CHAPTER I

Introduction and Scope of the Work
Chapter I

**General Introduction:**

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. Diabetes mellitus has two common forms, diabetes insipidus (Type I) and diabetes mellitus (Type II) in which blood glucose levels are elevated to pathological levels.

Type I diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. It accounts for about 10% of all diabetes and results from auto-immune mediated destruction of insulin secreting $\beta$-cells of the pancreas. In contrast Type II diabetes (formerly called non-insulin-dependent or adult-onset) results from the body’s ineffective use of insulin. It is a chronic and progressive metabolic disorder of carbohydrate and lipid metabolism and accounts for the remaining 90% of diabetes mellitus around the world, and is largely the result of excess body weight and physical inactivity.

Diabetes mellitus (DM), long considered as a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century. Diabetes is one of the most prevalent and serious disease in the world, because of the development of many severe complications. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke). Combined with reduced blood flow, neuropathy in the feet, increases the chance of foot ulcers and eventual limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. After 15 years of diabetes, approximately 2% of people become blind and about 10% develop severe visual impairment. Diabetes is among the leading causes of kidney failure. 10-20% of people with diabetes die because of kidney failure. The overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes.
Diabetes is a polygenic phenomenon which has both genetic and environmental and etiological factors with the increased prevalence of obesity in the general population, especially in young adults, the prevalence of diabetes is also on the rise, hence diabetes has been redefined as diabesity or obesity dependent diabetes mellitus.\(^9\)

Globally as of 2010 it was estimated that there were 285 million people with diabetes. According to world health organization (WHO) that number will be rise to 300 million by the year 2025. Diabetes is common in both the developed and the developing world. However, it remains uncommon in the underdeveloped world. Epidemiological reports show that India has highest number of diabetes in the world.\(^10\) Over 30 million people have now been diagnosed with diabetes in India and that number will be increased to 60-70 million in the coming years, 2025.\(^11\) Various epidemiological studies in India have shown that the prevalence and manifestation of diabetes are very high. The crude prevalence rate (CPR) in urban areas of India is found to be 9%. In rural areas, the prevalence is approximately 3% of the total population. It is quite evident from the above observations that diabetes has become a major health problem in India.\(^12\)

Considering the seriousness of diabetes, Indian council of medicinal research (ICMR) has considered this as one of the refractory disease. A number of lifestyle factors are known to be important for the development of Type II diabetes including obesity, lack of physical activity, poor diet, stress and urbanization. Type II DM is associated predominantly with a family history of diabetes. Women seem to be at a greater risk due to the gestational diabetes mellitus.\(^13\) Type II diabetes is attributed due to abnormality in glucose receptor in \(\beta\) cells so that they respond at higher glucose concentration, reduced sensitivity of peripheral tissue to insulin, reduction in insulin receptors (IRs), down regulation of IR and excess of hyperglycemic hormones.\(^14\) Patients with Type II DM often suffer from dyslipidemia in the form of high plasma triglycerides and low HDL cholesterol levels, both considered risk factors for coronary heart diseases.\(^15\) The disease is often associated with obesity, dyslipidemia and hypertension leading to cardiovascular risks.\(^16\) Type II DM occurs in older as well as in younger people due to the high caloric intake, sedentary lifestyles and lack of exercise.

Simple lifestyle measures have been shown to be effective in preventing or delaying the onset of Type II diabetes. To prevent Type II diabetes and its
complications, people should achieve and maintain healthy body weight. A proper diet and exercise are the foundations of diabetic care with a greater amount of exercise yielding better results.\textsuperscript{17} Aerobic exercise leads to a decrease in glycosilated hemoglobin (HbA1C) and improved insulin sensitivity.\textsuperscript{17} Resistance training is also useful and the combination of both types of exercise may be most effective. A diabetic diet that promotes weight loss is important.\textsuperscript{18} While the best diet type to achieve this is controversial. A low glycemic index diet has been found to improve blood sugar control. Culturally appropriate education may help people with Type II diabetes to control their blood sugar levels, for up to six months at least. If changes in lifestyle, in those with mild diabetes, has not resulted in improved blood sugars within six weeks oral medications should then be considered. Monotherapy is the first step of treating diabetes mellitus. However if the disease is advanced, combination therapy is recommended. Insulin is workhorse in late stage disorders.

Following is a brief review focusing on oral antidiabetic/hyperglycemic agents, their mechanism of action and the effects.

Oral antidiabetic/hypoglycemic agents can be classified into the following six classes.

