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Performance Evaluation of Functionalized Linear Peptides as Potential Vascular Endothelial Growth Factor Receptor Inhibitors: An *Insilico* Approach

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Abstracts
Breast tumors have caused significant devastation in females worldwide, presenting a great challenge to researchers. In this regard, the primary goal of researchers is to design and develop efficient drug-like compounds that can act as anti-vascular endothelial growth factor receptor agents that can down-regulate cancer. It was investigated how functionalized linear peptides inhibited vascular endothelial growth factor receptors. To optimize the investigated peptides, density functional theory using the 6-31G* basis set was used. Molecular docking was done to perform molecular assessments of the peptides under study as well as the vascular endothelial growth factor receptor (PDB ID: 2vpf). ADMET screening was also done using AdMETLab to evaluate the pharmaceutical properties and the toxicity status of the peptides. The optimized investigated compounds yielded several descriptors, such as frontier molecular orbitals (highest occupied molecular orbital energy and lowest occupied molecular orbital energy), band gap, polar surface area, polarizability, lipophilicity, and many more which revealed the inhibiting potential of these compounds to act as anti-vascular endothelial growth factor receptor agent. Furthermore, the computed binding affinity showed that, in comparison to the reference medications (5-fluorouracil), the investigated compounds showed greater inhibition of the vascular endothelial growth factor receptor. Molecular dynamic simulation was used to validate the findings. The ADMET screening revealed that the studied compounds are safer and more bioavailable than the referenced drug.
Keywords: *Functionalized; Cancer; Peptides; Proteins; Inhibitors; DFT; ADMET; MDS*
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Introduction

Cancer is still the primary cause of mortality in both industrialized and developing nations, raising concerns about public health. The death rate from this fatal disease remains high even with advancements in cancer therapy [1]. Cancerous cells can enter lymphatic or blood arteries, travel through the intravascular flow, and ultimately undergo metastasis. The mechanisms that lead to the development of new blood and lymphatic vessels are called angiogenesis and lymphangiogenesis. Both are required for the development of a new circulatory network that will eliminate waste and supply nutrition, oxygen, and immune cells. Like all solid tumors, breast cancer needs to undergo neovascularization (the creation of new blood vessels) to grow greater than a few centimeters in diameter. In addition to giving the tumor more nourishment, the extra veins may offer a means of tumor spread and dispersal [2].

Tumor neovascularization has a vital role in breast cancer, as demonstrated by clinical trials employing antiangiogenic therapies. The platelet-derived growth factor supergene family includes vascular endothelial growth factors (VEGFs), which are essential for controlling angiogenesis and lymphangiogenesis [3]. Most cancer cell types and some tumor stromal cells express it, making it one of the most important pro-angiogenic growth factors [4]. One potentially effective anti-angiogenic treatment for breast cancer and other solid tumors is to block the activity of VEGF. Furthermore, normal vascular endothelium does not include mutations that would enable drug resistance, in contrast to tumor cells, which are genetically unstable and can quickly develop resistance to numerous therapeutic drugs [2, 5].

To combat this deadly disease, it is imperative to develop new compounds with low cytotoxicity, high selectivity, and minimal acquired chemical resistance. This is because cancer cells have developed resistance to current anti-cancer chemotherapeutic drugs, which also have poor selectivity and adverse effects on normal cells [6]. Peptide-based drugs (less than 0.5 kDa) have emerged as a potential solution to address these problems, due to their superior potency over existing cancer therapies, high specificity, high tumor penetration, ease of synthesis, ease of chemical modification, increased tissue penetration, fewer side effects, and metabolic stability [6, 7]. Anticancer peptides do not have a specific mechanism of action, according to Camilo et al. (2014), this makes it extremely difficult to develop resistance against them [8]. However, there are limitations to the use of peptides. These restrictions include the peptides' brief plasma half-life, which is brought on by the presence of peptidases, and the potential immunogenicity they may elicit in the host [9]. Oral bioavailability presents an additional challenge because peptides undergo disintegration of their structure by digestive enzymes in the stomach, which alters their biological activity, as they transit down the digestive system [10]. Despite the drawbacks of peptides, over 150 peptides have been approved in clinical studies in the US, Europe, and Japan [11], with the US Food and Drug Administration having approved 63 of them [12]. Bacitracin, colistin, daptomycin, enfuvirtide, vancomycin, telavancin, teicoplanin, and dalbavancin are among the commercialized peptides [13].

