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Design, synthesis, *in silico* molecular docking and biological evaluation of novel oxadiazole based thiazolidine-2,4-diones *bis*-heterocycles as PPAR-γ agonists

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ABSTRACT

A library of novel 1,3,4-oxadiazole and 2-4-thiazolidinedione based *bis*-heterocycles **7 (a–r)** has been synthesized which exhibited significant PPAR-γ transactivation and blood glucose lowering effect comparable with the standard drugs Pioglitazone and Rosiglitazone. Compounds **7m** and **7r** did not cause body weight gain and were found to be free from hepatotoxic and cardiotoxic side effects. Compounds **7m** and **7r** increased PPAR-γ gene expression by **2.10** and **2.00** folds, respectively in comparison to the standard drugs Pioglitazone (**1.5** fold) and Rosiglitazone (**1.0** fold). Therefore the compounds **7m** and **7r** may be considered as potential candidates for development of new antidiabetic agents.

1. Introduction

Type 2 diabetes is a metabolic disorder which due to insulin resistance and impaired insulin secretion leads to hyperglycemia. Patients with type 2 diabetes suffers from several complications such as neuropathy, nephropathy, retinopathy, cardiovascular diseases and atherosclerosis [1,2]. In normal humans, up to 80% of insulin-stimulated glucose disposal occurs in the skeletal muscle, a major site of insulin resistance in type 2 diabetes [3].

2,4-thiazolidinediones (TZDs) are an important class of compounds that enhances insulin action (insulin sensitizers) and promote glucose utilization in peripheral tissues [4]. These are high-affinity ligands of peroxisome proliferator activated receptor-γ [5]. PPAR-γ, a member of a large family of ligand-activated nuclear hormone receptors is an important drug target for regulating glucose metabolism [6–9]. It increases insulin sensitivity in the adipose, muscle and hepatic tissues [10,11]. It leads to the channeling of fatty acids into adipose tissue and reducing their concentration in the plasma and thus alleviating insulin resistance and improving plasma glucose levels effectively [12–14]. 1,3,4-oxadiazoles are another important class of heterocyclic compounds which are known for a number of important pharmacological activities like hypoglycaemic, hypolipidemic, antimicrobial, antiinflammatory, analgesic, antimitotic and anticonvulsive activities [15–22].

Considering the biological importance of 2,4-thiazolidinediones and 1,3,4-oxadiazoles, we have conjugated thiazolidinediones with 1,3,4-oxadiazole under one construct through a methylene linkage to enhance the blood glucose lowering effect and minimize the side

Abbreviations: TZD, thiazolidinediones; STZ, streptozotocin; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; RT, reverse transcription; PCR, polymerase chain reaction.

