

SHORT COMMUNICATION

Docking Sulochrin and Its Derivative as α -Glucosidase Inhibitors of *Saccharomyces cerevisiae*Wening Lestari^{1,*}, Rizna Triana Dewi², Leonardus Broto Sugeng Kardono², and Arry Yanuar³¹Center for Radioisotopes and Radiopharmaceuticals Technology, National Nuclear Energy Agency, Puspiptek, Serpong 15314, Indonesia²Research Center for Chemistry, Indonesian Institute of Sciences, Puspiptek, Serpong 15314, Indonesia³Faculty of Pharmacy, Universitas Indonesia, Depok 16424, Indonesia

Received April 26, 2016; Accepted August 11, 2016

ABSTRACT

Sulochrin is known to have an activity as inhibitors of the α -glucosidase enzyme. In this report interaction of sulochrin to the active site of the α -glucosidase enzyme from *Saccharomyces cerevisiae* was studied by docking method. The crystal structure of α -glucosidase from *S. cerevisiae* obtained from the homology method using α -glucosidase from *S. cerevisiae* (Swiss-Prot code P53341) as a target and crystal structure of isomaltase from *S. cerevisiae* (PDB code 3A4A) as a template. These studies show that sulochrin and sulochrin-I could be bound in the active site of α -glucosidase from *S. cerevisiae* through the formation of hydrogen bonds with Arg213, Asp215, Glu277, Asp352. Sulochrin-I has stability and inhibition of the α -glucosidase enzyme better than sulochrin. The iodine atom in the structure of sulochrin can increase the activity as an inhibitor of the α -glucosidase enzyme.

Keywords: sulochrin; sulochrin-I; α -glucosidase inhibitor; *S. cerevisiae*

ABSTRAK

Sulochrin telah diketahui mempunyai aktivitas sebagai inhibitor enzim α -glukosidase. Pada laporan ini interaksi sulochrin terhadap sisi aktif enzim α -glukosidase dari *Saccharomyces cerevisiae* telah dipelajari melalui metode docking. Struktur kristal enzim α -glukosidase dari *S. cerevisiae* diperoleh melalui metode homologi menggunakan enzim α -glukosidase dari *S. cerevisiae* (Swiss-Prot code P53341) sebagai target dan struktur kristal isomaltase dari *S. cerevisiae* (kode PDB 3A4A) sebagai templet. Sulochrin dan sulochrin-I dapat terikat di sisi aktif enzim α -glukosidase dari *S. cerevisiae* melalui formasi ikatan dengan Arg213, Asp215, Glu277, Asp352. Sulochrin-I mempunyai stabilitas dan menghambat enzim α -glukosidase dari *S. cerevisiae* lebih baik dari sulochrin. Atom iodium pada struktur sulochrin dapat meningkatkan aktivitas sebagai inhibitor enzim α -glukosidase.

Kata Kunci: sulochrin; sulochrin-I; inhibitor α -glukosidase; *S. cerevisiae*

INTRODUCTION

Diabetes mellitus is a disease related to malfunction of insulin. In 2010 people with diabetes reached 220 million and in 2025 it is predicted to reach 300 million people [1]. Most diabetics are type 2 diabetes mellitus. Type 2 diabetes mellitus is characterized by the occurrence of postprandial hyperglycemia [2]. Control of postprandial hyperglycemia is an important step for the treatment of diabetes. It can be done by inhibiting the absorption of glucose through inhibition of carbohydrate hydrolyzed enzymes such as α -glucosidase and α -amylase [3-4]. The α -glucosidase enzyme converts carbohydrates into glucose [5-7]. Mechanism of α -glucosidase inhibitors is reversible inhibition, competitive to the α -amylase enzyme and pancreatic

digestive enzymes in the small intestine such as isomaltase, sucrase, and maltase. These enzymes can inhibit the absorption of glucose and it will be lowering the hyperglycemia after a meal [7-8].

