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Araştırma Makalesi

In Silico Studies of Two Biphenyl Based Oxime Containing Ligands

Güvenç GÖRGÜLÜ[1], Bülent DEDE[*2]

[1]*Mehmet Akif Ersoy University, Faculty of Education, Department of Science Education, Burdur, Türkiye*
[2]*Süleyman Demirel University, Faculty of Arts and Science, Department of Chemistry, Isparta, Türkiye*

**corresponding author e-mail: bulentdede@sdu.edu.tr*

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Abstract: Two biphenyl based ligands were tested for their molecular docking, ADME and toxicity properties *in silico*. Molecular docking studies performed with two factors (VEGFR-2 and EGFRK) which are known to be effective in tumor growth. Two ligands were similar in structure except one atom difference between ligands which is H and Cl. This small difference made an important impact on the molecular docking energy scores of ligand protein couples. The Cl atom containing ligand-protein complexes showed drastically elevated energy levels which might be due to higher electronegativity of Cl atom. ADME properties of two ligands were also alike except a few parameters as the inhibition of two conjugation enzymes (CYP2C19 ve CYP2C9). The biggest difference shown by the ligands were the elimination of carcinogenicity and mutagenicity of H containing ligand by Cl atom containing ligand. Druglikeness of two biphenyl based oxime containing ligands was also tested and the results of a single atom exchange were evaluated in terms of new drug design and discovery.

***Key words**: In Silico* study, Molecular docking, ADMET, Druglikeness

Oksim İçeren Bifenil Temelli İki Ligandın *in silico* Çalışmaları

Öz: İki bifenil temelli ligandın moleküler kenetlenme, ADME ve toksisite özellikleri *in silico* olarak incelendi. Moleküler kenetlenme çalışmaları, tümör büyümesinde etkili olduğu bilinen iki faktör (VEGFR-2 ve EGFRK) kullanılarak gerçekleştirildi. İki ligand, H ve Cl olan bir atom farkı dışında yapısal açıdan benzer olarak seçildi. Bu küçük fark, ligand protein çiftlerinin moleküler kenetlenme enerji değerleri üzerinde önemli bir etki meydana getirdi. Cl atomu içeren ligand-protein kompleksleri, Cl atomunun daha yüksek elektronegatifliğinden kaynaklanabilecek büyük enerji değerlerine sahip olarak bulundu. İki konjugasyon enziminin (CYP2C19 ve CYP2C9) inhibisyonu gibi birkaç parametre dışında iki ligandın ADME özelliklerinin benzer olduğu belirlendi. Ligandların gösterdiği en büyük farkın, H içeren ligandın kanserojenliğinin ve mutajenitesinin Cl atomu içeren ligand ile ortadan kaldırması olduğu tespit edildi. İki bifenil bazlı oksim içeren ligandın ilaç benzerliği de test edildi ve tek bir atom değişiminin sonuçları, yeni ilaç tasarımı ve keşfi açısından değerlendirildi.

***Anahtar kelimeler**: In Silico* çalışma, Moleküler kenetlenme, ADMET, İlaçbenzerlik

Güvenç GÖRGÜLÜ, guvencgorgulu@mehmetakif.edu.tr, ORCID: https://orcid.org/0000-0003-4740-7265
Bülent DEDE, bulentdede@sdu.edu.tr, ORCID: https://orcid.org/0000-0003-1416-7373

1. Introduction

Computer-aided drug design (CADD) is used for the rapid assessment of chemical databases to accelerate the early-stage development of new active compounds [1]. CADD can be structure or ligand originated which is essentially based on the chemical similarity to active compounds used [2,3]. This preliminary study relies on the elimination of the unrelated and vastly reducing the number of molecules to be studied. The typical role of CADD in drug discovery is to screen out large compound libraries into smaller clusters of predicted active compounds enabling optimization of lead compounds and by improving the biological properties and building chemotypes from a nucleating site by combining fragments with optimized function.

Among the CADD researches molecular docking studies comprise the major part in the preliminary studies. A designed ligand molecule can be tested for its binding capacity by picking up the optimal data for binding energy, fitness score, optimized energy of the complex (ligand & target molecule) with molecular docking study. The study also gives the number and location of possible hydrogen bonds formed. Plus, all binding poses are obtained as charming graphical data showing the proximity and orientation of the ligand molecule to the target protein [4].

Pharmacokinetics is the quantitative study of drug movement in and through the body expressed as the absorption, distribution, metabolism, excretion and toxicity (ADMET). Major elimination of the candidate molecules is achieved through molecular docking and pharmacokinetic studies [5,6].

Oxime containing compounds are extensively synthesized and characterized due to their coordination capacity which plays a major role in their chemical, biological, pharmacological and industrial capacity [7,8]. Since many oxime derivatives are still in use as pharmacological agents, it has become more important for new analogous compounds being synthesized, characterized and tested for druglikeness and toxicity. During these processes some new compounds will be extinguished and most of them will be eliminated.

