ORIGINAL ARTICLE

Docking and Pharmacokinetic Studies of Oxazolone Derivatives of p-Coumaric Acid as Anticancer Agents

Supriya A. Unavane[1,2], Rajesh B. Patil[1]

[1]Department of Pharmaceutical Chemistry, STES's Sinhgad College of Pharmacy, Pune, Maharashtra, India,
[2]Department of Pharmaceutical Chemistry, School of Pharmacy, Vishwakarma University, Pune, Maharashtra, India

Abstract

Introduction: Cancer is a leading cause of mortality leading to millions of deaths worldwide annually. It is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body. Protein tyrosine kinases (PTKs) are enzymes that regulate key cellular processes such as cell growth, differentiation, and survival. Targeted therapies such as tyrosine kinase inhibitors have been developed to block the aberrant PTK activity. P-coumaric acid is a phenolic acid of hydroxycinnamic acid family abundantly available in various fruits, vegetables, and cereals. It exhibits a wide range of pharmacological activities. It is reported to be active against various types of cancers, and hence, derivatives of p-coumaric acid can be developed as potential anticancer agents. **Methods:** In this study, we have designed derivatives of p-coumaric acid in combination with oxazolone ring. These compounds were docked on vascular endothelial growth factor receptor (VEGFR) receptor using AutoDock vina. All the compounds were further evaluated for their physicochemical properties and drug likeliness. **Results and Discussion:** All the compounds showed good binding affinity for the receptor with binding energy ranging from −9.8 to −10.7 kcaL/moL. All compounds have good bioavailability and none showed any violation of Lipinski's rule of five. **Conclusion:** The studies reveal that p-coumaric acid derivatives of oxazolones show good binding affinity for VEGFR. Monosubstitution on aromatic ring enhances the binding affinity whereas disubstitution causes a decrease in binding affinity. All the compounds possess good absorption, distribution, metabolism, and elimination properties, and hence, these molecules could be developed further as anticancer agents.

Key words: Docking, VEGFR, anticancer, p-coumaric acid, oxazolone, ADME

INTRODUCTION

Cancer is a leading cause of morbidity worldwide and poses significant challenges to global health systems. Advances in early detection, targeted therapies, immunotherapy, and personalized medicine have improved outcomes for many patients, yet the disease remains a challenging public health issue. Cancer is a complex disease characterized by the uncontrolled growth and spread of abnormal cells within the body. The genetic mutations and alterations in cellular processes disrupt normal cell cycle regulation, proliferation of malignant cells, evade apoptosis, and invade surrounding tissues. Protein tyrosine kinase (PTK) is the key enzymes that regulate critical signaling pathways involved in cell growth, differentiation, and survival. Dysregulation of PTKs, through mutations or overexpression, can lead to aberrant signaling that promotes tumor progression, angiogenesis, and metastasis.[1] Cancers such as lung, breast, and leukemia have been strongly linked to PTK abnormalities.[2] Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis. Overexpression of VEGF is observed in many cancers and inflammatory diseases.[3] Hence, efforts are directed toward the development of inhibitors of VEGF receptor (VEGFR). Targeting VEGFR with specific inhibitors has emerged as a promising therapeutic strategy, with drugs such as imatinib and erlotinib achieving success in clinical applications.[4]

Address for correspondence:
Supriya A. Unavane, STES's Sinhgad College of Pharmacy, S. No.44/1, Off. Sinhgad Road, Vadgaon Budruk, Pune - 411046, Maharashtra, India.
Phone: 020-24354720.
E-mail: supriya.unavane@yahoo.com

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p-Coumaric acid [Figure 1], a naturally occurring hydroxycinnamic acid, possesses antioxidant,[5] anti-inflammatory,[6] and antimicrobial[7] properties. Its anticancer effects are attributed to its ability to modulate multiple molecular pathways, including inhibition of tumor growth, induction of apoptosis, suppression of angiogenesis, and reduction of oxidative stress.[8] Studies have demonstrated that p-coumaric acid can target diverse types of cancer cells, such as breast, liver, and lung cancer while exerting minimal toxicity on normal cells.[9] Oxazolones are versatile molecules with varied biological activities. Some drugs possessing the oxazolone ring are listed in Figure 2. The oxazolone-containing compounds also exhibit anticancer effect by interfering with critical cellular processes, such as DNA replication, apoptosis induction, and inhibition of key enzymes involved in tumor growth.[10-12] Thus, they hold great promise as scaffolds for designing novel anticancer drugs. We have designed eight molecules which incorporate the p-coumaric acid with the oxazolone scaffold. This study aims to explore the anticancer activity of the designed oxazolone derivatives by predicting their binding interactions with the tyrosine kinase receptor using molecular docking and evaluate their pharmacokinetic profile using absorption, distribution, metabolism, and elimination (ADME) studies.

