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Design and synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid derivatives as PPARγ activators

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Abstract—The design and synthesis of novel series of 6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid (pyrimidone) derivatives that are high affinity ligands for peroxisome proliferators activated receptor γ have been reported as a potential substitute of 2,4-thiazolidinedione head group. The FlexX docking and radioligand binding affinity of some promising compounds of this series is comparable to that of thiazolidinedione based antidiabetic drugs currently in clinical use.

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetics.[1] It is predicted that world's diabetic population could rise to 220 million by the year 2010 partly due to a dramatic increase in the incidence of obesity and a sedentary lifestyle.[2] T2DM is a metabolic disorder which is associated with three basic pathophysiological abnormalities: impaired insulin secretion, excessive hepatic glucose production, and insulin resistance in skeletal muscle, liver, and adipose tissue.[3] It is now clear that aggressive control of hyperglycemia in patients with diabetes can prevent or delay the onset of complications such as retinopathy, nephropathy, and neuropathy.[4]

The peroxisome proliferators activated receptor γ (PPARγ) is a member of nuclear hormone receptor superfamily of ligand dependent transcription factors, which play a pivotal role in regulating adipogenesis, insulin sensitivity and glucose homeostasis.[5] Synthetic agonists of PPARγ including pioglitazone and rosiglitazone, had been proved clinically beneficial in decreasing the elevated plasma glucose levels in T2DM. However, edema and weight gain have been reported in patients after treatment with some of PPARγ agonists. It is unclear whether the side effects observed are PPAR receptor mediated or compound mediated.[6,7]

Therefore, there continues to be interest in new compounds for clinical development. This necessitated developing new antihyperglycemic agents that could be highly effective, safe, and devoid of side effects. This provides an opportunity to bring diverse class of ligands that could normalize both insulin and glucose levels (Chart 1).

The compounds of this class have few essential pharmacophoric elements. These comprise of an acidic group linked to a central flat ring and a large lipophilic substructure. Based on the crystal structure analysis and molecular modeling studies, a common U-shaped pharmacophore has been derived for PPARγ agonists. The thiazolidinedione (TZD) head group is anchored by four important H-bonds in the active site Ser289, His323, His449, and Tyr473.[8,9]

Current research trend has shifted toward non-thiazolidinedione insulin sensitizers. Bioisosteric replacement of thiazolidinedione by α-carbon substituted carboxylic acid, oxazolidine-2,4-dione, tetrazole, oxathiazole, carbonylated hydroxyurea, etc. had been reported in the literature.[10–15]

Earlier, we reported carbazole derivatives with the acyclic acidic head groups as PPARα/γ dual agonists with antioxidant property.[16,17] Sterically hindered open chain acid derivatives have been found efficient PPAR activators.[18] Recently compounds with pyran head instead of TZD were identified as novel PPARγ agonists.[19] The lipophilic fragment of promising compounds was

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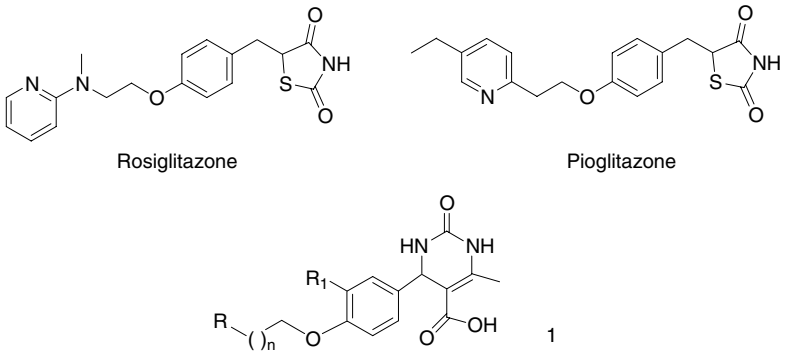


Chart 1. PPARγ agonists.

