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Araştırma Makalesi / Research Article

Molecular Docking and Reactive Sites Identification (Homo–Lumo, Mep) of Allicin and Diallyl Disulfide: Potential Anticancer Inhibitor

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Abstract

Natural products have historically made a significant contribution to pharmacotherapy, especially for cancer diseases. Garlic contains a variety of bioactive molecules with anticancer effects, including allicin and diallyl disulfide. In this study, optimization computations were performed in the Gaussian 09 W utilizing the DFT with functional B3LYP method/6-31++G(d,p) basis set for allicin and diallyl disulfide. Drug-likeness and ADME-Tox properties were examined. Molecular docking was achieved to research the biological knowledge of allicin and diallyl disulfide. The protein preferred in these computations is the crystal structure of the 5XGN, EGFR mutants T790M/C797S complex. The binding energies for the allicin and diallyl disulfide molecules-EGFR mutants T790M/C797S complex were computed as -8.3 kcal/mol and -8.2 kcal/mol respectively. Meaningful results were achieved for these two compounds.

Keywords: Allicin; Diallyl disulfide; DFT; HOMO-LUMO; Molecular docking; Garlic.

Allisin ve Diallil Disülfitin Moleküler Yerleştirme ve Reaktif Bölgelerinin Tanımlanması (Homo–Lumo, Mep): Potansiyel Antikanser İnhibitörü

Öz

Doğal ürünler tarihsel olarak, özellikle kanser hastalıkları için farmakoterapiye önemli bir katkı sağlamıştır. Sarımsak, allisin ve diallil disülfit dahil olmak üzere antikanser etkileri olan çeşitli biyoaktif moleküller içerir. Bu çalışmada, allisin ve diallil disülfit için fonksiyonel B3LYP yöntemi/6-31++G(d,p) temel seti ile DFT kullanılarak Gaussian 09 W'da optimizasyon hesaplamaları yapılmıştır. İlaca benzerlik ve absorpsiyon, dağılım, metabolizma, atılım ve toksisite (ADMET) özellikleri incelendi. Allisin ve diallil disülfitin biyolojik bilgisini araştırmak için moleküler yerleştirme gerçekleştirildi. Bu hesaplamalarda tercih edilen protein, 5XGN, EGFR mutantları T790M/C797S kompleksinin kristal yapısıdır. Allisin ve diallil disülfit molekülleri-EGFR mutantları T790M/C797S kompleksi için bağlanma enerjileri sırasıyla -8.3 kcal/mol ve -8.2 kcal/mol olarak hesaplandı. Bu iki bileşik için anlamlı sonuçlar elde edildi.

Anahtar Kelimeler: Allisin; Diallil disülfit; DFT; HOMO-LUMO; Moleküler yerleştirme; Sarımsak.

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1. Introduction

Cancer is clearly one of the most extensive worrisome diseases and one of the leading reasons for human death despite advancing technology and treatment methods (Chakraborty and Rahman, 2012; Bray et al., 2018). Detailed analysis of the pathways and mechanisms for the spread of cancer and the identification of several antitumor agents has led to significant advances in the protection and treatment of cancer (Zhao et al., 2021; Liu et al., 2021). Chemotherapy and irradiation are the gold standard approaches in cancer treatment worldwide, despite their toxicities (Miller et al., 2016; Pulte et al., 2010). The changes leading to cancer development are also controlled by many mediators, including protein tyrosine kinases and receptors (Kasmi et al., 2022and). Epidermal growth factor receptor (EGFR) is one of them, and is a tyrosine kinase receptor. It is overexpressed by different types of cancer, including lung, colon, pancreas, breast, and ovary (Mitsudomi and Yatabe, 2010). Tyrosine kinase inhibitors have become the mainstay in the treatment in non- mall cell lung cancer (NSCLC). Drugs such as Erlotinib (EGFR and HER2 tryrosine kinase inhibitors), Gefitinib, Crizotinib, Ceritinib have become attractive drugs for the treatment of NSCLC patients (Zhang et al., 2012).

On the other hand, the use of natural products from plants and their derivatives has produced remarkable clues for cancer treatment (Rayan et al., 2017; Choudhari et al., 2020). Up to 60% of the current anti-cancer drugs currently on the market and extensively adopted in clinical use are natural product derivatives (Abdalla et al., 2022). Classic examples of chemotherapeutic agents used in cancer treatment are the vinca alkaloids (Martino et al., 2018), etoposide (Baldwin and Osheroff, 2005), teniposide (Giaccone et al., 1988), irinotecan (Bailly, 2019), and taxanes (Huizing et al., 1995). Such medicaments are extremely efficient against various types of cancer; however, side effects (eg, hair loss, immunosuppression, and hematological toxicity) and high costs lead to the search for alternative treatments derived from natural products (Dehelean et al. 2021). It is also very important that cancer cells mutate and become resistant to these drugs (Housman et al., 2014). Therefore, in recent years, phytochemicals have been recognized as appropriate nominees for anti-cancer medicine improvement owing to their multiple effects on several targets with distinct mechanisms of action (Iqbal et al., 2017). A wide diversity of natural products such as flavonoids, polyesters, terpenoids, polyphenols, alkaloids, and other secondary metabolites have shown promising anticancer properties (Mohammed et al., 2023). Plant-based natural products cause fewer undesirable side effects due to their similarity to chemical components found in the human diet, which have significant tolerance-inducing abilities (Wangchuk, 2023).

