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A STUDY OF HETEROCYCLES AS A-AMYLASE INHIBITORS FOR THE TREATMENT OF DIABETES MELLITUS

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ABSTRACT

In order to cure diabetes mellitus, this study aims to use heterocycles as α-amylase inhibitors. The material presented in this study is derived from a review of literature that describes the structure and action mechanism of α-amylase. Additionally, the article provides a concise summary of the biological uses of heterocycles containing nitrogen and sulfur, as well as their function as inhibitors of α-amylase. A slightly modified version of the procedure outlined by Shetty et al. was used to conduct the experiment. The DMSO solvent was used to generate a stock solution with a concentration of 1 mg/mL. The three different concentrations of α-amylase were tested (25, 50, and 100 µg/mL), and the control group used the reagent solution without the test sample. Five milligrams of Aspergillus oryzae α-amylase enzyme was mixed with one hundred milliliters of 20 mM sodium-potassium buffer (pH 6.9) to create the enzyme solution. To make the starch solution, dissolve 500 mg of starch in 25 mL of 0.5 N NaOH. Then, boil the mixture at 100ºC for 5 minutes. Once the solution had cooled in ice water, 2M HCl was added to get the pH up to 7, and 100 mL of water was added to make the volume equal.

KEYWORDS: Heterocycles, Amylase Inhibitors, Diabetes Mellitus, α-amylase inhibitors, DMSO solvent.

INTRODUCTION

Carbocyclic compounds can be either aliphatic or aromatic; heterocyclic compounds, on the other hand, have at least one heteroatom—often nitrogen, oxygen, or sulfur—instead of carbon within the ring structure. One of the most important branches of organic chemistry is the study of heterocyclic molecules. They capture the interest of medicinal chemists, pharmacologists, and biologists due to their substantial biological and therapeutic

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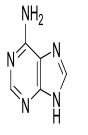
activity. Most medications have their basis in heterocyclic nucleus, making heterocyclic compounds a treasure trove of physiologically relevant molecules. The majority of the medications are heterocyclic compounds with five or six carbon atoms and one to three heteroatoms in their nucleus. For the greater good of humanity, it is easy to modify the structure of heterocycles to provide the desired activity.one, two Consequently, heterocycles have emerged as the primary building blocks for studies in organic chemistry. Genetic material, including DNA and RNA, is composed of the purines [adenine (1.1) and guanine (1.2)] and pyrimidines [cytosine (1.3), thymine (1.4) and uracil (1.5)].3,4 Puromycin is one example of a nucleoside antibiotic that inhibits protein synthesis; other examples include various pyrimidine and purine derivatives (1.6).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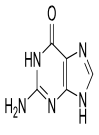
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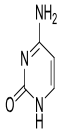
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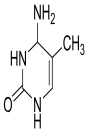
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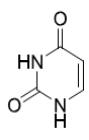
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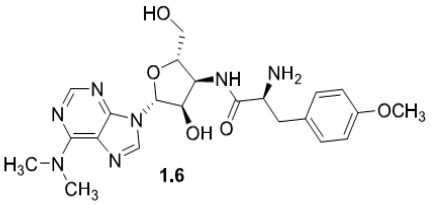
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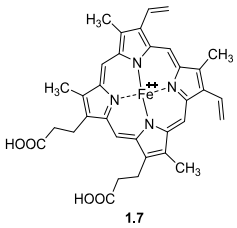
Natural examples of heterocyclic moieties include porphyrin ring derivatives like heme (1.7), an oxygen-transporting pigment, and chlorophyll (1.8), a photosynthesizing pigment.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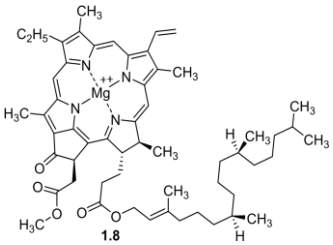
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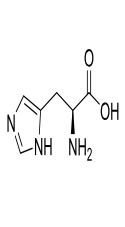
Some common heterocyclic compounds involved in biological processes include essential amino acids such as histidine (1.9), tryptophan (1.10), and proline (1.11), vitamins such as pyridoxine (1.12), biotin (1.13), ascorbic acid (1.14), α-tocopherol (1.15), thiamine (1.16), and riboflavin (1.17). Additionally, several natural compounds have heterocyclic systems.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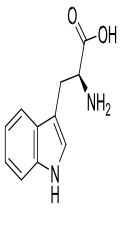
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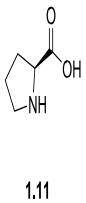
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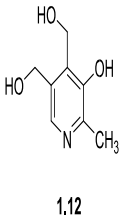
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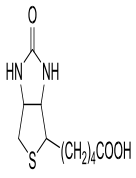
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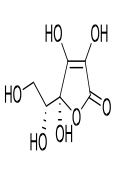
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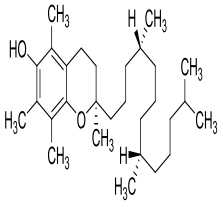
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Various natural materials have been utilized by humans for medicinal purposes since ancient times. These include quinine, an antimalarial medicine, penicillin, codeine, morphine, and atropine, which are narcotic analgesic opiate alkaloids.

