RHODANINE AS A SCAFFOLD: A SHORT REVIEW ON ITS SYNTHESIS AND ANTI-DIABETIC ACTIVITIES

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Abstract – Heterocyclic compounds play an important role in biological processes and synthetic medicinal chemistry, and comprise approximately half of the over 6 million compounds recorded to date in Chemical Abstracts. Owing to their high degree of structural variety, heterocycles have proven to be widely useful therapeutic agents and lead candidates in drug design. In this review, I outline recent studies on the synthesis of the rhodanine core, an important heterocyclic, and the anti-diabetic activities of its derivatives reported between 2007 and 2017.

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1. INTRODUCTION
Rhodanine is an important, five-membered heterocycle containing thioether and amino groups at positions 1 and 3, respectively. It was first discovered in 1877 by Nencki, who named it “Rhodaninsaure” in reference to its synthesis from ammonium rhodanide (ammonium thiocyanate in modern chemistry
terminology) and chloroacetic acid in water.\textsuperscript{1} It is structurally related to thiazolidine-2,4-dione and 2-iminothiazolidin-4-one, which contain oxo and imino groups at position 2, respectively, instead of the thioxo group (Figure 1). It is also related to 4-thioxothiazolidin-2-one, whose oxo and thioxo groups are switched with respect to their positions in rhodanine. Although these heterocycles appear to be very similar at first glance, analogous compounds based on such scaffolds usually exhibit drastically different biological activities.

![Chemical structures of rhodanine and its analogues](image)

Figure 1. Chemical structures of rhodanine and its analogues

Rhodanine derivatives with the exocyclic double bond at position five (I, Figure 2) are the most commonly synthesized rhodanine derivatives. 5-Arylmethylidenerhodanines (I) usually synthesized by base-catalyzed Knoevenagel condensation between rhodanines or \(N\)-substituted rhodanines and aromatic aldehydes, using either conventional or microwave heating. Following the introduction of a 5-benzylidene or 5-arylmethylidene moiety, the rhodanine ring becomes aromatic. The reaction usually gives the \(Z\) isomer, as confirmed by crystallographic\textsuperscript{2} and NMR data.\textsuperscript{3}

![Possible derivatization routes of the rhodanine ring](image)

Figure 2. Possible derivatization routes of the rhodanine ring
However, the exocyclic double bond, which is in conjugation with the carbonyl group at position 4 of the rhodanine moiety, is a potentially reactive site. As an electrophilic Michael acceptor, it can react with the nucleophilic amino acid side chains of target proteins, such as cysteine, to form a covalent adduct (Figure 3). On the other hand, the synthesis of compounds without the exocyclic double bond (II, Figure 2) involves either different ring closure reaction pathways or the reduction of the double bond of I. However, when the double bond is reduced, the compounds become more flexible with a new chiral center, and their electronic properties are altered, since the conjugation between the rhodanine moiety and aromatic ring at position 5 in unsaturated analogues is lost. These differences can lead to weaker activity of the saturated analogues than their unsaturated counterparts, likely owing to the loss of aromaticity of the heterocycle.

Figure 3. Addition of reactive cysteine thiol group to the exocyclic double bond of 5-arylmethylidene-rhodanines

According to the crystal structures of protein complexes with rhodanine-based inhibitors from the Protein Data Bank, the rhodanine heterocycle can participate in many spatially defined interactions. The rhodanine ring can engage in several types of interactions with amino acids in the binding sites of various proteins: (i) hydrogen bonds with rhodanine acting as a hydrogen bond acceptor or donor, (ii) hydrophobic interactions, (iii) π-π and cation-π interactions with amino acids with aromatic or charged side chains, such as 5-benzylidene-rhodanines, and (iv) interactions with metal ions such as Zn^{2+}. The rhodanine moiety has been utilized as a uracil mimic and (di)phosphate isostere. Owing to its unique properties, the rhodanine scaffold has high potential to impart useful biological activities.

For the past two decades, rhodanine and 2,4-thiazolidinedione have been raised as powerful anti-diabetic agents and effectively utilized in the treatment of type 2 diabetes mellitus in the form of ciglitazone, englitazone, pioglitazone, lobeglitazone, troglitazone, and netoglitazone which are the derivatives of the parent compound 2,4-thiazolidinedione. 2,4-thiazolidinedione binds easily to (PPAR)-γ (peroxisome proliferator-activated receptor agonists) and ameliorates insulin sensitivity involving an alteration in fat metabolism as well as abundant decline in rotating free fatty acids. Broadly, the rhodanine based molecules target the amino acids, which present in the active sites of the human pancreatic alpha-amylase (hPAA), HCV NS₃ protease, aldose reductase, β-lactamase, UDP-N-acetylmuramate/L-alanine ligase, anti-diabetic agents, cathepsin D, and histidine.
Some molecular properties, such as membrane permeability and bioavailability, are known to be directly related to certain parameters such as log P (partition coefficient), molecular weight, and number of hydrogen bond acceptors and donors. Lipinski’s rule of five\textsuperscript{18} yields a filter for drug-like properties: most molecules with good membrane permeability have log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond donors and acceptors ≤ 5, and number of rotatable bonds ≤ 5. The Lipinski parameters for rhodanine and thiazolidinedione are listed below (Table 1).

<table>
<thead>
<tr>
<th>Lipinski parameters</th>
<th>Rhodanine</th>
<th>Thiazolidinedione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log P</td>
<td>0.56</td>
<td>0.02</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>132.21</td>
<td>116.14</td>
</tr>
<tr>
<td>Hydrogen bond acceptors</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hydrogen bond donors</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. of rotatable bonds</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Both compounds satisfy the aforementioned conditions, and prove themselves \textit{a priori} as potential drugs and physiologically active compounds.

