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Review

Thiazine: Synthesis and Biological Activity

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Abstract: Thiazines are a class of heterocyclic molecules that have not been extensively studied for their pharmacological effects. Various methods for synthesizing thiazine derivatives can be found in the literature. This review examines various techniques for synthesizing thiazines using environmentally friendly approaches. Thiazine derivatives are synthesized compounds that exhibit various biological activities, such as antibacterial, antifungal, antitumor, antimalarial, antineoplastic, antiviral, anti-inflammatory, analgesic, and anticancer properties. These compounds are considered a valuable group of heterocyclic medicinal substances that merit additional research.

Keywords: Thiazine; Heterocyclic; Green synthesis; Biologically activity.

1.Introduction

More than fifty percent of all organic chemistry research globally is dedicated to heterocyclic synthesis [1]. Heterocyclic rings in biologically active compounds play essential functions in the development of drugs and demonstrate diverse biological activity [2, 3].
Thiazines are six-membered heterocycles with a single nitrogen atom and another sulfur atom in their structure [3, 4]. Thiazines are highly beneficial components in medical and pharmaceutical chemistry, known to provide a range of biological effects [5]. 1, 3-thiazines are significant due to their presence in cephalosporins and other medically essential chemicals such as Xylazin and Chlormezanone [6]. Thiazine is a heterocyclic structure with a ring with six members containing four carbon atoms, one nitrogen atom, and one sulfur atom at different positions. It exists as 1,2; 1,3; 1,4-thiazines, and its derivatives with N-C-S linkage have been utilized for various purposes such as antitubercular, antibacterial, antimicrobial, antitumor, insecticidal, fungicidal, herbicidal properties, as well as tranquilizers and dyes [7]. Additionally, 1,3-thiazine core structures exhibit significant potential as radiation protection agents [8]. 1,3-Thiazines are utilized in diverse chemical synthesis and conversions as intermediate compounds in reactions. Thiazines are chemical substances having the molecular formula C4H5NS [9, 10]. Thiazine is a six-membered heterocyclic ring structure that includes two heteroatoms (N and S) within the ring. Thiazine compounds can be classified as 1, 2-thiazine, 1, 3-thiazine, or 1, 4-thiazines [11].

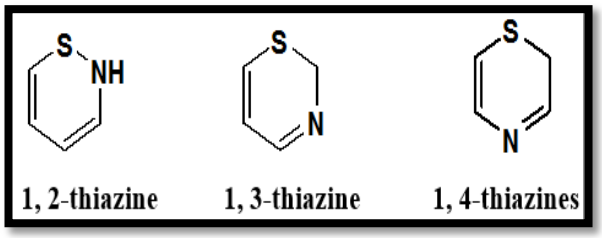

Fig. 1. Chemical structures of thiazines.

The review focuses on the role of various thiazine ring structures in heterocycles as antibacterial agents. This

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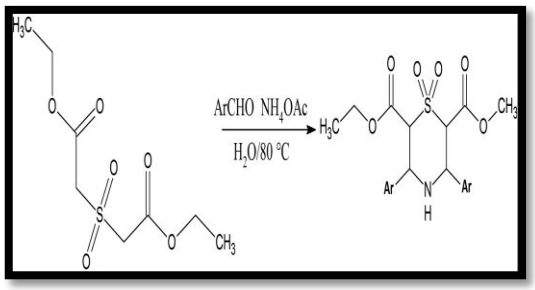
review aims to collect data on the antibacterial properties of thiazine compounds. The present study has established that substituted thiazines are promising antibacterial agents. We have chosen to examine various forms of substituted thiazines [12]. Heterocyclic molecules containing nitrogen and sulfur are highly important in medical chemistry [13]. Researchers have created several thiazine compounds with diverse biological effects, including anti-tubercular, anti-fungal, anti-bacterial, analgesic, and anti-inflammatory properties [14]. Several thiazine derivatives are in the development phase because of the versatility, chemical cleanliness, and manageability of the thiazine skeleton. Phenothiazines are a group of chemicals that are derivatives of thiazines [15]. Phenothiazines are utilized as a vermifuge for livestock and as a pesticide [16].

