Turkish Computational and Theoretical Chemistry

Turkish Comp Theo Chem (TC&TC)

Volume(Issue): 8(4) – Year: 2024 – Pages: 48-61

e-ISSN: 2602-3237

https://doi.org/10.33435/tcandtc.1437517

Received: 16.02.2024 ***Accepted***: 13.05.2024 *Research Article*

The discovery of new potent VEGFR2 inhibitors for potential anti-angiogenesis agent through a combination of structure-based virtual screening, molecular dynamics simulation and ADME-Tox prediction

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Abstract: The discovery of the importance of angiogenesis in the mechanisms of tumor growth has empowered the improvement of new particles that are utilized in the therapy of various cancers. The goal of this research was to identify novel compounds functioning as potent VEGFR2 inhibitors in silico. It is an interesting therapeutic target for developing new anti-angiogenic drugs. In this work, molecular simulation studies of enzyme inhibition was carried out by structure-based virtual screening with FlexX program of VEGFR2. This approach makes it possible to model the interactions between a protein and thousands of small chemical compounds. A collection of 6,000 compounds originating from the ZINC chemical library, were tested against the active site of VEGFR2. The ADME-Tox characteristics and molecular dynamics simulation of the potential compounds were also examined. At the end of this screening, the compounds ZINC01534124 and ZINC00588595 appear as new inhibitors theoretically more active towards VEGFR2. Again, these inhibitors have shown significant binding energy by interacting with important residues in the active site. Furthermore, the in silico prediction of a similar drug positively informs us about the ADME-Tox properties of these new compounds. Finally, the stable binding of VEGFR2 with ZINC01534124 and ZINC00588595 is shown using 100 ns molecular dynamics simulation. These findings point to the chemicals ZINC01534124 and ZINC00588595 as potential candidates for VEGFR2 inhibitor research. They might also act as a starting point for further chemical modifications in order to produce therapeutically relevant anti-angiogenic medications.

Keywords: VEGFR2, Anti-angiogenesis, Virtual screening, Molecular dynamics simulation, ADME-Tox.

1. Introduction

Cancer continues to be one of the leading causes of mortality globally, despite the treatment advancements made in the field of oncology over the past few decades [1]. Undoubtedly, a focused approach to cancer causes us to wonder how healthy cells might be distinguished from malignant cells. Attention then turns to the ability of a tumor to induce its own vascularization through the process of angiogenesis. It is the process through which novel blood vessels are formed from preexisting ones and it is highly significant and necessary throughout various physiological processes, including embryonic development, placenta implantation, tissue regeneration…etc. Angiogenesis can however become pathological when the growth of new capillaries becomes uncontrolled [2,3]. It also occurs during certain pathologies, in particular during the growth of tumors and the development of metastases. Targeting the vascular system that provides blood to a tumor is a recent conceptual innovation in cancer treatment [4,5]. As a result, consequently, there has been a lot of interest in the creation of anti-

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angiogenesis strategies that might stop tumor vascularization.

In reality, growth factors that interact with specific overexpressed receptors on the endothelial cells of the vessels close to the tumor can control angiogenesis, allowing for the separation of the tumor's neo-vessels from the resting vascularization. Therefore, targeting entails utilizing this overexpression to position itself between the factor and its receptor in order to block the angiogenic signal. The vascular endothelial growth factor receptor 2, often known as VEGFR2, is a new anti-angiogenic targeted drug [6].

VEGFR2 is a key enzyme in angiogenesis and one of two tyrosine kinase receptors. VEGFR2 is considered to be the main mediator of several physiological and pathological effects of VEGF these include proliferation, survival, migration and permeability [7, 8]. Thus, preventing tumor-induced angiogenesis by inhibiting VEGFR2 activity seems promising [9, 6].

The US Food and Drug Administration has approved bevacizumab (Avastin®), sunitinib malate (Sutent®, SU11248), and sorafenib (Nexavar®, BAY 43-9006) for the treatment of patients with particular types of cancer. All these medications inhibit VEGF signaling by blocking VEGFR. However, the use of anti-VEGF medications has been restricted due to significant adverse effects like hypertension, hemorrhage, and gastrointestinal perforation [10, 11]. Therefore, a more targeted and non-toxic chemical is urgently needed for the treatment of cancer.

Advances in computational procedures and computing power over the past two decades have made virtual screening a very important tool for identifying chemical starting points, inhibitors, and probes in various drug discovery activities [3].

To help drug development through virtual screening, many chemical compounds are currently accessible in numerous databases, such as the ZINC chemical library [12]. The term "virtual screening" summarizes a suite of computational techniques designed to analyze large compound databases to identify drug candidates, which is seen as a complementary step to experimental methods [13, 14].

Current research includes investigating the mode of inhibition of enzymes involved in angiogenesis; in particular, the combined analysis of structure-based virtual screening and molecular dynamics simulation to find new molecules with therapeutic potential against VEGFR2. As a crucial method of cancer therapy, anti-angiogenesis targeting VEGFR2 has been recommended.

2. Computational Method

2.1. Tools for virtual screening

In recent years, virtual screening has grown to be an essential step in the drug development process. It may be conceptualized as a funnel into which a large number of compounds, constituting the chemical library to be screened, are poured in order to acquire, via the use of a screening algorithm, a smaller number of chemicals, which will then be tested experimentally [15].

Three phases are involved in virtual screening, according to Kar and Roy [16]:

-Chemical library preparation;

-In silico screening, which varies depending on the size of the chemical library and the understanding of the 3D structure of a target protein;

-Results analysis, which leads to the identification of keys for experimental tests.