Boyd\textsuperscript{19} investigated the pharmaceutical importance of rhodanine and stated optimistically that rhodanine has the potential to lead to novel and patentable pharmaceutical compounds. Indeed, Murugana et al.\textsuperscript{20} reported that the anti-diabetic activity of rhodanine derivatives is much more forceful than that of rosiglitazone in improving stress condition. Bhatti et al.\textsuperscript{21} recorded that 2,4-thiazolidinedione derivatives exhibit better therapeutic potential such as pioglitazone\textsuperscript{22} and AD-5061\textsuperscript{23} in the avoidance and medication of diabetic complications for improving insulin resistance. Recent studies show that rhodanine inhibits the multiplication of echovirus and the development of virus-induced morphologic changes, rhodanine is more active than its derivatives and less toxic to the host cells.\textsuperscript{24} In addition, rhodanine derivatives possess anticonvulsant, antibacterial, antiviral, and anti-diabetic activities.\textsuperscript{15} Besides, to synthesize and design new anti-diabetic drugs with improved potency, it is very important to investigate anti-diabetic drugs at molecular and submolecular levels since their biological activities directly originate from their atomic structure and bonding ability.\textsuperscript{25} Moreover the knowledge about molecular interaction mechanisms as well as about the role of the functional group contributions to the physicochemical properties of the existing drugs is decidedly vital. In that sense electron-density features and the electrostatic molecular properties are highly crucial to throw light onto the reactivity as a main chemical origin of the biological properties of the molecules.\textsuperscript{26} An insight about structural features on the electron-density level is yielded to anticipate the interaction nature of the drug molecule with the active sites of the target molecule.
Devi used a combination of computational methods to reveal a picture of the anti-diabetic activities and molecule-receptor interactions between rhodanine and thiazolidinedione with human pancreatic alpha amylase protein (hPAA). The modern quantum chemical tools have been applied to study the electronic bonding and lone pair details, energy, electrostatic potential, dipole moment, and intermolecular interactions of rhodanine and thiazolidinedione, and to locate the regions that are susceptible to electrophilic and nucleophilic attacks. Studies using molecular docking, QM, and QM/MM dynamics approaches accompanied with electron-density descriptors have provided detailed information on the interactions between these two molecules and amino acid residues in hPAA. The O1 oxygen atom in rhodanine and O2 in thiazolidinedione form in-plane hydrogen bonds with the Arg195 and His299 residues. The S1 atom in both molecules is less reactive and does not form any significant contacts upon binding to the active site. Instead, it forms hydrogen bonds with water molecules. The NH fragment readily interacts with Asp197, and equilibrium between two different protonation states is achieved. The most preferable state corresponds to rhodanine with a deprotonated NH fragment and neutral side-chain of Asp197, whereas there are two conformations with comparable occupancies in the complex with thiazolidinedione. The ligand-protein interactions are strengthened if the molecule is negatively charged.

Figure 4. Interaction of the active site of the human pancreatic alpha-amylase, hPAA, with the rhodanine (left panel) or 2,4-thiazolidinedione (right panel) molecules. Electrostatic potential maps of the neutral ligands are shown at surfaces of electron density equal to 0.04e/Å³. The lower panel demonstrates the distance distribution between the NH group of ligand and Asp197 (rhodanine on the left graph and 2,4-thiazolidinedione on the right), blue graphs correspond to the r(Nligand…H1) and red to the r(OAsp197…H1).
Therefore, rhodanine would have a higher binding affinity than the 2,4-thiazolidinedione towards the active site of hPAA (Figure 4). Thus, the applied combination of computational methods throws light onto a more reliable picture of the anti-diabetic activity and also molecule-receptor interactions of the drugs rhodanine and 2,4-thiazolidinedione with hPAA.

As rhodanine-based compounds often comprise potent and selective modulators of target enzymes or receptors, they represent a significant class of heterocycles. Chemical modifications of the rhodanine core yield compounds with a wide range of biological activities. Thus, rhodanine-based compounds will remain a preferred scaffold in drug discovery.\textsuperscript{28} To enhance the speed, diversity, and efficiency in drug discovery, it is important to rely on combinatorial approaches for the discovery and optimization of new drugs.

There are various available routes to synthesize the rhodanine ring. Condensation followed by cyclization or multicomponent reactions (MCR), either in a step-wise manner or in one pot, have been successfully carried out to obtain the aforementioned class of heterocycles under various conditions. So far, rhodanine derivatives have been synthesized by assembling functionalized heterocycles via reactions of α-halogencarboxylic acid and maleic acid derivatives with carbon disulfide and amines, or of isothiocyanates with thioglycolates.\textsuperscript{29} A few multicomponent approaches based on the construction of functionalized rhodanine scaffolds have been developed recently using the three-component reaction of carbon disulfide, primary amines, and various substrates (e.g., arylpropiolates, dialkyl acetylenedicarboxylate, fumaryl chloride, 1-\textit{tert}-butyl 4-isopropylbut-2-ynedioate, 1,2-diaza-1,3-dienes, α-chloro-β,γ-alkenoate esters, ethyl chloroacetate, chloroacetyl chloride, bromoacetic acid, and maleic anhydride). However, these multicomponent protocols present a few drawbacks for combinatorial applications. For example, carbon disulfide is toxic, and the resulting chemical diversity is low due to the limited flexibility (and/or commercial availability) of the substrates. The first part of the review, covers advances made in the last ten years in rhodanine core synthesis. The synthetic methods were divided into four main classifications including multicomponent approaches, as well as from certain starting materials such as from bis(carboxymethyl) trithiocarbonates, α-halogen carboxylic acids, and isothiocyanates. The synthesis of target rhodanine compounds has been carried out using both conventional and non-conventional techniques. In the second part of the review I will focus on recently reported anti-diabetic activities of rhodanine based compounds.

2. RHODANINE SYNTHESIS

The number of new methodologies regarding the synthesis of rhodanine core has dramatically increased from year to year. All these transformations provide rapid access to new and original rhodanine compounds, affording the possibility of increasing structural diversity in a straightforward fashion.
starting from simple and common substrates. Here I have included some common synthetic procedures for rhodanine scaffold.

2-1. Multicomponent approaches (MCRs)

This section highlights the different processes used to establish rhodanine structure from simple and readily available starting precursors using MCRs. Recently, MCRs have garnered considerable attention from the chemical community because they facilitate the construction of architecturally complex molecules from relatively simple starting materials. Although significant progress has been made in this area, there is still a high demand for new processes aimed at the rapid assembly of heterocyclic molecules. 4-Thiazolidinones are an important group of heterocyclic compounds that have been subject to extensive studies. Among them, the rhodanine (2-thioxothiazolidin-4-ones) motif represents an important medicinal scaffold.

