INTRODUÇÃO

A enzima SIRT1 tem duas funções principais: catalisar a desacetilação de proteínas e atuar como um regulador de nutrientes. A enzima SIRT1 é responsible por desacetilação de proteínas e estabilização da atividade de desacetilase. A substituição do Glu230 com Lys resiste à atividade enzimática de redução da STACs. A composta de STACs de 4TO demonstrou interações hidrofóbicas com Leu215, Thr219 e Ile223 e interações de hidrogênio com Asn226, e com CNA (carba-nicotinamida-adenina-dinucleotídeo) ligado ao catalytic region. A complexo de SIRT1 com STACs mostra interações da STAC-1 com a STAC sem bond interactions at Glu230 e Arg446. O modelo ativo do complexo SIRT1 contém um STAC complex com a Ac-p53 substrato, indicando a presença de amino-acido-hidrofóbico-interações no Glu230 e Arg464. O complexo de SIRT1 com STAC composto mostra interações da STAC-1 com o catalytic binding domain (SBD). A ligação de STACs estimula a interação entre o catalytic region e a enzima SIRT1, aumentando a atividade da desacetilase. Substituição de Glu (E) 230 com Lys resultados disrupção enzimática atividade reduzindo a electrostático interações entre Glu230 e SBD Arg446 no substrate-binding site [13].

O modelo ativo de SIRT1 é uma complexo com o Ac-p53 substrato, indicando a presença de amino-acido-hidrofóbico-interações no Glu230 e Arg464. O complexo de SIRT1 com STAC composto mostra interações da STAC-1 com o catalytic binding domain (SBD). A ligação de STACs estimula a interação entre o catalytic region e a enzima SIRT1, aumentando a atividade da desacetilase. Substituição de Glu (E) 230 com Lys resultados disrupção enzimática atividade reduzindo a electrostático interações entre Glu230 e SBD Arg446 no substrate-binding site [13].

ASPECTO

A enzima SIRT1 tem duas funções principais: catalisar a desacetilação de proteínas e atuar como um regulador de nutrientes. A enzima SIRT1 é responsible por desacetilação de proteínas e estabilização da atividade de desacetilase. A substituição do Glu230 com Lys resiste à atividade enzimática de redução da STACs. A composta de STACs de 4TO demonstrou interações hidrofóbicas com Leu215, Thr219 e Ile223 e interações de hidrogênio com Asn226, e com CNA (carba-nicotinamida-adenina-dinucleotídeo) ligado ao catalytic region. A complexo de SIRT1 com STACs mostra interações da STAC-1 com a STAC sem bond interactions at Glu230 e Arg446. O modelo ativo do complexo SIRT1 contém um STAC complex com a Ac-p53 substrato, indicando a presença de amino-acido-hidrofóbico-interações no Glu230 e Arg464. O complexo de SIRT1 com STAC composto mostra interações da STAC-1 com o catalytic binding domain (SBD). A ligação de STACs estimula a interação entre o catalytic region e a enzima SIRT1, aumentando a atividade da desacetilase. Substituição de Glu (E) 230 com Lys resultados disrupção enzimática atividade reduzindo a electrostático interações entre Glu230 e SBD Arg446 no substrate-binding site [13].
The structure of SIRT1 PDB ID 5BTR (www.rcsb.org/structure/5btr) is the SIRT1 activator located in the allosteric region, a complex containing three resveratrol ligands (STL), and shows hydrogen bonding interactions at Glu222, Asn226, Ile344, Asp298, Asp292, and Glu320 and H2s at Gly415, Ile223, Glu294, Ile223, and Arg446.

Intection of 7-amino-4-methyl coumarin with 5BTR shows H2s at Phe412, Va414, His363, and Phe414 and hydrogen bond interactions at Arg446, Asn226, Gly415, Asp150, Glu416, and Val412 [12].

Therefore, the present study used an silico study with molecular docking and dynamic simulations of the SIRT1 enzyme (PDB IDs 4ZZI, 4ZZJ, 4ZZH, and 5BTR) to determine the bonding interactions of SIRT1 required for ligand selectivity and selective identification of bond interactions and target bond interactions with biological function [14,15].

MATERIALS AND METHODS

Materials

The following materials were used: IntelXeon(R) central processing unit ES620 at 2.40 GHz × 16, processor 2.6 GHz Intel Core i7, random access memory 32 GB 1600 MHz DDR3, and Graphics Intel Iris 15.36 MB. The operating system used was Linux Ubuntu 12.04 LTS with an uninterrupted power supply.

