J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 46(1): 23-34, 2022
Doi: 10.33483/jfpau.1008048

ORIGINAL ARTICLE / ÖZGÜN MAKALE

MOLECULAR DOCKING STUDIES OF COX INHIBITORS ON WILD-TYPE RAS

COX İNHİBİTÖRLERİNİN YABANİ-TİP RAS ENZİMİ ÜZERİNDE MOLEKÜLER DOKİNG ÇALIŞMALARI

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ABSTRACT

Objective: *In addition to its role in the formation mechanism of inflammation, the binding potential of COX inhibitors, which can inhibit tumorogenesis by induce apoptosis, has been explored by molecular docking studies on wild-type RAS enzyme.*

Material and Method: *KRAS enzyme (PDB ID: 4OBE), which consists is obtained by the x-ray crystallization method, was chosed considering the resolution. The 2D structures of ligand molecules were drawn in the ChemDraw 19.1. The MOE 2020 program was used to form the docking studies.*

Result and Discussion: *As a result of docking studies, it has been understood that the presence of aromatic structures in 3a and 3b ligand molecules is critical for ligand-receptor interaction. it has been understood that there must be a certain distance between the carbonyl group and the nonpolar part of the molecule for the molecule to bind to the receptor site with a high affinity. In the following stages, more effective anticancer drug molecules can be obtained by design molecules with an appropriate diameter and length, having functional groups containing the suitable electron donor or acceptor.*

Keywords: *RAS, COX inhibitors, docking, MOE, binding affinity*

ÖZ

Amaç: *Inflamasyon oluşum mekanizmasındaki rolünün yanı sıra apoptoz oluşumunu tetikleyerek tümorogenesisi inhibe edebilen COX inhibitörlerinin yabani-tip RAS enzimi üzerinde moleküler doking çalışmaları ile bağlanma potansiyelleri araştırılmıştır.*

Gereç ve Yöntem: *X-ışını kristalizasyon yöntemi ile elde edilen KRAS enzimi (PDB kodu: 4OBE) çözünürlük dikkate alınarak seçilmiştir.Ligand moleküllerinin 2 boyutlu yapıları ChemDraw 19.1'de çizilmiştir. Doking çalışmaları için MOE 2020 programı kullanılmıştır.*

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Submitted / Gönderilme: 11.10.2021 **Accepted / Kabul:** 22.10.2021

Sonuç ve Tartışma: *Docking çalışmaları sonucunda 3a ve 3b ligand moleküllerinde aromatik yapıların varlığının ligand-reseptör etkileşimi için kritik olduğu anlaşılmıştır. Molekülün reseptör bölgesine yüksek afinite ile bağlanabilmesi için karbonil grubu ile molekülün polar olmayan kısmı arasında belirli bir mesafe olması gerektiği anlaşılmıştır. İlerleyen aşamalarda uygun elektron verici veya alıcı içeren fonksiyonel gruplara sahip uygun çap ve uzunlukta moleküller tasarlanarak daha etkili antikanser ilaç molekülleri elde edilebilir.*

Anahtar kelimeler: *RAS, COX inhibitors, doking, MOE, bağlanma afinitesi*

INTRODUCTION

KRAS, NRAS, and HRAS are small GTPase proteins that attitude as cycling between inactive GDP-bound and active GTP-bound forms, transmitting signals from membrane bound receptors and expressed in all humans [1]. When Ras proteins are activated, "switch on" of downstream effectors that turn on genes, which are concerned in essential cellular processes such as cell growth, differentiation, and survival. It was identified as a retroviral oncogene by Harvey and Kirsten in the 1960s when sarcomas were excited in rodents from a murine leukemogenic virus preparation. Therefore, Kirsten rat sarcoma 2 viral oncogene homolog as it is named [2, 3].

