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Molecular Docking Approach of Some Quinoxaline Derivatives as Anticancer Agents Targeting VEGFR-2

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ABSTRACT

The vascular endothelial growth factor receptor-2 (VEGFR-2) has a crucial role in the angiogenesis of cancer. The growth of tumors was effectively prevented by inhibiting the VEGFR-2 regulatory pathway. Quinoxaline nucleus has been identified as a promising candidate that can potentially serve as a primary model for the design and synthesis of anticancer drugs that target VEGFR-2. The binding affinity of four quinoxaline-based derivatives towards the active site of the VEGFR-2 [PDB ID: 2OH4, resolution: 2.05] receptor obtained was investigated using a molecular docking approach. Quinoxaline compounds **III** and **IV** displayed binding interaction against the key amino acids of the VEGFR-2 with affinity values of -15.63 and -17.11 Kcal/mol, respectively. In addition, compounds **I** and **II** revealed affinity values of -12.13 and -11.93 kcal/mol, respectively. The present study revealed that the examined compounds **I, II, III,** and **IV** have good binding energy and interaction modes against the VEGFR-2 active site.

Key Words:
Anticancer, molecular docking, quinoxaline, VEGFR-2 inhibitors.

1. INTRODUCTION

Cancer has been identified as one of the most fatal diseases, ranking second in the category of disorders that pose serious risks to life [1]. According to the non-selectivity of drug resistance, the present chemotherapy for cancer contains several side effects. However there is an urgent requirement to develop new therapies that can inhibit the growth of cancer cells while having no or little adverse impact on normal cells [2]. An important component of biological processes is angiogenesis. Tumor development and metastasis depend on the vital mechanism of angiogenesis [3]. Abnormal angiogenesis causes harmful diseases including the occurrence of cancer [4,5].

Protein tyrosine kinases (PTKs) are a group of cell surface receptors that transmit signals to growth factors and hormones. PTKs have an essential function in the proliferation and growth of tumors[6–8]. PTKs are considered a good target for cancer treatments based on their role as essential components in a wide range of malignant disorders [9]. Angiogenesis is significantly regulated by protein kinases [10]. The important angiogenic factor known as vascular endothelial growth factor receptor 2 (VEGFR-2) which controls angiogenesis and contributes to the proliferation of tumors [11]. VEGFR-2 inhibitors attach to the ATP-binding site of VEGFR-2 to prevent angiogenesis and lymphangiogenesis. Some examples of VEGFR-2 inhibitors including sorafenib, vorolanib, acrizanib, telatinib, nintedanib, and sunitinib have been approved by the FDA (Figure 1) [12–17].

Quinoxalines is a synthetic nitrogen-heterocyclic component with linked pyrazine and benzene rings in the structure**.** The quinoxaline scaffold provides an excellent baseline for the identification of effective chemotherapy drugs. Quinoxaline derivatives exhibited strong anticancer activities according to evidence showing broad-spectrum efficiency against cancer treatment. Consequently, quinoxalines are highly selective ATP-competitive inhibitors for several kinases such as VEGFR, PDGFR, c-Met kinase, CDK1,2,4,6 and they have been identified as an important component for cancer therapies [18,19]. Several quinoxaline members have been reported as promising VEGFR-2 inhibitors [20–22]. The purpose of this study was to evaluate the inhibitory effect of quinoxaline compounds (**I, II, III,** and **IV**) towards theVEGFR-2 receptor.

