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Employing Eco-Friendly Approaches to Synthesize a Thiazole Derivative through the Utilization of Microwave Irradiation Techniques While also Investigating the Development of Antifungal and Antioxidant Activities

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Abstract: *Thiazoles are classified as azole heterocycles, which are aromatic five-membered heterocycles composed of one nitrogen atom and one sulphur atom. In recent times, considerable attention has been given to thiazoles, their derivatives, and isomers due to their extensive applications in various fields. These applications encompass agrochemicals, industrial purposes, photographic sensitizers, as well as their pharmaceutical and biological activities, notably antioxidant properties. The presence of thiazole moieties in compounds is a notable structural characteristic found in diverse natural products, including vitamin B and penicillin. Consequently, in this article, I present an array of thiazole-based heterocyclic frameworks, including monocyclic and bicyclic systems. I also delve into their synthesis methods and explore studies on their biological activities. Moreover, we discuss the modification of thiazole-based compounds at different positions to create new molecules with antioxidant activity.*

Keywords: encompass azole heterocycles, thiazoles, antifungal activity, antioxidants activity

I. INTRODUCTION

Thiazoles are a class of organic compounds composed of a five-membered ring containing nitrogen and sulphur atoms, with the presence of an isomer known as isothiazole. These thiazole compounds serve as a fundamental structure that can be found in numerous natural substances such as thiamine (vitamin B1), alkaloids, anabolic steroids, and flavones. Due to their versatility and usefulness, there has been a growing interest in synthesizing compounds incorporating the thiazole moiety for various applications. The significance of thiazoles lies in their wide range of applications in fields like photosensitizers, rubber vulcanization, liquid crystals, sensors, sunscreens, catalysts, dyes, pigments, and chromophores. Moreover, they hold a prominent position in modern medicinal chemistry due to their extensive applications in drug design and discovery. Thiazoles can be found in pharmaceuticals like bacitracin, penicillin antibiotics, and various synthetic drugs, including the short-acting sulpha drug sulfathiazole. Furthermore, thiazoles are utilized as antidepressant (pramipexole), antiulcer (nizatidine), anti-inflammatory (meloxicam), HIV/AIDS (ritonavir), and cancer treatment drugs (tiazofurin). Interestingly, thiazole is a more prevalent component in FDA-approved pharmaceuticals compared to other related five-membered heterocycles like isothiazole, thiophene, furan, isoxazole, and oxazole. In addition to their applications in medicine and chemistry, thiazole metal complexes are widely utilized in photocatalysis. These complexes have proven to be effective in various types of reactions, leading to the formation of biologically active fused heterocyclic moieties. Examples of such moieties include thiazolopyrimidine, imidazothiazoles, and thiazolopyridine. Overall, the unique structural properties and versatile applications of thiazoles make them a highly significant and influential component of various industries, ranging from pharmaceuticals to catalysis.

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II. STRATEGIES FOR THE SYNTHESIS OF DERIVATIVES CONTAINING 1, 3-THIAZOLE.

The thiazole ring system can be readily prepared using well-established techniques such as Hantzsch, Cook-Heilbron, and Gabriel methods. Several compounds, including thioamides, thiourea, ammonium thiocarbamate or dithiocarbamate, and their derivatives, can act as nucleophilic reagents in this reaction. In 1887, Hantzsch successfully synthesized the basic thiazole structure. This synthesis approach involves the cyclization and condensation of haloketones with thioamides, and it remains the most widely adopted method for obtaining thiazole compounds.

In contrast, Gabriel achieved the synthesis of thiazoles by treating α-acylaminoketones with precise amounts of P2S5 or Lawesson's reagent. Similarly, Cook-Heilbron employed versatile strategies for synthesizing substituted aminothiazoles. These methods involve various catalysts and utilized microwave irradiation techniques to synthesize thiazole derivatives.

III. UTILIZING ENVIRONMENTALLY SUSTAINABLE APPROACHES FOR SYNTHESIS: EMPLOYING MICROWAVE-ASSISTED SYNTHESIS (MAOS).

The synthesis of thiazole derivatives currently involves aggressive reaction conditions and excessive use of solvents and catalysts, which leads to wastage. However, to address these issues, eco-friendly method like the microwave irradiation technique is commonly employed for the synthesis of thiazole derivatives. This technique enables the rapid and efficient synthesis of a range of thiazoles without the need for solvents ***(Fig. 1).***

Additionally, a one-pot multicomponent reaction in an aqueous medium has been found to be economically feasible, non-toxic, and highly environmentally-friendly. Water, being a readily available medium, is considered as the most suitable solvent for the development of green chemistry techniques. By combiningN-bromosuccinimide, phenyl acetyleneand thiourea in an aqueous medium, substituted thiazole derivatives can be obtained in high yields ***(Fig. 2).***

Furthermore, the use of silica-supported tungstosilisic acid has proven to be an efficient and environmentally-friendly approach for synthesizing new substituted Hantzsch thiazole derivatives through a one-pot multicomponent procedure. By reacting 3-(Bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one with thiourea and substituted benzaldehydes in the presence of silica-supported tungstosilisic acid as a catalyst, either through conventional heating or ultrasonic irradiation, the desired derivatives can be synthesized ***(Fig. 3).***

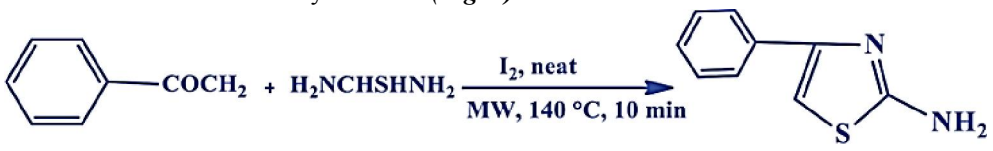

Fig. 1 synthesis of thiazoles under microwave irradiation.