Angiogenesis is one of the major factors in tumor growth and metastasis with a sequential mechanism. VEGFR-2 (vascular endothelial growth factor receptor-2) is often used as a parameter for being a potent tumorigenic and metastatic factor due to its angiogenic and lymphangiogenic effects [9]. Similarly, high expression levels of EGFRK (tyrosine kinase domain from the epidermal growth factor receptor) have been frequently observed in breast, prostate, ovarian and various squamous cell carcinomas in which overexpression positively correlates with shortened survival times and increased relapse rates [10].

VEGFR-2 and EGFRK show synergistic effects in tumor growth which makes them precise monitoring factors for cancer. Therefore, the inhibition of these carcinogenic factors became important. For this purpose, two of the previously designed, synthesized and characterized biphenyl based oxime containing ligands [11-13], namely; biphenyl-4-yl-oxo-acetaldehyde oxime (BHKO) and biphenyl-4-yl-oxo-chloro oxime (BCKO) were investigated for their molecular docking behaviors for VEGFR-2 and EGFRK. Revealing the binding properties of these two ligands to the VEGFR-2 expected to give valuable information about the antagonistic effects to the factor, in particular. Ligands were also tested for their ADMET properties.

2. Material and Method

Molecular docking studies were performed on SwissDock web server using EADock DSS algorithm [14]. High resolution crystal structures of VEGFR-2 (PDB ID: 2XIR) and EGFRK (PDB ID:1M17) were obtained from protein data bank (https://www.rcsb.org/). All visualizations of molecular docking studies were performed using UCSF Chimera software [15]. The GaussView 5.0.9 program was used to visualize the optimized geometries of the ligands [16]. ADME properties were executed by SwissADME web server to compile the information on the pharmacokinetics and pharmacodynamics of candidate molecules [17]. In addition, ligands were tested for their toxicity by ProTox-II web server [18].

3. Results

3.1. Molecular Docking Studies

Molecular docking simulations of the biphenyl derivatives were performed to understand in detail the various interactions between ligand and protein. Molecular docking studies started with the optimization of candidate ligands. In order to prepare the biphenyl derivatives for docking studies, their energies were minimized using the molecular mechanical method. On the other hand, waters and co-crystallized ligands were removed from the 3D crystal structures of the proteins. In addition, Kollman and Gastegier charges were calculated and polar hydrogens were added. Figure 1 shows the structures of biphenyl based BHKO and BCKO ligands.

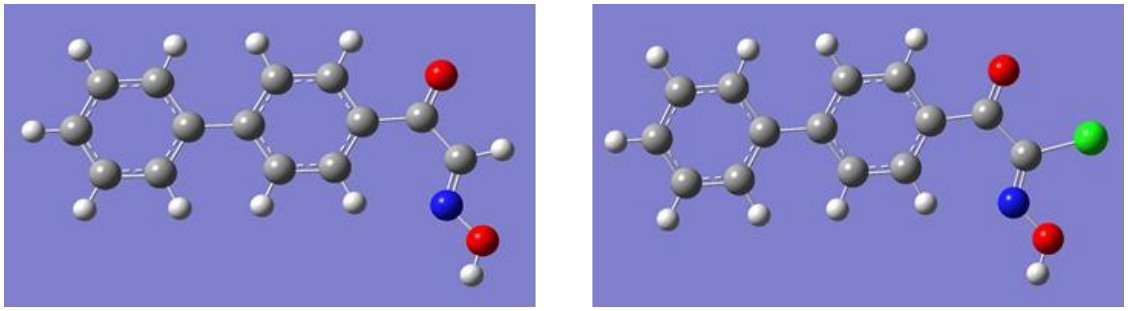


Figure 1. Optimized structures of BHKO (left) and BCKO (right) ligands

Both ligands were docked with VEGFR-2 and EGFRK proteins. Among a number of conformations, ligand-protein complexes with a higher number of formed hydrogen bonds, relatively higher full fitness scores and higher Gibbs free energies were chosen. The results were shown in Table 1.

Table 1. The molecular docking scores of ligand-protein chosen couples

TARGET PROTEIN	LIGAND	ΔG (kcal/mol)	FULL FITNESS SCORE (kcal/mol)	ENERGY (kcal/mol)	H-BOND LOCATION (Target&Ligand)	H-BOND LENGTH (Å)
VEGFR-2 (2XIR)	BHKO	-7.34	-1595.24	19.85	Asp 1046 -HN & carbonyl O	2.23
	BCKO	-7.31	-1574.57	26.62	Leu 1049 -HN & oxime N	2.39
EGFRK (1M17)	BHKO	-6.97	-2174.56	14.60	Cys 773 -HN & oxime O	2.31
	BCKO	-6.90	-2150.34	29.21	Cys 773 -HN & oxime O	2.21

Gibbs free energy of BHKO and BCKO ligands with VEGFR-2 protein has similar results as -7.34 and -7.31 kcal/mol, respectively. These data reveals that the reactions between the ligand and target were spontaneous. The two ligands coupled with the target proteins showed similar data in Gibbs free energies, full fitness scores and hydrogen bond lengths while the total energy of the molecules were vastly increased in BCKO-target couple which only differs with BHKO-target couple by the presence of an electronegative Cl atom instead of H. From the data, BHKO-VEGFR-2 couple seemed much more stable compared to BCKO-VEGFR-2 couple. The situation becomes more distinct for the BCKO-EGFRK couple which has twice as higher energy as the BHKO-EGFRK couple has. Figure 2 shows the ribbon shaped and space filled models for BHKO-VEGFR-2 couple with closer views. Green lines represent the hydrogen bonding between the protein and ligand.