Taran designed a simple and efficient method for constructing rhodanine derivatives 4a-f using a phosphine-catalyzed tandem umpolung addition and the intramolecular cyclization of bifunctional sulfur pronucleophiles on arylpropiolates. 4a-f were obtained separately in a one-pot process through the reaction of dithiocarbamates 3 (prepared in situ from amines and carbon disulfide) and arylpropiolates 1 in the presence of Bu3P (Scheme 1).

Scheme 1. Phosphine-catalyzed reaction of dithiocarbamates 3 with aryl propiolates 1 leading to rhodanine derivatives 4a–f

The strong nucleophilicity of the thiol group facilitates the chemoselective Bu3P-catalyzed R-S-addition of the bifunctional nucleophile on the alkyne. The resulting umpolung adduct would then undergo cyclization due to the proximity of the second nucleophile to the ester group (Scheme 2), resulting in the formation of sulfur heterocycle 4.
A facile and direct synthetic approach to rhodanine derivatives 6a,b via the three-component coupling of carbon disulfide, primary amines, and acetylenic esters under neutral conditions was reported by Alizadeh. The reaction of carbon disulfide with an amine in the presence of dialkyl acetylenedicarboxylate 5 proceeded spontaneously at room temperature in water and was complete within a few hours (Scheme 3).

A possible mechanism explanation is proposed in Scheme 4. Compounds 6a and 6b could result from the initial addition of the amine to carbon disulfide, and the attack of the resulting reactive alkylammoniumcarbodithioate on the acetylenic ester to yield intermediate 7. The cyclization of 7 and subsequent loss of ROH lead to compounds 6a and 6b.

Another relevant addition by Alizadeh in use fumaryl chloride instead of acetylenic esters in an easy, highly efficient, and simple one-pot approach for the synthesis of 2-thioxo-1,3-thiazolidin-4-one 9. The reaction between a primary amine and carbon disulfide in the presence of fumaryl chloride 8 in water afforded the title compounds in good yields 75–87% (Scheme 5).
The coupling of the 1,2-diaza-1,3-dienes with amines and carbon disulfide step may also be used as the basis for a rhodanine multicomponent synthesis. As shown in Scheme 6, the utility of 1,2-diaza-1,3-dienes in organic synthesis has been recognized owing to the ready accessibility and good reactivity of the highly electrophilic (C4) center that can lead to a variety of heterocyclic rings using a wide range of nucleophiles. Moreover, it is well-known that the reaction between amines and carbon disulfide and alkyl halides, epoxides, or Michael acceptors affords dithiocarbamates, and these reactions...
have a variety of applications in organic, medicinal, material, and agricultural chemistry. Favi’s research group\textsuperscript{38} reported a novel three-component synthesis of 5-hydrazinoalkylidene-rhodanine derivative 11, starting from aliphatic primary amines, carbon disulfide, and 1,2-diaza-1,3-diienes 10. The reaction gives 11 in good yields of 44–83\% (Scheme 6).

\begin{center}
\textbf{Scheme 6. One-pot synthesis of 5-hydrazinoalkylidene-rhodanines 11a–f}
\end{center}

The mechanism for the formation of hydrazinoalkylidene-rhodanines 11 suggested by the authors is summarized in Scheme 7, and involves an initial produced of intermediate A by the nucleophilic attack of the \textit{in situ} generated dithiocarbamic acid on the azo-ene system of 1,2-diaza-1,3-diene 10 \textit{via} a Michael-like 1,4-addition reaction. Next, the hydrazono-hydrazino tautomerization of intermediate A produces B, which is followed by the base-promoted intramolecular nucleophilic attack of the NH dithiocarbamic group on the ester moiety, resulting in the loss of an alcohol and formation of 11.

\begin{center}
\textbf{Scheme 7. Plausible mechanism for the formation of 5-hydrazinoalkylidene-rhodanine derivatives 11}
\end{center}
A very efficient route to rhodanine derivatives 5-(Z)-alkylidene-2-thioxo-1,3-thiazolidin-4-ones 15a–c has been developed by Posner et al.\textsuperscript{39} via the reaction of \textit{in situ} generated dithiocarbamates with racemic \(\alpha\)-chloro-\(\beta,\gamma\)-alkenoate esters 12. The multicomponent protocol involves the addition of the amine to carbon disulfide, followed by the \textit{in situ} exclusive S\textsubscript{N}2 displacement of chloride from \(\alpha,\beta,\gamma\)-trifunctional ester allylic chloride, carbon-carbon double bond isomerization creating conjugation with the ester group (\(\beta,\gamma\)-enoate \(\rightarrow\) \(\alpha,\beta\)-enoate), and finally a 5-exo-trig cyclization to produce 5-(Z)-alkylidene-rhodanines 15 in good yields (48–74\%) with diverse \textit{R} and \textit{R}' groups (Scheme 8). The method is mild and versatile, working successfully with a variety of simple as well as functionalized primary amines and with several different \(\alpha\)-chloro esters allowing preparation of a small library of new \(N\)-alkyl-5-alkylidene-rhodanines.

![Scheme 8. Formation of 5-(Z)-alkylidene-rhodanines 15a–c](image)

15a: \(R = \text{PhCH}_3, R' = -\text{CH}_2\text{CH}_2\text{OH}, 57\%\);
15b: \(R = n\)-pentyl, \(R' = -\text{CH}_2\text{Ph}, 48\%\);
15c: \(R = \text{cyclohexyl}, R' = -\text{CH}_2\text{Ph}, 74\%\)

An application of using ultrasound approach, reported by Shaabani and co-workers\textsuperscript{40} who successfully developed a novel one-pot sequential six-component reaction for the synthesis of rhodanine derivative 22. This MCR-based approach is an efficient, environmentally friendly, and expeditious procedure that affords direct access to a wide range of pharmacologically significant and structurally interesting
compounds. The syntheses of rhodanine-5-carboxylic acid was achieved in water under ultrasonic irradiation using readily available and inexpensive starting materials (2-chlorobenzylamine 17, carbon disulfide, and maleic anhydride 16. Subsequently, 4-nitrobenzaldehyde 20, 3,4-dimethylaniline 19, and tert-butyl isocyanide 21 were added. The reaction mixture was irradiated by ultrasound at room temperature for 90–120 min to produce moderate to high yields of the products without catalysts or additives. The desired product, 22, was isolated in 82% yield, which was higher than that obtained via the conventional stirring method (75%) (Scheme 9).

