A conceptual review of rhodanine: current applications of antiviral drugs, anticancer and antimicrobial activities

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Abstract

Rhodanines are accepted as advantaged heterocycles in medicinal chemistry as one of the 4-thiazolidinones subtypes. The aim of this paper is to analyze the features of rhodanine and its application in pharmacy and medicine. Some of the properties of rhodanine such as antiviral, anticancer, antimicrobial, and drug discovery have recently been reported. Although there are still vague points in the structure and mechanism of polymerization of this substance, there is a significant increase in the use of rhodanine in medicine. In this review paper, it can be said that we have provided a general overview of the recent advances in the rhodanine-based material which its application is more in the field of drug discovery and anticancer activity. The review starts with a summary of the antiviral activity of rhodanine-based materials and nanocomposites in general. Then in the next step, the detailed description is followed on their applications in the fields of anticancer activity, drug discovery, and an innovative type of rhodanine (RH) and thiohydantoin (TH) derivatives were created and combined in order to recognize tau pathology in the brains of patients with Alzheimer’s disease (AD). Through this review, we hope to promote rhodanine and its role in medicine and pharmacy becomes more prominent.

Introduction

So far, many uses of heterocyclic compounds have been recognized, and these compounds are widely used in chemistry and biosciences. Also, heterocyclic compounds play an essential role in the biological system of humans. In addition, with a general look at drugs such as antibiotics, antiviruses, antidiabetes, and antifungal, it can be easily understood that heterocyclic compounds are present in a wide range of these drugs. Thiazolidinone is endlessly being used to synthesize and also to design new compounds. Because of the different biological activities of thiazolidinone, it has become one of the strongest and the most important heterocyclic ring [1]. In fact, due to the group of antiabetic drugs such as Rosiglitazone Pioglitazine, etc, thiazolidine-2,4-diones is considered to be a known category of active biological compounds [2]. Thiazolidine-2,4-diones have a wide range of biological activities consist of antioxidant [3], anti-inflammatory [4,5], antibacterial [2,6–14], antifungal [15,16], and the most important one is anticancer [17–19], because nowadays, cancer is one of the most important causes of death all over the world and also anticancer drugs can be very effective. In order to synthesis polyrhodanine (PRh) and phenylalanine, Rhodanine (C\textsubscript{3}H\textsubscript{3}NSO\textsubscript{2}) monomer which is derived from thiazolidine is widely used [20]. Recently, scientists have focused on synthesizing antimicrobial factors and improving their antimicrobial features [21–25]. Five-membered heterocycles, which establish an attractive point for the fabrication of diverse biotic energetic particles are rhodanines (2-thioxo-1,3-thiazolidin-4-ones). Figure 1 illustrates the chemical configuration of the rhodanine monomer.

Applicable properties such as antifungal effects [26], anti-diabetic effects [27], antibacterial effects [28], antimalarial effects [29] and anti-inflammatory effects [30], all belong to valuable derivatives of rhodanine which play a major role in pharmaceutical and medical materials and also they have the ability to prevent many organisms like hepatitis C virus NS5B polymerase [31], PMT1 mannosyl transferase [32], penicillin binding protein (PBP) [33], HIV-1 integrase [34], JSP-1 phosphatases [35] and RNA polymerase [36]. As an interesting point, it can be said that one of the reasons why rhodanine is used in solar cells and colours is that it can regulate and manipulate electrochemical and spectral features [37]. As shown in Figure 2, rhodanine is a five-membered heterocycle including thioether and amino groups at positions 1 and 3, respectively. It is structurally related to thiazolidine-2,4-dione and 2-iminothiazolidine-4-one that include an oxo or imino group, respectively, instead of the thioxo group at position 2. It is also related to 4-thioxothiazolidin-2-one, which bears oxo and thioxo groups at positions opposite to those in rhodanine (Figure 2). These heterocycles have different biological
functions although they manifest to be very indistinguishable at first quick look.

