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An Overview on Anti Diabetic Drugs and Development

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Abstract—Diabetes mellitus is one of the world's major diseases and is the third leading cause of death in the United States after heart disease and cancer. In the India, about 2–6% population suffer from diabetes or related complication. Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. Mostly anti-diabetic drugs are administered orally except the insulin, exenatide, and pramlintide. There are different types of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, and many other factors. Treatments include the agents which increase the amount of insulin secreted by the pancreas, or increase the sensitivity of target organs to insulin, and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract. People are mainly focused on insulin, insulin analogues, oral hypoglycemic agents and various other complementary and alternate medicines to control the blood glucose levels in diabetes. The present review summarizes in brief about the drugs used for treatment of diabetes mellitus.

Keywords: Diabetes Mellitus, Glucose, Antidiabetic Drugs, PPAR, Insulin

INTRODUCTION

The word 'diabetes mellitus' [1] means, 'excessive excretion of sweet urine'. Diabetes mellitus is a group of metabolic diseases, characterized by hyperglycemia [2] resulting from defects in insulin secretion, action or both. Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs specially the eyes, kidneys, nerves, heart and blood vessels. Insulin is either not secreted in sufficient amounts or does not effectively stimulate its target cells, hyperglycemia occurs. In hyperglycemia blood glucose level becomes so high that glucose "spills over" in urine. However, cells starve since glucose stimulated entry into the cells is impaired. Apparent symptoms of hyperglycemia are excessive thirst and frequent urination. Chronic hyperglycemia causes damage to the eyes, kidneys, nerves, heart and blood vessels.

CAUSES OF DIABETES MELLITUS

Main causes of diabetes mellitus are:

- Genetic defects of beta-cell function [3].
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.

Endocrinopathies, i.e., changes in hormonal secretion and, Drugs or chemical induced.

TYPES OF DIABETES MELLITUS

- *Insulin dependant or juvenile-onset diabetes mellitus* (Type 1 Diabetes mellitus)
- *Non insulin dependant or maturity-onset diabetes mellitus* (Type 2 Diabetes mellitus)

TYPE 1: DIABETES MELLITUS

Insulin dependent diabetes mellitus (IDDM), i.e., patients require periodic doses of insulin it can occur at any age, commonly occurs in children, Characterized by the marked inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells. Kidney malfunctioning, nerve impairment, cardiovascular disease and retinal degeneration occur.

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Type 2: Diabetes Mellitus

Type 2 diabetes is non-insulin dependent diabetes mellitus (NIDDM). It accounts for about 90% of the diagnosed cases of diabetes and affects 18% of the population over 65 years of age. Insulin receptors on insulin responsive cells do not respond normally to insulin and are therefore called as "insulin resistant", thereby increasing blood glucose level.

GESTATIONAL DIABETES

Gestational diabetes is 'any degree of glucose intolerance with onset or first recognition during pregnancy'. The risk factors associated with developing gestational diabetes [4] mellitus includes the previous diagnosis of gestational diabetes mellitus. Overweight, obese or severely obese increases the risk by a factor 2.1, 3.6 and 8.6, respectively [5].

Insulin

The major function of insulin is to counter the concerted action of a number of hyperglycemia-generating hormones and to maintain low blood glucose levels. Because there are numerous hyperglycemic hormones, untreated disorders associated with insulin generally lead to severe hyperglycemia and shortened life span.

Insulin is stored in the body in the unit of six molecules but the active one is monomer. Insulin can aggregate and form interdigitated beta-sheets that can cause injection amyloidosis, and prevents the storage of insulin for long periods [6].

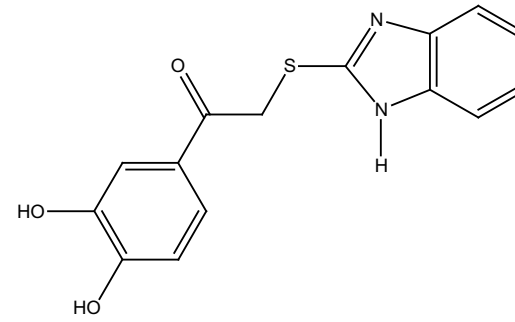
Use of Insulin for Treatment of Diabetes

According to UK perspective on diabetes study, insulin or its analogues are the standard treatment for type 1, gestational and some type of type 2 diabetes. The most common and serious reaction of insulin treatment is hypoglycemia. Severe hypoglycemia may lead to convulsions and coma. It is now known that hypoglycemia kills neurons more actively than starvation [7].

Glucagon Antagonists

Glucagon has a major role to maintain normal concentrations of glucose in blood. Glucagon is having the opposite effect of insulin to maintain glucose level in blood. Glucagon has the effect of increasing blood glucose levels by two pivotal metabolic pathways within the liver. These two pathways are by breakdown of glycogen stored in the liver and hepatic gluconeogenesis. Glucagon also appears to have a minor effect of enhancing lipolysis of triglyceride in adipose tissue by providing fatty acid fuel to most cells.

Glucagon antagonist has been investigated as potent anti-diabetic agents. The drugs being investigated in the patients with poorly controlled type-2 diabetes (1 and 2 Fig. 1).



