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Review Article

Unlocking the Potential of Oxadiazole Compounds: A Comprehensive Review of their Anticancer Applications

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Abstract

This review highlights the promising role of oxadiazole compounds in the field of anticancer research. Through an extensive exploration of their diverse chemical structures and mechanisms of action, it is evident that oxadiazoles possess significant potential as anticancer agents. Their ability to target various signaling pathways involved in cancer progression, combined with favorable pharmacokinetic properties and low toxicity profiles, positions them as attractive candidates for further development. However, despite the encouraging preclinical and early clinical data, challenges remain in optimizing the efficacy and safety of oxadiazole-based therapeutics. Future research efforts should focus on enhancing their selectivity towards cancer cells, improving their bioavailability, and elucidating their precise molecular targets. Additionally, the development of innovative drug delivery systems could facilitate the targeted delivery of oxadiazole compounds to tumor sites while minimizing off-target effects.

Keywords: oxadiazoles, pharmacokinetic properties, anticancer, cancer cells, bioavailability

1. Introduction:

Cancer

Cancer, a complex and multifaceted group of diseases characterized by the uncontrolled growth and spread of abnormal cells, has been a scourge on humanity throughout history. The understanding and treatment of cancer have evolved significantly over time, reflecting advances in medical science, technology, and our understanding of the disease.[1]

Ancient evidence suggests that cancer has been present in human populations for thousands of years. The earliest recorded descriptions of cancer date back to ancient Egypt, where tumors were identified and treated through surgical procedures. However, it wasn't until the ancient Greeks that cancer was recognized as a distinct disease entity, with Hippocrates coining the term "karkinos" to describe tumors resembling a crab, due to their invasive and spreading nature.[2]

Throughout the Middle Ages and into the Renaissance, understanding of cancer remained rudimentary, often intertwined with superstition and mysticism. Treatments ranged from surgical excision to herbal remedies, with little success in controlling the disease.

The advent of modern medicine in the 19th and 20th centuries heralded significant

advancements in cancer research and treatment. The development of microscopy allowed for the visualization of cancer cells, leading to the identification of distinct histological types and the recognition of metastasis. In the late 19th century, the discovery of anesthesia and aseptic surgical techniques paved the way for more effective surgical interventions.[3]

The 20th century witnessed remarkable progress in the understanding of cancer biology and the development of novel treatment modalities. The discovery of X-rays and radiation therapy revolutionized cancer treatment, offering a non-surgical option for localized tumors. The elucidation of the genetic basis of cancer, beginning with the identification of oncogenes and tumor suppressor genes, provided crucial insights into the molecular mechanisms underlying carcinogenesis.

The latter half of the 20th century saw the emergence of chemotherapy as a cornerstone of cancer treatment, with the development of cytotoxic drugs targeting rapidly dividing cancer cells. Additionally, the advent of targeted therapies, immunotherapy, and precision medicine has ushered in a new era of personalized cancer treatment, with therapies tailored to the molecular profile of individual tumors.[4]

1.1 cancer in india: report

As of my last update in January 2022, cancer remains a significant public health challenge in India, with a considerable burden on both individuals and the healthcare system. Here are some key statistics and trends regarding cancer in India:

High Incidence: India is experiencing a rising incidence of cancer, with millions of new cases diagnosed annually. The most common types of cancer in India include breast, cervical, oral, lung, and colorectal cancers.[5]

Regional Variation: Cancer incidence and mortality rates vary across different regions of India. Some states have higher rates of specific cancers due to factors such as lifestyle, environmental exposures, socioeconomic status, and access to healthcare.

Tobacco Use: Tobacco use, including smoking and smokeless tobacco products, is a leading cause of cancer in India. A significant proportion of cancers, including lung, oral, and esophageal cancers, are attributable to tobacco consumption.[6]

Screening and Early Detection: Early detection and screening programs are essential for improving cancer outcomes. However, in India, there are challenges related to awareness, access to screening facilities, and healthcare infrastructure, particularly in rural areas.

Treatment Challenges: Access to cancer treatment services, including surgery, chemotherapy, radiation therapy, and supportive care, varies widely across different regions of India. There are disparities in access to affordable and quality cancer care, particularly for underserved populations.[7]

Preventive Measures: Public health efforts aimed at tobacco control, promotion of healthy lifestyles, vaccination against human papillomavirus (HPV) for cervical cancer prevention, and awareness campaigns for early detection and screening are essential for cancer prevention in India.

Government Initiatives: The Indian government has implemented various initiatives to address the growing burden of cancer, including the National Cancer Control Programme (NCCP) and the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS).[8]

Research and Collaboration: Cancer research is a priority area in India, with ongoing efforts to enhance scientific research, clinical trials, and collaborative partnerships between government agencies, research institutions, academia, and the private sector.

