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PROCEEDINGS ABSTRACT

Recent advances in the design and synthesis of vascular endothelial growth factor receptor 2 antagonists: a review

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Angiogenesis, the process by which new blood vessels emerge from existing ones, is a tightly regulated physiological process vital to growth, tissue regeneration, and homeostasis. Abnormal angiogenesis is the feature of many pathologies and especially of cancer, where it facilitates the growth of tumours, their invasion, and their metastasis. The vascular endothelial growth factor (VEGF) signalling pathway is central to the regulation of angiogenesis, while the vascular endothelial growth factor receptor 2 (VEGFR-2) is the primary mediator of VEGF-induced endothelial activities. VEGFR-2 has become a key therapeutic target in cancer treatment due to its central role in promoting endothelial cell proliferation, migration, survival, and vascular permeability. The aim of this review was to critically assess recent developments in the design and synthesis of VEGFR-2 antagonists, with a focus on innovative small-molecule inhibitors, computational drug design methodologies, macromolecular therapeutic strategies, and emerging approaches to overcome resistance and toxicity associated with anti-angiogenic therapy. VEGFR-2 is a receptor tyrosine kinase with its structure consisting of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. VEGFR-2 stimulation through the VEGF binding induces receptor dimerization and autophosphorylation, thereby promoting angiogenesis *via* downstream signalling pathways. Detailed knowledge of the VEGFR-2 structure, particularly of its ATP-binding site, its hinge region, its hydrophobic pockets, and its activation loop, has enabled the rational design of selective VEGFR-2 inhibitors targeting its kinase activity. Recent progress in medicinal chemistry has led to the emergence of various classes of VEGFR-2 inhibitors that are more potent and selective. Amongst these, nicotinamide-thiadiazol hybrids exhibit high inhibitory activity and excellent anticancer capacity due to their effective interactions with the ATP-binding domain. Benzofuran derivatives, including clinically used agents such as sorafenib, have exhibited greater selectivity and cytotoxicity against hepatocellular carcinoma. On the other hand, peptide-tetrahydroisoquinoline conjugates represent an emerging design strategy to enhance solubility, target specificity, and pharmacokinetic properties through a hybrid molecular design. Urea-functionalized 2-oxoindolin-3-ylidene analogues have exhibited pronounced antiproliferative effects through the formation of essential hydrogen bonds with the kinase and the stabilization of inactive forms of VEGFR-2. Computational approaches have also been utilised, thereby enabling the discovery of VEGFR-2 inhibitors to proceed even faster: amongst these, the employment of three-dimensional quantitative structure–activity relationship modelling, molecular docking, and molecular dynamics simulations have

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allowed for accurate predictions of the ligand–receptor interactions, optimization of binding affinity, and determination of complex stability. Virtual screening and chemical space exploration have also increased the discovery of new scaffolds beyond the traditional kinase inhibitor chemotypes, thereby helping overcome the shortcomings of resistance and structural redundancy. In addition to small molecules, novel therapeutic platforms are currently being explored, including peptide–drug conjugates and bispecific antibody-drug conjugates, such as JSKN027, that combine VEGFR-2 targeting with immune checkpoint inhibition (e.g., PD-L1). These multipurpose systems could provide synergy by combining the anti-angiogenic effects with immunomodulatory and targeted cytotoxicity. Nonetheless, the acquired resistance, off-target toxicity, and lack of selectivity remain challenges despite the aforementioned tremendous pharmacological advancements. Combination therapies, biomarker-directed therapy, enhanced targeting specificity, and sophisticated drug delivery systems are among the strategies that can be used in order to overcome these problems. Moreover, recent advances in structure-based drug design, *in silico* approaches, and multifunctional therapeutics are radically reshaping the VEGFR-2-targeted therapeutics. Finally, the anti-angiogenic therapy for cancer is expected to improve in the future through the use of artificial intelligence and precision medicine approaches, thereby increasing both treatment safety and clinical efficacy.

Keywords

angiogenesis; *in silico* drug design; peptide–drug conjugates; therapeutics; VEGFR-2

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Conflicts of interest statement

None to declare.

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