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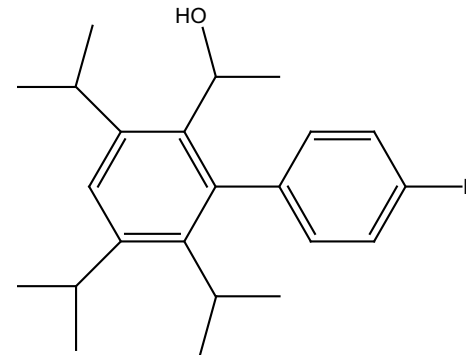

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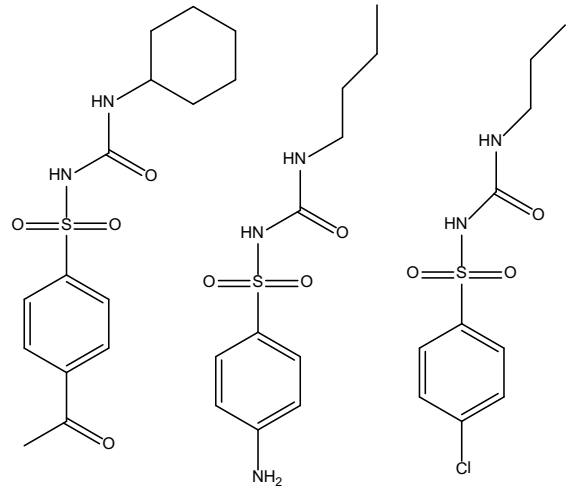
Fig. 1

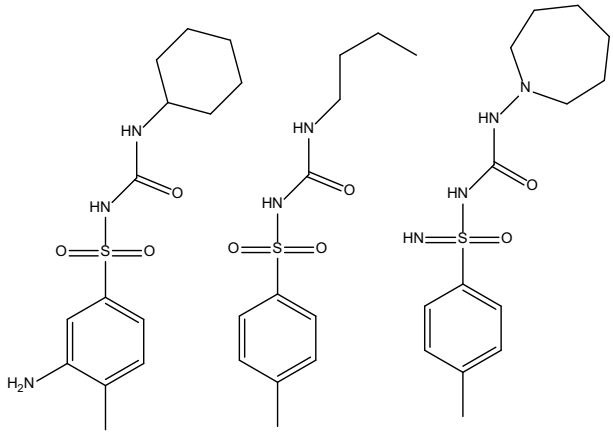
ORAL HYPOGLYCEMIC AGENTS

First and Second Generation Sulfonylureas (SUs)

The first-generation SUs include tolbutamide, acetohexamide, carbutamide, metahexamide, tolazamide and chlorpropamide (Fig. 2) and they are rarely used nowadays due to their severe side-effects. The major side-effects induced by SUs include hypoglycemia or even coma and binding to cardiac receptors, resulting in the failure of coronary vasodilatation and subsequent deleterious cardiac effects due to low specificity of the biological action, delayed time of onset and the long duration of the effect [8].



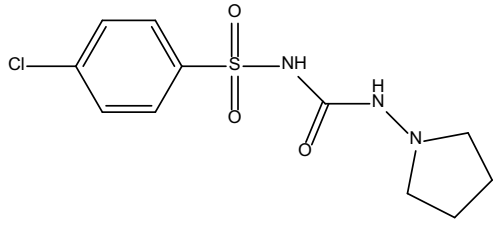
Acetohexamide Carbutamide Chlorpropamide



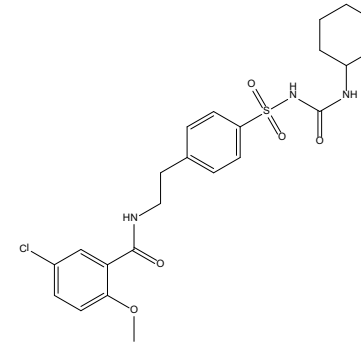
Metahexamide Tolbutamide Tolazamide

Fig. 2

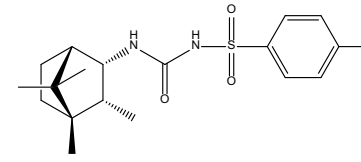
Second-generation SUs exhibit much safer and better biological effects, which is achieved by selective binding and a rapid onset of action. These improvements address the issues of SU induced hypoglycaemia as well as cardiovascular side-effects. The second generation SUs include glibenclamide (glyburide, Diabeta, Glynase and Micronase; Pfizer), glibornuride, glipizide (Glucotrol; Pfizer), gliquidone, glisoxepide, glyclopyramide, glimepiride (Fig. 3).