It takes a lot of time, effort, and complexity to identify and characterize novel anticancer peptides through experimentation, and there are a lot of flawed candidate molecules. The most common reasons for failures are low bioavailability brought on by proteases' quick peptide breakdown, undesirable side effects, and poor pharmacokinetics. Furthermore, a great deal of alterations and the addition of synthetic amino acids reduce the peptides' stability, which is necessary for the peptide to maintain its structure and perform its intended tasks [7]. Finding the peptide with the best activity, highest stability, and least amount of toxicity requires repeated alterations, which adds to the expense [14]. Therefore, there is a need for prior analysis to reduce the time, manpower, and cost of production, which plays an important role in preclinical evaluations of its toxic effects [15]. In silico drug, design identifies patterns and analyzes, models, and simulates molecules in systems that are like those found in nature by using the techniques of molecular simulation and bioinformatics to gather data on the transcriptome, genome, and proteome of organisms. This is currently employed to identify a pharmacological target, lead, or active molecule in preclinical tests, complementing the biological results [14].

In this report, some functionalized linear peptides were evaluated via in-silico approach as potential anti-vascular endothelial growth factor (VEGF) to down-regulate breast cancer. Density functional calculation was done to obtain selected descriptors that are related to the reactivity of the peptides. Molecular docking was done to observe non-bonding interaction existing between the peptides and vascular endothelial growth factor (PDB ID: 2vpf). Finally, ADMET screening will be conducted to identify the bioactive compounds that can be conveniently developed as possible safe anticancer therapeutics with no side effects.

Methodology

Ligand Optimization and Molecular docking

Five functionalized linear peptides were used for this study (Figure 1). The functionalized linear

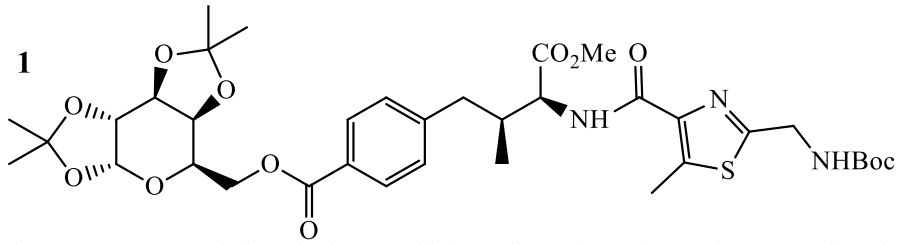
peptides were modelled using Spartan 14 [16] for the optimization of the studied compounds and 6-31G* serves as the basis set. The Lee–Yang–Parr correlation functional (B3LYP) [17] and Becke's gradient exchange correction [18] were used in the computations. The receptor used in this work was retrieved from protein data bank and it was subjected to treatment before carrying out further docking study. The small molecules and the water molecules downloaded with the protein were removed from the studied receptor before optimizing it using quickprep tool in molecular operating environment software (moe) so as to fix any missing amino acid residue and saved it in.moe format.

More so, the studied ligands were minimized and saved in moe format before docking processes. The refinement method used was induced fit with 30 poses and the result was saved in mdb format. The duration for the completion of each optimization was a function of the basis set used and the atom present in the compounds under investigation. A series of descriptors were obtained for additional analysis. The vascular endothelial growth factor receptor (PDB ID: 2vpf) was retrieved from the protein data bank and treated accordingly. The optimized ligands were docked into the binding location of the receptor using molecular operating environment software (MOE).

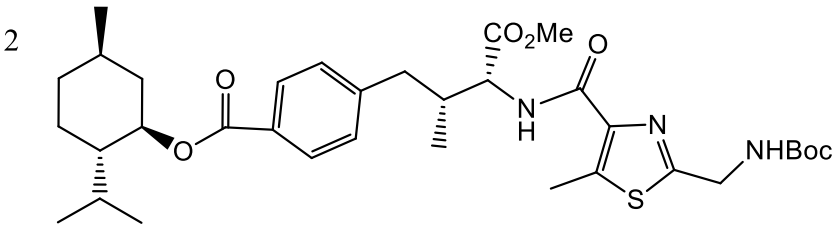
ADMET Screening

The examined peptide and reference drug were subjected to ADMETLab software for pharmacokinetics analysis. The acquired outputs were stated and construed.

