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DESIGNING, SYNTHESIZING, AND ASSESSING THE BIOLOGICAL ACTIVITY OF INNOVATIVE THIAZOLIDINEDIONE DERIVATIVES WITH DUAL FUNCTIONALITY

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Abstract

The pharmacological potential of derivatives of thiazolidine-2, 4-dione (TZD) as treatment agents for type 2 diabetic mellitus (T2DM) is examined in this research. The study clarifies the complex pharmacological profile of TZD derivatives by thoroughly examining their inhibitory effects on significant catalysts engaged with glucose digestion, like aldose reductase, α-amylase, α-glucosidase, protein tyrosine phosphatase 1B (PTP-1B), and di-peptidyl peptidase-4 (DPP-4). A manufactured methodology depicted in the Materials and Strategies segment was utilized to combine TZD subsidiaries. Further natural investigation showed that TZD subordinates fundamentally hindered the exercises of α-amylase and α-glucosidase, suggesting that they might postpone the gut's absorption of glucose. Understanding their pharmacological activities may be aided by mechanistic insights, such as interactions with enzyme residues and competitive mode of inhibition. Moreover, TZD compounds showed promise in addressing many pathways connected to the etiology of T2DM, indicating their adaptability as medicinal substances. The study emphasizes how crucial it is to do further investigation into the therapeutic potential of TZD derivatives and their wider implications for the treatment of diabetes.

Keywords: *Thiazolidine-2, 4-dione derivatives, Type 2 diabetes mellitus, Enzyme inhibition, Glucose metabolism, Pharmacological potential*

1. INTRODUCTION

A variety of variables, such as the rise of drug-resistant microorganisms and the emergence of novel infectious illnesses, make treating infectious diseases an ongoing challenge. Hospitalized patients, AIDS patients on immunosuppressive treatment, patients on anticancer therapy, and recipients of organ transplants all face significant therapeutic challenges. Despite the fact that there are many antibiotics and chemotherapeutics accessible for medical use, there is a significant demand for new classes of antimicrobial drugs due to the emergence of antibiotic resistance. Therefore, the development of novel, potent compounds as antibacterial agents is required.

Since they are versatile in their synthesis and have potential applications in medicine, small-ring heterocycles like sulfur and nitrogen have long been studied. Thiazoles have been shown to be essential in medicinal chemistry among the many heterocycles investigated as promising prospects in drug development.

A primary part of a few regular substances, including thiamine (vitamin B1), thiamine pyrophosphate (TPP), carboxylase, epothilones, and the expansive group of macrocyclic thiopeptide anti-microbials that incorporates thiostrepton and micrococcin P1. Many organic properties are connected to thiazole subsidiaries, like hypnotics, anticonvulsants, antimicrobial, antituberculous, bacteriostatic exercises, antiviral, antimalarial, anticancer, hypertension, irritation, schizophrenia, HIV diseases, and all the more as of late, fibrinojen receptor adversaries with antithrombotic movement and new inhibitors of bacterial DNA gyrase B for the therapy of agony. Derivatives of thiazoles are also used in the creation of medications to treat allergies.

The piperazine ring and amide moiety are common components of the molecular structures of several well-known pharmaceuticals today. Piperazines are present in physiologically active compounds with antifungal, antibacterial, antimalarial, and antipsychotic properties, making them one of the most significant building blocks in modern drug development.

Some thiazole-piperazine compounds were shown to have cholinesterase activity in our earlier investigation. We made a clever series of thiazoles-piperazine subsidiaries and analyzed their antibacterial and anticholinesterase capacities to get new organically dynamic mixtures.

Despite the fact that there are numerous antimicrobial prescriptions available, new antimicrobial specialists should be found with improved pharmacodynamic and pharmacokinetic characteristics and few or no unfavorable impacts. With regards to both Gram-positive and Gram-negative microbes, most of thiazolidinediones show solid bactericidal activity. The heterocyclic thiazolidine ring must be substituted for the aromatic moiety in order for thiazolidinedione derivatives to have bactericidal action.

