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Invited review

4-Thiazolidinones: The advances continue…

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ABSTRACT

The diversity in the biological response of 4-thiazolidinones has attracted the attention of many researchers to explore this framework for its potential. It is, therefore, of prime importance that the study of this topic and the development of new synthetic strategies should be based on the most recent knowledge, emerging from the latest research. This review is an endeavor to highlight the progress in the chemistry and biological activity of the 4-thiazolidinones, predominantly after 2006. The last section of the review encompasses the various patents granted on 4-thiazolidinone analogs/derivatives with World Intellectual Proprietary Organization (WIPO) and United State Patent Trademark Office (USPTO), particularly in the duration of the year 2000 to the year 2012.

1. Introduction

Heterocyclic compounds are an integral part of the chemical and life sciences and constitute a considerable quantum of the modern research that is being currently pursued throughout the world. Jeyaraman and Avila have reviewed the importance of heterocyclic and bicyclic compounds as intermediates in the synthesis of several physiologically active compounds [1]. These compounds are also found to be useful as intermediates for the synthesis of a variety of heterocyclic compounds [2]. 4-Thiazolidinone derivatives have attracted continuing interest over the years because of their diverse biological activities, such as anti-inflammatory, anti-proliferative, antiviral, anticonvulsant, anti-diabetic, anti-hyperlipidemic, cardiovascular, anti-tubercular, antifungal, and antibacterial. Compounds such as; ralitoline (anti-convulsant), etozoline (anti-hypertensive), pioglitazone (hypoglycemic) and thiazolidomycin (activity against streptomyces species), based on this pharmacophore are already in the market. In recent years, 4-thiazolidinone derivatives with antitumor activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines have become a promising area of research. Different researchers have reviewed the progress on the scaffold from time to time, such as Brown in 196 [3], Newkome et al. in 1977 [4], Singh et al. in 1981 [2], Abdel-Rahman et al. in 2001 [5], Verma et al. in 2008 [6], Hamama et al. in 2008 [7] and Jain et al. in 2012 [8]. Our group has also been continuously involved in researching this nucleus through chemical modifications with encouraging results [6,9–12]. The review summarizes current propensity in the 4-thiazolidinone synthetic chemistry and divulges the utility of this potent

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pharmacophore as a rich source of new compounds having promising biological activities. This assemblage recapitulates ongoing medicinal chemistry investigations worldwide, to explore novel chemical entities that can be useful in the treatment of many ailments.

2. Chemistry

The chemistry of 4-thiazolidinone was reviewed in depth by Brown in 1961 [3]. Thiazolidinones are a saturated form of thiazole, called thiazolidine, with a carbonyl group. 1,3-Thiazolidin-4-ones are heterocycles that have an atom of sulfur at position 1, a nitrogen at position 3 and a carbonyl group at position 4. New derivatives of 4-thiazolidinones have been obtained by modifications of the parent structure in several ways:

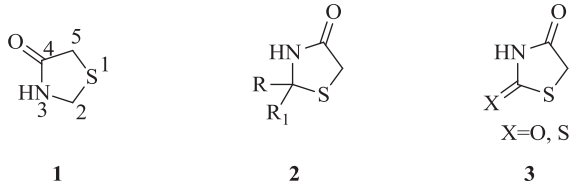
1. Substituents in the 2, 3 and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom at the 2-position (R and R_1 in **2** or X in **3**, of Scheme 1),
2. Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by **2** and **3**,
3. The carbonyl group of 4-thiazolidinone is highly unreactive. However, in a few cases, 4-thiazolidinone on reaction with Lawesson's reagent gives corresponding 4-thione derivative [13].

The unsubstituted 4-thiazolidinones are usually solids, often melting with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The 4-thiazolidinones not containing any aryl or higher alkyl substituents are somewhat soluble in water [3].

