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REVIEW ARTICLE **OPEN ACCESS**

A review on the 1,3,4-Thiadiazole as Anticancer Activity

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ABSTRACT
In this review study an attempt has been made of various mechanisms involved in cancer prevalence . This review study mechanism of action of 1,3,4 thiadiazole derivatives in the management of various cancers. These compounds have been investigated for their ability to inhibit cancer cell proliferation, induce apoptosis (programmed cell death), and inhibit specific molecular targets involved in cancer progression. 1,3,4-thiadiazole derivatives have shown promising anticancer activity in preclinical studies.
Keywords: *1,3,4-Thiadiazole, cell proliferation, apoptosis, topoisomerase.*

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INTRODUCTION

1,3,4-Thiadiazole is a heterocyclic organic compound composed of a five-membered ring containing three carbon atoms, one nitrogen atom, and one sulphur atom. The ring is planar and aromatic, exhibiting properties of aromatic compounds.1,3,4-Thiadiazole is known for its diverse range of applications in various fields, including medicinal chemistry, pharmaceuticals, agrochemicals, and materials science. It serves as a valuable building block for the synthesis of biologically active compounds, such as pharmaceutical drugs, pesticides, and herbicides[2].The presence of sulphur and nitrogen atoms in its structure imparts unique properties to 1,3,4-thiadiazole. It exhibits electron-deficient characteristics due to the electronegativity difference between sulphur and nitrogen, making it a potential candidate for electron transfer processes[3]. 1,3,4-thiadiazole derivatives have shown promising biological activities, such as antibacterial, antifungal, anti-inflammatory, anticancer, and anticonvulsant properties. The diverse range of activities exhibited by its derivatives has made 1,3,4-thiadiazole an attractive scaffold for the design and development of new therapeutic agents[4].

Anticancer Activity

1,3,4-Thiadiazole is a heterocyclic compound that has been investigated for its potential as an anticancer agent. Heterocyclic compounds have been widely studied in medicinal chemistry due to their diverse biological activities, including anticancer properties. Several studies have reported the synthesis and evaluation of 1,3,4-thiadiazole derivatives as potential anticancer agents. These derivatives can be modified to enhance their biological activity, improve their selectivity towards cancer cells, and reduce toxicity to healthy cells. Studies have shown that these compounds exhibit cytotoxic effects by inducing apoptosis (programmed cell death) in cancer cells[6]. They can also interfere with various cellular processes and signalling pathways involved in cancer progression and metastasis. For example, certain 1,3,4-thiadiazole derivatives have been found to inhibit specific enzymes or receptors that play crucial roles in cancer cell growth and survival. These include protein kinases, such as tyrosine kinases, which are involved in cell signalling pathways that regulate cell proliferation and survival. By inhibiting these kinases, 1,3,4-thiadiazole compounds can disrupt the abnormal growth and signalling of cancer cells. Additionally, some studies have shown that 1,3,4-thiadiazole derivatives possess antiangiogenic properties. Angiogenesis is the process of forming new blood vessels, which is critical for tumour growth and metastasis. Compounds that inhibit angiogenesis can help to starve tumours of their blood supply, thereby suppressing their growth and preventing the spread of cancer. [7].

1. Inhibition of cell proliferation: Many anticancer compounds, including those derived from heterocyclic scaffolds like 1,3,4-thiadiazole, target pathways involved in cell proliferation. They can interfere with DNA replication, disrupt cell cycle progression, or inhibit key enzymes involved in cell division, ultimately leading to the suppression of cancer cell growth.

2. Induction of apoptosis: Apoptosis is a programmed cell death mechanism that plays a crucial role in maintaining tissue homeostasis. Dysregulation of apoptosis is often observed in cancer cells, leading to uncontrolled cell growth. Anticancer compounds can activate apoptotic pathways in cancer cells, triggering cell death and inhibiting tumour growth. Specific mechanisms of apoptosis induction may involve targeting anti-apoptotic proteins, activating pro-apoptotic proteins, or disrupting mitochondrial function.

3. Inhibition of angiogenesis: Angiogenesis is the formation of new blood vessels, which is essential for tumour growth and metastasis. Anticancer compounds can interfere with angiogenesis by inhibiting the activity of growth factors involved in vessel formation or by blocking signalling pathways necessary for blood vessel development. By limiting the blood supply to tumours, these compounds can impede their growth and survival.

4. Inhibition of oncogenic signalling pathways: Many cancers are driven by aberrant signalling pathways that promote uncontrolled cell growth. Anticancer compounds may target specific molecular components of these pathways to disrupt their activity. For example, they can inhibit protein kinases involved in cell signalling cascades, block receptor tyrosine kinases, or interfere with downstream signalling molecules. By modulating these pathways, anticancer compounds can disrupt the growth and survival signals in cancer cells.

[8].

Few examples of pharmaceutical drugs that contain the 1,3,4-thiadiazole structure are as follows.

1. Thiazolidinediones (TZDs): TZDs are a class of drugs used in the treatment of type 2 diabetes. Pioglitazone and rosiglitazone, two widely prescribed TZDs, contain a 1,3,4-thiadiazole ring as a central structural component. These drugs act as peroxisome proliferator-activated receptor gamma (PPARγ) agonists, improving insulin sensitivity and glucose control.

