

Molecular Docking and Molecular Dynamic Simulation of 1,5-Benzothiazepine Chalcone Derivative Compounds as Potential Inhibitors for Zika Virus Helicase

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Received: January 2021
Accepted: March 2021
Published: March 2021

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Abstract

Zika virus caused of the emerging infections characterized by fever, Guillain-Barré syndrome (GBS) for adults. In the current work, we aimed to study the binding orientation of 1,5-benzothiazepine compounds as new potential agent against Zika virus inhibitor through molecular docking and molecular dynamic simulation. Since, 1-5-Benzothiazepines are particular interest for drug discovery and they also has some biological activities. However, their antiviral activities and *in silico* studies of the binding to their biological targets have not been extensively investigated. Molecular docking study of 1,5-benzothiazepine chalcone derivatives compounds with protein target 5GJB (PDB ID) and this protein was taken from the crystallographic structure. In this study, twelve 1,5-benzothiazepine chalcone derivative compounds were docked to the protein with the grid box along x, y and z radius of 26.85, 28.17 and 24.43 Å, respectively. Suramin was used as positive control. Thus, it can be used as a reference for design new inhibitors for Zika virus helicase. Based on the docking results, it is observed that compounds **MA3** and **MA8** are estimated to have activity as inhibitors for Zika virus helicase with binding free energy values of -4.6490 and -4.9291 kcal/mol, respectively. **MA3** and **MA8** were also stable during the MD simulations with the hydrogen bonding are still maintained before and after MD simulation. Furthermore, both of these compounds can be used an early stage for drug design and drug delivery process.

Keywords: docking, MD simulation, 1,5-benzothiazepine, Zika virus, suramin

Introduction

Zika virus (ZIKV) is a type of *Arbovirus* from the genus *Flavivirus*. This virus has a relationship with other *Arboviruses* like Dengue, Yellow Fever, Japanese Encephalitis, and West Nile Virus. This virus was first isolated in 1947 from saliva of a monkey in a study of Yellow Fever^[1]. There are some reports reported about the infections of Zika virus, one of them reported that in vitro studies on fibroblasts exposed to Zika virus shown high rates of infection from 24

to 48 hours after the onset of infection^[2]. Some symptoms were shown such as rash, fever, conjunctivitis, myalgia, arthralgia, weakness, and headaches^[1].

Tan et. al reported that suramin was used as potential ZIKV infection in Vero cells. Unfortunately, De-sulfated heparin analogues lose the inhibitory effect, this may cause that sulfonate group are critical for viral inhibition. In addition, the inhibitory effect of glycosaminoglycans and analogues against

ZIKV infection^[3]. Thus, there are no reports about vaccine for this virus and there is also no approved vaccine that can be used to attack this Zika virus until now. Since there are no vaccine to attack this ZIKV, patient has been treated using their immune responses^[4].

1,5-benzothiazepine chalcone has been synthesized by previous researcher^[5] derivative compounds consisted of seven-loop heterocyclic compound containing nitrogen and sulfur^[6]. 1,5-benzothiazepine chalcone derivative compound is a compound that has some biological activities such as antimicrobial^{[7]-[9]}, an anticonvulsant agent^[10], *Plasmodium falciparum* cytochrome *bc1* inhibitors^[11], anti-HIV^[12] and pulmonary anticancer^[13]. However, the antiviral activities like Zika virus inhibitor have not been extensively investigated.

The number of structural as well as non-structural protein from ZIKV that have enzymatic function. The drug design and drug discovery was used the enzymatic resolution at high resolution as the main target. NS3 helicase is one of the enzymatic function, its was able inhibition in ZIKV makes the virus unable to replicate and duplicate^[14]. Furthermore, in this research we used NS3 helicase with PDB ID 5GJB as the main target for ZIKV.