![Scheme 9. One-pot sequential synthesis of rhodanine derivative 22](image)

The proposed mechanism for the formation of 18 involves the formation of carbamodithioic acid 23 from a primary amine and carbon disulfide. The Michael addition of in situ prepared 23 to maleic anhydride affords intermediate 24, which forms an intramolecular amide bond via nucleophilic attack by nitrogen on the anhydride group to give 18 (Scheme 10).
2-2. From bis(carboxymethyl)trithiocarbonates

Xie described an convenient synthesis of N-phenyl-substituted rhodanine derivatives in 28–88% yields from various anilines via treatment of bis(carboxymethyl)-trithiocarbonate in water (Scheme 11).

On the other hand, Botta developed a fast and efficient protocol for the generation of substituted 5-arylidene-rhodanine in a sequential one-pot, two-step process combining the “Holmberg method” and Knoevenagel condensation under microwave-assisted conditions. Bis(carboxymethyl) trithiocarbonate (1 equiv) and an amine (1 equiv) were dissolved in DME, and the resulting mixture was heated at 90 °C under microwave irradiation for 10 min. In the second step, an aldehyde (R CHO, 1 equiv) was added, and the mixture was heated at 110 °C for 5 min under microwave irradiation. The products were isolated in high purities in moderate to good yields following precipitation from MeOH (Scheme 12).
Multicomponent, one-pot syntheses of rhodanines using carbon disulfide have been reported for the direct synthesis of highly substituted rhodanines by various authors, however these methods are usually inadequate for the synthesis of $N$-substituted rhodanines without substitution at position 5, and therefore do not yield products that offer the desired synthetic ‘freedom to operate’ in 5-position. Nitsche and Klein developed an improved one-pot process and straightforward protocol for the rapid synthesis of...
N-substituted rhodanine derivatives that do not carry additional substituents in the highly reactive position 5 and are thus valuable synthons to obtain rhodanine derivatives with the molecular complexity and diversity that are required in drug-discovery and enable the synthesis of a large number of N-substituted rhodanines from the corresponding amines under environmentally friendly conditions in high yields. Using the microwave assisted approaches shown in Scheme 13 at 160 °C, N-phenylrhodanines 30 has been produced in high purity via the reaction of 26 with anilines 29 in water and isolated in 32% yield.

Scheme 13. Microwave-assisted synthesis of N-substituted rhodanine 30

Lesyk\(^{44}\) reported the synthesis of 3-(benzothiazol-2-ylamino)-2-thioxo-4-thiazolidone 32 in 78% yield from (benzothiazole-2-yl)hydrazine 31 and trithiocarbonyl diglycolic acid 26 by refluxing in ethanol (Scheme 14).

Scheme 14. Synthesis of 3-(benzothiazol-2-ylamino)-2-thioxo-4-thiazolidone 32

Ono\(^{45}\) produced rhodanine derivative 34 in a yield of 81% through the reaction of glycine ethyl ester 33 with 26 in the presence of Et\(_3\)N (Scheme 15).

Scheme 15. Synthesis of rhodanine derivative 34
In another study by Biehl,\textsuperscript{46} 3-(aryl/alkyl-2-ylmethyl)-2-thioxothiazolidin-4-one derivative \textbf{36} was prepared in 52.9% yield by refluxing equimolar quantities of thiophen-2-ylmethanamine \textbf{35} and \textbf{26} in the presence of 0.5 equiv of potassium carbonate (Scheme 16).

\textbf{Scheme 16. Synthesis of \textbf{36}}

The arylsulfonamide functionality on the rhodanine moiety in compound \textbf{38} was produced using Powers’ approach.\textsuperscript{47} First, the formation of the arylsulfonylhydrazide was accomplished by treating sulfonyl chloride with hydrazine in THF at 0 °C, followed by an aqueous work-up. Second, arylsulfonylhydrazide \textbf{37} was treated with \textbf{26} in water at 95 °C for 22 h to produce 3-(arylsulfonylamino)rhodanine \textbf{38} in 41% yield (Scheme 17).

\textbf{Scheme 17. Synthetic approach used for the preparation of \textit{N}-substituted rhodanine \textbf{38}}

Harada\textsuperscript{49} carried out the synthesis of rhodanine \textbf{39} using trithiocarbonyl diglycolic acid and 1,10-carbonyldiimidazole in THF at room temperature in 1.5 h. An amine was added, and the mixture was refluxed for 4 h to give \textit{N}-substituted rhodanine derivatives \textbf{39} in 35–60% yields (Scheme 18).

\textbf{Scheme 18. Synthetic approach used for the preparation of \textit{N}-substituted rhodanine \textbf{39}}

\textbf{2-3. From α-halogen carboxylic acids}

Djafri\textsuperscript{50} reported that the reaction between carbon disulfide, aromatic amine \textbf{40}, and ammonium
hydroxide gives ammonium $O$-aryldithiocarbamate (DTC) salts \(41\). The reaction between the DTC and chloroacetic acid leads to $N$-arylthiazolidinones \(42\) (Scheme 19).

\[
\text{Scheme 19. Synthesis of compounds } 42
\]

Lesyk\(^{51}\) revealed that the reaction between carbon disulfide and amino acids in the presence of potassium hydroxide in aqueous solutions yields amino acid dithiocarbamates. Further reaction with potassium chloroacetate and cyclization with hydrochloric acid leads to rhodanine rings \(43\) with the amino acid moiety attached to the nitrogen at position 3 (N-3) (Scheme 20).

\[
\text{Scheme 20. Synthesis of compounds } 43
\]