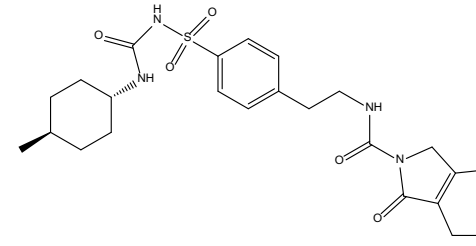
Glibenclamide



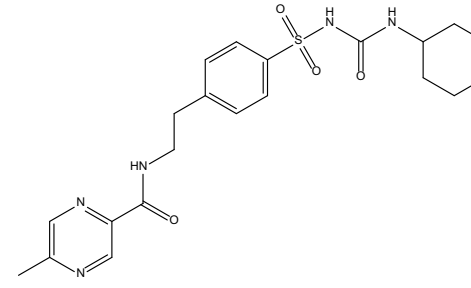
Glibornuride



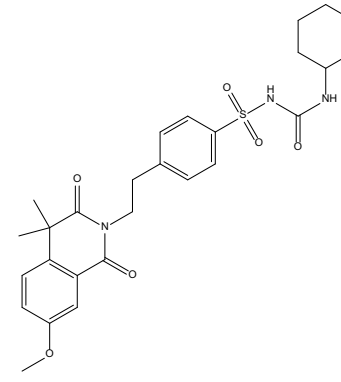
Glyclopyramide



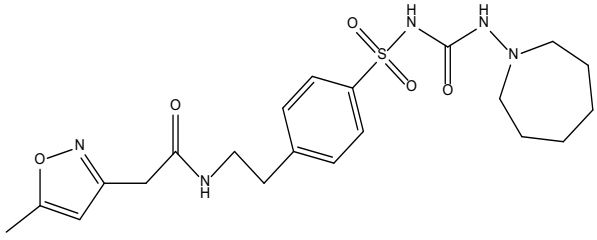
Glimepiride



Glipizide



Gliquidone



Glisoxepide

Fig. 3

The sulfonylureas used as hypoglycemic agent is usually p-substituted aromatic compounds with bulkier attachment on nitrogen of urea moiety; small substituents are usually not active. They stimulate the release of insulin from β cells. Mode of action of sulfonylureas is by affecting ATP sensitive potassium channel which is a complex of two sub units; a sulfonyl urea receptor and rectifying potassium channel. Sulfonylurea exhibits both insulin-secreting as well as extrapancreatic activities. Tolbutamide binds well to sulfonylurea receptor [9], metabolism occurs in liver, where tolbutamide and tolazamide undergo a rapid benzylic oxidation leading to inactive benzoic acid derivatives (Fig. 4).

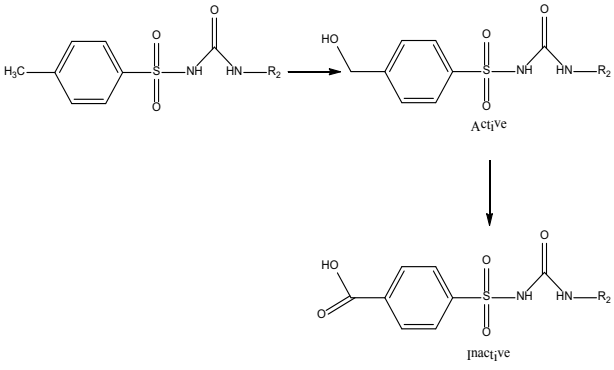


Fig. 4: Mettabolism of Tolbutamide

Various 2-arylsulfonylaminobenzothiazoles were synthesized and evaluated [10] for their protein tyrosine phosphatase-1D inhibitory activity. Compounds 3 and 4 have exhibited most promising activity as mixed-type inhibitors of PTP-1D. The *in vivo* anti-hyperglycemic activities of these compounds make them a suitable leads to develop new chemical entities for potential use in the treatment of T2DM. Also N-(3, 5-Difluoro-4-hydroxy-phenyl) benzenesulfonamide (5) [11] exhibited a comparatively improved aldose reductase inhibitory activity as well high antioxidant potential. Antioxidant property of compound 5 is additional indication for the ability of a compound to inhibit the formation of advanced glycation end products (AGEs) [12], that are implicated in the development of the long-term complications of diabetes [13].

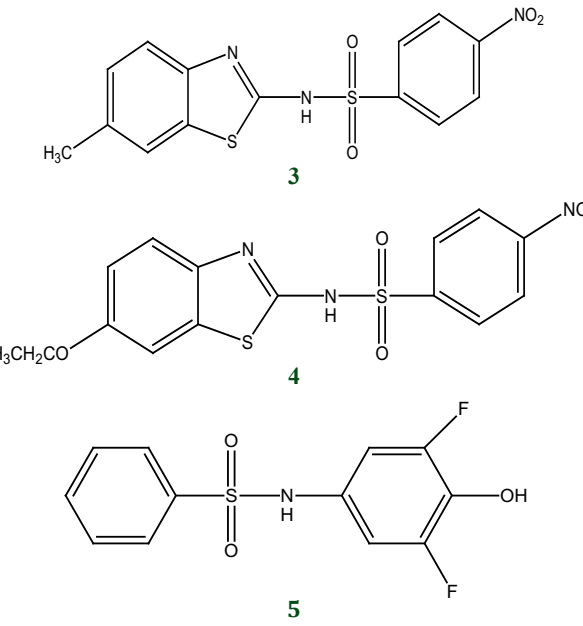


Fig. 5

Endothelial dysfunction and consequent reduction of biosynthesis of endogenous nitric oxide (NO) play an important pathogenetic role in the cardiovascular complications associated with type II diabetes. The pharmacodynamic characterization of drugs D and E [14] showed increasing hypoglycaemic activity with additional NO-donor effects, conferring vasorelaxing and anti-platelet properties of potentially great usefulness for diabetes-related cardiovascular disorders.

