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AN OVERVIEW OF THE SYNTHESIS OF GLIMPERIDE.

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ABSTRACT

The strong sulfonylurea derivative glimepiride has become well-known as an efficient oral antidiabetic medication for the treatment of type 2 diabetes mellitus. Glimepiride synthesis aids in the development of scalable and effective industrial production procedures, in addition to advancing our knowledge of its chemical structure. The importance of glimepiride in the treatment of diabetes emphasizes the need for more research to optimize its synthesis for a wider range of therapeutic uses. In order to create the intermediate sulphonamide, 3-ethyl-4-methyl-1H-pyrrol-2(5H)-one carbamate must first be prepared. This is followed by a reaction with 4-(2-amino-ethyl) benzene sulphonamide. Glimepiride and a novel purification method for rans-4-methyl cyclohexylamine HC1 and 4-[2-(3-Ethyl-4-methyl-2-carbony1 pyrrolidine amido) ethyl]benzene sulphonamide, which were utilized in the synthesis of glimepiride, were produced by this sulphonamide when it reacted with phenyl (trans-4-methylcyclohexyl)carbamate. Glimepiride is quickly absorbed when taken orally, and its strong ability to bind proteins affects where it ends up in the body. Glimepiride's broad hepatic metabolism, mainly through cytochrome P450 enzymes, offers a number of advantages over sulfonylurea therapy, which is now widely and effectively used for NIDDM patients. These advantages could make glimepiride a potentially significant advancement in therapy.

KEYWORDS: Glimepiride, Sulfonylurea, Type 2 Diabetes Mellitus, Hypoglycaemia, Insulin.

INTRODUCTION

285 million people globally suffer from diabetes, making it a serious public health issue (1). Renal failure, neuropathy, peripheral vascular disease, which increases the chance of limb loss, retinopathy, which increases the risk of blindness, and an increased risk of cardiovascular disease and stroke are among the complications associated with poorly controlled diabetes (2). The main objective of treating non-insulin-dependent (NIDDM) Type II diabetes is to get blood glucose levels back to normal in order to prevent hyperglycaemia and prevent, or at least postpone, the onset of diabetic late complications (3). The medical

field of diabetes mellitus (DM) is flourishing in both developed and developing nations. Genetic characteristics that make someone more susceptible to developing diabetes have likely come to light due to the rising prevalence of abundant nutrition in a large portion of the population (4). The pathophysiology of insulin resistance and/or a relative decrease in insulin production is what defines type 2 diabetes mellitus (T2DM). Since hyperinsulinemia is seen in preteens whose parents have diabetes, insulin resistance is thought to begin early in life. It is a complicated process that is made worse by obesity, especially central obesity (5). Glimepiride is the second generation of sulfonylurea. Second-generation sulfonylureas are efficacious, generally well-tolerated, and cost-effective options for the medical management of diabetes. Many comparative and non-comparative studies have evaluated the efficacy and safety of second-generation sulfonylureas in patients with type 2 diabetes (6). Glimepiride is an orally active, hypoglycaemic, sulfonylurea agent used in the treatment of type 2 diabetes (7). It works by stimulating the release of insulin from pancreatic beta cells, which helps to lower blood glucose levels (8). In a recent clinical trial, the incidence of hypoglycaemia was 7% in glimepiride-treated patients versus 33% in patients treated with glyburide (6). Sulfonylureas bind to receptor-like structures on the 3-cell that may be closely linked to or part of the potassium channels. The efficacy of various sulfonylureas to induce insulin secretion is closely correlated with their capacity to bind to these receptors (9). In order to attain the best blood glucose control, glimepiride is frequently used in addition to other diabetic drugs, such as metformin. This drug is a crucial tool in the treatment of type 2 diabetes, assisting patients in maintaining normal blood glucose levels and lowering their chance of developing complications from the disease (5). Diabetes has a variety of diffuse impacts, including an increased risk of aging-related impairment and several microvascular and macrovascular problems (1). Regarding the pharmacokinetic-effect relationships, the pharmacokinetics of the sulfonylurea, glimepiride, in risk groups of NIDDM patients are evaluated. A number of variables, including insulin sensitivity, glucose absorption, and regulatory systems, may make it difficult to define a distinct concentration-effect connection for sulfonylureas (10). Glimepiride possesses characteristics that point to potential clinical benefits over sulfonylureas that are currently on the market:

- Quicker beginning of action; comparable blood glucose reductions at lower insulin concentrations compared to other sulfonyl urea.
- Extended duration of action, enabling once-daily dosing and improving compliance.
- Less hypoglycaemia risk than other sulfonyl urea, particularly during the first few weeks of therapy (3).