Research on α -glucosidase inhibitor compounds has been carried out, *in silico*, *in vivo*, and *in-vitro*. Data from *in silico* study reported that interaction of α -glucosidase inhibitor through the formation of hydrogen bonds with the α -glucosidase residues. Interactions between sulfonamide derivatives and α -glucosidase from *Saccharomyces cerevisiae* occurs at Asp349, His348, Phe157, Tyr71, Phe177, Arg212 [6]. Salacinol derivatives also showed potential as α -glucosidase inhibitors, interaction with residues Asp327, His600, Asp542, Asp203, Arg526 in NtMGAM [9].

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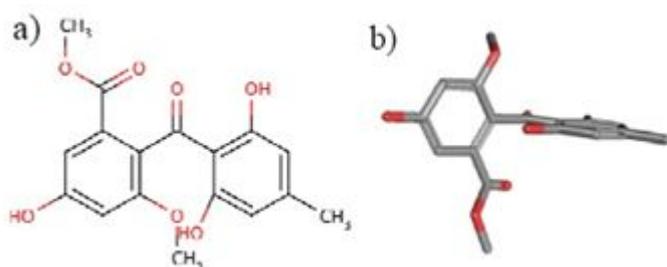


Fig 1. Sulochrin structure a) two dimension and b) three dimension

Methyl 2-(2,6-dihydroxy-4-methylbenzoyl)-5-hydroxy-3-methoxybenzoate (sulochrin) known as α -glucosidase inhibitors (Fig. 1). It could be isolated from the ethyl acetate extract of *A. Terreus*. *In silico* study shown that sulochrin can bind to the binding pocket in the crystal structure of *Thermotoga maritima* 4- α -glucanotransferase which has some similarities with the crystal structure of *S. cerevisiae* [10]. Sulochrin also interacts with the active site of human α -glucosidase at Asp587 with K_i with ΔG values of -6.90 kcal/mol [11]. *In vitro* study, reported that sulochrin has IC_{50} of 8.5 mg/mL when tested against *S. cerevisiae*. Sulochrin-I, a sulochrin derivative studied with the radioligand binding assay (RBA) method is reported to bind to the α -glucosidase from *S. cerevisiae* with K_d value of 26.316 nM [12]. Interaction of sulochrin and its derivative (sulochrin-I) with α -glucosidase of *S. cerevisiae* can be determined by docking these molecules (ligand and its receptor). The docking process will obtain the inhibition constants (K_i) and the free energy (ΔG) to form a stable conformation at the active site of the enzyme α -glucosidase. Currently, the crystal structure of the *S. cerevisiae* α -glucosidase is not yet available then docking process must be done using a homology structure of *S. cerevisiae* α -glucosidase. In this study, the homology was performed using *S. cerevisiae* α -glucosidase MAL12 obtained from Swiss-Prot (code P53341) as a target and the crystal structure of isomaltase from *S. cerevisiae* which was obtained from the PDB (PDB code 3A4A, 1.60 Å resolution) as a template [13]. Isomaltase from *S. cerevisiae* is known as oligo-1,6-glucosidase. This selection is based on the similarity of the amino acid sequence between α -glucosidase and isomaltase from *S. cerevisiae*.

EXPERIMENTAL METHOD

Materials

The material used in this work was a three-dimensional crystal structure of *S. cerevisiae* α -glucosidase which obtained from homology method using the SWISS-MODEL software. The target is the

S. cerevisiae α -glucosidase from Swiss-Prot with code number P53341. The template was crystal structure of *S. cerevisiae* oligo-1,6-glucosidase from the database PDB (code 3A4A). A compound which was going to be docked in the three-dimensional structure was sulochrin-I and this structure was prepared using the Chem3D software. The instruments of hardware and software were used. The hardware specifications was a computer equipped with 4 GB of RAM, Intel Xeon E5260 2.4 GHz, Graphic Card nVIDIA GeForce GT-680 (Taiwan), and Microsoft Windows XP operating system (USA). The software of a ChemOffice 2004 (licensed to Wening PRR), Open Babel (The Blueobelisk Group, USA), Autodock (The Scripps Research Institute, USA), PyMOL (DeLano Scientific LLC, Italy), PuTTY (www.PuTTY.org), Cygwin (Red Hat Inc., USA), SWISS-MODEL (<http://swissmodel.expasy.org>) [14-15], PROCHECK online (www.ebi.ac.uk/thrnton-srv/databases/pdbsum/generate.html), Clustal W2 (European Bioinformatics Institute, UK), were used.

Homology Modelling

Identification of homologs of α -glucosidase (Swiss-Prot code P53341) was carried out by performing sequence database searches with a standard tool, UniProt. The coordinate of the crystal structure *S. cerevisiae* oligo-1,6-glucosidase (PDB ID: 3A4A, 1.6 Å resolution) was used as a template to build the *S. cerevisiae* structure. Sequence alignment was performed by using the ClustalW2 program. The 3D model of the *S. cerevisiae* α -glucosidase was built by SWISS-MODEL software based on the *S. cerevisiae* oligo-1,6-glucosidase structure. The final protein model was evaluated by PROCHECK for the evaluation of Ramachandran Pot.

Molecular Docking Simulation

The 3D model of the *S. cerevisiae* α -glucosidase was used in docking analysis by using AutoDock. Hydrogen polar were added and Gasteiger charges were calculated. This research was used acarbose as a control for the docking simulation. The structure of sulochrin and sulochrin-I were built by using ChemOffice program. Acarbose, sulochrin and sulochrin-I were docked to *S. cerevisiae* α -glucosidase which used the same parameter for three compounds. Hydrogens polar were added and torsion number were calculated. Docking parameters were grid in 50 Å x 50 Å x 50 Å with X, Y and Z axis -21.727; -0.752; 18.637 respectively. Docking simulation runs with 100 runs using Lamarckian Genetic Algorithm. The free energy (ΔG) and inhibitions constant (K_i) scoring were then calculated.

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P53341|MAL12_YEAST      -MTISDHPETEPKWWKEATFYQIYPA SFKDSNNDGWGD LKGITSKLQYIK 49
3A4A_A|PDB ID          MTISSAHPETEPKWWKEATFYQIYPA SFKDSNDDGWGDMKGIA SKLEYIK 50
                        * *****:*****:*****:***:***:***
P53341|MAL12_YEAST      DLGVDAIWVCPFYD SPQQDMGYD ISNYEKVWPTYGTNEDCFELIDKTHKL 99
3A4A_A|PDB ID          ELGADAIWISPFYD SPQQDMGYDIANYEKVWPTYGTNEDCFALIEKTHKL 100
                        :*:***:*****:*****:*****:*****:*****:***:*****
P53341|MAL12_YEAST      GMKFIITDLVINHCSTEHEWFKESRS SKTNPKRDFWFFWRPPKGYDAEGKPI 149
3A4A_A|PDB ID          GMKFIITDLVINHCSEHEWFKESRS SKTNPKRDFWFFWRPPKGYDAEGKPI 150
                        *****:*****:*****:*****:*****:*****
P53341|MAL12_YEAST      PPNWKSFFGGSAWTFDETTNEFYLR LFA SRQVDLNWENEDCRRAI FESA 199
3A4A_A|PDB ID          PPNWKSFFGGSAWTFDETTNEFYLR LFA SRQVDLNWENEDCRRAI FESA 200
                        *****:*****:*****:*****:*****:*****
P53341|MAL12_YEAST      VGFWLDHGVDFRIDTAGLYSKR PGLPDSPIFDKTSKLQHPNWGSHNGPR 249
3A4A_A|PDB ID          VGFWLDHGVDFRIDTAGLYSKR PGLPDSPIFDKTSKLQHPNWGSHNGPR 250
                        **:*****:..*** ***:*:*.*. * .: : ****
P53341|MAL12_YEAST      IHEYHQLHRFMKNRVKDGREIMTVGEVAHGSDN--ALYTSAR YEVSEV 297
3A4A_A|PDB ID          IHEYHQLHRFMKNRVKDGREIMTVGEVAHGSDN--ALYTSAR YEVSEV 300
                        **:***:*:*****:*****:*.**: *****:***:***
P53341|MAL12_YEAST      FSFTHVEVGTSPFFRYNIVPFTL KQWKEIASNFLFINGTD SWATTYIEN 347
3A4A_A|PDB ID          FSFTHVEVGTSPFFRYNIVPFTL KQWKEIASNFLFINGTD SWATTYIEN 350
                        *.*:*.:*****:*****:*** ***:** *:*. * :*****:*. * **
P53341|MAL12_YEAST      HDQARSITRFADDS PKYR KISGKLL TLECSL TGLTYVYQGQEI GQINFK 397
3A4A_A|PDB ID          HDQARSITRFADDS PKYR KISGKLL TLECSL TGLTYVYQGQEI GQINFK 400
                        **:*****:***** * *****:*. :*****:*****:*****
P53341|MAL12_YEAST      EWPYEKYEDVDKNNY EIKK SFGKNSKEMKDFFKGIALLSRDHSRTPMP 447
3A4A_A|PDB ID          EWPYEKYEDVDKNNY EIKK SFGKNSKEMKDFFKGIALLSRDHSRTPMP 450
                        **:*****:*****:***:..*: ***:**.*:***:*****:***
P53341|MAL12_YEAST      WTKDKPNAGFTGPDVKPWFLLNE SF EQGINVEQESRDD SVLNFWKRALQ 497
3A4A_A|PDB ID          WTKDKPNAGFTGPDVKPWFLLNE SF EQGINVEQESRDD SVLNFWKRALQ 500
                        *:::*****:*. ***:** ***:** ***:** * :*****:*. **
P53341|MAL12_YEAST      ARKKYKELMIYGYD FQFIDLSDQ IFSFTKEYEDKTLFAALNFSGEEIEF 547
3A4A_A|PDB ID          ARKKYKELMIYGYD FQFIDLSDQ IFSFTKEYEDKTLFAALNFSGEEIEF 550
                        ** :*: :*****:*****:..:*****:***:*****:***: **
P53341|MAL12_YEAST      SLPREGASLSFILGNVD--DTDVSSRVLKPWEGR IYLVK 584
3A4A_A|PDB ID          SLPREGASLSFILGNVD--DTDVSSRVLKPWEGR IYLVK 589
                        .*:..*:..:*** :*. ***. *****: :

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Fig 2. Sequence alignment result between the template protein *S. cerevisiae* oligo-1,6-glucosidase (PDB ID 3A4A) and the target protein *S. cerevisiae* α -glucosidase (Mal12). The asterisks (*) indicate the conserved residues between the two protein. The red residues form the responsible for the break glycosidic bond

RESULT AND DISCUSSION

In silico study was carried out in order to determine the interaction between the ligand to its receptor. In this study, the receptor of a three-dimensional crystal structure of *S. cerevisiae* α -glucosidase was used. Unfortunately, its crystal structure is not yet available, therefore the homology modeling must be done in order to obtain a three-dimensional model of the structure. The first step in homology modeling was to determine the target and template. The target used in this study was the amino acid sequence of *S. cerevisiae* α -glucosidase MAL12 with 584 amino acids and obtained from Swiss-Prot (code P53341). The template used in this study was the crystal structure of *S. cerevisiae* oligo-1,6-glucosidase which was obtained from the PDB (PDBID 3A4A) with resolution 1.60 Å and 589 amino acids [16]. The selection of target and template are based on the

sequence similarity their amino acids. Oligo-1,6-glucosidase has amino acid residues which responsible for the break the glycosidic bond. These residues are His112, Asp215, Glu277, His351 and Asp352 [16]. The presence of these residues makes the crystal structure is suitable to be used as template in the homology process.