METHODS

Molecular docking studies were performed using AutoDock Vina[13,14] to predict the binding interactions and affinities of the compounds with the VEGFR. Marvin was used for drawing and displaying chemical structures [Figure 3], Marvin 24.3.0, 2024, ChemAxon (http://www.chemaxon.com) and optimized using AutoDock Tools. The ligands were converted into the PDBQT format ensuring appropriate torsional flexibility and charge assignments. The 3D structure of the target protein was obtained from the Protein Data Bank (PDB ID 3U6J) and was processed using Biovia Discovery Studio to remove water molecules and heteroatoms. Polar hydrogens were added, and Kollman charges were assigned using AutoDock Tools. The active site of the protein was identified, and a grid box was defined around this region for exploration of the binding site.

Docking simulations were performed with AutoDock Vina. The grid box dimensions were optimized to encompass the active site and surrounding residues. Nine different conformations of each ligand were generated and ranked according to their binding energies. The least energy conformation was further utilized to generate the protein-ligand complex and study different interactions between protein and ligand using Discovery Studio.

The ADME properties of compounds were predicted using SwissADME[15-17] (available at www.swissadme.ch.). The simplified molecular input line entry system formats of the compounds were obtained using Marvin Sketch which were used as inputs for the SwissADME tool to compute various properties such as molecular weight, polarity, hydrogen bond donors, hydrogen bond acceptors, lipophilicity, solubility, drug-likeness, gastrointestinal absorption, ability to cross blood–brain barrier, and metabolism which are important for assessing a drug's behavior *in vivo*.

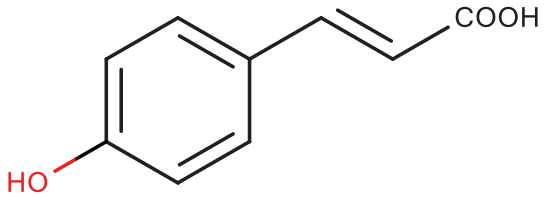

Figure 1: p-Coumaric acid

RESULTS AND DISCUSSION

The molecular docking analysis highlights the binding potential of the compounds with the target protein, revealing favorable interactions between the ligand and the receptor that contribute to their activity. The study shows

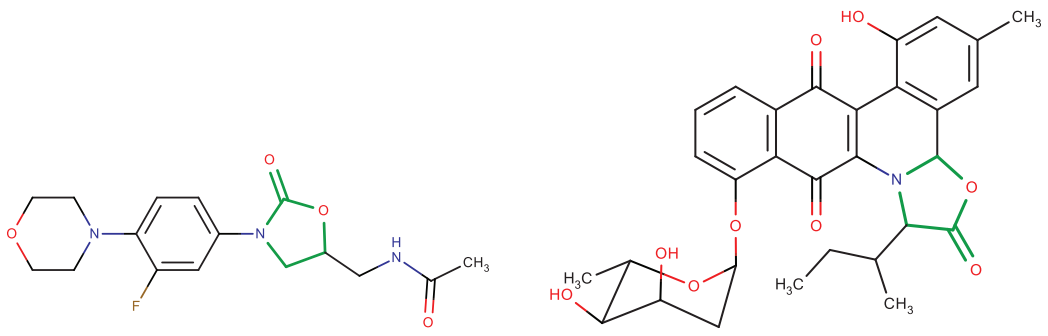

Figure 2: Drugs containing oxazolone ring

that all compounds (compounds 1–8) bind effectively to the active site residues of the protein [Table 1]. The binding energies of the compounds range from −10.7 to −9.8 kcaL/moL. All compounds form hydrogen bonds with key active site residues, including LYS868, THR916, CYS919, and ASP1046, indicating interactions with the protein's active site, which may contribute to their pharmacological effects.

