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Design, Synthesis and Anticancer Evaluation of Novel 1,3,4-Oxadiazole Derivatives as Potential VEGFR Inhibitors

Smriti[1], Rita Yadav[2], Chhoti Kumari[3], Rahul Kumar Saini[4], Shalini Bajaj[5], Subhranshu Panda[6]

[1]PG Scholar, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India-302017.

[2]Associate Professor, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India-302017.

[3]PG Scholar, Department of Pharmacology, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India-302017.

[4]PG Scholar, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Jaipur National University, Rajasthan, India-302017.

[5]Professor, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Jaipur National University, Rajasthan, India-302017.

[6]Professor, Department of Pharmaceutics, School of Pharmaceutical Sciences, Jaipur National University, Rajasthan, India-302017.

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ABSTRACT
Vascular endothelial growth factor receptors (VEGFRs) are attractive targets for anticancer therapy because angiogenesis is necessary for tumor growth, progression, and metastasis. Although several VEGFR inhibitors have demonstrated promise in clinical settings, their therapeutic potential is often limited by resistance, toxicity, and lack of selectivity. Therefore, there is still a need to find novel scaffolds that can offer potent, customized VEGFR inhibition with improved safety profiles. A common scaffold in medicinal chemistry among heterocyclic systems, the 1,3,4-oxadiazole nucleus possesses favorable physicochemical properties, metabolic stability, and versatile synthetic accessibility. Many 1,3,4-oxadiazole medications have demonstrated potent anticancer and anti-angiogenic effects by inhibiting VEGFR-mediated signaling pathways. This research discusses in depth the biological evaluation of 1,3,4-oxadiazole derivatives as VEGFR inhibitors, the synthesis processes for their generation, and the role of VEGFR in cancer angiogenesis. Significant issues about toxicity, translational development, and selectivity are extensively considered, along with trends in the structure–activity relationship (SAR) and comparison with clinically licensed VEGFR inhibitors. This study typically emphasizes the potential of molecules based on 1,3,4-oxadiazole as potential leads for next-generation anti-angiogenic anticancer medications.

1. INTRODUCTION:

One of the main global health issues and a major barrier to raising life expectancy globally is cancer. Cancer is one of the leading causes of mortality worldwide, according to data released by the World Health Organization (WHO) in 2019. Cancer is the first or second most common cause of death before the age of 70 in 112 out of 183 countries[1]. There is an urgent and compelling need to discover novel medications and therapies to successfully treat different types of cancer due to the rising incidence of cancer worldwide[2]. The hallmarks of cancer are a collection of traits and capacities that work together

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to propel the multistep process of normal cells turning into malignant cells. These include angiogenesis, tissue invasion and metastasis, self-sufficiency in growth signals, insensitivity to growth suppressive signals, and the capacity to avoid programmed cell death[3]. The transition to the invasive phase, the so-called angiogenic switch, and metastatic dissemination are linked to the evolution of many cancer types.

Complex communications between tumor cells, endothelial cells, extracellular matrix (ECM) components, and the production of several growth factors are necessary for the development and proliferation of new blood vessels from pre-existing arteries. The blood vessels, one of the biggest tissue masses, are essential for maintaining homeostasis, exchanging nutrients, metabolism, and tissue growth[4]. The development of aberrant blood vascular networks inside tumors as a result of an imbalance between pro- and antiangiogenic signals is known as pathologic angiogenesis. The father of angiogenesis research, Judah Folkman, proposed in 1971 that angiogenesis plays a crucial role in tumor formation. According to his theory, the development of new blood vessels is essential for a number of key processes inside tumors, such as the removal of waste materials, the provision of nutrition and oxygen to support tumor cells, and the facilitation of cancer cell spread. Furthermore, Folkman proposed that tumor size would be restricted to a volume of less than two mm^3 in the absence of new vascular creation[5].

Numerous pro- and anti-angiogenic chemicals precisely control the complex and dynamic process of angiogenesis. Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) are essential for both pathological and physiological angiogenesis. Vascular endothelial growth factors (VEGFs) are among the proteins released by cancer cells or by cells in the tumor microenvironment that promote the creation of blood vessels and are important in a number of malignancies[6]. VEGFRs are receptor tyrosine kinases that regulate endothelial cell migration, proliferation, and survival. Endothelial cell (EC) survival, mitogenesis, migration, and differentiation are all facilitated by the activation of the VEGF/VEGFR axis, which sets off a series of signaling networks. Furthermore, these chemicals encourage the movement of endothelial progenitor cells (EPCs) from the bone marrow into the peripheral circulation and increase vascular permeability.

Angiogenesis has been viewed as a desirable target for anticancer therapy, and VEGF/VEGFR targeting techniques have been thoroughly studied since neovascularization-defined as the creation of new blood vessels—is a crucial component in tumor growth and metastatic dissemination. With 20 years of clinical experience since the first US Food and Drug Administration-approved anti-angiogenic drug (AAD), which has been regularly used to treat a wide range of solid tumors, targeting tumor angiogenesis is the most validated therapy among many blood vessel-targeting therapies for various diseases[7]. Since overexpression and aberrant activation of VEGFR, especially VEGFR-2, have been shown in several solid tumors, VEGFR is an attractive target for the development of anticancer medications. Inhibiting VEGFR signaling has been shown to reduce tumor angiogenesis, which in turn reduces tumor growth and metastasis. The therapeutic efficacy of several VEGFR inhibitors that have been approved for clinical usage, including sorafenib, sunitinib, and pazopanib, is often limited by drug resistance, dose-limiting toxicity, poor selectivity, and adverse side effects. These limitations necessitate the constant search for novel, safer, more potent VEGFR inhibitors with improved pharmacological properties.

In recent years, heterocyclic compounds have garnered significant interest in the quest for anticancer drugs due to their favorable biological properties and structural diversity. The 1,3,4-oxadiazole nucleus has evolved into a special scaffold in medicinal chemistry. The 1,3,4-oxadiazole ring is a five-membered heterocycle containing two nitrogen and one oxygen atom. It has better metabolic stability, enhanced lipophilicity, and favorable hydrogen-bonding characteristics. Because of these characteristics, 1,3,4-oxadiazole derivatives can interact with a variety of biological targets, including kinases involved in the development of cancer[8].

1,3,4-oxadiazole compounds have been shown in numerous investigations to have a variety of biological effects, including as anticancer, anti-inflammatory, antibacterial, and anti-angiogenic properties. Numerous drugs based on 1,3,4-oxadiazole have shown strong VEGFR inhibitory effects and intriguing anticancer potential both *in vitro* and *in vivo*. This scaffold's adaptability allows for the strategic substitution of VEGFR at various locations to modify biological activity and selectivity. As a result, 1,3,4-oxadiazole derivatives have attracted more attention as possible candidates for the creation of novel anticancer drugs that target VEGFR[9]. In order to provide important insights for future anticancer drug development, this study attempts to thoroughly describe the design, synthesis, and anticancer evaluation of reported 1,3,4-oxadiazole derivatives with VEGFR inhibitory activity. It achieves this by highlighting important structural characteristics, synthetic methods, and

Journal of Molecular Science
Volume 36 Issue 2, Year of Publication 2026, Page 407-417
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biological results.

