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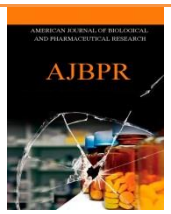

ANTIDIABETIC ACTION OF SULPHONAMIDE DERIVATIVES:A REVIEW

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ABSTRACT

Diabetic mellitus is a metabolic disorder which can be characterized by the hyperglycemic resulting from defect in the insulin secretion. Diabetic mellitus are of two types; insulin dependent and non- insulin dependent. Most commonly found diabetic mellitus is a non-insulin diabetic mellitus, which are characterized by destruction of pancreatic cell or decrease insulin secretion. There are many pharmacological and non-pharmacological treatments. Pharmacological treatment includes sulfonamides and biguanides that can be used to reduce the hyperglycemic effect. Sulfonamides are known as sulfa drugs. Sulfonamide that have the sulfonamide moiety of $S0_2NH_2$ have which are responsible for the various pharmacological action like hypoglycemic ,antivirus, antibacterial, anti-carbonic anhydrous, ant thyroid activity. But sulfonamidehas more anti-diabetic action and their derivatives like sulphonulurea stimulates insulin secretion from the beta cell of the pancreas and that associated with hyperglycemic and weight gain. These include drug such as tolbutamide and glibenclamide. It concluded that, the sulphonamide derivatives show useful results for hypoglycemic activity compared to that of the control and standard respectively. This review highlights antidiabetic activity of sulphonamide derivatives.

INTRODUCTION

The common metabolic syndrome, diabetes mellitus, is a major human health concern in the world and it is estimated to effect 300 million people by the year 2025.Several drugs such as sulfonylureas and biguanides are presently available to reduce the hyperglycemia in diabetes mellitus. These drugs have side effect and thus searching for new class of compounds is essential to overcome this problems.

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Diabetic mellitus is a metabolic disorder which can be characterized by the hyperglycemic resulting from defect in the insulin secretion. Diabetic mellitus are of two types; insulin dependent and non- insulin dependent. Most commonly found diabetic mellitus is a non- insulin diabetic mellitus, which are characterized by destruction of pancreatic cell or decrease insulin secretion. The chronic hyper glycemic patient is due to the dysfunction and the defect in the various organs like kidney, eye, nerves and blood vessels. The abnormalities in the metabolism of fat, protein and carbohydrate may leads to the efficient action of insulin on target tissue. A deficient action of insulin that may be due to the insufficient secretion of insulin from the pancreas by the decreases in the response of the tissues to the insulin.

They are many marked symptoms for hyperglycemia which include poly urea, weight loss, poly dyspnea and blurred vision. Symptoms for chronic hyper-glycaemia which include the susceptibility to action infection and impairment in growth. Long term complication of Diabetic mellitus that include blurring of vision, retinopathy and nephropathy that may leads to the renal failure, special dysfunction in cardiovascular symptoms. Many diabetes individuals cannot fit in to single class.

The main cause of type 1 diabetic mellitus is the absolute deficiency of the insulin secretion by the beta cells of pancreas. Symptoms of the beta cell destruction include production of islet cell auto antibodies, antibodies to glutamic acid decarboxylase, auto antibodies to insulin and auto antibodies to tyro nine phosphate.In this form of DM, the rate of beta cell distribution is depend up on the individuals, rapid in the case of infants and children and slow in the case of adults. In the case of adolescents an children the first manifestation of the DM is by the presence of the ketoacidosis .The patient having fasting type of hyperglycemia that may leads to severe due to various infections.