Protein preparation

Preparation of macromolecular three-dimensional structure was done by downloading macromolecules SIRT1 (PDB IDs: 4ZZI, 4ZZJ, 4ZZH, and 5BTR) was obtained from the Research Collaboratory for Structural Bioinformatics PDB (http://www.rscb.org/pdb) [16]. All macromolecules were clean-up from ligands, substrates, ions, and waters before minimization with Amber program [17].

Ligand preparation

The ligands used were the 4TO crystals of macromolecular SIRT1 (PDB IDs: 4ZZH). Minimization of ligand used the AMBER program, and 1NS compound (SIRT1 inhibitor) was used as a negative control.

Molecular docking validation

AutoDock4Zn was used to perform molecular docking in this study [18,19]. Validation of the autodock4Zn program measured the root mean square deviation (RMSD) value analyzed using the visual molecular dynamic (VMD) program and the initial crystall structure of PDB against the conformational crystal positioning after molecular docking was done.

Molecular docking

Molecular docking was performed using AutoDock4Zn, with ligand–macromolecular grid binding sites by determining npts and gridcenter. Analysis of the docking results in the form of affinity and RMSD binding values (for docking performance validation) of docking results to analyze ligand interaction with macromolecules used LigandScout (IntLigand, Austria) [20] and CHIMERA (UCSF/USA), respectively [21].

Molecular dynamics

The best compounds for molecular docking were selected for the molecular dynamics study, and the simulation was performed using Amber12 [17] for 50 ns.

General amber force field (GAFF) was used for ligand preparation [13]. Ligands and macromolecules topologies and coordinates were created in a vacuum and explicit waters environment. At this stage, the ligand structure was provided with an AM1–bond charge correction charge [14] using Antechamber software (UCSE USA) accessed via PDB. The file output was obtained in the form of *.mol2, and the antechamber result created a *.frcmod file.

Preparation of parameters and coordinates of macromolecule files containing Zn was performed online (http://mayoresearch.mayo.edu/mayo/research/camdl/zinc_protein.cfm).

Preparation of peptide minimization (substrate) used parameters and coordinates of peptide-containing (NArg His Lys Lys Leu Met CPhe) macromolecular files [22]. Preparation for the formation of NAD+ used NAD+ as a cofactor with a positive charge. The creation of macromolecules with NAD+ required NAD+lib and NAD+-frcmod parameter files were obtained from Ross Walker, and the coordinates were altered using the coordinates of the NAD+ file associated with the macromolecules. Further complexes of ligand: Zn: NAD+.

Macromolecules were used as topological and coordinate files with the addition of water molecules TIP3PBOX 12 Å, followed by minimization, heating, density, equilibration, and production.

Before continuing the dynamics simulation, verification of the system was balanced using the command "process_mdout. pl" to extract useful information from the output file: heat. out, density. out, and equil. out. A balanced system was seen from the temperature, density, and RMSD.

RESULTS AND DISCUSSION

The present study was performed by visualizing 4TO coocrystal interactions with SIRT1 macromolecules (SIRT1 PDB IDs 4ZZI, 4ZZJ, and 4ZZH) and one with three STLs (PDB ID 5BTR). Analysis of complex compound interactions (STACs) with SIRT1 activator receptors in the allosteric region was used to examine the bonding interactions that play an important role in ligand selectivity. Activator compounds act as sirtuin activators bound to the amino acid allostere site at residues 183–243 and generally interact at the hydrophobic chains at Thr209, Pro211, Pro212, Leu215, Thr219, Ile223, and Ile227 at the shape of the (helix-turn-helix) amino acid and one hydrophilic interaction at Asn226 (Supplemental Fig. 1). Visualization of macromolecular interactions with SIRT1 PDB IDs 4ZZI, 4ZZJ, 4ZZH, and 5BTR showed differences in the position of the allosteric region receptors. Residues at Glu220–Asn241 showed a flexible helix shape. As Fig. 1 shows, the superimposition of SIRT1 PDB ID 4ZZI demonstrates a more closed form between the allosteric and catalytic regions, containing 4TO ligand crystals in the allosteric region and 1NS ligand crystals in the catalytic region. SIRT1 PDB ID 4ZZJ contains CNA and 4TO ligand crystals in the allosteric region, and the allosteric area form was catalytically more open than that of 4ZZI. PDB 4ZZH showed an allosteric and catalytic form that was more open and contained only 4TO ligand crystals in the allosteric region. PDB 5BTR contained resveratrol compounds in the allosteric region adjacent to the catalytic region.

