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RESEARCH ARTICLE

SYNTHESIS AND α-GLUCOSIDASE INHIBITORY EVALUATION OF *N*-BENZENESULFONYL PYRIDAZINONE

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ABSTRAK

Turunan piridazinon diketahui memiliki berbagai aktivitas biologis, termasuk potensi sebagai antidiabetik melalui penghambatan enzim α-glukosidase. Pada penelitian ini, turunan *N*-benzensulfonil piridazinon, yaitu 6-(3-bromofenil)-2-(fenilsulfonil)piridazin-3(2*H*)-on **(7)**, telah disintesis dan dikonfirmasi strukturnya menggunakan analisis FTIR, ^{1}H-NMR, dan HRMS. Studi *molecular docking* dilakukan menggunakan struktur α-glukosidase lisosomal manusia (PDB ID: 5NN5) untuk memprediksi afinitas ikatan dan interaksi kunci pada sisi aktif enzim. Hasil *docking* menunjukkan bahwa senyawa **7** memiliki *binding score* (*S*) sebesar –10,96, lebih tinggi dibandingkan akarbosa (*S* = –18,24), serta menghasilkan interaksi ikatan hidrogen yang lebih sedikit. Uji penghambatan α-glukosidase secara *in vitro* menggunakan enzim α-glukosidase *Saccharomyces cerevisiae* menunjukkan aktivitas yang lemah, di mana senyawa **7** hanya menghambat enzim sebesar 2,5% pada konsentrasi 50 µM, dibandingkan 47,8% oleh akarbosa. Meskipun sesuai prediksi *docking*, kelarutan senyawa **7** yang sangat rendah diduga berkontribusi terhadap perbedaan signifikan aktivitas biologis tersebut. Dengan demikian, kerangka piridazinon tetap menjadi struktur yang menjanjikan untuk dimodifikasi lebih lanjut guna meningkatkan potensi dan khususnya kelarutan senyawanya.

Kata kunci: Antidiabetes, *docking*, inhibitor α-glukosidase, piridazinon.

ABSTRACT

Pyridazinone derivatives are known for a wide range of biological activities, including potential antidiabetic properties through α-glucosidase inhibition. In this study, the *N*-benzenesulfonyl pyridazinone derivative, 6-(3-bromophenyl)-2-(phenylsulfonyl)pyridazin-3(2*H*)-one (**7**) was synthesized and confirmed its structure by using FTIR, ^{1}H-NMR, and HRMS analyses. Molecular docking was performed using the human lysosomal α-glucosidase structure (PDB ID: 5NN5) to predict its binding affinity and key interactions within the active site. Docking results showed that compound **7** exhibited a binding score (*S*) of –10.96, lower than that of acarbose (*S* = –18.24), and formed fewer hydrogen-bond interactions. The *in vitro* α-glucosidase inhibitory assay using *Saccharomyces cerevisiae* α-glucosidase demonstrated weak activity, where compound **7** inhibited the enzyme by only 2.5% at 50 µM, compared to 47.8% inhibition by acarbose. Although the result as predicted, the poor solubility of compound **7** may have contributed to significant difference of their biological activity. Therefore, the pyridazinone scaffold remains a promising structural framework for further modification to enhance potency and specifically its solubility.

Keywords: Antidiabetic, α-glucosidase inhibitor, docking, pyridazinone.

INTRODUCTION

Diabetes mellitus is a chronic disease caused by insufficient insulin production or insulin resistance. According to the International Diabetes Federation (2025), in 2024 approximately 589 million people were living with diabetes and expected to increase to 853 million by 2050. The number of diabetes cases and affected individuals has continued to rise over the past few decades. One strategy to control blood glucose levels is by inhibiting the activity of the enzyme α-glucosidase. This enzyme functions to break down carbohydrates into glucose in the small intestine. Its inhibition can reduce the absorption of glucose into the bloodstream, thereby lowering blood glucose levels (Neetu *et al*., 2022).

The increasing prevalence and mortality associated with diabetes mellitus has driven extensive efforts to develop effective treatments and preventive strategies. Research on potential antidiabetic agents has been carried out through both the isolation of natural products and the synthesis route (Herfindo *et al*., 2025, Sakulkeo *et al.*, 2022). Advances in technology have enabled the design and synthesis of new drug candidates through structural modification of previously identified bioactive compounds. The discovery of new drugs through modification of known pharmacophores is considered more efficient and straightforward. One of potential candidate is pyridazinone compounds.

