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A Review on Thiazole Scaffolds and its Biological Activity

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ABSTRACT:

One of the most common heterocyclic compounds with five members that has both a nitrogen and a Sulphur atom is thiazole. Thiazole is an important molecule found in many natural and/or synthesized chemicals, which have a variety of therapeutic uses. Several modifications were made to the ring. The goal is to create new thiazole compounds and to evaluate their biological activities such as antibacterial, antidiabetic antimicrobial, anticancer, antitumor, antimalarial and anti-inflammatory activity and also a chemistry and physical characters of thiazole. As thiazole is of great importance in medical field.The synthesis were done in that synthesis of 2 ,4-,5-trisubstituted thiazole, synthesis of substituted aminothiazoles, synthesis of 2 hydroxythiazole derivatives, synthesis of 5-aminothiazole derivatives, synthsize of 2-phenyl5 alkyl- thiazole derivatives.

Key words: Thiazole; synthesis; biological activities.

Introduction

Thiazole is a heterocyclic compound with five membered that comprise sulfur and nitrogen atoms(C3H3NS) together with Isothiazole isomer Thiazole is also called as 1,3 Thiazole. originally Thaizole was characterized by Weber and Hantzch in 1887. Prop verified its composition in 1889[1]. Alkaloids, anabolic steroids, vitamin B1 – Thiamine, and many other naturally occurring substances contain thiazole, a basic stucture. A component of azole heterocycle, which also includes pyrazole, imidazole, isoxazoles, and oxazoles, is n-thiazole. Thiazole is organic heterocycle and it is aromatic also. In nature, thiazoles are widely distributed. Alomost in every organism, the α-keto acids undergo decarboxylation with the assistance of thiamine pyrophosphate coenzyme, which comprises a thiazolium ring that acts as electron sinkThe thiamine derivatives, as well as enzymes that the existence of B1 vitamin s necessary for the action, are universally found in all human cells. thiazoles are used in the process o f m a k i n g N -S f r e e complexes and carbine metals in transition. Due to their wide range of pharmacological actions, heterocyclic compounds are constantly producing novel therapeutic medicines. The heterocycle's capacity to bind to different enzymes' active sites or other regions accounts for their biological activity. The significant part of the pharmacophores of many significant pharmaceutical compounds is the thiazole. Molecules and the assessment of the biological activity they exihibit, antibacterial, antiprotozoal, antitubercular anthelminitics , antifungal , antiulcer , antineoplastic , antibiotic, anti-inflammatory , antimicrobial , anti-HIV , and also anticancer etc[2].

