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## Review Paper

### Evolution of Sulfonylureas in the Treatment of *Diabetes Mellitus*

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**Abstract:** *Diabetes Mellitus* is becoming fast growing epidemic all over the world. Despite several oral drugs available in the market, the most traditional as well as the most popular of them all are sulfonylureas. Sulfonylureas have been a foundation for maintaining glucose levels in type II diabetes. Although having many side effects, this class of compounds is still being used as the second-line recommended choice of oral glucose-lowering treatment after metformin. In the present review, various stages involved in the development of these drugs have been discussed through important case studies. The mode of action of sulfonylureas in biological system has been reviewed. Comparison of commercially available sulfonylureas has been made while discussing their chemical synthesis and metabolism inside gastrointestinal tract. A systematic study has been made on various antidotes that are available in the market to overcome hypoglycemia associated with the use of sulfonylureas.

## Introduction

### History of *Diabetes Mellitus*

The word '*diabetes*' was coined by Apollonius of Memphis around 250 BCE. Literally, "*diabetes*" is a Greek word which means a siphon to pass through and "*mellitus*" is a Latin word, meaning honeyed or sweet. Reports of diabetes are found in ancient Indian medicinal books and "Sushruta", an Indian doctor was aware of *diabetes* which he named as 'madhumeḥ' meaning honey combined with urine. The

famous Persian medical expert, "Avicenna" has discussed that an abnormal appetite, sexual dysfunctions and sweet urine as the symptoms of *Diabetes Mellitus* in his popular book, "The canon of medicine". Diabetes is a chronic metabolic disorder with the number of affected people expected to double in the next decade [1]. *Diabetes Mellitus* is associated with hyperglycemia (abnormal increase in blood glucose) resulting from defects in insulin secretion, insulin action, or both. Since several pathogenic processes have been involved in the development of diabetes, the diabetic condition may result in long-term damage, dysfunction, or even failure of various organs like kidneys, nerves, heart, eyes and

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blood vessels. Declining pancreatic  $\beta$ -cell function has been regarded as a major factor associated with progressive rising of plasma glucose levels and disease progression according to Belfast Diabetes Study [2] and United Kingdom Prospective Diabetes Studies UKPDS [3]. In both studies, extrapolation of data suggests that initial deterioration in the islet function may occur up to 15 years before diagnosis of the disease.

Polyuria (frequent urination), polydipsia (excessive thirst), weight loss, polyphagia (increased appetite), and blurred vision are some very common symptoms associated with marked hyperglycemia [4]. Impairment of growth and susceptibility to certain infections accompanies chronic hyperglycemia while acute hyperglycemia may be responsible for ketoacidosis or the nonketotic hyperosmolar (dehydration) syndrome [5]. Long-term diabetes can result in potential loss of vision, renal failure, gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes. The aim behind the treatment of diabetes is to prevent or delay the appearance of these diabetes related complications, decrease mortality, and maintain a good quality of life. *Diabetes Mellitus* can majorly be classified into Type I, Type II and Gestational diabetes [6]. The vast majority of cases of diabetes fall into former two categories. There is an absolute deficiency of insulin secretion in type I diabetes while in the other, much more prevalent category, type II diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.

Type I diabetes, accounts for only 5–10% of diabetic population, previously encompassed

by the terms insulin dependent diabetes because it results from a cellular-mediated autoimmune destruction of the  $\beta$ -cells of the pancreas. In this case, the patient eventually becomes dependent on insulin [7]. Type II diabetes also referred to as non-insulin dependent diabetes accounts for 90–95% of those with diabetes. This category includes individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. These individuals may not need insulin treatment to survive throughout their lifetime. The improvement in insulin sensitivity is thus a primary target for the preventing increase in the incidence of type II *Diabetes Mellitus* and its treatment. Several pharmacological drugs are being prescribed by medical practitioners for the management of diabetic condition. These therapeutic drugs have broadly been classified into sulfonylureas, biguanides, thiazolidinediones, Alpha-glucosidase inhibitors, DPP-4 inhibitors and insulin [8]. Sulfonylureas are the most primitive drugs among all these classes of oral antihyperglycemic drugs but are still in use, being potent and cost-effective glucose-lowering agents.

### Sulfonylureas

The first pharmacological approach for the oral glucose-lowering medications in the clinical practice was the introduction of sulfonylureas more than five decades ago [9]. All sulfonylureas (Scheme 1) contain a central *S*-substituted sulfonylurea structure with various groups terminating the urea *N'* end group [10]. These drugs have long been established in the treatment of diabetes and still a large number of people who are taking sulfonylureas, either as a first-line diabetes treatment or in combination with another diabetes medication, accounting for around 25% of newly initiated oral diabetes medications [11, 12].

However, several side effects have been reported to be associated with this class of drugs. After 10 years of follow-up made in the UKPDS, it was reported that the mean body weight change ranged from a minimum of 1.7 kg for glibenclamide to a maximum of 2.6 kg for chlorpropamide [13]. Also the treatment of patients with sulfonylureas had symptoms suggestive of hypoglycemia [14]. During the first year of the UKPDS, at least 30% of the sulfonylurea-treated patients suffered from hypoglycemia. This figure is however, similar to that observed in insulin-treated individuals. The relative risk of severe hypoglycemia in the UKPDS is much lower than the 27% observed in intensively treated type 1 diabetic patients reported by the Diabetes Control and Complications Trial (DCCT) [15] despite similar glycemic control. Furthermore, the patients exposed to sulfonylureas and exogenous insulin would have an increased risk of cancer-related mortality compared to patients who were exposed to the therapies that decrease circulating insulin levels [16]. Additionally, less common side effects include dermatological and hematological reactions and gastrointestinal disturbances. It can therefore be inferred from all these studies that the use of sulfonylurea drugs might contribute to increased morbidity and mortality of diabetic patients. However, the similar notion rose during the early stages of development of these drugs was later on criticized due to unclear methodology of the study [17]. Despite these drawbacks and continuous debates over the utility of sulfonylureas, these drugs are still in practice.

### **History behind the discovery of sulfonylureas**

The hypoglycemic effect of the sulfonylureas was first discovered in France

during World War II. It was rather serendipity occurred during the course of investigations of antibiotic properties of modified sulfonamides. Not much clinical application of these drugs came into picture until the synthesis of carbutamide after the war, in Germany, followed by the development of the agents called tolbutamide and chlorpropamide which were commonly used in the United States. However, a setback came when the University Group Diabetes Program (UGDP), designed a 12-center prospective trial to compare the efficacy of oral hypoglycemic treatment (tolbutamide) with insulin and diet alone. UGDP reported that the patients taking tolbutamide [18] have increased risk for cardiovascular mortality. Thereafter, several controversies were raised against the use of sulfonylureas [19] but by the late 1970s, use of these drugs once again increased, perhaps because the UGDP findings could not be confirmed [20, 21].

In the recent years, the laborious and extensive researches worldwide have upgraded these first generation sulfonylureas to the second and the third generation of compounds, which are far more potent than the original compounds (Table 1).

### **Mode of action of sulfonylureas**

Once the sulfonylureas had taken hold over the market in spite of various associated controversies, scientists had sought to determine the mechanism of their antihyperglycemic action. Initially, it was thought that an increase in insulin release is the primary action but in early 1970s, a serious concern regarding the insulin secretory effect of sulfonylureas was raised. Various attempts had been made to develop a basis for understanding of various aspects which might be playing important roles in the therapeutic action of these drugs. Finally

in 1990s, the mechanism of action of this class of compounds was found to be related with Adenosine triphosphate (ATP) sensitive potassium ( $K^+$ ) channels.

*Structure and function of ATP sensitive  $K^+$  channels ( $K_{ATP}$ ):* Glucose level in blood stream is maintained by insulin secretion from pancreatic  $\beta$  cells. The glucose metabolism in pancreatic  $\beta$  cells is the crucial step in glucose-induced insulin secretion. Pancreatic  $\beta$  cells are electrically excitable cells [22], and glucose regulates insulin secretion by controlling  $K^+$  permeability, which determines membrane potential [23, 24]. Thus, the  $K^+$  permeability of the  $\beta$ -cells is a critical determinant of glucose-induced insulin release.  $K_{ATP}$  channels were discovered originally in heart [25], and were later found in many other tissues including pancreatic  $\beta$  cells [26, 27], skeletal muscle [28], smooth muscle [29], brain [30], pituitary [31] and kidney [32]. Before the identification of  $K_{ATP}$  channels in pancreatic  $\beta$  cells, however, the molecule linking glucose metabolism and membrane potential was not known.

