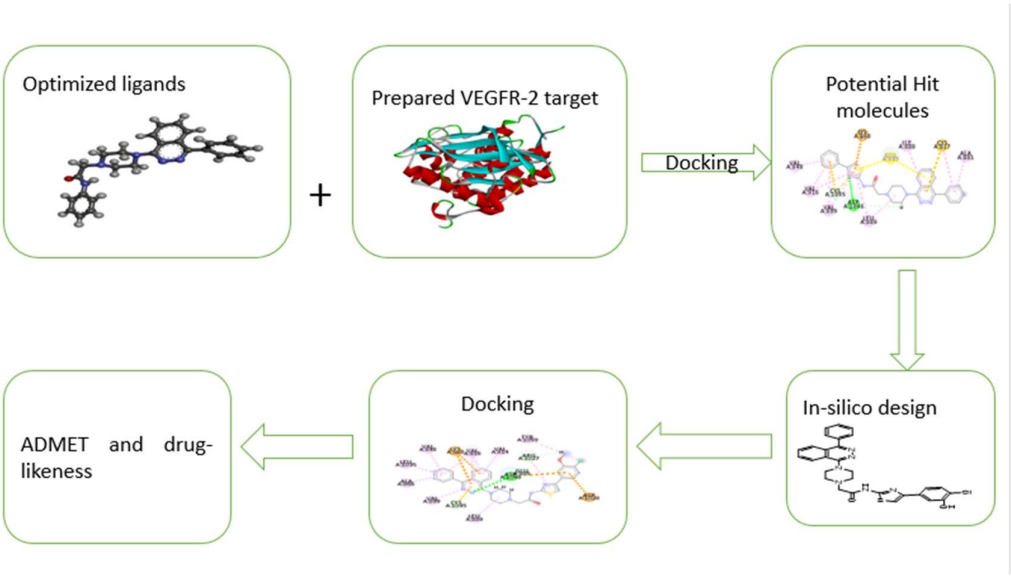
GRAPHICAL ABSTRACT



Introduction

According to reports from the World Health Organization (WHO), cancer is thought to be the condition that causes the most fatalities after coronary disease [1]. By 2030, thirteen million people are expected to have lost their lives to cancer [2]. The rate of survival is still unwelcoming despite all the recent advancements in the diagnosis and treatment of this disorder because of the predominantly antagonistic properties of the medications. Therefore, it is necessary to develop anticancer drugs that are safer and more effective [3]. Vascular endothelial growth factors (VEGFs) interacts with three different but structurally similar VEGF receptors (VEGFRs), which are transmembrane proteins with tyrosine kinase domains, in an overlapped manner (TK). There are three subtypes of VEGFRs: VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR-1 regulates the embryonic veins' progression, while lymphangiogenesis is controlled by VEGFR-3, embryonic vasculogenesis and tumor angiogenesis are both regulated by VEGFR-2 [4]. As a result, VEGFR-2 is the primary target for antiangiogenic therapy, and blocking it is an appropriate methodology for the development of new angiogenesis-reliant tumor drugs.

Among the different nitrogen containing heterocycles, phthalazines play an essential part in pharmaceutical chemistry and consequently have emerged as a pharmacophores. The phthalazine structural motifs have attracted huge attention as a result of their easy accessibility, diversified chemical reactivity, and extensive range of medicinal applications such as antibacterial, antifungal, antitumor, anti-inflammatory, and anticonvulsant activities [25]. Traditional drug design methods were too expensive, cumbersome, and slow because they had to go through every step of drug discovery process, from target exploration to registration. Between 2004 and 2008, there was a 50% fall in the likelihood of a drug candidate making it past the primary clinical trial stage and onto the market. Thus, in an attempt to improve the efficacy of the drug design approach, researchers are frequently utilizing the modern approaches [5]. Structure-based approaches of drug design and discovery have become simpler, faster, and

more effective as a result of advancements in bio-informatics and the availability of various computational chemistry softwares [6, 7].

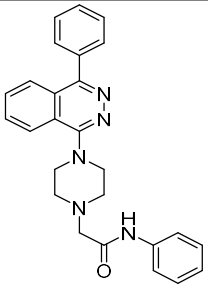
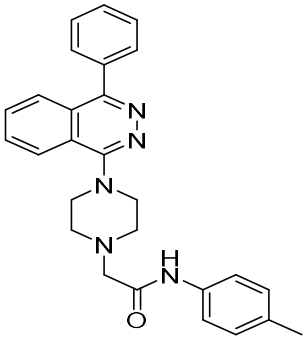
Molecular docking is one of the more dependable structure-based methods since it can be employed to screen vast molecular databases for hypothetically dynamic molecules as well as to isolate the most important molecular entities [8]. In the docking technique, ligand conformation (poses) predictions are made, and the binding energies of the poses are calculated using a scoring function obtained from a knowledge-based potential [9]. In our recent work, molecular docking approach was utilized for the virtual screening of diaryl-pyridinamine derivatives as estrogen receptor inhibitors targeting breast cancer [15]. However, structure based drug design using molecular docking approach and *in silico* study of pharmacokinetic features of the designed molecules have not been fully established. Hence, in this research, molecular docking approach was utilized in designing more potent Phthalazine derivatives as VEGFR-2 inhibitors. The pharmacological properties of the designed compounds were predicted to avoid drug failure after production.

