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Review Article

Development of Thiadiazole-Based VEGFR-2 Targeted Agents: A Comprehensive Review of Cytotoxic and Anticancer Activities

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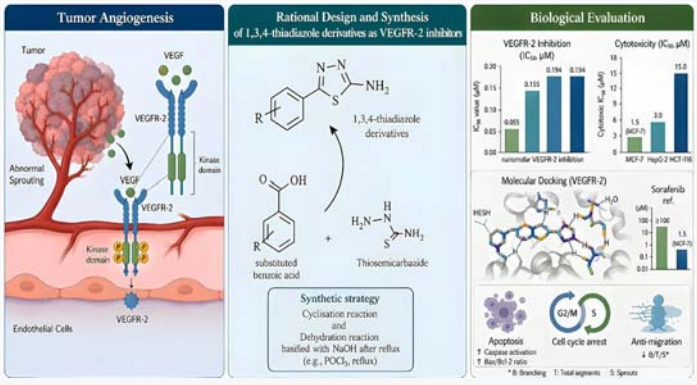
Abstract

One of the best-proven molecular targets in the treatment of cancer is vascular endothelial growth factor receptor-2 (VEGFR-2). Because it plays an important role in tumor angiogenesis, proliferation, and metastasis. FDA-approved VEGFR-2 inhibitors have proven to have clinical efficacy in managing various malignancies. Anti-cancer activity of approved agents such as sorafenib (IC_{50} = 1 µM - 10 µM), sunitinib (IC_{50} = 1 µM - 5 µM), and pazopanib (IC_{50} = 1 µM - 3 µM) has been demonstrated. However, their therapeutic use can result in off-target toxicities. Moreover, acquired resistance mechanisms have been observed as well. They also have poorly selective means of action. The 1,3,4-thiadiazole scaffold has become an important heterocyclic compound of medicinal chemistry due to its mesoionic character, versatility in structures, and pharmacological attributes. This review presents a systematic study of the earlier developments in the rational design, synthesis, SAR, and cytotoxicity evaluation of Thiadiazole-based VEGFR-2 inhibitors. In this review, the molecular mechanisms of VEGFR-2 inhibitors and their biological activities against a variety of cancer cell lines in terms of their ability to induce apoptosis, modulate cell cycle, anti-metastatic properties, and *in silico* approaches. The recently added Thiadiazole derivatives display very good VEGFR-2 inhibitory activities with IC_{50} values ranging from 0.055 to 0.194 µM, potent antiproliferation activities with IC_{50} values of 1.5-15 µM, good selectivity indices (3-20-fold), and anticancer activities through different mechanisms of action that are more favorable than the established drugs.

Graphical Abstract



More Information

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Introduction

Cancer is one of the most urgent social health emergencies in the whole world and especially in India, as the World Health Organization (WHO) GLOBOCAN 2025 report offers the central estimates according to the 2022 updates and forecasts. In the world, it was estimated in the year 2022 that there were about 20 million new cases of cancer resulting in about 9.7 million deaths, and it is projected that this figure will increase drastically to 35 million new cases by the year 2050. This epidemic is due to the aging of the world population, increased incidence of preventable risk factors such as smoking of tobacco, alcohol, poor nutrition, sedentary lifestyles, obesity, and environmental pollutants such as air pollution, and the chronic infectious agents like human papillomavirus (HPV), hepatitis B and C viruses, and Helicobacter pylori. Cancer related to lifestyle is predominant in high-income nations; infection contributes to it in much greater proportions in low- and middle-income nations, which incur 70 per cent of the world's cancer burden. WHO reported the different types of cancers spread worldwide with their numbers by 2025, as shown in Figure 1 [1,2].

In India, the disease has also become critically worrying as the number of new cases and deaths in 2022 is estimated at 1.41 million and over 1 million, respectively, placing it as the third-highest absolute incidence and the second-highest mortality despite its status as home to only 18% of the world population, but with 8.8% of cases. This unequal distribution is due to the combination of local risk factors such as high levels of tobacco consumption (both smoked (bidis) and smokeless (gutkha) which is linked to 30-50% of male cancers) and prevalence of HPV/hepatitis infections with low levels of vaccination coverage, alcohol use, nutritional deficiencies, poverty-oriented late-stage manifestations, and insufficient screening infrastructure which have led to a five-year survival rate of less than 30% compared to over 60 years in high-income countries The cancer profile in India does not follow global trends, and reflects the differences in socio cultural and epidemiological terms: breast cancer is the leading at 13.6% (rapidly increasing with urbanization, change in diet to processed food and consequence with delayed child bearing) and lip and oral cavity at 10.2% (India has contributed nearly half of the oral cancer cases in the world, with most of them due to betel quid chewing in combination with tobacco), cervix uteri cancer at 9.0 and in esophagus cancer at 5.0 The regional differences are stark, oral cancers in the northeast through habits of eating the areca nut, cervical in the south through lower awareness, and breast/lung in the urban areas, and compounded by over stretched health care systems and rural-urban differences (90% of the population, minimal services in the rural) versus urban (better access) [3,4].

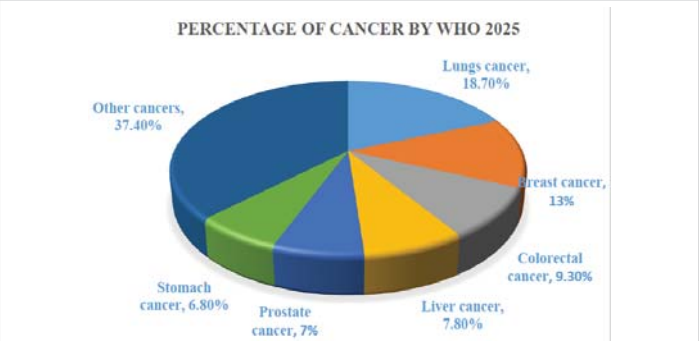


Figure 1: Percentage of cancer by WHO 2025.

Expanded global trends

It has been projected that there will be an increase of 77% in the number of low-human development index (HDI) countries by 2050, and hence there is a need to ensure equitable access to preventive, early-detection, radiotherapy (a 77% deficiency in low-HDI areas), and affordable treatments.

India challenges and variations

According to the National Cancer Registry Programme (NCRP) data on 43 registries, tobacco predominates in men (45% attribution) and infections in women (25%), and the Ayushman Bharat program is trying to close the gap but is experiencing challenges in implementation (Figure 2).

Angiogenesis

Angiogenesis refers to the process of formation of new blood vessels from existing ones, as shown in Figure 3. It is an essential biological process that gets critically deregulated in cancer. According to Hanahan and Weinberg, various cancer hallmarks, sustained angiogenesis is one such hallmark which leads to the supply of vascular oxygen for the rapid growth of the tumor and the spread of metastasis. The vascular system of a tumor allows nutrient, oxygen, and immune cell transfer and is regulated by pro- and anti-angiogenic factors working in balance [5,6].

Around 40 years ago, the discovery of the vascular permeability and angiogenesis-promoting factor led to the identification of VEGF family ligands and receptors (VEGFRs). The VEGF/VEGFR axis is essential for angiogenesis and is recognized as a primary mediator of tumor blood vessel development [7,8].

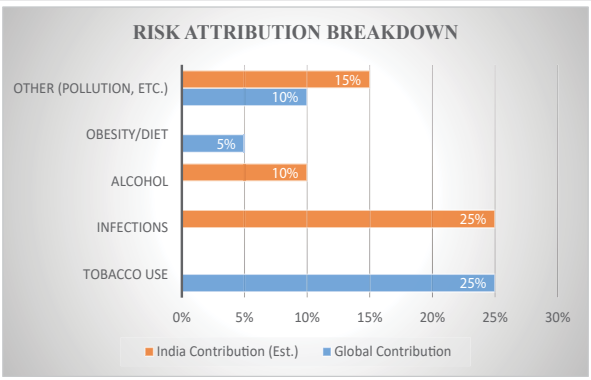


Figure 2: Risk Attribution Breakdown.