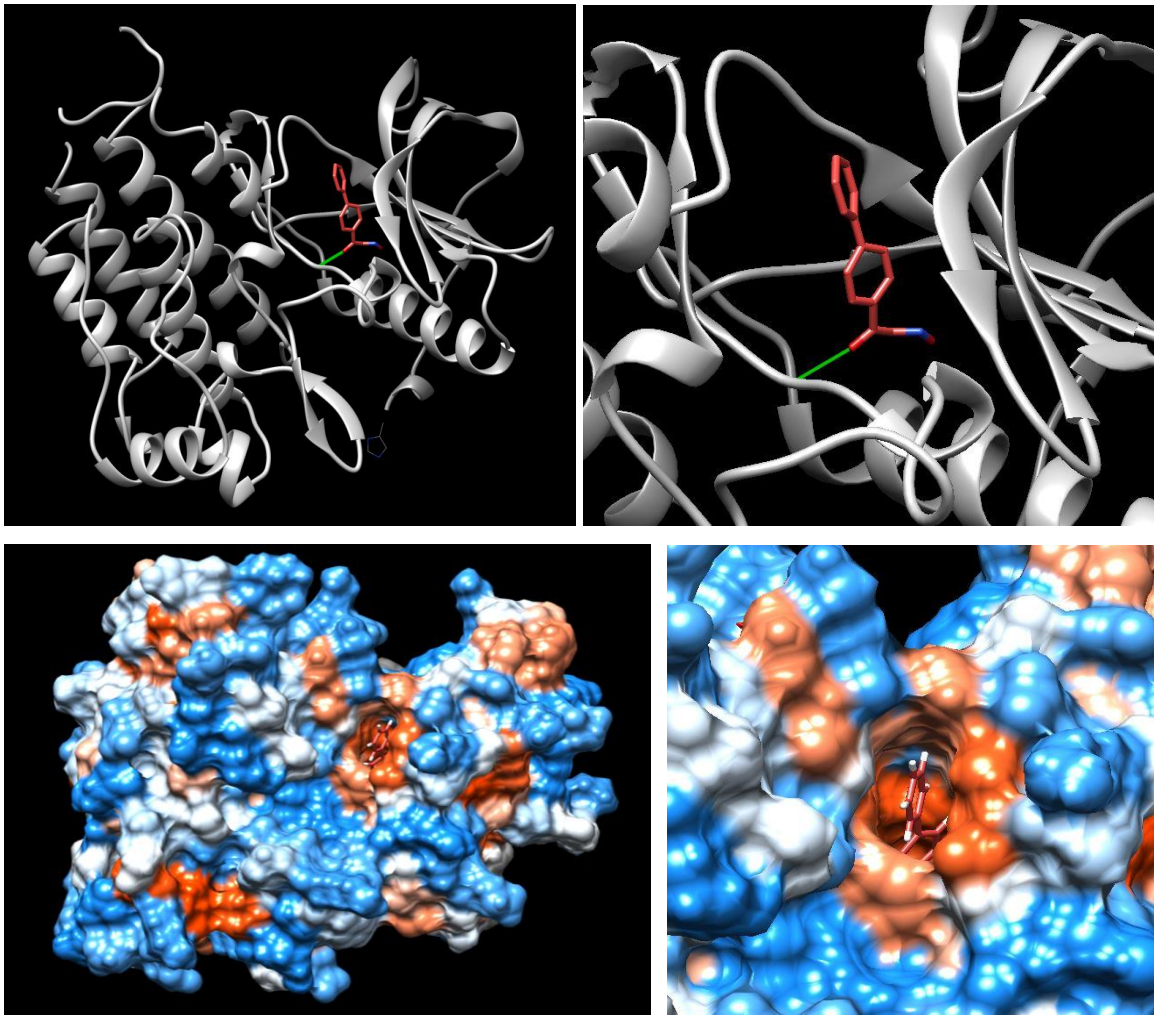


Figure 2. Ribbon shaped (above) and space filled (below), full (left) and closer (right) views for BHKO-VEGFR-2 couple.