Tiazolidinedione and its subordinates are of interest because of their great many organic and remedial applications. This moiety is of interest to researchers since it regulates a number of physiological processes. Numerous pharmacological activities require heterocyclic molecules that contain both nitrogen and sulfur. Specialists that have orchestrated a scope of thiazolidinedione subsidiaries and assessed them for their different natural properties have become inspired by this. We have attempted to gather biological characteristics of synthetically derived thiazolidinediones and their derivatives in the current investigation.

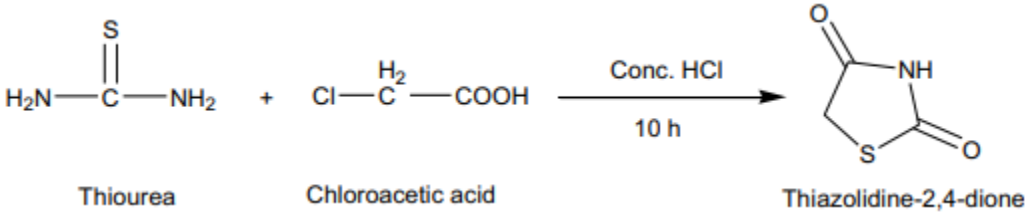

Figure 1: Synthesis of Substituted thiazolidine-2, 4- dione

1.1. Potential antibacterial properties of thiazolidinedione derivatives

Long-standing, communicable illnesses brought on by microbes resistant to drugs have gotten out of control, posing a severe danger to public health and a significant challenge in many nations around the globe. Because of the overuse of antimicrobial medicines in recent decades, there has been a prominent ascent in clinical medication obstruction; as a result, many infectious diseases are now incurable and cannot be effectively treated with standard anti-infective medications. The number of patients with immune suppression is steadily rising as a consequence of contemporary treatments and management strategies including bone marrow or solid organ transplants, as well as more recent, intense chemotherapy. Therefore, the discovery of new antimicrobial drugs is urgently needed to address the aforementioned issues.

Using the broth dilution method, Nawale et al. studied the in vitro antimicrobial movement against two types of Gram-positive microscopic organisms, Bacillus subtilis, Staphylococcus aureus, and Gram-negative microorganisms, Pseudomonas aeruginosa. They likewise incorporated another series of 5-Subbed 2, 4-thiazolidinedione subordinates.

2. LITERATURE REVIEW

Arineitwe, C., Oderinlo, O., Tukulula, M., Khanye, S., Khathi, A., & Sibiya, N. (2023) It is still required to look for new promising molecules for the therapy of this metabolic disease, even when standard pharmaceutical medications are helpful. Based on this, we have created four new thiazolidinedione (TZD) compounds and assessed their anti-diabetic qualities. N-arylpyrrole and TZD were used as the basis for the pharmacophore hybridization technique, which was used to create the TZD derivatives. The resulting compounds were evaluated against important liver (HEP-G2) cell line enzymes involved in glucose metabolism and utilization at various doses. Furthermore, docking experiments were used to activate the receptor-γ that is triggered by peroxisome proliferator. Strong binding, akin to rosiglitazone, was expected upon docking these compounds against PPAR-γ. As a result, when TZDD2 was added to the control, the liver cells' ability to absorb glucose was increased.

Hu, C., Liang, B., Sun, J., Li, J., Xiong, Z., Wang, S. H., & Xuetao, X. (2024) To create α-glucosidase inhibitors that may have antidiabetic properties, in particular, showed the highest inhibitory effect against α-glucosidase (IC50 = 2.35 ± 0.11 μM). Compound IT4's inhibitory mechanism on α-glucosidase was elucidated using kinetics investigations, molecular docking, CD spectra, fluorescence quenching, and 3D fluorescence spectra.

Sameeh, M. Y., Khowdiary, M. M., Nassar, H. S., Abdelall, M. M., Alderhami, S. A., & Elhenawy, A. A. (2021) The goal of this study was to use spectral data to manufacture safe anti-hyperglycemic derivatives containing thiazolidinedione fragment. Molecular docking simulations were run into the α-amylase and PPAR-γ active sites. We assessed the potency and radical scavenging abilities of α-amylase in vitro. Other participants showed little to negligible anti-diabetic efficacy. When compared to the evaluated biochemical parameters (HDL, LDL, and CH), all substances showed normal values. Good oral bioavailability was shown by the ADMET profile, and no carcinogenic impact was seen.

