

Research Article

***In-silico* Study on Pharmacokinetic Properties and VEGFR-2 Binding of Quininib Through Molecular Docking**

**Murtaza Jafari^{1,*} , Kamalluddin Zahedi² , Ahmad Reshad Haidari¹ ,
Mohammad Firdous Wahid¹ , Omar Azimi¹ **

¹Department of Pharmaceutics & Pharmacology, Cheragh Medical University, Kabul, Afghanistan

²Department of Chemistry & Biochemistry, Khatam-Al-Nabeien University, Kabul, Afghanistan

Abstract

Cancer growth depends on both the physiological process of angiogenesis, supported by binding of the vascular endothelial growth factor (VEGF) to endothelial cells of blood vessels, and on the interaction of angiogenic growth factors with receptors on endothelial cells, which promote angiogenesis through signaling pathways. The purpose of this *in-silico* study was to compare the binding of the small molecule inhibitor quininiib (QNB) to the VEGFR2 receptor with the binding of the standard anti-cancer drug axitinib using AutoDock 4.2 to predict and assess docking scores; and to categorize each compound's pharmacokinetic properties using the Swiss ADME (Absorption, Distribution, Metabolism, and Excretion) online tool. The results presented here demonstrate that quininiib is capable of binding to the areas of the VEGFR2 receptor corresponding to the following amino acids: LEU889, VAL898, VAL899, LEU1019, ASP1028, and ILE1044. These binding interactions involve primarily hydrophobic interactions, together with a hydrogen bond with ASP1046 and a docking score of -4.72 kcal/mol. In addition, it was found that QNB possesses a high level of gastrointestinal (GI) absorption and the ability to cross the Blood–Brain Barrier (BBB), as well as that it conforms to Lipinski's rule of five for oral administration. We can therefore conclude that quininiib has the potential to inhibit angiogenesis, which could thereby suppress the growth of cancer cells by binding to VEGFR2; and that even though its inhibition of VEGFR2 is lower than that of axitinib, there is potential for QNB to be developed as an orally administered agent following appropriate formulation and subsequent validation by further *in-vitro* and *in-vivo* studies.

Keywords

Molecular Docking, Quininib, VEGFR2, *In-Silico*

1. Introduction

Cancer is one of the most significant health issues worldwide, caused by abnormal cell growth, proliferation, and metastasis. The rates of cancer incidence and death are rising [1]. After cardiovascular disease, cancer is the second leading

cause of death globally. Among various types of cancer, lung cancer is the leading cause of death among cancer patients worldwide [2]. It accounts for 18% of cancer-related deaths [3], with 1.8 million people dying from it each year [4]. The

*Correspondence: Murtaza Jafari (murtaza.jafari@chreragh.edu.af)