Given the needs of today’s developing and developed countries, antibacterial drugs have emerged and their rates of use have recently increased [38]. Based on research, drug-resistant bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA), multi-drug resistant *Pseudomonas aeruginosa*, and multi-drug resistant *Escherichia coli* can create considerable problems and also cause fatal diseases [39–42], which, given the economic conditions, can seriously affect the general health of the community [43]. According to studies that have been done, it can be said that the use of pathogen can be an effective and suitable method for inhibiting antibiotic resistance. Therefore, in some studies, Gram-positive and Gram-negative pathogens have been utilized [44,45]. Although at first glance, using pathogen is appropriate but low evaluation efficiency is one of the drawbacks of this method and also some scientists have considered solutions to this problem. Recently, ceftolozane, daptomycin, Xifaxan®, telavancin, fosamil and ceftaroline as the novel antibiotics were subscribed and it can be said that dozens of antibiotics are currently in Phase 2 or Phase 3 clinical trials [46]. In fact, these kinds of drugs are not able to direct a wide range of bacterial resistance [47], so, developing novel antimicrobial factors, mainly drugs which can overcome drug resistance and also those with a novel drug target are very necessary. For example, indole is known as an intercellular signaling molecule and also it has the ability to control and adjust diverse features of bacterial physiology like plasmid strength, spore shaping, biofilm formation, and virulence and resistance to drugs. One of the main factors of the neurotransmitter serotonin and an indole derivative is amino acid tryptophan. So far, indoles have illustrated significant pharmacological functions and potent physiological activities like anti-HIV activity [48,49], anti-inflammatory and antioxidant [50], antiviral [51–53], antineoplastic [51,54,55] and antimicrobial [56,57]. Another derivative of indole is N-Arylsulfonylindoles, which can widely use for chemical drug studies and also act as anti-AIDS drugs [58], antifungal agents [59], 5-HT6 receptor antagonists [60]. But, based on research works, the antibacterial activity of N-arylsulfonylindoles has not been reported yet [61]. Previously, a certain group of rhodanine derivatives has been introduced which they demonstrated high inhibitory function against Gram-positive bacteria [62–67]. Other features of rhodanine derivatives are fully investigated in the following sections.

![Chemical structure of Rhodanine monomer](image1)

![Chemical structures of rhodanine and its analogues](image2)
Antiviral activity

In recent years, many activities of Rhodanine-containing compounds have been studied by scientists, mainly to control human immunodeficiency virus (HIV), hepatitis C virus (HCV) and dengue virus proteins. It can be said that, in order to reproduce HCV, non-structural protein 3 (NS3) obtained from HCV is a serine protease, which has an important role. Figure 3(1) shows the micromolar inhibitor of Rhodanine, which has been studied by numerous experiments. On the other hand, were not selective in contact with some of the relevant proteases such as trypsin, plasmin, chymotrypsin and elastase [68]. The interesting point in Figure 3(2) is that the bulkier hydrophobic classes based rhodanine also have the ability to cope with NS3 in the micromolar span but on the other hand, it has a suitable selective property against chymotrypsin [32].

Non-structural protein 5B (NS5B) polymerase is another HCV prey protein restrained through Rhodanines, which operates as a suitable catalytic subset of the viral condition. It can be said that through high-throughput operation [69] and also virtual covering (Figure 4(1)) [31], Low micromolar inhibitors of NS5B were recognized utterly. The compound shown in Figure 4(2) consists of controlling NS5B with an IC50 value of 200 nM which provides the next optimization.

In Figure 5, the specificity of the crystal structure of this type of controllers in cooperation with NS5B is illustrated, which is discussed covalent binding of the exocyclic double bond to the Cys366 thiol [69]. An important feature of rhodanine is that it has the ability to control HIV-1 integrase, this has a major role in speeding up the process of combination of viral cDNA into the human genome [70]. The researchers in their comprehensive study stated that one of the most effective inhibitors of the HIV virus is those that are found in their compounds, Rhodanine. Which, in addition to strong control has significant antiviral activity in the low micromolar range. For a better understanding of the topic, see Figure 6(1). On the other hand in Figure 6(2), low micromolar inhibition via Rhodanines of HIV-1 reproduction in MT-2 cells, that due to focus on the HIV-1 covering glycoprotein transmembrane subset gp41, has also been explained [71–73]. In addition, it can be said that Rhodanines have the ability to inhibit dengue virus protease NS2B-NS3 [74,75].