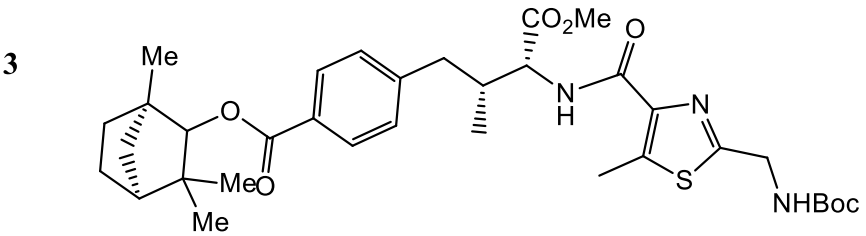
Absorption, distribution, metabolism, excretion, and toxicity are the pharmacokinetic features of drugs that are abbreviated to ADMET. This is referred to a pathway of how a drug is distributed in the systemic circulation and how it undergoes metabolism. A good drug candidate should possess both efficacy against the therapeutic target and attractive ADMET characteristics within the therapy dose range [19]. It is intended to be swiftly absorbed from the digestive tract, transported to the body's site of action, appropriately metabolized, go through biotransformation without impairing its function, and then eliminated without causing any harm [1].



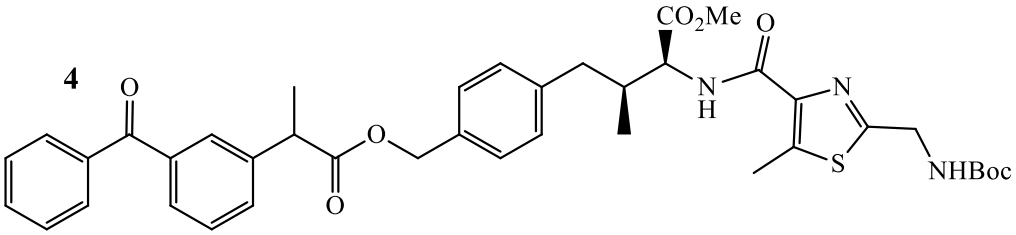
((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-yl)methyl 4-((2*S*,3*S*)-3-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylthiazole-4-carboxamido)-4-methoxy-2-methyl-4-oxobutyl)benzoate



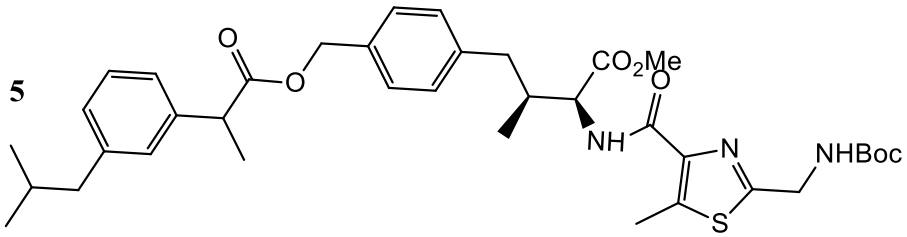
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-((2*R*,3*R*)-3-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylthiazole-4-carboxamido)-4-methoxy-2-methyl-4-oxobutyl)benzoate



(1*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl 4-((2*R*,3*R*)-3-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylthiazole-4-carboxamido)-4-methoxy-2-methyl-4-oxobutyl)benzoate



(2*S*,3*S*)-methyl 4-(4-(((2-(3-benzoylphenyl)propanoyl)oxy)methyl)phenyl)-2-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylthiazole-4-carboxamido)-3-methylbutanoate



(2*S*,3*S*)-methyl 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylthiazole-4-carboxamido)-4-(4-(((2-(3-isobutylphenyl)propanoyl)oxy)methyl)phenyl)-3-methylbutanoate

Figure 1: Two-dimensional structure of investigated functional linear peptides

Result and Discussion

The descriptors obtained from DFT calculations include energy of the highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied orbital (E_{LUMO}), energy gap, chemical potential (μ), global hardness (η), softness (σ), electrophilicity index (ω), dipole moment (DM), polar surface area (PSA), Ovality, lipophilicity (log P), hydrogen bond donor (HBD), and hydrogen bond acceptor (HBA).

