



Original article

Exploring the therapeutic potential of benzothiazine-pyrazole hybrid molecules against alpha-glucosidase: Pharmacological and molecular modelling based approach



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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder and a significant health problem all over the world. The current study elucidates the inhibitory potentials of the benzothiazine-pyrazole hybrid series against the α -Glucosidase enzyme. The molecular docking was employed to determine the binding affinity of synthetic compounds (ligands) with α -Glucosidase enzyme (receptor) active sites via the molecular operating environment (MOE). The molecular docking analysis revealed the best inhibitory interaction between certain synthetic compounds and the enzyme's active sites (α -Glucosidase). These compounds were further examined for drug-like properties, which necessarily validate the use of the compound as a drug. Then selected compounds were subjected to *in vitro* analysis to find the inhibitory potential with minimal dose. All compounds were docked into the active sites with the best binding pose and low rmsd values. The anti-diabetic analysis revealed that compound ST3 is more active against α -Glucosidase with IC₅₀ values 5.8 μ M as compared to acarbose which is 58.8 μ M. The present study exhibited compound 2c has a high proficiency in lowering blood glucose levels compared to acarbose. This study strengthened the scope of designing/synthesizing these benzothiazine-pyrazole hybrid molecules as anti-diabetic drug molecules in the pharmaceutical industry.

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1. Introduction

Diabetes mellitus is mainly characterized by hyperglycemia and disturbance/imbalance in carbohydrates, lipid, and protein metabolism (Abdelalim 2021). Hyperglycemia for an extended period may damage the vital body organs that may lead to neuropathy, nephropathy, cardiovascular diseases. DM is classified into two groups based on insulin secretion, Type I DM and type II DM. In type I DM, beta cells don't produce enough insulin to meet the body's requirements, and the glucose level increases in the blood-streams (Khademi et al., 2021). As it requires insulin, It is

also known as insulin-dependent diabetes mellitus. Secondly, Type II diabetes mellitus body cells become resistant to insulin due to pancreatic cells' low production of insulin hormone (Thaiyalnayaki 2021). Symptoms of post-prandial hyperglycemia include frequent urination, hunger, blurred vision, high blood sugar level right after the meal, and post-prandial plasma glucose level in diabetic patients is 200 mg/dL (Taj et al., 2019).

Diabetes, also known as the mother of all diseases and long-term hyperglycemia, may damage organs, including cardiovascular disorder, atherosclerosis, neuropathy, and nephropathy (Nanayakkara et al., 2021). Different type of enzymes within the body takes part in the breakdown and absorption of complex sugars into absorbable simpler sugars. An α -Glucosidase enzyme located in the brush border of the small intestine helps absorb simpler sugars in the upper jejunum of the small intestine (Taj et al., 2019). Another enzyme, α -Amylase also involved in the digestion of carbohydrates. Keeping in mind the importance of the primary purpose of this study is to inhibit the α -Glucosidase enzyme from stopping the absorption of simpler carbohydrates.

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α -Glucosidase inhibitors (AGIs) like acarbose, voglibose, and miglitol are available in the market, lowering the risk of hyperglycemia. AGIs inhibit the conversion of oligosaccharides by the enzyme that ultimately reduces the blood glucose level in type II diabetes. The available forms of AGIs have side effects like flatulence, diarrhea, and abdominal pain (Miller and Joubert 2021, Yang et al., 2021, Yu et al., 2021). Thus, there is a need to design an effective and safe drug against α -Glucosidase. For this purpose, a series of synthetic compounds are synthesized. pyrazolobenzothiazine 5,5-dioxide ring system is the structural hybrid of two bioactive heterocyclic compounds pyrazole and benzothiazine. pyrazole is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen atoms. Benzothiazine derivatives are best for biological activities such as., anti-inflammatory, anti-tumor, and anti-microbial activities (Kumar et al., 2012, Ahmad et al., 2014).

This study includes the *in-silico* molecular docking to find the potential drug compound from the series. Compounds selected from docking analysis are then subjected to *in-vitro* analysis (enzyme inhibition assay). However, ADMET analysis was also performed to check the drug-like properties of the synthetic compounds. And this will help to investigate the *in-silico* and *in-vitro* anti-diabetic activities of pyrazolobenzothiazine-5,5-dioxide derivatives to reduce the hyperglycaemic risk.