Both first and second generation sulfonylureas have the same clinical effectiveness but large difference in potency. These drugs produce a reliable glucose reduction in type 2 diabetes (6 & 7 in Fig. 6).

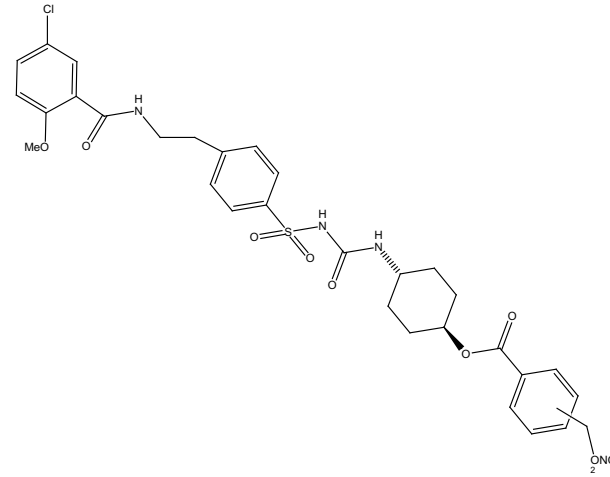


Fig. 6: 6; Meta, 7; Para.

Recently, new series of SUs were studied and found some potent compound (Fig. 7). Expression of this compound on PPAR-γ target genes were measured in 3T3-L1 fibroblasts and it was found better in comparison to standard drugs, rosiglitazone and glibenclamide. The compound shows significant enhancement in the expression of PPAR-γ genes [15].

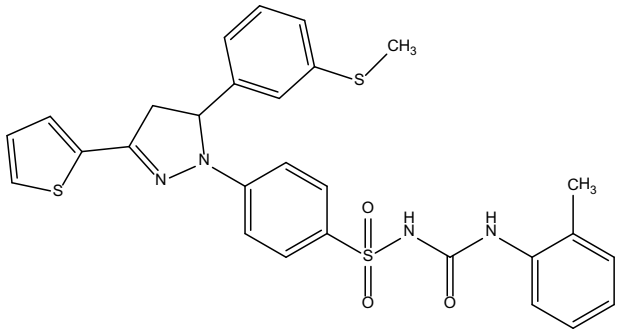


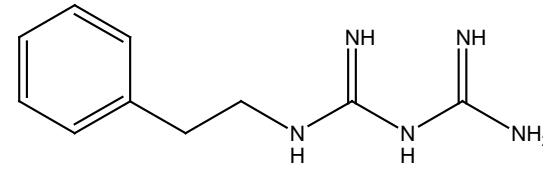
Fig. 7

Biguanides

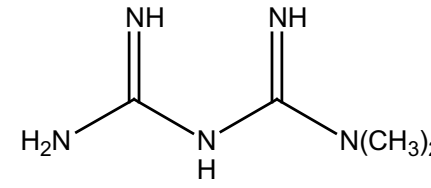
Biguanides are oral agents used for the treatment of mild to moderately severe T2DM patients to overcome insulin resistance, especially in obese patients who fail diet and exercise therapy (Fig. 8) [16,17]. Biguanides have a twofold mechanism of action: (i) they enhance peripheral muscle glucose uptake and utilization by making muscle and fat cells more sensitive to available insulin; and (ii) they inhibit hepatic glucose output by preventing the liver from making excessive glucose [18]. Biguanides are usually associated with a low risk of hypoglycemia, even in overdose, due to the fact that insulin secretion is not promoted.

Biguanides are described as insulin sensitizers. Complete mechanism of action of biguanides is still not clear but it acts in liver by decreasing excessive glucose production via reduced gluconeogenesis resulting from increased sensitivity of insulin [19]. The main action of biguanide drugs appears in the liver mitochondria via activation of adenosine-5'-monophosphate-activated protein kinase (AMPK) [20]. The therapeutic effect of metformine requires the presence of insulin and metformine does not stimulate the release of insulin or other factors, such as glucagon. In fact, metformine suppress the secretion of adiponectin, an insulin-sensitizing hormone [21]. Metformin is not metabolized and is cleared from the body by tubular secretion mediated by organic cation transporters and is excreted unchanged in the urine [22]. Metformin has a low risk of causing hypoglycaemia and lactic acidosis. However, metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders, lung disease and liver disease. Metformin is often used in combination with other oral antidiabetic drugs.

The most popular combination of metformin is used with rosiglitazone. Metformin is also used in combination with pioglitazone, glipizide, glibenclamide or glyburide, dipeptidyl peptidase (DPP)-4 inhibitors sitagliptin, saxagliptin, meglitinide repaglinide and Novo Nordisk. Furthermore, the Food and Drug Administration (FDA) also approved the combination of metformin and alogliptin under the trade name Kazano in 2013.