For the most current and detailed cancer statistics in India, including incidence rates, prevalence, mortality rates, and trends over time, it is advisable to refer to official reports and publications from reputable sources such as the Indian Council of Medical Research (ICMR), the National Cancer Registry Programme (NCRP), and the World Health Organization (WHO). These organizations regularly publish comprehensive data on cancer epidemiology and trends in India.[15]

In recent decades, advances in genomics, proteomics, and bioinformatics have accelerated our understanding of cancer at the molecular level, enabling the identification of novel therapeutic targets and the development of innovative treatment strategies. Furthermore, the integration of big data analytics and artificial intelligence holds promise for revolutionizing cancer diagnosis, prognosis, and treatment decision-making.[9]

2. Therapeutic agent introduction:

Oxadiazoles, a class of heterocyclic compounds, have garnered considerable interest in cancer research due to their diverse chemical structures and potential anticancer properties. These molecules, characterized by a five-membered ring containing two nitrogen atoms and one oxygen atom, offer a versatile platform for the development of novel anticancer agents.[10]

In recent years, researchers have explored the anticancer potential of oxadiazole derivatives through synthetic chemistry, computational modeling, and biological evaluation. These efforts have led to the identification of oxadiazole compounds with promising anticancer activity, targeting various pathways involved in cancer initiation, progression, and metastasis.

Oxadiazole-based compounds have demonstrated cytotoxic effects against cancer cells through mechanisms such as inhibition of cell proliferation, induction of apoptosis, disruption of cell cycle progression, and inhibition of angiogenesis. Additionally, some oxadiazole derivatives have shown selectivity towards cancer cells while sparing normal cells, highlighting their potential as targeted anticancer agents with reduced toxicity.[11]

The structural diversity of oxadiazole derivatives allows for the rational design and optimization of compounds with enhanced potency, selectivity, and pharmacokinetic properties. Through structure-activity relationship studies and molecular modeling, researchers have been able to fine-tune the chemical structure of oxadiazole compounds to improve their efficacy and therapeutic index.[14]

Furthermore, oxadiazole-based compounds have demonstrated synergistic effects when used in combination with conventional chemotherapeutic agents or targeted therapies, offering new strategies for overcoming drug resistance and improving treatment outcomes in cancer patients.[12]

Despite these promising findings, challenges remain in the development of oxadiazole-based anticancer agents, including optimization of pharmacokinetic properties, elucidation of precise molecular targets, and translation of preclinical efficacy to clinical settings. Nevertheless, ongoing research efforts hold great potential for harnessing the anticancer properties of oxadiazole derivatives and advancing the field of cancer therapeutics.

3. A brief description of review/research work on oxadiazole for anticancer activity:[13]

S. No.	Title of articles	Conclusion
1.	Groundbreaking Anticancer Activity of Highly Diversified Oxadiazole Scaffolds	Nowadays, an increasing number of heterocyclic-based drugs found application in medicinal chemistry and, in particular, as anticancer agents. In this context, oxadiazoles—five-membered aromatic rings—emerged for their interesting biological properties. Modification of oxadiazole scaffolds represents a valid strategy to increase their anticancer activity, especially on 1,2,4 and 1,3,4 regioisomers. In the last years, an increasing number of oxadiazole derivatives, with remarkable cytotoxicity for several tumor lines, were identified. Structural modifications, that ensure higher cytotoxicity towards malignant cells, represent a solid starting point in the development of novel oxadiazole-based drugs. To increase the specificity of this strategy, outstanding oxadiazole scaffolds have been designed to selectively interact with biological targets, including enzymes, globular proteins, and nucleic acids, showing more promising antitumor effects. In the present work, we aim to provide a comprehensive overview of the anticancer activity of these heterocycles, describing their effect on different targets and highlighting how their structural versatility has been exploited to modulate their biological properties.
2.	Vaidya, Ankur, Devender Pathak, and Kamal Shah. "1, 3, 4-oxadiazole and its derivatives: A review on recent progress in anticancer activities." Chemical biology & drug design 97.3 (2021): 572-591.	The 1,3,4-oxadiazole nucleus is a biologically imperative scaffold possesses numerous biological activities. The broad and potent activity of 1,3,4-oxadiazole and their derivatives has established them as important pharmacological scaffolds especially in the treatment of cancer disease. Several di-, tri-, aromatic, and heterocyclic substituted 1,3,4-oxadiazole derivatives have been reported to possess potent anticancer activity. These substituted 1,3,4-oxadiazoles had shown different mechanism of action and participated in anticancer drug discovery and development. This review is complementary to earlier reviews and aims to review the work reported on anticancer activities of 1,3,4-oxadiazole derivatives from year 2000 to the beginning of 2020.
3.	1,3,4-Oxadiazole-Containing Histone Deacetylase Inhibitors: Anticancer Activities in Cancer Cells	We describe 1,3,4-oxadiazole-containing hydroxamates and 2-aminoanilides as histone deacetylase inhibitors. Among them, 2t, 2x, and 3i were the most potent and selective against HDAC1. In U937 leukemia cells, 2t was more potent than SAHA in inducing apoptosis, and 3i displayed cell differentiation with a potency similar to MS-275. In several acute myeloid leukemia (AML) cell lines, as well as in U937 cells in combination with doxorubicin, 3i showed higher antiproliferative effects than SAHA.