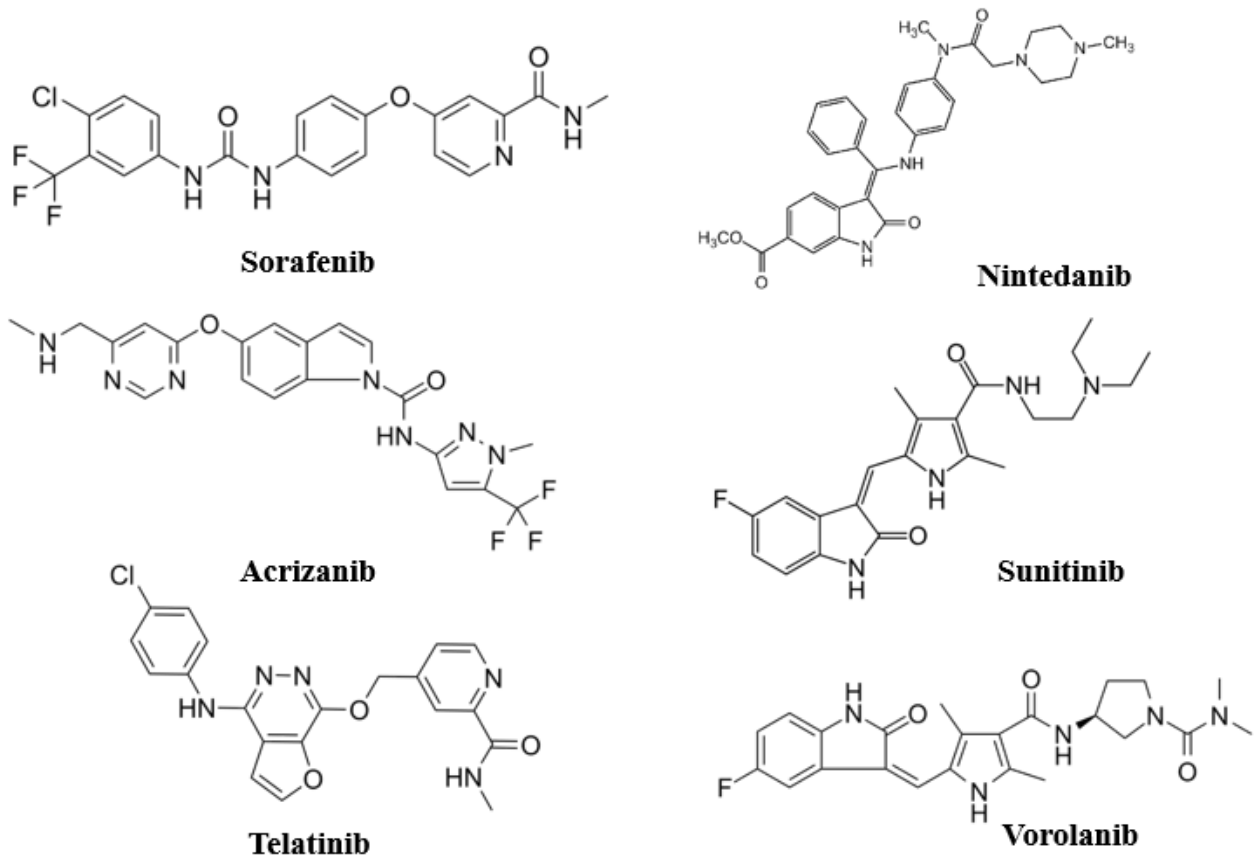

Figure 1. Some examples of FDA approved VEGFR-2 inhibitors drugs for cancer treatment.

2. MATERIALS AND METHODS

2.1 Chemistry

Quinoxaline compounds (**I, II, III**, and **IV**) was synthesized and characterized by El Rayes *et al.*, (2019) according to a previously published study [23].

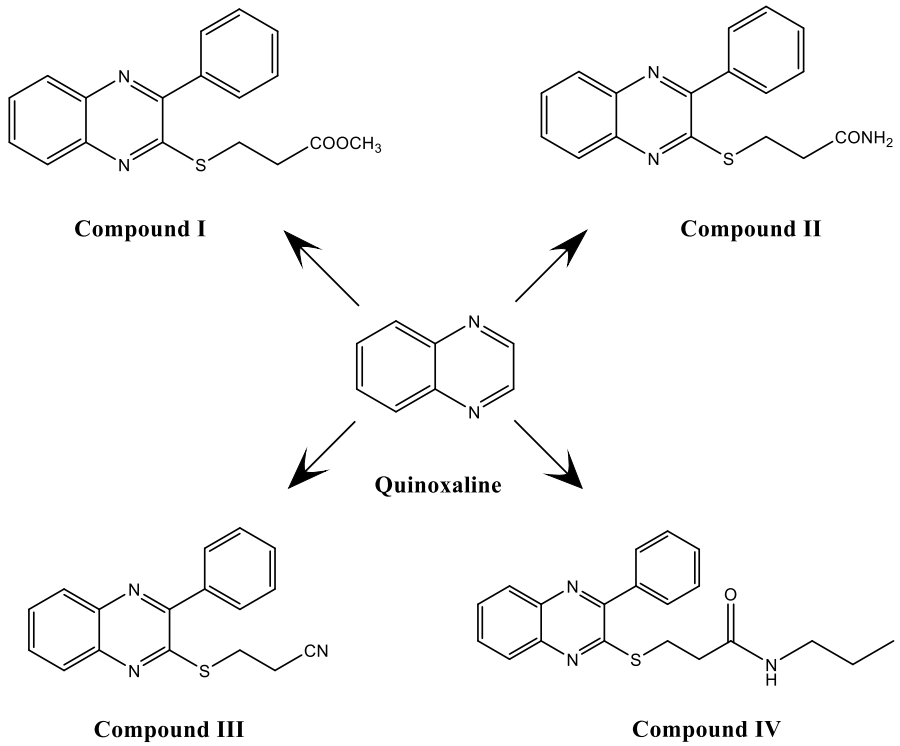

Figure 2. Quinoxaline derivatives: **I** [Methyl 3-((3-phenyl-1,2-dihydroquinoxalin-2-yl)-sulfanyl)]; **II** [3-((3-Phenylquinoxalin-2yl) sulfanyl) propenamide]; **III** [3-((3 Phenylquinoxalin-2-yl) sulfanyl) propanenitrile], and **IV** [*N*-Propyl-3-((3-phenylquinoxalin-2-yl) sulfanyl)- propenamide].