There are four different RAS proteins (HRAS, NRAS, KRAS4A and KRAS4B) encoded by three human Ras genes (HRAS, NRAS and KRAS) [4]. Because of their crucial role in signaling, mutation of the RAS gene family is implicated in human cancers [5]. These mutations cause sequential signal activation, thereby leading to the development of various cancers such as pancreatic, colorectal and lung malignancies [4]. Mutations in codons 12, 13 and 61 of Ras proteins are known to be associated with cancer [6]. Mutations of RAS proteins occur in more than 30% of human cancers [7]. Mutational profiles in different cancer types differ among of RAS gene isoforms [6].

For example, there is the most commonly mutation of KRAS with 86 % possibility, and it occurs mostly in pancreatic ductal, colorectal, lung, ovarian and endometrial carcinoma. On the other hand, while the isoform NRAS mutations were occured in cutaneous melanoma, hematopoietic malignancies, and colorectal cancer at amino acid 61. HRAS is the isoform mutated from amino acids 12, 13 and 61 in bladder and cervical cancers [7, 8].

For more than three decades, the importance of the numerous roles of RAS proteins in essential cellular processes has been identified. For this reason, inhibitor drug development studies are realized against these oncogenes. However, these studies have been quite challenging as the inhibition of wild-type RAS could be lethal [9].

Inflammation, which is the necessary defense mechanism to protection cellular homeostasis, is also a protective biological response of living mammalian tissue to harmful stimuli [10].

The inflammatory process is classified as acute or chronic. While acute inflammation takes minutes, a few hours, or several days to be protective, chronic inflammation results from uncontrolled acute inflammation that is amplified by long-term adverse stimuli such as an ongoing disease or

permanent cellular damage, ultimately leading to damaged tissues [10].

It mainly causes diseases including as cancer, asthma, rheumatoid arthritis, neurodegenerative disease, metabolic and cardiovascular disorders [11-17].

NSAIDs are known to have anticancer effects. NSAIDs act by inhibiting the COX-associated tumorigenesis mechanism, thereby making hazardous exposures less toxic. This mechanism is extremely related to the aero-digestive organs (i.e. lung and colon) submitted to a wide range of exogenous chemicals (i.e. xenobiotics) [18,19].

Increased the production of angiogenic growth factor [vascular endothelial growth factor (VGEF), basic fibroblast growth factor (bFGF) and transforming growth factor-beta (TGF-)] has been seen in cancer cells with overexpression of COX-2 [20]. These formations could be prevented by selective COX2 inhibitors with some non-selective COX inhibitor [20-22].

Though the antiapoptotic mechanisms continue to exist uncertain, many studies demonstrate the significance of COX-mediated apoptosis in cancers of the esophagus [23], gallbladder [24], CNS [25], head and neck [26], hematopoietic system [27], lung [28], and pancreas [29].

COX inhibitors disrupt the balance between cell proliferation and apoptosis, thereby causing tumor regression [30, 31].

In this study, we aimed to investigate the binding potential of drug molecules used as COX inhibitors to the KRAS enzyme.

MATERIAL AND METHOD

Molecular Docking Studies

Preparation of Protein Structure

As the KRAS enzyme, the enzyme that has not undergone any mutation in the amino acid sequence and did not covalently bond with the ligand during the crystallization process was chosen from the Protein Data Bank (www.rscb.org),the enzyme (PDB code: 4OBE [32], Guanosine-5'-Diphosphate as an inhibitor), which consists of two subunits and is obtained by the x-ray crystallization method, was used considering the resolution.

MOE 2020 (Molecular Operating Environment 2020) program was used to reduce the tension of the crystal structure and prepare the appropriate enzyme structure. Thanks to this program, polar and nonpolar hydrogens in the crystal structure of the macromolecules were first deleted and then added again, making the enzyme suitable. The resulting macromolecule structure protonated at the appropriate pH and temperature.

