Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 4, 2023, 372
https://doi.org/10.33263/BRIAC134.372

In Silico Drug Repurposing of 9*H*-Thioxanthene Based FDA-Approved Drugs as Potent Chemotherapeutics Targeting VEGFR-2 and COX-2

Shazia Parveen [1,*], Rua B. Alnoman [1,*], Abeer Abdullah Aljohani [1], Alhanouf Zeben Aljohani [1], Ibtisam Mansour Alotaibi [1], Leena Salah Al-Juhani [1], Mayada Hamad Aljohani [1], Rawan Oudah Aljohani [1]

[1] Department of Chemistry, Faculty of Science, Taibah University, Yanbu, 46423, Saudi Arabia
* Correspondence: shazia021@gmail.com (S.P.); rua-b-n@live.co.uk (R.B.A.);

Scopus Author ID 57187913400 (S.P.)
565610880000 (R.B.A.)

Received: 24.04.2022; Accepted: 3.06.2022; Published: 7.10.2022

Abstract: The approach of using existing drugs initially developed for one disease to treat other indications has found success across medical fields. This article emphasizes the drug repurposing of 9H-thioxanthene based on FDA-approved drugs for anticancer agents precisely targeting VEGFR-2 and COX-2. The investigated 9*H*-thioxanthene drugs **1-4** were analyzed for Lipinski's drug-likeness rule and ideal ADME parameters. The results show that all calculated physicochemical descriptors and pharmacokinetic properties are within the expected range. 9*H*-thioxanthene drugs **1-4** were subjected to molecular docking to determine their molecular interactions at the active sites of VEGFR-2 and COX-2. The molecular docking study revealed that all four 9*H*-thioxanthene drugs **1-4** were able to target VEGFR-2 and COX-2. In the future, these findings will be greatly favorable in augmenting the utility of the development of the investigated drugs **1-4** for cancer therapeutics specifically targeting VEGFR-2 and COX-2.

Keywords: 9*H*-thioxanthenes; VEGFR-2; COX-2; ADME; molecular docking.

1. Introduction

According to WHO's global cancer profile, ~9.6 million deaths have occurred worldwide due to cancer (https://www.who.int/health-topics/cancer). Cancer is a generic term used for a group of diseases characterized by an abnormal growth of cells beyond their usual boundaries, which may spread to adjoining parts or other organs [1]. Cancer originates due to genetic adaptations, but there might be other factors, including oncogenes activation, inactivation of both tumor suppressor genes, genes accountable for apoptotic activity, and chemically, physically, and biologically induced mutations. Cancer is characterized by loss of function due to the absence of differentiation, uncontrolled proliferation, invasiveness of adjacent tissues, and metastasis [2]. The mechanism of cancer is not yet understood completely. Presently existing anticancer drugs display poor selectivity that causes cytotoxicity for dividing cells leading to serious side effects, viz., immunosuppression, anemia, diarrhea, nausea, and alopecia [3]. Additionally, the acquired resistance of different cancer types is a major setback to cancer treatment approaches [4]. These factors necessitate discovering new, more active, and selective anticancer drugs.

The new drug development, preclinical research, and approval course are time-consuming. These long discovery methods unlock the doors for drug repurposing, also known as drug repositioning and reprofiling, as an alternate approach for reducing the time required to develop a drug [5–10]. Although drug repurposing is not novel, it has gained extensive motivation in the past decade: about one-third of the drug approvals in recent years corresponds to the drug repurposing approach, creating ~25% of the annual revenue for the pharmaceutical industry [11]. Pharmacophore-based procedures are currently a significant part of various computer-aided drug design plans. They have been productively utilized for assignments, viz. virtual screening, lead optimization, and de novo design [12].

Keeping this in mind, the present work intends on a drug repurposing approach of previously approved antipsychotic 9*H*-thioxanthene-based drugs, **1-4**, to explore their anticancer potential (Figure 1). They act as dopamine-2 (D2) receptor antagonists, suppressing dopamine's function in the brain. Antipsychotics containing thioxanthene are used to treat schizophrenia [13]. Neuroleptics such as phenothiazine and thioxanthene derivatives are commonly utilized. However, they exhibit various other fascinating qualities, such as antibacterial activity, anticancer properties, and the ability to suppress the growth of cancer cells [14].

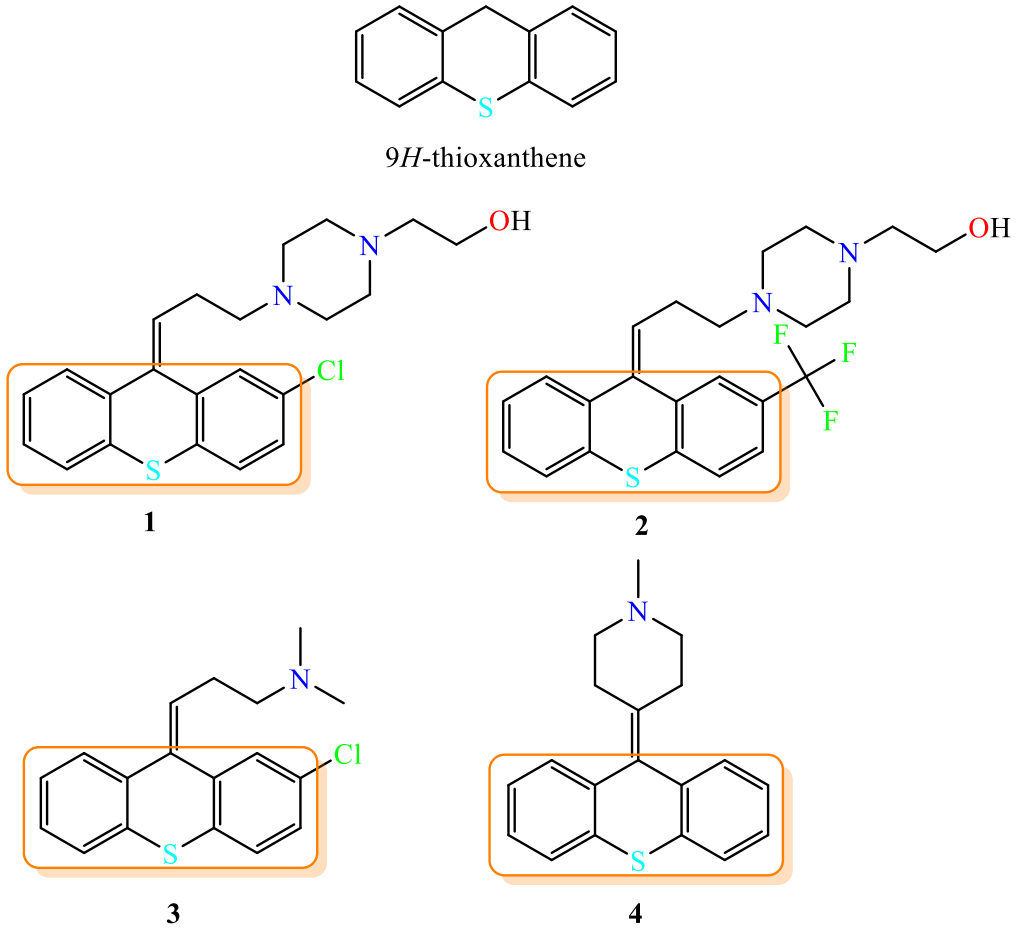

Figure 1. Structure of 9*H*-thioxanthene and its based FDA approved drugs; Zuclopenthixol (**1**), Flupentixol (**2**), Chlorprothixene (**3**), and Pimethixene (**4**).

