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THE INHIBITION EFFECTS INVESTIGATION OF METAL COMPLEXES OF SCHIFF BASES OF SOME SULFA DRUGS ON ALPHA-GLUCOSIDASE ACTIVITY

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DUNYA ABDULWAHHAB ABDULJABBAR ALTAIE

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By Dunya Abdulwahhab Abduljabbar ALTAIE

February 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

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Dunya Abdulwahhab Abduljabbar ALTAIE

Master of Science in Chemistry

Advisor: Assoc. Prof. Dr. Şevki ADEM

February 2022

Regulations of carbohydrate absorption via α-glucosidase enzymes competitive inhibition improve glycaemic control in patients with T2DM; thus, attempts to design new α-glucosidase inhibitors have become a point of interest. However, most investigations focus mainly on sugar mimics, which are challenging to tackle synthetically. In this *in vitro* study, nine derivatives of Sulfa-Schiff bases compounds were tested as α-glucosidase inhibitors. Spectroscopic techniques examined each analog activity. All of the ligand complexes were found to be active when screened for alpha-glucosidase inhibition and exhibited IC_{50} values ranging from 0.429 to 8.976 μM. Compounds (1, 4, 5, 7, 8, and 9) demonstrated impressive inhibitory potential against the α-glucosidase enzyme. All derivatives underwent a molecular docking procedure to clarify their ligand-receptor binding interactions.

2022, 42 pages

Keywords: Sulfa drugs Schiff base, Metal complexes, α-glucosidase inhibition,

ÖZET

BAZI SULFA İLAÇLARININ SCHIFF BAZLARININ METAL KOMPLEKSLERİNİN ALFA-GLUKOZİDAZ AKTİVİTESİ ÜZERİNDEKİ İNGİLTME ETKİLERİNİN İNCELENMESİ

Dunya Abdulwahhab Abduljabbar ALTAIE
Kimya Bilimi, Yüksek Lisans
Tez Danışmanı: Doç. Dr. Şevki ADEM
Şubat 2022

α-glukozidaz enzimleri yarışmalı inhibisyonu aracılığıyla karbonhidrat absorpsiyonunun düzenlemeleri, T2DM'li hastalarda glisemik kontrolü iyileştirir; bu nedenle, yeni *α*-glukosidaz inhibitörleri tasarlama girişimleri bir ilgi noktası haline geldi. Bununla birlikte, çoğu araştırma, esas olarak, sentetik olarak ele alınması zor olan şeker taklitlerine odaklanmaktadır. Bu *in vitro* çalışmada, Sulfa-Schiff baz bileşiklerinin dokuz türevi, a-glukozidaz inhibitörleri olarak test edildi. Spektroskopik teknikler, her bir analog aktiviteyi inceledi. Tüm ligand komplekslerinin, α-glukozidaz inhibisyonu için tarandığında aktif olduğu bulundu 0.429 ila 8.976 μM arasında değişen IC_{50} değerleri sergiledi. Bileşikler (1, 4, 5, 7, 8, 9) α-glukosidaz enzimine karşı etkileyici bir inhibitör potansiyel sergilemiştir. Tüm türevler, ligand-reseptör bağlanma etkileşimlerini netleştirmek için bir moleküler yerleştirme prosedürüne tabi tutuldu.

2021, 42 sayfa

Anahtar Kelimeler: Sülfa ilaçları Schiff bazı, Metal kompleksleri, α-glukozidaz inhibisyon

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Dunya Abdulwahhab Abduljabbar ALTAIE
Çankırı-2022

CONTENTS

LIST OF SYMBOLS

>	Greater than
°C	Celsius
µL	Microlitre
µM	Micrometre
2D	Two dimensional
3A4A	Crystal structure of α-glucosidase
3D	Three dimensional
IC_{50}	Half-maxımal ınhıbıtory concentratıon
mL	Millilitre
mM	Millimolar
mmol/L	millimoles per litre
nm	Nanometre
α	Alpha
β	Beta

LIST OF ABBREVIATIONS

ADA	American diabetes association
AGIS	Alpha-glucosıdase ınhıbıtors
ALR1	Aldehyde reductase
ALR2	Aldose reductase
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
CA	Antıcarbonıc anhydrase
CNS	Central nervous system
COX2	Cyclooxıgenase 2
CV	Cardıovascular
DM	Dıabetes mellıtus
DPP-4	Dıpeptıdyl peptıdase 4
FBG	Fastıng blood glucose
Gln	Glutamine
GLP-1	Glucagon-lıke peptıde-1
Glu	Glutamic acid
HBA1C	Haemoglobın a1c
Lys	Lysine
MVD	Molegro Vırtual Docker
NIDDM	Non–ınsulın-dependent dıabetıc mellıtus
OHAs	Oral hypoglycemıc agents
PPG	Postprandıal blood glucose
PPHG	Postprandıal hyperglycemıa
Pro	Proline
Ser	Serine
SU	Sulfonylureas
T2DM	Type 2 dıabetes mellıtus
Thr	Threonine
Tyr	Tyrosine
TZD	Thıazolıdınedıone

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1. INTRODUCTION

Alpha-glucosidases at the mucosal brush border of the small intestine catalyses the digestion of starch and disaccharides, which are predominant in the human regimen. Alpha-glucosidase enzymes located in the small intestine brush border, are especially capable of hydrolysing terminal 14-linked glucose residues to release a single α-glucose molecule (Bischoff 1994, Chiba 1997, Assefa *et al.* 2020). Pancreatic α-amylase a digestive enzyme that transforms dietary carbohydrates like starch into simple monosaccharides. These are further metabolized by α-glucosidases into glucose, which enters the bloodstream following absorption. Inhibiting both of α-amylase and α-glucosidase enzymes can thereby limit carbohydrate digestion, glucose absorption, and moderate blood sugar levels (Kajaria *et al.* 2013, Alqahtani *et al.* 2019) as a result; one of the medicinal strategies for lowering postprandial hyperglycaemia which is a serious manifestation of DM is to limit the digestion of dietary carbs.

Diabetes mellitus affects (382) million people worldwide; this number is anticipated to soar to (592) million by 2035, meaning that diabetes mellitus has the potential to become the world's major systemic metabolic disease (Guariguata *et al.* 2014). Diabetes is caused by a variety of pathogenic processes. These range from autoimmune destruction of beta-cells to insulin resistance abnormalities. It is also defined by abnormalities in glucose, protein, and lipid metabolism which is caused by insulin's ineffective action on target tissues. Inadequate insulin action is caused by diminished insulin synthesis and/or impaired tissue responses to insulin at one or more sites along the complex hormone action pathways. Insulin production and insulin action anomalies frequently coexist in the same patient, and it is not always evident which one is the primary cause of hyperglycemia (Alam *et al.* 2019).

Diabetes is classified into different main categories: Diabetes type 1 as a result of beta-cell destruction, usually leading to absolute insulin deficiency. Diabetes type 2 as a result of a increasing insulin secretory defect as an outcome of insulin resistance. Gestational diabetes mellitus which is a form of diabetes diagnosed in the second or third trimester of pregnancy.

Special types of diabetes prompted by other reasons, such as monogenic diabetes syndromes such as neonatal diabetes and maturity-onset diabetes of the young, exocrine pancreas diseases such as cystic fibrosis, and drug- or chemical-prompted diabetes such as in the treatment of HIV/AIDS or after organ transplantation (American Diabetes Association 2015)

Diabetes type 2 (T2DM) is a significant physiological condition defined by persistent hyperglycaemia induced by the progressive development of insulin resistance in liver and muscle, as well as compensatory insulin production from pancreatic β-cell disruption (Skyler *et al.* 2016, Kahn *et al.* 2014, Johansson *et al.* 2020). Diabetes type 2 is linked to a lower life span because it increases the risk of cardiovascular (CV) disease, peripheral neuropathy, stroke, amputation and kidney failure. This condition is distinguished by persistently elevated plasma glucose, an abnormal glucose tolerance test, obesity, and symptoms of impaired insulin. (Smushkin *et al.* 2010) Nonetheless, impaired glucose tolerance test with 2h plasma glucose levels in the oral glucose tolerance test of 7.8-11.0 mmol/L according to the ADA Expert Committee and impaired fasting plasma glucose levels between 6.1-6.9 mmol/L according to the World Health Organization are the parameters that indicate presence of type 2 diabetes. (Huang *et al.* 2014a, Sherwin *et al.* 2012, Huang *et al.* 2014b)

Diabetes type 2 therapy is dependent on a variety of patient variables, such as the degree of hyperglycemia, and readily available treatment interventions. Biguanides, sulphonylureas, glinides, thiazolidinediones, dipeptidyl peptidase IV inhibitors, and α-glucosidase inhibitors (Campbell *et al.* 1996) are the most thoroughly explored oral treatments (OHAs), biguanides such as metformin, thiazolidinedione (TZD), and sulfonylureas (SU) are the first line recommended interventions for T2DM (Stein *et al.* 2013, Inzucchi *et al.* 2012). Due to gradual loss of b-cell function and increasing insulin resistance, patients with T2DM who use mentioned OHAs eventually require PPG control with further therapy escalation (Cook *et al.* 2005, Riedel *et al.* 2007). Because of their positive influence on preserving β-cell activity, AGI-based interventions have gained prominence. Although there is limited evidence that AGIs directly impact insulin synthesis and action, lowering glucose toxicity and regulating PPHG, which maintains

pancreatic β-cells, may lead to an increase in insulin sensitivity and better management of T2DM (Chou *et al.* 2006, Joshi *et al.* 2015).