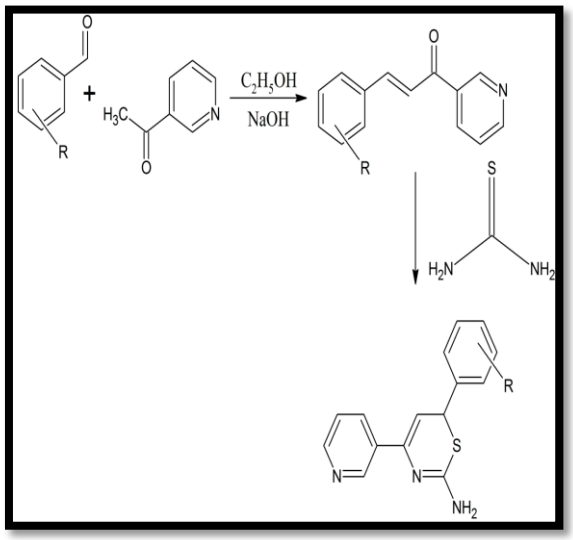
Green Syntheses of Thiazines compounds

Edayadulla and Ramesh prepared a chemical compound of 1,4-thiazine derivatives by reacting diethyl 2,2-sulfonyldiacetate with aldehyde derivative, followed by the addition of ammonium acetate at room temperature [17]. The reactants were agitated for 3 hours at 80°C, then cooled to room temperature. The molecule product was identified using several spectroscopic methods and analytical methods (Scheme 1). The compounds were found to be efficient anticonvulsants in tests conducted on animal models[18] .



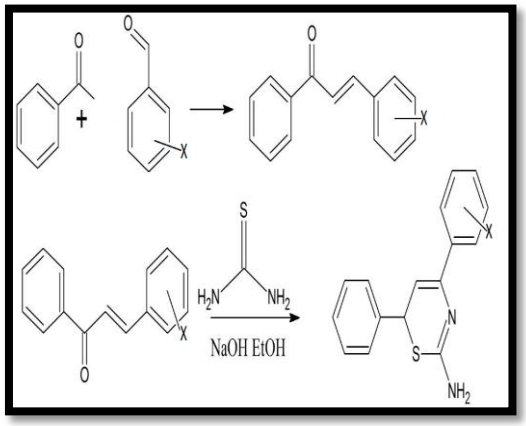
Scheme 1. Chemical equation of thiazine derivative synthesized [18].

Kadhim described a new azachalcone chemical formed by reacting acetylated pyridine with 4-hydroxybenzaldehyde. The resulting product was identified using infrared, ultraviolet, NMR spectroscopy, and C.H.N analyses. The chemical was examined for its antibacterial and antifungal characteristics and exhibited strong efficacy [19].



Scheme 2. Chemical equation of thiazine derivative synthesized [19].

Elarfi et al. reported that chalcone derivatives are produced through the reaction of acetophenone with benzaldehyde compounds. The subsequent stage of the this chemical reaction, the resulting product underwent a reaction with thiourea to produce thiazines and other associated chemicals. The results were analyzed using different technique of spectroscopy such as C.H.N analysis, EMIS, NMR, and FTIR. The bioactivity of thiazine derivative was assessed by antimicrobial tests [20].



Scheme 3. 1,3-Thiazine compounds derivatives [20].

Gayathri and colleagues found that thiazine derivatives with different compounds can be produced using microwave radiation. The produced compounds were verified and identified using TLC, C.H.N analysis, FTIR and NMR. The synthesized derivatives were tested for their antibacterial properties, demonstrating strong efficacy in both areas as described in Scheme 4 [21].

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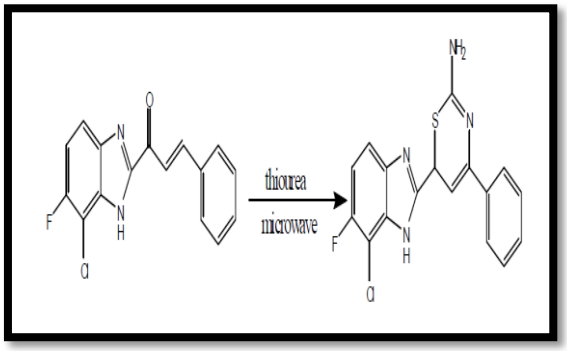
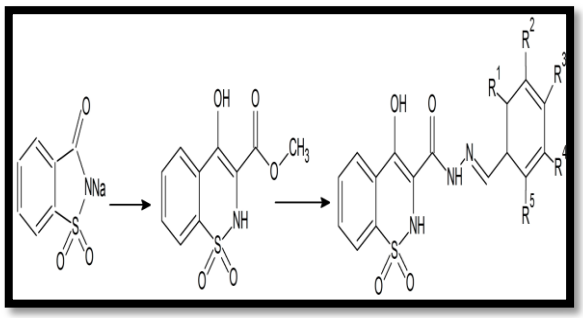


Scheme 4. General preapaed of thiazine compound by using microwave [21].

