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Computational Design and ADME Profiling of Thienopyrimidine-Based Dual VEGFR/EGFR Inhibitors for Anticancer Drug Discovery

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ABSTRACT

Colorectal cancer (CRC) remains a significant global health challenge, and the dual inhibition of EGFR and VEGFR represents a promising therapeutic approach. Thienopyrimidine derivatives have gained attention as versatile heterocyclic scaffolds with notable anticancer potential. In this study, sixteen thienopyrimidine-based compounds functionalized with benzene sulphonamide, piperazine, and primary amine groups were evaluated using an integrated in-silico methodology combining molecular docking and ADME profiling. The chemical structures were optimized using computational chemistry tools, and the target proteins-epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR), were retrieved from the Protein Data Bank (PDB IDs: 6Z4D and 3VNT, respectively). Docking simulations were carried out using AutoDock Vina to assess the binding interactions within the active sites of both targets. Among the tested compounds, PAS1o, PAS1p, and PAS1j demonstrated strong binding affinities, with docking scores below −9.0 kcal/mol for both EGFR and VEGFR, indicating potential dual-target inhibition. ADME properties were further predicted using SwissADME, focusing on parameters such as absorption, distribution, metabolism, excretion, and drug-likeness based on Lipinski's Rule of Five. Overall, the findings suggest that these thienopyrimidine derivatives hold promise as lead candidates for the development of dual EGFR/VEGFR inhibitors in colorectal cancer therapy.

Keywords: Colorectal Cancer, EGFR, Molecular docking, Protein Data Bank, SwissADME, Thienopyrimidine derivatives, VEGFR.

1. INTRODUCTION

Colorectal cancer (CRC) remains one of the most prevalent and deadly malignancies worldwide, ranking among the top three cancers in terms of both incidence and mortality rates [1]. Despite advances in screening, chemotherapy, and biologic agents, treatment outcomes for advanced CRC remain suboptimal due to drug resistance, tumour heterogeneity, and the activation of compensatory signalling pathways [2]. Among the molecular targets implicated in CRC progression, epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) are of particular clinical relevance. EGFR, a receptor tyrosine kinase, plays a pivotal role in regulating cell proliferation, survival, and differentiation via downstream signalling cascades such as the PI3K/AKT and RAS/RAF/MEK/ERK pathways [3]. Overexpression or dysregulation of EGFR is frequently observed in CRC and is associated with aggressive tumour behaviour and poor prognosis [4]. Several EGFR inhibitors, including monoclonal antibodies (e.g., cetuximab, panitumumab) and small molecules, have demonstrated clinical efficacy in EGFR-positive CRC cases [5]. In parallel, VEGFR, particularly VEGFR-2, is essential for tumour angiogenesis, enabling neovascularization and supporting tumor growth and metastasis [6]. The VEGF/VEGFR signalling axis is often upregulated in colorectal tumors, and its inhibition has been shown to impair blood vessel formation and enhance the efficacy of chemotherapeutic agents [7]. Anti-angiogenic agents such as bevacizumab, a monoclonal antibody targeting VEGF-A, have become integral components of CRC treatment regimens [8]. Notably, dual inhibition of EGFR and VEGFR has been proposed as a promising strategy to suppress both tumor growth and angiogenesis simultaneously, thereby addressing therapeutic resistance associated with monotherapies [9].

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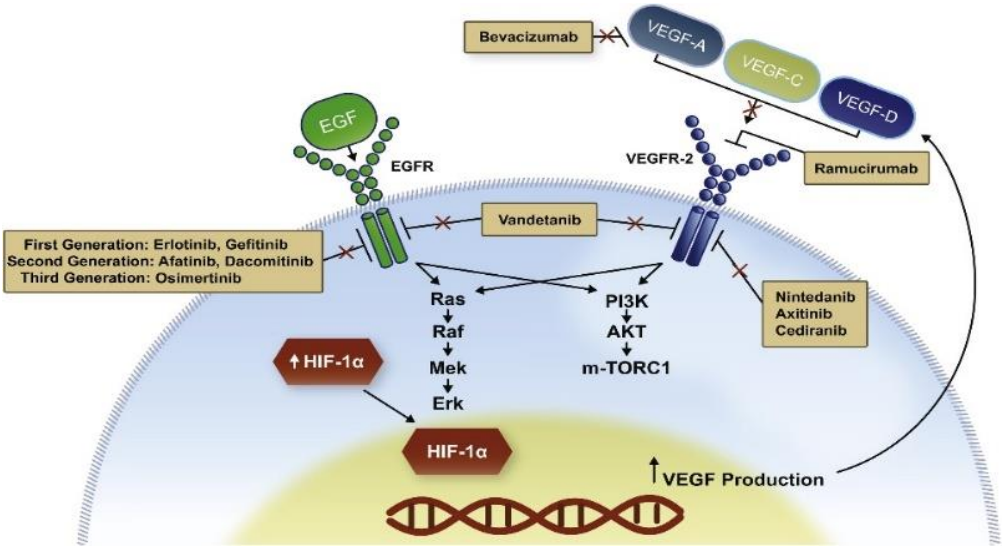

Fig. 1- Cross-talk between and inhibition of the VEGFR and EGFR pathways [9].