Ferro\(^{52}\) reported the synthesis of rhodanine derivatives \(44\) from commercially available amino acids, which cyclized with carbon disulfide and $\alpha$-chloroacetate to form substituted rhodanine derivatives \textit{via} microwave-assisted organic synthesis (Scheme 21).

\[
\text{Scheme 21. Synthesis of compounds } 44
\]
Klein\textsuperscript{43} reported a one-pot microwave-assisted method to rapidly synthesize $N$-substituted rhodanines $45$ from amines. Alkyl- and benzylamines could be converted into the corresponding rhodanines via an efficient, one-pot, and three-step protocol involving carbon disulfide and chloroacetic acid in short reaction times with in yields 13–81\% (Scheme 22).

\begin{center}
\begin{tikzpicture}
\node [rectangle, draw] (1) {\text{R=NH$_2$}}; \\
\node [rectangle, draw, below=of 1] (2) {1) CS$_2$, NaOH, MW}; \\
\node [rectangle, draw, below=of 2] (3) {2) ClCH$_2$CO$_2$H, MW}; \\
\node [rectangle, draw, below=of 3] (4) {3) HCl, MW}; \\
\node [circle, draw] (5) at (3) {$45$}; \\
\node [circle, draw] (6) at (5) {$R = \text{Me, 69\%; Et, 71\%; cyclopentyl, 59\%; Ph, 13\%; benzyl, 81\%}$}; \\
\end{tikzpicture}
\end{center}

Scheme 22. Synthesis of compound $45$

Ravi\textsuperscript{44} synthesized rhodanine compounds $47$ as outlined in Scheme 23. Ammonium dithiacarbamates $46$ were obtained by treating the respective amines with carbon disulfide and ammonia. In the second step, compounds $46$ were reacted with sodium chloroacetate at high temperatures to afford rhodanine derivatives $47$ in good yields.

\begin{center}
\begin{tikzpicture}
\node [rectangle, draw] (1) {\text{R=NH$_2$}}; \\
\node [rectangle, draw, below=of 1] (2) {1) CS$_2$, NH$_3$}; \\
\node [rectangle, draw, below=of 2] (3) {2) ClCH$_2$CO$_2$Na, 85–90 °C, HCl}; \\
\node [circle, draw] (4) at (3) {$46$}; \\
\node [circle, draw] (5) at (4) {$47$}; \\
\node [circle, draw] (6) at (5) {$R = \text{H, Ph}$}; \\
\end{tikzpicture}
\end{center}

Scheme 23. Synthesis of rhodanine derivatives $47$

Talele\textsuperscript{54} reported the synthesis of rhodanine derivative $49$ in 30\% yield from phenylalanine via cyclization of $L$-phenylalanine with carbon disulfide and sodium $\alpha$-chloroacetate (Scheme 24).

\begin{center}
\begin{tikzpicture}
\node [rectangle, draw] (1) {48}; \\
\node [rectangle, draw] (2) at (1) {$+$}; \\
\node [rectangle, draw] (3) at (2) {CS$_2$}; \\
\node [rectangle, draw] (4) at (3) {aq. NaOH}; \\
\node [rectangle, draw] (5) at (4) {ClCH$_2$CO$_2$Na, HCl, reflux}; \\
\node [circle, draw] (6) at (5) {$49$}; \\
\end{tikzpicture}
\end{center}

Scheme 24. Synthesis of rhodanine derivative $49$

A modified method for the synthesis of 2-thioxo-thiazolidin-4-one derivative incorporated with phenylalanine residue $49$ was introduced by Joghee.\textsuperscript{55} The amino acid was first converted to the corresponding ammonium salt and then reacted with carbon disulfide to yield the corresponding
dithiocarbamates. The dithiocarbamates were then reacted with sodium chloroacetate followed by cyclization under acidic conditions in presence of phosphorous oxychloride to yield products in which the N-terminal of the amino acid is converted to the corresponding 2-thioxothiazolidin-4-ones, 49 in a good yield 86%. The present method is simple and easy, the authors prepared the ammonium salt of dithiocarbamate rather sodium salt and the reaction completes at room temperature itself without heating and the dithiocarbamates are relatively more stable under cold conditions. Phosphorous oxychloride along with HCl was found to be useful in the cyclization step, as it enhances the yield (Scheme 25).

![Scheme 25. Synthesis of 2-thioxo-thiazolidin-4-one derivatives incorporated with phenylalanine](image)

Sharma\textsuperscript{56} described the synthesis of 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one 53 via the reaction between carbon disulfide, ammonia, and chloroacetic acid (Scheme 26).

![Scheme 26. Synthesis of rhodanine derivative 53](image)

Maleraju\textsuperscript{57} described the synthesis of 2-substituted-2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid derivatives 55 from amino acids 54, carbon disulfide, and the sodium salt of chloroacetic acid in KOH solution (Scheme 27).
Chauhan\textsuperscript{58} demonstrated the synthesis of rhodanine derivatives 57 from commercially available 4,7-dichloroquinoline, which was condensed with various diamines to afford 4-aminooquinoline derivative 56. 4-Aminooquinoline, carbon disulfide, and ethyl bromoacetate provided cyclized intermediate 3-((7-chloroquinolin-4-ylamino)alkyl)-2-thioxothiazolidin-4-one 57 in 78\% yield (Scheme 28).

