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COMPREHENSIVE REVIEW OF THE MEDICINAL AND BIOLOGICAL ROLES OF THIAZOLE AND ITS DERIVATIVES

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Abstract :
Thiazole, a five membered heteroaromatic ring, is an important framework of a large number of synthetic compounds. Its derivatives having a diverse range of medicinal and biological activities such as analgesic, antioxidant and antimicrobial including antimalarial, antifungal, antibacterial, antiallergic, anti-inflammatory, antipsychotic and antihypertensive. thiazole used effectively and additionally it is a non-cancer causing in nature. Describe diverse pharmacological activities and their pharmacological activity against different types of bacteria is the primary goal of this review paper. A new medicinally active thiazole and its derivatives are being actively designed by scientists due to their enormous biological significance. To help other researchers create new molecules of thiazole derivatives with stronger biological activities, this review explains the chemistry of thiazole, its synthesis pathway, and its biological activities. In recent decades, a large number of research articles about the synthesis and biological activity of thiazole derivatives have been located, rigorously examined, and organized.

INTRODUCTION

A series of significant work by Hofmann and Hantzsch in the late 19th century contributed to establish the research on thiazole synthesis chemistry. The thiazole ring, which belonging to the group of five-membered heterocyclic molecules and contains a strong S-C-N fragment, has been the focus of multiple investigations to date· discovering the presence of a thiazole derivative structure in the cyanine dyes as a sensitiser for photography. Thiazole ring, with its dyestuff property, is regarded as one of the first steps in its application in various commercial business fields.[1-2]

The strongly aromatic nut-like odour of the cocoa extract was initially discovered by Stoll et al. in 1967 as a consequence of thiazole derivative chemical substances.[3] The possibility that garnered the attention of the researchers was further supported by studies confirming that the thiazole groups have a strong taste constituent in modern food industry. However, the thiazole molecule is present in several synthetic categories of medicines as well as naturally occurring compounds like thiamine (often referred to as vitamin B1), thiamine pyrophosphate (TPP), bacitracin, epothilone and penicillin antibiotics. Earlier investigations have proven the unquestionable significance of thiazole-based substances' useful pharmacological function as antimicrobial, anti-diabetic, anticonvulsant, anti-inflammatory, antioxidant, anti-HIV, antitumor and more properties. The thiazole molecules, also known as 1,3-thiazole, is a heterocyclic molecule containing a chemical formula C3H3NS. It consists of a five-member ring which includes both nitrogen and sulphur heteroatoms throughout the entire cyclic structure. Sulphur is found in the initial position whereas nitrogen is found in the third place in the thiazole structure. [1,4,5,6]

Thiazole plays crucial role in several medicinal compounds. Examples of medications that contain thiazoles include the anti-inflammatory pharmaceuticals fanetizole, meloxicam, and fentiazac; the anti-HIV medication ritonavir; the antifungal medication ravuconazole; and the anti-neoplastic treatments tiazofurin and dasatinib. Recent studies have shown that the thiazole essential structure is used in drug design and the creation of new therapeutic medications. The thiazole ring in five-membered heterocycles has been used in a variety of ways during the lead identification and development process, such as as a spacer and as pharmacophoric and physiological isosteric components. Additionally,

the presence of thiazole rings in a drug's structure could be used to identify its physicochemical and pharmacokineticproperties. Determining the structural and biological significance of thiazoles is the aim of this overview.[7] More than 18 FDA-approved medicinal products contain the thiazole scaffold. Cefiderocol, marketed as Fetroja®, was the very first siderophore antibiotic approved by the FDA in 2019.This thiazole compound was discovered to be effective against an extensive spectrum of multi-drug-resistant Gram-negative bacteria, including Pseudomonas aeruginosa (P.aeruginosa) and is used to treat complex urinary tract infections in circumstances where no other treatment is available. Another thiazole-based medicine, alpelisib (brand name Pigray®), was approved once in 2019 for treatment of types of breast cancer. Breast cancer is one of the most prominent serious diseases globally as well as the second-biggest reason of cancer death, especially in developing nations. In 2018, the FDA approved Lusutrombopag is a medication that promotes platelet development in order to treat thrombocytopenia, including that which is brought on by chronic liver illness. Another example is cobicistat, which is a drug for the treatment of infections caused by the human immunodeficiency virus (HIV) by increasing the half-life of certain antiviral medications. The aim of this review is to highlight attention to recent developments in the identification of thiazole compounds that are biologically active. Since numerous reviews have been released, this one exclusively covers a brief period of time to till present day.[8,9]

