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"SULPHONYLUREA'S FUNCTION AND POTENTIAL BENEFITS FOR TREATMENT IN TYPE 2 DIABETES MELLITUS"

Gandigude Pallavi[1], Sangita kale [2], V.B.Panchabhai[3*]

Channabasweshwar Pharmacy College (Degree), Latur -413512, Maharashtra,India.

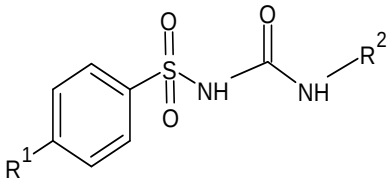
Abstract

Sulfonylureasare a class of organic compounds used in medicine and agriculture. All pharmacologically active sulfonylureas contain a central S-aryl sulfonylurea structure with a p-substituent on the phenyl ring and various groups terminating the urea N′ end group. Chemically, this functionality can be easily installed by reacting aryl sulfonamides with isocyanates. The current survey focused on some well-established method for preparation of sulphonylurea followed by their pharmacological profile. It is primarily used for the treatment of diabetes mellitus type 2 a pancreatic disorder. Though It also has some extrapancreatic effect like anti-cancer, diuretic, anti-inflammatory, anticonvulsant and neuroprotective agents etc which is discussed in our paper

Keywords: Sulphonylurea, Sulphonation,Antidiabetic,Anticancer,Anti-Inflammatory

Introduction

Sulfonylureas were discovered in 1942 by the chemist Marcel Janbonand co-workers. Sulfonylureas derivative contain a central S-aryl sulfonylurea structure with a p-substituent on the phenyl ring (R1) and various groups terminating the urea at N′ end group (R2). Chemically, this functionality can be easily installedby reacting aryl sulfonamides (R1-C6H4-SO2NH2) with isocyanates (R2-NCO)



Structure of sulphonylurea

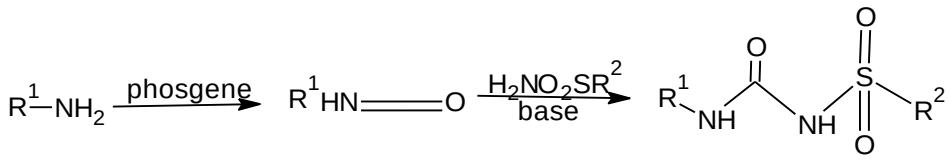
These compounds also exhibit a wide range of biological activities like antidiabetic, diuretic, histamine H3 receptor antagonism , thromboxane A2 receptor antagonism, antimicrobial, antimalarial, antitubercular, anticancer or cytotoxic and anti-inflammatory activity.

Sulfonylurea derivatives were the first oral hypoglycemic agents that have been in use for the treatment of type II diabetics for almost eight decades. All sulfonylurea hypoglycemic drugs act by releasing insulin from the β cells of pancreas. Along with their secretogogues action, sulfonylureas are also reported to have insulin sensitizers activities .Hence, medications which stimulate insulin secretion boosted by high glucose level with low side effects will be highly valued.