Several enzymes and metabolic pathways have been implicated in the development of cancer. The enzymes most frequently involved in carcinogenesis are vascular endothelial growth factor receptor-2 (VEGFR-2), cyclooxygenase-2 (COX-2). VEGFR-2 is a member of the VEGF tyrosine kinase receptor family (VEGFR-TK). It is responsible for normal and pathological changes in vascular endothelial cells [15]. The VEGFR-2 signaling pathway is

responsible for blood vessels' formation, function, and maintenance, all physiological processes that contribute significantly to nutrient supply in healthy tissues and tumors [16]. Due to its critical role in cancer angiogenesis, the VEGFR-2 receptor is the most important antiangiogenic target [17]. Several antiangiogenic inhibitors of VEGFR-2 have been discovered that target the ATP-binding site [18]. Angiogenesis is a progression of the production of new blood vessels from pre-existing ones. It is an indispensable physiological process for solid tumor cell proliferation by providing oxygen and nutrients to the tumor cells to boost their growth and metastasis [19,20]. VEGFR-2 is a tyrosine kinase receptor expressed in endothelial cells [21]. VEGFR-2 plays a crucial role in anti-angiogenesis and is an efficient target for inhibiting tumor cell proliferation and metastasis [22,23].

On the other hand, COX-2 enzymes are known to play a well-defined role in malignancies associated with chronic inflammation. The role of COX-2 overexpression in cervical cancer is well supported by evidence [24]. COX-2 is a highly inducible isoform that is rapidly upregulated in response to various pro-inflammatory agents, including cytokines, tumor promoters, and mitogens, especially in cells involved in inflammation, pain, fever, and tumors [25]. COX-2 plays important roles in tumor progressions, such as cell proliferation, inhibition of apoptosis, angiogenesis, invasiveness, and immunosuppression [26]; COX inhibitors may have a positive impact on reducing the development and growth of malignant tumors, thereby effectively promoting the development of anticancer drugs [27]. COX-2 is released by cancer-associated fibroblasts, macrophage type 2 (M2) cells, and cancer cells in the tumor microenvironment. It induces cancer stem cell-like activity and promotes apoptotic resistance, proliferation, angiogenesis, inflammation, invasion, and metastasis of cancer cells. It exerts most of its functions through its metabolite; thus, it appears to play the predominant role in initiating and promoting cancer progression [24].

Considering the above research findings, the current work focuses on the drug repurposing of 9H-thioxanthene drugs **1-4** for cancers, specifically targeting VEGFR-2 and COX-2 via molecular docking approaches. This study's outcome will help optimize the use of 9H-thioxanthene drugs **1-4** as anticancer drugs by contributing to the understanding of its yet unexplored molecular mechanisms of action.

2. Materials and Methods

2.1. In silico ADME profile.

In silico screening of pharmacological properties (ADME) and drug likeliness of the investigated drugs were performed by SwissADME (http://www.swissadme.ch/index.php) [28]. The analysis of distinct descriptors viz., calculated octanol/water partition coefficient, molecular weight, molecular volume, and the number of hydrogen bond donor and acceptor groups of all the drugs revealed that their penetrating ability in the biological membranes, as determined by the Lipinski rule of five [29]. Computational analyses to predict the core pharmacokinetics parameters such as blood-brain barrier (BBB) permeability, gastrointestinal (GI) absorption, P–glycoprotein–mediated efflux (Pgp) were also performed.

2.2. Molecular docking.

The molecular docking studies were performed by using AutoDock Vina [30]. The crystal structures of target proteins VEGFR-2 (PDB ID: 4ASD) [31] and COX-2 (PDB ID: 1CX2) [32] were downloaded from the Protein Data Bank (http://www.rcsb.org/pdb) in PDB

format and were prepared by AutoDock Tools [33]. The chosen grid parameters were x= 42.332, y= 33.590, z= 36.010 with 40·40·40 grid dimensions with COX-2 and x= -21.981, y= -1.141, z= -3.791 with 40·40·40 grid dimensions with VEGFR-2. The docked pose has been visualized using CHIMERA (www.cgl.ucsf.edu/chimera) and Discovery Studio visualizer.

3. Results and Discussion

3.1. In silico ADME profile

The chief considerations for pharmacokinetics are absorption, distribution, metabolism, and excretion [34]. The projected Lipinski's parameters molecular weight (MW), number of rotatable bonds (nrotb), number of hydrogen bond acceptors (nON), number of hydrogen bond donors (nOHNH), and lipophilicity (mLogP) and topological polar surface area (TPSA) for investigated drugs are shown in Table 1.

Table 1. Selected calculated physicochemical and pharmacokinetic properties of 9*H*-thioxanthene drugs, **1-4**.

Parameters	**Drugs**			
	1	**2**	**3**	**4**
mLogP (lipophilicity)	3.48	4.28	4.89	5.12
TPSA (Å²) (Total Polar Surface Area)	52.01	52.01	28.54	28.54
Molecular Weight (g/mol)	366.52	434.52	315.86	327.87
nHBA (number of hydrogen bond acceptors)	3	6	1	1
nHBD (number of hydrogen bond donors)	1	1	0	0
n violations (number of violated drug-likeness rules)	0	1	1	1
Nrotb (number of rotating bonds)	5	6	3	0
GI absorbtion (gastrointestinal)	High	High	High	High
BBB permeant (blood–brain barrier)	Yes	Yes	Yes	No
Pgp substrate (p-glycoprotein)	Yes	Yes	No	Yes

The outcomes of *in silico* properties of the drugs **1-4** displayed no noteworthy violations of Lipinski's rule of five (mLogP<4.15, MW<500, Hydrogen bond donors<5, and Hydrogen bond acceptors<10) [29], since all calculated physicochemical descriptors and pharmacokinetic properties are within the expected thresholds. TPSA measured the bioavailability of the drug molecule and is closely related to the hydrogen bonding potential and should be <160 Å [35]. According to this model, the chosen drugs showed satisfactory oral bioavailability in combination with lipophilicity, MW, polarity, solubility, saturation, and flexibility in an acceptable range, as shown in radar plots [36]. Drug likeness was determined by the number of free rotatable bonds and Lipinski's rule. Computational analyses were performed to predict the core pharmacokinetics parameters, such as gastrointestinal absorption and P-glycoprotein-mediated efflux, and the results are displayed in Table 1.

Bioavailability radar of investigated 9*H*-thioxanthene drugs, **1-4** given bySwissADME showed that they demonstrate favorably predicted physicochemical properties for oral bioavailability (Figure 2). The ideal space of six physicochemical parameters, size, polarity, lipophilicity, solubility, flexibility, and saturation for oral bioavailability, is located in the pink-colored area [36,37]. All four investigated 9*H*-thioxanthene drugs **1-4** are in the pink area. Ligand-based target prediction has proven highly performant and fast in predicting correct protein targets of compounds in drug discovery [38,39].