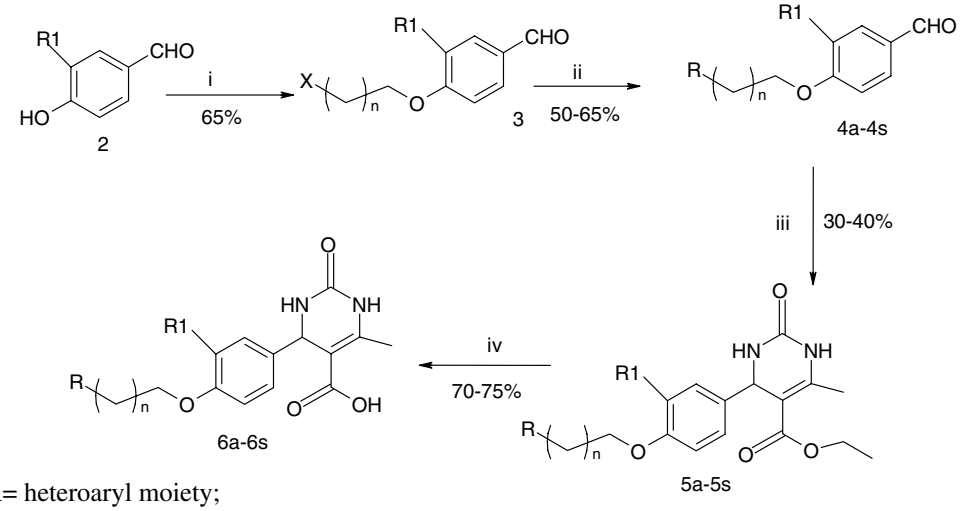
conjugated with a six-membered tetrahydropyrimidone group which is bioisosteric to thiazolidinedione with additional carbonyl functionality.

The prototype structures **1** are pyrimidone derivatives that are replacement for TZD group to develop new chemical entity that may retain the antihyperglycemic activity.

The molecular docking studies were performed on 1FM9 protein, viz. PPARγ employing the FlexX docking procedure using Sybyl 6.9 program installed on silicon graphics Octane2 workstation. FlexX is a fast automated program based on incremental construction procedure.[20] In this method flexibility of the ligands is considered including several conformations of ligands while maintaining a rigid structure for the biomolecule. Rosiglitazone was docked into the active site of the receptor to judge the discriminatory strength of the docking procedures and the choice of the crystal structure. The active sites were assigned at a radius of 8 Å around the reference ligand. FlexX run was submitted and the docking scores were obtained and analyzed. In the subsequent synthesis and biological evaluation of hit compounds, we found compounds **6a** to **6s** as high affinity ligands for PPARγ.

In this publication, we disclose the synthesis, in silico and in vitro evaluation of pyrimidone class of compounds for the first time. Further, we applied a receptor based approach to the validation of our hypothesis regarding substitution of pyrimidone moiety in place of TZD. This approach essentially searches for a ligand whose orientation and conformation achieve the highest degree of complementarity with respect to all details of the receptor's steric constraints and interaction geometrics.

The synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives **6a** to **6s** is depicted in Scheme 1. Commercially available 1,2-dibromoethane ($n = 1$); 1-bromo-3-chloropropane ($n = 2$) were refluxed with 4-hydroxy benzaldehyde or 4-hydroxy-3-methoxybenzaldehyde (**2**) in acetone in presence of anhydrous K_2CO_3 as base to give compound **3** in good yield. The reaction mixture was concentrated and extracted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, and concentrated. Further



Scheme 1. Reagents and conditions: (i) 1,2-dibromoethane ($n = 1$); 1-bromo-3-chloropropane ($n = 2$), X = Cl, Br , anhydrous K_2CO_3, acetone, 70 °C, 12 h; (ii) heteroaryl moiety (R), NaH, THF, 0 °C to rt, 4 h or heteroaryl moiety (R), K_2CO_3, acetone, 70 °C, 15 h; (iii) ethyl acetoacetate, urea, zinc triflate, acetonitrile, 80 °C, 12 h; (iv) 20% NaOH, EtOAc, rt, 2 h.