In silico Study of New Vascular Endothelial Growth Factor Receptor Inhibitors for The Treatment of Hepatocellular Carcinoma

Marwan Imad Jihad*, Monther Faisal Mahdi*

****Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mustansiriyah, Baghdad, Iraq..***

Article Info:

Received Dec 2022
Accepted Feb 2023
Corresponding Author email:
Email: marwanimadjihad@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0000-0002-2069-4121

DOI: https://doi.org/10.32947/ajps.v23i2.1023

Abstract:

Novel therapeutics are desperately needed for the difficult-to-treat and very lethal malignancy known as hepatocellular carcinoma (HCC). The first drug now authorized for the treatment of individuals with advanced HCC is sorafenib. To find novel Vascular Endothelial Growth Factor Receptor Inhibitors as prospective candidate therapeutics for HCC, an in-silico technique was used in this case. Docking investigations were conducted using the GOLD Suite (v. 5.7.1) from the Cambridge Crystallographic Data Centre (CCDC). The docking/scoring methods of CCDC were validated by reproducing the docking interactions and poses of Sorafenib. Based on their PLP fitness, compounds I–X and sorafenib were graded for their ability to inhibit VEGF. Compounds II, III and VIII among other ligands exhibit higher binding energies than the standard drug sorafenib that give PLP fitness value (80.4).

Key words: Hepatocellular carcinoma, Sorafenib, Vascular Endothelial Growth Factor, Cambridge Crystallographic Data Centre.

دراسة باستخدام الحاسوب لمثبطات جديدة لمستقبلات عامل النمو البطاني الوعائي لعلاج سرطان الخلايا الكبدية

مروان عماد جهاد*، منذر فيصل مهدي*

**** قسم الكيمياء الصيدلانية ، كلية الصيدلة ، الجامعة المستنصرية ، بغداد ، العراق.***

الخلاصة:

هناك حاجة ماسة لعلاجات الجديدة للأورام الخبيثة التي يصعب علاجها والقاتلة للغاية والمعروفة باسم سرطان الخلايا الكبدية. الدواء الأول المرخص به الآن لعلاج الأفراد المصابين بسرطان الكبد هو سورافينيب. للعثور على مثبطات جديدة لمستقبلات عامل النمو البطاني الوعائي كعلاجات محتملة لسرطان الخلايا الكبدية ، تم استخدام تقنية السيليكو في هذه الحالة. تم إجراء تحقيقات الإرساء باستخدام (الإصدار ٥,٧,١) من مركز بيانات التصوير البلوري في كامبريدج. تم التحقق من صحة طرق الالتحام من خلال إعادة إنتاج تفاعلات الالتحام للسورافينيب. بناء" على نتائج الارساء الجزيئي للمركبات المرشحة تم تصنيفها والسورافينيب اعتمادا على قدرتهم على تثبيط مستقبلات عامل النمو البطاني الوعائي. تُظهربعض المركبات طاقات ربط أعلى من عقارالسورافينيب الذي يعطي نتيجة ربط قيمتها ٨٠,٤

الكلمات المفتاحية: سرطان الخلايا الكبدية، سورافينيب، عامل النمو البطاني الوعائي، مركز بيانات التصوير البلوري في كامبريدج

Introduction

Over 700,000 people lose their lives every year to liver cancer, making it one of the top cancer killers globally. The most common form of liver cancer is hepatocellular carcinoma (HCC). HCC is still one of the deadliest forms of cancer, despite recent advances in therapy(1). Notably, the occurrence of HCC has been on the rise in recent decades, which places it among the ranks of the causes of mortality that are expanding at the quickest rate globally. This dismal outlook highlights the need for innovative treatments that are successful (2).

In addition to being one of the most common malignancies, liver cancer, also known as hepatocellular carcinoma (HCC), is one of the most aggressive forms of cancer that may develop in the digestive system. The incidence of HCC places it among the top 10 human malignancies diagnosed worldwide and among the top 5 cancers in terms of mortality attributable to the disease. The majority of instances of liver cancer are presented as HCC, although secondary liver cancers develop from metastases that originate from tumors located in other parts of the body, most frequently in the gastrointestinal system (3, 4).