Within this therapeutic landscape, thienopyrimidines have emerged as a structurally diverse class of heterocyclic compounds with demonstrated anticancer, antimicrobial, and kinase-inhibitory properties [10,11]. The fused thiophene-pyrimidine scaffold mimics purine structures and allows selective interaction with ATP-binding pockets of kinases, rendering thienopyrimidines attractive candidates for targeting receptor tyrosine kinases such as EGFR and VEGFR [12]. Prior studies have reported thienopyrimidine analogs exhibiting potent inhibitory activity against various kinases, including c-Src, EGFR, and VEGFR, with promising preclinical anticancer effects [13]. Recently, several EGFR/VEGFR-2 dual inhibitors have been discovered, such as vandetanib (ZD6474), which exhibited potent inhibitory activity against both EGFR and VEGFR-2. Furthermore, the presence of H-donor/acceptor group at the para position of the 4-anilino moiety, such as sulfonamide or amide group (compounds IV–VI), improved the binding to both EGFR and VEGFR-2 receptors and, as a result, enhanced the dual enzyme inhibitory activity. Finally, the presence of halide in the phenyl ring of 4-anilino or aryloxy moiety enhances the dual inhibitory activity (compound III, VII) [10]. Computer-aided drug design (CADD) has become a cornerstone of contemporary pharmaceutical research, offering efficient and cost-effective methods for lead compound optimization. It plays a vital role in understanding the molecular interactions between therapeutic candidates and their biological targets, such as enzymes, receptors, and transport systems.

Recognizing the potential of multi-targeted small molecules in CRC therapy, the current research study utilizes a computational strategy to investigate the inhibitory potential of substituted thienopyrimidine derivatives, specifically those bearing benzene sulphonamide and primary and secondary amine moieties, against EGFR and VEGFR, two key targets in colorectal cancer. Through molecular docking and ADME analysis, the compounds were evaluated for their binding affinity, interaction with target sites, and pharmacokinetic suitability. The outcomes aim to support the rational development of dual-targeted thienopyrimidine-based inhibitors for improved colorectal cancer treatment.

2. MATERIALS AND METHODS

A total of sixteen thiophene-linked pyrimidine derivatives were selected for evaluation. The molecular structures were drawn and optimized using ChemDraw to ensure accurate geometry for computational analysis. Molecular docking studies were carried out using AutoDock Vina, integrated within the PyRx Virtual Screening Tool, to predict the binding affinities of the compounds against target proteins EGFR and VEGFR. Following docking analysis, the top-performing compounds were subjected to ADME (Absorption, Distribution, Metabolism, and Excretion) profiling using the SwissADME online platform. This allowed for the prediction of pharmacokinetic properties and drug-likeness based on parameters such as Lipinski's Rule of Five, solubility, gastrointestinal absorption, and bioavailability.

2.1 Ligand Preparation

A series of novel substituted thienopyrimidine derivatives were synthesized and selected based on previously reported anticancer activities. The 2D structures of the compounds were drawn using ChemDraw and converted to 3D using Chem3D. Energy minimization was performed using the MM2 force field to obtain the most stable conformers. The minimized structures were saved in PDB format for further docking studies.