Frontier molecular orbitals (E_{HOMO} and E_{LUMO}) indicate a molecule's electron-donating and accepting abilities. The inhibitory efficiency can be enhanced by altering the transport process via the adsorption layer by increasing E_{HOMO} and decreasing E_{LUMO} values [20]. A higher E_{HOMO} value showed the compound with a better ability to donate electrons to neighbouring compounds and a better capacity of to inhibit the target protein [21]. Compounds with high E_{HOMO} values possess a greater tendency to donate electrons to the neighbouring compounds and it is expected to interact better with the target, while compound 2 with the smallest E_{HOMO} will be the least reactive. According to Oyebamiji et al. (2018), a compound's propensity to interact with the target is positively correlated with its E_{LUMO} value [22]. The studied compounds did not follow this trend. The band gap (BG) of a compound is very important; it reflects the reactivity and stability of a molecule. Lower energy gaps indicate higher reactivity, leading to stronger bonding of the ligand to the target protein, resulting in high bioactivity. Higher band gaps signify stability and low reactivity. The result shows that compound **3** has the lowest energy gap, indicating the best inhibition efficiency, while compound 2 with the highest BG has the least activity.

A molecule's stability and reactivity are described by its chemical hardness and softness. Chemical hardness resists electron cloud polarisation while softness favors chemical reactivity [23]. Lower hardness and higher softness values result in better ligand-receptor interaction [24]. A good correlation was observed between these values and the energy gap of the compounds. Based on energy gap, hardness, and softness, the reactivity order is 3>5>4>1>2. This suggests that compound 3 will be the best potential Vascular Endothelial Growth Factor Receptor Inhibitor, while compound 2 will be the least inhibiting strength against this receptor.

Reactivity can also be measured by chemical potential (μ). It is a measurement of a molecule's capacity to initiate a chemical reaction due to either external or internal energy. A lower value leads to better interaction while a higher value shows less reactivity [25]. From the result, compound 2 with the highest value has the least inhibiting potential against vascular endothelial growth factor receptor.

The electrophilicity index (ω), measures the electrophilic power and characterizes the biological activity of the molecule. Compound 3 is shown to have the highest electrophilicity index (ω). This further confirms why it has a higher capacity to block vascular endothelial growth factor receptors better than other studied compounds.

Dipole moment (DM) reflects the molecule's bond polarity and electron distribution. It's reported that compounds with higher DMs have superior inhibition ability and stronger interaction. In this study, compound 2 with the lowest inhibition efficiency, had the lowest value of DM.

Table 1: Calculated properties obtained from optimized functionalized linear peptides

	E_{HOMO}	E_{LUMO}	BG	η	σ	μ	ω	DM	PSA	OVA	LOG P	HBD	HBA
1	-14.93	-14.34	0.59	0.30	3.33	-14.64	363.27	5.52	96.388	1.58	4.18	0	13
2	-15.08	-14.41	0.67	0.34	2.94	-14.75	308.08	3.50	68.533	1.51	6.24	0	8
3	-14.80	-14.36	0.44	0.22	4.55	-14.58	483.13	7.63	70.998	1.62	6.00	0	8
4	-14.30	-13.76	0.54	0.27	3.70	-14.03	364.52	14.36	94.322	1.67	6.70	0	9

5	-14.66	-14.18	0.24	4.16	-0.48	433.20	6.40	72.078	1.64	6.79	0	8
					-14.42							

Table 2: Binding sites observed in considered VEGF

Site	Size	PLB	Hyd	Side	Residues
1	22	1.95	16	20	1:(ASP34 ILE35 PHE36 GLU42 ILE43 TYR45 ILE46 PHE47 SER50)
2	7	-0.22	9	17	1:(GLU38 TYR39 ARG56 ASN75 SER95 PHE96 LEU97)
3	19	-0.24	2	6	1:(GLY59 CYS60 CYS61 ASN62 ASP63 GLU64 LEU66 GLU67 CYS68)
4	3	-0.70	2	4	1:(ARG23 SER24 HIS27 ILE29)
5	11	-0.78	6	11	1:(THR71 LYS101 CYS102 GLU103)

Molecular Docking Studies

To determine the optimal shape and orientation of each ligand within the enzyme's active site, the docking scores calculated free binding affinities, as represented by Gibbs free energy (ΔG kcal/mol), and the interactions with each ligand's essential amino acids were investigated. Every complex was examined demonstrated a high affinity for binding to the receptor. They engage with the amino acid residue in the receptor's active site to form an accurate match inside it. The binding sites observed in considered VEGF, residues of proteins engaged in the interaction, binding score and nonbonding interaction formed are displayed in Tables 2.

The test compounds were docked to the vascular endothelial growth factor receptor (PDB ID: 2vpf) active site and the resulting complexes demonstrated that the test molecules inhibit the active site of the protein with binding affinity within the range of -7.02 and -7.47 Kcal/mol (Table 3). As reported by Oyebamiji *et al.*, 2023, the greater the compound's ability to inhibit correlates with the lower binding affinity value [26]. All the studied compounds have lower binding energies than the reference drug used. This indicates that these compounds had better affinity to the receptor than the standard hence they possess better anti-cancer activities. With a binding energy of -7.47 Kcal/mol, compound 1 exhibited the best binding interaction, this is not consistent with the molecular descriptors discussed earlier.