*$K_{ATP}$  channel* as the name suggests, is a type of potassium channel that is gated by ATP. ATP-sensitive potassium channels are composed of eight protein subunits (octamer). Four of these are members of the Inward-Rectifier Potassium ion channel family  $K_{ir}6.x$  (either  $K_{ir}6.1$  or  $K_{ir}6.2$ ), while the other four are SulfonylUrea Receptors (SUR) [33].  $K_{ir}6.2$  can function only when it is co expressed with the SUR subunit and is responsible for  $K_1$  conductance. The SUR subunits have three additional transmembrane domains, and contain two nucleotide-binding domains on the cytoplasmic side. These allow nucleotide mediated regulation of the potassium channel. This unit acts as a sensor of metabolic status. These SUR subunits are

also sensitive to sulfonylureas, MgATP, and some other pharmacological channel openers [34]. In pancreatic  $\beta$  cells, since these channels are ATP gated channels; the ATP/ADP ratio determines  $K_{ATP}$  channel activity. Under normal conditions, the  $K_{ATP}$  channels in pancreatic  $\beta$  cells are spontaneously active, allowing  $K^+$  ions to flow out the cell [35]. But as soon as there is increase in glucose level leading to increased glucose metabolism, the  $K_{ATP}$  channels close. This is because of consequent increased levels of ATP causing the membrane potential of the cell to depolarize, thus promoting insulin release. The depolarization and polarization of channels happens quickly and synchronously [36-38]. Sulfonylurea drugs have high affinity to bind with a SUR subunit of the  $K_{ATP}$  channel [39]. Thus, the acquiring of this receptor by a sulfonylurea drug inhibits flux of  $K^+$  through the channel pore leading to depolarization of the plasmalemma and thus inducing release of insulin (Fig. 1). However, it should be pointed out that the additional ion channels may also be targeted by sulfonylurea drugs [40-42].

## Synthesis and metabolism of some commercial sulfonylureas:

### I. First generation sulfonylureas

#### Tolbutamide

*Dose:* 500-3000 mg

*Synthesis:* The synthesis of tolbutamide involves addition reaction of *p*-toluenesulfonamide and butyl isocyanate as shown in Scheme 2a.

*Metabolism:* A rapid metabolic inactivation of *p*-ethyl group by oxidative metabolism leads to a relatively short duration of action. *p*-methyl group is first converted to the

hydroxymethylene primary alcohol then to the inactive acid (Scheme 2b).

*Side effects:* Salicylates displace tolbutamide from its binding site on plasma binding proteins which lead to increase in free tolbutamide concentration and thus hypoglycemic shock is usually observed [43, 44].

### **Tolazamide**

*Dose:* 100- 750 mg

*Synthesis:* To synthesize tolazamide, firstly *p*-toluenesulfonamide is reacted with ethylchloroformate in the presence of base to give corresponding carbamate. The ethoxy group of carbamate is displaced on heating with azepane and gives tolazamide (Scheme 3a).

*Metabolism:* Tolazamide undergoes metabolic inactivation by oxidative pathways similar to tolbutamide (Scheme 3b). But its action remains for longer duration than tolbutamide which may either be due to its slower rate of absorption from the gastrointestinal tract or the formation of active hydroxy metabolites which are more active than that formed in case of tolbutamide.

*Side effects:* Caution should be exercised in patients with history of liver, kidney, thyroid or heart problems, stomach problem, alcoholism, any allergy, who are taking other medications, during pregnancy and breastfeeding [45].

### **Acetohexamide**

*Dose:* 500- 1,500 mg

*Synthesis:* The diazotation of *p*-aminoacetophenone is carried out to form corresponding sulfonylchloride which is further converted to its amide (Scheme 4a). Sulfonamide so obtained is then reacted with

cyclohexaneisocyanate to give acetohexamide.

*Metabolism:* It gets rapidly metabolized by reduction of the acetyl carbonyl to L-(-)-hydroxyhexamide (Scheme 4b). This metabolized product is 2.5 times more active than the parent drug and has a longer half-life. Acetohexamide and L-(-)-hydroxyhexamide are also metabolized by omega-like oxidation of the cyclohexyl 4-position. The metabolism to dihydroxy metabolite lowers the activity. Further metabolism results in inactivation.

*Side effects:* Acetohexamide cannot be given to patients with renal and kidney disorders. Cases of hypoglycemia have also been reported [46].

### **Chlorpropamide**

*Dose:* 100-500 mg

*Synthesis:* The synthesis of chlorpropamide has been carried out by reacting *p*-chlorosulfonamide with *n*-propylisocyanate in the presence of mild base (Scheme 5a).

*Metabolism:* The half life period of chlorpropamide is relatively longer because of *p*-chloro substituent which protects the *p*-position from metabolic oxidation. 20% of a dose is excreted unchanged and remaining 80% is metabolized by omega and omega-1 type oxidation (Scheme 5b).

*Side effects:* Renal impairment and hypertension other than hypoglycemia is reported [47-48].

## **II. Second generation Sulfonylureas**

The second generation sulfonylureas have following advantages over first generation sulfonylureas [49].

- The presence of more nonpolar or lipophilic side chains result in increased hypoglycemic potency.
- Do not produce facial flushing after ethanol ingestion and are not uricosuric.
- Bind to human serum albumin by nonionic forces rather than binding by ionic forces as in several first generation drugs. Thus, anionic drugs such as salicylate do not displace glyburide from albumin as they do in earlier drugs making them safer to administer in the presence of concurrent administration of other pharmacologic agents.
- The amount and frequency of dose that need to be taken is lesser than for first-generation sulfonylureas.
- Preferred when there is poor function of the kidneys [50].

### Glibenclamide

*Dose:* 2.5 – 20 mg

*Synthesis:* *N*-phenethylacetamide is converted to *N*-phenethylsulfonamide. This sulfamide is coupled with 5-chloro-2-methoxybenzoylchloride and the product so obtained is reacted with cyclohexaneisocyanate to give glibenclamide (Scheme 6a).

*Metabolism:* Glibenclamide has prolonged biological effect due to the formation of active metabolites. It is metabolized primarily in the liver by oxidation of the cyclohexyl ring (omega and omega-1 type oxidations), of the four possible isomeric metabolites, the *cis*-3-OH and *trans*-4-OH compounds are the major ones formed (metabolism is shown in Scheme 6b).

*Side effects:* Hypoglycemia, Cholestatic jaundice and haemolysis is noted [51-53].

### Glipizide

*Dose:* 2.5-10 mg

*Synthesis:* 5-methylpyrazine-2-carboxylic acid and 2-phenylethanamine are reacted together to give carboxamide (Scheme 7). This carboxamide is reacted with chlorosulfonic acid and the resultant product is coupled with 4-nitrophenylcyclohexylcarbamate to give glipizide.

*Metabolism:* 90% of glipizide is metabolized by the liver while 10% is excreted unchanged by the kidney. It is metabolized same way as glibenclamide. In addition, some hydrolysis of the heterocyclic (electron deficient) amide may also occur.

*Side effects:* Hyponatremia, gastrointestinal side effects, disulfiram-like reactions and coproporphyrinuria have also been reported [54-56].

### III. Third generation sulfonylureas

#### Glimepiride

*Dose:* 1-4 mg

*Synthesis:* 3-ethyl-4-methyl-2-oxo-*N*-phenethyl-2*H*-pyrrole-1(5*H*)-carboxamide resulted from the reaction between 3-ethyl-4-methyl-1*H*-pyrrol-2(5*H*)-one and ethylphenylisocyanate is converted to its corresponding sulfonamide (Scheme 8a). The reaction of sulfonamide with 4-methylcyclohexaneisocyanate resulted in the synthesis of glimepiride.

*Metabolism:* Glimepiride is extensively metabolized by hepatic cytochrome enzymes into corresponding alcohol and carboxylic acid by sequential oxidation. The isozyme cytochrome P450 2C9 is involved in the formation of alcohol which then oxidized to carboxylic acid by one or more cytosolic (non-cytochrome) enzymes (Scheme 8b). Alcohol derivative possess about 1/3 the

activity of the parent drug while acid derivative is inactive.

*Side effects:* side effects of glimepiride include gastrointestinal tract disturbance, hypoglycemia, rarely thrombocytopenia, leukopenia, hemolytic anemia, and occasionally allergic reactions occur, [57, 58].