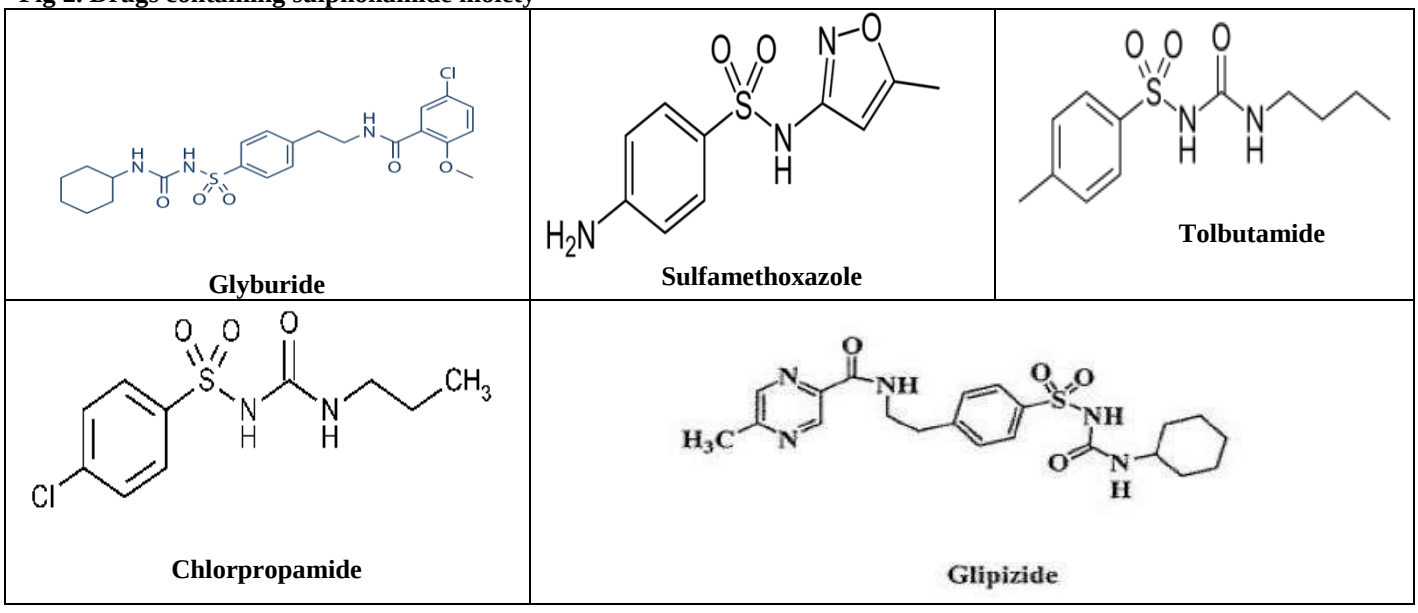
In type 2 DM, they have sufficient symptoms that include pathological and functional changes at the time but the DM that present long period of long time without any clinical symptoms even if the diabetes can be detected later. During this period, the diabetic that can be diagnose by the measuring the abnormalities in the carbohydrate metabolism by measuring the plasma glucose level in the fasting state or after the challenge in the oral glucose level. In some individuals, with diabetics they can treat hyperglycemic effect by weight reduction or by oral glucose lowering agent and by exercise. Some individual who have residual insulin secretion but they need adequate exogenous to control the glycemic level, they can even survive without it. But they have severity in the case of the patients having the beta cell destruction.

STRUCTURE OF SULPHONAMIDE

Fig. 1: Structure of sulphonamide

R groups simply represent any genomic side chain based on c-c and could be almost anything. Example R could be a methyl group, a benzene ring, an alkaline group or certain other groups. If the atom N contains two hydrogen's, the sulfonamide is classified primary, if there is a hydrogen atom it is secondary and if there is no hydrogen; present in the atom N then it is tertiary sulfonamide[1].

Fig 2. Drugs containing sulphonamide moiety



R Lavanya et al.,explaining sulfonylureas used as oral hypoglycaemic agents. Sulfonylureas contain sulphonamide functional group in their structure. General structure of sulphonylureas widely used in management of diabetes mellitus type 2. They act by increasing insulin release from the beta cells in the pancreas. Sufonylureas bind to and close ATP-sensiyive k channels in the cell membrane of pancreatic beta cells, which depolarizes the cell by preventing potassium from existing. This depolarization opens voltage –gated Calcium channels. The

rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of insulin[2].