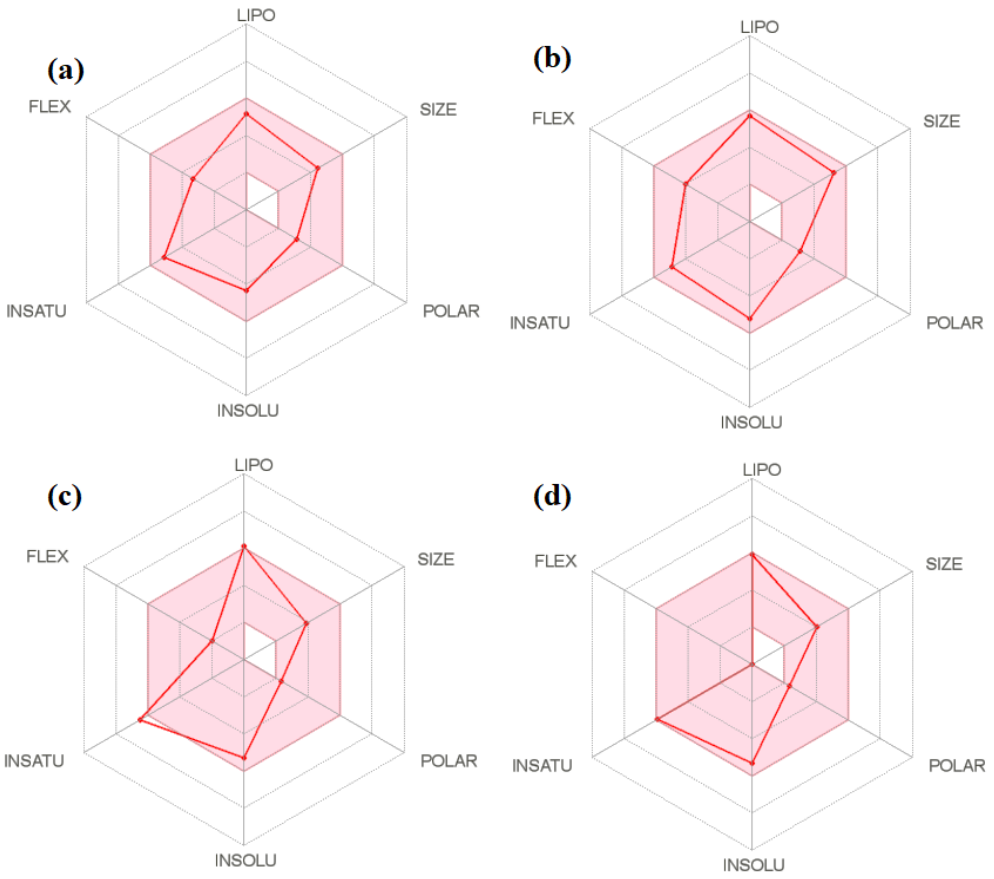

Figure 2. Bioavailability radar plot of 9*H*-thioxanthene drugs, **1-4**. POLAR (polarity), LIPO (lipophilicity), INSOLU (solubility), FLEX (flexibility), and INSATU (saturation).

3.2. Molecular docking.

Molecular docking is used in identifying and developing drug candidates and is a computational method to study the molecular activity of complexes at the molecular level [40–47]. The interactions between the structures of biological targets viz., protein or nucleic acid minimized at the molecular level with the molecular docking, and the drug candidate can be examined at the molecular level. Molecular docking gives binding energies, binding modes, and types of secondary chemical interactions between the target protein and the complex examined [48]. The Docking studies were performed to study the molecular binding pattern of 9H-thioxanthene-based FDA-approved drugs **1-4** within the active pocket of the crystal structures of the anticancer targets. The targets used for docking analysis with 9H-thioxanthene drugs **1-4** are VEGFR-2 and COX-2, which have been extensively revealed to contribute to apoptotic regulation, cell-cycle progression, transcriptional regulation, DNA damage repair, stem-cell self-renewal, metabolism, spermatogenesis, and neuronal function and anti-angiogenesis [19,20,22,23,49–54]. The ligand binding in the active site of a target is suggestive of the possibility that the ligand may be capable of driving functional alteration of the target molecules [55,56]. Drug-target interactions were also deciphered in terms of interacting amino acid residues, hydrogen bonding, docking energy analysis, and comparisons of active site amino acid residues and probable binding sites. The docking assessment of investigated drugs **1-4** within the active binding sites of targets is shown in Table 2.

Hydrogen bonding was also evaluated for the interaction of investigated drugs **1-4** with these three targets. Table 2 summarizes the amino acid residues involved in the hydrogen bonding of 9H-thioxanthene drugs **1-4** within the binding sites of VEGFR-2 and COX-2.

Overall binding strength is the result of various bonds, consisting of ionic, hydrophobic interactions, and Vander Waals forces, hydrogen bonds being the major contributors [57,58]. Hydrogen bonding also depends on the composition and 3D alignment of contacting amino acid residues at the prominent and active binding sites [59].

Table 2. Binding energies (kcal/mol) and amino acid residues involved in hydrogen bonding of 9*H*-thioxanthene drugs **1-4** within the binding sites of VEGFR-2 and COX-2.

Drug	Targets	Amino acids in the binding pockets	Receptor residues involved in Hydrogen bonding	Binding energy (kcal/mol)
1	VEGFR-2	Ala^{1050,1103}; Arg^{842,929,1032,1051}; Asn^{923}; Asp^{1052,1056,1058}; Gly^{841,1102}; Leu^{840}; Lys^{1055}; Phe^{1047}; Pro^{1057,1105}; Ser^{925,1104}; Thr^{926}; Trp^{1071}	Ser^{925}; Asp^{1052}; Gly^{1102}	-7.5
	COX-2	Ala^{562}; Arg^{311}; Asn^{570}; Asp^{268}; Cys^{569}; Gln^{270}; Glu^{308,339}; His^{242}; Ile^{558,343}; Leu^{246,567}; Lys^{243,253}; Phe^{247}; Ser^{563,566}; Thr^{269,561}	Ser^{563}	-7.6
2	VEGFR-2	Ala^{1031,1050,1103}; Arg^{929,1032,1051}; Asn^{923}; Asp^{1052,1056,1058}; Glu^{1097}; Glu^{841,1102}; Leu^{840}; Lys^{1055}; Phe^{1047}; Pro^{1057,1105}; Ser^{925,1104}; Thr^{926}; Trp^{1071}	Asp^{1052}; Glu^{1097}	-8.3
	COX-2	Ala^{562}; Arg^{245,311}; Asn^{70}; Asp^{268}; Cys^{569}; Gln^{270}; Glu^{308,339}; His^{242}; Ile^{558}; Leu^{246}; Lys^{243,253}; Phe^{247}; Ser^{566}; Thr^{269,561}	Glu^{308}; Arg^{311}; Glu^{339}; Ser^{566}; Asn^{570}	-8.0
3	VEGFR-2	Ala^{881}; Arg^{1027}; Asp^{814,1046}; Glu^{885}; Gly^{1048}; His^{1026}; Ile^{888}; Leu^{882,1049}; Ser^{884}	-	-6.4
	COX-2	Arg^{61}; Asp^{125}; Gln^{370,372,543}; Ile^{124}; Lys^{546}; Phe^{367}; Pro^{542}; Ser^{121}; Tyr^{122}	-	-6.2
4	VEGFR-2	Arg^{1032,1051}; Asn^{923}; Asp^{1052,1056,1058}; Lys^{1055}; Phe^{1047}	Asp^{1052}	-8.1
	COX-2	Asp^{58}; Glu^{553}; Gly^{551,552}; Cys^{57,59}; His^{320}; Lys^{56}; Met^{48}; Pro^{547}; Ser^{548}; Thr50; Val^{554}	-	-7.9

Ala- Alanine ; Arg-arginine ;Asn-Asparagine; Asp- Aspartic acid; Cys- Cysteine; Gln- Glutamine; Glu-Glutamic acid; Gly- Glycine; His-histidine; Ile- Isoleucine;Leu-leucine; Lys- Lysine; Phe-phenylalanine; Pro-Proline; Ser-serine; Thr- Threonine;Trp- Tryptophan; Val-Valine.