2. **Vegfr As A Target In Anticancer Therapy**

The most powerful inducer of neovasculature is vascular endothelial growth factor (VEGF), whose elevated expression is linked to poorer clinical outcomes in a variety of illnesses. Both angiogenesis and vasculogenesis, or the development of embryonic blood vessels, are regulated by VEGFs and their receptors, or VEGFRs. Numerous cancers have been found to have elevated VEGF mRNA expression, which frequently acts as a crucial prognostic indicator for cancer patients[10]. VEGF mRNA expression is upregulated by a number of growth factors, including EGF, TGF-α, TGF-β, keratinocytes growth factor, IGF-1, FGF, and PDGF, in addition to oxygen stress and nutritional deficiency. Moreover, it has been documented that hormones, cytokines, and oncogenes all cause VEGF production.

The VEGF receptors belong to the same subclass as PDGFR and FGFR receptors in the type III transmembrane tyrosine kinases (TKs) superfamily of receptors. They are made up of three domains: cytoplasmic, transmembrane, and extracellular. VEGFR-1, 2, and 3 are the three types of VEGF receptors. Vascular endothelial cells are the primary source of VEGFR-1 and VEGFR-2, while lymphatic endothelial cells are the primary source of VEGFR-3[11]. While VEGF-B and PIGF are specific ligands for VEGFR-1, VEGF-A binds to both VEGFR-1 and VEGFR-2. The only known ligands for VEGFR-3 are VEGF-C and VEGF-D, although they can also bind VEGFR-2. To put it another way, VEGF-A, -B, and PIGF have angiogenic effects, whereas VEGF-C and -D mostly contribute to lymphatic vessel development via activating VEGFR-3[12,13].

During embryogenesis, VEGF-A expression is elevated and then downregulated; nevertheless, in conditions of healthy and pathological angiogenesis, both VEGF-A and VEGFR-2 are upregulated once more. The primary mechanism that initiates angiogenesis by inducing endothelial cell proliferation, survival, sprouting, and migration as well as increasing endothelial permeability is VEGF-A signaling through VEGFR-2. Tyrosine residues are auto-phosphorylated and kinases are activated when VEGF-A binds to the VEGFR-2 receptor, causing the receptors to dimerize[14]. Phospholipase C (PLC), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), Ras, Src, and mitogen-activated protein kinases (MAPK) are all activated when these residues are phosphorylated. Protein kinase C (PKC) is activated as a result of this series of events, which also triggers the release of Ca^{2+} from internal reserves. PKC activation triggers the Raf/MEK/ERK pathway, which increases vascular permeability and cell proliferation by activating endothelial nitric oxide synthase activity. Via the action of Grb2, an adapter protein that binds pTyr1214 on VEGFR-2, ligand interaction to VEGFR-2 also initiates the Ras pathway; Through VEGF physiologic responses such cell proliferation, survival, migration, and endothelial cell arrangement, RAS activation enhances vascular tube development[15].

Folkman postulated in 1971 that angiogenesis is necessary for tumor growth and metastasis, and he later suggested that blocking angiogenesis could halt the spread of cancer. For a number of reasons, he believes that focusing on the tumor's vascular rather than the tumor itself could be a more successful approach. First of all, cancer is a broad category of diverse illnesses. Therefore, a therapeutic treatment that can successfully suppress angiogenesis is likely to be effective against a greater fraction of the disease, but a single chemotherapeutic agent cannot effectively treat cancer. Second, genetic abnormalities are continuously accumulated by cancer cells. Therefore, at a given stage of cancer, chemotherapeutics may not be able to effectively suppress the gene products that are aberrantly produced[16].

Thirdly, because angiogenic endothelial cells express particular cell-surface proteins that are lacking in endothelium or other cells, anti-angiogenic medications are less likely to have negative side effects such bone marrow suppression, gastrointestinal complaints, or hair loss. Because of its exceptional potency and selectivity for vascular endothelium, VEGF has been a key target in the pharmacological targeting of tumor vasculature. Additionally, VEGF is the only known angiogenic factor that increases the permeability of micro-vessels to circulating macromolecules. VEGF is the primary positive regulator of angiogenesis, Lymphangiogenesis, and vasculogenesis. It is produced in nearly all human tumor types, particularly in hypoxic areas of tumors and in blood vessels inside or close to tumors.

By preventing the development of malfunctioning blood vessels and lowering vascular permeability, VEGFR (vascular endothelial growth factor receptor) regulation lowers tumor growth and metastasis. This has great therapeutic potential, especially for disorders driven by angiogenesis and malignancy. VEGFR inhibitors, such as monoclonal antibodies and small-molecule tyrosine kinase inhibitors, have shown promise in treating tumors like renal cell carcinoma, colorectal cancer, and hepatocellular carcinoma, as well as ocular conditions such age-related macular degeneration.

Journal of Molecular Science
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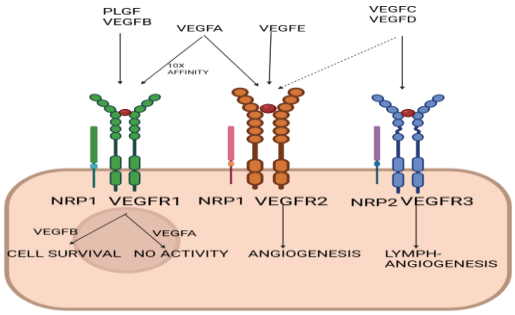

Figure 1: Vascular endothelial growth factor receptors' many roles: While VEGFB binding to VEGFR1 has been shown to increase cell survival, VEGFA binding to VEGFR1 does not result in significant receptor activation (in this scenario, the receptor works as a decoy). Although it has a lesser affinity, VEGFA can also bind to VEGFR2, which is thought to be a crucial regulator of angiogenesis that encourages the migration and proliferation of endothelial cells[17].

Table 1: VEGF/VEGFR Inhibitors for the treatment of Cancer: describes therapeutic targets and indications of clinically approved VEGFR inhibitors with their appropriate class.