Fig 3. Sulphanilamide

Various benzene sulfonamide derivatives were synthesised, by the two step reaction in which 2-bromo-1-(4-methoxyphenyl) ethanol was reacted with thiourea in refluxing ethanol yield 4-(4-methoxyphenyl)-thiazole -2-amine.The target compounds were synthesised by simple and facile condensation reaction of equimolar quantities of 2-amino thiazole with appropriate sulfonylchloride and evaluate their in vitro study. Abbas shafiee et al., reportedsome of the compounds demonstrated remarkable hypoglycaemic property, but with a degree of variation. Benzenesulfonamide derivatives showed a significant reduction in blood glucose compared to diabetic control rats at a dose of 100mg /kg po.Glibenclamide was taken as standard drug which showed a drop in blood sugar[3]

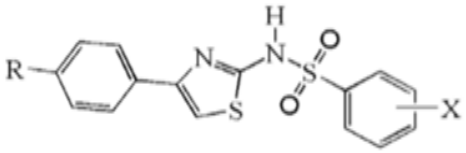


Fig 4. Benzenesulfonamide derivative

M. Akukulu Naidu et al reported the synthesis of novel Diarylsulfonylurea-chalcone hybrids.The key intermediate 1-(2-acetyl-3-pyridinyl)—tosyl urea was synthesised by reaction of tosylisocyanate with 2-2acetyl-3-aminopyridine and claisen-schmidt condensation of the intermediate with appropriate aromatic/heteroaromatic aldehydes under basic condition to give the corresponding derivatives and the hypoglycaemic activity was evaluated using animal models. In-vivo hypoglycaemic activity of the synthesiseddiarylsalfonylure-chalcone molecules showed that all the compounds possessed moderate to potential capacity to reduce the levels of glucose in the blood in type 2 normoglycemic and induced STZ[4].

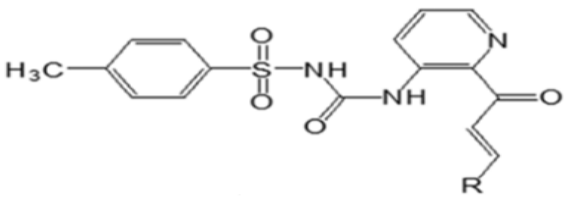


Fig 5. Diarylsulfonylurea-chalcone derivative

Abbas Ahmadi and coworkers obtained sulphonamide –benzothiazole derivatives by the addition of the triethylamine and 4-dimethylaminopyridine to a solution of 4-chlorosulfonyl-benzidine 2,4-thiazolidinedione.Then add 2-aminobenzothiazole and evaluate the antidiabetic action by 54 adult male NMRI rats with a blood sugar level of less than 150 mg /dl because the nine diabetic animals were randomly selected and housed three to four per cage in a colony room at controlled temperature under 12 hr light/dark cycle. All the experiments were conducted between 11a.m and p.m. Analysis of serum parameters Diabetes was induced in rats by intraperitoneal injection of streptozotocin at a dose of 70 mg/kg, dissolved in 0.1M cold citrate buffer (ph=4.5).Then the selected animals were randomly divided into six groups; There was no difference in serum glucose between the control group and the treatment group 4 days after the injection of STZ. However, on days9 and 16 following the application of STZ, a significant reduction in the glucose level was found in pioglitazone and other new compounds compared to the animals($p<0.05$).In the middle of the components, pioglitazone could have hyperglycaemic activity in comparison with other compounds[5] .

