European Journal of Medicinal Chemistry 129 (2017) 218–250

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship

Mohd. Javed Naim, Md. Jahangir Alam, Shujauddin Ahmad, Farah Nawaz, Neelima Shrivastava, Meeta Sahu, Ozair Alam*

Dept. of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, New Delhi, 110062, India

ARTICLE INFO

Article history:
Received 14 December 2016
Received in revised form
10 February 2017
Accepted 11 February 2017

Keywords:
Thiazolidinedione
PPARγ
Antihyperglycemic
Anticancer
Antimicrobial

ABSTRACT

Thiazolidinedione is an important heterocyclic ring system, a pharmacophore and a privileged scaffold in medicinal chemistry; is a derivative of thiazolidine ring which came into existence for its role as anti-hyperglycemic agent and a specific ligand of PPAR's (Peroxisome proliferator activated receptor). Exhaustive research has led to determination of its vast biological profile with wide range of therapeutic applications. This review covers recent pharmacological advancements of thiazolidinedione moiety along with structure activity relationship so as to provide better correlation among different structures and their receptor interactions.

Contents

Abbreviations: AI-2, Auto inducer-2; ATP, Adenosine triphosphate; ALR, Aldose reductase; COX, Cyclooxygenase; EC_{50}, Half maximal effective concentration; ED_{50}, Median effective dose; FFAR1, Free fatty acid receptor 1; FP-2, Cysteine protease falcipain-2; GPCR, G protein coupled receptors; GPR-40, G protein coupled receptors-40; HIV-1RT, Human immuno virus-1 Reverse transcriptase; IC_{50}, Inhibitory concentration; L-DOPA, L-dihydroxyphenylalanine; MIC, Minimum inhibitory concentration; NADH, Nicotinamide adenine dinucleotide; NIDDM, Non-insulin dependent diabetes mellitus; NO, Nitric oxide; iNOS, inducible nitric oxide synthase; NSAID, Non-steroidal anti-inflammatory drugs; PDF, Peptide deformylase; PGDH, Prostaglandin dehydrogenase; PI-3, Phosphoinositide-3; p.o, Per os (oral administration); PPAR, Peroxisome proliferator activated receptor; PTP-1B, Protein tyrosine phosphatase-1B; QS, Quorum sensing; SAR, Structure activity relationship; TZD, Thiazolidinedione.

* Corresponding author. Dept. of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, Hamdard University, New Delhi, 110062, India.
E-mail addresses: dr.ozairalam@gmail.com, oalam@jamiahamdard.ac.in (O. Alam).

http://dx.doi.org/10.1016/j.ejmech.2017.02.031
0223-5234/

1. Introduction

The thiazolidinediones (glitazones) are heterocyclic ring system which were introduced in the late 1990's as derivatives of thiazolidine ring for the treatment of type 2 diabetes mellitus (Fig. 1). They act through activation of PPAR's (Peroxisome proliferator activated receptor); a group of nuclear receptor with maximum specificity for PPARγ (PPARα, PPARβ & PPARγ are subtypes of PPAR) and regulates the genes controlling glucose homeostasis and lipid metabolism.

Thiazolidinedione consists of a five membered thiazolidine ring with carbonyl groups at 2 and 4 positions. Variable substitutions occur at 3 and 5 positions, but substitution at position 2 brings out greatest change in structure and properties of thiazolidinedione. Removal of oxygen at position 2 by sulphur gives rise to rhodanine derivatives whereas removal of sulphur at position 1 by oxygen gives rise to oxazolidinedione derivatives [1–4]. Due to its diverse and flexible nature, thiazolidinediones are found to exhibit wide range of pharmacological activities which includes Antihyperglycemic [5], Antimicrobial [6], Antiviral [7], Antioxidant [8], Aldose reductase inhibitors [9], Alpha glucosidase inhibitors [10], Anticancer [11], Anti-inflammatory [12], AI-2 quorum sensing inhibitors [13], Anti-plasmodial [14], Beta-3 agonists [15], COX inhibitors [16], FFAR1 agonists [17], GPR-40 agonists [18], 15-hydroxyprostaglandin dehydrogenase inhibitors [19], Hypolipidemic activity [20], LPS-induced NO production inhibitors [21], Neuroprotective [22], Peptide deformylase inhibitors [23], Phosphoinositide-3-kinase γ inhibitors [24], PPARγ agonists/modulators [25], PTP1B inhibitors [26], Tyrosinase inhibitors [27], and Xanthine oxidase inhibitors [28] (Fig. 2).