Owing to their nitrogen component AGIs act as competitive inhibitors, AGIs must coexist with carbohydrates near the location of enzyme activity in order to prohibit glucose absorption. All AGIs function by inhibiting α-glucosidase enzymes at the upper small intestine's brush boundary. However, some variances in inhibitory effects on distinct α-glucosidases may account for differences in adverse effect incidence. For instance, glucoamylase is inhibited by acarbose (commonly used AGI), which is followed by sucrase, maltase, and dextranase (Puls 1996, Hanefeld *et al.* 2007). On the other hand, it inhibits alpha-amylase but not beta-glucosidases such as lactase. Miglitol inhibits disaccharide digesting enzymes such as sucrase and maltase more effectively than acarbose, and it also inhibits maltase but not alpha-amylase (Junge 1996). It also has a poor interaction with the intestinal sodium-dependent glucose transporter as a pseudo monosaccharide (Joubert *et al.* 1990).

Considering the current concern about potential cardiovascular risk from diverse blood-glucose-lowering medications, the absence of such indications in the context of α-glucosidase inhibitor use is promising. Furthermore, cardiovascular risk factors such as postprandial hyperglycaemia, hypertension, excessive glucose fluctuation, and obesity appear to be influenced favourably. Unlike other blood-glucose-lowering therapies, there is no incidence of hypoglycemia, which is a risk predictor of CV mortality in and of itself. (Chiasson *et al.* 2002, Hanefeld *et al.* 2004, Standl *et al.* 2012). Overdoes of alpha-glucosidase inhibitors should not necessitate any particular treatment (Spiller *et al.* 2006). Although Glucosidase inhibitors can be easily administrated alongside insulin, sulfonylurea, or metformin (American Diabetes Association 2012) Breakthroughs can still be made decads after AGIs were first used in T2DM management due to risk discrepancies of AGIs such as acarbose inducement of liver damage due to long-term use. (Andrade *et al.* 1998, de la Vega *et al.* 2000) while Miglitol in contrast does not appear to pose a significant risk of liver damage. (Scott *et al.* 2000, Calson, 2000) considering this individuals who have a known diabetic ketoacidosis, intolerance to the medicine or inflammatory bowel disease, partial

intestinal blockage, colonic ulceration, or patients susceptible to intestinal obstruction should not use alpha-glucosidase inhibitors. Furthermore, they are not recommended in patients with chronic intestinal illnesses that cause severe digestion or absorption problems and in patients whose symptoms may worsen due to increased gas production in the gut. (Derosa and Maffioli 2012).

AGI intolerance with certain patients is the reason researchers still trying to develop better AGIs. Hence, finding active molecules from existing chemicals is the first and most crucial stage in AGIs drug discovery. Virtual screening may complete the screening of millions of compounds in a matter of days; after a chemical compound has been picked, it is subjected to spectroscopic and molecular docking experiments to investigate its potency and structural interactions with the target molecules. This study investigate several sulfa-Schiff base chemicals to find new AGI drug possibilities. As a result, combinations of sulfa-Schiff base ligands will be used and studied to see if these compounds can accomplish the same in vitro results as AGIs like Acarbose for DM treatment. The literature review chapter seeks to answer some of the AGI-related questions raised in this study. The in vitro research and virtual docking of the produced compounds will emphasize the materials and methods chapter. All thesis findings will be included in the Results; these discoveries will then be explored in the Discussion Chapter, leading to a complete conclusion inside the Conclusion chapter that will conclude all discoveries and knowledge throughout the thesis.

2. LITERATURE REVIEW

2.1 Background

The number of individuals diagnosed with type 2 diabetes has been on the rise for the last few decades due to an unhealthy diet and sedentary lifestyle. (Liu *et al.* 2017). Currently, the most successful treatment strategy for type 2 diabetes (NIDDM) is to reduce postprandial hyperglycemia (Kumar *et al.* 2011). The increase of plasma glucose concentrations after eating, which is known as Postprandial hyperglycemia, is influenced by a number of variables such as meal timing, portion, composition, insulin, and glucagon secretion (Ceriello 2003, Aisa *et al.* 2019) PPHG has been linked to microvascular problems, cognitive impairment, and cancer (Singh 2012). The current anti-diabetic pharmaceuticals can lower FBS levels, but they have minimum influence on postprandial glycemic response; thus, medications that control postprandial hyperglycemia, such as α-glucosidase inhibitors which act on the intestinal α-glucosidase enzymes, have been oftenly utilized (Baron 1998). This literature review shall try to answer some questions relating to AGIs usage in type 2 diabetes management as follows:

- What is the background of AGIs discovery and usage?
- What are the main clinical key findings of AGIs?
- What makes sulfonamides and their derivatives suitable candidates for diabetes treatment?
- What are the limitations of using sulfonamide and its derivatives in drug discovery development?

2.1 AGIs Discovery and Usage

Some researchers explained that Metformin is the first-line therapeutical medicine for (T2DM) management (Iron and Minze 2014, Garber *et al.* 2013). Metformin usage is the most agreed-upon remedy in the case of hyperglycemia, monotherapy administration (International Diabetes Federation 2012). However, Metformin administration is not always ideal for people with T2DM as it can exacerbate gastrointestinal problems. Along with Metformin cautions, the European Association for the Study of Diabetes advises that "sulfonylurea, meglitinide, or dipeptidyl peptidase 4 DPP-4 inhibitor" also cannot be used by patients who are at risk of Serious renal dysfunction or disorders that might abruptly affect renal function, which limits the ability in determining the correct medicine and who should be given that medicine. (Inzucchi *et al.* 2012). The American Association of Clinical Endocrinologists suggests getting a glucagon-like peptide-1 GLP-1 agonist if weight reduction is desired and recommends alpha-glucosidase inhibitors as appropriate metformin substitutes along with meglitinide, DPP-4, sulfonylurea, and GLP-1.so what are AGIs according to different works of literature, and how do they function?

During the 1990s, AGIs were permitted to manage T2DM (Stein *et al.* 2013, Bischoff 1994). Alpha-glucosidase inhibitors share the following characteristics:

- Sugar-mimicking structures
- Capability of forming ionic and hydrogen bonds with nucleophilically catalyzing residues
- Transition-state-like structures
- Ability to make ionic and hydrophobic interactions at sites other than the active site
- Presence of an epoxy or aziridine group that can form covalent bonds with enzymes. (Nakao *et al.* 2000, Hakamata *et al.* 2006, Hakamata *et al.* 2009)

AGIs can be defined as a distinct category of oral antihyperglycemic drugs that act by competitive and reversible inhibition of intestinal alpha-glucosidase for the treatment and mitigation of T2DM (International Diabetes Federation 2012, Garber *et al.* 2013, Joshi *et al.* 2015). Each of (Bischoff 1995, Hedrington and Davis 2019, Van de Laar *et al.* 2005, Zhu *et al.* 2013) explained that glucose absorption is hindered by blocking these enzymes, which reduces PPG and aids in controlling glycemic levels. Various national authorities have authorized three AGIs for drug regulation: acarbose, miglitol, and voglibose. AGIs can be administered as a single agent or as a combination treatment. The observed reduction in hemoglobin A1C (hba1c) is 0.8 percent when taken as monotherapy. The amount of HbA1c reduction is equivalent to the baseline HbA1c. The impact is more substantial 0.93 percent in higher >9 percent baseline HbA1c levels but less 0.56 percent in lower 7 percent baseline HbA1c levels. The average drop in FBG is 1.09 mmol/L, while the reduction in 1 hour PPG is 2.32 mmol/L.AGIs to be appear popular in Asian nations, notably China, where the class has demonstrated more capability in treating T2DM, which maybe attributed to carbohydrate-rich eastern diet. Acarbose, Voglibose, and Miglitol are the most effective treatments for PPHG, so what are the main clinical key findings of their administration?

2.2 Clinical Key Findings of AGIs Adminstration

The three current alpha-glucosidase inhibitors revealed a weaker blood-glucose-lowering impact than most other types of OHAs. (Cheng and Fantus 2005) and Several other researchers, Clinical investigations have shown an average hemoglobin A1c reducing effect of around 0.5 percent, 1.0 percent compared to placebo (Inzucchi 2002). Not unexpectedly, PPG levels are improved more than fasting levels (Lebovitz 1997). A modest decline in triglyceride levels was also revealed (Bayraktar *et al.* 1996). The proportional contributions of fasting plasma glucose and postprandial plasma glucose to HbA1c levels appear to differ according to glycemic management (Monnier and Colette *2009*). However, at lower HbA1c levels, PPG plays a more vital role in maintaining overall glycemic control (Monnier *et al.* 2003). Raised PPG levels impair glycemic control and aggravate cardiac events in individuals with normal FPG and HbA1c levels (Ning *et al.* 2010). As a result, the treatment of (PPHG) to minimize CV events in

T2DM patients is the focus of many researchers (Joshi *et al.* 2015). Hence (Acarbose, Voglibose, and Miglitol) are the most beneficial treatments for postprandial hyperglycemia. Still, the usage of AGIs should be avoided in individuals with gastrointestinal disorders Because of the high rates of adverse effects such as flatulence and diarrhea (Chiniwala and Jabbour 2011). Because of their low effectiveness in respect to other OHAs, AGIs inhibitors are seldom used alone. They are not recommended as first-line treatment for moderate to severe hyperglycemia (9.0 percent) (Canadian Diabetes Association and Cheng 2013).AGIs are also considered most effective when combined with other OHAs. Dosing should begin slowly, at 25 mg once a day, and steadily increase to 100 mg three times per day if tolerated. However, adverse digestive reactions restrict the tolerable dosage to 50 mg (Cheng and Fantus 2005). Due to these limitations of AGIs usage, there's a need to develop new ones that can stand alone in a monotherapy program and causes less significant side effects with the least amount of daily dosing possible. For that reason, this thesis wants to find familiar compounds that can be further developed and tested; the best of those compounds are sulfonamides, but what makes sulfonamides and their derivatives suitable candidates for diabetes drug discovery and development?