A) Sulfonylureas (Insulin Secretagogues)

B) Meglitinides/Metaglinides (Insulin Secretagogues)

C) Biguanides (Insulin Sensitzizers)

D) Thiazolidinediones (Insulin Sensitzizers, Peroxisome Proliferator Activated Receptor Gamma Agonists (PPAR γ))

E) α-Glucosidase Inhibitors (Carbohydrate Modulators)

F) DPP-IV Inhibitors (Sitagliptin)

Each class displays unique pharmacological properties. Figure 1 illustrates the likely sites of action of the currently available groups of oral hypoglycemic agents (OHAs). It emphasizes the importance of not just the pancreas and peripheral tissues (muscle and fat) in the pathogenesis of diabetes, but also the liver, gastrointestinal tract and indeed fat tissues, in the abdominal cavity (visceral fat). When deciding
which OHA or OHAs to be used, full consideration should be given to which sites of action are the targets for treatment.

**Fig 1: Mechanism of action of the oral hypoglycemic agents**

A) Sulfonylureas (Insulin Secretagogues)

Sulfonylureas work by stimulating insulin release from the beta cells of the pancreas and may slightly improve insulin resistance in peripheral target tissues (muscle, fat). On average, this class reduces glycosylated hemoglobin A1c (HbA1c) levels and fasting plasma glucose (FPG) concentrations. SUR-1 binding closes $K_{ATP}$ channels lowering the depolarization threshold of the membrane. Depolarization opens $Ca^{2+}$ channels increasing intracellular $Ca^{2+}$ levels and facilitates insulin release.

The sulfonylurea derivatives have been classified as first generation drugs and second generation drugs. The first generation drugs include glyburide, (1.1) glipizide, (1.2) tolbuamide, (1.3) chloropropamide, (1.4) and tolazamide, (1.5). Second generation drugs like gliclazide (1.6) is mostly used. It is found that the second generation drugs are more potent.
Hypoglycemia and weight gain are the two most frequent side effects of these drugs. Hypoglycemia is especially a problem with the first-generation agents because of their long half-lives.\textsuperscript{23}

**B) Meglitinides/Metaglinides (Insulin Secretagogues)**

The currently used metaglinides are repaglinide (1.7) and nateglinide (1.8) (a phenylalanine derivative). They are also insulin secretagogues. They bind to the ATP sensitive potassium ion channels on $\beta$-cells, but at a different site to sulfonylureas.\textsuperscript{24} However, they also need active $\beta$-cells to work.

Hypoglycemia and weight gain are the major side effects associated with these drugs.

**C) Biguanides (Insulin Sensitizers)**

The biguanides are insulinotropic agents and do not normally cause hypoglycemia. Several biguanides have been reported in the 1950s. These include metformin, (1.9) phenoformin, (1.10) and buformin. (1.11)\textsuperscript{25} Metformin is the most commonly prescribed oral agent.\textsuperscript{26} Although the molecular mechanisms of metformin are not completely understood. However, many studies have indicated that its primary effect is to inhibit the liver's production of glucose and to stimulate the process of transporting glucose into muscle, a process which requires insulin. Thus it only works when there is insulin around, for example in Type II diabetes and not in Type I diabetes, which is characterized by total insulin dependency.\textsuperscript{27} Metformin is the only
antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes.

Up to 30% of patients develop gastrointestinal complaints. Bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints with the metformin.\textsuperscript{28}

D) Thiazolidinediones (Insulin Sensitizers, Peroxisome Proliferator Activated Receptor Gamma Agonists (PPAR\textsubscript{\gamma}))

Thiazolidinediones (TZDs) enhance insulin action in muscle, fat and other tissues and are known as insulin sensitizers. TZDs act by activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptor with greatest specificity for PPAR\textsubscript{\gamma} (gamma).\textsuperscript{29} The nuclear receptor PPAR\textsubscript{\gamma} is activated by endogenous lipids and prostaglandins and modulates the transcription of a broad program of genes. The action of these agents requires the presence of insulin. TZDs may improve $\beta$ cell function by reducing free fatty acids. TZDs also increase the synthesis of certain proteins involved in fat and glucose metabolism, which reduces levels of certain types of lipids, and circulating free fatty acids.\textsuperscript{29} They do not directly affect insulin secretion, so they are not associated with hypoglycemia.

TZDs are effective in reducing glycosylated hemoglobin (HbA1c). TZDs generally decrease triglycerides and increase high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).\textsuperscript{30} The first TZD, troglitazone was approved in 1997 but was pulled from the market due to hepatotoxicity. Currently rosiglitazone and pioglitazone are the only TZDs available in the market.