According to the tests, HIV-1 and HIV-2 can be considered as harmful viruses that became commonplace among humans in the 20th century and in fact they were introduced as almost new pathogens [76]. Chimpanzees have been the main cause for transmission of this virus to humans, although some other factors have not been affected by the emergence and transmission of this virus [77–79]. Implementing the ”prevention and treatment” plan in the world to deal with human immunodeficiency virus type 1 (HIV-1) epidemic has led to a negligible reduction in the amount of infection worldwide. It is worth mentioning that the sexually transmitted infections (STIs), including HIV-1, has caused concern throughout the world, especially in deprived areas [80].

Figure 3. Hepatitis C virus NS3 inhibitors [136].
the other hand, since 2010, there has been no significant reduction in the number of people with this new HIV infection in most countries. Which can be considered as a worrying report. This means that the current efforts including treatment methods and easy access to anti-virus to reduce mortality have not been effective enough.

Scientists in previous studies presented several methods for the treatment of HIV in the early stages to prevent entry into the cell [81–83]. In fact, this can be attributed to increasing the availability of antiviral agents in effective and important preparations. A common feature of all the ways in which intracellular prevention has so far been proposed is that available drugs should penetrate both the mucosa and the membrane as it improves its effectiveness. As shown in Figure 7, during experiments on infectious viruses, scientists encountered compounds whose properties were highly regarded. After the introduction of Rhodanine, the scientists prepared and synthesized a series of rhodanine derivatives for further investigation. Following advanced trials and biological evaluations, researchers have come to the conclusion that these derivatives have a very high ability to control HIV-1 and HSV-1 and 2 replication at nanomolar concentration. They also identified the interdependence of these molecules on human albumin. In the next step, the preliminary ADME evaluation was performed successfully by determining the water sensitivity, permeability of the inactive membrane and the metabolic stability of the selected compounds. The researchers have stated that factors such as high level of inappropriate drug reactions and resistance in different parts of patients at drug concentrations below the optimal limit have limited the treatment of HIV infection [84].

Figure 8 illustrates the synthetic method for the final compounds 9a–f, which requires the preparation of the desired acid 6. Methyl 4–(5-formylfuran-2-yl)-2-hydroxybenzoate (5) was obtained through Suzuki reaction between commercially available 3 (methyl 4-iodosalicylate) and compound 4 (5-formyl-2-furanylboronic acid), in the next step, the acid analogue was made by fundamental hydrolysis (6). Using the information provided in the published articles, the Derivatives 9a–f, were prepared and synthesized. This process contains nucleophilic shift between the opportune amine and trithiocarbonate (7) to provide the superseded rhodanine mediumship (8a–f), followed by Knoevenagel condensation with aldehyde (6) catalyzed through the surplus of predominant amine. According to the same concepts as shown in Figure 8.

Different species of rhodanine compounds were studied in the laboratory. Some of these tests are summarized in Table 1, which analyzes the solubility (thermodynamics solubility), membrane permeability and microsomal stability of the liver. Considering the amounts of water solubility provided, its range can be from 0.1 to 0.88 µg/mL, but the important point is that the low level does not have a significant effect on the performance of the gel formulation. In fact the data did not reveal this truth. It has been accepted that in the experiments of researchers, the concentration of compounds in pre-gel solution was equal to the control solution values. In PAMPA experiments, the permeability of the inactive membrane was investigated, hence the range of all compounds was from 0.4 to $2.32 \times 10^{-6}$ cm/s. During the experiments, it was found that expansion of exposure time...
of the microbicide can cause the significant increase in local activity. In addition to all the points that have been mentioned so far, sustainability tests have indicated that all compounds exhibit favourable metabolic stability in human liver microsomes (>90%).

