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Recent development of VEGFR small molecule inhibitors as anticancer agents: A patent review (2021–2023)

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Highlights

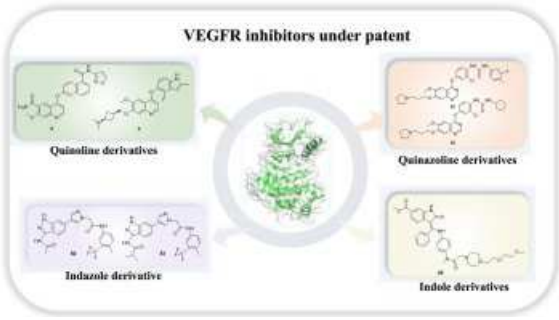
- SAR of VEGFR small molecule inhibitors under patents (2021–2023) are discussed.
- In vitro and in vivo pharmacological evaluation demonstrate anticancer potential.
- Quinoline derivatives are a predominant structural class among anti-VEGFR agents.

Abstract

VEGFR, a receptor tyrosine kinase inhibitor (TKI), is an important regulatory factor that promotes angiogenesis and vascular permeability. It plays a significant role in processes such as tumor angiogenesis, tumor cell invasion, and metastasis. VEGFR is mainly composed of three subtypes: VEGFR-1, VEGFR-2, and VEGFR-3. Among them, VEGFR-2 is the crucial signaling receptor for VEGF, which is involved in various pathological and physiological functions. At present, VEGFR-2 is closely related to a variety of cancers, such as non-small cell lung cancer (NSCLC), Hepatocellular carcinoma, Renal cell carcinoma, breast cancer, gastric cancer, glioma, etc. Consequently, VEGFR-2 serves as a crucial target for various cancer treatments. An increasing number of VEGFR inhibitors have been discovered to treat cancer, and they have achieved tremendous success in the clinic. Nevertheless, VEGFR inhibitors often exhibit severe cytotoxicity, resistance, and limitations in indications, which weaken the clinical therapeutic effect. In recent years, many small molecule inhibitors targeting VEGFR have been identified with anti-drug resistance, lower cytotoxicity, and better affinity. Here,

we provide an overview of the structure and physiological functions of VEGFR, as well as some VEGFR inhibitors currently in clinical use. Also, we summarize the in vivo and in vitro activities, selectivity, structure–activity relationship, and therapeutic or preventive use of VEGFR small molecule inhibitors reported in patents in the past three years (2021–2023), thereby presenting the prospects and insights for the future development of targeted VEGFR inhibitors.

Graphical abstract



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Introduction

Angiogenesis is the process of growing new blood vessels from existing ones, which is strictly regulated during tissue growth, wound healing, menstrual cycle, and embryonic development [1]. Vascular endothelial growth factor (VEGF) is a homodimeric protein that is secreted by various cells in both physiological and pathological conditions. The VEGF gene family primarily includes vascular endothelial growth factor A (VEGFA), placental growth factor (PLGF), VEGFB, VEGFC, and VEGFD [2], [3], [4]. VEGFRs, as the receptors of VEGF, are a type of receptor tyrosine kinase (RTK) composed of three members: VEGFR-1, VEGFR-2, and VEGFR-3 [5]. These three VEGFRs play a crucial role in the process of angiogenesis and neovascularization under pathological and physiological conditions [6]. VEGF and its receptors (VEGFRs) are important regulatory growth factors in endothelial cell vascularization, cell migration, and permeability. These functions contribute to the regulation of physiological and pathological processes of angiogenesis [7], [8], [9]. Among them, there have been numerous studies on the impact of tumor immunity. The VEGF/VEGFR pathway is regarded as a crucial driving factor in tumor angiogenesis. Apart from that, it can also inhibit tumor cell growth and the differentiation and function of various immune cells [10], [11], [12].

VEGFR-TKIs have shown excellent clinical efficacy in the treatment of many types of cancer. Currently, The Food and Drug Administration (FDA) has announced nine VEGFR-2 small molecule inhibitors that can act as anticancer drugs, including axitinib, cabozantinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib [13], [14]. However, these nine drugs have unavoidable side effects, such as cardiovascular toxicity and even severe hypertension. Studies have shown that lenvatinib is most likely to cause all levels of cardiovascular events and hypertension, and vandetanib is the most likely to have the highest risk of cardiotoxicity. In contrast, regorafenib and nintedanib did not increase the risk of heart damage [15], [16]. These small molecule inhibitors of VEGFR may not be selective, and as a result, a variety of non-VEGFR kinases may be inhibited, leading to adverse effects such as hypertension, hepatotoxicity, hyperglycemia, thrombocytopenia, proteinuria, and diarrhea [17]. The clinical use of VEGFR-TKIs produces many side effects that affect the clinical treatment effect, so it is necessary to develop VEGFR inhibitors with few toxic side effects and high selectivity.

