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"SYNTHESES OF PLATELET AGGREGATION OF THIAZOLES AND OXADIAZOLES"

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ABSTRACT:

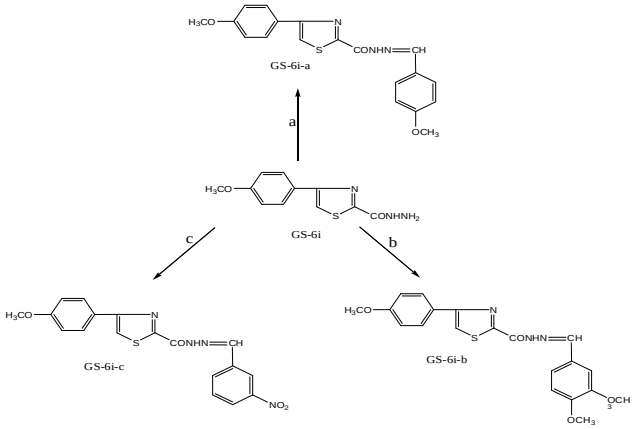
Aromatic heterocycles that are monocyclic or bicyclic include imidazoles, thiazoles, thiadiazoles, oxazoles, oxadiazoles, quinazolines, indoles, benzimidazoles, purines, pyrido pyrimidines, thiazolo pyrimidines, oxazolo pyrimidines, and thieno[2,3-d]pyrim Chemical compound libraries provide clear explanations and examples of these unique structures. This chapter presents a variety of heterocyclic scaffolds based on thiazole, including studies of their biological activities and the synthesis of monocyclic or bicyclic systems, both of which are uncommon in books and reviews. The primary significance of the synthetic route for various thiazole-based compounds is mentioned. In vitro tests on rabbit platelets demonstrated that diphenylthiazole derivatives and diphenylimidazole were effective inhibitors of platelet aggregation. Diphenylthiazole derivatives inhibited arachidonic acid-induced platelet aggregation in rabbit platelet-rich plasma more effectively than diphenylimidazole derivatives. Two diphenylimidazole and eight diphenylthiazole subordinates were assessed for ex vivo arachidonic corrosive and collagen-instigated platelet conglomeration inhibitory movement utilizing guinea pigs. Both in vitro and in vivo, these compounds displayed significant activity. Tenn had a 200-fold greater ex vivo activity than aspirin. The inhibition of cyclooxygenase was the mechanism by which 10n acted.

The thiazole moiety has been a significant heterocycle in chemistry for a number of decades. Because sulfur and nitrogen make up the thiazole ring, pi electrons can freely move from one bond to another, giving the ring its aromatic properties. The ring has many reactive positions due to its aromatic nature, including those for donor–acceptor, nucleophilic, oxidation, and other, might happen. When molecules with a thiazole ring enter physiological systems, their behavior is unpredictable and the system is reset in a different way. Biochemical pathways, enzymes, and receptors in biological systems may be stimulated or inhibited by these molecules. As a result, medicinal chemists have been concentrating their efforts on compounds containing thiazole in order to come up with novel treatments for a wide range of diseases. The purpose of this review is to provide readers with information about three main categories of molecules that contain thiazole: Thiazoles in their preclinical and developmental stages, thiazoles in clinical trials, and as treatment drugs. Preclinical studies on structure-based activity analysis and a compilation of thiazole-containing molecules from development and preclinical studies are highlighted. The authors anticipate that the current review will be successful in attracting the attention of medicinal chemists to the discovery of novel leads that could one day lead to the development of novel drugs.

KEYWORDS: *thiazoles, antimicrobial, neglected, anticonvulsant, anti-inflammatory, carbonic anhydise, antiviral, HIV, tuberculosis, antioxidant.*

INTRODUCTION :

Thiazole has a unique ring that carries nitrogen and sulfur atoms, making it a versatile entity in actions and reactions among the five-membered heteroaryl ring systems. The single pair of electrons in the sulfur atom of the thiazole ring is dislocated, meeting the Huckel rule condition for a minimum of six pi electrons. Thiazole undergoes various reactions, such as donor–acceptor intramolecular nucleophilic substitution photochemical reaction arylation cycloaddition oxidation transformation dimerization, etc. Although free thiazole cannot be found in nature, the ring of thiazole can be found in a number The Hantzsch thiazole synthesis, Cook–Heilbron synthesis, Herz synthesis, and modified Hantzsch synthesis are just a few of the older but still important methods for producing thiazole rings. Venugopala recently synthesized thiazole derivatives. Because the thiazole ring has an acidic proton at C-2, it is highly reactive and has evolved into a significant synthon for the production of numerous new chemical compounds. Due to the variety of their chemical, physical, and pharmacological properties, derivatives of thiazole have always piqued the interest of synthetic and biological chemists. By modifying the thiazole ring in various places, a variety of new compounds with a wide range of therapeutic potentials were produced, including antioxidant, anti-tubercular, antibacterial, antifungal, diuretic, anti-cancer, and anti-inflammatory effects. As a single nucleus or fused ring, thiazole is an essential component of natural antibiotics that look like penicillin.



