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Review Article

Insight into the Recent Advancement of 1,3,4 Oxadiazoles as Potential EGFR and Telomerase Inhibitory for Anticancer Activity

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ABSTRACT

Cancer is acknowledged as one of most perilous diseases, with significant challenges associated with existing anticancer therapies, including issues of drug resistance, narrow therapeutic windows, and the manifestation of severe and diverse adverse effects. Given the current state of oncology research, there is an urgent need to drive the development of innovative anticancer therapeutics that target unique molecular pathways to enhance the effective management of cancer. In this context, targeting the Epidermal Growth Factor Receptor (EGFR) and telomerase inhibition emerges as a promising strategy, with ongoing investigation focusing on 1,3,4-oxadiazole derivatives for this purpose. The findings of diverse researchers investigating these molecular frameworks have been systematically reviewed and analysed, culminating in a comprehensive summary. This review is centered on elucidating the Structure-Activity Relationships (SARs) and computational analyses of a range of 1,3,4-oxadiazole derivatives, specifically focusing on documented cytotoxicity, EGFR-TK inhibitory potential, and their efficacy as telomerase inhibitors in the context of anticancer activity. 1,3,4-Oxadiazole hybrids/derivatives with diverse substitutions exhibit efficacy as pharmacophores in achieving robust anticancer effects. Following a comprehensive literature survey, it is concluded that this review will undoubtedly furnish researchers with substantial insights to facilitate the design and synthesis of potent hybrids/derivatives capable of inhibiting EGFR and telomerase, thereby enhancing their therapeutic potential against cancer.

Keywords: 1,3,4-oxadiazole, Anticancer Activity, Cancer, EGFR-TK Inhibitors, Hybrids, Telomerase Inhibition, Telomerase.

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INTRODUCTION

According to Medicinal chemists who are engaged with anticancer researchs programs and 1,3,4-oxadiazoles will find the debate presented throughout to be a useful and essential resource. Cancer is a prime reason for early death in 134 countries in the world cancer entails aberrant cellular proliferation capable of metastasizing throughout the body, evolving from precancerous abnormalities to malignant tumors. Preventative measures can mitigate or eliminate exposure to risk factors by up to one-half.[1] Around 2.2 million cancer incidences were attributable to carcinogenic contamination in 2012.[2]

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Protein kinase inhibitors, alkylating agents, plant-derived compounds, and antimetabolites are chemotherapeutic drugs that help in cure of cancer.[3,4] Various molecular targets are exploited for the evolution of these antitumor agents. While chemotherapy remains pivotal in managing diverse cancer types, it is associated with substantial toxicity and the emergence of multidrug resistance against these agents.[5,6]

Heterocycles composed of nitrogen, mainly five-membered ring structures have captured interest because of their widespread occurrence in natural compounds. They are also present in many important parts of synthetic bioactive molecules.[7] Oxadiazoles have two nitrogen and an oxygen atom, which are an important structural category from a medical perspective.[8,9] Based on the arrangement of nitrogen atoms concerning oxygen atoms, it is classified as (a), (b) (c), and (d) shown in Figure 1. These motifs are regarded as biologically better pharmacophores because of their improved pharmacokinetics, demonstrate improved metabolic characteristics, enhanced water solubility, and reduced lipophilicity compared to alternative isomeric

oxadiazoles and the existence of the toxophoric linkage -N=C-O-.[10,11] 1,3,4 oxadiazoles can be easily synthesized and can bind up with different substituents in the various chemical reactions which may have high potential for having particular biological activity and support to important lead molecules for molecular stimulation.[12-14] Oxadiazoles display comprehensive activities with different substituents such as antibacterial,[15] vasodilatory,[16] AIDS,[17] antifungal,[18] anticonvulsant,[19] insecticide,[20] analgesic,[21] ulcerogenic,[22] plant growth regulatory,[23] anti-inflammatory,[24] hypolipidemic,[25] antitumor,[26] antimalarial,[27] CNS depressant,[28] antitubercular,[29] and antioxidant.[30] Not only therapeutic agents benefit but oxadiazoles can also have photo-stabilizing properties,[31] organic electroluminescent material[32] and fluorescent whiteners.[33] Some applications as the material of 1,3,4- oxadiazole derivatives fall under liquid crystal fields.[34] still tots of research required in this wonder moiety.

Raltegravir,[35] Tiodazosin,[36] Nesadipil,[37] Furamazole,[38] and Ziotentan,[39] are drugs which having 1,3,4-oxadiazole rings works as anticancer drugs (Figure 2). A known drug Setileuton (MK-0633) is used to cure respiratory disease by displaying strong 5-lipoxygenase activity, the 5 LO is also useful for treating cancer.[40]

Molecular Targets for 1,3,4-Oxadiazole Derivative

In the last few years, there has been outrageous research on anticancer agents and their development. Various molecular targets have been elucidated for 1,3,4-oxadiazoles such as encompassing vascular endothelial growth factor receptor (03), Endothelin receptor (ET1), Histone Deacetylase (HDAC), Glycogen Synthase Kinase-3 (GSK-3), Nuclear Factor κB (NF-κB), Methionine Aminopeptidase (MetAP), poly(ADP-ribose) Polymerase-1 (PARP-1), Thymidine Phosphorylase (TP), and Thymidylate Synthase (TS), telomerase, Focal-Adhesion Kinase (FAK), Epidermal Growth Factor Receptor (EGFR), etc.[41] Anticancer agents are divided into three categories. The first category includes chemotherapy drugs that obstruct DNA replication, the division of cells, mitosis, and topoisomerase inhibition. The second category comprises chemotherapy that particularly interacts with signaling intermediates, like tyrosine kinase and associated inhibitors. Finally, the third category of chemotherapy includes more sophisticated cancer treatments like PARP, HDAC, DNMTs, and proteasome inhibitors, in addition to others.[42]