CHEMISTRY

Structure of Glimepiride:

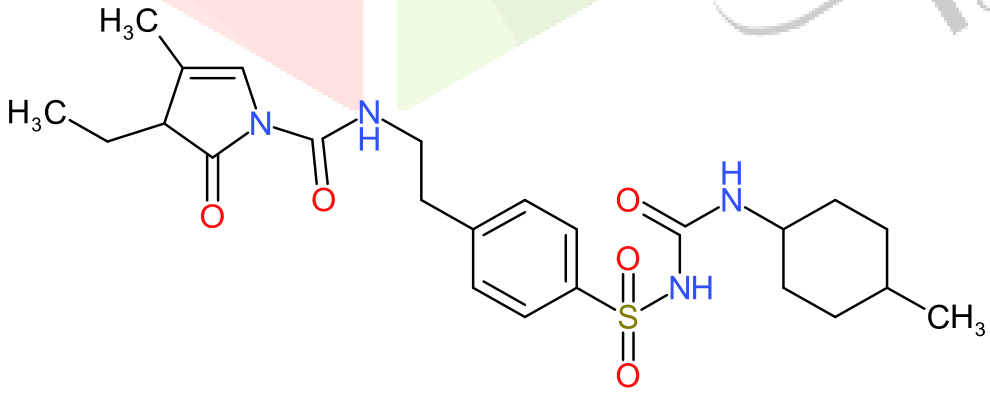


Figure 1 : Structure of Glimepiride

The most recent second-generation sulfonylurea for the management of type 2 diabetes is glimepiride. The US FDA classifies this medication as an oral hypoglycaemic agent (4). 1({p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl} sulfonyl)-3-(trans-4-methylcyclohexyl) urea is the IUPAC designation for glimepiride. Glimepiride, Amaryl, 1 [4 [2 (3 ethyl 4 methyl 2 oxo 3 pyrroline 1 carboxamide) ethyl] phenylsulfonyl] are some other names for it. 3[4 [2 (3 ethyl 4 methyl 2 oxo 3 pyrroline 1 carboxamide) ethyl]phenylsulfonyl]; hoe490; solos; 1 [4 [2 3 (hexyl-4-methyl urea); hoe490 (7). Glimepiride's chemical formula is C24H34N4O5S. Glimepiride has a molecular weight of 490.62 Da. It is a crystalline, odourless to almost odourless, white to yellowish-white powder that is basically insoluble in water (4). Glimepiride is

classified as having a place to lesson II of the Biopharmaceutical Classification Framework (BCS), which has destitute solvency and tall penetrability. The drug's solvency is destitute and subordinate on pH (11). It is taken orally; it is insoluble in water, somewhat soluble in methylene chloride (dichloromethane), extremely faintly soluble in methanol, and soluble in dimethyl sulfoxide (DMSO) (12). Glimepiride shows very low solubility at 37 °C in aqueous solutions. At pH 7, the drug's solubility increases marginally. Low dissolution and unexpected bioavailability could result from this low solubility (13). This molecule exists in two polymorphs, form I and form II. Form II is around 3.5 times more soluble than Form I (14).

Mechanism of Action:

Glimepiride attaches itself to receptors on the surface of pancreatic ß-cells that are dependent on adenosine triphosphate (ATP). Insulin release, a calcium influx, and potassium outflow result from the closure of these channels and membrane depolarization (15)(16). Glimepiride is integrated into a 65-kDa protein-binding site on the ß-cells, which appears to set it apart from the other sulfonylureas. Glyburide and the majority of other sulfonylureas are integrated into a 140-kDa protein (8). Glimepiride exhibits a two- to three-fold faster rate of association at the receptor site, an eight- to nine-fold faster rate of dissociation, and a significantly lower binding affinity for the ß-cell receptor when compared to glyburide (8). Theoretically, less fixed-receptor blockage than is seen with other sulfonylureas, a modification of insulin release, and a decreased potential for producing hypoglycaemia come from glimepiride binding at the specific 65-kDa protein-binding site (17). They block ATP-sensitive potassium (KATP) channels, which cause pancreatic β-cells to depolarize and let calcium enter. Insulin release into the bloodstream is accounted for by calcium, which functions as a second messenger (18). Sulfonylureas block ATP-dependent K' channels by binding to receptors. The beta cell membrane depolarizes as a result of the K' channel closing, decreasing its K' permeability. This activates voltage-dependent Ca2+ channels in the membrane, increasing intracellular calcium. Insulin-containing secretory granules are exocytosed when calcium ions attach to calm odium (19).