Validation of molecular docking

In the present study, AutoDock4Zn was used to visualize molecular docking. Validation of this AutoDock program measured the RMSD value analyzed using the VMD prgram. The initial crystall structure was balanced using the command "process_mdout. pl" to extract useful information from the output file: heat. out, density. out, and equil. out. A balanced system was seen from the temperature, density, and RMSD.

Molecular docking of macromolecular 4ZZI

The macromolecule receptor of 4ZZI has ligand crystals in the catalytic region as an activator. This ligand was 4TO {[(S)-N-[2-[1,3-oxazole-5-y]-phenyl]-7-[3-[trifluoromethyl] phenyl]-3,4-dihydro-1,4-methanopyrrodo [2,3-b] [1,4] diazepine-5 [2H]-carboxamide} in the
allosteric region as an activator. The molecular docking results of the 4TO obtained bond energy values of $\Delta G = -6.86 \text{ kcal/mol}$ and a $K_i$ value of $9.36 \mu M$ (predicted binding interaction).

Fig. 2 shows the 4TO ligand crystal compound interaction. 4TO bonded to the activating region of essential amino acids Ile223 and Ile227. The complex showed four hydrophobic features at amino acids namely Leu206 (HI), Thr219 (HI), Ile223 (HI), Ile227 (HI), Asn226 (hydrogen bond acceptor [HBA]), and Glu230. Docking of the 1NS compound (SIRT1 inhibitor) as a negative control on the allosteric region showed interactions at Thr219 (HBD) and Ile227 (HBD) and no HIs (Supplemental Fig. 2).

**Molecular docking of macromolecular 4ZZI**

The AutodockZn program was used to analyze docking of the ligand crystal molecule and the active compound SIRT1 with 4ZZI. The results obtained from the process showed a bond energy value of $\Delta G = -6.94 \text{ kcal/mol}$, a $K_i$ value of $8.24 \mu M$ (predicted binding interaction), and the complex interaction of ligand and receptor bonds.

Fig. 3 shows the 4TO compound interaction. The complexes demonstrate four hydrophobic features at amino acids namely Leu206 (HI), Thr209, Leu215 (HI), Thr219 (HI), Ile223 (HI), and Ile227 (HI) and show acceptor hydrogen bonding interactions (HBA) at Asn226. Docking of the 1NS compound (SIRT1 inhibitor) as a negative control on the allosteric region showed interactions at Gln222 (HBD) and Thr219 (HBD) and no HIs (Supplemental Fig. 2).

**Molecular docking of macromolecular 4ZZH**

The AutodockZn program was used to generate molecular docking of the crystal ligand molecule and the active compound SIRT1 with 4ZZH. The results were obtained using a bond energy value of $\Delta G = -7.61 \text{ kcal/mol}$ and $K_i = 5.6 \mu M$ (predicted binding interactions).

The 4TO compound showed interactions with four hydrophobic features of the amino acids namely Leu206 (HI), Leu215, Thr219 (HI), Ile223 (HI), and Ile227 (HI) and showed acceptor hydrogen bonding interactions (HBA) at Thr209 (HI) residues.

4TO compound interaction with macromolecules is shown in Fig. 4, showing interaction with four hydrophobic features at amino acids namely Leu206 (HI), Thr209, Leu215 (HI), Thr219 (HI), Ile223 (HI), and Ile227 (HI).

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![Fig. 1: Visualization superimposition crystal structure of protein data bank (4ZZI, 4ZZJ, 4ZZH, and 5BTR) shows the flexibility of allosteric region](image)

![Fig. 2: (a) Molecular docking of 4TO:4ZZI at the allosteric region. (b) Visualization of 4TO:4ZZI complex interactions at Thr219, Ile223, Ile227, Asn226 (hydrogen bond acceptor), and Glu230 using the LigandScout program. (c) Visualization of the 4TO:4ZZI complex using a mesh surface image generated by CHIMERA (hydrophilic, blue; hydrophobic, orange)](image)
Molecular docking of macromolecular 5BTR
Molecular docking 4TO with 5BTR using the AutodockZn program was obtained using a bond energy value of $\Delta G = -13.1 \text{ kcal/mol}$ and $K_i = 2.51 \times 10^{-4} \text{ M}$ (predicted binding interaction).