### Substituted benzenesulfonylureas

Several new derivatives of sulfonylureas have been synthesized and reported which showed comparable activity to that of commercial sulfonylureas. We have reported pyridazinone substituted benzenesulfonylurea which showed comparable activity to glicazide. Oral antihyperglycemic efficacies of thirteen compounds were assessed using an oral glucose tolerance test in normal and type II diabetic rat model. The compounds were given at 20 mg/kg b.w and almost completely prevented the rise of blood glucose of type II diabetic rats as compared with type II diabetic control [59]. We have also reported similar studies and one of the derivatives has been found to be more potent antihyperglycemic agent than glicazide and also the hypoglycemic effect is comparatively lesser [60]. The list of active compounds (I – XII) and their synthetic route has been displayed in Table 2 & Scheme 9 respectively. The pyridazinone derivatives of benzenesulfonylthiourea were also studied by our group and found that these compounds exhibited lesser antihyperglycemic activity as compared to glibenclamide [61].

### Sulfonylureas and their clinical trials

Since a debatable question was raised by UGDP study about the safety and effectiveness of sulfonylurea drugs in

ameliorating hyperglycemia, many studies have been carried out to evaluate the long-term results of sulfonylurea therapy in patients with *Diabetes Mellitus*. Here, some of these important studies and clinical trials carried out worldwide are listed. Balodimos and co-workers evaluated the effects of tolbutamide treatment for up to nine years in 3,387 patients [63]. For at least one month, satisfactory control was observed in 2,555 patients. During the course of study, 526 suffered primary failure while 499 suffered secondary failures with tolbutamide. Thus, nearly two-thirds (75.4 percent) achieved satisfactory control. Overweight and patients who had been on no or less than 20 U. of insulin per day were among the most effectively treated group. But the long term follow up was not made and only 430 patients were studied for six to nine years. Some investigators have interpreted this figure to mean that only 10 percent of patients respond to the therapy for greater than six years which although does not seem to be a valid conclusion. In 1965, a six-year investigation report was published by Bernhard [62]. According to this study, diabetes of 73.3 percent of the patients out of 8,538 diabetic patients was considered to be successfully controlled when treated with oral sulfonylurea. 455 i.e. 5.3 percent of patients suffered from primary failure while secondary failure was observed in remaining 1,258 cases. Diabetes more than five years old and being underweight were observed as the major reason for primary failures. 1,258 cases of secondary failures were seen among the patients associated with other complications like cardiovascular disorders, infectious diseases, or improper diet. Rest 5,052 patients were satisfactorily treated with sulfonylurea and the good response was maintained for five to six years. Of the 5,052 patients in satisfactory control on the oral sulfonylureas, 756 (15.0 percent) had been treated for five years and 741 (14.7 percent)

for six years. Therefore, majority of patients were responsive toward the treatment and were well treated and very less number of true primary and secondary failures were there.

Several other studies with less number of patients treated for shorter periods were done which present similar data [64, 65]. The results obtained in 200 diabetic patients treated with tolbutamide for five years were reported by De-Lawter and Moss [66]. Satisfactory control was observed in 13 percent patients, 10 percent had been switched to another agent. 22 percent has been suffered from primary failure, secondary failure were observed in 36 percent while the remaining patients were either dead or follow-up was lost. Another four years study was reported by Powell et al. on 676 patients treated with tolbutamide or chlorpropamide [67]. There were 67 primary failures (19 per cent), 66 secondary failures (11 per cent), 58 fairly controlled (10 per cent), and a major fraction i.e. 465 (79 per cent) were in good control. Another study was conducted for three years on diabetic patients with an objective to maintain the postprandial blood sugar below 150 mg/dl with oral sulfonylureas and diet therapy [68]. The usual medication of patients was substituted with identical placebo for six months, unless the degree of hyperglycemia forced a return to drug treatment. Placebo trials were carried out after every two years. 70.5 percent showed satisfactory response to the drug and 31.2 percent demonstrated satisfactory control even with the placebo substitute. Of 282 patients treated with tolbutamide, 29.5 percent were primary failures and 18.1 percent suffered secondary failures. While in case of chlorpropamide treated group, 36.4 percent developed primary failures, 14.9 percent secondary failures 16.9 percent responded well to placebo, and 30.8 percent

responded satisfactorily to the drug. In this study however, one major drawback in the methodology was that many patients did not meet the criteria for oral sulfonylurea therapy. On correcting this factor, the success rate was increased to 29.8 percent for tolbutamide and to 51.1 percent for chlorpropamide. Thereafter, similar studies have been reported showing the need for placebo controls for the patients who initially started with sulfonylureas. Tompkins and Bloom found the effects of discontinuing of sulfonylurea therapy [69]. Lev-Ran studied changes due to substituting chlorpropamide with placebo in 50 diabetic patients on long-term therapy [70]. The stability of 12 patients suffering from maturity-onset Diabetes Mellitus was studied by Charles and Donald [71]. A 12-week cross-over study design was done after careful examination of post dose variance individualized to the patient's requirements. Greater stability of fasting blood sugar and less glycosuria was observed in patients treated on tolazamide. Feldman suggested the patients with liver disease or significant renal disease should not be prescribed with glyburide. He also stated that the adverse effects of glyburide are lesser than chlorpropamide which is a first generation drug [72]. There are no definite reports on increasing risk of cardiovascular disease of diabetic patients when sulfonylureas were administered but long-term administration may lead to decrease in the resistance of muscle and liver to the action of insulin. Some studies demonstrated the feasibility of oral sulfonylurea treatment in Prenatal Diabetes Mellitus patients with Kir6.2 mutations even during infancy, and the superiority of this approach over insulin administration [73, 74]. Brogden et al. studied that glipizide is at least 100 times more potent than tolbutamide but the duration of action of glipizide is shorter than that of glibenclamide [75]. An increase in

immunoreactive insulin and a decrease in fasting blood glucose levels can be brought by a single dose of glipizide. Bo et al. showed the result of 14 years study done on the associations between mortality and treatments with different sulfonylureas of 1277 type 2 diabetic patients. It was confirmed during follow up that none of the patients treated with gliclazide died from cancer [76]. Vichayantraj et al. assessed 6 months cross-sectional survey on sulfonylurea treated patients with longitudinal phase evaluation. The survey suggested that marked reductions in HbA1c and fasting blood glucose are achievable by using oral sulfonylurea therapy in the treatment of diabetes [77].

During the clinical development of glimepiride, a total of 21 clinical studies with a minimum duration of two weeks were conducted in the United States and Europe. The study included four placebo-controlled, four active-controlled (with glyburide and glipizide), and three noncomparative trials (eight active controlled and two non-comparative). All the patients under study provided their medical history prior to trials. 6,500 patients were monitored for symptoms emerging because of treatment. Clinical laboratory abnormalities, discontinuations, deaths, and serious adverse events were also studied [78, 79].

### Sulfonylurea overdose

A very prompt outcome of high or overdose of sulfonylureas is hypoglycemia. The most popular oral drugs among patients with type II diabetes are the sulfonylureas. In 2007, there were 4,384 sulfonylurea exposures reported to the American Association of Poison Control Centers National Poison Data System, accounting for 34% of overdoses from oral hypoglycemics and antihyperglycemic drugs [80, 81]. In adults,

there may be many reasons for hypoglycemia like wrong dose, double dosing, drug interactions, impaired drug metabolism, or decreased drug excretion [82, 83]. Review of national poison center data reported 14 sulfonylurea-associated fatalities reported between 1992 and 1996 in adults aged 18 to 79 years.

### Antidotes for sulfonylurea induced hypoglycemia

**Restoration by 50% dextrose:** This has been one of the traditional methods used to overcome hypoglycemia associated with sulfonylureas. In this case, a continuous intravenous infusion of 10% dextrose at a rate of 250 ml/h with potassium supplements was commenced simultaneously [84]. But despite the continuous intravenous infusion of 10% dextrose, hypoglycemia (venous glucose 2.0 mM) recurred in almost all the cases studied.

**Diazoxide administration:** Diazoxide, an antihypertensive agent (Scheme 10), acts as a potassium channel opener and is used to reduce insulin release and limit rebound hypoglycemia [85]. It must be administered intravenously but its use could cause hypotension, nausea and vomiting [86, 87].