The data obtained and space-filled model views shows that BHKO ligand was docked with a high proximity in VEGFR-2 protein as seen from the Figure 2. The hydrogen bond was formed between the hydrogen of -HN group of amino acid 1046th (aspartic acid) and O of carbonyl group of the ligand. The pose of the most stable complex simulated between BHKO and EGFRK is given in Figure 3. In this complex, the calculated hydrogen bond with a length of 2.31 Å was found between -HN group of Cys 773 and oxime O of the ligand.

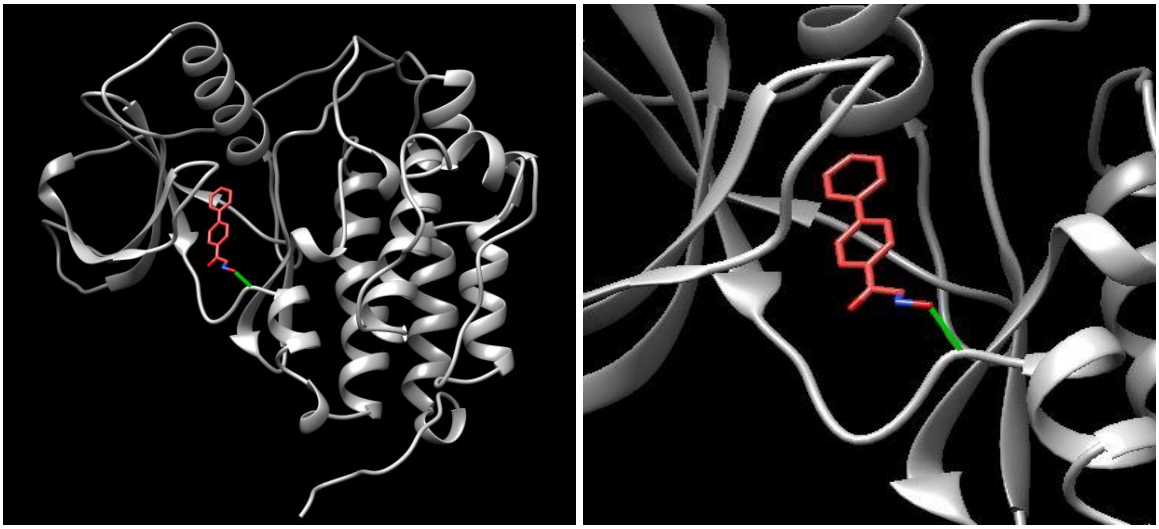


Figure 3. BHKO-1M17 couple; full (left) and closer view (right)

