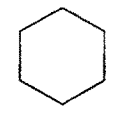
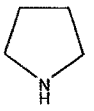
CHAPTER 1

INTRODUCTION

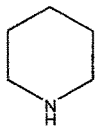
Chemistry of heterocyclic compounds is the most extensively explored branch of organic chemistry. The cyclic organic compounds have been categorized into homocyclic and heterocyclic compounds, classification being based upon the atoms constituting the ring. A *homocyclic* compound comprising of a ring formed by carbon atoms is known as *carbocyclic* compound. But if one or more hetero atoms are present as a part of the carbocyclic ring system then it is known as *heterocyclic* compound. These heteroatoms are usually nitrogen, oxygen or sulfur, but there are reports of other heteroatoms being present in the ring. The size of the ring may vary depending on the charge and stereochemistry of the heteroatom [1, 2].



cyclohexane



pyrrolidine

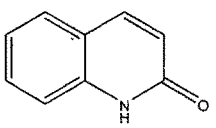


piperidine

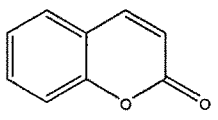
furan

thiophene

Some variants of these heterocyclic compounds such as quinolones, coumarin, synthesized by fusion of benzene with the heterocyclic ring system gives rise to a new class of heterocyclic compounds known benzoderivaties.



quinolin-2(1*H*)-one
(quinolinone)



2*H*-chromen-2-one
(coumarin)

These compounds are very useful in healthcare industry. Most of these heterocyclic compounds are either biosynthesized by plants or animals or are prepared synthetically. Three of the twenty amino acids, most of the essential vitamins are

examples of naturally occurring heterocyclic compounds. These compounds are also major components in nucleotides constituting DNA, RNA, chlorophyll, heme and others.

Heterocyclic compounds have major implications in various fields such as biochemistry, medicinal chemistry, material science and pharmaceuticals. Quinoxalines, triazoles, isooxazoles are regarded as important chemotherapeutic agents, and have clinical applications. Many pharmaceutical drugs as well as agrochemical products contain atleast one heterocyclic unit.

The field of heterocyclic chemistry has advanced substantially due the enormous research work done in this field. Heterocycles are known to be present in various biomolecules important for life, many vitamins, natural products, drugs and biologically active molecules such as antidiabetic compounds, antimalarial, antitumor, antifungal and others. Thus heterocyclic systems lay the foundation of new chemical entities with wide range of application due to their electronic, mechanical or biological properties.

Present research work is based on rationale of synthesis and applications of heterocyclic compounds, from medicinal chemistry point of view, as anti-diabetic and anti-cancer agents.

With the advances in industrialization, technology and improvement in health industry, although the quality of life and life expectancy of an individual has increased on one hand, it has resulted in amplification in the number of cases of "lifestyle diseases". Diabetes and cancer are two of the prominent lifestyle related health disorders and a major burden to global health care. Both, disorders have deleterious effect on human health worldwide and can often lead to medical complications. If left unattended or in advance stages, these diseases prove to be fatal to human life.

According to the definition given by American Diabetes Association, diabetes mellitus, also referred to as diabetes, is categorized as a group of metabolic diseases which have been symptomatically characterized by hyperglycemia or high blood sugar, caused due to lack of insulin secretion, insulin action or both [3]. Due to rampant increase in the number of cases of diabetes mellitus (DM), it has been reported that DM will reach epidemic proportions by the year 2025 [4, 5]. The National Diabetes Data Group (NDDG) had proposed the first classification of diabetes in 1979 [6]. After various revisions and modifications, the most recent classification has been published by WHO in 2006 [7]. The following is the classification for diabetes mellitus:

- Type 1 diabetes: also called as juvenile-onset diabetes (formerly called as Insulin-dependent diabetes mellitus) and although the mechanism is not entirely known, it is reported to be mostly caused by the auto-immune response against pancreatic β-cells. This form of diseases usually affects children or young adults.
- Type 2 diabetes: also termed as non-insulin dependent diabetes or adult-onset diabetes and is responsible for major cases of diabetes which are reported. The

patients generally exhibit insulin resistance and insulin deficiency and the diagnosis is possible at any age.

- Gestational diabetes (GDM): this form of diabetes is mostly prevalent during pregnancy. Such women exhibit high blood glucose and the symptoms generally disappear after pregnancy.
- Other types

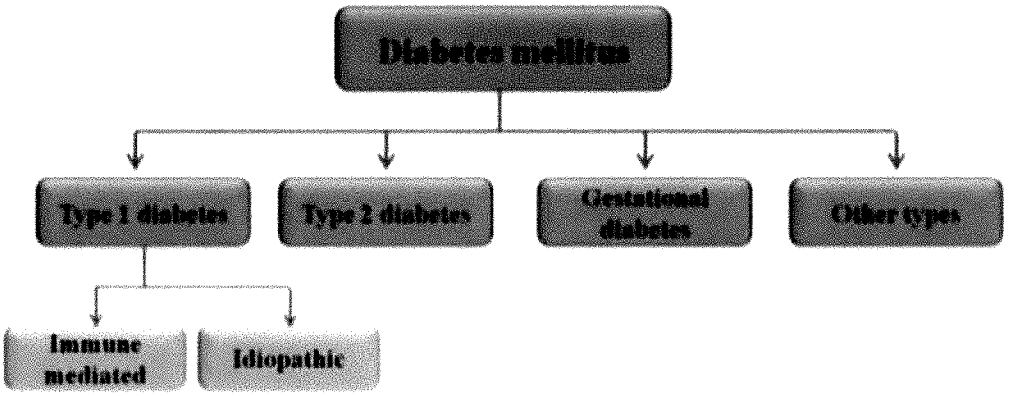


Figure 1.1: Classification of Diabetes mellitus [8]

The trends in most prevalent diseases in the human population were studied by experts in their respective fields and a comprehensive report was recently published in *The Lancet*. According to this report, there has been a significant increase in the number of deaths caused due to Diabetes in 2010 as compared to the data available in 1990 [9]. As can be seen in Figure 2, the rank of Diabetes soared from 15^{th} (in 1990) to 9^{th} (in 2010) in the category of diseases or risk factors responsible for largest number of deaths per year. Due to the alarming rate at which the percentage of deaths has increased because of Diabetes, it has become essential to take necessary measures in order to cure or prevent the disease.

