A complete review of thiazolidine-4-ones.

Devprakash¹ and Udaykumar A Bhoi.¹

¹Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Bharathinagara-571422, Karnataka, India.

Received on: 12-04-2011; Revised on: 18-05-2011; Accepted on: 21-06-2011

ABSTRACT
Thiazolidine-4-ones containing thiazole moiety, it had been synthesized by 6-amino Coumarin, Isatin, Primary amines and aromatic aldehydes. Thiazolidine-4-ones has been considered as a magic moiety because it posses almost all types of biological activities such as Antifungal, Antitubercular, Antimicrobial, Antioxidant, Antibacterial, Cytotoxic, Anti-inflammatory, Analgesic, Anti YFV (yellow fever virus) activities. Present article is sincere attempt to review of chemistry, different methods of synthesis, and pharmacological uses of thiazolidine-4-ones.

Key words: Thiazolidine-4-one, Spiro-thiazolidinone, Schiff bases, Biological activity.

INTRODUCTION

The chemistry of heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. Their study is of great interest both from the theoretical as well as practical importance. Various compounds such as alkaloids, essential amino acids, vitamins, hemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are large number of synthetic heterocyclic compounds, like pyrrole, pyrrolidine, furan, thiophene, pyridine, pyridine and thiazole having important application & many are important intermediates in synthesis. Heterocycles containing sulphur and nitrogen atoms in the core structure, it shows number of pharmacologically and biologically active compounds.

Thiazolidine-4-ones are usually solids, often melting with decomposition but the attachment of an alkyl group to the nitrogen lowers the melting point. Thiazolidine-4-ones are derivatives of thiazolidine with carbonyl group at the fourth position. The carbonyl group of thiazolidine-4-ones is highly un-reactive. Thiazolidine-4-ones are the derivatives, which belongs to important groups of heterocyclic compounds containing sulfur and nitrogen in a five member ring¹.

The nucleus is also known as a wonder nucleus, because it shows different types of biological activities². Thiazolidine-4-one substituted moieties have received considerable attention during last two decades as they are gifted with variety of activities and have wide range of therapeutics properties. Thiazolidine-4-ones and its derivatives offer enormous scope in the field of medicinal chemistry.

Thiazolidine-4-ones are important compounds due to their broad range of biological activities and pharmacological properties i.e. Antifungal²(12), Antioxidant³, Cytotoxic³, Anti-inflammatory⁴, Analgesic⁴, Anti YFV (yellow fever virus) activity⁴, Antitubercular⁴(10), Antimicrobial⁴(9,10,12,17,20), Antibacterial⁴(9,10,12,17,20). Thiazolidine-4-one derivatives possess different pharmacological and biological activities. Antibacterial activity is the most potent activity of thiazolidine-4-one. Antibacterial activity is strongly dependent on the nature of substituent at C-2 & N-3 position¹(2).

SAR of Thiazolidine-4-ones:
- Thiazolidine-4-one having 2,4-dimethyl amino phenyl at second position shows good antibacterial activity in all the species¹.
- Un-substituted phenyl group at the position 4 shows good antibacterial activity.
- The presence of para-fluorophenyl substituent decreased the cytotoxicity of thiazolidin-4-one derivatives against DLA cells.
- The un-substituted phenyl ring at third position shows less activity against gram negative strains and moderately effective against gram positive⁴.
- Thiazolidine-4-one having para nitro group at meta and para position of the aryl ring respectively, possess stronger antibacterial activity.
- Electron withdrawing moiety shows less activity compared to electron donating group eg. OCH₃ and NMe³.

Different methods for synthesis of Thiazolidine-4-ones:

Scheme-1:
Jubie, et al., synthesized series of 3-(methoxy phenyl)-2-aryl thiazolidin-4-one by the reaction with Schiff bases. The Schiff bases were synthesized by condensation of p-methoxy aniline with different substituted aromatic aldehydes. The obtained Schiff bases were subjected to condensation with mercaptoacetic acid to give the corresponding 4-thiazolidinones. The yield was found to be 42-62 %.

