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In silico study of four new phenoxybenzoic acid - isatin derivatives: targeting VEGFR and cancer

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ABSTRACT

Cancer remains a major global health challenge, necessitating the development of novel therapeutic agents. This study hypothesizes that phenoxybenzoic acid derivatives can effectively inhibit the vascular endothelial growth factor receptor (VEGFR; Protein Data Bank code: 4ASE); a key molecular target in cancer therapy. Four compounds – designated F1, F2, F3, and F4 – were designed and synthesized to test this hypothesis. Their molecular structures were sketched using ChemDraw Ultra version 12.0, and their binding affinities were evaluated through molecular docking simulations conducted with the Molecular Operating Environment (MOE) program. Docking scores and root-mean-square deviation values were analysed in order to assess the compounds' potential effectiveness. Compared to sorafenib, a clinically approved VEGFR inhibitor, the synthesized compounds exhibited significant binding affinities within the receptor's active site, supporting their potential as anticancer agents. These findings provide a rationale for further biological evaluation and optimization of these compounds for targeted cancer therapy.

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1. Introduction

Cancer remains one of the most life-threatening diseases due to its hallmark feature of uncontrolled cellular proliferation. Consequently, the development of high-quality anticancer agents – particularly those exhibiting potent biological activity, enzyme inhibitory properties, and minimal toxicity – is of paramount importance. Designing effective and safe chemotherapeutic agents for malignant conditions poses a significant challenge for medicinal chemists, whose efforts aim to elucidate the biochemical mechanisms underlying tumourigenesis and metastasis[1,2].

Among the most promising strat-

PHARMAKEFTIKI, 37, 2S, 2025 | 308-312

egies in oncology is targeted therapy, which enhances therapeutic efficacy while minimizing systemic toxicity. Multi-kinase inhibitors, especially tyrosine kinase inhibitors, represent a highly promising class of targeted anticancer agents. Kinases are enzymes that catalyse the phosphorylation of biomolecules, thereby regulating complex cellular processes such as motility, growth, proliferation, differentiation, and programmed cell death (apoptosis)[3].

A key angiogenic regulator implicated in tumour progression is the vascular endothelial growth factor (VEGF). VEGF exerts its pro-angiogenic effects by binding to specific kinase domains on vascular endothelial growth factor receptors (i.e., VEGFR1, VEGFR2, and VEGFR3). Among these, VEGFR2 – a receptor tyrosine kinase subtype – is primarily responsible for mediating angiogenesis[4]. This physiological process is essential for meeting the nutritional and oxygen demands of cells, tissues, and organs. However, dysregulated angiogenesis – whether excessive or insufficient – is associated with various pathological conditions, including malignancies, inflammatory disorders, and autoimmune diseases[5].

In cancer, aberrant angiogenesis leads to the formation of atypical vascular networks, which compromise the efficacy of conventional therapies and facilitate tumour expansion[6]. Antiangiogenic therapy has emerged as a compelling approach in oncology, as increased vascularity in malignant tissues correlates with tumour growth and proliferation[7]. The U.S. Food and Drug Administration (FDA) has approved several small-molecule inhibitors, including sunitinib and sorafenib, for the treatment of angiogenesis-dependent malignancies.

Benzoic acid and its derivatives exhibit a broad spectrum of biological activities, including flavouring, antioxidant, antibacterial, anticancer, diuretic, analgesic, anti-inflammatory, and local anaesthetic effects. Derivatives belonging to the diaryl / diphenyl ether class demonstrate antimicrobial, antifouling, and antiproliferative properties[8]. Diphenyl derivative bioisosteres interact with diverse biotarget families, and their unique electronic and spatial characteristics – modulated by structural substituents – enhance target binding and pharmacological versatility[9].

This study aims at evaluating the binding affinities of four synthesized phenoxybenzoic acid derivatives (designated F1, F2, F3, and F4) against VEGFR (Protein Data Bank code: 4ASE) by using molecular docking simulations. By comparing their docking scores and root-mean-square deviation (RMSD) values with those of sorafenib, we seek to assess their potential as anticancer agents.

