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Thiazolidine-2,4-diones derivatives as PPAR-γ agonists: Synthesis, molecular docking, in vitro and in vivo antidiabetic activity with hepatotoxicity risk evaluation and effect on PPAR-γ gene expression

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ABSTRACT

A library of conjugates of chromones and 2,4-thiazolidinedione has been synthesized by Knoevenagel condensation followed by reduction using hydrogen gas and Pd/C as a catalyst. Compounds **5c** and **5e** were most effective in lowering the blood glucose level comparable to standard drug pioglitazone. Compound **5e** exhibited potent PPAR-γ transactivation of 48.72% in comparison to pioglitazone (62.48%). All the molecules showed good glide score against the PPAR-γ target in molecular docking study. PPAR-γ gene expression was significantly increased by compound **5e** (2.56-fold) in comparison to standard drug pioglitazone. Compounds **5e** and **5c** did not cause any damage to the liver and may be considered as promising candidates for the development of new antidiabetic agents.

Type 2 diabetes is a complex metabolic syndrome resulting in high blood glucose due to impaired insulin action, which in turn stimulates glucose uptake in peripheral tissues such as muscle and fat. In normal humans, up to 80% of insulin-stimulated glucose disposal occurs in skeletal muscle, a major site of insulin resistance in type 2 diabetes.[1,2]

Recently, chemistry of 2,4-thiazolidinediones (TZDs) has attracted attention as they have been found to exhibit several biological activities,[3] such as antihyperglycemic,[4] anti-inflammatory,[5] antimalarial,[6] antioxidant,[7] antitumor,[8] cytotoxic,[9] antimicrobial,[10] and antiproliferative.[11] Thiazolidinediones are high-affinity ligands of peroxisome proliferator activated receptor-γ.[12] PPAR-γ, a member of a large family of ligand-activated nuclear hormone receptors is an important drug target for regulating glucose metabolism. PPAR-γ increases insulin sensitivity at adipose, muscle and hepatic tissues[13,14] thereby improving plasma glucose levels effectively.[15–17] PPAR-γ exists in two forms mainly PPAR-γ1, found in all the tissues except muscles and PPAR-γ2, found in adipose tissues and intestine. These are encoded by PPAR-γ gene in humans. Although TZDs are strong and specific activators of PPAR-γ capable of ameliorating diabetes mellitus by improving insulin resistance without inducing hypoglycaemia,[18] they are associated with side effects viz. weight gain, hepatotoxicity and fluid retention.[19]

Chromones are a group of naturally occurring compounds found in fruits and vegetables.[20,21] They are safe and are associated with low mammalian toxicity, making them excellent chemopreventive agents.[22] They are reported to exert an antihyperglycemic effect by promoting peripheral utilization of glucose or enhancing insulin sensitivity in diabetic animals.[23] Considering the biological importance of thiazolidinediones and chromones as antidiabetic agents, we have conjugated these two important ligands under one construct through a methylene linkage. We herein report the synthesis of thiazolidinedione and chromone based conjugates and their molecular docking studies and evaluation of their in vivo antidiabetic activity with hepatotoxicity risk evaluation, in vitro PPAR-γ activity and also the effect on the PPAR-γ gene expression.

Villsmeyer Hack reaction of substituted *o*-hydroxy acetophenones (**1a–k**) in presence of DMF and $POCl_3$ yielded 3-formyl

