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# An Overall Review of Different Derivatives That Activate Glucokinase Enzyme Having Multiple Actions to Treat Type 2 Diabetes

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**ABSTRACT**
Different derivatives like3,6-disubstituted2-pyridine carboxamide derivatives, Phenylethyl benzamide derivatives, Carboxypyridine benzamide derivatives, Pyrazole benzamide derivatives, Quinazoline-2,4 dione analogs**,** Ketopiperazine analogs, Cycloalkyl-fused N-thiazol-2-yl-benzamides derivatives, 1,4-disubstituted indazoles derivatives, 2,5,6-trisubstituted indole derivatives, Azaindole derivatives andPyrimidone derivatives was designed, synthesized and evaluated the pharmacological activity in mice. Such compounds activate the glucokinase by interaction between glucokinase activators and glucokinase receptors composed of different amino acids ARG 63,TYR 214, TYR 215, TYR 61, VAL 62, SER 64, THR 65, PRO 66, ILU 211, MET 210, ILU 159, ALA 456, VAL 455, VAL 452, LEU 451, MET 210.

**Keywords:** Diabetes mellitus, Glucokinase activator, metabolic disorder, glucose-6- phosphate, plasma glucose level

## I. INTRODUCTION

Chronic and metabolic disorder type 2 diabetes mellitus is characterized by elevated hepatic glucose production, insulin resistance, and pancreatic beta-cell dysfunction, and ultimately leads to hyperglycemia [1].Over the past 50 years, the number of diabetes patients has steadily climbed, as has the rate of obesity, which is one of the main causes of type 2 diabetes [2].

Hexokinase isozyme glucokinase, commonly referred to as hexokinase IV or hexokinase D is an enzyme. Its 465 amino acids make up its 50 kD molecular weight. The first stage in both glycogen production and glycolysis is the phosphorylation of glucose to glucose-6-phosphate, which the glucokinase enzyme promotes [3].

Humans and most other vertebrates have glucokinase in their brains, pancreas, guts, and liver cells. Compared to other hexokinases, glucose kinase has a lesser affinity for glucose and its activity was restricted to a small number of cell types. This decreased affinity for glucose causes variations in glucokinase activity. Glucokinase activators have also been demonstrated to increase hepatic glucose absorption and lower hyperglycemia in numerous animal models of T2D. In light of this, a unique strategy for treating T2D may be based on the numerous functions of GKAs [4-7].

Grimsby's significant finding of an allosteric activator binding site 20 away from the glucose binding site, there have been a plethora of publications from pharmaceutical companies describing how they are using GKAs to target this site. More than 100 GKA reports have been made. Glucokinase (GK), an enzyme that phosphorylates glucose, serves as a physiological glucose. Sensor is an important part of glucose homeostasis since it is present in glucose-responsive tissues like the liver and pancreas. The peculiar kinetic features of GK (Km for glucose 8 mM) and its restricted tissue distribution allow it to maintain plasma glucose levels in the physiological range through two mechanisms: (i) increasing insulin production from pancreatic ß-cells and (ii) raising hepatic glucose uptake [8-11].

Natural glucokinase mutations in humans are linked to either a loss or gain in the enzyme's activity, which results in the phenotypes of hyper and hypoglycemia, respectively. New information about the pathophysiology of Type-II Diabetes Mellitus has been revealed by this etiology. According to the literature, mice with a GK deficiency develop hyperglycemia, whereas

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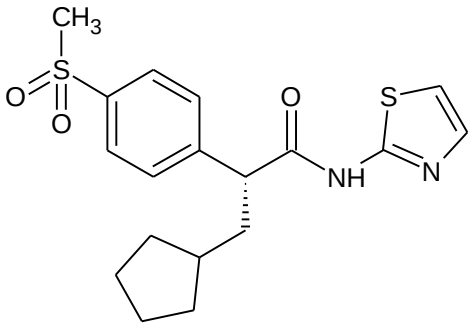
animals with hepatic GK over-expression displayed increased glucose tolerance. In Zucker diabetic fatty rats, GK expression in the liver declines throughout the disease, and correcting liver GK expression both returns plasma glucose levels to a range close to normal and normalizes hepatic glucose production. All of these findings imply that GK activation might be advantageous in the management of T2DM by lowering hyperglycemia. Several derivatives have discovered small compounds as glucokinase activators [12-17].