Structural Characteristics:

Thiazole, also known as 1,3-thiazole, is a readily apparent to pale yellow flammable liquid containing a pyridine-like odour along with its chemical composition is C3H3NS. It is a 5-membered ring that has two nitrogen and sulphur edges and three carbons. The system of numbers for naming the thiazole derivatives is shown below.

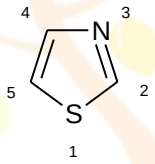


figure: 1

moiety is an essential component of vitamin B1 and epothilone. It is an aromatic chemically which adheres to Huckel's rule. Delocalization of a single pair of electrons from the sulphur atom completes the 6 π electrons.[7,10] The resonance forms are:

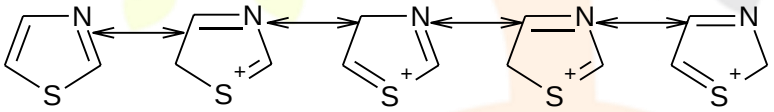


figure:2

Properties

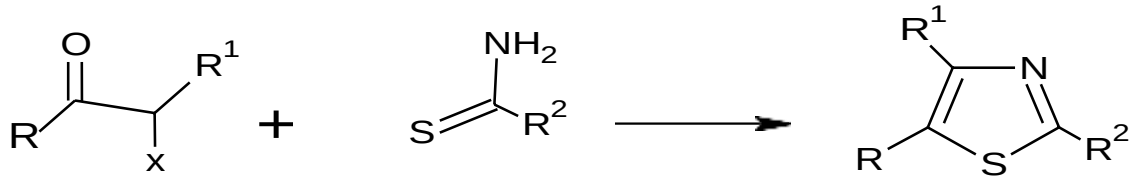
Physical properties

- Thiazole constitutes a light-yellow flammable liquid.
- It has tastes like pyridine.
- It is slightly dissolves in ether and alcohol but sparingly soluble in water.
- Its ionisation potential is 9.50 Ev and its density is 1.2 gm/cm3.
- It possesses a 1.61D dipole moment.
- It has a conjugated acid pKA of 2.5 and a boiling point between 116 and 118˚C.[7,10]

Thiazole derivatives

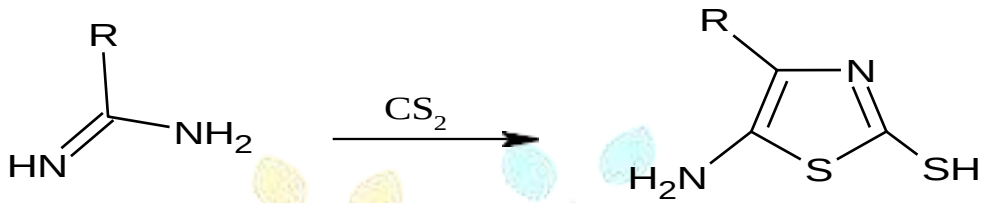
Chemistry of Thiazole Derivatives

Thiazole and its derived compounds can be synthesized using a number of procedures. Some of them are listed as follows: Hantzsch (1889) described synthesis of thiazole derivatives as well as the reaction between α-halocarbonyl compounds and thioamides or thiourea (Scheme 1).[7,11]