2.3 Sulfonamides and Their derivatives in Drug Discovery

Each of (Gul *et al*. 2016, Gokcen *et al.* 2016) and several other scientists considered Sulfonamide to be the foundation for several medication classes known as sulfa medicines. Sulfonamide refers to any molecule with a sulfonamide portion (SO2NH2) in its structure. These chemicals have received significant interest because of their many biological functions in the pharmaceutic and agricultural sectors (Boztaş *et al.* 2015). Sulfonamide compounds where R may be an aromatic, heterocyclic, or an aliphatic moiety represent a considerable variety of medications. Up to 30 pharmaceuticals comprising this functionality are in clinical use, including a broad range of therapeutical factors with anticarbonic anhydrase (CA), antiviral, antibacterial, diuretic, cyclooxygenase 2 (COX2) inhibitory, and protease inhibitor. These drugs are regularly used to treat diseases such as conjunctivitis, bacillary dysentery, meningitis, streptococcal pharyngitis, trachoma, nocardiasis, and malaria (Gulçin and Taslimi

2018). Due to its familiar structure and history, its derivatives have been studied to treat T2DM; for example, Metformin sulfonamide derivatives could have anticoagulant and antifibrinolytic properties, and therefore could be evaluated in the screening of effective pharmaceutical candidates for the treatment of Type 2 diabetes mellitus, which is characterized not only by hyperglycemia but also by an impaired balance with both of fibrinolysis and coagulation (Molyneux *et al*. 1990), (Ji *et al*. 2019) designed and produced quinoxalinone acyl sulfonamide derivatives and demonstrated the way to facilitate inhibition of aldehyde reductase (ALR1) /aldose reductase (ALR2) (Dräger *et al.* 1995). Patients with hyperglycemia, metabolic acidosis, and high ketone bodies in the blood circulation might have euglycemic incidents if their serum glucose levels are within permissible levels and since aldose reductase is a polyol pathway rate-determining enzyme, which phosphorylates glucose under euglycemic conditions. The mentioned research results are impactful for the treatment of type 2 diabetes (Apaydın and Török 2019). Studies of sulfonamide derivatives are encouraging, primarily the chalcones's, also known as α-β-unsaturated ketones (Di Carlo *et al*. 1999, Guida *et al.* 1997). They make up a substantial proportion of natural assets and are essential precursors for artificial manipulations. Chalcones and their chemically synthesized equivalents exhibit a wide variety of biological activity. The double bond conjugation of the carbonyl functional group is considered to be responsible for chalcones' bioactivity, whereas the apparent lack of this functionality renders them inert. They occur in trans and cis-forms and can be conveniently cyclized to produce flavanones via Michael's addition. Several typical synthetic procedures for chalcones synthesis incorporate ClaiseneSchmidt condensation under homogenous conditions in the presence of acid or base (Dhar 1981). Strong alkaline media such as natural phosphates and others have traditionally been used in their production (Climent *et al.* 2004, Daskiewicz *et al.* 1999). Numerous lewis acids have also been used (Iranpoor and Kazemi 1998, Nakano *et al.* 1987, Singh *et al.* 2014). Chalcone's investigations aspire to produce new drugs equivalent in reactivity to AGIs but without the limitations of the main known AGIs. Recent and comprehensive studies of Chaclons have been conducted: Yoshikawa and coworkers reported two sulfonium AGIs that naturally occur, salcinol (1) and kotalanol (2), from the Salacia reticulata plant (Yoshikawa *et al.* 1998). (Ghani 2015) compiled the latest sulfa drugs derivatives studies starting from (Seo *et al.* 2005) discovereing

eight novel sulfonamide chalcones (38-45) that inhibit a-glucosidase. The compounds (42-45) inhibited a-glucosidase with favourable results, (Wang *et al.* 2010), expanding research on prior work on sulfonamide chalcones by incorporating the phenylsulfonamide chalcone structure into the benzopyran backbone, resulting in 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives. The synthesis method produced more effective yeastglucosidase inhibitors compared to the simple sulfonamide chalcones, to (Ansari *et al.* 2005), offering a wide range of 2, 4-diaryl-2, 3-dihydro- and tetrahydro-1, 5-benzothiazepines from chalcones and tested them for -glucosidase activity. One chalcone (29) and several 1, 5-benzothiazepine derivatives (30, 31, 32, and 33) have been realized. Computational and Enzymological inquests on different synthetic furanochalcone products have granted intriguing hints to rat intestinal maltase's inhibitory activity and interactions with its active site. Although sulfonamides and their derivatives frameworks are familiar and understood in drug discovery programs, why there are some limitations with their developmental procedures?

2.4 Limitations of Using Sulfonamides and Their Derivatives in Drug Discovery

Each of (Asano *et al.* 1996, Apaydın and Török, 2019) elucidated that sulfonamide and its derivatives aid in developing new AGIs due to well-described libraries of its chemical compounds, which could be used to establish sulfa-Schiff bases ligands complexes that could be evaluated for multi-target activities and obtain permission for drug trials quite quickly than it would be if the structures were utterly new. Sulfonamides and their derivatives can be relatively hazardous and damaging to the environment; diligent evaluation throughout drug design is critical. For example, sulfonamide derivatives eliminate bilirubin from the transport protein albumin in humans, which leads to the increase of bilirubin levels in blood circulation and toxic adverse effects in the liver, CNS, and kidneys. With the inordinate usage of organic solvents such as dimethylformamide or highly reactive harmful starting ingredients in their synthesis, the waste from their production can also be very destructive to the environment, for example, thionyl chloride. Current, promising approaches for synthesizing sulfonamide derivatives in a "green" or non-toxic fashion that

demonstrated the synthesis without using organic solvents or reactive sulfur sources such as sulfonyl chloride were reported.

2.5 Summary

In summary, α-glucosidases are distinct OHAs approved for T2DM prevention and management. Although AGIs show less hypoglycemic effect and improved PPHG control, gastric withdrawal symptoms often limit the endurable dosage of these drugs, which drives the need to discover and develop similar therapeutic agents but with lesser negative side effects, thus the focus on Sulfonamide Owing to their recognizable structure and background. Sulfonamide derivatives have been explored to treat type 2 diabetes, for example, Metformin sulfonamide derivatives and Chalcones. One of the main limiting facets of these derivatives is their highly reactive hazardous starting ingredients and the waste from their synthesis that damages the environment. Nevertheless, emerging promising approaches for synthesizing sulfonamide compounds in a "green" or non-toxic manner have been reported.

3. MATERIALS AND METHODS

3.1 Equipments

- pH Meter with Glass Electrode for measuring alkalinity and acidity with calibration solutions (HCl, NaOH)
- Centrifuge for substrate preparation
- Hot Plate Magnetic Stirrer for buffer preparation
- Analytical Balance for the measurement and preparation of solid materials
- Microplate Spectrophotometer to measure absorbance

3.2 Regants

- Enzyme: α-Glucosidase from Saccharomyces cerevisiae
- Subsrate: p-nitrophenyl α-D-glucoside
- Buffer: Sodium phosphate
- Distilled Water
- Sulfa Schiff base compounds Figure 3.1

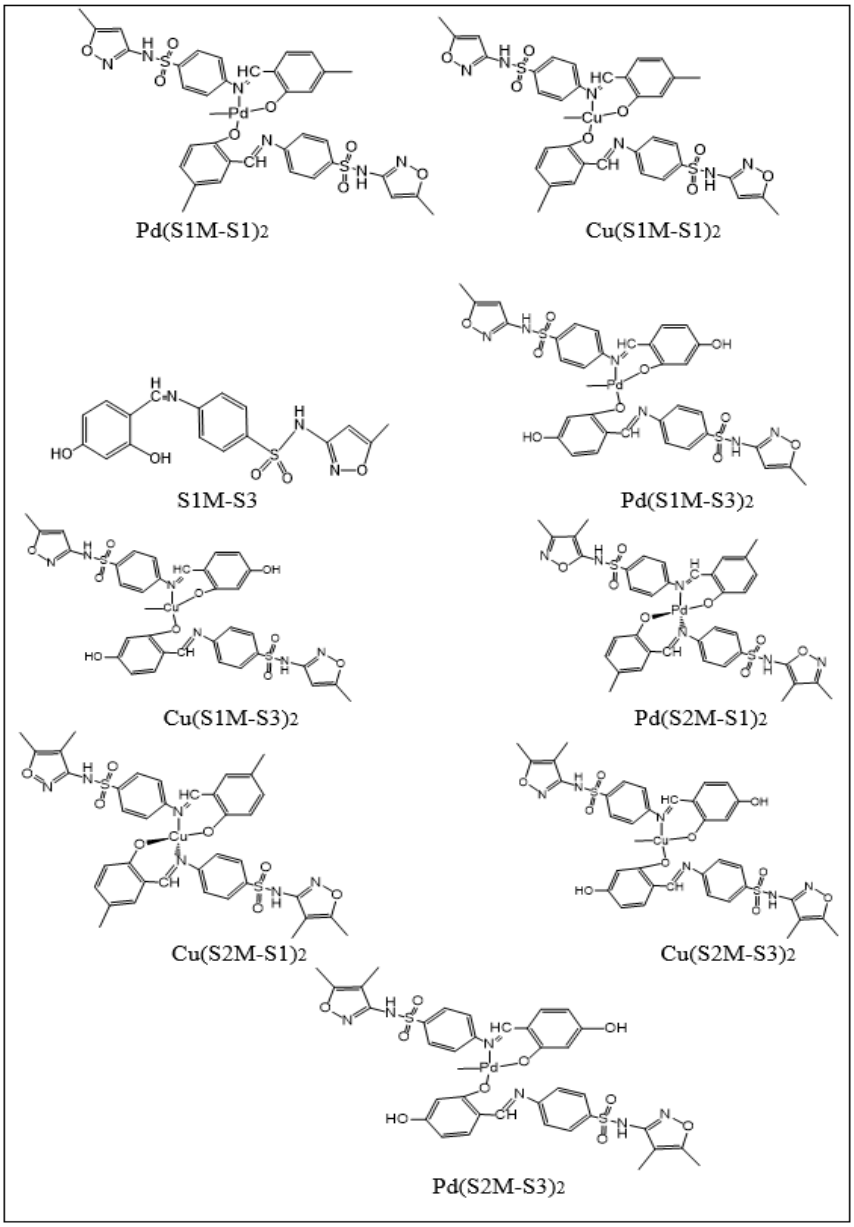

Figure 3.1 Chemical structures of sulfa-schiff base compounds

3.3 Solution Preparation

- Buffer solution (20 mM Sodium Phosphate with pH 6.8 at 20 °C): Buffer was weighed in grams then dissolved in 100 ml of distilled water with its pH adjusted to 6.8 using HCl and NaOH solutions.
- Enzyme (0.0025 units): Enzyme was dissolved at assay buffer as 0.0025 units,

- Substrate (2 mM): The substrate was calculated in grams then dissolved in buffer solution pH 6.8

3.4 Inhibitory Effects

The inhibitory activities of the sulfa drug derivatives compounds against Alpha-glucosidase enzyme was tested using (Li *et al.* 2016, and Wang *et al.* 2017) approach. Reaction mixture was displayed in Table 3.1.