Table X. Clinically Investigated VEGF/VEGFR-Targeted Therapeutics for Cancer Treatment

Therapeutic Class	Drug	Primary Molecular Target(s)	Major Therapeutic Applications	Ref.
Small-Molecule VEGFR Inhibitors	Sunitinib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β	Meningioma, pancreatic cancer, advanced renal cell carcinoma	18
	Golvatinib	VEGFR-2	Hepatocellular carcinoma, liver cancer, head and neck cancer	19
	Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α	Advanced renal cell carcinoma, soft tissue sarcoma	20
	Axitinib	VEGFR-1, VEGFR-2, VEGFR-3	Breast cancer, gastrointestinal stromal tumor, colorectal cancer, advanced renal cell carcinoma	21
	Foretinib	VEGFR-2, VEGFR-3, Tie-2	Gastric cancer, head and neck cancers	22
	Anlotinib	VEGFR-2, VEGFR-3, EGFR, PDGFR-α	Advanced renal cell carcinoma and other advanced solid tumors	23
	Sorafenib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β	Advanced solid tumors	24
	Tivozanib	VEGFR-1, VEGFR-2, VEGFR-3	Advanced renal cell carcinoma	25
Monoclonal Antibodies/Fusion Proteins	Fresolimumab	TGF-β1, TGF-β2, TGF-β3	Renal cancer, malignant melanoma	26
	Sevacizumab	VEGF-A	Colorectal cancer	27
	Trastuzumab	HER2	Breast carcinoma	28
	Aflibercept	VEGF-A, VEGF-B	Metastatic colorectal cancer	29
	Ramucirumab	VEGFR-2	Advanced gastric cancer, thyroid cancer, hepatocellular carcinoma, advanced renal cell carcinoma	30
	Bevacizumab	VEGF-A	Metastatic colorectal cancer	31
	Tanibirumab	EGFR*	Recurrent glioblastoma	32
	Sym004	VEGF-A*	Metastatic colorectal cancer	33
Antisense Oligonucleotides	BB-401	EGFR	Recurrent or metastatic head and neck cancer	34
	AP-12009	TGF-β2	Metastatic melanoma, advanced pancreatic cancer, recurrent glioma	35
	Veglin	VEGFR, PDGFR	Kaposi sarcoma, renal cancer	36

Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; TGF-β, transforming growth factor-beta.

3. 1,3,4-OXADIAZOLE SCAFFOLD IN MEDICINAL CHEMISTRY

An essential part of pharmacophores and ligand binding is oxadiazole. Oxadiazoles are a versatile lead compound that can be used to make potent bioactive medications. In certain cases, it can act as a flat aromatic linker to give the molecule the proper orientation. They combine with oxygen and nitrogen atoms to form a five-membered ring structure with the chemical formula C2H2N2O. Because of their broad range of biological activity, these compounds can be used as active agents in pharmacology and medicine. For example, they have anti-inflammatory and analgesic, antimicrobial, antiviral, antifungal, antitumor, and blood pressure-lowering qualities. Depending on where the heteroatoms are located, they are classified as 1,3,4-oxadiazoles, 1,2,5-oxadiazoles, 1,2,4-oxadiazoles, and 1,2,3-oxadiazoles[37].

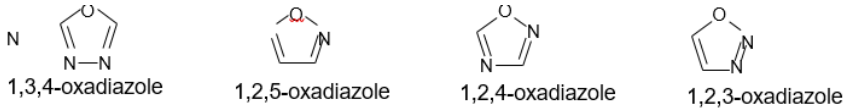

Fig 2: Isomeric forms of Oxadiazole: demonstrates structural variations according to the location of the heteroatoms within the five-membered ring.

Journal of Molecular Science

Unsubstituted 1,3,4-oxadiazole is the most stable isomeric structure among all isomeric oxadiazoles. A liquid with a boiling point of 150 °C is the fundamental unit of 1,3,4-oxadiazole. Liquids are also lower alkyl derivatives. Melting and boiling points are greatly raised by aryl substituents, particularly for symmetrical compounds. The kind of substituents on the heterocyclic ring affects how soluble 1,3,4-oxadiazoles are in water. 1,3,4-Oxadiazole is totally soluble in water when it has two methyl groups; aryl substituents considerably reduce its solubility[38]. 1.3,4-oxadiazoles are good bioisosteres of carbamates, amides, and esters. The azole (-N—C–O-) group increases the lipophilicity of the oxadiazole nucleus, which influences the drug's capacity to diffuse across membranes and reach the target. Pharmacokinetic characteristics may be significantly impacted by this. Compared to other isomeric oxadiazoles, 1,3,4-derivatives exhibit better metabolic stability, water solubility, and decreased lipophilicity. Because 1,3,4-oxadiazoles interact with different receptors by hydrogen bonding, they are regarded as good bioisosteres of carboxylic acids, esters, and carboxamides. Additionally, theyare said to significantly enhance pharmacological action. 1,3,4-oxadiazoles are nitrogen-containing heterocyclic compounds with significant pharmacokinetic properties and lipophilicity that may influence the drug's ability to permeate across membranes and reach the target[39].

The first 1,3,4-oxadiazole derivatives were created around the close of the 1800s. The novel structures were obtained via a variety of ways, such as cyclization of 1,2-diacylhydrazines by the action of dehydrating agents, thermal cyclization of 1-acylsemicarbazides, or interactions of suitable hydrazides with phosgene. In the 1950s and 1960s of the 20th century, this molecule was the subject of increased investigation. Scientists currently employ a variety of techniques to prepare 1,3,4-oxadiazole derivatives, some of which are refined versions of earlier techniques, such as cyclization oxydative reactions of N-acylhydrazones, cyclodehydration reactions of diacylhydrazines, or hydrazide reactions with carbon disulfide. Research on the 1,3,4-oxadiazole ring has significantly increased over the past 20 years[40].

Drug discovery research on 1,3,4-oxadiazole derivatives is still ongoing because of their varied biological actions and structural flexibility. They are attractive options for the creation of new therapeutic agents due to their capacity to interact with a variety of biological targets. These substances therefore have a great deal of potential in the pharmaceutical sector, opening the door to the development of novel and efficient therapies for a range of illnesses[41]. According to the literature, researchers have been creating novel compounds with the 1,3,4-oxadiazole core for a long time. These compounds have demonstrated a wide range of biological activity, such as anti-inflammatory[42], analgesic[43], anti-depressive[44], anticancer[45], and anti-diabetic effects.

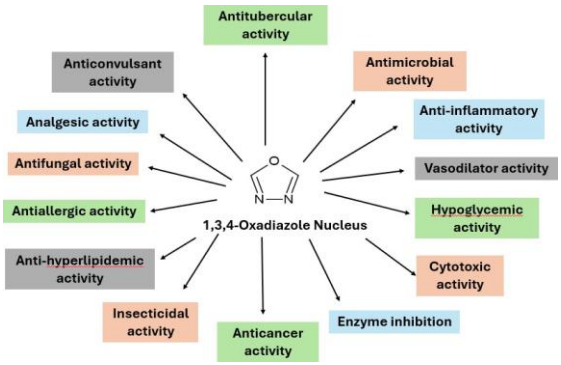

Fig 3: Biological activities of 1,3,4-Oxadiazole: An overview of the various biological actions linked to 1,3,4-oxadiazole derivatives, such as their analgesic, anti-inflammatory, anti-cancer, anti-angiogenic, and antibacterial properties.