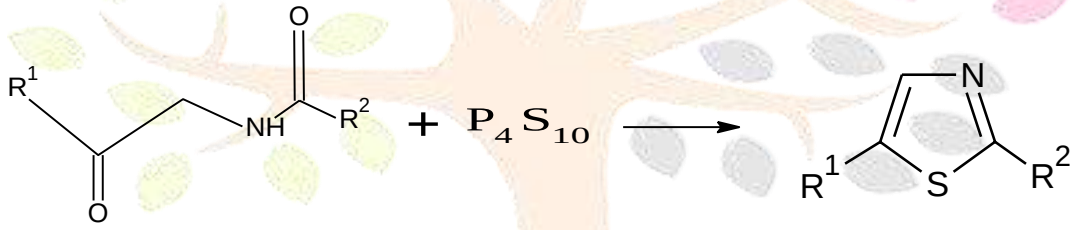
scheme 1. hantzsch synthesis of thiazole

The Cook–Heilbron method, which involves reacting an aminonitrile with carbon disulfide, is an additional method that produces thiazole derivatives such as 2,4-disubstituted 5-aminothiazole compound are synthesized. (Scheme 2).[12]



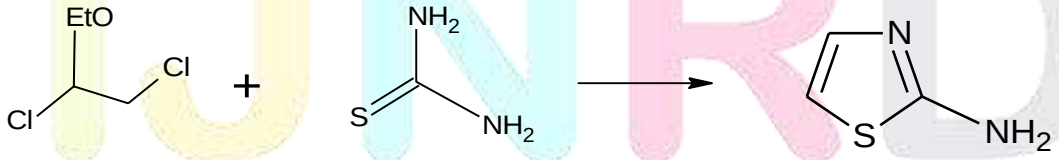
scheme 2. cook-heilbron thiazole synthesis.

The synthesis of thiazole derivatives can be obtained by the Robinson-Gabriel method, which involves rearrangement acylaminocarbonyl molecules in the presence of phosphorus pentasulfide at equilibrium quantity (Scheme 3).[13]



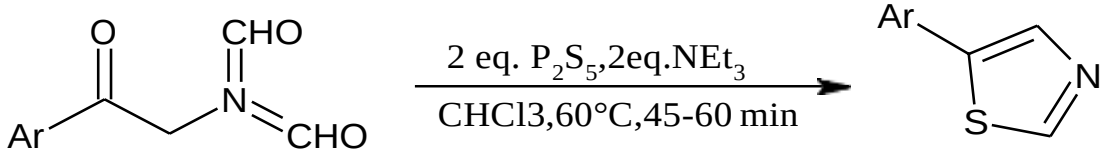
scheme 3. robinson-gabriel thiazole synthesis.

The nucleophilic attack of the thioamide sulfur atom on the alpha carbon of the alpha-halocarbonyl results in the formation of an intermediate, which undergoes dehydration to generate the identical thiazole. A particular variant of the previously mentioned process incorporates combining thiourea or its derivatives with 1,2-dichloro-1-ethoxyethane (Scheme 4).[8]



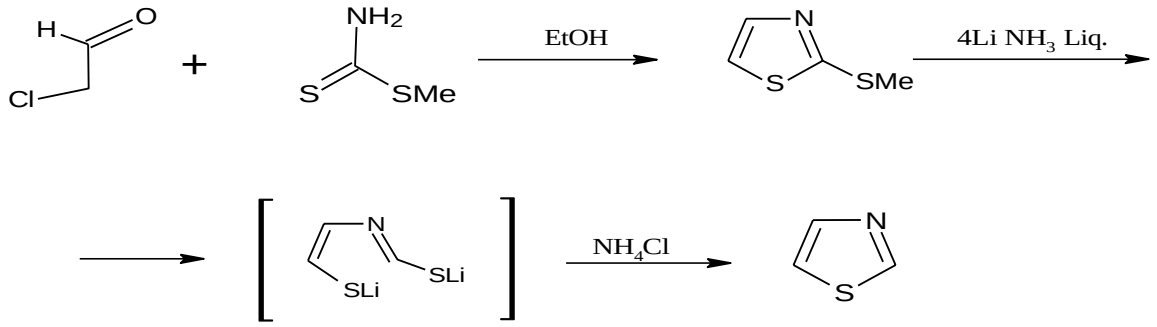
scheme 4. synthesis of 2-aminothiazole from thiourea and 1,2-dichloro-1-ethoxyethane.