Table 3.1 Solution and their volume used alpha-glucosidase activity assay

Solution	Volume (μL)
Buffer	100
Substrate	40
Enzyme	10
Distilled water	80
Temperature (^{o}C)	37
Wavelength (nm)	408

To determine the inhibitory effects of compounds, enzyme activity was assayed at five different sulfa Schiff base concentrations. Calculation of IC_{50} were done by solving the slope equation of activity percentage on x axis and each sulfa Schiff base compound final concentration on the y axis. Enzyme activity without inhibitors is accepted as control.

3.5 Moleculer Docking

Molecular docking is a technique often used to investigate the interactions between drug molecules and their targeted-receptors. The results of molecular docking provide vital information on drug-receptor interactions. İt is often used to estimate the activity and affinity of drug candidates' molecules by predicting their binding orientation with their intended targets (Rahim *et al.* 2020). The molecular docking procedure was carried out via the Molegro Virtual Docker tool. The crystal structure of α-D-glucose bound oligo-

1,6-glucosidase (3A4A), which has a 72 percent identical sequence with alpha-glucosidase, was utilized to construct Saccharomyces cerevisiae alpha-glucosidase (Liu *et al.* 2011). During the docking simulation, the following processes were carried: Addition of hydrogen atoms to the 3D structure of targeted protein residues was done via the MVD tool. The energy was reduced using the default parameters of Molegro Virtual Docker. The 3D structures of sulfa Schiff base compounds' were loaded into MVD as (mol) files (Sochacka and Baran 2012). MVD grid-based algorithm quickly identified the target cavity containing the side residues active sites. The number of cavity residues was reduced to a minimum. Throughout the minimization, side chains torsion angles were modified. The target backbone remained rigid during the docking simulation, but the amino acids side chains torsional angles close to the protein cavity were allowed to change. The side chains selected for energy reduction were decreased in areas close to the identified location after docking each ligand. When the side chains were rearranged, the energy of each ligand was reduced. To rearrange the side chains and reduce each ligand, ordinary non-softened potentials were applied. Because the amount of flexible torsions established during the docking run minimizes the complexity of the docking search, all flexible torsions in the ligands were set stiff during docking. To make the complexes, molecules in monoanionic and neutral states were docked individually to the cavity. Many separate runs were undertaken for each complex, each of which resulted in a single final solution (pose). When the docking run was completed, the lowest-energy result from each cluster was displayed; similar postures were removed, leaving just the highest-scoring one. The ten acquired postures were sorted according to their MolDock Score. The weighted reranking scores (Rerank Score) were used to examine the postures to increase the accuracy of the poses' ranked order. The posture with the lowest Rerank Score value for each complex was picked (Sochacka 2014).

4. RESULTS

4.1 Inibitory Activty Results

In Vitro studies of α-glucosidase inhibitory activity several ligand complexes were synthesized and evaluated against α-glucosidase inhibitory potential. All analogues displayed inhibition ranging between 0.429 to 8.976 μM when compared with the standard drug acarbose (IC_{50} = 0.80 μM). Among the series.ligand complexes 1, 4, 5, 7, 8 and 9 showed great inhibitory activity. 2 and 6 showed moderate inhibitory activity. 3 showed weak inhibitory activity. The inhibitory potential can be shown in this order judging by IC_{50} values of each analogue: $Cu(S2M\text{-}S1)_2$ > $Pd(S1M\text{-}S3)_2$ > $Cu(S2M\text{-}S3)_2$> $Pd(S2M\text{-}S3)_2$ > $Cu(S1M\text{-}S3)_2$ > $Pd(S1M\text{-}S1)_2$ > $Pd(S2M\text{-}S1)_2$ > $Cu(S1M\text{-}S1)_2$ > S1M-S3, Results for α-glucosidase inhibition by each ligand complex are shown in Figure 4.1. Their half maximal inhibitory concentration (IC_{50}) values were listed in Table 4.1.

Table 4.1 IC_{50} (μM) values, Moelcular docking scores and Hydrogen binding energies of sulfa-Schiff base compounds

No.	Inhibitor	MolDock Score	HBond	IC_{50} (μM)
1.	$Pd(S1M\text{-}S1)_2$	-219.731	-5.77043	0.825
2.	$Cu(S1M\text{-}S1)_2$	-250.473	-5.38617	2.217
3.	S1M-S3	-150.73	-10.4124	8.976
4.	$Pd(S1M\text{-}S3)_2$	-249.781	-10.8271	0.438
5.	$Cu(S1M\text{-}S3)_2$	-231.331	-3.37147	0.699
6.	$Pd(S2M\text{-}S1)_2$	-212.307	-0.508773	1.202
7.	$Cu(S2M\text{-}S1)_2$	-210.423	-0.0486618	0.429
8.	$Cu(S2M\text{-}S3)_2$	-183.1	-8.87229	0.494
9.	$Pd(S2M\text{-}S3)_2$	-194.64	-15.0851	0.514

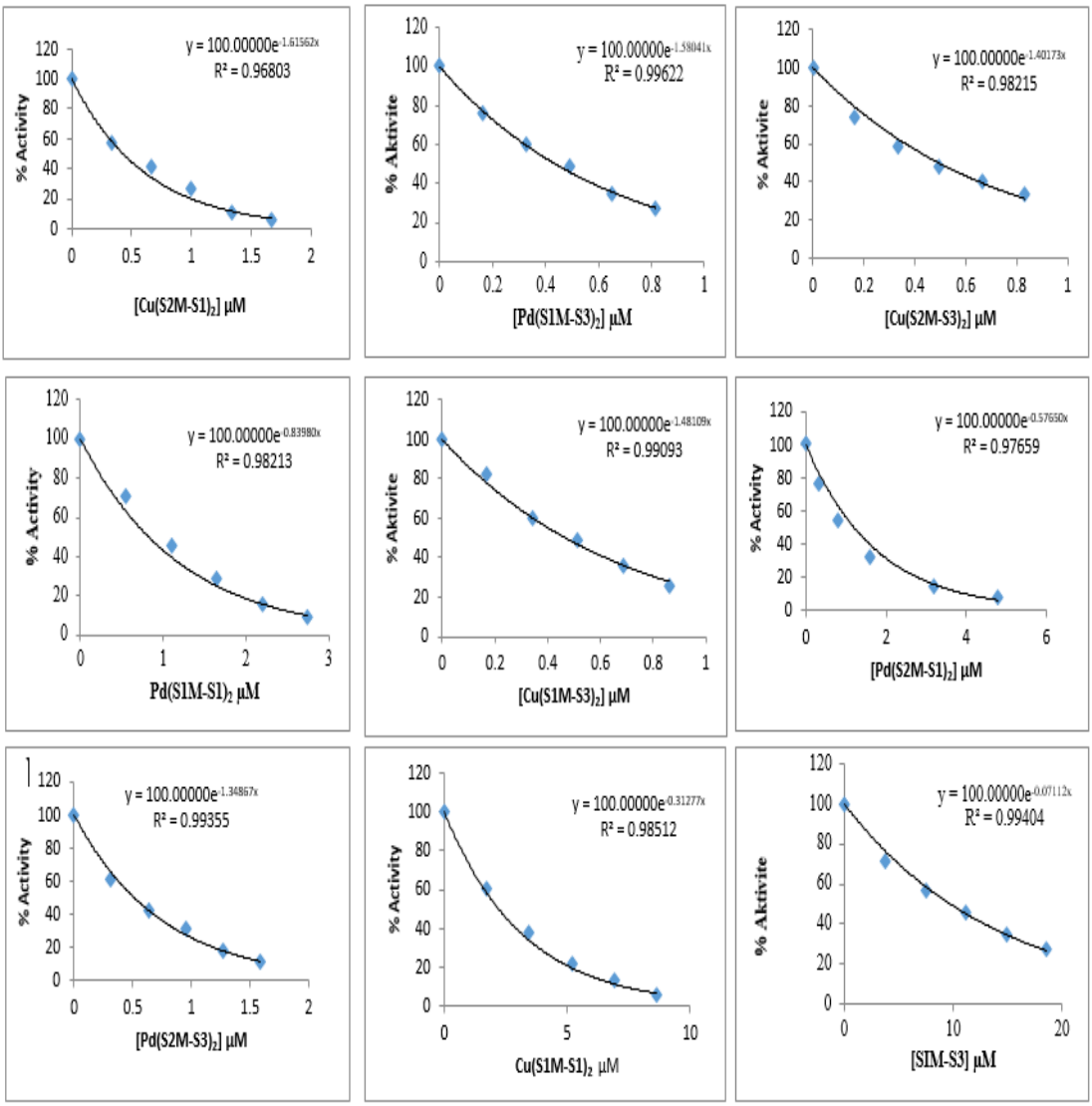

Figure 4.1 IC_{50} curves of sulfa Schiff base compounds Y-axis represent the remaining percentage of activity while the X-axis represent the concentration of each complex

4.2 Molecular Docking Results

For the past number of years there has been a lot of attention in computational modeling of drug candidates for alpha glucosidases. The binding relationship between the α-glucosidase enzyme and the sulfa Schiff base ligands was discovered via molecular docking.All compounds were well accommodated into the detected cavity of the alpha glucosidase enzyme. Each ligand was involved in various types of interactions with the cavity side residues. As shown in Figure 4.2 $Cu(S2M\text{-}S1)_2$ ligand showed hydrogen binding energy of -0.0486618 and a score function of -210.423 at cavity enclosed mainly by Gln279 steric interaction and Ser240 hydrogen bonding.