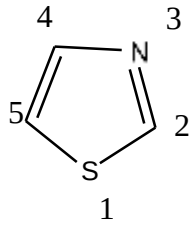

Fig 1:1,3 Thiazole

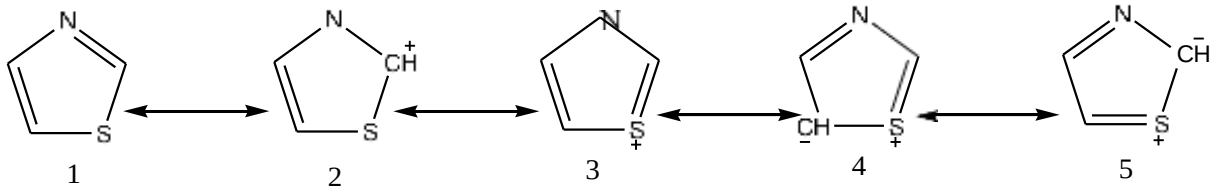

Fig 2:Resonance structure of thiazol

1. Review of Literature

1. S. A. Ibrahim and H. F. Rizk *et al*(2020), "Synthesis and Biological Evaluation of Thiazole Derivatives," in Azoles, A. Kuznetsov, Ed., Rijeka: IntechOpen, Stated that the creation and biological assessment of thiazole compounds, which are used in agrochemicals and medicines. several thiazole derivative synthesis techniques, such as Cook-Heilbron, Gabriel's synthesis, and Hantzsch Thiazole. antibacterial, anticancer, and antioxidant capabilities.This section highlights the importance of thiazole molecules in science and its potential for medicinal development.
2. C. Barba-Ostria *et al*., "Evaluation of Biological Activity of Natural Compounds: Current Trends and Methods," Molecules, vol. 27, 2022, stated that the inflammation is protective action taken by the particular live species against the dangerous pathogens also given the methods to evaluate in vitro antidiabetic characteristics.
3. S. Baliyan *et al*., "Determination of Antioxidants by DPPH Radical Scavenging Activity and Quantitative Phytochemical Analysis of Ficus religiosa," *Molecules*, vol. 27, no. 4, 2022, stated that theDPPH assay used to count antioxidant capacity ,indicating the plants potential in treating free Radical-related disorders
4. M. Balouiri, M. Sadiki, and S. K. Ibnsouda, "Methods for in vitro evaluating antimicrobial activity: A review," *J. Pharm. Anal.*, vol. 6, no. 2, 2016,stated that various biological assays used to determine the antimicrobial activity. It emphasizes the need for standardized testing methods to ensure reliable and comparable results across different studies.
5. N. TH, S. S. Nair *et al*, "A Review on Synthesis and Biological Activity of Thiazole and. Various methods for synthesizing thiazole and its derivatives are discussed, such as Gabriel Synthesis, Cook-Heilborn's Synthesis, and others.The document details the pharmacological activities of thiazole derivatives, including their use as antifungal, antibacterial, anticancer, antiviral, anti-TB its Derivatives," *Int. J. Pharm. Sci. Rev. Res.*, vol. 70, , 2021,stated that the Thiazole is described as a clear to pale yellow flammable liquid with a pyridine-like odour, and its molecular structure includes one sulfur atom and one nitrogen atom, and antioxidant agents.
6. C. Sanjai, S. S. Hakkimane *et al*, "A comprehensive review on anticancer evaluation techniques," *Bioorg. Chem.*, vol. 142, no. August 2023, p. 106973, 2024,stated that various analytical methods used in anticancer research, such as cell viability assays and genomics.It also explain the calorimetric and fluorescence assay for assessing drug efficacy and cell health.
7. V. Gupta and V. Kant *et al*, "A Review on Biological Activity of Imidazole and Thiazole Moieties and their Derivatives," Sci. Int, 2013, stated that the heterocyclic compounds, particularly those with five-membered ring like imidazole and thiazole which have wide range of biological activities ana therapeutic properties. Imidazoles have highlightened for their pharmacological activities including anti-viral,antiinflammatry, analgesic, antdepressant, anticancer,antimicrobial, and anthaishmanial effects. Thiazoles are highlightened for their structural similarity to imidazoles and their applications in various biologically active molecules,with activities such as antitumor, anti-inflammatry, antimicrobial, antifungal, anticonvulsant, and antibacterial.
8. M. S. Parvin, N. Das *et al*,"Evaluation of in vitro anti-inflammatory and antibacterial potential of Crescentia cujete leaves and stem bark Pharmacology and Toxicology," *BMC Res. Notes*, vol. 8,2015,stated that Human Red Blood Cells membrane stabilization and disc diffusion method used to evaluate antiinflammatory and antibacterial activity.

2. Physical characteristics

Thiazole is a transparent to yellow combustible substance. Thaizole is typically a flammable, pale yellow liquid with an odor similar to pyridine. It dissolves in ether and alcohol, but only very slightly water-soluble. It's pka is 2.5 and it's boiling point is between 116 and 118°C. The dipole moment of this object is 1.61D[1] .

3. Chemistry of a thiazole

A nitrogen and a sulfur atom are both present in the aromatic five- member ring of thiazole , a heterocyclic molecule . Thiazole and associated these are 1,3- azoles. They are identical containing the 1,2- azoles , referred to as isothiazole[2].

4. Methods of synthesis

4.1 Synthesis from α-halocarbonyl compounds

4.1.1 Reactions with thioamide

When thioamides and other α-halocarbonyl compounds were combined, alarge no. of thiazoles with multiple functional groups at position 2,4,or5[3][4] where produced.