SYNTHESIS OF GLIMEPIRIDE

A. Synthesis 1:

[2-(3-Ethyl-4-methyl-2-carbonyl pyrrolidine amido) ethyl] benzene is the product of glimepiride production, which begins with 3-Ethyl-4-methyl-3-pyro1idine-2-one and 2-phenyl ethyl isocyanate. By reacting with chloro-sulphonic acid and then treating the resulting 4-[2-(3-Ethyl-4-methyl-2-carbonyl pyrrolidine amido) ethyl] benzene sulphonamide, [2-(3-Ethyl-4-methyl-2-carbonyl pyrrolidine amido) ethyl] benzene is transformed into glimepiride (20). According to Fig. 2,

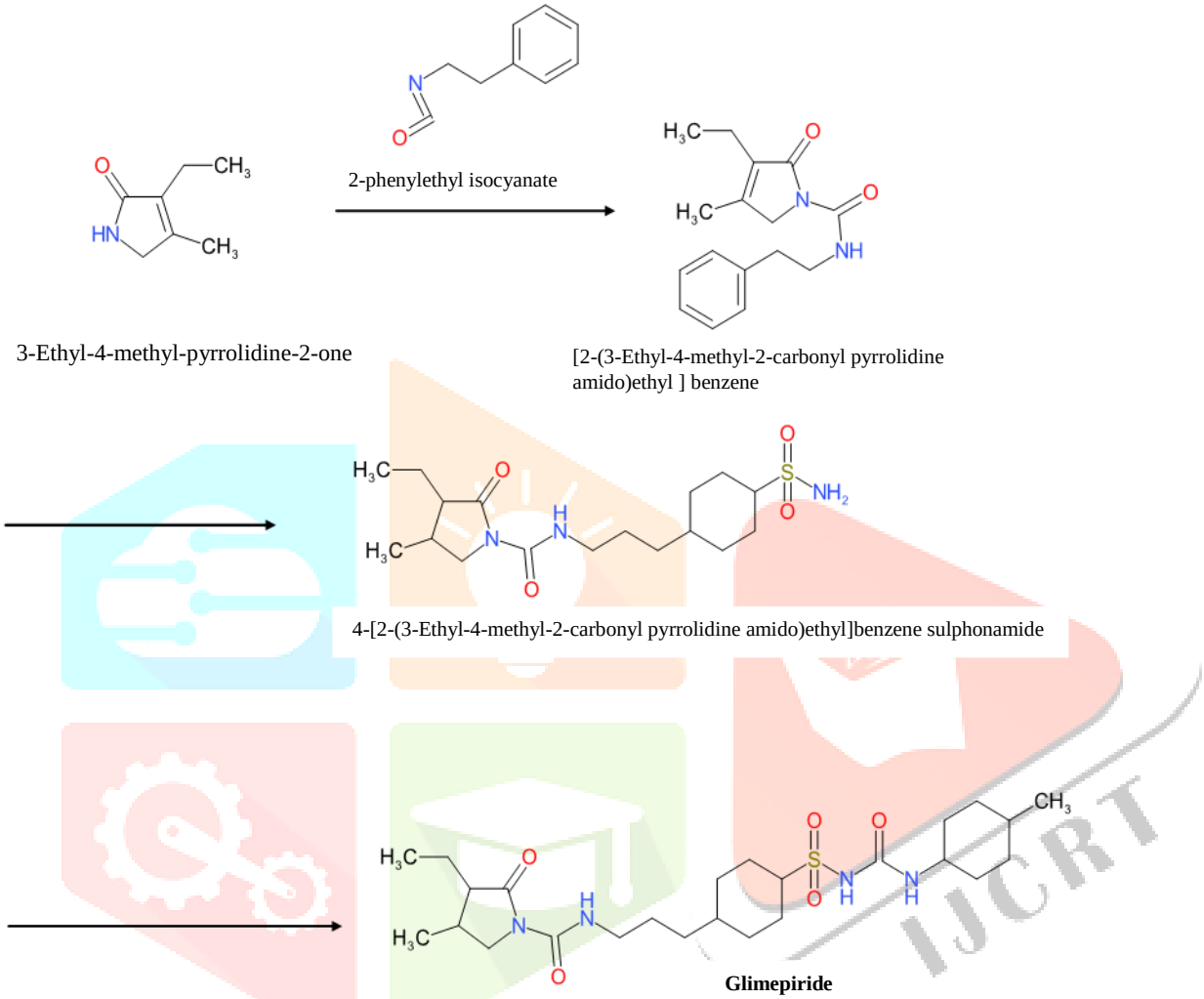


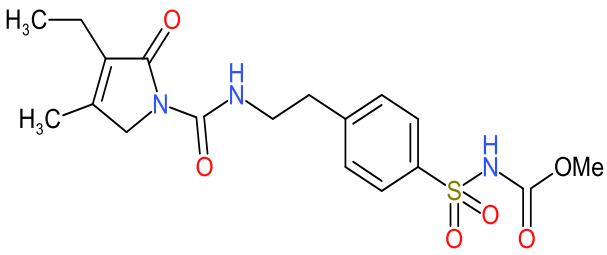
Figure 2 : synthesis 1

B. Synthesis 2:

The substances include yttrium nitrate pentahydrate (Y(NO3)3.6H2O) and pure glimepiride medication. 20 milliliters (80%) of ethanol were used to dissolve 12.25 g (0.025 mol) of glimepiride. To make the yttrium nitrate salt, 9.125 g (0.025 mol) of the salt were separately dissolved in 25 milliliters of ethanol. After adding the glimepiride solution gradually and stirring, the salt solution was refluxed for three hours while a diluted NaOH solution was added to keep the pH between 6.0 and 6.5. The complex split out after it cooled, and it was then cleaned again with ethanol, vacuum-dried, and recrystallized (21).

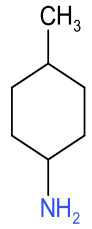