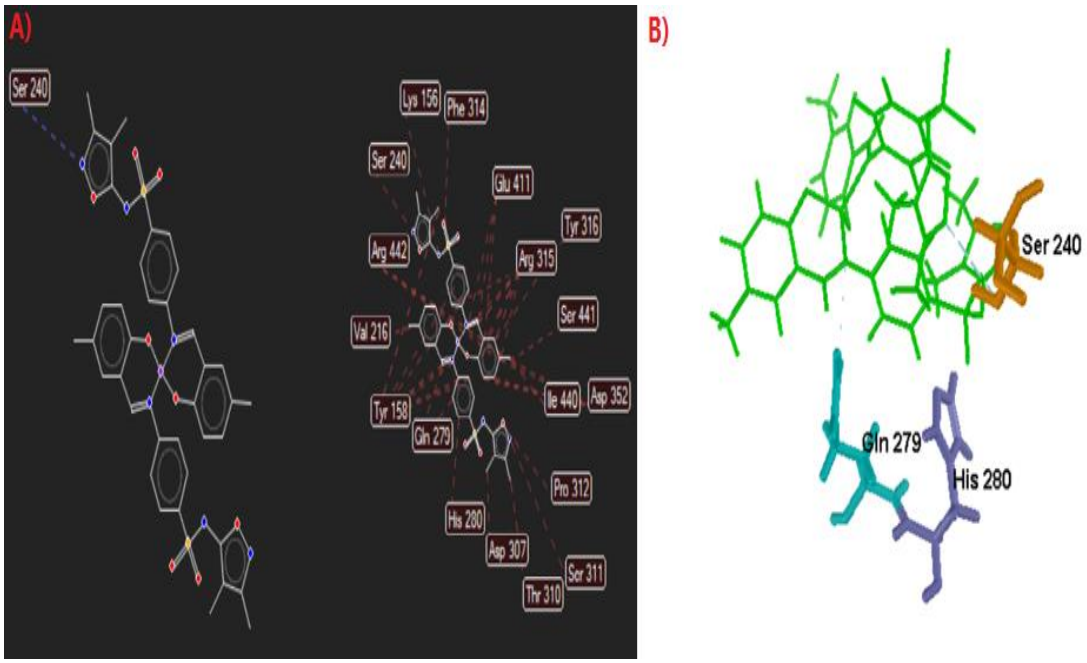

Figure 4.2 (A) 2D diagrams display steric and hydrophilic interactions of $Cu(S2M\text{-}S1)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Cu(S2M\text{-}S1)_2$ with α-glucosidase at labelled amino acid residues

As shown in Figure 4.3 $Cu(S2M\text{-}S3)_2$ ligand had a hydrogen binding energy of -8.87229 and a scoring function of -183.1. Its 3D structure showed steric interaction with Glu277 while its hydrogen bonds were with Asn415, Asp352, Asn350, Gln279 and Tyr347.

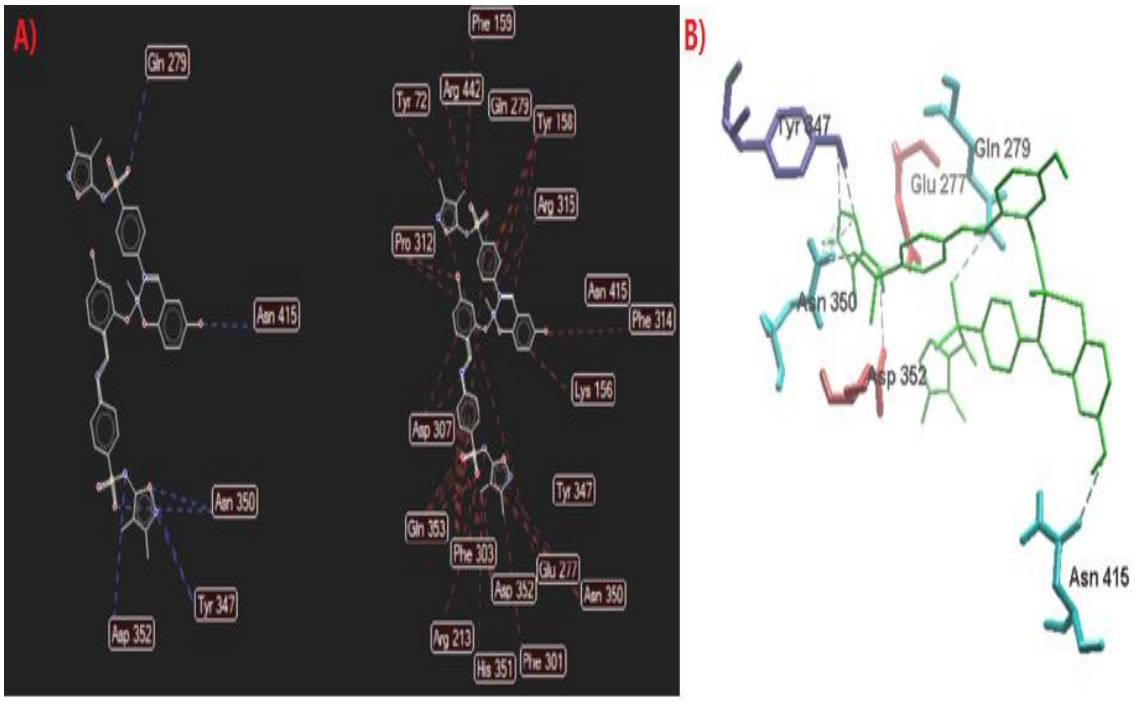

Figure 4.3 (A) 2D diagrams display hydrophilic and steric interactions of $Cu(S2M\text{-}S3)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Cu(S2M\text{-}S3)_2$ with α-glucosidase at labelled amino acid residues

As shown in Figure 4.4 $Pd(S1M\text{-}S3)_2$ ligand showed a hydrogen binding energy of -10.8271 and a scoring function of -249.781. Its 3D structure showed direct hydrophilic interactions with each of Asn415, .Arg315, Gln279, Arg442, Tyr158, Thr306, Asn350, and Asp215.

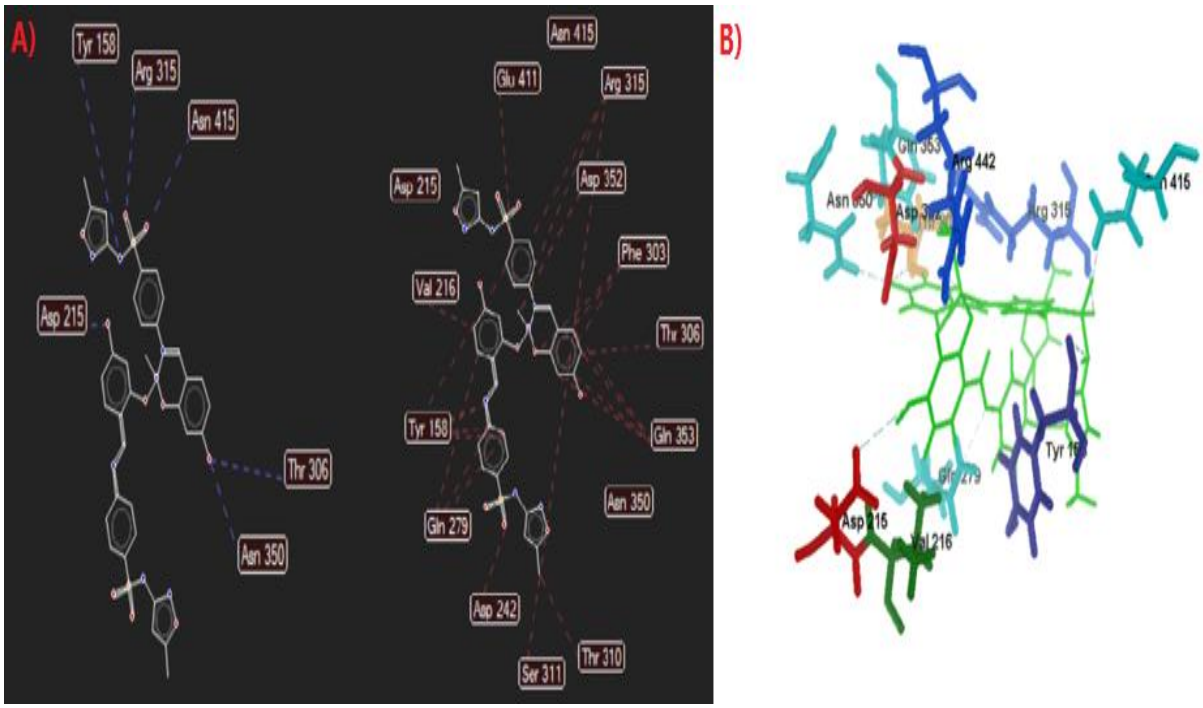

Figure 4.4 (A) 2D diagrams display hydrophilic and steric interactions of $Pd(S1M\text{-}S3)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Pd(S1M\text{-}S3)_2$ with α-glucosidase at labelled amino acid residues

As shown in Figure 4.5 $Pd(S2M\text{-}S1)_2$ this ligand had hydrogen binding energy of -0.508773 and a scoring function of -212.307. It showed hydrogen bond interaction and steric interaction with Ser240 while Lys156, Gln279, and Ser311 around it only showed steric interaction beside Thr310, which showed hydrophilic interaction.