SYNTHETIC STRATEGIES FOR 1,3,4-OXADIAZOLE DERIVATIVES

Ainsworth initially reported the synthesis of unsubstituted 1,3,4-oxadiazole in 1965. Formylhydrazone ethylformate was thermolyzed at air pressure to complete the synthesis[46]. The simplest N,N'-diformylhydrazine can be reacted with phosphorus pentoxide in the presence of polyphosphoric acid to produce basic unsubstituted 1,3,4-oxadiazole. Schwarzer et al.'s production method involves first heating the polyphosphoric acid to a temperature of roughly 100 °C before adding P2O5. The mixture can then be supplemented with hydrazine. For several hours, the reaction is conducted at a high temperature. Sodium bicarbonate can then be used to neutralize the resulting unsubstituted 1,3,4-oxadiazole[47]. N,N′-diacylhydrazines or N-acylhydrazones are the most widely used sources of 1,3,4-oxadiazole derivatives. Polyphosphoric acid (PPA), H2SO4, POCl3, SOCl2, (CF3SO2)2O, P2O5, BF3·OEt2, or Burgess reagent are the most commonly used cyclodehydrating agents for N,N′-diacylhydrazines. Furthermore, N-acylhydrazones can be oxidatively cyclized using oxidizing agents such ceric ammonium nitrate (CAN), Br2, KMnO4, PbO2, chloramine T, DDQ, or hypervalent iodine reagents to produce 1,3,4-oxadiazole derivatives. The literature also describes one-pot synthesis of oxadiazole groups from acid hydrazides using carboxylic acids and ortho-esters in the presence of an acid catalyst. Additional synthetic options include acylation, subsequent tetrazole ring opening and closure, conversion of 1,2,4-oxadiazole derivatives under UV radiation, and heterocyclization of semicarbazides, thiosemicarbazides, or selenosemi-carbazides[48].

Journal of Molecular Science
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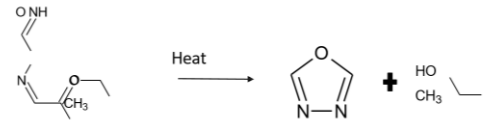

Fig 4: First preparation of 1,3,4-oxadiazole by thermolysis

Table 2: Different Synthetic Strategies For The Synthesis of 1,3,4-Oxadiazoles Derivatives And Their Potential Anticancer Action.

Category	Representative Compound/Scaffold	Key Synthetic Route	VEGFR Inhibition and Anticancer Activity	Reference
Aryl-substituted 1,3,4-oxadiazoles	Oxadiazole core substituted with aryl groups	Cyclodehydration followed by oxidation of acyl hydrazides or cyclization of hydrazides with carboxylic acid derivatives	Selective VEGFR-2 inhibition leading to significant cytotoxic activity against various cancer cell lines	49, 50
Alkoxy/Alkyl-substituted 1,3,4-oxadiazoles	Oxadiazole derivatives containing alkyl or alkoxy-substituted aryl rings	Conventional condensation followed by alkylation of key intermediates	Increased lipophilicity enhances VEGFR binding affinity, resulting in improved anticancer potency	51
Heteroaryl-linked 1,3,4-oxadiazoles	Thiophene-, quinoline-, or pyridine-linked oxadiazoles	Cyclization of hydrazides with heteroaryl carboxylic acids or aldehydes	Selective VEGFR inhibition with moderate to potent inhibitory activity (IC_{50} values in the low micromolar to nanomolar range), suppressing tumor cell proliferation	52
Sulfur-containing 1,3,4-oxadiazoles	Thioether- and thione-containing oxadiazole derivatives	Sulfurization of thiosemicarbazide intermediates using sulfurizing agents	Sulfur-containing linkages improve VEGFR inhibitory activity, resulting in enhanced cytotoxicity against cancer cells	53
Hybrid Molecules	Benzimidazole–oxadiazole hybrids	Cyclization strategy for simultaneous formation of benzimidazole and oxadiazole heterocycles	Hybridization enhances VEGFR inhibition and significantly improves antiproliferative activity	54
	Chalcone–oxadiazole hybrids	Claisen–Schmidt condensation followed by oxadiazole ring formation	Dual-targeting characteristics produce potent VEGFR inhibition and strong cytotoxic activity	54
	Oxadiazole–quinazoline hybrids	Amide or alkyl spacer-mediated coupling of oxadiazole and quinazoline pharmacophores	Enhanced inhibition of tumor cell growth through improved VEGFR-targeted activity	54
Novel Oxadiazole Derivatives	Lead compounds A, B, and C	Microwave-assisted synthetic methodology	Nanomolar VEGFR inhibition induces cell cycle arrest, growth inhibition, and pronounced cytotoxicity in cancer cells	55

Abbreviations: VEGFR, vascular endothelial growth factor receptor; IC_{50}, half-maximal inhibitory concentration.

4. ANTICANCER EVALUATION OF 1,3,4-OXADIAZOLES

A number of enzymes and growth factors, including telomerase, topoisomerase, histone deacetylase (HDAC), methionine aminopeptidase, thymidylate synthase, poly(ADP-ribose) polymerase, focal adhesion kinase, thymidine phosphorylase, glycogen synthase kinase-3, caspase-3, MMP-916−19 enzymes, epidermal growth factor, vascular endothelial growth factor, and nuclear factor κB, have specific roles in apoptosis, mitogenesis, angiogenesis, and metastasis pathways in tumors. According to Valente et al.'s research, amidic pharmacophores like hydroxamate and 2-aminoanilide, which are known to be successful in inhibiting HDAC in anticancer therapy, and bioisosteric displacement of the 1,3,4-oxadiazole ring increased cytotoxic and apoptotic activity at a similar rate[56].

In order to fully evaluate the therapeutic potential of 1,3,4-oxadiazole derivatives, anticancer evaluation has mostly employed in-vitro, enzymatic, anti-angiogenic, and in-vivo techniques. In order to ascertain the growth-inhibitory characteristics of 1,3,4-oxadiazole compounds against a variety of human cancer cell lines, such as breast, lung, colon, prostate, and cervical malignancies, in-vitro cytotoxic screening is most frequently carried out utilizing MTT and SRB assays. These tests evaluate cell survival and proliferation after treatment, allowing the computation of IC_{50} values that show the cytotoxic potential of the oxadiazole scaffold. The scaffold is appropriate for the creation of anticancer drugs since certain 1,3,4-oxadiazole derivatives have shown selective cytotoxicity toward cancer cells with relatively less harm to healthy cells.

VEGFR enzyme inhibition assays are frequently employed to examine the molecular mechanism of 1,3,4-oxadiazoles' anticancer activity, namely their anti-angiogenic properties. The ability of the synthetic oxadiazole derivatives to suppress VEGFR-2 kinase activity is evaluated in these studies using biochemical or cell-based kinase

assays. It has been shown that a variety of 1,3,4-oxadiazole compounds significantly lower VEGFR-2 phosphorylation, suggesting that the heterocyclic core facilitates effective interaction within the receptor's ATP-binding domain. This inhibition is in line with the medications' established antiproliferative effects in cancer cells and supports VEGFR-mediated signaling as their main target. Tests for endothelial cell proliferation, migration, and tube formation are used in both in vitro and *ex vivo* models to further evaluate the anti-angiogenic efficacy of 1,3,4-oxadiazole derivatives. These models assess how efficiently oxadiazole drugs suppress angiogenesis, a crucial stage in tumor growth and metastasis, by preventing the development of new blood vessels. Several derivatives have been shown to dramatically decrease the migration and development of endothelial cell tubes, supporting their potential as angiogenesis inhibitors and enhancing the results of VEGFR inhibition research.