A few representative examples of GKAs are shown in Figure.



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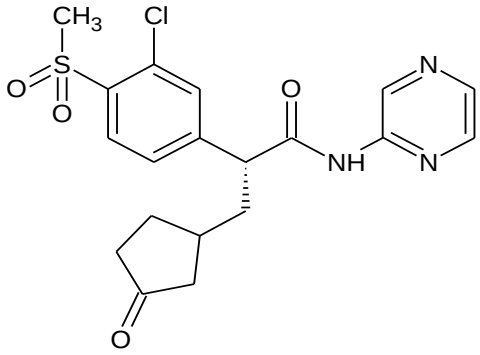
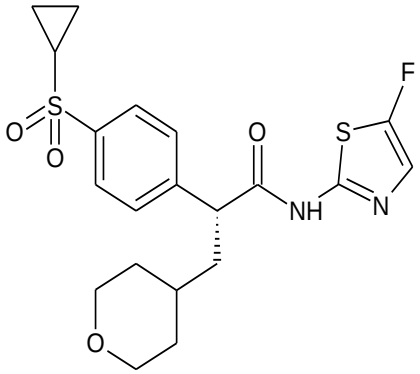
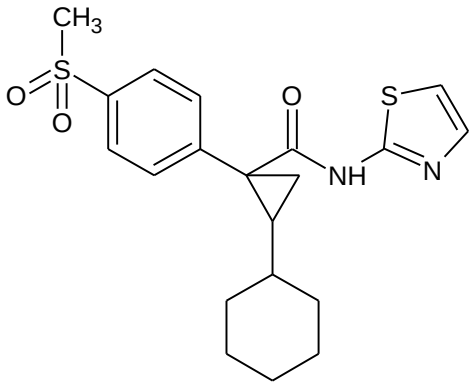


R-1440 (Piragliatin)



PSN GK1



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There are several classes of diabetic therapies available, but they do not achieve adequate glycemic control, and hence there is a need for the development of safe and effective therapies with a novel mode of action. The first line of oral therapy for type 2 diabetes mellitus is metformin and the second line of oral therapies are sulfonylureas, dipeptidyl-peptidase-4 inhibitors, and thiazolidinediones in combination with metformin. However, currently available antidiabetic agents have limited long-term efficacy and trade-offs in efficacy and safety or tolerability. Therefore, the clinical need for improved T2DM therapies remains high and diabetes patients are eager to have novel therapeutic options to safely achieve tight glycemic control [18-20].