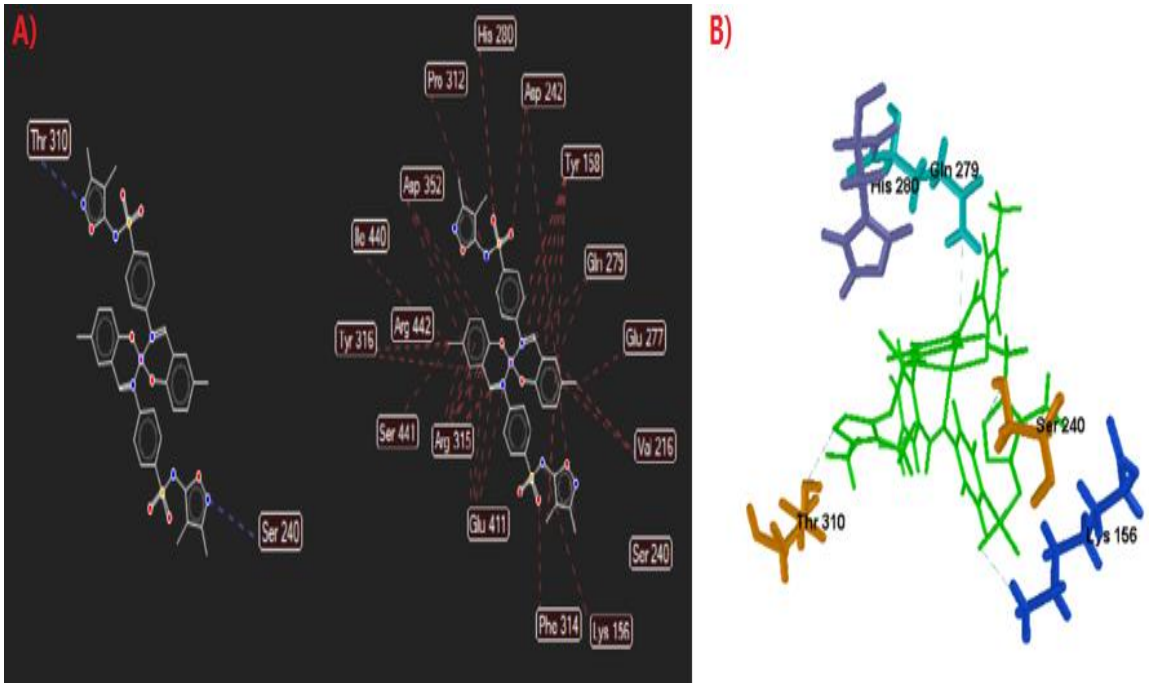

Figure 4.5 (A) 2D diagrams display hydrophilic and steric interactions of $Pd(S2M\text{-}S1)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Pd(S2M\text{-}S1)_2$ with α-glucosidase at labelled amino acid residues

As shown in Figure 4.6 $Pd(S2M\text{-}S3)_2$ ligand had hydrogen bonding energy of -15.0851 and a scoring function of -194.64. It also showed a hydrophilic and steric interaction with Ser311, Pro312, Asp415, Gln279, Arg442, Asp352, Asn350, Glu277, and Arg213.

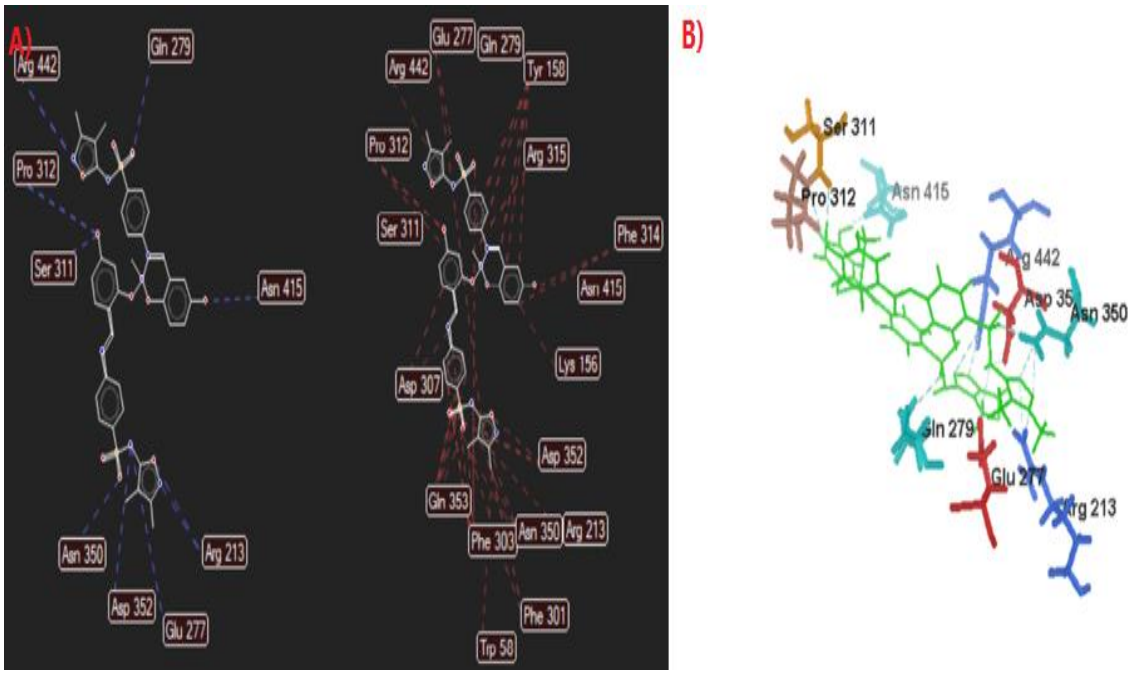

Figure 4.6 (A) 2D diagrams display hydrophilic and steric interactions of $Pd(S2M\text{-}S3)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Pd(S2M\text{-}S3)_2$ with α-glucosidase at labelled amino acid residues

As shown in figure 4.7 $Pd(S1M\text{-}S1)_2$ showed scoring function of -219.731 and a hydrogen binding energy of -5.77043. It showed hydrophilic interaction with each of the adjacent residues Asn415, Arg315 and Ser240.

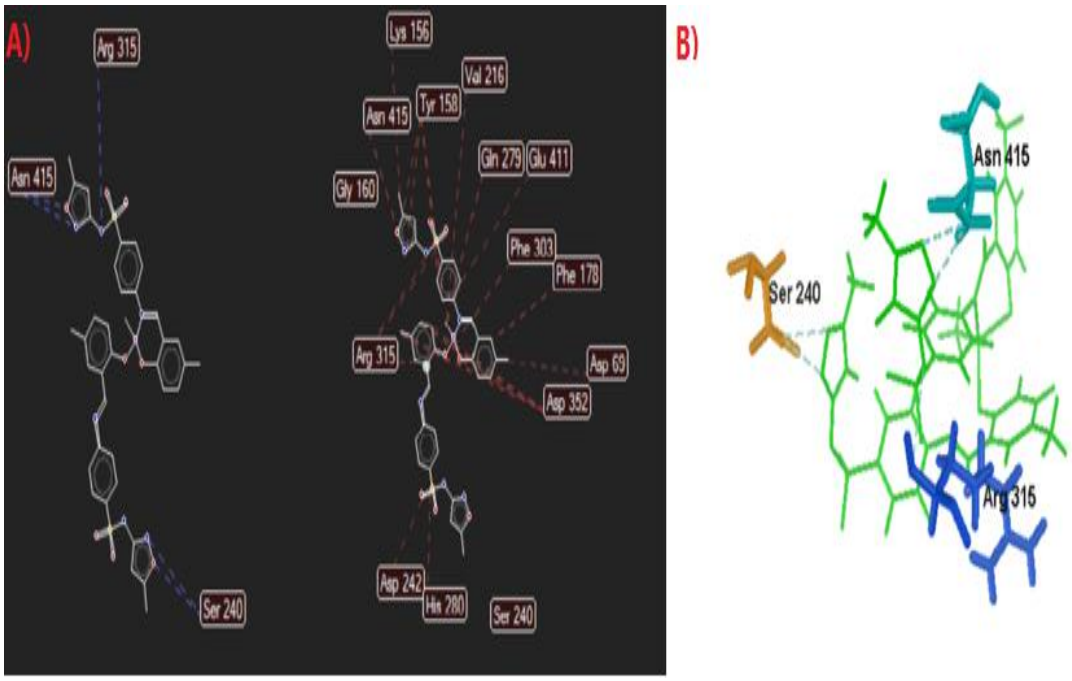

Figure 4.7 (A) 2D diagrams display hydrophilic and steric interactions of $Pd(S1M\text{-}S1)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Pd(S1M\text{-}S1)_2$ with α-glucosidase at labelled amino acid residues

As shown in Figure 4.8 S1M-S3 results had a scoring function of -150.73 and a hydrogen binding energy of -10.4124. It exhibited hydrophilic interaction with each of Arg442, Ser157, Ser241 and Lys156.