2. Sulfonamides: Sulfonamide derivative ---------- incorporate a 1,3,4-thiadiazole moiety in structure exhibit antimicrobial activity and are used to treat various bacterial and fungal infections. Acetazolamide, a carbonic anhydrase inhibitor used to treat glaucoma and epilepsy, contains a 1,3,4-thiadiazole ring.

3. Anticancer agents: Several compounds with anticancer activity incorporate the 1,3,4-thiadiazole structure.

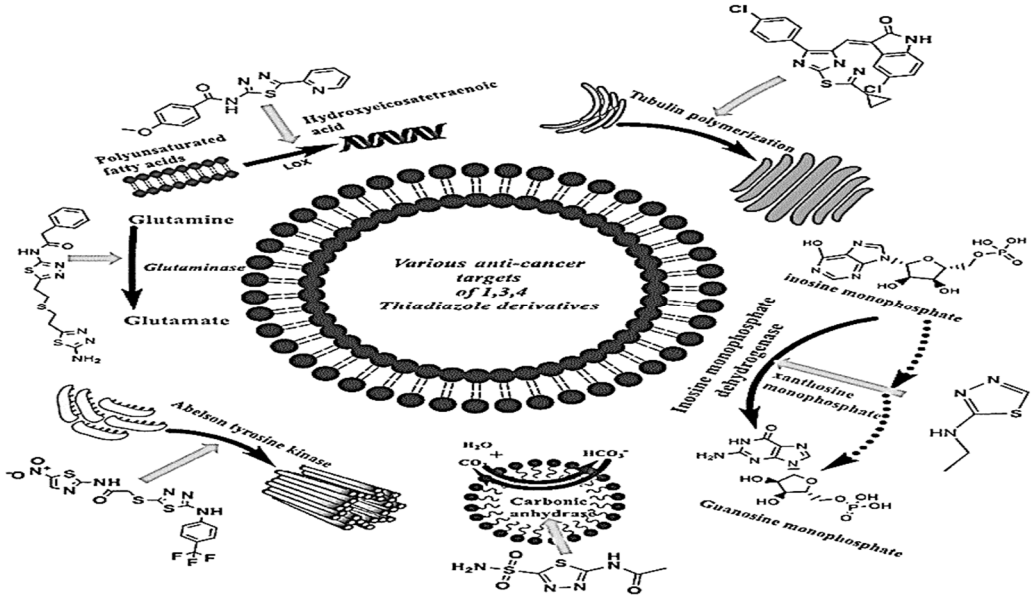

Fig 1 : Target different types of cancer cells.

There are various types of anticancer agents used to target different types of cancer cells. Here are some examples

1. **Chemotherapy drugs:** Chemotherapy is a widely used cancer treatment that involves the use of drugs to kill or inhibit the growth of cancer cells. Different types of chemotherapy drugs are used depending on the specific type of cancer. Examples include paclitaxel, cisplatin, doxorubicin, and methotrexate.

2. **Targeted therapies:** These drugs specifically target cancer cells by interfering with specific molecules or pathways involved in cancer cell growth and survival. Examples include monoclonal antibodies like trastuzumab for HER2-positive breast cancer, imatinib for chronic myeloid leukaemia (CML), and vemurafenib for BRAF-mutated melanoma.
3. **Hormone therapy:** This type of therapy is used for cancers that are hormone-dependent, such as breast and prostate cancer. Hormone therapy works by blocking the effects of certain hormones or inhibiting hormone production. Examples include tamoxifen for estrogen receptor-positive breast cancer and androgen deprivation therapy (ADT) for prostate cancer.
4. **Immunotherapy:** Immunotherapy drugs harness the body's immune system to recognize and attack cancer cells. They can stimulate the immune system to target cancer cells or inhibit the mechanisms that cancer cells use to evade immune detection. Examples include checkpoint inhibitors like pembrolizumab and nivolumab, which target proteins like PD-1 and PD-L1.
5. **Angiogenesis inhibitors:** These drugs target the process of angiogenesis, which is the formation of new blood vessels that tumours need to grow and spread. By inhibiting angiogenesis, these drugs can deprive the tumour of its blood supply. Examples include bevacizumab and sorafenib.
6. **Radiopharmaceuticals:** Radiopharmaceuticals are drugs that contain radioactive substances. They deliver radiation directly to cancer cells, killing them or inhibiting their growth. Examples include iodine-131 for thyroid cancer and radium-223 for bone metastases in prostate cancer[9].

It's important to note that the choice of anticancer agents depends on several factors, including the type and stage of cancer, individual patient characteristics, and treatment goals. Treatment plans are often personalised based on these factors, and multiple agents or a combination of therapies may be used for better efficacy. They can target various mechanisms involved in cancer cell growth and proliferation. Examples include compounds like 2-amino-5-(2,4-difluorophenyl)-1,3,4-thiadiazole, which has shown potent anticancer activity against different cancer cell lines [10].