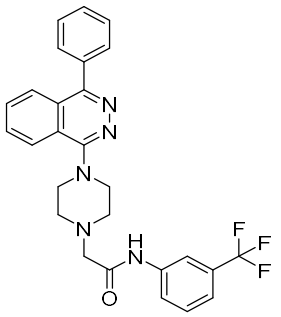
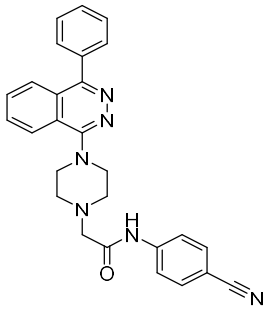
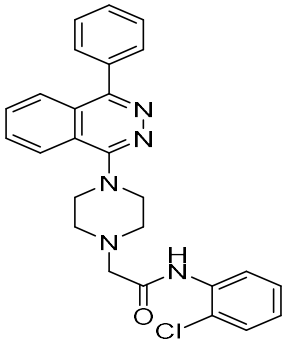
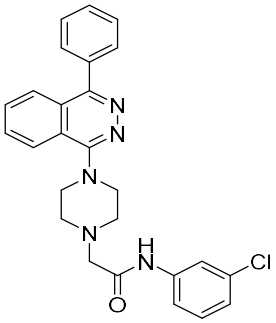
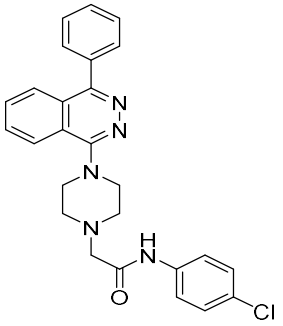
Methods

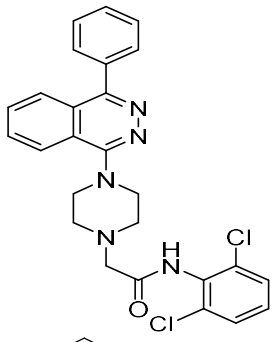
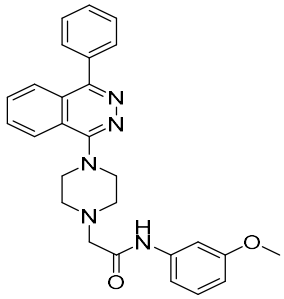
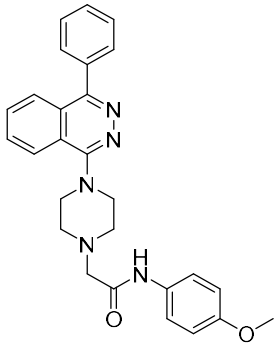
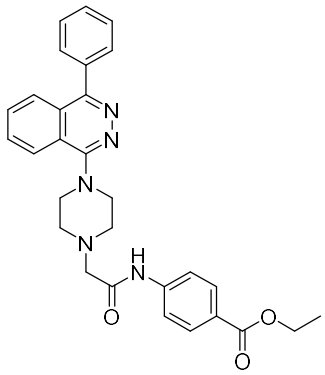
Data set collection and 2D structural drawings

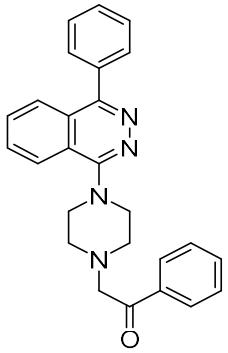
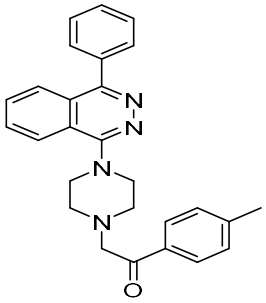
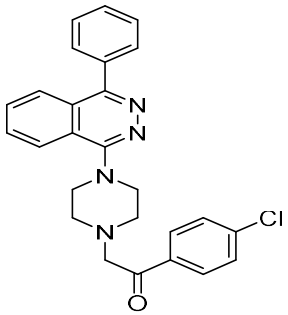
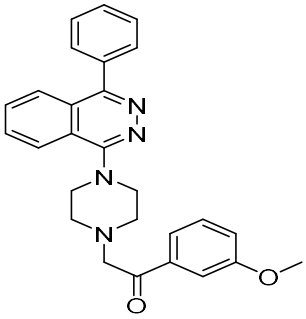
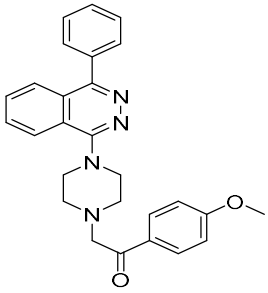
A series of 1-Piperazinylphthalazines derivatives as potential VEGFR-2 inhibitors were obtained from the work of Abouseri *et al.* [10]. Two dimensional structural drawing was carefully executed with the aid of the Perkin-Elmer ChemDraw software using ACS-1996 format, as presented in Table 1.

