Ö. Dilek et al. / Hacettepe J. Biol. & Chem., 2024, 52 (2), 129-138

Research Article

Hacettepe Journal of Biology and Chemistry

journal homepage: www.hjbc.hacettepe.edu.tr

Indole-Bearing Azo Compounds: Molecular Docking and in silico ADMET Analysis

İndol içeren Azo Bileşikleri: Moleküler Kenetlenme ve in siliko ADMET Analizi

Ömer Dilek[1], Tahir Tilki[2] and Çiğdem Karabacak Atay[3]

[1]Central Research Laboratory Application and Research Center, Isparta University of Applied Science, Isparta, Turkey.

[2]Department of Chemistry, Süleyman Demirel University, Isparta, Turkey.

[3]Department of Basic Education, Burdur Mehmet Akif Ersoy University, Burdur Turkey.

ABSTRACT

In this study, the interaction between the 12 indole-bearing azo compounds (a-l), which were previously synthesized by our research group, and two proteins, 2XIR and 5TGZ, was investigated using an *in silico* method. The ligand-protein interaction parameters and quantities were determined via molecular docking simulation studies. Since compound e has the lowest docking scores for both 2XIR and 5TGZ, it was selected for additional research on binding interactions. Both e-2XIR and e-5TGZ had docking scores that were lower than those of the control molecules. ADMET characteristics (absorption, distribution, metabolism, excretion, and toxicity) were anticipated using the ADMETlab 2.0 and ProTox-II server. Compound b was categorized as having the greatest levels of toxicity, falling into the sixth toxicity class.

Key Words

Molecular docking, 2XIR, 5TGZ, ADMET.

ÖZ

Bu çalışmada araştırma grubumuz tarafından daha önce sentezlenen 12 adet indol içeren azo bileşiği (a-l) ile iki protein (2XIR ve 5TGZ) arasındaki etkileşim *in silico* yöntem kullanılarak incelendi. Ligand-protein etkileşimi parametreleri ve miktarları, moleküler yerleştirme simülasyon çalışmaları yoluyla belirlendi. Bileşik e, hem 2XIR hem de 5TGZ için en düşük kenetlenme puanlarına sahip olduğundan bağlanma etkileşimleri üzerine ek araştırmalar için seçildi. Hem e-2XIR hem de e-5TGZ, kontrol moleküllerininkinden daha düşük kenetlenme puanlarına sahipti. ADMET özellikleri (emilim, dağılım, metabolizma, atılım ve toksisite), ADMETlab 2.0 ve ProTox-II sunucusu kullanılarak tahmin edildi. Bileşik b, altıncı toksisite sınıfına girerek en yüksek toksisite seviyelerine sahip olarak kategorize edildi.

Anahtar Kelimeler

Moleküler kenetlenme, 2XIR, 5TGZ, ADMET.

Article History: Oct 26, 2023; Revised: Dec 9, 2023; Accepted: Dec 9, 2023; Available Online: Feb 9, 2024.

DOI: https://doi.org/10.15671/hjbc.1381196

Correspondence to: Ö. Dilek, Central Research Laboratory Application and Research Center, Isparta University of Applied Science, Isparta, Turkey.

E-Mail: omerdilek@isparta.edu.tr

INTRODUCTION

Indole, a bicyclic heterocycle, is a preferred structure in the search for new drugs [1,2]. Many pharmacological properties, such as antiviral, antidiabetic, antioxidant, antihistamine, anti-inflammatory, antibacterial, antifungal, and anticholinesterase properties, are demonstrated by compounds containing indole [3-9]. It is thought to be one of the key scaffolds in demonstrating anticancer properties despite the aforementioned activities [10-12]. On the other hand, computational techniques offer benefits for studying compounds and its derivatives, as well as for investigating the possible uses of them in other domains. Specifically, by utilizing the electrical and physicochemical properties of indole, researchers can use computational methods to build new derivatives with superior features and potential therapeutic applications. These methods can also shed light on the drug's possible modes of action. Finding the precursor chemical and optimizing it are the most crucial phases in the production of a medication. The computer-aided drug design method known as molecular docking is frequently used to calculate ligand-protein interactions, which are crucial to various biochemical and biological processes [13]. Molecular docking is a tiny component of the CADD which may be like a facilitating technique for the determination of the lead in the pre-clinical phase [14]. The goal of molecular docking is to use computer-based programs to determine the native position, orientation, and conformation of the compound inside the active site of a large target molecule. These techniques work well and are less expensive than traditional drug research, which is costly and take more time.