In this study, the interaction energy of 6.000 compounds obtained from the ZINC chemical library was calculated relative with respect to the active site of VEGFR2 using virtual screening based on the structure of the enzyme target. Following the screening, the inhibitors that are still functional are submitted to a visual examination to show the numerous bonds that they suggested with the enzyme's active site. Additionally, an in silico study was conducted to examine the ADME-Tox and drug-likeness properties of the promising molecules. Finally, a molecular dynamics simulation of 100ns was performed for the potential compounds to evaluate their stability as potential anti-angiogenesis agents.

2.2. FlexX software (2.3.3, 2017)

The computer tool for predicting protein-ligand interactions was called FlexX [17]. This program makes predictions about the shape of the complex and an estimation of the binding strength for a specific enzyme and ligand. During molecular docking, FlexX takes into account three important parameters: the conformational flexibility of the ligand, the level or type of interaction between the protein and its ligand and finally, the classification

of the docking solutions (score function) by evaluating their interaction energy [18, 19]. This software looks for the most stable protein-ligand complex conformations using an incremental strategy (fragmentation/reconstruction) [20]. Ligands are divided into parts, and an initial fragment is positioned in various locations throughout the pocket before being scored using an easy but incredibly quick prescription method. The ligand is further constructed, fragment by fragment, from the n solutions inserted, and the intermediate solutions are compared to one another. The user receives the applications that scored the highest and survived the procedure [21].

Docking results performed by FlexX are generated in a text file. When an enzyme's interaction energy is reported in kj/mol, this file lists the top 1 to top 200 ligand positions in the enzyme's active site. Each pose has seven scores:X

Total-score = Match-score + Lipo-score + Ambig-score + Clash-score + Rot-Score + ΔG0

-Match-score = energy of level 3 and level 2 interactions between the different groups of atoms.

-Lipo-score = lipophilic contact energy.

-Ambig-score = energy of lipo-hydrophilic contacts.

-Clash-score = energy of steric obstruction.

-Rot-score = immobilization energy of the rotatable bonds of the ligand.

2.3. The VEGFR2 enzyme target

Knowledge of the 3D structure of proteins is a key element for a detailed understanding of their mechanism of action in a biological context. Thirty-two 3D structures of VEGFR2 are available on the PDB, identified by different codes. The 3VHE [22] complex was chosen for this study because it represents a compromise between good resolution (1.55 Å) and the presence of an inhibitor inside the active site (Figure 1).

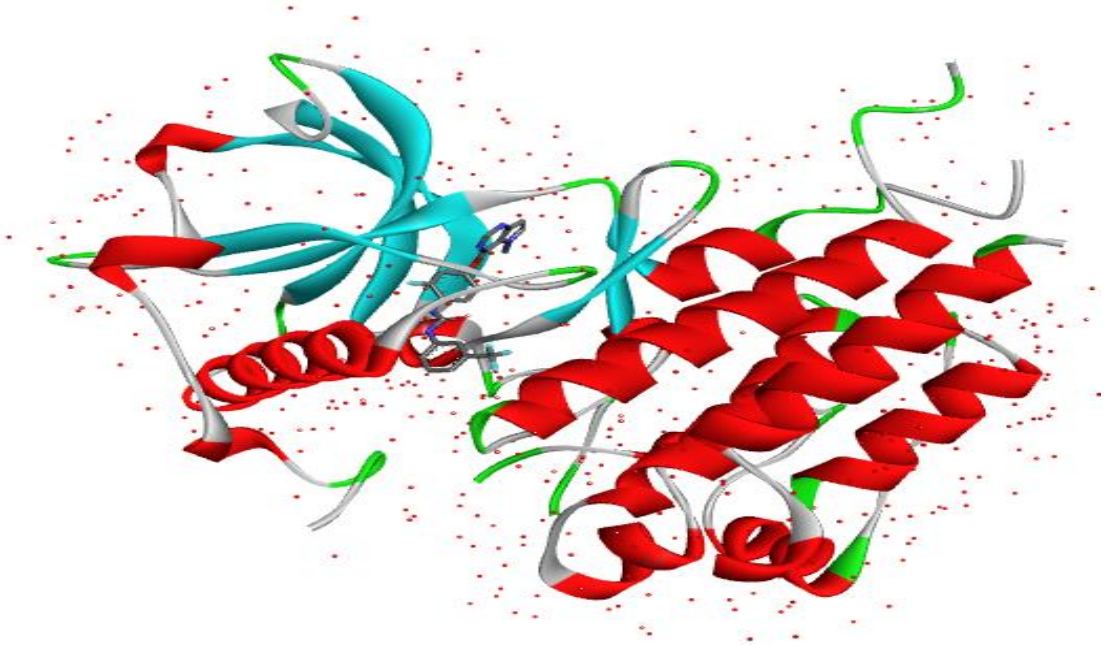


Figure 1. The VEGFR2 enzyme with ligand 42Q on the crystalized structure (PDB-ID: 3VHE), has been visualized by Discovery Studio Visualizer

2.4. The active site amino acids of the VEGFR2 enzyme (PDB-ID: 3VHE)

The active site is the region of the enzyme that allows substrate recognition and binding. This is essential for the catalytic activity of the enzyme. For this reason, the determination of the active site amino acids of our enzymatic target is crucial to being able to carry out a virtual screening. The following are the active site amino acids, according to FlexX software:

Leu840, Gly841, Val848, Val865, Ala866, Val876, Lys868, Glu885, Ile888, Leu889, Ile892, Val898, Val899, Val914, Ile915, Val916, Glu917, Phe918, Cys919, Lys920, Phe921, Gly922, Asn923, Met1016, Leu1019, Cyc1024, Ile1025, His1026,

Asn1033, Leu1035, Leu1036, Ile1044, Cys1045, Asp1046, Phe1047, Gly1048, Ala1050.