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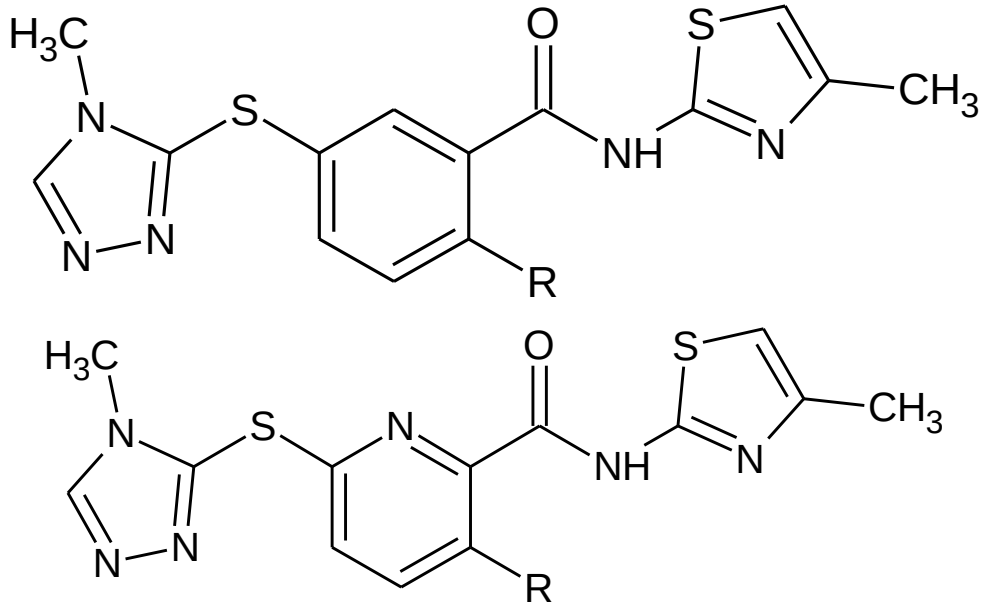
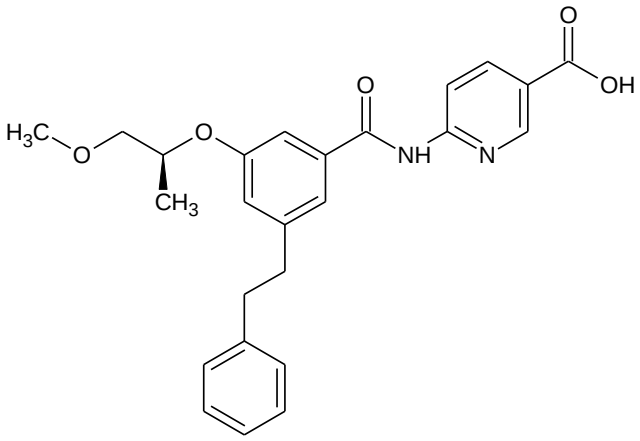
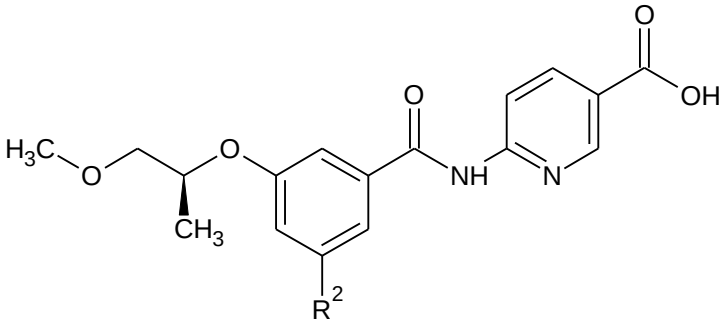
**Various derivatives which activate glucokinase and maintain blood glucose levels in the body are-**
**3,6-disubstituted 2-pyridine carboxamide derivatives**[21]**-**



**Phenylethyl benzamide derivatives**[22]**-**



**Carboxypyridine benzamide derivatives**[22]**-**



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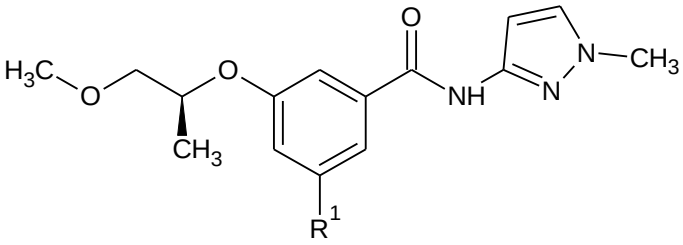
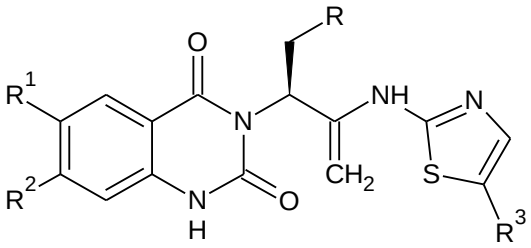
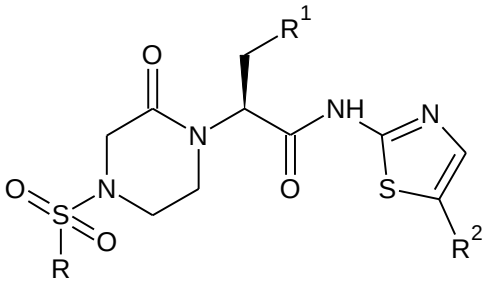
**Pyrazole benzamide derivatives**[22]-