TZDs scaffold has been found as core nucleus in various antidiabetic drugs of this class \textit{viz.}, pioglitazone, (1.13)\textsuperscript{31} rosiglitazone, (1.12)\textsuperscript{32} KRP-297,\textsuperscript{33} lobiglitazone (1.14)\textsuperscript{34} and DRF-2189 (1.15)\textsuperscript{35}
The major side effects of TZDs are associated with edema and weight gain. The weight gain may be due to a change in fat distribution with an increase in subcutaneous adipose fat and a decrease in visceral fat. It could also be due to an increase in plasma volume (i.e. edema).

**E) α-Glucosidase Inhibitors (Carbohydrate Modulators)**

α-Glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates specifically alpha glucosidase enzymes in the brush border of the small intestine. This inhibits the cleaving of di and oligosaccharides to monosaccharides such as glucose prior to absorption. This delays the absorption of glucose and alters the release of glucose dependent intestinal hormones. Acrabose, (1.18) Miglitol, (1.16) and Voglibases, (1.17) have been extensively studied for their hypoglycemic activity as α-glucosidase Inhibitors. Alpha-glucosidase inhibitors are used to establish greater glycemic control over hyperglycemia in diabetes mellitus Type II, particularly with regard to postprandial hyperglycemia. They may be used as monotherapy in conjunction with an appropriate diabetic diet and exercise, or they may be used in conjunction with other anti-diabetic drugs.
Gastrointestinal disturbances in the form of flatulence, abdominal pain and to lesser extent diarrhea are the adverse effects associated with the use of \( \alpha \)-Glucosidase Inhibitors.\(^{40}\)

**F) DPP-IV Inhibitors (Sitagliptin)**

Sitagliptin was the first DPP-IV inhibitor approved in 2006. Sitagliptin (1.19) significantly lowers blood glucose and HbA1c when used as monotherapy but these effects were not as potent as metformin.\(^{41}\) An advantage of exenatide or sitagliptin is reduction in HbA1c without weight gain commonly seen with insulin, sulfonylureas and TZD. Linagliptin (1.20) was recently approved by the FDA for treatment of type II diabetes.\(^{42}\)

The most common side effects of sitagliptin are gastrointestinal complaints and nasopharyngitis.

Current treatments, however, do not satisfactorily control glucose level, which is the primary purpose, nor do they prevent complications. If treatment with one drug fails to achieve this goal, i.e. monotherapy does not achieve glycemic levels goal then combination therapy is used.\(^{43}\)
Emerging Antidiabetic Targets

Aim of oral antidiabetic agents are not only to reduce the weight of obese patients and improve glycemic control but also to reduce the risk of cardiovascular diseases, reduce adverse effects and overcome compliances. The specific medications used in patients with type II diabetes are determined by clinical judgment about the likely balance between β-cell impairment and insulin resistance. Preventing hypoglycemia and improving compliance through less frequent dosing are the other important targets. Considering these targets the menu of medications has expanded greatly over the last decade. Following is a literature survey on emerging antidiabetic targets.

These emerging antidiabetic targets are roughly divided into four general areas based upon primary type of beneficial effects.\(^{44}\)

a. Modulators of Carbohydrate Metabolism/Disposition

b. Fat Cell and Lipid Level Modulators

c. Modulators with pleiotropic effects on carbohydrates, lipid or protein metabolism

d. Modulators of Insulin Sensitivity and Inflammation

a. Modulators of Carbohydrate Metabolism/Disposition

In non-diabetics, glucose generation and glucose disposal are tightly regulated and balanced to maintain euglycemia. Congenital and/or acquired defects in the enzymes mediating energy metabolism or any of the regulatory elements that control energy metabolism can yield worsening glycemic control. There are some enzymes which are responsible for this disposition of the carbohydrate metabolism. These includes the Glucokinase (GK) Activators,\(^{45}\) Fructose-1,6-Bisphosphatase (FBP) Inhibitors,\(^{46}\) Glycogen Phosphorylase (GP) Inhibitors,\(^{47}\) Sodium/Glucose Co-Transporter (SGLT) Inhibitors\(^{48}\) and Activators of AMP-Activated Protein Kinase (AMPK).\(^{49}\) These are the enzymes which are responsible for modulating the carbohydrate metabolism due to which glycemic control can be maintained or regulated.
Recently several carbohydrate metabolism modulators are developed and are at preclinical stage.