2. Materials and methods

2.1. Molecular docking

The 3D structure of an α -Glucosidase enzyme was retrieved from Protein Data Bank (PDB ID: 2QMJ). The retrieved structure was prepared for docking via removing ligand and solvent residues. The energy minimization and protonation of 3D structure was performed through Molecular Operating Environment (MOE, 2014.0901) on default parameters (Inc. 2016, Javaid et al., 2020). Docking site containing Asp(203), Asp(542), Asp(327), His(600), Arg(526) residues was selected through site finder, and dummies atoms were created on that site.

2D structure of synthetic compounds (Fig. 1) was drawn by Chem-Draw Ultra 12.0 and saved in '.sdf' format. (Li et al., 2004). The ligand optimization was done by adding partial charges through Protonate 3D and MMFF94X force field for energy minimization. (Inc. 2016). The optimized ligands were then added into the MOE ligand database for docking run. After docking, the best and top conformation were determined based on S-score, RMSD value, and interacting residues (Javaid et al., 2020).

2.2. Drug-likeness and ADMET analysis

Compounds with the best docking score and interaction were further checked for drug-likeness via Lipinski's rule of five (Ro5) (Benet et al., 2016). Drug likeness analysis of synthetic compounds was performed through online server Molinspiration (<https://www.molinspiration.com/>) and their physicochemical properties, and ADMET analysis was predicted through admetSAR. (<http://lmmd.ecust.edu.cn/admetSar2/>) (Yang et al., 2018).

3. In-vitro analysis

3.1. Sample preparation

Pyrazolobenzothiazine derivatives were synthesized according to our reported methodology (Ahmad et al., 2013). 10 mM stock solution of compounds ST1, ST2 and ST3 were prepared in dimethyl sulfoxide (DMSO, Sigma-Aldrich) and stored at room

temperature. The working solution of 500 μ M in DMSO was made for further enzyme inhibition analysis.

3.2. Enzyme inhibition assay (Anti-diabetic)

The enzyme α -Glucosidase (obtained from *Saccharomyces cerevisiae* (G5003, Sigma-Aldrich) was dissolved in phosphate buffer (pH 6.8, 100 mM). 12.5 μ L of each test compound (dissolved in DMSO), 40 μ L of the enzyme (0.5 U/mL), and 120 μ L of phosphate buffer (100 mM) were added in 96-well microtiter plates. The plates were incubated for 5 min at 37 °C. After incubation, 40 μ L of 5 mM *p*-nitrophenyl- α -D-glucopyranoside (Sigma Aldrich) was added to each sample solution and incubated for a further 30 min. After this, the absorbance of released 4-nitrophenol was measured at 405 nm and 37 °C using a microplate reader. DMSO and acarbose (Sigma-Aldrich) were used as negative control and positive control, respectively. The experiment was repeated thrice, and the inhibitory potential of synthetic compounds was calculated using the formula.

$$\%inhibition = \frac{Blank - Sample}{Blank} * 100$$

Where Blank indicates, the well contains only DMSO in place of the sample. MIC was performed through the microdilution method, and the IC50 of tested compounds was calculated.

3.3. Statistical analysis

All statistical analyses (standard deviation, percentage inhibition, and IC50) were performed through Microsoft excel 365.

4. Results

4.1. Molecular docking

Molecular docking was attained to determine the distinct conformation of the sample with α -Glucosidase (PDB: 2QMJ). The compounds were examined based on rmsd value, docking score, and binding residues. The RMSD value (route mean square value) calculates the deviation of a protein molecule from normal dimensions. The lowest rmsd indicates the best binding pose. The docking score predicts the binding affinity between two molecules that are docked. The lowest value of the docking score denotes a high efficiency of a ligand molecule to bind with protein. Interacting residues show the binding of the ligand with the desired pocket (binding site) of the protein molecule.

Among ten conformations, three compounds were selected that exhibited the best pose with low rmsd and docking scores. Compound ST1 has 1.597 rmsd and showed interaction with Arg (526), Asp(542), Asp(203), Asp(327) with -11.0127 docking score. Compound ST2 exhibit only three (Arg(526), Asp(542), Asp(327) with 1.760 and -11.572 rmsd and docking score respectively. Although compound ST3 has good rmsd (1.222) as compared to compound ST1 and ST2 but it interact only with two residues (Arg(526), Asp(327)). In comparison to these acarbose showed three interactions Asp(542), Asp(203), Asp(327) with 1.791 rmsd, and -16.312 docking score (Table 1). 2D interactions and a 3D map view of the ligand with the receptor (2QMJ) validate the best binding pose (Fig. 2).

4.2. Drug-likeness analysis

The drug-likeness of the proposed α -Glucosidase inhibitors was predicted through the Molinspiration server (Table 2). Compound ST3 passes the oral bioavailability and drug safety profiling as it showed less molecular weight < 400 Da and log p value < 120.