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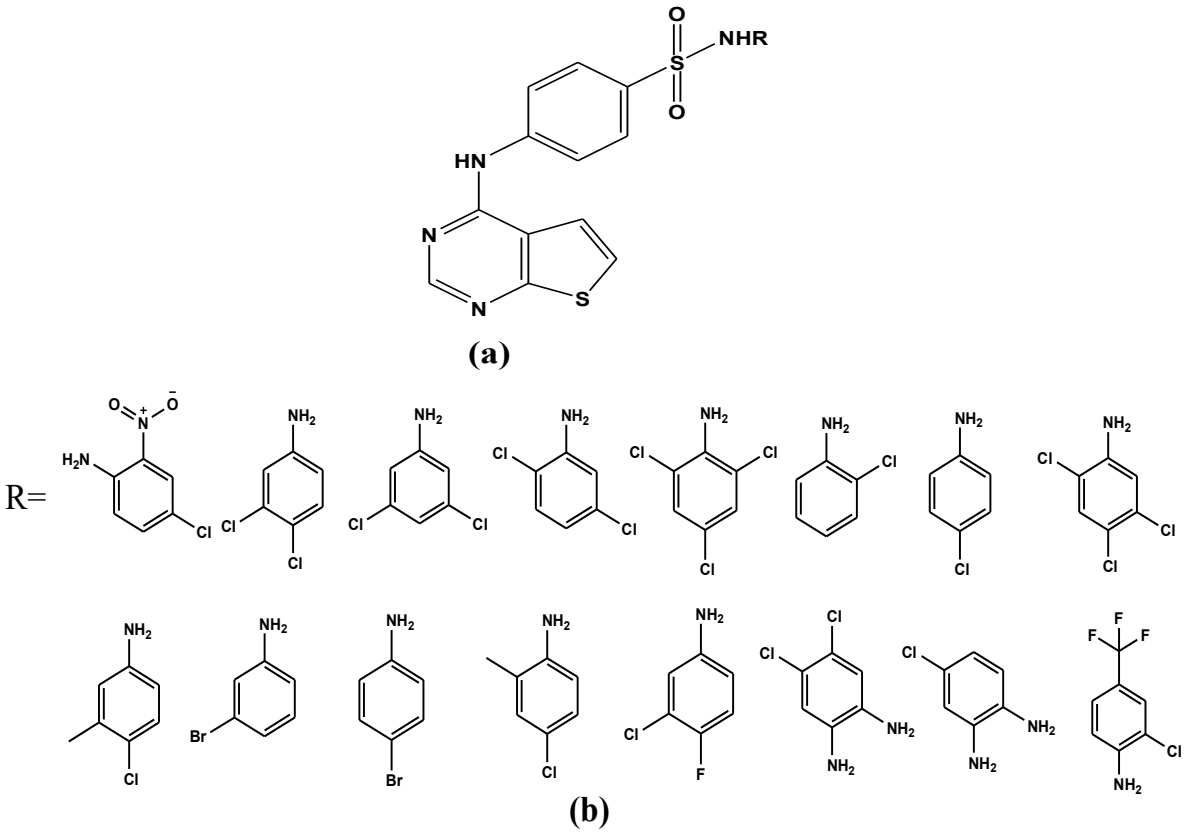

Fig. 2- (a) Basic Thienopyrimidine scaffold (b) Structures of Substitutions (R)

2.2 Protein Target Selection and Preparation

The target protein was retrieved from the National Center for Biotechnology Information (NCBI) database. The three-dimensional structures of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) were obtained from the RCSB Protein Data Bank (PDB IDs: 6Z4D, 3VNT) according to criteria of interest, such as Homo sapiens(organism), X-ray diffraction, chain, and interacting ligand were selected. Protein structures were prepared by removing water molecules and co-crystallized ligands, followed by the addition of polar hydrogens and assignment of Kollman charges using AutoDock Tools, such as Discovery Studio. The finalized protein files were saved in .pdb and PDBQT format.

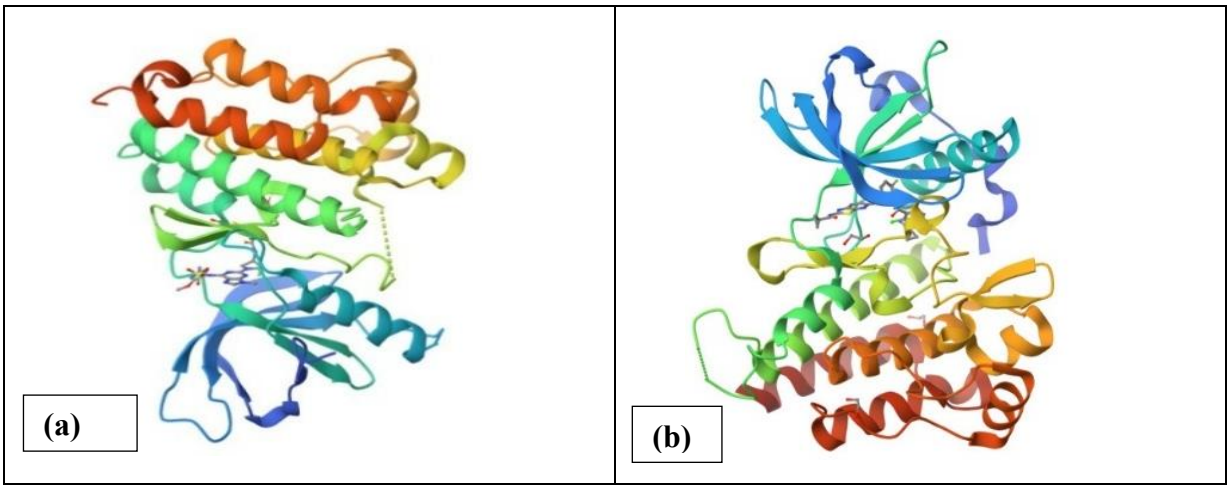

Fig. 3- 3D-Selection of target proteins (a) EGFR Protein (PDBID:6Z4D) (b) VEGFR Protein (PDBID:3VNT).