Zheng, Y., Lu, L., Li, M., Xu, D., Zhang, L., Xiong, Z., ... & Xu, L. (2024) Synthesis and evaluation of a series of chromone derivatives carrying thiazolidine-2,4-dione moiety were conducted in HepG2 cells stimulated with palmitic acid (PA) to assess their effects on the insulin pathway, interaction analysis, and PTP1B inhibitory activities. The findings demonstrated that, in comparison to the positive control drug lithocholic acid (IC50: 9.62 ± 0.14 μM). The CD spectra data verified that compound 9 interacted with PTP1B to alter its secondary structure. Molecular docking elucidated the intricate binding mechanism between PTP1B and compound 9. Compound 9 demonstrated a 19-fold increase in PTP1B selectivity compared to TCPTP. Furthermore, compound 9 might reverse the insulin resistance caused by PA via phosphorylating IRSI and AKT. According to CETSA findings, compound 9 considerably improved PTP1B's thermal stability.

Ibrahim, A. M., Shoman, M. E., Mohamed, M. F., Hayallah, A. M., & El-Din A. Abuo-Rahma, G. (2023) One of the favored heterocyclic rings, thiazolidinedione (TZD) has shown several biological uses in medicinal chemistry and drug development. The synthetic approaches of TZD and its derivatives, various synthetic methods for achieving the required region- and stereo-selectivity, and methods to improve reaction conditions, including microwave, one-pot, or ultrasonic synthesis, are all covered in this study. It focuses on the problems associated with synthesizing glitazones and converting other heterocycles to TZD. Furthermore covered are the chemical and biological properties of TZD as a result of N3 position replacement, C5 position alteration, annealing in intricate heterocyclic systems, and hybridization with additional pharmacologically appealing moieties.

3. METHODS AND MATERIALS

3.1. Biological Investigation

3.1.1. α-Amylase and Glucosidase Inhibition Analysis

With minor changes, the Worthington Catalyst Manual's methodology was utilized to discover the inhibitory movement of α-amylase. Tests were coordinated on the TZD auxiliaries at 10, 20, 30, 40, and 50 μg/mL. The through and through control included all of the reagents used, with the exception of the inhibitor compounds, while the positive control contained. As a clear, sodium phosphate cushion was utilized.

3.1.2. Alpha Glucosidase Inhibition Mechanism Analysis

To evaluate the dynamic constants and inspect the way of obstructing the normal compound α-glucosidase by the most excellent subordinate, the evaluation employed the Michaelis-Menten and Lineweaver-Burk plots. The growth of this synthetic was shown to be restricted at two clear core interests, 60 and 120 μg/mL, or twice its IC50, in both the presence and absence of TZDD3. Using GraphPad Gem 9.2.0, the Ki values were obtained by plotting the auxiliary centers (x-turn) versus the equivalent of the most extravagant speed. With GraphPad Gem 9.2.0, the inhibitory limit types were unquestionably determined. To summarize, 30 μL of α-glucosidase protein was separated in 0.02 M phosphate support and pre-brought forward with the recently referred auxiliary for 5 minutes at 37 °C in a 96-well plate. The reaction mixture was

supplemented with pNPG at the following concentrations: 0.125, 0.250, 0.500, 0.750, 1.000, 1.500, 2.000, 2.500, and 5.000 mM. After that, the mixture was tortured for 30 minutes at 37 °C.

3.1.3. Assessment of Protein Tyrosine Phosphatase Inhibitory Activity

With some modifications, the show described by Tune et al. A protein tyrosine phosphatase-1B (PTP-1B) restriction assay was subsequently performed. Sodium orthovanadate (Na3VO4) was used as a positive control and limits of 10, 20, 30, 40, and 50 µg/ml were determined.

3.1.4. Dipeptidyl Peptidase-4 Inhibition Analysis

In this study, we followed the item data for the DPP-4 inhibitor screening unit with some minor volume changes to allow measurements in 96-well plates.