The energy of the enzyme is minimized by deleting the water molecules and the ligands used for crystallization. The AMBER 99 (Assisted Model Building with Energy Refinement) internal package program was used as a force field and saved as the moe file extension in this energy minimizing process.

The surface of the macromolecule was scanned, and optimization processes were performed to find the active sites on the enzyme.

Ligand Preparation

The 2D structures of ligand molecules were drawn in the ChemDraw 19.1 (Perkin Elmer Informatics) program and, the database was created by transferring to the MOE system. Polar and nonpolar hydrogens were added to this data, converted into a 3D structure, and then saved as a .mdb file extension. Here, 33 different molecules (Table 2) were optimized by converting them into a ligand dataset. MMFF 94x (Merck Molecular Force Field) package program, appropriate for small molecules, was used for the required energy minimizing process. This process was performed at the smallest possible gradient value.

Protein-Ligand Modeling Simulation

Molecular docking studies examine protein-protein or ligand-protein interactions and, these interaction results score with the binding affinity scoring method and show the bonds in the interaction [33]. The MOE 2020 program was used to form the modeling files. Here, the region where the switch-II lobe is located was chosen as the most suitable active site for the enzyme. It was measured that there was a sufficient interaction area for the ligand molecule in these regions and the obtained value was compared with the sizes of the ligands. The modeling study was limited to the 30 most stable conformers with different torsion angles for each ligand. The data obtained from the modeling were interpreted according to the RMSD (Root Mean Square Deviation) and S (Score) value which indcicates the binding energy and binding affinity.

RESULT AND DISCUSSION

The S modeling value in MOE 2020 shows the bonding relationship between ligands and amino acids of the enzyme. Six different molecules (Table 1) were found to have better binding potential with KRAS protein taking into account the S value, binding energy, and RMSD values. In the docking studies, the presence of carboxyl acid or sulfonamide functional group in the NSAID molecules increased the hydrogen bond potential. It has been found that these polar structures increase the protein binding affinity as a hydrogen acceptor or donor. The presence of aromatic structures in the molecule is important for the interaction between the polar amino acid hydrogen and the π bonds of the molecule. In the pocket region of the receptor, Ser17, Gly13, Ile36, Lys16, Glu31 amino acids can be preferred as potential targets for hydrogen bonding. In addition, it has been understood that amino acids such as Gly 16, Thr 58, Ala 59, Asp30 are significant for receptor-ligand interaction in modeling.

In docking studies done using MOE, the low S (Binding affinity score) value is desirable. A hydrogen bond formed between the carboxylic acid functional group of the 3a molecule with the best

S-score and –NH2 at the 6th position of the Lys16 amino acid (Figure 1). Moreover, having two separate carbonyl groups in the molecule increased the potential for hydrogen bonding. A hydrogen bond was also formed between the 3a ligand molecule and the NH proton of Gly13. It has been understood that the presence of aromatic structures in 3a and 3b ligand molecules is critical for ligand-receptor interaction. As can be seen from the obtained binding energies (Table 1), it has been understood that there must be a certain distance between the carbonyl group and the nonpolar part of the molecule for the molecule to bind to the receptor site with a high affinity.

There are two potential binding sites in the active pocket of the enzyme molecule [34]. The binding site of the phosphate molecule in this region (P-loop) is important for the potential to form hydrogen bonds when designing new drug molecules. The pocket in this region has a diameter of about 6 Å, and it was observed that NSAID molecules with a width smaller than this value settle better in this pocket. In this context, the preference of electron acceptor and donor structures in the phosphate-binding region, as well as the diameter of the molecule, can be considered significant for activity in drug design. (Figure 4).