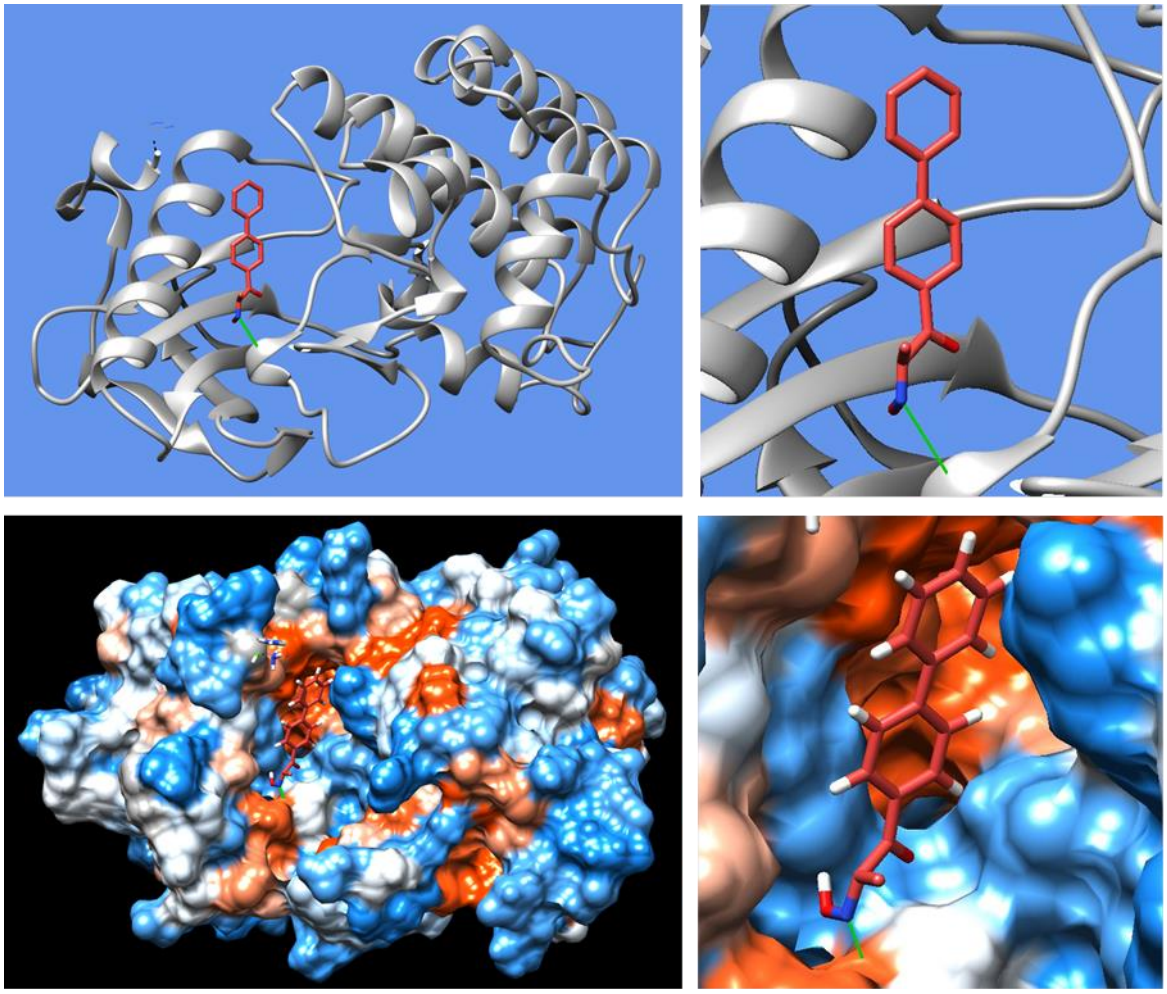


Figure 4. Ribbon shaped (above) and space-filled (below), full (left) and closer (right) views for BCKO-VEGFR-2 couple. Green line represents the hydrogen bond formed between BCKO and VEGFR-2.

In Figure 4 space-filled model (below) the red area corresponds to negative and the blue area is positive. The hydrogen bond formed between the ligand and VEGFR-2 protein is shown in green color. The hydrogen bond was formed between the hydrogen of -HN group of 1049th amino acid leucine and oxime nitrogen of the ligand.

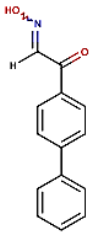
Not all the visuals related to the data in Table 1 were put in the manuscript for simplicity. Also, BHKO coupled figures kept with black background while BCKO coupled ones are kept with blue for the same reason.

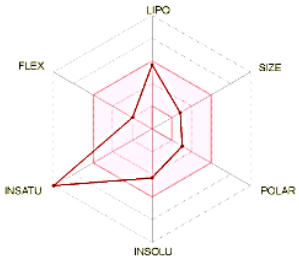
3.2. ADME Studies

Biphenyl based ligands were tested for ADME by SwissADME web server to compile the information on the pharmacokinetics and pharmacodynamics of candidate molecules. In addition, these ligands were tested for toxicity by ProTox-II web server.

Table 2. ADME table showing the physicochemical properties of BHKO (above) and BCKO (below) ligands

Molecule 1





SMILES O/N=C/C(=O)c1ccc(cc1)c1ccccc1

Physicochemical Properties	
Formula	C14H11NO2
Molecular weight	225.24 g/mol
Num. heavy atoms	17
Num. arom. heavy atoms	12
Fraction Csp3	0.00
Num. rotatable bonds	3
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	66.49
TPSA	49.66 Å²

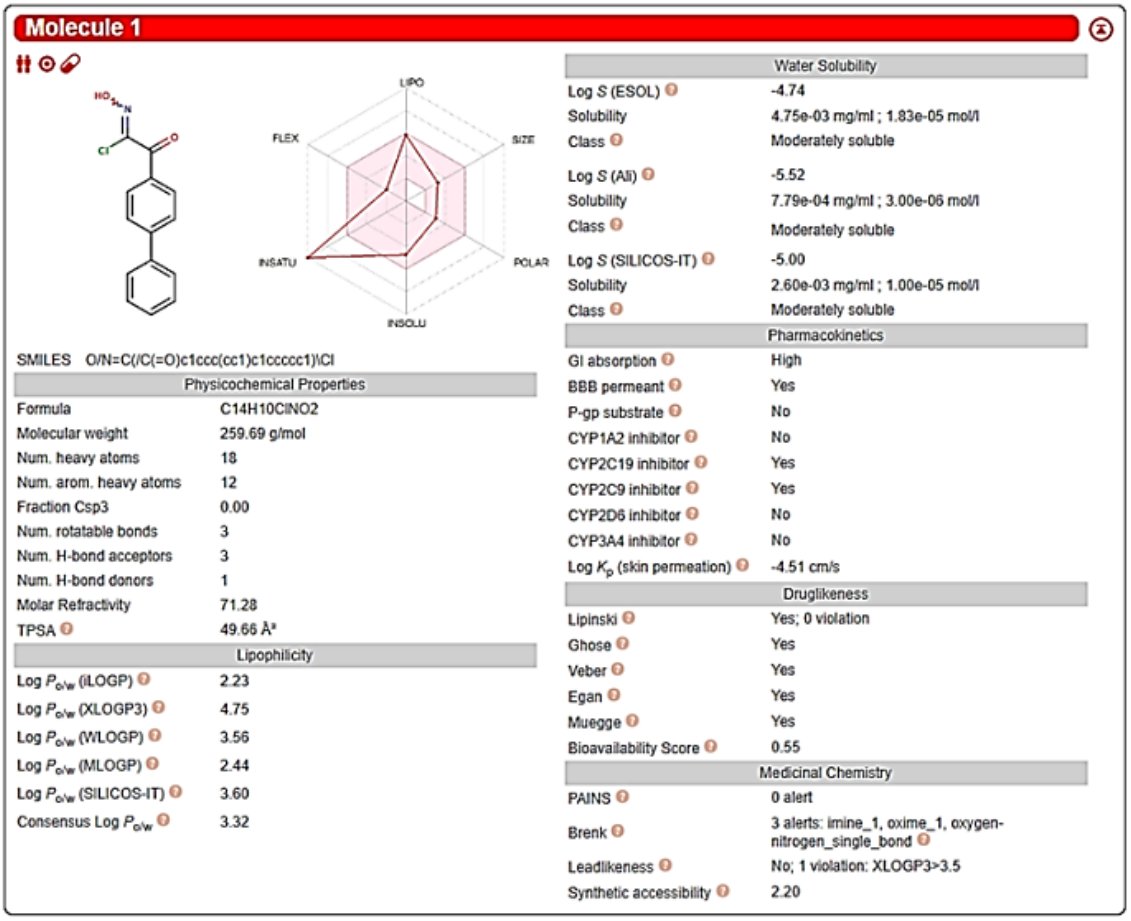
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.21
Log $P_{o/w}$ (XLOGP3)	4.38
Log $P_{o/w}$ (WLOGP)	3.00
Log $P_{o/w}$ (MLOGP)	2.19
Log $P_{o/w}$ (SILICOS-IT)	3.26
Consensus Log $P_{o/w}$	2.81

