An Overview of Chemistry and Antitubercular Activity of Thiazolidinediones
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Abstract

Thiazolidinediones (TZDs) constitute an important class of heterocyclic compounds which possess significant anti-tubercular activity along with various other activities like antimicrobial, anti-HIV, anti-inflammatory, antioxidant and anticonvulsant. Tuberculosis is serious health complication in which multidrug-resistance is challenging problem in treatment of tuberculosis. In the proposed article, we have shown new methods of synthesis of thiazolidinediones and antitubercular activity of the synthesized compounds. Various substituents (electron donating as well as withdrawing) like –methoxy, -chloro, -fluoro, and -hydroxy are attached at different positions on different aliphatic and aromatic substituents of thiazolidinedione ring amongst them, the compounds possessing electron withdrawing groups on substitutions have shown enhancement in the antitubercular activity.

Keywords: Thiazolidinediones, Synthesis, PPARg, Ligand, Biological activities, Glitazones.

ABBREVIATIONS

TB- Tuberculosis
HIV- Human Immunodeficiency Virus
MDRTB- Multidrug Resistant Tuberculosis
M. tuberculosis- Mycobacterium tuberculosis
MIC- Minimum Inhibitory Concentration
PPAR- Peroxisome proliferator-activated receptor gamma
MGIT- Mycobacteria growth incubator tube

INTRODUCTION

Thiazolidine-2, 4-diones (Fig.1) are sulphur and nitrogen containing pentacyclic compound, also known as glitazones. After the prototypical drug ciglitazone, the new class of heterocyclic compounds consisting of a five membered thiazolidine nucleus which is present in numerous biological activities like antidiabetic [1-3], antimicrobial [4-6], anti-inflammatory [6-7], anti-HIV [8], antioxidant [9] and anticonvulsant [10]. Thiazolidine-2, 4-diones are well-known pharmacophores introduced in the late 1990’s for the treatment of diabetes mellitus. These are five membered heterocyclic molecules which having thiazole nucleus with two carbonyl functional group at second and fourth carbon.

Fig-1: Chemical structure of 2, 4-thiazolidinedione

Tuberculosis is one of the top causes of death worldwide, caused by bacteria Mycobacterium tuberculosis. It is curable disease but multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. WHO estimates that there were 558000 new cases with resistance to rifampicin the most effective first-line drug, of which 82% had MDR-TB. Therefore, several new 2,4-thiazolidinediones have been synthesized and screened for their antitubercular activity against M. tuberculosis.
H37Rv strain have shown promising results indicating the potential of this scaffold in the development of novel anti-TB agents [11-12].

Thiazolidine-2, 4-dione scaffold is found to exhibit a significant antitubercular activity these findings attracted scientists to synthesize the thiazolidinedione derivatives and evaluated for their pharmacological activities. We could not find any review concerning about the new methods for synthesis of recently developed thiazolidinedione derivatives with their antitubercular activity. Therefore, this article attempts to review the new methods for the synthesis of thiazolidinediones along with their improved potential for treating tuberculosis. Compounds synthesized using the given synthetic strategies gives us a diversity of compounds with varying complexity and biological relevance.

Physical and chemical properties of 2, 4-thiazolidinedione
Thiazolidine-2, 4-dione is a white crystalline powder, sparingly soluble in water, methanol, ethanol, dimethylsulphoxide and ethyl ether. It has melting point of 123-125°C. Summary of it’s physical and chemical properties is depicted in Table 1 [13].