Tumor xenograft or allograft models are frequently used in published *in-vivo* evaluations to validate the anticancer effectiveness of suspected 1,3,4-oxadiazole compounds found in previous studies. In animal models, these investigations evaluate angiogenesis suppression, tumor growth inhibition, and overall tolerance. The results support the enzymatic and in vitro findings and demonstrate the 1,3,4-oxadiazole scaffold's promise as a workable foundation for the creation of new anticancer drugs. They also demonstrate that certain oxadiazole compounds can successfully decrease tumor volume without causing serious health problems.

Table 3: Representative 1,3,4-Oxadiazole Derivatives and Their Anticancer Activities [57]

Chemical Class	Representative Compound(s)	Reported Anticancer Activity
2,3-Dihydro-1,3,4-oxadiazole Derivatives	• 3-[(3-Chloroanilino)methyl]-5-(2-hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione • 3-[(4-Chloroanilino)methyl]-5-(2-hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione	Demonstrated superior anticancer activity compared with **cyclophosphamide** and **5-fluorouracil**, indicating enhanced cytotoxic potential.
2,5-Disubstituted-1,3,4-oxadiazoles	• (R)-2-Amino-N-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)propenamide • 5-Bromo-1-((4-chlorophenyl)((5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)amino)methyl)indoline-2,3-dione • {5-(4-Methylphenyl)-1,3,4-oxadiazol-2-yl}sulfanylacetic acid • 2-(3-Chlorobenzo[b]thiophen-2-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole • 3-(5-Benzyl-1,3,4-oxadiazol-2-yl)quinolin-2(1H)-one • 3-[5-(2-Phenoxymethyl-benzimidazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-2-p-tolyloxyquinoline	Activity comparable to **vorinostat**; improved cytotoxicity against **HT-29** and **HepG2** cells; significant reduction in tumor weight and viable cell count; time- and dose-dependent antiproliferative activity with **GI_{50} values of 1.41–15.8 µM** and **0.40–14.9 µM**, comparable to **mitomycin C**.
Toxophoric C=N-Linked 1,3,4-oxadiazoles	• 2-Amino-5-aryl-1,3,4-oxadiazole bearing toxophoric C=N linkage	Exhibited enhanced antiproliferative activity and significantly prolonged the lifespan of **Ehrlich Ascites Carcinoma (EAC)** tumor-bearing mice.
1,3,4-Oxadiazole–Thiazolidine-2,4-diones	• (E)-3-{[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione • (E)-3-{[5-(3-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione • (E)-3-{[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione	Displayed potent anticancer activity comparable to the vascular-disrupting agent **combretastatin**.
5-(3′-Indolyl)-1,3,4-oxadiazoles	• 3-[5-(Pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1H-indole • 3-[5-(Pyridin-3-yl)-1,3,4-oxadiazol-2-yl]-1H-indole • 3-{5-[4-(Benzyloxy)-3-methoxyphenyl]-1,3,4-oxadiazol-2-yl}-1H-indole	Exhibited potent cytotoxicity with **IC_{50} values around 1 µM**, indicating high efficacy against multiple cancer cell lines.
1,2,4-Oxadiazole-Linked 1,3,4-oxadiazoles	• 2-(3,4,5-Trimethoxyphenyl)-5-(4-(5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl)phenyl)-1,3,4-oxadiazole • 2-(3,4,5-Trimethoxyphenyl)-5-(4-(5-(3-nitrophenyl)-1,2,4-oxadiazol-3-yl)phenyl)-1,3,4-oxadiazole • 4-(3-(4-(5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)-1,2,4-oxadiazol-5-yl)benzonitrile	Demonstrated remarkable anticancer activity with **IC_{50} values ranging from 0.34 ± 0.025 to 2.45 ± 0.23 µM** against **MCF-7**, **A549**, and **MDA-MB-231** cancer cell lines.
1,2,3-Triazole-Linked 1,3,4-oxadiazoles	• 3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-phenyl-1,3,4-oxadiazol-2(3H)-one • 3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-(p-tolyl)-1,3,4-oxadiazol-2(3H)-one • 3-((1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(p-tolyl)-1,3,4-oxadiazol-2(3H)-one	Exhibited potent anticancer activity against **HeLa (cervical)**, **MDA-MB-231 (breast)**, **DU-145 (prostate)**, and **HepG2 (liver)** cancer cell lines.

Abbreviations: GI_{50}, concentration causing 50% growth inhibition; IC_{50}, half-maximal inhibitory concentration; HT-29, human colorectal adenocarcinoma cells; HepG2, human hepatocellular carcinoma cells; MCF-7, human breast adenocarcinoma cells; A549, human lung adenocarcinoma cells; MDA-MB-231, human triple-negative breast cancer cells; HeLa, human cervical cancer cells; DU-145, human prostate cancer cells; EAC, Ehrlich Ascites Carcinoma.

Journal of Molecular Science
Journal of Molecular Science
Volume 36 Issue 2, Year of Publication 2026, Page 407-417
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5. STRUCTURE ACTIVITY RELATIONSHIP OF 1,3,4-OXADIAZOLES

5.1 Impact of Substitution at Positions C-2 and C-5

The inhibitory activity of VEGFR is primarily regulated by substitution at the C-2 and C-5 positions of the 1,3,4-oxadiazole ring. The C-2 position is particularly important for receptor recognition and binding orientation in the VEGFR ATP-binding site. The inclusion of aryl or heteroaryl groups at C-2 improves hydrophobic interactions and π–π stacking with significant amino acid residues in the kinase domain. Electron-withdrawing substituents, such as nitro or halogen groups, increase the binding affinity at this site by stabilizing ligand-receptor interactions and changing the distribution of electrons.

However, changes in the C-5 position have a significant impact on potency and pharmacokinetic behavior. Bulky hydrophobic groups at C-5 increase affinity for VEGFR-2 by enhancing hydrophobic interactions within the binding pocket. Alkyl, aryl, or thio-substituents at this site have been shown to enhance cellular permeability and lipophilicity, hence increasing biological activity. Overall, dual substitution at both the C-2 and C-5 positions frequently results in compounds with enhanced anti-angiogenic and VEGFR inhibitory actions.

5.2 Aromatic vs. Heteroaromatic Rings' Function

VEGFR inhibition is significantly influenced by the type of substituents, whether aromatic or heteroaromatic, attached to the oxadiazole core. Phenyl and substituted phenyl groups are examples of aromatic rings that strengthen hydrophobic interactions with the VEGFR binding site, increasing efficacy. Specifically, because of their favorable steric alignment and decreased vulnerability to enzyme degradation, para-substituted phenyl rings have been linked to improved metabolic stability and selectivity.