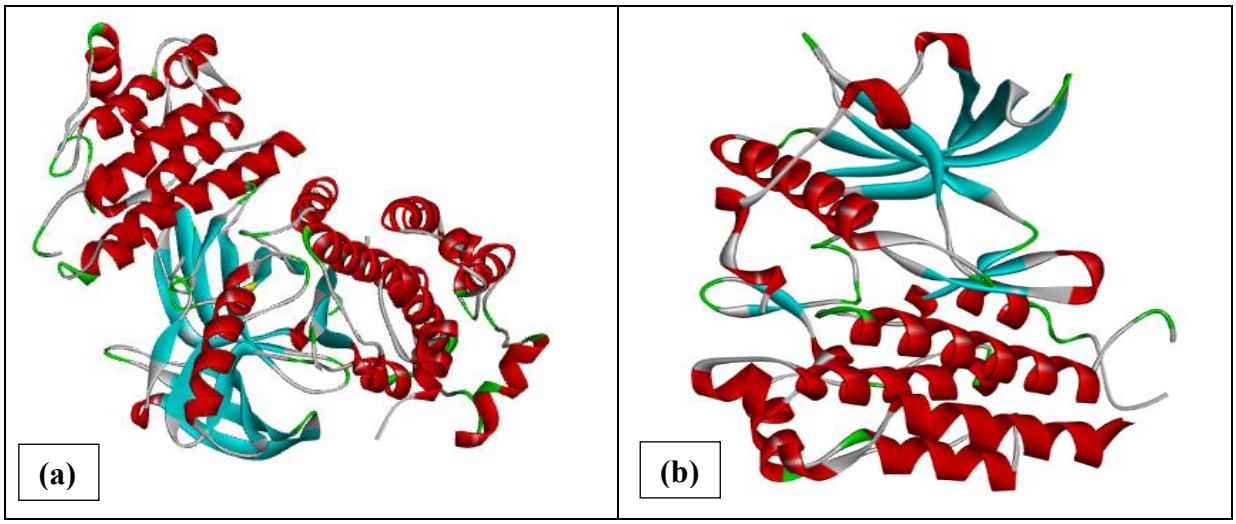

Fig. 4- 3D images of Purified target proteins (a) EGFR Protein (PDBID:6Z4D) (b) VEGFR Protein (PDBID:3VNT).

2.3 Molecular Docking Studies

A Docking study was conducted using AutoDock Vina by the PyRx—Virtual Screening Tool to evaluate the binding interactions between thienopyrimidine derivatives and the active sites of EGFR and VEGFR. The docking grid was centered on the active site residues, and exhaustiveness was set to a standard value to ensure reliable results. The docking scores (binding affinities) were recorded, and the ligand–receptor interactions were visualized using PyMOL and Discovery Studio Visualizer.

2.3.1 Procedure for Docking

The finalized protein structure was loaded into the PyRx virtual screening tool using the .pdb file format. It was then converted into the. pdbqt format through the "Make Molecule" function within the software. Ligands were added one by one, followed by energy minimization to ensure structural stability. These optimized ligand structures were also saved in. pdbqt format. Both protein and ligand files were selected for docking, and the active site of the protein was defined. A grid box was created to fully enclose the binding site, with the center coordinates at X, Y, and Z. Following the docking simulation, the results were saved as a CSV (Comma-Separated Values) file for further evaluation of binding affinities and molecular orientations. The docked complexes were visualized and interpreted using Discovery Studio Visualizer.

2.4 Binding Interaction Analysis

Following molecular docking, the binding affinities of the thienopyrimidine derivatives were assessed based on their docking scores, expressed in kcal/mol. These scores represent the estimated free energy of binding, where more negative values indicate stronger and more favourable interactions with the target protein. Compounds were ranked according to their binding energies against both VEGFR and EGFR to identify the most promising candidates. In addition to docking scores, the nature and number of key interactions—such as hydrogen bonds, hydrophobic contacts, π–π stacking, and electrostatic forces—were analysed using visualization tools like Discovery Studio and PyMOL. Compounds demonstrating strong binding affinities and forming multiple stable interactions within the ATP-binding pockets of VEGFR and EGFR were considered high-priority leads. Residues such as Cys919 in VEGFR-2 and Met793 in EGFR were particularly noted for their involvement in binding stability. The comparison of interaction energies across the compound series enabled the selection of top-performing molecules with the most favourable energetic profiles and interaction patterns. These prioritized ligands were subsequently subjected to ADME profiling to assess their drug-likeness and pharmacokinetic suitability.

2.5 ADME and Drug-Likeness Evaluation

The SwissADME tool was employed to evaluate the drug-likeness of the selected compounds based on Lipinski's rule of five, which considers key physicochemical properties such as molecular weight (MW), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), number of rotatable bonds (RTB), lipophilicity (Log P), and topological polar surface area (TPSA). These parameters are widely used to predict the oral bioavailability, membrane permeability, and overall pharmacokinetic suitability of compounds, helping to identify molecules with a higher probability of success as drug candidates.