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abnormal growth of cancer cells increases their demand for oxygen and nutrients, prompting an increase in angiogenesis to meet these needs [5]. Several chemical mediators, including Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), angiotensin, and interferons, regulate angiogenesis. Among these, VEGF is the most significant and influential in promoting angiogenesis and the development of lung cancer [6]. The VEGF family consists of five proteins: VEGFA, VEGFB, VEGFC, VEGFD, and Placental Growth Factor (PlGF) [7]. The effects of VEGF depend on its receptor binding. Generally, there are three types of VEGF receptors: VEGFR1, VEGFR2, and VEGFR3. VEGFR1 and VEGFR2 are crucial in the development and progression of cancer cells. VEGFA, VEGF, and PlGF bind to VEGFR1, leading to cancer cell metastasis. VEGFA, VEGF, VEGFC, and VEGFD bind to VEGFR2, promoting the growth and proliferation of cancer cells [8], while VEGFR3 is involved in lymph angiogenesis [9]. The activity of VEGFR2 is approximately ten times greater than that of VEGFR1 and is key to activating angiogenesis [10]. By binding to their receptors on endothelial cells, VEGF activates downstream signaling pathways, including the Phosphoinositide 3-Kinase (PI3K)/Akt pathway, which enhances cancer cell survival by inhibiting apoptosis and increasing cell metabolism; the Mitogen-Activated Protein Kinase (MAPK) pathway, which promotes lung cancer cell proliferation and differentiation; and the Ras/Raf/MEK/ERK pathway, which facilitates lung cancer cell growth [11]. Under normal conditions, a dynamic balance exists between pro-angiogenic and anti-angiogenic factors. However, in pathological conditions such as hypoxia, the expression of pro-angiogenic factors like VEGF increases, resulting in abnormal nonvascular growth [12]. Since VEGF and its receptors contribute to cancer cell growth, they are important targets in cancer therapy, with anti-angiogenic drugs playing a crucial role [13]. The growth and metastasis of cancer cells can be controlled using compounds that inhibit angiogenesis. The monoclonal antibody bevacizumab has been used to treat lung cancer [4]. *In-silico* studies enable the identification of target macromolecules involved in disease development. By examining their characteristics, compounds that can inhibit these macromolecules can be identified. These studies facilitate the analysis of VEGFR2, one of the most important targets in cancer therapy, and help in the search for receptors that inhibit angiogenesis in cancer cells, thereby stopping their growth [14]. Quinib (QNBs) are a group of small drug molecules with anti-angiogenic, anti-vascular permeability, anti-inflammatory, and anti-proliferative activities. Although this compound was discovered accidentally, its pharmacological properties have led to the synthesis of analogs as drugs. *In vivo* and *in vitro* studies have demonstrated that QNB has anti-angiogenic effects and can control the growth and proliferation of cancer cells [15]. Therefore, this *in silico* study investigates QNB as a potential agent targeting VEGFR2 for use as an anti-VEGFR drug or in cancer therapy, compared to a standard drug (axitinib).

2. Materials and Methods

2.1. Study Design

This *in-silico* study involved rigid and specific site molecular docking to examine the interaction between the ligand and protein. The ligand of interest was QNB, and the target protein was VEGFR2; it was used with axitinib (tyrosine kinase inhibitor).

2.2. Target Protein (VEGFR2) and Ligand (QNB) Preparation

The three-dimensional crystal structure of target protein VEGFR2 (4AG8) in Protein Data Bank (PDB) format was downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (<http://www.rcsb.org/pdb/home/home.do>). The preparation of the target protein (VEGFR2) was processed by using AutoDock 4.2 software (<http://autodock.scripps.edu/>). VEGFR2 was further cleaned by removing the non-essential water molecules, and polar hydrogens were added, and Kollman charges were computed (-14.44). For the preparation of the ligand (QNB), first, the three-dimensional structures of QNB in Structure Data File (SDF) format were downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and then converted from SDF format to PDB format by using the Open Babel Converter software (http://openbabel.org/wiki/Main_Page) to be suitable for molecular docking analysis. To investigate the structure, stability, and reactivity of the QNB, its Torsion angles and aromaticity were investigated. After this, the active sites of ligand binding in the VEGFR2 were identified by using literature reviews and online tools, like Click2Drug (<http://www.click2drug.org>) and UniProt (<https://www.uniprot.org>). After the minimization process and adding Kollman charges, the grid box resolution was set.

2.3. Molecular Docking Simulation

After the QNB and VEGFR2 preparation, molecular docking analysis was performed by AutoDock 4.2. The Lamarckian Genetic Algorithm was used to perform the docking calculations. The parameters of the Genetic Algorithm (GA) were set to default. For the QNB, 10 docking runs were performed, and the results were ranked based on the best binding energy. The final docked results were saved as a Docking Log File (.dlg). This file was opened again in AutoDock 4.2, and the conformation with the lowest binding energy was selected and saved in (.pdbqt) format. Then this file was converted to (.pdb) format by Open Babel, and the Protein-Ligand Interaction Profiler (PLIP) (<https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index>) and PDBsum (<https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/>) web servers were used to visualize and accurately observe the interactions between QNB and VEGFR2 and Ramachandran plot has been used to Validation of VEGFR2 structures, secondary structure investigation, and identification of errors in modeling.