The exhaustive research on thiazolidinediones resulted in several representative derivatives (troglitazone has been withdrawn from market due to its hepatotoxicity) and patents (Fig. 3, Table 1). Because of wide pharmacological profile; thiazolidinediones are still in research for better, safer and potential pharmacological agents [29–69].

Fig. 1. Structure of thiazolidinedione.

2. Pharmacological profile of thiazolidinediones

2.1. Antihyperglycemic agents

Hyperglycemia is a condition/lifestyle disease which leads to increase in glucose levels over prolonged periods due to insulin resistance in peripheral tissue and liver. Antihyperglycemic agents acts through ameliorating insulin resistance, enhancing insulin secretion and promoting utilization of glucose in tissues. Interaction of antihyperglycemic agents (TZD) with PPARγ receptors plays an important role in regulating glucose metabolism [70–72].

Kar et al. [73] designed and synthesized novel thiazolidinedione derivatives and evaluated them for glucose uptake activity as antihyperglycemic agent. Compound **1** was the most potent derivative with *in vitro* mean glucose uptake values of 34.71 mg/dl/45min and 47.65 mg/dl/45min in absence and in the presence of insulin against Rosiglitazone as the standard drug with 36.00 mg/dl/45min and 50.50 mg/dl/45min as *in vitro* mean glucose uptake values. Jawale et al. [74] synthesized thiazolidinedione derived sulfonylureas and evaluated them for antihyperglycemic activity. Compound **2** was found as the most potent derivative with 17.2% hyperglycemic activity against Metformin as the standard drug with 27.0% hyperglycemic activity. Datar et al. [75] designed and synthesized thiazolidinedione derivatives in which compound **3** appeared as the most potent derivative with a consistent decrease in the blood glucose level to 104 mg/dl for 120 min against Pioglitazone as the standard drug with 115 mg/dl. Kumar et al. [76] synthesized glitazones incorporated with glycine, aromatic and alicyclic amine moieties in which compound **4** appeared as the most potent analogue with 18.71 mg/dl/45min and 42.16 mg/dl/45min as *in vitro* mean glucose uptake values; in the absence and presence of insulin respectively using Rosiglitazone as the standard drug with 19.00 mg/dl/45min and 48.34 mg/dl/45min as *in vitro* mean glucose uptake values. Kumar et al. [77] synthesized TZD (thiazolidinedione) derivatives based on aryl-substituted cinnamic acid and investigated them for their anti-diabetic activity in streptozotocin-induced neonatal diabetic Wister male rats. (E)-methyl-3-(2,4-dimethoxyphenyl)-2-(4-(4-((2,4-dioxothiazolidin-5-yl)methyl) phenoxy)phenyl)acrylate **5** was found to be most potent compound with electron releasing di-substitutions on aryl ring for significant antihyperglycemic activity. Murugan et al. [78] synthesized novel dispiropyrrolidines through cycloaddition of thiazolidinediones and rhodanines and evaluated them for antidiabetic activity on male Wistar rats. Compound **6** was the most potent derivative with blood glucose lowering to 115.8 ± 1.8 mg/dl as compared to Pioglitazone as the standard drug. Mourao et al. [79] synthesized benzylidine thiazolidinedione derivatives and assessed them for their antihyperglycemic activity. Compound **7** was the most potent derivative with 51% reduction in glucose level and 59% reduction in triglyceride level at a dose of 30 mg/kg/day p.o. after 15 days using Rosiglitazone as the standard drug with 37% & 43% reduction in glucose and triglyceride level at a dose of 10 mg/kg/day p.o. Bhat et al. [80] synthesized novel thiazolidinedione