In their own experiments, researchers investigated the effect of rhodanine on two viruses. They described the effective factors for PrEP ways without the requirement of dual-factors production. They also found valuable facts about rhodanine, which proved the ability to control and restrain the viruses and prevent their entry into the cell by rhodanine. According to complex studies on primary samples, it has been found that the compounds can only affect certain species of viruses. In the end, scientists reported new ways

Figure 6. Representative inhibitors of (1) HIV-1 integrase and (2) gp41 [136].

Figure 7. 2D structures of HIV-1 inhibitors previously published [166].
Figure 8. Synthesis of aldehyde 6 and derivatives 9a–f. Synthesis scheme of aldehyde 6: (i) Pd (PPh3)2Cl2, Na2CO3, DMF/EtOH, RT, 1h; (ii) 1N NaOH (aq), MeOH/THF, reflux 2h. Synthesis scheme of derivatives 9a–f: (iii) DME, Et3N, MW(300 W), 90°C, 10 min. (iv) aldehyde 6, MW(300 W), 110°C, 5 min [166].

Table 1. Results of in vitro ADME analysis for selected rhodanine derivatives [166].

| Compound | Water Solub. (µg/mL) | Papp (1·10⁻⁶ cm/sec) | Metabolic Stability (%) | Kd HSA (µM) | Kd BSA (µM) |
|----------|----------------------|----------------------|------------------------|-------------|-------------|
| 1        | 0.88 ± 0.10          | 1.28                 | >90%                   | 0.63 ± 0.1  | 0.68 ± 0.1  |
| 2        | 0.52 ± 0.13          | 1.26                 | >90%                   | 0.96 ± 0.1  | 0.63 ± 0.1  |
| 9a       | 0.54 ± 0.08          | 0.4                  | >90%                   | 1.51 ± 0.2  | 1.08 ± 0.2  |
| 9b       | 0.10 ± 0.08          | 2.32                 | >90%                   | 1.57 ± 0.2  | 1.55 ± 0.3  |
| 9c       | 0.30 ± 0.07          | 1.23                 | >90%                   | 1.19 ± 0.1  | 1.05 ± 0.1  |
| 9d       | 0.25 ± 0.09          | 1.50                 | >90%                   | 1.09 ± 0.9  | 0.99 ± 0.9  |
| 9e       | 0.72 ± 0.12          | 0.92                 | >90%                   | 2.19 ± 1.0  | 1.07 ± 0.9  |
| 9f       | 0.73 ± 0.14          | 0.87                 | >90%                   | 2.23 ± 1.2  | 1.09 ± 0.9  |
to cope with the introduction of infection into the target cell, along with inhibition of cell toxicity, which can be used in future to improve the HIV prevention and treatment process.

**Anticancer activity**

One of the facts that are not covered today is the growth in the number of deaths among cancer patients, which is rising momentarily [85,86]. On the global scale, it can be said that each year, cancer can put to death many human beings in comparison with malaria, tuberculosis and AIDS. However, more effective treatments are needed in order to provide better efficacy and suitable treatment. The first point about the existing therapies is that their effectiveness is low, so it can be said that in this method of treatment it is only possible to focus on two cancer cells or their peers, which does not seem to be a very good feature. Then it can be noted that the toxicity of anticancer drugs, which have a significant degree of ability to constrain the treatment process and in the end, we must pay attention to various methods of chemotherapy, some of them are very hydrophobic and, therefore, have lost their importance [87]. Breast cancer can be considered as the second leading cause of female mortality among various types of cancers [88]. So far, techniques such as surgery or radiotherapy have been used most of the time. However, chemotherapy remains a commonly used treatment method for cancer. As mentioned above, in spite of endless efforts to develop new treatment of various types of cancer, cancer is still a major concern in today’s world. Therefore, in order to get better results, measures should be taken to find a new class of molecules with effective features against cancer cells. At this time, after a great deal of research on different molecules, five-membered heterocyclic molecules which have a thiazolidine nucleus with a carbonyl group on fourth carbon have been introduced, like rhodanine and its bioisostere 2,4-thiazolidinedione (TZD) derivatives that present unique cancer characteristics [89–96]. In this section, some of the interesting features of these very well-known substances are reviewed, for instance, cytotoxic activities [97] anti-diabetic [98], anti-oxidant [99], anti-microbial [7,100], anticonvulsant [101] anti-tubercular [100] and anti-inflammatory.