Garlic contains a diversity of bioactive compounds, including organosulfur compounds (Rouf et al., 2020), saponins (Diretto et al., 2017), flavonoids/isoflavonoids (Rekowska and Skupień, 2009),

terpenes (Kuete, 2017), and phenolic compounds (Tavares et al., 2021). Garlic (Allium sativum L.) is eaten as a nutrition globally and has been used as a conventional drug for centuries. It has numerous intriguing biological activities, containing antithrombotic, anticarcinogenic, antihypertensive, antiviral, antiparasitic, anti-inflammatory, antioxidant, antifungal, and antibacterial (El-Saber Batiha et al., 2020). Garlic extracts and garlic-derived compounds are receiving increasing attention due to their biological activities against different types of diseases. Some of the biologically effective compositions isolated from garlic (Martins et al., 2016; Bazaraliyeva et al., 2022) are given in Figure 1. Fresh garlic contains 0.4% alliin, allicin and essential oil, and 0.2-0.5% garlic oil. 94% of garlic oil forms from sulfur compounds (4.7-8.0% Diallyl Sulfide, 21.9-40.0% Diallyl Disulfide, 39.0-41.5% Diallyl Trisulfide) (Akan, 2014). These compositions have been noticed to have more than one pharmacological activity dedicated in Table 1.

Table 1. Bioactive properties of a few compounds isolated from Allium sativum L.

Compound	Activities
Ajoene	Antiprotozoal, Anticancer, Antiobesity
Allicin	Antibacterial, Antiviral, Antiprotozoal, Anticancer, Antioxidant, Antiinflammatory, Antidiabetic
Diallyl Sulfide	Antioxidant, Antiinflammatory, Anticancer
Diallyl Disulfide	Anticancer, Antifungal, Antioxidant
Diallyl Trisulfide	Antioxidant, Antifungal, Antiprotozoal, Antiviral

It has been reported that the organosulfur compounds of garlic effectively reduce serum cholesterol and triglycerides, inhibit the peroxidation of lipids, prevent cardiovascular diseases including atherosclerosis, and also play a role in tumor shrinkage (Talib, 2017). In addition, diallyl disulfide is an important organosulfur compound found in garlic. Recently, a few experimental works have shown that diallyl disulfide exhibits anti-tumor activity against many tumor cells, containing gynecological cancers, lung cancer, skin cancer, hematological cancers, and prostate (Mitra et al., 2022).

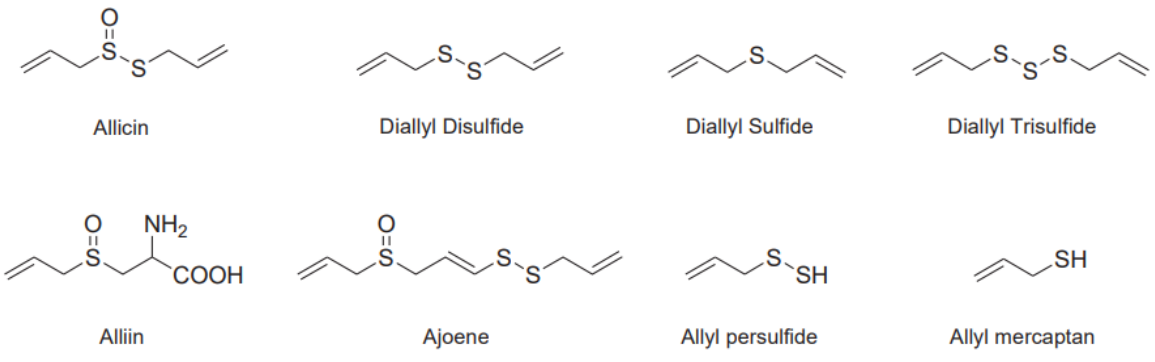


Figure 1. Structural formulas of some compounds isolated from Allium sativum L.

This study goals to investigate the present knowledge regarding the cancer prevention potency of allicin and diallyl disulfide compounds, as well as to sum up their mechanism of effect. Thus, it offers a computational approach to appraise the structural and biological properties of allicin and diallyl disulfide with their diverse states of function against the illnesses defined upstairs.

First, compounds were considered as optimal structures, and data were calculated on the basis set 6-31++G(d,p) using the Density Functional Theory (DFT) Becke3-Lee-Yang-Parr (B3LYP) method. HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies were computed for the two compounds in different environments. The chemical behavior of the compounds was analyzed through electronic parameters derived from DFT. In addition, a docking study was made to examine the binding conformation of the molecules at the 5XGN active site, and in silico ADME-Tox profile studies were accomplished.

2. Materials and Methods

2.1. Computational Methods

Quantum chemical computations supported by DFT were carried out using Gaussian 09 W program package (Frisch et al., 2009) at B3LYP/6-31++G(d,p) basis set. The obtained results were visualized by the Spartan ’10 package program (Wavefunction Inc., Irvine, CA). Some druggability, pharmacokinetics, and toxicity analyses were estimated owing to online web tools. The used web servers were ADMETlab (Guéniche et al., 2021), admetSAR (Desale et al., 2021), SwissADME (Daina et al., 2017), Pro Tox-II (Banerjee and Ulker, 2022), SwissTargetPrediction (Gfeller et al., 2014). The docking analyzes were accomplished using UCSF Chimera software with its AutoDock Vina tool (Butt et al., 2020). The 5XGN coded structure, which contains the three-dimensional structure coordinates of the EGFR kinase taken from the protein data bank (PDB), was used only with the Autodock Vina Program. By finding the appropriate binding coordinates of the protein, the results of the 5XGN structure with the smallest RMSD value and lowest binding energy were given. PubChem (Wang et al., 2009) was used for the 3D SDF formats of allicin and diallyl disulfide.

