Bioorganic Chemistry 73 (2017) 24–36

Contents lists available at ScienceDirect

Bioorganic Chemistry

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

Synthesis, molecular docking and anti-diabetic evaluation of 2,4-thiazolidinedione based amide derivatives

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ARTICLE INFO

Article history:
Received 2 March 2017
Revised 1 May 2017
Accepted 4 May 2017
Available online 6 May 2017

Keywords:
Antidiabetic
PPARγ
Thiazolidinedione
Molecular docking

ABSTRACT

A series of thiazolidinedione based amide derivatives were designed, synthesized and docked against the PPARγ receptor target. 11 compounds from the series with good glide scores were selected for *in vivo* antidiabetic study based on streptozotocin induced diabetic rat model. It was observed that 4 compounds (**6c**, **6e**, **6m** & **6n**) showed significantly good antidiabetic activity in comparison to rosiglitazone and pioglitazone as reference drugs. Compound **6c** appeared as the most potent derivative in lowering blood glucose level and showed excellent interaction with SER 342, ILE 281, pi-pi interaction with ARG 288 and halogen bond interaction with LYS 367. Further, PPARγ transactivation and gene expression studies of compound **6c** were carried out to investigate the possible mechanism of action through PPARγ modulation. Compound **6c** exhibited 53.65% transactivation and elevated PPARγ gene expression by 2.1 folds. The biochemical parameters (AST, ALT and ALP levels) were found within the range with no noteworthy damage to liver.

1. Introduction

Diabetes is a chronic metabolic syndrome which relates to impaired insulin secretion and peripheral insulin resistance. It consists of an array of dysfunctions characterized by hyperglycaemia as its initial symptoms which when left unnoticed leads to vascular diseases, nephropathy, vascular neuropathy, cardiovascular diseases etc. Categorized as Type I & II; Type II is found to be the most common among 80% of the affected population worldwide which can be tackled with changes in lifestyle and proper medications.

According to WHO reports; 30 million people were affected from diabetes in 1985 which increased to 185 million in 2000 and expected to double by 2030. These epidemic calculations put a demand towards the development of more potent and efficacious agents to control diabetes. [1–3] 2,4-thiazolidinediones (Glitazones) introduced in late 1990's are orally acting hypoglycaemic agents which have attracted attention round the globe because of their diverse biological profile showing anti-hyperglycaemic [4], anti-tumour [5], anti-oxidant [6], anti-malarial [7], anti-obesity [8] & anti-microbial activities [9,10]. TZD's acts as specific ligand for PPAR to ameliorate diabetes without causing hypoglycaemia. PPAR's (Peroxisome proliferated activated receptors) are ligand activated transcription factors of nuclear receptor superfamily [11] with a leading role in adipogenesis activation and insulin sensitivity [12]. Being an important molecular target; it is further classified as PPAR-α (NR1C1), PPAR-δ (NR1C2) & PPAR-γ (NR1C3) among which PPAR-γ is the most widely researched protein receptor. Rosiglitazone and pioglitazone are thiazolidinedione derivatives which act as PPAR-γ full agonist in ameliorating diabetes [13]. In spite of its excellent anti-diabetic action, TZD derivatives also possess undesirable side effects including weight gain, edema, anaemia, bone deformities. Being with a specified & well planned objective, it's still a challenge for medicinal chemists to avoid their undesirable effects while retaining the hypoglycaemic property of TZD derivatives. Some well-known thiazolidinedione derivatives are mentioned in Fig. 1. Recently our research group have reported a review on 2,4-thiazolidinedione moiety giving a very well description about its pharmacological profile and structure activity relationship [14].

We herein report the synthesis of amide based thiazolidinedione analogues with molecular docking studies, in vitro PPAR-γ