2.5. The ligand collection

The ZINC chemical compounds data base is a free chemical library containing over 35 million molecules commercially available for virtual screening [12]. Furthermore, ZINC classifies compounds into many categories: Standard, Clean, in stock and Boutique [23]. As we are looking for an active compound against VEGFR that can be directly purchasable, we have selected the "lead like in stock" subset of the ZINC chemical library which contains approximately 3.7 million structures. In order, identify only molecules of interest, it is common to filter the chemical library by a certain number of descriptors. In our instance, we managed these structures using the Screening Assistant program (http://screenassistant.sourceforge.net/).

2.5.1. Application of physico-chemical filters

Filters are intended to eliminate chemically reactive, toxic molecules with properties unsuitable for administration to humans or animals. In addition, molecular properties such as molecular mass, logP, the proportion of hydrogen bond donor and acceptor atoms and the number of bonds subject to rotation are the main selection criteria. Therefore, the purpose of these filters is to remove substances whose characteristics are too far from those of a drug.

2.5.2. Application of diversity filtering

The selection of compounds is based on the principle of similarity, according to which similar molecules must share comparable biological characteristics [24]. As a result, testing a single molecule from a similar group gives a reasonable estimate of the activity potential of other members of the same group. Thus, we will favor the screening of compounds with sufficiently different structures. This is with the aim of isolating several families of interest.

Applying these filters reduces our selection to approximately one million molecules. In total, 915 167 molecules were selected by Screening Assistant. However, the computer resources at our disposal limit our ability to test all these compounds; a diversity algorithm was applied to this set to ultimately select only 6 000 molecules to be screened by FlexX.

2.6. Molecular dynamics simulation

Molecular dynamics is a computer method that simulates the physical movements of atoms and molecules as they interact over time [25]. In this study, the molecular dynamics simulation of 100 ns was applied to both proposed inhibitors (ZINC00588595 and ZINC01534124) and the reference ligand (42Q) against VEGFR2 using GROMACS-2023.1 [26]. CHARMM36 force field [27] was used to prepare the protein topology, and the General force field (CGenFF) server was used to prepare the ligand topology. The type of box used in the solvation process was a dodecahedral unit cell shape and periodic boundary conditions with 10 Å were used to avoid the interaction of atoms when moving off the box edge. Ions were added using the steepest descent minimization algorithm, and sodium and chloride ions were used for protein neutralization. Energy minimization was applied to the complex to avoid steric clashes using the steepest descent minimization algorithm, force cutoff was set to 10.0 kJ/mol, and the maximum number of steps was 50000 steps. Next, two equilibration processes were applied; NVT and NPT equilibration using a modified Berendsen thermostat and leap-frog integrator for 50000 steps which are equivalent to 10 ps. Finally, MD simulation run for 100 ns with 2 fs at each step. The results obtained during a 100 ns MD simulation trajectory are interpreted by studying a number of factors including the root-mean-square deviation (RMSD), root-mean-square-fluctuations (RMSF), radius of gyration (Rg), solvent accessible surface area (SASA) and number of hydrogen bonds.

3. Results and discussion

3.1. Protocol for virtual screening

It is crucial to first investigate the processes underlying the interactions between the best inhibitor produced from the PDB and our enzymatic target in order to develop new, powerful inhibitors against VEGFR2.

The modeling of the 3VHE-42Q interaction simulated by molecular docking using FlexX allowed us to obtain a more stable complex with interaction energy equal to -40.725 Kj/mole. The RMSD between the crystallized and the redocked ligand 42Q was < 2 Å (0.52 Å) (Figure 2).The work of Oguro et *al* [22] shows that the incorporation of a diphenylurea moiety at the C4-position of the

pyrrolo[3,2-d]pyrimidine core via an oxygen linker resulted in compounds that were potent inhibitors of VEGFR2 kinase.

As a result, the 42Q inhibitor (1-{2-fluoro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)oxy]phenyl}-3-[3-(trifluoromethyl)phenyl]urea), is chosen as a reference model in order to identify from the ZINC chemical library new inhibitors of the enzymatic target VEGFR2.

In order to conduct our computations, we performed a virtual screening based on the structure of the VEGFR2 enzyme by the FlexX program of a collection of 6.000 compounds belonging to the "Lead Like in stock" category of the ZINC chemical library. With regard to the VEGFR2 enzyme, we compared the docking scores of these inhibitors (ΔG) with those of the reference inhibitor (42Q). Finally, after a docking-scoring protocol, we retained two molecules with high inhibitory potential.

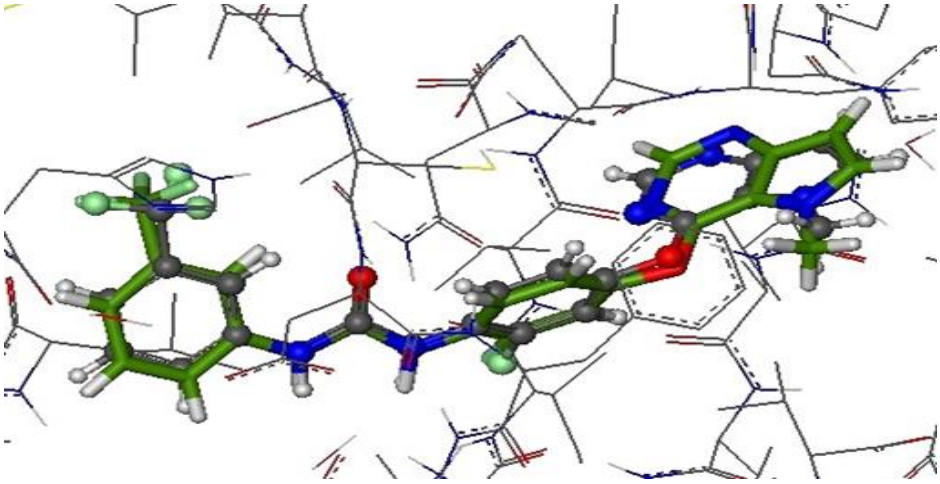


Figure 2. Superposition of the crystal conformation of the ligand extracted from 3VHE (colored in green) against the best predicted pose (RMSD = 0.52 Å)

Table 1. Chemical and structural data of compounds selected as candidates.