3. Findings and Discussion

3.1. Computational Structural Analysis

HOMO and LUMO, named as frontier molecular orbitals (FMOs), play a crucial role to predict the reactivity and stability of compounds (Yavuz, 2023). Since HOMO symbolizes the ability to

donate an electron and LUMO symbolizes the ability to accept an electron, the HOMO-LUMO energy difference elucidates the ultimate charge transference interaction within the molecule (Mary et al., 2015). The FMOs of the molecules of allicin and diallyl disulfide were computed by using DFT/B3LYP method with 6-31++G(d,p) basis set in the water, gaseous ambient, and methanol. The allicin and diallyl disulfide had the highest energy range (5.21504 eV and 5.33123 eV) for water media, respectively owing to the HOMO-LUMO areas and ΔE energy gaps shown in Table 2. Particularly, ΔE energy differences in liquid ambient were larger than in gaseous ambient. The great energy range value demonstrates that high energy was required to transfer the molecule from the stable case to the stimulated case. In gas and methanol ambiance, ΔE values were determined to be 5.06837 eV and 5.21041 eV for allicin, respectively, and 5.29912 eV and 5.30810 eV for diallyl disulfide, respectively. FMOs plot, energies of HOMO-LUMO, energy gap (ΔE) for allicin and diallyl disulfide in the gas media were shown in Figure 2.

Table 2. Molecular Orbital Energy (HOMO and LUMO) of allicin and diallyl disulfide in different ambient.

	Allicin				***Diallyl disulfide***			
Ambient	$E_{HOMO(a.u.)}$	$E_{LUMO(a.u.)}$	$\Delta E_{(a.u.)}$	$\Delta E_{(eV)}$	$E_{HOMO(a.u.)}$	$E_{LUMO(a.u.)}$	$\Delta E_{(a.u.)}$	$\Delta E_{(eV)}$
gas	-0.25053	-0.06427	0.18626	5.06837	-0.24256	-0.04782	0.19474	5.29912
water	-0.25753	-0.06588	0.19165	5.21504	-0.24769	-0.05177	0.19592	5.33123
methanol	-0.25730	-0.06582	0.19148	5.21041	-0.24678	-0.05171	0.19507	5.30810

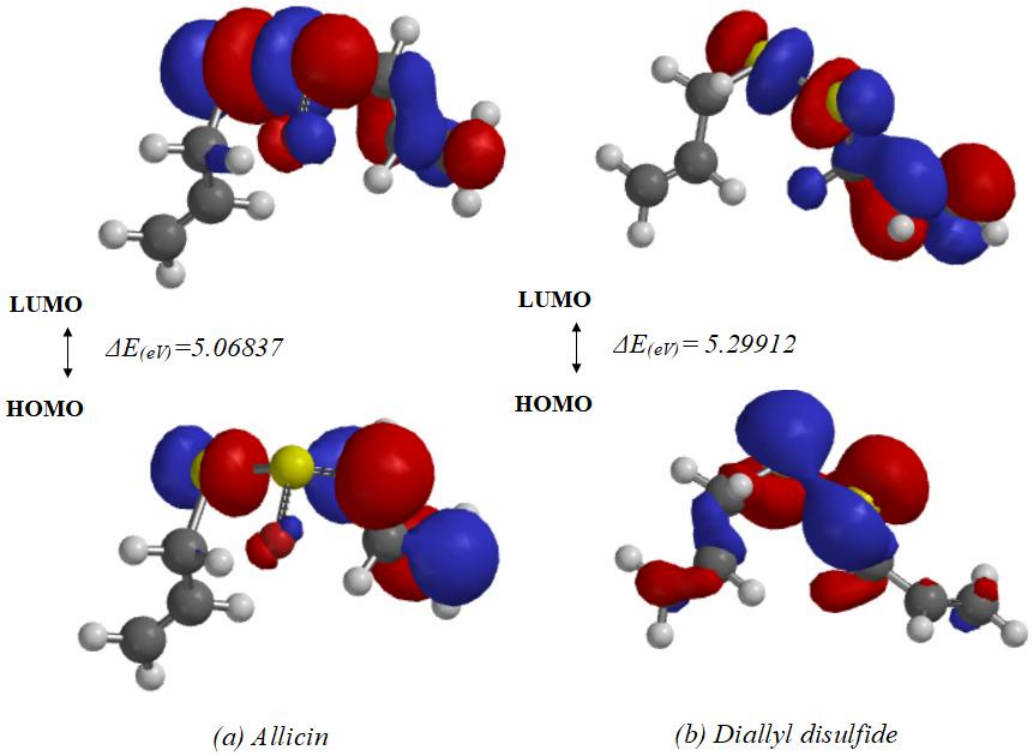


Figure 2. FMOs plot, energies of HOMO-LUMO, energy gap (ΔE) for allicin and diallyl disulfide in the gas media.

