RECENT ADVANCEMENT OF PYRIDINE MOIETY IN TREATMENT OF DIABETES

A Project Work Submitted

In Partial Fulfilment of the Requirements

For the Degree of

BACHELOR OF PHARMACY

Dhirendra Singh (Enrollment no: 18021020154)

Under the Supervision of

Mr. Rakesh Sahu

Assistant Professor

Galgotias University

Greater Noida

to the

Department of Pharmacy

GALGOTIAS UNIVERSITY

Greater Noida

May , 2022

CERTIFICATE

This is to certify that the project work entitled "*Recent advancement of pyridine moiety in treatment of diabetes "* is a bonafide research work done by Mr. Dhirendra Singh at Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, under the supervision and guidance of Mr. Rakesh Sahu, Assistant Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfillment for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2021-2022.

Date:

Place:

Prof. Pramod Kumar Sharma
Dean
School of Medical and Allied Sciences
Galgotias University
Greater Noida [U.P.]

BONAFIDE CERTIFICATE

This to certify that the project work entitled "**Recent advancement of pyridine moiety in treatment of diabete***s "* by MR. DHIRENDRA SINGH for the award of "Bachelor of Pharmacy" degree, comprises of the bonafide research work done by him at Department of Pharmacy, School of Medical & Allied Sciences, Galgotias University, Greater Noida under my guidance and supervision and to my full satisfaction.

[Guide]

Mr. Rakesh Sahu
Assistant Professor
Department of Pharmacy
School of Medical and Allied Sciences
Galgotias University
Greater Noida [U.P.]

DECLARATION

I hereby declare that the project work embodied in this project entitled " **Recent advancement of pyridine moiety in treatment of diabetes** *"* was carried out by me under the supervision and guidance of Mr. Rakesh Sahu, Assistant Professor, School of Medical and Allied Sciences, Galgotias University, Greater Noida. I have not submitted the matter embodied in this project or award of any other degree or diploma of any other university or institute.

Date:
Place:

Dhirendra singh
Name and Signature of candidate

Acknowledgement

It gives me immense gratification to place on record my profound gratitude and sincere appreciation to each and every one who have helped me in this endeavour.

I gratefully acknowledge Prof. Pramod Kumar Sharma, Dean, School of Medical and Allied Science, Galgotias University for his advice, supervision and crucial contribution which made a backbone of this research and so to this thesis.

I wish to express my gratefulness to Dr. Rakesh sahu, Assistant Professor, Department of Pharmacy, School of Medical and Allied Science, Galgotias University, Greater Noida for her constant guidance dealing the project.

I wish to express my gratitude to my colleagues and friends for encouragement and support.

Lastly, I have absolutely no words to express my feeling of gratitude to the staff members of marketing executive and sales representatives for their full co-operation and valuable suggestion in the completion of my project work.

DHIRENDRA SINGH

B. PHARM. [VIII SEM]

ENROLMENT NO. - 18021020154

GALGOTIAS UNIVERSITY

GREATER NOIDA

ABSTRACT

Diabetes mellitus is one of the common and very prevalent diseases affecting the citizens of both developed and developing countries. Type 2 diabetes accounts for nearly 80 to 90% of the cases reported. Prominent side-effects of existing drugs are the main reason for an increasing number of people seeking alternative therapies that may have less severe or no side-effects, hence the demand has arisen for using a more benign drug. Natural products have played an important role throughout the world in treating and preventing human diseases. In parts of the world where the population has restricted access to the healthcare system, the use of plants for the treatment of diabetes is widespread. Scientifically, very little is known about the mechanism of action of these traditionally used antidiabetic plants, thus preventing them from being used in standard diabetes care. Consequently, it is necessary to perform toxicological investigation of all plants empirically used in order to avoid the risk of the side effects related to phytotherapy. Recently, more research is being focused on elucidating the action of these plants and their active constituents.

Keywords : Pridine moiety, Diabetes, Treatment, modern-day trend, substituent impact.

CHAPTER : 1
INTRODUCTION

Diabetes mellitus is one of the common and very prevalent diseases affecting the population of both developed and developing countries. It is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances in carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, action or both [WHO, 1999].[1] The effects include long term damage, dysfunction and failure of various organs including progressive development of specific complications of neuropathy with risk of foot ulcers, nephropathy leading to renal failure and/or, retinopathy with potential blindness, Charcot joints and amputation including sexual dysfunction. Individuals with diabetes are at increased risk of peripheral vascular, cardiovascular and cerebrovascular diseases.[2] In the late 1970s, both National Diabetic Data Group [1979] and World Health Organization [1980] recognized two major forms of diabetes which they termed as type 1 diabetes [previously termed juvenile onset diabetes] or Insulin Dependent Diabetes Mellitus [IDDM] and type 2 diabetes or Non-Insulin Dependent Diabetes Mellitus [NIDDM]. Diabetes caused by a specific and identified underlying defects, such as genetic defects or diseases of the exocrine pancreas were placed under the third category known as "other specific types of diabetes".

Type 2 diabetes is a chronic and progressive syndrome representing heterogeneous disorders resulting by various combinations of insulin resistance and decreased pancreatic β-cell function caused by both genetic and acquired abnormalities [Olefsky, 1993; Kahn, 1994; Gerich, 1998]. In type 2 diabetic individuals, the blood glucose and insulin levels remain normal for many years until at a point of time when insulin resistance develops. Initially, β-cells compensate the insulin resistance by increasing insulin secretion leading to hyperinsulinemia. However, at later stages, β-cell function alters and fails to compensate for increasing insulin resistance leading to increase in blood sugar levels [Purrello and Rabuazzo, 2000] and eventually clinical diabetes is established.

1.1 Types of Diabetes

The study of disease transmission

In 2015, 415 million individuals were assessed to have diabetes, over 90% of whom had type 2 diabetes, with an extended increment to 642 million by 2040.[18] Epidemiology of type 2 diabetes is essentially influenced by ecological and hereditary variables. Hereditary variables apply their impact following openness to an obesogenic climate described by inactive conduct and over the top sugar and fat utilization. Genome-wide affiliation considers have prompted the identifi cation of regular variations of glycaemic hereditary attributes for type 2 diabetes, however these lone record for 10% of absolute quality difference, recommending that uncommon variations are important.[19]. The systems prompting improvement of type 2 diabetes in youngsters is almost like the more seasoned patients; albeit, the speed of beginning, seriousness, and exchange of diminished insulin affectability and inadequate insulin emission may be diverse in patients who foster the infection at a more youthful age.[20]

Diabetes is a gathering of metabolic sicknesses described by hyperglycemia coming about because of imperfections in insulin discharge, insulin activity, or both. The persistent high blood sugar of diabetes is related with lifelong haul harm, brokenness, and disappointment ofdifferent parts, particularly the eyes, kidneys, nerves, heart, and veins.

1.2 Type-I Diabetes

Safe Mediated Diabetes

Type I diabetes, which represents just 5 to 10% of those with blood sugar, recently incorporated by the terms insulin-subordinate diabetes or adolescent beginning sugar, results from a cell interceded immune system annihilation of the beta cells of the pancreas. 1 and generally a greater amount of these autoantibodies are available in 85 to 90% of people when fasting high blood sugar is at first identified. Type 1 diabetes* envelops diabetes that is basically a consequence of pancreatic beta cell obliteration with resulting insulin lack, which is inclined to ketoacidosis. This structure incorporates cases because of an immune system measure and those for which the etiology of beta cell annihilation is obscure.

1.3 Type II Diabetes

This type of diabetes, which represents ;90–95% of those with diabetes, recently alluded to as non–insulin subordinate diabetes, type 2 diabetes, or grown-up beginning diabetes, envelops people who have insulin opposition and for the most part have relative [instead of supreme] insulin insufficiency. In any event at first, and frequently all through their lifetime, these people needn't bother with insulin treatment to endure. There are likely various reasons for this type of diabetes. Albeit the particular etiologies are not known, immune system annihilation of b-cells doesn't happen, and patients don't have any of different reasons for diabetes recorded above or beneath. Most patients with this type of diabetes are large, and weight itself causes some level of insulin obstruction.