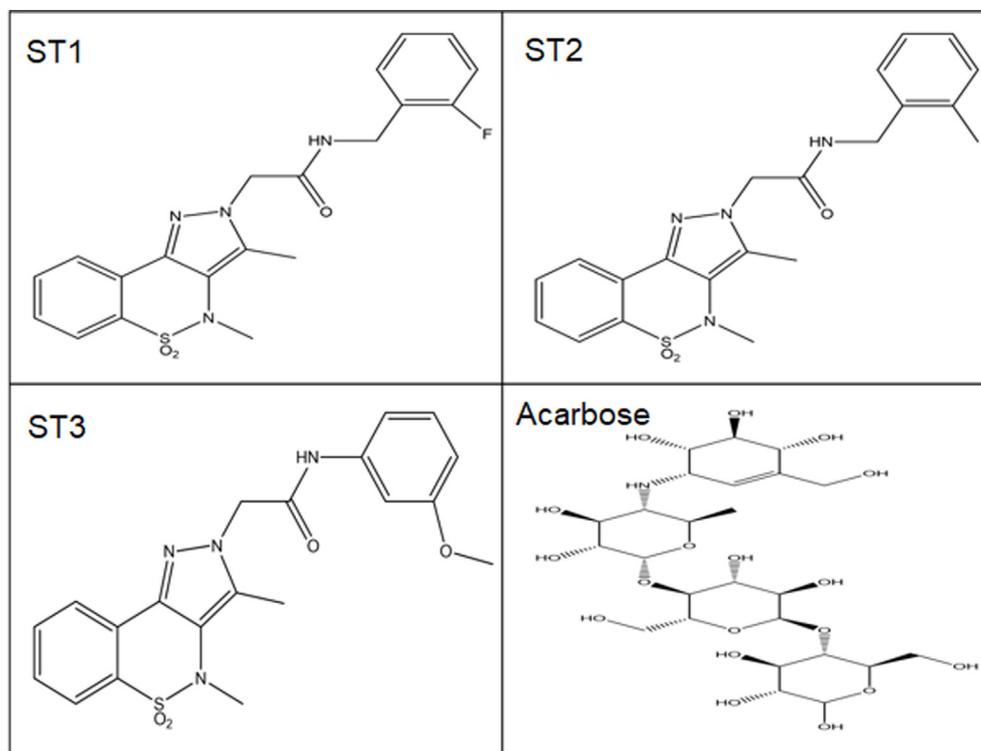


Fig. 1. Chemical structures for synthetic compounds.

Table 1
Interaction detail of three compounds into the active site of α -Glucosidase.

Structures Code	Docking Results			In-vitro IC50 μ M
	Docking Score	Interaction Residue	RMSD	
ST1	–11.0127	Arg (526), Asp(A203), Asp (542), Asp(A327)	1.597	65 \pm 0.021
ST2	–11.572	Arg (526), Asp (542), Asp(A327)	1.760	103 \pm 0.193
ST3	–13.665	Arg (526), Asp(A327)	1.222	5.8 \pm 0.251
Acarbose	–16.312	Asp-(203), Asp-(542), Asp-(327), His-(600), Thr-(205)	1.791	58.8 \pm 0.058

All three compounds are also proved non-carcinogens, non-toxic, and positive Human intestinal absorption and don't cross the blood–brain barrier (Table 3). All these parameters validate the use of synthetic compounds as a safe drug.

4.3. *In-vitro* enzyme inhibition assay

In-vitro enzyme inhibition for α -Glucosidase was achieved to determine the inhibitory effect of pyrazolobenzothiazine synthetic compounds and standard drug acarbose (IC50 at 58.8 μ M). Compared to acarbose compounds ST1, ST2, and ST3 showed IC50 at 65 μ M, 103 μ M, and 5.8 μ M concentrations, respectively, with high percentage inhibition (Table 1). Compound ST3 exhibits less IC50 among all the tested compounds with high efficacy so, it might be used as a potential drug for diabetes treatment.

5. Discussion

Diabetes mellitus, a metabolic disorder, results in hyperglycemia affecting a large population worldwide. Long-term hyperglycemia may damage other vital body organs functionality and lead to heart failure, neuropathy, retinopathy, and nephropathy. As it leads to organ failure, it has become a major concern nowadays. So, there is a need to lower the risk of hyperglycemia to minimize the diabetes complication (Taj et al., 2019). Many

drugs (acarbose, voglibose) are available in the market that are used as α -Glucosidase inhibitors. This study is being designed to investigate the therapeutic potential of synthetic compounds against hyperglycemia with fewer side effects and high potency (Taj et al., 2019).