3. RESULTS AND DISCUSSION

3.1 Molecular Docking Studies

To assess the binding affinity and potential dual inhibitory activity of the designed thienopyrimidine-based derivatives, molecular docking was performed against the tyrosine kinase domains of **EGFR (PDB ID: 6Z4D)** and **VEGFR (PDB ID: 3VNT)** using AutoDock Vina. The docking scores, which reflect the predicted binding energy between ligand and receptor, are summarized in **Table 1**. Several compounds demonstrated strong affinity toward both targets.

Notably, **PAS1d** exhibited the highest binding affinity toward EGFR with a docking score of **−9.9 kcal/mol**, followed by **PAS1j (−9.6 kcal/mol)** and **PAS1o (−9.4 kcal/mol)**. In the case of VEGFR, the most significant interaction was observed for **PAS1n**, which yielded a docking score of **−10.9 kcal/mol**, followed closely by **PAS1p (−10.0 kcal/mol)** and **PAS1o (−9.8 kcal/mol)**.

Compounds such as **PAS1o**, **PAS1p**, and **PAS1j** demonstrated strong dual-target activity, with docking scores below −9.0 kcal/mol for both EGFR and VEGFR, indicating their potential as dual kinase inhibitors.

Table 1. Docking Scores of Thienopyrimidine Derivatives against EGFR (6Z4D) and VEGFR (3VNT).

Compound Code	EGFR Score (kcal/mol)	VEGFR Score (kcal/mol)
PAS1a	-8.5	-8.9
PAS1b	-9.0	-9.3
PAS1c	-8.5	-8.3
PAS1d	-9.9	-9.2
PAS1e	-8.5	-9.3
PAS1f	-8.8	-8.2
PAS1g	-9.2	-8.2
PAS1h	-8.5	-9.1
PAS1i	-8.1	-9.3
PAS1j	-9.6	-9.2
PAS1k	-9.3	-8.2
PAS1l	-9.1	-9.5
PAS1m	-8.6	-8.0
PAS1n	-8.7	-10.9
PAS1o	-9.4	-9.8
PAS1p	-9.2	-10.0
Vandetanib	-7.7	-8.5

3.2 Evaluation of Dual Inhibitory Potential

Among the tested compounds, **PAS1o** and **PAS1p** emerged as the most promising candidates for dual inhibition of EGFR and VEGFR. Both compounds displayed docking scores significantly better than **Vandetanib**, a clinically approved dual inhibitor used as a reference, which has reported binding energies around **−9.3 kcal/mol (EGFR)** and **−9.6 kcal/mol (VEGFR)**.

- **PAS1o**: −9.4 kcal/mol (EGFR) and −9.8 kcal/mol (VEGFR).
- **PAS1p**: −9.2 kcal/mol (EGFR) and −10.0 kcal/mol (VEGFR).

This indicates that PAS1o and PAS1p not only mimic the dual-target activity of Vandetanib but may surpass it in terms of binding strength, particularly for VEGFR inhibition. Additionally, **PAS1n** displayed strong VEGFR selectivity, with the lowest docking energy recorded in the study (−10.9 kcal/mol), highlighting its potential as a highly specific VEGFR inhibitor.

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3.3 Binding Interaction Considerations

While specific binding site interactions were not visually examined in this phase, it is likely, based on the target protein structures-those key residues such as **Met793** and **Phe856** (EGFR), and **Cys919** and **Asp1046** (VEGFR) contribute to hydrogen bonding and π-interactions with the active compounds. Compounds showing high affinity are expected to stabilize within the ATP-binding clefts of these kinases, which is a common mechanism among known tyrosine kinase inhibitors. Further visualization using tools like Discovery Studio or PyMOL is recommended to confirm these hypotheses and guide structure-based optimization.

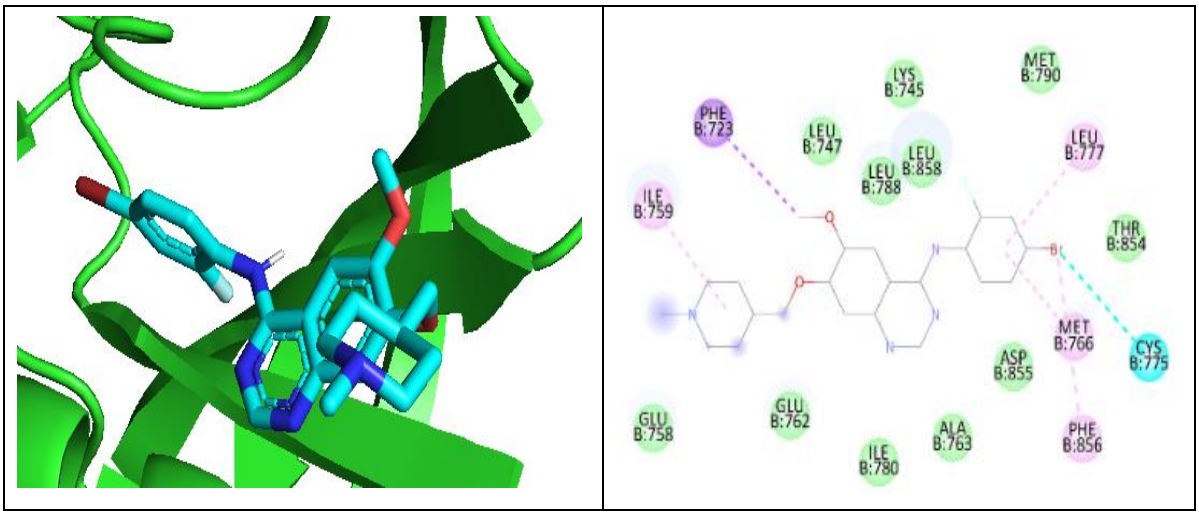

Fig. 5- 3D and 2D Diagram of Vandetanib-EGFR (PDB ID: 6Z4D) Complex.