The theoretical method known as molecular docking is designed to properly anticipate the interaction between macromolecules (target protein) and a relatively small ligand (5). In this regard, we used docking analysis to predict the docking models of the tested compounds in the binding pocket of the vascular endothelial growth factor (VEGF) protein (PDB code: 4ASD) complexes with sorafenib. This was accomplished by placing the tested compounds in the binding pocket and running the analysis. VEGF protein, is an essential target for the development of anticancer drugs in order to get insight into the mechanism of action of the compounds that have been examined (6). The Ras-Raf-ERK signal transduction pathway was induced as a result of the activation of VEGF, which led to its activation. This pathway leads to the growth of cells, which in turn leads to metastasis (7).

Methodology

Utilizing the CCDC GOLD Suite (v.5.7.1), the compounds' molecular docking investigation was completed. The protein, ligands, hydrogen bonding connections, quick contacts, and bond length measurement were all rendered visible using the CCDC Hermes visualizer tool (v. 1.10.1). The chemical structures of our ligands were drawn using ChemBioOffice (v. 17.1).

First, we used Chemdraw professional (v.16.0) to sketch out the chemical structure of our ligands. Then, we used Chem3D (version 16.0.0) with the MM2 force field to calculate the lowest possible energy states for our molecules. The crystal structure of the VEGF protein in association with sorafenib (PDB code: 4ASD) was used to dock the newly developed ligands. However, the protein data bank receptors were placed into GOLD's Hermes module. To verify the docking procedure, the co-crystallized ligands were redocked(8). In addition, polar hydrogen atoms were included for the purpose of achieving precise tautomeric states and ionization of amino acid (AA) residues (9). The VEGF kinase receptor protein structure is then prepared by eliminating the crystallographic water molecules (10, 11). Additionally, the reference ligand extraction was carried out from the receptor's active site.

Hermes visualizer software from the CCDC GOLD suite is used to set up the receptors for the docking procedure. The reference ligand interaction site is used to determine the active site. For the docking procedure, the protein binding site with all of the protein residues identified inside the (10 A°) of the reference ligand (12).

Default values were selected for all parameters utilized during the docking process. The top-ranked solution was kept as the default, and the option for early termination was deactivated. The number of produced poses was set to 10 and the number of generated poses was fixed. We employed the configuration model of chemscore kinase. CHEMPLP, a scoring function, is employed while using the piecewise linear potential. Based on docking performance, GOLD determines an individual's fitness score. The higher the fitness, the stronger the docking contact between a protein and a Ligand (13). Finally, the data were saved as mol.2 files, which detail the best binding strategy, binding free energy, and docked postures. These findings were carefully studied to determine the optimal binding and interaction of our proposed ligand with the receptor's amino acid residues (VEGF).

Results

The findings of the docking to determine the selectivity and binding energies of the ligands for the protein (VEGF) were achieved by examining the contact interactions between the protein's active binding sites and tested compounds. The VEGF inhibitory activity of compounds I-X and sorafenib, were ranked based on their PLP fitness. Docking analysis indicted that Glu885, Ile888, Val916, Cys919, Val848, Ala866, Val899, Lys920, Asp1046, Leu840, Leu889, Leu1019 and Phe918 amino acid residues of VEGF active site interact through hydrogen bonding and short contacts with our final ligands. The docking result of the inhibitors against the VEGF receptor is shown below in Table 1. The interactions of compounds I-X and sorafenib with the amino acids of VEFG receptor are shown in Figure 1.

Table (1): The binding energies for compounds I-X and standard sorafenib docked with VEGF.