C. Synthesis 3:

N-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl]sulfonyl] methylurethane can also be used to create glimepiride by reacting with trans-4-methyl cyclohexyl amine (20). According to Fig. 3,.

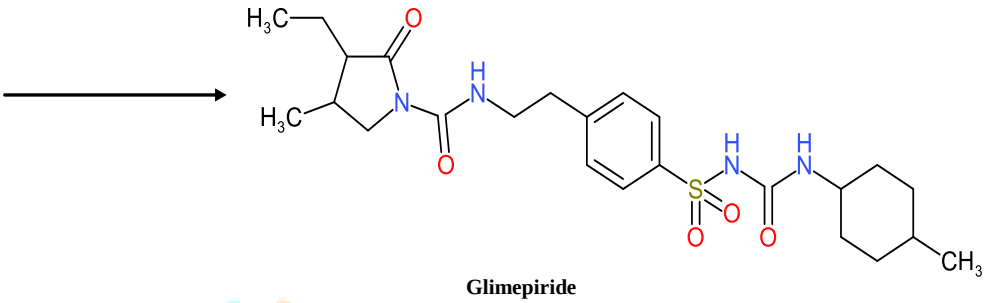


N-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]pheny1]sulfonyl] methylurethane

+



trans-4- methyl cyclohexyl amine



Glimepiride

Figure 3 : Synthesis 3

D. Synthesis 4:

To produce an isocyanate intermediate, 2-phenylethylamine is first treated with phosgene in the conventional production of glimepiride. The isocyanate then reacts with 3-ethyl-4-methyl-1H-pyrrol-2(5H)-one to produce 3-ethyl-4-methyl-2-oxo-N-(2-phenylethyl)-2,5-dihydroxy pyrrole-1-carboxamide. This intermediate is treated with chloro-sulfonic acid to yield sulfonyl chloride, which is then treated with ammonia to yield sulphonamide. This sulphonamide is either treated with trans-1-isocyanato 4-methylcyclohexane (Route II) or with an alkyl chloroformate to yield a carbamate that reacts with trans-4-methyl cyclohexylamine to yield glimepiride (Route I). Trans-(4-methylcyclohexyl)amine hydrochloride and phosgene were reacted to produce trans-1-isocyanato-4-methylcyclohexane in parallel (22) (23). According to Fig. 4,