Table 1. NSAID compounds and docking results showing the highest affinity

Docking Results			**Molecular properties**		
Molecules	S-Value	RMSD	MW	Log P	TPSA
3a	-6.1253	1.4724	254.28	3.40	54.37
4a	-5.9963	1.4197	357.79	3.93	68.53
1c	-5.9394	1.1059	250.2	3.04	57.53
3b	-5.6663	0.5745	242.27	3.67	46.53
3g	-5.4876	1.2526	293.32	4.03	63.33
3d	-5.4019	1.0822	206.28	3.07	37.3

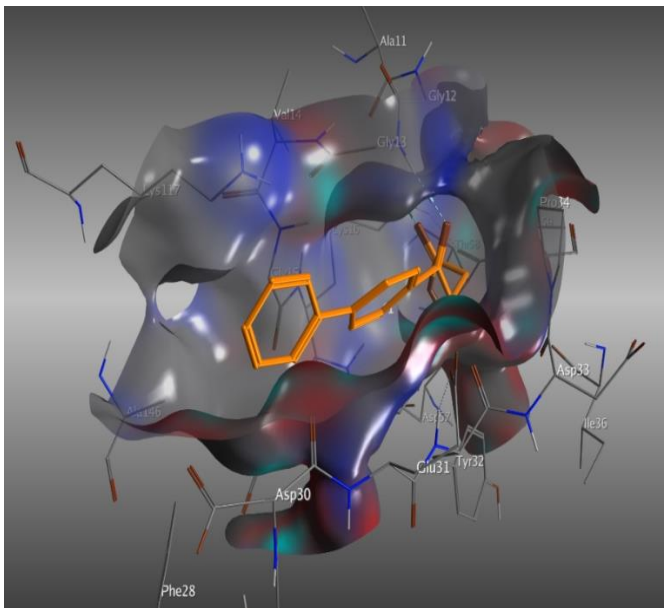


Figure 1. Binding pose of the 3a molecule with the active site of the KRAS enzyme (PDB ID: 4OBE)

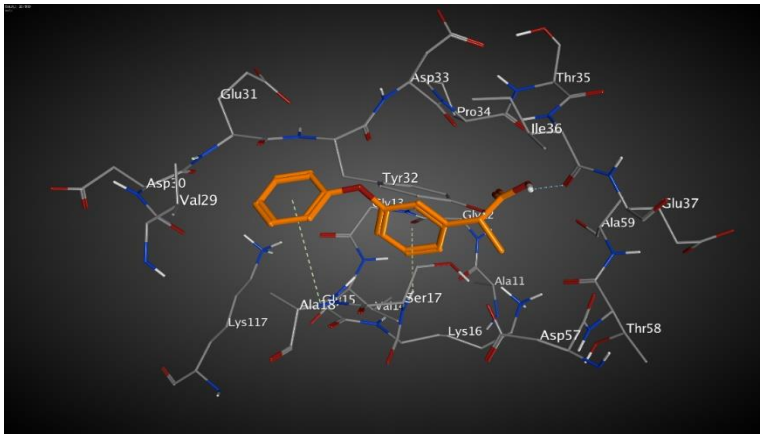


Figure 2. Binding pose of the 3b molecule with the active site of the KRAS enzyme (PDB ID: 4OBE)