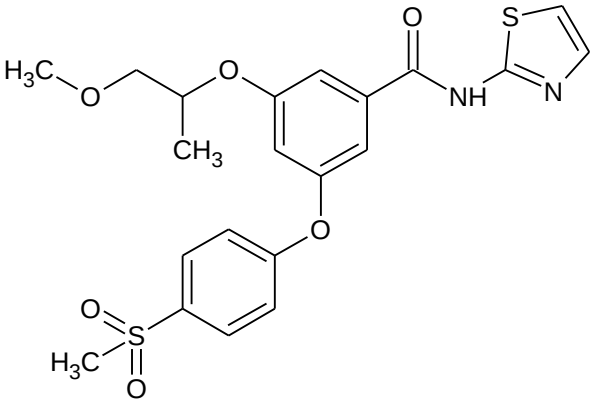
**Quinazoline-2,4 dioneanalogs**[23]-



**Ketopiperazine analogs**[23]-



**Cycloalkyl-fused N-thiazol-2-yl-benzamides derivatives**[24]-



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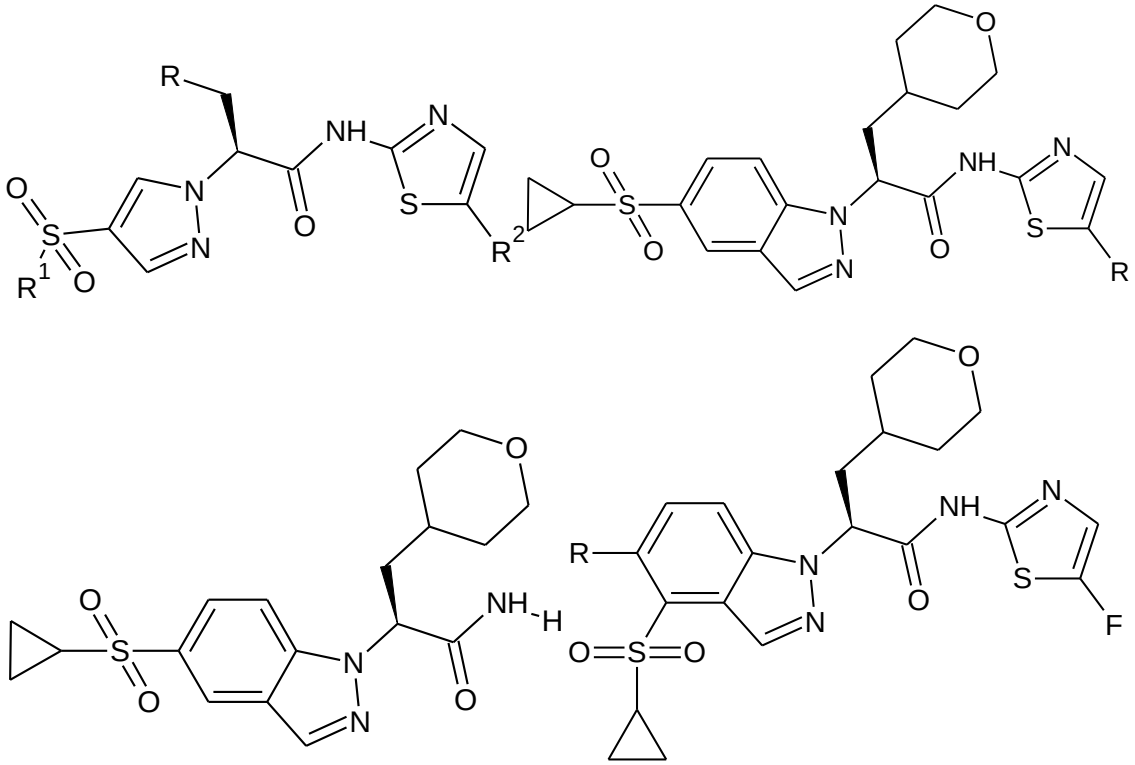
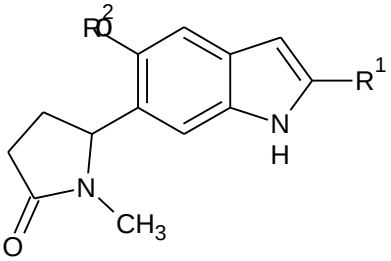
**1,4-disubstituted indazoles derivatives**[25]**-**