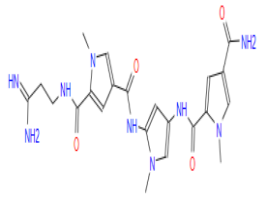
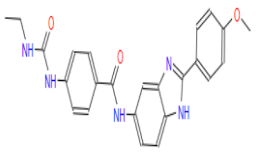
Inhibitor code	**Structure**	**Chemical name**	**Score Kj/mol**
ZINC 01534124		[1-amino-3-[[4-[[4-[(4-carbamoyl-1-methyl-pyrrole-2-carbonyl)amino]-1-methyl-pyrrol-2-yl]carbamoyl]	-48.647
ZINC 00588595		4-(ethylcarbamoylamino)-N-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]benzamide	-45.425

Table 2. The various interactions that the substance ZINC01534124 forms.

Ligand atoms	H-bonds interaction residue	**Distance (Å)**	Hydrophobic interaction residue
N_{19}-H_{38}	O_{E2}-Glu885	1.66	Gleu885, Asp1046, Cys1045, Lys868, Leu889, Val848, Ile888, Val899, Phe1047, Leu840,
O21	H-N-Asp1046	1.80	
N_{27}-H_{40}	O-Asp1046	1.62	
N_{32}-H_{44}	O-His1026	2.12	

N_{31}-H_{36}	O-Ile1025	2.00	Leu1035, Val916, Gly922 and Ala866
N_{32}-H_{43}	O-Asp1046	2.06	
N_{12}-H_{41}	O-2027	1.53	

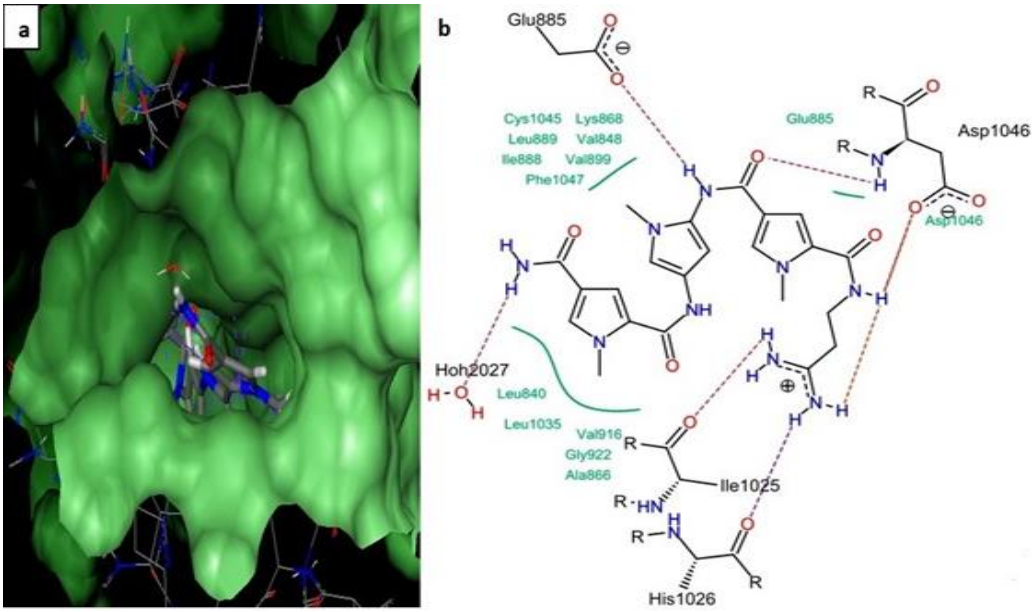


Figure 3. Docking of the inhibitor ZINC01534124 in the active site of VEGFR2. (a). Binding mode of compound ZINC01534124 with the active site of 3VHE. (b). Illustration of the links that the inhibitor ZINC01534124 made.

Table 3. The many interactions that the substance ZINC00588595 forms			
Ligand atoms	**H-bonds interaction residue**	**Distance (Å)**	**Hydrophobic interaction residue**
N_6-H_{34}	O-Cys919	1.68	Cys919, Phe918, Gly922, Leu1035, Phe1047, Leu840, Val916, Val848, Lys868, Ala 866, Leu889, Val899, Cys1045, As1046, Glu885, and Ile888
N_3-H_{36}	O-Lys920	1.84	
N_{38}	H-N-Asp1046	3.30	
O_5	H-H_2O2027	2.29	

