Design, synthesis and antidiabetic & antidyslipidemic activities of chalcone based hybrids
disease, heart failure, myocardial infarction, alzheimer’s disease, schizophrenia, bipolar disorder, fragile X syndrome and chronic fatigue syndrome.

Increasing evidence in both experimental and clinical studies suggests that oxidative stress plays a major role in the pathogenesis of both types of diabetes mellitus. Free radicals are formed disproportionately in diabetes by glucose oxidation, non-enzymatic glycation of proteins, and the subsequent oxidative degradation of glycated proteins. Abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes, increased lipid peroxidation, and development of insulin resistance. These consequences of oxidative stress can promote the development of complications of diabetes mellitus.

In condition of insulin resistance, glycemic control is maintained only if the pancreatic β-cells can increase its capacity to secrete insulin to compensate insulin for the extent of insulin resistance. The insulin secretagogues and sensitizers are therefore main stay for current treatment. Following are the targets which have been utilized for drug design against type-2 diabetes (fig 15).

<table>
<thead>
<tr>
<th>Targets</th>
<th>Class of Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation of insulin secretion</td>
<td>Sulphonylureas,</td>
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<tr>
<td></td>
<td>Benzoic acid derivatives</td>
</tr>
<tr>
<td>Suppression of hepatic glucose production</td>
<td>Biguanides</td>
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<tr>
<td>(gluconeogenesis)</td>
<td>Thiazolidinediones</td>
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<tr>
<td>Insulin sensitization</td>
<td></td>
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<tr>
<td>Reduction of postprandial plasma glucose</td>
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<td>excursion</td>
<td>Alpha-glucosidase inhibitors</td>
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Fig-15: Classes of agents available for treatment of type-2 diabetes
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2.1. Introduction: Diabetes mellitus is a chronic disease which is often simply referred as diabetes, a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin or cells do not respond to the insulin produced. The high blood sugar produces the classical symptoms of polyuria (frequent urination), polydypsia (increased thirst) and polyphagia (increased hunger). There are many types of diabetes mellitus but the two major types are type-1 (juvenile diabetes) and type-2 diabetes. All the forms of diabetes have different symptoms as well as different complications. Insulin is produced by the pancreas that manages the utilization of blood glucose as a source of energy into the cells. Type-1 diabetes refers to the condition where there is no insulin because of destruction of pancreatic cells by some auto-immune responses to metabolize glucose and leads to low levels of glucose in the blood. Type-2 diabetes is a condition where there is abnormally high glucose level in the blood. In this case pancreas is still able to produce insulin but the cells in the body are resistant to its effects. This is also known as “insulin resistant” or non-insulin dependent diabetes (NIDDM). Type-2 or NIDDM is the most common type of diabetes usually associated with hepatic and peripheral insulin resistance and impaired β-cell function. Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs (adipocytes and skeletal muscles) and impaired inhibition of hepatic glucose output. Long term disruption of glucose utilization causes macro- and micro-vascular diseases. The un-utilized glucose under oxidative stress forms reactive aldehydes which react with proteins, initiate inflammatory processes under endothelium ultimately narrowing the vascular passage and thus hindering supply of nutrients to organs.

2.2. Oxidative stress in diabetes: Oxidative stress represents an imbalance between the production and manifestation of reactive oxygen species and ability of biological system to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of tissues can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. In humans, oxidative stress is involved in many diseases. Examples include atherosclerosis, Parkinson’s
However, one particular concern is the tendency in most of the above treatments to achieve weight gain. Another problem associated with the sulphonylureas is that many patients who responded initially become refractory to the treatment over the time. In view of the problems associated with these therapies, there is a need to search newer drugs acting through different mechanisms. Currently few receptor based targets to enhance the metabolism of the glucose and lipids for diabetic control are being pursued for design of new classes of anti-diabetic drugs of which two we will discuss briefly which have formed the basis of our design and synthesis of molecules in present study. $\beta_3$-Adrenergic receptor agonist and peroxisome proliferators activated receptor (PPAR) stimulation to enhance metabolism are intensely being pursued.

2.3. $\beta_3$-Adrenergic receptor agonist: Induction of energy expenditure mechanisms particularly adaptive thermogenesis is currently being targeted for antidyslipidemic and antidiabetic drug design. Adaptive thermogenesis (non-shivering) process operates on exposure to cold or excessive caloric intake (so-called diet-induced thermogenesis) through the regulation by two major hormonal effectors: $\beta_3$-adrenergic agents and thyroid hormones. Fat cell selective $\beta_3$-adrenergic receptor agonists uncouple the ATP synthesis and divert the energy towards loss as heat through the activation of mitochondrial uncoupling proteins (UCP). Ultimately, adrenergic stimulation increases insulin sensitivity and glucose tolerance, leading to selective loss of adipose tissue mass in animal models. In 1984, compounds of the phenethanolamine (49 & 50) and phenoxypropanolamine classes having thermogenic properties were discovered for the first time. Among phenethanolamine compounds as thermogenic agents, Elly Lilly’s compound LY 377604 is found to be the most active.
2.4. Peroxisome Proliferators Activated Receptor (PPAR): Another target for metabolic enhancement is the Peroxysome-Proliferator Activated Receptors (PPARs) being studied for quite some time. PPARs, was first characterized as ligand-activated transcriptional factors belonging to nuclear hormone receptor family of adipocytes-specific gene expression and pre-adipocytes differentiation. Different types of PPARs agonists have been shown to have beneficial effects on the described characteristics of type-II diabetes. There are three sub types; commonly designated as PPAR-α, γ and δ. PPAR-α is mainly expressed in the liver, skeleton muscles and kidneys while PPAR-δ is ubiquitously expressed. PPAR-γ is mainly expressed in adipose tissue and is as master regulator of the differentiation and maturation of adipocytes.