Phenformin



Metformine

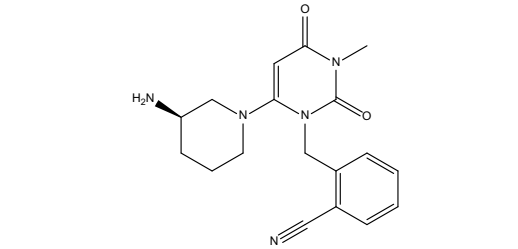
Fig. 8

Bile Acid Seuestrants

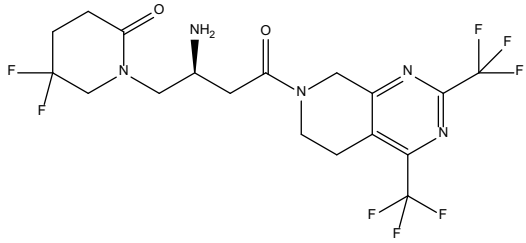
Cholestyramine and colestipol are first-generation bile acid sequestrants and antihyperlipidaemic agents that currently have a limited use due to their weak effect on lowering low-density lipoprotein cholesterol (LDL-C) and poor tolerability [23,24]. The second-generation bile acid sequestrants, such as colesevelam and colestimide (also called colestilan) have a glucose-lowering effect and improved tolerance, which has led to re-evaluation of their application as oral antidiabetic agents. Colesevelam is a bile acid-binding resin sequestrant, it is indicated as an adjunct to diet and exercise to reduce elevated LDL-C in patients with primary hyperlipidaemia as monotherapy and to improve glycaemic control in T2DM, including in combination with a statin [25,26]. The mechanism by which colesevelam improves glycaemia has not been fully understood but may involve enhanced meal-induced incretin secretion and altered farnesoid X receptor (FXR) signaling [24,26].

Gliptins (DPP-4 Inhibitors)

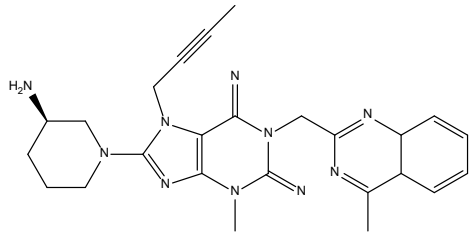
Dipeptidyl peptidase-4 (also known as adenosine deaminase complexing protein 2 or CD26) cleaves the two N-terminal amino acids from peptides with a proline or alanine in the second position, and inactivating both glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) [27,28]. Endogenously released GLP-1 has a short biological half-life around 1.5–5 min, whereas the serum half-life of GIP is approximately 7 min [29]. Upon secretion of GLP-1 and GIP both are rapidly degraded and inactivated by DPP-4. Therefore, DPP-4 inhibitors (Fig. 9) have been developed and to prevent degradation of endogenously released GLP-1 and GIP. Consequently, it enhanced plasma concentrations of active incretin, prolonging the actions of the incretin and leading to increased insulin levels [30].



Alogliptin



Gemigliptinz



Linagliptin

Fig. 9

The insulin-releasing effects of incretins are glucose dependent and the incretins have no insulinotropic activity at lower glucose concentrations (< 4 mmol/L), thus it reduces the chance of hypoglycaemia, which is one of the major concerns with other antidiabetic drug classes. Furthermore, DPP-4 inhibitors are the first substances that have a glucose-dependent dual action on α- and β-cell functions, stimulating insulin secretion and suppressing glucagon secretion under hyperglycaemic conditions. This dual action of incretin leads to an improved time-course of islet hormone secretion after a meal as well as in hyperglycaemia. The discovery of incretin therapy may help overcome the limitations of the classical treatment options for T2DM.

Dopamine D2 Receptor Agonists (Bromocriptine)

Bromocriptine (Fig. 10), a central-acting dopamine D2 receptor agonist used for the treatment of T2DM in 2009 [31]. This drug has been previously widely used in treatment of hyperprolactinaemia and galactorrhoea caused by pituitary tumours, Parkinson's disease, hyperprolactinaemia and neuroleptic malignant syndrome [31].

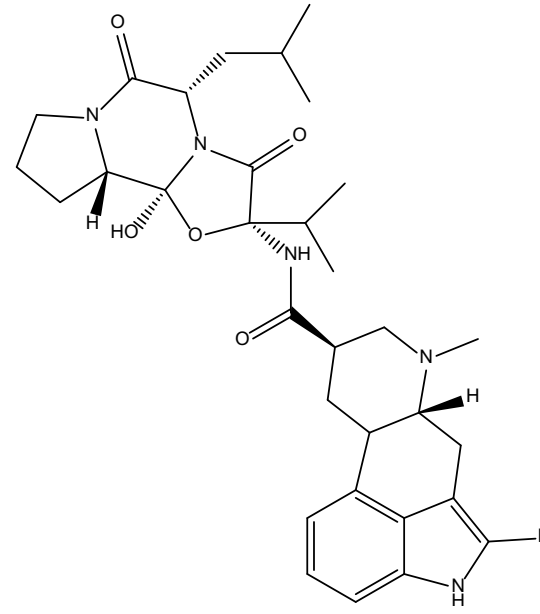


Fig. 10

The mechanism of action underlying how bromocriptine regulates glycaemic control is not clear, but data indicate that bromocriptine improves insulin sensitivity and other metabolic abnormalities [32]. Bromocriptine is a potent agonist at dopamine D2 receptors, serotonin (5-HT1, 5-HT2 and 5-HT6) receptors and α1- and α2-adrenoceptors. In addition, it is also a moderate agonist for dopamine D1 receptors and 1- and 2-adrenoceptors [31,32]. Bromocriptine inhibits glucose-stimulated insulin secretion by direct activation of α2-adrenoceptors on β-cells [33]. Clinical studies have shown that quick release (QR) bromocriptine