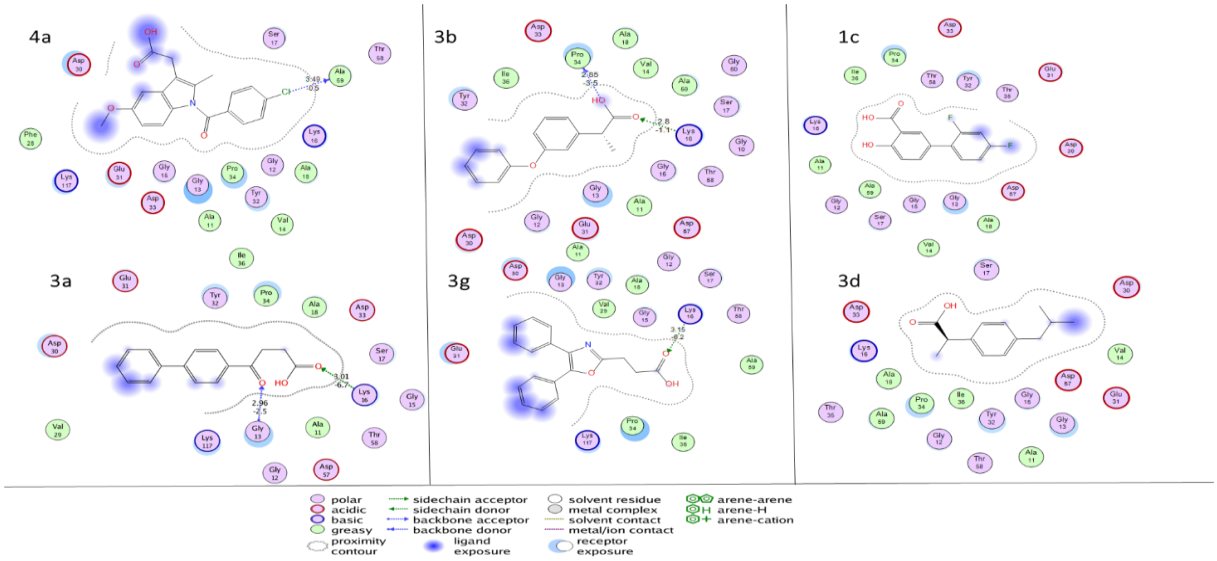


Figure 3. The active site of the human KRAS enzyme (PDB ID: 4OBE) and 2D binding poses with compounds 1c, 2a, 3a, 3b, 3g, 4a. Hydrogen bonding regions, binding energies, and distances are shown. Hydrogen bonds and polar-π, π - π, hydrophobic interactions are shown.

The second binding site of the enzyme is the area where GTP nucleosides are attached. In this region, a π-H bond is formed between the aromatic ring of the ligand and the -NH proton of the enzyme. Apart from this bond, this site is also a significant region for hydrophobic and π-π interactions. It was observed that the presence of structures such as naphthalene, heterocyclic rings, heteroaromatics, or aromatic rings with electron-donating groups increased the bonding. Furthermore, it can be assumed that a length above 10 Å between the polar part of the drug molecule and the aromatic ring is significant in creating a high interaction between the ligand and the protein. Among the NSAID molecules we docked (Table 3), it has been observed that the molecules complying with this rule had better binding energies. In salicylic acid derivative molecules such as 1a and 1b, a lower binding potential has been observed due to the short distance between the aromatic ring and the carboxylic acid.