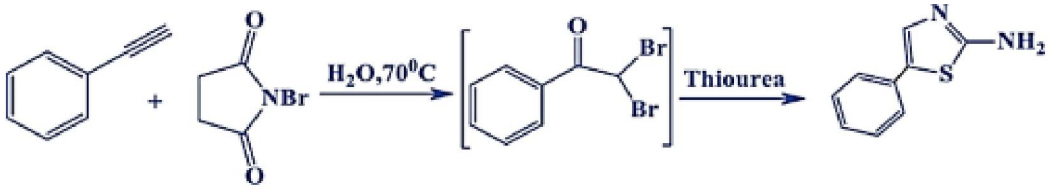

Fig. 2 Synthesis of 2-aminothiazolein aqueous medium.

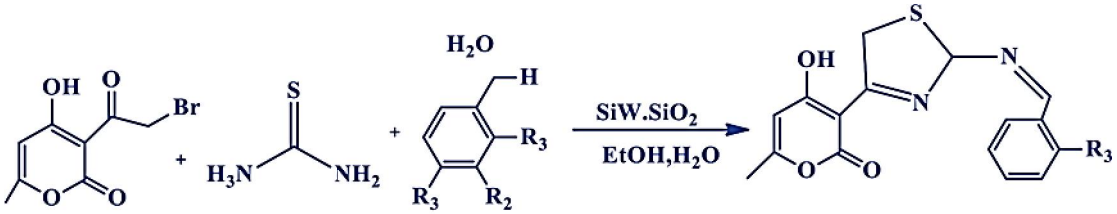

Fig.3 Synthes is of thiazole derivative

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IV. BIOLOGICAL IMPORTANCE OF THIAZOLES

Thiazole and its derivatives are highly potent compound classes that exhibit a wide range of activities. These include antibacterial, antifungal, antimalarial, antitubercular, antiviral, anti-inflammatory, antidiabetic, anthelmintic, anticonvulsant, antioxidant, anticancer, and cardiovascular activities. Furthermore, these compounds have been identified as novel inhibitors of bacterial DNA gyrase B. Notably, certain drugs already available in the market, such as masitinib, contain the thiazole nucleus.

V. ANTIFUNGAL ACTIVITY

A variety of 5-(2-substituted–1,3-thiazol-5-yl)-2-alkoxybenzamides and 5-(2-N-(substituted aryl)-1,3-thiazol-5-yl)-2-alkoxybenzamides. The objective was to test the antifungal properties of these synthesized compounds. Interestingly, certain derivatives of the compound***(IV.a.1)*** showed remarkable antifungal activity, as illustrated in ***Fig.4.***

Additionally, the synthesis of a unique collection of 2-thiazolylhydrazone derivatives. Also investigated how the different substituents affected both the thiazole ring and the anti-fungal activity of the compounds. During their experimentation, they discovered that some of the tested compounds exhibited significant antifungal activity, surpassing the effectiveness of clotrimazole. Notably, compound ***(IV.a.2)***displayed a particularly high potency against numerous *Candida* strains, as depicted in ***Fig.5.***

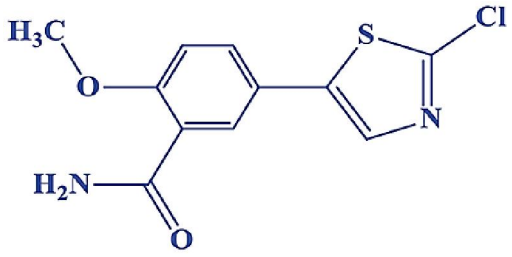

Fig. 4 : Structure of compound **(V.1)**

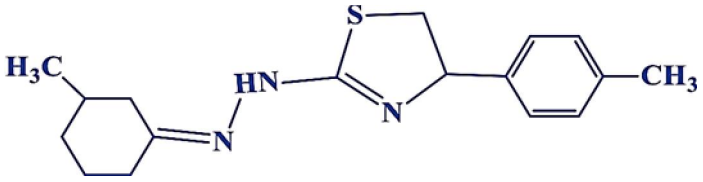

Fig. 5: Structure of compound **(V.2)**

VI. ANTIOXIDANT ACTIVITY

Antioxidants have garnered significant interest due to their crucial role in important biological and industrial processes. They are naturally produced within the human body, and yet they have the potential to cause damage to lipids, proteins, and DNA, leading to various diseases such as cancer, atherosclerosis, diabetes, cirrhosis, Alzheimer's, and inflammatory conditions. Thiazole and its derivatives serve as the fundamental structure in a range of pharmaceuticals with diverse biological activities.