Epidermal Growth Factor Receptor and Its Inhibitors

EGFR is a pivotal cell surface receptor that is pivotal in managing cell growth, multiplication, and survival.[43-45] It encompasses HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4), an integral part of the ErbB receptor family, all of which are tyrosine kinases. Activation of EGFR occurs upon binding with ligands like EGF and Transforming Growth Factor alpha (TGF-α).[46,47] EGFR initiates intracellular signaling cascades that regulate various cell processes once activated. EGFR overexpression or mutations have been implemented in the development and progression of various cancers, including head cancer, colorectal cancer, lung and neck cancer. Consequently, targeting EGFR has been a therapeutic strategy in cancer treatment. Activation of EGFR by EGF and TGF induces phosphorylation events that initiate a variety of intracellular signaling pathways, such as RAS, PI3K, and SFC. These signaling cascades promote cellular processes including proliferation, angiogenesis in tumors, cell motility, survival, and the upregulation of gene expression. as depicted in Figure 3.[48-50] There are several classes of EGFR inhibitors, including:

Monoclonal antibodies

These are engineered to interact with the extracellular domain of EGFR, thereby inhibiting ligand binding and subsequent receptor activation. Cetuximab and panitumumab are EGFR-targeting monoclonal antibodies and were initially cure of head cancer, colorectal cancer, and certain types of lung cancer.[51]

Tyrosine Kinase Inhibitors (TKIs)

It is type of targeted therapy. TKI targets the intracellular tyrosine kinase domain of EGFR and stops the phosphorylation and activation of downstream signaling pathways. They block some substances that slow the cell growth and proliferation process in cancerous cells. Gefitinib,[52] erlotinib,[53] and afatinib, etc are commonly used drugs for therapy having EGFR mutations and NSCLC in patients.[54] The main disadvantage is when TKIs are taken for a longer time, some cancer changes. When that happens, the process of slowing down the cell growth is no longer working due to TKI resistance being generated.

Dual EGFR and HER2 inhibitors

Some inhibitors affect both EGFR and HER2 receptors. An example is lapatinib, a dual inhibitor used to treat HER2-positive breast cancer. EGFR inhibitors have demonstrated considerable potential in various cancer types, especially in patients with specific EGFR overexpression or mutations.[55] However, these inhibitors can develop resistance over time, resulting in disease progression. Thus, ongoing research focuses on developing new inhibitors and combination therapies to counteract resistance and enhance treatment outcomes for cancer patients.

A variety of small molecules have been developed and evaluated as inhibitors of EGFR Tyrosine Kinase (TKIs). These compounds are categorized into various generations, such as the initial category (Erlotinib), which is attached to ATP-binding site of receptor reversibly. H- bonds must form with the amino acids Met 793 and Thr-790 located in the EGFR active site.[56] In the case of second-category kinase inhibitors like Neratinib, a covalent bond is created with the receptor's amino acid Cys797. However, because of the narrow therapeutic window, these chemicals are not very useful. The 3rd-category (Olmutinib) EGFR inhibitors form a hydrogen bond with Met793 and bind Cys797 covalently

and finally, 4th-category (EAI045) molecules bind with the allosteric site of the receptor.[57-62]

EGFR Gene

The EGFR gene, alternatively referred to as ERBB, HER1, mENA, ERBB1, PIG61, and NISBD2, is located on chromosome 7 at position p11.2, according to the GRCh38 genomic coordinates.[63-65] The transmembrane glycoprotein that the EGFR gene encodes comprises 31 exons.

EGFR TKIs Inhibitor Resistance

First and the foremost challenge in cancer treatment with EGFR-TKIs is the emergence of resistance. 1st-category medications are used to treat patients like Erlotinib and Gefitinib, they frequently develop resistance, often due to the T790M mutation, which reduces drug efficacy by weakening its influence with the ATP binding site. Second-category drugs like Afatinib and Dacomitinib aim to address this issue by incorporating a Michael acceptor to form a covalent bond with the Cys797 residue. However, these drugs are associated with significant side effects. 3rd-category EGFR inhibitors, such as Olmutinib and AZD9291, have been introduced to tackle these challenges.[66,67] Yet, during their clinical use, acquired resistance has reappeared. Primary resistance to 3rd-generation EGFR TKIs can arise through numerous mechanisms, including EGFR-driven amplification of ligands/receptors, mutations within the kinase domain's ATP site, and pathways not reliant on EGFR. These alternate pathways encompass changes in signaling components such as MET, FGFR, and IGF1R, alongside phenomena like phenotype conversion, EMT, and the shift to Small Cell Lung Cancer. Mutations in the ATP-binding site of the EGFR kinase domain directly weaken the binding affinity of EGFR inhibitors, reducing their effectiveness.[68,69]

Among the various resistance mechanisms, the tertiary mutation in the EGFR kinase domain poses a significant challenge. Several factors can contribute to primary resistance against third-generation EGFR TKIs. These include an increased production of ligands and receptors driven by EGFR, mutations in the ATP site within the kinase domain, and EGFR-independent pathways. These alternative routes encompass changes in signaling molecules such as MET, FGFR, and IGF1R, along with processes like phenotype conversion, Epithelial-Mesenchymal Transition (EMT), and the transformation to Small Cell Lung Cancer, which show potential in addressing the resistance issue. However, allosteric inhibitors have shown limited effectiveness.[70-72]

Overcoming Resistance of EGFR TKIS

EGFR TKIs Resistance is crucial in cancer treatment, and various approaches are being explored to tackle this obstacle.

Development of next-generation inhibitors-Researchers are currently engaged in the design and evaluation of next-generation EGFR inhibitors intended to target resistant mutations, such as the tertiary C797S mutation. These inhibitors are aimed at preserving or improving binding affinity, even when confronted with resistant mutations.[73]

Combination therapies-Pairing EGFR TKIs with either targeted therapies or conventional chemotherapy presents a hopeful strategy for overcoming resistance. This approach targets various signaling pathways concurrently, potentially averting or postponing the onset of resistance.[74]

Immunotherapy-Immunotherapeutic strategies, including immune checkpoint inhibitors, have demonstrated effectiveness in specific cancer types. Combining EGFR TKIs with immunotherapy may enhance antitumor immune responses and overcome resistance mechanisms.[75]

Exploring allosteric inhibitor-Despite facing obstacles, research persists on allosteric inhibitors focusing on alternative sites on EGFR. Although existing allosteric inhibitors may show restricted effectiveness, ongoing refinement of these compounds holds the potential for yielding more potent inhibitors capable of bypassing resistance mechanisms.[76,77]

Through the use of these various approaches, researchers seek to enhance patient outcomes. with EGFR-driven cancers by effectively overcoming resistance to EGFR TKIs.