2. Methodology

The computational analyses were performed on an MSI system equipped with an Intel Core™ i7-1355U central processing unit (CPU) operating at 1.70 GHz and 8.00 GB of random-access memory (RAM). The Molecular Operating Environment (MOE) 2015 software and ChemDraw Ultra version 12.0 were installed for molecular modelling and visualization. The docking protocol comprised two primary steps: (i) ligand preparation and (ii) protein preparation.

3. Results and Discussion

Molecular docking was employed in order to determine the optimal binding conformations of ligands within the active site of the target protein. The MOE software was selected for its capacity to generate detailed graphical representations of ligand-receptor interactions, thereby facilitating the visualization and characterization of binding events[10].

The docking simulations revealed that all four synthesized compounds selectively bound to VEGFR, occupying the same principal active site as sorafenib. A comparative analysis of the inhibitory effects and the amino acid interactions at the active site was conducted. Figure 1 provides a comprehensive overview of the interaction parameters for compounds F1 through F4, including docking scores (S-scores), RMSD values, and the key amino acid residues involved. Docking scores and RMSD values serve as indicators of binding affinity and structural alignment. The S-score reflects binding energy, while the RMSD quantifies the average interatomic distance between ligand atoms and the target site. Optimal binding is

PHARMAKEFTIKI, 37, 2S, 2025 | 308-312

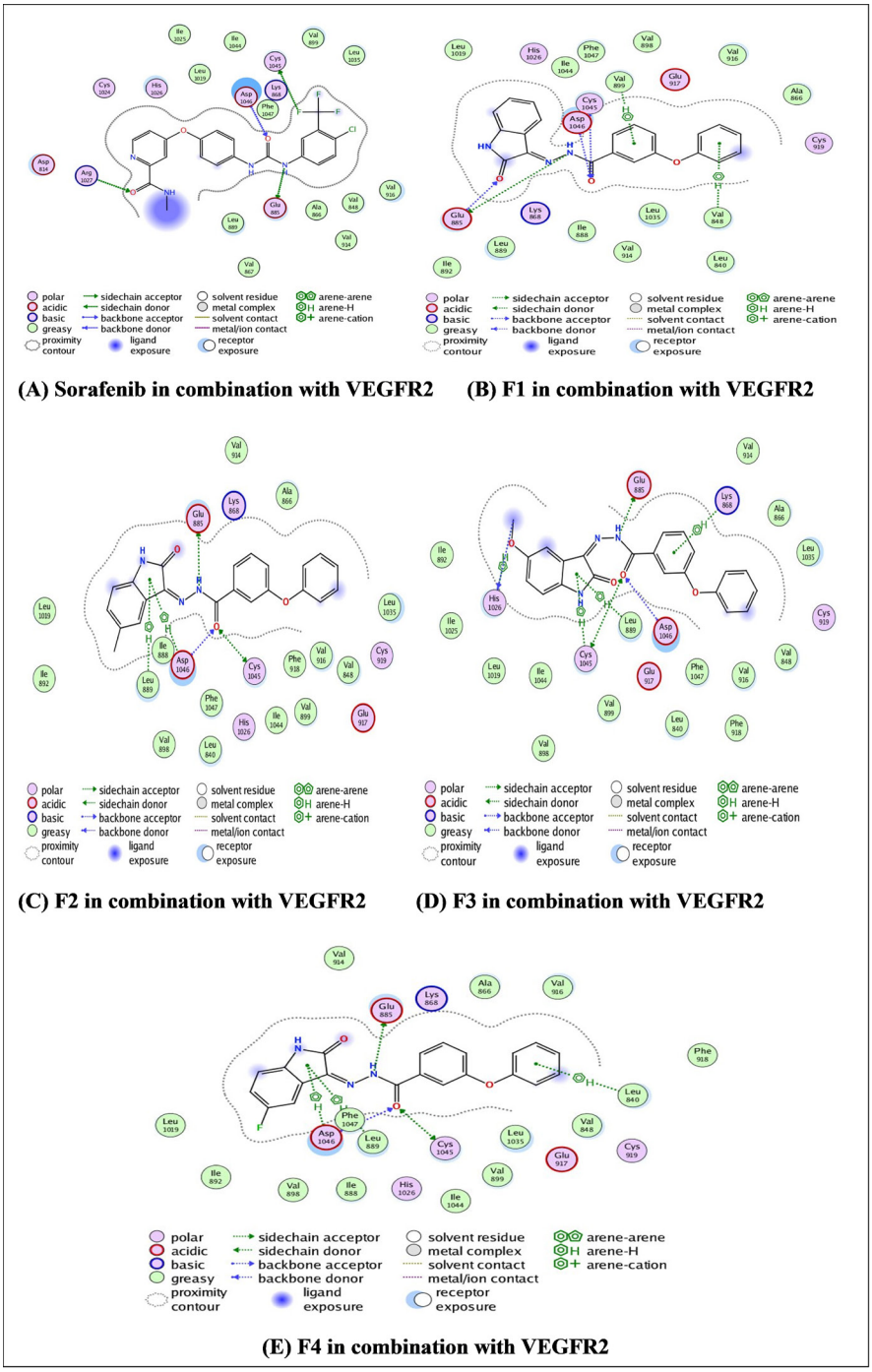

Figure 1. *Two-dimensional representations of the four designed compounds and of sorafenib bound to the vascular endothelial growth factor receptor-2 (VEGFR2). This figure illustrates the binding interactions of the four synthesized compounds and the reference drug sorafenib within the VEGFR2 active site. Images generated using the Molecular Operating Environment (MOE) software depict key molecular interactions (including hydrogen bonding and hydrophobic contacts), highlighting structural differences and similarities. This visual comparison provides insight into the inhibitory potential of the designed compounds, supporting the in silico predictions of their anticancer activity.*

PHARMAKEFTIKI, 37, 2S, 2025 | 308-312

indicated by lower RMSD values and more favourable (i.e., lower) S-scores.