VEGF is one of the most potent angiogenic factors involved in tumor growth. VEGF stimulates endothelial cell proliferation, migration, and tube formation by binding to VEGF receptor 1 and 2 (VEGFR-1 and VEGFR-2). Studies have shown that while the interaction between VEGF and VEGFR-1 plays a minor role in angiogenesis, while VEGFR-2 mediates the major angiogenic function of VEGF. Therefore, VEGFR-2 has been a therapeutic target for the creation of anticancer drugs. The Food and Drug Administration (FDA) approved small-molecule VEGFR-2 kinase inhibitors, demonstrating the significant anti-angiogenic effect of inhibiting the VEGFR-2 signaling pathway on human cancer [15].

Cannabinoid receptor 1 (CB1) is a therapeutically relevant drug target for controlling pain, obesity, and other central nervous system disorders. According to the World Health Organization, obesity is among the top 10 global health issues because it raises the risk of various cancers, heart attacks, and type 2 diabetes as well as comorbidities and mortality. The brain's Cannabinoid-1 (CB1) receptor has been confirmed as a viable target for the treatment of obesity [16].

By simulating the in vivo environment, ADMET (absorption, distribution, metabolism, excretion and toxicity) approach is used to determine the probable physicochemical features which are important to calculate ADMET parameters of drug candidates from absorption to excretion after taken inside.

Previously our research group has reported the synthesis of 12 indole-bearing compounds (a-l) and reported their molecular structures using HF and DFT methods with 6-31G(d), 6-311G(d), 6-311++G(d,p) and 6-31++G(d,p) basis sets [17]. Within the scope of this study, it was aimed to investigate of anticancer and anti-obesity properties of synthesized compounds and to determine ADMET properties using ADMETlab 2 and ProTox-II servers.

MATERIALS and METHODS

Synthesis of Compounds

The synthesis of 12 indole-bearing azo compounds (a-l) has previously been described by our research group [17]. The structures of compounds are displayed in Figure 1.

Computational Methods

Optimized geometries of compounds (a-l) were determined using Avogadro software and UFF parameters.

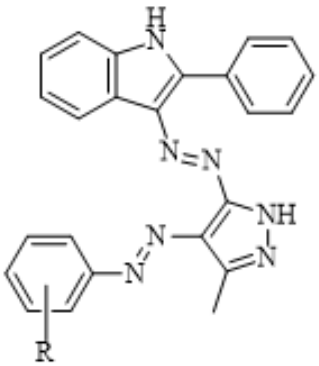
In silico studies

Target predictions

The compounds (a-l) were assessed by using SwissTargetPrediction [18] online server to do a systematic study.

Molecular docking studies

Molecular docking studies of the compounds (a-l) were carried out with the help of the AutodockVina 1.1.2 software [19]. UCSF Chimera 1.17.2 [20] and BIOVIA Discovery Studio Visualizer [21] softwares were used to visualize all obtained results. 2XIR and 5TGZ prote-



a: R; 2-NO_2 **b:** R; 3-NO_2 **c:** R; 4-NO_2 **d:** R; 2-CH_3 **e:** R; 3-CH_3 **f:** R; 4-CH_3 **g:** R; 3-OCH_3 **h:** R; 4-OCH_3 **i:** R; 2-Cl **j:** R; 3-Cl **k:** R; 4-Cl **l:** R; H

Figure 1. Structures of compounds.

ins were chosen for the molecular docking studies. The crystal protein structures were received from Protein Data Bank as pdb file [18]. The MODELLER program was used for the homology and modeling of protein three-dimensional structures [22]. Polar hydrogens and Kollman charges were introduced to the protein structures in place of water and other unconventional residues. The Dock Prep module in UCSF Chimera 1.17.2 was used to prepare the proteins. Active sites of 2XIR and 5TGZ were surrounded by a grid box 45 x 45 x 45 $Å^3$ using UCSF Chimera 1.17.2. The x, y, and z coordinates of the proteins' binding sites were taken from the literature [23,24]. Avogadro software and UFF parameters [25] were used to calculate optimized geometries of compounds. Then molecular docking studies were conducted using these optimized geometries.

ADMET predictions

Physicochemical properties and ADME parameters of compounds (a-l) were calculated using the ADMETlab 2.0 online server [26]. The toxicity parameters such as LD_{50} and acceptable usage range of compounds were identified using the ProTox-II online server [27].

RESULTS and DISCUSSION

Computational Details

Molecular structure

The optimized geometries of the indole-bearing azo compounds (a-l) calculated by Avogadro software and UFF parameters were displayed in Figure 2.

In silico studies

Target predictions

SwissTargetPrediction online server was used to guess which purpose the compounds (a-l) could be used for. Therefore, the compounds were drawn in chembiodraw and then were saved as .sdf file. These files were opened SwissTargetPrediction web server, target prediction properties were investigated, and the results were recorded. The results were shown Table 1.