Figure 3 displays the interacting amino acid residues between investigated 9*H*-thioxanthene drugs **1-4** and their respective targets. Figure 3 reveals that all four 9*H*-thioxanthene-based FDA-approved drugs **1-4** were found to bind to VEGFR-2 with binding energies of -7.5, -8.3, -6.4, and -8.1 kcal/mol, respectively (Figure 4). These negative binding affinities may explain the potent inhibition of compounds towards VEGFR-2 tyrosine kinases. The negative values also indicate that inhibition is thermodynamically favorable and spontaneous [60]. Figure 4 shows the 2D interaction of the drugs with amino acids of the VEGFR-2 enzyme.

These drugs were able to bind to the VEGFR-2 enzyme firmly and, therefore, could possibly inhibit its function. Table 2 summarizes the amino acid residues involved in the hydrogen bonding of investigated 9*H*-thioxanthene drugs **1-4** inside the target binding sites.

Also, within the active pockets of the COX-2 enzyme, the investigated drugs **1-4**, displayed in figures 5 and 6, revealed that they bind with the amino acids in the enzyme pocket with binding energies of -7.6, -8.0, -6.2, and -7.9 kcal/mol, respectively.

The results of ΔG values revealed that 9*H*-thioxanthene drugs **1-4** interacted with a greater binding affinity with VEGFR-2 in comparison to COX-2. From these docking results, we could suggest that the variations are due to the presence of amino acid residues mutual to the active binding sites, with small relation to the hydrogen bonds. Therefore the presence of the hydrogen bonds is independent of the mutual amino acid residues to active binding sites and the docking strength.

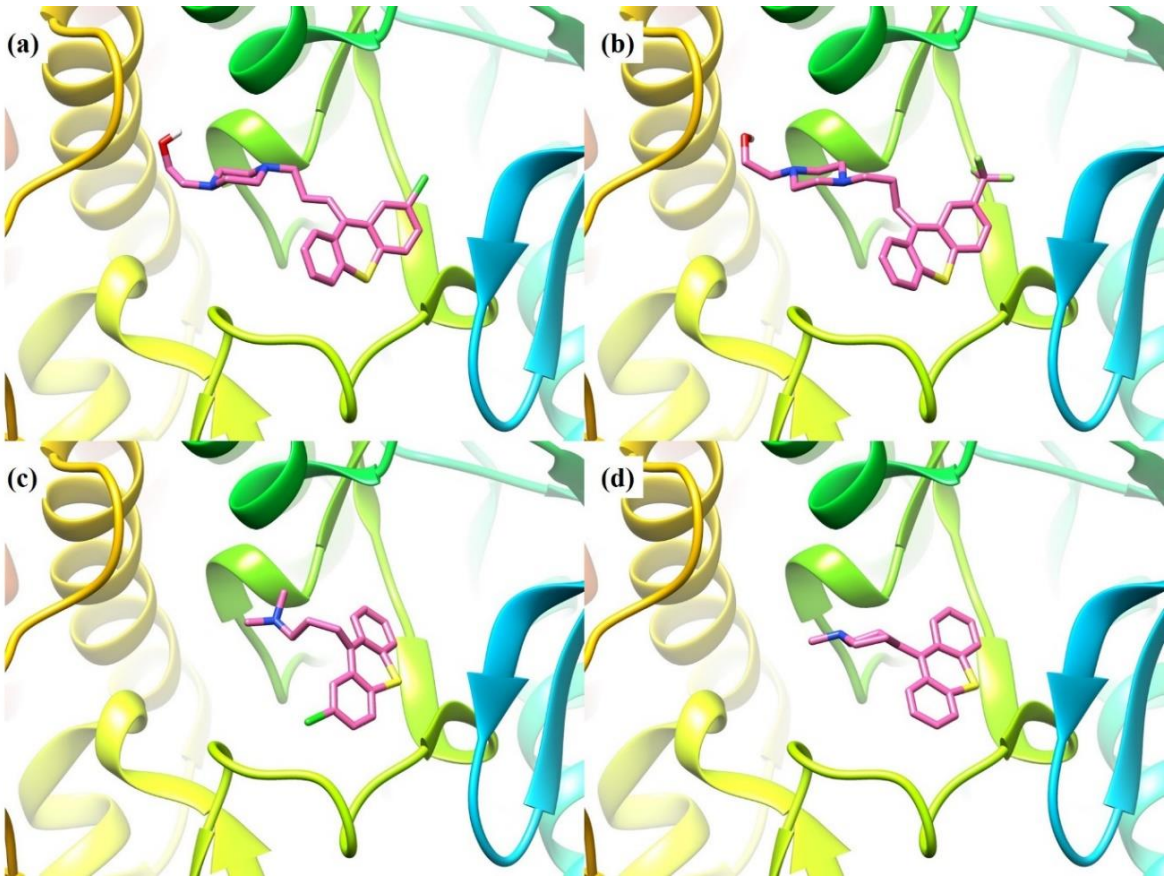

Figure 3. 3D alignment of the docked structures of 9*H*-thioxanthene drugs **1-4** (pink stick) in the corresponding binding pockets of target VEGFR-2.