Role of 1,3,4 oxadiazole Derivatives as an Anticancer Agent

The literature review indicates that various hybrid molecules with different structural cores, such as triazole-benzimidazole-chalcone,[78] benzimidazole-pyrazol,[79] chalcone benzimidazole,[80] quinazoline-chalcone,[81] thienoquinoline-2-carboxamide chalcone,[82] pyrazole-quinoline pyridine,[83] xanthine-chalcone,[84] 1,3,4-oxadiazolechalcones,[85] have been synthesized over time. These molecules have demonstrated significant inhibitory activity against EGFR-TK.

This review centers on documented 1,3,4-oxadiazole derivatives or hybrids serving as cytotoxic agents and EGFR inhibitors. These observations are bolstered by the structural representations of the least and most potent compounds, accompanied by their respective 50% Inhibitory Concentration (IC_{50}) values. Drawing insights from existing literature, our objective is to delineate the structural criteria crucial for the prospective advancement of cytotoxic agents and EGFR inhibitors.

Derivatives of 1,3,4-oxadiazoles as anticancer agent

1,3,4-oxadiazole compounds are characteristic heterocyclic substances known for their promising anti-cancer effects. They serve as potent bioisosteres of amides and esters, offering considerable pharmacokinetic benefits. This is attributed to the presence of the azole (-N=C-O-) group within the oxadiazole structure, which enhances lipophilicity and affects

the drug's capacity to reach its target through transmembrane diffusion.3,5-disubstituted derivatives of 1,3,4-oxadiazoles.

In 2011, a series of new 3,5-disubstituted 1,3,4-oxadiazole-2-thione derivatives were reported by S. Dash and co-workers and examined for their cytotoxic antitumor effects. Among these derivatives, Compound 1 is the most active with an inhibition rate of 73.9%, while Compound 2 is the less active with an inhibition rate of 52.2% (as depicted in Table 1). This investigation revealed substituent influence at the 5th position of the oxadiazole ring, whether electron-withdrawing or electron-donating, significantly impacted the anticancer potency. Compounds featuring substituents such as methyl, 2,4-dichloro phenyl groups, and hydroxyl exhibited notable antitumor effects. Furthermore, the availability of Cl atoms in the molecules amplifies the binding capacity of receptors.[86]

Substituted 1,3,4-oxadiazole derivatives

Ahsan *et al.* (2013) synthesized 10 analogs, out of these, two analogs were tested for their effectiveness against cancerous cells using a single-dose assay with 60 cell lines. Compound 3 (3, mean Growth Percent:95.37), featuring a 4-methoxyphenyl group at 5th position in the ring, exhibited stronger anticancer properties compared to compound 4 (4, mean Growth Percent:ss98.74), which had a 4-fluorophenyl group at the same position (as depicted in Table 1).[87]

1,3,4-oxadiazole with benzimidazole hybrid

Rashid *et al.* (2012) synthesized 25 variations of benzimidazoles incorporating an oxadiazole core. It is evaluated for its potential for *in vitro* anticancer activity. Among these, compound 5 (with a GI_{50} range of 0.797-17.8), featuring a substitution with 2,4-dichloro, is a promising main compound with significant growth inhibition activity (as illustrated in Table 1). This observation was made through a screening process involving five-dose level assay.

The examination of structure-activity relationships indicated that electron-donating groups, like -NH_2, positioned on the phenyl ring at the 5th position of the oxadiazole moiety, significantly impacted the anticancer activity. Moreover, on the 5th position of the oxadiazole ring, groups such as -$N(C_2H_5)_2$ and -O-C_6H_5 attached to the methyl group resulted in compounds having improved antitumor effects. Conversely, if electron-withdrawing groups are present diminished antitumor activity.[88]

1,3,4-oxadiazole Derivatives with substituted heterocycle

In 2012, Bondock and colleagues designed novel derivatives of 1,3,4-oxadiazole containing diverse pharmacophores and heterocyclic rings. Selected analogs were examined for their *in vitro* anticancer properties using the standard MTT method. Notably, Compound 6 emerged as the most potent member in this investigation, demonstrating significant efficacy against human HepG2 cells (with an IC_{50} of 12.4 μM), VERO cells (with an IC_{50} of 15.8 μM), and WI-38 cells (with an IC_{50} of 17.3 μM). Compound 7 exhibited considerable activity against HepG2 cells (with an IC_{50} of 21.2 μM) and moderate activity against MCF-7 cells (with an IC_{50} of 39.2 μM). On the other hand, Compound 8, containing a pyrazole ring, displayed the least potent activity with IC_{50} values ranging from 250.2 μM to 410.6 μM (as detailed in Table 1).[89]

1,3,4-Oxadiazole Derivatives with fatty acid analogs

Abdul *et al.* (2017) synthesized a new series of 5-long chain alkenyl/hydroxyalkenyl-1,3,4-oxadiazol-2-thiones. These analogs of fatty acids were subjected to cytotoxicity testing against various cancer cell lines using the standard MTT method. The results indicated medium to better activity for all compounds, and activity levels varying depending on the nature of fatty acid chain and the heterocyclic ring. Notably, Compound 9 contains a C10 terminal alkenyl fatty acid chain residue which is replaced at the 5-position of the 1,3,4-oxadiazol-2-thione, exhibited increases in potential against various human cancer cell lines (with IC_{50} values ranging from 08.94 to 35.32 μM).[90] Conversely, Compound 10 (with IC_{50} values ranging from 16.42 to 39.12 μM) shows least potent activity among the compounds tested (as outlined in Table 1).