In Figure 9, the pyridyl quinoline derivative GSK1059615 is known as a new ATP controller and great inhibitor of the PI3kS groups. This kind of inhibitor showed a great ability to control breast cancer cells [102,103]. As shown in Figure 9, Moorhy et al., have investigated 5-benzilidene-3-ethyl rhodamine (BTR-1), 3-dimethyl-2-thio-hydantoin (ITH-1), 3-ethyl-2-thio-2,4-oxazolidinedione (ITO-1) and realized that all the mixtures instigated cytotoxicity in a time and concentration-dependent procedure with an IC50 value of <10 μM and affected cell division through inducing a block at S phase, which eventually caused the activation of apoptosis [104]. All the cases that have been mentioned so far have been a small part of the treatment process, but more comprehensive and better efforts to improve the quality of treatment are needed [105,106].

**Antimicrobial activity**

Due to the emergence of diseases and the complexity of treatment, in the last 50 years, many efforts have been made to develop effective antibiotics. Rhodamine is one of the most well-known and key materials. It can be said that these groups of molecules have the same chemical structure as penicillin and have shown a favourable antibacterial activity during several experiments, which could attract researcher’s attention [62,107–109]. Figure 9 illustrates the antibacterial feature of a type of rhodamine-3-alkanecarboxylic acid derivatives with p-N,N-benzilidenedialkyl (phenyl)amine moieties at the position A on the gram-positive strains of staphylococci, micrococci and streptococci [110].

Furthermore, a group of rhodanines bearing N-arylsulfonylindole fragment at the position B have been introduced that were dynamic to gram-positive strains, particularly Staphylococcus aureus, including multi drug-resistant strains (MRSA) [61]. Rhodanine compounds have been investigated to be able to cope with bacteria such as *Staphylococcus aureus* and moderately operative against *Escherichia coli* which provides a wide range of applications [28]. Various derivatives of N-carboxymethyl rhodamine have been prominent examples of attempts to find antimicrobial agents in the last decade, which have been considered by scientists and have been continuously investigated. It may be argued that their high ability against gram-positive species, such as several strong separators, has highlighted the specificity of this molecule [66]. Also, resistance to gram-positive bacteria in esters and amides of rhodanine-3-acetic acids (C) with the same structure was completely investigated, including methicillin-resistant *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus aureus, Enterococcus sp.* and Mycobacteria.

It has been shown that with the development of molecules, the properties of inhibiting the growth of bacteria with low MIC and also the increasing effect of INH-resistant atypical myco bacteria can be mentioned [111]. In fact, based on extensive and fundamental studies on rhodanine derivatives, it can be seen that their activity against gram-positive bacteria is much more prominent than their function against gram-negative bacteria. Hence, the above comparison made it possible to guide the researchers to improve their properties. Integrating rhodanine grid with quinoline led in a line of compounds (D) demonstrating in vitro anti mycobacterial potency against MTB H37Ra and M. bovis BCG. During research in laboratories, the efficacy and high selectivity of
rhodanine-quinoline derivatives were carefully evaluated and tested. Based on these properties, it is possible to predict the presence of these compounds in antitubercular factors [112].