The researchers at Roche have first time reported an orally active GKA with the phenylacetamide Ro-28–167539 (1.21),\textsuperscript{50} which works through an allosteric increase in maximum velocity (Vmax). They also report a small molecule (1.22) that was found to directly activate AMPK.\textsuperscript{51}

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1.21 \quad 1.22
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b. Fat Cell and Lipid Level Modulators

Adipose tissue houses the long-term reservoir of metabolic energy which is largely stored as triacylglycerides within adipocytes. This energy source can be mobilized by a variety of factors including as a response to stimulation by the adrenergic system. At times of perceived danger, adrenaline is released which prepares many tissues for rapid energy utilization (i.e. generally increased glucose production). Therefore the modulators of fat cell and lipid level are important for the regulation of glucose level. There are four types of modulators which are Beta 3-Adrenergic Receptor (b3-AR) Agonists,\textsuperscript{52} Hormone Sensitive Lipase (HSL) Inhibitors,\textsuperscript{53} Adipocyte Fatty Acid Binding Protein (aFABP) Inhibitors\textsuperscript{54} and GPR40 (Free Fatty Acid Receptor 1 (FFAR1)) Ligands.\textsuperscript{55} Bristol-Myers Squibb reported a series of diphenyl azole inhibitors of aFABP (1.24).\textsuperscript{56} Recently they also reported an impressive broad scope preclinical validation of efficacy for (1.23)\textsuperscript{54a} using mouse models of DM-II and cardiovascular disease. (1.23) showed increased insulin sensitivity but not increased insulin secretion in diet-induced obese mice.
c. Modulators with pleiotropic effects on carbohydrates, lipid or protein metabolism

This class includes, Retinoic Acid X Receptor (RXR) Modulators, Liver X Receptor (LXR) Modulators, Farnesoid X Receptor (FXR) Modulators, Pan-Agonists, Directed Agonists, Selective Peroxisome Proliferator-Activated Receptor (PPAR) Modulators (SPPARM), Glucocorticoid Receptor (GR) Antagonists, 11Beta-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1) Inhibitors and Ghrelin Analogs and Growth Hormone Secretagogue Receptor (GHS-R) Ligands. RXR modulators, with the thiazolidinedione moiety core structure (1.25) designed and synthesized by Johnson and Johnson.

A new Thiazolidinedione (TZD), netoglitazone (1.26) was examined as a PPAR α/β/γ pan agonist by Upton et al. on plasma insulin, glucose and fatty acid concentrations and insulin sensitivity in obese fatty zucker rats.

d. Modulators of Insulin Sensitivity and Inflammation

This class has been divided in to subclasses, Insulin Receptor Tyrosine Kinase (IRTK) and Insulin Mimetics, Protein Tyrosine Phosphatase 1β (PTP1β) Inhibitors, Glycogen Synthase Kinase-3 (GSK3β) Inhibitors and Inhibitors of Kappa β Kinase (IKKβ).
Murata et al.\textsuperscript{69} (Bayer Yakuhin Ltd) have described synthesis of compounds with a pyridine core structure as selective IKK inhibitors (1.27, 1.28). Medicinal chemistry research has generated a very potent series of GSK3 inhibitors with pyrimidine and pyrazine-based core structures. Examples such as (1.29)\textsuperscript{70} have nanomolar IC50 values for inhibition of GSK3284 and demonstrated hypoglycemic activity in db/db and ZDF mice (25% reduction in glucose at 30 mg/kg in db/db) and improved glucose disposal.

![Chemical structures](attachment://1.27.png) ![Chemical structures](attachment://1.28.png) ![Chemical structures](attachment://1.29.png)

However, the evaluations of emerging targets require the interpretation of all the available data, but particularly important is validations of in vivo efficacy at the preclinical or clinical level. This data set must be interpreted with consideration of the expected activity profile for the target.

From the above emerging targets some targets for which the clinical prospects are favorable. Still several emerging targets would have to be considered problematic due to known liabilities and/or unproven beneficial effects.

From the above reports it seems that, there is everlasting scope for the synthesis of newer therapeutic agents for type II diabetes. The SAR studies show that some time minor change in the heterocyclic nuclei influences the pharmacological profile of the parent nucleus and enhances its activity. Therefore recently considerable efforts have been directed towards the syntheses of new drug molecules for the treatment of Type II diabetes by introducing alternative bioactive heterocyclic moieties on the molecular frames of the existing clinically used antidiabetic agents.

An enormous amount of research, directed on synthesizing new molecular frames having pharmacologically active heterocycles such as thiazoles, 4-thiazolidinones, pyrazolines/pyrazoles, isoxazolines/isoxazoles, pyrimidines etc. has been carried with hope to obtain compounds with enhanced hypoglycemic activities
and to explore them as future medicaments. Following is the brief account of the bio applications of these heterocycles.

