Adıyaman University Journal of Science
https://dergipark.org.tr/en/pub/adyujsci
DergiPark AKADEMİK
ISSN 2147-1630
e-ISSN 2146-586X

# Analysis of Interactions of NHC Type Molecules and NHC-Ag Complexes with VEGFR-2 and DNA: A Molecular Docking Study

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**Received:** 13.12.2020 **Accepted:** 12.05.2021 **Published:** 30.06.2021

**Abstract**

Molecular docking is an important tool in drug research. Thanks to these calculations, the type and magnitude of interactions of the molecules with target molecules are evaluated. It is also possible to perform more detailed analyzes than known experimental methods in an easy and economical way by using the results obtained with current scientific developments and examine interactions with different target molecules depending on bioactivity type. Cancer researches show that vascular endothelial growth factor is effective in the growth and proliferation of cancer cells. Inhibition of the receptor that regulates the release of this factor may be an efficient method for designing an anticancer agent. One of these receptors is VEGFR-2. This receptor can be used as a target molecule in cancer research. In addition, the interaction of molecules with DNA is important in terms of getting insight for future studies. In this study, the interaction of 1-allyl-3-benzylbenzimidazolium, 1-allyl-3-(naphthylmethyl)benzimidazolium, 1-allyl-3-(anthracen-9-yl-methyl)benzimidazolium,chloro[1-allyl-3-benzylbenzimidazolium-2-ylidene]silver(I), chloro[1-allyl-3-(naphthylmethyl)benzimidazolium-2-ylidene]silver(I), chloro[1-allyl-3-(anthracen-9-yl-methyl)benzimidazolium-2-ylidene]silver(I) with VEGFR-2 and DNA were analyzed by molecular docking methods.

***Keywords:*** Molecular docking; N-Heterocyclic carbenes; VEGFR-2; Silver complexes.

* Corresponding Author DOI: 10.37094/adyujsci.838918

# NHC Tipi Moleküllerin ve NHC-Ag Komplekslerin VEGFR-2 ve DNA ile Etkileşimlerinin Analizi: Moleküler Doking Çalışması

**Öz**

Moleküler doking, ilaç araştırmalarında önemli bir araçtır. Bu hesaplamalar sayesinde moleküllerin hedef moleküllerle olan etkileşimlerinin türü ve büyüklüğü değerlendirilir. Güncel bilimsel gelişmelerle elde edilen sonuçlar kullanılarak, bilinen deneysel yöntemlere göre daha detaylı analizleri kolay ve ekonomik bir şekilde gerçekleştirmek ve biyoaktivite tipine bağlı olarak farklı hedef moleküller ile etkileşimleri incelemek de mümkündür. Kanser araştırmaları vasküler endotelyal büyüme faktörünün, kanser hücrelerinin büyümesi ve çoğalmasında etkili olduğunu göstermektedir. Bu faktörün salımını düzenleyen reseptörün inhibisyonu, bir antikanser ajanı tasarlamak için etkili bir yöntem olabilir. Bu reseptörlerden biri VEGFR-2'dir. Bu reseptör, kanser araştırmalarında bir hedef molekül olarak kullanılabilir. Ayrıca moleküllerin DNA ile etkileşimi ileride yapılacak çalışmalara ışık tutması açısından önemlidir. Bu çalışmada, VEGFR-2 ve DNA ile 1-allil-3-benzilbenzimidazolyum, 1-allil-3-(naftilmetil)benzimidazolyum, 1-allil-3 (antrasen-9-il-metil)benzimidazolyum, kloro[1-allil-3-benzilbenzimidazolyum-2-iliden]gümüş(I), kloro[1-allil-3-(naftilmetil)benzimidazolyum-2-iliden]gümüş (I), kloro[1-allil-3-(antrasen-9-il-metil)benzimidazolium-2-iliden]gümüş(I) bileşiklerinin etkileşimi moleküler doking yöntemleriyle analiz edildi.