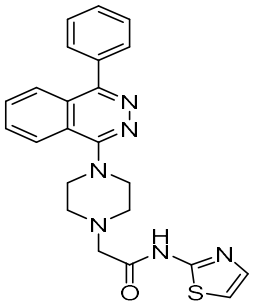
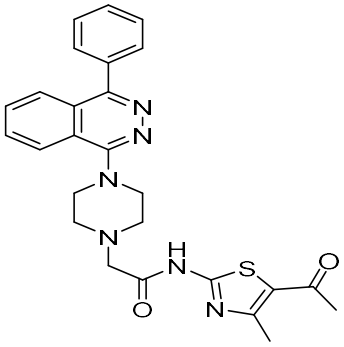
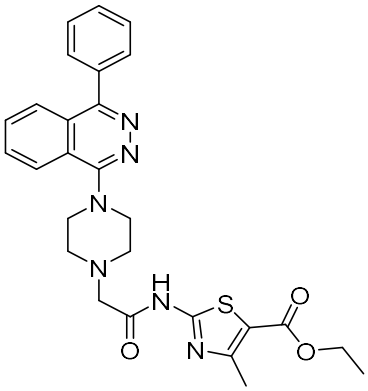
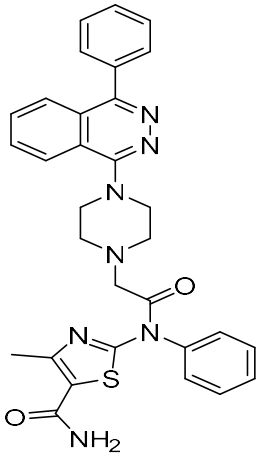
Table 1. 2D Structures of the 1-Piperazinylphthalazine analogs and their docking scores with the VEGFR-2 active site

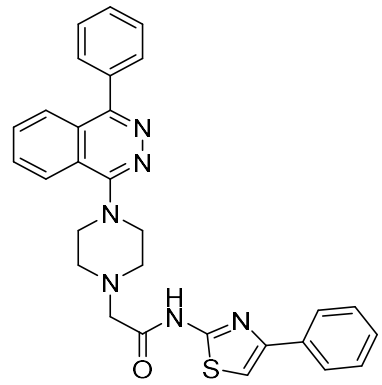
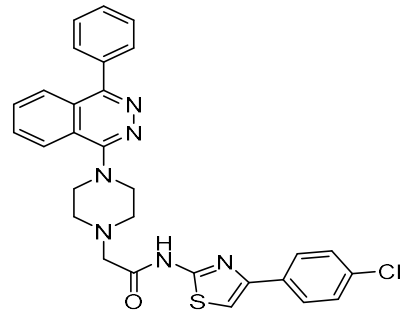
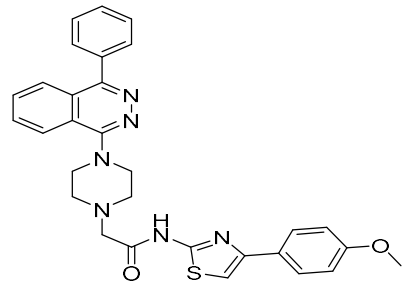
ID	Structure	MolDock score (Kcal/mol)	Re-rank score (Kcal/mol)
1		-141.628	-102.972
2		-125.292	-94.7259

3		-132.007	-109.985
4		-141.427	-107.839
5		-123.917	-102.303
6		-124.782	-105.654
7		-136.955	-103.402

8		-128.142	-105.035
9		-126.728	-107.065
10		-127.516	-109.004
11		-136.306	-95.8354

12		-122.677	-86.4617
13		-120.066	-13.1988
14		-139.167	-104.597
15		-138.287	-89.4703
16		-142.101	-94.038

17		-132.672	-93.3303
18		-154.125	-50.7487
19		-143.429	-106.307
20		-163.346	-89.5449

21		-146.77	-115.096
22		-151.651	-115.757
23		-153.388	-113.179
Sorafenib		-144.289	-113.368

Ligand optimization

One of the crucial steps in docking simulation utilized to achieve the most desirable molecular geometries with least energy is the ligand optimization. The procedure was carried out using the B3LYP/6-31G* basis set and density functional theory (DFT) calculations [11]. The 3D structure of one of the optimized ligands is displayed in Figure 1. The optimized ligands were saved in the recognized pdb file format for subsequent studies.

VEGFR-2 target retrieval and preparation

The protein data bank online resource was utilized in downloading the X-ray crystallized structure of the VEGFR-2 target protein with Sorafenib ligand (PDB ID: 4ASD) [12]. The target was prepared using the BIOVIA discovery studio visualizer by removing all varieties of water molecules, co-crystallizing Sorafenib, and then optimizing hydrogen ions. In addition, the prepared protein was stored in pdb format and displayed in Figure 2 [13].