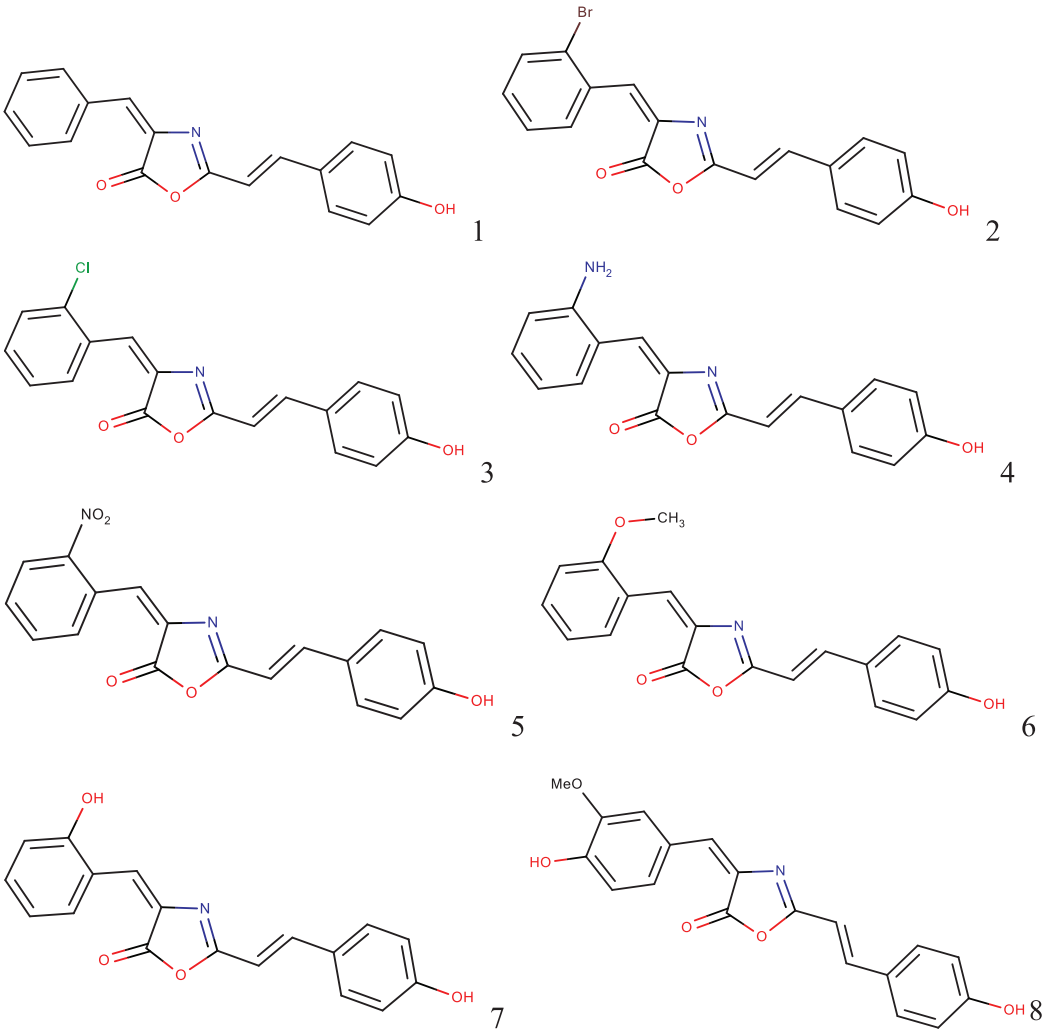

Figure 3: Structures of compounds under study

Table 1: Docking results for compounds 1–8

Compound No.	Binding energy (kcaL/moL)	No. of H bonds	Distance (A°)	Interacting amino acids
1	−10.3	1	2.46	LYS868
2	−10.5	1	3.06	THR916
3	−10.5	1	3.10	THR916
4	−10.4	1	3.15	THR916
5	−10.7	1	3.34	CYS 919
6	−10.5	1	3.04	THR916
7	−10.5	1	3.10	ASP1046
8	−9.8	1	3.38	CYS919
Co-crystal ligand	−12.7	2	2.06 1.91 2.3	CYS 919 ASP 1046 ASP 1046

Compound 5, which contains a strong electron-withdrawing group, exhibits the lowest binding energy compared to the other compounds. It forms a hydrogen bond with CYS919 present in the active pocket of the receptor [Figure 4]. This is followed by compounds 2, 3, 6, and 7, which contain bromo, chloro (weakly electron-withdrawing), methoxy, and hydroxy (electron-donating) groups, respectively, and show similar binding energies. Compound 1, which lacks any substituents on the aromatic ring, shows moderate binding energy, while Compound 8, which has two substitutions, demonstrates the highest binding energy.