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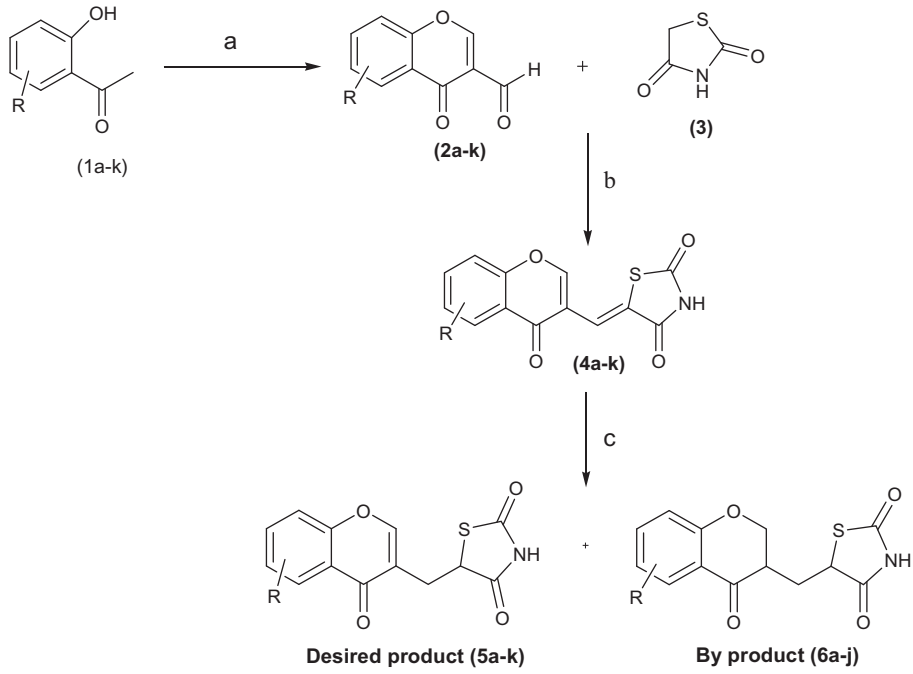
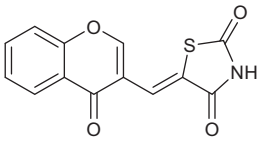
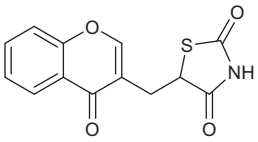
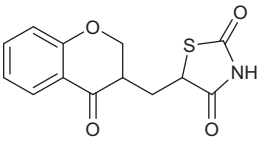
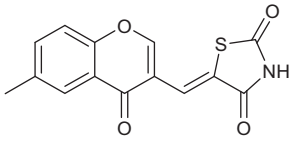
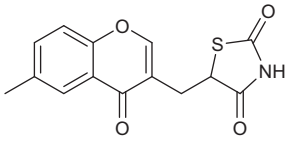
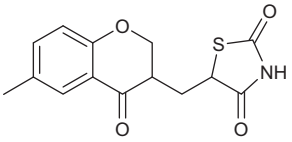
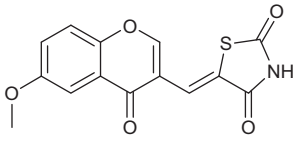
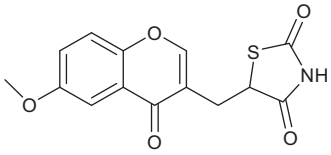
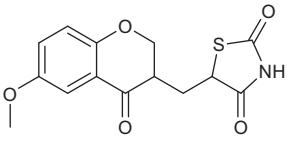
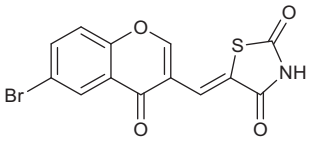
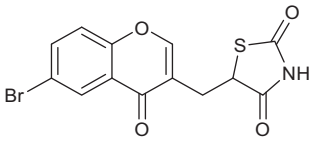
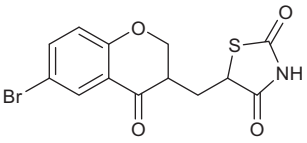
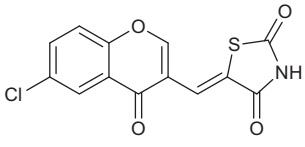
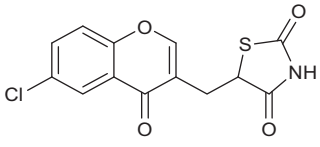
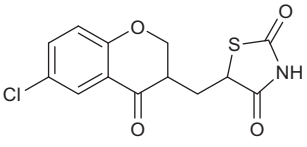
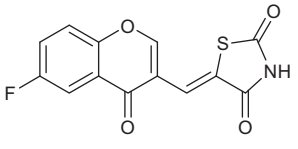
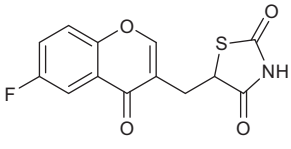
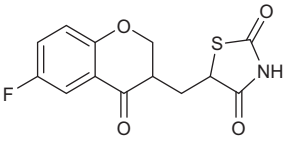


Scheme 1. Reagents and conditions:(a) DMF, $POCl_3$, 0-(−5)°C;(b) sodium acetate, acetic acid, 120–140 °C; (c) Pd/C, H_2 gas, 30 psi, rt, 10–12 h.

Table 1
Physical data of the synthesized compounds

S.No.	Reactant (**4**)	Desired product (**5**)	yield (%)	By product (**6**)	Yield (%)
a			50		30
b			65		20
c			70		20
d			65		25
e			60		20
f			65		21

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