Pyridazinones are derivatives of oxo-pyridazine that exhibit a wide range of bioactivities, making them promising candidates for drug development. Several studies have reported pyridazinones to possess analgesic and anti-inflammatory (Hassan et al., 2022), antidiabetic (Assila et al., 2024, Fatisa et al., 2025), antihypertensive (Siddiqui et al., 2010), and anticancer activities (El-Nagar et al., 2024). In particular, (Rathish et al., 2009)successfully synthesized benzenesulfonylurea-substituted pyridazinones, which showed *in vivo* antidiabetic activity and inhibited the increase in blood glucose levels in rats by 67.4%.

Based on the above considerations, herein we reported the synthesize of *N*-benzenesulfonyl pyridazinone derivative using a sealed-vessel reactor. The synthesized compound was evaluated for its ability to inhibit α-glucosidase through *in vitro* studies utilizing α-glucosidase from *Saccharomyces cerevisiae.*

METHODS

Instruments

The instruments used in this study included a Monowave 50 microwave reactor (Anton Paar), spectroscopic and analytical measurements were carried out using UV–Visible spectrophotometer (Genesys 10S UV–VIS v4.0022L9N175013), a high-performance liquid chromatography (HPLC) system (UFLC Prominence–Shimadzu LC Solution, UV Detector SPD-20AD), an FTIR spectrophotometer (Shimadzu IR Prestige-21), an NMR spectrometer (Agilent 500 MHz, DD2 console system), and a mass spectrometer (Waters LCT Premier XE, positive mode).

Materials

The chemicals used in study were reagent grade and used without further purification which includes 3-bromoacetophenone (Sigma-Aldrich), glyoxylic acid (Merck), hydrazine hydrate (Merck), glacial acetic acid (Merck), benzenesulfonyl chloride (Merck), potassium carbonate (Merck), acetonitrile (Merck), sodium hydroxide (NaOH) (Merck), TLC plates GF_{254} (Merck), and α-glucosidase enzyme (Sigma-Aldrich). Meanwhile, organic solvent used for purification steps were distilled commercial solvents.

Procedure

Synthesis of pyridazinone (5)

Pyridazinone **5** synthesis was carried using method reported in literature (Fatisa et al., 2025). A mixture of 3-bromoacetophenone **1** (1 equiv, 3 mmol), glyoxylic acid **2** (1 equiv, 3 mmol), and glacial acetic acid (3 mL) was placed in a capped pressure tube and reacted in a Monowave 50 reactor for 6 h at 120 °C. After the formation of the oxobutanoate intermediate **3**, hydrazine hydrate **4** (1 equiv, 3 mmol) was added to the reaction mixture, followed by further heating in the Monowave reactor for 3 h at 120 °C. The reaction progress was monitored using thin-layer chromatography (TLC).

After completion, reaction mixture was then poured into ice cubes and neutralized by the addition of 6 N NaOH solution. The mixture was allowed to stand in a refrigerator for overnight to ensure maximum precipitation. The resulting solid was collected by filtration. Crude product was recrystallized in methanol to afford 6-(3-bromophenyl)pyridazin-3(2*H*)-one **5**.

Synthesis of N-benzenesulfonyl pyridazinone (7)

N-benzenesulfonyl pyridazinone **7** synthesis was carried using method reported in literature (Fatisa et al., 2025). A mixture of 6-(3-bromophenyl)pyridazin-3(2*H*)-one (**5)** (1 mmol), benzenesulfonyl chloride **6** (1.1 mmol), potassium carbonate (2.5 mmol), and acetonitrile (15 mL) was placed in round bottom flask and stirred at room temperature for 8 h. The reaction progress was monitored using thin-layer chromatography (TLC). After completion, the solvent was removed and the resulting solid was then extracted with a 1:1 mixture of distilled water and ethyl acetate. The ethyl acetate layer was collected and evaporated using a rotary evaporator. The resulting solid was purified by column chromatography to afford 6-(3-bromophenyl)-2-(phenylsulfonyl)pyridazin-3(2*H*)-one **7**.