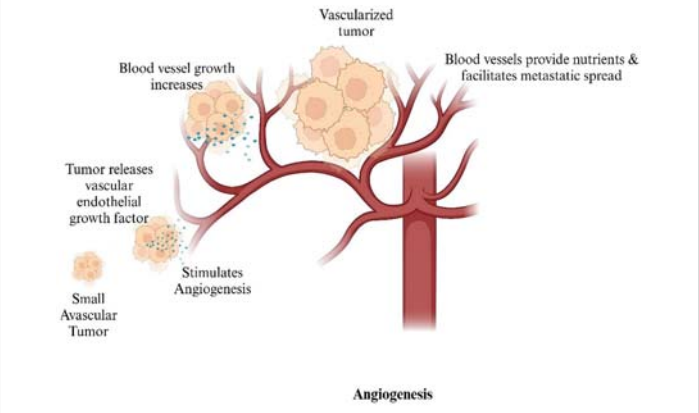


Figure 3: Tumor angiogenesis.

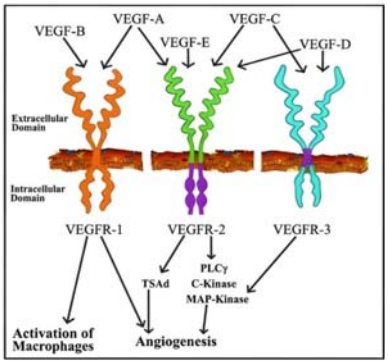


Figure 4: Types of VEGFR receptors.

The tumor angiogenic pathways function through diverse mechanisms, including sprouting angiogenesis, intussusceptive angiogenesis, vascular co-option, vascular mimicry, and glomeruloid angiogenesis, which are normally activated by varied angiogenic stimulators and their receptors [9,10]. Among the three main VEGF receptors, VEGFR-1, VEGFR-2, and VEGFR-3, as shown in the given (Figure 4), VEGFR-2 emerges as one of the key and critical mediators in tumor angiogenesis and is recognized as a major therapeutic target for combating the angiogenesis phenomenon [11,12].

The growth, survival, and metastasis of solid tumors depend on angiogenesis. Moreover, VEGFR-2, which is the receptor for VEGF, is overexpressed in many human solid tumors. Thus, it makes VEGFR-2 an attractive target for anti-cancer therapy. The protein VEGFR-2 is involved in tumor angiogenesis, and its high expression in a variety of tumor types has made it a target for anticancer therapy [13,14]. VEGFs are vascular endothelial growth factors that are responsible for directing angiogenesis and vasculogenesis. VEGFR-2 is the receptor of VEGF and during various physiological reaction it regulate response of the receptor. VEGF is mainly expressed in endothelial cells and performs cell differentiation, cell proliferation, migration, and survival [15].

VEGFR-2: Molecular architecture and clinical validation

VEGFR-2 is a receptor tyrosine kinase that mediates the effect of VEGF in angiogenesis, as the major receptor of VEGF. It is also called KDR (Kinase insert Domain Receptor) or Flk1. Receptor tyrosine kinases are widely conserved molecules ranging from a prokaryote to man, which take an active part in the phosphorylation of the tyrosine residues in the proteins, resulting in alterations in protein function. Deregulation of kinases due to mutation and transcriptional or post-translational modifications ultimately leads to the onset of pathological conditions, including cancer [16,17]. Among the various kinases, the VEGF/VEGFR-2 signaling cascade is an important target to develop novel small-molecule inhibitors for the therapy of abnormal angiogenesis associated with cancer. Due to advances in the knowledge of the catalytic domain and DFG-motif (Aspartate-Phenylalanine-Glycine) region, selective DFG-in (type I) and DFG-out (type II) VEGFR-2/KDR inhibitors were successfully developed, and some are in different phases of clinical trials. The DFG-out (inactive) conformation has significant advantages over the DFG-in (active) conformation concerning the affinity of ATP at the catalytic domain [18,19].

The clinical validation of VEGFR-2 as a therapeutic target is evidenced by multiple FDA-approved inhibitors. Several anti-angiogenic drugs, like ramucirumab, sunitinib, axitinib, and sorafenib, showing good survival rates, have been developed and FDA-approved against VEGFR-2 [20,21].However, clinical application of available VEGFR-2 inhibitors has been challenged by limited efficacy and a wide range of side effects, potentially due to inadequate selectivity for VEGFR-2. Analysis of residual kinase activity of a panel of 270 kinases showed that highly selective VEGFR-2 inhibitors displayed greater selectivity compared with reference inhibitors, highlighting that toxicities associated with available VEGFR-2 inhibitors are thought to be partly due to their effects against kinases other than VEGFR-2 [22].

The clinical utility of VEGFR-2 inhibition has been firmly established through decades of controlled trials, with approved agents now spanning multiple tumor types and lines of therapy. Among the small-molecule inhibitors, sorafenib holds particular historical significance as one of the earliest multi-kinase agents to demonstrate survival benefit in solid tumors, earning regulatory approval for unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and radioiodine-refractory differentiated thyroid carcinoma [23]. Sunitinib, similarly broad in its kinase coverage, extended this paradigm by showing meaningful progression-free survival gains in advanced renal cell carcinoma and subsequently in imatinib-resistant gastrointestinal stromal tumors and progressive pancreatic neuroendocrine tumors, establishing multi-targeted VEGFR inhibition as a viable first-line strategy in these settings [24]. Axitinib emerged as a more selective second-generation agent, designed specifically to address the shortcomings of earlier inhibitors; it is now standard of care for advanced renal cell carcinoma following failure of at least one prior systemic regimen, with particular benefit

observed in patients whose disease progressed on sunitinib or cytokine-based therapies [25]. Pazopanib, with clinical outcomes comparable to sunitinib in treatment-naive renal cell carcinoma, extended the therapeutic reach of VEGFR-2 blockade into soft tissue sarcomas refractory to prior chemotherapy, demonstrating that anti-angiogenic strategies are not exclusively confined to epithelial malignancies [26]. Lenvatinib, a structurally distinct inhibitor with a broader receptor kinase profile encompassing VEGFR-1/2/3, FGFR1–4, RET, KIT, and PDGFRα, has since been approved across radioiodine-refractory thyroid cancer, unresectable hepatocellular carcinoma, and advanced renal cell carcinoma in combination regimens with everolimus and pembrolizumab, underscoring the expanding role of VEGFR-targeted agents within immuno-oncology combinations. Cabozantinib introduced a mechanistically important refinement by simultaneously targeting VEGFR-2, MET, and AXL — receptor axes that are frequently co-activated during acquired resistance to first-generation anti-angiogenic therapy — and has demonstrated efficacy in advanced renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer following prior treatment [27]. Beyond small molecules, ramucirumab, a fully human monoclonal antibody directed against the extracellular ligand-binding domain of VEGFR-2, has validated receptor-level blockade as a distinct and effective approach, with approvals spanning gastric and gastro-oesophageal junction adenocarcinoma, metastatic non-small cell lung cancer, colorectal cancer, and hepatocellular carcinoma [28]. Taken together, the patient populations deriving the most consistent benefit from VEGFR-2-directed therapy include those with clear-cell renal cell carcinoma histology, tumors characterized by elevated VEGF/VEGFR-2 pathway activity, and patients whose disease has progressed beyond first-line cytotoxic or targeted regimens — a clinical reality that underscores the urgent need for structurally novel inhibitors capable of improved selectivity and a more favorable tolerability profile. It is precisely against this backdrop that the rational development of thiazole-based VEGFR-2 inhibitors acquires its clinical significance.