3.1.5. Silico Docking of Peroxisome Proliferator–Activated Receptor-γ

The 3D diamond structure of peroxisome proliferator-qualified gamma receptor (PPAR-γ) was extracted from a protein database. Protein placement wizard in AutoDock 4. 2 was used to create proteins for docking. Ligands were organized using Openbabel 2.4.1 programming to provide pbdqt structures and ChemDraw AcdLabs programming to create .dxt plans. The components of the organizing center around the X, Y, and Z axes were 60 × 60 × 60.

3.1.6. Statistical Analysis

Every experiment was conducted twice and in duplicate. Each examination's information were genuinely investigated utilizing GraphPad Crystal 9.2.0. To decide the meaning of the distinction between a test compound and the outright control, further factual investigation was completed utilizing a one-way ANOVA and a Tukey-Kramer post hoc test. Estimates of absorbance or fluorescence were used for the factual analysis prior to any normalization. The significance of the facts was recognized at the $p < 0.05$ level.

4. RESULTS

4.1. α-Amylase Function

The inhibitory effects of TZD subordinates on α-amylase activity are shown in Figure 5. As opposed to the control, TZDD3 showed fixation subordinate inhibitory activity, with focuses more than 30 µg/mL exhibiting measurable importance. Looking at TZDD1, 2, and 4 to the control, all dosages showed critical inhibitory activity. Acarbose showed a critical inhibitory movement at all measurements. TZDD2 had unparalleled inhibitory execution among the four TZD auxiliaries broke down in the α-amylase block investigate, with an IC50 worth of 18.24 µg/mL.

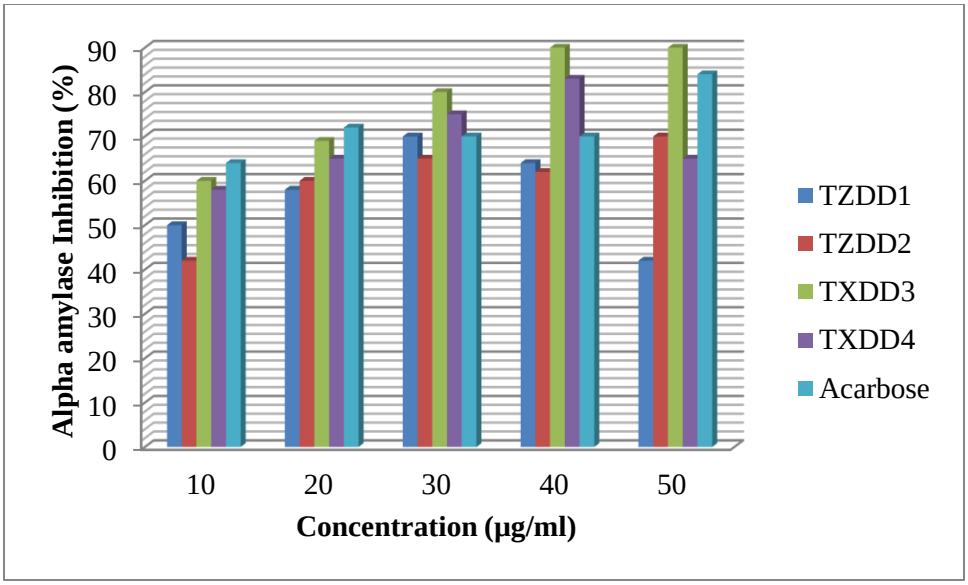

Figure 1: Restraint of α-amylase movement by TZD subsidiaries (10-50 µg/mL). Results are in a bunched segment. Information is displayed as mean ± standard deviation. Bullets (*) show critical factual contrasts contrasted with the control explore (p esteem < 0.05). Mistake bars address standard blunders of the means.