α-Glucosidase Inhibitory Activity Assay

The α-glucosidase inhibitory assay was performed using a 96-well microplate. The assay was carried out using the protocol as reported by Supasuteekul et al. with minor modification. Each well contained 10 µL of sample (1 mM), 40 µL of phosphate buffer (pH 6.8), 25 µL of *p*-NPG substrate solution (3 mM), and 25 µL of α-glucosidase enzyme solution (0.2 U/mL). The mixture was incubated at 37 °C for 30 minutes. After incubation, the reaction was terminated by adding 100 µL of 0.1 M Na_2CO_3. The absorbance of the released p-nitrophenol was measured at 405 nm using a microplate reader. The percentage inhibition was calculated using the formula below.

$$\% \text{ Inhibition} = (1 - A_s / A_c) \times 100$$

A_s is the absorbance value of the sample, A_c is the absorbance value of the negative control. Each experiment was performed in triplicate.

Molecular Docking

Molecular docking studies were performed using MOE 2019.0102. The crystal structure of human lysosomal α-glucosidase (PDB ID: 5NN5) was retrieved from the Protein Data Bank, and the ligands, 6-(3-bromophenyl)-2-(phenylsulfonyl)pyridazin-3(2*H*)-one

7 and acarbose (as a positive control), were prepared in ChemDraw Pro 12.0 and converted to 3D structures in MOE. Ligands were protonated and energy-minimized using the MMFF94X force field, while the receptor was prepared by removing water molecules, repairing missing atoms, protonation, charge assignment, and energy minimization. The docking protocol was validated via redocking of the natural ligand moranolin, with RMSD values below 2 Å considered acceptable (Herfindo et al., 2023). Docking simulations were then conducted using standard MOE parameters with 100 poses generated, and the best binding conformation was selected based on the binding score (*S*). Ligand–residue interactions were visualized in 2D using Discovery Studio Visualizer v21.1.0.20298.

RESULTS AND DISCUSSION

Synthesis and Characterization

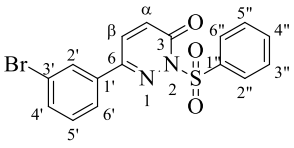
In this study, *N*-benzenesulfonyl pyridazinone (**7)** was synthesized by two-steps reaction (**Figure 1).** Firstly, pyridazinone, 6-(3-bromophenyl)pyridazin-3(2*H*)-one (**5)**, prepared via a one-pot synthesis method. The compound was prepared from the reaction of three starting materials: 3-bromoacetophenone (**1)**, glyoxalic acid (**2**,) and hydrazine hydrate (**4)** in pressure tube. In this reaction, glacial acetic acid used as a catalyst. The reaction proceeds *via* an enolic intermediate formed through an aldol condensation, which subsequently reacts with hydrazine hydrate to yield the desired product with 90.6% yield.

N-benzenesulfonyl pyridazinone (**7**) was synthesized from the previously obtained pyridazinone (**5**) via a substitution reaction with benzenesulfonyl chloride (**6**). The product was purified by column chromatography using a gradient system of *n*-hexane and ethyl acetate. Due to its limited solubility, the compound was obtained in 15.7% yield. The reaction mechanism is illustrated in **Figure 2.**

The disappearance of the N–H stretching vibration at ~3200 cm^{-1} in the FTIR spectrum of compound **7** indicates successful reaction, consistent with the formation of the expected product. Furthermore, the ^{1}H-NMR spectrum of the synthesized pyridazinone (**7**) showed the presence of Hα and Hβ protons. Hα appeared at a chemical shift of δ 6.96, while the more deshielded Hβ proton appeared at δ 7.66, both as doublets with a coupling constant of J = 9.8 Hz.

The aromatic protons of the two rings appeared in the δ 7.38–8.23 range. The proton at C5' gave a triplet at δ 7.38 (J = 7.9 Hz), while the proton at C2' appeared as a singlet at δ 7.98. The proton at C4' appeared as a doublet at δ 7.79 (J = 8.3 Hz). The proton at C6' showed a multiplet due to overlapping with protons at C3" and C5", appearing in the δ 7.56–7.64 range. A triplet signal corresponding to C4" appeared at δ 7.72 (J = 7.5 Hz). Finally, protons at C2" and C6" gave identical doublets at δ 8.23 (J = 7.3 Hz), consistent with their chemically equivalent environment **(Table 1)**.