Scheme for synthesis of sulphonylurea

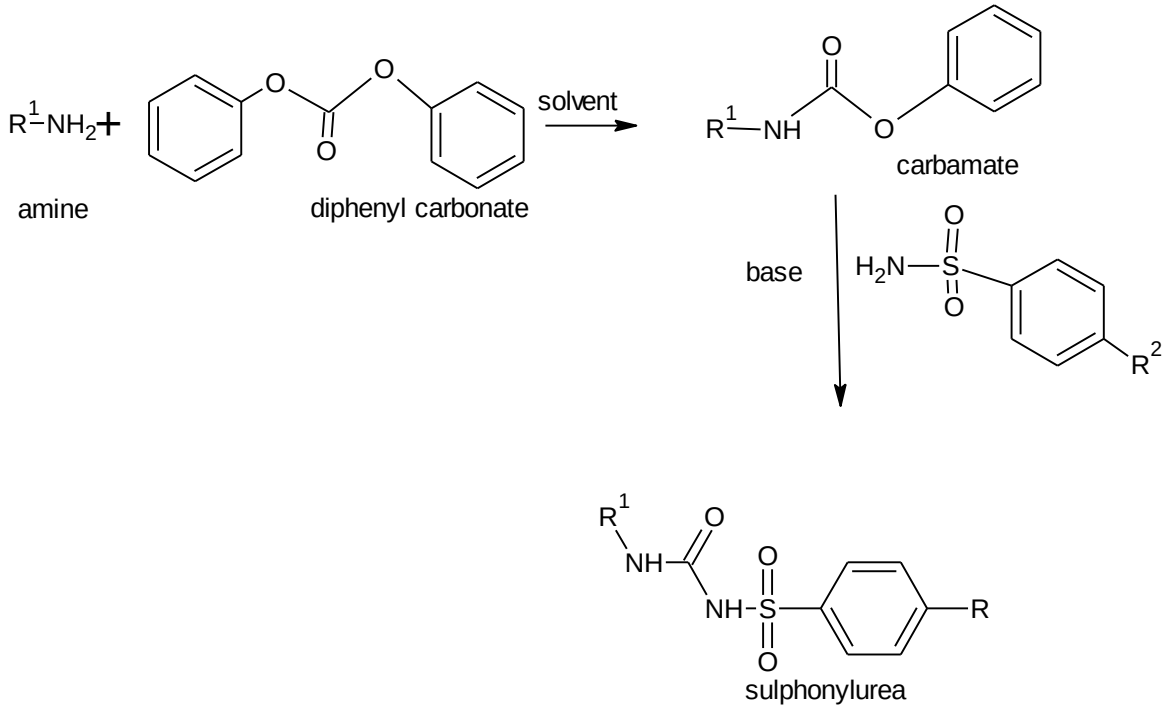
Scheme 1

isocyanate synthesis involves the use of phosgene,22 a highly toxic chemical, which requires special handling on scale.23 Similarly carbamate of sulfonamides are prepared from chloroformates which are, subsequently, synthesized from phosgene.



Scheme 2

As most of the antidiabetic sulfonylureas have aliphatic N-side chains therefore N-alkyl O-aryl carbamates are required for the synthesis of these molecules. Keeping in view the low cost of aryl carbonate such as diphenyl carbonate (DPC), it appeared a synthetic challenge to prepare N-alkyl O-aryl carbamates from the reaction of aryl carbonated with primary amines. Therefore, our investigation started with the reaction of diphenyl carbonate with primary aliphatic amines to produce carbamates as the key intermediates which were thenconverted in to sulfonylureas. The overall process executed to synthesize various sulfonylureas is depicted in Scheme 2.



Sulphonylurea action

Drugs that bind to sulphonylurea receptors and close KATPchannels have been used for many years to stimulate insulin release in subjects with Type 2 diabetes.Although the first and second generation agents (e.g. tolbutamide, chlorpropamide, glibenclamide, gli-clazide, glimepiride) possess a sulphonylureagroup,this is not essential for drug activity.

Interactions between sulphonylureas and nucleotides

The simplistic interpretation of the data discussed above is that the sulphonylureas and glinides are a heterogeneous group of drugs that would exhibit different degrees of cross-reactivity with cardiovascular KAT P channels in vivo. Under physiological conditions, however, a number of additional factors need to be taken into consideration, such as the effects of cytoplasmic nucleotides.

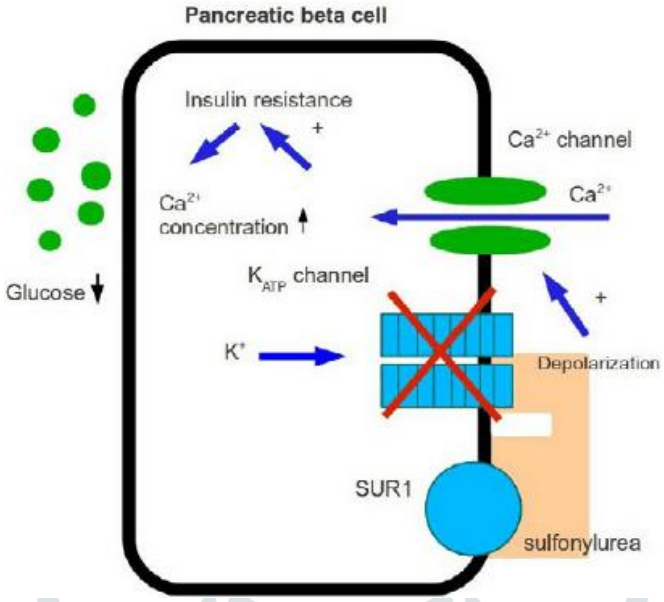
Therapeutic aspects of sulfonylurea

It was found that sulfonylureas have different types of activity along with antidiabetic activity. The different researcher reported some of the activities like antidiabetes, anticancer, diuretic. anti-inflammatory, antimalarial, antitubercular etc.Some of the case studies are described below.