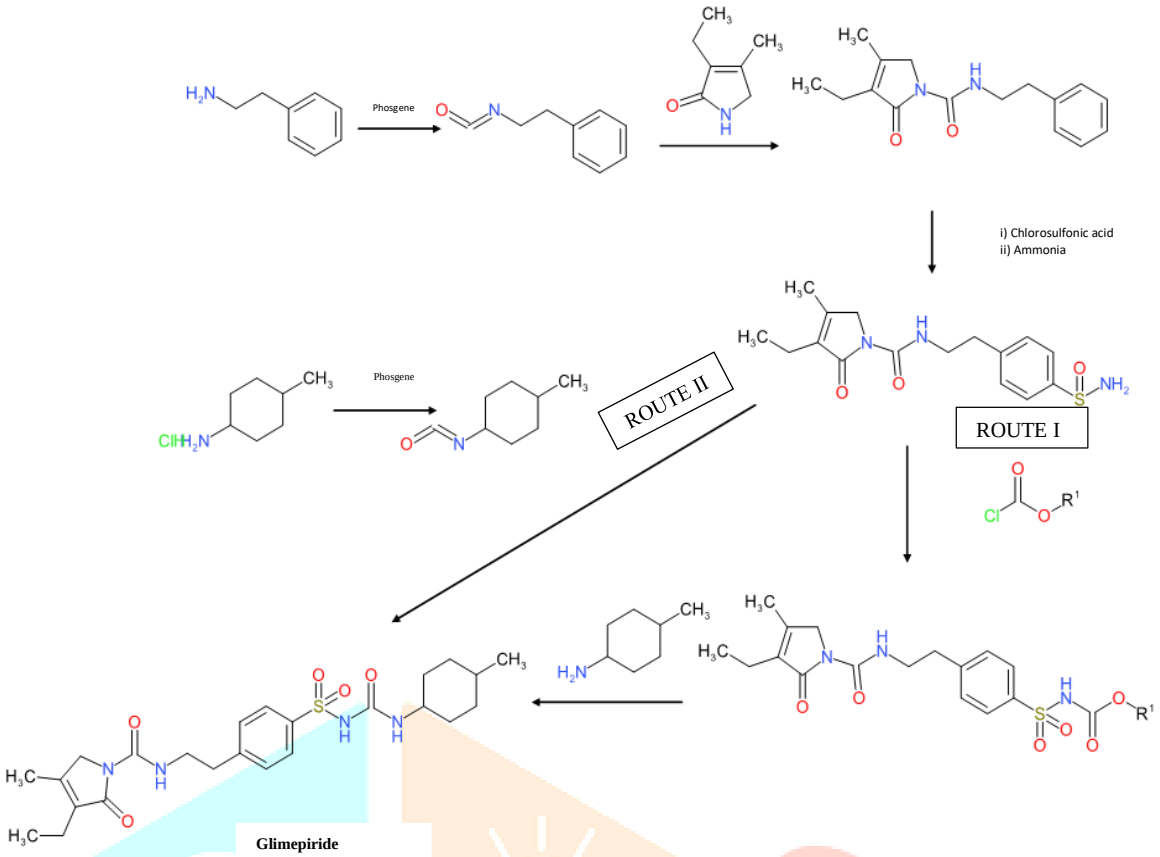


Figure 4: Synthesis 4

E. Synthesis 5:

In order to create the complex, the ligand and metal salt solutions (80% DMF) were mixed in 1:2 molar ratios at room temperature. The pH was then kept between 6.5-8 by adding a diluted NaOH solution. White-colored crystals were formed by refluxing the combination content for three hours at 800 °C and then cooling it down (24) (25).

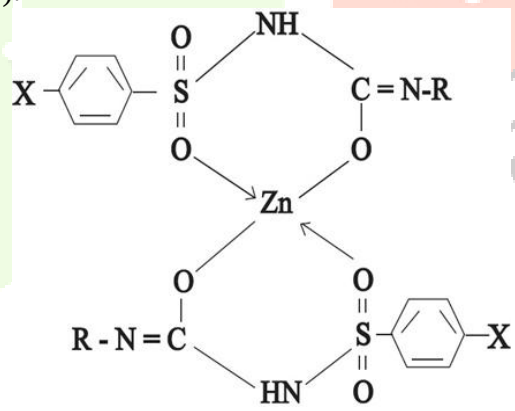


Figure 5: Structure of Glimepiride zinc complex (25).