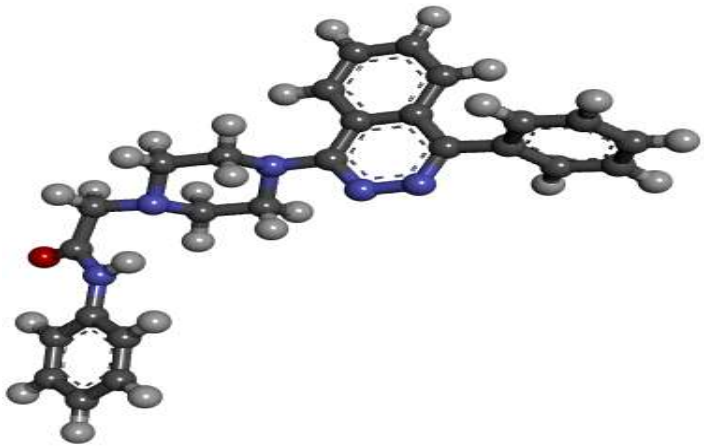


Figure 1. 3D structure of an optimized ligand

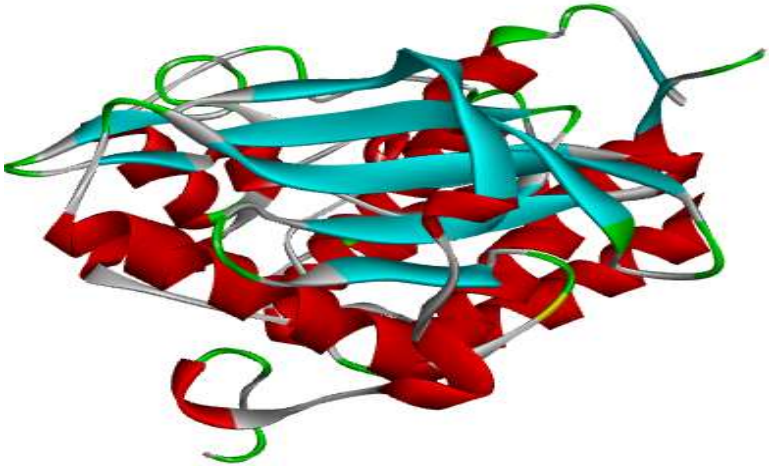


Figure 2. 3D structure of the prepared VEGFR-2 target

Docking studies

In this work, docking simulation was performed with the aid of Molegro Virtual Docker (MVD) program as it gives more reliable results compared to other docking software. Prior to the docking process, the prepared VEGFR-2 target in pdb layout was imported to the Software's work space for the electrostatic surface creation and prediction of the active pocket, which was set into a confined sphere with X, Y, and Z coordinates of -27.60, -8.97, and -6.00Å. The optimized ligands were then imported to the MVD work space for the simulation which was executed using 0.30Å GRID resolution, 2.0Å root mean square deviation (RMSD) for an assembly of poses with 100.00 energy penalty scores. Moreover, the docking algorithm was set for an extreme of 1500 circles with overall populace of 50. The docking simulation was run for at least 50 times for the 5 poses, and the computation of the best poses were centered on the MolDock and Re-rank scoring functions [14,15]. Discovery studio v3.5 application was used in the visualization and interpretation of the ligand-protein binding modes.

Validation of docking protocol and drug design

To validate the docking algorithm employed in this study, the co-crystal ligand was redocked with the principal active site of the VEGFR-2 target. The original pose was then superimposed with the redocked pose using discovery studio software as shown in Figure 7, and RMSD score was computed [8]. Furthermore, the binding affinity of the co-crystal ligand was opted as a standard for the design template isolation, which was later structurally modified by introduction and substitution of various active fragments for the design of more potent and safer hypothetical drugs [15].

Pharmacological profile prediction

The appraisal of drug-likeness and basic ADMET status of a potential drug candidate is obligatory at the preliminary phase of drug production as they facilitate the disclosure of any unwanted properties of the molecules. The predictions were executed via the prominent Lipinski's rules thru the SwissADME online tool, meanwhile, pkCSM web tool was employed for the ADMET profiling [16].

Results and Discussion

Docking study

The results of docking studies performed between the optimized ligands and the predicted VEGFR-2 active site were placed in Table 1. Furthermore, Sorafenib was also redocked into the primary active site and the outcome of superimposition of the initial and redocked pose reliably validated the docking protocol of the algorithm used in this study with RMSD value of 1.03Å. Moreover, binding scores of Sorafenib (MolDock score = -144.289 Kcal/mol, Re-rank score = -113.368 Kcal/mol) were used as a yardstick for the isolation of potential hit molecules among which compounds 21 and 22 with binding affinities of -146.77, and -151.651 Kcal/mol MolDock scores and -115.096, and -115.757 Kcal/mol Re-rank scores exceeding that of Sorafenib were isolated as lead molecules in this work.