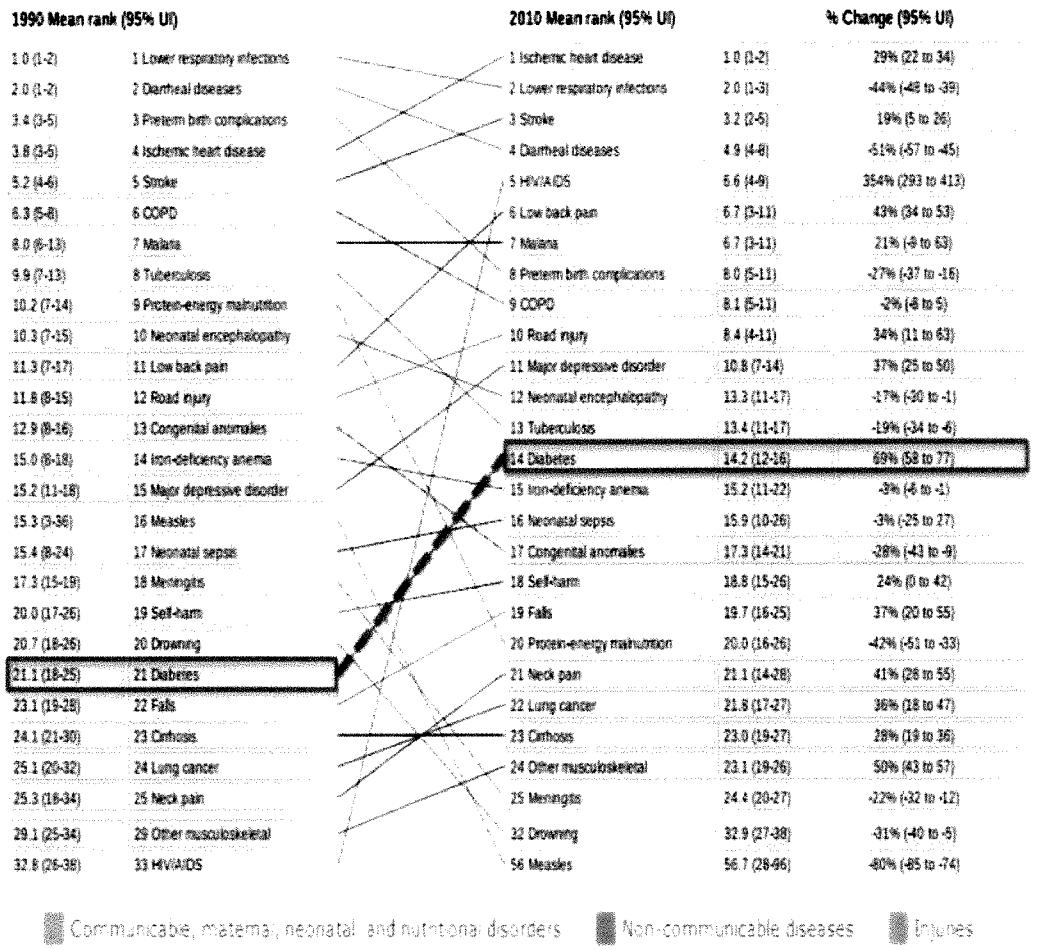


Figure 1.2: Arrow diagram depicting increase in the rank of Diabetes amongst other diseases and risk factors

Important factors responsible for (hallmarks of) type 2 diabetes are [10]:

(i) body-cell resistance to insulin (insulin resistance)

(ii) increased hepatic glucose production (e.g. from glycogen degradation)

(iii) lowered insulin mediated glucose transport into muscles and adipose tissues

(iv) impaired β-cell function leading to loss of early phase of insulin release in response to hyperglycemic stimuli (β-cell dysfunction) [11]

Insulin plays a major role in diabetes. It was first isolated in 1922 by Banting and Best and is known to regulate glucose homeostasis and other physiological functions [12]. Insulin is a polypeptide hormone secreted by the β-cells of Islet of Langerhans of pancreas. It is secreted as proinsulin (inactive form), which further processed by proteases in Golgi apparatus to form insulin. In biological systems uptake of insulin happens with the help of receptors present on fat or muscle cells of the body. This polypeptide hormone consists of 51 amino acid residues, having molecular weight of 5808Da, and the chains A and B are cross-linked to each other by disulphide bridges [13-15]. Insulin is able to undergo dimerization by forming hydrogen bonds between the ends of two B-chains [16]. Insulin is usually stored in the body in hexameric form, wherein three dimers come together in presence of zinc ions. Figure 3 illustrates the secondary structure of human insulin in dimeric and hexameric forms. The Physiological functions of insulin include glucose uptake into liver, muscles and fat cells. Thus insulin is an anabolic hormone promoting the synthesis of glycogen, triglycerides and proteins by promoting glucose uptake into cells of tissues, and hence essential to regulate the level of glucose in the body. Studies have been done to synthesize analogues of insulin and their potency has been as compared to the wild-type human insulin [14]. In order to modify the ADME (Absorption, Distribution, Metabolism and Excretion) properties of these analogues, chemical modifications are made at the side chains of C-terminus or N-terminus amino acids.

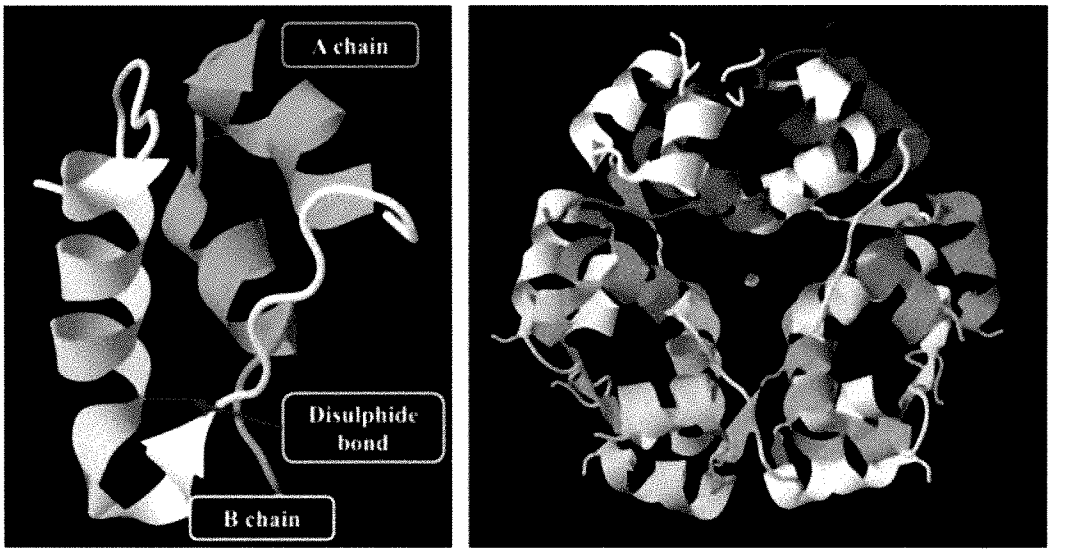


Figure 1.3: Crystal structure of a) monomeric form of human insulin and b) hexameric form of human insulin