Table 3: Calculated Scoring, amino acid residue, and types of non-bonding interactions

Compounds	Scoring	Amino Acid residues and non-bonding interactions
1	-7.47327328	PRO 49 (A) pi-H
2	-7.21955061	ASN 100 (A) H-donor
		ASN 100 (A) H-donor
		CYS 102 (A) H-acceptor
3	-7.24292612	LYS 107 (A) H-acceptor
		PHE 17 (A) pi-H
4	-7.42495394	CYS 60 (A) pi-H
5	-7.02247334	LYS 108 (A) H-acceptor
5-FU	-6.8451376	CYS 102 (A) H-acceptor
		HIS 27 (A) pi-H
		PRO 28 (A) pi-H

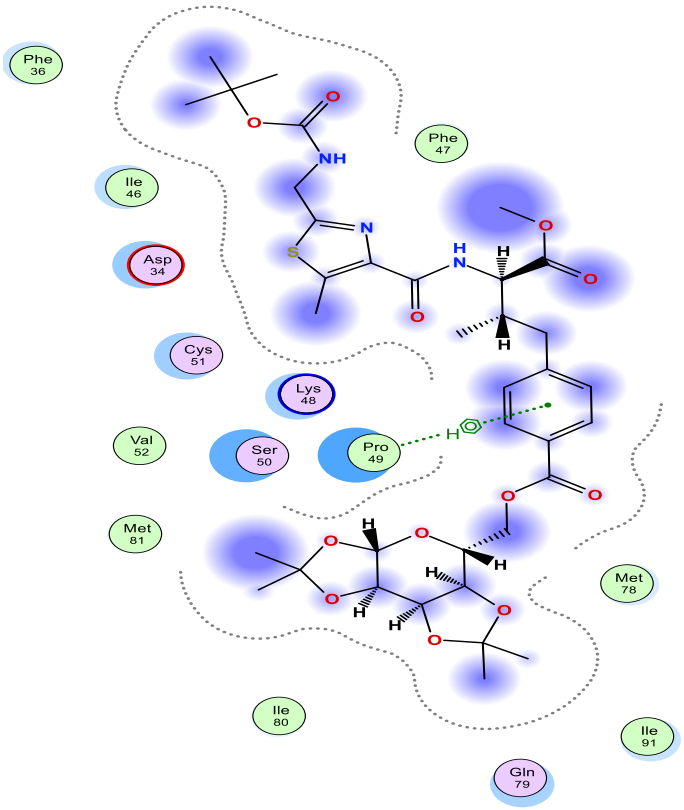


Figure 2: Compound 1 with amino acid residues in the active site of VEGF

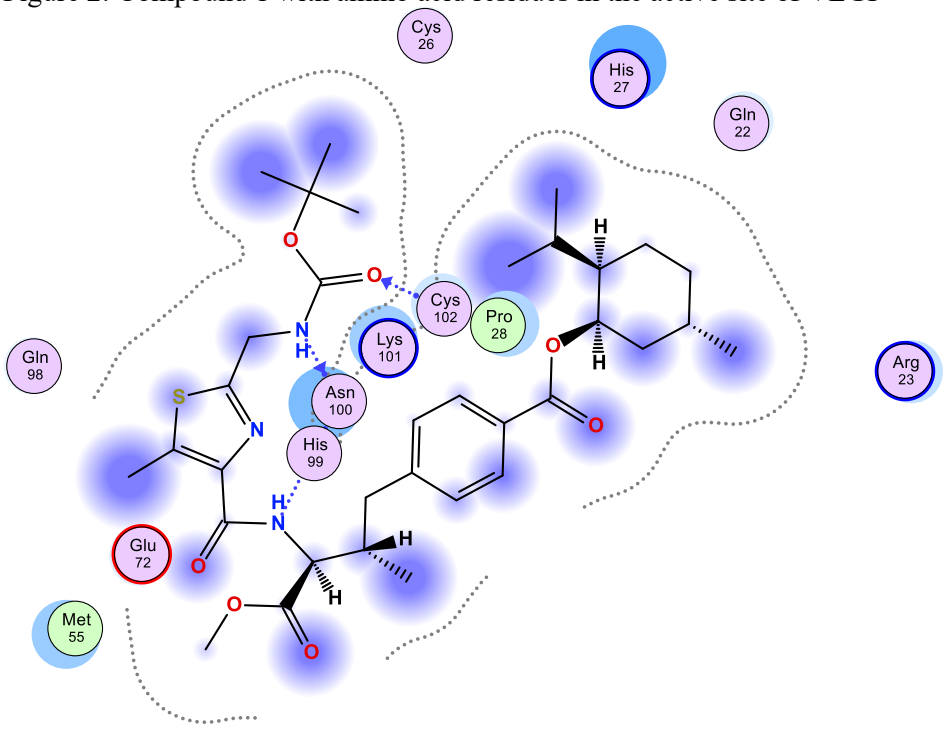


Figure 3: Compound 2 with amino acid residues in the active site of VEGF

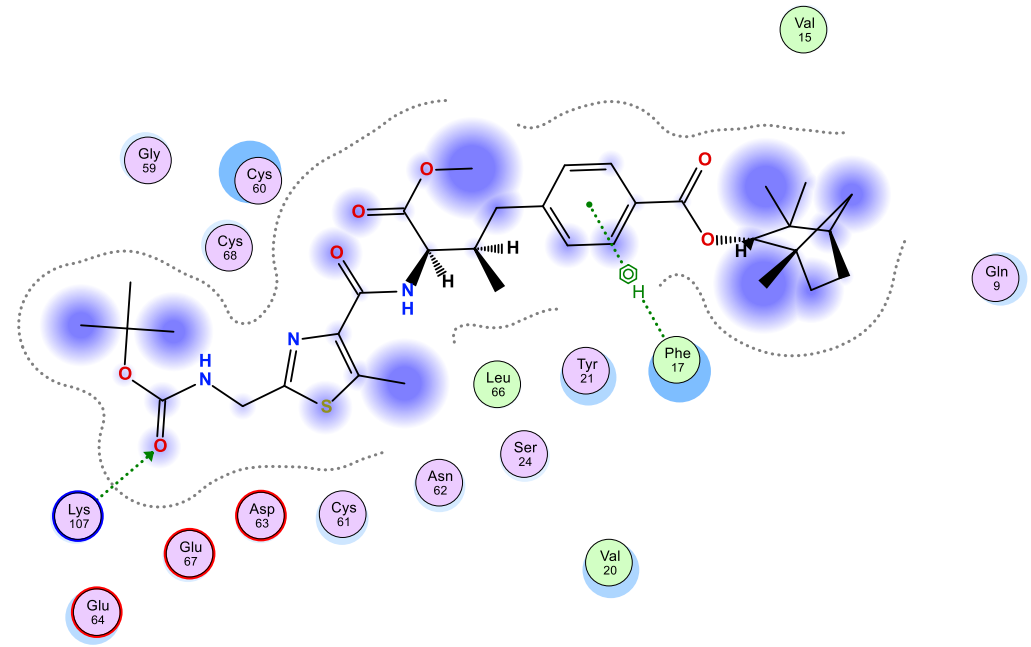


Figure 4: Compound 3 with amino acid residues in the active site of VEGF

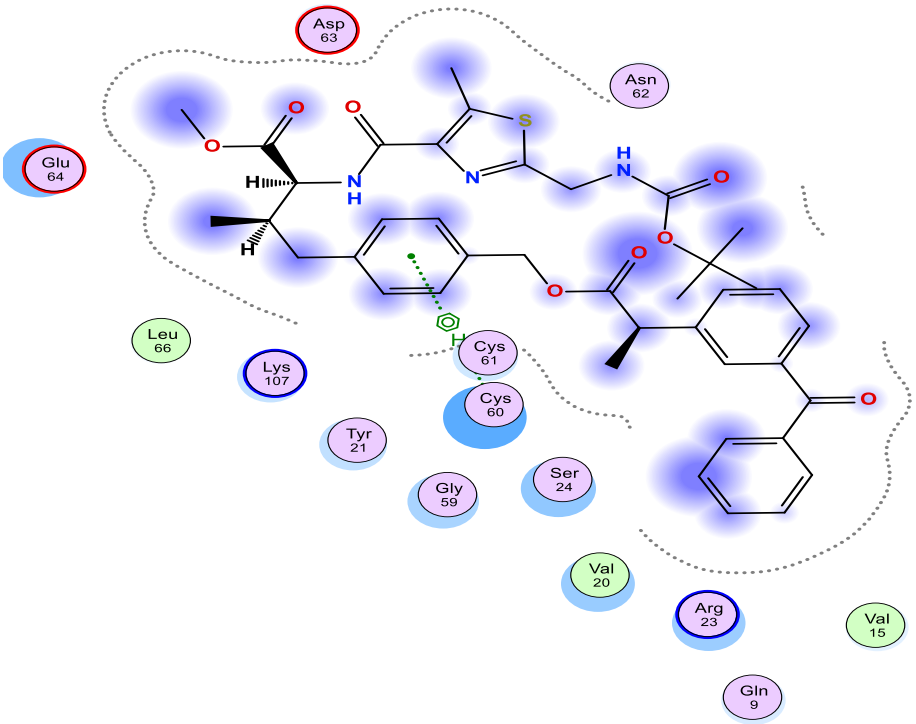