The addition of extra hydrogen-bond donors or acceptors supplied by heterocyclomatic rings, such as pyridine, thiazole, and quinoline, enables greater interactions with the hinge area residues of VEGFR. These rings often enhance binding selectivity and can boost water solubility. Because heterocyclomatic substitutions provide a balance between potency, selectivity, and pharmacokinetic features, they perform better than basic aromatic rings in many known derivatives, making them perfect for drug design that targets VEGFR.

5.3 Functional Groups That Improve Inhibition of VEGFR

Certain functional groups found in the oxadiazole scaffold significantly boost VEGFR's inhibitory action. Hydrogen bond-forming substances such amines, amides, ureas, and sulfonamides improve anchoring inside the ATP-binding pocket by interacting with crucial residues implicated in kinase activation. The binding interactions seen with well-known VEGFR inhibitors are often similar to these functions.

Additionally, electron-withdrawing compounds like halogens and trifluoromethyl moieties increase binding affinity by stabilizing ligand–receptor interactions and enhancing lipophilicity. Substitutes that can form hydrophobic contacts inside the allosteric areas significantly boost VEGFR inhibition. The anti-angiogenic activity, VEGFR-2 selectivity, and potency are all increased by the addition of these functional groups, which makes 1,3,4-oxadiazoles an appropriate scaffold for anticancer medications that target VEGFR.

6. COMPARISON WITH STANDARD VEGFR INHIBITORS

Table 4: Comparison Between 1,3,4-Oxadiazole-Based Vegfr Inhibitors And Standard Marketed VEGFR Inhibitors With Respect To Potency, Selectivity, Toxicity, And Clinical Status

Aspect	Oxadiazole Derivatives	Standard VEGFR Inhibitors
IC50	Higher as compared to marketed drugs	Lower as compared to Oxadiazole derivate
VEGFR Inhibition	*In-vitro* studies showed the highest inhibition. Effect varies as per the structure of derivative	Clinical data proves the VEGFR inhibition
Selectivity	More VEGFR selectivity as compared to other kinases	Can act on other kinases such as PDGFR, KIT along with VEGFR
Clinical status	Oxadiazole derivates have shown its effects n preclinical studies, confirming its presence in experimental studies. Clinica studies need to be carried.	Already approved and marketed
Efficacy against tumors	Have the potential to treat cancer due to its anti-angiogenic properties	Enhanced survival of cancer patients
Toxicity	Due to higher selectivity and specificity, it may cause	Severe adverse effects are observed

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	reduction in toxicity	
Chemical flexibility	Highly modifiable scaffold (easy SAR optimization)	Limited flexibility
Limitations	Lack of clinical studies	Resistance, adverse effects, non-selectivity

7. CHALLENGES AND FUTURE PERSPECTIVES

7.1 Challenges

A number of obstacles prevent 1,3,4-oxadiazole-based VEGFR inhibitors from being clinically translated, despite promising preclinical results. Many derivatives still inhibit kinases such as PDGFR, EGFR, and KIT off-target, which makes selectivity a significant drawback that could have negative consequences. Because the majority of research is limited to in-vitro cytotoxicity and a small number of in-vivo models, toxicity and safety features are also poorly understood.

The absence of pharmacokinetic and metabolic information, such as oral bioavailability, plasma stability, and long-term tolerance, presents another difficulty. Direct comparisons between reported compounds are further complicated by differences in production and biological evaluation techniques. Oxadiazole derivatives have not been sufficiently studied for drug resistance, which is a drawback of existing VEGFR inhibitors. The lack of clinical research highlights the discrepancy between encouraging lab results and real therapeutic use.

7.2 Future perspectives

Future research should concentrate on creating highly selective VEGFR-2 inhibitors by molecular docking and logical structure-based drug design. Pharmacokinetic factors including solubility and metabolic stability need to be taken into consideration in order to bring lead medications closer to clinical development. Dual-target tactics and hybrid pharmacophores can be employed to get around resistance mechanisms and boost treatment effectiveness. Standardized in-vivo angiogenesis models and comprehensive toxicity profiles are required to validate safety and translational potential. Nanotechnology-based drug delivery techniques may also improve tumor targeting and reduce systemic toxicity. With further interdisciplinary research, 1,3,4-oxadiazole derivatives hold significant promise as next-generation anti-angiogenic medications for the treatment of cancer.

CONCLUSION:

The 1,3,4-oxadiazole scaffold provides a versatile and physiologically significant foundation for the development of novel VEGFR-targeted anticancer medications. Extensive synthetic flexibility and favorable pharmacological properties have led to the production of several molecules with potent anti-angiogenic and anticancer properties. According to SAR studies, strategic replacement at the C-2 and C-5 sites is crucial for enhancing VEGFR inhibition, selectivity, and cellular efficacy. Even though most oxadiazole medications are still in the preclinical stage, their relative benefits over traditional VEGFR inhibitors, such as improved selectivity and reduced toxicity, highlight their therapeutic potential. Resolving problems with pharmacokinetics, safety, and clinical validation will be essential to future progress. Overall, 1,3,4-oxadiazole-based VEGFR inhibitors present a promising platform for the rational creation of safer and more potent anti-angiogenic anticancer therapies.

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REFERENCES:

1. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries - Sung - 2021 - CA: A Cancer Journal for Clinicians - Wiley Online Library. Accessed January 8, 2026.
2. https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21660
3. Chhikara BS, Parang K. Global Cancer Statistics 2022: The Trends Projection Analysis.
4. Accessed January 8, 2026. https://digitalcommons.chapman.edu/pharmacy_articles/938
5. Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discov*. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059
6. Frontiers | Exploring the Immunological Mechanisms