Water Solubility	
Log *S* (ESOL)	-4.32
Solubility	1.08e-02 mg/ml ; 4.78e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.14
Solubility	1.63e-03 mg/ml ; 7.26e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.39
Solubility	9.20e-03 mg/ml ; 4.08e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.56 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: imine_1, oxime_1, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW<250, XLOGP3>3.5
Synthetic accessibility	2.06



As the radar chart shows five of the six rules for druglikeness were provided by both of the executed ligands according to the SwissADME predictions. The INSATU violation in the radar chart refers to the ratio of sp^3 hybridized of C atoms to the total number of C atoms. No C atoms have sp3 hybridization for both ligands; therefore, the Csp3 fraction was zero as seen in Table 2. The official paper of SwissADME [14] also stated; for any deviation of the radar chart has been represented a suboptimal physicochemical property for oral bioavailability. Even the terms oral absorption and oral bioavailability do not refer the same meaning they are frequently used interchangeably by highly respected and cited publications. They also seem strictly correlated including the transit time (gut wall and liver passing times) to the calculations [19]. In our case a deviation from the pink area with INSATU value of SwissADME radar chart seems to make our ligand useless. We used another formula to calculate the percentage absorption of our ligand based on the PSA (polar surface area) method [20]. The percentage absorption value of the both ligands was obtained as 91.87% which may eliminate the inconvenience on the druglikeness of our ligands. In addition, both ligands provide the Lipinski's rule of five with zero violation as shown in Table 2 and 3.

Table 3. Physicochemical properties of BHKO and BCKO ligands subjected to Lipinski's Rule of Five

Physicochemical Properties						
	LIPINSKI'S RULE of FIVE					
	TPSA ($Å^2$)	Consensus Log $P_{o/w}$	MW (g/mol) ≤ 500	Log $P_{o/w}$ (MLogP) ≤ 4.15	H Bond Donor Atoms ≤ 10 (N or O)	H Bond Acceptor Atoms ≤ 5 (NH or OH)
BHKO	49.66	2.81	225.24	2.19	1	3
BCKO	49.66	3.32	259.69	2.44	1	3

In Table 2, pharmacokinetics part BHKO does not interact any of the conjugation enzymes while BCKO inhibits two of them which are CYP2C19 and CYP2C9. This is probably due to the electronegative Cl atom in BCKO which is again the only difference between two ligands.

Both ligands show high absorption rates. In Figure 5, the red plot in the middle of egg yolk shows the ligands can pass blood-brain barrier (BBB) besides the human gastrointestinal absorption (HIA). The red color of the dot refers to the info that the ligand is not a substrate for P-glycoprotein (shown as PGP-) which is an important criterion for pharmacokinetics [21]. The model was formed by plotting WLOGP vs. TPSA (lipophilicity vs. topological polar surface area) in a boiled egg model which shows the passive absorptive states. Egg orientation in the analytical coordinate also gives information about the acceptable values for WLOGP and TPSA. For BHKO and BCKO ligands both red dots located in the middle part of yolk revealing that they have the highest absorptive states for HIA and BBB.

