CHAPTER - 1

INTRODUCTION
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Type 2 diabetes mellitus is a metabolic disorder of biochemicals like carbohydrate and fat. The insufficient or deficit in insulin secretion makes the improper metabolism of glucose which is a major cause of diabetes mellitus (Anirban et al., 2005). Diabetes is the major problem throughout the world, especially in developed countries. There are more than 220 million people are suffered from this disorder and by 2025 it is expected to reach in around 300 million (Simon et al., 2010). The major prevalence and injurious effect on the physical as well as the psychological state of the patient become a major concern of medical expert. Due to its incurable status at present, the drug is only choice to control of diabetes. Nearly 80% patients of noninsulin dependent diabetes mellitus (NIDDM) are commonly treated by the oral hypoglycemic agents to control the diabetic symptoms. The key factor in the pathogenesis of NIDDM are insulin resistance and impaired insulin secretion so the treatment should be directed toward restoring metabolic normality by improving insulin secretion and reducing insulin resistance.

Insulin resistance is a condition in which the uptake of glucose by skeletal muscle gets reduced because insulin activates the glucose transport in skeletal muscle where it stored as glycogen. This may lead the increased blood glucose level in type 2 diabetes patient (Henriksen et al., 2006). The glycogen synthase kinase-3 (GSK3) is an enzyme which performs important role in the regulation of insulin resistance activity by affecting insulin-stimulated glucose transport (Oreña et al., 2000). Glycogen synthase is an enzyme that responsible for the assimilation of free glucose to glycogen particle, thus level of glucose gets balanced in the body (Jensen et al., 2009). Glycogen synthase kinase-3 is serine/threonine kinase tends to inhibit glycogen synthase by its phosphorylation (Lee et al., 2012). An efficient GSK-3 inhibitor may help to manage the problem of glucose level by promoting glycogenesis in diabetic patients (Embi et al., 1980). The sulfonylurea agents are one of the options from oral hypoglycemic agents options to achieve these goals (DeRuiter, 2003).
It is considered as the hypoglycemic effect of sulfonylurea compounds are exerts by promoting the insulin secretion from receptor of pancreatic β-cell (Kecskemeti et al., 2009). Sulfonylureas are got bind with the ATP-sensitive K+ (KATP) channels in the cell membrane of β-cell in the pancreas, that prevent the outward movement of potassium ion after depolarization of the cell. The voltage-gated Ca2+ channels now open due to depolarization and raise the intracellular calcium which leads to improved fusion of insulin granules with the membrane of the cell and thus secretion of insulin is occurs (Proks et al., 2002).

![Diagram of mechanism of sulfonylurea drugs in beta cells of pancreas.](#)

**Fig.1: Mechanism of action of sulfonylurea drugs in beta cells of pancreas.**

However some publications suggest that the first generation sulfonylureas (chlorpropamide, glycyclamide, metahexamide, tolazamide and tolbutamide) having limited/ specific site for binding with plasma membrane of β-cell due to poor penetration ability (Flatt et al., 1994). It may be due to lower lipophilicity or due to ionized form of sulfonylureas.
To overcome these limitations, second generation sulfonylureas (glibenclamide (glyburide), glibornuride, gliclazide, glipizide, glimeperide) have developed which so potent stimulator of insulin secretion give a success for the control of type 2 diabetes. But the hurdles are still there as the second generation sulfonylureas are leads the hyperinsulinemia that causes the weight gain or hypoglycemia in diabetics (Hamaguchi et al., 2004).
Beside the antidiabetic profile of sulfonylureas, some of the sulfonylurea containing derivatives are also been evaluated for the H$_3$ receptor antagonist very efficiently (Ceras et al., 2012). The best thing of the sulfonylurea, it is a group of functional pharmacophore like sulfonamide which has been established as an effective inhibitor of metalloenzyme carbonic anhydrase that is very useful for reducing intraocular pressure in glaucoma (Vullo et al., 2004). From the urea moiety of the sulfonylurea molecule, we may search for the anti-inflammatory activity (Zarghi et al., 2008). The antimicrobial character of sulfonylurea drugs has also studied against the resistant bacteria strain (Krajacic et al., 2005). The urea moiety of sulfonylurea derivatives was suggested as the bioisosteres of cyclic acylurea of
phenytoin an anticonvulsant drug. After evaluation of the activity, these were showed an equal response to the phenytoin which may explore the way for working with sulfonylurea as an anticonvulsant drug (Masereel et al., 1997).