Table 1: IC50 values for TZD auxiliary in inhibitory activity testing for aldose reductase, α-amylase, α-glucosidase, PTP-1B, and DPP-4 (n/a = not important)

The Inhibitory Activity Assays' IC50 values (µg/mL)					
Compounds Name	**Structure α–Amylase**	**α–Glucosidase**	**AR**	**PTP-1B**	**DPP-4**
TZDD1	35.76 ± 3.42	267.26 ± 22.68	38.63 ± 6.45	unstable	64.13 ± 6.68
TZDD2	29.35 ± 1.21	265.48 ± 5.46	91.36 ± 8.87	247.98 ± 5.17	42.82 ± 4.35
TZDD3	36.86 ± 1.82	47.91 ± 1.51	68.54 ± 8.71	unstable	64.73 ± 5.46
TZDD4	35.17 ± 3.37	786.81 ± 3.56	47.88 ± 6.21	367.67 ± 2.58	82.72 ± 3.43
Acarbose	56.11 ± 7.81	55.73 ± 8.54	n/a	n/a	n/a
Quercetin	n/a	n/a	45.82 ± 22.26	n/a	n/a
Na3VO4	n/a	n/a	n/a	Unstable	n/a
Sitagliptin	n/a	n/a	n/a	n/a	4.42 ± 1.56

4.2. Alpha-Glucosidase Activity

Figure 6 illustrates how TZD subordinates reduce the activity of α-glucosidase. TZDD1-4 showed quantifiable importance for inhibitory adequacy at all doses as compared to the control. At every measurement, acarbose exhibited a crucial inhibitory movement. Among the four TZD subordinates that were dissected, TZDD3 had a stronger inhibitory impact in the effort to restrict α-glucosidase, as evidenced by a lower IC50.A decrease in Vmax and Km deviated from the uncontrolled reaction was found by the powerful analysis of α-glucosidase restriction using Michaelis-Menten and the Lineweaver-burk plot engine evaluation by TZDD3.

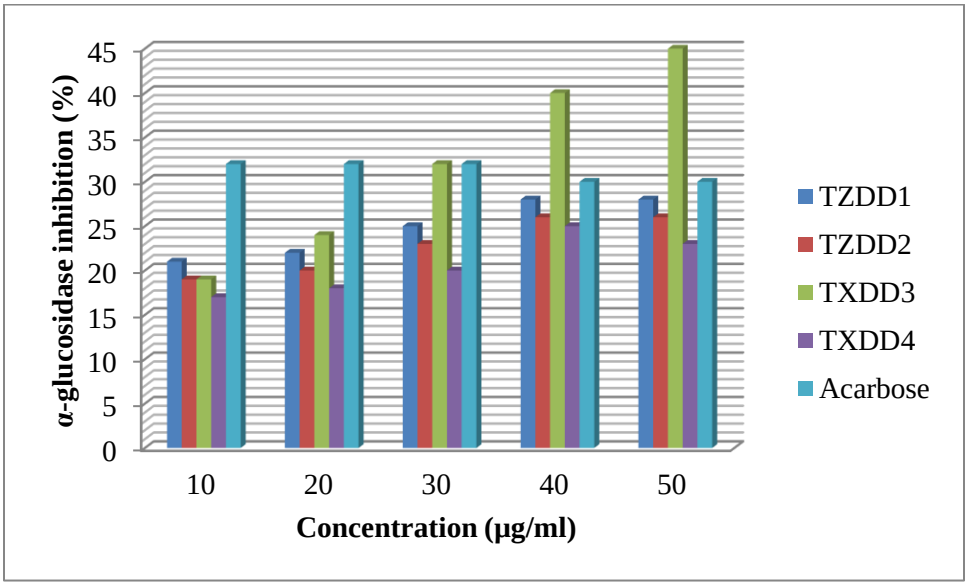

Figure 2: Results are in a grouped segment. Data are shown as mean ± standard deviation. Reference marks (*) show colossal authentic differences stood out from the control investigate (p regard < 0.05). Goof bars address standard mix-ups of the means. The right bolt pointing at the example at 0.0 demonstrates the negative control, which has zero percent block for data normalization

Table 2: Michaelis-Menten experiments, TZDD3 are introduced to the substrate to assess its influence on α-glucosidase inhibition

	Control	**TZDD3 (60 µg/mL)**	**TZDD3 (120 µg/mL)**
Vmax	42.37	60.52	43.87
Km	4.368	11.35	5.665