DIABETES MELLITUS

Among the most prevalent non-communicable metabolic diseases, diabetes mellitus is defined by persistently high blood glucose levels (hyperglycemia) and abnormalities in the metabolism of carbohydrates, lipids, and proteins due to an inadequate or nonexistent insulin secretionInsulin, a peptide hormone produced by the pancreatic β-cells of the islets of Langerhans, primarily functions to regulate blood glucose levels, which typically increase in response to food consumption. Hence, hyperglycemia occurs in diabetes patients due to abnormalities in insulin synthesis and its usage. Metabolizing carbs and fats also relies on insulin, which reduces blood glucose levels via increasing glucose uptake by cells, activating glycogenesis, and inhibiting glycogenolysis. Additionally, it slows the process by which fats are converted into free fatty acids and ketone molecules.

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Type 1 diabetes mellitus, type 2 diabetes mellitus, prediabetes, gestational diabetes mellitus, and insulin-dependent diabetes mellitus are the several subtypes of diabetes mellitus. Among these, type-2 diabetes is a global epidemic that has already impacted about 200 million people and is projected to reach 642 million by the year 2040.36-38 The most significant side effects of diabetes include polydipsia, kidney disease, nephropathy, impaired vision, increased hunger, and high blood pressure.39 These problems impact over half of all diabetic patients and can be deadly in some cases. As a result, diabetes is acknowledged as a serious condition in many parts of the world.

The most difficult part of managing diabetes mellitus is getting blood glucose levels back to normal.41 Treatment options for diabetes mellitus include dietary changes, physical activity, and sometimes the use of oral hypoglycemic medications such as sulphonylureas, biguanides, thiazolidinediones, peroxisome proliferator-activated receptors, and acarbose42,43. However, a variety of side effects and toxicity are linked to the usage of oral antihyperglycemic medications.

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Due to their role in catalyzing metabolic activities and their extreme substrate selectivity, enzyme inhibitors should be considered as potential new therapeutic targets in the fight against this illness.46 Research into the rate of carbohydrate digestion and monosaccharide absorption is necessary for the prevention of hyperlipidemia, dysbetalipoproteinemia, obesity, diabetes, and other related conditions. Postprandial glycemic management can be achieved in part by slowing the rate of glucose absorption after carbohydrate digestion. A widely recognized therapeutic approach involves delaying glucose absorption with the use of carbohydrate hydrolyzing enzymes, such as α-amylase and α-glucosidase.47 The reason why α-amylase inhibitors have a unique place is because α-amylase starts the hydrolysis of polysaccharides.

1.3 α-Amylase

The 13th family of glycoside hydrolases (GH13) include α-amylase, an endoamylase that is mostly found in plants, microorganisms, and higher creatures (EC 3.2.1.1). Hydrolyzing the α-D-(1,4)-glycosidic linkage in starch49–52 while maintaining the α-anomeric structure in the end products is its primary function. The hydrolysis of glycosidic bonds in starch requires many amylolytic enzymes, but the process cannot begin without α-amylase.53 Because of its capacity to facilitate the hydrolysis of α-(1,4)glycosidic bonds in starch, it is regarded as a prime target for the creation of therapeutic medicines for type-2 diabetes.54,55 In the treatment of type 2 diabetes mellitus, inhibiting αamylase lowers plasma glucose levels, also known as postprandial blood glucose.

1.4 STRUCTURE ANALYSIS OF TAKA-AMYLASE A (TAA)

Researchers have described the natural α-amylase structure at the three-dimensional level and analyzed its structural and inhibitory calcium locations.

The molecular weight of the Aspergillus oryzae α-amylase, which is also known as "Taka-amylase A" or 1,4-α-D-glucan glucanohydrolase, is 52.53 kDa. There is just one molecule of tata-amylase A, and it has 478 amino acid residues, four disulfide bonds, one free sulfhydryl group, and one calcium ion. Its thorough biochemical characterization made it one of the first glycosylhydrolases to get such attention. There are two domain assignments in tama amylase: d7taaa1 (95 residues) and d7taaa2 (381 residues).

The α-amylase secondary structure has four L-cystine protein modification legends and

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is composed of a wide arrangement of 34% α-helices and 21% B-sheets. d7 Taaa1 is devoid of acarbose and calcium binding sites. Ca2+, an ion of calcium, is situated at the point where the A and B domains of the catalytic protein come together.