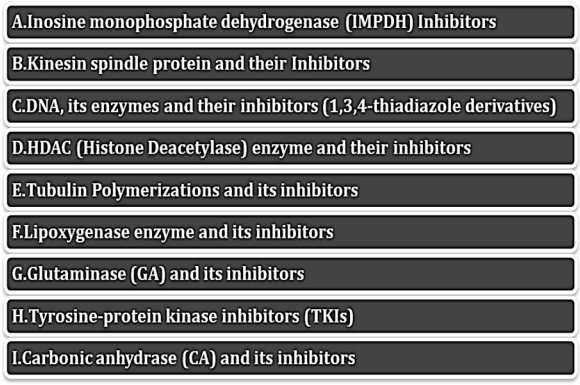

FIG 2: All Anticancer Activity of 1,3,4-Thiadiazole

A.Inosine monophosphate dehydrogenase (IMPDH) inhibitors :

Inosine monophosphate dehydrogenase (IMPDH) inhibitors are a class of drugs that target the enzyme inosine monophosphate dehydrogenase, which plays a crucial role in the de novo synthesis of guanine nucleotides, essential for DNA and RNA synthesis. These inhibitors are used in the treatment of various diseases, including autoimmune disorders and certain cancers. The mechanism of action of IMPDH inhibitors involves the inhibition of IMPDH enzyme activity, which leads to a decrease in the production of guanine nucleotides[11]. This disruption in guanine nucleotide synthesis can have several effects on cell function, particularly affecting rapidly dividing cells such as immune cells and cancer cells. One of the important IMPDH inhibitors is 1,3,4-thiadiazole. The thiadiazole moiety is a heterocyclic compound containing three nitrogen and two sulphur atoms arranged in a specific pattern. It has been found to possess inhibitory activity against IMPDH. The role of 1,3,4-thiadiazole in IMPDH inhibition can be attributed to its structural features, which allow it to bind to the enzyme's active site and interfere with its catalytic function. The specific interactions between 1,3,4-thiadiazole and the active site of IMPDH are thought to involve hydrogen bonding and hydrophobic interactions, leading to the inhibition of the enzyme's enzymatic activity[12]. By inhibiting IMPDH, 1,3,4-thiadiazole and other IMPDH inhibitors disrupt the production of guanine nucleotides, which are necessary for the synthesis of DNA and RNA. This disruption can ultimately lead to the suppression of immune responses in autoimmune disorders and the inhibition of cell proliferation in certain cancers. It's worth noting that while IMPDH inhibitors, including 1,3,4-thiadiazole, have shown promise in the treatment of various diseases, their specific mechanisms of

action and clinical applications may vary depending on the specific compound and the targeted condition. Further research and development are still ongoing to explore the full potential and therapeutic applications of IMPDH inhibitors in different disease contexts[13].

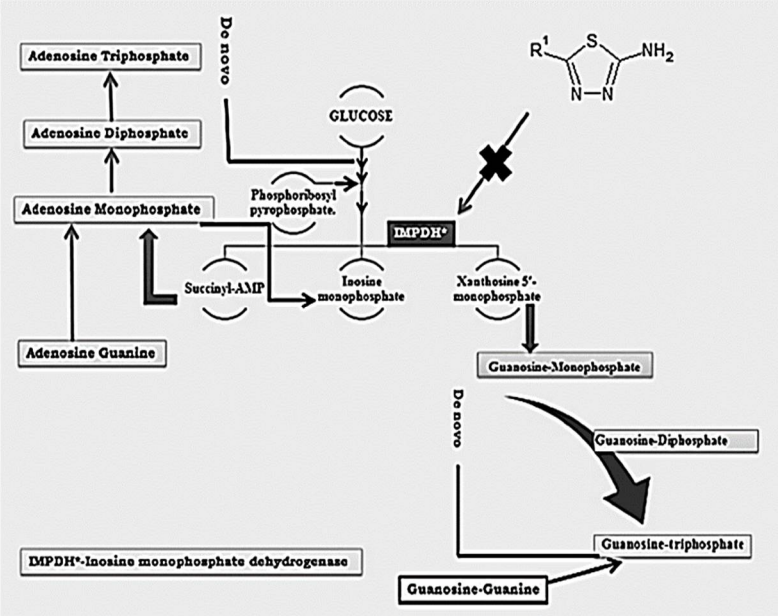

FIG 3 : IMPDH Cycle for 1,3,4-Thiadiazole

B.Kinesin spindle protein and their Inhibitors:

Kinesin spindle proteins (KSPs), also known as Eg5 or KIF11, are motor proteins that play a critical role in mitosis, specifically in the assembly and maintenance of the mitotic spindle. The mitotic spindle is a complex structure responsible for proper chromosome segregation during cell division. KSPs are involved in the movement and positioning of microtubules within the spindle, ensuring the separation of duplicated chromosomes into two daughter cells. The mechanism of action of KSP inhibitors involves interfering with the ATPase activity of KSPs, which is necessary for their motor function. One class of KSP inhibitors that has been extensively studied is the family of compounds known as 1,3,4-thiadiazoles[14]. These compounds have shown promising anti-mitotic activity by specifically targeting KSPs. 1,3,4-thiadiazole derivatives exert their inhibitory effect on KSPs by binding to the ATP-binding site of the motor domain, which is essential for ATP hydrolysis and microtubule movement. By occupying this site, they prevent ATP from binding and inhibit the motor activity of KSPs, leading to mitotic arrest and cell death. The binding affinity and selectivity of 1,3,4-thiadiazole compounds to KSPs are attributed to their structural features. The presence of a 1,3,4-thiadiazole core, which is a five-membered heterocyclic ring containing three nitrogen and two sulphur atoms, contributes to the formation of critical interactions with the ATP-binding pocket of KSPs. The additional substituents on the ring further enhance the potency and specificity of the inhibitor. By inhibiting KSPs, 1,3,4-thiadiazole compounds disrupt the normal mitotic process, leading to the accumulation of cells in the mitotic phase, known as mitotic arrest. Prolonged mitotic arrest triggers apoptotic pathways, eventually causing cell death[15-16].