Type 2 Diabetes Mellitus is usually caused due to the following defects: a) impaired insulin action in tissues such as skeletal muscles, liver and adipocytes b) defect in insulin secretion due to β-cell dysfunction and c) insulin resistance. Defects in insulin secretion i.e. either it is insufficiently produced or is ineffective on its target tissues, results in elevated blood glucose level or hyperglycemia [17]. The excess glucose in the blood subsequently spills over in urine, during diabetic condition (Greek: diabetes-siphon or running through; mellitus-sweet). Hence, there is "scarcity in plenty" as the body cells are starved of glucose despite its very high concentration in the blood. Deficiency of insulin thus results into chronic hyperglycemia, which in turn disrupts the carbohydrate, fat and protein metabolism. If the disease is left untreated, serious damage is caused to the heart, eyes, kidneys, blood vessels and nerves. Its symptoms include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (constant hunger), weight loss and blurred vision [3]. Insulin resistance is

mainly due to impaired insulin-mediated glucose clearance into target tissues. Insulin resistance in non-diabetic as well as type 2 diabetics is associated with a cluster of metabolic abnormalities, which are collectively termed as the metabolic syndrome [11]. Metabolic syndrome is associated with a markedly increased incidence of coronary, cerebral and peripheral artery disease [18]

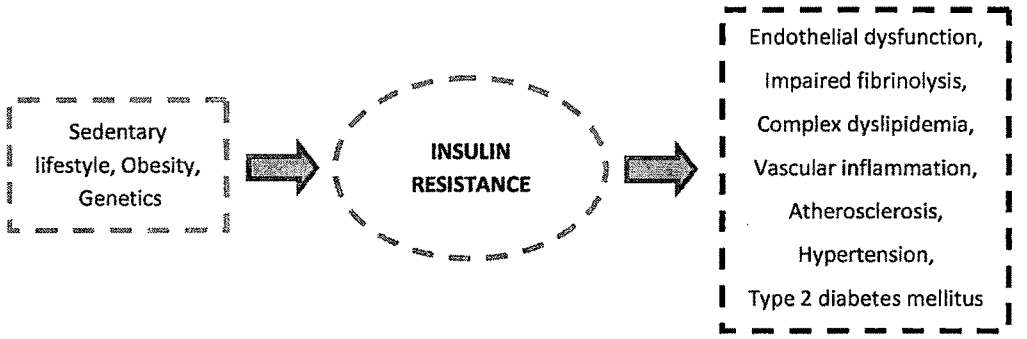


Figure 1.4: Insulin resistance and metabolic syndrome.

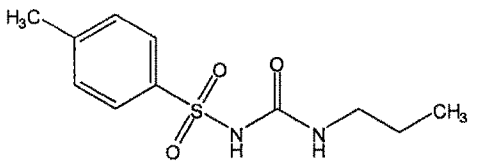
The World Health Organization recommends the oral glucose tolerance test (OGTT) while the fasting plasma glucose is the recommended method by the American Diabetes Association (ADA) for the diagnosis of diabetes [Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a WHO/IDF consultation **2006**]

Diagnostically, an individual is considered to be diabetic when

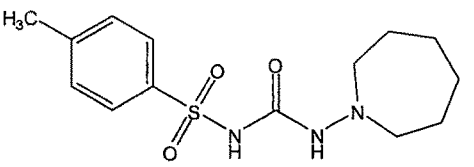
- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)
- Plasma glucose ≥ 11.1 mmol/l (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (Hb A1C) ≥ 6.5%

Hence, management of Type 2 Diabetes Mellitus can be achieved by controlling hyperglycemia thereby significantly reducing the risk of microvascular and macrovascular complications. At an early stage diet control and exercise helps to achieve normal body weight in turn reducing insulin resistance [19]. However, in most of the cases, dependence on exogenous insulin, drug intervention or both are required to control the blood glucose levels.

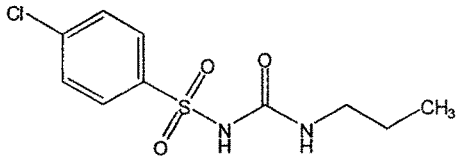
At present therapy for Type 2 Diabetes Mellitus involves various targets/approaches, which reduce hyperglycemia by enhancing insulin secretion by pancreatic β-cell. The first line therapy involves use of sulfonylurea insulin secretagogues [20-22], which acts on ATP dependent K^+ channels and sulfonylurea receptors. Sulfonylureas induce insulin secretion and suppress gluconeogenesis in the liver. The first generation sulfonylureas include tolbutamide, tolazamide, acetohexamide and chlorproamide. All have similar efficacy and require bulky hydrophores and acidic proton on sulphonylurea.



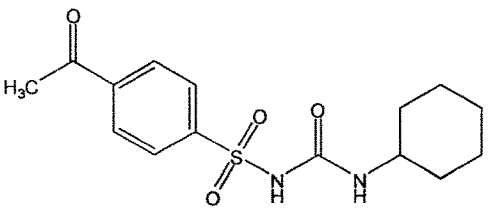
Tolbutamide



Tolazamide



Chlorpropamide



Acetohexamide

Figure 1.5: First generation Sulfonylureas.

Sulphonylureases operate by closing K^+ gate in absence of glucose, which in turn opens Ca^{+2} gate and allows Ca^{+2} influx thereby increases insulin secretion.

The second-generation agents have more rapid onset. Few examples of such drugs are glibenclamide (glyburide), glimepiride and glipizide. They act through different receptor but mechanism of action remains same. Among second generation sulphonylureases, Glimepiride acts longer for sustained insulin secretion. The major drawback of sulfonylureas is hypoglycemia and weight gain.

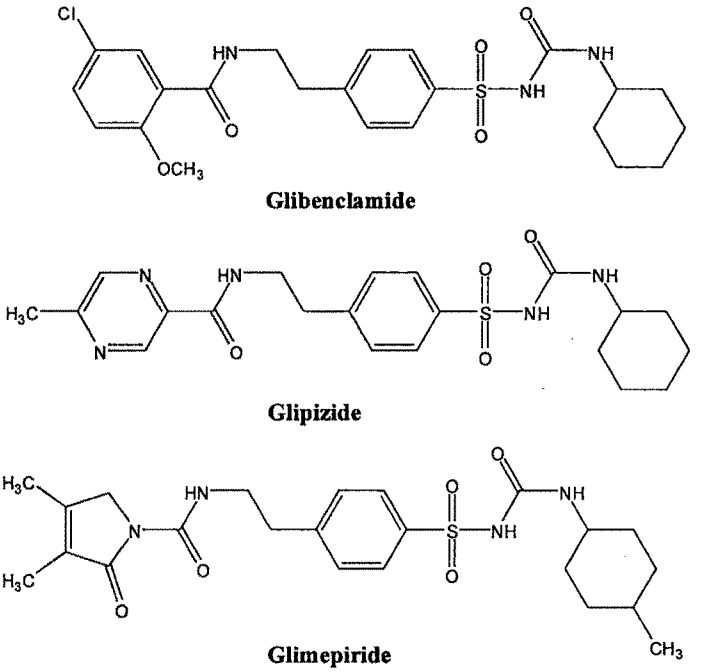
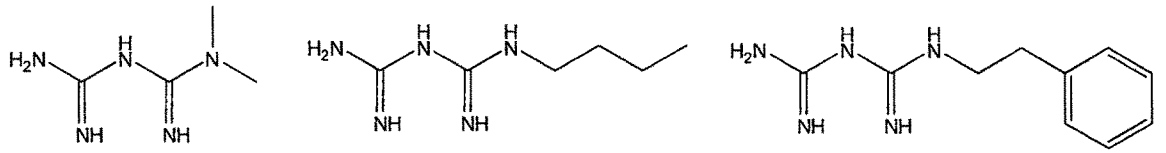