In addition, there are distinctive and modern techniques for the production of thiazole derivatives. N,Ndiformylaminomethyl aryl ketones were treated with Triethylamine and phosphorous pentasulfide in chloroform resulting in 5-arylthiazoles. The method reaction gives 5-arylthiazoles in significant yields (Scheme 5).[.[14]



scheme 5. synthesis of 5-arylthiazoles.

The fascinating thiazole synthesis takes place by reduction of 2-methylthiothiazole (Scheme 6).[.[15]



scheme 6. synthesis of thiazole by reduction of methylthiothiazole.

Pharmacological Activities:

Antifungal and Antibacterial Agents

Fungi and bacteria are growing increasingly resistant to antimicrobial therapy as a result of broad-spectrum antimicrobial actions and a limited number of medicinal products. To address this issue, a number thiazole-containing compounds have been developed for the treatment of bacterial and fungal infections.

The condensation of 2-bromo-4-methoxy acetophenone with 2-acetylpyridine thiosemicarbazone formed a pyridinyl thiazole ligand containing a hydrazone moiety. Researchers additionally developed a cobalt complex by treating the ligand with cobalt precursor. Gram-positive bacteria (Bacillus subtilis, Streptococcus fecalis, and Staphylococcus aureus) and gram-negative bacteria were used to investigate the antibacterial qualities of the ligand and its complex.(Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Klebsiella pneumonia, and Proteus vulgaris).[18]

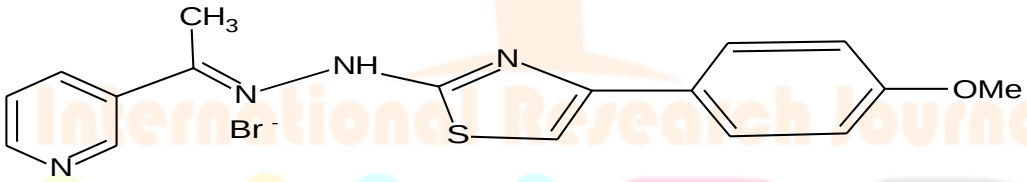
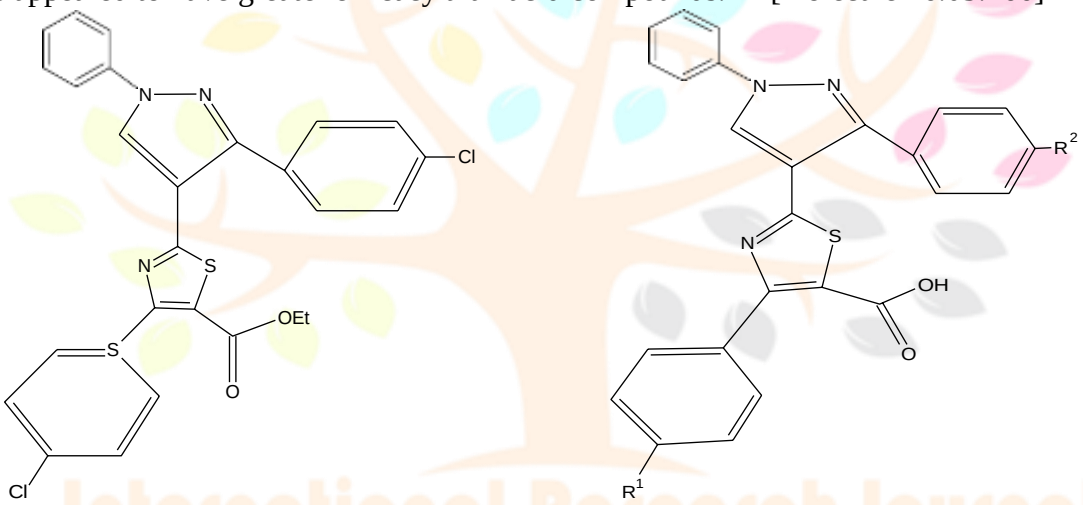