The 1,3,4-Thiadiazole Scaffold in Drug Discovery: The impact of heterocycles cannot be understated. Medicinal chemistry contains numerous drug molecules based on heterocyclic structures. In fact, 75% of the drug molecules approved by the FDA and still available on the market contain heterocycles. Over the next ten years, a far larger proportion of novel drugs that will incorporate nitrogen-containing heterocyclic structures is forecasted. Five-membered heterocycles with two heteroatoms, mainly nitrogen and sulphur, have gained a lot of attention for their biological properties and good drug-like properties [29,30].

The 1,3,4-thiadiazole scaffold has emerged as a privileged moiety in cancer drug discovery due to its mesoionic character, structural diversity, and molecular pharmacology. Notably, the N-N-C-S motif and sulfur atom of thiadiazole significantly contribute to VEGFR-2 binding through key molecular interactions. A systematic analysis of different publications from the last decade led to the extraction and evaluation of thiazole-based VEGFR-2 inhibitors, with chemical space, structure-activity relationships as shown below (Figure 5), substitution patterns, selectivity, toxicity, and essential binding interactions (ATP or allosteric site) with VEGFR-2 being critically examined [31,32].

The chemistry of 1,3,4-thiadiazole is one of the most interesting scaffolds for synthesizing new drug molecules due to its numerous pharmacological activities. Several modifications in the thiazole ring have been made, proving it to be more potent and highly effective with a less toxic scaffold for various biological applications [33]. During recent years, small molecules containing five-member heterocyclic moieties have become the subject of considerable growing interest for designing new antitumor agents, with 1,3,4-thiadiazole being one of [34,35].

Rationale, scope, and organization

This comprehensive review addresses the critical need for selective and efficacious VEGFR-2 inhibitors by systematically analyzing recent advances in thiazole-based inhibitor development. The review is structured to give: thorough coverage of VEGFR-2 structural biology, signaling pathways, and role in cancer, in-depth analysis of 1,3,4-thiadiazole chemistry, synthetic strategies and structural diversity, a systematic overview of recent reports of thiadiazole-based VEGFR-2 inhibitors including design strategies, synthetic pathways, and biological testing, and extensive structure-activity relationship investigations [36,37]. Extensive cytotoxicity studies across various cancer cell lines with selectivity studies; mechanistic studies such as apoptosis pathways, cell cycle regulation, and anti-metastatic effects; future outlook and translational prospects [38].

VEGFR-2: Structural biology, signaling mechanisms, and cancer biology molecular architecture and structural features of VEGFR-2

The conserved three-dimensional structure of receptor

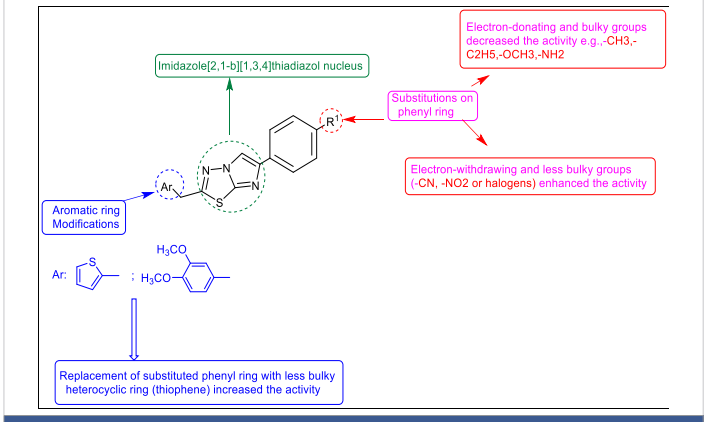


Figure 5: SAR of thiadiazole.

tyrosine kinases (RTKs) has been observed in prokaryotes to humans and actively participates in the phosphorylation process of tyrosine residues in proteins, which results in the alteration of protein function. The human genome encodes two kinds of tyrosine kinases: non-receptor tyrosine kinases (NRTKs) and receptor tyrosine kinases (RTKs), with VEGFR-2 belonging to the RTK superfamily [39,40].

VEGFR-2 is a receptor that regulates the process of vasculogenesis and angiogenesis through catalytic receptor tyrosine kinases. The structure of the protein has three major structural domains. They include an extracellular ligand-binding domain having seven immunoglobulin (Ig)-like domains (D1-D7), a single-pass transmembrane helix, and an intracellular segment with the tyrosine kinase catalytic domain, as shown in the given figure (Figure 6) [41,42]. According to the research, D2 and D3 are the primary binding sites for VEGF-A, and the ligand with a high affinity binds to it via a sandwich-like molecular structure [43-45].

The intracellular tyrosine kinase domain contains the ATP-binding site, activation loop, and multiple tyrosine residues that undergo autophosphorylation upon receptor activation. In the catalytic domain, between the front and back cleft, a smaller gatekeeper residue (Val916) is present; therefore, selectivity against VEGFR-2 could be precisely achieved [46,47]. This structural feature distinguishes VEGFR-2 from many other kinases that possess larger gatekeeper residues, creating opportunities for developing selective inhibitors [48,49].

The DFG motif, consisting of Asp-Phe-Gly residues, serves as a molecular switch controlling the kinase activation state. Small molecule first-generation type I, DFG-in, and second-generation type II, DFG-out, VEGFR-2 inhibitors exhibit clinical benefits in the treatment of aberrant angiogenesis associated with cancer [50,51].

VEGF-mediated VEGFR-2 activation and signal transduction

The VEGFs and their VEGFRs (receptors) have critical roles in vasculogenesis and angiogenesis. Angiogenesis is a major mechanism involved in many physiological and pathological processes. It plays an important role in the proliferation, migration, and survival of endothelial cells, which further leads to tubulogenesis and finally the formation of vessels. The VEGF/VEGFR-2 system precisely controls the signaling cascade pathways in this series [52,53].

The VEGF binding to the IgD2 and IgD3 domains of VEGFR-2 induces the dimerization of the receptor, subsequently causing activation and trans-autophosphorylation of the tyrosine kinase, and then initiating intracellular signaling cascades. Finally, the VEGF-activated VEGFR-2 stimulates and mediates a variety of signaling transduction, biological responses, and pathological processes in angiogenesis [54,55].

Several crucial phosphorylated sites within the VEGFR-2 intracellular domains mediate several key signaling processes. Tyr801, Tyr951, Tyr1175, and Tyr1214 in the VEGFR-2 intracellular domains mediate key signaling processes including PLC-PKC, TSAd-Src-PI3KAkt, SHB-FAK-paxillin, SHB-PI3K-Akt, and NCK-p38-MAPKAPK2/3 pathways [56]. Individual phosphotyrosine sites recruit their respective effector proteins, forming a complex signaling network, which coordinates various cell responses necessary in angiogenesis [57].

The process of angiogenesis causes cancer formation. Scientists study the PI3K pathway, which is a signaling pathway based on inositol phospholipids, as shown in the given figure (Figure 7). The signaling pathway known as PI3K/AKT/mTOR is quite conserved and is found in eukaryotes. It is involved in cell survival, growth, and cell cycle progression[58,59].. Through analyzing the molecular structure and signaling pathways of VEGFR-2, a VEGFR-2-targeted therapeutic strategy should be considered for the treatment of VEGF/VEGFR-2-associated diseases through blocking the signaling pathways, inhibiting the expression of genes, blocking the binding of ligands and receptors, and preventing the proliferation, migration, and survival of vascular endothelial cells expressing VEGFR-2 [60-62].