Therefore, VEGFR-2 has become one of the most crucial therapeutic targets for various types of cancer. Furthermore, due to the synergistic effect of VEGFR with other factors, the combination of VEGFR inhibitors with other inhibitors can effectively target tumor cells and the tumor microenvironment. To optimize therapeutic efficacy and expand the range of anti-tumor treatment, it demonstrates a superior anti-tumor effect compared to the blockade of a single target [18], [19], [20]. This provides a foundation for the combination of VEGFR inhibitors with other inhibitors.

Research has shown that many small molecule inhibitors of VEGFRs have been developed, which impact RTK-dependent oncogenic pathways by competing with the ATP binding site in the RTK domain. This process inhibits the enzymatic activity, suppressing the growth and metastasis of cancer [21]. In recent years, VEGFR inhibitors have attracted widespread attention. At present, VEGFR inhibitors hinder their clinical efficacy due to their limited clinical efficacy and potential toxicity. Therefore, it is necessary to develop new strategies to improve clinical efficacy and toxicity. This article provides an overview of important structure–activity relationships, inhibitory effects, pharmacological mechanisms, and the use of VEGFR inhibitors reported in patents for the treatment or prevention of cancer.

Section snippets

Biological structure

The molecular weight of VEGFR-2 is approximately 230 kDa, and the human VEGFR-2 gene is located at chromosome locus 4q11-12 and encodes 1356 amino acids [22]. VEGFR-2 (Fig. 1) is typically composed of multiple regions, including an extracellular kinase domain consisting of seven immunoglobulin Ig-like segments, a transmembrane domain, a membrane-proximal domain, and a catalytic tyrosine kinase domain composed of a kinase insert segment split by a tyrosine kinase domain and a carboxy-terminal…

VEGFR inhibitors in clinical use

Most of the drugs in clinical practice are small molecule inhibitors that target VEGFR, and these inhibitors have shown therapeutic efficacy for different types of cancer. Currently, targeting tumor angiogenesis by inhibiting VEGFR has become a successful strategy for cancer therapy [63]. VEGFR-TKIs can be divided into two categories, namely VEGFRs-selective and non-selective inhibitors. Selective inhibitors are drugs that have a higher selectivity for VEGFRs, while non-selective inhibitors are …

VEGFR inhibitors in patents

In recent years, many small molecules of VEGFR have been on the public. The effective VEGFR inhibitors not only improve selectivity, but also reduce cytotoxicity, anti-drug resistance, and have a wider range of therapeutic applications. In this context, we provide a succinct summary of VEGFR inhibitors reported in patents over the past three years. The review primarily focuses on the structural features, structure–activity relationships (SAR), selectivity, inhibitory efficacy, and potential…

Conclusion and perspective

At present, anti-angiogenic therapy is one of the effective strategies for the treatment of a variety of cancers. Ramucirumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody. Ramucirumab can target VEGFR-2 and block angiogenesis that mediates tumor cells, and it is used to treat a variety of cancers. Drug resistance to anti-VEGFR therapy remains a challenge in the treatment of cancer patients. The most common

side effects of ramucirumab monotherapy include fatigue, decreased…

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CRediT authorship contribution statement

Jing Zeng: Writing – original draft. **Qichuan Deng:** Writing – original draft. **Zheng Chen:** Writing – original draft. **Shuang Yan:** Writing – review & editing. **Qin Dong:** Writing – review & editing. **Yuyu Zhang:** Writing – review & editing. **Yuan Cui:** Writing – review & editing. **Yuxin He:** Writing – review & editing. **Ling Li:** Writing – review & editing. **Jianyou Shi:** Writing – review & editing.…

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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References (111)

N. Ferrara *et al.*
Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells
Biochem. Biophys. Res. Commun. (1989)

X.J. Liu *et al.*
Recent development of multi-target VEGFR-2 inhibitors for the cancer therapy
Bioorg. Chem. (2023)

T.C. Elebiyo *et al.*
Reassessing vascular endothelial growth factor (VEGF) in anti-angiogenic cancer therapy
Cancer Treat Res. Commun. (2022)

R.D. Meyer *et al.*
The carboxyl terminus controls ligand-dependent activation of VEGFR-2 and its signaling
J. Biol. Chem. (2004)

J. Li *et al.*
Immunoregulation mechanism of VEGF signaling pathway inhibitors and its efficacy on the kidney
Am. J. Med. Sci. (2023)

B. Witzenbichler *et al.*
Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis in the setting of tissue ischemia
Am. J. Pathol. (1998)

A. Basolo *et al.*
Effects of tyrosine kinase inhibitors on thyroid function and thyroid hormone metabolism
Semin. Cancer Biol. (2022)

B. Goel *et al.*
Therapeutic approaches for the treatment of head and neck squamous cell carcinoma – an update on clinical trials
Transl. Oncol. (2022)

S. Fogli *et al.*
Optimizing treatment of renal cell carcinoma with VEGFR-TKIs: a comparison of clinical pharmacology and drug-drug interactions of anti-angiogenic drugs
Cancer Treat. Rev. (2020)

S. Tanno *et al.*
Human small cell lung cancer cells express functional VEGF receptors, VEGFR-2 and VEGFR-3
Lung Cancer (2004)

View more references

Cited by (0)

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