1,3,4-Oxadiazole Derivatives with substituted pyridine

El-Sayed and co-workers (2019) reported a new series of 12 heterocycles oxadiazoles and all were analyzed for their COX-1 and COX-2 inhibitory activity. Nine out of twelve compounds

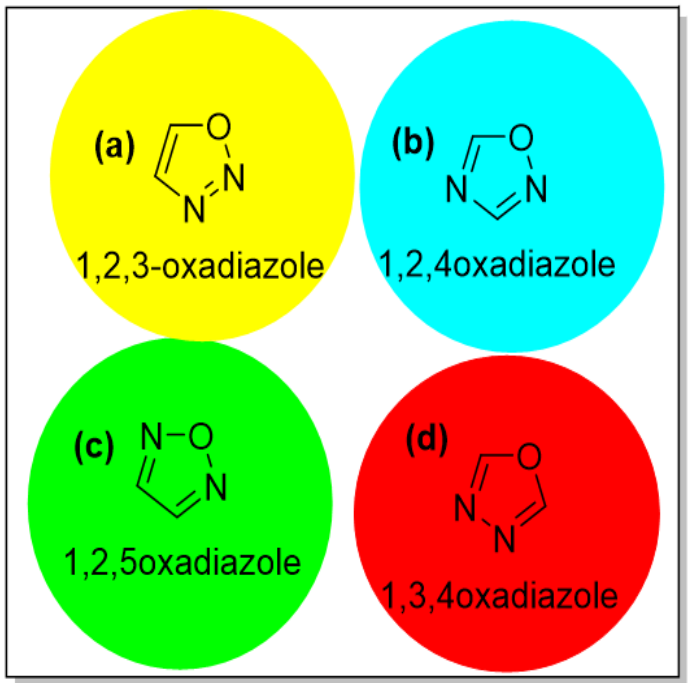
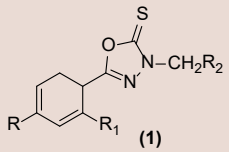
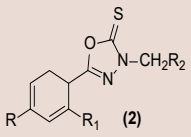
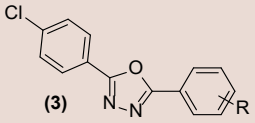
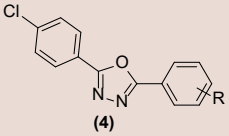
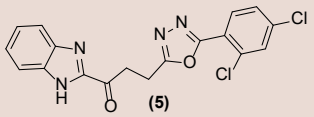
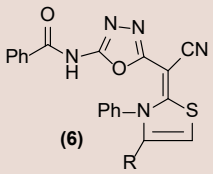
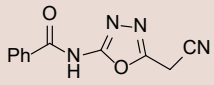
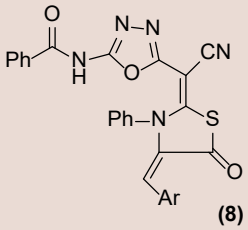
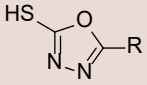
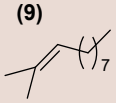
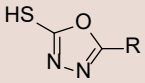
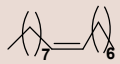
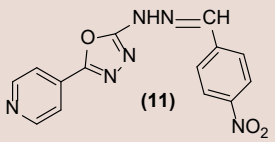
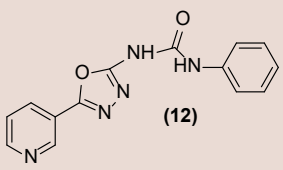
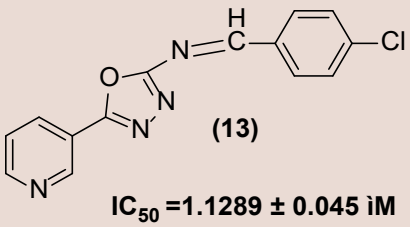


Figure 1: Regio-isomers of oxadiazoles.

Table 1: **1,3,4-oxadiazole derivatives with most potent and least potent structure, along with, along with their pharmacological effect and reference molecule.**

Sl. No.	Most Potent Derivative	Least Potent Derivative	Standard Used
1.	 (1) **R= -OH, R_1= -H, R_2= 2- amino pyridine (Tumor Inhibition= 73.9%)**	 (2) **R= -Cl, R_1= -Cl, R_2= - 2-Aminopyridine (Tumor Inhibition=52.2%)**	5-fluorouracil (TI_{50}= 93.0%) Structure
2.	 (3) **R= 4-methoxy (mean Growth Percent: 95.37)**	 (4) **R= 4-fluoro (mean Growth Percent: 98.74)**	--
3.	 (5) GI_{50}= 0.797-17.8		GI_{50}= 6.59
4.	 (6) **R= -Me (IC_{50}-12.4 iM-17.3 iM)**  (7) **(IC_{50}-12.4iM-17.3 iM)**	 (8) **Ar= 1.3-diphenyl pyrazol-4-yl (IC50-250.2iM-410.6 iM)**	5-fluorouracil: IC_{50}- 2.3µM-8.6 µM
5.	 (9) R=  **(IC_{50} = 08.94 -35.32 iM)**	 (10) R=  **= 16.42 -39.12 iM) (IC_{50}**	5-fluorouracil: IC_{50}= 2.78-8.91µM Doxorubicin: IC_{50}=2.35- 9.23 µM
6.	 (11) **Potent: IC_{50} =0.4123 ± 0.022 iM**  (12) **Most potent: IC_{50} =0.2757 ± 0.013 iM**	 (13) **IC_{50} =1.1289 ± 0.045 iM**	Erlotinib IC_{50}= 0.4178 ± 0.014 µM

2

tested for cytotoxic activity by MTT assay against renal cancer cell line. From those compounds, compounds 11,12 and 13 were tested against tyrosine kinase EGFR enzyme using kinase inhibitory assay. Compound 12 exhibited nearly double the efficiency compared to reference drug Erlotinib, with an IC_{50} value of 0.2757±0.013 µM. Among the compounds tested, Compound 11 demonstrated the highest potency, with an IC_{50} value of 0.4123±0.022 µM (as depicted in Table 1). It was observed that the 2nd position of the oxadiazole ring substitution with phenyl urea is crucial for enhanced activity against EGFR tyrosine kinase.[91]