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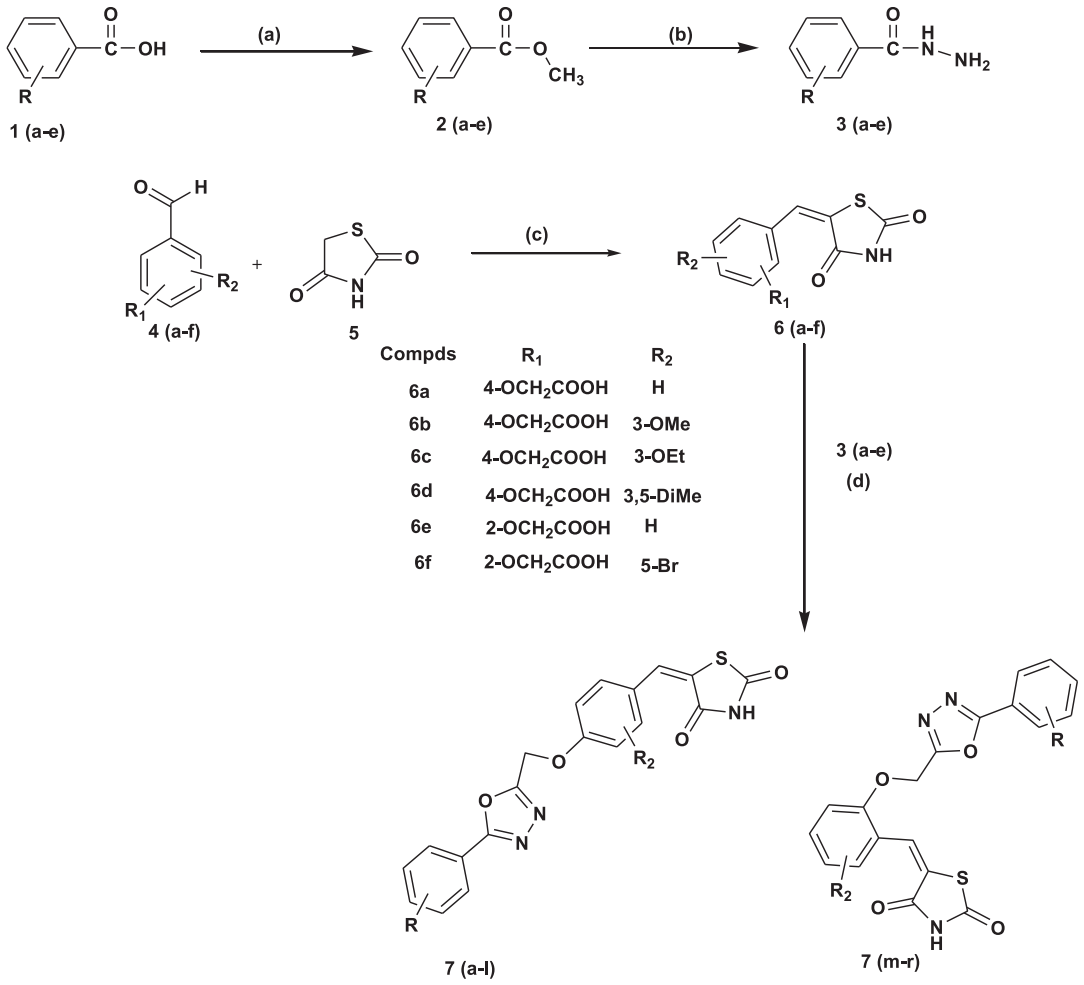

Compds	R_1	R_2
6a	4-OCH_2COOH	H
6b	4-OCH_2COOH	3-OMe
6c	4-OCH_2COOH	3-OEt
6d	4-OCH_2COOH	3,5-DiMe
6e	2-OCH_2COOH	H
6f	2-OCH_2COOH	5-Br

Reagents and conditions: (a) MeOH, H_2SO_4, Reflux, 1-2 h; (b) $NH_2NH_2.H_2O$, Abs. alcohol, 6-8 h; (c)EtOH, NaOH, 0-(-5) °C, 10-12 h; (d) $POCl_3$, RT, 10-12 h.

Compds	R_2	R	Compds	R_2	R
7a	H	H	7j	3-OMe	2-OEt
7b	3-OMe	H	7k	H	Phenyl
7c	3-OEt	H	7l	H	-O-CH_2-2,6-diCl
7d	3,5 DiMe	H	7m	H	H
7e	H	4-Cl	7n	H	4-Cl
7f	3-OMe	4-Cl	7o	H	4-Br
7g	H	4-Br	7p	H	2-OEt
7h	3-OMe	4-Br	7q	-5-Br	H
7i	H	2-OEt	7r	H	-O-CH_2-2,6-diCl

Scheme 1. Synthetic route for novel 1,3,4-oxadiazole-thiazolidine-2,4-diones based *bis*-heterocycles.

effects. We herein report for the first time, the synthesis and *in silico* molecular docking studies of oxadiazole and thiazolidinedione based *bis*-heterocycles **7 (a–r)** against PPAR-γ target. The compounds showing good docking score (>−7.20) were screened for their *in vitro* PPAR-γ transactivation activity. Compounds **7b**, **7h, 7k, 7m** and **7r** showing significant PPAR-γ transactivation activity were further evaluated for their *in vivo* antidiabetic activity and hepatotoxicity. Two compounds **7m** and **7r** showing the most potent *in vitro* and *in vivo* antidiabetic activity were finally evaluated for their cardiotoxic risk evaluation as well as effect on PPAR-γ gene expression.

2. Results and discussion

2.1. Chemistry

Treatment of different aromatic acids **1 (a–e)** with MeOH in presence of a few drops of conc. H_2SO_4 yielded methyl esters of