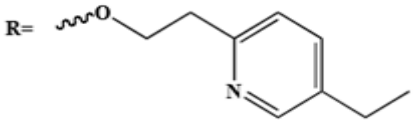


Fig 6. Sulphonamide–benzothiazole derivative

Hb Zhang et al, reported excellent hypoglycaemic activity of certain sulfonylurea derivatives. The reported compound can be used in the treatment of diabetes with cardiovascular and nephropathy complications. The targeted compound affects the release of insulin from pancreatic islets of isolated rats and the transport of glucose in the adipocytes of rats[6].

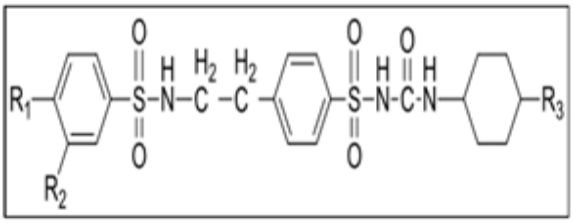
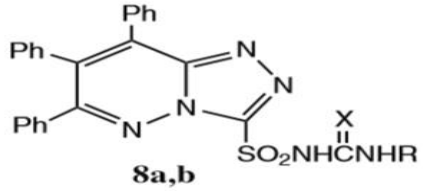


Fig 7. Sulfonylurea derivatives

Ali Deeb et al., synthesized some pyridazinesulphonamides by a mixture of 3-sulfonylchloride and ammonium hydroxide was stirred and refluxed. Then the solution was neutralized with 6N HCl. Then the solid product was filtered and evaluate the hypoglycemic activity by using the reference drug was Glipizide.Standard environmental condition such as temperature ($26+2^0$C)and relative humidity were

maintained. All the animals were fed with rodent pellet diet and water was allowed ad-libtum conditions.The animals fasted for 24h before induction of diabetes.The induction of hyperglycemia involves the intra-peritoneal injection of freshly prepared alloxan monohydrate. Fourty eight hrs later, blood samples were collected from 8h fasted animals from the retro-orbital plexus in capillary tubesand serum was separated within 30 min.Study indicate that the compounds were found to reduce the glucose levels in animals and demonstrated significant antidiabetic activity [7].



8a,b

a , R = Ph , X = O
b , R = Et , X = S

Fig 8. Pyridazinesulphonamides

Farah Yousef *et al*., develop various structural activity relationship that Glyburide and glipizide; more potent sulfonylurea members .The mechanism of anti-hyperglycaemic agents action is the increase of insulin hormone secretion from pancreatic beta cells[8].

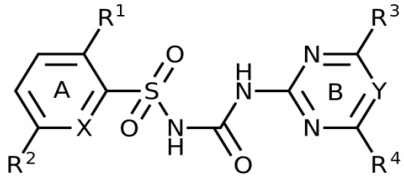


Fig 9. Sulfonyl urea derivative

The targeted trisubstituted sulfonylurea derivatives were prepared and confirmed by various spectroscopic and elemental analyses. Mass spectra and NMR data were helpful to conclude the molecular formula and weight as well as the chemical condition of atoms in the structure along with the data from the elemental analysis. The progress and completion of synthetic reactions were evaluated by the TLC. The type 2 diabetes were induced by streptozotocin i.p injection in rat successfully and then the anti-diabetic study was evaluated. In glucose fed normal rats these compounds reduced the more than 80% of blood glucose as compared to control. These compounds either possessed simply phenyl ring on to the second amine of sulfonylurea or nitro group at the para position in compound to produce significant blood glucose lowering activity. The para-m ethoxy derivatives were given a little inferior activity compare to rest of the compounds. While chloro and hydroxyl derivatives were given considerable blood glucose lowering effect. The unsubstituted phenyl ring is favourable for activity and the presence of electron withdrawing nitro moiety in phenyl ring increases the activity very significantly.