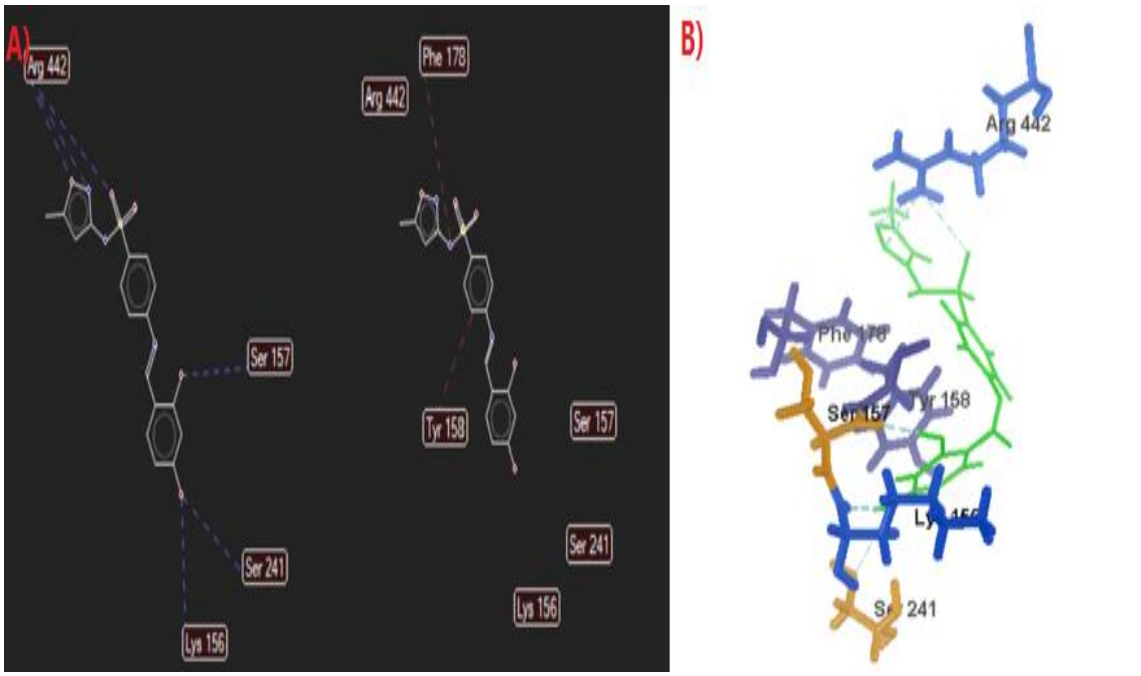

Figure 4.8 (A) 2D diagrams display hydrophilic and steric interactions of S1M-S3 in the active sites of the receptor. (B) 3D illustrations show interactions of S1M-S3 with α-glucosidase at labelled amino acid residues

As shown in Figure 4.9 $Cu(S1M\text{-}S3)_2$ showed a scoring function of -231.331 and a hydrogen bonding energy of -3.37147 it also had hydrophilic and steric interactions with Arg446, Arg442, Asp69, Gln353, Thr306, Ser240, and Arg315.only Arg446 did not interact sterically.

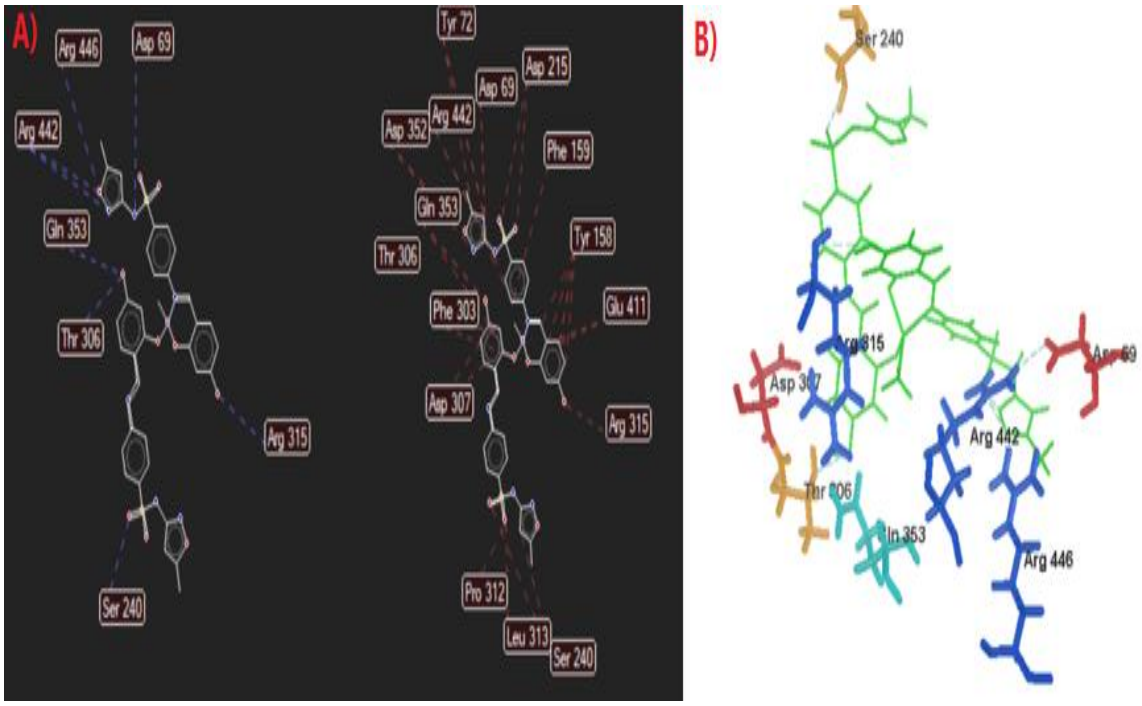

Figure 4.9 (A) 2D diagrams display hydrophilic and steric interactions of $Cu(S1M\text{-}S3)_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of $Cu(S1M\text{-}S3)_2$ with α-glucosidase at labelled amino acid residues

As shown in Figure 4.10 Cu(S1M-S1)$_2$ showed a scoring function of -250.473 and a hydrogen binding energy of -5.38617 it did also interact hydrophilically and sterically with the following residues Tyr158, Gln 279, Arg442, Arg315, Tyr316 with Tyr158 and Gln279 showing steric interaction and Arg446 only showing hydrophilic interaction.

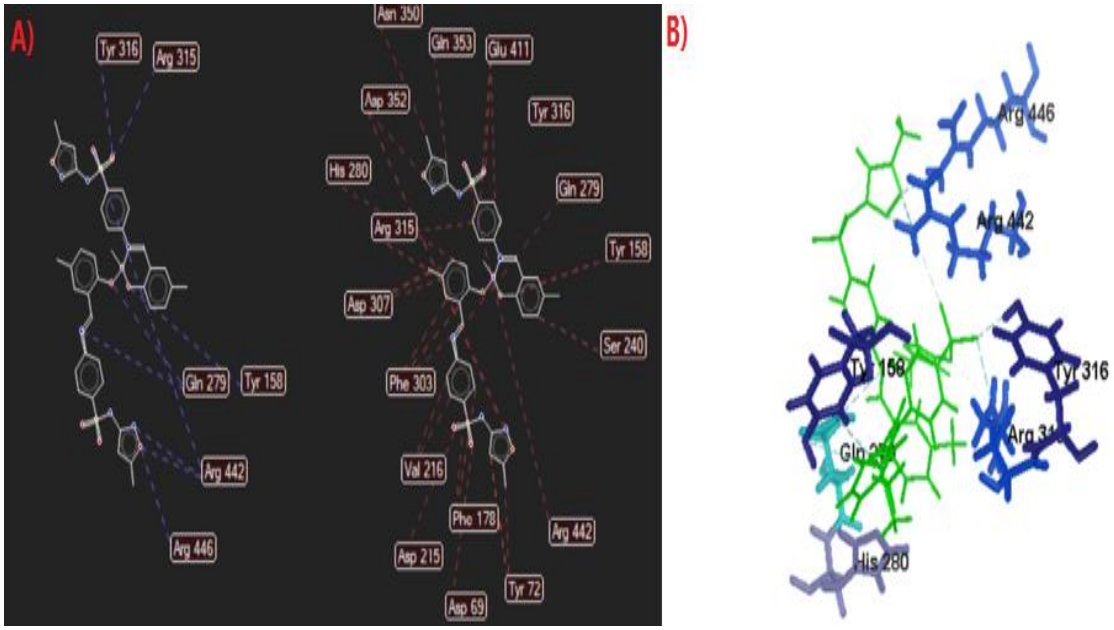

Figure 4.10 (A) 2D diagrams display hydrophilic and steric interactions of Cu(S1M-S1)$_2$ in the active sites of the receptor. (B) 3D illustrations show interactions of Cu(S1M-S1)$_2$ with α-glucosidase at labelled amino acid residues

5. DISCUSSION

Alpha-glucosidase was chosen and synthesized, robust compounds with decent IC_{50} values were permitted to dock with the active residues of the α-glucosidase using the most basic parameters, Placement: Triangle Matcher and Rescoring: London dG. Ten conformations were created for each molecule, and the top-ranked conformations of each chemical were selected (Rahim *et al.* 2020). The molecular docking experiments investigated the required configuration for all nine potent compounds, and each one was determined to be a good fit in the active site of the alpha-glucosidase. $Cu(S1M\text{-}S3)_2$ with a good IC_{50} value of 0.699 μM and a scoring function of -231.331 formed 8 hydrogen bonds with the cavity engulfed by Arg446, Arg442, Asp69, Gln353, Thr306, Ser240, and Arg315 most interactions were both hydrophilic and steric beside Arg446 it did not show steric interactions. Arg315 interacted with the ligand through the lone pair donation of the amine's nitrogen within the residue with the hydroxyl group of the ligand's phenol ring. Ser 240 interacted through the hydroxyl group of the residue to form a strong hydrogen bond with the oxygen of the ligand's sulfone. Thr306 formed hydrogen bonds on each side of the interaction by interacting with the hydroxyl group of the amino acid residue and the hydroxyl of the ligand's phenol ring. Gln353 amide group donated a lone pair and formed a covalent hydrogen bond with the hydroxyl of the ligand's Phenol ring. Arg442, Arg446 nitrogens of the guanidino group acted as a donor and formed hydrogen bonds by donating/sharing lone pairs to both the oxygen and nitrogen of the isoxazole ring. Asp69 carbonyl oxygen atom acted as an acceptor and formed a strong hydrogen bond with the donating nitrogen within the amine group of the ligand. $Cu(S2M\text{-}S1)_2$ had the highest IC_{50} value of 0.429 μM and a score function of -210.423; it formed 2 hydrogen bonds at a cavity enclosed mainly by Gln279 steric interaction Ser240 hydrogen bonding. Ser240 hydrogen bond formed via the interaction of the hydroxyl oxygen atom with the nitrogen atom of isoxazole within the ligand; meanwhile, Gln279 nitrogen of amide group acted as a lone pair donor to form steric and hydrophilic interaction with the carbon of the cyclic compound. $Cu(S2M\text{-}S3)_2$ with a high IC_{50} of 0.494 μM and a scoring function of -183.1 formed 9 hydrogen bonds with Asn415, Asp352, Asn350, Gln279, and Tyr347 only Glu277 residue showed steric interaction. Asn 415 oxygen of carbonyl group acted as an accepting atom with the