**2,5,6-trisubstituted indole derivatives**[26]**-**



**Azaindole derivatives**[27]**-**

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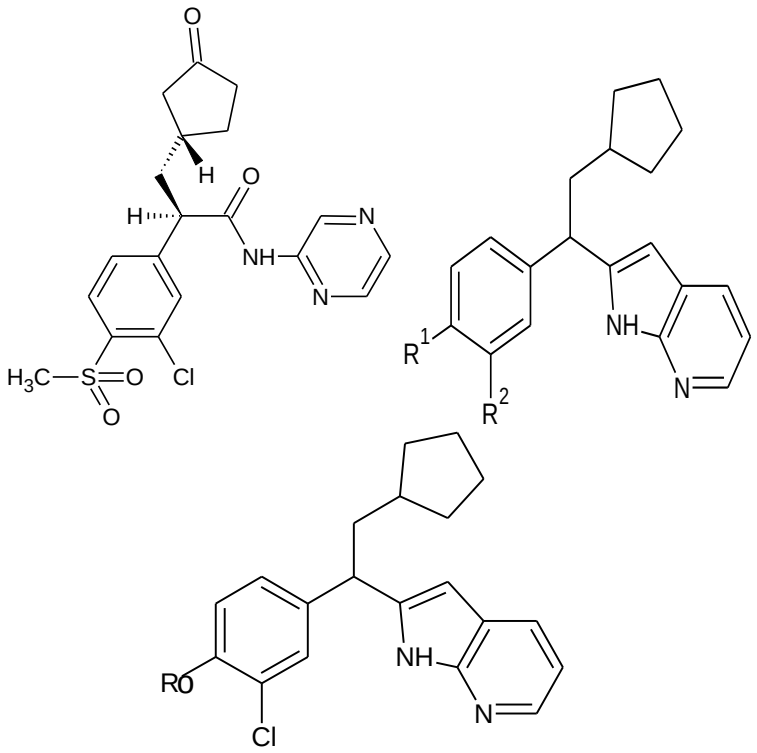
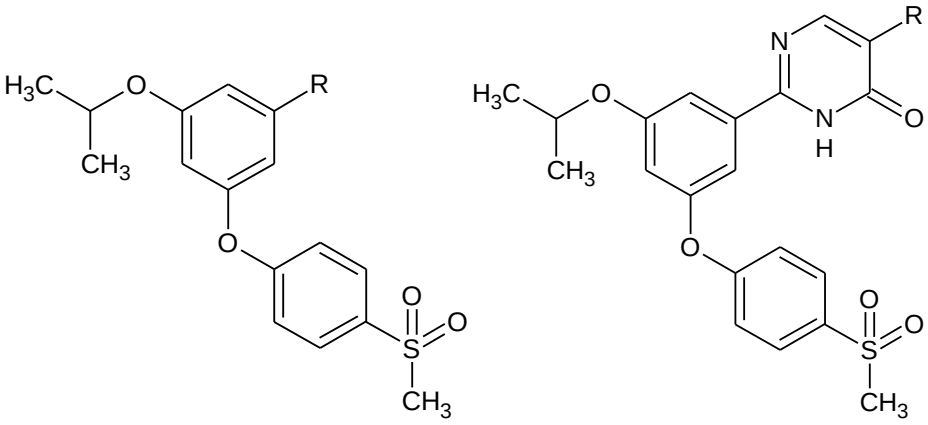


**Pyrimidone derivatives**[28]-



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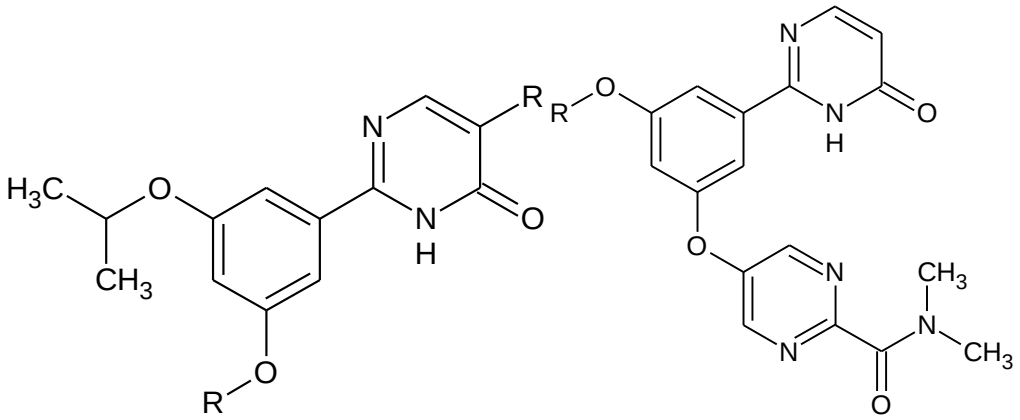