1.4 Hereditary Defects of the beta Cell

A few types of blood sugar are related with monogenetic abandons in beta cell work. These types of diabetes are habitually portrayed by beginning of hyperglycaemia at an early age. They are alluded to as development beginning sugar of the youthful and are described by impeded insulin discharge with insignificant or no deformities in insulin activity.

1.5Hereditary Defects in Insulin Action

there are uncommon reasons for diabetes that outcome from hereditarily decided anomalies of insulin activity. The metabolic irregularities related with transformations of the insulin receptor may go from hyperinsulinemia and unassuming hyperglycemia to serious diabetes.

Illnesses of the Exocrine Pancreas

Any interaction that diffusely harms the pancreas can cause diabetes. Obtained measures incorporate pancreatitis, injury, disease, pancreatectomy, and pancreatic carcinoma. Except for that brought about by malignant growth, harm to the pancreas should be broad for diabetes to happen; adrenocarcinomas that include just a little part of the pancreas have been related with diabetes.

1.1 Other specific types of diabetes

Genetic defects of the β-cell Monogenetic defects in β-cell function are frequently characterized by onset of hyperglycemia at an early age, generally before 25 years. They are referred to as maturity Chapter I – Introduction - 3 onset diabetes of the young [MODY] and are characterized by impaired insulin secretion with minimal or no defects in insulin action. Abnormalities at six genetic loci on different chromosomes have been identified so far. Genetic abnormalities that result in the inability to convert pro-insulin to insulin have been identified and such traits are inherited in an autosomal dominant pattern. Therefore, the resultant glucose intolerance is mild. Similarly, production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a limited number of families with only mildly impaired or even normal glucose metabolism.[3]

1.2 Defects in insulin action

The metabolic abnormalities associated with mutations of the insulin receptor and genetically determined abnormalities of insulin action may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Alterations in the structure and function of insulin receptor cannot be demonstrated in patients with insulin-resistant lipoatrophic diabetes. Therefore, it is assumed that the lesion[s] must reside in the post receptor signal transduction pathways. Earlier, this syndrome was termed as type A insulin resistance.

1.3 Diagnosis Criteria

The diagnostic value of the fasting plasma glucose concentration from the former level of 7.8 mmol/L [140 mg/dL] and above to 7.0 mmol/L [126 mg/dL] and above is the major change recommended in the diagnostic criteria. For whole blood, the former 6.7 mmol/L [120 mg/dL] is reduced to 6.1 mmol/L [110 mg/dL] and above. This value represents the upper end of the range that corresponds in diagnostic significance in many individuals to that of the 2h post load concentration, which is not changed [Table 1.1]. This equivalence has been established from several population based studies and represents an optimal cut–off point of fasting plasma glucose concentration.

Table 1: Criteria for the diagnosis of diabetes [5]

1	A1c ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
2	FPG ≥ 126 mg/dL [7.0 mmol/L]. Fasting is defined as no caloric intake for at least 8 h.*
3	2h plasma glucose ≥ 200 mg/dL [11.1 mmol/L] during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
4	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL [11.1 mmol/L].

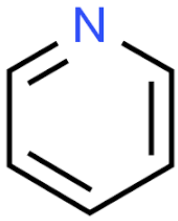


Fig : 1 Chemical Structure of pyridine

Pyridine is a fundamentally important chemical compound with the formula C_5H_5N
It is a liquid with a distinctively putrid, fishy odor. Its molecules have a six-membered ring structure that

can be found in many compounds, including the nicotinamides.

This compound has numerous applications. It is both a versatile solvant and a building block for a variety of other Organic compound. It is a starting material in the manufacture of insecticides, herbicies, pharmaceuticals, food flavorings, chemicals,, and disinfectants. In addition, it is a denaturant for antifreeze mixtures and is sometimes used as a ligand in coordination chemistry.

1.4. Properties of pyridine

Table 2 : Physical Properties of pyridine

Formula	**Molecular weight**	**Density**	**Melting point**	**Boiling point**	**Acidity**	**Dipole moment**
C_5H_5N	79.1 g mol^{-1}	0.9819g/cm^3	-41.6°C , 232K , -43°F	115.2°C , 388K , 239°F	5.25 pK_a	2.2 D

Chemical Properties of pyridine

Given the electronegative nitrogen in the pyridine ring, the grain is generally electron lacking. That's why it enters lower directly into electrophilic sweet concession responses than benzene derivations. Also, Pyridine is precipitously inclined to nucleophilic concession, as vindicated by the simplicity of metalation by solid organometallic bases.

The reactivity of the Pyridine structure can be honored for three emulsion gatherings. With electrophiles, electrophilic concession happens where Pyridine communicates ambrosial parcels. With nucleophiles, Pyridine responds at positions 2 and 4, and along these lines carries on like imines and carbonyls. The response with numerous Lewis acids brings about the expansion to the nitrogen speck of Pyridine, which is like the reactivity of tertiary amines. The capacity of Pyridine and its accessories to oxidize, shaping amine oxides[N- oxides], is also a element of tertiary amines.

The nitrogen focal point of the Pyridine structure includes an essential solitary brace of electrons. This single brace does not cover with the sweet- smelling π- frame ring. Thus Pyridine is necessary, having chemical parcels like those of tertiary amines. Protonation gives pyridinium, C5H5NH. The pKa of the conjugate sharp[the pyridinium cation] is 5.25. The structures of Pyridine and pyridinium are nearly identical.

Different Pyridine Uses

Pyridine is dissolvable and is added to ethyl liquor that makes it unfit for drinking. It's changed to particulars analogous as sulfapyridine, a medicine dynamic against bacterial and viral contaminations; pyribenzamine and pyrilamine, as antihistaminic drugs; and piperidine, which is employed in elastic drug, and as a crude substance material; and wateranti- agents, bactericides, and dressings. Mixes not using Pyridine, still, containing its ring structure incorporate niacin and pyridoxal, both B nutrients; isoniazid, an antitubercular medicine; and nicotine and a numerous different nitrogenous plant particulars. Pyridine uses in the chemical industriousness and enterprises as a significant crude material, used in dental consideration particulars for cleaning, used as a dissolvable which is applicable for dehalogenation, Pyridine uses in medicinals, radiator fluid blends as a denaturant, Pyridine uses as a sulfonating specialist, used in colors and maquillages, soap, a ligand in the chemical wisdom. Samples 1. Which is the common outgrowth of Pyridine that is mainly factory in mammals? Through oxidation, Mammals synthesize nicotinic acid whose coenzyme forms are nicotinamide adenine dinucleotide[NAD]. 2. Which plant is considered to be the natural source of Pyridine? Pyridine is generally present in the leaves and roots of Atropa belladonna

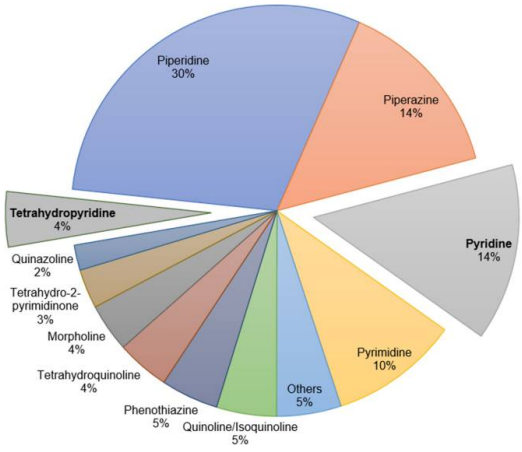


Fig 3 : Contribution Of pyridine in viral contamination

1.5 Pyridine Health Side Effects

Though pyridine is a useful emulsion, employed in every implicit field. But if consumed by humans, it might prove dangerous. The inflexibility depends upon the quantum of consumption and mode. Pyridine

can enter the mortal body while breathing, drinking, or consuming anything that has the presence of that chemical. Once the input is done, this chemical can irritate the nose, leading to coughs and whooshes. Due to which health problems like headaches, dizziness, fatigue be, and major symptoms may indeed lead to death. And if pyridine consumption is through the mouth, further than 50 of it's absorbed into your body. In some cases, skin mislike happens, due to which any future exposure leads to skin rashes. Pyridine is a ignitable liquid and a fire hazard.