Substituents:

Scheme-2:
Gurupadaya et al., synthesized various 7-chloro-6-fluroro-2-arylidenylaminobenza(1,3)(2a-2h) by the condensation of 7-chloro-6-fluroro-2-aminobenza(1,3) thiazole(1) with different aromatic aldehydes. Cyclization of Schiff base with thioglycolic acid produced 3-(7-chloro-6-fluroro-benzothiazol-2-yl)-2-substituted-arylthiazolidin-4-ones (4a-h).
Compound | Ar | R |
--- | --- | --- |
DS1 | 4-F-C₆H₄ | 4-Cl |
DS2 | 4-F-C₆H₄ | 2-Cl |
DS3 | 4-F-C₆H₄ | 3-NO₂ |
DS4 | 4-F-C₆H₄ | 4-N(CH₃)₂ |
DS5 | 4-F-C₆H₄ | 2-OH |
DS6 | 2,6-(CH₃)₂C₆H₄ | 4-NO₂ |
DS7 | 2,6-(CH₃)₂C₆H₄ | 4-OH |
DS8 | 3-Cl, 2-CH₃C₆H₄ | 2-Cl |
DS9 | 3-Cl, 2-CH₃C₆H₄ | 2-Cl |

Scheme-4:
Ranjan et al. synthesized 2-Isonicotinoylthiosemicarbazide-1,3-thiazolidine-4-one by reaction of Isonicotinoyl thiosemicarbazide with chloroacetic acid in absolute alcohol and anhydrous sodium acetate.

Scheme-5:
Visagaperumal et al. synthesized some new 3-substituted-1, 3-thiazolidine-4-ones by the reaction of 3-(4-nitrophenyl)-1-(pyridin-4-yl-carbonyl)-1H-pyrazole-4-carbaldehyde and different substituted aromatic amines in the presence of toluene. The synthesis of 2-[3-nitrophenyl-1-(pyridin-4-ylcarbonyl)-1H-pyrazol-4-yl]-3-substituted-1,3-thiazolidine-4-one 3a-j was carried out in three steps, first by the condensation of isoniazid with 4-nitroacetophenone in the presence of glacial acetic acid to give N²-[1-(4-nitrophenyl) ethylenediamine] benzohydrazide, secondly Vilsmeier Haack complex was treated with it to give 3-(4-nitrophenyl)-1-(pyridin-4-yl carbonyl)-1H-pyrazole-4-carbaldehyde, which on treatment with different substituted aromatic amines and thiglycolic acid in the presence of toluene afforded the title compound. Cyclization of 3-(4-nitrophenyl)-1-(pyridin-4-yl-carbonyl)-1H-pyrazole-4-carbaldehyde carried out by the reaction with thiglycolic acid.

Scheme-6:
Ketan et al. synthesized new series of compounds namely 3-chloro-4-(2''-4''-dichlorophenyl)-4-methyl-1-(substituted-1''3''-benzothiazol-2''yl)-azetidin-2-ones and 2-(2''4''-dichlorophenyl)-2,5-dimethyl-3-(substituted-1''3''-benzothiazol-2''-yl)-1,3-thiazolidine-4-ones by the reaction of Schiff base derivatives with chloroacetyl chloride in presence of triethylamine thiolactic acid respectively.

Scheme-7:
Liu et al. synthesized five derivatives of 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and series of their 5-arylidine derivatives, were tested for antifungal activity against seven agricultural fungi. The thiazolidinones (1) was obtained by crystallisation from ethanol and melting point was found to be 173-175°C.
**Method-1**

\[
\begin{align*}
\text{Method-2} & \quad \text{Method-2} \\
\end{align*}
\]

2a= Ar= C_H, Ar'= o-2CN C_H; 2b= C_H, Ar'= m-2CN C_H; 2c= C_H, Ar'= o-Cl C_H; 2d= p-Cl C_H, Ar'= o-2CN C_H; 2e= p-Cl C_H, Ar'= m-2CN C_H.

**Scheme-8:**

Rajiv et al\(^{11}\), synthesized some new N1-[2- [2-substituted-phenyl-5-substituted-benzylidene-1,3-thiazolidine-4-one]-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazoles, 6(a-n) conventional and green approach methods in terms to yield and reaction time along with antimicrobial activity against Bacillus subtilis, Escherichia coli, Klebsiella pneumonia and Streptococcus aureus bacteria and Aspergillus niger, Aspergillus flavus, Fusarium oxysporum and Trichoderma viride fungi in vitro at 50 and 100 ppm concentrations.

**Scheme-9:**

Desai et al\(^{11}\), synthesized various 2-(4-chlorophenyl)-N-(4-oxo-2-arylthiazolidin-3-yl) acetamides by the cyclization of (Z)-N-arylidenec-2-(chlorophenyl)-acetohydrazides 1 and N-(1-aza-2-arylvinyl)(4-[5-oxo-2-phenyl-4-phenylmethene)](2-midazolinyl)phenoxy carboxamides in the presence of thioglycolic acid and 1:4 dioxane.

**Scheme-10:**

Vandana Tiwari et al\(^{11}\), used Zeolite 5A\(^{o}\) for the synthesis of 2-(2-chloroquinoline-3-yl)-3-substituted phenyl thiazolidin-4-ones starting from N-aryl-2-chloroquinolin-3-yl-azomethine and thioglycolic acid under microwave irradiation.