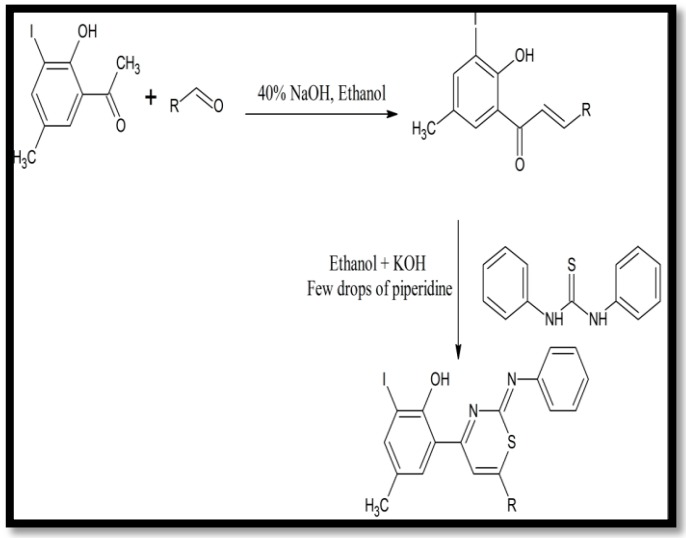
Zia-ur-Rehman and coworkers developed a range of analogs of thiazine derivatives. The sodium saccharin was N-alkylated with methyl chloroacetate using ultrasonic irradiation. The products were dissolved in DMSO. This method provides the added convenience of being able to be conducted at reduced temperatures and within a brief timeframe. It was subsequently reacted with hydrazine and benzaldehydes to produce the products needed in a large quantity as described in scheme 5 [22].



Scheme 5. General synthesis of some benzothiazine derivatives [23].

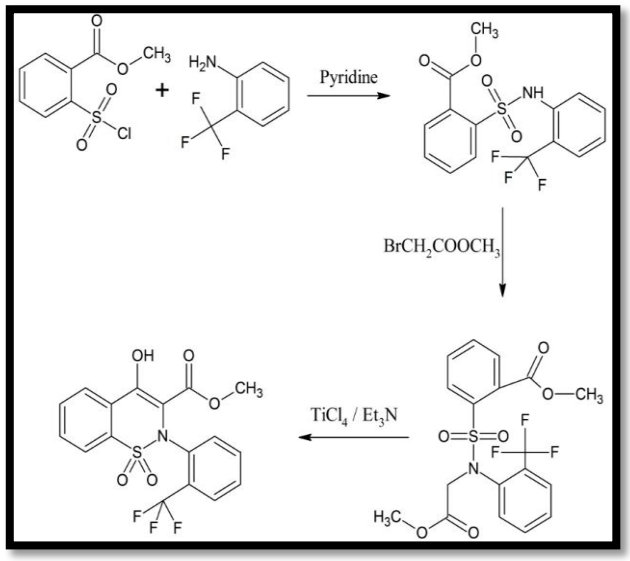
Some compounds exhibit strong antibacterial characteristics, although most products display antioxidant effects. The research group has recently broadened the manufacturing of 1,2-thiazine compound, resulting in an excellent product result [24]. Zia-ur-Rehman and coworkers conducted crystallographic research on 1,2-benzothiazine compounds to analyze their molecular structure by focusing on bond dimensions, angles of bonds, and different structural phases [23].

Dighade and coworkers, produced several chalcones by mixed acetophenone derivative with various aldehydes. The thiazine products were identified and classified by EIMS, FTIR and NMR, as shown in Scheme 6 [25].



Scheme 6. General synthesis of 1,3-thiazine derivatives [25].