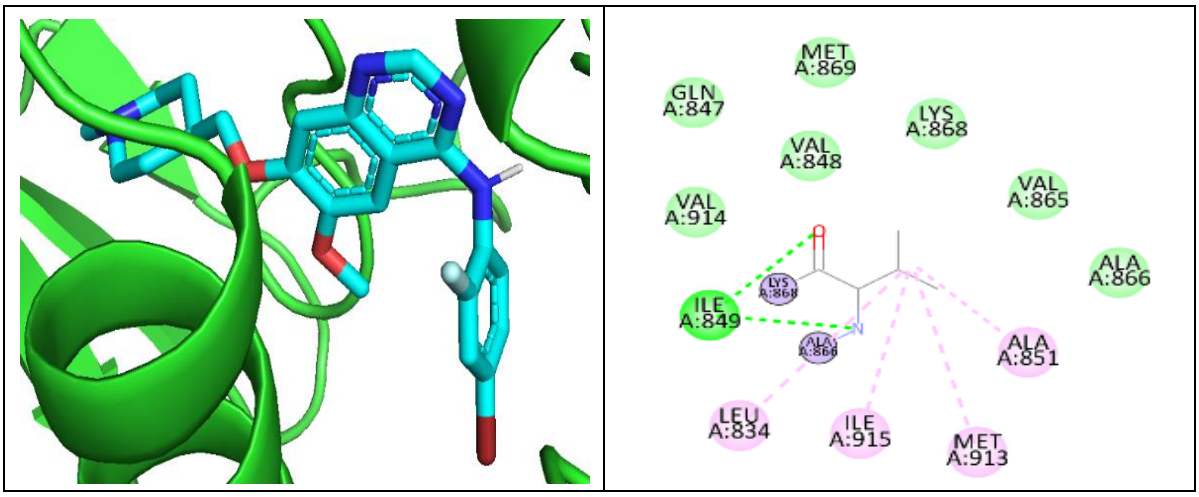

Fig. 6- 3D and 2D Diagram of Vandetanib-VEGFR (PDB ID: 3VNT) Complex.

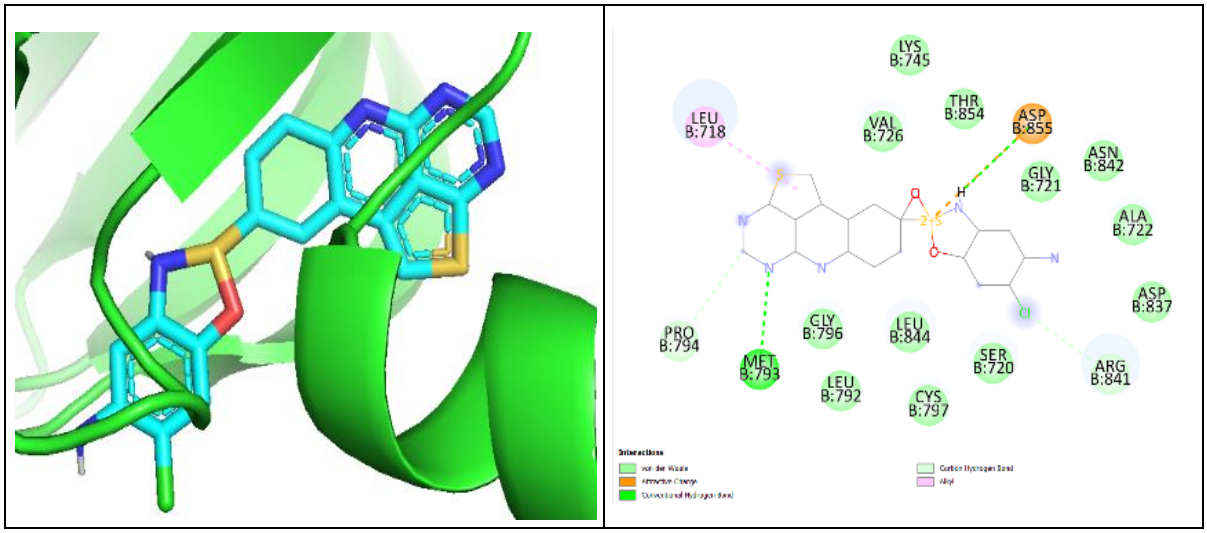

Fig. 7- 3D and 2D Diagram of PAS1d-EGFR (PDB ID: 6Z4D) Complex.