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Parameters</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Appearance</td>
<td>White needle like crystals.</td>
</tr>
<tr>
<td>2.</td>
<td>IUPAC name</td>
<td>1,3-thiazolidine-2,4-dione</td>
</tr>
<tr>
<td>3.</td>
<td>Molecular formula</td>
<td>C₃H₇NO₂S</td>
</tr>
<tr>
<td>4.</td>
<td>Molecular Weight</td>
<td>117.13 g/mol</td>
</tr>
<tr>
<td>5.</td>
<td>Melting point</td>
<td>123-125°C</td>
</tr>
<tr>
<td>6.</td>
<td>Boiling point</td>
<td>178-179°C</td>
</tr>
<tr>
<td>7.</td>
<td>Density</td>
<td>1.408</td>
</tr>
<tr>
<td>8.</td>
<td>Refractive index</td>
<td>1.513</td>
</tr>
<tr>
<td>10.</td>
<td>Log P</td>
<td>-0.031</td>
</tr>
<tr>
<td>11.</td>
<td>Storage</td>
<td>Store below +30°C.</td>
</tr>
<tr>
<td>12.</td>
<td>Thin layer chromatography</td>
<td>Rᶠ value-0.6 [Mobile phase- Chloroform: Methanol (4.5:0.5; v/v)]</td>
</tr>
</tbody>
</table>

Structural characterization of 2, 4-thiazolidinedione
The 2,4-thiazolidinedione can be structurally characterized by using Infra-red spectroscopy which shows peaks for secondary amine at 3387cm⁻¹ (N-H Stretch), Carbonyl group at 1687cm⁻¹ (C=O Stretch), C-S at 622cm⁻¹ (Stretch) and by using Mass spectroscopy which gives mass fragment at ESI⁺-117.01 [M+H]⁺. The Proton NMR at 400 MHz in DMSO-d₆ shows peaks at 12.50 for one hydrogen of N-H and 4.39 for two hydrogens of -CH₂-. Summary of the characterization tools are depicted in Table 2 [14].

Table-1: Physical and chemical properties of 2, 4-thiazolidinedione

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameter</th>
<th>Functional group</th>
<th>Wavelength (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>IR spectral data (KBr)</td>
<td>Secondary amine N-H Stretch</td>
<td>3387</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbonyl C=O Stretch</td>
<td>1687</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-S Stretch</td>
<td>622</td>
</tr>
<tr>
<td>2.</td>
<td>Mass spectral data</td>
<td>ESI⁺- 117.01 [M+H]⁺</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>'H-Nuclear Magnetic Resonance spectral data (Dimethylsulfoxide-d₆, 400 MHz)</td>
<td>12.50 (1H; S; NH), 4.39 (2H; S; CH₃)</td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of action 2, 4-thiazolidinedione

Thiazolidinediones are synthetic ligands for the PPAR\textsubscript{\textgamma} (peroxisome proliferator-activated receptor gamma) receptors. In the cell, PPAR\textsubscript{\textgamma} forms a heterodimer with the retinoid X receptor (RXR). When induced by 2,4-thiazolidinediones, a conformational change occurs in the heterodimer and co-repressor complexes, this promotes binding of the PPAR\textsubscript{\textgamma}–RXR complex to PPAR\textsubscript{\textgamma} response elements (PPRE) in target genes and alteration of the transcription of these genes. PPREs are found in a number of genes involved in lipid metabolism and energy balance, including those encoding for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl CoA synthase, malic enzyme, glucokinase and the GLUT4 glucose transporter [15-17].

Methods of synthesis and antitubercular activity of 2, 4-thiazolidinedione

The 2, 4-thiazolidinediones have been synthesized by using conventional, solid phase and microwave assisted methods. The derivatives were screened for their antitubercular activity against \textit{M. tuberculosis} H37Rv strain by using different methods like Middlebrook 7H9 agar medium, BACTEC mycobacteria growth incubator tube system, Lowenstein Jensen and Microplate alamar blue assay (MABA) method.