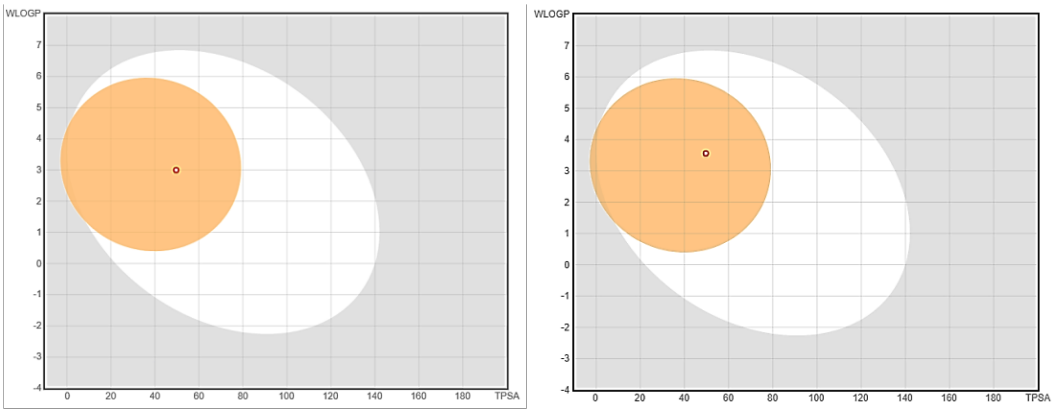


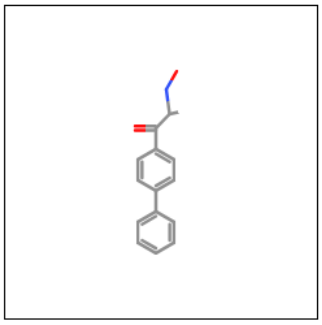
Figure 5. BOILED-Egg model for BHKO (left) and BCKO (right) ligands which refer to the predictions for human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation

3.3. Toxicological Studies

Both ligands were tested for a detailed toxicity profile. Table 4 shows a general profile for the executed molecules. LD_{50} and toxicity class of the ligands are seen in the middle. Also the similarity of the interested molecules with the molecules in the database are compared and resulted as the average similarity. Accuracy of the software is also predicted. The geometry and the identification of the molecules are also given in Table 4.

Table 4. Oral toxicity predictions for BHKO (above) and BCKO (below) ligands

Oral toxicity prediction results for input compound



Predicted LD50: 1200mg/kg

Predicted Toxicity Class: 4

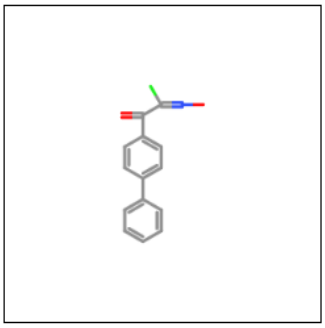
1 2 3 4 5 6

Average similarity: 67.25%

Prediction accuracy: 68.07%

Name	User defined
Molweight	226.25
Number of hydrogen bond acceptors	3
Number of hydrogen bond donors	0
Number of atoms	18
Number of bonds	19
Number of rings	2
Number of rotable bonds	4
Total charge	0
Molecular Polar Surface Area	49.33

Oral toxicity prediction results for input compound



Predicted LD50: 2000mg/kg

Predicted Toxicity Class: 4

1 2 3 4 5 6

Average similarity: 58.31%

Prediction accuracy: 67.38%

Name	User defined
Molweight	259.69
Number of hydrogen bond acceptors	3
Number of hydrogen bond donors	0
Number of atoms	18
Number of bonds	19
Number of rings	2
Number of rotable bonds	3
Total charge	0
Molecular Polar Surface Area	49.66

In Table 4 both ligands were sketched and predicted for LD_{50} which is higher for BCKO ligand but the range they resided is Toxicity Class 4 for both ligands. Not significantly, BCKO is less toxic. Both ligands also share similar molecular properties with an only exchange in Cl and H atoms.