ligand's phenol ring. Gln 275 amide nitrogen acted as a donating group with the oxygen of the ligand's sulfone. Glu277 oxygen of its carbonyl group acted as an acceptor with the substituted methyl of the ligand. Asp352 Oxygen atom of carbonyl group interacted as an acceptor with the amine of the ligand's sulfonamide. Asn350 nitrogen of amide group acted as a donor with the accepting oxygen and nitrogen of the isoxazole cyclic ring. Tyr347 hydroxyl group interacted with the ligand's electronegative atoms of isoxazole and formed hydrogen bonds. Pd(S1M-S3)$_2$ had a high IC$_{50}$ of 0.438 μM and a scoring function of -249.781; it formed 9 hydrogen bonds and steric interactions with each of Asn415, Arg315, Gln279, Arg442, Tyr158, Thr306, Asn350, and Asp215. Asn415 amide group interacted as a donor with the sulfone oxygens. Tyr158 carbonyl oxygen atom interacted as an acceptor with the sulfonamide nitrogen atom. Arg315 amine group atoms interacted with the sulfone oxygen. Arg442 nitrogen of amide interacted as a donor with the oxygen of the ligand. Asp215 carbonyl oxygen interacted with the hydroxyl of the ligand's phenol ring. Asn350 amine interacted as a donor with the hydroxyl group of the ligand's phenol ring. Thr306 hydroxyl groups on both ligand and receptor complex interacted. Gln279 amide group interacted with the nitrogen of ligand. Pd(S2M-S1)$_2$ with a moderate IC$_{50}$ of 1.202 μM and a scoring function of -212.307 formed 2 hydrogen bonds. Interactions with Ser240 were both steric and hydrophilic. Thr310 interactions were hydrophilic while Lys156, Gln279, Ser311 only showed steric interactions. Thr310 hydroxyl interacted with the nitrogen of the cyclic ligand. Gln279 amide group interacted with a carbon atom within the ligand as a donor. Serin 240 hydroxyl group interacted through hydrogen bonding with the nitrogen of the isoxazole of the ligand compound. Lys156 amine interacted as a donor with the nitrogen atom within the ligand. Pd(S2M-S3)$_2$ had a good IC$_{50}$ of 0.514 μM with a scoring function of -194.64; it formed 11 hydrogen bonds with the engulfing residues Ser311, Pro312, Asp415, Gln279, Arg442, Asp352, Asn350, Glu277, Arg213 all interactions were both hydrophilic and steric. Ser311 oxygen of the carbonyl group interacted with the hydroxyl of the ligand's phenol ring, Pro312 nitrogen of the amine group interacted with the hydroxyl of the ligand's phenol ring. Asn415 carbonyl of oxygen interacted with the hydroxyl of the ligand's phenol ring, Gln279 nitrogen of amide interacted with the sulfone oxygen as a donor, Arg442 amide nitrogen interacted with the nitrogen of the isoxazole substituted ring as a donor, Asp352 oxygen of carbonyl group interacted

with the nitrogen of the sulfonamide group, Asn350 amine group interacted as a donor with both nitrogen and oxygen of the cyclic ligand ring, Glu277 oxygen atom interacted with the nitrogen of the sulfonamide within the ligand, Arg213 nitrogen of guanidino group acted as donated with the nitrogen and oxygen of the isoxazole ring. Pd(S1M-S1)$_2$ with IC_{50} of 0.825 μM and scoring function of -219.731 formed 5 hydrogen bonds with both hydrophilic and steric interactions with each of these residues Asn415, Arg315, and Ser240. Asn415 interacted as a donor through the nitrogen of the amide group with the nitrogen and oxygen of the isoxazole ring of the ligand. Ser240 hydroxyl group reacted with the nitrogen and oxygen of the substituted isoxazole ligand aromatic ring. Arg315 amine group acted as a donor with the nitrogen of sulfonamide within the ligand. Cu(S1M-S1)$_2$ had a decent IC_{50} value of 2.217 μM, and a scoring function of -250.473 formed 9 hydrogen bonds. It did interact sterically, and hydrophilically with the following residues Tyr158, Gln 279, Arg442, Arg315, Tyr316, Arg446 only showed hydrophilic interactions. Gln279 amine group interacted as a donor with the oxygen and nitrogen of the ligand's isoxazole. Tyr158 hydroxyl interacted with the oxygen within the cyclic ring of the ligand. Arg315 amine interacted as a donor with the ligand oxygen atom of sulfonamide. Tyr316 hydroxyl interacted with the oxygen atom of sulfonamide within the ligand compound. Arg442 and Arg 445 both interacted as donors through their activating amide groups with the oxygen and nitrogen of the isoxazole ligand ring. S1M-S3 with the least potent IC_{50} value of 8.976 μM and a scoring function of -150.73 formed 5 hydrogen bonds it exhibited hydrophilic and steric interaction with each of Arg442, Ser241, Ser157, and Lys156. Arg442 interacted as a donor through the amide group with nitrogen and oxygen of the substituted isoxazole ligand ring. Ser157 oxygen interacted as an acceptor with the hydroxyl of the ligand. Lys156 carbonyl oxygen acted as an acceptor with the hydroxyl of the ligand's phenol ring. Ser241 interacted through the hydroxyl groups on both sides of the ligand-receptor complex. The observed results indicated that the presence of electron-donating moieties (Alcohol and Amino groups) and ring activation at ortho and para locations could be ascribed to the potency of all ligands; these sites tend to be taken by incoming groups faster, resulting in higher enzyme activity (Uddin *et al.* 2020). In this scenario, the biological activity of the compounds against a receptor (alpha-glucosidase) is mainly determined by its binding, which is determined by its

electrostatic property and steric orientation. Minor structural variations are frequently associated with a significant level of biological variety (Tripathi *et al.* 2013, and Zhou *et al.* 2006), demonstrating the importance of the inhibitor's ability to form hydrogen bonds with the alpha-glucosidase catalytic residues in the inhibitory activity. Such hydrogen bonds can generally develop between an acceptor on the enzyme residue and the inhibitor's donor vise-versa. The phenyl hydroxyl group was essential for the ligand's inhibitory effects (Misra *et al.* 2012). The oxygen and nitrogen in the isoxazole cyclic group, the nitrogen in the amine group, and the oxygen and nitrogen in the sulfonamide group were all required for hydrogen bond formation. The ligand nitrogen and oxygen atoms played a significant role in forming hydrogen bonds with amino acids at the active site. Docking experiments further revealed that the ligand's isoxazole ring methyl groups induce steric hindrance during the molecule's contact with the alpha-glucosidase enzyme. The presence of two methyl groups may have further reduced the compound's interactions and flexibility, resulting in poor binding affinity (Alyar *et al.* 2019). Finally, sulfa-Schiff bases ligands have demonstrated the potential for new practical uses, such as the development of novel therapeutic reagents for diabetes. The alpha-glucosidase inhibitory activity of docked complexes was assessed. Almost all of them showed good -glucosidase inhibition with IC_{50} values ranging from 0.429 to 8.976 μM low micro-molar and starting concentrations ranging from 0.3949 mM to 2.6809 mM. $Cu(S2M\text{-}S1)_2$ with an IC_{50} value of 0.429 μM, the 2 Schiff base copper complex demonstrated the most potent inhibitory activity of the produced compounds. In terms of drug design, simultaneous administrations of tested ligands may be a potential technique for increasing inhibitory efficacy. This virtual inhibition analysis suggested that this class of sulfa drug derivatives may provide a novel chemical class of therapeutic medicines for type 2 diabetes treatment (Zheng and Ma 2016).

6. CONCLUSIONS AND RECOMMENDATION

The metabolic condition Diabetes type 2 is distinguished by persistent hyperglycemia. It is associated with a lower life expectancy due to an increased risk of heart disease, stroke, peripheral neuropathy, blindness, renal failure, and amputation. AGIs are a subclass of oral hypoglycemic agents that are approved for the prevention and treatment of type 2 diabetes. Three AGIs, acarbose, miglitol, and voglibose, are available for the treatment of type 2 diabetes. Despite the fact that these AGIs are safe drugs, a recent systematic search for novel alpha-glucosidase inhibitors was conducted using high-throughput screening of pharmaceutical libraries. Along the compounds discovered, sulfa drug derivatives were chosen to interact with ligands containing Schiff bases because of the high occurrence and usefulness of these chemical structures in biological processes, as well as their potential utility in the development of novel therapeutic medicines. In this thesis, 9 ligand complexes of sulfa drug compounds were tested in vitro using docking and spectroscopic approaches. Cu(S2M-S1)2 with two substituted active iso-oxazole rings and two sulfonamide accepting groups displayed the most potent inhibitory efficacy among these compounds, with an IC50 value of 0.429 μM, making it as effective as a typical acarbose drug. The findings suggested that utilizing metal ions in sulfa- Schiff base compounds could be a potential path for improving alpha-glucosidase inhibitory activity. It may also potentially lead to developing a unique chemical class of therapeutic drugs for the treatment of type 2 diabetes.

Recommendations

- Further studying the correlation between sulfa-Schiff bases ligands and α-glucosidase inhibition.
- Further studying the in vivo reaction to Copper and Palladium sulfa-Schiff bases ligands.
- Further studying the correlation between different Copper and Palladium sulfa-Schiff bases ligands on alpha glucosidases side residues.

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