Sulfonylureas as Antidiabetic agent

Sulfonylureas stimulate insulin secretion from pancreatic β-cells and are widely used to treat type 2 diabetes. The principal target of sulfonylureas is the ATP-sensitive potassium (KATP) channel, which plays a major role in controlling the β-cell membrane potential. Inhibition of KATP channels by sulfonylureas causes depolarization of the β-cell membrane; which in turn, triggers the opening of voltage-gated Ca2+channels by eliciting Ca2+influx and a rise in intracellular Ca2+to stimulates the exocytosis of insulin-containing secretory

granules.

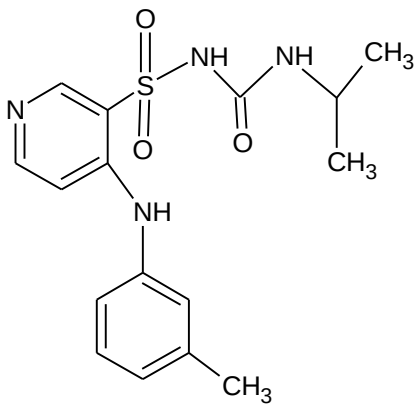


Sulfonylureas as anticancer

Glibenclamide increases NADPH oxidase and mitochondrial respiratory chain ROS production followed by the release of proapoptotic factors and caspase activation. Membrane depolarization by glibenclamide and TRAIL (Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand) induces ER (Endoplasmic Reticulum) stress-mediated apoptosis. .

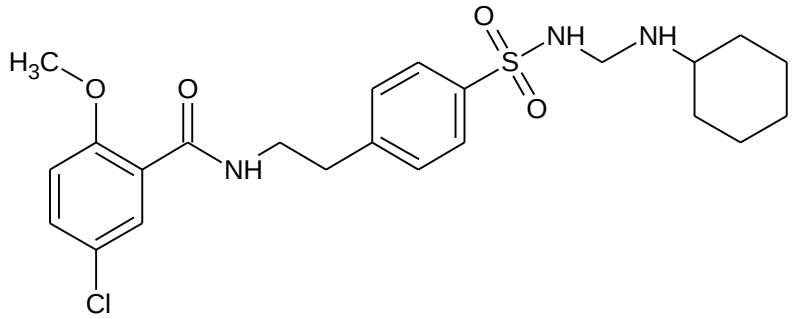
Sulfonylureas as diuretics

Torasemide (rINN) or torsemide(USAN) is a pyridine-sulfonyl urea type loop diuretic. The actions of torsemide can be mediated by several mechanisms operating within the thick, medullary segment of ascending loop of henle .



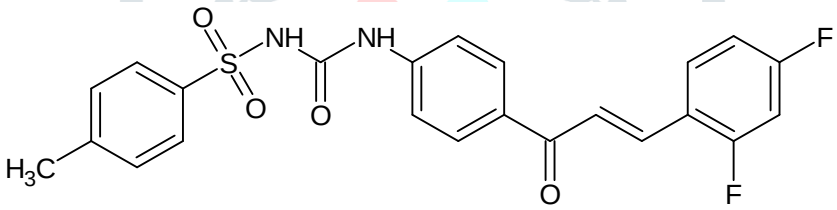
Sulfonylureas as anti-inflammatory agents

Recently, a wide range of anti-inflammatory effects of glibenclamidehas been reported in different articles. Some of them are reported here.



Antimalarial Activity

Leon CI et al had developed a series of sulfonylureas and tested their antimalarial activities. The Study also included the inhibition of in vitro development of a chloroquine-resistant strain of Plasmodium falciparum, in vitro hemoglobin hydrolysis, hemozoin formation, and development of Plasmodium berghei in murine malaria.



New Trends in the Development of Oral Antidiabetic Drugs

1) Sulphonylureas (SUs)

SUs act as a specific blockers of a particular class ofK+channels in pancreatic beta cells, known as ATP-sensitiveK+ channels hese channels were first discoveredin cardiac myocytes and later were found in othertissues, including pancreatic beta cells.

2) Nonsulfonylureas

- Benzoic Acid Derivatives (Glinides)

Repaglinide is an enantiomer of 2-etoxy-4-[2[[-3-methyl-1-[2-(1-pieridinyl) phenyl]-butyl] amino]-oxoethyl] benzoicacid, a member of the carbamoylmethyl benzoic acid family(glinides), which is structurally distinct from the traditionalsulfonylureas (SUs) but shows some chemical resemblanceto the nonsulfonylurea moiety of the glibenclamide molecule.