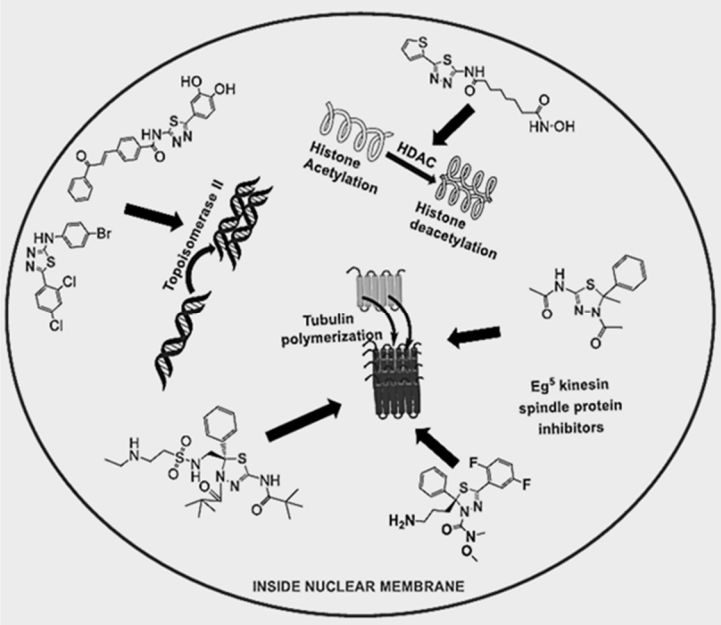

FIG 4 : Kinesin spindle protein(KSP) cycle for 1,3,4-Thiadiazole

The selective inhibition of KSPs provides a potential therapeutic strategy for cancer treatment since rapidly dividing cancer cells are particularly reliant on proper mitotic spindle function. It is worth noting that while 1,3,4-thiadiazole compounds have shown promise as KSP inhibitors, the development and optimization of these inhibitors are ongoing, and their clinical use is still under investigation. As with any potential drug candidate, further research and clinical trials are necessary to determine their efficacy, safety, and potential side effects before they can be approved for clinical use[17].

C.DNA, its enzymes and their inhibitors (1,3,4-thiadiazole derivatives):

DNA is a molecule that contains the genetic instructions for the development, functioning, and reproduction of all living organisms. Enzymes play a crucial role in DNA replication, repair, and transcription, while inhibitors can interfere with the normal functioning of these enzymes. One class of compounds known as 1,3,4-thiadiazoles has been studied for their potential as enzyme inhibitors in various biological processes, including DNA-related mechanisms[18]. Enzymes involved in DNA processes, such as DNA polymerases, topoisomerases, and helicases, are critical for DNA replication, repair, and gene expression. These enzymes have specific functions and mechanisms of action in maintaining the integrity and stability of the DNA molecule. 1,3,4-thiadiazole derivatives have been investigated for their potential inhibitory effects on DNA-related enzymes. These compounds can act through various mechanisms to disrupt the normal functioning of these enzymes, leading to inhibition of DNA replication, repair, or transcription. Here are some possible mechanisms and actions of 1,3,4-thiadiazole derivatives.

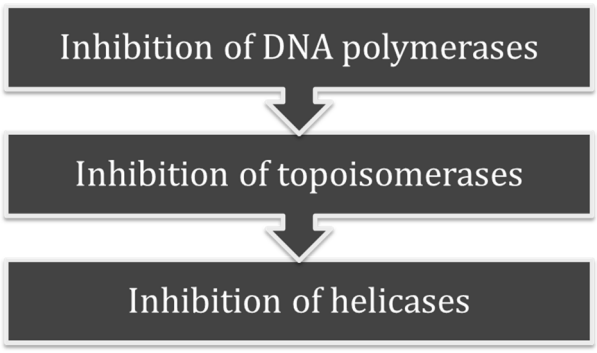

Fig 5 : Steps for DNA enzymes and their inhibitors

DNA polymerases are enzymes responsible for DNA replication and synthesis. Some 1,3,4-thiadiazole derivatives have been found to inhibit the activity of DNA polymerases by binding to their active sites and preventing the incorporation of nucleotides into the growing DNA strand. This inhibition can lead to the

disruption of DNA replication and subsequent cell death. Topoisomerases are enzymes involved in the regulation of DNA supercoiling, which is crucial for DNA replication and transcription[19-20]. Certain 1,3,4-thiadiazole derivatives have shown inhibitory effects on topoisomerases by interfering with their ability to break and rejoin DNA strands, thus disrupting the normal topological changes required for DNA processes. Helicases are enzymes involved in unwinding the DNA double helix during replication and transcription. Some 1,3,4-thiadiazole derivatives have demonstrated inhibitory effects on helicases by interfering with their ATPase activity or blocking their interaction with DNA. This inhibition can impair the unwinding of DNA, leading to the inhibition of DNA replication or transcription. The role of 1,3,4-thiadiazole derivatives as enzyme inhibitors in DNA-related processes has been studied to develop potential therapeutic agents for various diseases, including cancer and viral infections. By selectively targeting DNA-related enzymes, these compounds can disrupt critical cellular processes and potentially inhibit the growth and proliferation of cancer cells or the replication of viruses[21-22].