Figure 1.6: Second generation sulfonylureas

Biguanides induces their anti-hyperglycemic effect by inhibiting glucose synthesis in liver [21-23]. The exact mechanism of action for this class is still unknown. Some examples of biguanides are phenformin, buformin, metformin. Amongst these different biguanides, metformin is the most potent. Metformin helps the patients with NIDDM (non-insulin dependent diabetes mellitus) by decreasing basal hepatic glucose output, thus lowering fasting plasma glucose concentrations and in turn

improving insulin sensititvity [23]. If the metformin therapy is taken for prolonged duration it increases the blood lactate concentrations and reduction in plasma triglyceride concentrations.

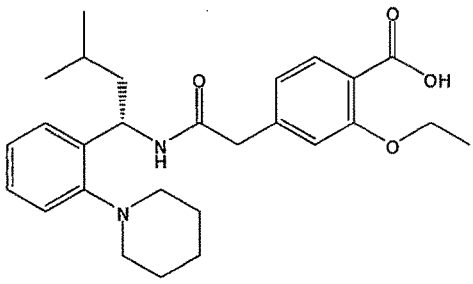
Some of the advantages of biguanides is that they are not protein bound and hence are not metabolized. They are rapidly excreted from the kidney and are highly bioavailable. Usually, they are used in monotherapy or in conjunction with sulfonylureas [23].



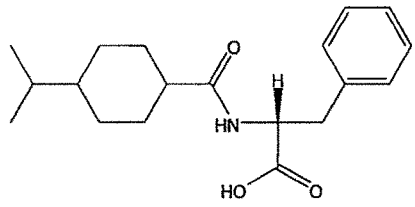
Metformin **Buformin** **Phenformin**

Figure 1.7: Anti-hyperglycemic biguanides.

Meglinitides analogues improve early-phase insulin secretion by binding to sulfonylurea receptor 1 on the pancreatic β-cell and closing the K^+ ATP channel but at a site different from that of sulfonylurea receptor e.g. nateglinide, repaglinide [21-24]. The advantage of meglinitides over other drugs available for diabetes is rapid stimulation of insulin secretion with low risk of hypoglycemia (since its action is confined to intermediate concentrations of glucose).



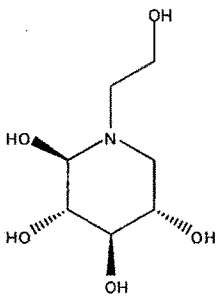
Nateglinide



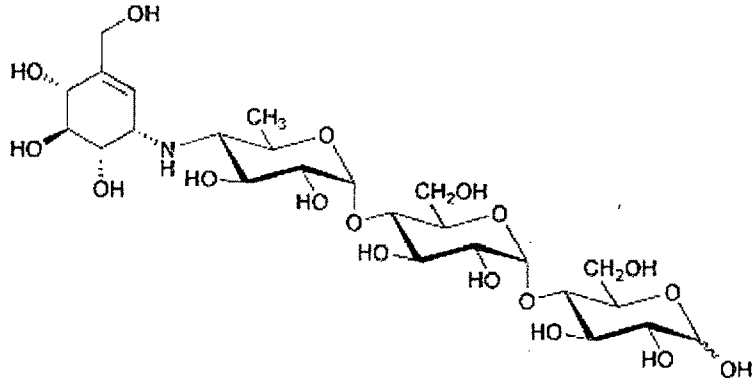
Repaglinide

Figure 1.8: Anti-diabetic meglinitides analogues.

α-glucosidase inhibitors inhibit absorption of complex sugars/glucose by interfering with the action of α-glucosidase present in the small intestinal brush border. Some examples of α-glucosidase are acarborse and miglitol. They are less potent than the sulfonylureas and exhibit side-effects which include abdominal bloating, diarrhea and flatulence [21-22]. These inhibitors significantly reduce postprandial glycemia and have excellent safety profile.



Miglitol



Acarbose

Figure 1.9: Potent α-glucosidase inhibitors.

Thiazolidinedione act as peroxisome proliferator activated receptor-γ (PPAR-γ) agonist which increases gene expression for insulin release, fatty acid oxidation and insulin sensitivity while decreasing gene expression for lipid production [20, 25-27]. Troglitazone was withdrawn from the market due to serious hepatotoxicity while rosiglitazone is the most potent thiazolidinedione [27].

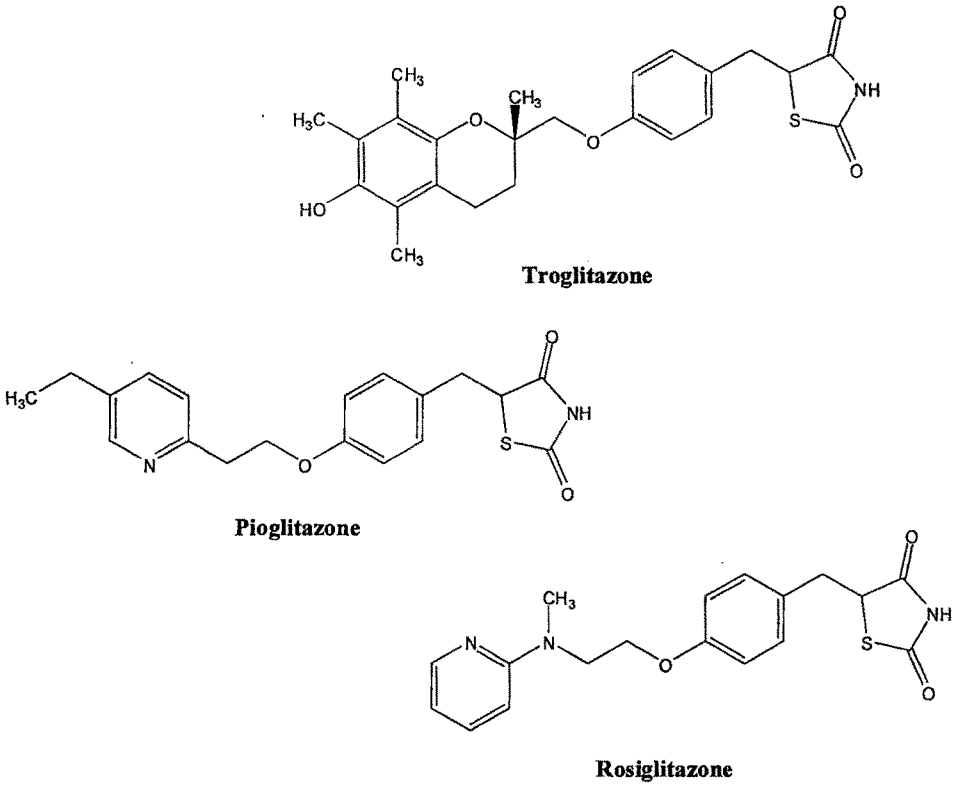


Figure 1.10: Thiazolidenediones as PPAR-γ agonist.