**Scheme-11:**

Raga Basawaraj et al\(^{11}\), synthesized 3-[(1E)-1-(5-chloro-3-methyl-1-benzofuran-2-yl) ethylidene][amino]-2-substituted phenyl-1,3-thiazolidin-4-one derivatives by reaction of substituted benzaldehyde[1-(5-chloro-3-methyl-1-benzofuran-2-ethylidene] hydrazones with thioglycolic acid in the oil-bath at 115-120 °C for 12 hrs.

**Biological activity:**

**Antibacterial activity:**

1) Vinita et al\(^{11}\), have been screened compounds 5a-i for their antimicrobial activity by cup plate method and have found to exhibit significant activity against B.Subtilis. E.coli at different concentration (50 and 100 µg/ml) using DMSO as solvent. The results of antibacterial activity shows that compound 5f and 5i have good activity compared to the standard.
2a= (Ar=4-CH$_3$), 2b= (2-OH-), 2C=(2-OH-5-Br-)  
3) Aamer et al\textsuperscript{5b}, carried out \textit{in vitro} evaluation of antibacterial activity by disk diffusion method (Kirby-Bauer method) against different bacterial strains. All the compounds 2a-2i exhibited promising inhibitory activity against the four bacterial strains compared to the standard drug ciprofloxacin.

Fungicidal activity:
1) Gowri Chandra Sekhar et al\textsuperscript{15}, synthesized compounds most of them were found to possess moderate activity against tested fungi. Compounds 3d and 3h were found to be most active against Aspergillus flavus and Candida albicans respectively. The antifungal activities of test compounds were compared with standard Salicylic acid (20 - 30 mm) and Clotrimazole (25 - 30 mm).

Anti-YFV activity:
Drmarajan et al\textsuperscript{16}, evaluated all compounds compound were also evaluated for their inhibitory effects on the replication of YFV in green monkey kidney (Vero) cells (ATCC CCL81), by means of a cytopathic effect reduction assay [12]. The antiviral activity of the compounds was expressed as the effective concentration required to inhibiting the viral cytopathic effect by 50% (EC50). The minimum cytotoxic concentration was expressed as CC50, the concentration required to reduce cell growth by 50%. Six compounds (DS1-3, DS6-7 and DS14) were found to prevent the YFV infection of the cells at concentrations that had no effect on cell growth. Four compounds (DS1-3 and DS14) were found to be more effective than ribavirin (EC50 values of 28.0 µm). The compound DS-1 emerged as the most potent anti-YFV agent with EC50 of 6.9 µm and CC50 more than 100 µm.

**Antitubercular activity:**
Sriram et al\textsuperscript{6d}, screened synthesized compounds for the antitubercular activity against \textit{mycobacterium tuberculosis} H37R\textsubscript{v} using resazurin microplate assay 25 (REMA) at the concentration of 1, 10, 50µg/ml. All the compounds have given mild activity at 50µg/ml especially 3d have given a good activity at 1 and 10 µg/ml.

The literatures survey shows that thiazolidine-4-ones has diverse biological potential, and the easy synthetic procedures for synthesis have taken attention of the chemists, pharmacologists and researchers.

Thiazolidine-4-ones can be synthesized by using coumarin derivatives, isatin derivatives, primary and secondary amines. Cyclization of compounds can be
carried out by using thioglycolic acid and chloroacetyl chloride. By heterocyclization of Quinoline-imines with thioglycolic acid using zeolite 5Å under microwaves afforded 2-(2-chloroquinoline-3-yl)-3-substituted phenyl thiazolidin-4-one. Microwave irradiation process is fastest synthesis procedure for thiazolidine-4-ones. Substitution is possible at 2, 3 and 5 position of thiazolidine-4-ones.

Thiazolidin-4-one have a broad spectrum of pharmacological properties i.e. Antifungal, Anti-tubercular, Antimicrobial, Antioxidant, Cytotoxic, Anti-inflammatory, Analgesic, Anti YFV (yellow fever virus) activities. Antimicrobial is the most potent activity of the thiazolidine-4-ones. Anticancer and anti HIV are most encouraging activities of thiazolidin-4-ones for the researchers for the development of newer anticancer and anti HIV agents, which is requirement of today medicinal field.

ACKNOWLEDGMENT:
We are thankful to the Dr. T. Tamizmani, Principal, Bharathi College of Pharmacy, for providing library facilities.

REFERENCES:

Source of support: Nil, Conflict of interest: None Declared