Numerous review articles have emphasized the significance of the thiazole nucleus in the design and optimization of newer bioactive drug candidates. However, none of these articles presented a chronological significance of the thiazole moiety. In recent decades, the thiazole moiety has received a lot of attention. The current review article aims to educate readers about some of the new aspects of the thiazole platform, such as thiazole-ring-bearing drugs that are clinically used for a variety of diseases, thiazole-containing drug candidates that are either in the preclinical development or clinical trial stages, and so on.

The design, synthesis, and production of molecules with the potential to treat human diseases is one of the primary goals of organic and medicinal chemistry. Combinatorial chemistry has made it possible to access chemical libraries based on special structures over the past ten years. Heterocyclic scaffolds have received particular attention because they are a class of compounds that have been shown to be useful in medicinal chemistry. Numerous molecules with two heteroatoms and five-membered rings are biologically active. One of those is the thiazole ring. Due to its numerous pharmaceutical applications, thiazole is an excellent pharmacophore nucleus. Antioxidant, analgesic, antibacterial, anticancer, antiallergic, antihypertensive, anti-inflammatory, antimalarial, antifungal, and antipsychotic properties abound in its derivatives. More than 18 medications approved by the FDA contain the thiazole scaffold. Cefiderocol, which was the first siderophore antibiotic to be approved by

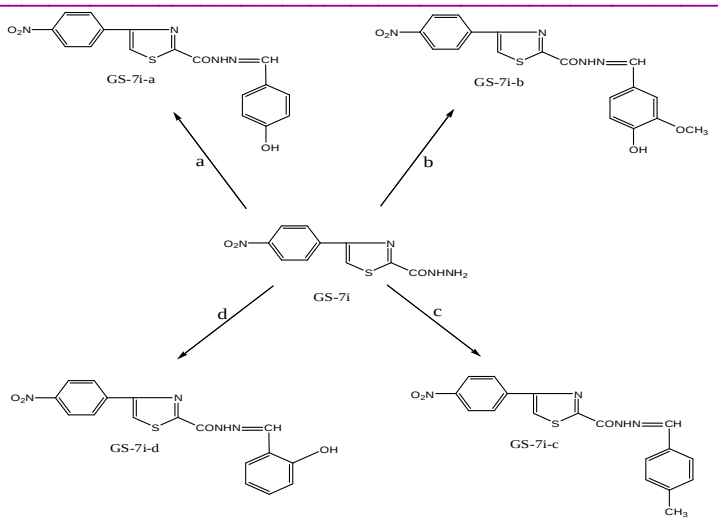
the FDA under the brand name, is one of them. This thiazole derivative was found to be active against a wide range of multi-drug-resistant Gram-negative bacteria, including Pseudomonas aeruginosa. It is used to treat complicated urinary tract infections when no other treatment is available. Alpelisib, which is a thiazole-based drug, was approved Breast cancer is the second leading cause of cancer-related death worldwide, primarily in less developed nations, and is one of the most severe diseases. Lusutrombopag is a medication that was approved in 2018 to treat thrombocytopenia, such as thrombocytopenia associated with chronic liver disease, by stimulating platelet formation. Cobicistat, a drug that extends the half-life of some antiviral medications, is another example. It is used to treat human immunodeficiency virus infection.