Rationally, the main goal is to explore the potency of 1,5-benzothiazepine chalcone derivative compounds to bind with the active site of the Zika virus helicase receptor. In silico study such as molecular docking and molecular dynamic simulation (MD) are able to identify the promising compounds with high activity and also less toxicity according to the binding free energy value^[15]. To date, chalcone derivative heterocycles like 1,5-benzothiazepine chalcone derivative compounds have not extensively studied for the Zika virus inhibitors. In addition, there are not many reports about discovering new inhibitors for Zika virus using computational like molecular docking and MD simulation. The aim of this study is to determine the potentiality of the 1,5-benzothiazepine

chalcone derivative compounds as new inhibitors for Zika virus helicase using molecular docking and MD simulation with suramin as a positive control.

Experimental

Materials

The computational research was performed using computer LG Intel(R) Core (TM) i7-8700 CPU, 3.20 GHz, with 16,0 GB of RAM, ChemDraw Professional 15.0, Molecular Operating Environment (MOE 2019.0101, CCG), Windows 10. Twelve of 1,5-benzothiazepine chalcone derivative compounds^[5], protein target 5GJB^[16] from modeling helicase enzyme crystallographic, and suramin was used as a positive control.

Methods

Ligand preparation

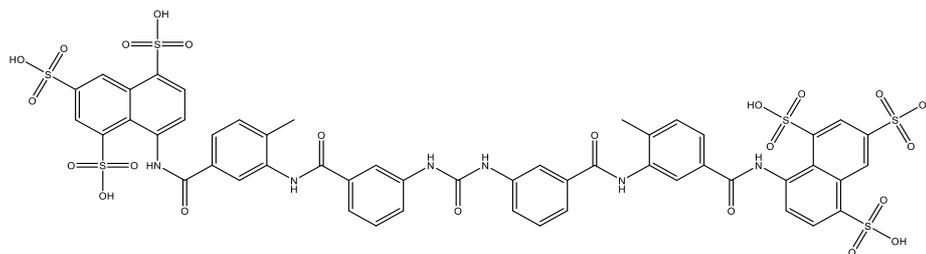
The molecular structure of twelve 1,5-benzothiazepine has been synthesized^[5] and suramin were sketched using ChemDraw Professional software thus, saved with .cdx format and then converted into pdb format using discovery studio visualizer (DSV, Biovia) software package. The molecular structures of twelve 1,5-benzothiazepine chalcone derivative compounds and suramin are depicted in Table 1.

Protein preparation

Three-dimensional structures of 5GJB were obtained from the protein databank (www.rcsb.org) in the .pdb. format with resolution of 1.7Å. Then, the initial ligand and water molecules should be removed. Next is adding hydrogen atoms and energy minimization. The last stage is fixed the energy minimization for backbone atoms and also alpha carbons. Protein was prepared using MOE 2019.01 (Chemical computing group) software package.

Table 1. Molecular structure of the ligand

Code	Structure	Code	Structure
MA1		MA2	
MA3		MA4	
MA5		MA6	
MA7		MA8	
MA9		MA10	
MA11		MA12	

Suramin**Molecular docking**

Molecular docking was performed using MOE 2019.01 (Chemical computing group). It was begun with set up some docking parameters, CHARMM27 (Chemistry HARvard Macromolecular Mechanics) was selected as force field. The dimension along x, y and z radius were set up to be 26.85, 28.17 and 24.43 Å, respectively. The lowest binding free energy was selected as the best docking conformation from all the emerged results.

Molecular dynamic simulation

MD simulation was performed for 1,5-benzothiazepine chalcone derivative compounds-protein complexes using NAMD (Nanoscale Molecular Dynamics program v 2.9) software package. In this case, CHARMM27 was selected as the best force field. Modeled protein was achieved for each direction of coordinated structure using TIP3P water box with the distances of 2.5 Å.

