HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN AND SULPHUR – FOCUS ON FEW BIOLOGICAL ACTIVITIES

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ABSTRACT

In the recent past, heterocyclic compounds containing sulphur and nitrogen were gaining much importance. Among them, substituted thiazolidine derivatives have been extensively studied because of their synthetic feasibility, varied chemical behaviour, diverse biological activities and different applications. The current review focuses on the methods of synthesis, spectroscopic characterization and few biological activities of thiazolidines. This review mainly summarizes the potential antimicrobial and anti-inflammatory activity when substituted at 2,3 and 4 positions mainly in thiazolidine ring.

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INTRODUCTION

Thiazolidines are a class of heterocyclic organic compounds with 5-membered saturated ring having nitrogen and sulfur in the 1st and 3rd positions. Thiazolidine, a sulphur analogue of oxazolidine, is also known as tetrahydrothiazole with molecular formula C₃H₇NS and molecular weight 89.16.

Synthesis of thiazolidines

In early 1930’s Birch et.al. and Shinohara studied cysteine reactivity in the presence of formaldehyde and observed loss of activities assigned to –SH group, like reducing capability and chelation[1,2]. In continuation of this study, Schubert has first described the reactions of cysteine with various aldehydes and has produced evidence that the latter reacts with cysteine to form a thiazolidine-4-carboxylic acid[3]. The most widely used method for the preparation of thiazolidine and its homologs involve the reaction of carbonyl compounds with α-aminothiols. Aldehydes, ketones or their derivatives such as acetals, thioacetals or Schiff’s bases have been used. Among these α-aminothiols, cysteine and its decarboxylation product cysteamine, play an important role.

The parent compound, thiazolidine hydrochloride (3) is obtained in very high yield, by the reaction of cysteamine hydrochloride (1) with aqueous formaldehyde (2) at ambient temperature. (Scheme 1)

The amino group of L-cysteine was protected as (4R)-1, 3-thiazolidine-4-carboxylic acid (4) used for the synthesis of functionalized 1, 3-diamines by the way of Curtis reaction (Scheme 2).

The reaction of ethyl cyanothioacetate (5) with an amine and aromatic aldehydes afford diversely substituted 5-arylidene-2-iminothiazolidin-4-one derivatives (6) (Scheme 3).
The adduct of allylisothiocyanate and dimethyl malonate (7) cyclizes in the presence of halogen to give the corresponding thiazolidine (8) (Scheme 4)[4].

A simple method for the synthesis of 1, 3-thiazolidines by the in situ reaction of thioephedrines (9) with carbonyl compounds has been reported. A synthetic route to 1, 3-thiazolidines (10), starting from the respective aminothiols and formaldehyde is shown in Scheme 5. [5]

In a similar way, acid hydrolysis of sulfonic acid group of compounds (11) in 30% aqueous HCl afforded the corresponding aminothiol hydrochlorides. In order to avoid their oxidation after neutralization with 30% aqueous NaOH, the carbonyl compound (dissolved in CH₂Cl) was added before the base, cyclization occurred without formation of unwanted disulfides to give the corresponding thiazolidines (12) (Scheme 6) [6].
The thiazolidines were obtained by two methods; the first one, starting from guaiphenesin or the other 3-(aryloxy)-1,2-propanediols (13) involving the oxidative cleavage of a 1,1-diol with sodium periodates followed by the reaction of the crude aldehydes (14) with the appropriate 2-mercaptoethylamine (15) derivatives (Scheme 7) [7].