Thiazole-Derived Treatment Drugs

A wide range of natural and synthetic molecules with varying degrees of biological activity contain the thiazole ring. By making it easier to make acetylcholine, for example, vitamin B1 with thiazole helps the nervous system function normally. Previously, some thiazole analogues were utilized as potent medications for the central nervous system. Pramipexole was used to treat Parkinson's disease because it had dopamine D2 agonist activity and had a 2-amino-thiazole moiety linked to a cyclohexane ring that was structurally similar to dopamine's catechol ring. A drug based on aminothiazoles called riluzole has been approved for the treatment of Lou Gehrig's disease. Ritonavir is an antiretroviral drug with a protease suppressor that is used to stop HIV from spreading. Nizatidine is a histamine-receptor suppressor that is used to control peptic ulcers and gastroesophageal reflux disease by reducing the production of stomach acid. Organosulfur sulfa drugs like sulfathiazole are used to treat bacterial infections for a short time. By preventing the histamine receptor from being activated, famotidine reduces stomach acid production. Dasatinib is a tyrosine kinase suppressor that works against Abl and Src, which are both forms of Abelson's murine leukemia and sarcoma. It has been found to have immunomodulatory properties. The drug has been supported to oversee persistent myeloid leukemia . Febuxostat, a suppressor of the enzyme xanthine oxidase that is not specific for purine, is used to treat gout-associated hyperuricemia. The medication clomethiazole is used to treat sleep issues. Niridazole is prescribed for the treatment of periodontitis in addition to its use as a schistosomicide. Fentiazac, a new non-steroidal anti-inflammatory, is used to treat pain in the muscles and joints. Amiphenazole is used to treat opiate or barbiturate poisoning. Most of the time, abafungin is applied topically to treat various fungi-caused skin infections. As a result of voreloxin's interaction with topoisomerase II and binding to DNA, DNA double-strand cracks, a G2 stop, and ultimately cell death are brought about. Voreloxin is currently being used to treat a variety of cancers. Aztreonam, also known as azactam, is an antibiotic made with penicillin that is used to treat conditions caused by Gram-negative bacteria.

Thiazole Bearing Drug Candidates under Intensive Clinical Investigations

As was mentioned in the previous section, a greater number of drug-bearing thiazole rings are now utilized in the treatment of a variety of diseases, and medicinal chemists all over the world continue to hold out hope for the discovery of some of the most effective medications in this class. Numerous potential drug molecules have been tailored for clinical use as a result of ongoing research. Some of them have completed clinical trials and are awaiting regulatory bodies' final approval, while others are beginning clinical trials. We have listed a number of therapeutic candidates that have the potential to become treatments for a number of diseases in the coming days.



Due to its numerous pharmaceutical applications, thiazole is an excellent pharmacophore nucleus. Antibacterial, antifungal, antimalarial, anticancer, antiallergic, antihypertensive, anti-inflammatory, and antipsychotic biological activities are among the many biological activities of its derivatives. In fact, the thiazole scaffold is present in more than 18 drugs that have been approved by the FDA and in numerous experimental drugs. Objective: Methods: To provide a synopsis of the most recent research on the biological activities of compounds with thiazole rings: From 2015 to the present, the subjects were the subject of a literature review. Because they were previously analyzed in available peer reviews, older publications were not included. Results: In the past five years, nearly 124 research articles on the synthesis and biological activities of thiazole derivatives were discovered, critically analyzed, and arranged.

Chemistry of Thiazole Derivatives

Thiazole and its derivatives can be synthesized in a variety of ways. A few are listed below: According to Hantzsch, the primary method for the synthesis of thiazole derivatives is the reaction of alpha-halocarbonyl compounds with thioamides or thiourea. The reaction mechanism involves the nucleophilic attack of the sulfur atom of the thioamide on the alpha carbon of the alpha-halocarbonyl, followed by the formation of an intermediate by dehydration to the corresponding thiazole. Concentrating thiourea or its derivatives with 1,2-dichloro-1-ethoxyethane is one variation of the above synthesis. The Cook–Heilbron method, which involves the reaction of an aminonitrile with carbon disulfide, is another method for the production of thiazole derivatives. Thiazole derivatives can be synthesized using the Robinson–Gabriel method, which is based on the cyclization of acylaminocarbonyl compounds in the presence of stoichiometric amounts of phosphorus pentasulfide. This method is used to synthesize 2,4-disubstituted 5-aminothiazole derivatives. The reduction of 2-methylthiothiazole serves as the conduit for an intriguing thiazole synthesis. Additionally, new approaches to the synthesis of thiazole derivatives have emerged in recent times. Sheldrake and other reported that N,N-diformylaminomethyl aryl ketones were treated with phosphorus pentasulfide and triethylamine in chloroform to produce 5-arylthiazoles. Tang et al. report high yields of 5-arylthiazoles from the reaction. reported the copper-catalyzed type condensation of oximes, anhydrides, and potassiumthiocyanate for the synthesis of 5-arylthiazoles. Wang and co. 4,5-disubstituted thiazoles were produced by the base-induced cyclization of active methylene isocyanides like tosylmethyl isocyanide, ethyl isocyanoacetate, and arylmethyl isocyanides with methyl arene- and hetarenecarbodithioates. These thiazoles were made from simple aldehydes, amines, and sulfur in the presence of molecular