***Anahtar Kelimeler**:* Moleküler doking; N-Heterosiklik karbenler; VEGFR-2; Gümüş kompleksleri.

## 1. Introduction

Angiogenesis which is defined as the formation of new blood vessels from pre-existing vasculature takes place in processes such as cell growth and wound healing [1, 2]. However, recent studies display that excessive angiogenesis causes pathological problems such as tumor formation, increase in existed tumor and metastasis [3, 4]. In this case, controlling the systems that regulate angiogenesis could be a hopeful way for cancer therapy. Vascular endothelial growth factor (VEGF) is a signal protein that positively regulates vascular endothelial cells [5]. The activity of VEGF is controlled by vascular endothelial growth factor receptors (VEGFR) that are structurally similar to each other and these are VEGFR-1 (Flt-1), VEGFR-2 (KDR / Flk-1) and VEGFR-3. VEGFR-2 is a type of tyrosine kinase and is major regulator of endothelial cells in both physiological and pathological angiogenesis [6]. Studies confirmed that overexpression of VEGFR-2 has been monitored in breast, colorectal, ovarian, and thyroid cancers [7-9]. Indeed,

VEGFR-2 could be considered as a target for fighting against cancer, and many articles on this strategy have been published recently [10-14].

DNA is the essential target for designing more effective molecules and the detection of the interaction of new molecules with DNA is still an active scientific field [15-17]. Understanding the interactions of metal complexes with DNA sequences is important for the analysis of tumor inhibition mechanisms and design new molecules for effecting the selected parts of DNA [18].

N-heterocyclic carbenes (NHCs) is a family of molecules whose many properties have been studied since the first synthesized [19, 20]. NHCs, which are well-known for their catalytic activity, can be easily synthesized and modified due to their electron-rich and neutral sigma donor properties [21, 22]. In addition, many NHC-metal complexes have been synthesized, and their bioactivities have been frequently studied. Particularly, the antibacterial activity of the ruthenium and rhodium complexes is well known [23, 24]. After the improvement in metal-based anti-cancer drugs, the anti-cancer properties of metal-NHC complexes have also been frequently studied [25, 26]. Good results have been especially obtained from anti-cancer activity studies of Au-NHC complexes [27]. Moreover, the anti-cancer research of Ag-NHC complexes that are generally known as anti-infective has positively progressed [28].

Molecular docking method is accepted as an essential tool for investigating the interactions between new molecules and biological macromolecules such as DNA, proteins, enzymes [29-32]. It is possible to have an idea about the properties of molecules that have not been synthesized with this method [33]. Moreover, it is very useful to have foresight for designing new molecules by comparing the experimental bioactivity results. In this study, VEGFR-2 and DNA were selected as a cancer target molecule and interaction of previously synthesized [34] 1-allyl-3-benzylbenzimidazolium [**1a**], 1-allyl-3-(naphthylmethyl)benzimidazolium [**1b**], 1-allyl-3-(anthracen-9-yl-methyl)benzimidazolium [**1c**], chloro[1-allyl-3-benzylbenzimidazolium-2-ylidene] silver(I) [**2a**], chloro[1-allyl-3-(naphthylmethyl) benzimidazolium-2-ylidene]silver(I) [**2b**], chloro[1-allyl-3-(anthracen-9-yl-methyl)benzimidazolium-2-ylidene]silver(I) [**2c**] (Fig. 1) with VEGFR-2 and DNA were analyzed by molecular docking methods.