CONVENTIONAL METHOD

2, 4-thiazolidinediones with substituted benzylidene ring

Pattan \textit{et al.} [18] synthesized benzylidene-2,4-thiazolidinedione derivatives from chloroacetic acid and thiourea by using scheme 1 and 2, derivatives were screened for antitubercular activity by Middlebrook 7H9 agar medium against \textit{M. tuberculosis} H37RV strain using streptomycin as standard drug which showed sensitivity at MIC value (25-100 µg/mL). The derivatives synthesized by scheme 1 and 2, the N-methylisonicotinamide substituted derivatives showed sensitivity at MIC values (50 and 100 µg/mL).

[Chemical structures for synthesis of 4-chloroacetyl-benzylidene-2, 4-thiazolidinedione derivatives and Thiazolyl benzenesulfonamide-condensed 2,4-thiazolidinediones are shown in schemes 1 and 2.]

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µg/mL) and Isoniazid (MIC value 0.2 µg/mL) were used as standard drugs. Results revealed that final thiazolidinedione analogs possessing electron-donating group (-chloro) at C-2, C-3 and C-4 positions of the phenyl ring displayed highest inhibition at a constant concentration level (MIC value 62.5 µg/mL) against *M. tuberculosis* H37Rv strain.

**Scheme 3: Synthesis of (Z)-4-((3-benzoyl-2,4-dioxothiazolidin-5-yldiene)methyl)-N-(4-substituted phenylthiazol-2-yl) benzenesulfonamides.**

**Dichlorobenzoylthiazolidine-2,4-diones containing substituted benzylidene ring**

Shaikh *et al.* [20] prepared 2,4-thiazolidinedione derivatives possessing dichlorobenzoyl and substituted benzylidene ring by using Knoevenagel condensation reaction of 2,4-thiazolidinediones with aromatic aldehydes as shown in scheme 4. The synthesized compounds were screened against *M. tuberculosis* H37RV strain using rifampicin as reference drug (MIC value 40 µg/mL). Results revealed that 4-methoxy and 4-dimethylamino substituted compounds showed very good activity with MIC value (25-50 µg/mL) and compounds having 3,4-dichlorobenzoyl, 4-methyl and 3,4,5-trimethoxy substitution showed comparable activity with MIC value (62.5-100 µg/mL).
Thiazolidinediones incorporated with Pyridine and 1, 3, 4-Oxadiazole

The 2,4-thiazolidinediones with pyridine and 1,3,4-oxadiazole synthesized from (Z)-5-benzylidene-thiazolidine-2,4-dione as shown in scheme 5 by Patel et al. [21] were investigated for antitubercular activity against *M. tuberculosis* H37Rv strain. Rifampicin was used as reference drug (MIC value 40 µg/mL). The results show that compounds bearing 4-fluoro and 4-methoxy substitution was most active amongst the tested compounds with MIC value (50 µg/mL).

Ethyl-pyridin-ethoxy-benzylidine conjugated 2, 4-thiazolidinediones

Patel et al. [22] synthesized 2,4-thiazolidinediones conjugated with ethyl-pyridin-ethoxy-benzylidine from 2-(5-ethylpyridin-2-yl)ethanol as depicted in scheme 6 and examined them for antimycobacterial activity against *M. tuberculosis* H37Rv strain using rifampicin as reference drug (MIC value 40 µg/mL). Results indicated that compounds containing N, 6-dimethylbenzo[d]thiazol-2-amine substitution showed better activity with MIC value (25 µg/mL) and N, 5-dimethylthiazol-2-amine and N-methyl-5-nitrobenzo[d]thiazol-2-amine substituted compounds showed good activity with MIC value (50-62.5 µg/mL).
Arylidene thiazolidine-2, 4-diones

Ponnuchamy et al. [23] synthesized arylidene thiazolidine2,4-diones from 2,4-thiazolidinedione and 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethan-1-one as depicted in scheme 7 which were screened for their antimycobacterial activity against *M. tuberculosis* H37Rv strain in high throughput screen using isoniazid as reference drug with EC₅₀ value (0.18 µM). Among the screened compounds, the compounds with substituted thiophene-2-carbaldehyde was found to be most active having EC₅₀ value (6 µM).

