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Synthesis of Novel Thiosemicarbazones and Their Molecular Docking Simulations as Inhibitors of α-Amylase and α-Glycosidase Enzymes

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Abstract: In this study, a new chiral aldehyde featuring an isoxazolidine scaffold was synthesized. This compound served as a precursor for the preparation of three novel isoxazolidine-thiosemicarbazone hybrids. In a molecular docking study (MDS), compound 7a emerged as the top performer, showing the highest binding affinity with binding energies of -8.5 kcal/mol for alpha-amylase and -7.5 kcal/mol for alpha-glucosidase.

Keywords: *Molecular docking simulation, isoxazolidine, thiosemicarzone, 1,3-dipolar cycloaddition, imidazolidinone.*

1. INTRODUCTION

Thiosemicarbazones (TSCs) are organic compounds derived from thiosemicarbazide and carbonyl compounds. TSCs are a dynamic class of compounds with applications spanning from medicine to materials science [1-4], and as ligands in coordination chemistry [5-7]. The ability of TSCs to interact with metal ions plays a crucial role in their diverse biological applications and activities [8-11]. TSCs exhibit a wide range of biological activities, including antidiabetic [12], anticancer [13], antimicrobial [14], antioxidant [15], and anti-inflammatory [16], making them a valuable candidate for drug development and therapeutic applications.

On the other hand, isoxazolidines (ISXs) are a class of heterocyclic compounds that contain a five-membered ring with three carbon atoms, one nitrogen atom, and one oxygen atom. These derivatives are significant due to their diverse biological activities and applications such as antidiabetic [17,18], anticancer [19], antimicrobial [20] and antioxidant activities [21].

In addition to this, hybrid heterocycles are gaining significant attention in biomedical research for their potential to merge multiple pharmacophoric structures into a single molecular entity [22]. This integration can lead to compounds with unique and enhanced biological activities, making them promising candidates for drug development and therapeutic applications [23]. In this study, our primary objective is to develop new hybrid compounds that integrate ISX and thiosemicarbazide moieties. By merging these two chemical entities, we aim to synthesize a series of novel isoxazolidine-thiosemicarbazide derivatives with potentially enhanced biological and chemical properties. The resulting hybrid compounds are anticipated to exhibit unique chemical structures, which could lead to novel applications or improved efficacy in pharmaceutical or other chemical fields. We want to emphasize that the proposed hybrid compounds feature a pyrazole core, which is recognized as a valuable building block in both organic synthesis and medicinal chemistry because of its biological significance and chemical versatility.

2. MATERIALS AND METHODS

2.1. Chemistry

2.1.1. General methods

All chemicals and reagents used in this study were of analytical grade and purchased from standard suppliers unless otherwise specified. Solvents were used either as received or dried and distilled using standard methods prior to use. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AVANCE III (Qassim University, College of science) operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. Coupling constants (J) are given in Hertz (Hz). Data for ^{1}H NMR are reported as: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants where applicable.

2.1.2. Synthesis of ISX 5

Nitrone **3** (1 mmol) and 1-allyl-3-methyl-1H-pyrazole-4-carbaldehyde **4** (1 mmol) were sequentially added to 10 mL of toluene in a 50 mL flask and stirred at reflux for 48 hours. After evaporating the solvent, the residue was subjected to chromatography on silica gel using a 7:3 Cyclohexane/EtOAc mixture to yield ISX **5**.

2.1.3. Synthesis of isoxazolidine-thiosemicarbazide derivatives **7a-c**

ISX **5** (1 mmol) and thiosemicarbazide **6a-c** (1 mmol) were added sequentially to ethanol in a 25 mL flask, along with a catalytic amount of glacial acetic acid. The mixture was stirred and refluxed for 16 h. After evaporating the solvent, the residue was chromatographed on silica gel using a 6:4 cyclohexane/ EtOAc mixture to yield novel isoxazolidine-thiosemicarbazide derivatives **7a-c**.