Table 1. Chemical shift of compound **7**



Position	δ_H (ppm)	J (Hz)
α	6,96	9,8
β	7,66	9,8
2'	7,98	-
4'	7,79	8,3
5'	7,38	7,9
6', 3'', 5''	7,64 – 7,56	-
2'', 6''	8,23	7,3
4''	7,72	7,5

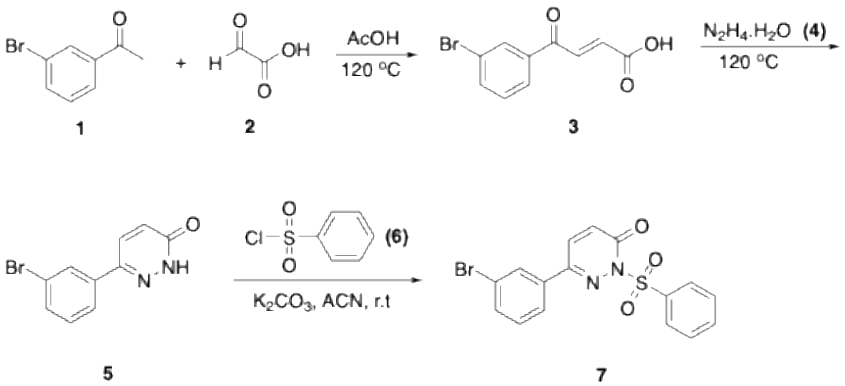


Figure 1. Reaction scheme of *N*-benzenesulfonyl pyridazinone (**7**) synthesis.