Bunker and colleagues produced with described a set of thiazine analogs [18]. The benzothiazine production was accomplished in 3 stages using benzoate derivative with aniline derivative as beginning components [18]. The 1,2-benzothiazine compounds were stated to be beneficial, according to Scheme 7 [26].



Scheme 7. Synthesis of thiazine derivative [26].

Biological Activities of Thiazine compounds

Heterocyclic thiazine compounds play a vital role in pharmacological chemical synthesis because of their beneficial therapeutic characteristics. Thiazines, a type

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of heterocyclic compound, have diverse medicinal properties, including antitumor, antipsychotic medication, anti-inflammatory effects, and antibacterial properties. Thiazine compounds have a diverse array of advantageous characteristics. The next paragraphs will cover each activity individually [27].

Antimicrobial Effects

Phenothiazines and their new derivatives demonstrate significant biological effects in living organisms and in controlled laboratory conditions. These chemicals exhibit efficacy against diseases. The chemicals' effects were tested on several organisms, including mammals infected with dangerous bacteria and viruses and cell lines. The 1,3-thiazine moiety is the active component of cephalosporins, which are β-lactam antibiotics effective against a wide range of Gram-positive and certain Gram-negative pathogenic bacteria [28].

Cephalosporins exhibit a comparable mechanism for working with penicillins and possess a similar β-lactam ring structure. Nevertheless, they have more atoms in their side rings, as shown in figure 2. Many penicillin-resistant organisms are susceptible to cephalosporins, with a few variations. Cephalosporin resistance is frequently encountered in bacteria, such as intestinal bacteria, which exhibit the ability to most third and fourth-generation medicines [29].

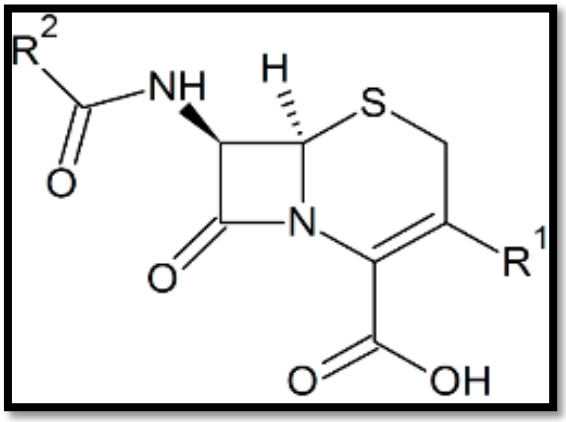

Fig. 2. Cephalosporin structure.

Antitubercular Effects

Mycobacterium TB is a very drug-resistant infectious organism, necessitating the development of novel medications to combat its difficulties [30]. Koketsu and coworkers produced approximately eight distinct 5,6-dihydro-4H-1,3-thiazine analogs and evaluated their inhibitory effects on mycobacterium organisms in addition to showing inhibitory actions. Many of these chemicals have substantial antitubercular effects at low concentrations, indicating that 1,3-thiazine compounds possess promising antimycobacterial properties [31].

Antimalarial Effects

A need for thiazine-based antimalarial medicines has a long history, starting in 1891 when Guttmann and Ehrlich utilized thiazine pigments to treat disease. Thiazine pigments exhibit high potency and selectivity in inhibiting the spread of plasmodium.

The marine sponge Plakortis lita from Australia contains four thiazine-based compounds known as thiaplakortones. Between these, thiaplakortone A is among the most effective against all chloroquine-sensitive and -resistant types of Plasmodium falciparum, showing an IC50 concentration ranging from 51 to 6.6 nM. Complete production of thiaplakortone is accessible, and many additional compounds for resistance to drugs plasmodium types can be made using this known approach. Thiaplakortone derivatives with amide and urea groups were produced and tested for their effectiveness against malaria [32].

Antifungal Properties

Certain thiazine compounds exhibit antifungal characteristics. For instance, Vicentini and coworkers, developed pyrazole compounds of 1,3-thiazine. They conducted tests on rice blast disease linked to Magnaporthe grisea. The thiazine compounds can hinder fungal development within a level ranging from 10 to 200 $\mu g \cdot mL^{-1}$. In certain instances, they are capable of halting the development of mycelium at a concentration of 10 $\mu g \cdot mL^{-1}$. Therefore, such thiazine compounds have remarkable antifungal properties. Substituted forms of 1,4-benzothiazines, together with their annelated derivatives [33], have significant pharmacological importance due to their potential applications as antimicrobials, antivirals, antibacterials, and antifungal medicines [34].