The 4TO ligand revealed bonds at the activating regions of essential amino acids Ile223 and Ile227. The complex showed hydrophobic features at amino acids namely Leu206 (HI), Thr219 (HI), Ile223 (HI), and Ile227 (HI) (Fig. 5). Docking of the 1NS compound (SIRT1 inhibitor) as a negative control on the allosteric region showed interactions at Leu206 (HBD) and no HIs (Supplemental Fig. 2).

Molecular dynamic simulation
Molecular dynamic simulation of 4TO compounds against 4ZZI, 4ZZJ, 4ZZH, and 5BTR receptors was performed for 50 ns using the Amber program. Analysis of the dynamics simulation result was carried out considering RMSD, RMSF, and hydrogen bonding conditions, and the binding energy was calculated using the MMGB/PBSA method.

RMSD
Conformational changes of the 4TO compound during the simulation were seen from the RMSD values. The RMSD curve for 50 ns showed a change in the stability of the 4TO complex dynamic simulation that corresponded to 4ZZI, 4ZZJ, 4ZZH, and 5BTR receptors. In Fig. 6, the 4TO:4ZZI, 4TO:4ZZJ, and 4TO:5BTR complexes showed an RMSD range of 2Å, whereas the 4TO:4ZZH complex had a RMSD range of 3Å.

RMSF
RMSF is the measure of the deviation between the atomic positions of each protein residue, i.e., the difference in fluctuations in the movement of each residue during the simulation is measured for 50 ns. Fig. 7 shows the RMSF value of the complex molecular dynamic simulation between the 4TO ligand (ligand crystal) and 4ZZI, 4ZZJ, 4ZZH, and 5BTR receptors. The 4ZZH receptor showed fluctuations in the N-terminal domain of all RMSF compared with 4ZZI, 4ZZJ, and 5BTR receptors that did not show fluctuations, indicating that binding of the 4TO compound to the receptor is more stable.
Fig. 6: Root mean square deviation and conformational changes of receptor structure at an interval of 10 ns (a). Zn:4ZZI, (b). peptide: Zn: NAD+:4ZZJ, (c). Zn:4ZZH, and (d). peptide: Zn:5BTR with 4TO at 300 K.
Hydrogen bond analysis

As an activator of SIRT1 PDB ID 4ZZJ, the 4TO ligand crystal shows the presence of hydrogen bond interactions at Arg234–Asp475 (NH–O) 2.83Å, Arg234–His473 (NH–O) 2.84Å, and Arg234–Val459 (NH–O) 3.01 Å [7]. The VMD program was used to perform hydrogen bond strength analysis (% occupancy) of 4TO with SIRT1 PDB IDs 4ZZI, 4ZZJ, 4ZZH, and 5BTR from molecular dynamic simulations for 50 ns. Based on the molecular dynamic simulations, 4TO in complex with 4ZZI and 4ZZH receptors did not show any hydrogen bond interactions between Glu230 (allosteric regions) and Arg446 (catalytic region).

Fig. 9 shows the binding of 4TO ligand to the allosteric region but not to the activator of SIRT1.

The results of the hydrogen bond strength (% occupancy) in the complex of the 4TO ligand with 4ZZJ receptor indicated the presence of important amino acid interactions, namely Glu230–Arg446, 51%; Arg234–Asp475, 65.1%; Arg234–His473, 22.50%; and Arg234–Val459, 11.7%. The hydrogen bond strength (% occupancy) in the complex of the 4TO ligand with the 5BTR receptor showed the presence of important amino acid interactions, namely Glu(E)230–Arg(R)446, 65.80%; Arg(R)234–Asp(D)475, 70.9%; Arg(R)234–His(H)473, 33.3%; and Arg234–Val459, 4.9% (Fig. 10). The results of this analysis indicate that the SIRT1 activator is showed by hydrogen bond interactions between Glu230 and Arg234 (allosteric region) with Arg446, Val459, His473, and Asp475 (catalytic region) which are close to the bound substrate region.

Free energy calculation (ΔG)

The result of the ΔG bond energy calculated from the molecular docking with AutoDock4Zn was then recalculated to determine the free bonding energy from the 4TO compound with SIRT1 PDB IDs 4ZZI, 4ZZJ, 4ZZH, and 5BTR using the MM-GBSA method, with simulation dynamics carried out for 50 ns. This was performed to ensure that the bond energy was more selective [23], and the energy value of the 4TO ligand bond with 4ZZJ receptor using the MM-GBSA method was calculated, while MMPBSA measured bond energy on simulation dynamics for 50 ns.
The calculation of the compound complex of 4TO ligand crystal with peptide: Zn:NAD+:4ZZJ found a value of MMGBSA (ΔG_{total}) = −31.4729 kcal/mol, ΔG_{total} = ΔG_{gas} + ΔG_{solv} = −51.2942 + 19.8212 = −31.479 kcal/mol. Fig. 11 shows an example of the calculation. Fig. 12 shows the overall results.