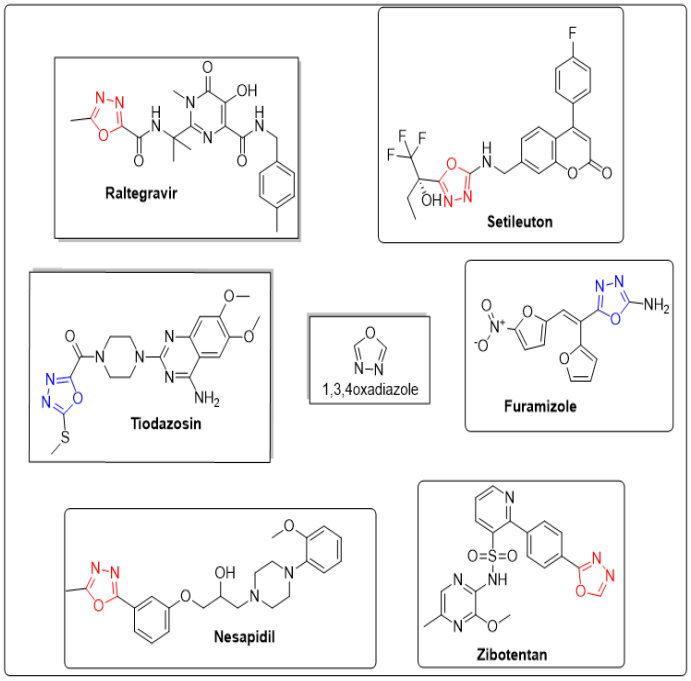


Figure 2: Drugs having 1,3,4-oxadiazole moiety.

Structural activity relationship of 1,3,4-Oxadiazole and its derivatives as EGFR inhibition

The basic structure of the 1,3,4-Oxadiazole and its derivatives plays an important role in the inhibition of EGFR and acts as a potential anticancer agent.

Telomerase Inhibitors

Telomerase is a specialized ribonucleoprotein present in mammalian cells, with a distinct role in maintaining and stabilizing telomeres, facilitating chromosomal integrity, and promoting cell proliferation.[92,93] Its function involves maintaining and replenishing telomere length through the addition of hexameric (TTAGGG) repeats, facilitating cell proliferation (Figure 5).[94-96] In cancer cells, activation of telomerase occurs, regulating telomere length. Reactivation of telomerase is prevalent in approximately 85% of advanced human tumors, indicating its significant role in tumor formation. Consequently, targeting telomerase has been suggested as a key approach for the progress of anti-cancer drugs.[97,98] In cancer cells, telomerase is reactivated through multiple routes, including heightened transcriptional activation of TERT and/or TER, reduction in transcriptional inhibitors of TERT, alterations in the TERT gene promoter region

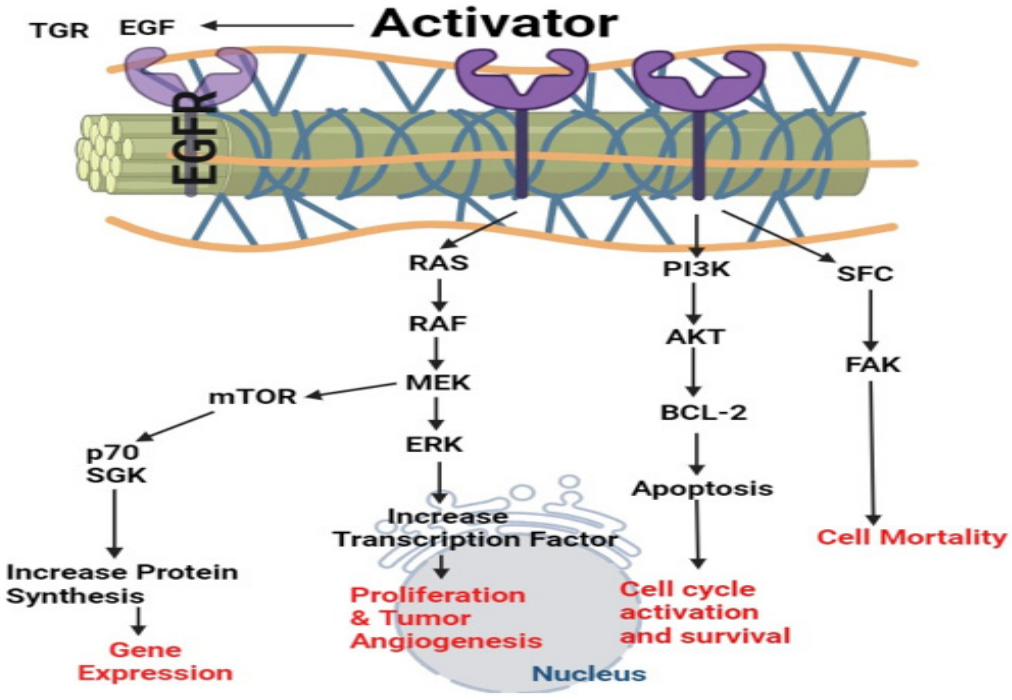


Figure 3: The role of EGFR and EGFR inhibitors in cancer.

Table 2: Components and Functions of Telomerase subunit.

Sl. No.	Subunit	Functions	References
1.	p-23	Facilitate the assembly of telomerase by efficiently folding a specific group of reverse transcriptases.	107
2.	hTERT	The rate-limiting part of telomerase also helps by using its own RNA template for DNA synthesis.	108
3.	Dyskerin	The role of ribosomal RNA involves converting uridine to pseudouridine through isomerization.	109
4.	hsp90	Assist in the formation of telomerase and enable increased telomerase function.	107
5.	hTERC	Work as a guide for DNA synthesis	110
6.	TEP1	Obtain and arrange telomerase substrates, hTR, hTERT, and other important regulatory factors.	111