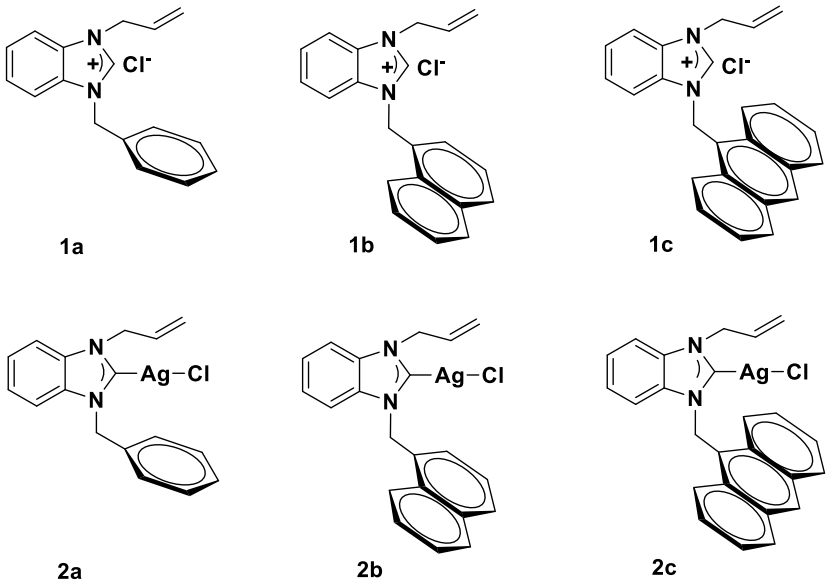


**Figure 1:** Allyl substituted benzimidazolium molecules and their Ag complexes

## 2. Materials and Methods

### 2.1. Molecular docking method

Before the molecular docking process, molecules are optimized with ORCA package program. DFT calculations were performed with ORCA version 2.8 using the BP86 functional with a def2-SVP def2-SVP/J basis set, the tightscf, and KDIIS SOSCF options for geometry optimizations [35, 36]. Molecular dockings were performed by using AutoDock 4.2. with both vascular endothelial growth factor receptor-2 (PDB id: 1YWN) and DNA dodecamer (PDB id: 1BNA) crystal structures which are obtained from RCSB protein data bank [37]. Water in the proteins was removed and polar hydrogen atoms and Kollman charges were evaluated for target molecules in the docking process. Gasteiger charges, randomized starting positions, optimizations, and torsions have been evaluated for ligand molecules. The genetic algorithm population was used as 150 while applying Lamarkian genetic algorithms.

## 3. Results

Molecular docking became a common method for bioactivity and drug design studies [38, 39]. In many published texts, experimental studies are supported by computational methods such as molecular docking [40, 41]. The action mechanisms and interactions of the molecules with biological macromolecules such as proteins and enzymes can be analyzed with this method. Besides, unlike the well-known and frequently used methods, these computational methods guide the future studies by using different target molecules [42, 43]. Due to the positive results obtained

from drug research of metal-based molecules, the bioactivity analysis of newly synthesized and characterized complexes is one of the important fields of chemical research and promising results have been obtained for many complexes. Cancer is still one of the major health problems in the world [44]. Therefore, it is important to investigate the anti-cancer activity of inorganic molecules. In cancer research, the standard procedures are in vitro [45, 46]. The studies show that anti-cancer agents affect with different mechanisms in different cancer types. For example, the vascular endothelial growth factor that is controlled by VEGF receptors is effective in cell growth, the proliferation of cancer cells, and metastasis. Among receptors, VEGFR-2 is efficient in thyroid, colorectal, and breast cancer cases. VEGFR-2 has also become a target molecule since the inhibition of VEGFR-2 can be used as a method in cancer treatment [47, 48].