CHAPTER :2

Monotherapy of antidiabetic drugs for the treatment of T2DM.

Monotherapy for the treatment of T2DM is targeted for reduction of glycosylated hemoglobin [HbA1c] up to 0.5 to 1.5% [44]. Further control of postprandial glucose level becomes more pertinent for improvement of HbA1c when the value meets the recommended value of less than 7% [45]. Metformin is the drug of choice for first line treatment. In conditions where metformin is contraindicated in certain patients or the patients experience associated complications on metformin use, use of other available hypoglycemic agents is chosen as first line treatment for the said disease condition [48-50]The details of the drugs that are appropriate for the treatment of T2DM are entailed in Table 2.1.

Table 2.1 Antidiabetic drugs for treatment for Diabetes

Name of the drug	**Pharmacological study**	**outcome**
Alpha Glucosidase inhibitors [AGIs]	Voglibose, the alpha glucosidase inhibitor was studied for control over post prandial blood sugar [PPBS] and cardioprotective action in T2DM patients. The antidiabetic activity acarbose, voglibose and miglitol were studied and compared for antihyperglycemic effect along with their propensity to develop cardiovascular risks associated with T2DM.	Voglibose was found to have better control as compared with other antidiabetic drugs over PPBS with lesser cardiovascular risks. Its efficiency was established in pre-diabetic elderly patients with hepatic impairment or renal complications where other antidiabetic drugs failed to show the desired therapeutic action. Voglibose had inhibitory effect on glucagon secretion. It was also effective in reduction of HbA1c and reduction of cardiovascular risks. As compared to acarbose and miglitol, voglibose demonstrated very less drug reaction owing to the administered low dose.

	Study on the effect of voglibose, before and after meal in patients with and without impaired glucose tolerance and compared with other alpha glucosidase inhibitor like miglitol and acarbose.	
Amylin analogs	A crossover investigation was done to assess the effectiveness of two alpha glucosidase inhibitor, voglibose and acarbose in T2DM patients.	Pramlintide slowed the rate of gastric emptying, suppressed the secretion of glucagon after food intake, increased satiety and reduced the rate of food intake.
Dipeptidyl Peptidase - IV inhibitors	A new DPP – IV inhibitor, anagliptin was assayed by LC – HRMS for its effect on serum glucagon and GIP level which maintains the glucose homeostasis.	It was found that teneligliptin was a potent, competitive and long lasting DPP – IV inhibitor which showed good reduction in postprandial hyperglycemia and dyslipidemia post single and repeated administration

Table 2.2 : Conbination therapy of antidiabetic drugs for treatment of T2DM

Name of the drug combinations	**Pharmacological study**	**Outcome**
Vildagliptin	The study was designed to investigate the relationship of the difference between observed and predicted glycated hemoglobin [dopHbA1c] and the actual HbA1c reduction after the patients were administered	The investigation of dual therapy of Vildagliptin resulted in a greater reduction in HbA1c in patients with dopHbA1c less than zero.

	with Vildagliptin in T2DM patients.	
Metformin with Sulfonylurea/ anti-hyperglycemic agents	The study was aimed for the outcomes of triple oral hypoglycaemic therapy compared with basal insulin therapy.	In case of patients receiving basal insulin, major adverse cardiovascular events and hypoglycaemic event were noted in comparison to the patients receiving oral hypoglycaemic agent as add-on therapy.
Alpha glucosidase inhibitors and DPP-IV inhibitors	Linagliptin, a DPP – IV inhibitor was tested alone or in combination of voglibose or Exendin – 4 for effect on glycaemic control in T2DM patients.	The combination of linagliptin and voglibose was found to reduce bodyweight, improve glycaemic control and reduce plasma insulin significantly as compared to linagliptin alone. The combination of Linagliptin and exendin – 4 had no effect on plasma GLP- 1. The combination of linagliptin and voglibose was more significant in control of glycaemic control than the individual drug therapy.

Table 2.3 Novel drug delivery system for antidiabetic drugs for T2DM

Types of delivery system	**Class of drug**	**Name of drug**	**Polymer used**	**Outcome**
Liposome	Biguanides	Metformin	Glycerolphosphate–Chitosan Microcomplexation [GP/CH Microcomplex]	2.5 fold longer Tmax with a 40% improvement in bioavailability were observed with the GP/CH microcomplex of metformin. GP/CH microcomplexes proved as potential carriers for highly water- soluble antihyperglycemic drug, allowing its controlled release and improved oral bioavailability.

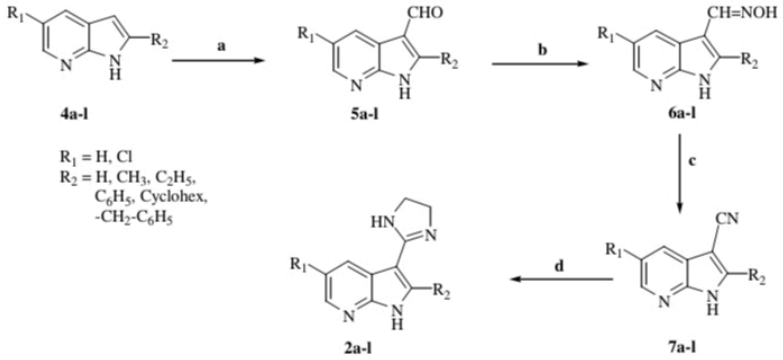
Niosome	Insulin Secretagogues	Repaglinide	Span 60, cholesterol	The cholesterol: surfactant ratio in the formulation was found to be responsible for drug entrapment efficiency. Maximum entrapment of the drug was found for cholesterol: surfactant at a ratio of 4:7. Additionally, the formulation showed good oral bioavailability of 89% *in vivo*. Niosomes enhanced bioavailability of the entrapped drug The study reported that the niosomal system is an effective carrier with sufficient drug entrapment and prolonged release profile
Polymeric Nanoparticles	Biguanides	Metformin	Chitosan-PLGA	Burst release of metformin from the nanoparticle was approximately20% in just 30 minutes whereas 98% of drug was released at 144 hrs in phosphate buffer of pH 6.8 Initial burst release of 74–80% was observed followed by a sustained release [92%–100%] in a time period of 12 hrs and 24 hrs for Eudragit®RSPO NPs and Eudragit®RSPO/PLGANPs, respectively The nanosystem was able to cause burst release of metformin within 22 – 24 hrs of administration followed by a sustained release for 15 days.
Nanoemulsion	Insulin Secretagogues	Repaglinide	Span 80, Tween 80, olive oil and acetone Sefsol-218, Tween 80 and Transcutol	This formulation resulted in high therapeutic efficiency with 4-5-fold increase in oral bioavailability of liraglutide. AUC of 49.58 mg h/mL, with C_{max} of 11.12 mg/mL and T_{max} of 4 hrs was observed for the

			Labrafac PG, Tween 80, and propylene glycol	nanoemulsion. A dose of 1 mg/kg was able to reduce the blood glucose level by a maximum of 67%. Improved dissolution rate with higher % of drug release was observed for the nanoformulation when compared to pure drug.