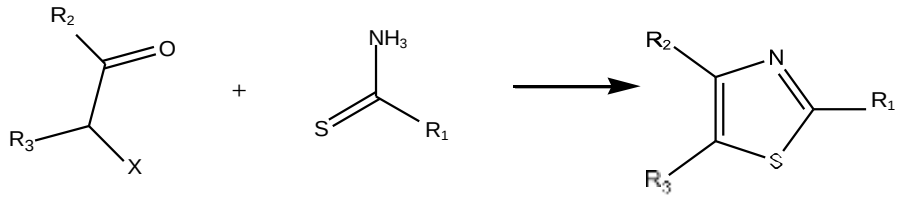

Fig 3:Synthesis of 2,4,5-trisubstituted thiazole

4.1.2 Reaction with n-substituted thiourea

2-N-substituted thiourea compounds and halocarbonyl compounds reacted to produce monosubstituted or disubstituted aminothiazoles[4][5].

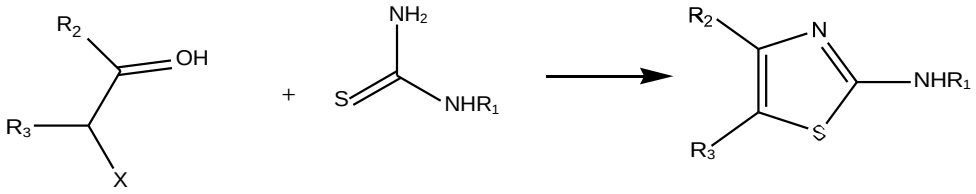

Fig 4:Synthesis of substituted Aminothiazoles

4.1.3 Reaction with esters of thiocarbamic acid

2 Hydroxythiazole derivatives were produce by the condensation of α-halocarbonyl compounds with thiocarbamates [6][7].

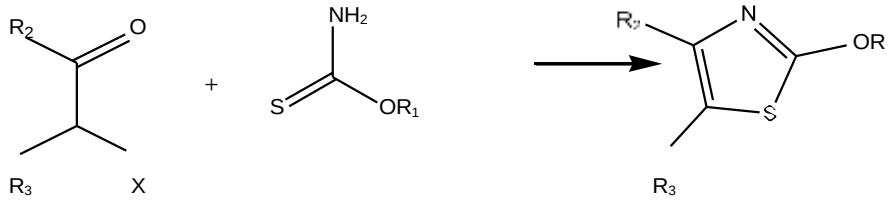

Fig 5:Synthesis of 2-hydroxythiazole

4.2 Synthesis from α-aminonitrile compounds

4.2.1 Reaction with the carbon disulfide:

When tcarbon disulfide and alpha-aminonitriles are condensed, 2-mercapto-5-amino thiazoles are produced these can be further processed to yield 5-amino thiazoles that are substituted in position 2 in[4]

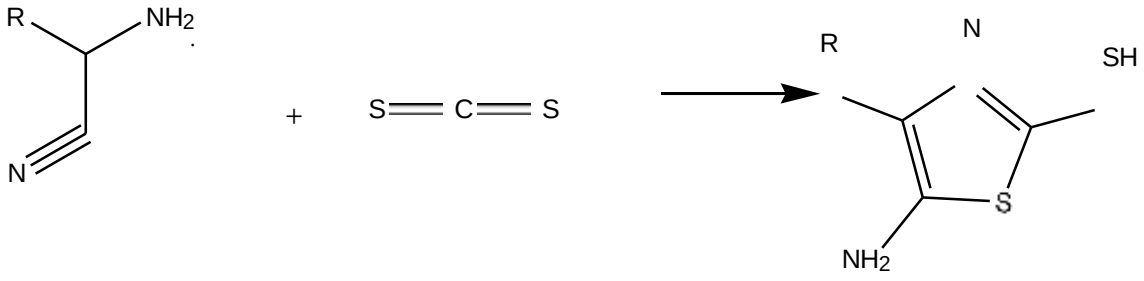

Fig6:synthesis of5-aminothiazole derivatives

4.3 Reaction with ester and salts of dithioacids

Alpha-aminonitriles were reacted with the salts or esters of dithioformic and dithiophenacetic acids to generate 5-aminothiazoles in good yields in [4].