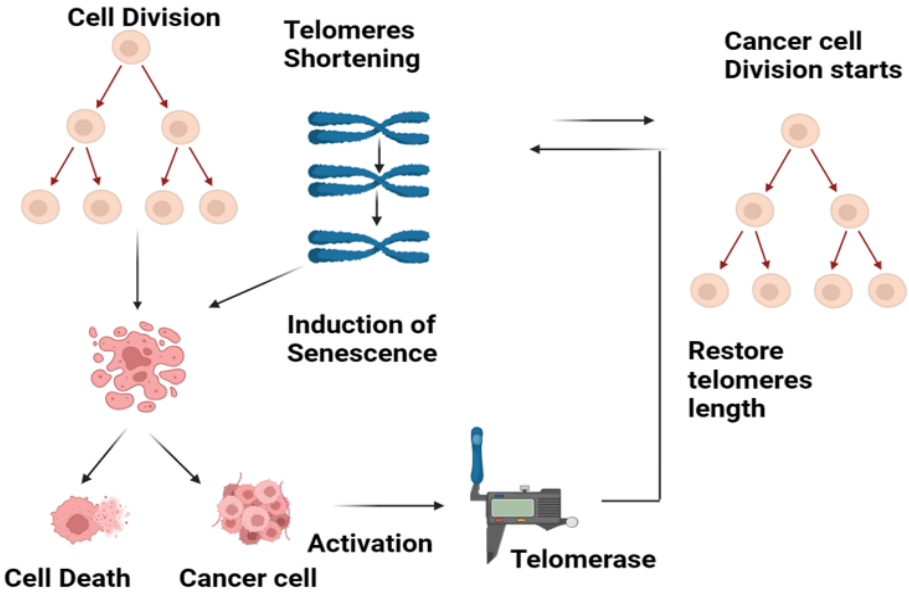


Figure 4: Telomerase enzyme activation in cancer cells.

resulting in heightened activation, and impact of different kinases that phosphorylate and boost TERT activity.[99]

In yeast telomerase, the involvement of ATP in its function was initially noticed. Here, for telomerase binding, the catalytic helicase unit reveals a single-stranded substrate. This activity triggers a structural alteration in the telomerase ribonucleoprotein complex or its associated protein(s), leading to a reduction in the dissociation rate of the complex.[100] In contrast to the yeast enzyme, human telomerase displays processivity even without ATP, whereas the mouse enzyme tends to function distributively even when ATP is present. The regulation of telomerase activity by ATP is specific to yeast telomerase.[101,102] Additionally, experimental evidence concerning the human enzyme revealed the presence of Deoxyadenosine Triphosphate (dATP) as a necessary substrate for synthesizing human telomere repeats. These findings indicate that dATP, serving as a substitute for ATP, plays a crucial part in preserving the processivity of both yeast and human telomerase-catalyzed reactions.[103]

Telomerase

Telomerase, an enzyme with reverse transcriptase activity, operates exclusively within cancerous cells, as illustrated in Figure 5A Its role supports incessant cell division by extending the G-overhang of telomeres and maintaining their length. Telomerase achieves telomere extension through a series of steps, including substrate binding, reverse transcription of telomere DNA, and translocation of the enzyme along the elongated substrate to sustain the extension process.[104]

The key components of telomerase comprise six subunits: hTERC, hsp90, hTERT, TEP1, dyskerin and p23,[105,106] as outlined in Table 2. Among these, hTERC and hTERT function as the central

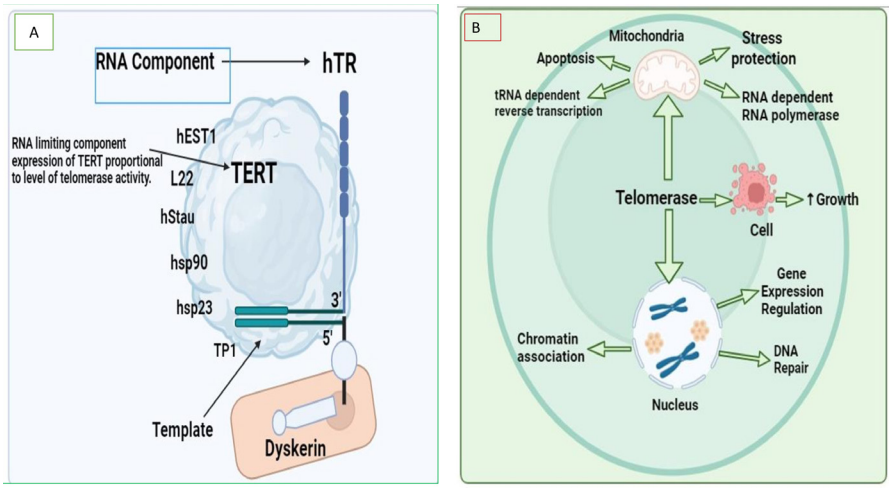
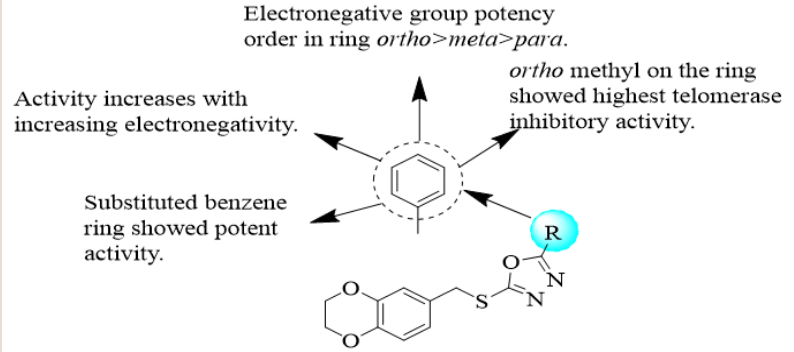
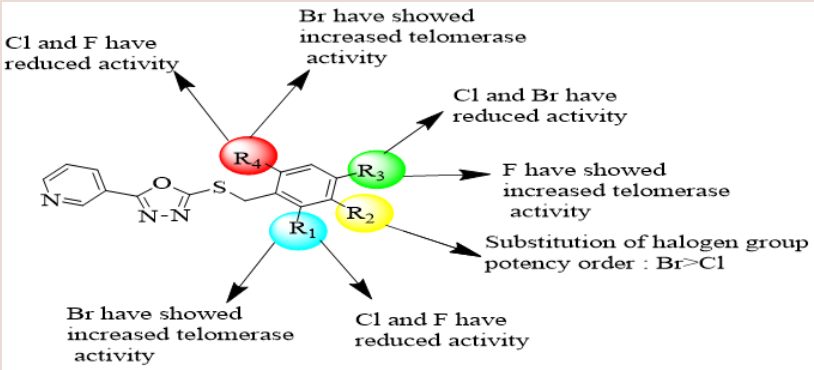
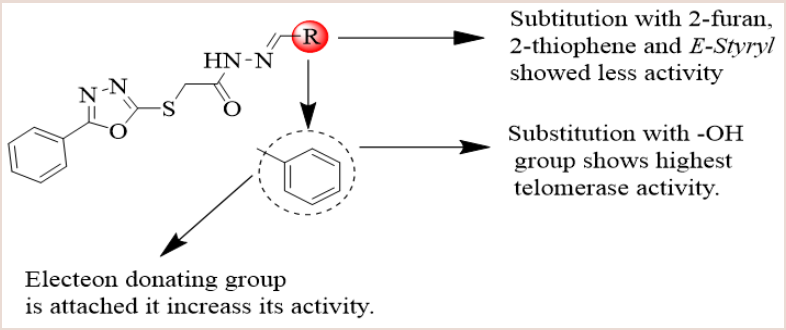