5

1H NMR (δ) 0.76 (d, 3H, J= 6.4 Hz, CH_3); 0.80 (d, 3H, J= 6.8 Hz, CH_3); 0.83 (d, 3H, J= 7.2 Hz, CH_3); 0.86-0.93 (m, 1H); 1.17 (t, 1H, J = 12.4 Hz); 1.34 (dd, 1H, J = 7.6 and 10.8 Hz); 1.40 (quin, 1H, J = 6.8 Hz); 1.61-1.64 (m, 2H); 1.76-1.82 (m, 3H); 2.26 (ddd, 1H, J = 4.4, 8.8 and 12.4 Hz); 2.45 (s, 3H, CH_3); 2.69 (s, 3H, NCH_3); 2.73 (dd, 1H, J = 5.6 and 12.8 Hz); 3.97 (d, 1H, J= 8.8 Hz); 4.11 (dd, 1H, J = 8.4 and 13.6 Hz); 4.17-4.24 (m, 1H); 4.30 (dd, 1H, J = 2.8 and 13.6 Hz); 7.88 (s, 1H); 9.85 (s, 1H, *H*C=O).

13C NMR (δ) 12.8; 18.4; 21.9; 22.4; 24.1; 24.3; 26.0; 29.6; 34.4; 35.6; 40.5; 48.0; 54.3; 65.5; 74.8; 89.3; 121.6; 135.7; 150.9; 172.1 (C=O); 183.9 (HC=O).

7a

1H NMR (δ) 0.75 (d, 3H, J= 6.4 Hz, CH_3); 0.80 (d, 3H, J = 6.8 Hz, CH_3); 0.85-0.90 (m, 1H); 1.16 (t, 1H, J= 12.0 Hz); 1.32 (dd, 1H, J= 4.4 and 12.0 Hz); 1.39 (quin, 1H, J = 6.8 Hz); 1.57-1.67 (m, 2H); 1.77-1.80 (m, 1H); 1.83-1.87 (m, 1H); 2.24 (dd, 1H, J = 8.4 and 12.4 Hz); 2.41 (s, 3H, CH_3); 2.68 (s, 3H, CH_3); 2.74 (ddd, 1H, J = 5.6, 6.8 and 12.4 Hz); 3.98 (d, 1H, J= 8.8 Hz); 4.10 (dd, 1H, J= 8.0 and 13.6 Hz); 4.17-4.30 (m, 1H); 4.29 (dd, 1H, J= 2.8 and 13.6 Hz); 7.21 (t, 1H, J= 7.2 Hz); 7.37 (t, 2H, J= 8.0 Hz); 7.63 (d, 2H, J= 7.6 Hz); 7.68 (s, 1H); 7.98 (s, 1H); 9.05 (s, 1H); 10.50 (s, 1H).

13C NMR (δ) 13.5; 18.4; 22.0; 22.3; 24.0; 24.2; 26.0; 29.5; 34.4; 35.7; 40.5; 47.9; 54.0; 65.5; 75.1; 89.3; 114.7; 124.0; 125.9; 128.7; 131.8; 136.6; 137.8; 148.0; 172.2 (C=O); 174.8 (C=S).

7b

1H NMR (δ) 0.75 (d, 3H, J = 6.4 Hz, CH_3); 0.78 (d, 3H, J = 6.4 Hz, CH_3); 0.81 (d, 3H, J = 6.8 Hz); 0.78-0.82 (m, 1H); 1.15 (t, 1H, J = 12.4 Hz); 1.31 (dd, 1H, J = 3.6 and 12.4 Hz); 1.38 (quin, 1H, J = 6.8Hz); 1.57-1.66 (m, 1H); 1.77 (brd, 2H, J = 12.8 Hz); 1.82-1.85 (m, 1H); 2.22 (ddd, 1H, J = 3.6, 8.8 and 12.4 Hz); 2.34 (s, 3H, CH_3); 2.67 (s, 3H, CH_3); 2.71 (ddd, 1H, J = 4.8, 7.6 and 12.4 Hz); 3.19 (d, 3H, J = 4.4 Hz, NHCH_3); 3.96 (d, 1H, J = 8.8 Hz); 4.07 (dd, 1H, J = 7.6 and 13.6 Hz); 4.13-4.19 (m, 1H); 4.25 (dd, 1H, J = 4.0 Hz); 7.22 (d, 1H, J= 4.0 Hz); 7.64 (s, 1H); 7.86 (s, 1H); 10.10 (s, 1H).