Figure 5: Compound 4 with amino acid residues in the active site of VEGF

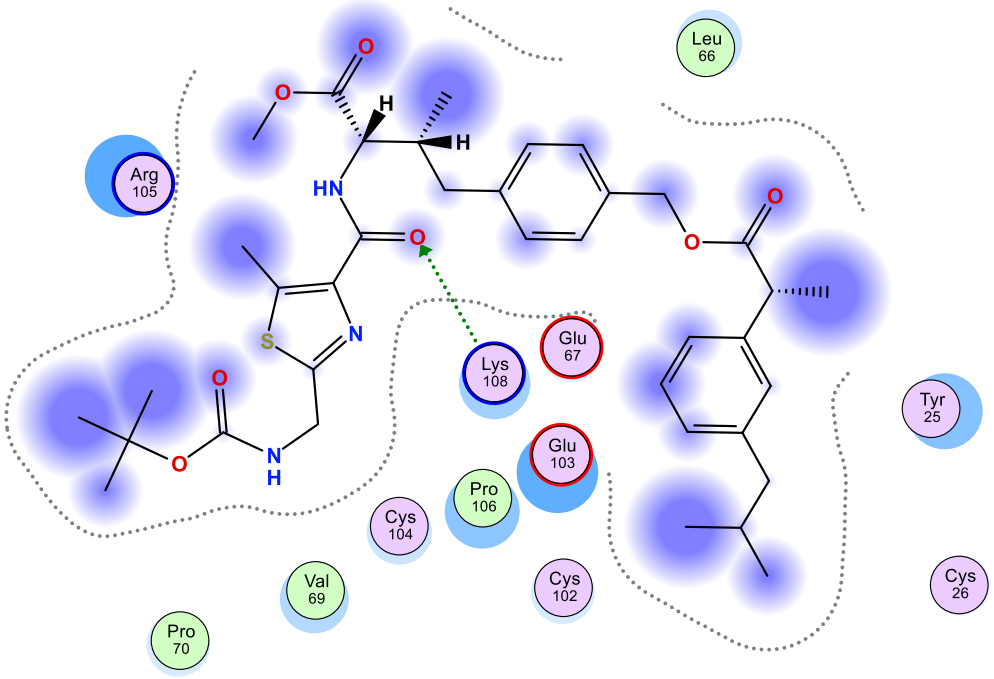


Figure 6: Compound 5 with amino acid residues in the active site of VEGF

Pharmacokinetics Prediction

Using admetLab, the pharmacokinetics prediction of the investigated compounds was performed to assess the compounds' potential toxicity in a living system as well as their ability to be absorbed, distributed, metabolized, and removed. From the result (Table 5), The studied compounds and standard demonstrated low absorption in the intestine according to the Caco-2 Permeability. The low absorption may be due to their small molecular size. All of the compounds under investigation, except the standard, do not inhibit or substrate P-glycoprotein (P-GB) permeability. The mitochondria are the primary location of all chemicals, including the standard.

Drug metabolism is crucial because it accounts for nearly half of drug excretion via Cytochrome P450 enzymes. Drug metabolism has a significant impact on its therapeutic effects. Of the CYP450 enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 have been investigated the most; they are responsible for metabolizing almost 90% of all drug compounds [27]. From Table 5, all the studied compounds are inhibitors of CYP2C19 and CYP3A4 except standard. All compounds are inhibitors of CYP2C19 and CYP3A4 except standard. All compounds are also substrates of CYP3A4 except standard. Compounds 1, 4, and 5 are inhibits CYP1A2 while compounds 2, 3, and standard are not inhibitors of CYP1A2. All compounds are inhibitors of CYP2C9 except compound 2 and standard. None of the compounds was a substrate of CYP2C9 and CYP2D6 and at the same time, none was an inhibitor of CYP2D6.