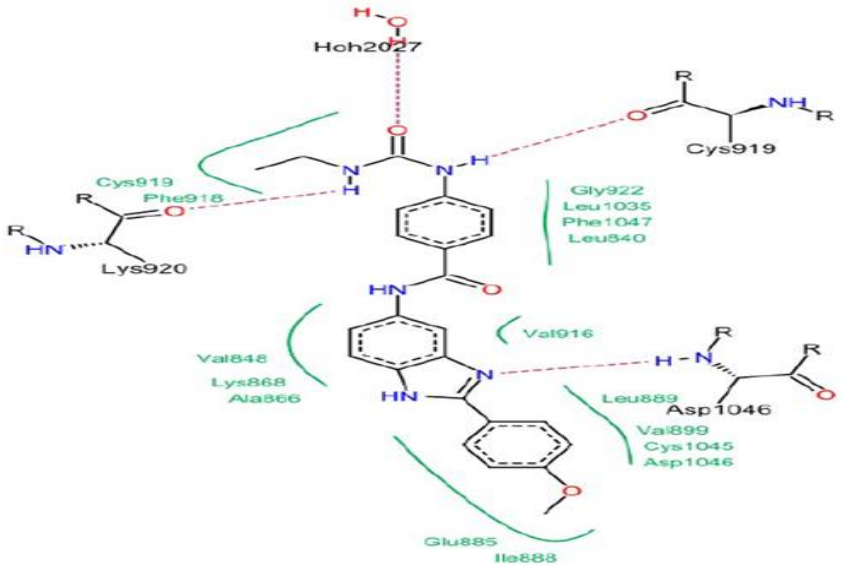


Figure 4. Representation of the binding mode predicted by FlexX between VEGFR2 and ZINC00588595

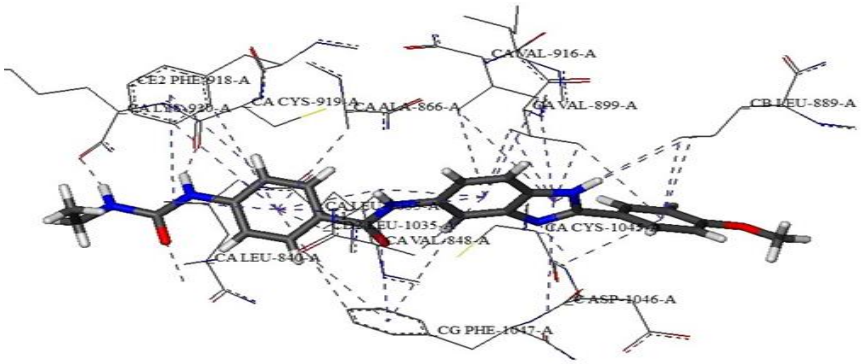


Figure 5. Representation of the hydrophobic interactions formed between the compound ZINC00588595 and the active site of 3VHE

Table 4. Lipinski's rule criteria for the two inhibitors studied.						
Criteria	**Molecular weight (g/mol)**	**Log P**	**Number H-bond donors**	**Number H-bond acceptors**	**Number rotatable bonds**	**Synthetic accessibility**
ZINC 01534124	481.5	–0.52	6	5	9	3.85
ZINC 00588595	429.5	3.21	4	4	6	2.84

Table 5. ADMET properties of the top-two ligand		
Criteria	**ZINC01534124**	**ZINC00588595**
GI absorption	Low	High
BBB permeant	No	No
CYP1A2 inhibitor	No	Yes
CYP2C19 inhibitor	No	Yes
CYP2C9 inhibitor	No	Yes
CYP2D6 inhibitor	No	Yes
CYP3A4 inhibitor	No	Yes
Carcino_Rat	positive	negative
Carcino_Mouse	positive	negative
Ames_test	non-mutagen	non-mutagen
hERG_inhibition	medium_risk	medium_risk

3.2. Candidates' molecules chosen

Following a screening procedure, the substances listed in Table 1 were identified as new potent inhibitors of our enzyme target, VEGFR2.

3.3. Prediction 0of the best compounds' interaction mode

In this part, different bonds are involved between the active site of VEGFR2 and the two inhibitors described above. This research should help to improve knowledge of the structural behavior of the target of interest and potential interactions with its inhibitors.

3.4. VEGFR2-ZINC01534124 interaction

The [1-amino-3-[[4-[[4-[(4-carbamoyl-1-methyl-pyrrole-2-carbonyl)amino]-1-methyl-pyrrol-2-yl]carbamoyl] inhibitor which the ID code is ZINC01534124, gives the best interaction energy (-48.647 Kj/mole). The visual analysis of the interactions between this inhibitor and our enzyme was shown in Figure 3. The existence of various bonds between this inhibitor and the VEGFR2 enzyme reflects the interaction energy (Figure 3a). Seven hydrogen bonds are formed between the substance ZINC01534124 and the amino acids in the active site of VEGFR2 (Figure 3b). The summary of these many bridges was represented in the Table 2.

3.5. VEGFR2-ZINC00588595 interaction

We were able to create a stable complex with an interaction energy of -45.425 Kj/mole thanks to the modeling of the VEGFR2-ZINC00588595 interaction simulated by docking using FlexX (Figure 4). Hydrophobic interactions and the formation of numerous hydrogen bonds are essentially contributes to this energy. Table 3

provides an overview of the lengths and spatial orientations of the various bonds that were found.

The involvement of the residues Cys919, Phe918, Gly922, Leu1035, Phe1047, Leu840, Val916, Val848, Lys868, Ala 866, Leu889, Val899, Cys1045, As1046, Glu885, and Ile888 in the stability of the VEGFR2-ZINC00588595 complex is also crucially important because it permits the formation of numerous hydrophobic type interactions (Figure 5).

3.6. ADME-Tox profile prediction

Because it is the primary factor in the tardy and expensive failure of candidate molecules in drug design, the characteristics of absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) must be taken into consideration during the development of a novel medication [28]. It is significant to highlight that computer models complement experimental procedures by rapidly providing predicted and reliable results. These computer models aid pharmaceutical companies in choosing drug candidates before expensive clinical trials by predicting the pharmacokinetic, physicochemical, and therapeutic characteristics of small compounds [29, 30]. These prediction models are now accessible through free online resources, including the following: SwissADME (http://www.swissadme.ch) and PreADMET (https://preadmet.webservice.bmdrc.org).