![Scheme 7](image)

The second method involves a nucleophilic substitution of phenyl thiolates or aryloxy salt (16) with bromoacetaldehyde diethyl acetal to give the acetal (17), which are then converted into the desired thiazolidines (18) in acidic medium. (Scheme 8)

![Scheme 8](image)

**SPECTRAL FEATURES OF THIAZOLIDINES**

Mass spectral fragmentation of thiazolidine-4-carboxylic acid derivatives:

The mass fragmentation of thiazolidine analogues follows majorly four pathways:

1. C-2 alkyl/aryl cleavage
2. 1,3-cleavage
3. 1,4-cleavage
4. 2,5-cleavage

![Spectral Features](image)

Earlier, Pasto D. J, while studying the mass fragmentation of oxothiolane analogues, has suggested cleavage of alkyl group α-to both hetero atoms. Similar phenomenon was observed (figure 2.2) in the thiazolidines also and the ion obtained due to fragmentation of C-2 substituent is usually very intense if the substituent is an alkyl group. But in case of aryl substituents at C-2 position, this fragment ion is found to have an intensity ≤ 20.
THERAPEUTIC POTENTIAL OF THIAZOLIDINES AND ITS DERIVATIVES

The importance of thiazolidine nucleus is well established in the field of pharmaceutical chemistry. Various pharmacological activities such as antiproliferative, hepatoprotective, antihypertensive, antiabetic, platelet activating factor antagonist, thromboxane A2 receptor antagonists, antitussive, calcium antagonist, antipyretic, anti-inflammatory, anthelmentic, analgesic, mucolytic, anti-tubercular, antiviral, anticancer and antiHIV activities are associated with compounds having thiazolidine nucleus. In view of this activities, the review provides the information that potential activity of the thiazolidine derivatives may increase with the change in positions of the substitutions.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Structure</th>
<th>SAR</th>
<th>Activity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Presence of X may be responsible for the anti-tubercular activity</td>
<td>&gt;90%</td>
<td>The compounds with more than 90% inhibition were obtained by S-alkylation with acetonitrile. It results the cyano group did not have any role in increasing the activity [8]</td>
</tr>
<tr>
<td></td>
<td>1a)X=CH3, Ar =3-NO2,C6H4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b)X=C6H5, Ar =3-NO2,C6H4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Substituents(X) on aromatic ring of 4-thiazolidine ring are responsible for the activity</td>
<td>6.25µg/mL</td>
<td>Kucukguzel et al. reported antimycobacterial activity of substituted 4-thiazolidinones. They have reported 90-</td>
</tr>
<tr>
<td></td>
<td>2a)X=NO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b)X=F</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.3 Hydroxyl and methoxy groups are responsible for the activity 0.31µg/ mL Compounds without any substitution did not show any activity[9] 98% of activity[9]

1.4 2-pyridyl and 2-hydroxy 5-methoxyphenyl group are essential for anti-tubercular activity IC₅₀ 6.22µg/mL Zitouni et al. reported the synthesis of N-pyridyl-N’-thiazolylhydrazine[10]

1.5 Substitution(X) on the ring with chloro group and nitro group are responsible for the activity[11] 1.5a-2.75µg/mL 1.5b-2.50µg/mL 1.5c-2.75µg/mL 1.5d-2.75µg/mL 1.5e-2.50µg/mL 1.5f-2.50µg/mL 1.5g-2.75µg/mL Nitro group containing compounds showed more activity than Cl and Br substituted compounds

1.6 X=NHCOCH₃ X=NHCH₂COOH X=NHCOCH₃Cl The activity of the compounds may be due to the substitution(X) on thiazolidine ring [12] >90% inhibition Acetate derivatives when converted to hydrazide derivatives shown more activity

1.7 Electron withdrawing substituents Chloro, bromo, nitro groups are responsible for the activity[13] 1.7a-1.75µg/ml 1.7b-3.25µg/ml 1.7c-3.50µg/ml 1.7d-2.25µg/ml 1.7e-1.25µg/ml 1.7f-1.50µg/ml 1.7g-1.75µg/ml The order of activity is NO₂ >Cl> Br

1.8 The activity of compounds depends on electron withdrawing nature of the substituted groups [14] 1.8a-2.50µg/ml 1.8b-2.25µg/ml 1.8c-2.50µg/ml 1.8d-2.25µg/ml 1.8e-2.50µg/ml The sequence of the activity is following the order NO₂ >Cl> Br

X 1.8a-3-cl 1.8b-2-Cl 1.8c-4-Br 1.8d-3-Br 1.8e-4-NO₂
Some more compounds showing anti-tubercular activity[9,12,15]

![Chemical structures](image)

Table II- Compounds Showing Anti-Cancer Activity[16,17].