D.HDAC (Histone Deacetylase) enzyme and their inhibitors:

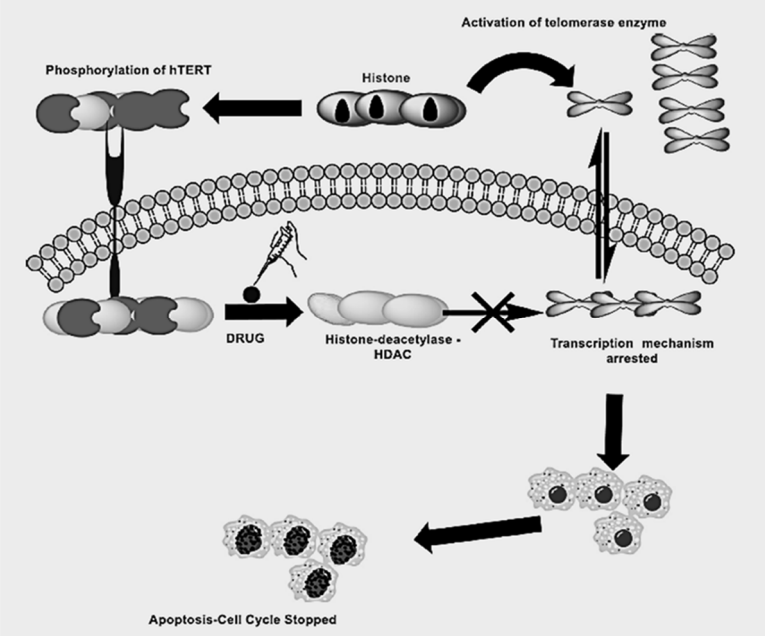

Fig 6 : HDAC (Histone Deacetylase) enzyme for 1,3,4-Thiadiazole

Histone deacetylases (HDACs) are a group of enzymes that play a crucial role in gene expression regulation by removing acetyl groups from lysine residues on histone proteins. This process leads to chromatin condensation, making the DNA less accessible for transcription factors and inhibiting gene expression. HDAC inhibitors (HDACis) are small molecules that can block the activity of HDAC enzymes, resulting in an increase in histone acetylation and modulation of gene expression. The mechanism of action of HDAC inhibitors involves binding to the active site of HDAC enzymes, thereby preventing them from removing acetyl groups from histones[23]. This inhibition leads to an accumulation of acetylated histones, resulting in an open chromatin structure. The increased accessibility of DNA allows for enhanced binding of transcription factors and other proteins involved in gene expression regulation, leading to changes in gene transcription. 1,3,4-Thiadiazole is a heterocyclic compound that has been investigated for its potential as an HDAC inhibitor. It possesses a sulphur atom and three nitrogen atoms in its ring structure. The role of 1,3,4-thiadiazole derivatives as HDAC inhibitors involves their ability to bind to the active site of HDAC enzymes and inhibit their activity[24]. By acting as HDAC inhibitors, 1,3,4-thiadiazole compounds can modulate gene expression and have potential therapeutic applications in various diseases. Increased histone acetylation resulting from HDAC inhibition has been associated with the activation of tumour suppressor genes, cell cycle arrest, induction of apoptosis, and inhibition of angiogenesis in cancer cells. Furthermore, HDAC inhibitors have shown promise in the treatment of neurodegenerative diseases, inflammatory disorders, and cardiovascular conditions. It's important to note that the specific effects and mechanisms of 1,3,4-thiadiazole derivatives as HDAC inhibitors may vary depending on the compound's structure, dosage, and the specific HDAC isoforms targeted. Extensive research is still ongoing to explore

the therapeutic potential and optimise the efficacy of HDAC inhibitors, including 1,3,4-thiadiazole derivatives, in various disease contexts[25].