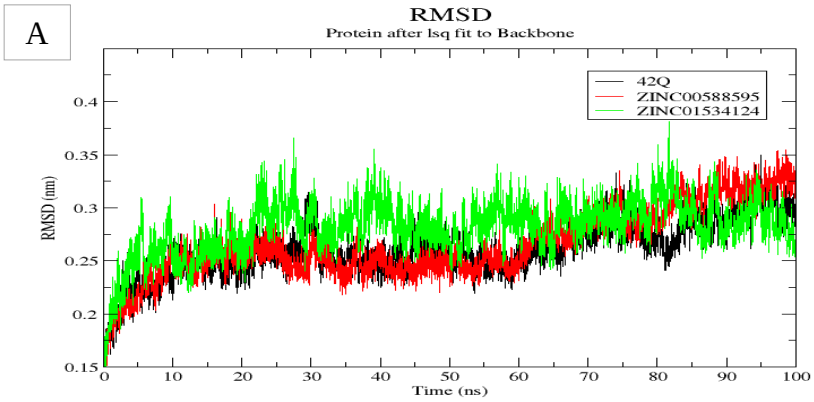
3.6.1. Physicochemical properties

Using the SwissADME service, we estimated the physico-chemical properties of the most effective VEGFR2 inhibitors.

At the conclusion of this test, the substances ZINC01534124 and ZINC00588595 satisfy Lipinski's criteria, suggesting that these inhibitors can be administered orally without creating any issues. Furthermore, one of the key issues to resolve during optimization relates to the compounds' synthetic accessibility. The range for this criterion's score was 1 to 10. The difficulty of synthesizing a compound has increased with the increase in its value [31]. The results of Table 4 indicated that for values less than five, the chemical production of the inhibitors ZINC01534124 and ZINC00588595 appears to be feasible.

3.6.2. Prediction of ADME-Tox properties

A potent drug candidate must be quickly and thoroughly absorbed from the gastrointestinal system, delivered precisely to the body's site of action, metabolized without impairing physiological functions, and removed in the proper amount and without causing damage. In order to confirm our choice and go toward the chemical with the highest potential to be a drug candidate, a number of parameters were predicted in silico.



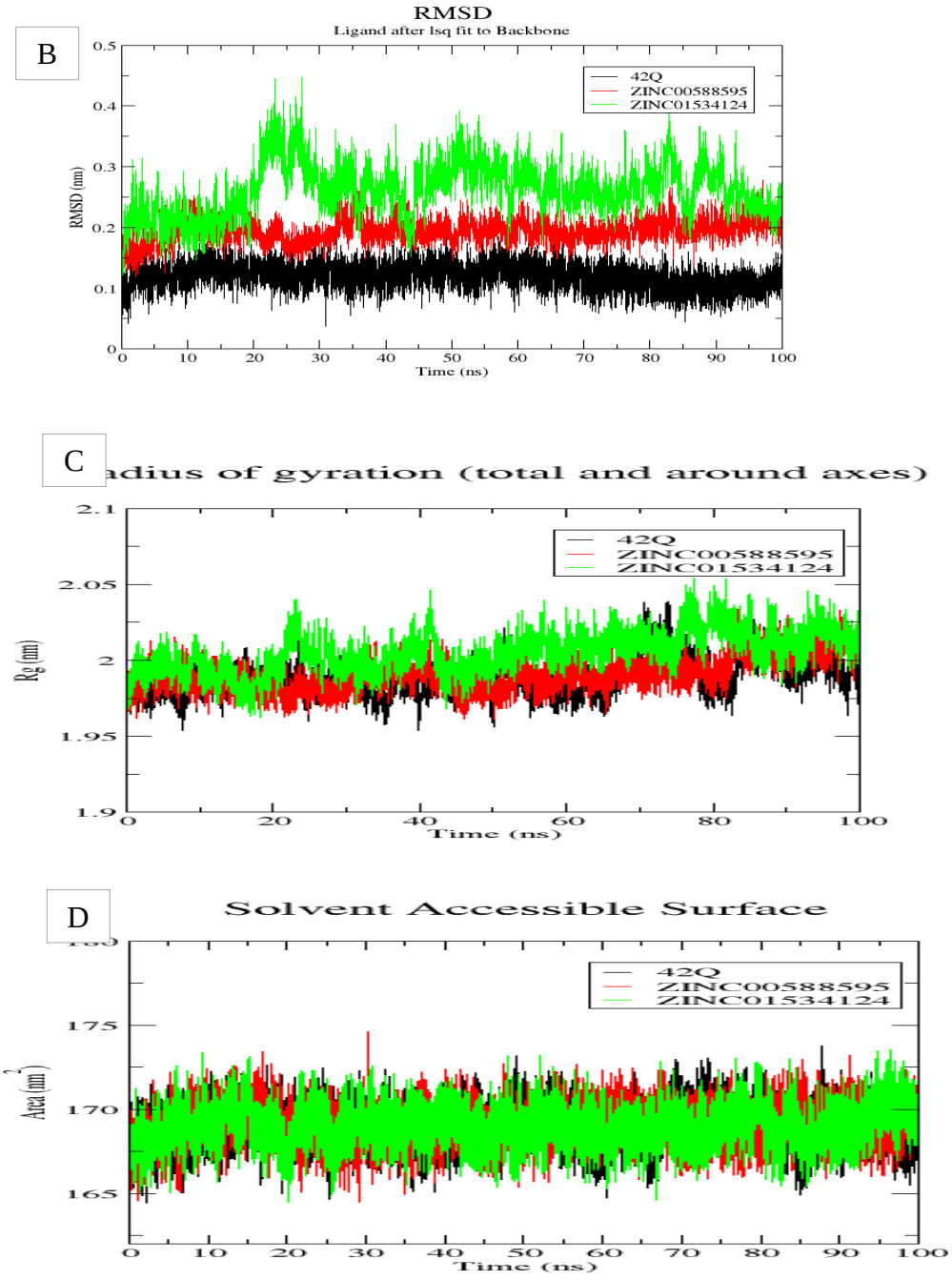
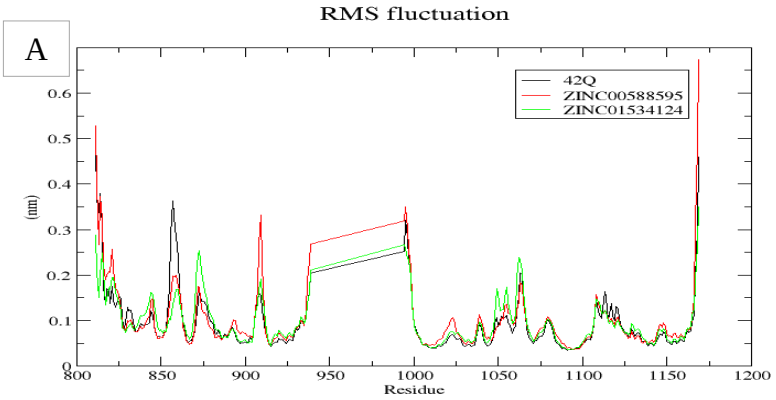
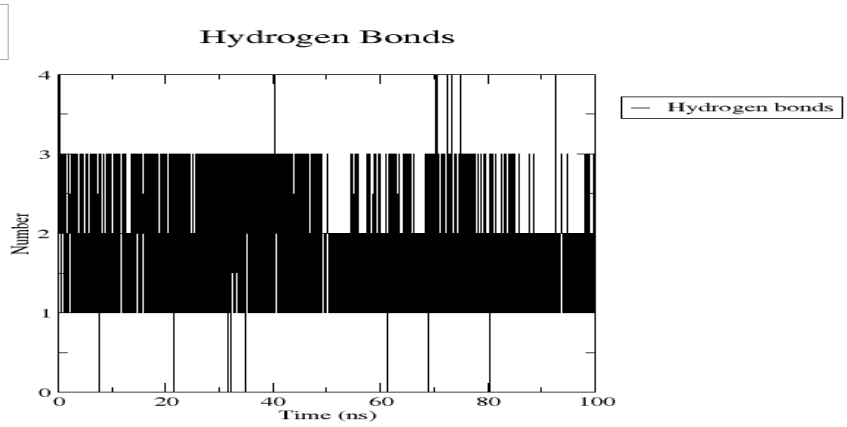