Crystal structure of *S. cerevisiae* oligo-1,6-glucosidase (PDB code 3A4A) was aligned with the *S. cerevisiae* α -glucosidase MAL12 (Swiss-Prot code P53341) using the ClustalW2 program. This alignment would be able to identify the similarity sequence of the above-mentioned molecules. The results showed that the alignment similarity of amino acid sequence between the *S. cerevisiae* oligo-1,6-glucosidase and *S. cerevisiae* α -glucosidase MAL12 was 71.92% as shown in Fig. 2. The percentage of similarity above 40% indicates that the crystal structure of *S. cerevisiae*

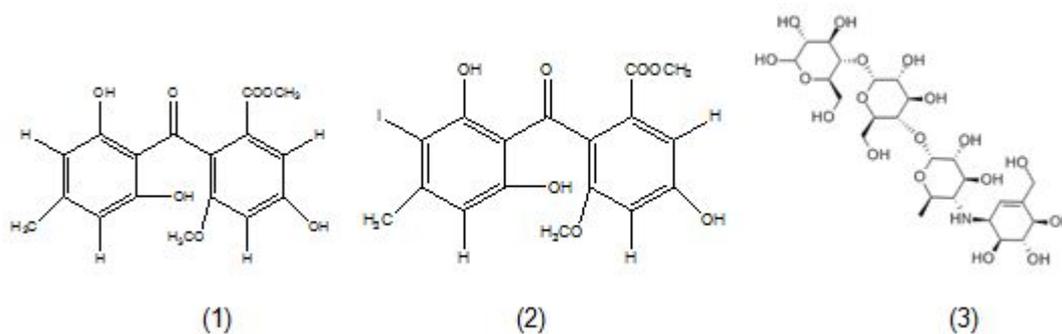


Fig 3. Sulochrin (1), sulochrin-I (2) and acarbose (3) structures

Table 1. Free energy (ΔG) of ligand to *S. cerevisiae* α -glucosidase (PI: experiments 1, PII: experiments 2, PIII: experiments 3, ACR: acarbose, S: sulochrin, A: sulochrin-I)

Ligand	Free Energy (ΔG) with AutoDock program (kcal/mol)									
	Best Energy					Best Cluster				
	PI	PII	PIII	Mean	SD	PI	PII	PIII	Mean	SD
ACR	-12.27	-12.28	-12.09	-12.21	0.107	-10.06	-10.04	-10.2	-10.1	0.087
S	-4.82	-4.9	-4.75	-4.82	0.075	-4.76	-4.76	-4.75	-4.76	0.006
A	-6.67	-6.72	-6.75	-6.71	0.040	-6.59	-6.60	-6.55	-6.58	0.026

oligo-1,6-glucosidase was qualified as a template in the process homology modeling [8]. In a recent publication, homology modeling of α -glucosidase was performed with *Bacillus cereus* (O16GB) as a template and the percentage of similarity was found to be 58.4% [8].

Homology modeling of *S. cerevisiae* α -glucosidase was performed using an SWISS-MODEL software that can be accessed at <http://swissmodel.expasy.org>. Homology modeling process was done using target *S. cerevisiae* α -glucosidase MAL12. The result from this process was QMEAN Z-score a value that describes the quality of a model by providing an estimate of the 'degree of nativeness' of the structural features observed in a model and useful measure quality of theoretical models. Rasouli and Fazeli-Nasab reported that a model with QMEAN Z-score between 0 and 1 was considered to be a good quality model [17-19]. The value of QMEAN Z-Score calculated for *S. cerevisiae* α -glucosidase MAL12 was off -0.019. This result shows *S. cerevisiae* α -glucosidase MAL12 was a good quality of the model because of the estimated reliability of the model was very much close to the value of 0, the value which was considered to be a good quality model.

The evaluation of the obtained models was performed using the PROCHECK program through Ramachandran plot. This evaluation gave the percentage of residual in most favorable regions of 87.7% and 0.2% in disallowed region. The percentage of residues in most favorable regions illustrates the quality of protein models. The above-mentioned results indicated that the model developed was qualified to be used for molecular docking process.