Insulin-secretagogues such as sulfonylureas, meglinides (e.g. repaglinide) both induce hypoglycemia. Metformin is the only anti-diabetic drug which is known to reduce the rate of any diabetes related endpoint. Although these drugs help in reducing hyperglycemia but are unable to maintain long term glycemic control thereby necessitating the use of combination drug therapies. In adverse cases, when all these medications fail, exogenous insulin is administered to control the blood glucose levels.

Various drug classes with their site and mechanism of action and side effects have been listed in Table 1.

Drug Class	Examples	Molecular target	Site of action (Primary tissue target)	Mechanism of Action	Side Effects
Sulfonylureas (SU)	Glypizide, Glymepiride	SU receptor 1/ ATP-K channel	Pancreatic β-cells	Stimulate insulin secretion	Hypoglycemia, weight gain
Biguanide	Metformin	Unknown	Liver, muscle	Inhibition of hepatic glucose output	Gastrointestinal disturbances, lactic acidosis
Meglitinides	Nateglinide, Repaglinide	SU receptor 1 (different binding site from SU)	Pancreatic β-cells	Stimulate insulin secretion	Hypoglycemia, weight gain.
α-glucosidase inhibitor	Acarbose, Miglitol	α-glucosidase	Intestine	Retards carbohydrate absorption in the gut.	Gastrointestinal disturbances
Thiazolidinediones	Pioglitazone, Rosiglitazone	PPAR-γ agonist, PPAR-γ/α dual agonist	Adipose, muscle, liver. Adipose, muscle, liver.	Increase insulin sensitivity, anti-inflamatory. Insulin sensitizing, anti-inflamatory, lipid lowering.	Weight gain, oedema, anemia.
GLP-1 analogues	Exenatide, Liraglutide	GLP-1 receptor	Pancreatic β-cells	Stimulate insulin secretion and β-cell differentiation.	Gastrointestinal disturbances, nausea and weight loss.
Insulin		Insulin receptor	Liver, muscle, adipose	Correct insulin deficiency	Hypoglycemia, weight gain.

Table 1.1: Classification of various insulin secretagogues targets for the treatment of type 2 diabetes mellitus.

Thus the major side effects of all these drug classes are hypoglycemia and weight gain. Hence, newer approaches involving glucose-dependent insulin secretion (GDIS) are needed for regulation of blood glucose to overcome these side effects.

In response to nutrient ingestion, peptide hormones called incretins are released by the gastrointestinal tract, which stimulates insulin secretion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones serving as enhancer of glucose dependent secretion of insulin from pancreatic β-cell. Both these hormones play an important role in glucose-dependent insulin secretion (GDIS). However, in patients with type 2 diabetes mellitus the incretin effect is either greatly impaired or completely lost [28].

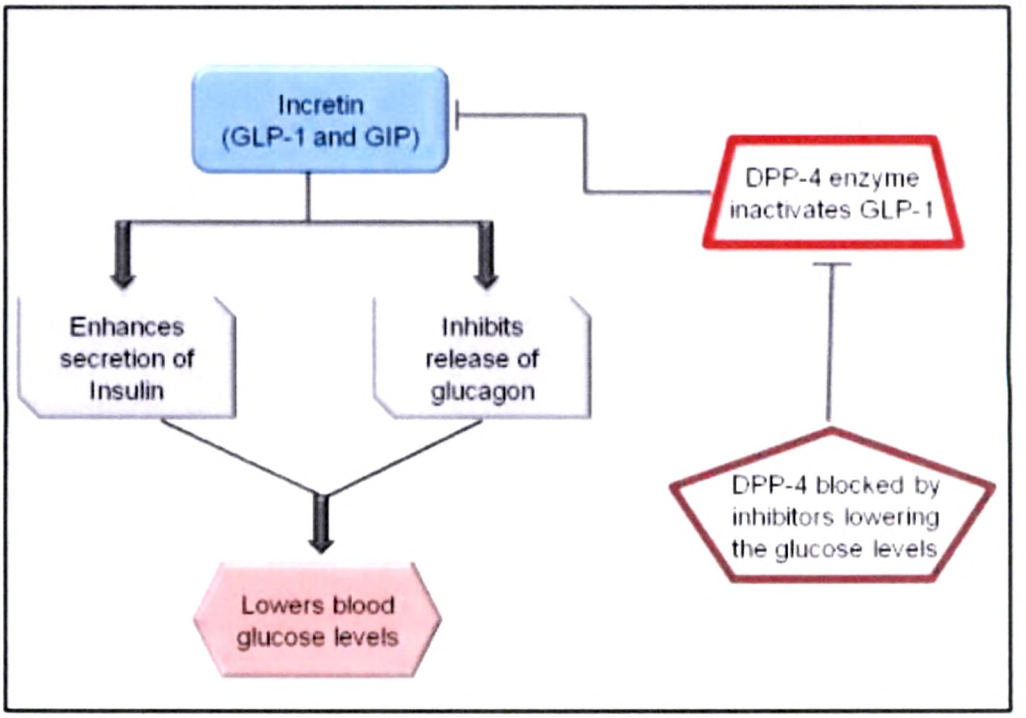


Figure 1.11: The biological role of incretin hormones and DPP-4 along with DPP-4 inhibitors.

GLP-1 is synthesized in the body as a result of tissue-specific processing of proglucagon gene. It is approximately 50% homologous to glucagon. GLP-1 is a 37 amino acid peptide hormone secreted by intestinal L-cells in response to food intake [29-31]. It is the most potent insulinotropic hormone known and has become a promising target for the treatment of type 2 diabetes. The active form of GLP-1 (7-36 residue) amide exhibits several biological effects [32-35] which includes

- glucose-induced stimulation of insulin biosynthesis and secretion
- inhibition of glucagon secretion or release
- slowing of gastric emptying
- reduce appetite by induction of satiety and
- induce pancreatic β-cell proliferation

These biological effects of GLP-1 is beneficial in controlling glucose homeostasis without the induction of hypoglycemia in the patients with type 2 diabetes [36]. The active form of GLP-1(7-36 residues) amide is enzymatically degraded, *in-vivo*, by a serine protease dipeptidyl peptidase IV (DPP-IV) thereby rendering it inactive as GLP-1(9-36 residues) amide [37, 38].