This suggests that derivatives with strong electron-withdrawing substituents bind more effectively to the receptor. Compounds with a monosubstitution exhibit moderate binding, while disubstituted compounds experience a significant reduction in binding capacity.

Based on the SwissADME analysis [Table 2], all compounds analyzed (compounds 1–8) exhibit molecular below 500 Da, ensuring that they are sufficiently small for optimal absorption. Each compound has <5 hydrogen bond donors and <10 hydrogen bond acceptors. All compounds exhibit moderate lipophilicity, with log P < 5. Hence, all compounds obey Lipinski's rule and show no violations. All the compounds have moderate total polar surface area which indicates good permeability through membranes optimal for drug absorption. Compounds 1–7 are not inhibitors of CYP3A4 and hence can be metabolized in the liver.

The bioavailability radar [Figure 5] displays various properties of compounds such as lipophilicity, size, polarity, insolubility, insaturation, and flexibility. All compounds have all properties within range except for insaturation indicating higher degree of unsaturation.

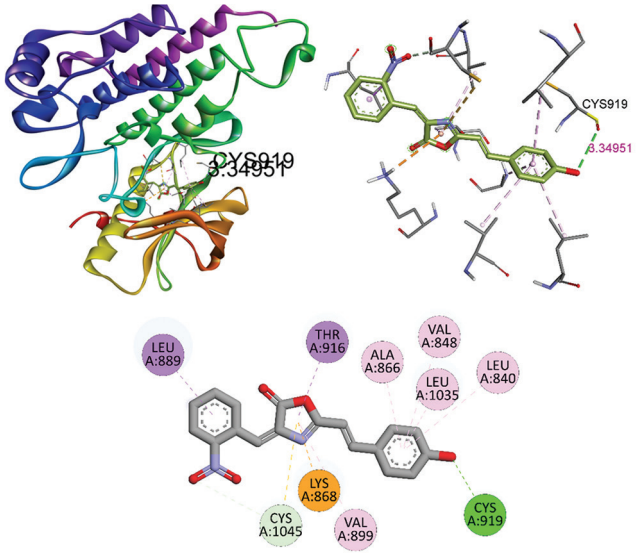

Figure 4: Compound 5 in complex with the receptor 3U6J

Table 2: Pharmacokinetic and drug-likeness parameters determined using SwissADME

Compound No.	Formula	Mol. Wt.	#H-bond acceptors	#H-bond donors	TPSA <140	XLOGP3	Solubility	GI absorption	BBB permeation	CYP3A4 inhibitor	Lipinski #violations
1	$C_{18}H_{13}NO_3$	291.3	4	1	58.89	3.63	Moderate	High	Yes	No	0
2	$C_{18}H_{12}BrNO_3$	370.2	4	1	58.89	4.32	Moderate	High	Yes	No	0
3	$C_{18}H_{12}ClNO_3$	325.75	4	1	58.89	4.26	Moderate	High	Yes	No	0
4	$C_{18}H_{14}N_2O_3$	306.32	4	2	84.91	2.95	Moderate	High	No	No	0
5	$C_{18}H_{13}N_2O_5$	337.31	6	2	108.55	3	Moderate	High	No	No	0
6	$C_{19}H_{15}NO_4$	321.33	5	1	68.12	3.6	Moderate	High	Yes	No	0
7	$C_{18}H_{13}NO_4$	307.3	5	2	79.12	3.28	Moderate	High	No	No	0
8	$C_{20}H_{17}NO_5$	351.35	6	1	77.35	3.57	Moderate	High	Yes	Yes	0

