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Analysing Oxadiazole Derivatives for Their Anticancer Activity: A Review

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Abstract

Innovative ways are needed to effectively treat cancer, which continues to be one of the most difficult medical problems of our day. A new class of chemicals with promising cancer therapeutic potential has evolved in the last few years: oxadiazole derivatives. This study summarizes what is now known about oxadiazole-based medications, including how they work, what their pharmacological characteristics are, and what we have learned from recent advances in both clinical and preclinical research.

Keywords: Cancer, Oxadiazole derivatives, Anticancer activity, Mechanisms of action, Pharmacological properties, Preclinical studies, Clinical trials.

Introduction

The condition known as cancer is defined by the uncontrolled growth and multiplication of cells, which often results in metastasis and death. In spite of the fact that conventional cancer therapies like chemotherapy and radiation therapy are helpful to a certain degree, they sometimes come with significant adverse effects and have limits in terms of their effectiveness. In light of this, there is an urgent need for the development of innovative therapeutic medicines that are capable of specifically targeting cancer cells while sparing normal cells. Oxadiazole derivatives have attracted a lot of interest owing to the diversity of biological functions that they possess, including the ability to fight cancer.[1]

Chemical Composition of Oxadiazole Derivatives

The heterocyclic complex oxadiazole has five members, with two nitrogen atoms positioned next to each other and one oxygen atom. Because of their distinct structure, oxadiazole derivatives are easily modified to produce a large variety of analogues with different pharmacological characteristics. These substances may be produced in a variety of ways, giving researchers creative freedom to create compounds with improved anticancer properties.[2]

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Mechanisms of Action

The curative properties of oxadiazole derivatives are mediated by a number of different mechanisms, such as the reduction of cell growth, the activation of apoptosis, and the interference with signaling pathways that are essential for the advancement of cancer. It has been discovered, for example, that some oxadiazole chemicals have the ability to block important enzymes that are involved in the process of DNA replication and repair. This, in turn, causes DNA damage and causes cancer cells to undergo apoptotic differentiation. On top of that, some derivatives have anti-angiogenic capabilities, which means that they prevent the production of new blood vessels, which is essential for the growth of tumours and the spread of metastases.[3]

Properties of a Pharmacological Nature

When it comes to establishing the effectiveness and safety profiles of oxadiazole derivatives, the pharmacokinetic and pharmacodynamic aspects of these compounds are quite important. Certain oxadiazole-based drugs have been shown to exhibit favourable pharmacokinetic properties, including excellent oral bioavailability, metabolic stability, and tissue distribution, according to studies. In addition, in order to increase the therapeutic efficacy of these medications, attempts have been made to improve their solubility and to allow for more targeted administration of the medication.[4]

Studies at the Preclinical and Clinical Levels

Preclinical investigations have provided compelling evidence supporting the anticancer potential of oxadiazole derivatives across various cancer types, including breast, lung, colon, and prostate cancer. These studies have elucidated the mechanisms of action and demonstrated the efficacy of oxadiazole-based compounds in inhibiting tumor growth and metastasis in animal models. Furthermore, several oxadiazole derivatives have progressed to early-phase clinical trials, showcasing promising results in terms of safety, tolerability, and preliminary efficacy in cancer patients.[5]

A Short Summary of The Review and Research Work Concerning Phthalimide for Anticancer Activity: *George A. Naclerio ET. Al.*

Synthesized newer N-(1,3,4-oxadiazol-2-yl) benzamides with potent antibacterial activity against N. gonorrhoeae. 18C and18D exhibited highly acceptable tolerability to human colon cells. New N-(1,3,4-oxadiazol-2-yl) benzamides is towards N. gonorrhoeae, proceeded to test their 18A, 18C, and 18D were active against other Gram-positive and Gram-negative pathogens. When assessed using a Caco-2 bidirectional permeability assay, 18D showed a remarkable ability to cross Caco-2 bilayers, indicating that it would have favorable systemic absorption. OCF3-modified N-(1,3,4-oxadiazol-2-yl) benzamides can be added to the list of novel antibacterial agents with novel scaffolds [6]