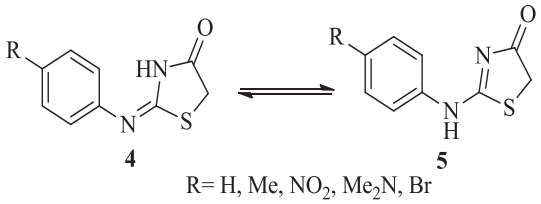
2.1. Stereochemistry

Various optical, geometrical and regioselective isomers [14–16] of 4-thiazolidinone derivatives have been reported by different workers. Ramsh et al. reported that 2-imino-4-thiazolidinone and its 2-aryl derivatives exist in the crystal state as the amino tautomers (Scheme 2) [17,18]. A detailed study of imino–amino tautomerism in 2- iminothiazolidin-4-one and its derivatives has also been reported by *Akerblom* [19]. The infrared spectroscopy data showed that in the crystal state, imino isomer is predominant whereas in the solution, amino isomer predominates [6].

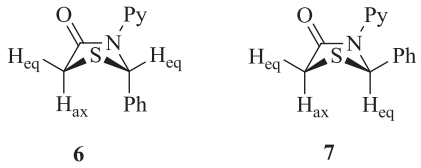
The 2,3-disubstituted 4-thiazolidinones exist as two diastereoisomers **6** and **7** (Scheme 3). Vigorita et al. conducted the conformational studies on various 2-aryl-3-(2-pyridyl)-4-thiazolidinones and found that the preferred configuration **6** is that in which the C(2) proton and one of the methylene protons are in *cis*-1,3 diequatorial relationship. This is due to the fact that the phenyl group prefers the axial orientation to avoid the steric crowding with pyridyl group [6,20].



Scheme 1. Structure of 4-thiazolidinone nucleus with substituents at various positions (**1**, **2**, **3**).



Scheme 2. Tautomerization of 2-imino-4-thiazolidinone (**4**, **5**).



Scheme 3. Stereochemistry of 4-thiazolidinones (**6**, **7**).

During a study on a recently synthesized series of 2-(substitutedphenyl)-3-[3-(*N*,*N*-dimethylamino) propyl]-1,3-thiazolidin-4-ones active as H_1 antagonists, 1H NMR data showed that the geminal protons of the three methylene groups, α, β, and γ, belonging to the alkylamine side chains of the series were not equivalent and were coupled to each other in a *gauche-anti* conformation. The chemical shift difference (~0.9 ppm) between the geminal α-CH_2 protons was very large and could be ascribed to an unusual intramolecular interaction, such as a hydrogen bond, between the amidic oxygen of the thiazolidinone ring and hydrogen of the α-CH_2.

Molecular mechanics calculations of the low energy conformations of all derivatives were carried out by TRIPOS force field of SYBYL (a comprehensive computational tool kit for molecular design and analysis). Geometrical optimizations were realized with the semiempirical quantum mechanical method AM1, available in the Molecular Orbital Package (MOPAC) program. Two low energy conformers, **8** and **9** (Scheme 4), showed a *gauche-anti* conformation of the alkylamine chain and the H–Cα–N3–C4=O atoms lying on the same plane in agreement with an attractive interaction between the carbonyl oxygen and α-CH_2 hydrogen. When X = Y, the two thiazolidinone planes are equal; **8** and **9** have the same energy and are equally probable, and ^{1}H NMR spectrum shows only one α-CH_2 signal. When X # Y, Ha # Hb, the two low-energy minimized conformers, **8** and **9**, contribute differently to the Ha and Hb shifts, and 1H NMR spectrum shows two α-CH_2 signals [21].

3. Synthesis

Literature survey reveals that several substituted thiazolidinones have been prepared from different synthetic routes [21–52]. The main synthetic routes to 1,3-thiazolidin-4-ones **12** involve three components (an aldehyde, an amine, and mercaptoacetic acid), either in a one or two-step process (Scheme 5). The reactions proceed by initial formation of an imine, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization on elimination of water. The most common protocol to remove the water is by azeotropic distillation. Dicyclohexyl-carbidiimide (DCC), which is extensively used in peptide synthesis dehydration, strongly promotes the dehydration here too.

Some improved protocols have been reported by Shrivastava et al. and Rawal et al. wherein *N*,*N*-dicyclohexyl carbodiimide/2-(1H-benzotriazo-1-yl)-1,1,3,3 tetramethyluranium-hexafluorophospate is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and