2.4. In-silico Analysis of QNB (Lipinski Screening), Molecular Properties, and ADME Analysis

Lipinski's Rule of Five has been used to evaluate the pharmacokinetics of QNB, particularly its ability to be absorbed orally (oral bioavailability). According to this rule, a drug molecule is most likely to be well absorbed in the human body if it meets these five properties. QNB was analyzed using the software (<https://scfbio-iitd.res.in/software/drugdesign/lipinski.jsp>), which applies the five rules of QNB. The Swiss ADME (Absorption, Distribution, Metabolism, and Excretion) online tool (<http://www.swissadme.ch>) was also used to investigate the molecular properties of QNB. Any chemical compound that is to be used as a drug must undergo pharmacokinetic analyses before use. This principle allows for more accurate drug formulation (dosage form) to be designed and for determining which route of administration provides the most suitable bioavailability. In this study, the Swiss ADME online tool was used to study the pharmacokinetics of the QNB.

3. Result

3.1. Molecular Docking Simulation

QNB as a ligand docked with VEGFR2 by using AutoDock 4.2 software, and after docking, to determine the best-suited conformation of ligand and protein interaction was determined by binding energy (kcal/ mol) in 10 different interacting conformations. The most lower binding energy of QNB with VEGFR2 was calculated (-4.72 kcal/ mol) with LEU889, VAL898, VAL899, LEU1019, ASP1028, ILE1044, and ASP1046 amino acid binding sites (Figure 1). From the binding results of QNB with VEGFR2, it is clear that QNB had relatively good binding energy and they were able to bind to VEGFR2 as a drug. Among the observed interactions between QNB and VEGFR2, six interactions had hydrophobic bonds, and only one interaction had a hydrogen bond. In this hydrogen bond, the ASP1046 was identified as the donor and the O3 atom of the QNB as the acceptor. The hydrogen bond angle was calculated to be 171.17. Other information related to VEGFR2 with QNB interactions is also shown in Table 1.

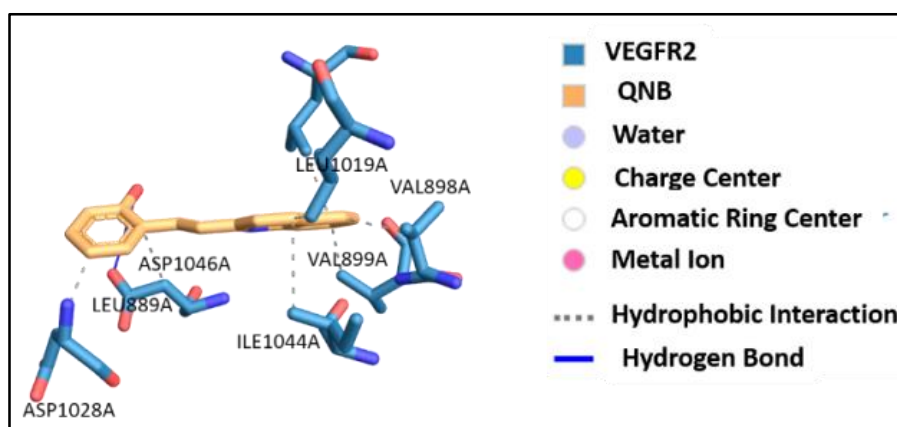


Figure 1. Interaction of VEGFR2 with QNB using the Protein–Ligand Interaction Profiler (PLIP). QNB by forming interactions with LEU889, VAL898, VAL899, LEU1019, ASP1028, ILE1044, and ASP1046 of VEGFR2 and one hydrogen bond with ASP1046, can inhibited VEGFR2 activity. QNB: quininib, VEGFR2: vascular endothelial growth factor receptor 2.

Table 1. The interaction results of VEGFR2 with QNB using the Protein–Ligand Interaction Profiler.

N	Residue	AA	Distance (Å)	QNB Atom	VEGFR2 Atom
1	889A	LEU	3.28	2945	722
2	898A	VAL	2.89	2942	810
3	899A	VAL	2.92	2945	819
4	1019A	LEU	3.11	2941	1436
5	1028A	ASP	3.48	2931	1534
6	1044A	ILE	3.73	2941	1692
8	1046A	ASP	3.00	2929	1707

The Ramachandran plot shows that most of the spots are concentrated in the red and brown regions, indicating that the VEGFR2 structure is spatially stable and well modeled. A few spots in the yellow or white regions (undesired) can be normal,

especially if those spots are related to GLY and PRO, or specific positions such as loops. The Ramachandran plot and secondary structure of VEGFR2 are shown in (Figure 2).