From the results given Table 1, the compounds (a-l) were prone to cannabinoid receptor 1 and Vascular endothelial growth factor receptor 2. When the literature studies investigated and examined, mostly 2XIR and 5TGZ proteins were studied intensely. Also, there were many studies related to molecular docking studies of 5TGZ protein with pyrazole moiety [23,28,29]. So 2XIR and 5TGZ proteins were chosen for molecular docking studies.

Molecular docking studies

By using 2XIR and 5TGZ proteins molecular docking studies of compounds (a-l) were investigated. The 3D binding site coordinates of 2XIR and 5TGZ were taken from the literature [23,24]. The all synthesized compounds were individually docked selected regions of both 2XIR and 5TGZ proteins. The lowest docking scores with RMSDlb and RMSDub were chosen to investigate the binding modes of synthesized compounds. The docking scores of compound-protein complexes were given in Table 2, the poses of complexes formed between ligands and proteins are given in Figure 3. Whi-

le the docking lowest docking score was -9.9 kcal/mol (between compound b, e and 2XIR), the highest docking score was -9.4 kcal/mol (between compound g and 2XIR). When the docking scores of compound (a-l)-5TGZ complexes examined; the docking lowest docking score was -9.6 kcal/mol (between compound e and 5TGZ), the highest docking score was -8.6 kcal/mol (between compound l and 5TGZ).

Compound e was chosen to further investigation of binding interactions because of it has the lowest docking score both 2XIR and 5TGZ. Interactions between ligand and protein can be different types such as Van der Wails, Hydrogen bonding, etc. When the interactions of compound e-2XIR and compound e-5TGZ complexes were examined, both complexes have conventional hydrogen bond. Hydrogen bond of compound e-2XIR complex was between ASP 181 of 2XIR and hydrogen of pyrazole N-H with 2.86 Å while Hydrogen bond of compound e-5TGZ complex was between GLN 22 of 5TGZ and hydrogen of pyrazole N-H with 2.46 Å.

N,2-dimethyl-6-(7-(2-morpholinoethoxy)quinolin-4-yloxy)benzofuran-3-carboxamide (https://www.rcsb.org/ligand-validation/2XIR/00J) and 4-[4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)pyrazol-3-yl]phenyl]but-3-ynylnitrate (https://www.rcsb.org/ligand-validation/5TGZ/ZDG) compounds was used as a control molecules respectively for 2XIR and 5TGZ. Also geometries of these compounds were optimized by using Avogadro software and UFF parameters before molecular docking studies. The docking parameters were given in Table 3. When the docking scores of compound e were compared with control molecules, docking scores of both compound e-2XIR and compound e-5TGZ were lower than docking scores of both control-2XIR and control-5TGZ.

The other interactions between compound e-2XIR, compound e-5TGZ, control-2XIR and control-5TGZ complexes, bond lengths were shown in Figure 4.