figure 3: pyridinyl thiazole ligand with antimicrobial activity

Anti-inflammatory Agents

The mechanism that organisms react to different stimuli is through inflammation. Various inflammatory diseases, including psoriasis, asthma, and arthritis, require long-term or continuous treatment. Nonsteroidal anti-inflammatory medications (NSAIDs) are the most commonly used medications for the treatment of chronic as well as acute inflammation, pain, and fever. However, its long-term clinical use is associated with serious adverse reactions, such as gastrointestinal (GI) issues, kidney disease, adverse cardiovascular events. Bleeding and nephrotoxicity.
Neutralization of tumor necrosis factor (TNF), leukotriene receptor blockers, cytokine or leukotriene inhibitors, and other significant elements of the inflammatory reaction for systemic medical conditions are among the therapeutic alternatives being researched for inflammation control. However, the primary objective remains cyclooxygenase (COX), an enzyme responsible for the first step of arachidonic acid conversion into prostaglandins (PGs). Classical NSAIDs, especially indomethacin, inhibit both isoforms of COX-1, which is constitutively expressed in most organs and tissues and promote the synthesis of PGs responsible for the controlling of physiological cellular activities; COX-2 is primarily induced by several stimuli such as cytokines, mitogens, and endotoxins in regions of inflammation. consequently, their therapeutic consequences predominantly attributed to the reduction in inflammatory substances PGs formed by COX-2, whereas their adverse reactions are caused by the inhibition of constitutive COX-1 variant. synthesis and development of a new class of pyrazolyl thiazole carboxylates along with associated acid compounds as well as an in vivo analysis for their anti-inflammatory potential using a rat paw edema technique derived from carrageenan. With inhibitory percentages ranging from 89.59% to 93.66%. A, B, and C were the most active molecules. Ester compounds appeared to have greater efficacy than acid compounds.[19] [molecule 26.03.166]

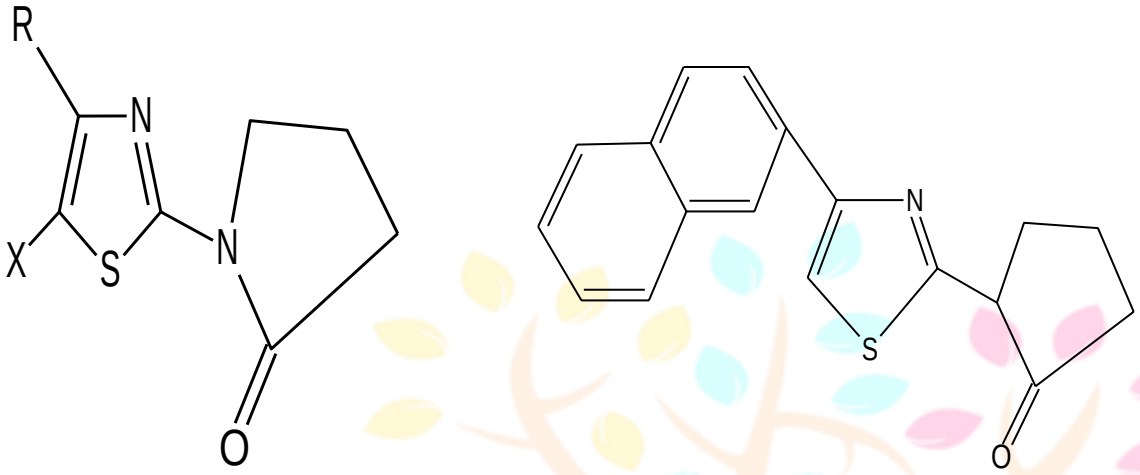


R1=F, R2=H
R1=FOMe, R2=Cl

figure 4: structure of pyrazolyl thiazole carboxylates and thiazole bearing pyrozole derivatives.