4.3. Aldose Reductase Activity

The impact of TZD auxiliaries on aldose reductase activity restriction is shown in Figure 7. Each TZD subsidiary showed inhibitory activity; in any case, the inhibitory movement of TZDD1 was fixation subordinate. Whenever TZDD1-4 was diverged from the control, all measurements showed enormous inhibitory action. Exactly as expected, quercetin showed a critical inhibitory effect at all doses. TZDD1 displayed unmatched inhibitory execution among the four TZD subordinates assessed in this aldose reductase deterrent attempt, with an IC50 worth of 36.45 µg/mL (Table 1)

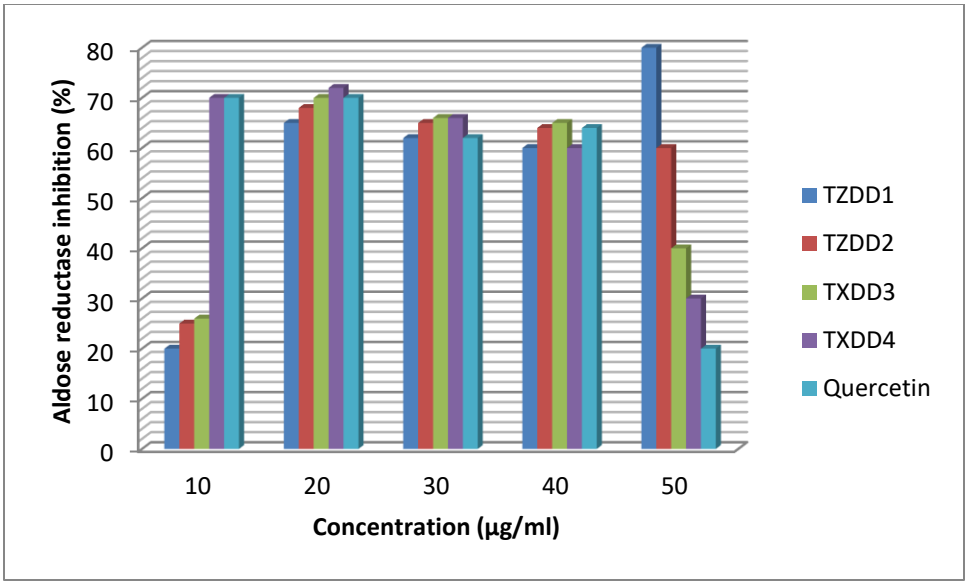

Figure 7: Results are in a grouped segment. Data is shown as mean ± standard deviation. Slugs (*) show immense quantifiable differentiations stood out from the control attempt (p regard < 0.05). Botch bars address standard goofs of the means. The right bolt pointing at the example at 0.0 means the negative control, which has zero percent restriction for data normalization.

4.4. Activity of Protein Tyrosine Phosphatase 1B

The impact of TZD subordinates on protein tyrosine phosphatase 1B activity obstacle is shown in Figure 3. Diverged from the control, all measurements had enormous ($p < 0.05$) inhibitory movement, except for TZDD4, which displayed unassuming inhibitory action. With an IC50 worth of 245.71 µg/mL TZDD2 was the best of the four TZD subordinates concentrated on concerning protein tyrosine phosphatase restraint.