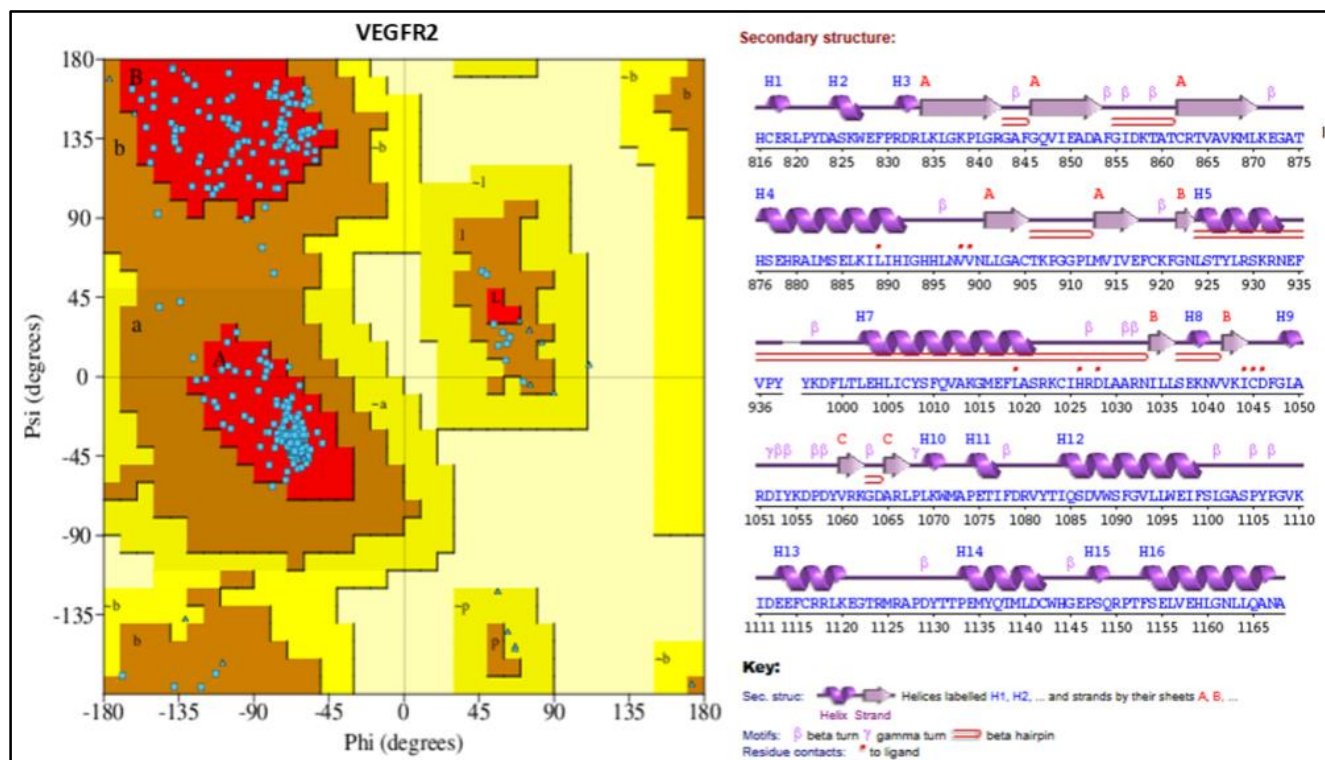


Figure 2. Ramachandran plot and secondary structure of VEGFR2 using the PDBsum. It represents the spatial angles of the peptide chain in VEGFR2, indicating that the spatial states (conformations) are suitable for the bonds between atoms in the backbone. VEGFR2: vascular endothelial growth factor receptor 2.

