OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing

October 15-17, 2013 Hampton Inn Tropicana, Las Vegas, NV, USA

Synthesis and evaluation of some novel thiazolidinedione derivatives as PPAR-α/γ dual agonists

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Thiazolidinediones (TZDs) or glitazones are an important class of drugs which act by increasing the transactivation activity of PPARs, as a result of which, they reduce hepatic glucose production and increase peripheral utilization of glucose and promote lipid metabolism. These actions, therefore, ensure reduced preload and after load on β-cells and lipid homeostasis. In addition, unlike sulfonylureas, these agents are devoid of mechanism based hypoglycemic side effects. There is, therefore, an excellent rationale for the use of TZDs in the management of T2DM. Unfortunately, the clinically used TZDs (troglitazone, pioglitazone and rosiglitazone) suffered with some serious side effects like idiosyncratic hepatotoxicity, fluid retention, weight gain, bladder cancer, etc., as a result of which both troglitazone and rosiglitazone were banned and the pioglitazone label was updated for the risk of bladder cancer.

In recent years, however, new approaches have been made to address the problems associated with current TZDs. One of these is the development of molecules which possess both PPAR-α/γ dual agonistic activities. These molecules have been claimed to achieve a broad spectrum of metabolic effects by improving insulin resistance, hyperglycemia and atherosclerotic dyslipidemia. This presentation talks on the synthesis and evaluation of *in silico* and *in vitro* binding activities of 11 novel (5Z)-5-[4-(3-phenoxypropoxy)benzylidene]-1,3-thiazolidine-2,4-dione derivatives as PPAR-α/γ dual agents. All the compounds show good binding to both PPAR-α and γ receptors, in the *in vitro* binding assay. The *in silico* studies show diverse possible potential of these molecules to act as agonists and partial agonists/antagonists. These molecules, therefore, may have a potential in the treatment of type 2 diabetes mellitus without the reported adverse effects of the clinically used agents of this class.

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