The calculation of the compound complex of 4TO ligand crystal with peptide: Zn:NAD+:4ZZJ showed a range of bonding energy values as follows: MMGBSA ΔG = 1.4979 kcal/mol (−34.461—to−26.6982) and MMPBSA ΔG = 1.4592 kcal/mol (−30.343—to−28.5751). The bond energy of 4TO:peptide:Zn:NAD+:4ZZJ showed a range of bonding energy values as follows: MMGBSA ΔG = 4.7973 kcal/mol (−31.4729—to−26.6756) and MMPBSA ΔG = 4.1432 kcal/mol (−32.6292—to−28.486). The 4TO:Zn:4ZZI bond energy indicates the range of bond energy enzymes as follows: MMGBSA ΔG = 10.9523 kcal/mol (−36.2616—to−25.3093) and MMPBSA ΔG = 10.8905 kcal/mol (−37.4334—to−26.5429). The bond energy of 4TO:Zn:5BTR:Ac:peptide showed a range of energy values as follows: MMGBSA ΔG = 10.56 kcal/mol (−40.6255—to−30.0653) and MMPBSA ΔG = 8.6762 kcal/mol (−34.6713—to−25.9951). The results obtained from

Fig. 10: Hydrogen bond strength (% occupancy) of important amino acid interactions in the complex of 4TO:4ZZJ and 4TO:5BTR

Fig. 11: Calculation of free bonding energy (MMGBSA) in 4TO: peptide:Zn: NAD+:4ZZJ complex.
the four different receptors (4ZZI, 4ZZJ, 4ZZH, and 5BTR) showed that the strength of the 4TO bond to 5BTR was stronger than that of the other receptors because the receptor form was more closed. A small difference in MM-GB(PB)SA range values was seen in the interaction between 4TO-Zn-4ZZI.

CONCLUSIONS

The present study describes an in silico study of SIRT1 bond interaction using a simulation approach of molecular dynamics over 50 ns using the Amber program. Analysis of activator ligand (4TO) binding to the SIRT1 receptor (PDB IDs 4ZZI and 5BTR) showed selectivity of the ligand by marked hydrophobic bond features on Leu206, Ile223, Asn226, Ile227, and Glu230 of the 4ZZI and 5BTR receptors.

Hydrogen bond interactions between Glu230 and Arg234 (allosteric regions) with Arg446, Val459, His473, and Asp475 (catalytic areas) ensured that they became close to the bounding substrate area. The bond energy values obtained for 4TO interacting with 4ZZJ using the MM-GB(PB)SA calculation using AMBER were as follows: MMGBSA ΔG = -31.4729-26.675 and MMPBSA ΔG = -32.6292-28.486. The bond energy values of the 4TO interaction with 5BTR were as follows: MMGBSA ΔG = -40.6255–30.0653 and MMPBSA ΔG = -34.6713–25.9951. These results are important for drug discovery and development as they give insight into target interaction of the bonds to the more selective SIRT1 activator [24-26].

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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Supplemental Fig. 1: (A) (i) Visualization of 4ZZI. (ii) The structure of the 4T0:4ZZI complex shown as a mesh surface image generated by CHIMERA (hydrophilic, blue; hydrophobic, orange). (iii) Three-dimensional image generated using LigandScout. (B) (i) Visualization of 4ZZJ. (ii) The structure of the 4T0:4ZZJ complex shown as a mesh surface image generated by CHIMERA (hydrophilic, blue; hydrophobic, orange). (iii) Three-dimensional image generated using LigandScout. (C) (i) Visualization of 4ZZH. (ii) The structure of the 4T0:4ZZH complex shown as a mesh surface image generated by CHIMERA (hydrophilic, blue; hydrophobic, orange). (iii) Three-dimensional image generated using LigandScout. (D) (i) Visualization of 5BTR. (ii) The structure of the resveratrol:4ZZJ complex shown as a mesh surface image generated by CHIMERA (hydrophilic, blue; hydrophobic, orange). (iii) Hydrogen bond interaction at the allosteric region.

Supplemental Fig. 2: Molecular docking of the 1NS compound (SIRT1 inhibitor) as a negative control in the allosteric site.