3.2. Lipinski Screening and Molecular Properties, and ADME Analysis of QNB

Lipinski's Rule of Five is a simple guideline for assessing the "oral bioavailability" of compounds. If a compound violates more than one of these four conditions, it is unlikely to be well absorbed by the body when taken orally. This rule mainly applies to small molecules. QNB is a small molecule ($C_{17}H_{13}NO$) with a molecular weight of 247.29 g/mol, 3.04 MLOGP, two hydrogen bond donors, one hydrogen bond acceptor, and 79.14 molar refractivity, so QNB does not violate

the Lipinski rule of five. Table 2 shows QNB's compliance with Lipinski's rules. The physicochemical properties of QNB are analyzed along six main axes: lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), water insolubility (INSOLU), unsaturation (INSATU), and acceptor capacity (FLEX). The closer the properties are to the center, the more drug-like the compound is. In this chart, QNB has the appropriate size and affinity, is slightly polar, slightly insoluble, and relatively saturated. Generally, for good oral absorption, solubility may need to be improved. The bioavailability radar chart of QNB is shown in (Figure 3).

Table 2. Lipinski rule, molecular properties, and ADME analysis of QNB.

N	Lipinski Rule of Five	QNB	Violate
1	Molecular mass less than 500 Dalton Molecular weight ≤ 500	275.29	No
2	High lipophilicity (expressed as log P less than 5) MLOGP ≤ 5	3.04	No

N	Lipinski Rule of Five	QNB	Violate
3	Less than 10 hydrogen bond acceptors N or O ≤ 10	2	No
4	Less than 5 hydrogen bond donors NH or OH ≤ 5	1	No
5	Molar refractivity should be between 40- 130.	79.14	No
Molecular Properties of QNB			
1	TPSA (Topological Polar Surface Area)	33.12 Å ²	
2	Solubility class	Moderately soluble	
3	Synthetic accessibility (from 1 very easy to 10 very difficult)	2.25	
ADME analysis of QNB			
1	GI absorption	High	
2	BBB permeant	Yes	
3	P-gp substrate	No	
4	CYP1A2 inhibitor	Yes	
5	CYP2C19 inhibitor	Yes	
6	CYP2C9 inhibitor	No	
7	CYP2D6 inhibitor	Yes	
8	CYP3A4 inhibitor	No	
9	Log K _p (skin permeation)	-4.87 cm/s	

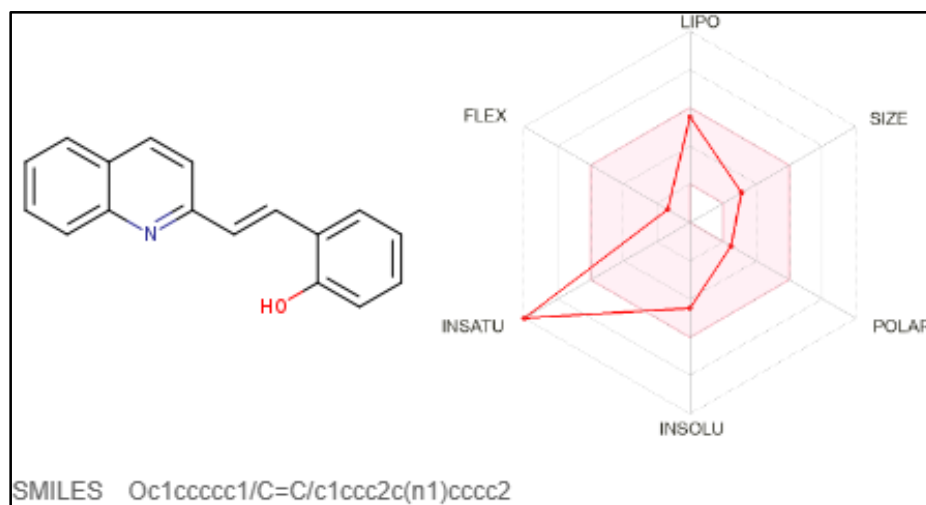


Figure 3. Bioavailability radar chart from the SwissADME online tool of QNB. This chart shows that the QNB has suitable pharmacokinetic properties and can be formulated as an oral drug. QNB: quininib.

4. Discussion

Angiogenesis is a complex physiological process involved in the growth and differentiation of vascular endothelial cells. It also contributes to the growth and metastasis of cancer cells [16]. This process is regulated by chemical signals in the body, with VEGF being one of the most crucial messengers that

plays a key role in angiogenesis. VEGF also promotes tumor growth and is considered a fundamental therapeutic target in cancer; inhibiting its activity can halt the growth, proliferation, and spread of cancer cells [17].