2.1 Synthesis of potential drug having pyridine moiety for treatment of diabetes

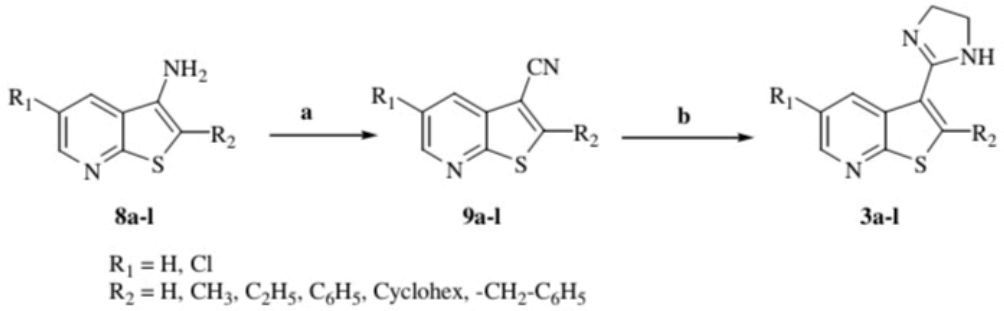
1.Inhibitor of all the test compounds showed glucose and concentration dependent insulin secretion.

Bahekar et al [46] The synthesis of 2,5-disubstituted-3-(4,5-dihydro-1H- imidazol-2-yl)-thieno[2,3-b]pyridine (3a–l) was con- ducted, by the condensation of 2,5-disubstituted-thieno[2,3-b]pyridine-3-carbonitrile (9), with EDA, using P_2S_5.



Scheme 1: Reagents and conditions: (a) HMTA/acetic acid, 6 h, reflux; (b) NH_2OH/HCl, 60 °C; (c) Acetic anhydride, 4 h, reflux; (d) EDA/P_2S_5, 120 °C, 5 h.

Compound 9 (yields 66–72%) was pre- pared from 2,5-disubstituted-thieno[2,3-b]pyridin-3-yla- mine (8) by Sandmeyer reaction, in which the diazonium salt was generated in situ, using a mixture of sodium nitrite ($NaNO_2$) and HCl, followed by the addition of a mixture of copper(I) cyanide, in an excess of sodium cyanide solution. Compound 8 was pre- pared in turn starting from 2-mercapto-5-substituted-nicotinonitrile, via Thorpe–Ziegler isomerization.

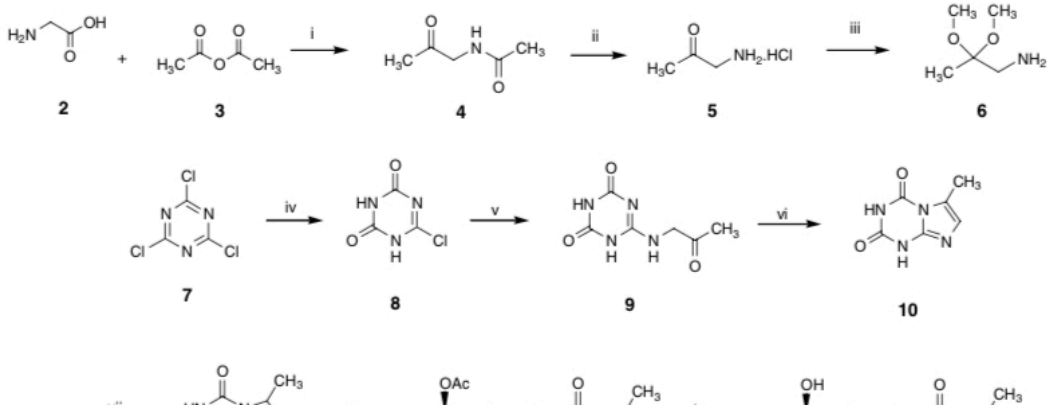


Scheme 2 : Reagents and conditions: (a) HCl/NaNO2/CuCN/NaCN, reflux, 3 h; (b) EDA/P2S5, 120 °C, 5 h.

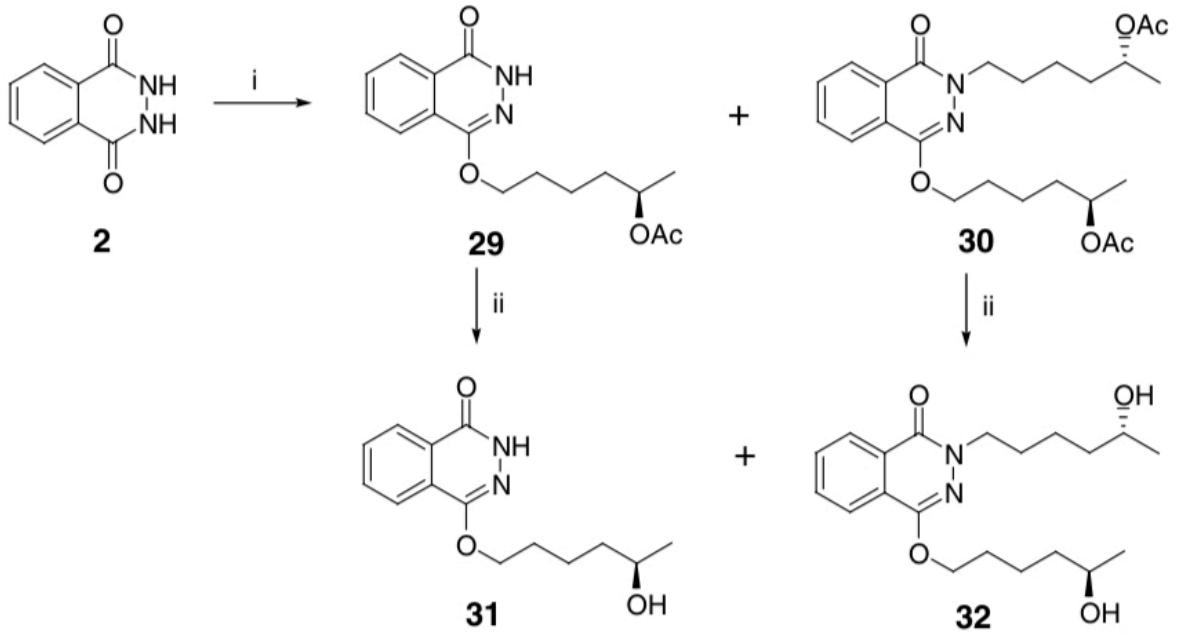
2. Inhibitor of b-cells from Th1 cytokine-induced

Cui et al [47] LSF, 1-(5-R-hydroxyhexyl)-3,7-dimethylxanthine) is an anti-inflammatory agent that protects b-cells from Th1 cytokine-induced dysfunction and reduces the onset of Type 1 diabetes in non-obese diabetic (NOD) mice.

.



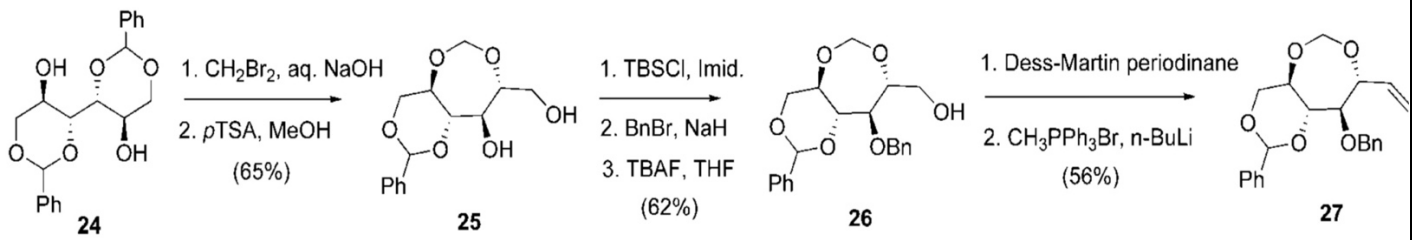
Scheme 3: Reagents and conditions: (i) pyridine, reflux, 6 h, 78%; (ii) HCl, H2O, reflux, 6 h, 60%; (iii) trimethylorthoformate, MeOH, p- toluenesulfonic acid monohydrate, reflux 24 h, then 3 N NaOH, 49%; (iv) NaOH, H2O; (v) 6, H2O, reflux, 3 h, 17%; (vi) H2SO4, 95 °C, 1.5 h, 35%; (vii) NaOH, CH3I, H2O, acetone, rt, 24 h, 34%; (viii) 5-(R)-acetoxy-1-chlorohexane, NaH, DMSO, 70–80 °C, overnight; (ix) 1 M HCl in ether, MeOH, rt, 12 h, 60% two steps.