The eight legends that bind the Ca2+ ion include: the two sets of carboxylate oxygen atoms surrounding Asp175 in a bidentate fashion with bond lengths of 2.54 Å and 2.85 Å, respectively; the side chain carbonyl oxygen atoms surrounding Asn121 (2.51 Å), three molecules of water (2.41, 2.46, and 2.76 Å), and the main chain carbonyls surrounding Glu162 (2.51 Å) and His210 (2.54 Æ). Further binding sites for acarbose with d7taaa2 are as follows: Gln35(A), Asp340(A), Arg344(A), Asp206(A), Glu230(A), His210(A), Gly234(A), Arg204(A), Asp297(A), Lys209(A), His121(A), and Trp83(A). There are 89 β-strands, 12 β-bridges, 38 S-bends, 60 twists, 363/10 helices, and 130 α-helices in a single polypeptide chain.

CATALYTIC MECHANISM OF A-AMYLASE

α-Amylase is responsible for facilitating the breakdown of the glycosidic link while maintaining the anomeric state. A double-displacement reaction is the catalyst. As a first step in these processes, the oxocarbenium ion transition state forms a glycosyl-intermediate, an intermediate that is covalently bonded; the intermediate is then hydrolyzed. Glu230 acts as a bronsted acid in the described mechanism, which first encourages the exit of the leaving group by protonating the glycosyl oxygen and cleaving the α-linkage. Additionally, the formation of a covalently bonded glycosyl-intermediate with a β-configuration was caused by the attack of the nucleophile (Asp206) from the opposite direction (first walden inversion). The following step involves attacking a deprotonated proton donor, which forms an activated water molecule. Afterwards, α-glucose is produced when this activated water molecule attacks from the other side, which is known as the second walden inversion (Path-I). The general preservation of the α-configuration was the outcome of two succeeding inversions at the anomeric carbon. Figure 3 shows that the enzyme can do more than just retain configuration; it can also catalyze transglycosylation by attacking the anomeric carbon of the covalent intermediate with the hydroxyl groups of sugars and alcohols. The 2-deoxy-2,2-difluoroglucosides and 5-fluoroglycosyl fluorides were used to capture the covalently bound intermediate.

α-AMYLASE INHIBITORS

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According to a literature review, α-amylase inhibitors can slow down digestion and absorption in the beginning stages of digestion, which results in a substantial delay in postprandial hyperglycemia and a positive impact on insulin resistance.62 New treatments for metabolic illnesses like type-2 diabetes and obesity can be developed through the design of α-amylase inhibitors.63 Acarbose, voglibose, and miglitol are α-amylase inhibitors that have been extensively used in clinical practice and have proven to be highly effective in managing hyperglycemia. But despite this, these medications are linked to a host of GI side effects, including flatulence, diarrhea, and abdominal pain.64,65 that necessitate the identification of novel, efficient α-amylase inhibitors.55.66 cents

The discovery of new hypoglycemic medications relies heavily on a wide variety of chemicals that contain heterocyclic and fused heterocyclic groups. Since these heterocyclic compounds offer antidiabetic characteristics and the ability to produce new powerful pharmacological molecules, a lot of research has shifted towards them. These compounds contain nitrogen and sulfur. times Oral-hypoglycemic medications are glitazones e.g., rosiglitazones68(1.33), pioglitazone's (1.34) and troglitazones69(1.35), dipeptidyl peptidase IV inhibitor (DPP-4 inhibitor) e.g., sitagliptin70(1.36), alogliptin71,72(1.37), teneligliptin (1.38), α-glucosidase inhibitors e.g., miglitol (1.39), acarbose (1.40) and voglibose (1.41), sulfonylureas e.g., glipizide (1.42), glimepiride (1.43) etc. Some people took these medications and experienced a variety of unwanted side effects.

CONCLUSION

The chemistry of heterocyclic compounds is one of the most imperative extents of organic chemistry. They are associated with significant therapeutic and biological activities which draw the attention of medicinal chemists, pharmacologists and biologists. Heterocyclic compounds are the gold mines of biologically relevant compounds as most of the drugs are based on heterocyclic nucleus. Most of the drugs are five- and sixmembered heterocyclic compounds containing one to three heteroatoms in their nuclei. The structure of heterocycles can be easily manipulated to achieve the desired activity for the benefit of mankind. Although variety of heteroatoms has been integrated in the heterocycles, but the heterocyclic systems which comprise of nitrogen and/or sulphur, are the center of attraction in organic and medicinal chemistry, due to their vast biological significance such as

antineoplastic, anticancer, antimicrobial, antiHIV, antimalarial, antidiabetic etc.

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