Molecular electrostatic potential (MEP) analysis is considered an efficient tool for deciding and evaluating the reactivity and chemical properties of molecular systems (Suresh et al., 2022). MEP is a precious notion in molecular modeling computations as it may offer well accurate information on the active sites of several chemical structures (Bulat et al., 2010). Also, it is crucial in evaluating the chemical addition nature through which a chemical structure is most possible to go through; either electrophilic or nucleophilic addition (Bayoumy et al., 2020). MEP is symbolized by dissimilar colors; red, blue, and green illustrate the areas of negative, positive, and zero electrostatic potential, respectively. The positive regions are related to nucleophilic reactivity and the negative regions to electrophilic reactivity. As seen in Figure 3, since the MEP map is analyzed it can be seen that negative regions are located on S atoms in the chain, these areas have excellent electrophilic attack effect. The positive areas appear to be deployed on the unsaturated carbon chains. These areas are suitable for nucleophilic attacks.

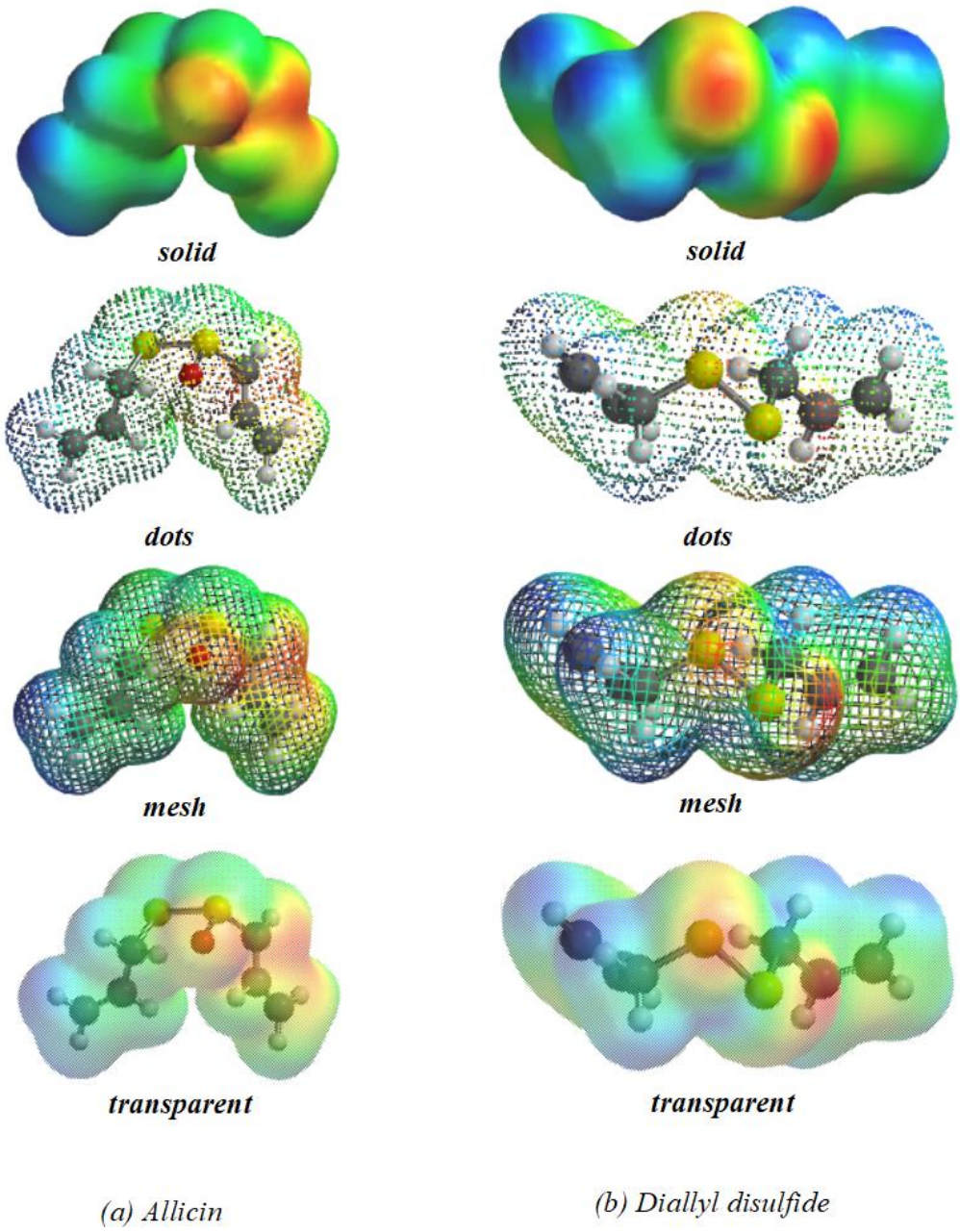


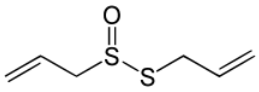
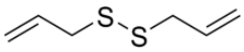
Figure 3. Molecular electrostatic potential map of the allicin and diallyl disulfide.