Eid E. Salama et.al

Synthesized and characterized of new 2-amino-1,3,4-oxadiazole derivatives(19a-19q) All compound were evaluated for their biological activity against gram-negative bacteria Salmonella typhi. where compounds C,D, L, M and N showed significant activity. Structures of the new synthesized compounds were confirmed using the spectral analysis such as IR, 1 H NMR and 13C NMR and mass spectrometry [7]

Sreenivasulu et. al

They have created and synthesised a newer series of ten unique derivatives of 2,5-bis(indolyl)-1,3,4-oxadiazoles (1a -1j). Using the MTT assay, the in vitro cytotoxicity effects of the compounds that were synthesised were evaluated against four different human cancer cell lines, namely A549, MDA-MB-231, MCF-7, and HeLa. Compound 1a demonstrated a high level of cytotoxicity on the MCF-7 cell line, with an IC50 value of 1.8 µM. Compound 1b demonstrated superior antitumor activity against three cancer cell lines, namely lung (A549), breast (MCF-7), and cervical (HeLa), with IC50 values of 3.3 µM, 2.6 µM, and 6.34 µM,[8]

Anish Kumar Kadambar et.al

Synthesized of one-pot three-component azide-alkyne cycloaddition of 5-chloro-1- phenyl-pyrazole-4-carbaldehyde with 2-(prop-2-yn-1-ylthio)-5-((substituted phenoxy) methyl1,3,4-oxadiazole and sodium azide The newly synthesized compounds 29d, 29i, and 29k were showed in vitro anti-inflammatory activity being comparable with that of the standard drug diclofenac sodium. it is characterized by spectral and analytical data. The QSAR models for the observed anti-inflammatory activity were successfully developed. The docking studies of the compounds which showed excellent activity in bovine serum albumin denaturation assay strongly bind to the active site of the COX-2 when compared to the other molecules.it is used for the development of non-steroidal anti-inflammatory drugs[09]

Singhai et. al.

Synthesized a newer novel series of substituted 1,3,4-oxadiazole derivative(22a-22h) was synthesized starting from amine with 1-cyclopropyl-6-fluoro-7(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III) and characterizes them by physicochemical & spectral analysis (IR &^{1}H NMR). These Compounds 22a, 22d, 22e, 22f, and 22 h showed the maximum activity against all Gram-positive and Gram-negative organisms [10]

Ali et. al

During this study, a novel series of 1,3,4-oxadiazole/chalcone hybrids, designated as 6a-6x, was synthesized, discovered using several spectroscopic approaches, and physiologically assessed for their potential to inhibit EGFR, Src, and IL-6. In MTT tests, the compounds that were synthesized displayed strong to moderate cytotoxic effects against K562, KG-1a, and Jurkat leukaemia cell lines. The compounds themselves exhibited anticancer activity, notably against leukaemia, with 6v being the most powerful of the compounds under investigation. The findings presented in the study reveal that compound 6a displayed antitumor activity throughout a wide spectrum, with a GI50 spanning from 0.32 to 11 µM. Additionally, the selectivity ratio at the GI50 level was found to be between 0.65 and 1.20. Furthermore, compound 6v demonstrated the capability to block the proliferation of all nine of the cell lines that were experimented with, with the concentration of TGI ranging from 1.28 to 23.60 µM. In the range of concentrations, compound 6v had LC50 values that ranged from 5.28 to more than 100 µm [11]

Bhupender Singh Rawat et. al

Synthesized and Characterization of Substituted Aniline Oxadiazole Derivatives(23a-c),(24a-c),(25a-k),(26a-K),(27a-k),(28a-k),(29a-k),(30a-k). It is a five membered heterocyclic structure and exist in four isomeric forms out of its four isomers 1, 3, 4- oxadiazole exhibited a wide range of biological activities.Isomeric forms of ortho/meta/ para toluidine, is converted to 3- methyl-N-(5- substituted phenyl)-1, 3, 4 oxadiazol-2yl-methyl aniline. The synthesized compounds show significant anti-inflammatory activity. Compound 27g, 28c, 29a and 29g shows very good response against standard drug indomethacin. It can also be concluded that the introduction of nitro group &fluoro group in para positions significantly increases or shows very good response [12]