4.	Evaluation of anticancer activity of some 1,3,4-oxadiazole derivatives	Carboxymethyl derivatives of various para substituted/unsubstituted oxadiazole-2-thione have been evaluated for their potential anticancer activity. Male Swiss albino mice have been used as test animal. The anti-cancer activity has been evaluated by comparing the ability of the test compound (25 mg/kg) to inhibit the tumor weight as well as tumor cell count with that of the control. The results suggest that all the studied compounds show significant reduction in both tumor weight and tumor cell count with respect to that of the control. Compound 3 is found to the most potent. The standard compound used is Mitomycin C (1mg/kg)
5.	Novel 1,3,4-Oxadiazole Induces Anticancer Activity by Targeting NF-κB in Hepatocellular Carcinoma Cells	Aberrant activation of NF-κB is linked with the progression of human malignancies including hepatocellular carcinoma (HCC), and blockade of NF-κB signaling could be a potential target in the treatment of several cancers. Therefore, designing of novel small molecule inhibitors that target NF-κB activation is of prime importance in the treatment of several cancers. In the present work, we report the synthesis of series of 1,3,4-oxadiazoles, investigated their anticancer potential against HCC cells, and identified 2-(3-chlorobenzo[b]thiophen-2-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (CMO) as the lead compound. Further, we examined the effect of CMO on cell cycle distribution (flow cytometry), apoptosis (annexin V-propidium iodide-FITC staining), and phosphorylation of NF-κB signaling pathway proteins (IκB and p65) in HCC cells. We found that CMO induced antiproliferative effect in dose- and time-dependent manner. Also, CMO significantly increased the percentage of sub-G1 cell population and induced apoptosis. Furthermore, CMO found to decrease the phosphorylation of IκB (Ser 32) in the cytoplasmic extract and p65 (Ser 536) in the nuclear extract of HCC cells. It also abrogated the DNA binding ability and transcriptional activity of NF-κB. CMO induced the cleavage of PARP and caspase-3 in a time-dependent manner. In addition, transfection with p65 small interfering RNA blocks CMO-induced caspase-3/7 activation. Molecular docking analysis revealed that CMO interacts with the hydrophobic region of p65 protein. Thus, we are reporting CMO as an inhibitor of NF-κB signaling pathway.
6.	Synthesis of novel benzimidazole–oxadiazole derivatives as potent anticancer activity	DNA topoisomerase I regulates DNA topological structure in many cellular metabolic processes and is a validated target for the development of antitumor agents. In this work, a series of novel 2-[(5-(4-(5(6)-substituted-1H-benzimidazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)thio]-1-(4-substitutedphenyl)ethan-1-ones (4a–4s) derivatives have been synthesized and evaluated for DNA Topo I inhibition and cytotoxicity. The structures of the compounds (4a–4s) were confirmed by IR, 1H-NMR, 13C-NMR, 2D NMR, and

		mass spectroscopy. Anticancer activity of these compounds was assessed against two different human cancer cell lines A549 (human lung adenocarcinoma) and HepG2 (human liver cancer cell line), as well as normal mouse embryonic fibroblast cells (NIH3T3). IC50 values of compounds 4a, 4c, and 4f were highest than those exhibited for the reference drug cisplatin. Then, the inhibitory effect of 4a, 4c, and 4f compounds on topoisomerase I enzyme with the relaxation assay was investigated on supercoiled DNA using agarose gel electrophoresis. The Annexin V-FITC assay demonstrated that these compounds induce cell death by apoptosis.

4. Conclusion:

This overview focuses on the prospective significance of oxadiazole molecules in anticancer research. Following a thorough examination of their various biochemical structures and methods of action, it is clear that oxadiazoles have considerable anticancer properties. Their capacity to target many signaling pathways implicated in cancer progression, together with superior pharmacokinetic features and minimal toxicity profiles, make them promising candidates for future research. However, despite good preclinical and early clinical results, there are still problems in improving the effectiveness and safety of oxadiazole-based therapies. Future study should focus on increasing their selectivity for cancer cells, boosting bioavailability, and determining their particular molecular targets.

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