Scheme 4: Reagents and conditions: (a) HCl/$NaNO_2$/CuCN/NaCN, reflux, 3 h; (b) EDA/P_2S_5, 120 °C, 5 h.

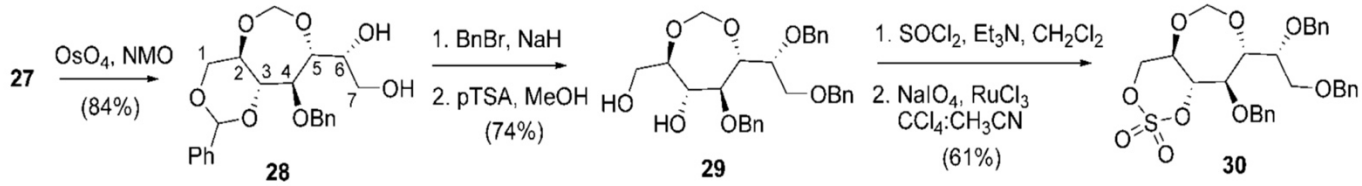
3. Inhibitor of aqueous extracts of Salacia

Jayakanthan et al [48]This initial synthetic strategy relied on the selective nucleophilic attack of *p*-methoxybenzyl (PMB)-protected 4-thio-D-arabinitol at the least hindered carbon atom of two different, selectively protected 1,3-cyclic sulfates to afford the sulfonium sulfates.

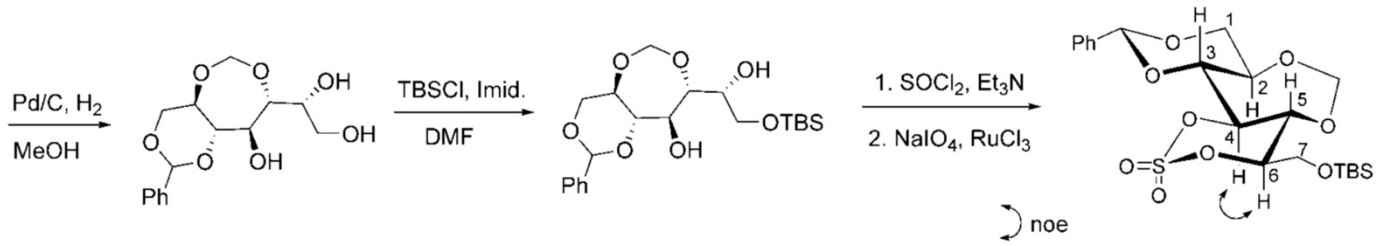


Scheme 5 : di-*O*-benzylidene-D-mannitol,was treated with dibromomethane in the presence of aqueous sodium hydroxide and tetra-*n*-butylammonium bromide as catalyst;removal of one of the benzylidene

groups using catalytic *p*-toluenesulfonic acid (PTSA) in methanol then gave the diol in 65% yield over two steps.



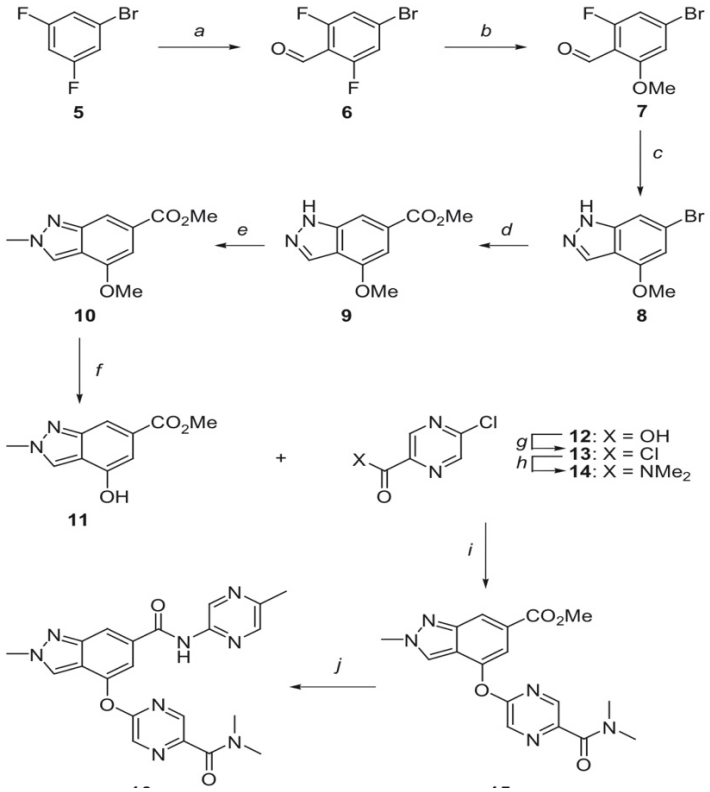
Scheme 6 : treatment of the olefin under OsO4-catalyzed dihydroxylation conditions gave a diastereomeric ratio of 7:1, with the major isomer in 84% yield



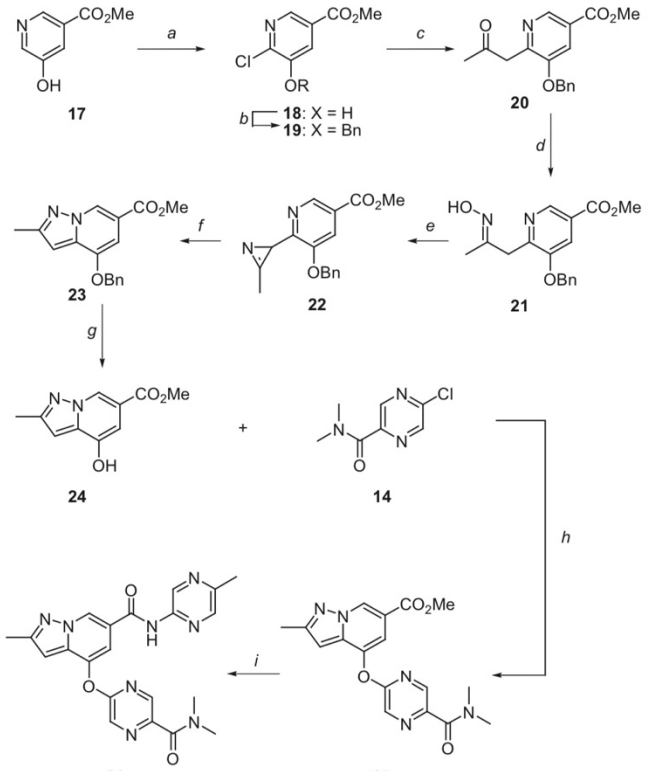
Scheme 7 : Stereochemistry at the newly formed stereogenic center (C-6) of compound , it was converted into the tricyclic derivative.

4. Inhibitor of indazole and pyrazolopyridine

Pfefferkorn et al [49] the identification and optimization of 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 (42) as a potent activator with favorable preclinical pharmacokinetic properties and in vivo efficacy.



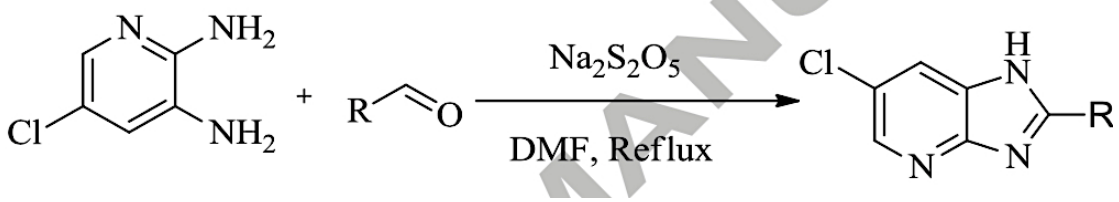
Scheme 8 : Synthesis of representative indazole 16. Reagents and conditions: (a) diisopropylamine, n-BuLi, THF, DMF, □70 °C, 2 h, 63%; (b) NaOMe, MeOH, 0 °C – reflux, 3.5 h, 71%; (c) N_2H_4–H_2O, ethylene glycol, 95 °C, 24 h, 83%; (d) CO, $Pd(OAc)_2$, BINAP, Et_3N, MeOH, 50 psi, 80 °C, 24 h, 87%; (e) trimethyloxonium tetrafluorobo- rate, ethyl acetate, 23 °C, 16 h, 86%; (f) i) BBr_3, DCM, 0 °C, 48 h; ii) MeOH, cat. H_2SO_4, reflux, 2 h, 78%; (g) $(COCl)_2$, cat. DMF, DCM, 23 °C, 18 h, quant.; (h) Me_2N–HCl, Et_3N, DCM, 0 – 23 °C, 4 h, 85%; (i) Cs_2CO_3, CuI, DMF, 110 °C, 3 h, 63%; (j) 2-amino-5- methylpyrazine, Me_2AlCl (1.0 M in hexanes), DME, 90 °C, 16 h, 46%.



Scheme 9 : Synthetic method for the synthesis of 26. Reagents and conditions: (a) NaOCl, water, 0 °C, 1 h; (b) benzyl bromide, NaH, DMF, 23 °C–reflux, 40 min, 30%; (c) isopropenyl acetate, Bu_3SnOMe, $Pd(dba)_2$, S–Phos, toluene, 100 °C, 16 h, 36%; (d) NH_4OH-HCl, MeOH, aq. NaOH, 70 °C, 1 h; (e) trifluoroacetic anhydride, Et_3N, DME, 23 °C, 16 h; (f) $FeCl_2$, 75 °C, 2 h, 36% over 3 steps; (g) H_2, 10% Pd/C, EtOH, ethyl acetate, 30 psi, 23 °C, 16 h; (h) K_2CO_3, DMF, 60 °C, 16 h; (i) 2-amino-5-methylpyr- azine, Me_2AlCl (1.0 M in hexanes), DME, reflux, 16 h, 43%.

5. Inhibitor of antiglycation, antioxidant and β –glucuronidase

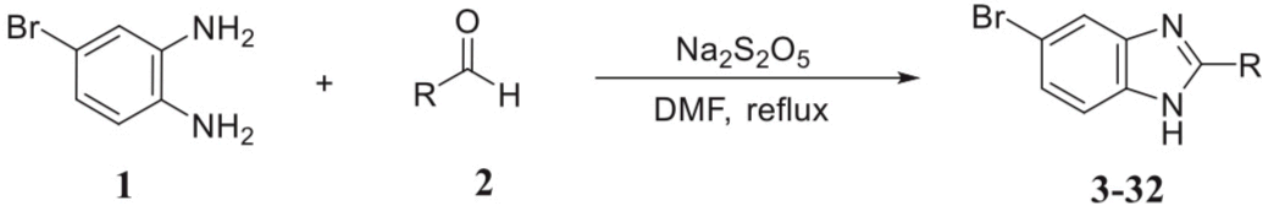
Taha et al [50] 6-chloro-2-Aryl-1H-imidazo[4,5-b]pyridine and its analogues consist of a versatile heterocyclic pharmacophore which is extremely important in organic chemistry due to their diverse biological activities



Scheme 10 : Synthesis of 6-chloro-2-Aryl-1H-imidazo[4,5-b]pyridine 1-26 derivatives

6. Inhibitor of Baker's yeast α-glucosidase enzyme.

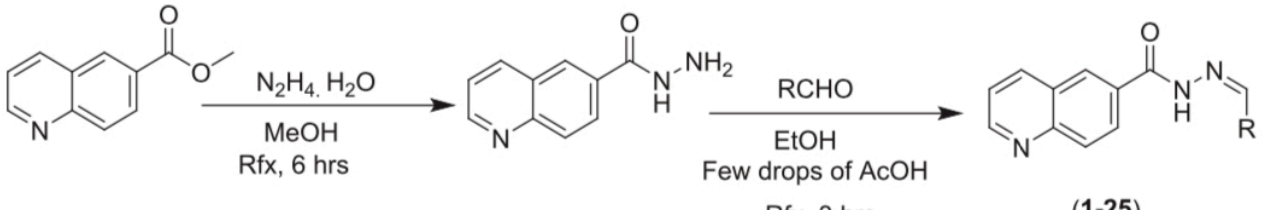
Taha et al [51] IC_{50} values for all com- pounds were in the range of 13.5–93.7 μM with compound 15, a 2,4-dihydroxy-substituted analog, displayed the most potent activity potential.



Scheme 11 : Synthesis of 2- phenyl-1H-imidazo[4,5-b] pyridines (3–32)

7. Inhibitar of quinoline

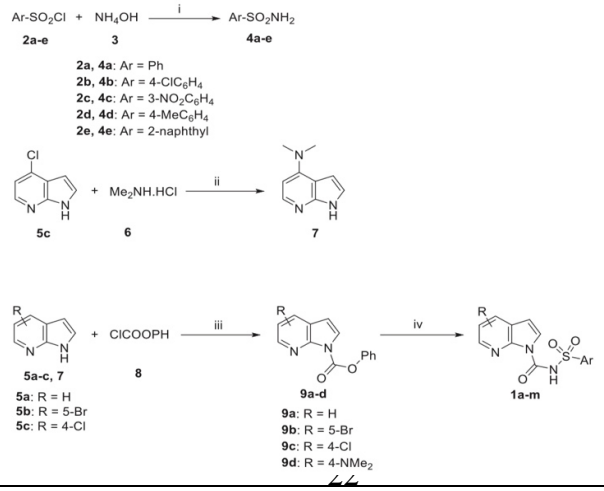
Taha et al [52] an inhibitor against α-glucosidase enzyme under positive control acarbose. From the activity profile it was found that analogs with values respectively showed most potent inhibition among the series even than standard drug acarbose . Here in the present study analog was found with many folds better α-glucosidase inhibitory activity than the reference drug.



Scheme 12 : Synthesis of quinoline-based Schiff base derivatives

8. Inhibitor of Ecto-nucleotide pyrophosphatases/phosphodiesterases

Ullah et al [53] reported as antidiabetic agents, therefore, we synthesized and investigated series of sulfonylurea derivatives 1a-m possessing pyrrolo [2,3-b]pyridine core as inhibitors of NPP1 and NPP3 isozymes that are over-expressed in diabetes.



Scheme 13 : Reagents and reaction conditions: (i) MeOH, rt, 5e10 min; (ii) 180 □C (fusion), 5 h; (iii) TEA, THF, 0 □C, 2 h; (iv) K_2CO_3, CH_2Cl_2, rt, overnight.

CHAPTER 3
CONCLUSION

Diabetes is a slow killer with no known curable treatments. However, its complications can be reduced through proper awareness and timely treatment. Three major complications are related to blindness, kidney damage and heart attack. It is important to keep the blood glucose levels of patients under strict control for avoiding the complications. One of the difficulties with tight control of glucose levels in the blood is that such attempts may lead to hypoglycemia that creates much severe complications than an increased level of blood glucose. Researchers now look for alternative methods for diabetes treatment. The goal of this paper is to give a general idea of the current status of diabetes research. The author believes that diabetes is one of the highly demanding research topics of the new century and wants to encourage new researchers to take up the challenges. The rising pattern of sedentary lifestyle and the higher incidence of obesity has contributed to an ever-increasing number of patients with diabetes, generating a massive demand for anti-diabetic medication and prompting companies to invest more on research and development for developing targeted formulations. Nanotechnology guarantees to bring in plenty of genuine ground breaking therapeutic advancements in our daily existence.