All synthesized compounds (F1–F4) exhibited S-scores comparable to that of sorafenib, thereby suggesting similar inhibitory potential. The respective S-scores were -8.54 (F1), -7.82 (F2), -7.16 (F3), and -8.20 (F4), with corresponding RMSD values of 1.96, 1.57, 1.80, and 1.07.

The compound N'-(2-oxoindolin-3-ylidene)-3-phenoxybenzohydrazide incorporates an indolinone (isatin) core (which is a well-established scaffold in kinase inhibitors) alongside a phenoxybenzohydrazide moiety. The indolinone core mimics adenosine triphosphate (ATP) binding, rendering it suitable for targeting kinases such as VEGFR2, while the phenoxy group enhances hydrophobic interactions within the receptor pocket.

Docking simulations conducted using MOE demonstrated that all ligands adopted similar orientations within the VEGFR2 active site, which is flanked by a membrane-binding domain that facilitates substrate entry. The results confirmed the anticancer (antiangiogenic) potential of the synthesized compounds, with most ligands exhibiting strong binding affinities relative to sorafenib.

Compound F1 yielded the highest S-score (-8.54), indicating that the absence of substitution (hydrogen) may enhance its orientation within the receptor pocket. The F4 derivative, featuring fluoro-substitution, formed stabilizing hydrogen bonds with key amino acid residues, resulting in a lower RMSD (1.07) and a strong docking score (-8.20). In contrast, the unsubstituted inhibitor displayed a higher RMSD (1.96) but retained a favourable docking score (-8.54). These findings underscore the potential of the synthesized compounds as VEGFR2 inhibitors and warrant further experimental validation.

4. Conclusion

This *in silico* study, conducted using the MOE program, successfully designed and evaluated VEGFR2 tyrosine kinase inhibitors incorporating diphenyl ether and isatin moieties. The obtained molecular docking results confirmed strong binding affinities, with compound F1 demonstrating the highest S-score (-8.54) and compound F4 forming stabilizing hydrogen bonds due to fluoro-substitution. These findings highlight the promise of these compounds as VEGFR2 inhibitors for anticancer therapy and support their further biological evaluation.

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None.

Conflicts of interest

None exist.

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