Since rhodanine (2-thioxothiazolidin-4-one) is one of the fundamental factors in the field of medicinal chemistry, it can be used for chemical modifications. Subsequently, materials such as N-3 and/or “active methylene” C-5 substitution can be found that are capable of generating potential new bioactive compounds and thus the new window has opened to medical science. As mentioned in previous sections, rhodanine has interesting properties which they can inhibit diverse enzymes, for instance deoxyxylulose 5-phosphate reductoisomerase [113], cholinesterases [114,115], 15-lipoxygenase [114], aldose reductase [116], dolicholphosphate mannose synthase [117], gyrase B [118], Mur ligases [119] and also augmentation of pathogenic protozoa [117], fungi [120], bacteria [31,113,121,122] and Mycobacterium tuberculosis [123] in whole-cell covering tests. It has been proven in the laboratory that rhodanines including those with C-5 substitution have the special ability to inhibit microbial enzymes and extensive anti-microbial activity. In the past, new antimicrobial agents have been identified and reported clearly [124–128]. They assessed antecedently reported N-phenylamides and phenyl esters of rhodanine-3-acetic acid, new salicylaldehyde-based C-5 arylmethyldene derivatives of the RAA and their reciprocal conjugates against Gram-positive and Gram-negative bacteria mycobacteria, and also eight fungal types. In fact, it could be said that a group of 20 microbes was introduced and all of them were major pathogens of the human body, this means that with intelligent screening, early detection of the antimicrobial activity of the compounds can be achieved successfully.

**Drug discovery**

So far, many compounds have been involved in drug discovery processes, which are discussed in detail in previous studies, the purpose of this section is to investigate the role of rhodanines (2-thioxo-1,3-thiazolidin-4-one) and related substances like 2,4-thiazolidinediones, 2-amino(imo)-4-thiazolidinones, 2-R- and 2-yldene-4-thiazolidinones derivatives in this field [96,129–134]. It has been accepted that rhodanine
core based molecules play an essential role in pharmacy because they are very rich in it [74,135,136]. Multiple ligand method is one of the new and effective ways in the emergence and development of new drugs, therefore according to the characteristics of rhodanine, it can be widely utilized. In addition, it can be said that the desirable feature of this method is more efficiency and also reduced costs and risks. There may be various benefits to this method, but the main advantage is that there are lower drug–drug interactions in comparison with drug cocktails or multicomponent drugs [137]. In pharmaceutical chemistry, we face some interesting and different approaches and one of them is the hybrid pharmacophore approach [138,139]. Finally, it can be said that since rhodanine is simply influenced by various chemical optimizations, it is considered a favourable factor [140,141]. An interesting example is PI3γ kinase inhibitor, containing chemically similar thiazolidinedione fragment, which means that rhodanine can be used as a basic ingredient in fragment-based drug design [142]. In fact, it can be said that effective and desirable methods have been presented so far in which the methods required for the synthesis of rhodanine core and its derivatives are fully described [66,129,134,143–146]. According to studies, it is possible to synthesize them in chemical methods that are used for other materials such as 4-thiazolidinone subtypes (2,4-thiazolidinediones, 2-amino(imino)-4-thiazolidinones, 2-R-4-thiazolidinones), they are thus divided into three main sections, as shown in Figure 11: (1) synthesis of the rhodanine core and

dithiocarbamate method

\[ R - \text{NH}_2 + \text{CS}_2 + \text{HalCH}_2\text{COOH} \]

Holmberg method

\[ R - \text{NH}_2 + \text{HOOC} \]

thiocyanate based method

\[ \text{NH}_2\text{SCN} + \text{HalCH}_2\text{COOH} \]

Structure of the most referred sub-types

\( X = \text{various fragments} \) (alkyl, aryl, heteryl)

![Diagram of rhodanine synthesis and transformation](image-url)

**Figure 11.** General approaches to rhodanines synthesis and transformation [170].
its N3 substituted derivatives; (2) alternation of the main core; (3) synthesis of the rhodanine derivatives in the one-pot or multistage reactions.

So far, scientists have made many studies in the field of drug recognition and also they have proposed extensive activities titled pan assay interference compounds (PAINS) and periodic hitters in various screening. Rhodanine containing compounds are non-specialized collectors that deal with target proteins and also Michael receptors. Finally, it can be said that because of their colour, they have the ability to interact photometrically in biologic assessments [136].