**Binding interaction of glucokinase activators with their receptors**

Such compound showed hydrogen bond interaction between the nitrogen atom of the thiazole ring with amino acid residues ARG 63 where as the N-atom of the pyridine ring with amino acid residues TYR 214 of glucokinase allosteric site[29].The other amino acids found in the cavity of glucokinase receptors are TYR 61, VAL 62, SER 64, THR 65, PRO 66, ILU 211, MET 210, ILU 159, ALA 456, VAL 455, VAL 452, LEU 451, MET 210.

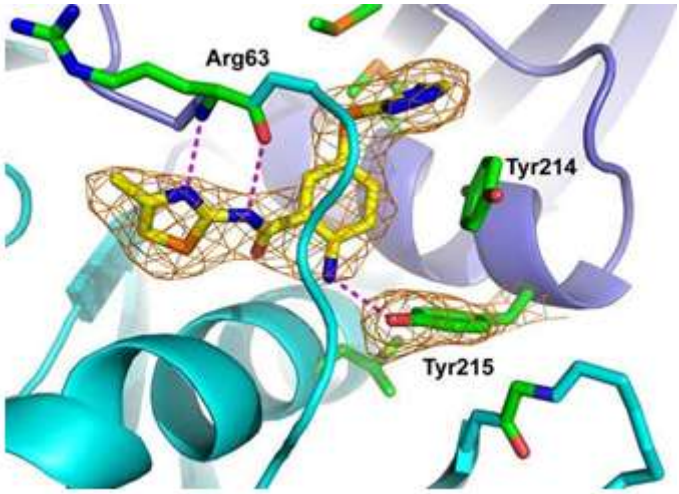


**Figure 1: Interaction between compound and receptor**

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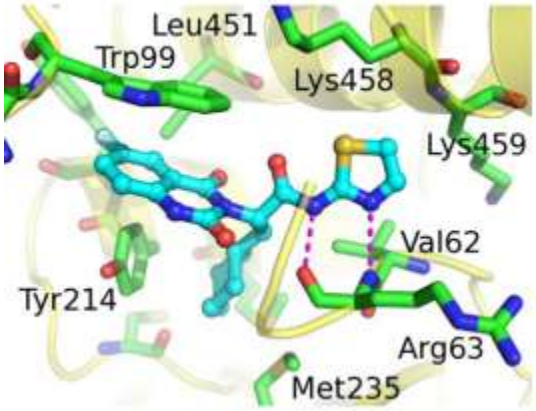


**Figure 2: Co-crystal structure of compounds in the GK allosteric site**

## II. CONCLUSION

Glucokinase is crucial to maintaining glucose homeostasis throughout the body. By speeding up and becoming more affine to glucose, glucokinase activator increases the activity of the glucokinase enzyme.

The medicines that are now available on the market for the treatment of type 2 diabetes mellitus do not provide adequate glucose control for a prolonged period. Hepatotoxicity, nephrotoxicity, insulin resistance, and postprandial hypoglycemia are all side effects of currently marketed medications that have a single mode of action. A novel medication with several mechanisms of action is still urgently needed to control glucose levels with higher and longer-lasting potency.

The results of the literature review showed that small-molecule glucokinase activators might be able to solve these issues because they have multiple mechanisms of action, including stimulating the pancreatic beta cells to secrete insulin and reabsorbing glucose from the blood into the hepatic cells. As a result, it is possible to predict that glucokinase activators will have anti-diabetic effects.

Hence, the objective of the present study is to synthesize molecules ofthese different derivatives like3,6-disubstituted2-pyridine carboxamide derivatives, Phenylethyl benzamide derivatives, Carboxypyridine benzamide derivatives, Pyrazole benzamide derivatives, Quinazoline-2,4 dione analogs**,** Ketopiperazine analogs, Cycloalkyl-fused N-thiazol-2-yl-benzamides derivatives, 1,4-disubstituted indazoles derivatives, 2,5,6-trisubstituted indole derivatives, Azaindole derivatives and Pyrimidone derivatives to bedesigned, synthesized and evaluated the pharmacological activityas glucokinase activator.

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