PPAR-α agonists (fig 16), fibrate primarily decreases serum triglyceride levels and increase high-density lipoprotein cholesterol (HDL-C) levels, but they also improve glucose tolerance in type-II diabetic patients. PPAR-γ agonists (fig 17), the insulin sensitizers also have a range of clinical effects including improvement of insulin sensitivity, glucose tolerance and lowering of blood glucose levels in type-II diabetic patients. Thiazolidinediones (TZDs) work to lower blood sugar by increasing the muscle, fat and liver’s sensitivity to insulin. Thiazolidinediones increase the amount of certain fat particles, called LDL.

![Clofibrate (16)](image1)

![Finofibrate (17)](image2)

![Ciprofibrate (51)](image3)

![LY 518674 (52)](image4)

Fig-16: PPAR-α agonists
The TZDs were synthesized as potentially hypolipidemic derivatives of clofibrate but then developed as antidiabetic agents because of their unexpected insulin sensitizing action *in-vivo*. TZDs are high-affinity PPAR ligands, with the rank order of their binding affinities mirroring anti-hyperglycemic activity, suggesting a role for this receptor in mediating their antidiabetic action. TZDs enhance peripheral sensitivity to insulin and to a lesser degree, decreases hepatic glucose production by activating PPAR-γ receptors. Adverse effects include weight gain, anemia and abnormalities in liver enzyme levels.

KRP-297 (55) is the first reported example of PPAR-α/γ dual agonist. Dual acting PPAR agonists were designated to combine the beneficial effects seen with insulin sensitizers and fibrates. They might also reduce the weight gain associated with adipogenesis resulting from PPAR-γ activation through simultaneous stimulation of lipid-oxidation and decreased adiposity after PPAR-α activation. In addition, KRP-297 improves abnormal lipid metabolism in obese rats. Besides KRP-297, some other compounds like 56 & 57 are also in clinical trials (fig 18).
2.5. Present work:
The studies described in first chapter have established that the diabetes and dyslipidemia under oxidative stress condition both result into endothelial dysfunction leading to morbidity and mortality due to macro and micro-vascular complications. Therefore it requires the future generation of drugs to be of hybrid nature acting on multiple targets to tackle endothelial dysfunction as well as the diabetes or dyslipidemia. In present study, we have taken up the designing of hybrid molecules having antioxidant property as well as pharmacophores either of the above two targets so that the compounds besides exhibiting anti-diabetic activity can also mitigate the vascular complications. We have selected chalcones which have antioxidant property of its own, as the base skeleton to graft pharmacophores for β3-adrenergic receptor and PPAR-α receptors. Chalcones are among the most ubiquitous group of polyphenolic compounds in foods of plant origin. They have also shown a variety of biological activities including antibacterial,\textsuperscript{17} antiallergic,\textsuperscript{18} antiinflammatory,\textsuperscript{19} antioxidant\textsuperscript{20} and anticancer\textsuperscript{21} effects. Recently chalcones and their derivatives have also been reported for anti-diabetic\textsuperscript{22} and anti-dyslipidemic\textsuperscript{23} activities. These studies thus also favor the choice of chalcones as safe base skeleton for grafting various pharmacophores. The below presented prototype molecules A-G (fig 19) were designed and taken-up for synthesis and structure activity relationship (SAR) studies.
Fig-19: Prototypes under taken for synthesis and their biological evaluation

The work on prototype A has already progressed quite well in our laboratory and a compound (58) has been picked up for detail study based on the preliminary screening results.\(^{24}\) To assist further studies on this molecule it was chosen for large scale synthesis for its iterative biological screening, preparation of its optical isomers (59, 60) to locate the best active enantiomer. It was also planned to study its pharmacokinetic and pharmacodynamic behavior and isolation of its major metabolites. During its bio-distribution studies, a major metabolite (61) was identified by LC-MS/MS (fig 20). This metabolite has also been prepared and studied for its biological efficacy as anti-diabetics. All these studies are described in chapter 1. After closely studying the mechanism of action of \(\beta_3\)-adrenergic receptor in literature and finding its similarity with parathyroid hormone (PTH) action, it was tested for its bone anabolic activity and found to be active as PTH. The antiosteoporotic activity of this compound is mentioned in next section of the chapter.
The synthesis and biological activities of another variant B with oxypropanolamine in B ring of the chalcone along with prototype C & D lacking carbinol moiety for SAR studies are described in next chapter. These compounds have also exhibited good anti-hyperglycemic and anti-dyslipidemic activities. Prototype molecules E & F with PPAR-α pharmacophore having good lipid lowering activity comparable to clofibrate are described in chapter 3. The chapter also describes the synthesis of chalcone prototype (G) with oxypropanolamine as well as fibrate moiety on another side in the same molecule is also reported. Biological evaluations of these molecules are under process. Experimental and biological activities of all synthesized compounds are reported in chapter 3 and 4 respectively.
2.6. References:


