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RECENT TARGET BASED DISCOVERY OF ANTI-DIABETIC AGENTS

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Keywords:

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ABSTRACT: Diabetes is the most common lifestyle disease associated with many serious worries including diabetic ketoacidosis, cardiac problems, kidney failure, non ketotic hyperosmolar coma, foot ulcers, eye damage etc. All these complications develops due to abnormalities in carbohydrate metabolism and insulin synthesis resulting in high blood sugar with symptoms such as elevated hunger and thirst, polyuria, glycosuria, lethargy etc. The article is focused on different targets of diabetes.

INTRODUCTION: Type 2 diabetes mellitus or non-insulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes is a chronic metabolic disorder characterised by hyperglycaemia (fasting and post-prandial). Due to its increasing incidence across the globe, it affects nearly about 5% of the total population in the urbanizednations.[1, 2] and accounts for about 90% of all the diagnosed cases, thereby becoming one of the biggest challenges in 21st century [3-5] leading to hyperglycaemia, insulin resistance and obesity, etc. [6-8]. According to the International Diabetes Federation (IDF), the global prevalence of diabetes is predicted to grow from 366 million in 2011to 552 million by 2030 [9]. The major incidence of diabetes mellitus will occur in Asia, mainly China and India (57 million in India). [10, 11]

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It is a widespread syndrome leading to insulin resistance in target tissue, adipose tissue, liver and skeletal muscles and disproportionate glucose production by liver.[12-16] Resistance to insulin is a major health factor in diabetes mellitus [17]. In order to avoid severe complications and to obtain desirable blood sugar levels, improving sensitivity to insulin must be the first task. Thiazolidinedione's (TZDs) are found to be excellent examples for improving sensitivity to insulin and avoiding serious complications [18], but are avoided due to its side effects such as liver toxicity, retention of fluid etc.[19] Four major pharmacological agents available widely for treatment of diabetes includes insulin secretagogues sulfonylureas [20-22], bigunides [23-27], glitazones [28-32] and acarbose.[33-35]

Although variousanti-diabetic drugs have been synthesized for the treatment, but still many of them have a number of serious side effects [36]. Development of anti-diabetic drugs with minimal side effects and relatively low costs is still a challenge to the medical system. [37]

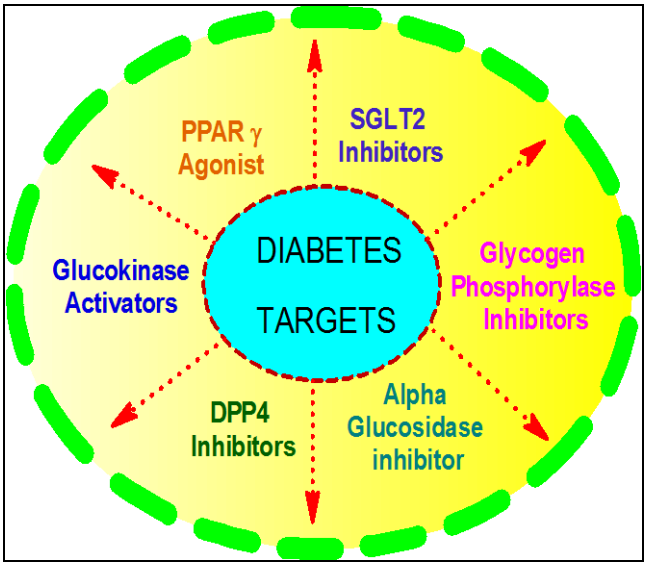


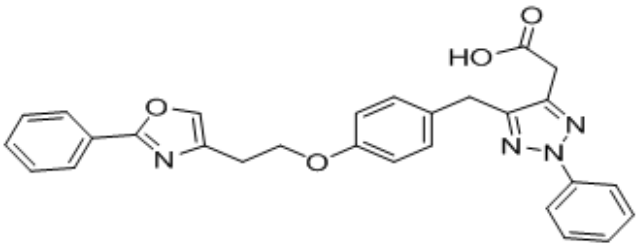
FIG.1: DIFFERENT TARGETS OF DIABETES

Molecular targets of anti-diabetic agents:

PPAR gamma agonists:

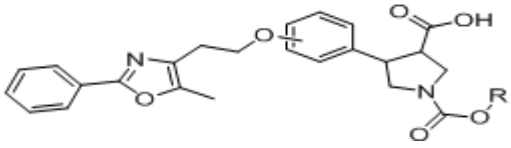
Peroxisome proliferator-activated receptors (PPARs) are ligand activated nuclear hormone receptors which plays an important role in glucose metabolism [38]. It has three subtypes which are identified as PPARα, PPARγ and PPARδ. PPARαis mainly expressed liver, heart, kidney [39] and includes fibrate class of drugs (fenofibrate, gemfibrozil) [40, 41]. PPARγagonists mainly comprises of the thiazolidinedione (TZD) class of anti-diabetic agents (rosiglitazone, pioglitazone) [42, 43].

Zhang.H.*et al* [44] has designed, synthesized and carried out structure–activity relationships of a novel series of N-phenyl-substituted pyrrole, 1,2-pyrazole and 1,2,3-triazole acid analogs as PPAR ligands.



(1)

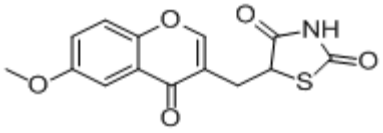
Zhang. H. *et al* [45] has designed, synthesized and carried out structure–activity relationships of a novel series of 3,4-disubstituted pyrrolidine acid analogs as PPAR ligands. 1,3- and 1,4-oxybenzyl pyrrolidine acid series were characterized by spectral analysis.



(2)

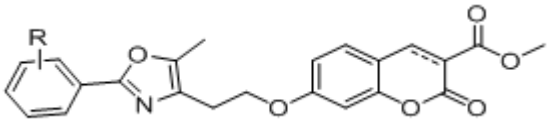
R = Et, Ph

Nazreen.S.*et al* [46] has synthesized a library of conjugates of chromones and 2,4-thiazolidinedione by Knoevenagel condensation followed by reduction using hydrogen gas and Pd/C as a catalyst.



(3)

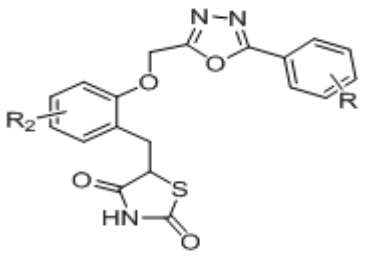
Yu.J.*et al* [47] has synthesized a series of benzopyran derivatives and evaluated for PPAR a/g. agonist activities. All of the synthesized compounds were characterized by spectral analysis.



(4)

R= p-Ph, p-OMe. p-tBu, p-Me, m-Me, m-CF_3, p-F, m-F, m-NO_2

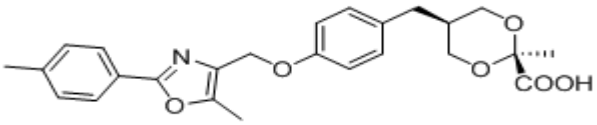
Nazreen.S.*et al* [48] has synthesized a novel series of 1,3,4-oxadiazole and 2-4-thiazolidinedione based bis-heterocycles which exhibited significant PPAR-g transactivation and blood glucose lowering effect comparable with the standard drugs.



(5)

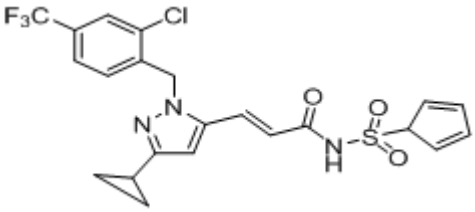
R= H, HR_2= H, O-CH_2-2,6-diCl

Pingali.H.*et al* [49] has designed and synthesized a novel series 1,3-dioxane carboxylic acid derivatives to aid in the characterization of PPAR a/c dual agonists. The Lead compound 2-methyl-c-5-[4-(5-methyl-2-(4-methylphenyl)- oxazol-4 ylmethoxy)-benzyl]-1,3-dioxane-r-2-carboxylic acid exhibited potent hypoglycemic, hypolipidemic and insulin sensitizing activity.



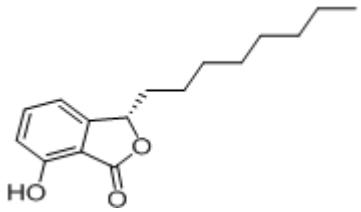
(6)

Rikimaru.k. *et al* [50] has designed, synthesized and carried out the structure–activity relationships of novel benzylpyrazole acylsulfonamides as non-thiazolidinedione (TZD), non-carboxylic-acid-based peroxisome proliferator activated receptor (PPAR) c agonists.



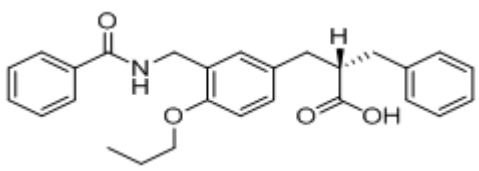
(7)

Xio.B. *et al* [51] has synthesized 20 analogson the basis of a marine fungal phthalide (paecilocin A) skeleton, and characterized them with spectral analysis.



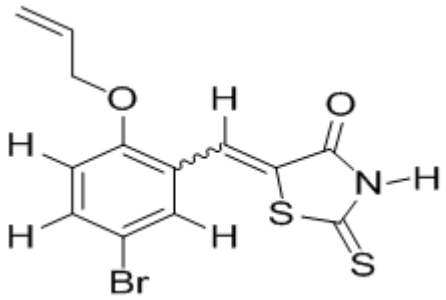
(8)

Ohashi.M. *et al* [52] has designed an synthesized a series of a-benzyl phenylpropanoic acid-type hPPARc partial agonists with improved aqueous solubility and characterized by spectral analysis.



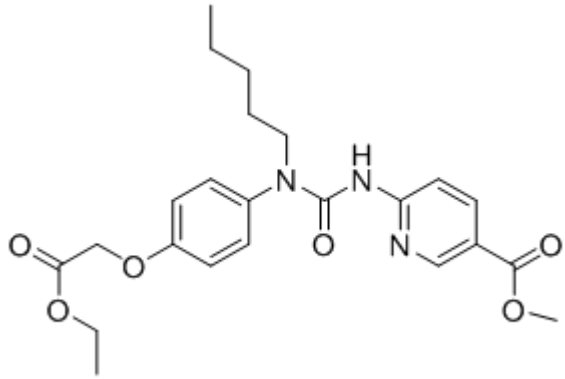
(9)

Zhou.L.*et al* [53] has designed and synthesized a series of 2-thioxo-4-thiazolidinone derivatives and evaluated them on peroxisome proliferator activated receptor g (PPARg) binding activities.



(10)

Zhang. L. *et al* [54] has designed and synthesized a series of novel phenyl urea derivatives which can simultaneously activate glucokinase (GK) and peroxisome proliferator-activated receptor g (PPARg). The possible binding mode of these compounds with GK and PPARg were predicted by molecular docking simulation.

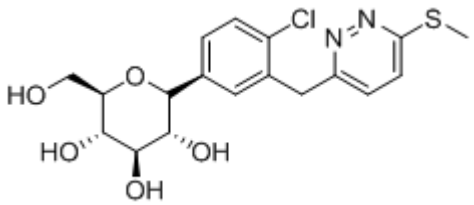


(11)

SGLT2 Inhibitors:

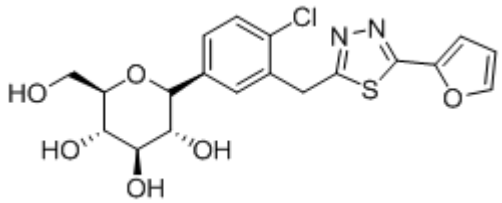
SGLT2 inhibitors are high capacity Sodium-dependent glucose co-transporters that have low-affinity, and located exclusively at the apical domain of the epithelial cells in the early proximal convoluted tubule. It accounts for 90% of the total renal glucose absorptions.[55, 56]

Kin.M.J.*et al* [57] has designed and synthesized novel C-aryl glucoside SGLT2 inhibitors containing pyridazine motif. Among all the synthesized compounds, pyridazine containing methylthio moiety 22l orthiadiazole ring were found to be most potent.



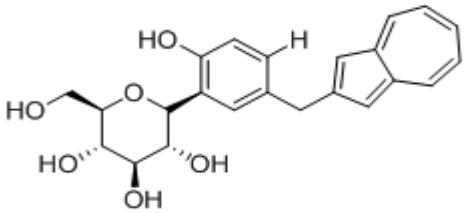
(12)

Lee. J. *et al* [58] has designed and synthesized novel C-aryl glucoside SGLT2 inhibitors containing 1,3,4-thiadiazole moieties. Among all the synthesized compounds, biaryl-type compounds containing pyrazine 9, 2-furan, and 3- thiophene were found to be most potent.



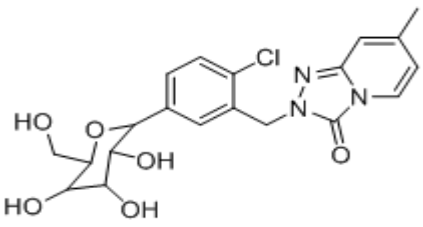
(13)

Ikegai.K.*et al* [59] has synthesized a series of C-glucosides with azulene rings in the aglycon moiety and the inhibitory activities toward hSGLT1 and hSGLT2 were then assessed. The compound having 3-[(azulen-2-yl)methyl]phenyl group was identified as a lead compound for further optimization.



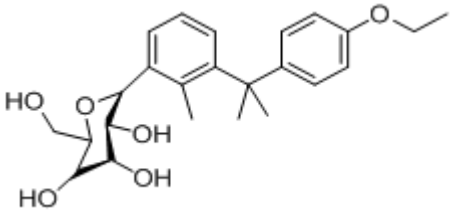
(14)

Guo.C.*et al* [60] has designed, synthesized and carried out structure– activity relationship (SAR) of C-glycosides with benzyltriazolopyridinone and phenylhydantoin as the aglycone moieties as novel SGLT2 inhibitors.



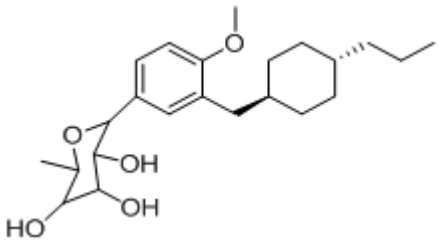
(15)

Zhao.J.W.*et al* [61] has designed and synthesized a series of gem-dimethyl-bearing C-glucosides as SGLT2 inhibitors, with anhydrous aluminium chloride-mediated Friedel-Crafts alkylation reaction.



(16)

Zhang.S.*et al* [62] has designed and synthesized seven cyclohexane-bearing C-glucoside derivatives as SGLT2 inhibitors and then characterized by spectral analysis.

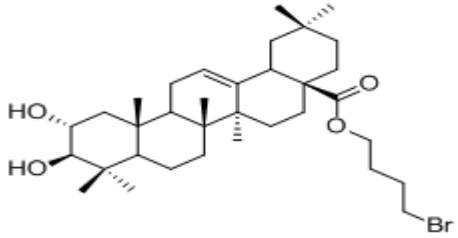


(17)

Glycogen Phosphorylase Inhibitor:

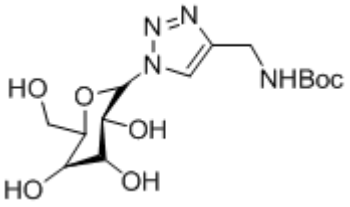
Glycogen phosphorylase inhibitors inhibits the enzyme glycogen phosphorylase which is responsible for glycogen conversion to glucose and related metabolites.[63] Pharmacological inhibition of GP has been proved to be an effective therapeutic approach for treating diseases caused by abnormalities in glycogen metabolism, such as type 2 diabetes, myocardial ischemia, and tumors.[64-66]

Wen.X.*et al* [67] has synthesized a series of maslinic acid derivatives and their effect on rabbit muscle glycogen phosphorylase was evaluated and their SAR has been discussed.



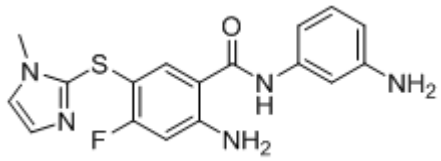
(18)

Goyard.D.*et al* [68] has synthesized a series of eight GP inhibitor candidates from per acetyl glucopyranosyl azide by click-chemistry. The N-Boc-protected amine was the best inhibitor (IC50 = 620 lM) unpredictablysomewhatsuperior than the 2-naphthylamido substituted analogue (IC50 = 650 lM).



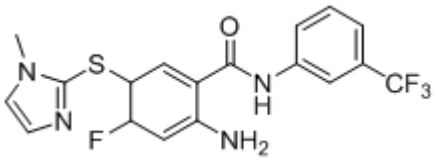
(19)

Chen.L.*et al* [69] has designed and synthesized a series of novel benzamide derivatives and their inhibitory activities against glycogen phosphorylase (GP) in the direction of glycogen synthesis by the release of phosphate from glucose-1-phosphate were evaluated and their structure activity relationship has been established.



(20)

Zhang.L.*et al* [70] has synthesized a series of benzamide derivatives which can simultaneously inhibit glycogen phosphorylase (GP) andactivate glucokinase (GK) and their structure–activity relationship (SAR) has been established.

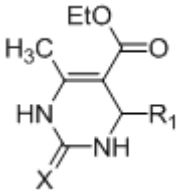


(21)

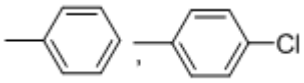
Alpha Glucosidase Inhibitors:

α-Glucosidase inhibitors reversibly inhibits the enzyme α-Glucosidase which is responsible for hydrolysing carbohydrates to produces α-D-glucose, which enters blood stream, and increases postprandial blood glucose levels, finally leading to diabetes. Thus, for the control and prevention of diabetes, a-glucosidase inhibitors are of particular interest [71, 72].

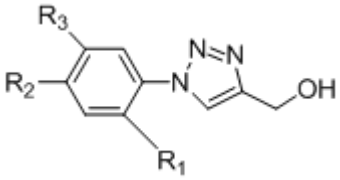
Yar.M.*et. al* [73] has synthesised dihydropyrimidines by N-acetyl glycine (NAG) catalysed reaction of aromatic aldehydes with ethyl acetoacetate and urea/thiourea by a new conventional and efficient method. The method is also applicable for various substituted aldehydes as well as urea and thiourea.



(22)

R_1 = 

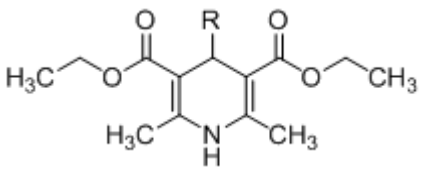
Gonzaga.D.*et. al* [74] has synthesised two series of non-glycoside triazoles and screened against baker's yeast a-glucosidase (MAL12) and porcine pancreatic a-amylase activity (PPA).



(23)

R_1 = H, Cl
R_2 = H, OCH_3
R_3 = H, Cl.

Niaz.H.*et. al*[75] has synthesised1,4-Dihydropyridine-3,5-dicarboxylate derivatives *via* Hantzsch reaction and evaluated for their *α*-glucosidase inhibitory activity and their structures were then characterized by different spectroscopic techniques.



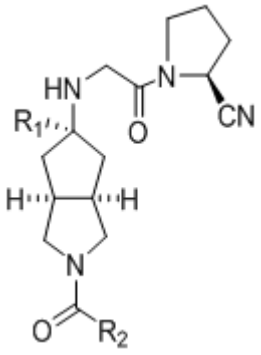
(24)

R = NO_2

DPP4 Inhibitors:

Dipeptidyl peptidase 4 inhibitors have been identified as novel therapeutic agents for the treatment of diabetes and includes sitagliptin, saxagliptin, vildagliptin and linagliptinas approved agents for the treatment of type 2 diabetes, DPP4 inhibitors do not shows signs of weight gainalong with very low incidence of hypoglycemic events[76-80].

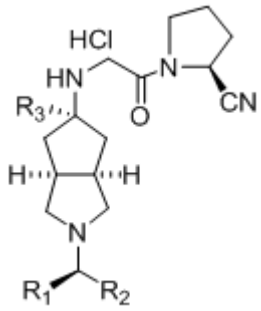
Cho. T. P. *et. Al* [81] has synthesiseda series of novel azobicyclo[3.3.0]octane derivatives and evaluated as dipeptidyl peptidase 4 (DPP-4) inhibitors.



(25)

R_2 = $N(CH_3)_2$, $NHCH(CH_3)$, $N(CH_2)_4$, $N(CH_2)_5$, $N(CH_2\ CH_2)_2O$

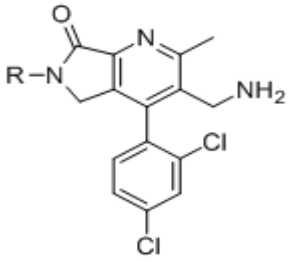
Cho. T. P. *et. Al* [82] has synthesiseda series of novel bicyclo[3.3.0]octane derivatives have been synthesized and found to be dipeptidyl peptidase 4 (DPP-4) inhibitors.



(26)

R_1 = H, OH, OMe, OEt
R_2 = H, OMe
R_3 = H (α), H (β).

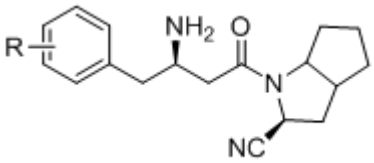
Wang. W. *et. a l* [83] has designed, synthesized and carried out SAR of 7-oxopyrrolopyridine-derived DPP4 inhibitors.



(27)

R = Butanol, 4- OMe-Bn.

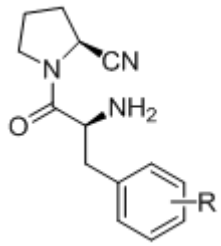
Ji, X. *et. al* [84] has designed and synthesized a series of novel b-amino pyrrole-2-carbonitrile derivatives.



(28)

R = H, 2- Cl, 2-Me, 3-F, 4-F, 4- I.

Wang, J. *et. al* [85] has synthesised a novel series of pyrrolidine-2-carbonitrile and 4-fluoropyrrolidine-2-carbonitrile derivatives and found to act as dipeptidyl peptidase-4 (DPP-4) inhibitors.



(29)

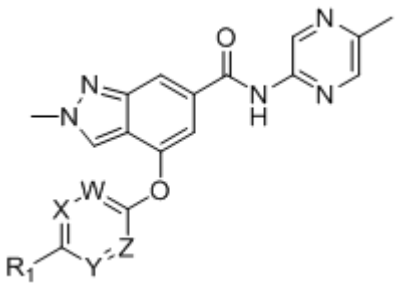
R = H, 2-F, 4- Me, 4- OMe, 4- NH_2, 4- Cl, 4- Br.

Glucokinase Activators:

Glucokinase is an enzyme which is responsible for the regulation of glucose homeostasis. In the liver, it regulates the uptake and output of hepatic glucose, whereas in the pancreas it actsas a glucostat and establishes the threshold for β-cell glucose-stimulated insulin secretion.

Pharmacologically it is envisioned that activation of glucokinase in the liver and pancreas would be an effective strategy for lowering blood glucose by up-regulating hepatic glucose utilization, down-regulating hepatic glucose output and enhancing glucose-stimulated insulin secretion[86, 87].