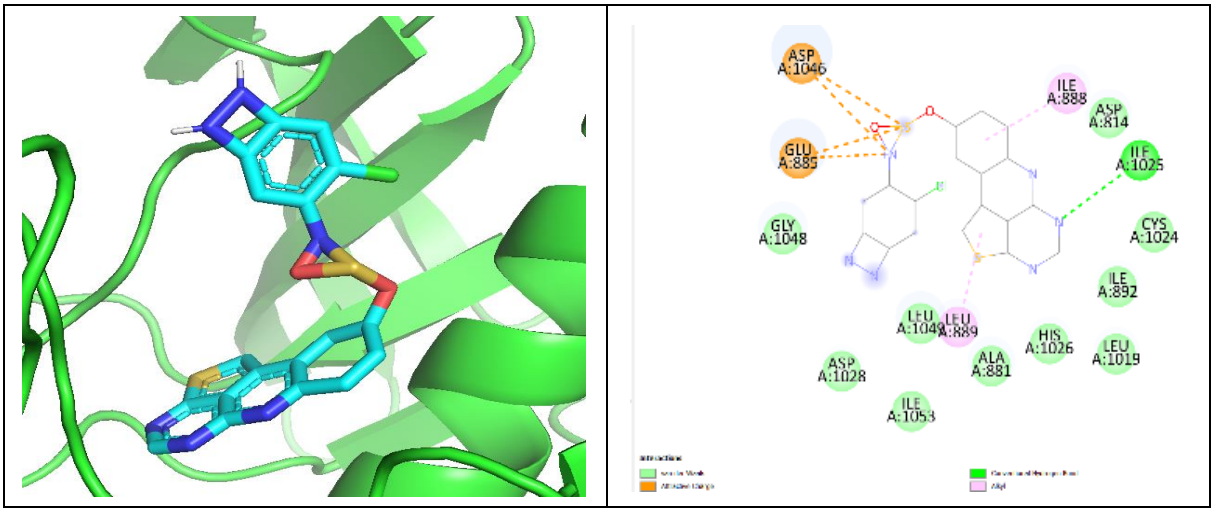

Fig. 8- 3D and 2D Diagram of PAS1n-VEGFR (PDB ID: 3VNT) Complex.

3.4 Implications for Anticancer Therapy

The strong binding affinity of PAS1 derivatives, especially PAS1o, PAS1p, PAS1d, and PAS1n, suggests their promise as lead scaffolds for the development of dual EGFR/VEGFR-targeting agents. This is particularly relevant in the context of colorectal cancer, where overexpression of both VEGFR and EGFR is associated with tumour growth, angiogenesis, and resistance to therapy.

Given their favourable docking profiles, these compounds warrant further evaluation through:

- ADME profiling
- Molecular dynamics simulations
- In vitro kinase inhibition assays
- Cytotoxicity studies in relevant cancer cell lines

3.5 ADME Analysis and Drug-Likeness Evaluation

To assess drug-likeness and pharmacokinetic behavior, ADME profiling was carried out using SwissADME for the most promising thienopyrimidine analogues. All tested compounds complied with Lipinski's Rule of Five, indicating suitability for oral administration. Their molecular weights were under 500 g/mol, with hydrogen bond acceptors (HBA) and donors (HBD) in acceptable ranges. The topological polar surface area (TPSA) values were consistent across the derivatives (~146.62 Å²), indicative of moderate membrane permeability. The gastrointestinal (GI) absorption for all derivatives was predicted to be low, likely due to relatively high TPSA values, which may hinder passive diffusion. None of the compounds were predicted to cross the blood–brain barrier (BBB), an advantageous trait for minimizing central nervous system toxicity. Additionally, the compounds were identified as non-substrates of P-glycoprotein (P-gp), reducing concerns related to drug efflux and resistance mechanisms. The consensus LogP values (ranging from 2.11 to 3.77) suggest moderate lipophilicity, favourable for oral bioavailability without compromising aqueous solubility. Solubility predictions using the ESOL model showed most compounds to be poorly soluble, except PAS1o, which was classified as moderately soluble, potentially due to its structural conformation or substituent effects. Bioavailability scores were uniformly 0.55, suggesting moderate oral bioavailability and drug-likeness. However, all compounds were predicted to inhibit key cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2C9, and CYP3A4), indicating a possible risk of metabolic interactions. These results highlight the need for further metabolic stability studies and structure optimization to reduce CYP inhibition liability.

Table 2. Drug likeness and ADME properties of Thienopyrimidine Derivatives.