In this study, we examined how the chemical compound QNB interacts with VEGFR2 using molecular docking studies to assess its potential as a cancer therapy by inhibiting angiogenesis. QNB can bind to VEGFR2 through hydrogen bonds

and multiple hydrophobic interactions, with a calculated binding energy of -4.72 kcal/mol. A single hydrogen bond is formed between QNB and the amino acid ASP1046. Pharmacokinetic analyses and Lipinski's rules suggest that QNB can be developed as an oral drug and formulated for suitable administration. Various *in silico* studies on VEGF inhibition and angiogenesis indicate that molecular docking can predict the likelihood of ligands binding to target proteins. These studies include both synthetic and plant-derived compounds used to inhibit VEGF activity. For example, Lutfiya et al. compared the interaction of 50 plant compounds with VEGF to that of the drug Triamcinolone (standard drug) via molecular docking. Their results showed that 6 of these plant compounds could potentially interact with VEGF and inhibit angiogenesis [17]. Besides plant compounds, synthetic chemicals can also inhibit VEGF activity by binding to its receptors. One of the main targets is VEGFR2, which is a key receptor in cancer treatment. New pyrazoline derivatives outperform the standard drugs Vantalanib and Sorafenib in inhibiting VEGFR2, forming hydrogen bonds and π - π interactions with amino acids CYS919, LYS868, and PHE1047 in VEGFR2 [18]. 2-furybenzimidazole derivatives interact with amino acids GLU885, ASP1046, and CYS919 in VEGFR2 [19]. Thiazole hybrid derivatives with fluorinated indenoquinoline form hydrogen bonds with CYS919 and hydrophobic interactions with VAL848, ALA866, LYS868, LEU840, VAL899, VAL916, and CYS1045 in VEGFR2 [20]. Phthalazine derivatives show better VEGFR2 inhibition than Vantalanib and Sorafenib by binding to VEGFR2 with lower energy, forming hydrogen bonds and hydrophobic interactions [21]. 2-furybenzimidazoles exhibit stronger binding to VEGFR2 than standard drugs like Sorafenib and Tamoxifen. Benzothiazole and benzoxazole derivatives also show stronger binding than Sorafenib [22]. Additionally, some protein-derived compounds can inhibit VEGF activity; for example, SPARC (Secreted Protein Acidic and Rich in Cysteine) can inhibit angiogenesis by binding to VEGFR1 [23]. The chemical structure of a ligand plays a vital role in its binding affinity to the target protein, with 2-phenyl substitutions in the benzimidazole ring facilitating hydrophobic interactions with residues such as Ile888, Leu889, Ile892, Val899, Leu1019, Ile1025, and Ile1044 in VEGFR2 [24]. Based on molecular docking results, some compounds demonstrate better docking scores compared to standard drugs [25]. Overall, these results suggest that QNB can inhibit angiogenesis and, considering its pharmacokinetic and dynamic profile, could be formulated as an oral drug. Nevertheless, further *in vivo* and *in vitro* studies are necessary to evaluate its pharmacological effects and safety. The binding of QNB to the VEGFR2 is lower than that of axitinib (forms stronger bonds with the VEGFR2 by forming 4 hydrogen bonds and 12 hydrophobic interactions). In this case, due to the strong binding of the drug to the protein, it can be introduced as an effective compound in binding to the target protein.

5. Conclusion

Angiogenesis is one of the most important biological processes that plays a role in the rapid growth of cancers and their metastasis. By increasing angiogenesis, the transfer of O_2 and nutrients to cancer cells and tissues increases, which ultimately leads to the growth of cancer cells. Hormone A increases angiogenesis by VEGF binding to its receptors on the surface of endothelial cells. The growth of cancer cells can also be stopped by inhibiting angiogenesis. Various compounds can inhibit angiogenesis by binding to the VEGF receptors. This *in silico* study shows that QNB can bind to proteins and inhibit angiogenesis by binding to LEU889, VAL898, VAL899, LEU1019, ASP1028, ILE1044, and ASP1046 of VEGFR2, with binding energy of -4.72 kcal/mol, and considering its pharmacokinetic properties, it can be used as an oral drug by preparing a suitable formulation after *in vitro* and *in vivo* studies.