3.2. Molecular Docking

In this study, a show of molecular docking of allicin and diallyl disulfide molecules with the target protein complex crystal structures of EGFR mutants T790M/C797S (PDB code 5XGN) has been ensured, owing to AutoDock Vina in UCSF Chimera 1.16 (Pettersen et al., 2004). The crystal structure of 5XGN was acquired from the RSCB PDB website, with a resolution of 3.00 Å. The docking results were visualized using BIOVIA Discovery Studio Visualizer (Biovia, 2017). The outcomes of the docking studies were in the shape of 2D and 3D structures to assist visualize and examine the interaction model of the ligand-protein complex. While these positions were defined in

the docking method, the binding site (active site) of a protein was defined from the place where the inhibitor was bound, since it was a protein with a known crystal structure. Good energy values of the docking results (-8.3 kcal/mol, -8.2 kcal/mol, respectively) for both the allicin molecule and the diallyl sulfide molecule are shown in the Table 3. Allicin molecule constituted secondary interactions (van der Waals and hydrogen bonding) with the EGFR mutants T790M/C797S complex and also, the diallyl disulfide molecule constituted secondary interaction (van der Waals) with the same complex. These interactions were shown in Figure 4.

Table 3. Molecular docking results of the allicin and diallyl disulfide molecules with PDB ID: 5XGN.

Molecule Name	Molecular structure	Binding Energy (kcal/mol)	RMSD	Amino Acid Residues
Allicin		-8.3	1.315	LYS49, GLU66, MET70, CYS79, LEU92, MET94, ASP159, PHE160
Diallyl disulfide		-8.2	1.767	LYS49, GLU66, ALA67, MET70, CYS79, LEU81, LEU92, MET94, PHE160

The best interaction of the allicin compound was determined as van der Waals interaction, attractive charge interaction, Sulfur-X interaction, alkyl interaction, and hydrogen bond interactions including LYS49, GLU66, MET70, CYS79, LEU92, MET94, ASP159, PHE160 residues. Also, the best interaction of the diallyl disulfide compound was determined as van der Waals interaction, Sulfur-X interaction, alkyl interaction, and π-alkyl interaction including LYS49, GLU66, ALA67, MET70, CYS79, LEU81, LEU92, MET94, PHE160 residues.

Conventional hydrogen bonds (NH•••O, OH•••O, OH•••N, and NH•••N) represent the fundamental stabilizing forces in biomolecular structure. Van der Waals forces are crucial in the formation of protein-ligand complexes, and diverse studies have shown that these interactions are very important in determining the binding affinity of the ligand to the protein. On the other hand, interaction types such as π-alkyl bonds help increase the hydrophobic interaction of the ligand in the binding pocket of the receptor. These types of bonds, also encountered in docking analyses are important for the structural integrity of many biological molecules including proteins and DNA, and are also very crucial for drug-receptor interactions.

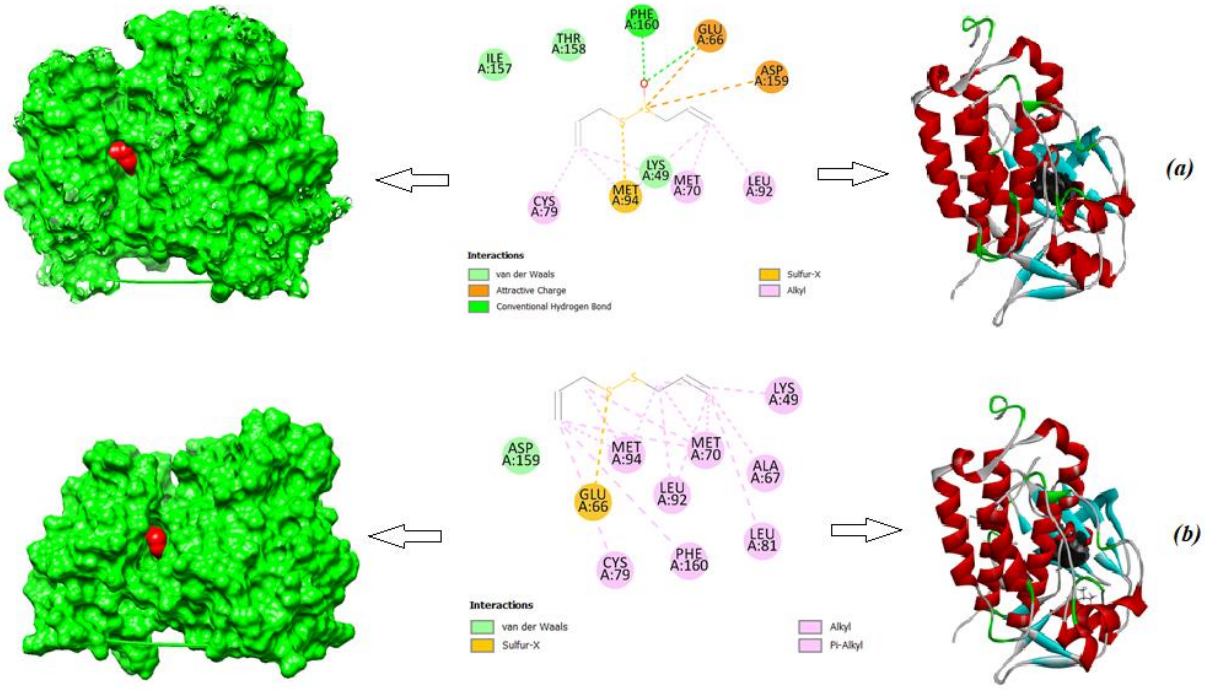


Figure 4. Graphs of the protein-ligand interaction for the most steady complexes of (a) allicin and (b) diallyl disulfide molecules.