Compounds	VEGF Binding Energy (PLP Fitness)	Amino Acids Included in H-bonding and short contact Interactions
Sorafenib	80.4	Glu885 Cys919 Asp1046
I	79.1	Glu885 Val848 Ala866
II	85.8	Ala866 Glu885 Cys919
III	91.5	Ala866 Val899 Lys920 Asp1046
IV	78.2	Glu885 Ile888 Val916
V	70.9	Glu885 Cys919
VI	72.6	Leu840 Val899
VII	77.4	Leu840 Val848 Ala866 Val899
VIII	83.6	Leu889 Cys919 Leu1019 Asp1046
IX	78.1	Val899 Val916 Cys919
X	76.5	Val899 Val916 Phe918

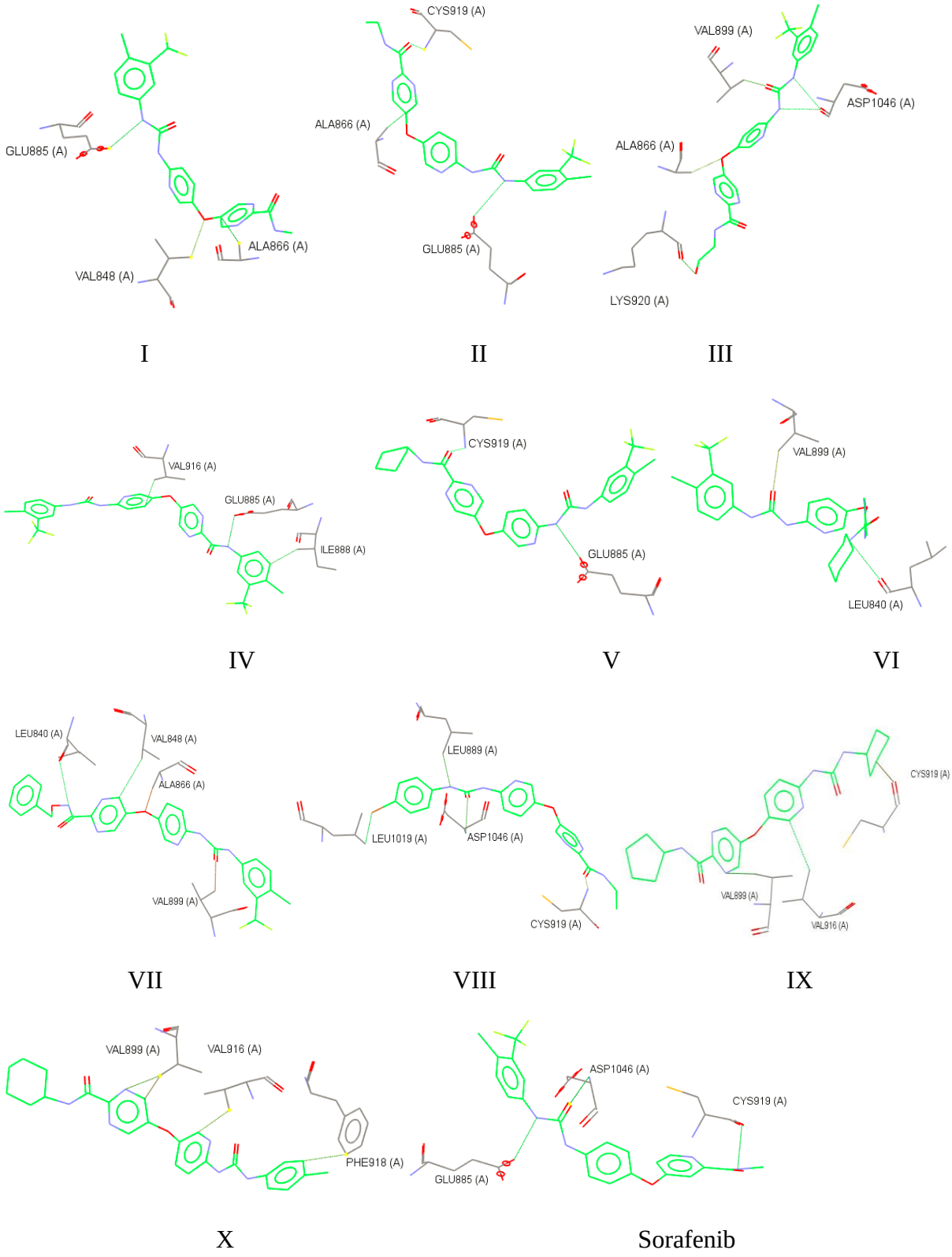

Figure (1): Interaction of compounds I-X and sorafenib with the amino acids of VEFG receptor active site.