Compound 21 interacted with the target via a conventional and carbon-hydrogen bonds with ASP1046 and CYS1045 at 1.76, 2.95, and 2.69Å. Electrostatic Pi-anion and Pi-cation interactions with LYS868 and GLU885. Pi-sulfur interactions with CYS817, and CYS1045, and hydrophobic interactions with LEU889, VAL899, VAL916, VAL848, ILE888, CYS817, and ALA881 as demonstrated in Figure 3. Meanwhile compound 22 interacted with the target binding site via carbon-hydrogen bonds with ASP814, and HIS1026 at 2.73, and 1.93Å. Electrostatic Pi-anion and Pi-cation interactions with LYS868 and ASP1028, Pi-sigma interaction with LEU889, Pi-sulfur interaction with CYS1045, and hydrophobic interactions with ALA866, VAL848, LYS868, VAL916, ARG1027, PRO1068, VAL899, and CYS1045, as shown in Figure 4.

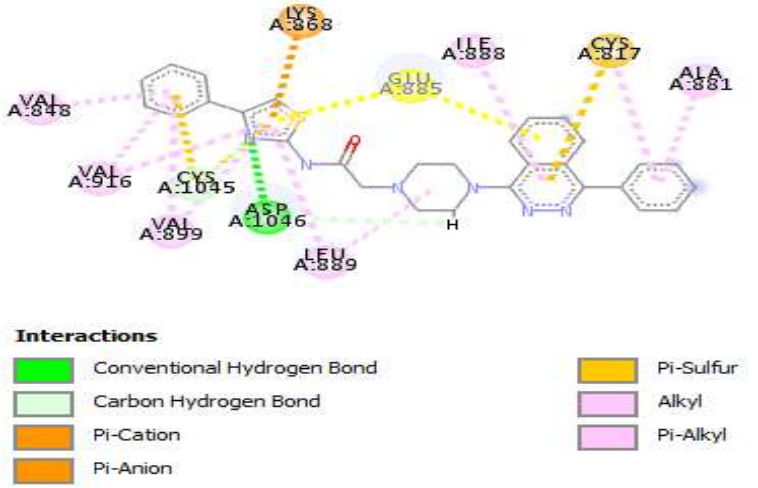


Figure 3. 2D interactions of compound 21 with the 4ASD active site.

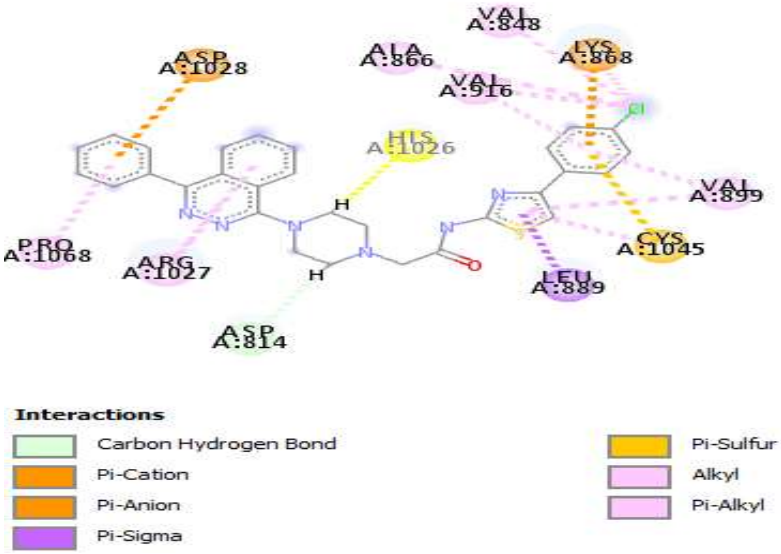


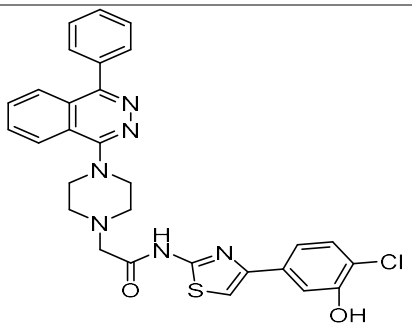
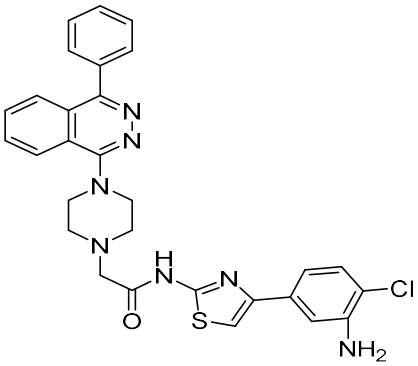
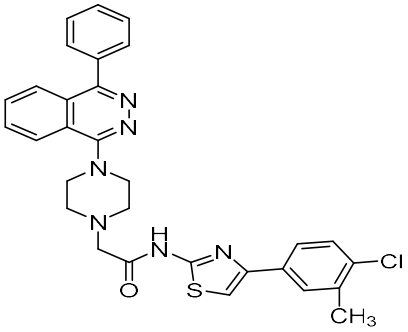
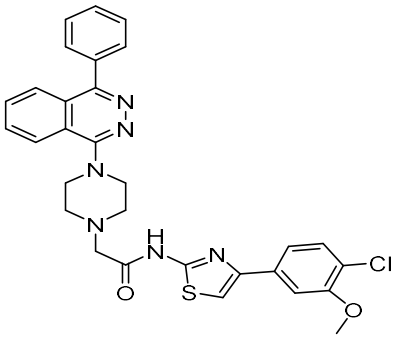
Figure 4. 2D interactions of compound 22 with the 4ASD active site.