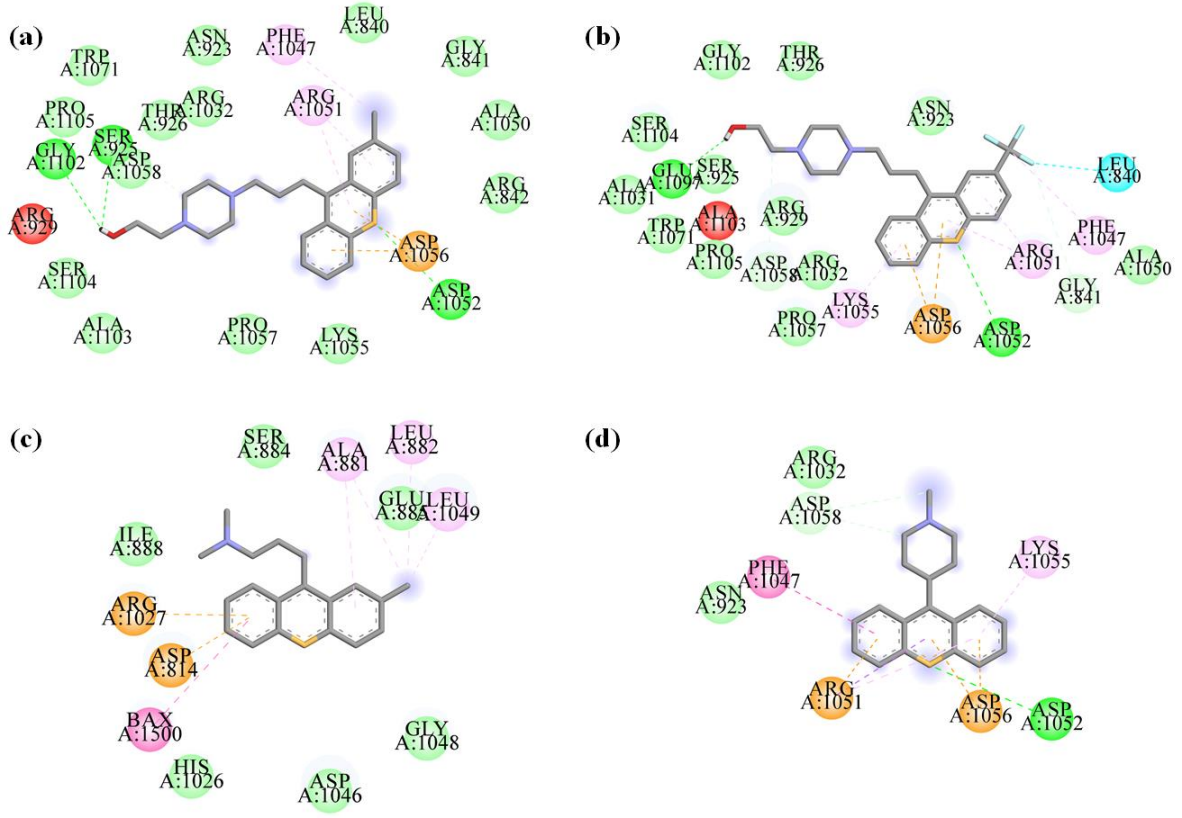

Figure 4. The 2D interaction of 9*H*-thioxanthene drugs **1-4** with the amino acids of the active site of VEGFR-2 enzyme.

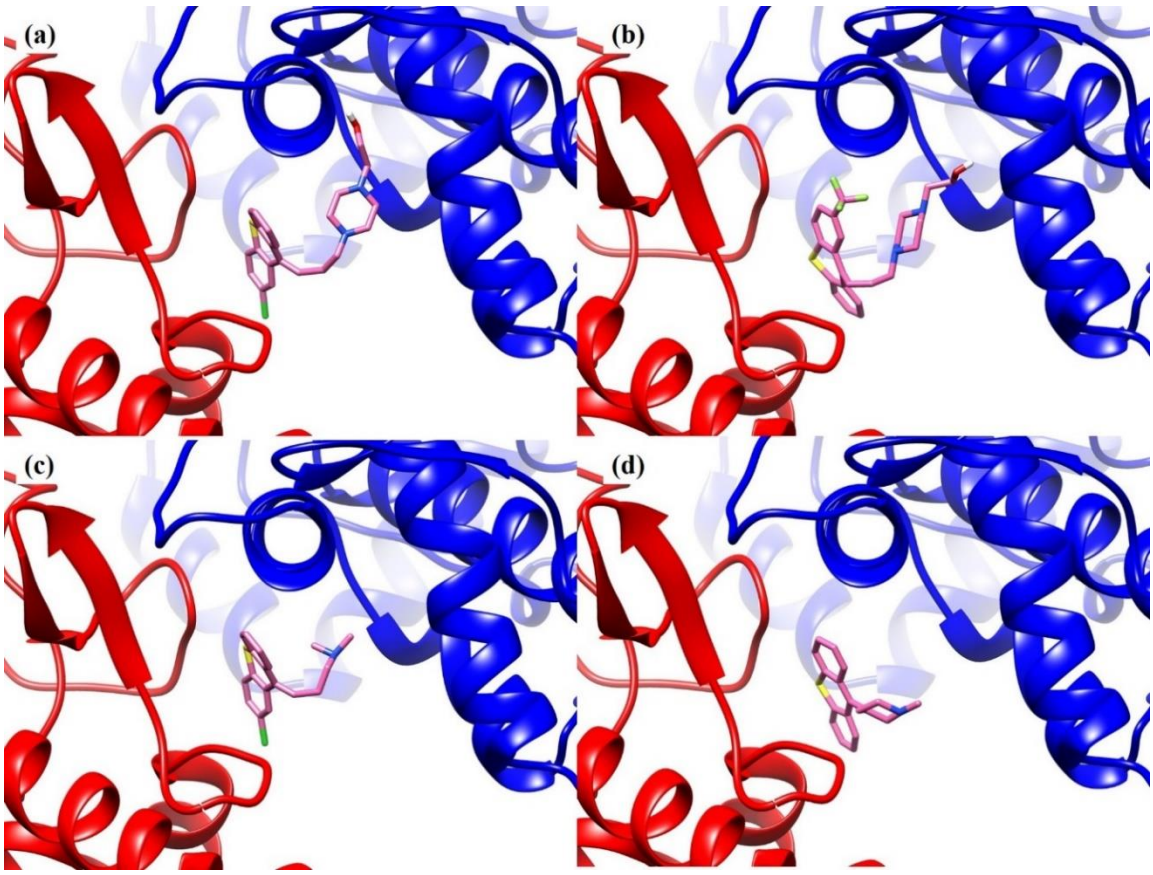

Figure 5. 3D alignment of the docked structures of 9*H*-thioxanthene drugs **1-4** (pink stick) in the corresponding binding pockets of target COX-2.

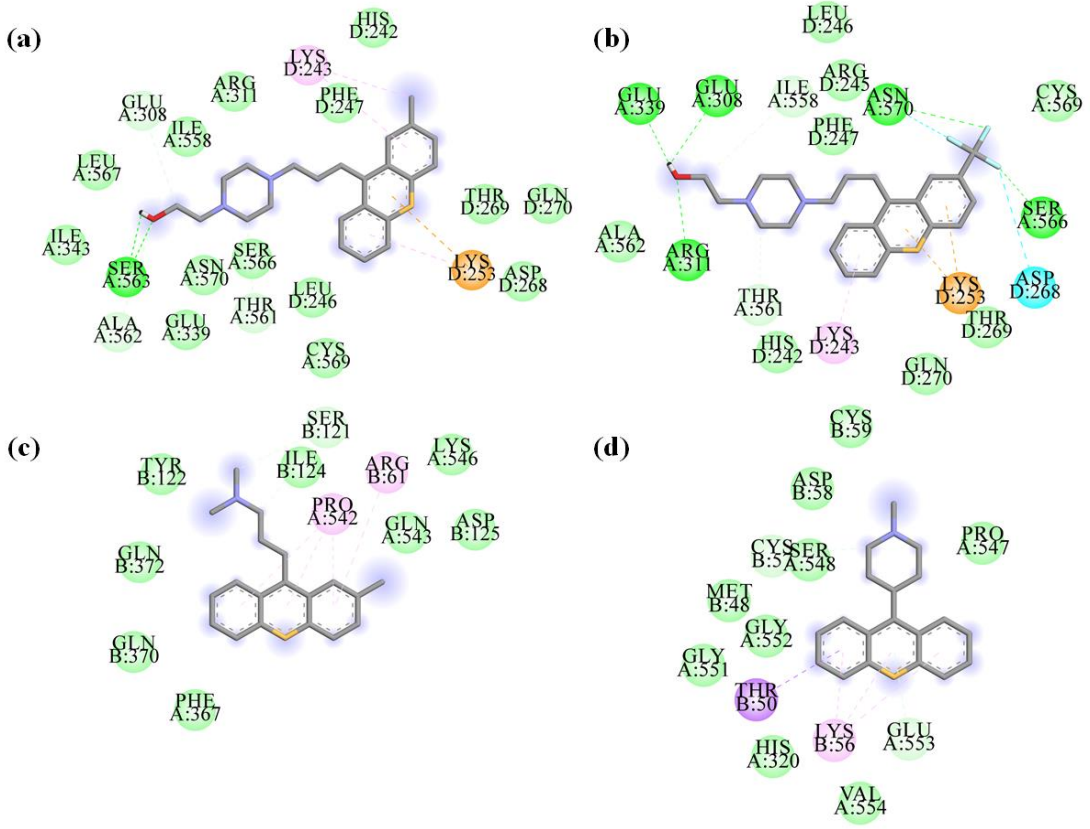

Figure 6. The 2D interaction of 9*H*-thioxanthene drugs **1-4** with the amino acids of the active site of COX-2 enzyme.