The system was heated using NVT ensemble from 0 to 300 K over 100 ps. Time scale was set up for 50 ns for each system in an isothermal isobaric ensemble (NPT) in periodic boundary conditions. Temperature and pressure were set as a coupling for 1.0 ps. Conformation of each coordinates were then saved every 0.1 ps during the sampling process. From this simulation, some conformations were generated for then the best conformation was selected for further binding free energy calculation.

Results and Discussion

Docking plays an important role in the rational drug design which are often used to predict the

appropriate orientation and binding site of small molecule to their target protein to ascertain their affinity and activity^[17]. Molecular docking has the advantage of filtering large compound databases at a relatively lower cost compared than experimental methods, it is also time-saving, cost-effective, and more productive. In the previous study, it was reported that molecular docking was able to identify promising compounds that could be solutions in the health sector in the future, namely by predicting a ligand-receptor binding site model^[15]. In this study, molecular docking is begun with the selection of protein as a target and ligands. These ligands were attached to the protein. The ligand structure of 1,5-benzothiazepine and positive control (suramin) from ChemDraw was copied and pasted into the MOE program for then create a new database. Meanwhile, 3D protein crystallography extraction is available on the website www.rcsb.org/pdb in PDB format. 5GJB protein crystallography is carried out by deleting the native ligand on the protein structure. The main goal is to explore the potency of 1,5-benzothiazepine chalcone derivative compounds to bind with the active site of the Zika virus helicase receptor. The water molecules in the protein must be removed, this is to avoid the bonding between these water molecules with the protein and it can interfere the data analysis^[18]. The protein provided in protein databank, it needs to add the hydrogen atom to ensure that each atom in the molecule has a charge during receptor preparation^[19] because in general the interactions that occur between ligands and receptors are in the form of hydrogen bonds. Energy minimization is also important when preparing protein against alpha carbon, backbone atoms, and sidechain atoms to

stabilize the bonds protein-ligand. The docking process is carried out for 10 times for each ligand in order to obtain the best binding free energy value^[20]. The docking results are presented in Table 2.

There are some parameters used to analyze the docking results such as Root Mean Square Deviation (RMSD), the docking method is valid if it has a RMSD less than 2 Å^[18]. The RMSD value describes the deviation value from errors that occur when docking. Smaller of the RMSD value indicated that the error deviation in the

docking is also small. The binding free energy is useful for describing how the test ligand can binds well with the receptor. The lower value of the binding free energy is indicated that the binding between ligand and receptor is more stable^[21]. Hydrogen bonding is also become parameter to select the best conformation of docking results. Generally, hydrogen bond can be defining as one of the most non-covalent bonds found in the biological systems^[22]. This bonding occurs between positively charged hydrogen atoms and atoms that have high electronegativity such as O, N, and F^[23].

Tabel 2. Docking results

Code	Parameter					
	Binding Free Energy (kcal/ mol)	RMSD	Factor of Binding with Suramin	Hydrogen Bond	Van der Waals Bond	Hydrophobic Bond
MA1	-4.7422	0.6881	Lys607, His603	Lys610	Glu579, Glu611	Lys610, Lys607, Lys616
MA2	-4.3766	2.0469	Arg388, Ala264	Arg388	-	Arg388, Arg226
MA3	-4.6490	1.3074	Asp574, Glu573	Arg367, Glu573	Asp574, Asp602, Glu573	Arg367
MA4	-4.7583	2.5208	Arg388, Asp291, Ala264	-	Asp291	Arg226, Arg388
MA5	-4.5734	1.3242	His603, Glu573, Asp574	Ser601	Asp574, Glu573	Arg367
MA6	-4.2467	1.0413	Asp574	Asp574	Asp574	Arg367
MA7	-4.5490	1.9705	His603, Glu573, Asp574	-	Asp574, Glu573	Arg367
MA8	-4.9291	1.4669	Glu573, His603, Asp574	Arg367	Glu573, Asp574, Asp602	Arg367
MA9	-4.7536	0.9691	-	Lys537	-	Lys537, Arg538, Arg269
MA10	-4.4337	0.7039	Arg388, Lys389	Arg388	-	Arg388, Lys389
MA11	-4.9251	1.4280	-	Pro277	Glu256, Asp259	Arg275, Arg242, Arg218, Arg269
MA12	-4.5822	3.4292	-	-	-	Arg538, Lys537, Arg269
Suramin	-8.2270	4.6001	-	Asp574, Lys389	Glu573, Asp574, Asp291	Lys607, Lys389, Arg388
Native Ligand	-8.9053	4.5597	Asp574, Glu573, His603	Arg367, Arg343, Asp574	Glu573, Asp574	Arg367, Arg439, Arg343