In this study, the interactions between VEGFR-2 and NHC/Ag-NHC molecules that were previously analyzed for anti-cancer activities were investigated by the molecular docking method. **1a** has interacted with the region that formed by Leu887, Ile890, Val896, Val897, Leu1017, Cys1043, Cys1022, and Arg 1025 amino acids of VEGFR-2 with the binding energy of -5.74 kcal/mol. Effective alkyl and pi-alkyl interactions were noted, while no H-bond interaction was detected. The amide-pi stacked with Arg1025 and pi-cation with Cys1043 interactions of the molecule are remarkable. Although it is not high enough, van der Waals interactions have been noted for **1a** with Glu883, Ile1023, His1024, Ile1042, and Asp1044. **2a**, which is the silver complex of the **1a**, interacts with approximately the same region of VEGFR-2 with -6.18 kcal/mol binding energy. While the **2a** molecule represented pi-anion interactions with Glu 883 and Asp1044, amide-pi stacked interaction between benzimidazole ring of the molecule and Cys1043 was recorded. **2a** showed effective alkyl and pi-alkyl interactions, like **1a**. While alkyl and pi-alkyl interactions were calculated between Ile886, Ile890, Val896, Leu1017, Cys1022, and **2a**, van der Waals interactions were recorded with Leu887, Val897, Ile1023, His1024, Arg1025, and Ile1042. Binding properties and areas of **1b** and VEGFR-2 are different from **1a** and **2a**. The alkyl and pi-alkyl interactions of Val897, Leu887, Val846, Lys866, Ala864, and Cys917 with **1b** are efficient (Table 1, Fig. 2, and Fig. 3).

**Table 1:** Molecular docking results of the molecules for VEGFR-2 target

| Molecules | Bind. Aff.* | Amino Acids Residue |
|---|---|---|
| | | **VEGFR-2 (1ywn)** |
| **1a** | -5.74 | Arg1025 (Pi-Cation), Cys1043 (Amide-Pi Stacked), Leu887, Ile890, Val896, Val897, Leu1017, Cys1022 (Pi-Alkyl), Glu883, His1024, Ile1023, Ile1042, Asp1044 (van de Waals) |
| **1b** | -6.97 | Val914, Leu1033 (Pi-Sigma), Phe916 (Pi-Pi Stacked), Val846, Ala864, Lys866, Leu887, Val897, Cys917 (Pi-Alkyl), Glu883, Asp1044 (Carbon Hydrogen Bond), Val865, Val912, Glu915 (van der Waals) |
| **1c** | -7.40 | Ile886 (Pi-Sigma), Arg1025 (Pi-Cation), Leu887, His889, Val896, Leu1017, Cys1022 (Pi-Alkyl), Glu883, Val897, His1024, Ile1042, Asp1044 (van der Waals) |
| **2a** | -6.18 | Glu883, Asp1044 (Pi-Anion), Cys1043 (Amide-Pi Stacked), Ile886, Ile890, Val896, Leu1017, Cys1022 (Pi-Alkyl), Leu887, Val897, Ile1023, His1024, Arg1025, Ile1042 (van der Waals) |
| **2b** | -6.76 | Ile886 (Pi-Sigma), Arg1025 (Pi-Cation), Cys1043 (Amide-Pi Stacked), Val896, Leu1017 (Pi-Alkyl), Glu883, Ile890, Val897, Ile1023, His1024, Ile1042, Asp1044 (van der Waals) |
| **2c** | -7.03 | Leu1033 (Pi-Sigma), Leu838, Val846, Ala864, Val914, Cys917 (Pi-Alkyl), Gly839, Val897, Glu915, Phe916, Lys918, Gly920, Asn921 (van der Waals) |

* Binding Affinity in kcal/mol.

Furthermore, the pi-sigma interactions between the benzimidazole residue and Val914, between naphthalene and Phe916 and, also pi-pi stacked interactions with Leu1033 can be examined in Fig. 2. In addition, carbon hydrogen-bonds of **1b** with Glu883 and Asp1044 were recorded. The binding energy of **1b** molecule with VEGFR-2 was calculated as -6.97 kcal/mol. The **2b**, which is the Ag complex of the **1b** ligand, differs from **1b** in terms of both binding site and binding types. Pi-alkyl interactions with Cys1022, Leu1017, and Val896, pi-cation interaction with Arg1025, pi-sigma interaction with Ile886, and amide-pi stacked interaction with Cys1043 contributed to the binding energy of **1b** with -6.76 kcal/mol. In addition, van der Waals interactions of the molecule can be pursued in the Fig. 2. It is noteworthy that **1c** performs less van der Waals interaction compared to other ligands. The binding energy was calculated for **1c** as -7.40 kcal/mol with the contribution of pi-cation, pi-sigma, amide-pi stacked and alkyl interactions. It can also be analyzed in Fig. 2 that **2c** makes only van der Waals, pi-sigma, and alkyl interactions. The binding energy of **2c** was calculated as -7.03 kcal/mol (Table 1, Fig. 2, and Fig. 3).