***In silico* design**

Compound 22 with the highest binding affinities was chosen as a template for the design purpose, and its structure was adjusted by adding electron releasing -OH, $-NH_2$, $-CH_3$, and $-OCH_3$ groups to the ortho- and meta- positions of the p-chlorophenyl group. These groups tend to release electrons to the ring system through a positive inductive effect, elevating the basic character and, as a result, the binding affinities of the designed compounds [17]. Five hypothetical compounds with binding affinities ranging from -159.014 to -1669.245 Kcal/mol MolDock scores and -121.591 to -134.697 Kcal/mol Re-rank scores were designed, their 2D structures and the binding scores are presented in Table 2. Their residual interactions with the VEGFR-2 target are illustrated in Table 3, and the binding modes of

designed compounds 4, and 5 (with highest binding affinities) were discussed and compared to that of the design template in this work.

Table 2. 2D structures of the designed compounds and their docking scores

ID	Structure	MolDock score (Kcal/mol)	Re-rank score (Kcal/mol)
1		-159.782	-122.691
2		-161.221	-121.591
3		-159.014	-125.183
4		-169.245	-134.697

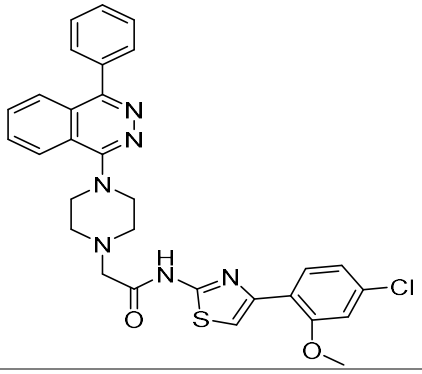
5		-166.137	-128.528

Table 3. Residual interactions of lead compounds and the designed compounds with the VEGFR-2 active site.

ID	Hydrogen bonds	Distance (Å)	Hydrophobic interactions	Electrostatic and other interactions
		Lead compounds		
21	ASP1046 CYS1045 ASP1046	1.76 2.95 2.69	LEU889, VAL899, VAL848 VAL916, ILE888, CYS817 ALA881	LYS868 GLU885 CYS817 CYS1045
22	ASP814 HIS1026	2.73 1.93	LEU889, ALA866, VAL848, ARG1027, PRO1068, VAL899, CYS1045, LYS868, VAL899, VAL916	LYS868 ASP1028 CYS1045
		Designed compounds		
1	LYS868 ASP1046 HIS1026	2.89 2.32 2.04	ALA866, VAL848, ARG1027, LEU1067, PRO1068, LEU889, VAL899, CYS1045, LYS868, VAL899, VAL916	LYS868 MET1072
2	LYS868 VAL914 ASP1046 HIS1026	2.93 2.29 2.93 2.03	ALA866, VAL848, ARG1027, LEU1067, PRO1068, LEU889 CYS1045, LYS868, VAL899, VAL916	LYS868 MET1072
3	ASP814 HIS1026	2.79 2.04	ALA866, VAL848, VAL914, ARG1027, LEU1067, PRO1068, VAL899, CYS1045, LYS868, VAL899, VAL916	LYS868 ASP1028 CYS1045
4	ASP1046 CYS1045 ASP1046 GLU885 GLU885 ARG1027	1.79 3.07 2.11 1.77 3.00 2.72	LEU889, TYR1059, VAL899, LYS868, VAL914, VAL848, ALA866, VAL916, LEU1035, ARG1027	LYS868 ASP1028 ASP1046 CYS1045

5	LYS868 ASP1046 GLU885 ASP1046 HIS1026 ASP1046	2.97 2.83 3.01 2.68 1.97 2.61	ALA866, VAL848, ARG1027, LEU1067, PRO1068, LEU889 VAL899, CYS1045, VAL848 LYS868, VAL899, VAL916	LYS868

Designed compound 4 interacted with the VEGFR-2 target via a conventional hydrogen bond with ASP1046 at 1.79Å and carbon-hydrogen bonds with CYS1045, ASP1046, GLU885, and ARG1027 at 3.07, 2.11, 1.77, 3.00, and 7.71Å. Electrostatic Pi-anion and Pi-cation interactions with LYS868, ASP1028, and ASP1046. Pi-sulfur interaction with CYS1045 and hydrophobic interactions with LEU889, TYR1059, VAL899, LYS868, VAL914, VAL848, ALA866, VAL916, LEU1035, and ARG1027 as presented in Figure 5.