Convulsion is a disorder at cortical neurons of brain in which the recurrent neuronal firing takes place. The overproduction of this impulse leads the transitory loss of consciousness and other brain related dysfunction. This neuronal firing results from the prolong depolarization of neuronal membrane due to an opening of voltage-gated Na\(^+\) channels which initiate the action potentials repeatedly (Köhling et al., 2002). Voltage-gated sodium channel is the target for various cyclic anticonvulsant drugs i.e. phenytoin, carbamazepine, lamotrigine (Lipkind et al., 2010), phenobarbitals (Rajak et al., 2010). Sulfonylureas are chemical bioisosteres of the cyclic acylurea moiety present in phenytoin, a potent anticonvulsant drug (Masereel et al., 1991). This bioisosteric relation made the test compounds vulnerable to produce anticonvulsant effects via the same mechanism as the phenytoin exhibits.

It has also suggested that the activity can be attributed due to its ability to inhibit astrocytic Na\(^+\) 2HCl K+ co-transport same as torasemide which having sulfonylurea in its structure. Torasemide has the similar action as the furosemide that obstructs kainic acid-induced electrical discharges observed from the cortex (Hochman et al., 1995) and it is neuroprotective agents, for instance antagonizing the N-methyl-D-aspartate (NMDA) and non-NMDA receptors on evaluation for antiepileptic activity.

![Diagram of Torasemide](image-url)
In silico (docking) study is the best way to develop mechanism based molecules, which could identify more precisely the bonding requirements in structure with targeted protein molecule. The bonding interaction of test molecule with the individual residue in the protein structure could more helpful to find the way of interaction and orientation of molecule at the targeted site. It also helpful in the explanation of the mechanism of action of test compounds. In the present work, the GSK3 is an enzyme which can be taken as protein residue to find whether the approach of test compound in the blood glucose lowering effect occurring or not. In a similar way, the anticonvulsant activity can be justified by taking voltage-gated sodium channel as targeted protein residue.

The general structure of the sulfonylurea contains an aryl moiety along with the sulfonyl group and urea molecule which are arranged in the following manner:

\[
\text{Ar} + \text{SO}_2 + \text{HCONH} \rightarrow \text{ArSO}_2\text{NHCONH}
\]

The Ar and R portions of this general structure provide lipophilic character whereas the -SO2-NH-CO-NH- moiety is hydrophilic. All of these functional groups are required for activity, but the lipophilic Ar and R groups account for the differences in potency (sulfonylurea receptor SUR binding), metabolism, duration, and routes of elimination (DeRuiter, 2003).

The aryl sulfonylureas are weak organic acids (pKa = 5.6) and are largely ionized at physio-logical pH. This ionization contributes significantly to drug potency, SUR (affinity), extensive plasma protein binding of these agents (>95%). Also, alkalinization of the urine enhances ionization and elimination (shortens half-life).
Chapter 1

Introduction

To avoid the problem of short half-life could be possible to substitute the first nitrogen group of sulfonylurea which may prevent the ionization of this nitrogen this may be contributed to the longer half life.

Thus, the objective of the present research work is to prepare and evaluate the trisubstituted and bisubstituted sulfonylurea molecule for blood glucose lowering (antidiabetic) as well as the effect on CNS disorder like anticonvulsant activity, containing different heteroaryl and substituted aryl group in animal models. The work is also extended to investigate the possibility of an anticonvulsant profile of designed molecule by mean of different in vivo models. Following are some pharmacophoric changes that can be achieved by the synthesis.

![Normal sulfonylurea](image1)  ![N-substituted sulfonylurea](image2)