Compound	MW (g/mol)	HBA	HBD	TPSA (Å²)	LogPcons	GI Absorption	BBB Permeability	P-gp Substrate	CYP Inhibition	ESOL Solubility	Bioavailability Score
PAS1d	457.55	7	2	146.62	3.11	Low	No	No	1A2, 2C19, 2C9, 3A4	Poor	0.55
PAS1j	453.91	6	2	146.62	3.21	Low	No	No	1A2, 2C19, 2C9, 3A4	Poor	0.55
PAS1k	461.99	6	2	146.62	3.77	Low	No	No	1A2, 2C19, 2C9, 3A4	Poor	0.55
PAS1n	466.03	6	2	146.62	2.58	Low	No	No	1A2, 2C19, 2C9, 3A4	Poor	0.55
PAS1o	456.92	6	2	146.62	2.11	Low	No	No	1A2, 2C19, 2C9, 3A4	Moderate	0.55
PAS1p	468.04	6	2	146.62	3.55	Low	No	No	1A2, 2C19, 2C9, 3A4	Poor	0.55
Vandetanib	475.36	6	1	93.02	4.00	high	No	yes	1A2, 2C19, 2C9, 2D6, 3A4	Moderate	0.55

Thus, PAS1o, PAS1p, PAS1d, and PAS1n emerged as the most promising thienopyrimidine derivatives, showing strong binding affinities toward EGFR and VEGFR, with PAS1o and PAS1p outperforming the reference drug Vandetanib as potential dual inhibitors, and PAS1n exhibiting exceptional VEGFR selectivity (−10.9 kcal/mol). All compounds complied with Lipinski's rules, displayed moderate lipophilicity, low gastrointestinal absorption, no blood-brain barrier permeability, and were non-P-gp substrates, indicating favourable drug-likeness. PAS1o showed moderate solubility, whereas others were poorly soluble, and all were predicted to inhibit multiple CYP enzymes, suggesting potential drug–drug interaction risks. These findings highlight PAS1o, PAS1p, PAS1d, and PAS1n as strong lead candidates for further development of dual EGFR/VEGFR-targeted therapies in colorectal cancer.

4. CONCLUSION

The present study employed a comprehensive in silico approach to evaluate a series of thienopyrimidine derivatives as potential dual inhibitors of VEGFR and EGFR, key targets implicated in colorectal cancer. Molecular docking studies revealed that several analogues, particularly PAS1n, PAS1p, PAS1o, and PAS1j, demonstrated strong binding affinities towards both VEGFR (PDB ID: 3VNT) and EGFR (PDB ID: 6Z4D), with docking scores surpassing that of the reference drug vandetanib. Binding interaction analyses further supported their high-affinity interactions through favourable hydrogen bonding and hydrophobic contacts within the active sites of both kinases. ADME profiling indicated that all top-performing compounds adhered to drug-likeness criteria and exhibited moderate oral bioavailability. Although poor aqueous solubility and CYP enzyme inhibition were noted for most derivatives, these challenges are considered manageable through structural optimization or formulation strategies. Overall, the findings suggest that thienopyrimidine scaffolds, particularly those functionalized with sulphonamide and aniline moieties, hold promise as dual-target anticancer agents. The study provides a valuable foundation for further in vitro and in vivo evaluations, as well as lead optimization efforts for the development of effective targeted therapies against colorectal cancer.

5. FUTURE SCOPE

The present computational investigation highlights the potential of thienopyrimidine-based scaffolds as dual VEGFR/EGFR inhibitors, offering a promising avenue for anticancer drug development. However, to translate these findings into clinically viable therapies, several future directions are recommended:

1. In vitro Validation: The top-performing compounds should be synthesized and tested for cytotoxicity against colorectal cancer cell lines, particularly those overexpressing VEGFR and EGFR, to confirm their antiproliferative activity and kinase inhibition profiles.

2. Pharmacokinetics and Toxicity: Preclinical pharmacokinetic studies are required to evaluate absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters in animal models to assess the drug-likeness and therapeutic index of these molecules.

3. Structural Optimization: Given the moderate solubility and predicted CYP450 inhibition, structural modifications and prodrug strategies could be explored to enhance oral bioavailability and reduce metabolic liabilities.

4. Molecular Dynamics Simulations: Advanced computational techniques such as molecular dynamics (MD) simulations and binding free energy calculations (MM-PBSA/MM-GBSA) can provide insights into the stability of protein–ligand complexes over time.

5. Formulation Development: For compounds with poor aqueous solubility, nanoformulation approaches such as liposomes, solid lipid nanoparticles, or polymeric carriers could be developed to improve delivery and bioavailability.

6. In vivo Efficacy Studies: Promising lead candidates should undergo in vivo anticancer evaluations using xenograft or orthotopic models to assess tumor regression and systemic toxicity.

By addressing these future aspects, the current study can evolve into a robust drug discovery pipeline for the development of selective and potent dual-targeted anticancer agents for colorectal cancer therapy.

6. ACKNOWLEDGMENT

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7. CONFLICT OF INTEREST

The authors declare no conflict of interest.

8. FUNDING

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Conflict of Interest Statement:
The authors have no conflicts of interest to declare.