Singh and Chauhan\textsuperscript{59} reported a novel synthesis of ketene dithioacetal rhodanines 59 and 60 via reactions of primary amines, carbon disulfide, ethyl chloroacetate 58, and alkyl halides in dimethylformamide (DMF). Potassium carbonate efficiently catalyzes the reaction at room temperature give the products in moderate to good yields of 44–70\% (Scheme 29).
A plausible mechanism for the formation of ketene dithioacetal rhodanines is presented in Scheme 30. The initial step is the nucleophilic attack of the amine on carbon disulfide to afford key intermediate A, which reacts with ethyl chloroacetate to form intermediate B, which undergoes an intramolecular cyclization to give rhodanine derivative C. The deprotonation of C affords enolate D, which reacts with carbon disulfide to form thiolate E. Monothiolate anion F undergoes mono-alkylation with an alkyl halide to afford dithio alkyl ester G. Then, G undergoes enolization and another alkylation to give the corresponding ketene dithioacetal-rhodanine.
Similarly, Azizi and coworkers developed a practical and rapid one-pot synthesis that yields arylidene rhodanine derivatives in high yields (70–95%) through the condensation of primary amines, aldehydes, ethyl chloroacetate, and carbon disulfide in polyethylene glycol (PEG) either at room temperature or with ultrasonic irradiation (Scheme 31). Under the ultrasound activation the reaction proceeded rapidly and gave the corresponding product in quantitative yield within 2–7 min.

$$\begin{align*}
R-\text{NH}_2 + \text{CS}_2 + &\quad \text{CS}_2 \quad 2 \\
\text{Cl} \quad \text{O} \quad \text{O}
\end{align*}$$

**Scheme 31.** Synthesis of substituted rhodanine derivatives 61 with various amine and aldehyde components

A solvent- and catalyst-free synthesis of 2-thioxo-1,3-thiazolidin-4-ones systems has been developed recently by Heravi, based on the reaction between primary amines, carbon disulfide, and chloroacetyl chloride (Scheme 32). The 2-thioxothiazolidin-4-one derivatives thus obtained in excellent yields (>85%).

$$\begin{align*}
R-\text{NH}_2 + &\quad \text{CS}_2 + \quad \text{Cl} \quad \text{O} \quad \text{Cl} \\
2 
\end{align*}$$

**Scheme 32.** Synthesis of 2-thioxo-1,3-thiazolidin-4-one 63 via three-component reaction

Guiheneuf et al. synthesized 3-(4-oxo-2-thioxo-thiazolidin-3-yl)propanoic acid 66 in 44% yield via the reaction of β-alanine with carbon disulfide and bromoacetic acid in aqueous potassium hydroxide (Scheme 33).
Scheme 33. Synthetic approach for the preparation of \(N\)-substituted rhodanine 66

2-4. From isothiocyanates

Cosse\(^{63}\) reported the synthesis of rhodanine derivative 68 in 42\% yield over three steps starting from the corresponding aniline. 4-Methoxyaniline 67 was first converted into the corresponding isothiocyanate. The isothiocyanate was then treated with thioglycolic acid; the resulting dithiocarbamate subsequently cyclized into rhodanine 68 upon refluxing in acetic anhydride (Scheme 34).

Scheme 34. Synthesis of rhodanine derivative 68

Ono\(^{45}\) reported the synthesis of 3-(2-(1H-imidazol-4-yl)ethyl)-2-thioxoimidazolidin-4-one 70 in 79.5\% yield through the reaction of histamine with ethyl isothiocyanatoacetate 69 in the presence of Et\(_3\)N in acetonitrile for 10 min at room temperature (Scheme 35).

Scheme 35. Synthesis of rhodanine 70

Helal\(^{64}\) reported an efficient method for the synthesis of rhodanine derivative 73. The reaction involved the cyclocondensation of cyclohexyl-isothiocyanate 71 with sulfanylacetic acid 72 in 1,4-dioxane in the presence of triethylamine under reflux (Scheme 36).
Scheme 36. Synthesis of rhodanine derivative 73

Li described the synthesis of N-methyl-4-(4-(4-oxo-2-thioxothiazolidin-3-yl)phenoxy)picolinamide 75 in 66% yield from 2-sulfanylacetic acid and 4-(4-isothiocyanatophenoxy)-N-methylpicolinamide 74 in 1,4-dioxane (Scheme 37).

Scheme 37. Synthesis of rhodanine derivative 75

A large number of therapeutic agents are synthesized with the help of rhodanine nucleus. During recent years there have been some interesting developments in the biological activities of rhodanine derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities.

3. RHODANINES AS ANTI-DIABETIC AGENTS

Type 2 diabetes mellitus is a metabolic disease in which the body loses its ability to control glucose levels within the normal range. This is caused by either altered insulin secretion by the pancreas, or the development of insulin resistance by different organs, especially skeletal muscles. This chronic disease has high morbidity and mortality rates, and poses an economic burden on developing countries. A recent study by the WHO revealed that approximately 200 million people 20 to 80 years old have diabetes globally, and this figure is expected to increase to 366 million by 2030. Prolonged exposure to uncontrolled hyperglycemia in patients leads to several complications, such as retinopathy, neuropathy, cataracts, nephropathy, and cardiovascular issues. Rhodanines can be used in the treatment of type 2 diabetes mellitus by acting as PPARγ agonists, as well as in the treatment of diabetes complications by inhibition of aldose reductase. Among the possible treatment routes for diabetes, the polyol pathway has been studied extensively. Aldose reductase (ALR),
the first and rate-limiting enzyme of the polyol pathway is responsible for the conversion of glucose into sorbitol (Figure 5).\textsuperscript{26}

The progression of chronic complications due to diabetes is thought to be linked to excess free glucose in insulin-insensitive tissues, which leads to the increased formation of sorbitol through the polyol pathway. Numerous observations have implicated aldose reductase (ALR) in diabetic complications. Specifically, ALR catalyzes the NADPH-dependent reduction of glucose to sorbitol, which is then oxidized to fructose by sorbitol dehydrogenase. ALR has a low affinity towards glucose, so under normal conditions, there is little flux of glucose through the polyol pathway. ALR inhibition thus represents an attractive approach to prevent or control the progression of chronic diabetes complications.\textsuperscript{27}

Accordingly, aldose reductase inhibitors (ARIs) have recently become an attractive therapeutic strategy.\textsuperscript{28}

Over the last two decades, a variety of ARIs with different pharmacophores have been synthesized and tested for their efficacy in several diabetic complications (Figure 6). On the basis of their chemical structures, they can be classified into three general groups: (i) carboxylic acid derivatives (such as Zopolrestat, Epalrestat, Zenarestat, Ponalrestat, Tolrestat, and the recently developed Lidorestat); (ii) spirohydantoins (include Sorbinil, Ranirestat, AND-138, and Fidarestat); and (iii) flavonoids (such as Resveratrol and Quercetin).
Quercetin and Resveratrol). However, most tested compounds failed in clinical trials because of side effects or poor efficacy. The only exception is Epalrestat, which is currently used for the treatment of diabetic neuropathy in Japan, China, and recently, in India.