E.Tubulin Polymerizations and its inhibitors :

Tubulin polymerization is a critical process for the formation of microtubules, which are important components of the cytoskeleton in eukaryotic cells. Microtubules play essential roles in various cellular processes, including cell division, intracellular transport, and maintenance of cell shape. During tubulin polymerization, tubulin dimers, which consist of α- and β-tubulin subunits, assemble into protofilaments. Protofilaments then associate laterally to form a cylindrical structure, ultimately resulting in the formation of microtubules. This polymerization process is regulated by various factors, including the concentration of tubulin, the presence of GTP (guanosine triphosphate), and the binding of stabilising or destabilising agents. Several compounds have been identified as inhibitors of tubulin polymerization. These inhibitors interfere with different stages of tubulin assembly and can be broadly categorised into two groups: microtubule-stabilising agents and microtubule-destabilising agents. Microtubule-stabilising agents, such as taxanes (e.g., paclitaxel) and epothilones, enhance tubulin polymerization by promoting microtubule assembly and stabilising microtubule structures. They bind to the tubulin subunits and prevent microtubule depolymerization, leading to the accumulation of stable microtubules[26]. This disruption of normal microtubule dynamics interferes with crucial cellular processes, ultimately leading to cell cycle arrest and cell death. On the other hand, microtubule-destabilising agents, like colchicine and vinca alkaloids (e.g., vincristine and vinblastine), inhibit tubulin polymerization by binding to tubulin subunits and preventing their assembly into microtubules. These inhibitors interfere with the lateral association of tubulin protofilaments, resulting in the disruption of microtubule formation and the formation of abnormal tubulin aggregates. Consequently, microtubule-destabilising agents disrupt essential cellular functions, including mitosis, and induce cell cycle arrest and cell death. 1,3,4-Thiadiazole is a heterocyclic compound that has shown potential as an anticancer agent by targeting tubulin polymerization. Some derivatives of 1,3,4-thiadiazole have been identified as microtubule-destabilising agents. These compounds bind to tubulin subunits and interfere with tubulin assembly, leading to the destabilisation of microtubules. The exact mechanism of action of 1,3,4-thiadiazole derivatives may vary depending on the specific compound and its chemical structure. Overall, the role of 1,3,4-thiadiazole and its derivatives in inhibiting tubulin polymerization is to disrupt microtubule formation and function, ultimately affecting vital cellular processes and potentially leading to cell death. However, it's important to note that the development and use of specific compounds as inhibitors of tubulin polymerization require further research and investigation to determine their effectiveness and safety profiles[27].

F.Lipoxygenase enzyme and its inhibitors :

Lipoxygenases (LOX) are a family of enzymes that play a crucial role in the metabolism of arachidonic acid, a fatty acid found in cell membranes. These enzymes catalyse the oxidation of arachidonic acid to produce bioactive lipid mediators called leukotrienes. Leukotrienes are involved in various physiological and pathological processes, including inflammation, immune responses, and allergic reactions. Inhibitors of lipoxygenase enzymes are compounds that can interfere with the activity of these enzymes, thereby reducing the production of leukotrienes. One class of compounds that has been studied as lipoxygenase inhibitors is 1,3,4-thiadiazole derivatives. The mechanism of action of these inhibitors involves several steps:

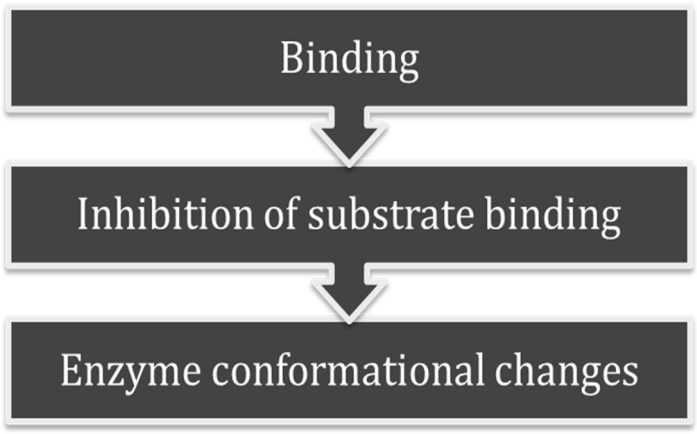

Fig 7 : Steps of Lipoxygenase enzyme and its inhibitors for 1,3,4-Thiadiazole.

1,3,4-thiadiazole derivatives bind to the active site of the lipoxygenase enzyme. The active site is the region of the enzyme where the substrate (arachidonic acid) normally binds. By occupying the active site, 1,3,4-thiadiazole inhibitors prevent the binding of arachidonic acid to the enzyme. This prevents the enzymatic conversion of arachidonic acid to leukotrienes. The binding of the inhibitor induces conformational changes in the enzyme structure, which can further hinder the catalytic activity of the lipoxygenase enzyme. These changes may involve alterations in the active site geometry or disruption of essential interactions required for enzymatic activity[28].

By inhibiting lipoxygenase activity, 1,3,4-thiadiazole derivatives can effectively reduce the production of leukotrienes. This inhibition can have anti-inflammatory and immunomodulatory effects, making these compounds potential candidates for the development of therapeutic agents targeting inflammatory diseases, such as asthma, rheumatoid arthritis, and inflammatory bowel disease. It's worth noting that the specific mechanism and action of 1,3,4-thiadiazole derivatives may vary depending on the structural characteristics of individual compounds within this class. Further research and development are needed to fully understand their precise mechanisms of action and optimise their therapeutic potential[29].

G.Glutaminase (GA) and its inhibitors:

Glutaminase (GA) is an enzyme that catalyses the hydrolysis of glutamine, an amino acid, into glutamate. This enzyme plays a crucial role in various cellular processes, including energy metabolism, neurotransmission, and biosynthesis of nucleotides and amino acids. Aberrant glutaminase activity has been associated with several diseases, including cancer, neurodegenerative disorders, and autoimmune diseases[30]. Inhibitors of glutaminase have gained significant attention as potential therapeutic agents for various diseases. One class of compounds that has shown promise as GA inhibitors is 1,3,4-thiadiazole derivatives. These compounds possess a core structure consisting of a thiadiazole ring, and they can be chemically modified to enhance their inhibitory activity and selectivity towards glutaminase.