3.3. Druggability and ADMET Properties

Druglikeness, such as permeability, metabolic stability, solubility, and transporter effects develop drug discovery and have critical point to successful drug nominees (Di et al., 2009). In silico approaches lend considerably early pharmaceutical study and are particularly major in goal and lead discovery. It also enables early discovery of drug-like properties, thanks to fundamental molecular features such as polarity, hydrogen bonding, and molecular weight which are studied in silico (Kerns and Di, 2003). In recent years, ADME-Tox studies are requisite in modern drug discovery and development stage (Pantaleão et al., 2022). Owing to in vitro and in vivo approaches being time-consuming, labor-intensive, and costly, in silico methods have been extensively utilized to estimate the ADME features of pharmacologically active chemical molecules (Shaker et al., 2021). It was used many in silico web tools such as SwissADME, ADMETlab, and admetSAR to predict ADME properties of the allicin and diallyl disulfide molecules.

Lipinski rule, Veber rule and Ghose rule are some of the rules that help evaluate lipophilicity, water solubility and drug similarity of ligands (Goktas et al., 2023). The ligands used in the study were found to satisfy most of the Lipinski, Veber, and Ghose rules. It was shown relative results of the calculated ADME/Tox values for allicin and diallyl disulfide molecules in Table 4 and Table 5, respectively.

Table 4. Admet properties predicted for the allicin compound.

	SwissADME	**ADMETlab**
	Physicochemical Properties	
Formula	$C_6H_{10}OS_2$	$C_6H_{10}OS_2$
Molecular weight	162.27 g/mol	162.02 g/mol
Number heavy atoms	9	9
Number aromatic heavy atoms	0	0
Fraction Csp^3	0.33	0.333
Number rotatable bonds	5	5
Number hydrogen bond acceptors	1	1
Number hydrogen bond donors	0	0
Molar refractivity	45.88	-
TPSA	61.58 $Å^2$	23.06 $Å^2$
Lipophilicity		
$LogP_{o/w}$	1.61	1.325
Water Solubility		
LogS	-1.34	-1.556
Solubility	$7.39e^{+}00$ mg/ml	-
Absorption		
GI absorption	High	-
Distribution		
BBB permeation	Yes	0.512
P-gp substrate	No	0.005
Metabolism		
CYP1A2 inhibitor	No	0.069
CYP2C19 inhibitor	No	0.061
CYP2C9 inhibitor	No	0.014
CYP2D6 inhibitor	No	0.098
CYP3A4 inhibitor	No	0.079
$LogK_p$ (skin permeation)	-6.36 cm/s	-
Drug-likeness		
Lipinski	Yes (0 violation)	Yes
Ghose	No (1 violation)	-
Veber	Yes	-
Medicinal Chemistry		
PAINS	0 alert	0 alert
Brenk	2 alert: disulphide, isolated_alkene	-
Leadlikeness	No; 1 violation: MW<250	-
Synthetic Accessibility	3.60	5.675
Bioavailability Score	0.55	0.275

In Figure 5, the red plot in the middle of egg yolk displayed that the ligands can pass both blood-brain barrier (BBB) and the human gastrointestinal absorption (HIA). The red color of the dot demonstrated the information about the ligand is not a substrate for P-glycoprotein (PGP-) which is a significant criteria for pharmacokinetics (Gundogdu, 2023). According to this study, allicin and diallyl disulfide ligands both red dots situated in the within part of yolk disclosing that they have the high absorptive states for HIA and BBB.

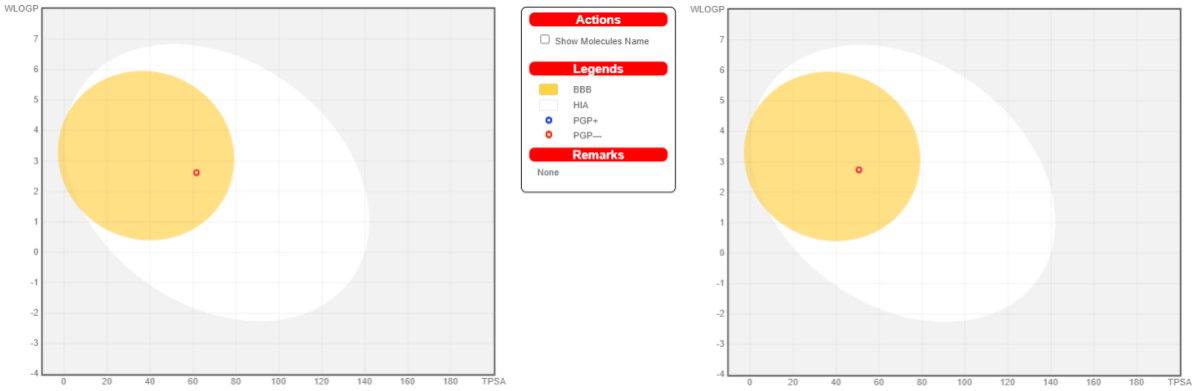


Figure 5. BOILED-Egg model for allicin (left) and dially disulfide (right) ligands.

Table 5. Admet properties predicted for the dially disulfide compound.