Glipizide is a second generation sulphonylurea with promising hypoglycaemic activity. It acts by stimulating the release of insulin from the beta –cells of pancreases. Glipizide is absorbed rapidly, uniformly with good mean oral bioavailability. It offers several advantages such as long and short action, high potency and also does not accumulate in plasma on repeated oral administration safely profile and effectiveness of glipizide has been well documented in commendable number of experimental models and clinical studies. It is generally well tolerated and categorized as Bio pharmaceutics Classification System class 1 drug due to poor water solubility and good permeability. Various analytical methods have been reported for determination of glipizide in biological fluids. The present articles provide a comprehensive review on various analytical methodologies, pharmacology, pharmacokinetics, clinical evaluation, toxicology and therapeutic applications [9].

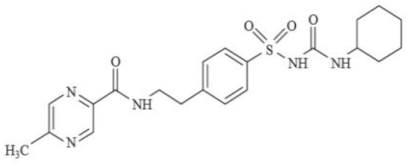


Fig 10. Glipizide

Carbonic anhydrous inhibitors are in clinical use as anti-glaucoma, diuretics, antiepileptic and management of altitude sickness, and under investigation as anticancer, anticonvulsant and antiobesity agents. Sulphonamides have been known for decades as carbonic anhydrous inhibitors and are in clinical use. Sulphonamide derivatives of p-hydroxybenzoic acid and trihydroxybenzoic acid were synthesized [10].

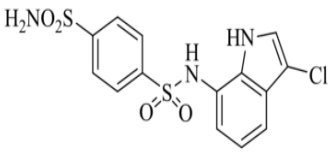


Fig 11. Sulphonamide derivatives

There are important points regarding the possible hypoglycemic effects of sulfasalazine and suggest possible underlying mechanism(s) accounting for sulfasalazine-induced hypoglycemia**.** They describe a case of reversible sulfasalazine-induced hypoglycemia, review the literature, and discuss a potential mechanism accounting for sulfasalazine-induced hypoglycemia. A 63-year-old man with Crohn disease treated with sulfasalazine and type 2 diabetes complicated by end stage renal disease was

admitted for treatment of persistent hypoglycemia. Insulinoma was initially suspected, but localization studies including endoscopic ultrasound were negative. This raised the possibility of sulfasalazine induced hypoglycemia. Three days after sulfasalazine was stopped, he became normoglycemic. Hypoglycemia has not recurred since discontinuing sulfasalazine [11].

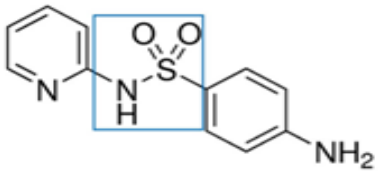


Fig 12. Sulfasalazine

There are some pyridazine sulphonamides by a mixture of 3-sulfonylchloride and ammonium hydroxide was stirred and refluxed. Then the solution was neutralized with 6N HCl. Then the solid product is filtered and evaluates the hypoglycemic activity by using the reference drug was Gliclazide. Standard environmental condition such as temperature ($26+2^0$C) and relative humidity were maintained. Study indicate that the compounds were found to reduce the glucose levels in animals and demonstrated significant ant diabetic activity.

A novel class of sulfonylurea and thiourea derivatives substituted with pyridazinetriazolopyridazine were designed and synthesized. The target compounds were assayed for their effects on the insulin release of alloxan-induced diabetic rats. The result showed that derivatives have significant anti –hyperglycemic effect in an experimental model of diabetes mellitus. No significant difference in cholesterol levels were observed between the diabetic group and diabetic group that received the test compounds.

CONCLUSION

In summary, we have developed various sulphonamide like benzene sulphonamide, pyridazine sulphonamides, Diaryl sufonylurea chalcone hybrids, bemzothiazole sulfonamide, sulfasalazine, sulfonamide, flouropyrzone sulfonylurea etc. They have various activities like anti-diabetic, anticancer, antibiotic, anti-oxidant, antimicrobial, antiviral, etc. It concluded that, the sulphonamide derivatives show useful results for hypoglycemic activity compared to that of the control and standard respectively.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

No interest.

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