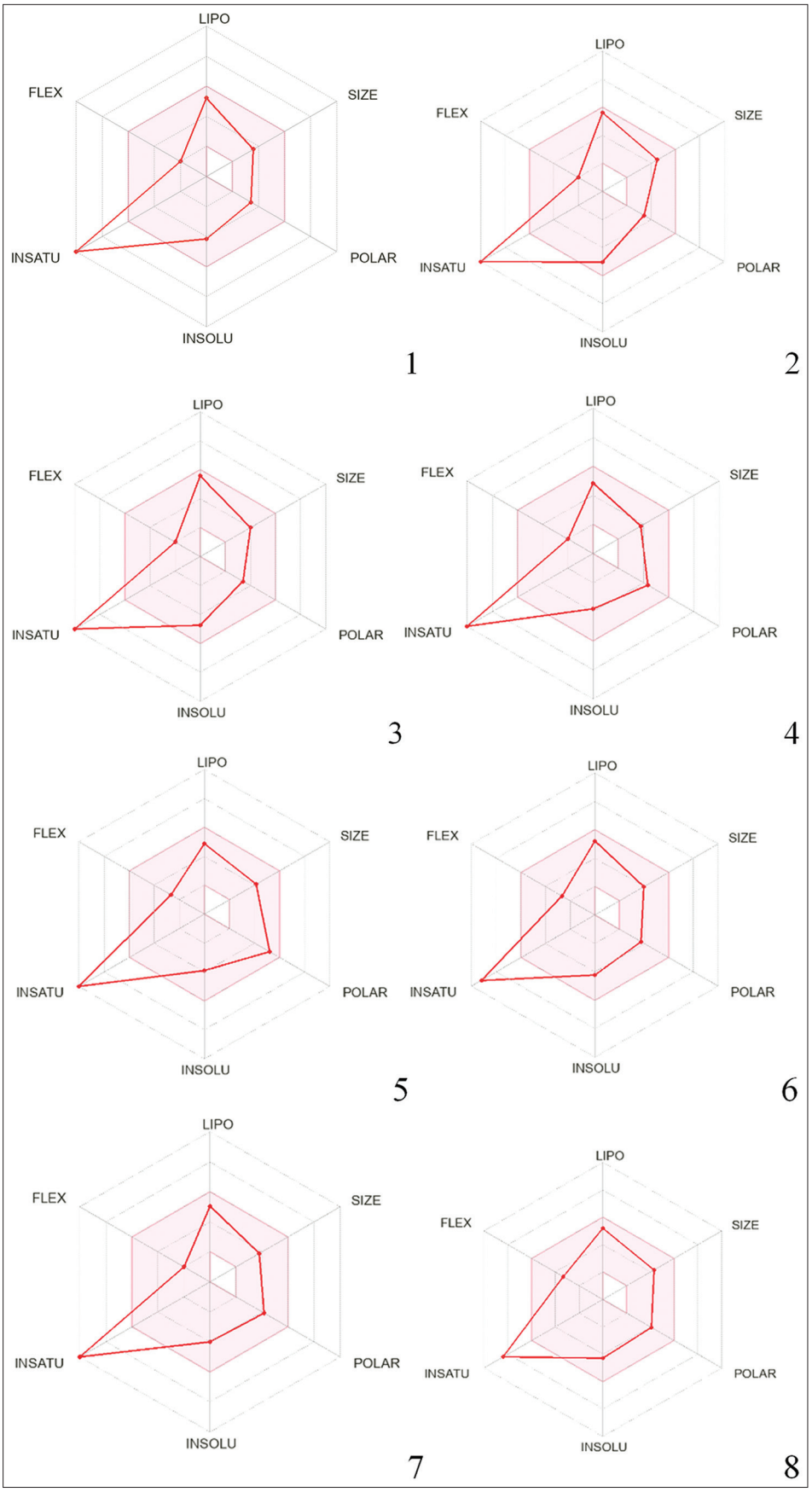

Figure 5: Bioavailability radar of compounds 1–8

CONCLUSION

Cancer remains a disease of concern with the need for better and safer therapies. p-Coumaric acid being a natural compound with proven anticancer activity can be conjugated with versatile ligands like oxazolones to form new safer compounds. The molecular docking studies of the designed compounds 1–8 show binding affinity for the VEGFR and form drug-protein complexes. Compound **5** possesses a better binding potential as compared to other agents. Compounds with monosubstitution have better binding affinity whereas the binding affinity drastically reduces for disubstituted compound. Further, the pharmacokinetic evaluation of all compounds proves that none of the compounds violate Lipinski's rule. All the compounds possess moderate solubility, polarity, and lipophilicity. Their moderate topological polar surface area values indicate favorable permeability and absorption characteristics, making them promising candidates for drug development. In addition, since they are not inhibitors of CYP3A4, they have a lower risk of causing unwanted drug interactions and will likely be metabolized efficiently in the liver. These findings provide valuable insights into the design of more effective compounds for further experimental validation and development of these compounds as potential anticancer agents.

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