Ligand–protein interactions were found out via molecular docking of pyrazolobenzothiazine compounds with the α -Glucosidase enzyme. Compounds 3 having oxygen atom at benzene ring showed low rmsd (1.222) and best binding pose (Arg (526) and Asp(A327), as compared to acarbose and other tested compounds. It was observed that compound ST1 having fluorine atom at 2 possess –11.012 docking score, rmsd value 1.597 with residues Arg (526), Asp(A203), Asp (542), and Asp(A327). Compound ST2 has a –11.572 docking score, rmsd 1.760, and residues Arg (526), Asp (542), and Asp(A327). All molecular docking results predict the active potential of synthetic compounds Table 2. Molecular docking analyses of synthetic compounds are also reported in different studies that validate the use of synthetic compounds as a potential drug in diabetes (Khan et al., 2021, Saddique et al., 2021, Saleem et al., 2021, Shareghi-Boroujeni et al., 2021). The drug-likeness and safety profiling of test compounds also strengthens the study because compound ST3 passes all the drug safety tests and rules and is predicted as non-toxic and non-carcinogens.

These compounds were further exposed to *in-vitro* anti-diabetic analysis to check the inhibitory concentration of synthetic compounds against α -Glucosidase based on high docking profile. All

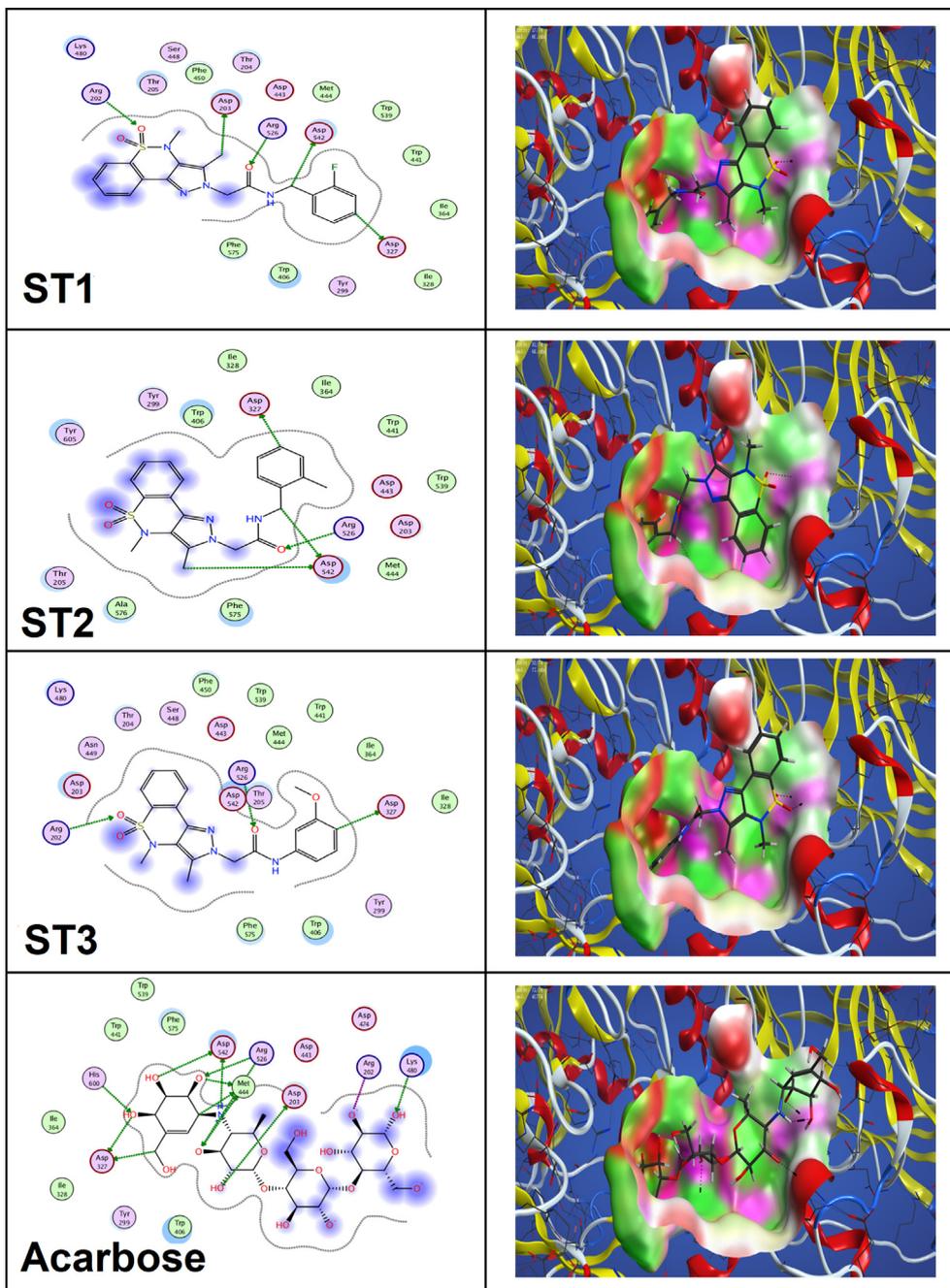


Fig. 2. The binding poses of compounds.

Table 2
Results of compounds examined for Lipinski rule.

virtual hits	Oral Bioavailability			ADMET	Drug Safety Profiling GSK 4/400 RULE
	LRO5	Veber rule	Egan rule		
1	✓	✓	✓	×	×
2	✓	✓	✓	×	×
3	✓	✓	✓	✓	✓

✓; Compounds fulfilled the criteria, ×; couldn't pass the criteria

the compounds show high inhibition of α - Glucosidase. But only compounds ST3 showed IC₅₀ at a concentration of 5.8 μ M compared to other tested samples ST1 and ST2 that exhibits high IC₅₀ at 65 μ M, 103 μ M concentration respectively (Table 2).

Synthetic compounds anti-diabetic activity has already been performed, showing its potential to inhibit α - Glucosidase enzyme with minimal IC₅₀ (Gong et al., 2017, Azimi et al., 2021, Saleem et al., 2021).

Table 3
ADMET Profiling Enlisting Absorption, Metabolism and Toxicity related drug-like parameters of synthetic compounds.

ADMET analysis																	
	BBB	HIA	solubility	P-gp			CYP450 substrate			CYP450 inhibitor				CYP IP	AMES toxicity	cocarcinogens	
				substrate	Inhibitor	ROCT	2C9	2D6	3A4	1A2	2C9	2D6	2C19				3A4