**Administration of Octreotide:** Octreotide is a synthetic peptide analogue of somatostatin (Scheme 11). It binds to G protein-coupled somatostatin-2 receptors in pancreatic  $\beta$ -cells and results in decreased calcium influx and thus inhibits of insulin secretion. Clinical trials have been done with both subcutaneous and intravenous administration. The subcutaneous administration is generally adopted in doses ranging from 40 to 100  $\mu$ g in adults and 1 to 10  $\mu$ g/kg in children [88]. In a paediatric case, a 1 $\mu$ g/Kg intravenous dose was used [90]. Whenever there is a need to take

octreotide along with standard therapy of diabetes, usually, a short term treatment of upto 12-72 hrs is sufficient but in some rare cases administration may be required for several days, especially with long-acting sulfonylureas [91]

Several trials have already been carried out to prove the efficacy of octreotide. Some of the very early studies have been listed here, covering almost all age groups affected by hypoglycemia. Krentz and coworkers [92] reported that the administration of octreotide prevented reoccurrence of hypoglycemia on a nondiabetic patient with sulfonylureas-induced hypoglycemic coma, who relapsed despite revival with intravenous lozenges of 50% glucose and continuous 10% glucose infusion. The reoccurrence of hypoglycemia was significantly controlled by injecting 50 $\mu$ g octreotide subcutaneously after every 12 hrs. The utility of octreotide in treating sulfonylureas-induced hypoglycemia have been confirmed by various clinical trials [93, 94]. Nzerue and coworkers [95] reported the case in which a patient suffering from long and prolonged hypoglycemic episodes has been fully recovered after only two subcutaneous doses of octreotide. The recovery of patient was ineffective of the fact that he was suffering from chronic renal failure. Green and Palatnik [96] reported the case of a 20-year-old woman who ingested 900 mg gliburide. The ingestion resulted in hypoglycemia which was quickly brought under control by 100  $\mu$ g intravenous administration of octreotide. Before administering octreotide, treatment with intravenous glucose, glucagon, and diazoxide had been tried but failed in controlling the reoccurrence of hypoglycemia. An observational series was reported by McLaughlin and colleagues [97] that reviewed the reports of treating nine adult patients with octreotide. Out of these nine patients, six had ingested gliburide and

three had ingested glipizide and were treated for sulfonylurea-induced hypoglycemia from 1995 to 1998. The study suggested that more relapsing of hypoglycemia could be prevented by administration of octreotide for extended period. Crawford and Perera studied a successful management of sulfonylureas-induced hypoglycemia with octreotide [98] in two diabetic patients suffering from impaired renal functions. Frequent hypoglycemic episodes were observed when one of them underwent emergency bypass surgery due to sudden cardiac arrest. Reoccurrence of hypoglycemia was observed in spite of gliclazide discontinuation and intravenous infusion of glucose 10%. However, an intravenous infusion of octreotide (30 ng/Kg /min) was maintained for 13 hours and the patient was discharged home 2 days later. In the case of second patient, hypoglycemic coma occurred despite glibenclamide discontinuation. The supplementation with intravenous boluses of glucose 50% and continuous infusion of glucose 10% were also ineffective but a single subcutaneous injection of 50  $\mu$ g octreotide normalized blood glucose level and no further episodes of hypoglycemia occurred. Charles J. et al. reported a random trial of 40 patients; of which 18 were on placebo while 22 were treated with 75  $\mu$ g of octreotide subcutaneously. It was observed that treatment with placebo did not long for longer duration while addition of octreotide to standard treatment increased serum glucose value to significant level [99]. Octreotide has not been adequately studied for the treatment of children. Benjamin et al. studied eight patients with hyperinsulinemic hypoglycemia of infancy [100]. All were given octreotide subcutaneously 3-4 times. The treatment was discontinued in five patients after 9 months while remaining were continued with the treatment. Paul and Craig also examined the efficacy of

octreotide in nine infants and found that a long term treatment with octreotide was successful [101]. A 5-year-old child who was erroneously given glipizide in repeated doses over 3 days diagnosed with hypoglycemia. In spite of glucose supplementation (up to 18 g/hour), recurrent hypoglycemia developed. An intravenous administration of 25 µg octreotide resulted in a rapid increase in glycemia and glucose administration was completely stopped 4 hours later. Another case is of a 16-month-old child admitted one hour after accidental ingesting glyburide [97]. Recurrent hypoglycemia developed despite continuous infusion of 10% dextrose and 50% glucose. 10 µg octreotide intravenously over 15 min was given 5 hour after ingestion and glucose level was then maintained with 10% glucose infusion, without any additional bolus. A second dose of octreotide had to be given 8 hours later. After second octreotide injection, glucose 10% infusion was completely stopped. All these clinical trials suggest that octreotide can be used in effective treatment whenever reoccurring

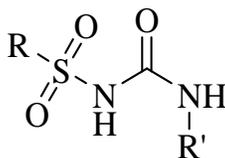
hypoglycemia induced by sulfonylureas has been diagnosed [102]. The use of octreotide is far better than the use of glucose supplementation and consequent insulin release and can safely be used in adults as well as in children.

In summary, the sulfonylureas have been regarded as potent antihyperglycemic agents but structural changes need to be carried out in order to eliminate various adverse effects related to them. However, studies are being made on the inclusion of other pharmacological agents (as per the requirement of patient) like octreotide in the treatment or prescribing them along with other antihyperglycemic agents which may lead to better treatment.

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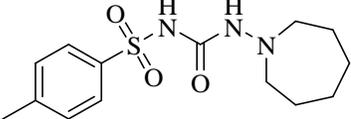
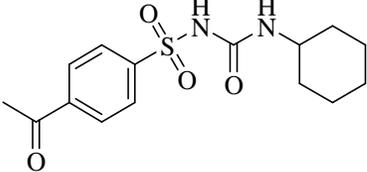
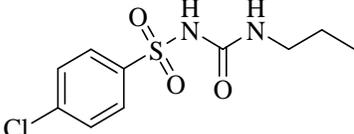
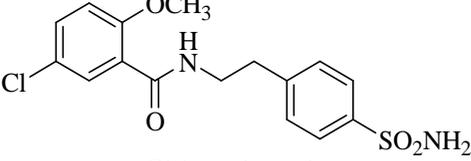
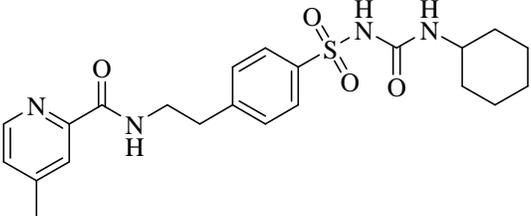
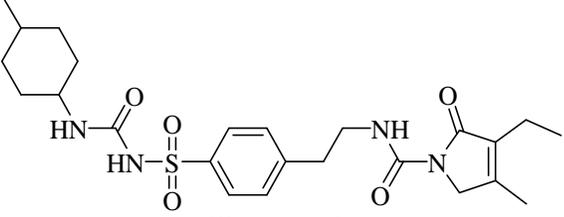
### Schemes and Figures