4. Conclusions

Computational approaches are evolving day by day to improve the drug discovery process. The current study is based on drug repurposing of 9*H*-thioxanthene drugs against anticancer chemotherapeutic targets, *viz.,* VEGFR-2 and COX-2. The ADME properties and drug-likeness of 9*H*-thioxanthene drugs **1-4** were also assessed, suggesting their good oral bioavailability. 9*H*-thioxanthene drugs **1-4** were screened against VEGFR-2 and COX-2 through *in-silico* approaches to find more potent inhibitors. In structure-based drug discovery, the binding site unlocks the active residues interacting with the small molecule and is undoubtedly essential for molecular docking. Thorough data regarding the binding pocket is obligatory for structure-based drug discovery. The molecular docking study showed that all four investigated 9*H*-thioxanthene exhibited inhibitory effects on the chosen enzymatic targets. The docking results revealed that all four 9*H*-thioxanthene drugs were able to bind to VEGFR-2 with more affinity in comparison to COX-2. Thus, these drugs can be analyzed through experiments in future clinical trials of drugs against VEGFR-2 and COX-2. However, it requires further study to elucidate this hypothesis.

Funding

This research received no external funding.

Acknowledgments

The authors are grateful to Taibah University.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Rosenberg, S.A. Progress in Human Tumour Immunology and Immunotherapy. *Nature* **2001**, *411*, 380–384, https://doi.org/10.1038/35077246.
2. Cairns, J. The Origin of Human Cancers. *Nature* **1981**, *289*, 353–357, https://doi.org/10.1038/289353a0.
3. Demaria, M.; O'Leary, M.N.; Chang, J.; Shao, L.; Liu, S.; Alimirah, F.; Koenig, K.; Le, C.; Mitin, N.; Deal, A.M.; et al. Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse. *Cancer Discov.* **2017**, *7*, 165–176, https://doi.org/10.1158/2159-8290.CD-16-0241.
4. Mansoori, B.; Mohammadi, A.; Davudian, S.; Shirjang, S.; Baradaran, B. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. *Adv. Pharm. Bull.* **2017**, *7*, 339–348, https://doi.org/10.15171/apb.2017.041.
5. Parvathaneni, V.; Kulkarni, N.S.; Muth, A.; Gupta, V. Drug Repurposing: A Promising Tool to Accelerate the Drug Discovery Process. *Drug Discov. Today* **2019**, *24*, 2076–2085, https://doi.org/10.1016/j.drudis.2019.06.014.
6. Ancidoni, A.; Bacigalupo, I.; Remoli, G.; Lacorte, E.; Piscopo, P.; Sarti, G.; Corbo, M.; Vanacore, N.; Canevelli, M. Anticancer Drugs Repurposed for Alzheimer's Disease: A Systematic Review. *Alzheimers. Res. Ther.* **2021**, *13*, 96, https://doi.org/10.1186/s13195-021-00831-6.
7. Mottini, C.; Napolitano, F.; Li, Z.; Gao, X.; Cardone, L. Computer-Aided Drug Repurposing for Cancer Therapy: Approaches and Opportunities to Challenge Anticancer Targets. *Semin. Cancer Biol.* **2021**, *68*, 59–74, https://doi.org/10.1016/j.semcancer.2019.09.023.
8. Song, Y.; Yang, X.; Yu, B. Repurposing Antidepressants for Anticancer Drug Discovery. *Drug Discov. Today* **2021**, https://doi.org/10.1016/j.drudis.2021.10.019.
9. Kaushik, I.; Ramachandran, S.; Prasad, S.; Srivastava, S.K. Drug Rechanneling: A Novel Paradigm for Cancer Treatment. *Semin. Cancer Biol.* **2021**, *68*, 279–290, https://doi.org/10.1016/j.semcancer.2020.03.011.
10. Sherin, D.R.; Manojkumar, T.K. Exploring the Selectivity of Guanine Scaffold in Anticancer Drug Development by Computational Repurposing Approach. *Sci. Rep.* **2021**, *11*, 16251,