2.2Docking Studies

From the Protein Data Bank, the crystal structure of VEGFR-2 was obtained [PDB ID: 2OH4, resolution: 2.05]. AutoDock Vina software was used to conduct the docking study. Firstly, water molecules were eliminated from the crystal structure of VEGFR-2. A selected chain was protonated and put through an energy-minimization step. After that, the target protein's active site was identified. Using ChemBioDraw Ultra 14.0, each of the examined compound's structures was provided. Then, the protonated 3D structures were subjected to energy-minimization processes. Docking the co-crystallized ligand to the isolated pocket of the active site was previously used to validate the docking approach. The tested compounds were finally docked using the dock tool, and then the results of the docking procedure were displayed.

3. RESULTS

3.1 Docking Studies

Four examined compounds (**I, II, III,** and **IV**) were docked inside the binding site of VEGFR-2 (PDB ID: 2OH4) and showed good affinity and interactions with the key amino acids. The binding affinity and interaction bonds between the docked derivatives and the binding site of the target receptor VEGFR-2 were shown in (**Table 1 and Figure 3**). Results indicated that compounds (**III** and **IV)** showed the highest binding interaction against the key amino acids of 2OH4 with affinity values of -15.63 and -17.11

Kcal/Mol, respectively, compared with sorafenib as a VEGFR-2 inhibitor. Additionally, compounds (**I** and **II)** revealed affinity values of -12.13 and -11.93 kcal/mol, respectively. Furthermore, Compounds (**II** and **IV**) formed two hydrogen bonds with crucial amino acids Asp1044 and Glu883. Also, compounds **I** and **III** formed a hydrogen bond with Asp1044.

Table 1. Docking results of sorafenib and four compounds (**I, II, III**, and **IV)** against VEGFR-2 (PDB ID: 2OH4).

No.	Binding Scores (Kcal/Mol)	Type on interaction	Bond length (A°)	Amino Acid
I	-12.13	H-acceptor	2.05	ASP 1044
II	-11.93	H-acceptor	1.87	ASP 1044
		H-donor	1.97	GLU 883
III	-15.63	H-acceptor	2.13	ASP 1044
IV	-17.11	H-acceptor	1.99	ASP 1044
		H-donor	1.75	GLU 883
Sorafenib	-21.57	H-acceptor	1.59	ASP 1044
		H-donor	1.83	GLU 883
		H-donor	1.99	GLU 883

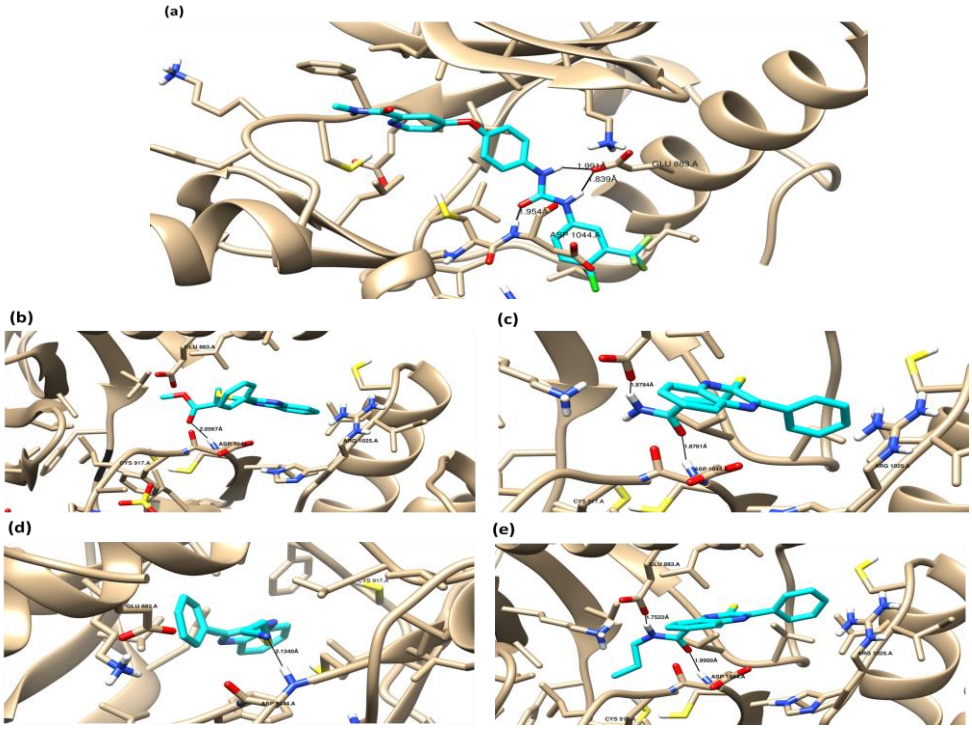

Figure 3. Three-dimensional (3D) binding mode of the most active poses of four compounds (cyan) at the VEGFR-2 active site: (a) sorafenib as a reference ligand (b) compound **I**; (c) compound **II**; (d) compound **III** and (e) compound **IV.**