	SwissADME Physicochemical Properties	**ADMETlab**
Formula	$C_6H_{10}S_2$	$C_6H_{10}S_2$
Molecular weight	146.27 g/mol	146.02 g/mol
Number heavy atoms	8	8
Number aromatic heavy atoms	0	0
Fraction Csp^3	0.33	0.333
Number rotatable bonds	5	5
Number hydrogen bond acceptors	0	0
Number hydrogen bond donors	0	0
Molar refractivity	45.19	-
TPSA	50.60 $Å^2$	0.0
Lipophilicity		
$LogP_{o/w}$	2.39	2.452
Water Solubility		
LogS	-1.80	-3.508
Solubility	2.30e+00 mg/ml	-
Absorption		
GI absorption	High	-
Distribution		
BBB permeation	Yes	0.799
P-gp substrate	No	0.031
Metabolism		
CYP1A2 inhibitor	No	0.848
CYP2C19 inhibitor	No	0.78
CYP2C9 inhibitor	No	0.269
CYP2D6 inhibitor	No	0.268
CYP3A4 inhibitor	No	0.712
$LogK_p$ (skin permeation)	-5.63 cm/s	-
Drug-likeness		
Lipinski	Yes (0 violation)	Yes
Ghose	No; 2 violations: MW<160	-
Veber	Yes	-
Medicinal Chemistry		
PAINS	0 alert	0 alert
Brenk	2 alerts: disulphide, isolated_alkene	-
Leadlikeness	No; 1 violation: MW<250	-
Synthetic Accessibility	3.12	3.936
Bioavailability Score	0.55	0.919

SwissTargetPrediction is a web-based tool designed to predict the most likely protein targets of small molecules. Thanks to the program, it was tried to predict probable target proteins. The predicted results for each compound were shown in Figure 6 and Figure 7. In Figure 6, the allicin molecule could be an inhibitor of 40% possibility for the enzyme, 13.3% for family A G protein-coupled receptor, 13.3% for kinase, and 13.3% for lyase. The computed other three particular objectives were predicted as phosphatase, family C G protein-coupled receptor, and electrochemical transporter.

Target	Common name	Uniprot ID	ChEMBL ID	Target Class
11-beta-hydroxysteroid dehydrogenase 1	HSD11B1	P28845	CHEMBL4235	Enzyme
Acyl coenzyme A:cholesterol acyltransferase	CES1	P23141	CHEMBL2265	Enzyme
Carboxylesterase 2	CES2	O00748	CHEMBL3180	Enzyme
Carbonic anhydrase XII	CA12	O43570	CHEMBL3242	Lyase
Carbonic anhydrase IX	CA9	Q16790	CHEMBL3594	Lyase
Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor
Adenosine A1 receptor *(by homology)*	ADORA1	P30542	CHEMBL226	Family A G protein-coupled receptor
Metabotropic glutamate receptor 4	GRM4	Q14833	CHEMBL2736	Family C G protein-coupled receptor
Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase
Serine/threonine-protein kinase Aurora-A	AURKA	O14965	CHEMBL4722	Kinase
Dopamine transporter *(by homology)*	SLC6A3	Q01959	CHEMBL238	Electrochemical transporter
Heme oxygenase 1 *(by homology)*	HMOX1	P09601	CHEMBL2823	Enzyme
Arachidonate 15-lipoxygenase	ALOX15	P16050	CHEMBL2903	Enzyme
Dual specificity phosphatase Cdc25A	CDC25A	P30304	CHEMBL3775	Phosphatase
Poly [ADP-ribose] polymerase-1	PARP1	P09874	CHEMBL3105	Enzyme

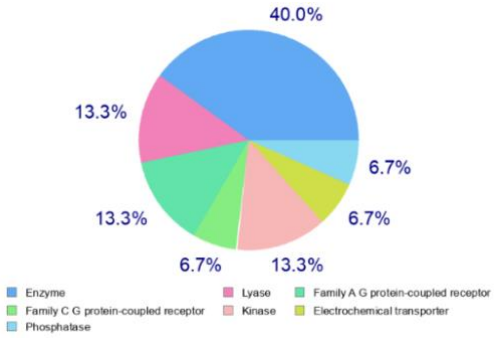


Figure 6. Distribution of the predicted biological targets for allicin molecule.

On the other hand, diallyl disulfide could be an inhibitor of 28.6% probability both for the lyase and enzyme, 14.3% for nuclear receptor, 14.3% for hydrolase, and 14.3% for voltage-gated ion channel. The calculated particular objectives were displayed in Figure 7.

Target	Common name	Uniprot ID	ChEMBL ID	Target Class
Carbonic anhydrase I	CA1	P00915	CHEMBL261	Lyase
Carbonic anhydrase IX	CA9	Q16790	CHEMBL3594	Lyase
Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase
Gamma-butyrobetaine dioxygenase	BBOX1	O75936	CHEMBL2163175	Enzyme
Monoglyceride lipase	MGLL	Q99685	CHEMBL4191	Enzyme
Androgen Receptor	AR	P10275	CHEMBL1871	Nuclear receptor
Transient receptor potential cation channel subfamily A member 1	TRPA1	O75762	CHEMBL6007	Voltage-gated ion channel