https://doi.org/10.1038/s41598-021-95507-4.
11. Naylor, S.; Kauppi, D.M.; Schonfeld, J.M. Therapeutic Drug Repurposing, Repositioning and Rescue: Part II: Business Review. *Drug Discov. World* **2015**, *16*, 57–72, https://www.ddw-online.com/therapeutic-drug-repurposing-repositioning-and-rescue-part-ii-business-review-888-201504/.
12. Seidel, T.; Wieder, O.; Garon, A.; Langer, T. Applications of the Pharmacophore Concept in Natural Product Inspired Drug Design. *Mol. Inform.* **2020**, *39*, minf.202000059, https://doi.org/10.1002/minf.202000059.
13. Debord, J.; Merle, L.; Bollinger, J.-C.; Dantoine, T. Inhibition of Butyrylcholinesterase by Phenothiazine Derivatives. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 197–202, https://doi.org/10.1080/1475636021000003165.
14. Poulsen, M.; Dastidar, S.G.; Roy, D.S.; Palchoudhuri, S.; Kristiansen, J.E.H.; Fey, S.J. A Double-Edged Sword: Thioxanthenes Act on Both the Mind and the Microbiome. *Molecules* **2022**, *27*, 196, https://doi.org/10.3390/molecules27010196.
15. Ahmed, M.F.; Santali, E.Y.; El-Haggar, R. Novel Piperazine–Chalcone Hybrids and Related Pyrazoline Analogues Targeting VEGFR-2 Kinase; Design, Synthesis, Molecular Docking Studies, and Anticancer Evaluation. *J. Enzyme Inhib. Med. Chem.* **2021**, *36*, 308–319, https://doi.org/10.1080/14756366.2020.1861606.
16. Uzun, S.; Korkmaz, Y.; Wuerdemann, N.; Arolt, C.; Puladi, B.; Siefer, O.G.; Dönmez, H.G.; Hufbauer, M.; Akgül, B.; Klussmann, J.P.; et al. Comprehensive Analysis of VEGFR2 Expression in HPV-Positive and -Negative Opscc Reveals Differing VEGFR2 Expression Patterns. *Cancers (Basel).* **2021**, *13*, https://doi.org/10.3390/cancers13205221.
17. Abdelgawad, M.A.; El-Adl, K.; El-Hddad, S.S.A.; Elhady, M.M.; Saleh, N.M.; Khalifa, M.M.; Khedr, F.; Alswah, M.; Nayl, A.A.; Ghoneim, M.M.; et al. Design, Molecular Docking, Synthesis, Anticancer and Anti-Hyperglycemic Assessments of Thiazolidine-2,4-Diones Bearing Sulfonylthiourea Moieties as Potent VEGFR-2 Inhibitors and PPARγ Agonists. *Pharmaceuticals* **2022**, *15*, https://doi.org/10.3390/ph15020226.
18. Alanazi, M.M.; Eissa, I.H.; Alsaif, N.A.; Obaidullah, A.J.; Alanazi, W.A.; Alasmari, A.F.; Albassam, H.; Elkady, H.; Elwan, A. Design, Synthesis, Docking, ADMET Studies, and Anticancer Evaluation of New 3-Methylquinoxaline Derivatives as VEGFR-2 Inhibitors and Apoptosis Inducers. *J. Enzyme Inhib. Med. Chem.* **2021**, *36*, 1760–1782, https://doi.org/10.1080/14756366.2021.1956488.
19. Nazer, B.; Humphreys, B.D.; Moslehi, J. Effects of Novel Angiogenesis Inhibitors for the Treatment of Cancer on the Cardiovascular System: Focus on Hypertension. *Circulation* **2011**, *124*, 1687–1691, https://doi.org/10.1161/CIRCULATIONAHA.110.992230.
20. Gotink, K.J.; Verheul, H.M.W. Anti-Angiogenic Tyrosine Kinase Inhibitors: What Is Their Mechanism of Action? *Angiogenesis* **2010**, *13*, 1–14, https://doi.org/10.1007/s10456-009-9160-6.
21. Vittorio, S.; Seidel, T.; Germanò, M.P.; Gitto, R.; Ielo, L.; Garon, A.; Rapisarda, A.; Pace, V.; Langer, T.; De Luca, L. A Combination of Pharmacophore and Docking-Based Virtual Screening to Discover New Tyrosinase Inhibitors. *Mol. Inform.* **2020**, *39*, 1900054, https://doi.org/10.1002/minf.201900054.
22. Goel, H.L.; Mercurio, A.M. VEGF Targets the Tumour Cell. *Nat. Rev. Cancer* **2013**, *13*, 871–882, https://doi.org/10.1038/nrc3627.
23. Huang, L.; Huang, Z.; Bai, Z.; Xie, R.; Sun, L.; Lin, K. Development and Strategies of VEGFR-2/KDR Inhibitors. *Future Med. Chem.* **2012**, *4*, 1839–1852, https://doi.org/10.4155/fmc.12.121.
24. Akhtar, W.; Marella, A.; Alam, M.M.; Khan, M.F.; Akhtar, M.; Anwer, T.; Khan, F.; Naematullah, M.; Azam, F.; Rizvi, M.A.; et al. Design and Synthesis of Pyrazole–Pyrazoline Hybrids as Cancer-associated Selective COX-2 Inhibitors. *Arch. Pharm. (Weinheim).* **2021**, *354*, 2000116, https://doi.org/10.1002/ardp.202000116.
25. Regulski, M.; Regulska, K.; Prukała, W.; Piotrowska, H.; Stanisz, B.; Murias, M. COX-2 Inhibitors: A Novel Strategy in the Management of Breast Cancer. *Drug Discov. Today* **2016**, *21*, 598–615, https://doi.org/10.1016/j.drudis.2015.12.003.
26. Huang, M.; Chen, Q.; Xiao, J.; Liu, C.; Zhao, X. Prognostic Significance of Cyclooxygenase-2 in Cervical Cancer: A Meta-Analysis. *Int. J. Cancer* **2013**, *132*, 363–373, https://doi.org/10.1002/ijc.27686.
27. Ghosh, N.; Chaki, R.; Mandal, V.; Mandal, S.C. COX-2 as a Target for Cancer Chemotherapy. *Pharmacol. Reports* **2010**, *62*, 233–244, https://doi.org/10.1016/S1734-1140(10)70262-0.
28. Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: Updated Data and New Features for Efficient Prediction of Protein Targets of Small Molecules. *Nucleic Acids Res.* **2019**, *47*, W357–W3664, https://doi.org/10.1093/nar/gkz382.
29. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25, https://doi.org/10.1016/S0169-409X(96)00423-1.
30. Trott, O.; Olson, A.J. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading. *J. Comput. Chem.* **2009**, https://doi.org/10.1002/jcc.21334.
31. McTigue, M.; Murray, B.W.; Chen, J.H.; Deng, Y.-L.; Solowiej, J.; Kania, R.S. Molecular Conformations, Interactions, and Properties Associated with Drug Efficiency and Clinical Performance among VEGFR TK Inhibitors. *Proc. Natl. Acad. Sci.* **2012**, *109*, 18281–18289, https://doi.org/10.1073/pnas.1207759109.
32. Kurumbail, R.G.; Stevens, A.M.; Gierse, J.K.; McDonald, J.J.; Stegeman, R.A.; Pak, J.Y.; Gildehaus, D.;