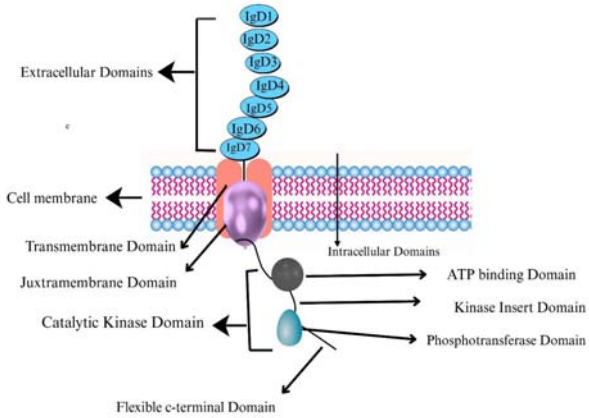


Figure 6: Molecular architecture of VEGFR-2.

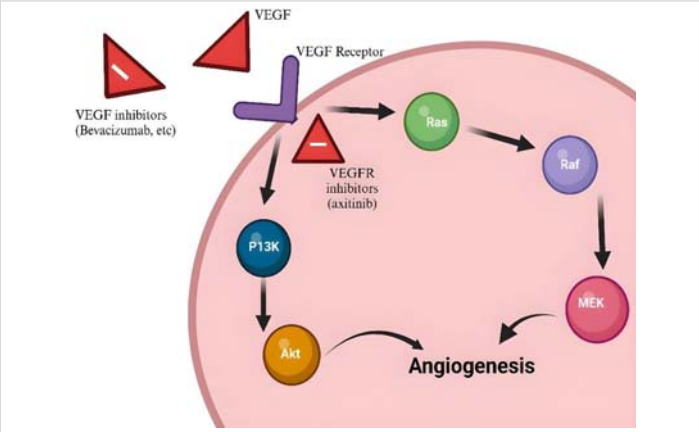


Figure 7: VEGFR activation and signal transduction.

Tumor angiogenesis and VEGFR-2 signaling represent critical processes in cancer progression. The tumor angiogenic pathways function in diverse mechanisms via sprouting angiogenesis, intussusceptive angiogenesis, vascular co-option, vascular mimicry, and glomeruloid angiogenesis, which are normally activated by varied angiogenic stimulators and their receptors intertwined to give rise to specialized signaling pathways [63,64].

VEGFR-2 is an important receptor that mediates tumor angiogenesis and has been estimated as an important therapeutic target. Numerous tumor types are observed for the widespread expression of vascular endothelial growth factor receptor 2 (VEGFR2), which regulates tumor angiogenesis. VEGFR-2 on cancer cells drives tumor angiogenesis to sustain tumor growth [65-67].

The hypoxic tumor microenvironment further upregulates VEGF expression through HIF1 activation, creating a pro-angiogenic feedback loop. Hypoxia is a common feature of solid tumors and develops because rapid growth outstrips oxygen supply and impaired blood flow due to the formation of abnormal vessels. Hypoxia can activate angiogenesis, thereby enhancing invasiveness and risk of metastasis, increasing survival of tumor cells, and suppressing anti-tumor immunity while hampering therapeutic response [68,69].

In pancreatic cancer, VEGF levels correlate with disease stage, tumor burden, and survival. Nevertheless, the efficacy of anti-VEGFR-2 therapies (tyrosine kinases, monoclonal antibodies) is limited due to the emergence of resistance mechanisms through the activation of other vascularization pathways. According to experts, the emergence of acquired resistance remains a major obstacle restricting the broad clinical success of molecular targeted therapies [70-72].

As a result of exposure to molecular targeted agents, VEGFR-2 expression gets induced, indicating the significance of VEGFR-2 signaling in molecular targeted therapy for cancer patients. Combination treatment of EGFR-TKIs and VEGFR-2 inhibitors may help overcome EGFR-TKI resistance. The importance of creating more selective and effective VEGFR-2 inhibitors is highlighted by these findings, as it may help overcome resistance [73].

Clinical validation and limitations of current VEGFR-2 inhibitors

More than a dozen approved drugs demonstrate the clinical validation of VEGFR-2 as a therapeutic target. The introduction of sorafenib in 2005 has seen approval of drugs targeting the VEGF/VEGFR pathway for roughly 20 solid tumor types, normally with combination therapy. The following compounds (2a-2d series) are multi-kinase inhibitors: Sunitinib, Pazopanib, Axitinib, Regorafenib, Cabozantinib, and Lenvatinib, as shown in the given figure (Figure 8) [74].

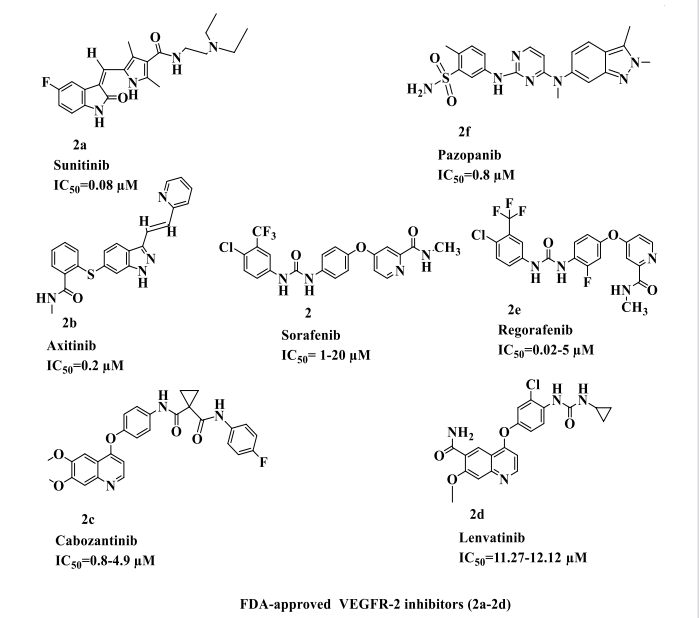


Figure 8: FDA-approved VEGFR-2 inhibitors (2a-2d).

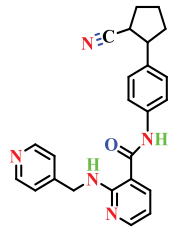
Rivoceranib is a medication that inhibits a certain critical process in our body. The ANGEL study evaluated the effects of rivoceranib in patients with advanced or metastatic gastric or gastroesophageal junction cancer as a 3rd-line or 4th-line therapy. In patients treated with rivoceranib, PFS Progression-Free Survival), ORR(Objective Response Rate), and DCR Disease Control Rate) were all enhanced compared to placebo, and there was a prespecified 4th-line OS(Overall Survival) benefit as shown in the given (Figure 9) [75,76].

Despite clinical success, several challenges limit the therapeutic potential of current VEGFR-2 inhibitors. The widespread side effects linked to these VEGFR-2 inhibitors—hypertension, epistaxis, proteinuria, and upper respiratory infection—motivate researchers to search for new VEGFR-2 inhibitors with better pharmacokinetic profiles. Toxicities associated with available VEGFR-2 inhibitors are thought to be partly due to their effects against kinases other than VEGFR-2 [77,78].

The survival benefit has been modest in most tumor types, and there are currently no biomarkers in routine clinical use for identifying which patients are most likely to benefit from treatment. Nevertheless, the ability of these agents to reprogram the immunosuppressive tumor microenvironment into an immunostimulatory one [79,80].

Chemistry, synthesis, and structural diversity of 1,3,4-thiadiazole derivatives

Five-membered heterocyclic systems incorporating nitrogen along with oxygen or sulfur atoms have gained substantial attention in recent years as privileged scaffolds in the rational design of novel anticancer agents, as shown in the given figure (Figure 10). Within this class, thiazole derivatives

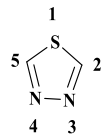


VEGFR-2 (KDR):
IC_{50} ~1 µM – 16 µM

3
Rivoceranib

N-(4-(2-cyanocyclopentyl)phenyl)-2-((pyridin-4-ylmethyl)amino)nicotinamide

Figure 9: Structure of rivoceranib.