lowers HbA1c by 0.6%–1.2% either as monotherapy or in combination with other antidiabetic drugs [31].

Peroxisome Proliferator-Activated Receptors (PPARs)

The peroxisome proliferator-activated receptor belongs to the family of nuclear receptors including the oestrogen receptors, thyroid hormone receptors, retinoic-acid receptors (RARs) and retinoid-X receptors (RXRs) [34]. PPARs are the group of nuclear receptors that control the carbohydrate metabolism by altering the expression of the genes involved, consists of three different genes, PPARα, PPARβ/δ, PPARγ. PPARα shows distinct tissue distributions [35,36] and associated with different ligands [37]. These are highly expressed in liver, skeletal muscles and heart, PPARγ is highly expressed in adipose tissues but is also expressed in intestines, breast tissues etc. PPARβ/δ is expressed in highest level in skin and skeletal muscle. At submicromolar levels, a class of thiazolidinediones (TZDs) activates PPAR-γ and are used pharmaceutically for the treatment of type 2 diabetes because they sensitize tissues to insulin.[38] PPAR-γ may be the biochemical target of TZDs [39]. PPAR-γ contains the general structural features of other nuclear receptor-family members, including a central DNA-binding domain and a carboxy-terminal domain that mediates ligand binding, dimerization and transactivation functions.

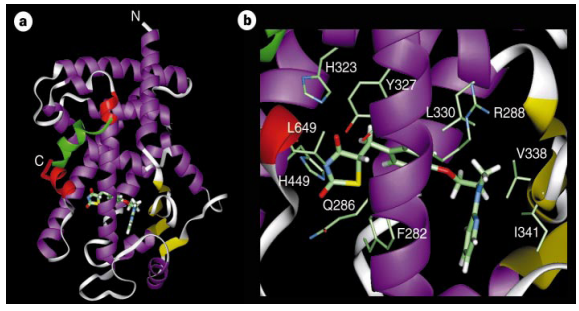
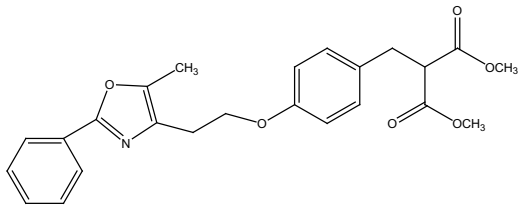


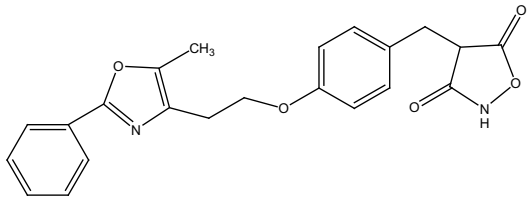
Fig. 11: Binding of Rosiglitazone with PPARγ.

Rosiglitazone, antidiabetic drug of glitazone series, occupies about 40% of the ligand-binding [40] site in the ternary complex. In general, the ligand is in a U-shaped conformation, wrapping around H3 with its central benzene ring directly behind H3 and the TZD head group and pyridine ring wrapping around H3 (Fig. 11). The TZD head group makes several specific interactions with amino acids in H3, H4, H10 and the AF-2 helix (Fig. 11). The carbonyl groups of the TZD form hydrogen bonds with two histidine residues, H323 and H449. Y473 in the AF-2 helix forms a secondary hydrogen bond with H323. The partly negatively charged nitrogen of the TZD head group is within hydrogen bonding distance of the Y473 side chain hydroxyl group. A buried lysine residue, K367, forms another secondary hydrogen bond with rosiglitazone, at residue H449. All of these primary and secondary hydrogen bonds result in a fixed conformation of the TZD head group and of the participating amino acids. Next to the head group, the sulphur atom of the TZD ring is positioned in a hydrophobic region of the PPAR-γ. After activation by specific ligands, PPARs binds to the regulatory regions of DNA of the genes, thus regulating the transcription of genes involved in glucose homeostasis pocket formed by F363, Q286, F282 and L469. The central benzene ring of the ligand occupies a very narrow pocket between C285 and M364. The bridging oxygen atom between the benzene ring and the pyridine ring provides vital geometry for the pyridine ring, which occupies the pocket between H3 and the β-sheet. Rosiglitazone has one chiral atom in the head group that is in the S configuration, even though a racemic mixture was used for crystallization. Substituted carboxylic acids can act as bio-isosteric replacements for the TZD head group, maintaining high affinity binding and receptor activation. It is predicted by above findings that these carboxylic acids conserve the key interactions with H323 and H449, and that this molecular recognition may be important for the binding of other acidic ligands. Several naturally occurring carboxylic acids, including essential fatty acids, oxidized lipids and prostaglandin J2 metabolites, can bind and activate PPAR-γ at micromolar concentrations.[41] According to above studies, it is proposed that all of these hydrophobic carboxylic acids bind to PPAR, and that the key interactions involving the histidine residues required for TZD binding are conserved with the acid groups.