F. Synthesis 6:

The reaction of 3-ethyl-4-methyl-1H-pyrrol-2(5H)-one with diphenyl carbonate in the presence of NaH produced phenyl 3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (a) with an isolated yield of 65%. The intended sulfonamide intermediate b was produced in an 85% yield by reacting intermediate a with 4-(2-aminoethyl) benzene sulfonamide. In a subsequent step, amine reacted with diphenyl carbonate to create the N-phenoxy-carbonyl derivative of trans-4-methylcyclohexylamine (c) in an isolated yield of 84%, utilizing our previously published procedure for related compounds. Glimepiride was produced in the last stage by the reaction of intermediates b and c (22) (26). As depicted in Figure 6,

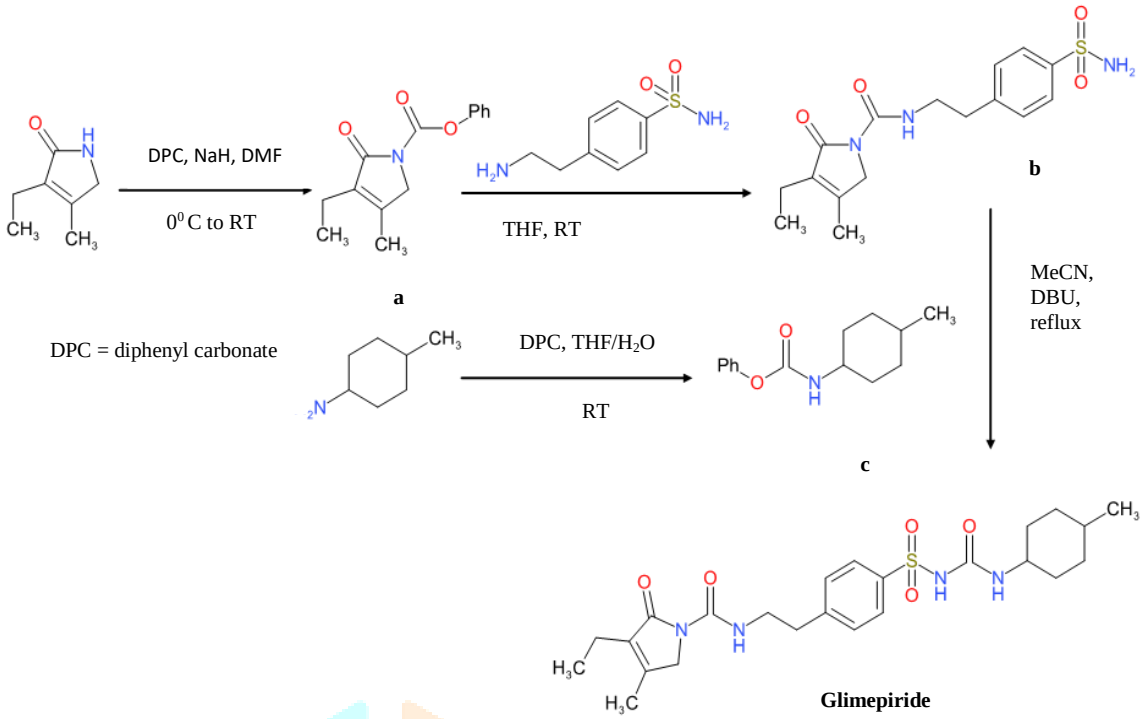


Figure 6 : Synthesis 6

G. Synthesis 7:

For homogeneity, GMP 1.258 g was mixed in 15 mL of double-distilled ethanol and agitated for 30 minutes. Similarly, MF 1.36 g was similarly dissolved into a homogenous solution in 15 milliliters of distilled ethanol. Equal portions of each (15 mL GMP, 15 mL MF) were then added to a 100 mL RB flask for refluxation. After refluxing the mixture for eight hours to get the temperature down to 50 °C ± 5 °C, 0.1 gm of cadmium chloride was added dropwise, and aqueous (2 N) NaOH was slowly added to bring the pH of the mixture down to 8. For 12 hours, the combined solution was refluxed continuously at 60 °C ± 5 °C. When the refluxation was finished and the mixture was allowed to settle to room temperature, the compound's pink crystals became visible. Following their separation by filtration, the resulting crystals were repeatedly cleaned—first with triple-distilled water and then with ethanol (27). like in Figure 7.