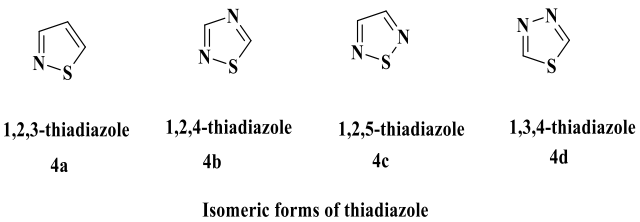
4
1,3,4-thiadiazole

Figure 10: Structure of 1,3,4-thiadiazole.

have emerged as particularly attractive pharmacophores due to their diverse biological activities. Recent literature is beginning to point out the important antitumor potential of compounds based on thiadiazole, with particular focus on compounds that have a single, unfused, 2,5-disubstituted thiadiazole ring. A number of these derivatives have shown significant cytotoxic effects, with some being even more active than known reference anticancer drugs in preclinical studies. Part of the explanation of the strong therapeutic utility of the thiazole nucleus is to be found in its Bioisosteric similarity to pyrimidine, a structural motif which occurs in three of the five DNA and RNA nucleobases. Due to this structural similarity, thiazole derivatives have the potential to bind to nucleic acid-related biological processes, and thus, they may interfere with DNA replication and other cellular activities that are critical to the cellular growth of cancer. This property highlights why thiazoles are promising molecular scaffolds in the creation of second-generation anticancer therapeutics [81-83].

Structurally, the thiazole nucleus is known to exist in various isomeric forms depending on the relative orientation of the nitrogen and sulfur heteroatoms in the five-membered ring. According to these position changes, there are four different isomeric forms of thiadiazole, namely 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, as shown in the following (Figure 11). The isomers have different electronic and steric properties, which may have a considerable impact on target selectivity and biological performance [84].

Such a wide range of diverse biological activities of thiazole derivatives can be explained by the fact that they have a high capacity to interact with a variety of biological



1,2,3-thiadiazole 4a | 1,2,4-thiadiazole 4b | 1,2,5-thiadiazole 4c | 1,3,4-thiadiazole 4d

Isomeric forms of thiadiazole

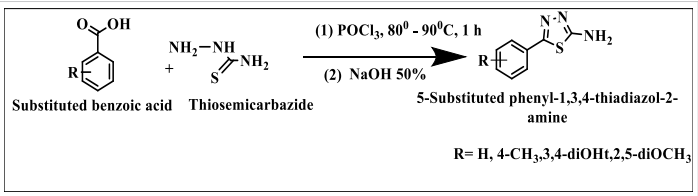
Figure 11: Distinct isomeric forms of thiadiazole.

targets via a broad range of non-covalent and coordination-based interactions. These are hydrogen bonding, van der Waals interactions, hydrophobic forces, as well as metal ion coordination that work together to make them bind together, as well as their pharmacological versatility. This type of interactional versatility allows thiazole scaffolds to interact well with enzymes, receptors, and nucleic acid-related targets [85,86].

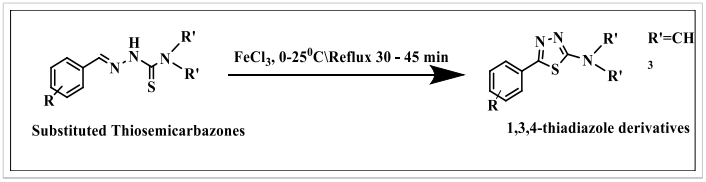
General synthetic methodologies and strategies

1,3,4-thiadiazole derivatives can be synthesized in a variety of ways, such as cyclization of linear organic derivatives. Various synthetic methods have been designed, and each has its benefits in terms of yields, reaction conditions, and the availability of starting materials [87,88].

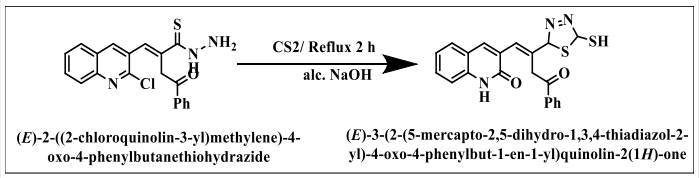
Cyclization of Acylthiosemicarbazides: This is done by reacting acylthiosemicarbazides with dehydrating reagents, including phosphorus oxychloride, concentrated sulfuric acid, or polyphosphoric acid, in the presence of heating conditions. The process of cyclization is carried out by the nucleophilic attack of the terminal nitrogen on the carbon atom of the carbonyl group, and then the removal of water to produce the thiadiazol ring [89].



Oxidative Cyclization of Thiosemicarbazones: Oxidative cyclization of thiosemicarbazones can be performed using reagents like ferric chloride, iodine, or oxidizing agents to form 1,3,4-thiadiazoles. The technique has the advantage of mild reaction conditions and the ability to tolerate different functional groups. [90].



Reaction of Hydrazides with Carbon Disulfide: Acyl or acid hydrazide reacts with carbon disulfide in the presence of a base (usually potassium hydroxide) and produces 2-mercapto1,3,4- thiadiazole. These thiol derivatives are very versatile intermediates that can be further functionalized by alkylation, acylation, or even oxidation reactions [91].



Green Chemistry Approaches: Modern synthetic strategies include the synthesis catalyzed by microwaves, solvent-free conditions, and recyclable catalytic systems that are recyclable. [86]. These techniques reduce the reaction time, yield higher yields, and are less polluting. An example is the naphthamide derivatives that were made using microwave-assisted synthesis in a four-step procedure to produce compounds that have strong VEGFR-2 inhibitory effects [92,93].

Molecular hybridization and multi-pharmacophore approaches

Molecular hybridization, combining two or more pharmacophoric units into a single molecular entity, has emerged as a powerful strategy for developing improved therapeutic agents. This approach leverages the complementary properties of different scaffolds to achieve synergistic effects, multi-target inhibition, or improved pharmacokinetic profiles [94,95].

New benzothiazole hybrids linked to thiadiazole moieties have been synthesized and evaluated as VEGFR-2 inhibitors. A new series 5a-5d of 2-aminobenzothiazole hybrids linked to 1,3,4-thiadiazole aryl urea moieties was synthesized as shown in Figure 12, with compounds 5a-5d series showing a strong impact on cancer cell lines. The most promising compounds exhibited nanomolar VEGFR-2 inhibition, demonstrating the potential of combining thiazole with other privileged scaffolds [96-98].

Novel quinazolines bearing 1,3,4-thiadiazole-aryl urea derivatives were designed as anticancer agents. A novel series 6a-6d of 1-(5-((6-nitroquinazoline-4-yl) thio)-1,3,4-thiadiazol-2yl)-3-phenylurea derivatives was synthesized to evaluate their cytotoxic potencies against multiple cancer cell lines, as shown in the given (Figure 13). Computational investigations, including molecular dynamics, frontier molecular orbital analysis, Fukui reactivity descriptors, and electrostatic potential surface studies, were performed to illustrate structure-activity relationships [99,100].

Expedition of sulfur-containing heterocyclic derivatives as cytotoxic agents in medicinal chemistry reveals that sulfur heterocyclic frameworks represent fundamental structures of diverse synthetic analogs with myriad therapeutic activities [101,102]. The incorporation of five and six-membered sulfur-containing scaffolds such as thiazoles, thiadiazoles, thiazolidinediones, and others has unveiled their effects through multiple mechanisms, including inhibition of tyrosine kinases, topoisomerase, tubulin, COX, DNA synthesis, and PI3K/Akt and Raf/MEK/ERK signaling pathways, as shown in the given (Figure 14) [103,104].