3-1. Rhodanines as ARIs

Bagul described the synthesis, biological activity, and structure-activity relationships of a series of Epalrestat analogues. The synthesized compounds were evaluated in vitro for their ability to inhibit ALR activity, using Epalrestat as the reference compound. Compounds 76, 77, 78, 79, and 80 (Figure 7) exhibited more than 50% inhibition, which was comparable to that of Epalrestat. Compound 80 was found to be the most potent ARI, with an IC50 value of 0.22 mM (the IC50 value of Epalrestat is 0.4 mM). Other compounds, namely 76, 77, 78, and 79, exhibited excellent inhibitory activities with respective IC50 values of 0.75, 0.67, 0.69, and 0.86 mM.

Figure 7. A) Potential structural modification of Epalrestat. B) New Epalrestat analogues
Replacing the methyl group in Epalrestat with an electron-withdrawing nitrile group on the olefin chain did not have a considerable influence on the activity. ARI activity studies of compound 79 revealed that replacing the phenyl group in Epalrestat with a thiophene residue also did not significantly affect the ARI activity. Compound 77 has a furan ring and exhibited excellent activity, which was comparable to that of Epalrestat. In compounds 78 and 79, the acetic acid group of rhodanine is replaced with just rhodanine; their ARI activities suggest that the acetic acid end group is not mandatory for ARI activity. Further, compound 78 has a substituent in the para position of the phenyl ring. The observation that compounds without the acetic acid end group (78 and 79) still exert ARI activity is new and interesting, especially in terms of understanding the function of small molecules and macromolecular interactions. In compound 80, replacing acetic acid with benzoic acid resulted in excellent activity (0.22 mM). The structural changes introduced in these Epalrestat analogues revealed novel structure-activity relationships.

Agrawal reported a series of substituted 5-phenylbenzoates containing rhodanine moieties, and evaluated their in vitro ALR inhibitory activities using Sorbinil as a reference (Figure 8). Sorbinil is an aldose reductase inhibitor being investigated for treatment of diabetic complications including neuropathy and retinopathy. Preliminary structure-activity relationship determinations revealed that rhodanine derivatives exhibited improved ALR inhibitory activities. Among the synthesized compounds, (4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl) 2-chlorobenzoate 81 showed an IC_{50} value of 1.82 µM, which was very similar to that of Sorbinil (1.32 µM). In contrast, analogues 82 (5.89 µM) and 83 (12.5 µM) bearing 4-chloro or 2,4-dichlorobenzoate substituents on the 5-arylidene moiety produced no or only moderate ALR inhibition. Electron-withdrawing groups at the 2nd position of the terminal phenyl ring imparted favorable activity as in 81 (1.82 µM), whereas electron-withdrawing groups at the 4th position resulted in decreased activity as in 82 (5.89 µM). Similarly, di-substituted electronegative derivatives in 83 exhibited less activity with IC_{50} value of 12.5 µM. Meanwhile, electropositive and bulky groups in the 4th position, such as 4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl 4-methoxybenzoate 84, resulted in comparable activity; specifically, its IC_{50} value of 2.57 µM was better than that of the corresponding 4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl 3,4-dimethoxybenzoate 85 (2.68 µM). The displacement of the para methyl group of 86 to the ortho position of the 5-benzylidene ring in 87 markedly increased the inhibition from 5.82 to 3.65 µM. Rhodanine derivatives 81 and 84 exhibited ALR inhibitions at micromolar concentrations (IC_{50} = 1.82 and 2.57 µM, respectively), making them good starting points for future drug discovery programs.
3-2. Rhodanines as PPARγ modulators

Peroxisome proliferator-activated receptors (PPARs) are well known transcription factors that directly control the expression of genes involved in lipid and glucose metabolism. They function as cellular lipid sensors to activate transcription in response to the binding of cognate ligands (generally fatty acids and their eicosanoid metabolites). The biological mechanism of PPARs has been well described elsewhere. Among the three isotypes of PPARs (PPARα, PPARβ, and PPARγ), PPARγ is most studied in drug discovery. PPARγ was initially identified as a key regulator of adipogenesis, however it also plays an important role in type 2 diabetes, cellular differentiation, insulin sensitization, atherosclerosis, and cancer. PPARγ is activated by several lipophilic ligands, including long-chain polyunsaturated fatty acids, arachidonic acid metabolites derived from the cyclooxygenase and lipoxygenase pathways, and fatty acid-derived components of oxidized low-density lipoprotein. Anti-diabetic thiazolidinedione drugs such as Troglitazone, Rosiglitazone, Pioglitazone, and Ciglitazone represent a class of synthetic ligands with high affinities towards PPARγ. Other compounds that can function as ligands include certain non-steroid anti-inflammatory drugs (NSAIDs) such as indomethacin, ibuprofen, flufenamic acid, and fenoprofen. In addition, non-thiazolidinedione derivatives such as ragaglitazar, tesaglitazar, GW-409544, GW-0072, L-764406, and MCC-555 are also synthetic PPARγ ligands. Therefore, the development of new drugs with insulin-sensitizing and cholesterol/triglyceride-lowering effects is of general interest.

Murugana et al. synthesized a series of dispiropyrrolidines, performed molecular docking studies with 1FM9 protein, and screened the synthesized compounds for anti-diabetic activities. The synthesized
compounds exhibited attractive anti-diabetic properties and were found to be more effective than Rosiglitazone in ameliorating stress. Compounds 88 and 89 displayed promising anti-diabetic activities (Figure 9). Compound 89 was more active, fit better within the active site of PPARγ, and attained the best score of 71.2 amongst all tested molecules when compared with Rosiglitazone (96.48). It showed important additional H bonding interactions with the Tyr473 residue in the active site of PPARγ, due to the methoxy group, which is present at the 4th position of the phenyl ring in compound 89.