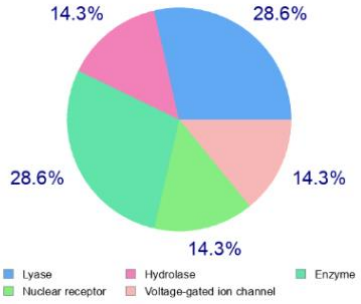
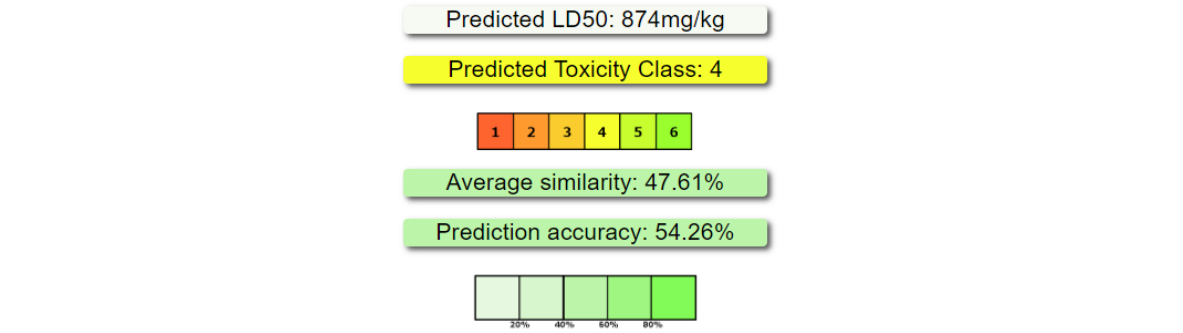


Figure 7. Distribution of the predicted biological targets for diallyl disulfide molecule.

The toxicity studies were carried out using the Pro-Tox II. The predicted results for allicin and diallyl disulfide were displayed in Figure 8 and Figure 9 respectively. According to the evaluation of the toxicity data, it could achieve some results for the allicin molecule: The allicin had no toxicity

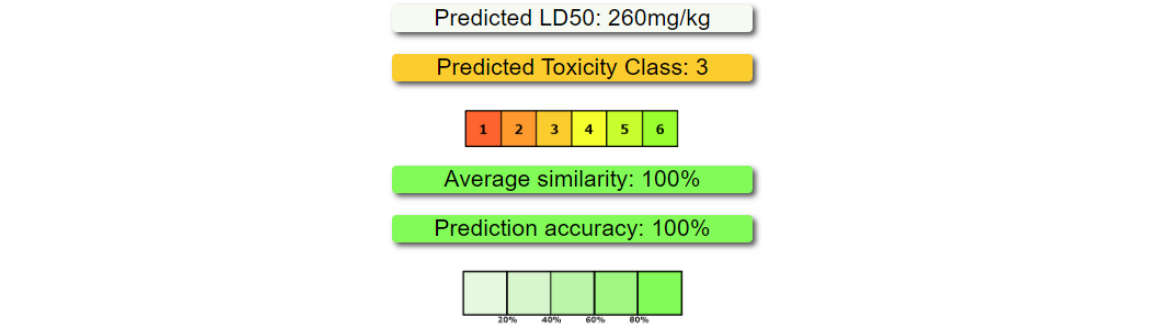
structure. The allicin molecule had no cytotoxic, carcinogenic, immunotoxic, or mutagenic efficacies considering the toxicity tool used. Considering Pro Tox-II, the allicin was categorized as toxicity grade 4. The diallyl disulfide didn't illustrate cytotoxic, mutagenic, or immunotoxic efficacies but had carcinogenic and phosphoprotein (tumor supressor) p53 effects. The diallyl disulfide was categorized as toxicity grade 3.



Toxicity Model Report

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.73
Toxicity end points	Carcinogenicity	carcino	Inactive	0.64
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.61
Toxicity end points	Cytotoxicity	cyto	Inactive	0.74
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
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	0.96
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.91
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.89
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.83
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.83
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.94
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.56
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.93

Figure 8. The toxicity estimate of allicin molecule by Pro-Tox II.



Toxicity Model Report

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.80
Toxicity end points	Carcinogenicity	carcino	Active	0.56
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.55
Toxicity end points	Cytotoxicity	cyto	Inactive	0.83
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	1.0
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.95
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.95
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.99
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Active	1.0
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.98

Figure 9. The toxicity estimate of diallyl disulfide molecule by Pro-Tox II.

4. Conclusions and Recommendations

The quantum chemical descriptors of the allicin and diallyl disulfide molecules were calculated by the DFT/B3LYP method with 6-31++G(d,p) basis set. The energy value gap between the HOMO and LUMO is a significantly stable index. The HOMO-LUMO energy gap of the allicin molecule was lower than that of the diallyl disulfide molecule, reaffirming theoretically that it has high chemical reactivity and low kinetic stability. Allicin is an unstable compound and readily converts over time or later to various more stable sulfide compounds, including diallyl sulfide, diallyl disulfide, and diallyl trisulfide. According to the demonstrated results of MEP calculations, the studied molecules have included both nucleophilic active sites and electrophilic attack sites. Studied molecules have low binding energies which could be regarded as encouraging inhibitors for cancer. It was seen to have the lowest binding energies of -8.3 kcal/mol and -8.2 kcal/mol of allicin and diallyl disulfide molecules, respectively. The allicin molecule displayed an admissible drug-likeness property and had no cytotoxicity, carcinogenicity, mutagenicity, or immunotoxicity. On other the hand diallyl disulfide molecule with respect to the Pro Tox-II estimates exhibited no cytotoxic,

mutagenic, or immunotoxic efficacies but had carcinogenic and phosphoprotein (tumor supressor) p53 effects. Useful results were achieved with these two compounds.

Statement of Conflicts of Interest

The author declares no conflicts of interest with respect to the content, authorship, and/or publication of this article.

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