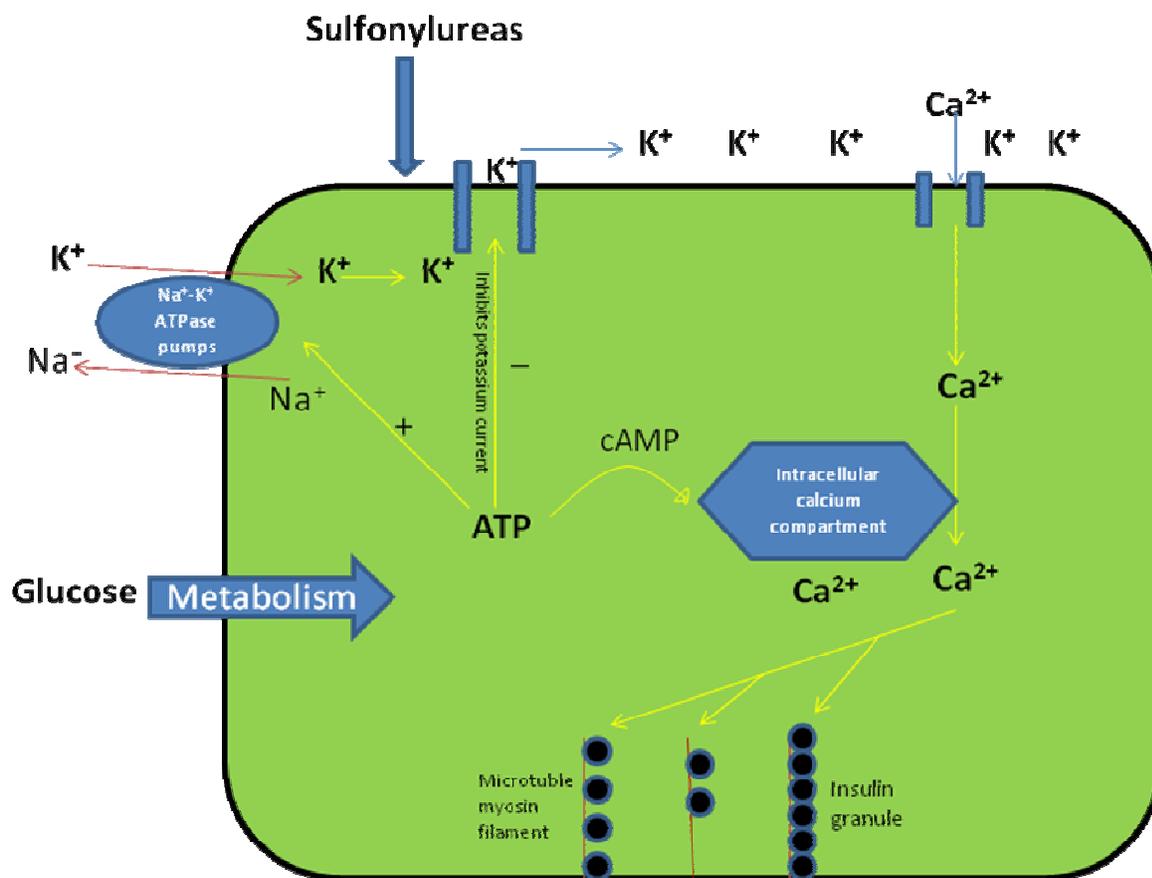


**Scheme 1:** General structure of Sulfonylureas.

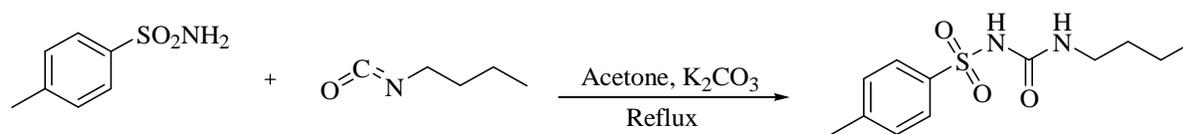
**Table 1:** Some commercial sulfonylureas and their classification.

First generation sulfonylureas	<p>Tolbutamide</p>
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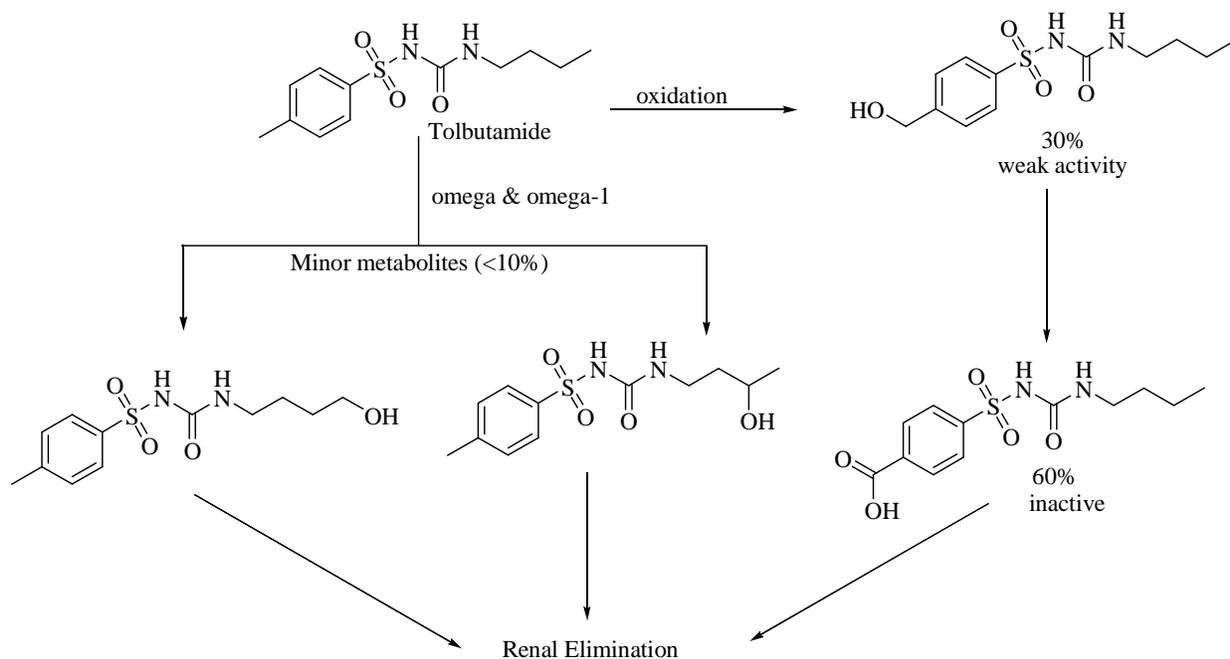
	 <p>Tolazamide</p>  <p>Acetohexamide</p>  <p>Chlorpropamide</p>
Second generation sulfonylureas	 <p>Glibenclamide</p>  <p>Glipizide</p>
Third generation sulfonylureas	 <p>Glimepiride</p>



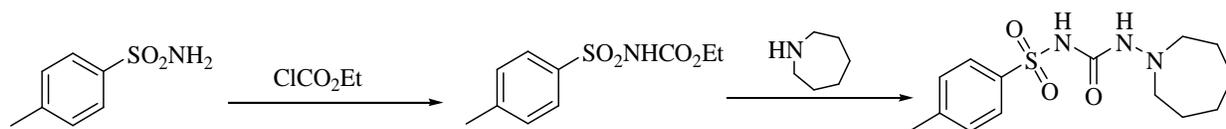
**Fig. 1:** Schematic representation of mode of action K<sub>ATP</sub> channels and sulfonylureas.



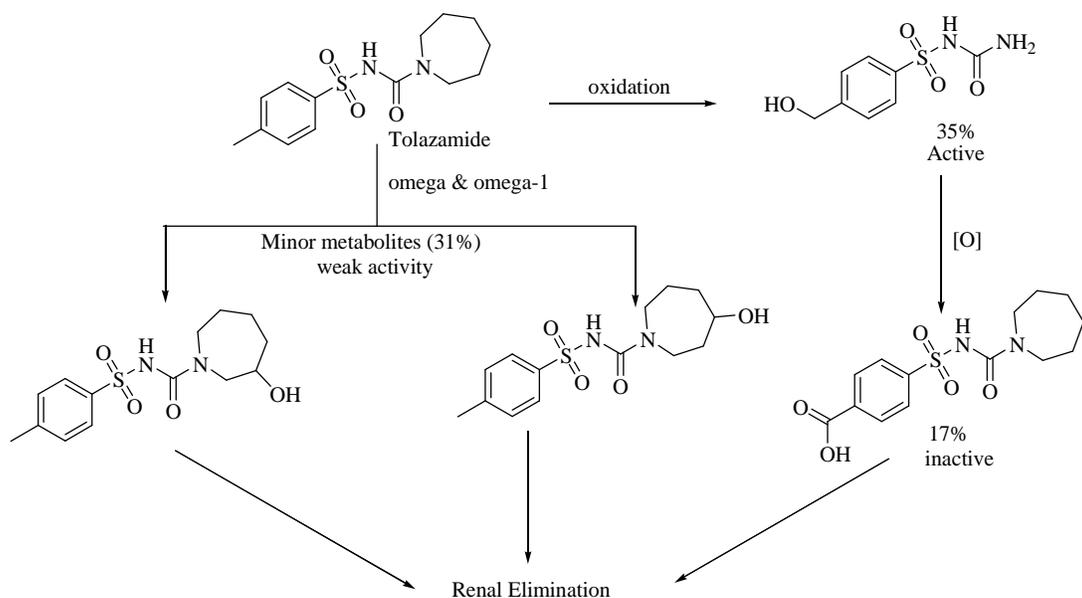
**Scheme 2a:** Synthesis of tolbutamide.



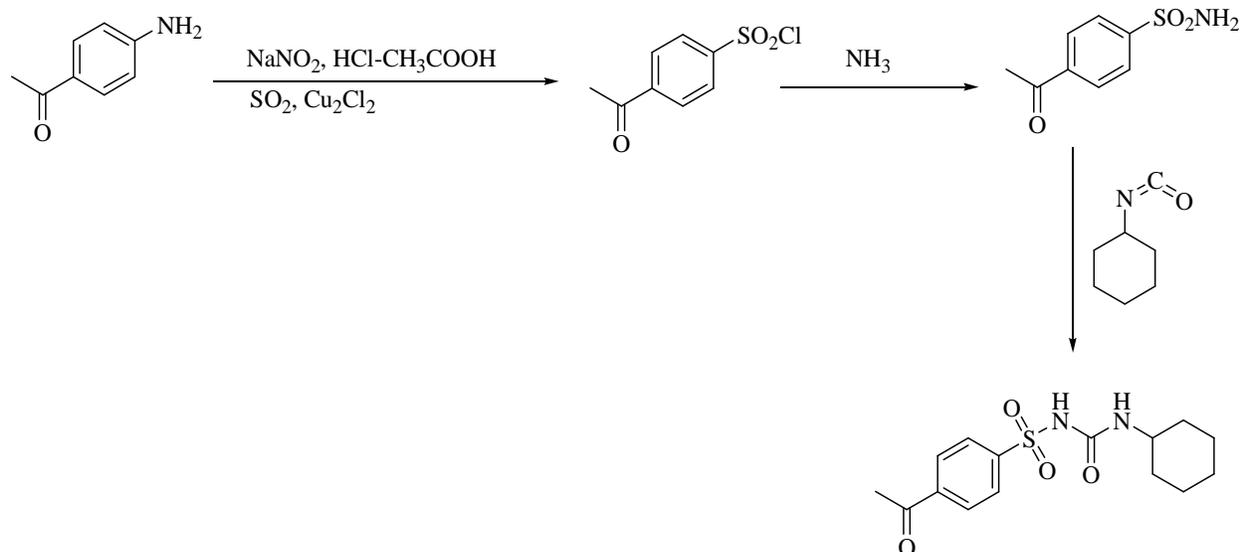
Scheme 2b: Metabolism of tolbutamide.