The treatment generally prescribed for non-insulin dependent diabetes mellitus (NIDDM) is a combination of diet, exercises, and oral hypoglycemic agents, commonly sulfonylurea and biguanides [42]. However, sulfonylurea therapy leads to many problems associated with primary and secondary failure of efficacy, incidence of hypoglycaemia [43] and obesity [44]. Thus, drugs that reverse the onset of insulin resistance fulfil a major unmet medical need for the treatment of NIDDM [45]. Replacement of the thiazolidine-2,4-dione ring by an isoxazolidine-3, 5-dione (JTT-501) (Fig. 12) [46,47] and its non-cyclic 1, 3-dicarbonyl derivatives (JTP20993) and compound 8 (Fig. 12) [48] led to compounds which showed very interesting insulin-sensitizing activity in 3T3-L1 cells and hypoglycemic activity in genetically diabetic KKAy mice.



JTP20993



JTT-501

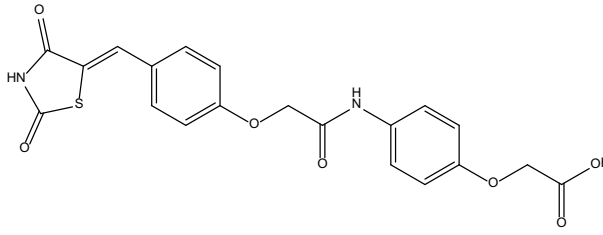


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Fig. 12

A series of benzazolonic heterocycles, which could replace the 2-phenyloxazole of JTP20993, bearing a 1, 3-dicarboxylic functionality as potent and selective PPARγ agonists have been synthesized [49] and the SAR studies demonstrated that 2(3H)-benzothiazolone seemed to be the most potent nitrogen heterocycle of the series (9).

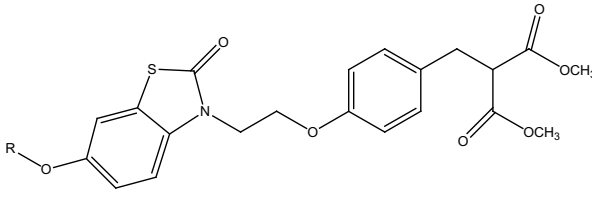

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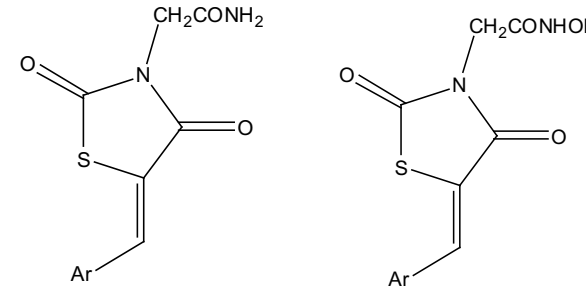
Fig. 13

The Aldose reductase (ALR2) inhibitory data of some 5-arylidene-2, 4-thiazolidinediones [50] can be considered as promising ARIs and allowed to extend their structure–activity relationships. The introduction of an additional aromatic ring or an H-bond donor group on the 5-benzylidene ring was shown to be very favourable for the ALR2 inhibitory effectiveness of these compounds. The *in vitro* evaluation of (5-arylidene-2, 4-dioxothiazolidin-3-yl) acetamides (10) [51] and analogous N-hydroxyacetamides (11) (Fig. 14) highlighted that the replacement of the carboxylic anionic head of acids at 3-position with the carboxamide or N-hydroxycarboxamide group produces a general decrease in the in vitro ALR2 inhibitory effect, whereas insertion of the N-hydroxyacetamide chain on N-3 (compounds 10) gave a general improvement in activity.



10 11

Fig. 14

The main side effect of glitazones is water retention leading to edema, with significant water retention, leading to decompensation of potentially previously unrecognized heart failure. Recent studies have shown there may be increased risk of attack with rosiglitazone. Pioglitazone treatment, in contrast, has shown significant protection from both micro and macro-vascular cardiovascular events and plaque progression. These side effects are the requirement of development of new molecules with potent antidiabetic activities with least side effects.

Saroglitazar was the first glitazar to be approved for the treatment of T2DM. It is marketed under the trade name Lipaglyn. The average terminal half-life of saroglitazar is 5.6 h and it is not eliminated via the renal route [52] Single oral doses of saroglitazar up to 128 mg are well tolerated [52] Bezafibrate is a fibrate drug used for the treatment of hyperlipidaemia. It helps lower LDL-C and triglyceride and increase HDL in the blood. Like the other fibrates, bezafibrate is a PPARα agonist; some studies suggest it may also have modulating effects on PPARγ and PPARδ [53,54].