Many medication candidates are hazardous and end up failing before they ever get to clinical trials [28]. The compounds' level of toxicity was established. The term "acute oral toxicity" describes the adverse reactions that result from taking a chemical substance orally [27]. All the substances, including the reference ligand, showed high oral toxicity. AMES (Salmonella typhimurium reverse mutation assay) is a pharmacological screening technique that evaluates the medicinal compounds' carcinogenicity factors [29]. None of the studied compound, including the reference ligand, are toxic according to the results of the AMES experiment.

A key component of drug analysis during the design and development process is drug solubility.

Aqueous solubility (Log S) affects drug dissolution, with lower Log S values being preferable. The compounds' Log S values which range from -1.1327 to -4.415 suggest good aqueous solubility. and none was found to be carcinogenic. Controlling cardiac anxiety and maintaining a normal heartbeat depend on the potassium channel known as the human ether-a-go-go-related gene (hERG) [30]. Human ether-a-go-go was weakly inhibited by both the standard and the substances under study. High acute oral toxicity was demonstrated by every tested substance.

Table 5: Pharmacokinetics properties of compounds

Parameter	1	2	3	4	5	5-fu
AMES Toxicity	-	-	-	-	-	-
Acute Oral Toxicity (c)	III	III	III	III	III	III
Aqueous solubility	-3.4318	-4.4152	-4.2709	-3.7932	-3.7932	-1.1327
Blood Brain Barrier	-	-	-	-	-	+
Biodegradation	Not ready biodegradable	Not ready biodegradable	Not ready biodegradable	Not ready biodegradable	Not ready biodegradable	Not ready biodegradable
Caco-2 Permeability	-	-	-	-	-	-
Caco-2 Permeability	0.9580	0.8844	0.8680	1.0417	1.0417	1.0136
Carcinogens	-	-	-	-	-	-
CYP450 2C9 Substrate	-	-	-	-	-	-
CYP450 2D6 Substrate	-	-	-	-	-	-
CYP450 3A4 Substrate	+	+	+	+	+	-
CYP450 1A2 Inhibitor	+	-	-	+	+	-
CYP450 2C9 Inhibitor	+	-	+	+	+	-
CYP450 2D6 Inhibitor	-	-	-	-	-	-
CYP450 2C19 Inhibitor	+	+	+	+	+	-
CYP450 3A4 Inhibitor	+	+	+	+	+	-
CYP Inhibitory Promiscuity	+	+	+	+	+	Low
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	Weak inhibitor	Weak inhibitor	Weak inhibitor	Weak inhibitor	Weak inhibitor
Human Intestinal Absorption	+	+	+	+	+	+
P-glycoprotein Substrate	+	+	+	+	+	-

Acute Oral Toxicity	0.5509	0.5310	0.5420	0.5281	0.5289	0.4387
P-glycoprotein Inhibitor	+	+	+	+	+	-
Renal Organic Cation Transporter	-	-	-	-	-	-
Rat Acute Toxicity	2.7002	2.7894	2.7442	2.7289	2.7289	2.2529
Subcellular localization	Mitochondria	Mitochondria	Mitochondria	Mitochondria	Mitochondria	Mitochondria

Conclusion

Five Functionalized linear peptides were investigated by insilico method. By optimizing these compounds with DFT simulations, reactivity descriptors such as HOMO and LUMO energies as well as band gap energy were obtained. Every chemical was positioned in the active site of the vascular endothelial growth factor receptor (PDB ID: 2vpf) to investigate its anticancer properties in more detail. Compounds 1 through 5 showed good inter- and intramolecular interactions, high binding affinity, and stability in the binding pocket of VEGFR-2 target proteins, according to the results of the computational analysis. Understanding protein-ligand complex stability, reactivity, and interaction profiling as well as the mechanistic insights into the inhibitory mechanism of VEGFR-2-ligand complexes is made easier with the use of this information. Additionally, compared to reference medications, all examined compounds have better pharmacokinetic features.

Also, none of the studied compounds showed any type of toxicity, therefore, they are good therapeutic candidates. This work is entirely in silico. Therefore, to gain a deeper understanding of the pharmacological and biological actions of these ligands in the therapy of VEGFR-2, more in vivo or in vitro investigation should be conducted, and the compounds could be synthesized.

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