2, 4-thiazolidinediones bearing 2-amino-6-thiocyanato benzothiazole derivatives

The 2,4-thiazolidinediones bearing 2-amino-6-thiocyanato benzothiazole were synthesized from aniline as depicted in scheme 8 by Shaikh et al. [24] which were screened against *M. tuberculosis* H37RV strain with reference drug rifampicin (MIC value 40 µg/mL). Results showed that 3,4,5-trimethoxy, 4-chloro and 3-bromo substituted compounds showed good activity with MIC value (25-50 µg/mL) and compounds having 4-fluoro, 3-methoxy-4-hydroxy, 4-methoxy and 4-dimethylamino substitution showed comparable activity with MIC value (62.5-100 µg/mL).
Thiazolidinedione clubbed with Imidazolones

Khan et al. [25] synthesized 2,4-thiazolidinediones clubbed with imidazolones from benzoylglycine and benzaldehyde as depicted in scheme 9 and examined for antimycobacterial activity by using L. J. method by using rifampicin as reference drug which showed activity at MIC value (40 µg/mL). The results indicate that compounds having 4-hydroxy, 3-methoxy and 5-nitro substituents on benzene showed better activity with MIC value (25 µg/mL) and compounds having unsubstituted thiophene, 4-hydroxy, 4-methoxy, and 2,5-dimethoxy substituents on benzene showed good activity with MIC value (50-62.5 µg/mL).

SOLID PHASE SYNTHESIS
Thiazolidinedione combined with Pyrimidine conjugates

Šlachtová et al. [26] demonstrated the solid phase synthesis of 2, 4-thiazolidinediones combined with pyrimidine conjugates from Wang resin as shown in scheme 10. Antimycobacterial activity of synthesized compounds was evaluated against M. tuberculosis H37Rv strain (NCTC 7416) using isoniazid as standard drug which showed activity at MIC value (0.125 µg/mL). The results indicate that thiazolidinedione that having (trifluoromethyl) benzene substitution showed the highest antitubercular activity against M. tuberculosis H37Rv strain with MIC value (256 µg/mL).
Microwave assisted synthesis

Thiazolidinedione with imidazo[2,1-b][1,3,4]thiadiazole

The 2, 4-thiazolidinediones with imidazo [2,1-b] [1, 3, 4] thiadiazole were synthesized from 2,2,2-trifluoroacetic anhydride and hydrazinecarbothioamide as depicted in scheme 11 by Alegaon et al. [27] which were assessed for antitubercular activity against M. tuberculosis H37Rv strain (ATCC 27294) using the Microplate Alamar Blue assay (MABA) method with standard drug, Isoniazid (MIC value 1.56 µg/mL) and Rifampicin (MIC at 0.78 µg/mL). The results of the antitubercular activity screening revealed that all compounds did not show any considerable activity except compound which is substituted with -chloro group showed antitubercular activity with MIC value (3.12 µg/mL).
CONCLUSION
After brief study of existing synthesized thiazolidinedione derivatives we can conclude that the scaffold exhibit various biological activities like antimicrobial, antioxidant, anticancer, antioxidant, anti-inflammatory, antitubercular. In present article we have emphasized on antitubercular activity of thiazolidinediones bearing various substitutions. Substitution of alkyl /aryl groups on nitrogen exhibits potent antitubercular activity. Attachment of benzene sulfonamide to N-substituted thiazolidinedione scaffold bearing electron donating group on heterocyclic ring improved activity in comparison with unsubstituted compound. Substitution of bioactive heterocycles like pyridine, oxadiazole, benzylidine at fifth position increases the antitubercular activity against M. tuberculosis. Some derivatives bearing simultaneous substitutions at nitrogen and fifth position in scaffold exhibits remarkable antitubercular activity. From the above findings one must consider thiazolidinediones as potential antitubercular agents for development.

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