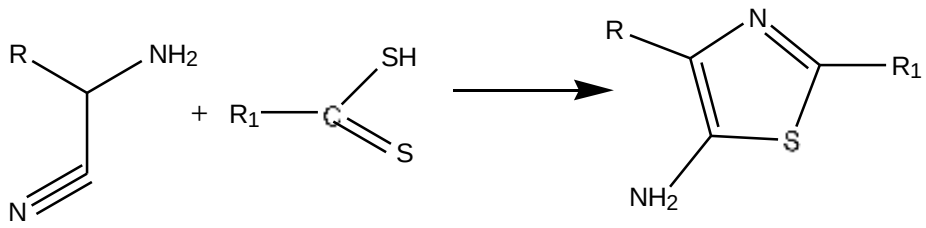

Fig7: Synthesis of5-aminothiazoles derivatives

4.4 Gabriel's synthsis

Gabriel originally classified this response in1910. A good yield of 2-phenyl-5-alkyl-thiazole was produced by the reaction of phosphorus pentasulfide with acylaminoketonein [4].

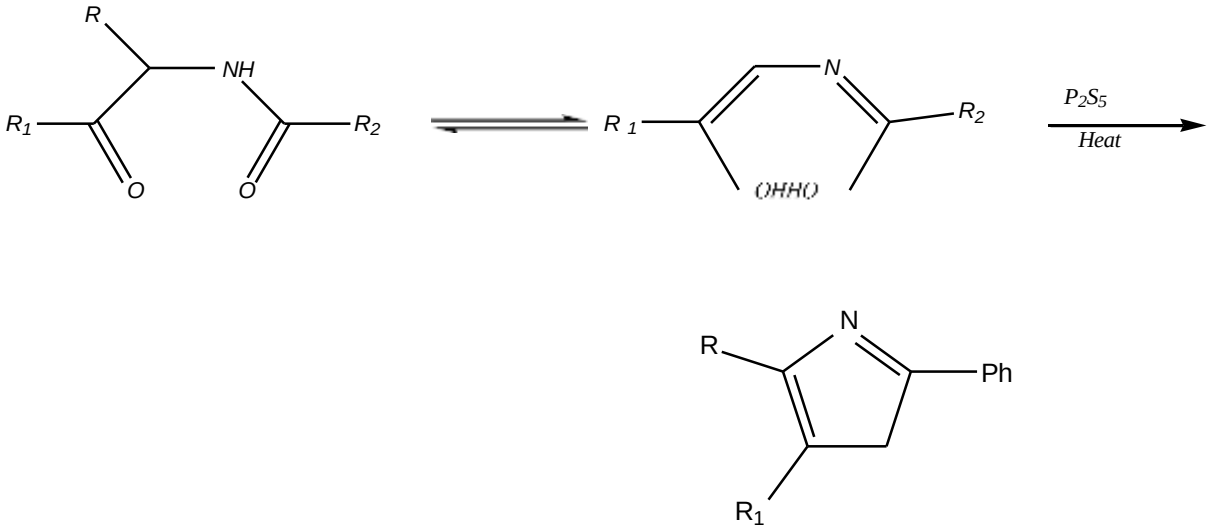

Fig8:Synthesis of 2 phenyl-5-alkyl thiazole derivatives R1

4.5 Synthesis with eco-friendly methods

4.5.1 Using microwave assisted synthesis

Strong reaction conditions and catalyst and solvent waste are part of the production of thiazole derivatives. In order to address these drawbacks,environmentally friendly processes such as the microwave irradiation approach are frequently employed in the production of thiazole derivatives. Microwave heating is used in solvent –free environment to synthesize a class of thiazoles in timely and elegant manner[5][8].