Figure 6. Structural dynamics of VEGFR2 kinase domain RMSD (A), ligands RMSD (B) VEGFR2 kinase domain radius of gyration (C), SASA values (D) calculated during the 100 ns of MD trajectories

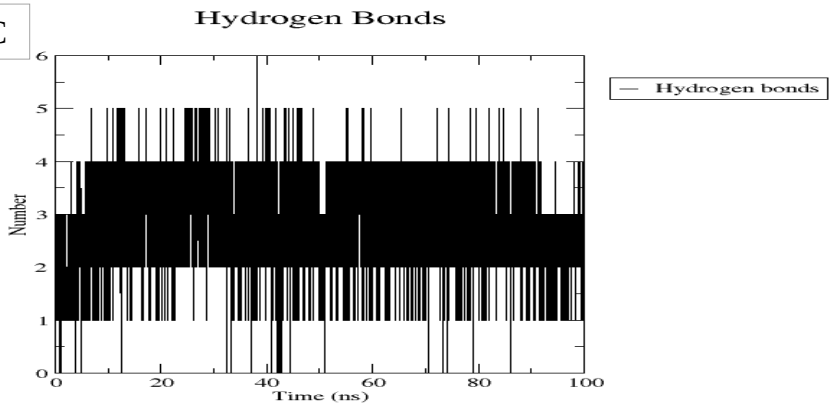
A


RMS fluctuation
42Q
ZINC00588595
ZINC01534124
(nm)
Residue

B


Hydrogen Bonds
Hydrogen bonds
Number
Time (ns)

C


Hydrogen Bonds
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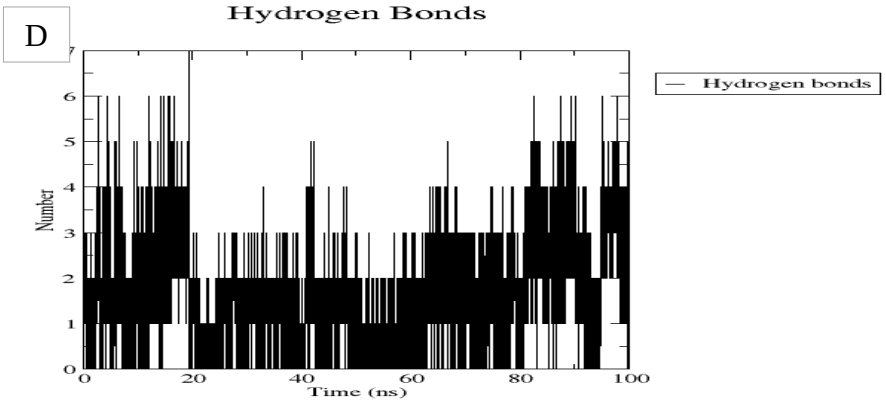

Figure 7. Structural dynamics calculated during the 100 ns of MD trajectories; Root Mean Square fluctuation (RMSF) of protein backbone (A), number of H-bonds formed with 42Q (B), ZINC00588595 (C) and ZINC01534124 (D)

According to Table 5, the compound ZINC01534124 showed a low possibility of gastrointestinal absorption. On the other hand, the inhibitor ZINC00588595 has a high gastrointestinal absorption, which allows it to cross the gastrointestinal barrier to reach the blood. Additionally, none of the chemicals under investigation crosses the blood-brain barrier. ZINC01534124 is not a cytochrome P450 isoenzyme (CYP) inhibitor, which prevents the biotransformation of drugs. Compared to ZINC00588595, a substance that blocks all CYPs. Understanding this inhibition is crucial for identifying medication interactions and minimizing risk.