13C NMR (δ) 13.2; 18.3; 22.0; 22.3; 24.0; 24.2; 26.0; 29.5; 30.9; 34.4; 35.6; 40.4; 47.9; 54.0; 65.5; 75.1; 89.3; 114.8; 131.2; 136.0; 147.9; 172.1 (C=O); 177.6 (C=S).

7c

1H NMR (δ) 0.74 (d, 3H, J = 6.4 Hz, CH_3); 0.78 (d, 3H, J = 6.8 Hz, CH_3); 0.81 (d, 3H, J = 6.8 Hz, CH_3); 0.84-0.91 (m, 1H); 1.15 (t, 1H, J = 12.4 Hz); 1.31 (dd, 1H, J = 4.0 and 10.6 Hz); 1.37 (quin, 1H, J = 6.8 Hz); 1.60-1.65 (m, 2H); 1.75-1.79 (m, 2H); 1.81-1.84 (m, 1H); 2.23 (ddd, 1H, J = 4.0, 8.8 and 12.0 Hz); 2.35 (s, 3H, CH_3); 2.67 (s, 3H, NCH_3); 2.72 (dd, 1H, J = 5.6 and 12.0 Hz); 3.98 (d, 1H, J = 8.8 Hz); 4.09 (dd, 1H, J= 8.4 and 13.6 Hz); 4.14-4.18 (m, 1H); 4.27 (dd, 1H, J = 2.4 and 13.6 Hz); 6.70 (s, 1H); 7.02 (s, 1H);7.67 (s, 1H); 7.97 (s, 1H); 10.46 (s, 1H).

13C NMR (δ) 13.3; 18.3; 22.0; 22.3; 24.0; 26.0; 29.5; 29.6; 34.4; 35.7; 40.4; 47.9; 54.0; 65.5; 75.1; 89.3; 114.6; 131.7; 137.6; 148.1; 172.2 (C=O); 177.1 (C=S).

2.2. Molecular docking:

Molecular docking simulations were conducted to investigate the interactions between compounds **7a-c** and their respective targets, α-amylase HPA and α-glucosidase HLAG. The objective was to determine the optimal binding orientations of the compounds within the catalytic sites of the enzymes.

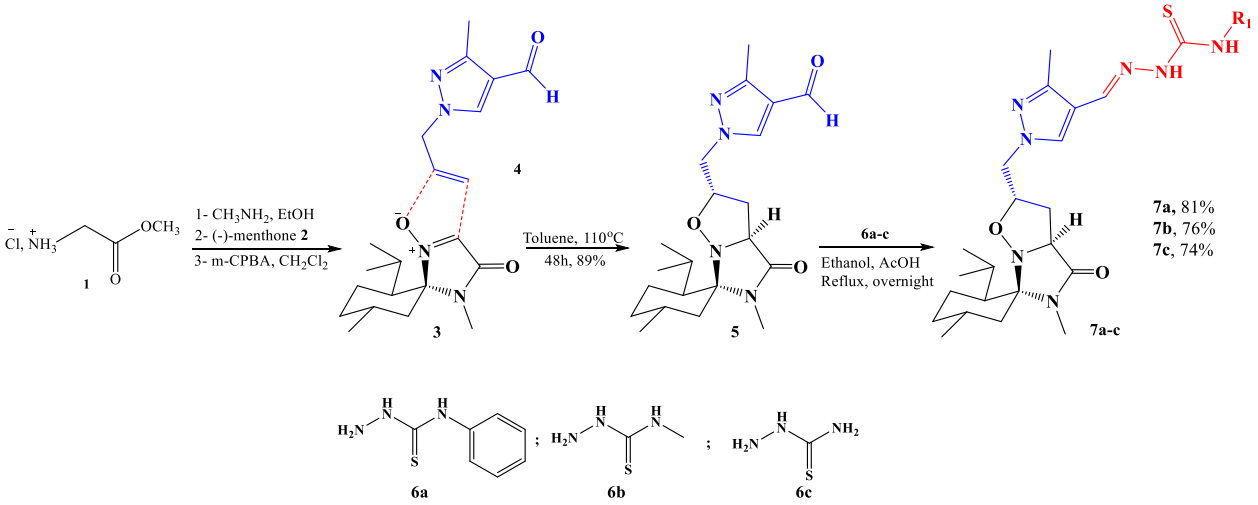
The 3D structures of α-amylase HPA (PDB: 5E0F) and α-glucosidase HLAG (PDB: 5NN8) were obtained from the Protein Data Bank. After removing water molecules and ligands, the protein structures were prepared for docking by adding Gasteiger charges and polar hydrogens using AutoDock Tools 1.5.2 (ADT) and converting them to PDBQT format [24].