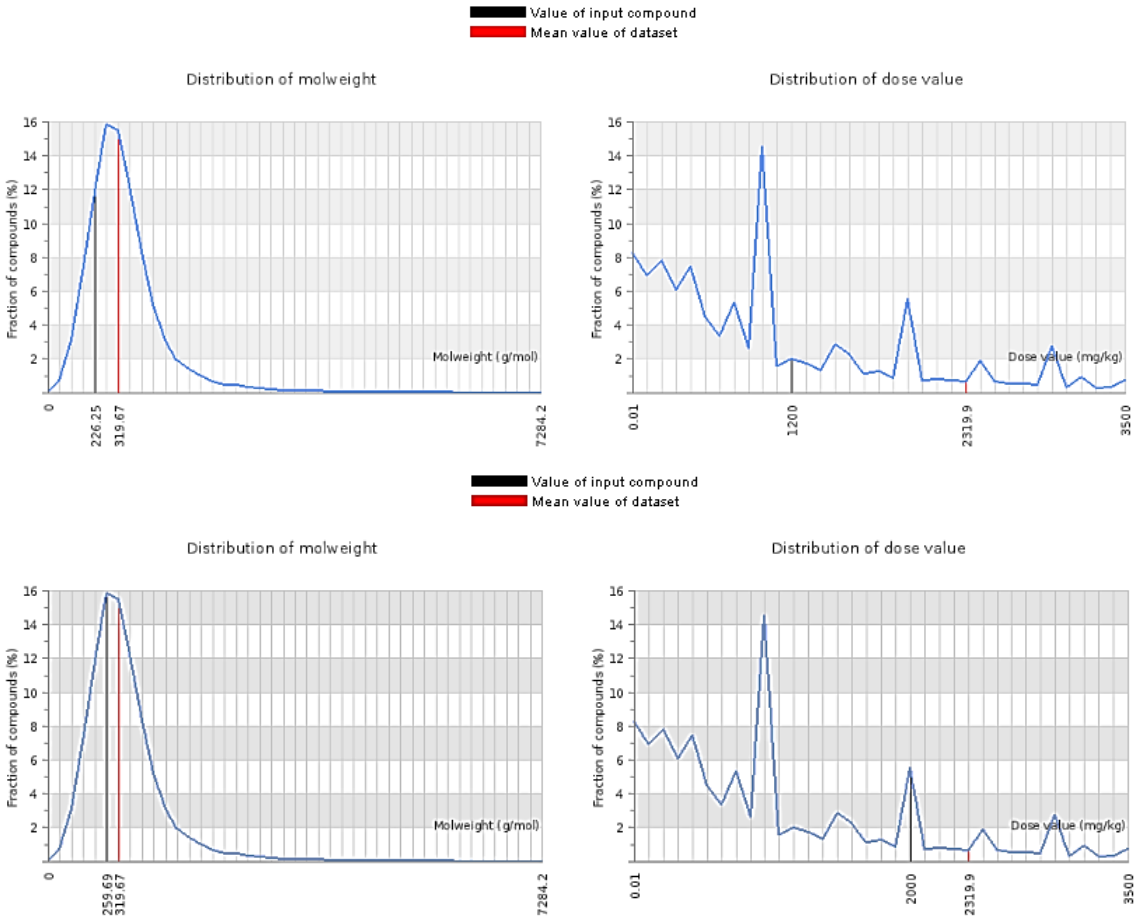


Figure 6. The molecular weight and administrated dose of BHKO (left) and BCKO (right) are compared with the commercially active agents' average molecular weight and dose.

In Figure 6 mean values of molecular weights and dose values for the commercial agents in the market (limited to the agents in the database of ProTox-II) are compared to the molecule of interest. Both ligands' molecular weight and dose values were below the mean value of dataset.

Table 5. Toxicity test results of the BHKO (above) and BCKO (below) ligand in toxicologically important parameters

Toxicity Model Report

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.53
Toxicity end points	Carcinogenicity	carcino	Active	0.50
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Active	0.58
Toxicity end points	Cytotoxicity	cyto	Inactive	0.69
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.77
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.92
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.78
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.95
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.93
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.93
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.78
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.92
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.90

Toxicity Model Report

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Active	0.55
Toxicity end points	Carcinogenicity	carcino	Inactive	0.51
Toxicity end points	Immunotoxicity	immuno	Inactive	0.98
Toxicity end points	Mutagenicity	mutagen	Inactive	0.58
Toxicity end points	Cytotoxicity	cyto	Inactive	0.75
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.67
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.85
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.74
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.86
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.90
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.84
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.84
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.59
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.83
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.74

In Table 5; toxicologically important parameters were interpreted. BHKO ligands' carcinogenicity and mutagenicity is 50% and 58% active where the mean value of the dataset is given as 88% and 79%, respectively. All other parameters were inactive for BHKO ligand. For BCKO only hepatotoxicity was 55% active where the mean value for the drugs in the market was given as 82%.

4. Conclusion and Comment

The molecular docking capacities of both ligands were similar. The carcinogenic effect in the BHKO ligand was eliminated by the H & Cl exchange. As we stated before, the only difference between ligands were Cl replaced by H atom. This is a huge difference for a drug candidate having carcinogenic and mutagenic effects which can be eliminated by a "click" movement indicating the importance of the redesign of the drugs. Drug resistance and side effects can be eliminated by the reconstruction of the drugs already on the market.

Author Statement

Güvenç GÖRGÜLÜ: Investigation, Software, Visualization, Original Draft Writing, Review and Editing.
Bülent DEDE: Methodology, Original Draft Writing, Review and Editing.

Acknowledgment

As the authors of this study, we declare that we do not have any support and thank you statement.

Conflict of Interest

As the authors of this study, we declare that we do not have any conflict of interest statement.

Ethics Committee Approval and Informed Consent

As the authors of this study, we declare that we do not have any ethics committee approval and/or informed consent statement.

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