On the other hand, the prediction of toxicity shows that the ZINC00588595 inhibitor exhibits negative carcinogenic properties in the test on mice and rats, while the ZINC01534124 inhibitor exhibits positive carcinogenic properties. Studies on rodent toxicity have been crucial in finding substances that might be dangerous to humans. However, the two substances under study have a non-mutagenic impact and cannot hence cause genetic alterations, as was reported. We also found a low risk of these chemicals inhibiting the hERG gene. Keeping this gene blocked might result in cardiac arrest.

3.7. Molecular dynamics simulations

The conformational changes of protein-ligand complex were examined using two methods; root-mean-square deviation (RMSD) and solvent accessible surface area analysis through the 100 ns MD simulation to assess the stability of the simulated system. These parameters were calculated after re-centering and re-wrapping the complex within the unit cells using the trjconv function of GROMACS.

The RMSD plot (Figure 6A) indicates the stability of VEGFR2 kinase domain where the 2 hits and the native ligands bound to it and gives an insight into the conformation changes throughout the 100 ns MD simulation. The RMSD of the backbone shows very stable fluctuation for both the co-crystallized ligand (42Q) and ZINC00588595 throughout the trajectory showing low oscillation around 0.25 nm. On the other hand, ZINC01534124 shows less stability with higher oscillation, fluctuating between 0.25 and 0.35 nm. Similar RMSD results are shown for the ligands upon binding to our target protein as shown in figure 6B. Both 42Q and ZINC00588595 were fluctuating around only 0.1 nm which a very stable acceptable range while ZINC01534124 shows also higher ones.

The compactness of the protein backbone of the three complexes was studies via visualizing their radius of gyration (Rg) during the whole simulation (Figure 6C). Protein backbone showed a higher compactness and in turn stability when bound to both 42Q and ZINC00588595 than ZINC01534124. This stability was also confirmed via SASA plot which showed to be very stable, with very low fluctuation ranging between 165 and 172 nm2 for the three complexes during the whole simulation (Figure 6D).

The root mean square fluctuation (RMSF) of the backbone residues was also calculated to evaluate the rigidity/flexibility of residues throughout the 100 ns MD simulation. As shown in Figure 7A, all the three complexes show the same RMSF patterns where residues involved in the interaction with the ligand show very low fluctuation (< 0.2 nm).

Protein-ligand binding is often thought to be aided by H-bonds [32]. They are crucial in establishing the specificity of the ligand binding as well as indicating the high affinity of the ligand for the receptor's active site [33]. To assess the stability of this binding, number of H-bonds formed during the 100 ns simulation were calculated (figure 7 B, C and D). It is clear that co-crystallized ligand was able to maintain at least 2 H-bonds during the whole simulation with an ability to form a third one especially during the first 50 ns. Regarding, ZINC00588595 an average of 3-4 H-bonds was formed allover the trajectory explainng its high stability observed in both RMSD and Rg plots. On the other hand, ZINC01534124 was able to form up to 6 H-bonds but non of them was stable during the 100 ns. This illustrates why they show good binding affinity while been docked in the target receptor while showing an unstable trajectory with a high fluctuation pattern.

These findings demonstrate that the inhibitor ZINC00588595 has a strong and consistent interaction with the VEGFR2 enzyme more than ZINC01534124.

4. Conclusions

Theoretical methods that predict how a ligand will interact with its receptor are complimentary to experimental methods and occasionally enable their interpretation. For biology, pharmacy, and medicine to evolve as best they can, theoretical and experimental techniques must work in harmony. One of the keys to an increasingly easy process for the discovery of a therapeutic need is unquestionably the existence of such a research environment. Numerous research published recently demonstrated the significance of VEGFR2 in the search for new drugs [10]. VEGFR2 has emerged as a key therapeutic target for cancer anti-angiogenesis treatment because it targets endothelial cells that promote tumor development rather than actual cancer cells [34, 38]. In this work, we used a structure-based virtual screening technique to find two novel putative inhibitors of VEGFR2 from the Zinc databank that target the active site of VEGFR2. The compounds ZINC01534124 and ZINC00588595 have an excellent ADME-Tox profile and possibly strong inhibitory activity towards our target. Furthermore, a total of 100 ns molecular dynamics simulation revealed that the two inhibitors ZINC01534124 and ZINC00588595 formed stable complexes with VEGFR2 drug target. As compared to the reference inhibitor, the compound ZINC00588595 revealed great stability during the whole 100 ns MD simulation. These findings are thus very encouraging for the advancement of our strategy and the potential therapeutic uses of the compounds under investigation. However, it is still necessary to test these inhibitors on our target directly. In this context, research on these two compounds and their many variants is ongoing in an effort to discover novel anti-angiogenic drugs.

ACKNOWLEDGEMENT

This work was supported by the Algerian Ministry of Higher Education and Scientific Research (MERS) (F01220060052).

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