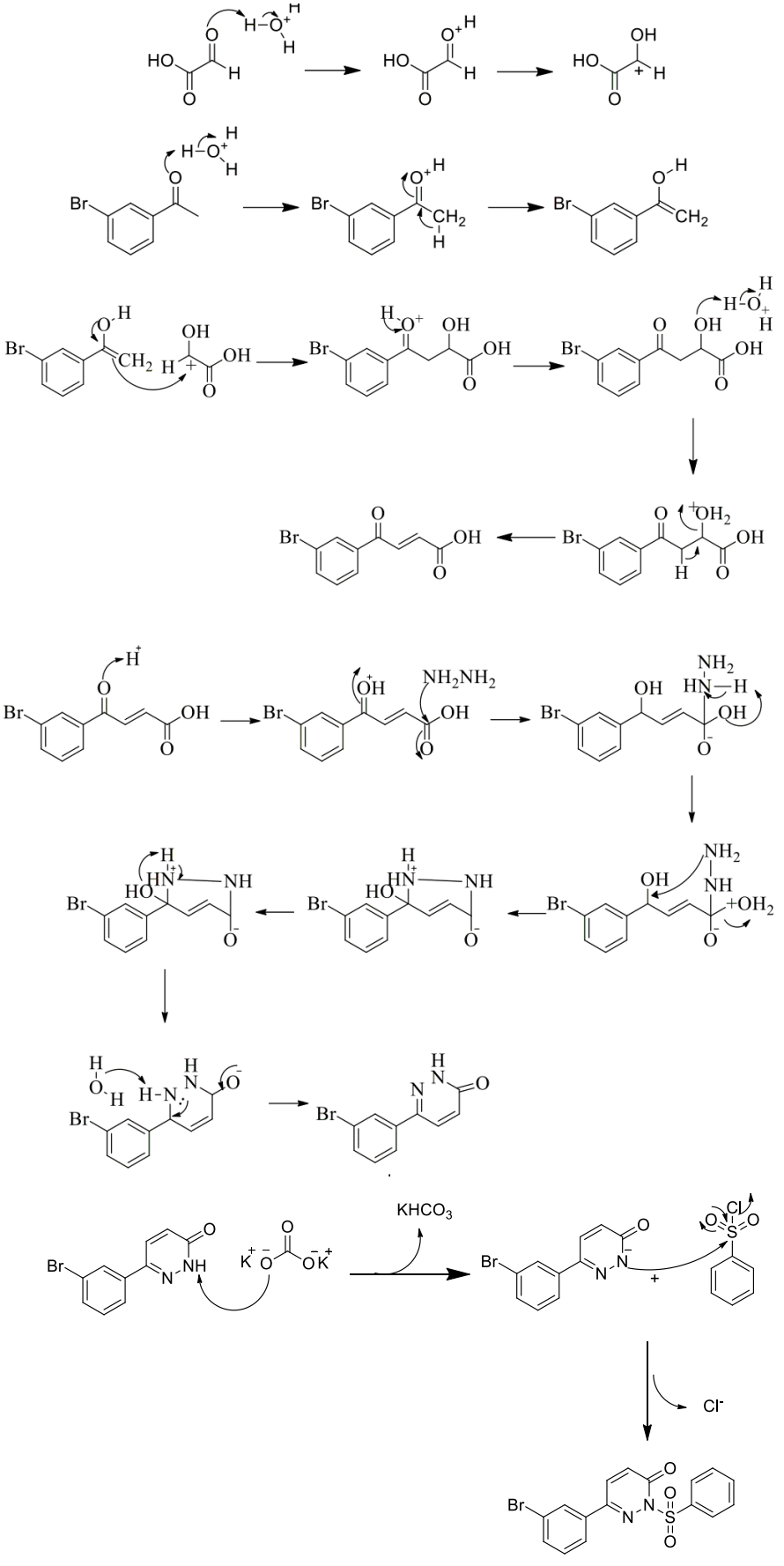


Figure 2. Reaction mechanism of *N*-benzenesulfonyl pyridazinone **7** formations.

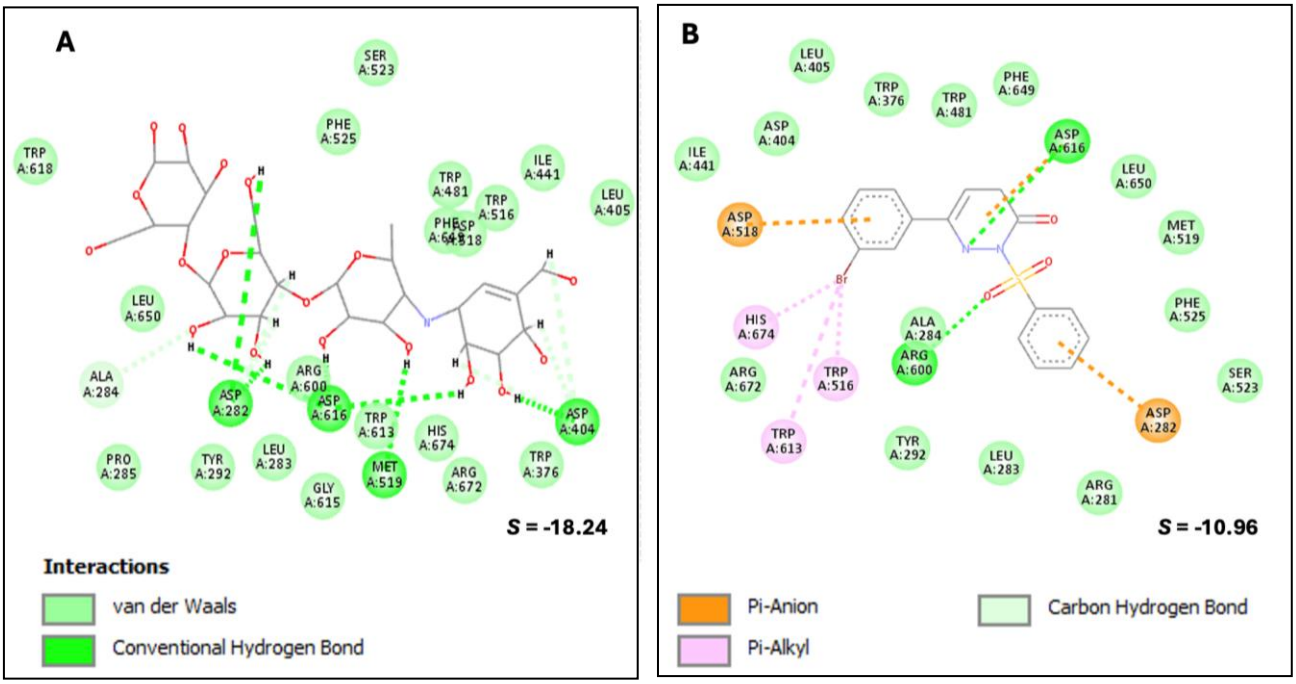


Figure 3. 2D binding interactions of acarbose (A) and compound 7 (B).

HRMS analysis showed a molecular ion peak $[M+H]^+$ at m/z 390.9758 (100% abundance), in agreement with the calculated value of 390.9752 for $C_{16}H_{12}BrNO_3S$. Collectively, these data confirm that the synthesized compound corresponds to the intended target *N*-benzenesulfonyl pyridazinone (**7**).