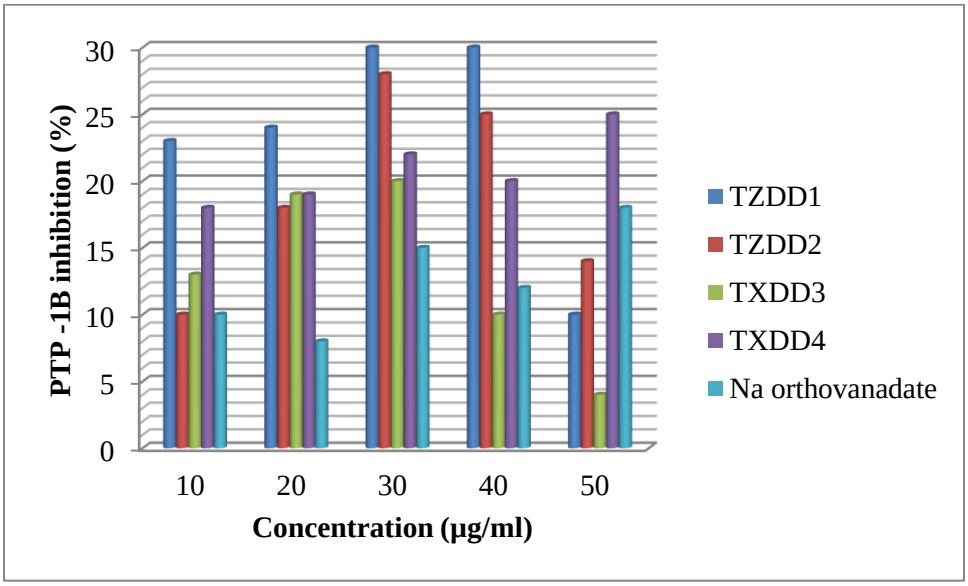

Figure 3: TZD subsidiaries decline protein tyrosine phosphatase 1B action. Results are in a gathered portion. Data are shown as mean ± standard deviation. Markers (*) show enormous genuine differences appeared differently in relation to the control investigate. bars address

standard goofs of the means. The right bolt pointing at the check at 0.0 implies the negative control, which has zero percent limitation for data normalization.

4.5. DPP-4 Activities

The impact of TZD auxiliaries (10, 20, 30, 40, and 50 µg/mL) on DPP-4 inhibitory development is shown in Figure 9. Rather than the control, TZDD2 displayed a nearly expanded movement that was huge at all fixations. Contrasting TZDD1 and 3 with the control, there was next to no inhibitory activity that was not measurably critical ($p < 0.05$). Sitagliptin had a substantial ($p < 0.05$) inhibitory effect on DPP-4 at all concentrations. A decreased IC50 indicates that TZDD2, out of the four TZD subsidiaries examined, was more viable in stifling DPP-4 movement (Table 1). In all four TZDD studies, there was no evidence of dose-dependent activity.

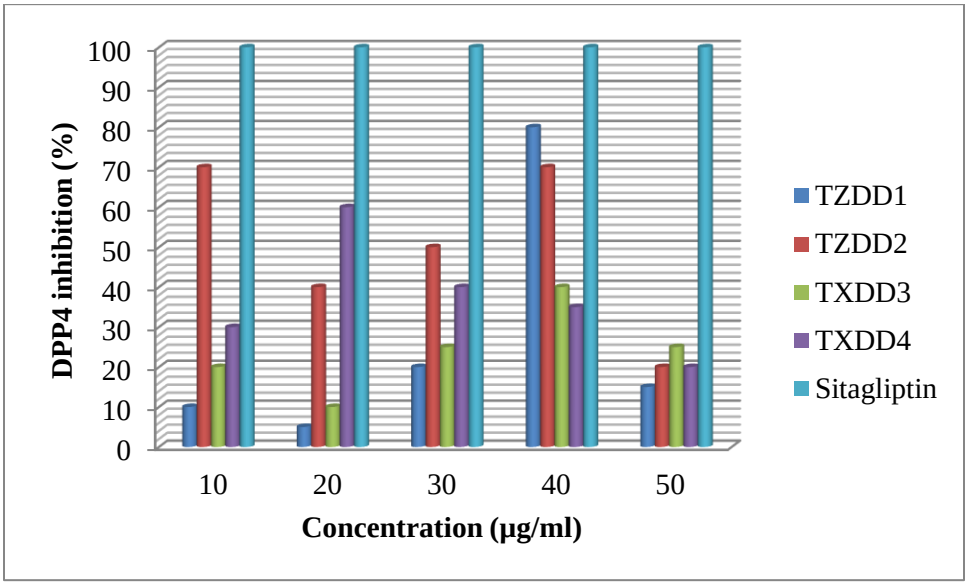

Figure 4: Restraint of DPP-4 action by TZD subordinates (10-50 µg/mL). Results are in a bunched section. Information is displayed as mean ± standard deviation. Indicators (*) show huge measurable contrasts contrasted with the control explore (p esteem < 0.05). Mistake bars address standard blunders of the means. The right bolt pointing at the benchmark at 0.0 means the negative control, which has zero percent hindrance for information standardization.