Docking grids were defined using ADT, with dimensions and centers specified for each enzyme. For HPA, the grid box was centered at (−7.946 Å, 10.438 Å, −21.863 Å) with dimensions of x = 80, y = 72, and z = 66 points. For HLAG, the grid box was centered at (x = −12.175 Å, y = −35.415 Å, z = 88.753 Å) with dimensions of x = 74, y = 70, and z = 90 points. The ligands were optimized using the conjugate gradient AMMP technique built into the VEGA ZZ program [25] and converted to PDBQT format. AutoDock Vina software [26] was employed to perform the docking calculations, with an exhaustiveness parameter set to 32.

The resulting conformations were analyzed using ADT, and the types of interactions between ligands and receptors were determined using Discovery Studio Visualizer [27].

3. RESULTS AND DISCUSSION

The reaction sequence starts with the synthesis of nitrone **3** from glycine methyl ester **1** and (-)-menthone **2**, using the procedure outlined in the literature [28-30]. The resulting nitrone undergoes a 1,3-DC with 1-allyl-3-methyl-1H-pyrazole-4-carbaldehyde **4** (available commercially from Sigma Aldrich), producing ISX **5** with a 90%. This is followed by a condensation reaction between ISX **5** and various thiosemicarbazides **6a-c**, resulting in hybrid isoxazolidine-thiosemicarbazones **7a-c** (scheme 1).



Scheme 1. Synthesis of isoxazolidine-thiosemicarbazide derivatives **7a-c**.

In our previous work, we confirmed that for H-3 and H-4 protons in the syn orientation, the coupling constant ranges from 7.7 to 9.0 Hz, while for those in the anti-position, the coupling constant is weak or even negligible ($0 \leq J_{3,4}$ (anti) ≤ 3.7 Hz). For H-4 and H-5 protons in the anti- orientation, the coupling constant falls between 8.7 and 11.7 Hz, whereas in the *syn* position, the coupling is weaker.

Analysis of the ^{1}H NMR spectrum of ISX **5** revealed a strong coupling constant between the H-3 and H-4a protons ($J_{3\text{-}4a}$ = 8.8 Hz), as well as an absence of coupling between H-3 and H-4b ($J_{3\text{-}4b}$ = 0 Hz), indicating that the H-3 and H-4a protons are in syn configuration. In addition, a coupling constant of 7.5 Hz between the H-4b and H-5 protons was observed, which also suggests a syn configuration for these protons (Figure 1). These results are in agreement with previously published data [28-30].

The ^{13}C NMR spectra of compounds **7a-c** show a singlet at 172.2 ppm (172.1 ppm for **7b**), corresponding to the carbon of the carbonyl group of the amide, as well as a signal at 174.8 ppm (177.6 ppm for **7b** and 177.1 ppm for **7c**), attributed to the thiocarbonyl group.