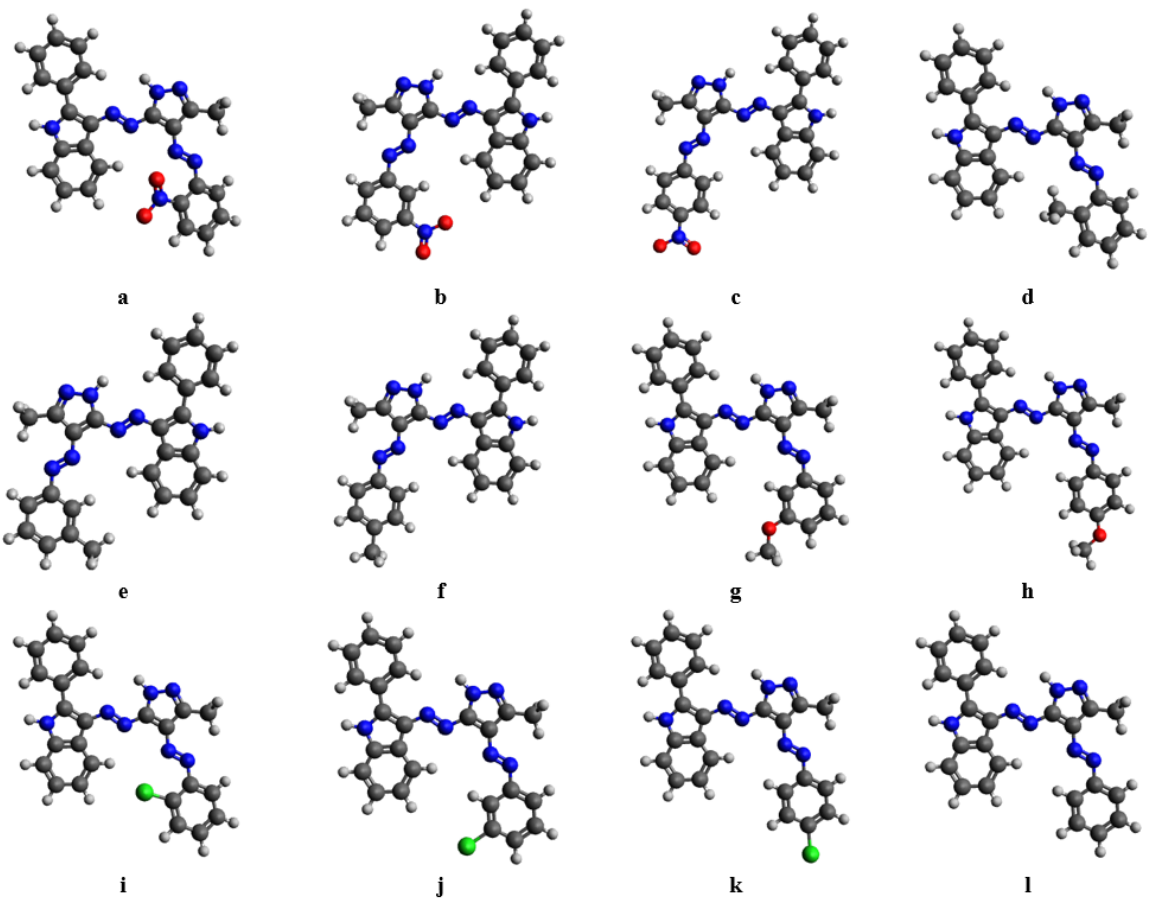


Figure 2. Optimized geometries of compounds (a-l) by using Avogadro software and UFF parameters.

Table 1. Swiss target prediction results.

Compound	SwissTargetPrediction Results
a	60% Kinase
b	40% Kinase
c	33% Protease 26% Kinase
d	46% G protein-coupled receptor, Family A
e	33% G protein-coupled receptor, Family A 33% Kinase
f	53% Kinase
g	40% Kinase
h	27% Kinase 27% G protein-coupled receptor, Family A
i	40% G protein-coupled receptor, Family A %27% Kinas
j	%27% G protein-coupled receptor, Family A 20% Kinase
k	33% G protein-coupled receptor, Family A 33% Kinase
l	40% G protein-coupled receptor, Family A 20% Kinase

ADMET predictions

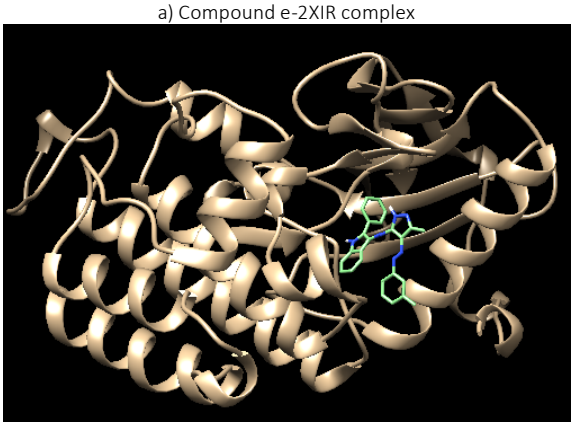
Physicochemical properties of compounds have a crucial role for determining ADME parameters. Physicochemical properties of a drug molecule directly impact its ADME properties, influencing how the drug is absorbed, distributed, metabolized, and excreted within the body. These interactions are important considerations in drug discovery and development. Physicochemical properties like molecular weight (Mw), Topological Polar Surface Area (TPSA) solubility (LogS), lipophilicity (LogP), hydrogen bond acceptor atoms (HBA), hydrogen bond donor atoms (HBD) affect ADME parameters of compounds. LogS influences the absorption of a drug. Poorly soluble drugs may have difficulty dissolving in the gastrointestinal tract, which can hinder absorption. LogP affects a drug's distribution between aqueous and lipid phases. A higher LogP value suggests greater lipid solubility, which can influence both absorption and distribution. LogP also affects a drug's ability to cross cell membranes. A balance is needed, as overly lipophilic drugs may have difficulty dissolving in the bloodstream or being metabolized. Mw can impact absorption. Large molecules may have difficulty crossing biological barriers like cell membranes.