The recent discovery that peroxisome proliferator-activated receptor γ (PPAR γ) targeted anti-diabetic drugs function by inhibiting Cdk5-mediated phosphorylation of the receptor has provided a new viewpoint to evaluate and perhaps develop improved insulin-sensitizing agents. As the prevalence of obesity continues to rise, therapies started to treat the metabolic syndrome and its associated conditions are of increasing importance. Novel thiazolidinedione (GQ-16), that retains similar anti-diabetic efficacy as rosiglitazone in trial yet does not elicit weight gain or edema, common side effects associated with full PPAR γ

activation. Further characterization of this compound shows GQ-16 (Fig. 15) to be an effective inhibitor of Cdk5-mediated phosphorylation of PPAR γ [55].

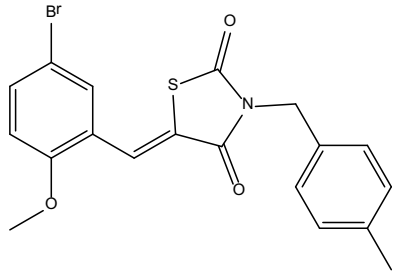
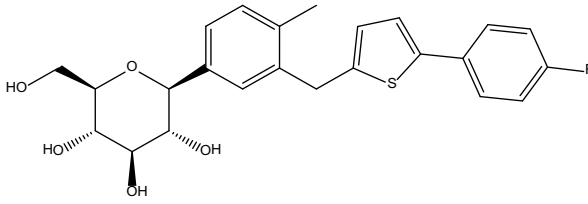


Fig. 15. (GQ-16).

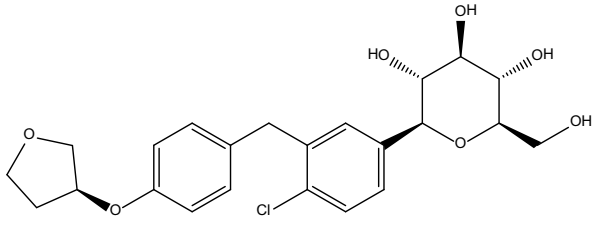
SGLT2 Inhibitors: A New Class of Diabetes Medications

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of diabetic medications used for the treatment of type 2 diabetes. SGLT2 is a protein in humans that facilitates glucose reabsorption in the kidney. SGLT2 inhibitors lower blood glucose level by blocking the reabsorption of glucose in the kidney and increasing the glucose excretion [56]. Inhibition of SGLT2 leads to the decrease in blood glucose due to the increase in renal glucose excretion. This class of drugs offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in the muscle cells, decreased gluconeogenesis and improved first phase insulin release from the beta cells.

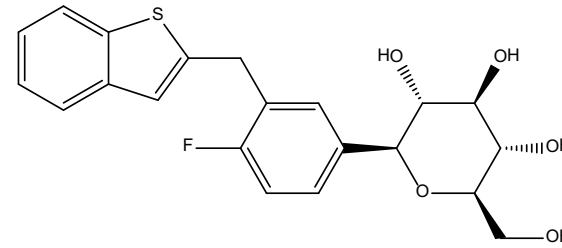
Drugs in the SGLT2 inhibitors class include empagliflozin, canagliflozin, dapagliflozin, ipragliflozin (Fig. 16) [57]. There are many side effects but vaginal yeast infections and urinary tract infections are the most common side effects associated with these inhibitors with the greatest risk being in female patients and those men who are uncircumcised [58].



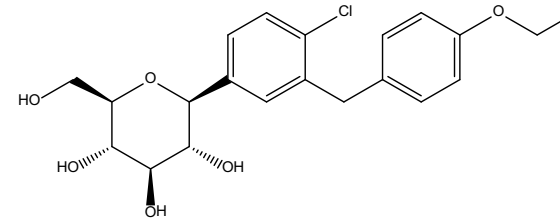
Canagliflozin



Empagliflozin



Ipragliflozin



Dapagliflozin

Fig. 16

CONCLUSION AND FUTURE DIRECTION

Despite the fact that now a variety of antidiabetic agents are available for the treatment T2DM patients albeit there are shortcomings in diabetes treatment at present and the search for optimal therapy is ongoing. Putting aside common side-effects, such as weight gain and hypoglycaemia, current diabetes therapies do not address the key driver of this condition, namely β-cell dysfunction, and do not alter the progressive nature of the insulin secretory deficit. In addition, the pathophysiology of the disease is only partially understood and there are currently no antidiabetic agents that can effectively reduce excessive cardiovascular risk associated with T2DM. Therefore, development of new antidiabetic drugs should not only address blood glucose levels, but also aim to halt disease progression, restore β-cell function and, in the long run, reduce T2DM-associated complications, such as cardiovascular risks. In conclusion, the examples highlighted in this review convincingly demonstrate the short comings of antidiabetic therapy, while at the same time they emphasize the need for truly new safer and effective antidiabetic drugs.

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