Designed compound 5 interacted with the VEGFR-2 target via three conventional hydrogen bonds with LYS868, ASP1046, and GLU885 at 2.97, 2.82, and 3.0Å. Two carbon-hydrogen and single Pi- donor hydrogen bonds with ASP1046, HIS1026, and ASP1046 at 2.68, 1.97, and 2.61Å. Pi-cation and Pi-sigma interactions with LYS868. And hydrophobic interactions with ALA866, VAL848, LYS868, ARG1027, LEU1067, PRO1068, LEU889, VAL899, CYS1045, and VAL916, as depicted in Figure 6.

The dominant interactions between the designed entities and the residues of the VEGFR-2 active site are ultimately driven by hydrogen bonds [18]. According to Figures 5 and 6, the designed compounds 4 and 5 made six conventional and carbon-hydrogen bonds with the VEGFR active site residues, compared with the template's two conventional and carbon-hydrogen bonds (Figure 2). Their better docking scores compared with the template and consequently more effective binding with the target may be due to the large difference in the number of hydrogen bonds they formed. Hence, it is evident that through molecular docking approach, the structural features that can improve the potency of a drug candidates can be appraised leading to the design of more effective hypothetical drugs. *In silico* aided techniques utilized in this work reduces the expenses and duration of drug development processes. However, these computational studies rely mostly on statistics, as such, experimental validation of the results through laboratory synthesis of the designed compounds and their *in vivo* and in-vitro testing on targets is required for their affirmation as the novel drugs.

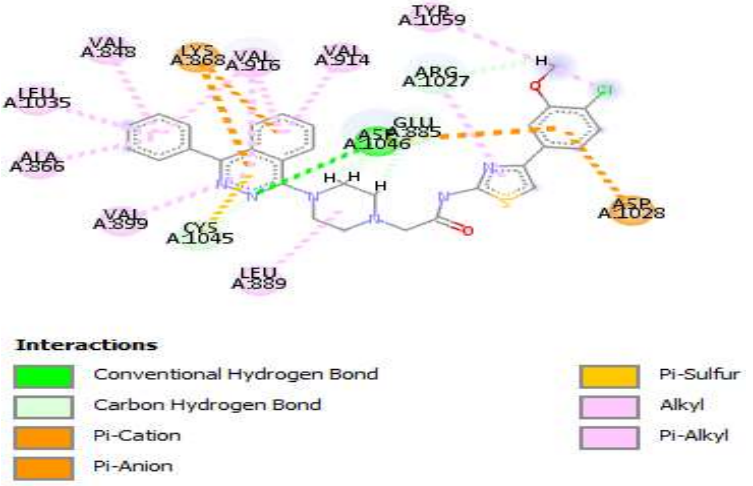


Figure 5. 2D interactions of designed compound 4 with the 4ASD active site.

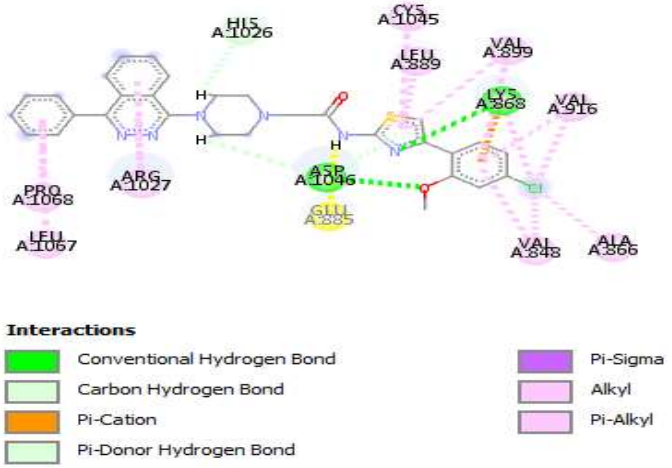


Figure 6. 2D interactions of designed compound 5 with the 4ASD active site.

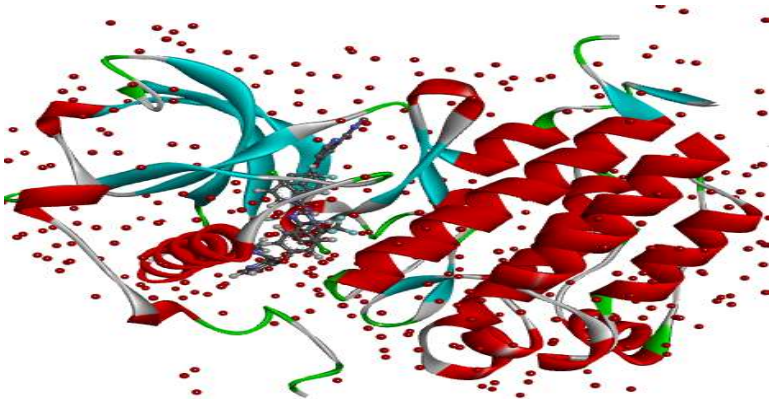


Figure 7. 3D superimposed structure of the initial and redocked pose of Sorafenib with the VEGFR-2 active site