4.6. Determination of PPAR-γ Activation in Silico

The restricting energies, RMSD values, and associations fundamentally showed the commencement. The correspondence between the TZD subordinates and the PPAR-γ protein is shown in Figure 10. These blends showed various joint efforts, including as hydrogen security interchanges, with the stores of the PPAR-γ protein. Furthermore, rosiglitazone created an interaction with Л-cations. Remarkably, Table 3 also revealed that the derivatives had lower RMSD values than rosiglitazone. With its least restricting energy, assessed hindrance steady, and adaptation, TZDD4 has the most practically identical collaboration to the norm utilized. TZZD1 and the protein's dynamic site are not displayed in the chart since they can't embrace a two-layered conformity. Table 3 shows the LBE, RMSD, and EIK, which were gotten from docking examinations.

Table 3: Lower bound energy (LBE), TZD lower constraint constant (EIC) and root mean square deviation (RMSD) study from docking tests, 298.

Compound	LBE (kcal/mol)	EIC, ki (nM)	RMSD Values
TZDD1	−13.12	2.66	32.56A
TZDD2	−11.51	34.66	36.428A
TZDD3	−9.95	441.41	34.553A
TZDD4	−8.82	63.48	35.288A
Rosiglitazone	−7.54	561.69	35.258A

5. DISCUSSION

In this study, N-heterocycles as stations on N-3 of the TZD platform to establish a TZD subsidiary were used, as various mixtures with these main backbones are known to have organic effects. Our methodology for monitoring type 2 diabetes was to create pharmacological moieties that could target many targets. The effect of TZD subsidiaries on the exercises of α-glucosidase (15-half hindrance) and α-amylase (≥50%) may demonstrate that, as far as clinical practice, unassuming doses are expected to defer the stomach's retention of glucose. In view of the Lineweaver-Burk plot and the high protein liking (Km = 4.556) of TZDD3, acarbose appears to have achieved a cutthroat component of hindrance. This could imply that the subordinate's dynamic utilitarian gathering rivals the substrate to connect to the chemical's dynamic site, obstructing the breakdown of perplexing sugars. Intensifies that show action against α-amylase are repressed by hydrogen bonds and hydrophobic communications with the amino corrosive buildups of the chemical, as indicated by many examinations. The distinguishing proof of lipophilic amino corrosive buildups, including Leu162, Leu165, and Ile235, in the α-amylase active region may provide crucial insights into hydrophobic interactions with inhibitor chemicals. Furthermore, it's possible that functional groups such aliphatic CH groups, carboxylic acid groups, and methoxy groups are essential for binding. We may further propose that, by ¸-stacking, the derivatives' methyl groups and lipophilic tail create hydrophobic contacts with the α-amylase's binding site's amino acid residues. The protein inhibitor complex might get more grounded via hydrogen bonding between the amino acid residues and the ketone group that is conserved on 4C.

6. CONCLUSION

The study's conclusion emphasizes the possibility of subordinates of thiazolidine-2,4-dione (TZD) as feasible choices for the treatment of type 2 diabetic mellitus (T2DM). The study clarifies the complex pharmacological profile of these derivatives by means of a methodical examination of their inhibitory effects on important enzymes involved in glucose metabolism, specifically α-amylase, α-glucosidase, aldose reductase, protein tyrosine phosphatase 1B (PTP-1B), and di-peptidyl peptidase-4 (DPP-4). The compounds of TZD were shown to have noteworthy inhibitory action against α-amylase and α-glucosidase, indicating their ability to postpone the absorption of glucose in the gastrointestinal tract. Understanding their pharmacological activities may be aided by mechanistic insights, such as interactions with

enzyme residues and competitive mode of inhibition. The research also emphasizes the ability of TZD derivatives to target many pathways involved in the etiology of T2DM, demonstrating their flexibility as therapeutic agents. Overall, the results highlight the need for further investigation into the therapeutic potential of TZD derivatives and their wider implications for the treatment of diabetes.

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