In addition, hydrogen bonds can also be formed between the H atom with the phenyl ring contained in a medicinal compound^[24]. There is also another binding such as van der Waals interaction and hydrophobic bonds which are supporting bonds to determine whether a compound has good activity or not.

Compounds **MA3** and **MA8** have the lowest binding free energy values. The smaller (negative) of the binding free energy value, it is indicated that, the smaller energy required for the ligand-protein interactions. So that the binding between ligand and protein become more stable and increased their predicted activity^[25]. Two hydrogen bonds are formed in **MA3** compound. Much more hydrogen bonds formed are predicted to increase the ligand

activity as an inhibitor of the Zika virus helicase. In addition, these two compounds also have factor of binding (i.e., measure of probability that a tested compound will bind to the same amino acid residues to which the control compound, suramin binds) calculated by docking may predict which compounds will be more active Zika helicase inhibitors.

Compounds **MA3** and **MA8** were predicted to be active as inhibitors for Zika virus helicase, it was observed in their spatial arrangement using DSV as depicted in Figure 1. Superimposition describes the shape and the best poses of the ligand. It was seen from the compounds that overlap between the test compound and control positive compound.

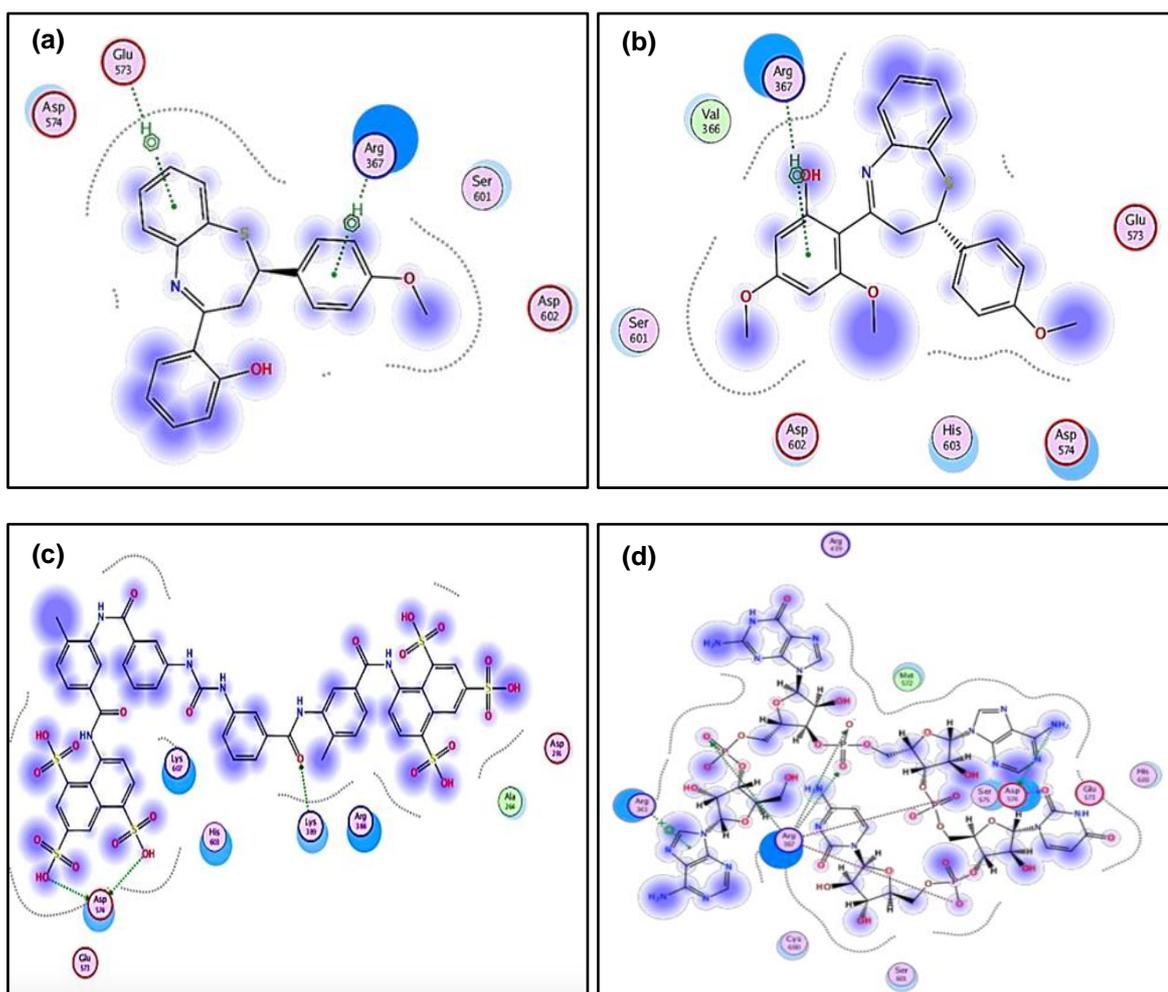


Figure 1. Visualization from ligand interactions of (a) **MA3**, (b) **MA8**, (c) native ligand and (d) suramin.

From the superimposed results, it is found that **MA3** and **MA8** compounds have the same conformations and orientations with the native ligands in the 5GJB protein (i.e., Based on Figure 2), **MA3** and **MA8** compounds shown specificity with the hydrophobic amino acid residues and also hydrogen bonds through Arg367, Glu573 through van der Waals bonds. Thus, **MA3** and **MA8** compounds can inhibit the Zika virus helicase with the same mechanism as the native ligand.

MA3 and **MA8** were exhibited crucial binding affinities (i.e. hydrogen bond) with residue

Arg367 at the protein active site which seems to be significant for activity prediction. Hence, **MA3** and **MA8** considered potentially active as ZIKV and can be further utilized in drug designing process.

MD simulation was applied to **MA3** and **MA8** to ensure that the interaction between ligand and protein are still maintained^[26]. Visualization of the MD simulation are presented in Figure 3. The efficiency of hydrogen bonding for both of these compounds i.e., **MA3** and **MA8** were checked before and after MD simulation for 50 ns and 300K.