Underlying the Anti-vascular Endothelial Growth Factor Activity in Tumors. Accessed January 8, 2026. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2019.01023/full
7. Guo Z, Jing X, Sun X, Sun S, Yang Y, Cao Y. Tumor angiogenesis and anti-angiogenic therapy.
8. *Chin Med J (Engl)*. 2024;137(17):2043-2051. doi:10.1097/CM9.0000000000003231
9. Ghalehbandi S, Yuzugulen J, Pranjol MZI, Pourgholami MH. The role of VEGF in cancer-induced angiogenesis and research progress of drugs targeting VEGF. *Eur J Pharmacol*. 2023;949:175586. doi:10.1016/j.ejphar.2023.175586
10. Targeting angiogenesis in cancer therapy: lessons learned and paths forward: Expert Review of Anticancer Therapy: Vol 0 , No ja - Get Access. Accessed January 8, 2026. https://www.tandfonline.com/doi/full/10.1080/14737140.2025.2599893?src=
11. Nayak S, Gaonkar SL, Musad EA, Dawsar AMA. 1,3,4-Oxadiazole-containing hybrids as potential anticancer agents: Recent developments, mechanism of action and structure-activity relationships. *J Saudi Chem Soc*. 2021;25(8):101284.
12. doi:10.1016/j.jscs.2021.101284
13. Significance of 1,3,4-Oxadiazole Containing Compounds in New Drug Development - PubMed. Accessed January 8, 2026. https://pubmed.ncbi.nlm.nih.gov/33349230/
14. Sopo: Expression profiles of VEGF-A, VEGF-D and VEGFR1... - Google Scholar. Accessed January 11, 2026.
15. https://scholar.google.com/scholar_lookup?title=Expression%20profiles%20of%20VEGF-A%2C%20VEGF-
16. D%20and%20VEGFR1%20are%20higher%20in%20distant%20metastases%20than%20in%20matched%20primary%20high%20grade%20epithelial%20ovarian%20cancer&publication_year=2019&author=M%20Sopo&author=M%20Anttila&author=K%20Hamalainen
17. (PDF) VEGF receptor signalling - In control of vascular function. Accessed January 11, 2026. https://www.researchgate.net/publication/7148150_VEGF_receptor_signalling_-
18. _In_control_of_vascular_function
19. Elebiyo TC, Rotimi D, Evbuomwan IO, et al. Reassessing vascular endothelial growth factor (VEGF) in anti-angiogenic cancer therapy. *Cancer Treat Res Commun*.
20. 2022;32:100620. doi:10.1016/j.ctarc.2022.100620
21. Park SA, Jeong MS, Ha KT, Jang and SB. Structure and function of vascular endothelial growth factor and its receptor system. *BMB Rep*. 2018;51(2):73-78. doi:10.5483/BMBRep.2018.51.2.233
22. Lee C, Kim MJ, Kumar A, Lee HW, Yang Y, Kim Y. Vascular endothelial growth factor signaling in health and disease: from molecular mechanisms to therapeutic perspectives. *Signal Transduct Target Ther*. 2025;10:170. doi:10.1038/s41392-025-02249-0
23. Patel SA, Nilsson MB, Le X, Cascone T, Jain RK, Heymach JV. Molecular Mechanisms and Future Implications of VEGF/VEGFR in Cancer Therapy. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2023;29(1):30-39. doi:10.1158/1078-0432.CCR-22-1366
24. Role of VEGFs/VEGFR-1 Signaling and Its Inhibition in Modulating Tumor Invasion: Experimental Evidence in Different Metastatic Cancer Models. Accessed January 11, 2026. https://www.mdpi.com/1422-0067/21/4/1388
25. Lal N, Puri K, Rodrigues B. Vascular Endothelial Growth Factor B and Its Signaling.
26. *Front Cardiovasc Med*. 2018;5. doi:10.3389/fcvm.2018.00039
27. Butz H, Ding Q, Nofech-Mozes R, Lichner Z, Ni H, Yousef GM. Elucidating mechanisms of sunitinib resistance in renal cancer: an integrated pathological-molecular analysis. *Oncotarget*. 2017;9(4):4661-4674. doi:10.18632/oncotarget.23163
28. Clinical Development of c-MET Inhibition in Hepatocellular Carcinoma. Accessed January 13, 2026. https://www.mdpi.com/2079-9721/3/4/306
29. VEGFR-2 inhibitors and the therapeutic applications thereof: a patent review (2012-2016): Expert Opinion on Therapeutic Patents: Vol 27, No 9. Accessed January 13, 2026. https://www.tandfonline.com/doi/abs/10.1080/13543776.2017.1344215
30. Kidney Cancer, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology in: Journal of the National Comprehensive Cancer Network Volume 15 Issue 6 (2017).
31. Accessed January 13, 2026. https://jnccn.org/view/journals/jnccn/15/6/article-p804.xml
32. Goltsov AA, Fang B, Pandita TK, Maru DM, Swisher SG, Hofstetter WL. HER2 Confers Resistance to Foretinib Inhibition of MET-Amplified Esophageal Adenocarcinoma Cells. *Ann Thorac Surg*. 2018;105(2):363-370. doi:10.1016/j.athoracsur.2017.09.003
33. Development of Second-Generation VEGFR Tyrosine Kinase Inhibitors: Current Status
34. | Current Oncology Reports. Accessed January 13, 2026. https://link.springer.com/article/10.1007/s11912-011-0154-
35. 3?utm_source=getftr&utm_medium=getftr&utm_campaign=getftr_pilot&getft_integrator=sciencedirect_contenthosting
36. Ruan H, Li X, Yang H, et al. Enhanced expression of caveolin-1 possesses diagnostic and prognostic value and promotes cell migration, invasion and sunitinib resistance in the clear cell renal cell carcinoma. *Exp Cell Res*. 2017;358(2):269-278.
37. doi:10.1016/j.yexcr.2017.07.004
38. Emerging oral VEGF inhibitors for the treatment of renal cell carcinoma: Expert Opinion on Investigational Drugs: Vol 28, No 2. Accessed January 13, 2026. https://www.tandfonline.com/doi/abs/10.1080/13543784.2019.1559296
39. Zhao H, Wei J, Sun J. Roles of TGF-β signaling pathway in tumor microenvirionment and cancer therapy. *Int Immunopharmacol*. 2020;89:107101.
40. doi:10.1016/j.intimp.2020.107101
41. Novel anti-angiogenic therapeutic strategies in colorectal cancer: Expert Opinion on Investigational Drugs: Vol 25, No 5. Accessed January 13, 2026. https://www.tandfonline.com/doi/abs/10.1517/13543784.2016.1161754
42. Trastuzumab in the Treatment of Breast Cancer | BioDrugs. Accessed January 13, 2026. https://link.springer.com/article/10.1007/s40259-016-0162-9
43. A Review of Anti-Angiogenic Targets for Monoclonal Antibody Cancer Therapy. Accessed January 13, 2026. https://www.mdpi.com/1422-0067/18/8/1786
44. Wu J biao, Tang Y ling, Liang X hua. Targeting VEGF pathway to normalize the
45. vasculature: an emerging insight in cancer therapy. *OncoTargets Ther*. 2018;11:6901-6909. doi:10.2147/OTT.S172042
46. Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev*.
47. 2020;86:102017. doi:10.1016/j.ctrv.2020.102017
48. Kong DH, Kim MR, Jang JH, Na HJ, Lee S. A Review of Anti-Angiogenic Targets for Monoclonal Antibody Cancer Therapy. *Int J Mol Sci*. 2017;18(8):1786.
49. doi:10.3390/ijms18081786
50. Efficacy of Sym004 in Patients With Metastatic Colorectal Cancer With Acquired Resistance to Anti-EGFR Therapy and Molecularly Selected by Circulating Tumor DNA Analyses: A Phase 2 Randomized Clinical Trial | Colorectal Cancer | JAMA Oncology | JAMA Network. Accessed January 13, 2026.
51. https://jamanetwork.com/journals/jamaoncology/fullarticle/2671608
52. Le BT, Raguraman P, Kosbar TR, Fletcher S, Wilton SD, Veedu RN. Antisense
53. Oligonucleotides Targeting Angiogenic Factors as Potential Cancer Therapeutics. *Mol Ther Nucleic Acids*. 2019;14:142-157. doi:10.1016/j.omtn.2018.11.007

54. Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee SS. Therapeutic miRNA and siRNA: Moving from Bench to Clinic as Next Generation Medicine. *Mol Ther - Nucleic Acids*. 2017;8:132-143. doi:10.1016/j.omtn.2017.06.005
55. Kerr DA, Busarla SVP, Gimbel DC, Sohani AR, Nazarian RM. mTOR, VEGF, PDGFR, and c-kit signaling pathway activation in Kaposi sarcoma. *Hum Pathol*. 2017;65:157-165.
56. doi:10.1016/j.humpath.2017.05.002
57. Khamkar T, Kadam R, Mali SS, Udugade B, Singh S. Recent Advances in Synthetic Approaches for 1,3,4-Oxadiazole Derivatives: A Comprehensive Review on Therapeutic Applications. doi:10.2174/0118741045372896250619051210
58. Luczynski M, Kudelko A. Synthesis and Biological Activity of 1,3,4-Oxadiazoles Used in Medicine and Agriculture. *Appl Sci*. 2022;12(8):3756. doi:10.3390/app12083756
59. A V, D P, K S. 1,3,4-oxadiazole and its derivatives: A review on recent progress in anticancer activities. *Chem Biol Drug Des*. 2021;97(3). doi:10.1111/cbdd.13795
60. Glomb T, Świątek P. Antimicrobial Activity of 1,3,4-Oxadiazole Derivatives. *Int J Mol Sci*. 2021;22(13):6979. doi:10.3390/ijms22136979
61. Updates on synthesis and biological activities of 1,3,4-oxadiazole: A review: Synthetic Communications: Vol 47, No 20. Accessed January 17, 2026.
62. https://www.tandfonline.com/doi/abs/10.1080/00397911.2017.1360911
63. Zabiulla, Gulnaz AR, Mohammed YHE, Khanum SA. Design, synthesis and molecular docking of benzophenone conjugated with oxadiazole sulphur bridge pyrazole pharmacophores as anti inflammatory and analgesic agents. *Bioorganic Chem*.
64. 2019;92:103220. doi:10.1016/j.bioorg.2019.103220
65. Kaur J, Soto-Velasquez M, Ding Z, et al. Optimization of a 1,3,4-oxadiazole series for inhibition of Ca2+/calmodulin-stimulated activity of adenylyl cyclases 1 and 8 for the treatment of chronic pain. *Eur J Med Chem*. 2019;162:568-585.
66. doi:10.1016/j.ejmech.2018.11.036
67. Tantray MA, Khan I, Hamid H, Alam MS, Dhulap A, Kalam A. Synthesis of benzimidazole-linked-1,3,4-oxadiazole carboxamides as GSK-3β inhibitors with in vivo antidepressant activity. *Bioorganic Chem*. 2018;77:393-401.
68. doi:10.1016/j.bioorg.2018.01.040
69. Glomb T, Szymankiewicz K, Świątek P. Anti-Cancer Activity of Derivatives of 1,3,4-Oxadiazole. *Mol Basel Switz*. 2018;23(12):3361. doi:10.3390/molecules23123361
70. Banik BK, Sahoo BM, Kumar BVVR, et al. Green Synthetic Approach: An Efficient Eco-Friendly Tool for Synthesis of Biologically Active Oxadiazole Derivatives. *Molecules*.
71. 2021;26(4):1163. doi:10.3390/molecules26041163
72. Schwärzer K, Tüllmann CP, Graßl S, Górski B, Brocklehurst CE, Knochel P. Functionalization of 1,3,4-Oxadiazoles and 1,2,4-Triazoles via Selective Zincation or Magnesiation Using 2,2,6,6-Tetramethylpiperidyl Bases. *Org Lett*. 2020;22(5):1899-1902. doi:10.1021/acs.orglett.0c00238
73. Luczynski M, Kudelko A. Synthesis and Biological Activity of 1,3,4-Oxadiazoles Used in Medicine and Agriculture. *Appl Sci*. 2022;12(8):3756. doi:10.3390/app12083756
74. Hatti I, Sujana O, Nookaraju M, Suresh J, Aparna Seetharam K, Raju RR. Rational design, synthesis, and anticancer evaluation of pyridine and substituted aryl linked 1,3,4-oxadiazole derivatives. *Results Chem*. 2024;11:101755.
75. doi:10.1016/j.rechem.2024.101755
76. Srilaxmi D, Reddy AG, Sireesha R, et al. Design and Synthesis of Different Aryl Substituted 1,3,4-Oxadiazole-imidazo[1,5-a]pyridine Derivatives as Anticancer Agents. *Russ J Gen Chem*. 2022;92(5):891-897. doi:10.1134/S107036322205019X
77. Sonu Jangir SJ, Satish S. "A Design and Synthesis of Some New 1, 3, 4-Oxadiazole Analogues for Using Anticancer Agents." *Int J Pharm Res Appl*. 2025;10(3):1248-1267. doi:10.35629/4494-100312481267
78. Anti-Cancer Activity of Derivatives of 1,3,4-Oxadiazole. Accessed January 27, 2026. https://www.mdpi.com/1420-3049/23/12/3361
79. View of A Review Exploring Therapeutic Effect of 1,3,4-Oxadiazole Compounds | Journal of Drug Delivery and Therapeutics. Accessed January 27, 2026. https://jddtonline.info/index.php/jddt/article/view/5979/5662
80. Nayak S, Gaonkar SL, Musad EA, Dawsar AMA. 1,3,4-Oxadiazole-containing hybrids as potential anticancer agents: Recent developments, mechanism of action and structure-
81. activity relationships. *J Saudi Chem Soc*. 2021;25(8):101284. doi:10.1016/j.jscs.2021.101284
82. Samanta A, Maji A, Paul A, Mishra SS, Nahar S, Maity TK. 1,3,4-Oxadiazole-based EGFR inhibitors as anticancer therapeutics: SAR study and binding mode of interaction analysis. *Eur J Med Chem Rep*. 2025;14:100265. doi:10.1016/j.ejmcr.2025.100265
83. Yurttaş L, Evren AE, Kubilay A, Aksoy MO, Temel HE, Akalın Çiftçi G. Synthesis of Some New 1,3,4-Oxadiazole Derivatives and Evaluation of Their Anticancer Activity. *ACS Omega*. 2023;8(51):49311-49326. doi:10.1021/acsomega.3c07776
84. Vaidya A, Pathak D, Shah K. 1,3,4-oxadiazole and its derivatives: A review on recent progress in anticancer activities. *Chem Biol Drug Des*. 2021;97(3):572-591. doi:10.1111/cbdd.1379