- Alpha2 Antagonists and Imidazoline Receptor Agonists

These drugs binding to the alpha2 or imidazoline Ireceptors in pancreatic cells stimulate insulin secretion.During the past ten years, it has been established that a range of imidazoline drugs can stimulate insulin

secretion from pancreatic β-cells.The stimulation ofinsulin secretion by imidazolidines occurs in response to theclosure of ATP-sensitive K+channels

Extra-pancreatic action of sulfonylureas

Many of these actions have re-quired concentrations of sulfonylureas far in excess of the therapeutic levels usually attained in the plasma.the extra-pancreatic effects of sulfonylurea drugs can be divided into different groups:

- Effects probably related to anti-diabetic action: enhancement of insulin stimulation of carbohy-drate transport in skeletal muscle; enhancement of insulin action on the liver.
- Effects possibly related to anti-diabetic action: Direct effects on the liver: inhibition of triglycer-ide lipase; limitation of anionic substrate move-ment across the inner membrane of hepatic mitochondria; inhibition of ketosis; inhibition of glucose output.

Pharmacokinetics

Although with time and different quantities, all sulfonylureas are absorbed by the intestine after oral intake, each one with its specific absorption time and bioavailability. Hyperglycemia can re-duce the absorption of sulfonylureas as it impairs intestinal motility, thereby reducing the absorp-tion of all orally administered drugs. This same phenomenon occurs for food intake as well. For this reason, to optimize their absorption, sulfony-lureas should be taken 30 min before meals, and their dosage should be increased every 2 weeks if glycemic control has not been reached. The typical starting dose should be low (for example gliben-clamide 2.5 mg or glimepiride 2 mg).

Side effects

Sulfonylureas are usually well tolerated. The most common side effect is hypoglycemia, more common with long-acting sulfonylureas such as chlorpropamide and glibenclamide . How-ever, all sulfonylureas may cause hypoglycemia, usually due to an excessive dosage.In addition to the use of longer-acting drugs such as glibenclamide or chlorpropamide, it is necessary to recognize other situations at risk of hypoglycemia.

Issues with sulfonylurea Treatment

Although SUs have been the mainstay of pharmacologic management of T2DM, concern has been raised over their potential role in β-cell failure, blunting of IPC, weight gain, hypoglycaemia, and mortality risk. This section will focus on the concerns related to SUs usage. A thorough search of the literature pertaining to each of these issues was performed to frame evidence based recommendations.

1) β-cell apoptosis

As SUs act by stimulating insulin release from β-cells, there is concern regarding SU induced "β-cell exhaustion". In UKPDS and ADOPT, majority of patients treated with glibenclamide experienced a loss of effective antidiabetic response after an initial excellent response (secondary failure). Gliclazide is therefore less likely to induce β-cell failure or secondary SU failure as compared to conventional SUs.

2) β-cell de-differentiation

Evidence suggests that β-cell de-differentiation, rather than cell death, is responsible for β-cell failure in T2DM. According to Talchai et al., stressed β-cells undergo de-differentiation, where the expression of β-cell specific genes and enzymes that process pro-insulin to insulin is reduced De-differentiated β-cells reverted to progenitor-like cells expressing neurogenin3, Oct4, Nanog, and L-Myc, consequently expressing non β-cell hormones such as somatostatin and glucagon.Thus β-cell de-differentiation may account for reduced β-cell mass and insulin secretion in patients with T2DM.

CONCLUSION

From the above discussion, it can be concluded that the various methods had been reported for the preparation of sulfonylureas derivatives. It can be prepared by chloro-sulfonation and amidation between sulfonamides and isocyanates. Beside this Claisen-Schmidt condensation is also a reported reaction for the preparation of sulfonylurea. The literature also proves the pancreatic and extrapancreatic effect of sulfonylureas. They have an extrapancreatic effect like,diuretics, anti-inflammatory, anticancer, antimalarial etc. SUs are the main stream of pharmacotherapy in the management of patients with T2DM. Their well-established glycaemic efficacy, safety and tolerability support their use as an integral part of diabetes treatment. Given the fact that many of the clinical concerns associated with the use of SUs are agent-specific, and do not pertain to the class as such, a careful choice of specific SU should be considered beneficial.

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