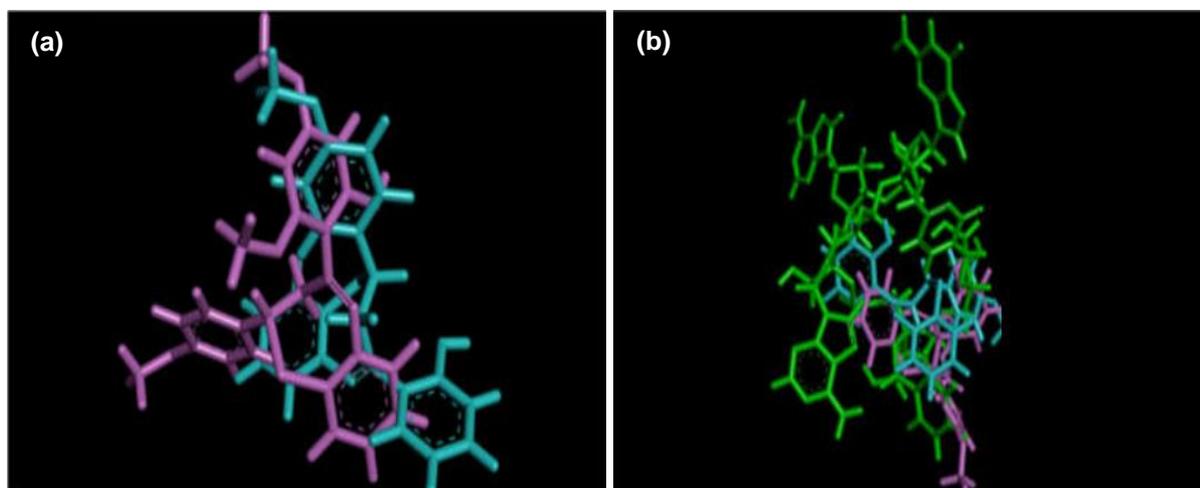


Figure 2. Superimposed (a) **MA3** (blue) and **MA8** (purple) (b) **MA3**, **MA8**, and Native Ligand (green) used DSV.

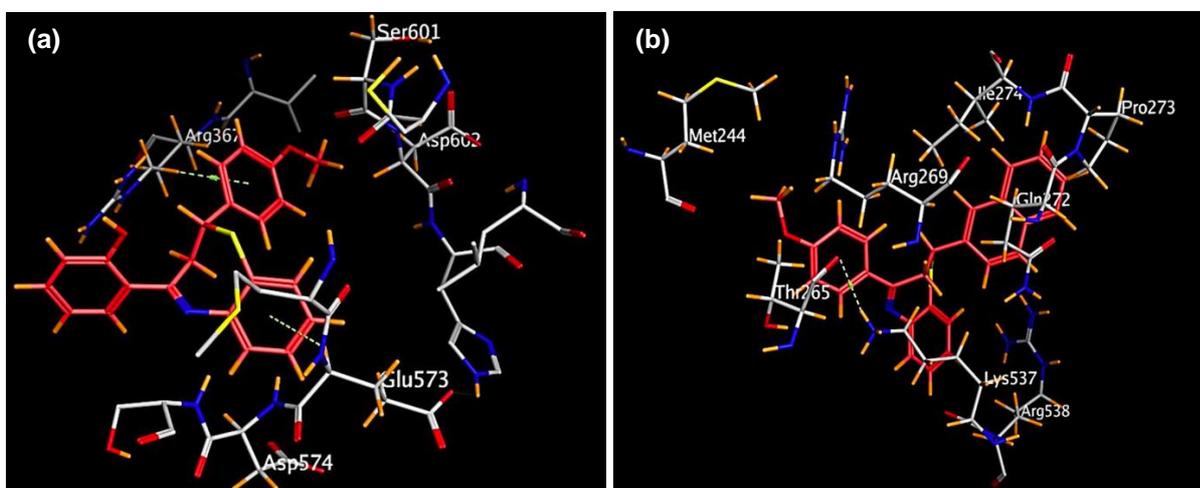


Figure 3. Visualization of MD simulation for compound (a) **MA3** and (b) **MA8**.

Based on the MD results, the conformation of MA3 and MA8 were maintained to bind well with same residues before and after MD simulation process. In addition, the existence of the hydrogen bond distance is less than 2.9 Å. It is indicated that both of these compounds can be used as potential inhibitor for Zika virus helicase.

Conclusions

MA3 and MA8 compounds have met all the expected docking parameters, besides that they also have a greater number of amino acid matches against positive control and also the lowest value of binding free energy compared than other compounds. These two compounds were also able to maintain the hydrogen bonding with the distances less than 2.9 Å. Furthermore, these two compounds can be used as an early stage for drug design and drug discovery against Zika virus helicase.

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