Molecular Docking Analysis

The inhibitory activity of *N*-benzenesulfonyl pyridazinone (**7**) against α-glucosidase was investigated through molecular docking. Docking studies were performed using the crystal structure of human lysosomal α-glucosidase (PDB ID: 5NN5), which is complexed with moranolin, a natural ligand known to inhibit α-glucosidase.

Moranolin was subjected to redocking to validate the docking protocol. Water molecules surrounding the ligand in the crystal structure were removed prior to docking to avoid interference with hydrogen bonding, thereby optimizing ligand–receptor interactions and achieving the most favorable conformations (Xuan-Yu et al., 2011). The redocking results showed a excellent overlap with the original ligand (RMSD = 0.29 Å), confirming the method's reliability (Shamsian et al., 2024).

Docking results **(Table 2)** showed the binding score of acarbose was –18.24, which is lower than that of compound **7** (–10.96). These results suggest that the binding affinity of compound **7** is lower than that of acarbose.

For compound **7**, the compound formed two hydrogen bonds with Arg600 and Asp616, while other hydrophobic interactions were observed with Asp282, Trp516, Asp518, Trp613, Asp616, and His674 (**Figure 3)**. These interactions likely contribute to the stabilization of the ligand within the active site, although the number of hydrogen bonds is limited compared to the reference ligand.

Table 2. Binding interactions of docked compounds.

Cpd	*S*	Interactions	
		H-bond	Other
7	-10,96	Arg600, Asp616	Asp282, Trp516, Asp518, Trp613, Asp616, His674
Acarbose	-18,24	Asp282, Ala284, Asp404, Met519, Asp616	Asp282, Ala284, Asp404

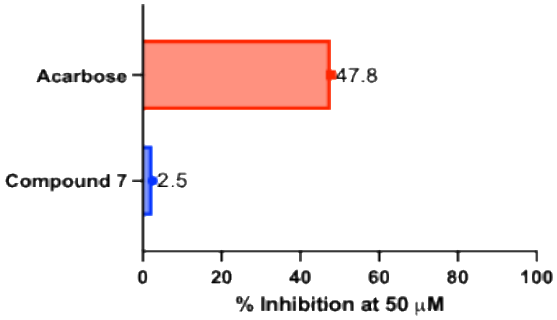


Figure 4. Inhibitory activity of tested compounds

In comparison, acarbose, the positive control, exhibited a stronger binding affinity. Presumably due to acarbose formed multiple hydrogen bonds with Asp282, Ala284, Asp404, Met519, and Asp616, in addition to other hydrophobic interactions with Asp282, Ala284, and Asp404. The higher number of hydrogen bonds and the more negative binding energy indicate a stronger and more stable interaction with the enzyme active site.

***In vitro* α-Glucosidase Inhibitory Evaluation**

The α-glucosidase from *Saccharomyces cerevisiae* (EC 3.2.1.20) was used to evaluate the inhibitory activity of compound **7**. The *in vitro* assay showed that compound **7** exhibited negligible activity, with only 2.5% inhibition at 50 μM, whereas acarbose inhibited the enzyme by 47.8% at the same concentration **(Figure 4)**. These findings are consistent with the molecular docking results, which predicted that compound **7** would have lower binding affinity and weaker inhibitory activity compared to acarbose. In addition, the poor solubility of compound **7** may have contributed to its low inhibitory effect observed in the assay.

CONCLUSIONS

In this study, *N*-benzenesulfonyl pyridazinone, 6-(3-bromophenyl)-2-(phenylsulfonyl) pyridazin-3(2*H*)-one **(7),** was successfully synthesized and structurally confirmed through spectrometry analyses. Molecular docking studies against human lysosomal α-glucosidase showed that compound **7** exhibits a lower binding affinity compared to acarbose. Consistent with the docking result, the *in vitro* α-glucosidase inhibitory assay using *Saccharomyces cerevisiae* α-glucosidase demonstrated that compound **7** showed minimal inhibition. The low solubility of the compound may also have contributed to its weak biological response. Overall, *N*-benzenesulfonyl pyridazinone (**7**) did not exhibit strong α-glucosidase inhibitory activity; however, its scaffold may serve as a basis for future structural optimization to improve potency and solubility.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest in writing is article.

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