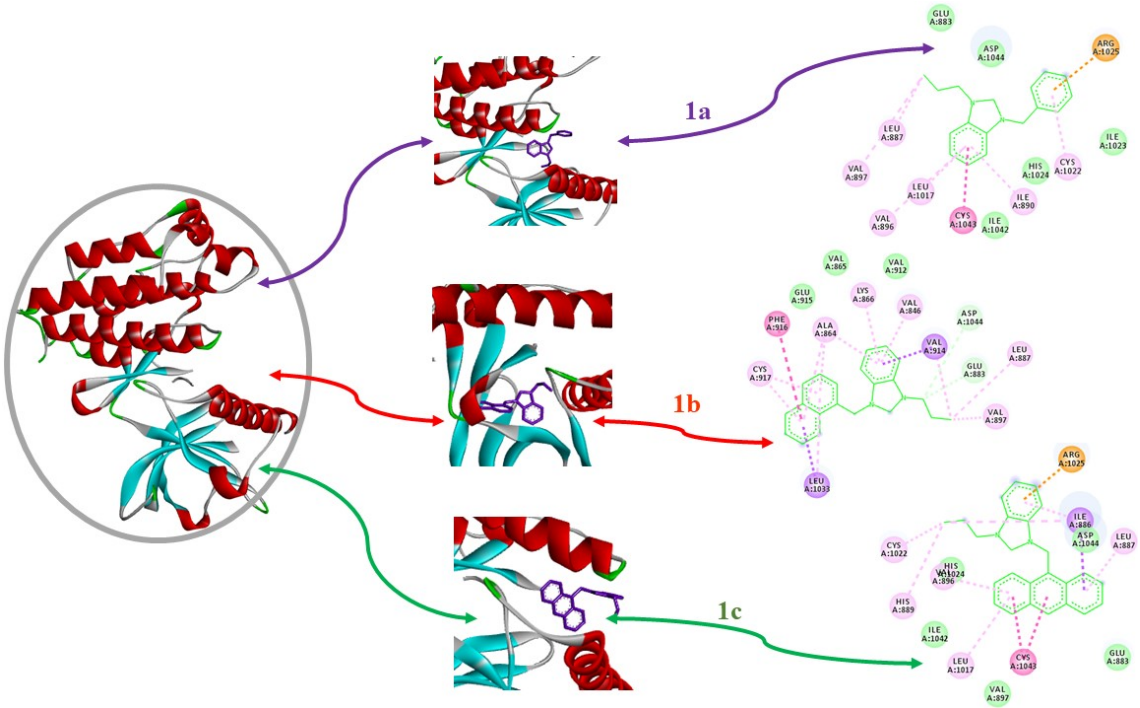


**Figure 2:** Graphical illustration of the interactions between VEGFR-2 and the molecules (center: ribbon style crystallographic structure of VEGFR-2; the arrows guided the interactions, purple: **1a**; red: **1b**; green: **1c**)