1	-	+	-3.53	+	-	-	-	-	+	-	-	-	+	+	high	-	-
2	-	+	-3.36	+	-	-	-	-	+	-	-	-	+	-	high	-	-
3	-	+	-3.82	+	-	-	-	-	+	-	+	-	+	+	high	-	-

ADMET, absorption distribution metabolism elimination and toxicity; BBB, blood-brain barrier; HIA, human intestinal absorption; CYP450, cytochrome P450; CYP IP, CYP inhibitory promiscuity; ROCT, renal organic cation transportation; +, present; -, not present.

Pyrazolobenzothiazine is a class of compounds with many reported activities like anti-cancer, anti-HIV anti-oxidant, and antibacterial activity (Kumar et al., 2012, Ahmad et al., 2014). The already registered pyrazolobenzothiazine compounds have anti-diabetic activities at a minimum dose of 4.7 μM (Taj et al., 2019). *In-silico* and *in-vitro* analysis of synthetic compounds confirm their anti-diabetic potential provides a non-toxic and economical alternative for hyperglycemic drugs. Furthermore, the titled compounds were studied through molecular docking. Molecular docking helps to predict a protein's interactive behavior with a small molecule that can either be a ligand or another protein (Sethi et al., 2019, Tahir Ul Qamar et al., 2019). It provides an ideal tool for the virtual screening of compounds for drug designing and discovery.

Moreover, virtual screening reduces the effort in terms of human resources and cost to discover a new compound with targeted biological activity. (Vilar et al., 2008, Khalid et al., 2020). The study demonstrated that synthetic compounds ST1, ST2, and ST3 possess high anti-diabetic potential. Among these, ST3 exhibited high activity at a low dose (5.8 μM). Based on the docking score, the studied compound showed excellent binding affinity.

6. Conclusion:

In-silico molecular docking and anti-diabetic activity of compounds ST1, ST2, and ST3 are reported first time in this research. The current study highlights the top three active synthetic compounds that exhibit good inhibitory potential against α -Glucosidase. Among three compounds, ST3 showed higher activity at a low concentration (5.8 μM) than the positive control acarbose and other tested samples. However, the ST3 compound is non-toxic and non-carcinogenic and passes all the drug safety profiles. Therefore, it was concluded that ST3 might be a potential drug against hyperglycemia with fewer side effects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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