<table>
<thead>
<tr>
<th>S.No</th>
<th>Structure</th>
<th>Activity</th>
</tr>
</thead>
</table>
| 2.1  | ![Structure](image) | LogGI50 = -5.41  
LogGI50 = -5.49 |
| 2.2  | ![Structure](image) | LogGI50 = -5.61  
LogGI50 = -5.61 |
| 2.3  | ![Structure](image) | 2.3a-0.19±0.06µM  
2.3b-0.50±0.12 µM  
2.3c-1.1±0.4 µM  
2.3d-2.9±2.4 µM  
2.3e-2.2±0.4 µM  
2.3f-1.2±0.1 µM  
2.3g-3.4±0.2 µM  
2.3h-3.4±1.6 µM  
2.3i-3.4±1.6 µM  
2.3k-1.6±0.2 µM |
| 2.3a | R=CH3    | 2.3b | R=C2H5   |
| 2.3c | R=C6H5CH2 |
| 2.3d | R=C6H5(CH2)2 |
| 2.3e | R=4-F-C6H4CH2 |
| 2.3f | R=3-F-C6H4CH2 |
| 2.3g | R=4-Cl-C6H4CH2 |
| 2.3h | R=3-Cl-C6H4CH2 |
| 2.3i | R=4-CF3-C6H4CH2 |
Some more compounds which are showing anti-cancer activity [12, 18]
Table III-Compounds Showing Anti-Inflammatory Activity.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Structure</th>
<th>SAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Bromine on both the aromatic rings showed percentage inhibition[9]</td>
</tr>
<tr>
<td>3.2</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Methoxy group in the structure is responsible for the activity[9]</td>
</tr>
<tr>
<td>3.3</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Absence of 5-arylmethylidene moiety in the structure enhanced anti-inflammatory activity [9]</td>
</tr>
<tr>
<td>3.4</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>Presence of 2,4 dichlorophenylring in the central position and terminal piperidine on left side is responsible for activity [9]</td>
</tr>
<tr>
<td>3.5</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>Presence of chloro group at meta position showed activity due to inhibition of COX-1, COX-2[8]</td>
</tr>
<tr>
<td>3.6</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>Compounds with substitution R' = CH&lt;sub&gt;3&lt;/sub&gt; showed potential anti-inflammatory activity [8]</td>
</tr>
<tr>
<td></td>
<td>3.6a) R = H, R' = H, R'' = H, R''' = H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.6b) R = H, R' = CH&lt;sub&gt;3&lt;/sub&gt;, R'' = H, R''' = H</td>
<td></td>
</tr>
<tr>
<td>3.7</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>Presence of thiazolidinone ring have shown better activity[12]</td>
</tr>
</tbody>
</table>
CONCLUSIONS
Thiazolidine ring possessing substitutions at 2, 3 and 4 positions is showing favourable antitubercular activity whereas the substitutions at 2,3,4 and 5 positions respectively are favouring anticancer activity. The compounds showing anti-inflammatory activity showed potent activity when there is a substitution at 2, 3, and 4 positions of the thiazolidine ring and position 5 substitution has very less effect on activity. Electron withdrawing groups like methoxy and halogen groups enhanced the anti-inflammatory activity. Similarly for antitubercular activity also the thiazolidine ring in combination with halogens is showing good activity. For optimum activity the thiazolidine ring can be fused with other aromatic or heterocyclic rings without disturbing the electron cloud on sulphur and nitrogen. So we recommend further research to find a novel antitubercular and antimicrobial derivatives of thiazolidine moiety.

ACKNOWLEDGEMENTS
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3) Schubert M.P., Ibid., 111,671 (1935) ; 114, 341 (1936)