A small collection of compounds with thiazole scaffolds and structural diversity in positions 2 and 5 was created by Sanz-Cervera. Miura et al. found that the intermediate -amido--ketoesters

produced by double acylation of a protected glycine react with Lawesson's reagent to produce 1,3-thiazoles. reported the use of a rhodium catalyst to create 2,5-disubstituted thiazoles from 1-sulfonyl-1,2,3-triazoles and thionoesters. Chinnaraja and Rajalakshmi produced novel hydrazinyl thiazole derivatives with a high yield and purity using microwave irradiation. In the past, Kiran et al. By cyclizing tosylmethyl isocyanide with -oxodithioesters in the presence of KOH and ethyl isocyanoacetate with -oxodithioesters in the presence of DBU/EtOH, respectively, we were able to produce 4-methylthio-5-acylthiazoles and 4-ethoxycarbonyl-5-acylthiazoles. Mamidala and others reported the reaction of thiocarbohydrazide, aldehydes, and -halocarbonyl coumarins in a molar ratio of 1:2:1 under microwave heating to produce new coumarin-based thiazole derivatives. A variety of solvents were utilized.

Thiazole-Bearing Compounds in Pre-Clinical Investigations

A group of neurological conditions is epilepsy. Unprovoked, excessive, sudden, and self-regulated neuronal firing causes seizures in all types of epilepsies. Due to excessive neuronal discharge, the intricate pattern of the brain's integrative activity is lost. Palliative care is used to treat the condition, and over time, resistance to the medication develops. Additionally, the numerous side effects of current medications necessitated the creation of a new class of medications to address these issues. Thiazole is a well-known platform for the creation of numerous classes of bioactive compounds. A series of trisubstituted thiazole derivatives were synthesized by the reaction of an appropriate aldehyde solution in dry diethyl ether with methyl dichloroacetate, which was then transformed into final products. Current research trends show that numerous newly developed thiazole agents with high lipophilicity are capable of stopping seizures to the same extent as treatment. The ability of these substances to inhibit carbonic anhydrase was examined. The SAR study revealed that the essential requirements for activity were the presence of a free amino group at the position, a carboxylic acid moiety at the 4-position, and a phenyl ring at the position of the thiazole scaffold. This compound was the most potent inhibitor among the synthesized compounds.

Thiazoles as Antimicrobial Agents

Over the years, new chemical entities bearing thiazole have significantly advanced biochemical science. They are the drug industry's most celebrated basic moiety due to their distinctive properties. Scientists are putting in a lot of effort to create novel, biologically active thiazole derivatives due to their enormous biological significance. This review examined the antibacterial properties of several thiazoles and their derivatives. Researchers will benefit from the ongoing study of thiazoles as antimicrobials in designing and synthesizing various active molecules. From benzothiazolidine derivatives, a variety of thiazole-quinolinium derivatives with aliphatic amino and/or styrene substituents were synthesized and further investigated for their antibacterial properties against various Gram-positive and Gram-negative bacteria. The finding suggested that the most potent and efficient bacteriostatic agents against multi-drug-resistant bacteria were the synthesized compounds. In short, the SAR study focused on small group requirements like where the quinoline fragment should be placed. When a solution of sodium carbonate in anhydrous dimethylformamide was added dropwise to a solution of chloroacetyl chloride, the resulting product was used in multistep reactions to produce the novel methylthiazole-based thiazolidinones derivatives. All of the compounds had antibacterial properties, with some of them particularly effective against B. cereus and E. coli. In terms of antibacterial activity against three resistant pathogens, compound 48e performed better than ampicillin and streptomycin, the standard medications. E. coli and P. aeruginosa. Compounds significantly reduced the development of biofilms associated with P. aeruginosa by more than half at a concentration equal to the MIC. The bacterial strain was tested for antimicrobial activity using novel benzothiazole derivatives that were synthesized. The compounds that were synthesized had the greatest antimicrobial activity against all of the bacterial strains that were tested. The substitution of a phenyl ring with hydroxy and nitro groups and the substitution of dihydrobenzothiazole with methyl and bromo groups may both account for the high

activity of these two compounds. A Claisen–Schmidt condensation reaction was used to create novel chalcones based on thiazole.