Discussion

With a PLP fitness of 91.5 and strong H-bonding with amino acids, compound (III) tops the charts as illustrated in Table (1). Among the ligands, compounds II, III, and VIII have greater binding energies than the gold standard medication sorafenib, which contributes to PLP's fitness value (80.4). As illustrated in Figure (1) compound (III) forms three H-bond, two of them through N-H of the urea group with Asp1046 and one H-bond with Lys920 through O-H of the alcohol group accompanied by brief interactions that strengthen the bond and provide PLP value (91.5). Compound (II) forms two H-bond through N-H of the urea group with Glu885 and one H-bond with Cys919 through carbonyl of the amide group along with other brief interactions as illustrated in Figure (1) and gives PLP value (85.8). While compound (VIII) that gives PLP fitness value (83.6) forms two H-bond through carbonyl of urea group with Asp1046 and one H-bond with Cys919 through carbonyl of amide group along with short contact as shown in Figure (1).

Conclusion

In comparison to the reference ligand sorafenib, all of the proposed compounds produce good docking data. Compounds II, III and VIII gives the highest PLP fitness value even higher than sorafenib, this indicating a small substitution on the NH of amide group is important for activity, in addition presence of urea moiety is also essential.

References

1- Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet. 2018;391(10125):1023-75.

2- Rybakova Y, Gonzalez JT, Bogorad R, Chauhan VP, Dong YL, Whittaker CA, et al. Identification of a long non-coding RNA regulator of liver carcinoma cell survival. Cell death & disease. 2021;12(2):1-14.

3- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011;61(2):69-90.

4- Tabor E. Hepatocellular carcinoma: global epidemiology. Digestive and Liver Disease. 2001;33(2):115-7.

5- Shah UA, Joshi HV, Patel JK, Savjani J, Patel VK, Choudhary K, et al. Molecular docking studies of novel dihydro Pyrimidine derivatives as potential antibacterial agents.

6- Abbas WAK, Alzubaidi SHA, Aljaleeli AND, Al-Mugdadi SFH. Vascular Endothelial Growth Factor (VEGF-C) Protein Expression Related with Lymphangiogensis in Iraqi Cervical Cancer Patients. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2019;19(4):28-40.

7- Talib WH, Al Kury LT. Parthenolide inhibits tumor-promoting effects of nicotine in lung cancer by inducing P53-dependent apoptosis and inhibiting VEGF expression. Biomedicine & Pharmacotherapy. 2018;107 :1488-95.

8- Hajalsiddig TT, Osman ABM, Saeed AE. 2D-QSAR modeling and molecular docking studies on 1 H-Pyrazole-1-carbothioamide derivatives as EGFR kinase inhibitors. ACS omega. 2020;5(30):18662-74.

9- Allawi MM, Mahdi MF, Raauf AM. Synthesis, anti-inflammatory, molecular docking and ADME studies of new derivatives of ketoprofen as cyclooxygenases inhibitor. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2019;19(4):125-39.

10- Khalifa NM, Al-Omar MA, Alkahtani HM, Bakheit AH. Kinase Inhibitors of Novel Pyridopyrimidinone Candidates : Synthesis and In Vitro Anticancer

Properties. Journal of Chemistry. 2019;2019.
11- Ibrahim MT, Uzairu A, Shallangwa GA, Uba S. In-silico activity prediction and docking studies of some 2, 9-disubstituted 8-phenylthio /phenylsulfinyl-9h-purine derivatives as Anti-proliferative agents. Heliyon. 2020;6(1):e03158.
12- Muhsin YF, Alwan SM, Khan AK. Design, Molecular Docking, Synthesis of Aromatic Amino Acids Linked to Cephalexin. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2021;21 (3):25-34.
13- Lee A, Hong S, Kim D. KRDS: a web server for evaluating drug resistance mutations in kinases by molecular docking. Journal of cheminformatics. 2018;10(1):1-10.