The selectivity index (SI) serves as one of the most informative parameters in evaluating whether a newly synthesized compound preferentially targets cancer cells over healthy tissue. In the studies reviewed here, SI is derived from the ratio of the cytotoxic concentration causing 50% reduction in normal cell viability (CC_{50}) to the half-maximal inhibitory concentration against the cancer cell line (IC_{50}),

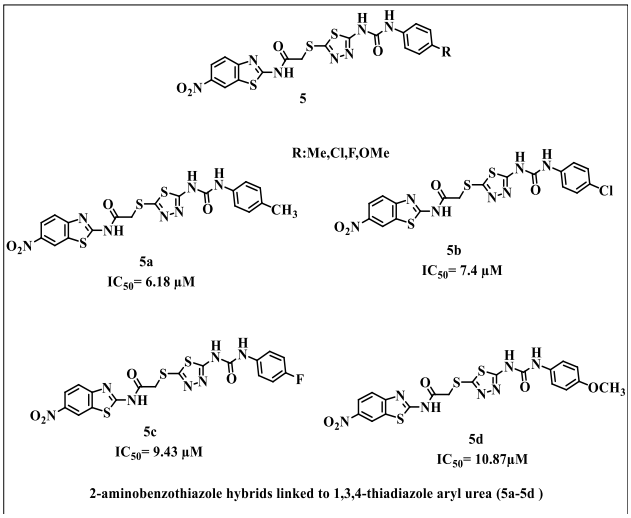


Figure 12: 2-aminobenzothiazole hybrids linked to 1,3,4-thiadiazole aryl urea moieties (5a-5d).

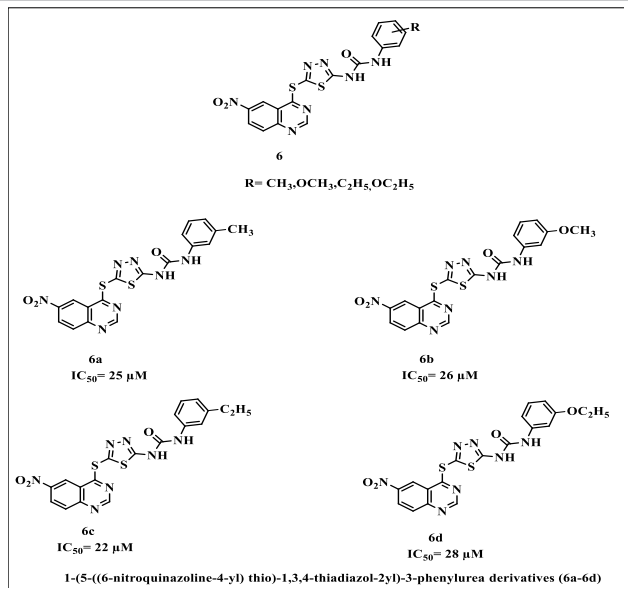


Figure 13: 1-(5-((6-nitroquinazoline-4-yl) thio)-1,3,4-thiadiazol-2yl)-3-phenylurea derivatives (6a-6d).

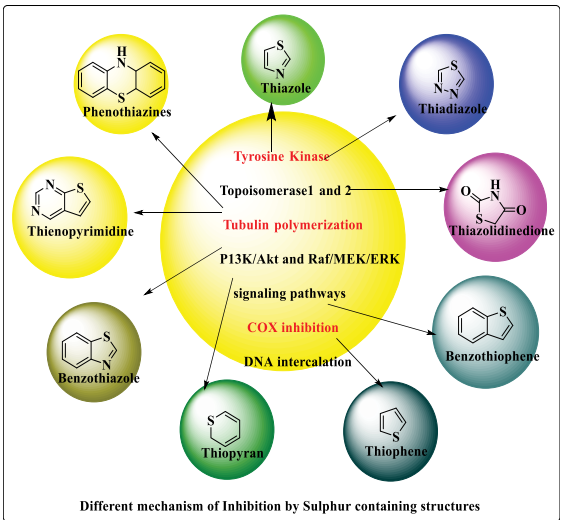


Figure 14: Different mechanisms of Inhibition by sulphur-containing structures.

expressed as SI = CC_{50} (normal cells) / IC_{50} (cancer cells) [105]. A compound yielding a high SI value is therefore one that kills cancer cells at concentrations far below those harmful to normal tissue — a distinction of considerable practical importance in drug development. Cell viability in both normal and cancerous populations is routinely assessed using the MTT assay, a well-established colorimetric method based on mitochondrial reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide [106]. Across the studies cited in this review, assay conditions are broadly consistent: cells are seeded at approximately 5×10^3 per well in 96-well plates, exposed to serial dilutions of the test compound (typically ranging from 0.001 to 100 µM) for 48 hours at 37°C under a humidified atmosphere containing 5% CO_2, after which MTT reagent is added and absorbance measured. Sorafenib, with a VEGFR-2 inhibitory IC_{50} of approximately 0.041 µM, is consistently used as the positive reference control, providing a meaningful benchmark against which the potency of novel thiazole derivatives can be judged. For normal cell cytotoxicity assessment, the choice of cell line varies by study but commonly includes WI-38 human embryonic lung fibroblasts, HDF human dermal fibroblasts, WISH human amnion epithelial cells, or MCF-10A non-tumorigenic breast epithelial cells [107]. As a general interpretive threshold, an SI greater than 2 is taken as evidence of meaningful selectivity toward cancer cells, while values exceeding 10 reflect a particularly wide therapeutic window. Where SI values are reported across the compounds discussed in this review, they are evaluated against these criteria to give an honest picture of each compound's safety profile relative to its antiproliferative potency.

Recent advances: Thiadiazole-based VEGFR-2 inhibitors (2020-2025) 2,3-dihydro-1,3,4-thiadiazole derivatives as potent VEGFR-2 inhibitors

The reduced form of the thiadiazole scaffold, 2,3-dihydro-1,3,4-thiadiazole, has shown exceptional promise as a core structure for VEGFR-2 inhibitor development. Discovery of new thiadiazole-based VEGFR-2 inhibitors through rational design, synthesis, cytotoxicity assessment, and apoptosis induction studies has yielded highly promising candidates [102,108-110].

The approved inhibitor sorafenib and others targeting vascular endothelial growth factor receptor-2 (VEGFR-2) have had off-target toxicities and resistance issues. As already established, the drug target is involved in cancer therapy. This study aimed at the design and development of novel thiazole-based vascular endothelial growth factor receptor 2 inhibitors that are more selective and safer. A series (7a-7e)of 2,3-dihydro-1,3,4-thiadiazole compounds was designed and synthesized [111].

In vitro cytotoxicity was determined against MCF-7, HepG-2, HCT-116, and normal WI-38 cells. Compound 7b was the most potent among the series of 7a-7e and selective with IC_{50} values of 9.49 µM for MCF-7 and 12.89 µM for HepG-2 and more than three selectivity indices. The compound caused over 70% apoptosis and dual-phase (S and G2/M) cell cycle arrest, as shown in Figure 15 [112].

VEGFR-2 inhibition was demonstrated with IC_{50} = 0.055 µM, comparable to sorafenib. Molecular docking, 200-ns molecular dynamics simulations, density functional theory calculations, and *in silico* toxicity profiling supported experimental findings. Computational studies confirmed stable binding at VEGFR-2 active sites, and compound 7b is a promising thiazole-based candidate with notable *in vitro* potency, selectivity, and mechanistic activity [113].