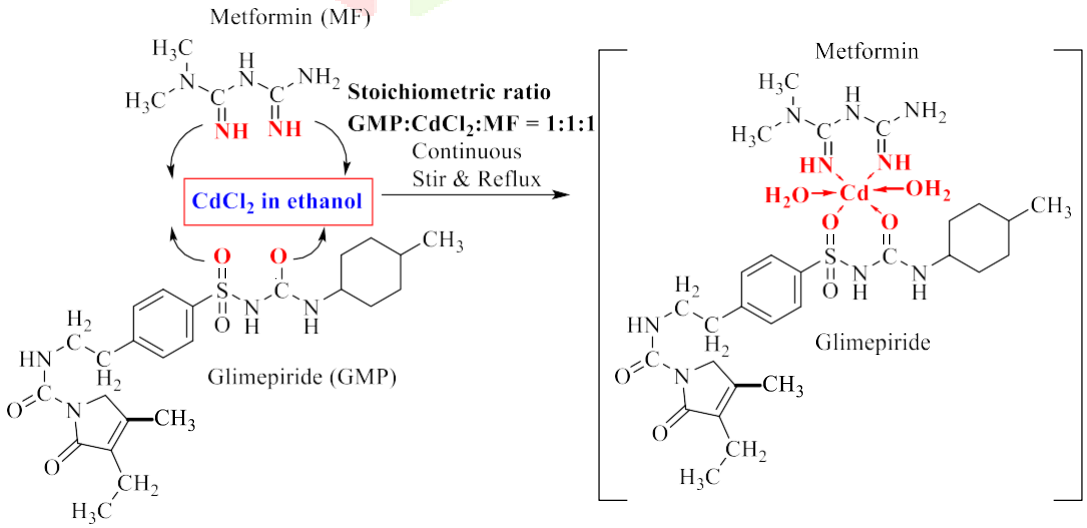


Figure 7 : cadmium complex of glimepiride–metformin (27).

H. Synthesis 8:

80 g of carbamate in a reaction vessel. Reflux was achieved by heating 27.2 g of trans-4-methylcyclohexyl amine, 11.5 g of 4-dimethyl amino pyridine, and 1.6 L of toluene together. The reaction constant's entire volume was maintained while the toluene was extracted using distillation. The mass was cooled to 25 to 30° C once the reaction was complete in order to precipitate the glimepiride, which was then filtered and cleaned with 800 mL of toluene. After drying the filtered sample, 88 g of glimepiride (95% yield) with a purity of 99.5% was obtained (28).

I. Synthesis 9:

A minimal quantity of 80% DMF was used to dissolve a weighed quantity of glimepiride (2 mol). Separately, the neodymium trioxide was dissolved in the same solvent to create the solution. To improve the solubility, a few drops of alkali NaOH solution were added to the metal solution. A diluted NaOH solution was added to the ligand solution at ambient temperature, and the metallic solution was added gradually while stirring. The mixture was then refluxed for two to four hours, from 25 to 27, at 800 °C. After the solutions were allowed to crystallize for 18 to 20 hours at room temperature, lustrous, gray crystals of the complex were produced. These crystals were then filtered, cleaned, and dried, and their melting temperatures were noted (29).

J. Synthesis 10:

41.0 g of pivalate VII was added to a combination of 70.0 g of ethyl [4-(2-{[(3-ethyl-4-methyl-2-oxo-2,5-di hydro- 1 H-pyrrol-1-yl)carbonyl] aminoethyl)phenyl] sulfonyl carbamate (IV, RIEt) in 840 ml of toluene after it had been combined. The mixture was refluxed for four hours after that. After cooling to 150 °C, the solid part was drained off and washed with cold toluene. 74.5 g (92%) of the crude product were produced, with a 98.5% HPLC content. The crude product was then refined by freezing and draining it after three hours of triple boiling in toluene (820 ml). With a 99.5% HPLC content (or 99.7% of the trans-isomer), the yield was 68.5 g of glimepiride (84%). Melting point: between 206 and 207 °C (30).

PHARMACOKINETIC

Following oral treatment, glimepiride is absorbed quickly and entirely. Food intake has no effect on oral bioavailability, which is around 100% (15) (31). Two to three hours after oral dosing, peak serum concentrations happen (15). Like other sulfonylureas, glimepiride is substantially coupled to plasma proteins, absorbed from the gastrointestinal tract with great efficiency, and processed extensively in the liver (7). The sulfonylureas are quickly absorbed by the human digestive system. The drug's lipophilicity and solubility at intestinal pH determine how well it is absorbed via the digestive system (2). Serum proteins firmly bind all sulfonylureas. The main protein to which they are attached is albumin. The second-generation sulfonylureas have significantly lower blood concentrations and therapeutically efficacious dosages (2). CYP2C9 metabolizes almost all drugs before they are eliminated unaltered in the urine (32). Glimepiride is converted by the CYP2C9 enzyme to the cyclohexylhydroxymethyl derivative (M1), which is then further broken down by cytosolic enzymes to produce the carboxyl derivative (M2) (15). Glimepiride has an elimination half-life of five hours following a single dose and nine hours following several doses (31). Sulfonylureas are normally removed by the liver through metabolism, with the metabolites excreted by the kidneys sometimes having some action (10). A more marked and extended release of insulin may underlie glimepiride's more powerful and sustained reduction of blood glucose. In actuality, glimepiride's insulin-releasing activity in type 2 diabetic patients is longer—24 hours—but it also has lower peak levels of C-peptide and insulin (at 4 hours) during fasting (33). The peak plasma concentration (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$), and area under the plasma concentration-time curve from time zero to 12 hours [AUC(0-12)] and from time zero to infinity [AUC(0-∞)] were used to characterize the pharmacokinetics of glyburide and glimepiride (34). The existence of diabetic complications did not change the safety profile of glimepiride (35).