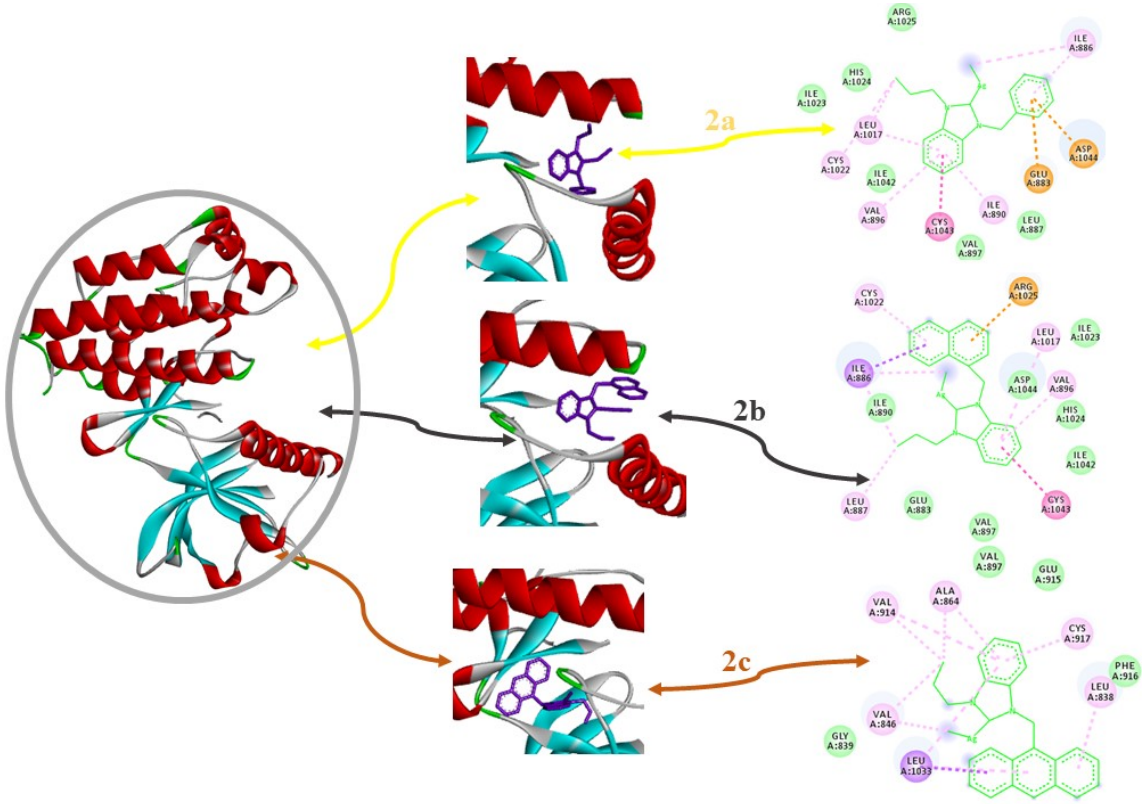


**Figure 3:** Graphical illustration of the interactions between VEGFR-2 and the molecules (center: ribbon style crystallographic structure of VEGFR-2; the arrows guided the interactions, yellow: **2a**; grey: **2b**; brown: **2c**)

In experimental studies of the molecules, activity values were examined both for different cancer types and different intervals. Binding energies are generally considered as a suitable criterion for comparing experimental and theoretical results. According to the theoretical results detailed above, it is possible to say that **1c** is the most active of the ligands while the most active complex is **2c**. These results agree with experimental results [34]. On the other hand, the experimental activity results of complex molecules were higher than the ligands, but the theoretical results were not compatible with this result.

One of the most frequently used analyzes when examining the activity of molecules is evaluating the position of the interactions of molecules with DNA [49]. The interaction of molecules with DNA is important in terms of getting insight for future studies [50]. DNA Dodecamer structure (pdb id:1BNA) was used to analyze the interaction (Fig. 4). All of the molecules interact with nearly the same region of DNA. **1a** with Cyt9 and Gua10, **1b** was interacted with Thy7 and Thy8, **1c** was interacted with Gua10 and Cyt11. The Ag complexes of these molecules were interacted with the similar region of DNA. **2a**, **2b**, and **2c** were interacted with Cyt9 and Gua10. It is noteworthy that unlike **2a** and **2b**, **2c** was also interacted with Thy7.