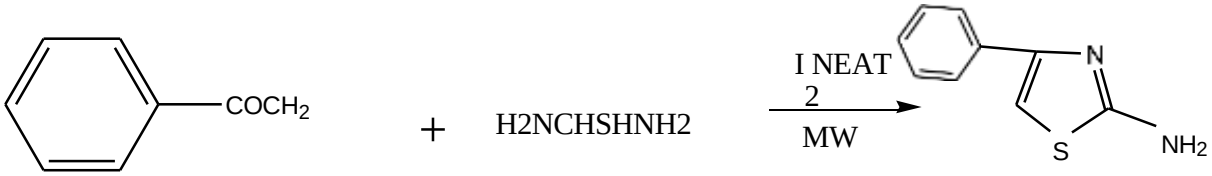

Fig9: Synthesis of thiazoles under microwave irradiations

5. Biological activity of thiazole and its derivatives

5.1 Antibacterial and antifungicidal activity ISO 22196 Standard Method

With very little adjustments, the ISO 22196 was completed. Filterable 90 mm Petri dishes were filled with 50 mm x 50 mm sections of the film and unstructured smooth control films. Once the ultimate bacterial concentration of 6×105 CFUs/mL was reached, 400 microliers of serially diluted bacteria inoculum were pipetted onto the test surfaces. To ensure that the bacterial inoculum was evenly distributed across the surface, a 40 mm by 40 mm piece of Stomacher bag was placed over it. For a full day, the specimens were grown at 35 °C with a relative humidity of greater than 90%. In order to extract

the germs from the plastic samples' surfaces, 10 milliliters of Soybean Casein Lecithin Polysorbate (SCDLP) broth were introduced into the Petri plate. To guarantee that the samples were thoroughly cleaned, the SCDLP was taken then released at least four times. A total of ten SCDLP serial dilutions were prepared in PBS, and 50 µL of dilutions numbered 10–4, 10–5, 10–6, and 10–7 were cultivated on Tryptic soy agar plates containing 5percent sheep blood. Dishes were kept for growth for twenty-four hours at 35 °C. To calculate the amount of living bacteria per cm2, the amount of colonies per dish was counted and utilized, as per the following equation:

$$N=(100\times C\times D\times V)/A$$

where V is the volume of SCDLP in milliliters, A is the film's surface area (in centimeters), D is the dilution factor, and C is the average CFU count[9].

5.2 Antidiabetic activity

422 million individuals globally suffer from diabetes, a global health issue. Untreated, this disease causes severe multi-organ failure and 1.5 million deaths annually. Elevated blood glucose levels are one of its hallmarks. A diverse class of compounds known as antihyperglycemic medicines is produced chemically or extracted from natural sources. Their purpose is to either decrease or stop the rise of blood glucose levels. α-amylase inhibition and α-glycosidase inhibition utilized to assess the in vitro antidiabetic qualities of natural compounds[10].

Procedures: In contrast to the new, innovative MAE methodology, two traditional extraction methods—Cold maceration and Soxhlet—were employed.

Soxhlet extraction method: Comprehensive Using traditional equipment, a precise 50 g sample of powdered material was used for the soxhlet extraction process. 80% methanol was used as the extraction solvent during the process. Following extraction, the methanol solvent was removed by centrifuging the mixture in a rotating evaporator set to 40°C and low force. Methanol extract free of solvent was then assessed.

Cold maceration method: A closed conical flask was used for the maceration process, which lasted 72 hours. 50 g of powdered compound and 80percent methanol were used as the solvent in both cases. The suspension was centrifuged after maceration, and the supernatant evaporated under reduced pressure. The resulting solvent-free methanol extracts were assessed in a similar manner[11].