Docking simulation was performed on sulochrin, methyl 2-(2,6-dihydroxy-3-iodo-4-methylbenzoyl)-5-hydroxy

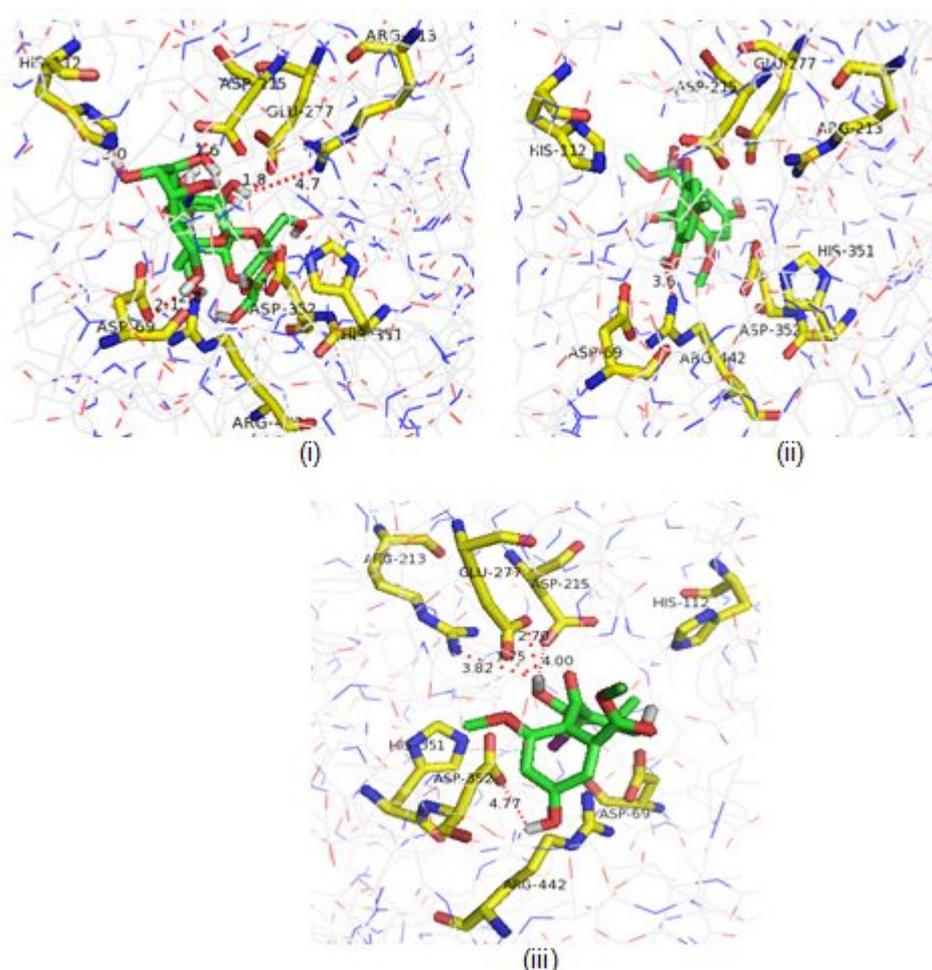
-3-methoxybenzoat (sulochrin-I) and acarbose as a control (Fig. 3). Docking was run using AutoDock 4.2 with Lamarckian Genetic Algorithm (Lamarckian GA). A number of the evaluation was chosen the long category with RMSD 0.5 Å. The analysis showed that acarbose has the lowest of the free energy (ΔG), -12.21 ± 0.07 kcal/mol. The free energy for sulochrin and sulochrin-I were -4.82 ± 0.07 and -6.71 ± 0.04 kcal/mol, respectively. This results indicating that acarbose has the most stable bond when it interacts with the *S. cerevisiae* α -glucosidase compared with sulochrin and sulochrin-I (Table 1). This analysis also showed that sulochrin-I has more stable bond than the sulochrin when interacted with *S. cerevisiae* α -glucosidase. This result suggests that the presence of iodine atoms in the sulochrin molecule improving the stability of sulochrin-*S. cerevisiae* α -glucosidase. Inhibition constants (K_i) of acarbose, sulochrin, sulochrin-I are shown in Table 2. It can be seen that acarbose has the smallest K_i value compared to that of sulochrin, sulochrin-I. K_i values of acarbose, sulochrin, sulochrin-I were $1.13 \cdot 10^{-3} \pm 0.2 \cdot 10^{-3}$, 293.69 ± 35.77 and 12.03 ± 0.83 μ M respectively. These results suggest that acarbose has the best ability to inhibit of α -glucosidase. The presence of iodine atoms in sulochrin was found to decrease K_i values sulochrin from 293.69 to 12.03 μ M (sulochrin-I). Lowering K_i value of iodinated sulochrin indicated the increasing of its ability to inhibit the activity of α -glucosidase. Inhibition of α -glucosidase occurs through the formation of hydrogen bonds between ligands (i.e. acarbose, sulochrin and sulochrin-I) with the active site of *S. cerevisiae* α -glucosidase (Table3). Based on results in Table 3, it can be suggested that acarbose interacts with all active