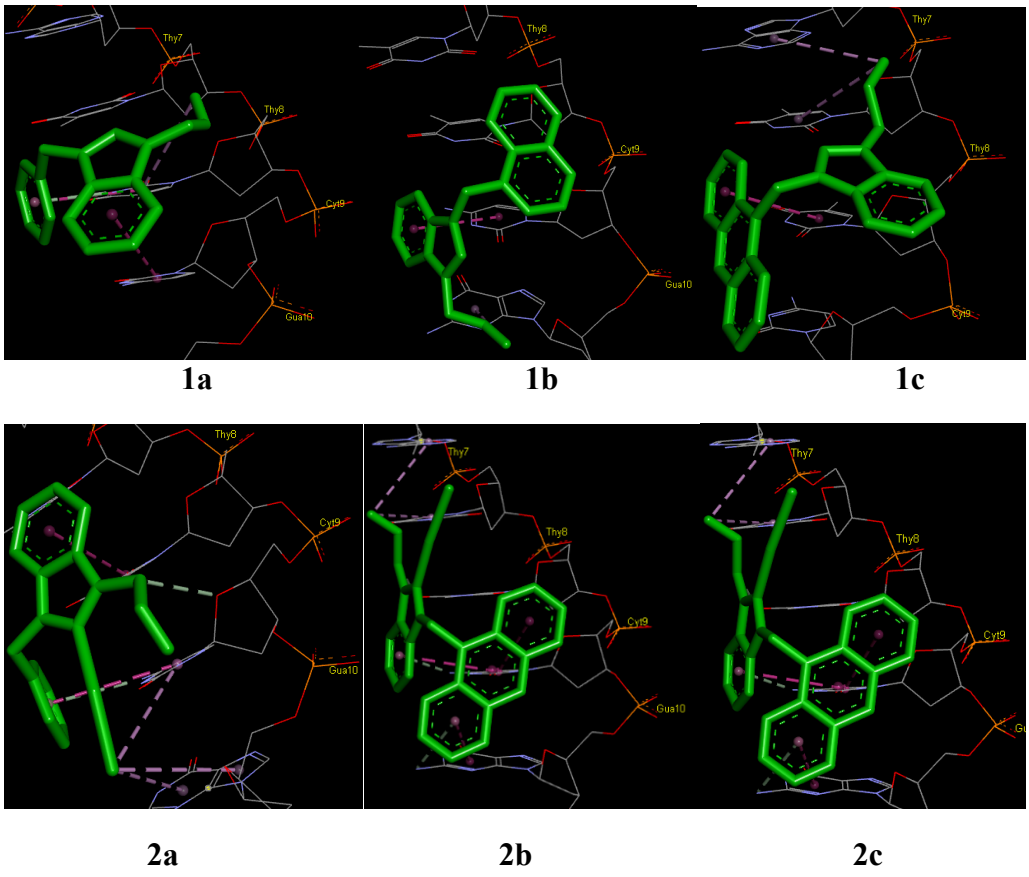


**Figure 4:** Graphical illustration of the interactions between DNA dodecamer and the molecules

## 5. Conclusions

The developments in *in-silico* studies in recent years are remarkable. Therefore, these methods are considered essential tools in bioactivity and drug design studies. Most of the empirical work is now supported by theoretical calculations. Molecular docking studies are one of the leading *in-silico* studies. In this study, molecular docking analysis of the complexes, whose activity was experimentally investigated previously, was performed. The first molecular docking analysis was performed using VEGFR-2, which is effective in the cell growth, proliferation of cancer cells, and metastasis. The obtained results are partially consistent with the experimental results. Secondly, the interaction of molecules with DNA was analyzed. As it is known, many mechanisms of action are known to be effective in cancer treatments. One of them is analyzed in this study. The augmentation of these studies is important in terms of getting foresight in future studies. In the future, it is planned to continue *in-silico* studies with different target molecules of different effect mechanisms.

## Acknowledgement

The authors would like to thank the Technological and Scientific Research Council of Turkey (TÜBİTAK-3001, Project Number: 118R045).

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