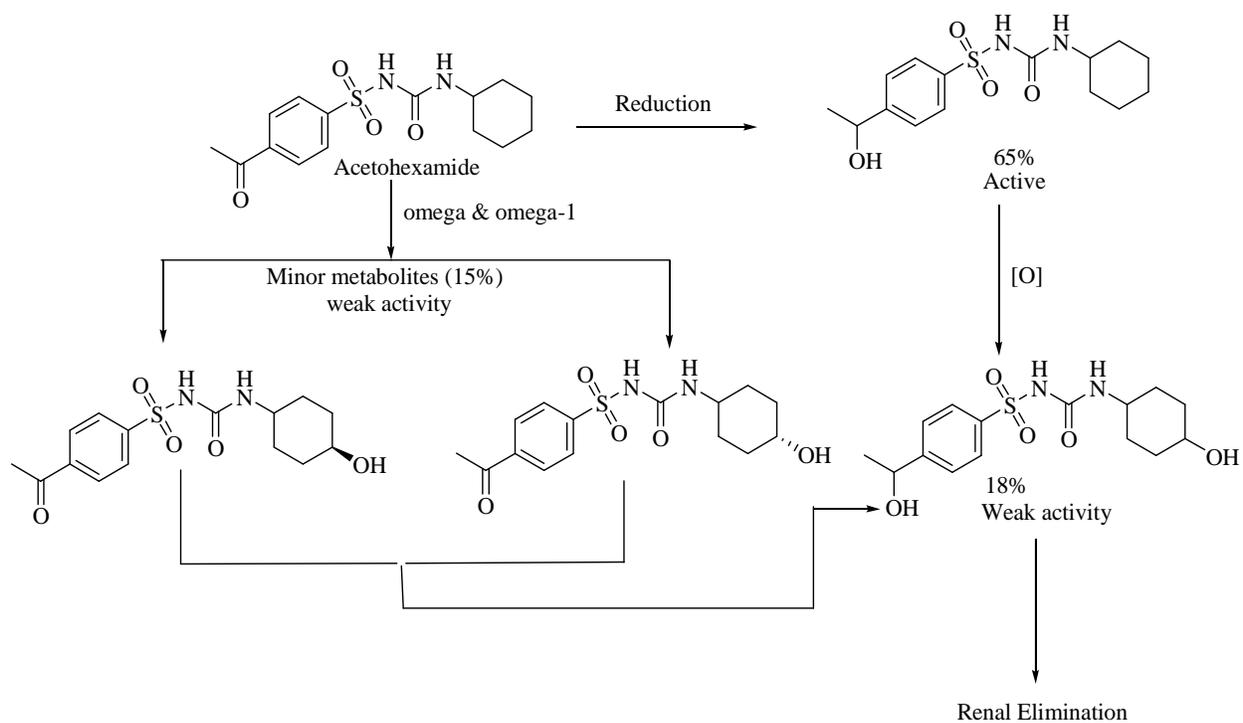
Scheme 3a: Synthesis of tolazamide.



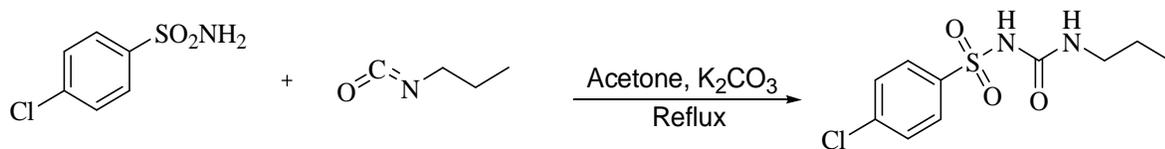
Scheme 3b: Metabolism of tolazamide.



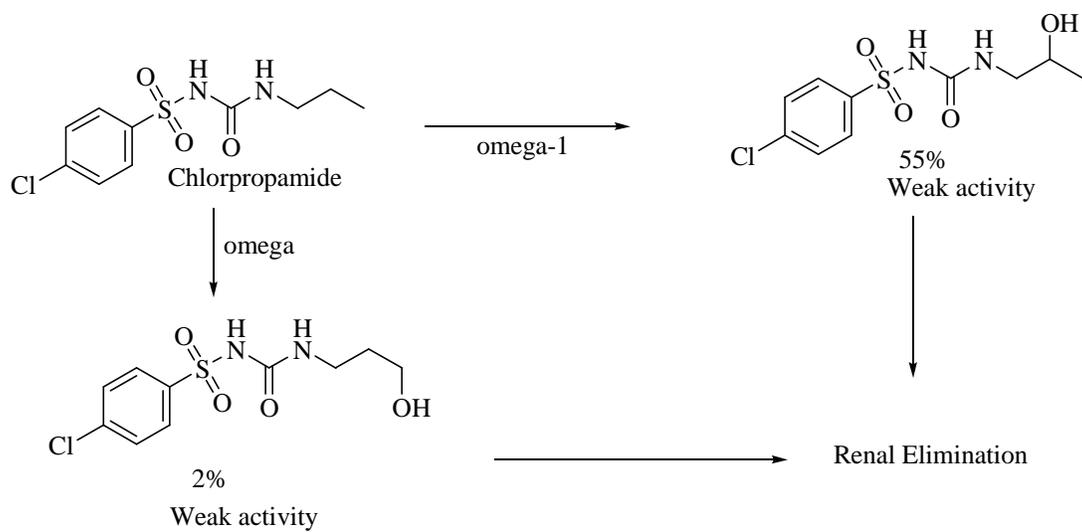
**Scheme 4a:** Synthesis of acetohexamide.



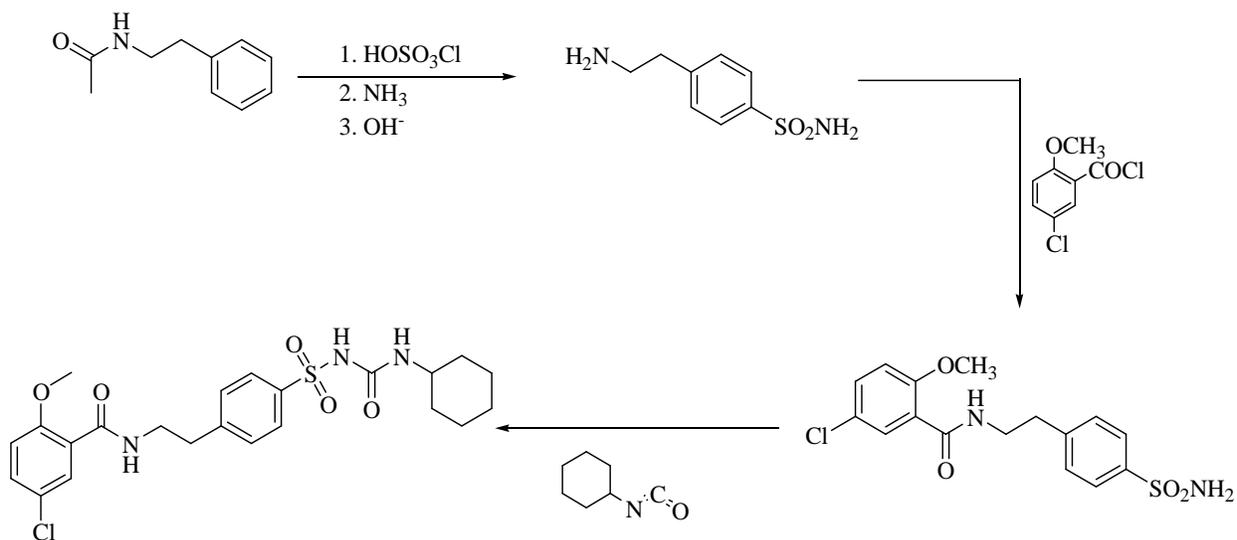
**Scheme 4b:** Metabolism of acetohexamide.