Table 2. Inhibition constants (Ki) of ligand to *S. cerevisiae* α -glucosidase (PI: experiments 1, PII: experiments 2, PIII: experiments 3, ACR: acarbose, S: sulochrin, A: sulochrin-I)

Ligand	Inhibition constant (Ki) with AutoDock program (μM)									
	Best Energy					Best Cluster				
	PI	PII	PIII	Mean	SD	PI	PII	PIII	Mean	SD
ACR	1.01×10^{-3}	1×10^{-3}	1.38×10^{-3}	1.13×10^{-3}	0.2×10^{-3}	42.58×10^{-3}	43.39×10^{-3}	33.25×10^{-3}	0.039	0.0056
S	294.17	257.68	329.23	293.69	35.77	321.78	329.23	325.32	321.78	3.74
A	12.92	11.91	11.26	12.03	0.830	14.63	15.75	15.027	15.14	0.56

Table 3. Ligand interaction on active site of *S. cerevisiae* α -glucosidase (\checkmark indicate interaction with distance $\leq 5\text{\AA}$, - indicate no interaction, ACR: acarbose, A: sulochrin-I)

Ligand	Residues of <i>S. cerevisiae</i> α -glucosidase							
	Asp69	His112	Arg213	Asp215	Glu277	His351	Asp352	Arg442
ACR	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	-	\checkmark	\checkmark
Sulochrin	-	-	-	-	-	-	-	\checkmark
A	-	-	\checkmark	\checkmark	\checkmark	-	\checkmark	\checkmark

**Fig 4.** Interaction of (i) acarbose, (ii) sulochrin, (iii) sulochrin-I with active sites of *S. cerevisiae* α -glucosidase

sites on *S. cerevisiae* α -glucosidase (i.e. Asp69, His112, Arg213, Asp215, Glu277, His351, Asp352 and Arg441) except His351, while sulochrin only interacts with Arg442 and sulochrin-I interacts with residues Arg213, Asp215, Glu277, Asp352, Arg442. The difference in these

interactions causes acarbose have the most stable and good inhibitory ability.

The results of the analysis of docking indicate that the ligands visually occupy the active sites of *S. cerevisiae* α -glucosidase as shown in Fig. 4. Those

corresponding active sites are Asp69, His112, Arg213, Asp215, Glu277, His351, Asp352 and Arg441 [15].

CONCLUSION

The three-dimensional model structure of the *S. cerevisiae* α -glucosidase was obtained by homology using *S. cerevisiae* α -glucosidase MAL12 (Swiss-Prot code P53341) as a target and the crystal structure of *S. cerevisiae* oligo-1,6-glucosidase (PDB code 3A4A, 1.60 Å resolution) as a template. Interaction of sulochrin to the active site of the α -glucosidase enzyme from *S. cerevisiae* has been studied by docking method. Model compounds of sulochrin-I were found to form a more stable bond and better inhibition capability towards α -glucosidase enzymes compared to that of sulochrin. The presence of iodine atoms on sulochrin was found enhancing its inhibitory action towards the α -glucosidase enzymes. Sulochrin-I could be bound in the active site of α -glucosidase from *S. cerevisiae* through the formation of hydrogen bonds with Arg213, Asp215, Glu277, Asp352.

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