DPP-IV was first identified in 1966 [39]. It is also known as T-cell antigen CD26 (DPP-IV, EC 3.4.14.5). This serine exopeptidase is found in a variety of mammalian tissues and body fluids particularly on the surface of certain T-lymphocyte subsets, either membrane bound or as a soluble enzyme and has several biological roles which include its role as a peptidase responsible for the degradation of incretin hormones namely GLP-1 and GIP [40, 41]. It also contributes to extracellular matrix binding [42-43] and functions as adenosine deaminase (ADA) binding protein [44].

Previous studies have shown that GLP-1 remains strongly insulinotropic even though its secretion levels are reduced in the case of type 2 diabetics as compared to non-diabetic control [45-48]. Although GLP-1 has strong insulinotropic effects, but its poor pharmacokinetic profile leads to the development of GLP-1 agonists being resistant to DPP-IV. Peptides though clinically efficacious, have to be administered either subcutaneously or intravenously. Furthermore, peptides have drawbacks for clinical application due to their low bioavailability, proteolytic ability, rapid biliary excretion and short duration of action. This creates a scope for discovery of synthetic non-peptide derivatives. Consequently, inhibition of DPP-IV has gained importance as new treatment of type 2 diabetes.

If the action of DPP-IV is inhibited, then the half-life of endogenous GLP-1 increases, which has been reported to improve glucose excursion in diabetics. Consequently, inhibition of DPP-IV and prevention of incretin degradation can ultimately produce pharmacological effects especially in diabetes.

The potency and efficacy of GLP-1 can be enhanced upon inhibition of DPP-IV, thereby stimulating insulin secretion. Also, as GLP-1 is secreted on ingestion of food, hypoglycemia and exhaustion of pancreatic β-cells, common side effects of most anti-hyperglycemic drugs, is not observed. Thus small molecule DPP-IV inhibitors, which prolong the beneficial effects of endogenous GLP-1 as well as stabilize GIP, have been pursued as a new drug class.

Vildagliptin (NVP-LAF237), sitagliptin (MK-0431) and alogliptin are some of the most potent DPP-IV inhibitors in the market.

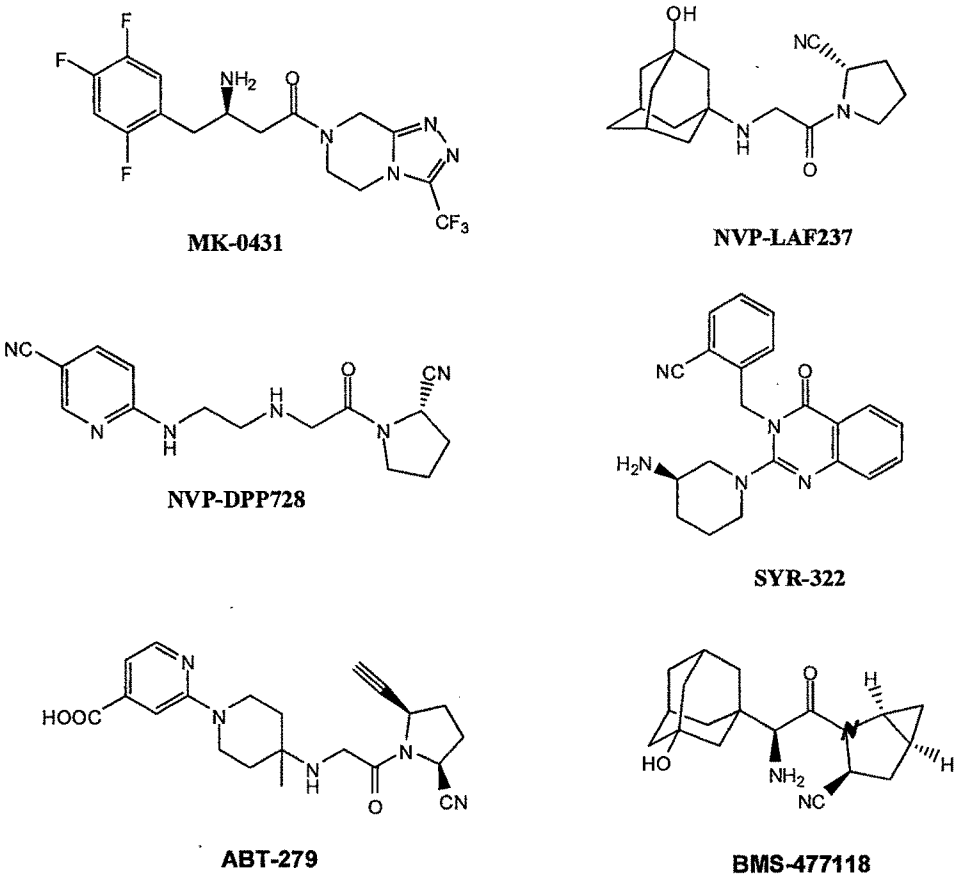


Figure 1.13: Some potent DPP-IV inhibitors.

Crystal structure of Viladagliptin bound to DPP-IV and the interacting residues of DPP-IV bound to Vildagliptin are shown in the Figure.

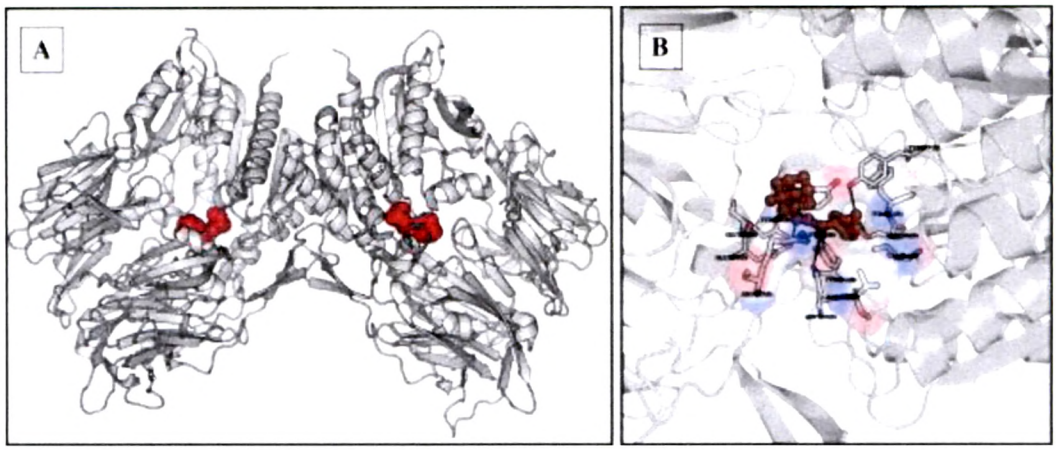
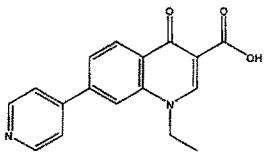


Figure 1.14: A) Crystal structure of DPP-IV with Viladagliptin bound to it and B) binding site and the interacting residues of DPP-IV bound to Vildagliptin.
Source: DOI: 10.2210/pdb3w2t/pdb

Most common feature in the design of all these inhibitors is the glycine moiety contributing the protonable nitrogen at the P2 site. A major part of the work presented in the following chapters is dedicated to design, syntheses and biological evaluation of small molecules containing glycine motif as DPP-IV inhibitors.