The anticancer, apoptotic, and VEGFR-2 inhibitory design and synthesis of thiadiazoles led to the discovery of remarkably active compounds. VEGFR-2 inhibitors are important in the treatment of cancer as they inhibit tumor angiogenesis. The

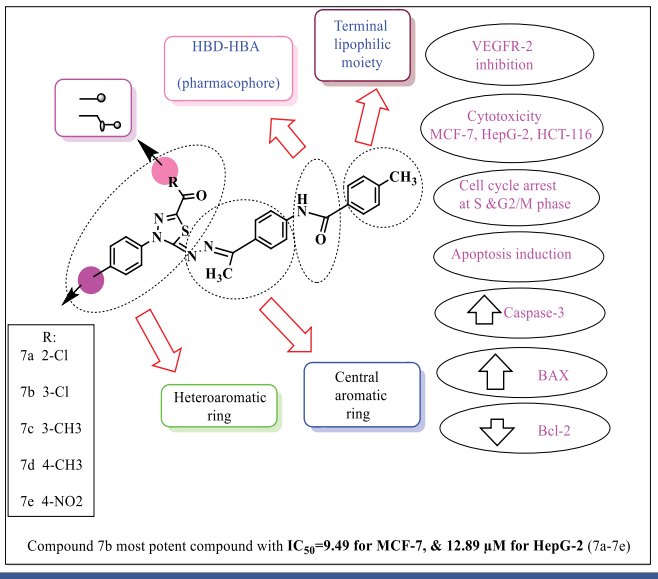


Figure 15: 2,3-dihydro-1,3,4-thiadiazole (7a-7e).

synthesized compounds were screened for antiproliferative activity against human cancer cell lines (HCT-116, MCF-7, and HepG-2) and WI-38 as normal cells using sorafenib as a reference drug [114].

The compound 8(4,5-dihydro-1,3,4-thiadiazole) was the most potent anti-proliferative compound tested and displayed strong VEGFR-2 inhibition with an IC_{50} of 41.51 µM, more potent than sorafenib, IC_{50} =53.32 µM. The work showed that 8 slowed MCF-7 cells in their cell cycle analysis at the G2 phase. The low level of apoptosis (2%) was increased with an IC_{50} of 700 µM after 48 h incubation, 53%, and associated with a greater than 12-fold increase in Bax/Bcl-2 ratio and activation of caspase-8/9. Moreover, 8 decreased the wound closure of MCF-7 cells to 5.28%, indicating strong anti-metastatic properties shown in the given (Figure 16) [115].

Dual BRaf/VEGFR-2 inhibitory thiadiazoles

The development of dual-target inhibitors represents an advanced strategy in cancer therapy, addressing multiple oncogenic pathways simultaneously. New 1,3,4-thiadiazole-based dual BRaf/VEGFR-2 inhibitors with potential anti-breast cancer activity have been developed. This study reported the design, synthesis, and biological evaluation of a novel series 9a-9f of 1,3,4-thiadiazole-based derivatives as dual BRaf/VEGFR-2 kinase inhibitors with potential anticancer activity. Among the whole series 9a-9f synthesized compounds, 9b emerged as the most potent candidate, exhibiting strong cytotoxicity against MDA-MB-231 and MCF-7 breast cancer cell lines (IC_{50} = 9.66 and 15.83 µM, respectively), with minimal toxicity toward normal WI-38 and WISH cells, reflected by favorable selectivity indices as shown in Figure 17. Compound 9b, featuring a unique structural assembly of a 2,3-dihydro-1,3,4-thiadiazole core, para-methoxyphenyl group, and sulfonamide-linked methylpiperidine moiety, exhibited superior dual-inhibitory activity with IC_{50} values of 0.75 µM for BRaf and 58.13 µM for VEGFR-2. Flow cytometry and gene expression analysis revealed that the compound induces G1-phase cell cycle arrest and promotes apoptosis through upregulation of BAX and caspases-8/9, with downregulation of Bcl-2. Structure-activity relationship analysis indicated that substitution with electron-donating groups enhanced cytotoxic potency. Molecular docking and molecular dynamics simulations confirmed stable binding to active sites, supported by Glide scores (-25.47 and -31.64 kcal/mol) and MMGBSA energies, while DFT(Density Functional Theory) calculations further validated the compound's electronic stability and reactivity [116].

Identification of benzothiazoles bearing 1,3,4-thiadiazole as antiproliferative hybrids targeting VEGFR-2 and BRAF kinase yielded compounds (10a-10f) with exceptional properties, demonstrating remarkable cytotoxicity with IC_{50} values ranging from 3.58 to 15.36 µM against three cancer cell lines, showing IC_{50} values of 38.77-66.22 µM against normal cell lines, significantly safer than sorafenib, as shown in Figure 18. Compound 10f exhibited the capacity to Inhibit both BRAF and VEGFR-2 enzymes with IC_{50} values similar to sorafenib (0.071 and 0.194 µM, respectively) and caused G2-M- and S-phase cycle arrest as shown in Figure 18 [117].

The new thiazole derivatives produced as VEGFR-2 inhibitors with anticancer and proapoptotic activities, out of which compound 10f was produced, which demonstrated cytotoxic activity against MCF7 breast cancer cells (IC_{50}: 6.13 µM) higher than that of sorafenib (IC_{50}: 7.26 µM). The compound has potent VEGFR-2 inhibition (IC_{50}: 40.65 µM), more potent than sorafenib (IC_{50}: 53.32 µM). Apoptosis analysis revealed primarily late apoptosis or necrosis (21.81%), with treatment increasing expression of proapoptotic gene BAX (4.19 ± 0.34-fold) and suppressing antiapoptotic Bcl-2 (0.38 ± 0.02-fold),

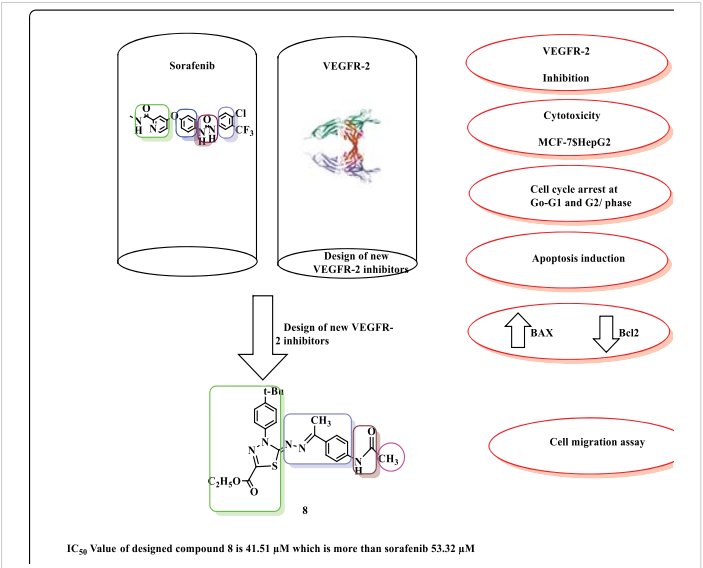


Figure 16: 4,5-dihydro-1,3,4-thiadiazole compound Promising Activity.

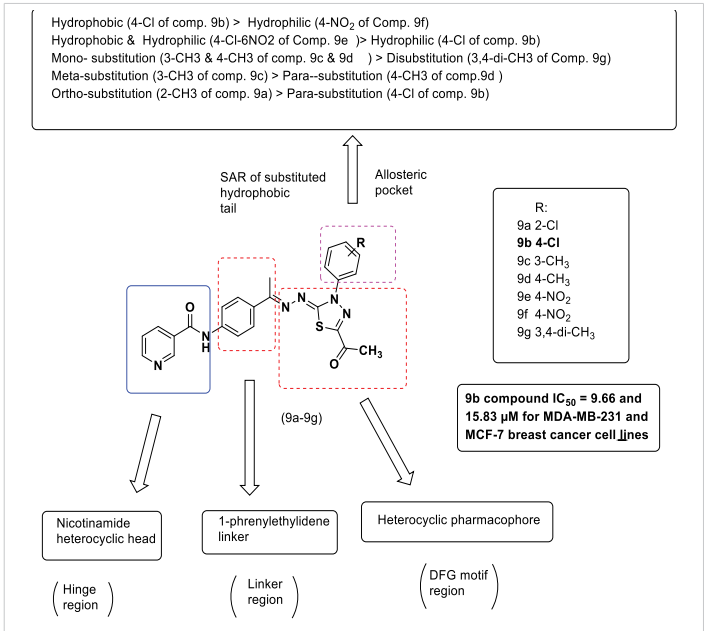


Figure 17: New 1,3,4-thiadiazole based dual BRaf/VEGFR-2 inhibitors (9a-9g).