Physicochemical properties like Mw, LogP, HBA and HBD are searched in Lipinski's rule of five. If one property is out of range, it is acceptable for Lipinski's rule. When Lipinski's rule of five was investigated in all compounds, it was concluded that the compounds (a-l) have the all criteria except LogP (Table 4). TPSA value is also important as gets through of substances from cell membranes. The TPSA value of the substance should be less than 140 $Å^2$. When the predicted TPSA values of all compounds were examined, the all values were lower than 140 $Å^2$

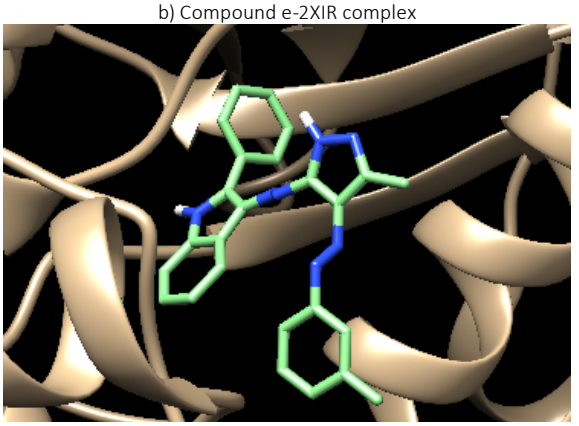
Table 2. Docking Results of Compounds (a-l) with 2XIR and 5TGZ proteins.

Compound	Docking Score with 2XIR (kcal/mol)	Docking Score with 5TGZ (kcal/mol)
a	-9.8	-9.5
b	-9.9	-9.1
c	-9.7	-8.8
d	-9.8	-8.8
e	-9.9	-9.6
f	-9.6	-9.1
g	-9.4	-9.0
h	-9.5	-9.1
i	-9.7	-9.5
j	-9.8	-8.8
k	-9.7	-8.8
l	-9.6	-8.6
Coligand	-9.8 [24]	-8.3

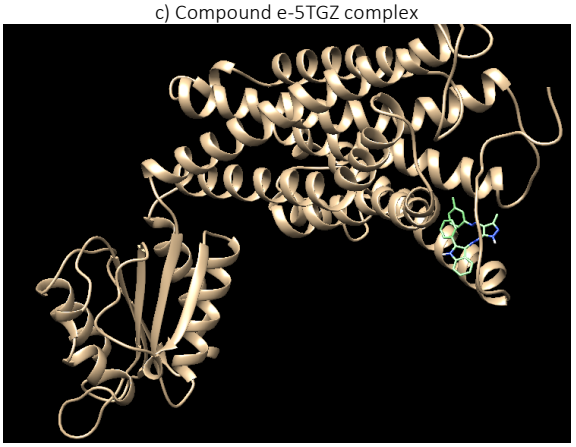
a) Compound e-2XIR complex



b) Compound e-2XIR complex



c) Compound e-5TGZ complex



d) Compound e-5TGZ complex

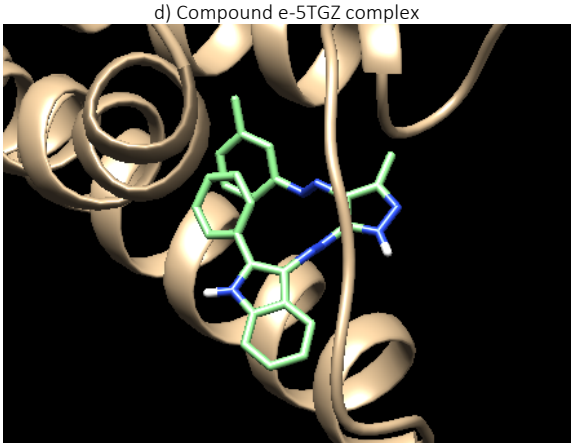


Figure 3. Molecular Docking Simulation poses of compound e with 2XIR and 5TGZ proteins.

Table 3. Molecular docking parameters within the ligand-target molecule couples.

Ligand-Target	ΔG (kcal/mol)	H bond Location (Length, Å)
Compound e-2XIR	-9.9	ASP 181 & Pyrazole N-H (2.86 Å)
Compound e-5TGZ	-9.6	GLN 22 & Pyrazole N-H (2.46 Å)
Control-2XIR	-9.8	ASP 1046 & Amide N-H (2.31 Å)
Control-5TGZ	-8.3	PHE 14 & Carbonyl O (2.59 Å) PHE 14 & Amide N-H (2.66 Å) HIS 87 & Nitro O (2.12Å)