Anticonvulsant

In 2015, the synthesis of two new class of molecules with thiazole rings, and the anticonvulsant activity of these molecules was determined. Thirteen novel 1-(thiazole-2 yl) pyrrolidin-2 -ones with a broad structure were developed. Three seizure models have been used to establish the activity which are follows MES, PTZ, and picrotoxin. 1-(4-(naphthalen-2-yl) pyrrolidin-2-one was determined to be the most potent chemical substances; (Figure 5) shows that with a PTZ effective dosage (ED50) value of 18.4 mg/kg in mice. Additionally, a computational evaluation involving docking studies and the prediction of pharmacokinetic parameters was carried out.[20] [molecule 26.03.166]



a) **b)**

a: R=F
b: R=Cl

figure 5: structures of 2,4,5-trisubstituted thiazoles (a), 2-(thiazole-2-yl) isoindoline-1,3-diones (b) and 2-(cyclopentylmethylene) hydrazinyl-1,3-thiazoles.

Anti-Oxidant agents

Thiazole compound of antioxidant activity (Figure 6). when the molecule compared with standard ascorbic acid it demonstrated greater potency towards erythrocyte hemolysis (0.85%).[21]

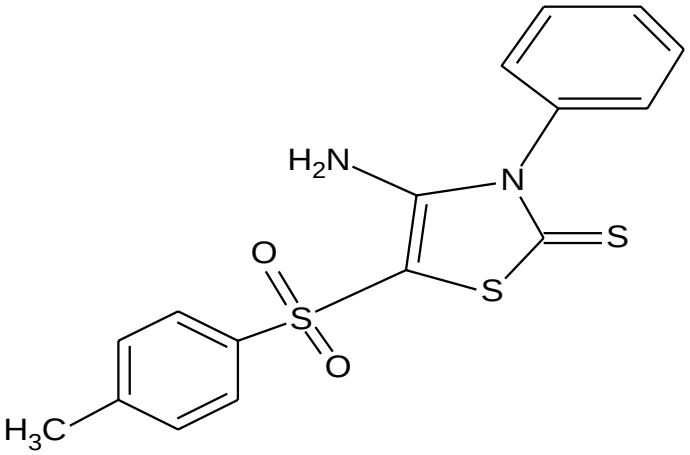
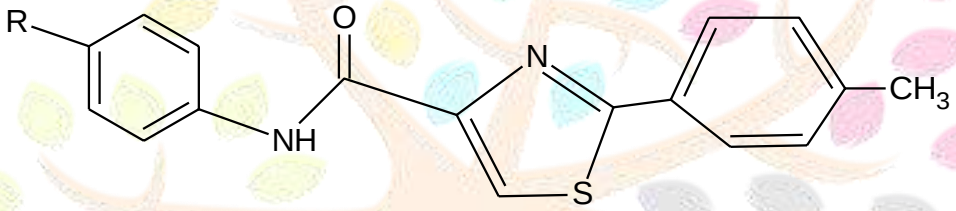


figure 6: thiazole derivative as potent anti-oxidant agent

Anticancer Agents

a novel group of thiazole compounds (Figure 7), and they investigated the anticancer properties of these compounds against human carcinoma cell lines SKNMC (neuroblastoma), Hep-G2 (hepatocarcinoma), and MCF-7 (breast cancer). The compounds containing nitro groups at the para position and chloro groups at the meta position have indicated the highest anticancer activity against Hep-G2 and SKNMC cells, with IC50 values of 10.8 and 11.6 μM, respectively.[22]