Table 2. NSAID drug molecules and S-Values

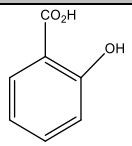
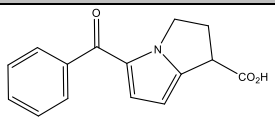
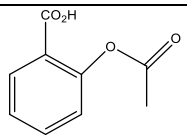
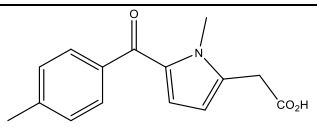
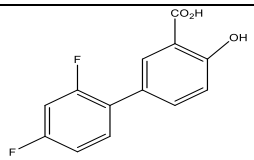
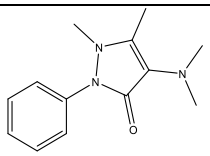
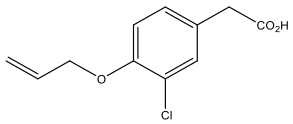
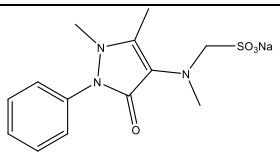
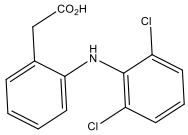
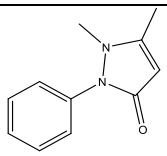
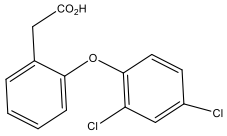
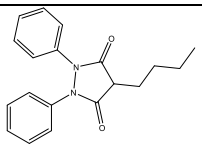
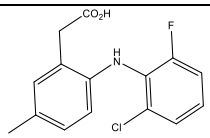
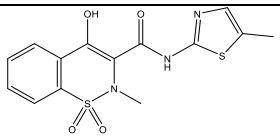
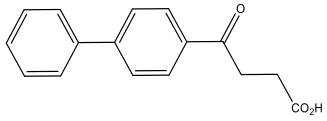
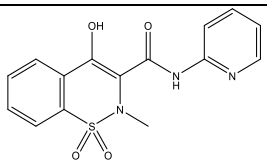
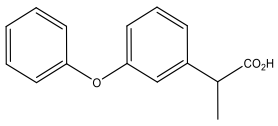
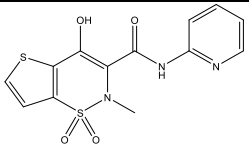
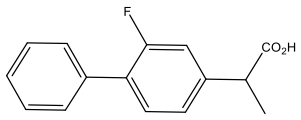
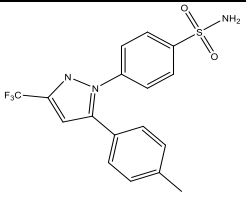
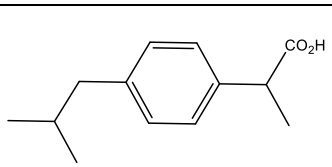
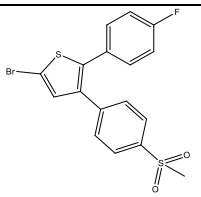
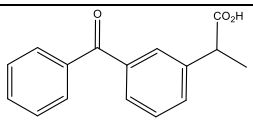
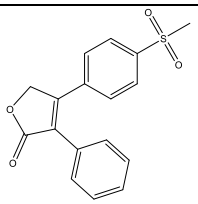
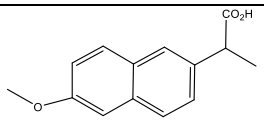
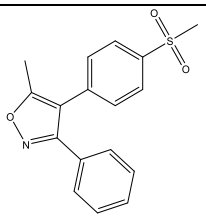
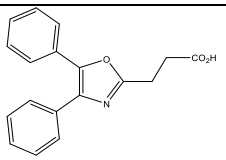
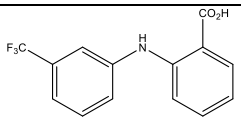
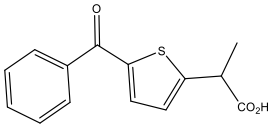
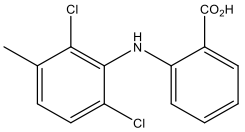
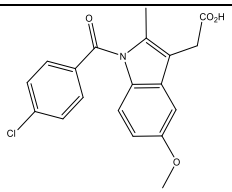
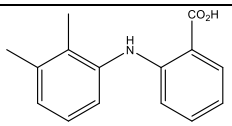
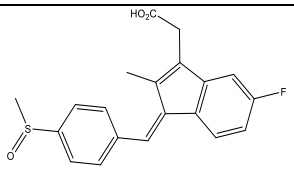
Compound		S Value	Compound		S Value
1a		-4.4984	**4c**		-4.8728
1b		-4.1726	**4d**		-4.7131
1c		-5.9394	**5a**		-3.8434
2a		-5.3677	**5b**		-5.0768
2b		-4.9669	**5c**		-3.9116
2c		-4.3277	**5d**		-4.6868
2d		-4.5919	**6a**		-4.7468
3a		-6.1253	**6b**		-4.5565
3b		-5.6663	**6c**		-4.5324
3c		-5.2392	**7a**		-4.5095