Tiwari et. al

Thus it can be concluded that the oxadiazole derivatives possibly possess significant antitumor activity in both in vitro and in vivo. 1,3,4-oxadiazole derivatives were synthesized and were tested for IC50 values through brine shrimp lethality assay and MTT assay on HeLa and A549 cell lines. Four compounds, 11a, 11b and 11c showed potential cytotoxicity activity with low IC50 value. These compounds produced considerable cytotoxic effect on Hep-2 and A549 cancer cell lines Among the tested compounds [13]

Ahsan et. al

Synthesized a newer novel series of 2,5-disubstituted-1,3,4-oxadiazole analogs (8a-j) was synthesized starting from 2-aminopyrimidine. Some of the compounds were screened for in vitro anticancer activity as per

(NCI US) Protocol on leukemia, melanoma, lung, colon, CNS, ovarian, renal and prostate and breast cancer cell lines. N-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}pyrimidin-2- amine (8a) showed maximum activity with growth percent of 61.19 (UO-31; Renal cancer) and 76.82 (MCF; Brest Cancer) and N-{[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]methyl}pyrimidin-2-amine (8e) showed maximum antibacterial activity among the series, comparable to the standard drug ciprofloxacin with MIC ranging from 4-8 µg/ml while N-{[5-(3,4- dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}pyrimidin-2-amine (8g) showed maximum antifungal activity among the series, less active than the standard drug fluconazole with MIC 4 µg/ml [14]

Kikkeri P. Harish

Synthesized a new series of novel 2-methyl-2-[3-(5-piperazin-1-yl- [1,3,4] oxadiazol-2-yl)-phenyl]-propionitrile derivatives 32a–o, 33a–c, 34a–d and 35a–d. the synthesized compound were characterized by 1 H NMR, 13C NMR, and mass spectral studies and the synthesized compounds shows significant potent anticonvulsant activity. Among the synthesized compounds, 32d, 32e, 32f, and 32h showed excellent anticonvulsant activity. Therefore, the nature of groups in sulfonyl moiety is very important for anticonvulsant activity in MES model [15]

Conclusion

Oxadiazole derivatives are highly promising compounds that have shown remarkable effectiveness in fighting cancer. Their effectiveness is derived from a variety of mechanisms that help fight cancer cells, along with favourable pharmacological qualities. Their collective potency positions them as strong contenders in the arsenal of cancer therapeutics. These diverse mechanisms of action work together to hinder cell proliferation, promote apoptosis, and interfere with vital signalling pathways that are essential for cancer progression. These actions together contribute to their ability to hinder tumour growth and metastasis. In addition, the positive pharmacological properties of these substances, including their high oral bioavailability and metabolic stability, greatly enhance their potential for therapeutic use. Positive results from preclinical studies and early-phase clinical trials continue to support the potential of oxadiazole derivatives in cancer treatment. These investigations have not only revealed the anticancer mechanisms, but have also shown the safety, tolerability, and initial effectiveness in cancer patients.However, in order to fully unlock the power of oxadiazole-based drugs in the fight against cancer, ongoing research efforts are absolutely necessary. Efforts focused on enhancing the structure-activity relationships of these compounds are crucial for maximising their effectiveness and reducing any potential negative effects. Furthermore, it is essential to continue exploring the underlying mechanisms of action in order to gain a comprehensive understanding of their therapeutic impact. Advancing clinical development through larger-scale trials is crucial for establishing the efficacy of treatments across diverse cancer types and patient populations.

Essentially, the continuous pursuit of scientific inquiry and clinical investigation is crucial for fully unlocking the therapeutic potential of oxadiazole derivatives in the fight against cancer. [16-19]

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