Bioorganic & Medicinal Chemistry xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Review

Thiazolidine-2,4-diones: Progress towards multifarious applications

Viral S. Jain, Dhagash K. Vora, C. S. Ramaa *

Department of Pharmaceutical Chemistry, Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D. Belapur, Navi Mumbai 400614, Maharashtra, India

ARTICLE INFO

Article history:
Received 4 December 2012
Revised 8 January 2013
Accepted 10 January 2013
Available online xxxx

Keywords:
Thiazolidine-2,4-dione
Anti-hyperglycaemics
Aldose reductase inhibitors
Anti-cancer
Anti-inflammatory
Anti-arthritics
Anti-microbials

ABSTRACT

The promising activity shown by compounds containing thiazolidine-2,4-dione nucleus in numerous categories such as anti-hyperglycaemics, aldose reductase inhibitors, anti-cancer, anti-inflammatory, anti-arthritics, anti-microbials, etc. has made it an indispensable anchor for development of new therapeutic agents. Varied substituents on the thiazolidine-2,4-dione nucleus have provided a wide spectrum of biological activities. Importance of this nucleus in some activities like, peroxisome proliferator activated receptor γ (PPARγ) agonism and PPARγ-dependent and -independent anti-cancer activities are reviewed separately in literature. Short reviews on biological importance of this nucleus are also known in literature. However, owing to fast development of new drugs possessing thiazolidine-2,4-dione nucleus many research reports are generated in short span of time. So, there is a need to couple the latest information with the earlier information to understand the current status of thiazolidine-2,4-dione nucleus in medicinal chemistry research. In the present review, various derivatives of thiazolidine-2,4-diones with different pharmacological activities are described on the basis of substitution pattern around the nucleus combined with the docking studies performed in the active site of the corresponding receptors with an aim to help medicinal chemists for developing an SAR on thiazolidine-2,4-dione derived compounds for each activity. This discussion will further help in the development of novel thiazolidine-2,4-dione compounds.

Contents

* Corresponding author. Tel.: +91 022 27572131/1122; fax: +91 022 27574515.
E-mail address: sinharamaa@yahoo.in (C.S. Ramaa).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.01.029

1. Introduction

One of the main objectives of organic and medicinal chemistry is to design, synthesize and produce molecules possessing value as human therapeutic agents. Compounds containing heterocyclic ring systems are of great importance receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry.[1] As an example, five-membered ring heterocycles containing three carbon atoms, one nitrogen atom, and one sulfur atom, known as thiazoles (**A**) are of considerable interest in different areas of medicinal chemistry.[2]

Thiazolidine-2,4-dione (TZD) is a heterocyclic ring system with multiple applications. Thiazolidine-2,4-dione inhibits corrosion of mild steels in acidic solution. These are also used in analytical chemistry as highly sensitive reagents for heavy metals[3] and as a brighter in electroplating industry.[4]

In 1982 a number of TZDs were intensively studied for their anti-hyperglycaemic property. The first representative of this class was ciglitazone, whereas other derivatives like englitazone, pioglitazone and troglitazone followed soon. The thiazolidine-2,4-dione nucleus has been reported for being responsible for majority of their pharmacological actions. Henceforth, thiazolidine-2,4-dione derivatives have been studied extensively and found to have diverse chemical reactivities and broad spectrum of biological activities.

We, in our laboratory, have been investing our efforts in developing novel TZD molecules and have explored and achieved success in establishing their anti-hyperglycaemic and anti-cancer potential. Even though these molecules have been established for a long time now, their structural and therapeutic diversity makes them interesting enough to be explored in depth.

Therefore, this review article is an exhaustive attempt to abridge all the various chemical and therapeutic aspects of thiazolidine-2,4-diones.

2. Chemistry

1,3-Thiazolidine-2,4-diones (**C**) are derivatives of thiazolidine (**B**) with two carbonyl groups at the 2 & 4 positions. Substituents in the 3 & 5 positions may be varied. The pK_a of thiazolidinedione has been reported to be 6.82.[5]

2.1. Synthesis

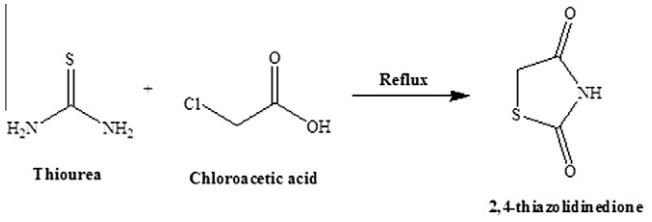
The thiazolidinedione ring can be synthesized using both conventional as well as microwave method. Conventional method is carried out by refluxing chloroacetic acid and thiourea using water as a solvent for 12 h and cooled to yield white crystals of thiazolidine-2,4-dione (Scheme 1).[6]

The reported microwave assisted synthesis of thiazolidine-2,4-dione ring (Scheme 2) involves a two-step reaction. In the first step, chloroacetic acid and thiourea are stirred under ice cold condition to obtain a white precipitate of 2-imino-thiazolidin-4-one (**i**) intermediate, which in the second step is further irradiated with microwave at 250 W for 5 min to obtain white crystals of thiazolidine-2,4-dione (**ii**).[7]

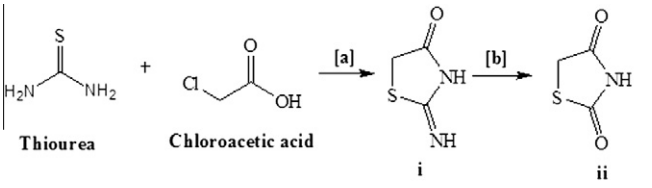
2.2. Tautomerism

Since thiazolidine-2,4-dione (**C**) contains two carbonyl groups and an α-hydrogen it has an ability to undergo tautomerism[8] and different tautomers obtained are shown in Figure 1. It undergoes either amide-imidol (**b**,**c**) type of tautomerism or keto-enol (**d**) type of tautomerism or both (**e**).[9] Of all different tautomeric forms mentioned tautomer (**a**) is found to be stable.

There are various pharmaceutical drugs containing the TZD ring capable of undergoing tautomerism that usually involve migration of proton (prototrophy) from one site to another within the molecule.[8]



Scheme 1. Conventional method for synthesis of thiazolidine-2,4-dione.



Preperation of Thiazolidine-2,4-dione: [a]0-5^{0}C, water, for stirring for 15 min
[b]MW-250W, 5min

Scheme 2. Microwave assisted synthesis of thiazolidine-2,4-dione ring.

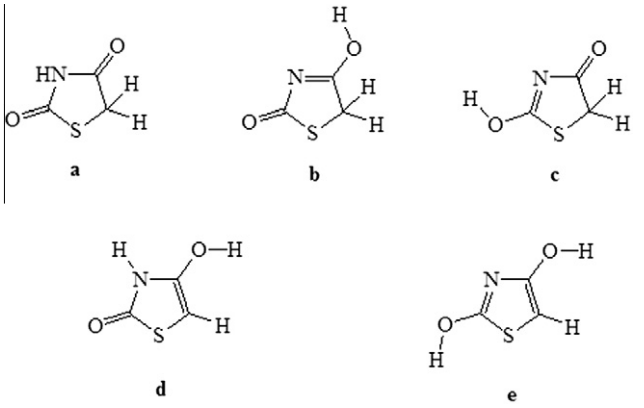


Figure 1. Different tautomers of thiazolidine-2,4-dione.