5.3 Antimicrobial activity

Acinetobacter baumannii, Pseudomonas aeruginosa, Enterococcus sp., Staphylococcus aureus, Enterococcus sp., and Candida species with inherent and active resistance to fluconazole are just a few examples of the multidrug-resistant strains that have spurred research in field of antimicrobial drug design and development.These days, hybrid compounds with a thiazole nucleus combined with additional pharmacophore characteristics are given special consideration. Several heterocycles, including pyrazole, triazole, 1,3,4-oxadiazole, pyridine, 1,4-dihydropyridine, indole, quinoline, pyrimidine, pyrazine, triazine, and thiophene, were combined with thiazole to create a variety of hybrid molecules that were then tested as antimicrobial agents [12][13]. Additionally, new hydrazones and Schiff bases with thiazole scaffolds have shown promising antibacterial action [14][15]. Six trimethyl[(5-substituted-1H-indol-2-yl)carbonyl]–-1-Fourth-{[4-(substitutedthiazol-2-yl)iminoethyl)phenyl] hydrazono}- 2-pyrazolin-5-one Both traditional and microwave techniques were used to create derivatives. 35 different bacterial and fungus strains were used to assess the antibacterial properties of the produced compounds[16]..

Agar disk-diffusion method:

Agar disk-diffusion testing, first employed in 1940, is the standard method for routine antibiotic susceptibility testing in many clinical microbiology laboratories. The Clinical and Laboratory Standards Institute (CLSI) now provides a number of accredited and recognized standards for testing on yeasts and bacteria. Inspite of that not every fastidious bacteria can accurately examined by this method, standardization have been developed to check some fastidious bacilli pathogens, such as streptococci, H. influenzae, Haemophilus parainfluenzae,

N. gonorrhoeae, and Neisseria meningitidis, using specific culture media, varied incubation conditions, and interpretive criteria for restriction zones. A standardized inoculum of the test organism is utilized to inoculate agar plates in this commonly used technique. After that, filter paper discs with a diameter of about 6 mm are filled with the test material and placed on the agar's surface at the designated concentration.The ideal setting has been established for the Petri dishes. A antimicrobial agent that permeates the agar usually inhibits the test microorganism's ability to germinate and develop. Next, the overall size of the growth zones that impede growth is ascertained. Furthermore, the minimum inhibitory concentration (MIC) cannot be determined using the agar disk-diffusion approach since the amount of the antimicrobial agent that diffused in agar medium cannot be quantified. It is still possible to calculate an estimated minimum inhibitory concentration (MIC) for a variety of bacteria and drugs by comparing the inhibitory zones with stored algorithms.Still, the disk diffusion assay offers many benefits over other methods, such as comfort of use, low cost, the ability to test a large area of bacilli and antimicrobial medications, and the comfort of managing the findings. Additionally, numerous research investigations have shown that antibiotherapy depending on the antibiogram of the causal agent is highly desired for patients with bacterial infections [17].

5.4 Anticancer activity

As an in vitro assay, colorimetric and fluorometric assays are used to assess cytotoxicity and preliminary anticancer efficaciousness for cell viability. These tests are easy to use and reasonably priced. The reagent used to quantify the total number of living cells based on dehydrogenase activity (mitochondrial) is the primary distinction between the colorimetric and fluorometric assays.

Calorimetric assay:

Colorimetric and fluorometric assays are utilized as an in vitro method to evaluate cytotoxicity and preliminary anticancer efficaciousness for maintaining cell viability. These assessments are inexpensive and simple to apply. The main variation in both colorimetric and fluorometric assays is the reagent used to determine the overall amount of live cells based on dehydrogenase activity (mitochondrial).

MTT/MTS Assay:

The MTT assay measures the decrease of tetrazolium salt to an insoluble formazan in the mitochondrion of living cells, with an optical density of 570 nm, due to the action of mitochondrial dehydrogenases. Reducible activity is used to calculate the number of live cells. To dissolve the insoluble formazan product into solution, a solubilizing solution is added in this instance.

Method:

Replace the used media for attaching cells in each well with new medium after discarding the old one. Next, add the stock solution for MTT. Maintain MTT stock solution as a countermeasure. The plate is incubated for four hours at 37 °C. Add DMSO to each well and mix well to dissolve the formazan that is formed. Measure the absorbance at 570 nm following a 10-minute incubation period at 37 °C.

Another variant of the MTT assay that has been updated is the MTS assay. The process used here is based on the decrease of the tetrazolium compound by living cells, which results in a dyed formazan that dissolves in the growing media.

Method:

Add the MTS reagent to the newly prepared cell culture medium. Incubate for 0.5 to 4 hours under standard culture conditions. Once the plate has been shaken immediately, measure the absorbance at 490 nm.

