QSAR AND MOLECULAR MODELING STUDIES IN IMIDAZOPYRIDINETHIAZOLIDINE-2,4-DIONES: PPARγ AGONISTS

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Abstract. Physicochemical and Pharmacophoric mapping based QSAR studies have been performed on a set of imidazopyridine thiazolidine-2,4 diones to identify essential structural and electronic features for PPARγ agonist activity. The 2D QSAR studies revealed that the activity is mainly influenced by electronic parameters where the contribution of field effect and Hammet constant is positive while that of resonance is negative. The 3D QSAR studies using Apex 3D expert system led to the identification of the pharmacophore in terms of common biophoric sites and secondary sites for interacting with PPARγ receptors. Among the several pharmacophore models, the best model had $R^2 = 0.69$, chance $= 0.09$, size $= 3$, match $= 0.68$. Both the approaches showed good correlation between experimental and observed biological activity in both training ($r > 0.8$) and test set ($r = 0.75$ for 2D and $r = 0.68$ for 3D QSAR model) with statistical significance $> 99.5\%$.

Introduction
Type-2 diabetes is a debilitating disease caused by improper energy storage and utilization. The global incidence of this disease is estimated to be 120 million at present and is likely to grow to 200 million by the year 2010. Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin sensitive target organs such as adipocytes and skeletal muscle. It leads to hyperglycemia, which may also play a role in

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the etiology of a wide spectrum of metabolic disorders such as obesity, hypertension, atherosclerosis, neuropathy, nephropathy, retinopathy etc\textsuperscript{5}. As the exercise enhances tissue responsiveness to insulin, the combination of diet and exercise is the primary treatment for non-insulin dependent diabetes mellitus (NIDDM) patients\textsuperscript{3}. Since, dietary adherence is difficult for most patients, medication is essential for many NIDDM patients. Most commonly used oral hypoglycemic agents are sulfonylureas which have the disadvantages such as primary and secondary failure of efficacy as well as the potential for induction of severe hypoglycemia\textsuperscript{4}. So there is a need for new chemical entities, which may effectively reduce insulin resistance. The search for the drugs that reverse the insulin resistance without stimulating insulin release from \(\beta\)-cells also fulfill a major medical need in the treatment of NIDDM and is of current interest. The pioneering discovery of ciglitazone, a thiazolidine-2,4-dione derivatives (TZDs) and several of its analogues have led to the identification of possible molecular targets peroxisome-proliferator activated receptor (PPAR\(\gamma\)), selectively expressed in adipocytes\textsuperscript{5-9}. The TZDs are found to be the promising compounds capable of ameliorating NIDDM by improving insulin resistance without inducing hypoglycemia. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue, resulting in the correction of elevated plasma level of glucose without the occurrence of hypoglycemia.

In continuation of our previous work in this area\textsuperscript{10,11,12} here we report both the identification of essential structural and physicochemical parameters important for the PPAR\(\gamma\) agonistic activity of imidazopyridine thiazolidine-2,4 diones\textsuperscript{13} by the application of 2D and 3D QSAR analysis.

**Material and Methods**
All the twenty-two molecules were divided into training set (18) and test set (4) for 2D and 3D QSAR analysis (Table 1).