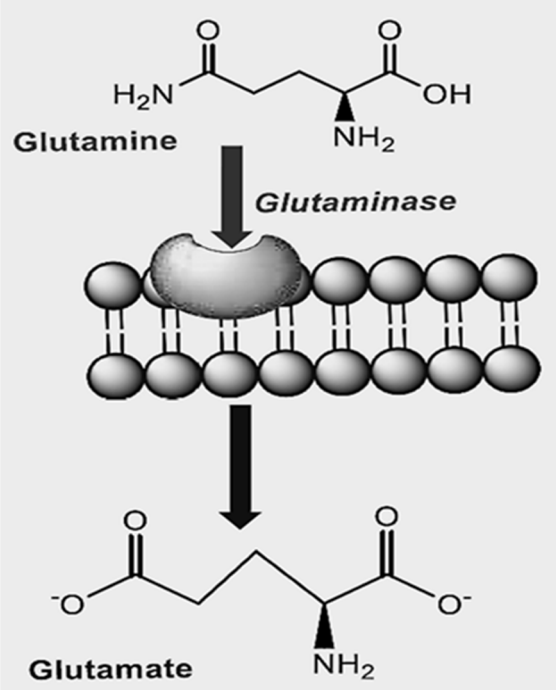

Fig 8 : Steps of Glutaminase (GA) and its inhibitors

The mechanism of action of 1,3,4-thiadiazole inhibitors involves binding to the active site of glutaminase and interfering with its catalytic activity. These inhibitors can act through different mechanisms, such as competitive inhibition, non-competitive inhibition, or mixed inhibition. Competitive inhibitors compete with the substrate (glutamine) for binding to the active site of the enzyme. Non-competitive inhibitors, on the other hand, bind to a different site on the enzyme, causing a conformational change that reduces its catalytic activity. Mixed inhibitors can bind to both the active site and an allosteric site, affecting the enzyme's function[31-32]. By inhibiting glutaminase, 1,3,4-thiadiazole compounds decrease the production of glutamate from glutamine. This disruption in glutamine metabolism can have several effects

on cellular processes. For example, cancer cells often rely on increased glutaminase activity to support their high demand for energy and building blocks for proliferation. Inhibiting glutaminase can therefore lead to a decrease in energy production and impair cancer cell growth. Additionally, glutamine is an important precursor for the synthesis of neurotransmitters and nucleotides. Inhibiting glutaminase can alter these pathways and affect neurotransmission and nucleotide synthesis, which may have implications for neurodegenerative disorders and autoimmune diseases. It's important to note that while 1,3,4-thiadiazole inhibitors show promise as potential therapeutic agents, further research is needed to fully understand their mechanism of action, optimise their potency and selectivity, and evaluate their safety and efficacy in various disease contexts[33].

H.Tyrosine-protein kinase inhibitors (TKIs) :

Tyrosine-protein kinase inhibitors (TKIs) are a class of drugs that specifically target and inhibit the activity of tyrosine kinases, which are enzymes involved in the regulation of cell signalling pathways. TKIs have been developed as targeted therapies for various types of cancers, including leukaemia, breast cancer, lung cancer, and gastrointestinal stromal tumours (GISTs).1,3,4-Thiadiazole is a heterocyclic compound that has been investigated for its potential as a pharmacophore in the development of tyrosine kinase inhibitors. It is known to possess certain chemical properties that can interact with the ATP-binding site of tyrosine kinases and disrupt their enzymatic activity[34]. Here's a general mechanism of action for tyrosine-protein kinase inhibitors, including those containing the 1,3,4-thiadiazole moiety:

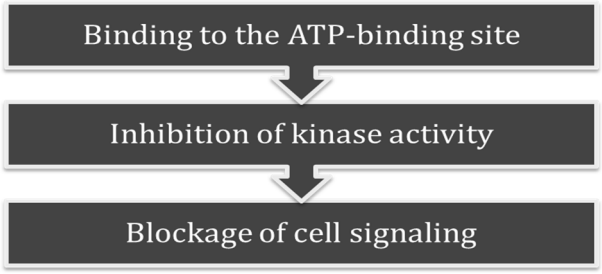

Fig 9 : Steps for Tyrosine-protein kinase inhibitors (TKIs)

TKIs, including those with the 1,3,4-thiadiazole structure, are designed to mimic the structure of ATP, the natural substrate of tyrosine kinases. They have a similar shape and chemical properties, allowing them to competitively bind to the ATP-binding site of the tyrosine kinase. Once bound to the ATP-binding site, the TKI prevents ATP from binding to the tyrosine kinase. As a result, the tyrosine kinase cannot phosphorylate its target proteins, which are crucial for transmitting signals within the cell. This inhibition of tyrosine kinase activity disrupts the downstream signalling pathways involved in cell growth, proliferation, and survival. By inhibiting the tyrosine kinase activity, TKIs interfere with the activation of signalling pathways that are essential for cancer cell growth and survival. These pathways often involve tyrosine kinases such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). By blocking these pathways, TKIs can inhibit tumour growth and metastasis [35].