Other types of activity

In today’s world, there are many therapeutic treatments for Alzheimer’s disease, so rhodanine derivatives have been investigated for this purpose. Several 5-arylidenerhodanine-3-carboxylic acids had the ability to control protein tau accumulation, whose natural task is to brace the microtubule lattice in order to convey organelles and vesicles in nerve cells, required for the interactions between cells and as a result for brain function [147]. Also it can be said that, in order to diagnosis tau pathology in the brains of patients with Alzheimer’s disease, a series of thiohydantoin and rhodanine (34) and derivatives can create and design [148]. In recent years, it has been proven that, rhodanine and thiohydantoin derivatives can affect destabilization, creation and augmentation of masses such as tau [147]. One of the most prominent features of these derivatives is their dependence on the dose and the ability to restrict the growth of tau accumulation and destabilize it, showing their direct effect on interactions and binding with the mass. As illustrated in Figure 12, some researchers created and combined three new radiiodinated rhodamine and thiohydantoins and derivatives and also they worked on their biotic features in vivo NFT screening factors and finally analyzed and developed them. It might be said that before these experiments, never rhodanine and thiohydantoins derivatives been used to identify tau pathology in the AD brain [148].

If we consider the sulphur atoms of 4-thiazolidinone as an effective agent for liver toxicity, then we have only referred to a hypothesis that is not certain because there are no fundamental studied and also it is clear that toxicity depends on the individual structure of each compound and cannot be detected and evaluated only by the presence of one factor [149]. With precursor studies on thiazolidinones, its anticancer activity can be recognized and also it was found that most active compounds do not have notable toxicity to normal cells. In addition, rhodanines are organized as non-mutagenic [150] and comprehensive work on the clinical results of the rhodanine-based Epalrestat indicated that it is well tolerated. The most important conclusions in the anti-inflammatory 4-thiazolidinones are connected with their capability to restrict isoforms of cyclooxygenase (COX) and lipooxygenase (LOX) and related operations associated with prostaglandine synthesis [108]. For instance Darbufelone (5-(3,5-diterbutyl-4-hydroxybenzylidene)-thiazol- 4-one can be mentioned as a prime sample [151]. Furthermore, this 3,5-disubstituted rhodanine derivative indicated the notable reduction in formalin-induced paw edema higher than that of celecoxib and gastrointestinal safety profile as celecoxib in gastric ulcerogenic operation analyze [152]. By studying many articles, we have proposed that, when ketones exist, advanced technique for the chemoselective reduction of aldehydes are very distinguished and gained notable consideration or even through usage of some additives materials such as thermoplastic thermoplastic, (PET, ABS, SAN) [153–155], nanotube [156,157] resins [158,159] graphene oxide in polymer composite for X-ray radiation shielding [160] and features of nanocomposites, linear low density polyethylene, ethylene-co-vinyl acetate and nano-clay particles through electron rays [161]. Due to the features mentioned, rhodanine may also be used to do this in the future. As a point, it can be said that if exocyclic sulphur is presented in the thioxo group of rhodanines, then interesting electronic features can be considered for this action, which can participate in many important interactions. Because rhodanines are usually high-throughput screening (HTS) hits that are difficult to modify to guide compounds, therefore they were identified as pan assay interference compounds (PAINS). Figure 13(A) illustrated that, rhodanines experienced simplistic reaction with nucleophiles through Michael addition to the exocyclic double bond [136].

As an essential point, it can be said that recently, 10 crystal structures of rhodanine derivatives in complex with proteins available in the RCSB Protein Data Bank have been recognized. The common feature of all these structures is they have an exocyclic double bond. As shown in Figure 13(B) there is a covalent bond between the inhibitor and a cysteine residue in the allosteric binding site which it relates to the crystal structure of 5-benzylidenerhodanine-containing controllers in complex with the HCV RNA polymerase NS5B. Finally, the reversibility of this inhibition process was proved [69].

The researchers, with long-term tests on rhodanine, found interesting electrical features and their positive performance in biological experiments. Rhodanine containing compounds

Figure 12. Chemical structure of rhodanine and thiohydantoins derivatives reported previously [148].
are non-specialized collectors that deal with target proteins and also Michael receptors. Finally, it can be said that because of their colour, they have the ability to interact with photo-metrically in biologic assessments [136].