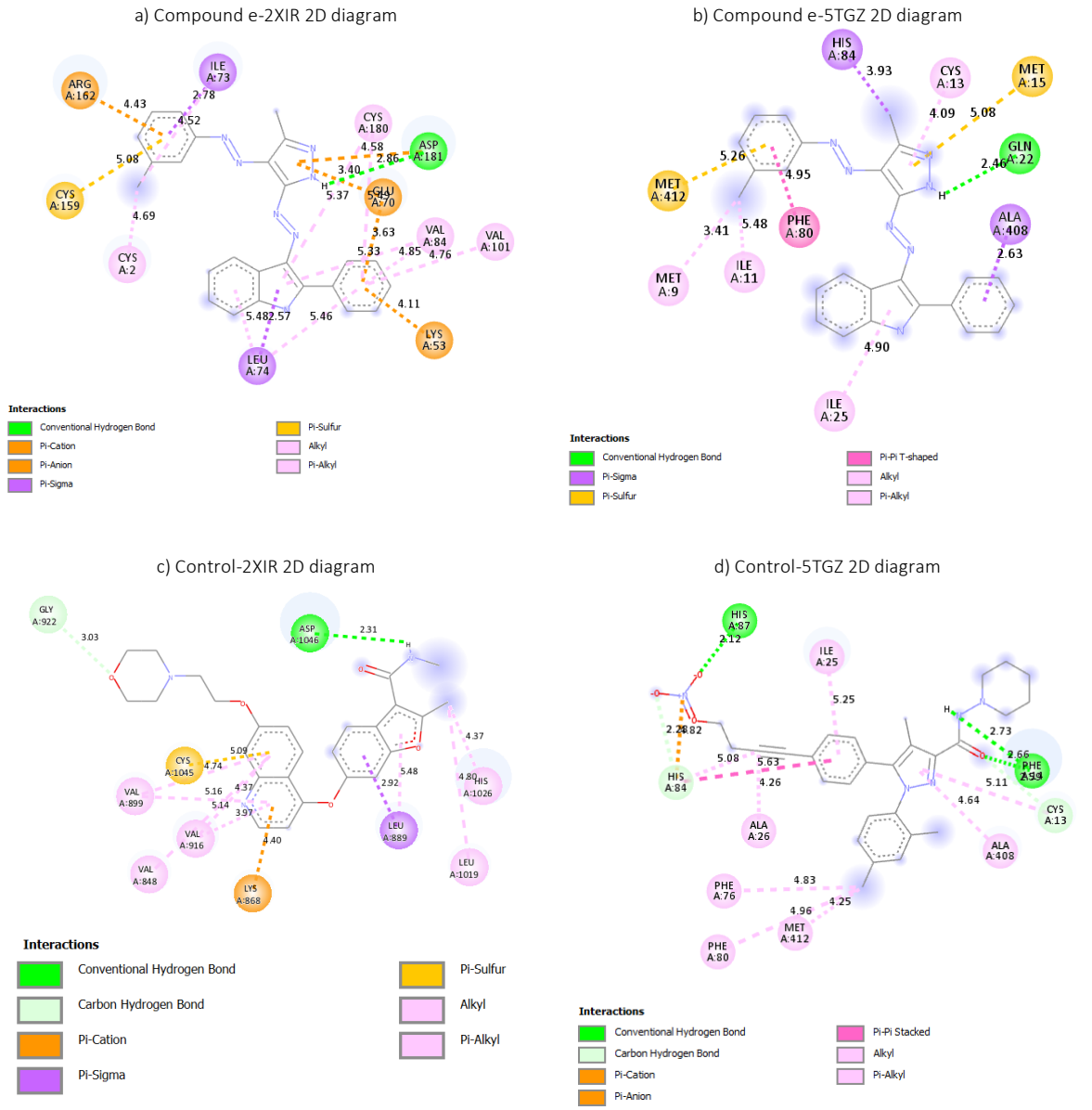


Figure 4. 2D diagrams of compound-protein couples.

Table 4. Physicochemical, lipophilicity, solubility, pharmacokinetics and drug-likeness properties of the compounds (a-l).

Compound	ADME Parameters	Predicted Toxicity Parameters (LD_{50} (mg/kg)/ Toxicity Class)
a	Mw:450.16 g/mol; LogP: 5.502 HBA:10; HBD: 2; TPSA: 137.05 Å^2 Lipinski Rule: Yes	5000/5
b	Mw:450.16 g/mol; LogP: 5.494 HBA:10; HBD: 2; TPSA: 137.05 Å^2 Lipinski Rule: Yes; Pfizer Rule: Yes	9000/6
c	Mw:450.16 g/mol; LogP: 5.544 HBA:10; HBD: 2; TPSA: 137.05 Å^2 Lipinski Rule: Yes;	5000/5
d	Mw:419.19 g/mol; LogP: 6.059 HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes;	5000/5
e	Mw:419.19 g/mol; LogP: 6.061 HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes	5000/5
f	Mw:419.19 g/mol; LogP: 6.094 HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes;	5000/5
g	Mw:435.18 g/mol; LogP: 5.672 HBA:8; HBD: 2; TPSA: 103.14 Å^2 Lipinski Rule: Yes;	200/3
h	Mw:435.18 g/mol; LogP: 5.697 HBA:8; HBD: 2; TPSA: 103.14 Å^2 Lipinski Rule: Yes;	200/3
i	Mw:439.13 g/mol; LogP: 6.079 HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes;	5000/5
j	Mw:439.13 g/mol; LogP: 6.223 HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes;	5000/5
k	Mw:439.13 g/mol; LogP: 6.275 HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes;	5000/5
l	Mw:405.17 g/mol; LogP: 5.629; HBA:7; HBD: 2; TPSA: 93.91 Å^2 Lipinski Rule: Yes;	5000/5