Thiazoles have played an important role in the field of medicinal chemistry. There are several hypoglycemic agents having thiazole nucleus as active pharmacophore shows antidiabetic activity. The researchers of Glaxo Smith Kline have reported thiazole-phenyl (i.e. biaryl) compound (1.30) with propanoic acid segments.\(^5\) Which is GPR40 antagonists and would be promising as pancreas-directed anti-diabetic agents that prevent lipotoxicity. Agonists may be useful as insulin secretagogues. A large number of thiazole derivatives have received considerable attention as potential anti-inflammatory, anticonvulsant, anti tubercular activities.\(^7\) Famotidine (1.31) and Nizatidine (1.32) are Thiazole derivatives used as antiulcerative agents.\(^7\) Tiamine, (1.33) Vitamin B1 is composed of thiazole nucleus.

Pyrazoline/pyrazole has occupied a unique place due to wide spectrum of pharmacological activities. Numerous pyrazoline/pyrazole derivatives have been found to possess effective antidiabetic, antifungal, antibacterial, antidepressant anticonvulsant, antitumour, analgesic etc activities.\(^7\) Pyrazole is an important core nucleus of various drugs viz. celecoxib, (1.34) zoniproide, (1.35) and PNU-32945 (1.36). These drugs act as COX-2 inhibitors sodium hydrogen ion exchanger inhibitors and HIV reverse transcriptase inhibitors.\(^7\) Pyrazoles are also emerged as potential antihyperglycemic agents. SAH 57-749 (1.37), a pyrazole derivative has shown antidiabetic activity.\(^7\)
Isoxazoles/isoxazolines are well explored class of compounds, used in the curative treatment of some of the diseases. Isoxazoline derivatives have received considerable attention as potential antimicrobial and antitubercular agents.\textsuperscript{76} The isoxazoles derivatives like valdecoxib (1.38), glisoxepid (1.39) and sulfamethaxazole (1.40) possess significant activity and are used in the treatment of inflammation, diabetes and bacterial infections.\textsuperscript{77}

Pyrimidines are the privileged scaffold and show promising biological activities. Numerous pyrimidine derivatives have been found to possess effective antiprotozoal, coccidiostat, antibacterial, antifungal, antihypertensive and antiviral.\textsuperscript{78} Lobeglitazone, (1.41) Bacimethin (1.42) and Sulfadimide (1.43) are having pyrimidine moieties and display antidiabetic, antibacterial and antibiotic activities respectively.\textsuperscript{79} Some pyrimidines are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia.
In recent years, thiazolidinone and its derivatives are become very important heterocyclic compounds and widely studied for their synthesis and biological activities. Some of the thiazolidinones are found to possess interesting biological activities such as anticancer, antimalarial, tuberculostatic, antihistaminic, anticonvulsant, antibacterial and antiarrhythmic etc. Etozolin, (1.44) hexythiazox (1.45) and lestostenine (1.46) are thiazolidinones derivatives and are known as diuretic, acracidal and nucolytic agents respectively.

Thiazolidinediones (TZDs) have been the subject of extensive research because of their deep involvement in the regulation of different physiological processes. Type II diabetes mellitus (Type II DM) has been revolutionized with the advent of 2, 4-thiazolidinedione class of molecule. 2, 4-Thiazolidinedione scaffold is concomitant with various antidiabetic drugs viz. ciglitazone, (1.47) englitazone (1.48) and netoglitzazone (1.49). These are highly active aldose reductase inhibitors, which possess a prospective for the treatment of diabetic complications.
Modification of the 2,4-thiazolidinedione ring leads to various kinds of pharmacological activities. Recently more efforts are being directed towards the synthesis of newer analogs of 2,4-thiazolidinediones by introducing bioactive heteryl moieties for obtaining the drugs to overcome the diabetic complications associated with Type II diabetes.

Considering the biological and pharmaceutical significance shown by the above referred heteryl nuclei and knowing the enhancement in bioactivities of the parent ring system on incorporating other heteryl pharmacophores here it was thought worthwhile to undertake the syntheses of new bioactive heterocycles with hope to obtain molecules with high efficacy and less side effects by following cost effective synthetic routes.

Keeping this aspect in mind, the synthetic work for obtaining new biodynamic heterocycles and their precursors/intermediates has been carried. For obtaining the required precursors/intermediates and the desired products/molecules, various successful attempts have also been made to develop modified convenient synthetic routes for getting the products rapidly and with the high yields.

Hence, the present work entitled, “Syntheses of Newer Therapeutic Agents for Diabetes Mellitus” was undertaken. The details of the synthetic work, characterizations of the intermediates and the desired products and the biological assay of some of the newly synthesized molecules have been presented in the forthcoming six Chapters of this thesis.
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