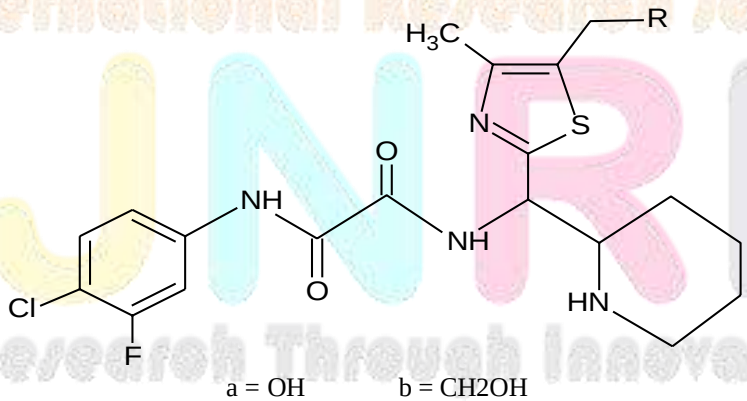


R = o – NO2, m-NO2, p-NO2, m-Cl, p- Cl, p-Cl, p-F

figure 7: 2-phenylthiazole-4-carboxamides having anticancer activities.

Antiviral Agents

The synthesis of thiazole derivatives containing an oxalamide unit (Figure 8), and these compounds examined for the HIV virus. Both compounds have greater effectiveness against HIV-1, determined by the scientific evidence. By inhibiting the CD-4 binding site the chemicals aim to damage the HIV virus. As a result, the molecules prevent the virus from infecting the host cell.[23]



a = OH b = CH2OH

figure 8: thiazole carrying oxalamides moiety.

Marketed Formulations

Pramipexole, Acinitrazole, Sulfathiazole, Bleomycin, Tiazofurin, Ritonavir, Cinalukast, Nizatidine, Fenetizole, and Meloxicam are among the clinically utilized medicines or potential medications containing thiazoles.

Pramipexole

- Tetrahydro benzothiazole derivatives such as pramipexole are formed as di-HCL salts (side chains NH and hetero N) of single (S- (-)) isomers which are medicinally active.
- Pramipexole is readily absorbed after oral administration.

Mechanism of action

It is authorized to treat Parkinson's disease using a non-ergot dopamine agonist. Individuals with severe Parkinson's disorder and those who have never taken levodopa benefit from pramipexole's potential to alleviate motor abnormalities. Pramipexole reduces the Dopamine production and synaptic release in healthy dopaminergic systems by functioning on presynaptic D2 and D3 dopamine glutamate receptors.[24]

Sulphathiazole

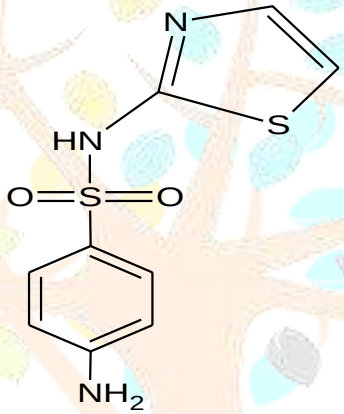


figure: 10

- Sulfathiazole is a fast-acting sulfa medicinal product.
- It used to be an effective oral and topical antibacterial.
- It works well against a variety of harmful pathogens, including gram-positive and gram-negative.
- Although no longer consumed by humans, it is still used in cattle.

Mechanism of Action:

Sulfathiazole interacts with the synthesis of folic acid a compound that bacteria require to growth thereby preventing further development of bacteria.[7]

Conclusion:

Thiazole Derivative have been reported to possess broad spectrum of medicinal activities like antifungal, antibacterial, anti-inflammatory, anticonvulsant, antiviral, antioxidant and anticancer. The presence of thiazole ring in many drugs such as fanetizole, meloxicam, fentiazac, ritonavir, ravuconazole, Tiazofurin, dasatinib, febuxostat etc. Various recent new drugs developments in thiazole derivatives show better effect and less toxicity. The thiazole nucleus plays a crucial role in discovering novel medications to treat numerous diseases. This review emphasizes the latest scientific and biological applications of thiazole derivatives with various therapeutics objectives.

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