I assessed the antioxidant potential of these compounds***(IV.b.1)***using a spectro-photometric method, employing either the DPPH radical or the Fe (TPTZ)3+ complex, as well as EPR spectroscopy. The results revealed that the synthesized compounds exhibited remarkable antioxidant activity ***(Fig.6).***Bozdag-Dundar et al. synthesized a series of 2,4-dichlorothiazolyl thiazolidine-2,4-dione and 4-chloro-2-benzylsulfanylthiazolyl-thiazolidine-2,4-dione derivatives, which were then tested for their antioxidant properties. Among these compounds***(IV.b.2),*** one exhibited the most effective scavenging activity against superoxide anions ***(Fig. 7).***

Gouda et al. synthesized 2-amino thiazole derivatives and investigated their antioxidant activity. Through an analysis of structure-activity relationship (SAR), they concluded that three compounds ***(IV.b.3)***possessed potent antioxidant properties (Fig. 8). Additionally, a series of N2-[2-chloro-4(3,4,5-trimethoxyphenyl)azetidin-1-yl)]-N4-(substituted aryl)-1,3-thioazol-2,4-diamine compounds***(IV.b.4)*** were synthesized and subjected to an in vitro evaluation of their

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antioxidant properties. The results, depicted in Fig.9, indicated that certain synthesized compounds displayed robust antioxidant activity based on their IC50 values.

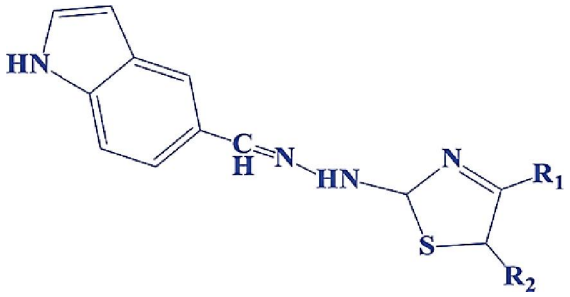

Fig.6: Structure of compound ***(IV.b.1)***

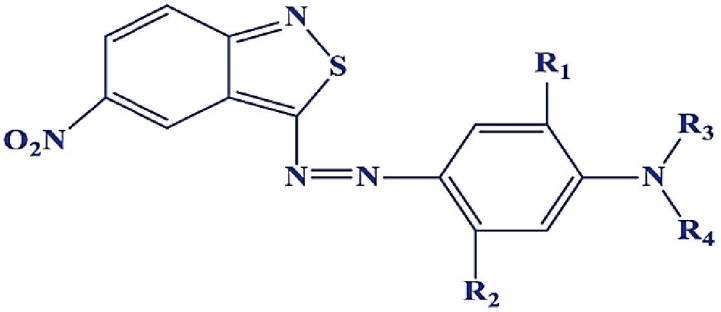

Fig.7: Structure of compound ***(IV.b.2)***

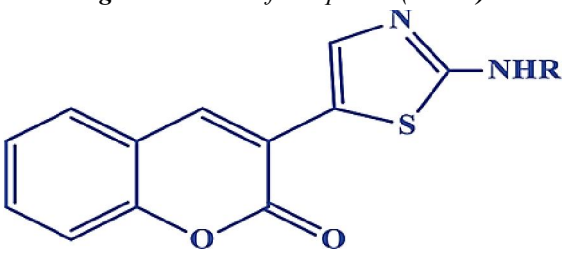

Fig.8: Structure of compound **(IV.b.3)**

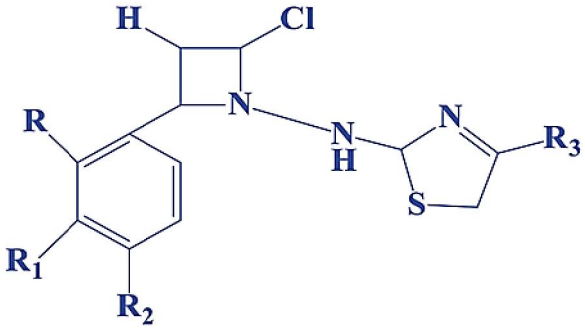

Fig.9: Structure of compound **(IV.b.4)**

VII. CONCLUSION

Thiazole compounds have gained significant significance in modern organic and medicinal chemistry due to their wide-ranging pharmacological and medicinal attributes, including antioxidant and antifungal properties. The presence of a thiazole ring in various drugs like penicillin, pramipexole, tiazofurin, meloxicam, and nizatidine has inspired chemists to devise novel thiazole frameworks. The thiazole nucleus plays a crucial role in the discovery of new leads and drugs for diverse diseases. This article delves into the commonly employed methods for synthesizing stable thiazole derivatives, elucidating their essential electronic characteristics, and highlighting their significant chemical reactivity. Special emphasis is given to the utilization of thiazole in dyes, their metal complexes, and various other applications of thiazole dyes. Furthermore, our attention is directed towards the biological applications of thiazole derivatives.

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