In the initial phase of reactions, ethanone compounds reacted with a variety of aromatic aldehydes. The resulting products underwent subsequent multistep reactions to produce the final compounds. The antimicrobial properties of these newly synthesized compounds were investigated. All of the compounds have demonstrated antibacterial properties that are superior to those of ampicillin and, in many instances, to those of streptomycin. In addition, the antifungal activity was significantly higher than that of the standard medications bifonazole and ketoconazole. Among the blended mixtures, seemed, by all accounts, to be 10-and 56-crease more intense contrasted with streptomycin and ampicillin, individually. A close examination of the SAR revealed that the primary requirement is the presence of a chloro- and fluoro-substituted phenyl ring. Organic synthesis was used to create thiazolidinones, thiazole and benzothiazole derivatives, and other compounds. Microdilution was used to measure the antimicrobial activity. Due to the presence of a methoxy group on the benzothiazole moiety, title compound 51 demonstrated the greatest antimicrobial activity among the synthesized compounds. Starting with thiourea and 1-adamantyl bromomethyl ketone, some thiazole derivatives with multiple ring systems were made. In the first step, thiazol-2-amine was obtained, and in the presence of mercaptoacetic acid, it reacted with variously substituted aromatic aldehydes to produce the desired compounds.

Synthesis of 2-Aminothiazoles

Facchinetti and others reported that the solvent-free, simple, quick, and environmentally friendly synthesis of aminothiazoles and selenazoles without the use of a catalyst can be achieved through the Hantzsch condensation of 2-bromoacetophenones with thiourea or selenourea. With good yields, this reaction is carried out in a short amount of time. palladium acetate was used as a catalyst to make substituted aminothiazoles from potassium thiocyanate and vinyl azides. Ferric bromide was used to make 4-substituted 5-thiocyano-2-aminothiazoles by coupling oxime acetates with isothiocyanates in a copper-catalyzed way to make a variety of substituted and disubstituted aminothiazoles. A one-pot, three-component reaction of primary amines, potassium thiocyanate, and -nitro epoxides, as described by, is another method for the synthesis of polysubstituted aminothiazoles. Castagnolo used a domino alkylation-cyclization reaction of propargyl bromides with thioureas and thiopyrimidinones under microwave irradiation to quickly and efficiently produce 2-aminothiazoles and 5H-thiazolo pyrimidin-5-ones. Narender described how to make amino carboxylates by halogenating keto esters with N-bromosuccinimide, then cyclizing them with thiourea. De Andrade described how to make aminothiazoles in a single pot with readily available esters and tribromoisocyanuric acid by monohalogenating them in an aqueous medium and then reacting with thiourea.

Biological Activities of Thiazoles

Due to the rise in bacterial resistance, which is exacerbated by the appearance of multidrug-resistant strains such as Staphylococcus aureus, Enterococcus, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter cloeacae, and Candida sp., medicinal chemists are paying close attention to the design and development of antimicrobial agents with various modes of action at the moment. with fluconazole acquired resistance being a factor in numerous human infections. For a number of decades, new antimicrobial drugs were not developed very well, resulting in a lack of highly active antibiotics against resistant Gram-negative bacteria. As a result, it is obvious that novel agents with novel modes of action that target both sensitive and resistant strains are required.

Thiazole Derivatives as Anticancer Agents

In the majority of nations around the world, cancer is one of the major issues affecting public health. Genetic abnormalities, either inherited or acquired, are linked to the disease. There are a plethora of antitumor medications in the literature and on the market; Sadly, the majority of them are

toxic and develop resistance, which may result in treatment failure. As a result, there is a lot of interest in creating promising new drug prototypes. Braga and co. investigated the cytotoxicity of a number of thiazole derivatives against three different human cancer cell lines: in addition to normal cell lines. At a concentration of 50, compounds were tested in vitro, while the reference drug etoposide was examined at.