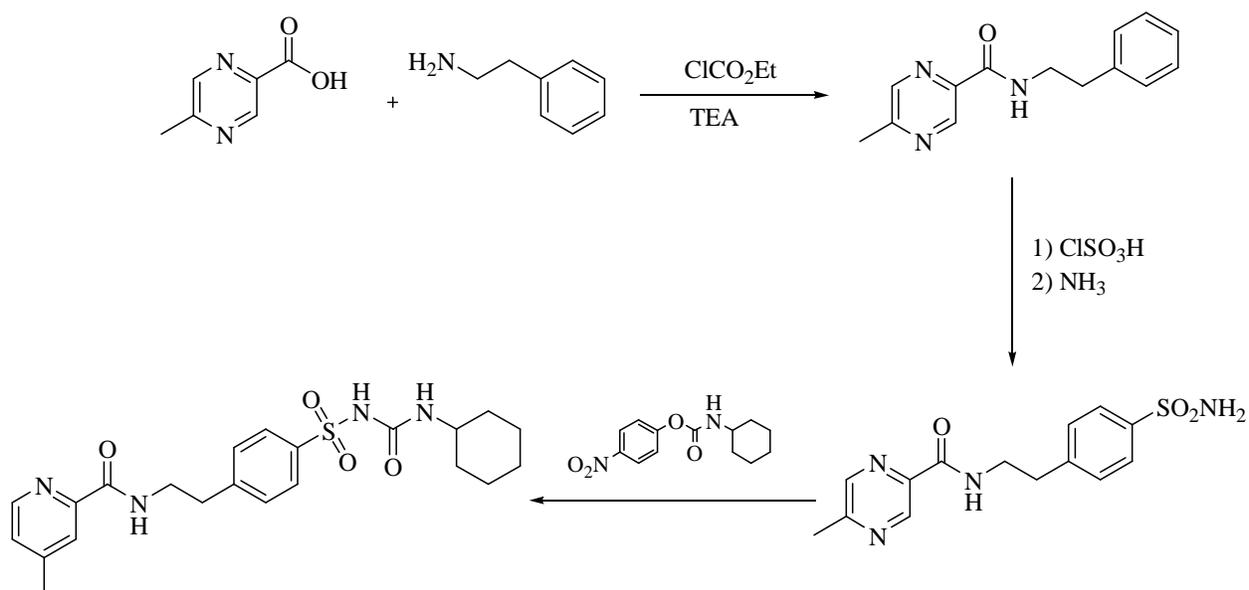
Scheme 5a: Synthesis of chlorpropamide.



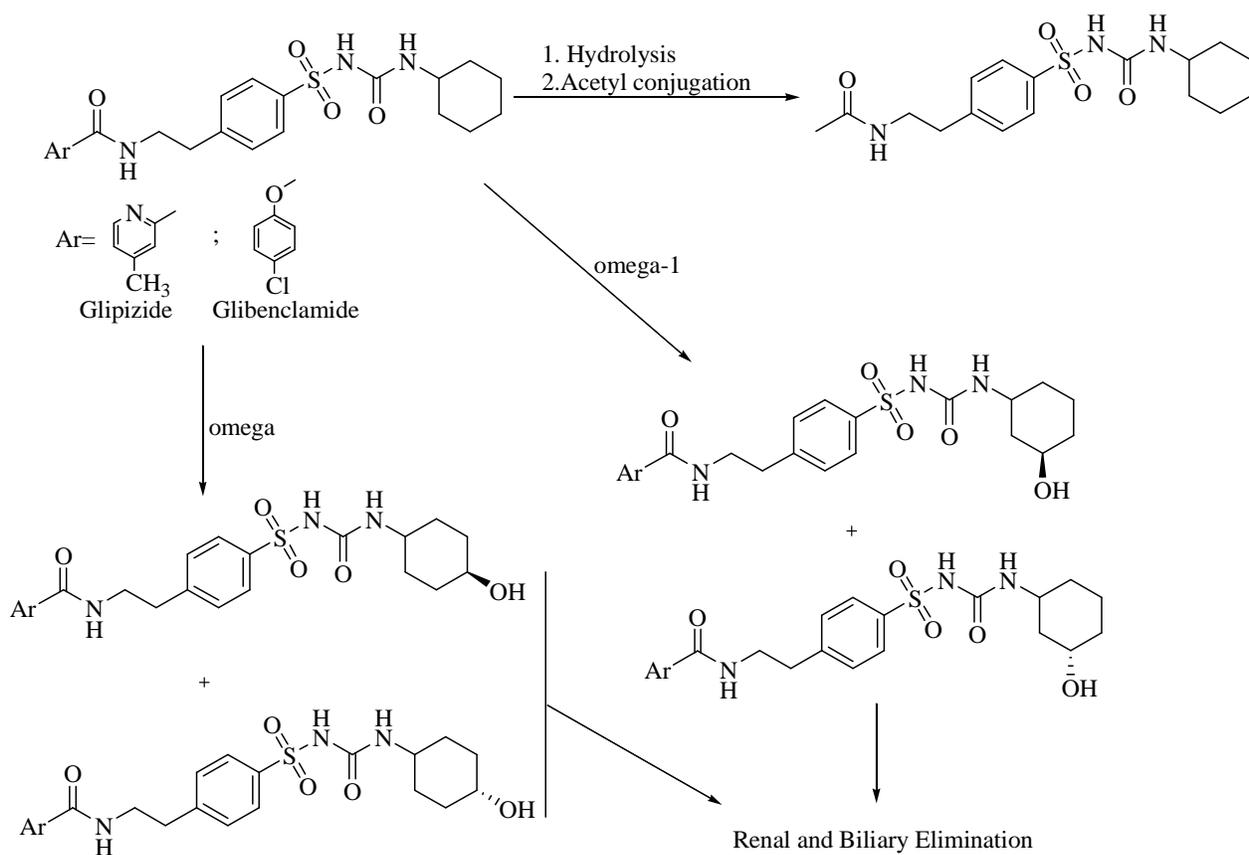
Scheme 5b: Metabolism of chlorpropamide.



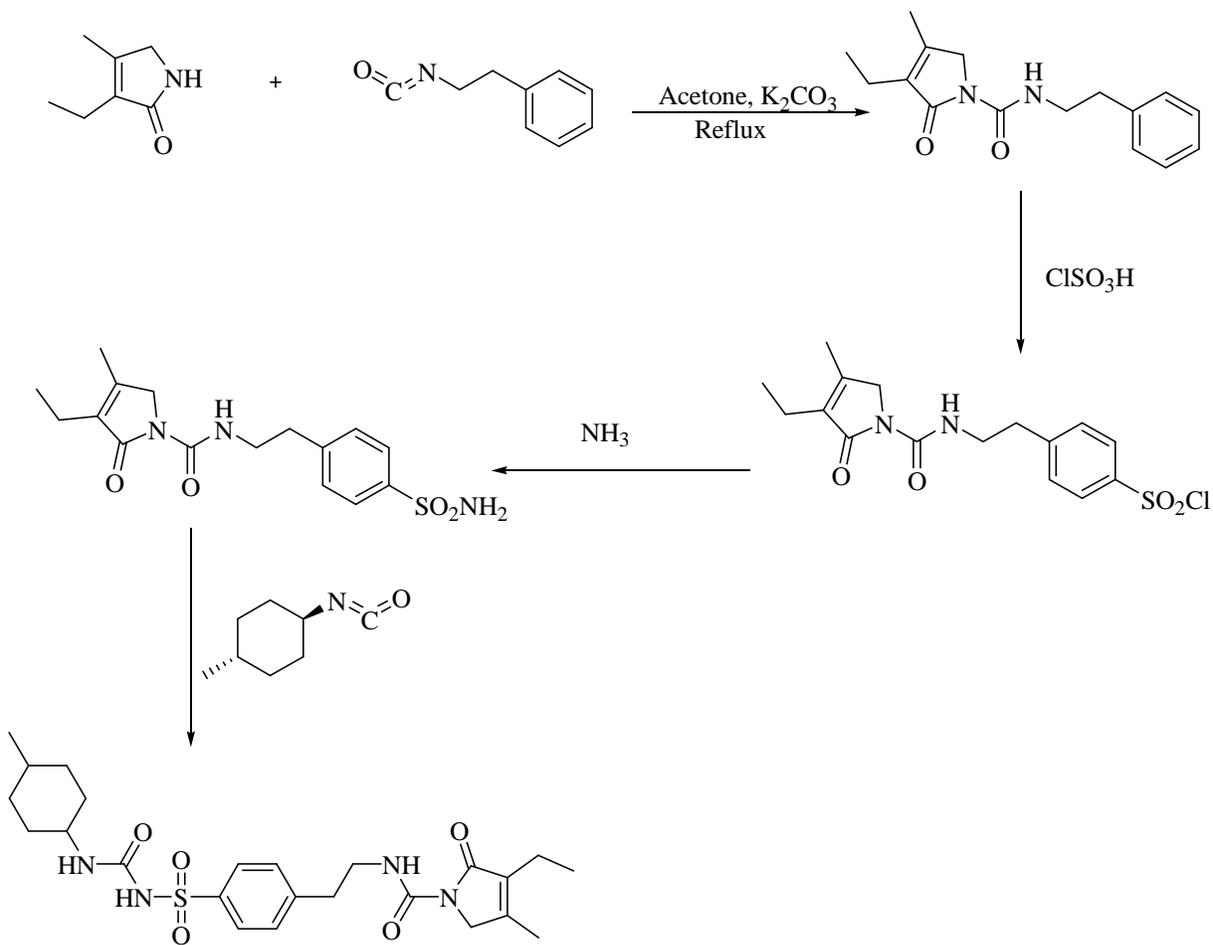
Scheme 6a: Synthesis of glibenclamide.