4. DISCUSSION

A number of novel quinoxaline compounds were produced and identified by El Rayes *et al.* (2019) as having strong anti-tumor properties against HCT-116 and MCF-7 cancer cells [23]. Furthermore, more evaluations were needed to evaluate and explain the mechanism of cancer cell death by these derivatives. The nucleus of quinoxaline exhibits promising anti-tumor properties [24–27]. Similar inhibitory properties of quinoxaline derivatives against the VEGFR-2 receptors [28–30]. The present investigation revealed the good binding affinity of the four tested compounds (**I, II, III,** and **IV**) towards the VEGFR-2 active site using a molecular docking approach. Compounds (**II** and **IV**) showed interaction at the VEGFR-2 binding site and formed two hydrogen bonds with the crucial amino acids ASP 1044 and GLU 883. Also, compounds (**I** and **III**) produced one hydrogen bond with amino acid ASP 1044. The structure of the terminal hydrophobic tail has a significant impact on the activity of the compounds under study. The carbonyl moiety in each compound (**I, II**, and **IV**) interacts with ASP 1044 as an H-bond acceptor. While GLU 883 served as the H-bond donor to form an H-bond with the nitrogen atom in compounds (**II** and **IV**). In order to interact with the ATP active site of VEGFR-2 efficiently, the chemical structure of VEGFR-2 inhibitors must contain four pharmacophoric properties (**Figure 4**). In the hinge region of the ATP binding site, a heterocyclic moiety is required for the formation of a hydrogen bond. The distance between the DFG domain and the hinge space can be occupied by a spacer group. H-bond acceptor and donor groups have been found at the pharmacophore moiety. The hydrophobic moiety, has the potential to interact hydrophobically with the ATP binding site's allosteric hydrophobic pocket [31–33].

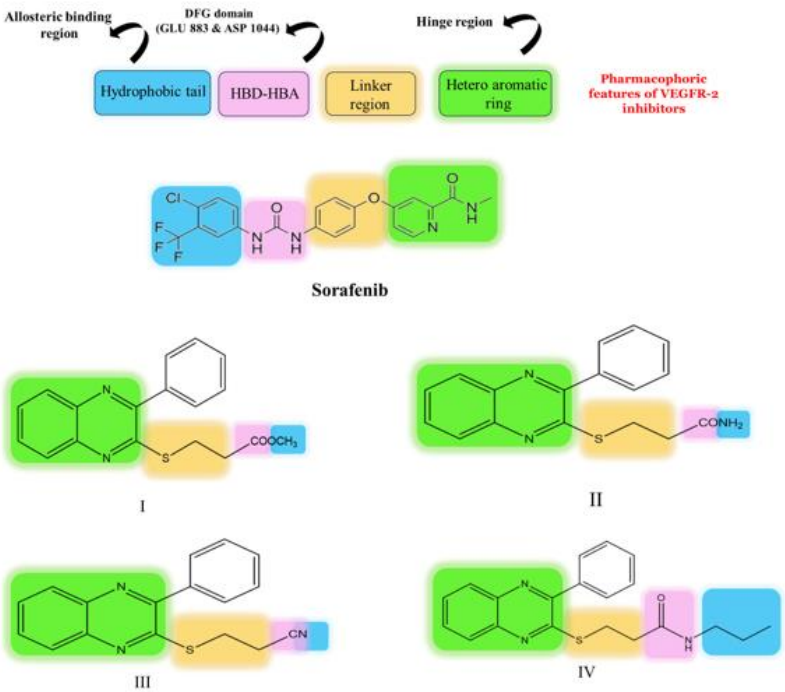

Figure 4. Pharmacophoric properties of VEGFR-2 inhibitors and schematic summary for the rationale of four compounds.

5. CONCLUSION

The present *in silico* study shed the light to the potentiality of some quinoxaline-based derivatives as antiproliferative agents of cancer cells through inhibition of the VEGFR-2 receptor. Therefore, these results provide a starting point for the research on using quinoxaline compounds as a promising anti-tumor agent targeting the VEGFR-2. *In vitro* and *in vivo* studies will advise further investigation of the inhibitory activity of compounds against the VEGFR-2 receptor.

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