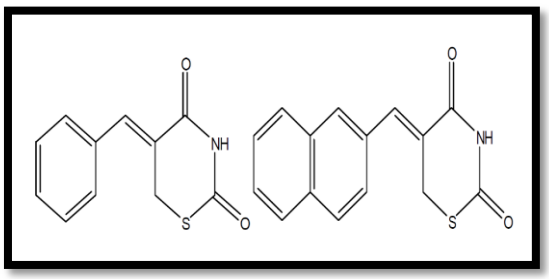

Fig. 3. Structure of thiazinediones.

Ha and co-workers described a skin-lightening substance derived from manufactured 1,3-thiazine chemicals. The thiazine compounds hinder the function of tyrosinase

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enzymes into a number of cells and obstruct the pigment production process, resulting in anti-melanogenesis actions [35]. The 1,2-thiazine 1-oxides are valuable for creating various linked types of pyrrole and benzodiazepines with anti-tumor effects [36].

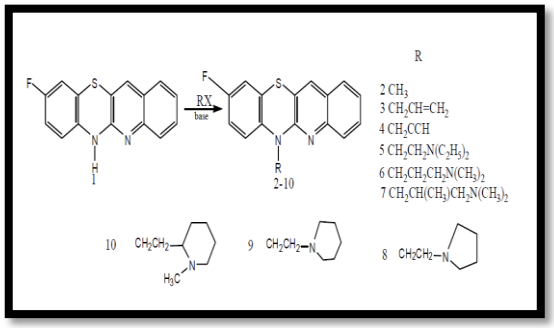

Fig. 4. Tetracyclic azaphenothiazine synthesis.

Anti-inflammatory properties

The thiazine compounds found in the Aplidium ascidian subspecies from New Zealand are believed to have anti-inflammatory properties via inhibiting the formation of oxide by neutrophils [37]. Chia and colleagues developed various thiazine compounds linked with chemical compounds and quinones that inhibit the generation of free radicals by neutrophils in the laboratory at a low level. Therefore, they could serve as potential NSAID substitutes. Some thiazine compounds have demonstrated anti-inflammatory in nature and analgesic properties at reduced dosages and are also considered safe in terms of stomach irritation at reduced concentrations [38].

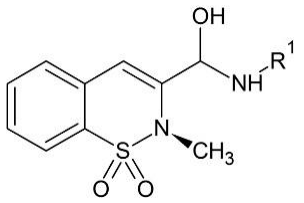

Fig. 5. Structure of 1,2-thiazine derivative.

Antidiabetic Effects

Aldose reductase is a crucial enzyme in complications of diabetes that is an acceptable target for diabetes medical care. 1,2-benzothiazine derivatives have been developed and tested for their effectiveness against the enzyme aldose reductase. The double halogenated benzene analogs exhibited the greatest effective reduction [39].

Conclusions

Thiazines are an important group of heterocyclic chemicals with promising applications in treating many infectious and inflammatory diseases, as indicated by existing evidence in the literature. The review described the development and production of many different thiazine derivatives using procedures such as radiation with microwaves, solvent, single synthesis, and other sustainable methods that can be readily applied in biomedical and pharmaceutical research. Thiazine research has captured the attention of medicinal chemists and biochemists to a significant degree, demonstrating that this powerful chemical has the potential to be used in creating bioactive drugs. This review offers initial information, and its references will significantly assist pharmaceutical scientists in developing improved, highly efficient, cost-effective, and readily accessible thiazine derivatives. Moreover, it may be inferred that various different variations of thiazine, which would exhibit potent pharmacological properties.

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Author's Contributions

Tamam Mahdi Salih[1], Asmaa A. Jawad[2], Moustafa A. Gouda [3], Abbas K. Abbas[4], Reem Husam Al-Tabra[5] are Conceived and designed the analysis, and wrote this review

Ethics

This study was conducted under approval by the medical ethics committee at Al-Nahrain University (2024). Parents and agreement provided verbal and written consent for publication was obtained from both participants and researchers.

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