6. Recommendations

The *in-silico* study has helped generate numerous recommendations following the findings of the study. The first recommendation made is that additional *in-vitro* studies will need to be run in order to confirm the *in vitro* ability of QNB to inhibit VEGFR-2 and that QNB possesses and/or has the *in vitro* anti-angiogenic capabilities. The second recommendation is that pharmacodynamics studies and pharmacokinetics studies should be performed in preclinical models in order to identify the pharmacodynamic properties and the pharmacokinetic properties of QNB *in vivo*. QNB is expected to be able to cross the BBB and to produce clinically significant actions. Also, additional studies to establish Quininib's binding affinity to VEGFR-2 via structural and medicinal chemistry techniques would allow QNB to have a much higher potency when compared to standard anti-VEGFR-2 agents such as axitinib. Based on Quininib's favorable ADME properties and that QNB meets all criteria from Lipinski's Rule of Five, additional studies to develop oral drug development formulations would provide valuable information for enhancing the chemical stability and therapeutic efficacy of QNB.

Finally, future studies employing molecular dynamics simulation and free energy calculation methodologies would be helpful in providing greater insight into the stability and dynamics of the Quininib-VEGFR-2 Complexes over time. In conclusion, the results generated from such studies would further support the development of QNB as a potent anti-angiogenic cancer therapy to be delivered orally.

Abbreviations

ADME	Absorption, Distribution, Metabolism, and Excretion
BBB	Blood-Brain Barrier

EGF	Epidermal Growth Factor
FGF	Fibroblast Growth Factor
GA	Genetic Algorithm
GI	Gastrointestinal
MAPK	Mitogen-Activated Protein Kinase
PDB	Protein Data Bank
PI3K	Phosphoinositide 3-Kinase
P-gp	P-glycoprotein
PIGF	Placental Growth Factor
PLIP	Protein–Ligand Interaction Profiler
QNB	Quininiib
RCSB	Research Collaboratory for Structural
PDB	Bioinformatics Protein Data Bank
SDF	Structure Data File
SPARC	Secreted Protein Acidic and Rich in Cysteine
TPSA	Topological Polar Surface Area
VEGF	Vascular Endothelial Growth Factor

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Author Contributions

Murtaza Jafari: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resource, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Kamalluddin Zahedi: Conceptualization, Data curation, Project administration, Resources, Software, Validation, Writing – review & editing.

Ahmad Reshad Haidari: Conceptualization, Formal analysis, Investigation, Software, Validation.

Mohammad Firdous Wahid: Data curation, Investigation, Resources, Validation, Writing – review & editing.

Omar Azimi: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Validation.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

Murtaza Jafari is a member of the Department of Pharmaceutics & Pharmacology at Cheragh Medical University, Kabul, Afghanistan. He holds a Doctor of Pharmacy (Pharm D) degree and a Master's (MSc) in Cellular and Molecular Biology. His research interests include nanotechnology and bioinformatics.

Kamalluddin Zahedi holds a Master's (MSc) degree in Analytical Chemistry and is a member of the Department of Chemistry & Biochemistry at Khatam-Al-Nabeien University, Kabul. His research focuses on bioinformatics and nanotechnology.

Ahmad Reshad Haidari is a Doctor of Pharmacy (Pharm D) and head of the Department of Pharmaceutics & Pharmacology at Cheragh Medical University. His research areas include pharmacology, bioinformatics, and nanotechnology.

Mohammad Firdous Wahid is a Doctor of Pharmacy (Pharm D) and a Master's (MSc) in Clinical Pharmacy, and a faculty member in the Department of Pharmaceutics & Pharmacology at Cheragh Medical University. His research interests cover pharmaceutical and biomedical sciences.

Omar Azimi holds a Master's (MSc) degree in Medical Laboratory Technology and is a member of the Department of Pharmaceutics & Pharmacology at Cheragh Medical University, Kabul. His research interests include medical and biomedical investigations.