Discussion

So far, many methods have been proposed for the synthesis of thiazolidinone derivatives, so initially, a series of compounds were introduced (Figure 14) and then synthesized. The researchers used α-chloroacetic acid (A) and thiourea (B) at first, in order to start the synthesis of thiazolidine-2,4-dione. Figure 15 illustrates the Synthesis of thiazolidine-2,4-dione(TZD) (D) by chloroacetic acid and thiourea [1]. Also, in some studies, it is recommended that, if the reaction is under cold conditions and after that irradiated with the microwave, it can lead to the simplicity of the process and also increase of efficiency [162]. A group of other researchers synthesized all compounds through Knoevenagel Condensation reaction (Figure 16) and in order to obtain the acidic compounds (A6, A12, A17, A23), some thiazolidinedione ester compounds (A3, A9, A15, A20) were hydrolyzed. This test was conducted to evaluate the anti-cancer properties of these compounds against two hepatocellular carcinoma (HCC) cell lines, Huh7 and Plc/Prf/5 (Plc) cell lines using sulforhodamine B assay. Also, it can be said that IC50 values were utilized for some candidates like A4, A15, A21, in five different HCC (Huh7, Plc, Snu449, HepG2, Hep3B) and one breast cancer (Mcf7) cell line. As a practical point, it can be stated that compounds A4, A15, and A21 may be used in the future to improve anticancer drugs [163]. In another experiment, a group of compounds was studied which had thiazole nucleus in their structure. Using the reactions of the thiosemicarbazones with a series of α-halo carbonyl compounds, these new compounds were prepared. Actually, it can be said that the thiosemicarbazones derivatives were reacted also with hydrazonyl chlorides to get the corresponding tri-substituted and tetra-substituted thiazoles. The structure of these novel compounds has been verified by numerous experiments and spectral data. In comparison with, the ketoconazole, as the reference drug, it is easy to say that some of these new compounds illustrated better function against two fungal strains, such as Aspergillus flavus, and Aspergillus niger in addition...
to three yeast strains, like Saccharomyces cerevisi, Candida albicans NRRL Y-477, and Candida Pathological specimen [164]. Then, we can refer to the Synthesis of Silver/Polyrhodanine Nanotubes. In an ordinary method, silver nitrate (5.9 × 10⁻³M) was dissolved by ethanol in 200 ml after that, rhodanine monomer (7.5 × 10⁻³M) was injected in the silver nitrate solution at 60 °C. Strong magnetic stirrer was utilized during the entire production process, in order to had high shear flow. Through centrifugal precipitation, after 24 h, polyrhodanine nanotubes modified with silver nanoparticles were precipitated and washed with ethyl alcohol to eliminate the remaining reagents. For about 72 h, the nanotubes

![Formula of the compounds A1–A23](image)

**Figure 16.** Formula of the compounds A₁–A₂₃ [163].
were under vacuum at 25°C for being dried. All steps of synthesis of silver/polyrhodanine nanotubes are shown in Figure 17 [165].

**Conclusion**

Much effort has been devoted to the shape control synthesis of Poly rhodanine because it provides an effective strategy for tuning the physical and chemical properties of a Polymer. Thiazolidione is an adaptable nucleus and its derivatives are very interesting materials that have been very prominent in medicine and pharmacy. Actually, the antiviral, anticancer, antimicrobial areas are the three main applications of thiazolidione derivatives like rhodanine. Due to the demanding for Poly rhodanine with specific properties for dedicated applications, developments of novel techniques for creating the functional method with desired morphologies and properties are constantly required. Therefore, the efficient and rapid approach for the fabrication of synthesis of Polyrhodanine using different methods were described. Several of the above methods proved to be extremely effective in detecting drug accumulation in cancer tissue, and effective against human immunodeficiency virus (HIV), hepatitis C virus (HCV), dengue virus proteins and Antimicrobial activity holding a great promise for application in image-guided cancer chemotherapy. It’s believed that Poly rhodanine provides interesting perspectives for applications in biomedical fields. Recent developments in applications ranging from diagnosis to treatment provide a mirror image of future horizons.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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