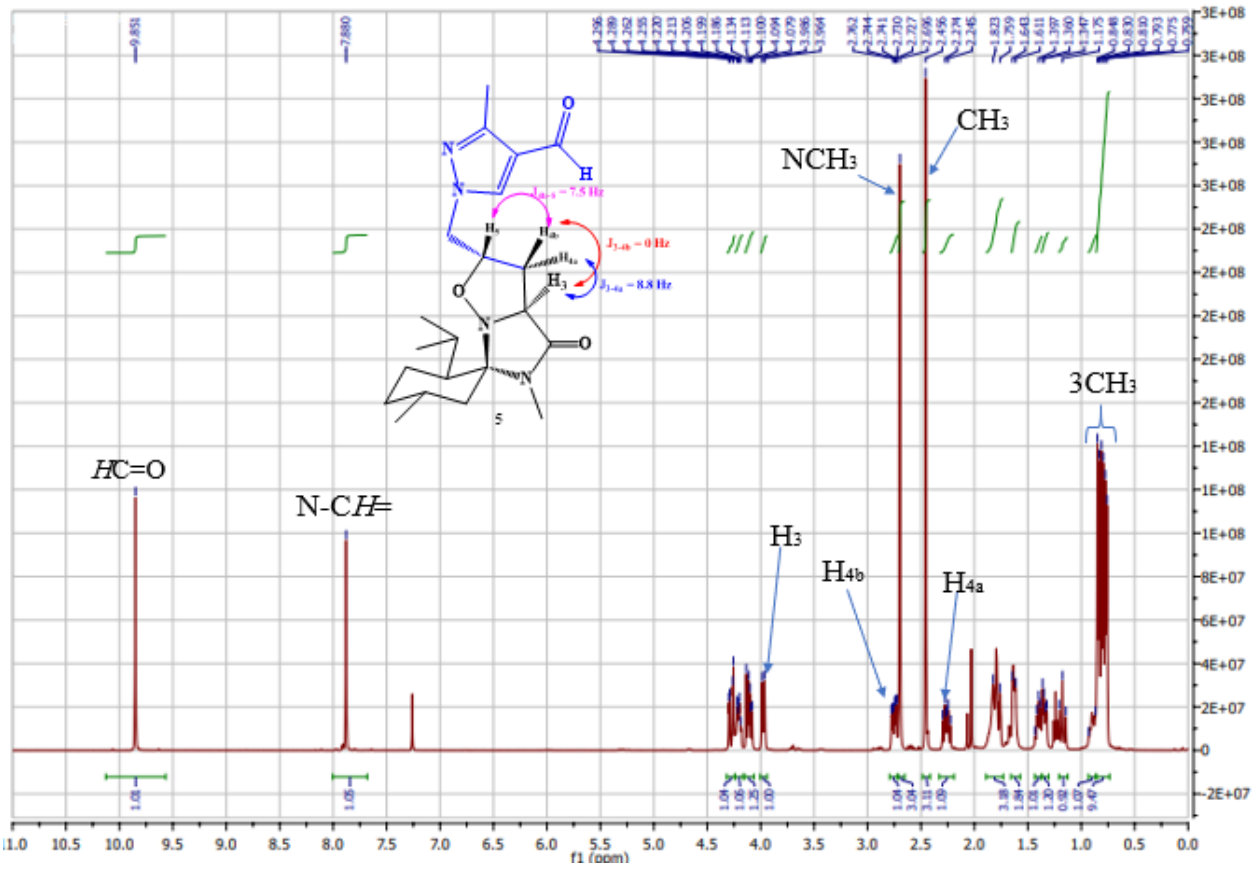


Figure 1. Structure and 1H NMR spectrum of **5**

4. Molecular docking studies:

This computational study aimed to investigate the interactions between novel compounds **7a-c** and the catalytic sites of α-amylase and α-glucosidase. Molecular docking was employed as a crucial tool in structure-based drug design to identify potential binding interactions [31]. The results demonstrated favorable binding energies for all complexes, with **7a** exhibiting the highest affinity (-8.5 kcal/mol for alpha-amylase and -7.5 kcal/mol for α-glucosidase) as shown in Table 1.

Further analysis revealed that compound **7a** forms stable interactions with multiple amino acid residues within the catalytic regions of both enzymes. These interactions, as depicted in Figures 2 and 3, contribute to the strong binding affinity observed for **7a**.

Table 1: Docking binding energies (kcal mol−1) of complexes with α-glucosidase and α-amylase of **7a-c.**

	α-amylase	α-glycosidase
7a	-8.5	-7.5
7b	-8.3	-6.9
7c	-7.8	-7.4

The docking analysis of compound **7a** with alpha-amylase revealed several key interactions (Figure 2). Compound **7a** forms a hydrogen bond with Glu233 at a distance of 2.15 Å. It also engages in a Pi anion interaction with Asp197, with a distance of 3.93 Å. Additionally, a Pi sulfur interaction occurs between **7a** and His201 at 4.60 Å, while a Pi sigma interaction is observed with Trp59 at 3.67 Å. Alkyl interactions are noted with Leu165 (4.46 Å), Trp58 (5.89 Å), and His305 (4.09 Å). Van der Waals interactions were identified with the following amino acids: Ile235, Ala198, Arg195, Asp197, His299, Asp300, Tyr62, Leu162, Thr163, and Gln63.