The toxicity properties of compounds (a-l) were investigated using the Protox-II online server, which is a widely used tool for predicting toxicity in chemical compounds. The lethal dose (LD_{50}) values of compounds were determined between 200-9000 mg/kg (Table 4). Compound b have the highest LD_{50} value (9000 mg/kg), while compounds g and h have the lowest LD_{50} value (200 mg/kg). Furthermore, the estimated toxicity classes for the substances were established on the Protox-II web server, which ranks compounds from the worst (class 1) to the best (class 6) based on their predicted toxicity. Compound b was classified into the sixth toxicity class, which indicates the lowest toxicity levels. (Table 4).

CONCLUSION

In this study, the molecular docking simulation method was used to investigate how 12 indole-bearing azo compounds (a-l) interacted with the 2XIR and 5TGZ proteins. Docking values ranged from -9.9 to -8.3 kcal/mol. The greatest results came from the e-2XIR and e-5TGZ complex, with docking scores of -9.9 kcal/mol and -9.6 kcal/mol, respectively. Also, it was discovered that LD_{50} value of compound b was extremely high (9000 mg/kg). It was determined as a result that the compound b had extremely little toxicity. Acceptable limits were reached for all of the compounds' (a-l) computed ADMET and drug similarity parameters. The successful outcomes show that deeper research in anticancer and anti-obesity fields is required for these compounds.

References

1. F. de Sa Alves, E. Barreiro, C. Manssour Fraga, From nature to drug discovery: The indole scaffold as a privileged structure, Mini Rev. Med. Chem., 9 (2009) 782–793.
2. P.F. Lamie, J.N. Philoppes, Design, synthesis, stereochemical determination, molecular docking study, in silico pre-ADMET prediction and anti-proliferative activities of indole-pyrimidine derivatives as Mcl-1 inhibitors, Bioorg. Chem., 116 (2021) 105335.
3. H. Abdel-Gawad, H.A. Mohamed, K.M. Dawood, F.A.-R. Badria, Synthesis and antiviral activity of new indole-based heterocycles, Chem. Pharm. Bull (Tokyo)., 58 (2010) 1529–1531.
4. Y. Li, H. Wu, L. Tang, C. Feng, J. Yu, Y. Li, Y. Yang, B. Yang, Q. He, The potential insulin sensitizing and glucose lowering effects of a novel indole derivative in vitro and in vivo, Pharmacol. Res., 56 (2007) 335–343.
5. M.S. Estevão, L.C. Carvalho, D. Ribeiro, D. Couto, M. Freitas, A. Gomes, L.M. Ferreira, E. Fernandes, M.M.B. Marques, Antioxidant activity of unexplored indole derivatives: Synthesis and screening, Eur. J. Med. Chem., 45 (2010) 4869–4878.
6. S. Battaglia, E. Boldrini, F. Da Settimo, G. Dondio, C. La Motta, A.M. Marini, G. Primofiore, Indole amide derivatives: synthesis, structure–activity relationships and molecular modelling studies of a new series of histamine H1-receptor antagonists, Eur. J. Med. Chem., 34 (1999) 93–105.
7. M.A.A. Radwan, E.A. Ragab, N.M. Sabry, S.M. El-Shenawy, Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents, Bioorg. Med. Chem., 15 (2007) 3832–3841.
8. 8.A.Y. Alzahrani, Y.A. Ammar, M.A. Salem, M. Abu-Elghait, A. Ragab, Design, synthesis, molecular modeling, and antimicrobial potential of novel 3-[(1H -pyrazol-3-yl)imino] indolin-2-one derivatives as DNA gyrase inhibitors, Arch. Pharm (Weinheim)., 355 (2022) e2100266.
9. S. Ghanei-Nasab, M. Khoobi, F. Hadizadeh, A. Marjani, A. Moradi, H. Nadri, S. Emami, A. Foroumadi, A. Shafiee, Synthesis and anticholinesterase activity of coumarin-3-carboxamides bearing tryptamine moiety, Eur. J. Med. Chem., 121 (2016) 40–46.
10. S. Dadashpour, S. Emami, Indole in the target-based design of anticancer agents: A versatile scaffold with diverse mechanisms, Eur. J. Med. Chem., 150 (2018) 9–29.
11. H. Sachdeva, J. Mathur, A. Guleria, Indole Derivatives as Potential Anticancer Agents: A Review, J. Chil. Chem. Soc., 65 (2020) 4900–4907.
12. K. Kaur, V. Jaitak, Recent Development in Indole Derivatives as Anticancer Agents for Breast Cancer, Anticancer Agents Med. Chem., 19 (2019) 962–983.
13. W. Cui, A. Aouidate, S. Wang, Q. Yu, Y. Li, and S. Yuan, Discovering Anti-Cancer Drugs via Computational Methods, Front Pharmacol., 11 (2020) 733.
14. M. H. Baig, K. Ahmad, G. Rabbani, M. Danishuddin, and I. Choi, Computer aided drug design and its application to the development of potential drugs for neurodegenerative disorders, Curr. Neuropharmacol., 16 (2018) 740–748.
15. H. M. Patel et al., Design and synthesis of VEGFR-2 tyrosine kinase inhibitors as potential anticancer agents by virtual based screening, RSC Adv, 5(2015) 56724–56771.
16. R. Hanachi et al., Structural, QSAR, machine learning and molecular docking studies of 5-thiophen-2-yl pyrazole derivatives as potent and selective cannabinoid-1 receptor antagonists, New Journal of Chemistry, 45 (2021) 17796–17807.
17. Ç. Karabacak, Ö. Dilek, Synthesis, solvatochromic properties and theoretical calculation of some novel disazo indole dyes, J. Mol. Liq., 199 (2014) 227–236.
18. A. Daina, O. Michielin, V. Zoete, SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules, Nucleic Acids Res., 47 (2019) W357–W364.
19. O. Trott, A.J. Olson, AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem., 31 (2010) 455–461.
20. E.F. Pettersen, T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E.C. Meng, T.E. Ferrin, UCSF Chimera—A visualization system for exploratory research and analysis, J. Comput. Chem., 25 (2004) 1605–1612.
21. BIOVIA (2021) Discovery Studio Visualizer, version 21.1.0.20298. Dassault Systèmes, San Diego, CA
22. B. Webb, A. Sali, Comparative Protein Structure Modeling Using MODELLER, Curr. Protoc. Bioinformatics, 54 (2016) 5.6.1-5.6.37.