It's important to note that the exact mechanism of action can vary depending on the specific TKI and the target tyrosine kinase being inhibited. Different TKIs may have different binding affinities and selectivity for specific tyrosine kinases, leading to variations in their therapeutic effects and potential side effects. Overall, tyrosine-protein kinase inhibitors, including those containing the 1,3,4-thiadiazole structure, act by competitively binding to the ATP-binding site of tyrosine kinases, thereby inhibiting their enzymatic activity and interfering with crucial signalling pathways involved in cancer cell growth and survival [36].

I.Carbonic anhydrase (CA) and its inhibitors:

Carbonic anhydrase (CA) is an enzyme that catalyses the reversible conversion of carbon dioxide (CO2) and water (H2O) into bicarbonate ions (HCO3-) and protons (H+). This enzymatic reaction is crucial for various physiological processes, including acid-base balance, respiration, and electrolyte transport. 1,3,4-Thiadiazole is a heterocyclic compound that has been investigated for its potential as a carbonic anhydrase inhibitor (CAI). CAIs are compounds that can bind to the active site of CA and inhibit its enzymatic activity[37]. Here's an overview of the mechanism and action of CAIs, including 1,3,4-thiadiazole:

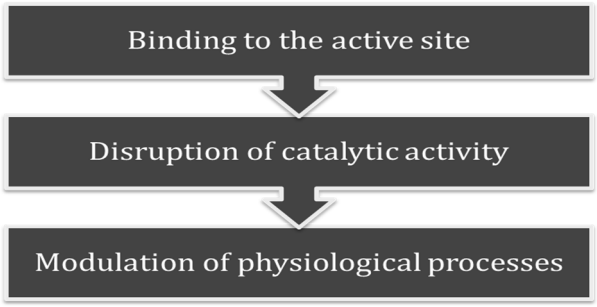

Fig : 10 : Steps Involving in Carbonic anhydrase (CA) and its inhibitors for 1,3,4-Thiadiazole.

CAIs, including 1,3,4-thiadiazole derivatives, have a similar structure to the substrate of CA, CO2. They can bind to the active site of CA, which contains a zinc ion coordinated with three histidine residues. The inhibitor molecule coordinates with the zinc ion and interacts with amino acid residues in the active site. By binding to the active site, CAIs interfere with the catalytic activity of carbonic anhydrase. They can block the access of CO2 to the active site or hinder the release of the reaction products (HCO3- and H+). This disruption leads to a decrease in the rate of the CA-catalysed reaction. Inhibiting carbonic anhydrase activity can have various physiological effects. For example, CAIs can reduce the production of H+ ions in the stomach, thereby decreasing the acidity of gastric acid and providing relief for conditions like gastric ulcers. Inhibition of CA in the kidneys can also affect the reabsorption of bicarbonate ions, influencing the acid-base balance in the body[38].

Regarding 1,3,4-thiadiazole specifically, it is a heterocyclic compound that has been studied as a potential CAI due to its structural properties and ability to interact with the zinc ion in the active site of CA. However, the exact mechanism of action and efficacy of 1,3,4-thiadiazole derivatives as CAIs may vary depending on the specific chemical structure and modifications made to the compound. It's worth noting that CAIs have therapeutic potential for various conditions, including glaucoma, epilepsy, edema, and cancer. However, the development and use of CAIs as drugs require careful consideration of their selectivity, pharmacokinetics, and potential side effects to ensure their safety and efficacy[39].

CONCLUSION

1,3,4-Thiadiazole is a heterocyclic compound that has been studied for its potential applications in various fields, including medicinal chemistry and drug discovery. While there is ongoing research on the effects of 1,3,4-thiadiazole derivatives on cancer cells, it's important to note that I can provide general information based on existing knowledge up until September 2021, and there might have been advancements in this area since then. Some studies have reported that certain 1,3,4-thiadiazole derivatives exhibit potent cytotoxicity against various cancer cell lines, including breast, lung, colon, prostate, and leukemia cells. These compounds have been shown to interfere with multiple signaling pathways involved in cell growth and survival, such as the PI3K/Akt pathway and the MAPK/ERK pathway. Furthermore, 1,3,4-thiadiazole derivatives have been explored for their potential to overcome multidrug resistance, which is a significant challenge in cancer treatment. Some studies have suggested that these compounds can sensitize drug-resistant cancer cells to chemotherapy agents, enhancing their cytotoxic effects. It's important to note that the development of any potential anticancer drug involves extensive research, including in vitro studies (cell culture experiments), in vivo studies (animal models), and ultimately clinical trials in humans. The effectiveness and safety of 1,3,4-thiadiazole derivatives as anticancer agents are still being investigated, and their use in clinical practice is not yet established. In summary, 1,3,4-thiadiazole derivatives have shown promising anticancer activity in preclinical studies, but further research is needed to fully understand their mechanisms of action, optimize their efficacy, and evaluate their safety profile. Continued exploration of these compounds and their derivatives may lead to the development of novel therapeutic options for cancer treatment in the future.

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