Another most dreaded disease with high mortality rate, ranked after the cardiovascular diseases, is Cancer. Uncontrolled cell division and proliferation are hallmark of cancer. Cancerous cells are bestowed with indefinite proliferative capability; this feat is achieved by sustaining growth signals and escaping growth signal suppressors. Cancer cells become immortal by resisting cell death by evading immune surveillance. After indefinite growth cancer cells induce angiogenesis which is followed by invasion and metastasis [49]. Once cancer cells metastasize the disease spreads and proves to be fatal. Thus early detection of cancer is desired for medical intervention. Since cancer cells grow in between normal tissues, synthesis of selective drug for cancer is the biggest challenge, for the drug should cause apoptosis of the cancerous cells and not affecting the surrounding normal tissues.

Various natural and synthetic molecules are reported to exhibit anti-cancer activity [50].



Rosoxacin

Quinolones have promising pharmacological potential due to its drug-like properties and structural similarity to some specific targets and hence have gained importance. Quinolones form the basic framework of many biologically active molecules exhibiting a broad spectrum of bioactivities, primarily, antimicrobial [51, 52], anti-cancer [53-55] and anti-viral [56, 57] activity. Since past five decades, 4(1*H*)-quinolone-3-carboxylic acid derivatives are widely used as antibiotics. Also, 4-(aminomethyl)quinolin-2(1*H*)-one derivatives and various quinolone linked with coumarins via ether linkage have been studied for their anti-microbial and analgesic activities [58, 59]. Various 2-quinolone derivatives have been reported as inducible nitric oxide synthase (iNOS) inhibitors and potent anti-platelet agents [60, 61].

Fluoroquinolones have been approved by WHO as a second line drug for the treatment of tuberculosis. The potential of fluroquinolones as first line drug due to its good pharmacological profile, absorption and penetration into host macrophages is still being investigated. Farnesyl transferase inhibitor, tipifarnib, a 3-aryl-2-quinolone derivative is in its clinical trial stage for the treatment of leukemia and breast cancer [62]. Joseph *et al.*, have reported 3-aryl-2-quinolone derivatives as anti-tumor agents [63].

In the last concluding part, synthesis of 4-aminomethyl-2(1*H*)-quinolone derivatives have been synthesized and their anti-cancer activity against lung cancer A549 cell line has been studied.

References

[1] Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd edn., Longman/Wiley, Harlow/Chichester, **1992**.

[2] Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th edn., Blackwell Science, Oxford, **2000**.

[3] American Diabetes Association. *Diabetes Care*, **2009**, *33*, S62.

[4] King, H., Aubert, R. E.; Herman, W. H. *Diabetes Care*, **1998**, *21*, 1414.

[5] Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. *Diabetes Care*, **2004**, *27*, 1047.

[6] Gavin III, J. R.; Alberti, K.G.M.M.; Davidson, M. B.; DeFronzo, R. A.; Drash, A.; Gabbe, S. G.; Genuth, S.; Harris, M. I.; Kahn, R.; Keen, H.; Knowler, W. C.; Lebovitz, H.; Maclaren, N. K.; Palmer, J. R.; Raskin, P.; Rizza, R. A.; Stern, M. R. *Diabetes Care*, **1997**, *20*, 1183.

[7] World Health Organization. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation.* Geneva: World Health Organization, **2006**, p. 1-50.

[8] Ahmad, S. and Maraschin, J. *Classification of Diabetes*, in *Diabetes*. **2013**, Springer New York. p. 12-19.

[9] Salomon, J. A.; Wang, H.; Freeman, M. K.; Vos, T.; Flaxman, A. D.; Lopez, A. D.; Murray, C. J. *Lancet*, **2012**, *380*, 2144.

[10] DeFronzo, R. A. *Med Clin North Am* **2004**, *88*, 787.

[11] Leahy, J. L. *Archives of Medical Research* **2005**, *36*, 197.

[12] Bell, G. I.; Pictet, R. L.; Rutter, W. J.; Cordell, B.; Tischer, E.; Goodman, H. M. *Nature*, **1980**, *284*, 26.

[13] Brange, J.; Langkjoer, L. *Pharm Biotechnol,* **1993**, *5*, 315.

[14] Favero-Retto, M.P.; Palmieri, L. C.; Souza, T. A. C. B.; Almeida, F. C. L.; Lima, L. M. T. R. *European Journal of Pharmaceutics and Biopharmaceutics*, **2013**, *85*, 1112.

[15] Ryle, A.P.; Sanger, F. *Biochem J*, **1954**, *58*(330th Meeting), p. v-vi.

[16] Timofeev, V. I.; Chuproy-Netochin, R. N.; Samigina, V. R.; Bezuglov, V. V.; Miroshnikovb K. A.; Kuranova, I. P. *Acta Crystallogr Sect F Struct Biol Cryst Commun,* **2010**, *66*, 259.

[17] Tripathy, D.; Chavez, A. O. *Curr Diab Rep*, **2010**, *10*, 184.

[18] Moller, D. E. *Nature* **2001**, *414*, 821.

[19] Stoffers, D. A.; Ferrer, J.; Clarke, W. L.; Habener, J. F. *Nature Genet* **1997**, *17*, 138.

[20] Philippe, J.; Raccah, D. *Int J Clin Pract* **2009**, *63*, 321.

[21] Krentz, A.J.; Bailey, C. J. *Drugs* **2005**, *653*, 385.

[22] Tahrani, A. A.; Piya, M. K.; Kennedy, A.; Barnett, A. H. *Pharmacol Ther* **2010**, *125*, 328.

[23] Bailey, C. J.; Turner, R. C. *N Engl J Med* **1996**, *334*, 574.

[24] Black, C.; Donnelly, P.; McIntyre, L.; Royle, P. L.; Shepherd, J. P.; Thomas, S. *Cochrane Database Syst Rev* **2007**, *2*, p. CD004654.

[25] Kahn, S. E.; Haffner, S. M.; Heise, M. A.; Herman, W. H.; Holman, R. R.; Jones, N. P.; Kravitz, B. G.; Lachin, J. M.; Colleen O'Neill, M.; Zinman, B.; Viberti, G. *N Engl J Med* **2006**, *355*, 2427.

[26] Nissen, S. E.; Wolski, K. *N Engl J Med* **2007**, *356*, 2457.