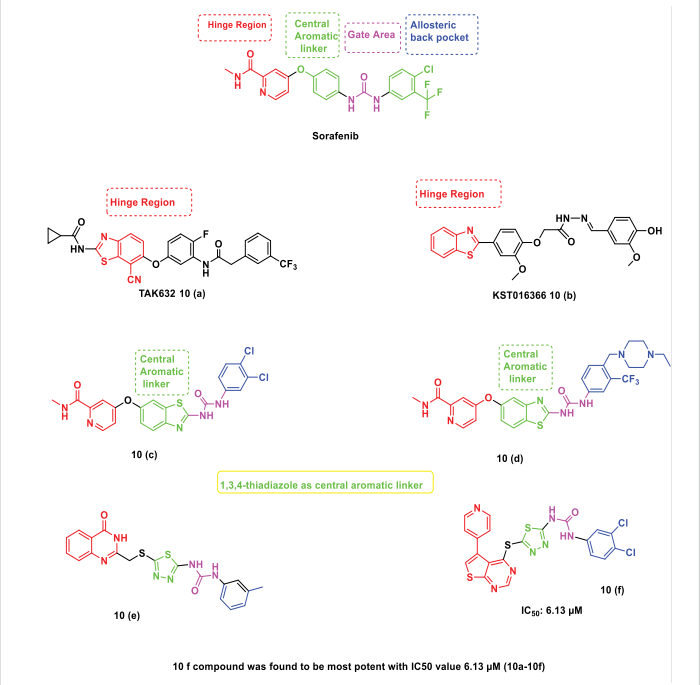


Figure 18: Benzothiazoles bearing 1,3,4-thiadiazole (10a-10f).

resulting in a dramatic 11.03-fold increase in BAX/Bcl-2 ratio. Caspase-8 and caspase-9 levels were elevated by 2.99- and 4.13-fold, respectively, confirming activation of both intrinsic and extrinsic apoptotic pathways [118-120].

Different biological activities of thiadiazole

1,3,4-Thiadiazole is a five-membered aromatic heterocycle containing two nitrogen atoms and one sulfur atom positioned at the 1, 3, and 4 positions of the ring. The thiazole scaffold is widely studied for its diverse pharmacological activities, exhibiting bioactivity as an anticancer agent toward human cancers, along with antibacterial, diuretic, antitubercular, and antifungal properties, as shown below (Figure 19) [117,121-123].

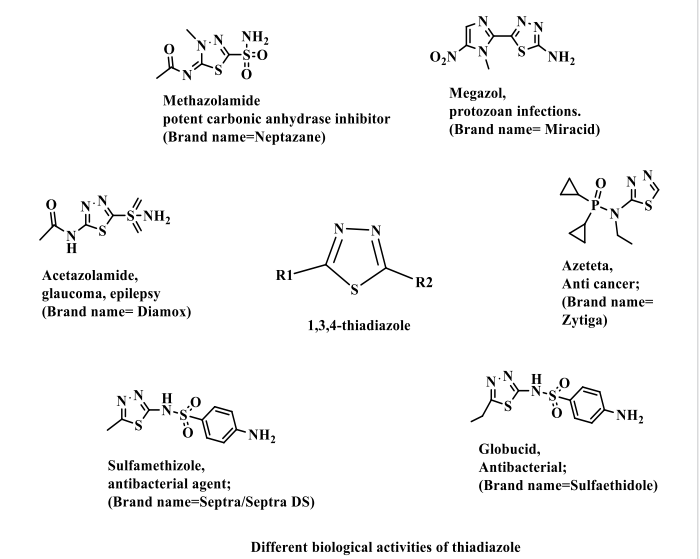


Figure 19: Different activities of thiazole.

The unique pharmacological profile arises from distinctive electronic properties. The thiazole ring consists of sulfur and nitrogen in such a fashion that electrons are free to move from one bond to another, rendering aromatic properties. On account of its aromaticity, reactive positions exist where donor-acceptor, nucleophilic, and oxidation reactions may take place [124-127].

The mesoionic character of the 1,3,4-thiadiazole ring involves delocalization of electrons across the heterocyclic system, with the sulfur atom playing a crucial role in electron distribution. The N-N-C-S motif and sulfur atom of thiadiazole significantly contribute to VEGFR-2 binding through key molecular interactions. The nitrogen atoms, with their lone pairs of electrons, serve as effective hydrogen bond acceptors, facilitating interactions with biological macromolecules [128,129].

The heteroatom used to form the thiadiazole ring is based on a benzene ring or a simple aromatic. Thiadiazole derivatives have been known to display diverse pharmacological activity, and several of their related compounds have multiple biologically active constituents and various applications that have been clinically approved. In recent years, several biologically active thiazole and bisthiazole derivatives have been reported in the literature due to their great medicinal importance [130-132].

Conclusion

The overall discussion of thiazole-based VEGFR-2 inhibitors that have been developed in the last five years shows conclusively that the 1,3,4-thiazole scaffold forms a privileged heterocycle that can be used to come up with selective, potent, and safe anticancer agents. The systematic screening of more than 151 thiazole analogs demonstrates some regular trends in nanomolar to sub-micromolar VEGFR-2 inhibitory potentials, strong cytotoxic action in a variety of cancer cell lines, and desirable selectivity indices that can differentiate between cancer and normal cells.

The existence of critical molecular determinants such as the essential N-N-C-S motif, optimal linker lengths (3-5 bonds), the significance of electron-donating substituents, and the strategic positioning of halogen atoms has been detected by studies of structure-activity relationships.

Consistent mechanistic evidence indicates that VEGFR-2 inhibitors that contain thiadiazole will induce apoptosis by activating both intrinsic and extrinsic pathways, disrupt cell cycle progression at numerous points, and prevent cancer cell migration and invasion. The multi-mechanistic profile observed across these thiazole derivatives, taken together with their generally favorable in vitro selectivity relative to established agents like sorafenib, makes a reasonable case for their continued investigation as VEGFR-2-targeted anticancer candidates. That said, it would be premature to draw firm conclusions from the current body of evidence alone. Virtually

all of the data discussed in this review originates from cell-based in vitro experiments, and while such findings are a necessary and valuable first step, they cannot by themselves reliably predict how a compound will behave in a living biological system. Factors such as metabolic stability, tissue distribution, off-target organ toxicity, and pharmacokinetic behavior — none of which are adequately captured by cell culture models — will ultimately determine whether the promising selectivity profiles reported here translate into genuine therapeutic benefit. Any comparison with sorafenib or other clinically approved agents in terms of safety or efficacy must therefore be treated cautiously at this stage, as the absence of head-to-head in vivo data leaves such comparisons necessarily incomplete. Moving forward, it will be important for researchers working in this area to bridge this gap by subjecting the most promising lead compounds to rigorous animal model studies, encompassing both efficacy assessment in tumor-bearing models and thorough pharmacokinetic and toxicological profiling. Only through such validation can the current in vitro promise of thiazole-based VEGFR-2 inhibitors be meaningfully translated into preclinical candidates worthy of further advancement.

The combination of medicinal chemistry, structural biology, computational modeling, and systems biology methods has enabled the discovery and optimization of thiazoles against the mitigation of VEGFR-2. With the continued development of studies, the compounds may prove to be of great benefit to cancer patients. They may be more selective, less toxic, and have the potential to overcome resistance mechanisms of therapeutic agents currently in use. Thiadiazole-based derivatives are supported by strong evidence according to the review. VEGFR-2 inhibitors are a promising class of next-generation anticancer agents worthy of further investment and clinical translation.

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