***In silico* drug-likeliness and ADMET profiling**

The ADMET and pharmacological profiles of the designed molecules were predicted to verify that they possess drug-like features, and are depicted in Tables 4 and 5. The designed compounds are presumed to be feasible drug candidates because they comply with the Lipinski's rule by only breaching one of the criteria (MW>500), as indicated in Table 5. A molecule only exhibits drug-related challenges by violating more than two of the Lipinski's rules [19]. The excellent permeability and bioavailability of the designed molecules were demonstrated by their bioavailability scores of 0.55 [20]. Moreover, the compounds are easily synthesizable as their synthetic accessibility scores are less than 0.5 when referred to the scale 1 (easily synthesizable) and 10 (challenging to synthesis). Furthermore, the designed entities demonstrate the excellent human intestinal absorption (HIA) scores above 90% disclosing excellent absorbance by the human intestine as molecules are only poorly absorbed when their HIA scores falls below 30% [21]. Assessments of the blood-brain barrier and central nervous system permeation were used to determine the degree of permeability of a molecule. An easy BBB permeant profile was indicated by a log BB > 0.3, whereas a bad BBB distribution was indicated by a log BB < -1. Log PS > -2 indicates simple CNS distribution and log PS < - 3 suggests poor dispersion. While predicted logPS scores of the designed entities revealed the promising CNS permeant, predicted logBB scores of the designed entities revealed the non-potentiality of crossing the blood-brain barrier [22]. As the primary liver protein system responsible for oxidation (phase-1 metabolism), Cytochrome P450 (CYP450) are a category of super enzymes that facilitate the drug's metabolism, as in the case of this research. In addition, the designed compounds were discovered to be both substrates and inhibitors of this class of enzyme, cytochrome CYP3A4 inhibition being a crucial phenomenon in this study [22]. The term "clearance" refers to the drug's systemic concentration in relation to its rate of excretion. Low clearance score predicted a prominent perseverance of the drugs in a human [23]. All of the designed compounds have clearance scores below 0.5, which indicates that the molecules will be effectively eliminated from the body. Furthermore, it is critical to consider the toxicity level because it ultimately contributes to the drug success. Only the designed compound 2 displays a positive AMES toxicity status; the other designed compounds pose no significant toxicity risks when administered orally [24].

Table 4. Drug-likeliness properties of the designed molecules.

ID	Molecular weight	Number of H-bond acceptors	Number of H-bond donors	mlogP	Bioavailability score	Synthetic accessibility
1	557.07	6	2	2.61	0.55	3.99
2	556.08	5	2	2.61	0.55	4.04
3	555.09	5	1	3.59	0.55	4.07
4	571.09	6	1	2.80	0.55	4.10
5	571.09	6	1	2.80	0.55	4.16
RO5	<500	<10	<5	<5		

Table 5. Predicted ADMET properties of the designed compounds.

S/No	Absorption	Distribution		Metabolism							Excretion	Toxicity
				Substrate			CYP Inhibitors					
	Intestinal Absorption (Human)	BBB Permeability	CSN Permeability	2D6	3A4	1A2	2C19	2C9	2D6	3A4	Tolerance clearance	AMES Toxicity
1	96.468	-1.577	-2.128	NO	YES	NO	YES	YES	NO	YES	0.275	NO
2	95.605	-1.452	-2.113	NO	YES	NO	YES	YES	NO	YES	0.438	YES
3	92.719	-1.203	-1.864	NO	YES	NO	YES	YES	NO	YES	0.347	NO
4	93.081	-1.424	-2.180	NO	YES	NO	YES	YES	NO	YES	0.258	NO
5	93.139	-1.425	-2.180	NO	YES	NO	YES	YES	NO	YES	0.231	NO

Conclusion

In this research, molecular docking was performed between the optimized structures of 1-Piperazinylphthalazine derivatives as ligands and the predicted VEGFR-2 active site residues to identify the lead molecules and a template which will be utilized to design safer and improved derivatives. The docking protocol of the algorithm utilized in this work was validated by redocking the co-crystallized ligand (Sorafenib) with the initial VEGFR-2 binding site and the RMSD score computed between superimposed complexes of the initial and redocked poses of Sorafenib was found to be 1.03Å. Moreover, the binding affinities of Sorafenib (MolDock score = -144.289 Kcal/mol, Re-rank score = -113.368 Kcal/mol) was utilized as a yardstick for the adoption of lead molecules among which compounds 21 and 22 with binding affinities of -146.77, -151.651 Kcal/mol MolDock scores, and -115.096, and -115.757 Kcal/mol Re-rank scores exceeding that of Sorafenib were explored. Compound 22 was utilized as a design template from which five hypothetical compounds with binding affinities ranging from -159.014 to -166.245 Kcal/mol MolDock scores and -121.591 to -134.697 Kcal/mol Re-rank scores were designed via the introduction of electron releasing -OH, $-NH_2$, $-CH_3$, and $-OCH_3$ groups to the ortho and meta positions of the p-chlorophenyl group. To avoid drug failure after development, drug-likedness and ADMET properties were predicted, and it was observed that the designed molecules exhibits drug-likedness features with welcoming ADMET properties which poses no serious toxicity threat. Hence, they could be utilized as the novel VEGFR-2 inhibitors.

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