XXT Assay:

In this experiment, the tetrazolium ring is broken down by viable cells using mitochondrial dehydrogenase activity as a proxy for viable cell activity. Here, the water soluble substance is called Formazan (orange in colour).The XTT reagent's cytotoxic properties cause the cells under study death, allowing for only one evaluation. This is a sensitive, fast, easy-to-use, and highly precise test.

Method:

Fill each well with 100 µL of the ready-to-use XTT reagent. At 37 °C, incubate for 4 hours. Check the absorbance at 450 and 660 nm. Determine the particular absorbance.

Crystal violet staining(CVS):

Adherent cells are identified using this technique. The test involves coloring the corresponding cells since the dye binds to both the proteins and DNA of living cells. A quick and accurate screening method is the crystal violet assay. strategy for ascertaining how growth inhibition and cell survival are affected by chemotherapy or any other substances. It is not impacted by variations in the metabolic function of the cell and is quick and accurate when assessing cell viability in a range of conditions. Consequently, research including medications that modify cell metabolism should not use this test to calculate the ratio of live cells, use a microplate reader that features an excitation/emission filter range of 560–590 nanometer. This technique was developed by Zizheng Zou and colleagues .

Method: Place 50 µL of 0.1% CVS mixture into each well and let it sit at room temperature on a rocker for 20 minutes. Three complete washings are performed on the cells. at least a two- hour period of room temperature air drying are spent on the wells. A reading is taken at 590 nm after adding 10% acetic acid and incubating for an additional 20 minutes[18].

5.5 Antioxidant activity

DPPH RSA was used to test the Antioxidant activity

A 1,1-diphenyl2-picryl hydrazyl (DPPH) method was used to assess the drug's free RSA. A standard solution were prepared by mixing 24 milligrams of 1,1-diphenyl2-picryl hydrazyl in 100 milliliters of methyl alcohol. A acceptable mixture with absorbance of roughly 0.973 at 517 nm was obtained by filtering the DPPH stock solution with methanol. A test tube was filled with hundred microliters of sample extract and three mililiters of DPPH working solutions.As a standard, three milliliters of 1,1-diphenyl2-picryl hydrazyl containing solution in hundred Microliters of methyl alcohol has often served. Following that, the tubes was left in total blackness for a half hour. So, at 517 nm, the absorbance had been calculated. To calculate the percentage of antioxidants, or RSA, the below formula was adopted:

% of Antioxidant Activity =[(Ac-As)÷Ac]×100

whereby absorbance of the testing item is As, Ac is control reaction absorbance[19]. By disabling activities or eliminating free radicals through electron donation, antioxidants counteract the damaging effects of free radicals on biological systems. Chemistry (ABTS, DPPH, FRAP, ORAC, CUPRAC) and biochemistry (oxidation of LDLassay,TBARS assay)assays are two examples of in vitro techniques that can be used to detect this inhibition or neutralization. Still, due to their ease of use, quickness, and low price, the first ones are chosen over the second. Due to their capacity for scavenging, a

number of metabolites and phytoconstituents, such as polysaccharides, flavonoids, phenolic compounds, and anthocyanins, have demonstrated antioxidant capabilities.Considering how frequently these compounds occur in natural settings, studying their antioxidant qualities is an essential component of nearly all research on biological processes.

ET reaction-based analysis and HAT reaction-based analysis are two types of chemical-based tests. But some 2,2-azino-bis-3ethylbenzothiazoline-6-sulphonic acid and 2,2-Diphenyl-1- picrylhydrazyl, for example—combine the two processes. Because they evaluate the prevent of radicals which does not exist in biological systems (DPPH•, ABTS•+), or decreasing capacity based upon a single particular ion (Fe3+), numerous approaches (e.g., ABTS, DPPH, FRAP) have limited biological relevance. The assay known as Oxygen Radical Absorbance Capacity (ORAC) is an exception to this rule. It tracks the suppression of the physiologically significant peroxyl radical (ROO•) and uses chemiluminescence to measure the ability of various oxygen and reactive nitrogen species to sequester light [10].