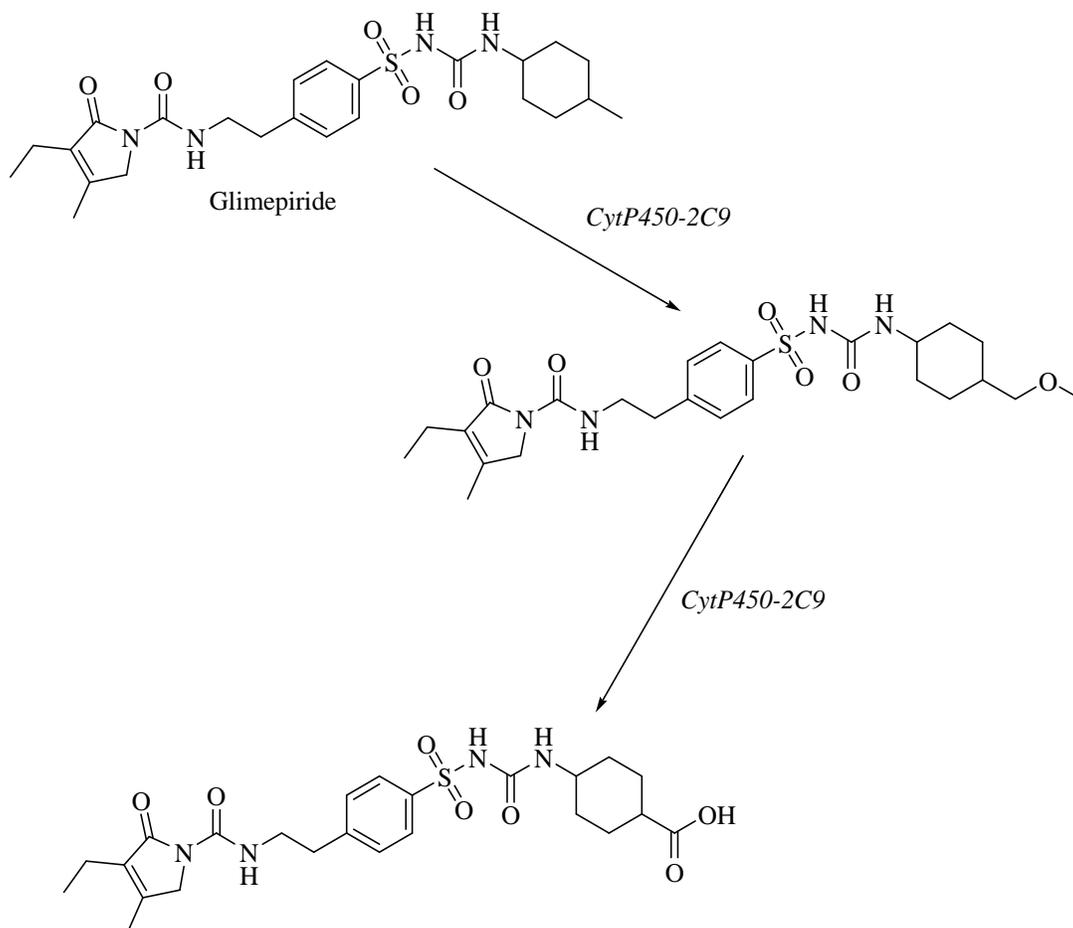


Scheme 7: Synthesis of glipizide.

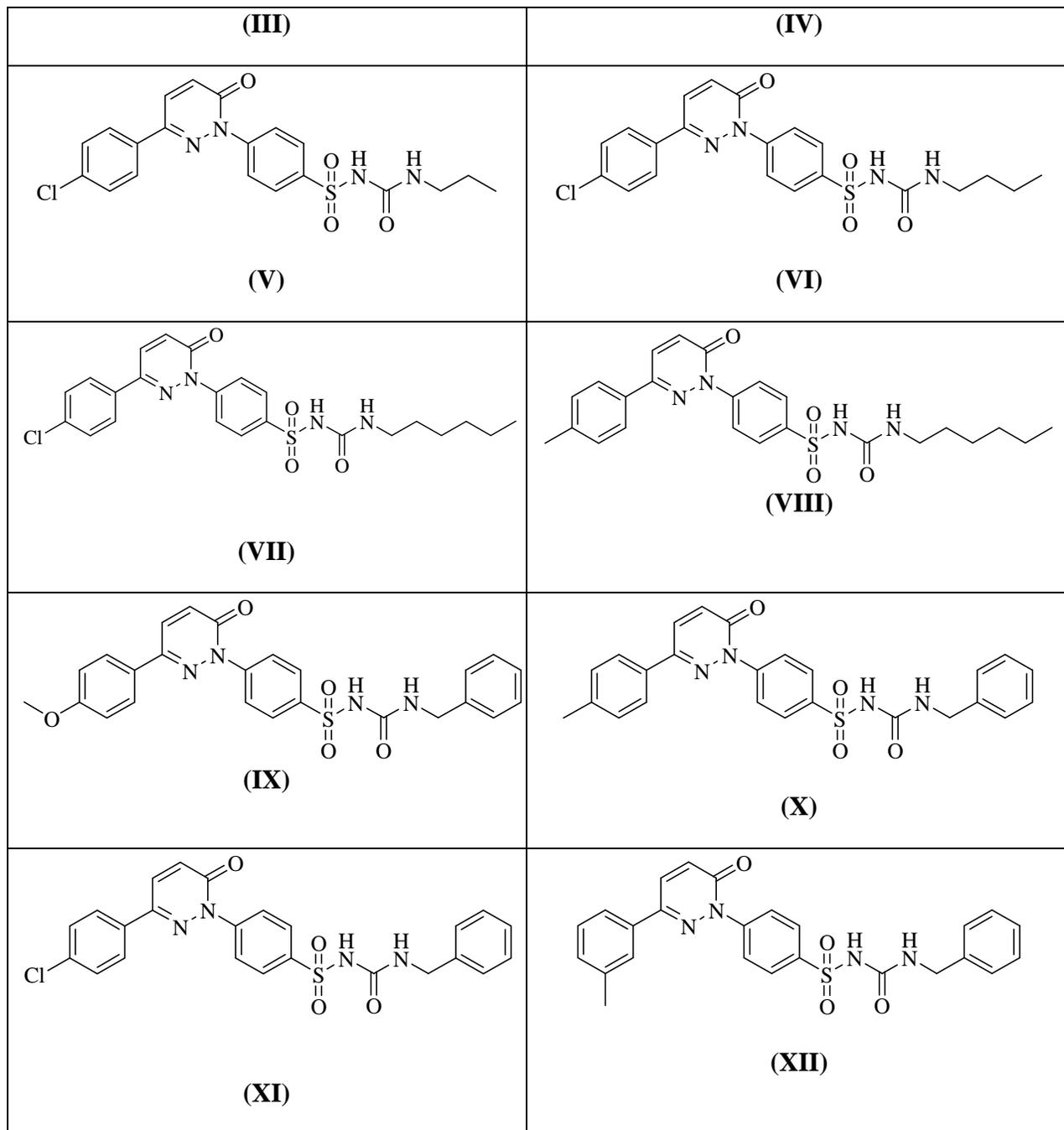


Scheme 6b: Metabolism of glibenclamide/glipizide.

**Scheme 8a:** Synthesis of glimepiride.

**Scheme 8b:** Metabolism of glimepiride.**Table 2:** List of active benzenesulfonylurea derivatives (I – XII).

<p><b>(I)</b></p>	<p><b>(II)</b></p>





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