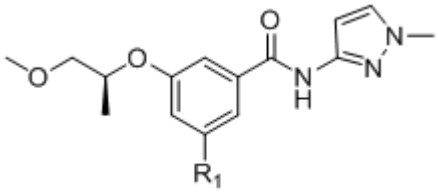
Pfefferkorn. J. A. *et. al* [88] has synthesised a series of novel indazole and pyrazolopyridine based activators leading to the identification of 4-(6-(azetidine-1-carbonyl)-5-fluoropyridin-3-yloxy)-2-ethyl-N-(5-methylpyrazin-2-yl)-2H-indazole-6-carboxamide as a potential candidate.



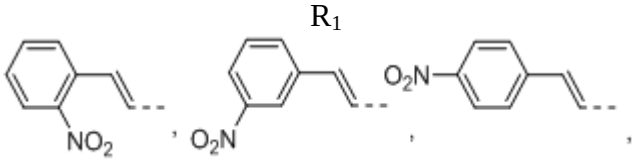
(30)

R_1 = C(O)NMe2, SO2Me, SO2Et.

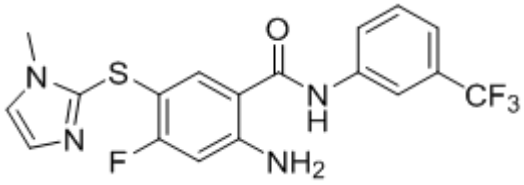
Park. K. *et. al* [89] .has synthesised novel benzamide derivatives and tested at in vitro assay by measuring fold increase of glucokinase activity at 5.0 mM glucose concentration.



(31)

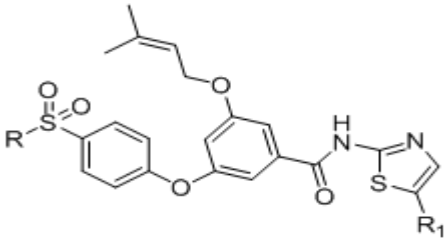


Zhang. L. *et. al* [90] has designed and evaluated a series of benzamide derivatives which can simultaneously inhibit glycogen phosphorylase (GP) and activate glucokinase (GK). The structure–activity relationships (SAR) of these compounds were also established.

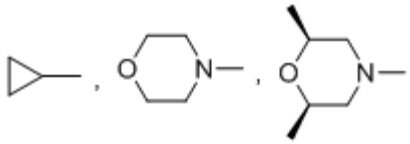


(32)

Mao. W. *et. al* [91] has designed a series of benzamide derivatives and their SAR studies as glucokinase activators were described.



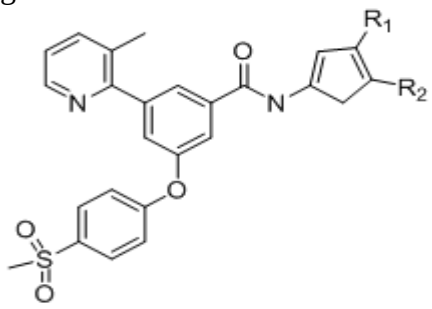
(33)



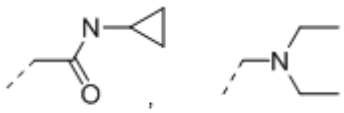
R =

R_1 = F, H

Park. K. *et. al* [92] has designed and synthesized novel heteroaryl-containing benzamide derivatives and screened using an in vitro assay measuring increases in glucose uptake and glucokinase activity stimulated by 10 mM glucose in rat hepatocytes. From a library of synthesized compounds, 3-(4-methanesulfonylphenoxy)-N-[1-(2- methoxy-ethoxymethyl)-1H-pyrazol-3-yl]-5-(3-methyl pyridin-2-yl)-benzamide was identified as a potent glucokinase activator.



(34)



R_1 = H,

R_2 = H

CONCLUSION: The article is focused on different targets of diabetes which can be explored with different inhibitors/activators for better treatment of this lifestyle disease.

CONFLICT OF INTEREST: The authors confirm that this article content has no conflicts of interest.

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