REFERENCE :

1. R. Tundis, M. Loizzo, F. Menichini, Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update, Mini Reviews in Medicinal Chemistry, 10 [2010] 315-331.
2. H. Chen, K. Ouyang, Y. Jiang, Z. Yang, W. Hu, L. Xiong, N. Wang, X. Liu, W. Wang, Constituent analysis of the ethanol extracts of Chimonanthus nitens Oliv. leaves and their inhibitory effect on α-glucosidase activity, International Journal of Biological Macromolecules, 98 [2017] 829-836.
3. S. Kasturi, S. Surarapu, S. Uppalanchi, J.S. Anireddy, S. Dwivedi, H.S. Anantaraju, Y. Perumal, D.K. Sigalapalli, B.N. Babu, K.S. Ethiraj, Synthesis and α-glucosidase inhibition activity of dihydroxy pyrrolidines, Bioorganic & Medicinal Chemistry Letters, 27 [2017] 2818-2823.
4. Joshi, S. R., Standl, E., Tong, N., Shah, P., Kalra, S., & Rathod, R. Therapeutic potential of α-glucosidase inhibitors in type 2 diabetes mellitus: an evidence-based review. Expert. Opin. Pharmaco. 16 [2015] 1959-1981.
5. Mahmood, N. A review of α-amylase inhibitors on weight loss and glycemic control in pathological state such as obesity and diabetes. Comp. Clin. Path. 25 [2016] 1253-1264.
6. K. Ogurtsova, J.D. da Rocha Fernandes, Y. Huang, U. Linnenkamp, L. Guariguata, N.H. Cho, D. Cavan, J.E. Shaw, L.E. Makaroff, IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040, Diabetes Res. Clin. Pract. 128 [2017] 40–50.
7. N. Al-Hassan, Definition of diabetes mellitus, Br. J. Gen. Pract. 53 [2003] 567–568.
8. W.T. Cade, Diabetes-related microvascular and macrovascular diseases in the physical
9. therapy setting, Phys. Ther. 88 [2008] 1322-1335.
10. D. Care, 2. Classification and diagnosis of diabetes, Diabetes Care 38 [2015] 8-16.
11. into oral anti-diabetic drugs: Finding needle in the haystack, Eur. J. Med. Chem. 103 [2015] 133-162. [b] K. Wang, L. Bao, K. Ma, J. Zhang, B. Chen, J. Han, J. Ren, H. Luo, H. Liu, A novel class of α-glucosidase and HMG-CoA reductase inhibitors from Ganoderma leucocontextum and the anti-diabetic properties of ganomycin 1 in KK-A^y mice, Eur. J. Med. Chem. 127 [2017] 1035-1045. [c] K. Wang, L. Bao, N. Zhou, J. Zhang, M. Liao, Z. Zheng, Y. Wang, C. Liu, L. Wang, W. Wang, S.J. Liu, H. Liu, Structural modification of natural product ganomycin 1 leading to discovery of a α-glucosidase and HMG-CoA reductase dual inhibitor improving obesity and metabolic dysfunction in vivo, J. Med. Chem. 61 [2018] 3609-3625. [d] S. Rocha, D. Rebeiro, E. Fernandes, M. Freitas, Systematic review on anti-diabetic properties of chalcones, Curr. Med. Chem. 25 [2018] DOI: 10.2174/0929867325666181001112226
12. Wang S, Yuan XH, Wang SQ, Zhao W, Chen XB, Yu B. FDA-approved pyrimidine-fused bicyclic heterocycles for DIABETES therapy: synthesis and clinical application. Eur J Med Chem.

13. Bull JA, Mousseau JJ, Pelletier G, Charette AB. Synthesis of pyridine and dihydropyridine derivatives by regio- and stereoselective addition to N-activated pyridines.
14. Boström J, Brown DG, Young RJ, Keserü GM. Expanding the medicinal chemistry synthetic toolbox. Nat Rev Drug Discov.
15. Wang L, Bharti KR, Pavlov PF, Winblad B. Small molecule therapeutics for tauopathy in Alzheimer's disease: walking on the path of most resistance. Eur J Med Chem. 2021;209:112915. doi:10.1016/j.ejmech.2020.112915
16. Yerragunta V, Patil P, Anusha V, Kumaraswamy T, Suman D, Samhitha T. Pyrimidine and its biological activity: a review. PharmaTutor. 2013;1[2]:39–44.
17. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. 2015. http://www.diabetesatlas.org/ [accessed Oct 6, 2016]
18. Grarup N, Sandholt CH, Hansen T, Pedersen O. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. Diabetologia 2014; 57: 1528–41.
19. Gungor N, Bacha F, Saad R, Janosky J, Arslanian S. Youth type 2 diabetes: insulin resistance, β-cell failure, or both? Diabetes Care 2005; 28: 638–44.
20. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab 2002;4:201e8.
21. .. Rosenstock J, Goldstein BJ, Vinik AI, et al. Effect of early addition of rosiglitazoneto sulphonylurea therapy in older type 2 diabetes patients [>60 years]: the Rosiglitazone Early vs. Sulphonylurea Titration [RESULT] study. Diabetes Obes Metab 2006;8:49e57.
22. Rosenstock J, Rood J, Cobitz A, et al. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. Diabetes Obes Metab 2006; 8:643e9.
23. Rosenstock J, Rood J, Cobitz A, et al. Initial treatment with rosiglitazone/ metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab 2006;8:650e60.
24. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011;378:182-97.
25. Nathan DM, Buse JB, Davidson MB, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203.
26. Bolen S, Feldman L, Vassy J, et al. Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386-99.
27. Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int 2012 January 18 [Epub ahead of print].
28. Nathan DM, Buse JB, Davidson MB, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203
29. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.

30. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.
31. . Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
32. Stewart, R.; Liolitsa, D.: Type 2 diabetes mellitus, cognitive impairment and dementia. Diabetic Medicine 1999, 16, 93-112.
33. Han, W.; Li, C.: Linking type 2 diabetes and Alzheimer's disease. Proceedings of the National Academy of Sciences 2010, 107, 6557-6558.
34. Soreq, H.; Seidman, S.: Acetylcholinesterase—new roles for an old actor. Nature Reviews Neuroscience 2001, 2, 294-302.
35. Rosas-Ballina, M.; Olofsson, P. S.; Ochani, M.; Valdés-Ferrer, S. I.; Levine, Y. A.; Reardon, C.; Tusche, M. W.; Pavlov, V. A.; Andersson, U.; Chavan, S.: Acetylcholine- synthesizing T cells relay neural signals in a vagus nerve circuit. Science 2011, 334, 98- 101.
36. He, X.-C.; Feng, S.; Wang, Z.-F.; Shi, Y.; Zheng, S.; Xia, Y.; Jiang, H.; Tang, X.-c.; Bai, D.: Study on dual-site inhibitors of acetylcholinesterase: Highly potent derivatives of bis- and bifunctional huperzine B. Bioorganic & Medicinal Chemistry 2007, 15, 1394-1408.
37. Holmstedt, B.: Distribution and determination of cholinesterases in mammals. Bulletin of the World Health Organization 1971, 44, 99.
38. Schliebs, R.; Arendt, T.: The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. Journal of Neural Transmission 2006, 113, 1625-1644.
39. Cuello, A.: Structure and functions of acetylcholinesterase and butyrylcholinesterase.
40. Cholinergic Function and Dysfunction 1993, 139 Elsevier Science Publishers.
41. Grutzendler, J. Morris, J. C. Cholinesterase inhibitors for Alzheimer's disease. Drugs
42. 2001, 61, 41-52.
43. Yar, M.; Bajda, M.; Mehmood, R. A.; Sidra, L. R.; Ullah, N.; Shahzadi, L.; Ashraf, M.;
44. Ismail, T.; Shahzad, S. A.; Khan, Z. A.: Design and synthesis of new dual binding site cholinesterase inhibitors: in vitro inhibition studies with in silico docking. Letters in Drug Design & Discovery 2014, 11, 331.
45. Yar, M.; Bajda, M.; Shahzadi, L.; Shahzad, S. A.; Ahmed, M.; Ashraf, M.; Alam, U.; Khan, I. U. Khan, A. F. Novel synthesis of dihydropyrimidines for α-glucosidase inhibition to treat type 2 diabetes: In vitro biological evaluation and in silico docking. Bioorganic Chemistry 2014, 54, 96-104.
46. Yar, M.; Bajda, M.; Shahzad, S.; Ullah, N.; Gilani, M. A.; Ashraf, M.; Rauf, A.; Shaukat, A.: Organocatalyzed solvent free an efficient novel synthesis of 2, 4, 5-trisubstituted imidazoles for α-glucosidase inhibition to treat diabetes. Bioorganic Chemistry 2015, 58, 65-71.
47. R. Khursheed, S. Singh, S. Wadhwa, B. Kapoor, M. Gulati, R. Kumar, et al., Treatment strategies against diabetes: Success so far and challenges ahead, Eur. J. Pharmacol. 862 [2019] 172625, https://doi.org/10.1016/j.ejphar.2019.172625.
48. [2] S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030, Diabetes. Care 27 [2004] 1047–1053, https://doi.org/10.2337/diacare.27.5.1047.
49. [3] C. Wong, H. Al-Salami, C. Dass, Potential of insulin nanoparticle formulations for oral delivery and diabetes treatment, J. Control. Release 264 [2017] 247–275, https://doi.org/10.1016/j.jconrel.2017.09.003.

50. [4] A. Chaudhury, C. Duvoor, V.S.R. Dendi, S. Kraleti, A. Chada, R. Ravilla, et al., Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management, Front. Endocrinol. 8 [2017] 1–12, https://doi.org/10.3389/ fendo.2017.00006.
51. [5] K.R. Feingold, et al., in: K.R. Feingold, B. Anawalt, A. Boyce [Eds.], Oral and Injectable [Non-insulin] Pharmacological Agents for Type 2 Diabetes, MDText. com, Inc., South Dartmouth [MA], 2000. Endotext [Internet]. [Updated 2019 Jul 8], Available from: https://www.ncbi.nlm.nih.gov/books/NBK279141/.
52. [6] S.Tan,J.MeiWong,Y.Sim,S.Wong,S.MohamedElhassan,S.Tan,etal.,Type1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention, Diabetes. Metab. Syndr. 13 [2019] 364–372, https://doi.org/10.1016/j.dsx.2018.10.008.
53. [7] E. Souto, S. Souto, J. Campos, P. Severino, T. Pashirova, L. Zakharova, et al., Nanoparticle Delivery Systems in the Treatment of Diabetes Complications, Molecules 24 [2019] 4209, https://doi.org/10.3390/molecules24234209.
54. [8] S.Uppal,K.S.Italiya,D.Chitkara,A.Mittal,Nanoparticulate-baseddrugdelivery systems for small molecule anti-diabetic drugs: An emerging paradigm for effective therapy, Acta. Biomater. 81 [2018] 20–42, https://doi.org/10.1016/j. actbio.2018.09.049.
55. [9] M.M. Abbasi, H. Valizadeh, H. Hamishehkar, P. Zakeri-Milani, Inhibition of P- glycoprotein expression and function by anti-diabetic drugs gliclazide, metformin, and pioglitazone in vitro and in situ, Res. Pharm. Sci. 11 [2016] 177–186. PMCID: PMC4962298.
56. [10] T. Kobori, S. Harada, K. Nakamoto, S. Tokuyama, Functional Alterations of Intestinal P-Glycoprotein under Diabetic Conditions, Biol. Pharm. Bull. 36 [2013] 1381–1390, https://doi.org/10.1248/bpb.b13-00369.
57. [11] M. Okur, I. Karantas, P. Siafaka, Diabetes Mellitus: A Review on Pathophysiology, Current Status of Oral Pathophysiology, Current Status of Oral Medications and Future Perspectives, ACTA Pharm Sci. 55 [2017] 61, https://doi.org/10.23893/ 1307-2080.aps.0555.
58. [12] A. Mayorov, Insulin resistance in pathogenesis of type
59. A. Philis-Tsimikas, C. Wysham, E. Hardy, J. Han, N. Iqbal, Efficacy and tolerability of exenatide once weekly over 7 years in patients with type 2 diabetes: An open-label extension of the DURATION-1 study, J. Diabetes. Complicat. 33 [2019] 223–230, https://doi.org/10.1016/j.jdiacomp.2018.11.012.
60. C. McAdam-Marx, H. Nguyen, M. Schauerhamer, M. Singhal, S. Unni, X. Ye, et al., Glycemic Control and Weight Outcomes for Exenatide Once Weekly Versus Liraglutide in Patients with Type 2 Diabetes: A 1-Year Retrospective Cohort Analysis, Clin. Ther. 38 [2016] 2642–2651, https://doi.org/10.1016/j. clinthera.2016.11.003.
61. J. Rosenstock, M. Hanefeld, P. Shamanna, K. Min, G. Boka, P. Miossec, et al., Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in Type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin [GetGoal-S], J. Diabetes. Complicat. 28 [2014] 386–392, https://doi.org/10.1016/j. jdiacomp.2014.01.012.
62. M. Hassanein, R. Sahay, K. Hafidh, K. Djaballah, H. Li, S. Azar, et al., Safety of lixisenatide versus sulfonylurea added to basal insulin treatment in people with type 2 diabetes mellitus who elect to fast during Ramadan [LixiRam]: An international, randomized, open-label trial, Diabetes. Res. Clin. Pract. 150 [2019] 331–341, https://doi.org/10.1016/j.diabres.2019.01.035.
63. L. Van Gaal, E. Souhami, T. Zhou, R. Aronson, Efficacy and safety of the glucagon- like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young [<50 years] obese patients with type 2 diabetes mellitus, J. Clin. Transl. Endocrinol. 1 [2014] 31–37, https://doi.org/10.1016/j. jcte.2014.03.001.

64. X. Cai, C. Li, J. Zhou, Y. Dai, Y. Avraham, L. Sun, et al., Novel glucagon- and OXM- based peptides acting through glucagon and GLP-1 receptors with body weight reduction and anti-diabetic properties, Bioorg. Chem. 95 [2020] 103538, https:// doi.org/10.1016/j.bioorg.2019.103538.
65. I. Lingvay, A. Catarig, J. Frias, H. Kumar, N. Lausvig, C. le Roux, et al., Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes [SUSTAIN 8]: a double-blind, phase 3B, randomized controlled trial, Lancet. Diabetes. Endocrinol. 7 [2019] 834–844, https://doi.org/10.1016/s2213-8587[19]30311-0.
66. P. Men, S. Qu, Z. Song, Y. Liu, C. Li, S. Zhai, Lixisenatide for Type 2 Diabetes Mellitus Patients Inadequately Controlled on Oral Antidiabetic Drugs: A Mixed- Treatment Comparison Meta-analysis and Cost–Utility Analysis, Diabetes. Ther. [2020], https://doi.org/10.1007/s13300-020-00857-3.
67. M. Mirabelli, E. Chiefari, P. Caroleo, B. Arcidiacono, D. Corigliano, S. Giuliano, et al., Long-Term Effectiveness of Liraglutide for Weight Management and Glycemic Control in Type 2 Diabetes, Int. J. Env. Res. Publ. Health 17 [2020] 207, https:// doi.org/10.3390/ijerph17010207.