Iyashiro, J.M.; Penning, T.D.; Seibert, K.; et al. Structural Basis for Selective Inhibition of Cyclooxygenase-2 by Anti-Inflammatory Agents. *Nature* **1996**, *384*, 644–648, https://doi.org/10.1038/384644a0.
33. Morris, G.M.; Ruth, H.; Lindstrom, W.; Sanner, M.F.; Belew, R.K.; Goodsell, D.S.; Olson, A.J. Software News and Updates AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility. *J. Comput. Chem.* **2009**, *30*, 2785–2791, https://doi.org/10.1002/jcc.21256.
34. Cheng, W.; Yuan, Y.; Qiu, N.; Peng, P.; Sheng, R.; Hu, Y. Identification of Novel 4-Anilinoquinazoline Derivatives as Potent EGFR Inhibitors Both under Normoxia and Hypoxia. *Bioorganic Med. Chem.* **2014**, *22*, 6796–6805, https://doi.org/10.1016/j.bmc.2014.10.038.
35. Veber, D.F.; Johnson, S.R.; Cheng, H.Y.; Smith, B.R.; Ward, K.W.; Kopple, K.D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623, https://doi.org/10.1021/jm020017n.
36. Abdel-Mohsen, H.T.; Abood, A.; Flanagan, K.J.; Meindl, A.; Senge, M.O.; El Diwani, H.I. Synthesis, Crystal Structure, and ADME Prediction Studies of Novel Imidazopyrimidines as Antibacterial and Cytotoxic Agents. *Arch. Pharm. (Weinheim).* **2020**, *353*, https://doi.org/10.1002/ardp.201900271.
37. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* **2017**, *7*, 42717, https://doi.org/10.1038/srep42717.
38. Cereto-Massagué, A.; Ojeda, M.J.; Valls, C.; Mulero, M.; Pujadas, G.; Garcia-Vallve, S. Tools for in Silico Target Fishing. *Methods* **2015**, *71*, 98–103, https://doi.org/10.1016/j.ymeth.2014.09.006.
39. Ding, H.; Takigawa, I.; Mamitsuka, H.; Zhu, S. Similarity-Basedmachine Learning Methods for Predicting Drug-Target Interactions: A Brief Review. *Brief. Bioinform.* **2013**, *15*, 734–747, https://doi.org/10.1093/bib/bbt056.
40. Husain, A.; Bedi, S.; Parveen, S.; Khan, S.A.; Ahmad, A.; Iqbal, M.A.; Farooq, A.; Ahmed, A. Furanone-Functionalized Benzothiazole Derivatives: Synthesis, in Vitro Cytotoxicity, ADME, and Molecular Docking Studies. *Zeitschrift für Naturforsch. B* **2022**, *77*, 41–53, https://doi.org/10.1515/znb-2021-0146.
41. Alnoman, R.B.; Parveen, S.; Khan, A.; Knight, J.G.; Hagar, M. New Quinoline-Based BODIPYs as EGFR/VEGFR-2 Inhibitors: Molecular Docking, DFT and in Vitro Cytotoxicity on HeLa Cells. *J. Mol. Struct.* **2022**, *1247*, 131312, https://doi.org/10.1016/j.molstruc.2021.131312.
42. Mohammed, F.F.; Hagar, M.; Parveen, S.; Alnoman, R.B.; Ahmed, H.A.; Ashry, E.S.H.E.; Rasheed, H.A. 2-(Alkylthio)-3-(Naphthalen-1-Yl)Quinazolin-4(3H)-Ones: Ultrasonic Synthesis, DFT and Molecular Docking Aspects. *Polycycl. Aromat. Compd.* **2021**, https://doi.org/10.1080/10406638.2021.1878245.
43. Parveen, S.; Hagar, M.; B. Alnoman, R.; Ahmed, H.A.; El Ashry, E.S.H.; Zakaria, M.A. Synthesis, Docking and Density Functional Theory Approaches on 1,3-Bis-3-(4-Chlorophenyl)-2,3-Dihydroquinazolin-4(1H)-on-2-Thioxopropane toward the Discovery of Dual Kinase Inhibitor. *Polycycl. Aromat. Compd.* **2021**, 1–12, https://doi.org/10.1080/10406638.2021.1871636.
44. Parveen, S. Biophysical and Theoretical Investigation of Benzo[c]Coumarin Functionalized Schiff Base with Human Serum Albumin. *Chem. Pap.* **2021**, *75*, 2339–2351, https://doi.org/10.1007/s11696-020-01496-5.
45. Husain, A.; Bhutani, M.; Parveen, S.; Khan, S.A.; Ahmad, A.; Iqbal, M.A. Synthesis, in Vitro Cytotoxicity, ADME, and Molecular Docking Studies of Benzimidazole-Bearing Furanone Derivatives. *J. Chinese Chem. Soc.* **2021**, *68*, 362–373, https://doi.org/10.1002/jccs.202000130.
46. Alnoman, R.B.; Hagar, M.; Parveen, S.; Ahmed, H.A.; Knight, J.G. Computational and Molecular Docking Approaches of a New Axially Chiral BODIPY Fluorescent Dye. *J. Photochem. Photobiol. A Chem.* **2020**, *395*, 112508, https://doi.org/10.1016/j.jphotochem.2020.112508.
47. Hagar, M.; Chaieb, K.; Parveen, S.; Ahmed, H.A.; Alnoman, R.B. N-Alkyl 2-Pyridone versus O-Alkyl 2-Pyridol: Ultrasonic Synthesis, DFT, Docking Studies and Their Antimicrobial Evaluation. *J. Mol. Struct.* **2020**, *1199*, 126926, https://doi.org/10.1016/j.molstruc.2019.126926.
48. Kaya, S.; Erkan, S.; Karakaş, D. Computational Investigation of Molecular Structures, Spectroscopic Properties and Antitumor-Antibacterial Activities of Some Schiff Bases. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2021**, *244*, 118829, https://doi.org/10.1016/j.saa.2020.118829.
49. Warren, C.F.A.; Wong-Brown, M.W.; Bowden, N.A. BCL-2 Family Isoforms in Apoptosis and Cancer. *Cell Death Dis.* **2019**, *10*, 177, https://doi.org/10.1038/s41419-019-1407-6.
50. Lim, S.; Kaldis, P. Cdks, Cyclins and CKIs: Roles beyond Cell Cycle Regulation. *Dev.* **2013**, *140*, 3079–3093, https://doi.org/10.1242/dev.091744.
51. Tigan, A.S.; Bellutti, F.; Kollmann, K.; Tebb, G.; Sexl, V. CDK6-a Review of the Past and a Glimpse into the Future: From Cell-Cycle Control to Transcriptional Regulation. *Oncogene* **2016**, *35*, 3083–3091, https://doi.org/10.1038/onc.2015.407.
52. Malumbres, M.; Barbacid, M. To Cycle or Not to Cycle: A Critical Decision in Cancer. *Nat. Rev. Cancer* **2001**, *1*, 222–231, https://doi.org/10.1038/35106065.
53. Malumbres, M.; Barbacid, M. Cell Cycle, CDKs and Cancer: A Changing Paradigm. *Nat. Rev. Cancer* **2009**, *9*, 153–166, https://doi.org/10.1038/nrc2602.
54. Selvam, C.; Mock, C.D.; Mathew, O.P.; Ranganna, K.; Thilagavathi, R. Discovery of Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) Inhibitors by Ligand-Based Virtual High Throughput Screening. *Mol. Inform.* **2020**, *39*, minf.201900150, https://doi.org/10.1002/minf.201900150.

55. Kojetin, D.J.; Burris, T.P. Small Molecule Modulation of Nuclear Receptor Conformational Dynamics: Implications for Function and Drug Discovery. *Mol. Pharmacol.* **2013**, *83*, 1–8, https://doi.org/10.1124/mol.112.079285.
56. Schena, A.; Griss, R.; Johnsson, K. Modulating Protein Activity Using Tethered Ligands with Mutually Exclusive Binding Sites. *Nat. Commun.* **2015**, *6*, 7830, https://doi.org/10.1038/ncomms8830.
57. Papaneophytou, C.P.; Grigoroudis, A.I.; McInnes, C.; Kontopidis, G. Quantification of the Effects of Ionic Strength, Viscosity, and Hydrophobicity on Protein-Ligand Binding Affinity. *ACS Med. Chem. Lett.* **2014**, *5*, 931–936, https://doi.org/10.1021/ml500204e.
58. Zhao, X.; Xu, Z.; Li, H. NSAIDs Use and Reduced Metastasis in Cancer Patients: Results from a Meta-Analysis. *Sci. Rep.* **2017**, *7*, 1875, https://doi.org/10.1038/s41598-017-01644-0.
59. Chelliah, V.; Blundell, T.L.; Fernández-Recio, J. Efficient Restraints for Protein-Protein Docking by Comparison of Observed Amino Acid Substitution Patterns with Those Predicted from Local Environment. *J. Mol. Biol.* **2006**, *357*, 1669–1682, https://doi.org/10.1016/j.jmb.2006.01.001.
60. Riadi, Y.; Alamri, M.A.; Geesi, M.H.; Anouar, E.H.; Ouerghi, O.; Alabbas, A.B.; Alossaimi, M.A.; Altharawi, A.; Dehbi, O.; Alqahtani, S.M. Synthesis, Characterization, Biological Evaluation and Molecular Docking of a New Quinazolinone-Based Derivative as a Potent Dual Inhibitor for VEGFR-2 and EGFR Tyrosine Kinases. *J. Biomol. Struct. Dyn.* **2021**, 1–7, https://doi.org/10.1080/07391102.2021.1890221.