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http://dx.doi.org/10.1016/j.bioorg.2017.05.007
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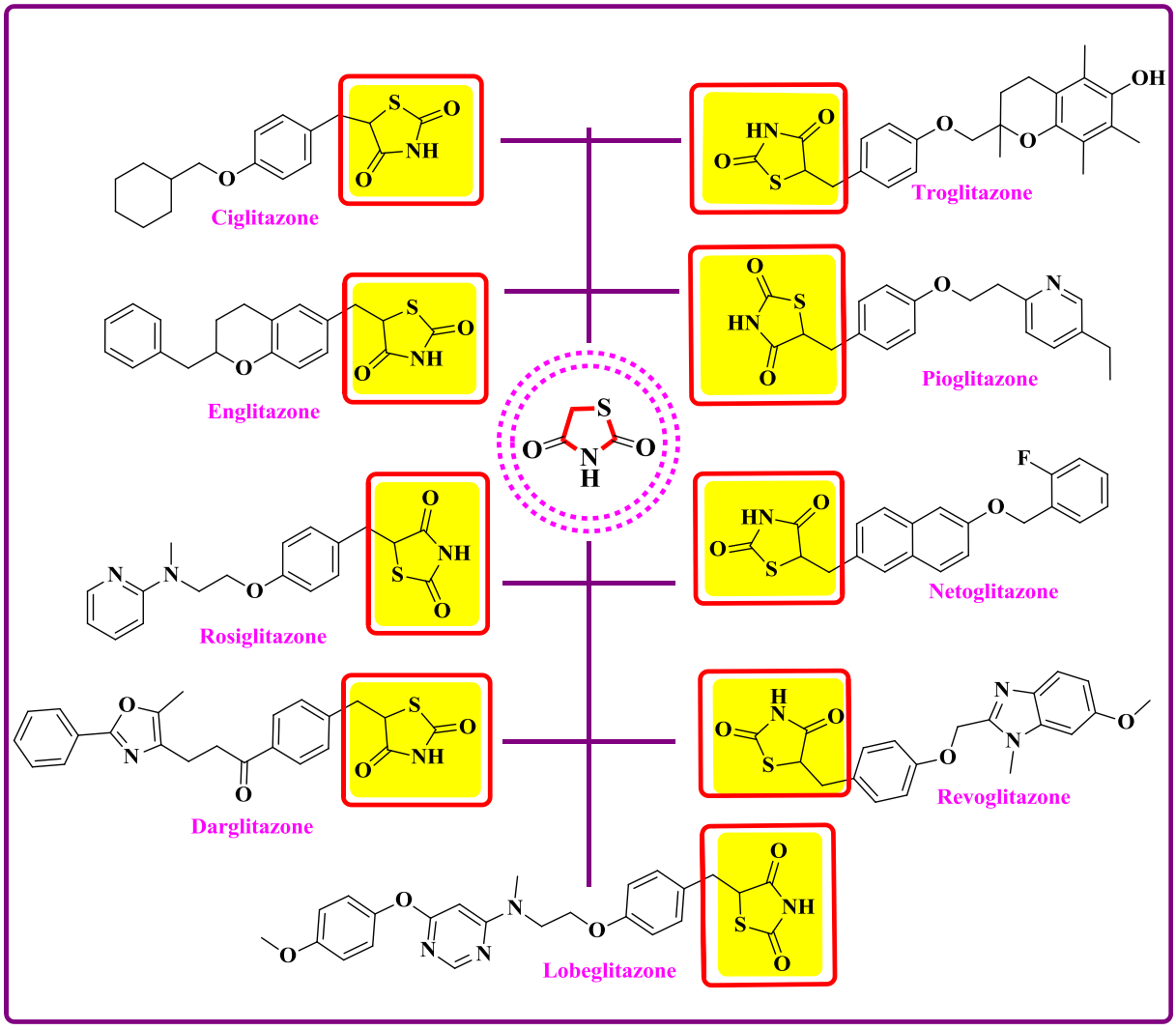

Fig. 1. Representative drugs of thiazolidinedione moiety.

assay, *in vivo* anti-diabetic activity, PPAR-γ gene expression along with hepato-toxicity studies. Substituted acetophenones/aryl ketones were treated with phenyl hydrazine in absolute ethanol under acidic conditions to obtain substituted hydrazones **3(a-q)** which then undergoes Villsmeyer Hack reaction in the presence of DMF & $POCl_3$ yielding pyrazole carbaldehydes **4(a-q)**. Knoevenagal condensation of TZD and **4(a-q)** yielded 2,4-thiazolidinedione derivatives **5(a-q)** which then further reacted with 2-chloroacetamide in the presence of acetonitrile as solvent to finally yield amide based TZD derivatives **6(a-q)** (Fig. 2) consisting of central pyrazole ring, additional aryl ring, hydrophobic tail and an acid functionality/acid group/acid head such as thiazolidinedione which interacts with the PPARγ active site. Other acidic heads that interacts with PPARγ active sites includes carboxylic acids [15], Oxazolidinediones [16] & acylsulfonamides [17] etc.

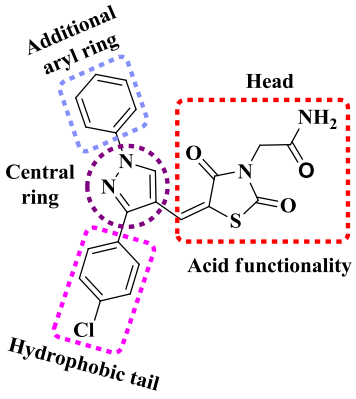

Fig. 2. Designed molecule.

2. Results & discussion

2.1. Chemistry

The titled compounds (**6a–q**) were synthesized as per the route mentioned in Scheme 1**.** The compounds (**3a-q**) were synthesized by treating substituted acetophenones/aryl ketones (**1a-q**) with phenyl hydrazine (**2**) to form hydrazones which then undergoes Vilsmeier-Haack reaction in the presence of $POCl_3$ and DMF to give pyrazole carbaldehydes (**4a-q**). These resulting carbaldehydes undergoes Knoevenagal condensation with 2,4-thiazolidinedione to yield **5a-q** which were then finally treated with 2-chloroacetamide to yield derivatives **6a-q**. The structures were then characterized by FT-IR, ^1H and ^{13}C NMR (Bruker-400 NMR spectrometers) and Mass spectrometry (ESI-MS, Water). Elemental