23. S. Russo, W.F. De Azevedo, Advances in the Understanding of the Cannabinoid Receptor 1 – Focusing on the Inverse Agonists Interactions, Curr. Med. Chem., 26 (2019) 1908–1919.
24. Ç. Karabacak Atay, Ö. Dilek, T. Tilki, B. Dede, A novel imidazole-based azo molecule: synthesis, characterization, quantum chemical calculations, molecular docking, molecular dynamics simulations and ADMET properties, J. Mol. Model., 29 (2023) 226.
25. M.D. Hanwell, D.E. Curtis, D.C. Lonie, T. Vandermeersch, E. Zurek, G.R. Hutchison, Avogadro: an advanced semantic chemical editor, visualization, and analysis platform, J. Cheminform., 4 (2012) 17.
26. G. Xiong, Z. Wu, J. Yi, L. Fu, Z. Yang, C. Hsieh, M. Yin, X. Zeng, C. Wu, A. Lu, X. Chen, T. Hou, D. Cao, ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties, Nucleic Acids Res., 49 (2021) W5–W14.
27. P. Banerjee, A.O. Eckert, A.K. Schrey, R. Preissner, ProTox-II: a webserver for the prediction of toxicity of chemicals, Nucleic Acids Res., 46 (2018) W257–W263.
28. R. Hanachi, R. Ben Said, H. Allal, S. Rahali, M.A.M. Alkhalifah, F. Alresheedi, B. Tangour, M. Hochlaf, Structural, QSAR, machine learning and molecular docking studies of 5-thiophen-2-yl pyrazole derivatives as potent and selective cannabinoid-1 receptor antagonists, New J. Chem., 45 (2021) 17796–17807.
29. G.S. Amato, A. Manke, D.L. Harris, R.W. Wiethe, V. Vasukuttan, R.W. Snyder, T.W. Lefever, R. Cortes, Y. Zhang, S. Wang, S.P. Runyon, R. Maitra, Blocking Alcoholic Steatosis in Mice with a Peripherally Restricted Purine Antagonist of the Type 1 Cannabinoid Receptor, J. Med. Chem., 61 (2018) 4370–4385.