Based on the research conducted by Ramasubbu and his colleagues [32], the active site of α-amylase comprises a cluster of polar amino acids, including Glu-233, Asp-236, Arg-61, Lys-200, Asp-300, Leu-165, and Asp-197, alongside non-polar and aromatic residues such as Ile-235, Tyr-258, His-299, His-305, Trp-58, Tyr-62, Ala-307, Ser-163, Trp-59, and His-101. Williams et al. [33] discovered that myricetin binds to the enzyme's active site, forming hydrogen bonds with Gln-63, His-101, and Asp-197, as well as hydrophobic contacts with Tyr-62 and Leu-

165. Additionally, Mudgil and his team [34] reported that the control compound acarbose interacts with key residues within the α-amylase active site, including Trp-58, Trp-59, Tyr-62, Tyr-151, Leu-162, Ser-163, Leu-165, Ile-235, Gly-306, Gln-63, Lys-200, Asp-300, and His-305.

When comparing our findings with interactions reported in the literature, several common amino acids were identified. These include Glu233, Asp197, Leu165, Trp58, Trp59, His305, Tyr62, Ile235, Asp300, Gln63, Leu162, Thr163, and His299. This overlap indicates that these residues are potentially significant in the binding mechanism of α-amylase with various ligands.

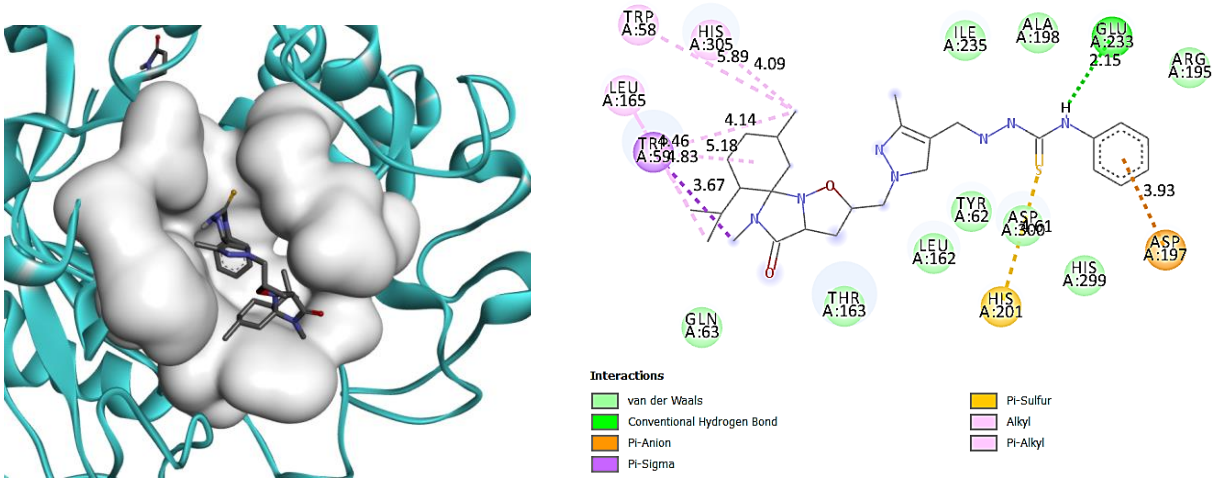


Figure 2. 3D and 2D views of the interaction of **7a** with surrounding amino acids of **α-amylase**

The docking analysis of compound **7a** with alpha-glycosidase revealed several significant interactions (Figure 3). Compound **7a** forms a hydrogen bond with Ser676 at a distance of 2.77 Å. Additionally, it exhibits alkyl interactions with Leu677 (5.49 Å), Leu678 (5.43 Å), Phe525 (4.29 Å), and Ala555 (5.33 Å). Van der Waals interactions were observed with several amino acids, including Leu650, Arg600, Asp616, Asp282, Arg281, Asn524, Ser323, Met519, Trp481, Phe649, and Trp376.