Synthesis of Thiazole

Numerous methods for the synthesis of thiazole derivatives were developed by various research groups, including Hantzsch, Tchernic, Cook-Heilborn, and Gabriel, to assess the significance of thiazoles and their derivatives. In recent times, thiazole derivatives were produced using a microwave and a variety of catalysts, including ammonium-12-molybdophosphate, cyclodextrins, iodine, and silica chloride, in organic solvents at a higher temperature. There are a variety of methods for making thiazole compounds that can be broken down into the part structures shown below. It is observed that the earliest of these structures is the most significant and adaptable of all the thiazole formation methods. It allows alkyl, aryl, aralkyl, or heterocycles to be taken in any one of the carbons of the thiazole ring with a workable and first reactant. Condensation of a compound with two heteroatoms on the same carbon and one halogen and one carbonyl function attached to two adjacent carbon atoms is the core of this method, which is better known by its German inventor, Hantzsch. Compounds like thiourea, thioamide, ammonium thiocarbamate, or dithiocarbamate and its derivatives can serve as nucleophilic reagents in this reaction.

Biological importance of thiazoles

Antibiotics, bacteriostatics, CNS regulators, and high-sales diuretics are just a few of the many medical chemistry applications for thiazole moiety-containing compounds. For the treatment of HIV infections, inflammation, and hypertension, the thiazole framework has found widespread application in drug development. Aminothiazoles are well-known for being novel adenosine receptor antagonists and estrogen receptor ligands. Other equivalents are used as schistosomicidal and anthelmintic medications, as a component of herbicides, or as fungicides that stop Xanthomonas from growing in vivo. Sherif. et al. syntheses of the thiazolylantipyrine and thiadiazolylantipyrine series of compounds, with the thiazolylantipyrine series having superior antibacterial properties to the thiadiazolylantipyrine series. Compounds 17 to 19 of the thiazolylantipyrine series are widely regarded as the more potent antimicrobial members identified in this study, possessing a broad spectrum of antibacterial activity against both Gram positive and Gram negative bacteria.

General Synthetic Routes to Thiazolo

Thiazole ring condensation can use pyrimidines with a nitrogen-containing substituent at position 5 as precursors for a variety of thiazolo pyrimidines. Diethyl amino-, nitro-, or acetylamino-malonate can be organized into 5-amino- or 5-nitropyrimidines by reacting with coupling reagents like thiourea, urea, guanidine, and amidines under alkali conditions. Oxygen is transformed into sulfur and the thiazole ring is closed by the reaction of the 4,6-dihydroxypyrimidine analog with a pyridine thionation reagent. Thiazolo pyrimidines are also produced when 5-amino-6- mercaptopyrimidines and reagents like phosgene, formic acid, and acid anhydride interact. Deoxygenation is all that is required to produce thiazolopyrimidines from 6-chloro-1,3-dimethyl-5-nitropyrimidinone, which can be obtained by reaction with mercapto compounds and monitored by base-catalyzed dehydrative cyclization. The anticipated thiazolopyrimidines can be produced by either oxidative deoxygenation with dimethylformamide at reflux temperature or reductive deoxygenation with sodium dithionite on the thiazolopyrimidine oxides.

Zablotskaya A and others prepared thiazole-containing trimethylsilyl ethers with various hydroxyl groups. All of the analyzed compounds have antihypoxic properties and can extend the lives of hypoxic mice by 20-78%. In most cases, the derivatives with and without silylation exhibit antihypoxic activity. The unique xanthine oxidase inhibitor febuxostat 29, which was approved by the FDA in, is

another example of a drug with a thiazole ring. Non-competitive inhibition of xanthine oxidase is how this inhibitor works. As a result, less of the oxidation product uric acid is produced. As a result, it is a very well-planned treatment for gout hyperuricemia.

CONCLUSIONS

The chronology of thiazole-derived compounds has been organized and presented in a systematic manner in this review article. There are three main sections to this review: Thiazoles in their preclinical and developmental stages, thiazoles in clinical trials, and as treatment drugs. With a few exceptions, research conducted prior to 2010 was included in the preclinical investigation section. There were 11 subsections in the preclinical investigation section: Thiazole as an anticonvulsant, an antimicrobial, an antitubercular, an antiinflammatory, an antimalarial, an antiviral, an antidiabetic, an anti-A1 receptor, and a bioactive agent. This review's numerous thiazole compounds appeared to be more potent than reference drugs, indicating that they are excellent candidates for further development and modification that could result in new drugs.

From the reaction of chloride, chloroacetone, -bromoketones, ethyl chloroacetate, and 2,3-dichloroquinoxaline, a novel series of substituted thiazolyl derivatives with antimicrobial properties was screened in good to excellent yield. With a range of MICs, compound 46 demonstrated effective antibacterial and antifungal properties. The electron-drawing group was found to be the result of the structure-based activity analysis. at the phenyl ring's p-position was necessary for the antimicrobial activity.

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