5.6 Anti-inflammatory activity

Preparation of blood samples for membrane stabilization assay:

An approach to investigate the in vitro anti-inflammatory effect is the membrane stabilization of human red blood cells (HRBCs). A healthy volunteer's blood was drawn and combined with an same amount of Alsever solution (Two percent dextrose, 0.8 percent sodium citrate, 0.5 percent citric acid, and 0.42 percent NaCl) two weeks previous to the experiment. Prior to usage, each blood specimen was kept for twenty-four hours at 4 °C. The liquid that remained was extracted after it was centrifuged for five minutes at 2500 rpm. After centrifuging the cell suspension for five minutes at 2500 rpm, it was clear with sterile saline solution (0.9 percent w/v NaCl). This procedure was carried out 3 times until the supernatant was colorless and clear, at which point the packed cell volume was determined. To use in the tests, the cellular component was reconstituted to a forty percent suspension (v/v) using phosphate buffered saline (10 mM, pH 7.4)[20]. An organism's immune system uses inflammation as a defense mechanism against dangerous outside substances including infections, poisons, or irritants. This system promotes the healing process by assisting in the recovery from illnesses, infections, and tissue injury.Pro-inflammatory mediators like LPS, IL-1β, IFN-γ, and NF-κB can activate

macrophages, which in turn can activate the COX and LOX pathways, leading to the production of nitric oxide,TNF-α,and IL-6. To determine the in vitro anti-inflammatory qualities of natural compounds, all of these pro-inflammatory mediators are investigated. Non- steroidal medications have been demonstrated to suppress the reduction in prostaglandin levels and the synthesis of arachidonic acid, which help to lessen pain and inflammation. Nevertheless, there are a number of negative consequences linked to their use, such as headaches, indigestion, allergic responses, and an increase in cardiovascular problems. Fortunately, because of their wide range of biological activities, plants contain an amazing variety of phytoconstituents,which are excellent sources for drug development. Particularly, studi1es have demonstrated the anti-inflammatory properties of flavonoids, anthocyanins, and some polyphenols. Likewise, the inflammatory process is inhibited by secondary metabolites including sulfated polysaccharides from Sargassum cristaefolium, a brown alga, and atranorin from lichens[10].

6. Summary

Thiazole is a 5-membered heterocyclic ring which having sulphur as well as nitrogen in it as a heteroatom. Also known as 1,3 thiazole.It is organic heterocycle. It was described by Weber and Hantzch in 1887.latter on verified its composition in year 1889. Many naturally occurring susstances contains pyrazole, imidazole, isothiazole, and also oxazoles. Because of its wide range of pharmacological actions,heterocyclic compounds are constantly producing novel therapeutic medicines. It binds to different enzymes active sites or other regions for their biological activity.Thiazole is transparent to yellow combustible substance,it is flammable.dissolves in alcohol.

Synthesis of thiazole and its derivative from different compounds and different methods. Such as synthesis fromα-halocabonyl comounds,synthesis fromα-aminonitrile compounds,reaction with ester and salts of dithioacids,gabreil's synthesis,synthesis with eco-friendly methods. In all that synthesis of 2,4,5-trisubstituted thiazole, synthesis of aminothiazoles, synthesis of 2-hydroxythiazole,synthesis of 5-aminothiazole derivatives, synthesis of2phenyl-5-alkyl thiazole thiazole derivatives.

Various biological activities have been evaluated such that antibacterial, antidiabetic, antimicrobial, anticancer, antioxidant and anti-inflammatory activities.

Antibacterial activity is examine using ISO 22196 standard method.Antidiabetic activity is examined using soxhlet extraction method and cold maceration.Antimicrobial activity is identifyby agar disk-diffusion method.Two techniques use for anticancer activity is calorimetric and fluoroscence assay.In that calorimetric assay is analysed it has different methods like MTS/MTT assay,XTT assay,Crystal violet staining etc.In antioxidant activity DPPH RSA used test its activity against oxidative agents.Membrane stabilization assay used to denote the anti-inflammatory activity.

7. References

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