Table 2 (*continued*). NSAID drug molecules and S-Values

3d		-5.4019	**7b**		-4.7326
3e		-4.8891	**7c**		-5.1170
3f		-4.9346	**7d**		-4.7906
3g		-5.4876	**8a**		-4.5991
3h		-4.4148	**8b**		-5.0570
4a		-5.9963	**8c**		-4.5346
4b		-4.1314			

As a result, the KRAS enzyme is known very important in the formation of some cancer cells [35]. A more effective anticancer drug molecule can be designed by considering the 3D structure of the pocket in the active site of the enzyme and using the data from this docking study. In the following stages, more effective anticancer drug molecules can be obtained by design molecules with an appropriate diameter and length, having functional groups containing the suitable electron donor or acceptor.

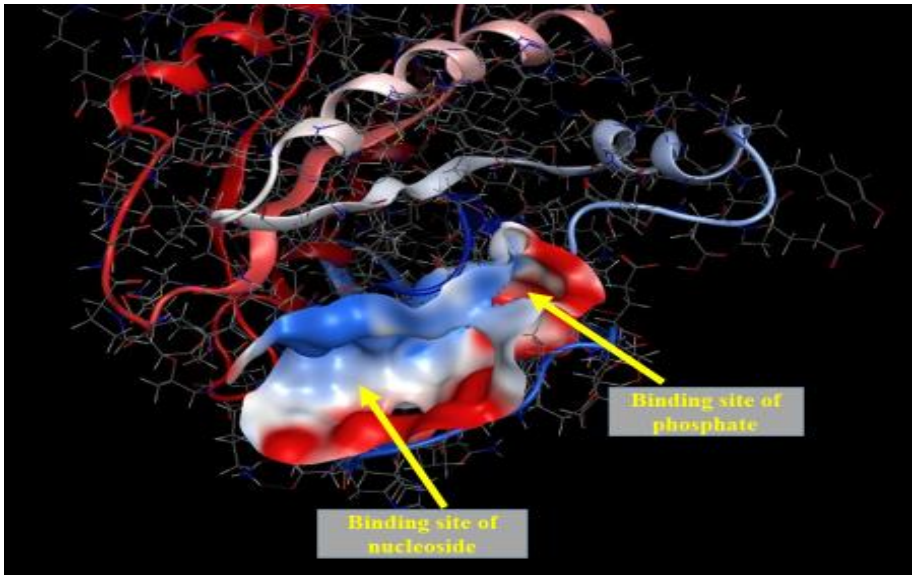


Figure 4. Binding sites and 3D structure of the active pocket of the wt-KRAS enzyme

Table 3. Binding energy values of NSAIDs which are a derivative of propionic acid and salicylic acid

Molecules	S-Value	Receptor	Bond	Distance (Å)	Energy (Kcal/Mol)
3a	-6.1253	Gly13	H-bond acceptor (HBAs)	2.96	-2.5
		Lys16	H-bond acceptor (HBAs)	3.01	-6.7
3b	-5.6663	Pro34	H-bond donor (HBDs)	2.85	-3.5
		Lys16	H-bond acceptor (HBAs)	2.80	-1.1
1a	-4.5459	Ser17	H-bond donor (HBDs)	3.18	-1.2
		Lys16	H-bond acceptor (HBAs)	2.76	-10.0
1b	-4.1726	Glu162	H-bond donor (HBDs)	3.05	-2.4

AUTHOR CONTRIBUTIONS

Conception: *D.K.*; Design: *D.K., H.O.*; Supervision: *D.K., H.O.*; Resources: *D.K., H.O., Z.A.*; Materials: *D.K., H.O., Z.A.*; Data Collection and/or processing: *D.K., H.O.*; Analysis and/or interpretation: *D.K., H.O*; Literature search: *D.K., H.O., Z.A.*; Writing manuscript: *D.K., H.O., Z.A.*; Critical review: *D.K., H.O.*; Other: *Z.A.*

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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