Figure 5: A. Telomerase structure B. Function of telomerase.

Table 3: SAR of 1,3,4-Oxadiazole and its Derivatives.

Sl. No.	Compounds with SAR	References
1.		133
2.		130
3.		131
4.		132

subunits governing telomerase activity. Aberrant regulation of telomerase function is associated with numerous diseases.

Functions of Telomerase

Telomerase possesses various functions beyond telomere length maintenance, referred to as extra-telomere functions as illustrated in Figure 5B. These include safeguarding both the mitochondria and nucleus through apoptosis reduction, chromatin interaction, enhancing stress resistance, RNA-dependent RNA polymerization, DNA repair, supporting cell viability, regulating gene expression, and aiding in neuroprotective signaling.[112-116]

DNA damage repair

The hTERT component of telomerase plays a crucial function in DNA replication and repair mechanisms by upregulating genes implicated in the response to DNA damage. This process results in a reduction of spontaneous chromosomal abnormalities in G1 phase cells and enhances efficiency of DNA repair processes. Recent investigations suggest that telomerase's involvement in the DNA damage response extends beyond merely repairing double-strand breaks, encompassing various other forms of DNA repair, such as nucleotide excision. These findings indicate a potential role of telomerase in the DNA damage response that operates independently of its conventional function in maintaining telomere length.[117,118]

Gene Expression Regulation

TERT governs the expression of genes within mitochondria and inhibits certain genes associated with the processes of angiogenesis and metastasis.[119] Additionally, p65, cyclin D1, VEGF, β-catenin, and Mac-2BP modulate the level of transcription.[120,121]

RNA Dependent RNA Polymerase (RDRP)

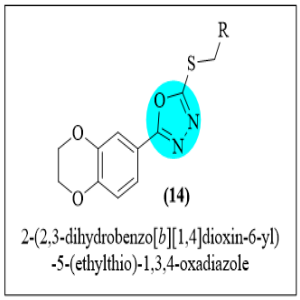
TERT interacts with the RNA section of mitochondria, specifically binding with the RNA processing enzyme RMRP, to form a complex. Within this complex, TERT functions as an RNA-Dependent RNA Polymerase (RDRP), transforming RMRP into double-stranded RNA (dsRNA). Subsequently, the enzyme Dicer processes this dsRNA into some meddling RNA (siRNA), which then regulates the levels of endogenous RMRP. This feedback mechanism, mediated by TERT-RMRP-RDRP, maintains RMRP levels through negative feedback control. Decreased RMRP levels, influenced by the activity of RDRP, enhance cellular proliferation.[122,123]

Chromatin connection

Telomerase plays a role in modifying epigenetic features and regulating chromatin structure. Elevated levels of hTERT contribute to the continued activity of DNA 5-methylcytosine transferase-I in regular human fibroblasts,[124] whereas decreased expression of hTERT results in alterations in the general organization of chromatin.[125]

Reducing apoptosis

Telomerase diminishes apoptosis by boosting resistance against specific DNA-damaging agents, functioning separately from its role in lengthening telomeres. It heightens the susceptibility of mitochondrial DNA (mtDNA) to hydrogen peroxide, leading to oxidative harm. The TERT component of telomerase carries a signal for mitochondrial localization, directing it to mitochondria. Mutations in this region of TERT result in the loss of mitochondrial targeting, leading to reduced levels of mtDNA damage in cells with mutated Htert.[126-129] Telomerase is crucial in promoting cellular immortality and driving carcinogenesis by enabling ongoing cell division and inhibiting replicative senescence. Various strategies can impede telomerase activity, such as RNA interference, gene therapy, Antisense Oligonucleotides (AS-ODNs), dominant negative hTERT, immunotherapy, G-quadruplex stabilizers, hammerhead ribozymes, small molecule inhibitors, Reverse-Transcriptase Inhibitors (RTIs) and. Among these strategies, 1,3,4-oxadiazole derivatives stand out as potential candidates for telomerase inhibition. Certain specific derivatives within this class are being investigated. Zhang and colleagues (2011) conducted the synthesis of novel 1,3,4-oxadiazole derivatives incorporating the 1,4-benzodioxan moiety (14) and evaluated their potential as telomerase inhibitors with the standard TRAP-PCR-ELISA method. The compounds demonstrated significant antitumor efficacy across four cancer cell lines (HEPG2, HELA, SW1116, and BGC823) when compared to the established anticancer agent, 5-fluorouracil. Compound 14 with o-methyl substituted phenyl ring displays robust telomerase inhibition with IC_{50} = 1.27±0.05 μM against SW1116 cell lines.[130]

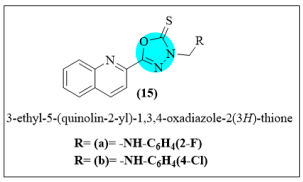


(14)

2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(ethylthio)-1,3,4-oxadiazole

Novel 1,3,4-oxadiazole derivatives incorporating the 1,4-benzodioxan moiety

Sun and colleagues (2013) documented a collection of quinoline derivatives (15) with selective potential as telomerase inhibitors, as depicted below. Evaluation via the TRAP-PCR-ELISA assay revealed that all synthesized compounds demonstrated telomerase inhibition. Notably, compounds 15a and 15b exhibit potent telomerase inhibitory activity with IC_{50}= 0.8+0.1 μM and 0.9+0.0 μM and displayed significant broad-spectrum antitumor effects across three cancer cell lines (HepG2, SGC-7901, and MCF-7).[131]