Adverse Drug Reaction

There were no ADRs that were discovered to be lethal, life-threatening, or in need of hospitalization for treatment. ADRs brought on by oral hypoglycaemic agents are somewhat frequent. When consumed by patients, they can induce a variety of discomforts, although they are not expected to be fatal (36). The two most frequent side effects of sulfonylurea medication in individuals with type 2 diabetes mellitus are hypoglycaemia and weight gain. The negative effects of sulfonylureas, especially the risk of hypoglycaemia, frequently restrict their usefulness (37). Gastrointestinal disturbances, such as diarrhoea, gastric discomfort, stomach pain, and distension in the abdomen, are examples of mild adverse effects (38). Anaemia, agranulocytosis, pancytopenia, cholestatic jaundice, vasculitis, and transient alterations in liver function are among the extremely uncommon but potentially fatal side effects; however, there is no proof to connect them to the medication (7). Glimepiride levels were lowered by 56.9% in fasting blood sugar (FBS) and 32.3% in postprandial blood sugar (PPBS) (39). One or more symptoms or indicators consistent with a hypoglycaemic episode with a blood glucose level that confirms the condition was referred to as hypoglycaemia (40). Comparing it to traditional sulfonylureas, its cardiovascular risk has decreased (38).

DRUG INTERACTION

When two drugs are provided concurrently or quickly after one another, the term "drug interaction" describes how one drug alters the response to the other (41). During the course of sulphonyl urea treatment, approximately 20% of patients had a potential drug-drug interaction with a CYP2C9 inhibitor (42). Eighty-nine percent of diabetic patients (80.9%) had at least one possible clinically relevant diabetic foot infection (DDI) that needs to be monitored while receiving therapy (category C) (43). Glimepiride metabolism, as a percentage, was 9.06%. In glimepiride + atorvastatin and glimepiride + rosuvastatin, the percentages of glimepiride that were metabolized were 2.05% and 6.03%, respectively (44). Oral antidiabetic medications are primarily affected by DDIs through the processes of CYP enzyme activation, inhibition, and transduction. There are two types of CYP enzyme inhibition: irreversible enzyme inactivation and reversible (usually complementary) inhibition. As the concentration of the inhibitor decreases, reversible inhibition also disappears (45). A novel class of anti-type 2 diabetes medications known as sodium-glucose co-transporter-2 (SGLT2) inhibitors lowers blood glucose levels by enhancing the excretion of excess glucose through the urine and blocking renal glucose reabsorption (46). Serum insulin levels rose when glimepiride and A. vera were administered together. It has been determined that A. vera increased glimepiride's hypoglycaemic impact (47). The mean estimated area under the plasma concentration-time curve (AUC) of glimepiride was 2.41 times higher when gemfibrozil was used (48). Hypoglycaemia risk is increased while taking aspirin and glimepiride together (49). There was a clear indication of enzyme stimulation by the extract in the herbal-drug interactions between glimepiride and A. indica (50).

CONCLUSION:

Glimepiride synthesis is a difficult procedure requiring a number of processes and chemicals. Overall, the synthesis method for glimepiride signifies a noteworthy accomplishment in the field of medication development and emphasizes the significance of ongoing study and ingenuity in this domain. Research has indicated that glimepiride is a highly promising treatment for type 2 diabetes, as it can effectively lower blood glucose levels and improve insulin sensitivity. Glimepiride has a number of advantages over sulfonylurea therapy, which is now extensively and effectively utilized for NIDDM patients. These advantages could make glimepiride a significant contributor to improved therapy. For the preparation of glimepiride, a practical, economical, and efficient approach has been established.

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