![Chemical structures](image)

blood glucose level (mg/dL)  
115.3 ± 2.2*  
115.8 ± 1.8†  
97.4 ± 4.5

Figure 9. *In vivo* anti-diabetic activity screening of dispiropyrrolidine derivatives. *p < 0.01 compared to the respective control; the results were analyzed by ANOVA and student t-test

Choi et al. identified (β-carboxyethyl)-rhodanine derivatives as potential PPARγ agonists. Specifically, an *in vitro* assay revealed the nanomolar-scale binding affinity of 90 (Figure 10). In a cell-based transactivation assay, it exhibited PPARγ agonistic activity similar to that of Rosiglitazone, a well-known PPARγ agonist with an IC₅₀ value of 876 nM.

![Chemical structures](image)

IC₅₀ = 876 nM  
IC₅₀ = 269 nM

Figure 10. (β-Carboxyethyl)-rhodanine derivatives as PPARγ agonists

Prachand screened (Z)-4-(4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl substituted benzoate derivatives 91 for their anti-diabetic activities (Figure 11). Some compounds showed better activities than the reference (Rosiglitazone) in reducing blood glucose levels, and considerably improved efficacies and
biological responses. These results suggest that PPARγ is a promising target for the management of type 2 diabetes, and that rhodanine analogues could elicit anti-diabetic activity from the receptor.

![Chemical structure of compound 91 and Rosiglitazone](image)

**Figure 11.** (Z)-4-(4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl substituted benzoate as PPARγ agonistic

Kapoor\(^{24}\) identified a novel series of glitazone derivatives, and screened them for anti-hyperglycemic activities in a fructose-induced diabetic animal model. Pioglitazone was used as a reference standard. Rhodanine-substituted compound \(92\) (Figure 12) showed anti-hyperglycemic activity with a maximum blood glucose reduction of 40%. The presence of an ether linkage is the primary requisite for anti-hyperglycemic activity in this case. The condensation of benzylidene with lipophilic moieties (i.e., benzothiazole) enhanced the activity of the synthesized derivative.

![Chemical structure of compound 92 and Pioglitazone](image)

**Figure 12.** Anti-hyperglycemic evaluation of compound \(92\); the basal blood glucose level was considered to be 100% for calculating the percentage decrease with \(n = 3\). The results are expressed as mean ± SEM, and the data were analyzed using one-way ANOVA followed by Dunnett test, **\(p < 0.01\)

A significant advance in the development of small-molecule PPARγ receptor agonists was the discovery of new substituted rhodanines exemplified by compound \(93\), as reported by Kumar.\(^{95}\) When subjected to an *in vitro* glucose uptake assay using a rat hemi-diaphragm in the absence or presence of insulin to confirm its anti-diabetic activity, compound \(93\) showed considerable glucose uptake activity as compared to Rosiglitazone, a standard drug (Figure 13).
in the absence of insulin (mg/dL/g/45 min)  & 29.06 ± 0.44* & 36.00 ± 1.00**  

in the presence of insulin (mg/dL/g/45 min) & 38.29 ± 0.71* & 50.50 ± 1.50**  

Figure 13. In vitro glucose uptake of rhodanine derivative 93 and Rosiglitazone, a standard drug in the presence and absence of insulin. *p < 0.05 and **p < 0.01 compared to the respective control, using one way-ANOVA followed by Dunnett’s post-test

4. CONCLUSION

In conclusion, this review article seeks to provide an up-to-date overview of the latest advances involving the development of straightforward and diversity-oriented reactions to construct rhodanine skeletons which have always been of a paramount chemical significance for pharmaceutical and synthetic chemists. In this review, we have presented the recent major advances in the synthesis of rhodanine-based compounds. The synthesis of target rhodanine compounds has been carried out using both conventional and non-conventional techniques. The non-conventional (microwave and ultrasonic irritation) pathways showed advantages like ecofriendly and safe procedures, as well as spectacular accelerations, higher yields under mild reaction conditions, shorter reaction times, and simple work ups as compared to the conventional techniques. Apart from notable synthetic advancements, we have clearly shown that numerous outstanding achievements revealed that these structures possess extensive potential applications as medicinal drugs. In particular, a large number of rhodanine-based compounds as PPARγ agonists and Aldose reductase inhibitors, have been successfully developed, marketed, and extensively used in the clinic in preventing and treating diabetes with low toxicity, high bioavailability, and good biocompatibility and curative effects such as Epalrestat, a drug currently used for the treatment of diabetes complications.

The structure-activity relationship (SAR) of the reported compounds revealed that the choice of a suitable substitution pattern including electron-donating, electron-withdrawing groups as well as some heterocyclic moieties, on the basic skeleton plays a key role in regulating the biological potential of the synthesized compounds. This would also help medicinal chemists to choose appropriate functional groups in order to design more effective and safer molecules for treatment of anti-diabetic.

However, some limitations still subsist for several methods due to the use of harsh reaction conditions and restricted substrate generality. The scope of some described reactions needs to be expanded with the use of sterically encumbered substrates with optimal yields of the products. It is also highly desirable to
focus on developing more eco-friendly processes which are in accordance with the green chemistry protocols. The extensive medicinal potentiality will ineluctably draw more and more researchers to engage in the medicinal research of rhodanine derivatives. Much effort will contribute to structural modification of clinical drugs to retain the advantages of these drugs and overcome their shortcomings. One important strategy is to employ some functional groups or structural fragments that are helpful for improving physicochemical properties and affinity with target sites to modify clinical drugs. This intention is to increase their anti-diabetic activities. To conclude, rhodanines will probably remain an important scaffold in drug discovery, owing to their wide spectrum of pharmacological activities and amenability towards structural modifications that enable the development of potent and selective drugs.

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REFERENCES


34. A. Alizadeh and N. Zohreh, *Synlett, 2009, 2146*.
60. N. Azizi, M. Hasani, M. Khajeh, and M. Edrisi, **Tetrahedron Lett.**, 2015, **56**, 1189.
64. M. H. Helal, **Der Pharma Chem.**, 2016, **8**, 149.
68. S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, **Diabetes Care**, 2004, **27**, 1047.
71. R. J. Young, D. J. Ewing, and B. F. Clarke, **Diabetes**, 1983, **32**, 938.
73. M. Dunlop, **Kidney Int.**, 2000, **58**, S3.

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