(15)

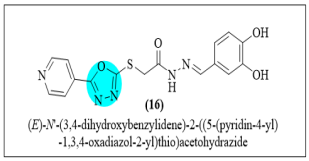
3-ethyl-5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione

R= (a)= -NH-C_6H_4(2-F)

R= (b)= -NH-C_6H_4(4-Cl)

Novel 1,3,4-oxadiazole derivatives incorporating the quinoline moiety

Zhang and co-researchers (2014) recently documented the telomerase inhibitory potential of 1,3,4-oxadiazole derivatives featuring pyridine and acyl-hydrazone components. Assessment of their anticancer efficacy via the TRAP-PCR-ELISA assay revealed that Compound **16** displayed the most substantial antitumor activity across four distinct cancer cell lines (HEPG2, MCF7, SW1116, BGC823). Additionally, it showcased the highest shows potent telomerase inhibitory activity against the SW1116 cell line with IC_{50}=1.18±0.14 µM concerning staurosporine.[132]



(16)

(*E*)-*N*'-(3,4-dihydroxybenzylidene)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide

Novel 1,3,4-oxadiazole derivatives incorporating pyridine and acyl-hydrazone

Structural Activity Relationship of 1,3,4-Oxadiazole and its Derivatives by Telomerase Inhibition. Structural Activity Relationship (SAR) analysis of 1,3,4-oxadiazole and its derivatives reveals crucial insights into their potential as telomerase inhibitors, pivotal in anticancer drug development. By systematically modifying the chemical structure, researchers discern patterns correlating molecular architecture with biological activity. These derivatives interact with telomerase, impeding its function, and thus hindering cancer cell proliferation. SAR elucidates optimal structural features enhancing potency, selectivity, and pharmacokinetic properties. Such understanding guides rational drug design, facilitating the synthesis of potent telomerase inhibitors with improved therapeutic profiles. Harnessing SAR enables the iterative refinement of compounds, expediting the formation of novel anticancer agents with enhanced efficacy and reduced toxicity for clinical applications. SAR of 1,3,4-Oxadiazole and its Derivatives is given in Table 3.

CONCLUSION

In conclusion, the exploration of 1,3,4-oxadiazoles as potential EGFR and telomerase inhibitors for anticancer activity presents a promising avenue in cancer therapeutics. Through extensive research and experimentation, these compounds have demonstrated significant inhibitory effects on key cancer-promoting pathways, highlighting their potential as effective anticancer agents. The multifaceted mechanisms of action, including interference with EGFR signaling and telomerase activity, offer a dual-targeted approach that could enhance treatment efficacy and overcome resistance mechanisms. Additionally, the structural diversity and synthetic versatility of oxadiazole derivatives provide ample opportunities for further optimization and development of potent anticancer drugs. Taking into consideration the SAR of the molecules that inhibit the EGFR, electron groups attached at position 5, increase its activity whereas electron withdrawing diminishes the EGFR activity and the availability of alkenyl small FA chain displays better activity. To inhibit telomerase enzyme, the electron-withdrawing groups attached at the benzene ring increase the activity and as the electronegativity increases the activity increases Although challenges related to pharmacokinetics, toxicity, and clinical application remain, the strong preclinical evidence highlights the need for ongoing research into the therapeutic potential of 1,3,4-oxadiazoles in cancer treatment. Ultimately, the development of these novel compounds offers promise for advancing cancer therapies and enhancing patient outcomes in the battle against this devastating disease.

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ABBREVIATIONS

AIDS: Acquired immunodeficiency syndrome; **CNS:** Central nervous system; **PARP:** Poly (ADP-ribose) polymerase inhibition; **HDAC:** Histone deacetylase; **DNMTs:** DNA Methyltransferases; **EGFR:** Epidermal growth factor receptor; **ERBB:** Erythroblastic oncogene B; **TKIs:** Tyrosine kinase inhibitors; **IGF1R:** Insulin-like growth factor receptor; **EMT:** Epithelial-Mesenchymal Transition; **ATP:** Adenosine triphosphate; **MCF-7 Cells:** Michigan Cancer Foundation-7; **COX:** Cyclooxygenase; **dATP:** Deoxyadenosine triphosphate; **hsp 90:** Heat shock protein 90; **TEP1:** Telomerase-associated protein 1; **bhTERC:** Human telomerase RNA component; **hTERT:** Human telomerase reverse transcriptase; **DNA:** Deoxyribonucleic acid; **RDRP:** RNA-dependent RNA polymerase; **RNA:** Ribonucleic acid; **AS-ODNs:** Antisense oligonucleotides; **RTIs:** Reverse-transcriptase inhibitors. **NSCLC:** Non-small cell lung cancer, **FGFR:** Fibroblast growth factor receptor, **IGF1R:** Insulin-like growth factor receptor; **EMT:** Epithelial-Mesenchymal Transition.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

cancer is one of the leading causes of the early death of human beings. Now a heterocyclic compound plays an important role in treating various types of cancer. One of the most targeted sites of cancer treatment are inhibition of FGFR and telomerase. Five-membered heterocyclic rings with two nitrogen atoms and one oxygen atom make 1,3,4-Oxadiazoles. This isomer is becoming more popular rather than other isomers because of its metabolic stability, lower lipophilicity, better thermal stability, and aqueous solubility. From the former literature review, it has been found that numerous 1,3,4-oxadiazole derivatives are prepared and reported as promising anticancer agents. Important heterocyclic compounds with a wide range of biological functions include 1,3,4-Oxadiazoles. They can be mono- or disubstituted, and because of their low lipophilicity and thermal stability, they may serve as an essential anchor for drug design and discovery. They demonstrated the inhibition of many cancer targets as well as cancer-fighting potential. Medicinal chemists who are engaged with 1,3,4-oxadiazoles and anticancer research programs will find the debate presented throughout to be a useful and essential resource.

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