Roig-Zamboni and colleagues [35] discovered that 1-deoxynojirimycin binds to the human lysosomal acid α-glucosidase (GAA) catalytic site, interacting with residues such as Asp-404, Trp-376, Ile-441, Leu-405, Trp-516, Trp-481, Met-519, Asp-518, Arg-600, Asp-616, Trp-613, Asp-645, His-674, Arg-672, and Phe-649. In a separate study, Adinortey et al. [36] identified catalytic residues within alpha-glucosidase, including Asp-282, Asp-404, Asn-

524, Phe-525, Arg-600, Asp-616, His-674, Asp-281, Leu-283, Ala-284, Trp-376, Leu-405, Ile-441, Trp-481, Trp-516, Asp-518, Met-519, Ala-555, Trp-613, and Phe-649, which interact with acarbose.

When comparing our findings with interactions reported in the literature, several common amino acids were identified. These include Trp376, Trp481, Met519, Arg600, Asp616, Asp282, Asn524, Phe525, Phe649, and Ala555. These residues are mentioned in the literature as being significant for catalytic activity. The overlap of these amino acids with our docking results underscores their potential importance in the binding mechanism of α-glycosidase with various ligands.

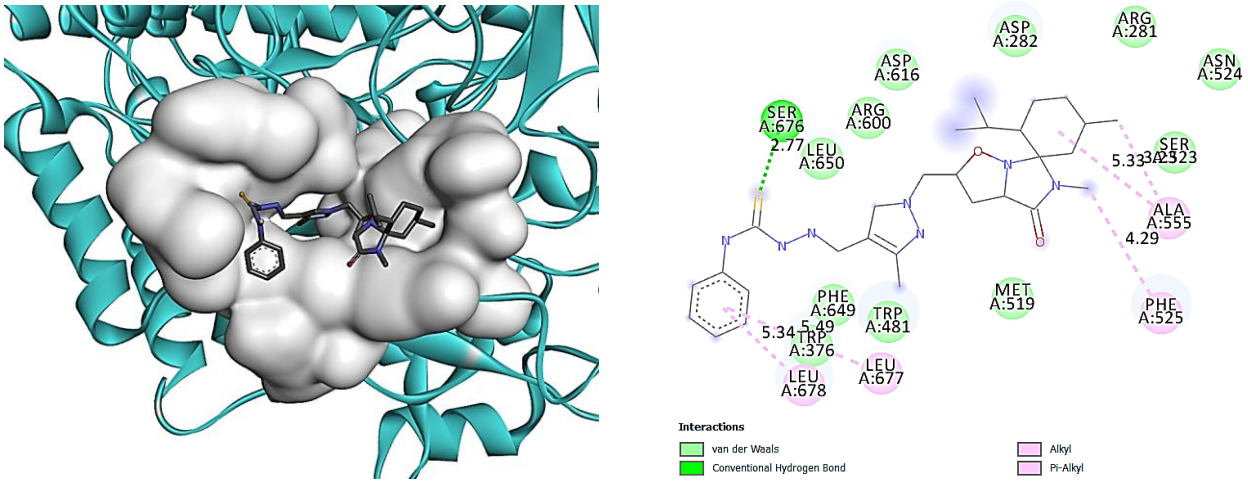


Figure 3. 3D and 2D views of the interaction of **7a** with surrounding amino acids of α- glycosidase

Conclusion

In this study, we detailed the synthesis of four new compounds and examined their docking simulations with α-amylase and α-glycosidase enzymes. The results showed favorable binding energies for all complexes, with compound **7a** demonstrating the highest affinity, displaying binding energies of -8.5 kcal/mol for α-amylase and -7.5 kcal/mol for α-glucosidase.

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الملخص باللغة العربية

اصطناع مركبات ثيوسياميكاربازون جديدة ومحاكاة الالتحام الجزيئي لها كمثبطات لإنزيمات α-أميلاز و α- جليكوسيداز

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في هذه الدراسة، تم تخليق ألدهيد حلقي جديد يتميز بهيكل إيزوكسازوليدين. وقد تم استخدام هذا المركب كمقدمة لتحضير ثلاثة هياكل هجينة من إيزوكسازوليدين-ثيوسياميكاربازون جديدة. في دراسة الالتحام الجزيئي(MDS) ، ظهرت المركب 7 aكأفضل أداء، حيث أظهر أعلى تقارب ارتباط مع طاقات ارتباط بلغت -8.5 كيلو كالوري/مول لإنزيم-α أميلاز و -7.5 كيلو كالوري/مول لإنزيم-α جليكوسيداز.

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