[27] Yki-Jarvinen, H. *N Engl J Med* **2004**, *351*, 1106.

[28] Holst, J. J.; Gromada, J. *Am J Physiol Endocrinol Metab,* **2004**, *287,* 199.

[29] Drucker, D. J. *Endocrinology* **2001**, *142*, 521.

[30] Holst, J. J.; Orskov, C.; Nielsen, O.V.; Schwartz, T. W. *FEBS Lett.* **1987**, *211*, 169.

[31] Ross, S. A.; Gulve, E. A.; Wang, M. *Chem Rev*, **2004**, *104*, 1255.

[32] Rachman, J.; Barrow, B. A.; Levy, J. C.; Turner, R. C. *Diabetologia* **1997**, *40*, 205.

[33] Nauck, M. A.; Wollschlager, D.; Werner, J.; Holst, J. J.; Orskov, C.; Creutzfeldt, W.; Willms, B. *Diabetologia* **1996**, *39*, 1546.

[34] Drucker, D. J. *Gastroenterology* **2002**, *122*, 531.

[35] Nauck, M. A.; Niedereichholz, U.; Ettler, R.; Holst, J. J.; Orskov, C.; Ritzel, R.; Schmiegel, W. H. *Am. J. Physiol.* **1997**, *273*, E981.

[36] Knudsen, L. B. *J. Med. Chem.* **2004**, *47*, 4128.

[37] Deacon, C. F.; Nauck, M. A.; Toft-Nielson, M.; Pridal, L.; Willms, B.; Holst, J. J. *Diabetes* **1995**, *44*, 1126.

[38] Kieffer, T. J.; McIntosh, C. H. S.; Pederson, T. A. *Endocrinology* **1995**, *136*, 3585.

[39] Hopsu-Havu, V. K.; Glenner, G. G. *Histochemie* **1966**, *7*, 197.

[40] Deacon, C. F.; Johnsen, A. H.; Holst, J. J. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 952.

[41] Mentlein, R.; Gallwitz, B.; Schmidt, W. E. *Eur. J. Biochem.* **1993**, *214*, 829.

[42] Bauvois, B. *Biochem. J.* **1988**, *252*, 723.

[43] Loster, K.; Zeilinger, K.; Schuppan, D.; Reutter, W. *Biochem. Biophys. Res. Commun.* **1995**, *217*, 341.

[44] Kameoka, J.; Tanaka, T.; Nojima, Y.; Schlossman, S. F.; Morimoto, C. *Science* **1993**, *261*, 466.

[45] Nauck, M. A.; Kleine, N.; Orskov, C.; Holst, J. J.;Willms, B.; Creutzfeldt, W. *Diabetologia* **1993**, *36*, 741.
[46] Toft-Nielson, M.; Madsbad, S.; Holst, J. J. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 3853.
[47] Toft-Nielson, M.; Madsbad, S.; Holst, J. J. *Diabetes* **1996**, *45*, 552.
[48] Vilsboll, T.; Krarup, T.; Deacon, C. F.; Madsbad, S.; Holst, J. J. *Diabetes* **2001**, *50*, 609.
[49] Hanahan, D.; Weinberg, R. A. *Cell* **2011**, *144*, 646.
[50] Dobson, R. A.; O'Connor, J. R.; Poulin, S. A.; Kundsin, R. B.; Smith, T. F.; Came, P. E. *Cell* **1980**, *18*, 738.
[51] Letafat, B.; Emami, S.; Mohammadhosseini, N.; Faramarzi, M. A.; Samadi, N.; Shafiee, A.; Foroumadi, A. *Chem. Pharm. Bull.* (Tokyo), **2007**, *55*, 894.
[52] Srivastava, B. K.; Solanki, M.; Mishra, B.; Soni, R.; Jayadev, S.; Valani, D.; Jain, M.; Patel, P. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1924.
[53] A. Ryckebusch, D. Garcin, A. Lansiaux, J. Goossens, B. Baldeyrou, R. Houssin, C. Bailly, J. Hénichart, *J. Med. Chem.* **2008**, *51*, 3617.
[54] Ferlin, M. G.; Chiarelotto, G.; Gasparotto, V.; Dalla Via, L.; Pezzi, V.; Barzon, L.; Palù, G.; Castagliuolo, I. *J. Med. Chem.* **2005**, *48*, 3417.
[55] Gasparotto, V.; Castagliuolo, I.; Chiarelotto, G.; Pezzi, V.; Montanaro, D.; Brun, P.; Palù, G.; Viola, G.; Ferlin, M. G. *J. Med. Chem.* **2006**, *49*, 1910.
[56] Tabarrini, O.; Stevens, M.; Cecchetti, V.; Sabatini, S.; Dell'Uomo, M.; Manfroni, G.; Palumbo, M.; Pannecouque, C.; De Clercq, E.; Fravolini, A. *J. Med. Chem.* **2004**, *47*, 5567.
[57] Cecchetti, V.; Parolin, C.; Moro, S.; Pecere, T.; Filipponi, E.; Calistri, A.; Tabarrini, O.; Gatto, B.; Palumbo, M.; Fravolini, A. *J. Med. Chem.* **2000**, *43*, 3799.
[58] Kalkhambkar, R. G.; Kulkarni, G. M.; Kamanavalli, C. M.; Premkumar, N.; Asdaq, S.M.B.; Sun, C. M. *Eur. J. Med. Chem.* **2008**, *43*, 2178.
[59] Kalkhambkar, R. G.; Aridoss, G.; Kulkarni, G. M.; Bapset, R. M.; Mudaraddi, T. Y.; Premkumar, N.; Jeong, Y. T. *Monatsh Chem.* **2011**, *142*, 305.
[60] Bonnefous, C.; Payne, J. E.; Roppe, J.; Zhuang, H.; Chen, X.; Symons, K. T.; Nguyen, P. M.; Sablad, M.; Rozenkrants, N.; Zhang, Y.; Wang, L.; Severance, D.; Walsh, J. P.; Yazdani, N.; Shiau, A. K.; Noble, S. A.; Rix, P.; Rao, T. S.; Hassig, C. A.; Smith, N. D. *J. Med. Chem.* **2009**, *52*, 3047.
[61] Priya, N.; Gupta, A.; Chand, K.; Singh, P.; Kathuria, A.; Raj, H. G.; Parmar, V. S.; Sharma, K. *Bioorg. Med. Chem.* **2010**, *18*, 4085.
[62] Sparano, J. A.; Moulder, S.; Kazi, A.; Coppola, D.; Negassa, A.; Vahdat, L.; Li, T.; Pellegrino, C.; Fineberg, S.; Munster, P.; Malafa, M.; Lee, D.; Hoschander, S.; Hopkins, U.; Hershman, D.; Wright, J. J.; Kleer, C.; Merajver, S.; Sebti, S. M. *Clin. Cancer Res.* **2009**, *15*, 2942.
[63] Joseph, B.; Darro, F.; Behard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 2543.