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Research Article

In-Silico Studies of *Brucea javanica* (L.) Merr. as Potential Inhibitors of Influenza A H5NI Neuraminidase

Rina F. Nuwarda*, Kiva Agita, Andhara M. Belinda, Putri Maharani, Denisa Z. Yulia, Nadiyah S. Athaya, and Bilqis N. Almattin

Departement of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Indonesia

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*Corresponding author: rina.nuwarda@unpad.ac.id

Abstract

The H5N1 avian influenza continues to be endemic in Indonesia, posing threats to the poultry farming industry and public health. Type A virus is the most lethal and frequently evolves resistance against NA drugs; therefore, the exploration of novel neuraminidase (NA) inhibitors is crucial. Studies showed that Brucea javanica extract inhibits the activity of the H5N1 NA enzyme. Using the molecular docking technique, this study sought to ascertain the *in-silico* activity of *B. javanica* compounds in relation to H5N1 NA. By utilizing molecular docking simulation, we conducted the *in-silico* study and predicted the toxicity and pharmacokinetic profile, in addition to their drug-likeness according to Lipinski's Rule of Five. The result showed that bruceantinol had a ΔG of -8.93 kcal/mol and Ki of 0.28 μM and interactions with six important amino acid residues. The HIA and Caco-2 values were 47.935% and 19.871%, respectively, whereas the PPB and BBB values were 39.591% and 0.049%, respectively. Neither is this substance carcinogenic nor mutagenic. Low binding energy and the most favored interaction with H5N1 NA were observed for bruceantinol. Although failed to comply with Lipinski's rule of five, bruceantinol still exhibits potential as a prospective NA inhibitor.

Keywords: antiviral, *Brucea javanica*, H5N1, molecular docking, neuraminidase.

Studi *In-Silico Brucea javanica* (L) Merr. Sebagai Inhibitor Potensial Neuraminidase H5N1 Influenza A

Abstrak

Virus flu burung H5N1 yang ada di Indonesia hingga saat ini bersifat endemis dan hingga kini menjadi penyakit yang membebani zona peternakan unggas serta masih menimbulkan masalah kesehatan masyarakat. Virus influenza tipe A merupakan tipe influenza yang paling berbahaya dan sering terjadi resistensi. Seiring berkembangnya resistensi virus terhadap obat penghambat Neuraminidase (NA), dibutuhkan penemuan penghambat NA baru. Penelitian sebelumnya menunjukkan bahwa ekstrak Brucea javanica memiliki kemampuan menghambat aktivitas enzim NA virus H5N1. Penelitian ini bertujuan untuk mengetahui aktivitas *in-silico* senyawa *B. javanica* menggunakan metode penambatan molekular terhadap H5N1 NA. Studi *in-silico* dilakukan dengan simulasi penambatan molekuler, memprediksi profil farmakokinetik dan toksisitas senyawa, serta drug-likeness yang mengacu pada Lipinski's Rule of Five. Hasil penelitian menunjukkan bahwa bruceantinol memiliki free binding energy sebesar -8,93 kkal/mol dengan konstanta inhibisi 0,28 μM dan terdapat interaksi dengan enam residu asam amino penting. Nilai HIA dan Caco-2, yaitu sebesar 47,935% dan 19,871%, sementara nilai PPB dan BBB sebesar 39,591% dan 0,049%. Senyawa ini juga tidak bersifat mutagenik dan karsinogenik. Bruceantinol ditemukan memiliki energi ikat yang rendah dan interaksi paling disukai oleh H5N1 NA. Walaupun tidak memenuhi aturan Lipinski, bruceantinol masih berpotensi untuk dapat dikembangkan menjadi inhibitor NA.

Kata Kunci: antivirus, *Brucea javanica*, H5N1, molecular docking, neuraminidase.

1. Introduction

Influenza is an infectious respiratory illness caused by the influenza virus. This virus infects the throat, nose, and occasionally the lungs. Influenza symptoms can range from mild to severe and can even result in death.[1] There are three types of influenza viruses: influenza A, B, and C, with influenza A being the most dangerous and capable of causing a pandemic due to the high mutation rate and its high risk of forming variants that are more lethal and virulent. Swine flu (H1N1) and bird flu (H5N1) are two influenza A viruses.[2] Avian influenza virus, also known as bird flu, is a single-stranded RNA virus with two layers of glycoproteins named hemagglutinin (HA) and neuraminidase (NA).[3] The H5N1 bird flu virus is endemic in Indonesia, threatening not only the poultry farming industry but also public health. Because this bird flu virus mutates more easily than other types of viruses and is more resistant to NA inhibitor drugs, the development of novel drug candidates is needed to combat this virus.

Brucea javanica, also known as Buah Makassar, belongs to the kingdom Plantae and falls under the subkingdom *Tracheobionta*. It is classified as a super division *Spermathopyta*, division *Magnoliophyta*, and class *Magnoliopsida* (dicotyledons). Further, it is categorized under the subclass Rosidae, order Sapindales, family Simaroubaceae, genus Brucea, and the species *Brucea javanica* (L.) Merr. B. javanica can thrive in both young teak forests and secondary forests in Indonesia.[4]

B. javanica contains a number of secondary metabolites including glycosides (brucealin, kosamine, and yatanoside A and B), phenols (bruceolic acid, brucenol), quassinoid (bruceantinol), and alkaloids (yatanine, brucamarine). The seeds contain several secondary metabolites, including bruceine A, B, C, E, F, G, H, and brusatol. The fruit's flesh also has secondary metabolites such as fatty oil, oleic acid, linoleic acid, stearic acid, and palmitoleic acid. High levels of tannins and saponins are also found in both its leaves and fruit. *B. javanica* exhibits therapeutic properties for various ailments, including gastrointestinal disorders (such as dysentery and diarrhea), coughs, fever, rheumatism, cancer, microbial infections, inflammation, oxidative stress, malaria, tumors, tuberculosis, parasitic infestations, and serves as an effective antibiotic.[5-7]

Prior research has demonstrated that *B. javanica* extract possesses the capability to inhibit the activity of the NA enzyme of the H5N1 and H1N1 viruses.3,6 Therefore, in this study, we aimed to assess the *in-silico* activity of ten *B. javanica* compounds against H5N1 NA using the molecular docking method.

2. Method

2.1. Instruments

A personal computer with Intel ® Core ™ i5-7200U CPU @ 2.50 GHz with Turbo Boost up to 3.1 GHz and 8 GB RAM was employed to run the computational simulation.

2.2. Materials

The crystal structure of H5N1 avian influenza NA complexed with oseltamivir carboxylate (OTV) for molecular docking validation was downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank website (www.rcsb.org) using the PDB ID: 2HU4. The Autodock Tools 1.5.6 software was utilized to perform a molecular docking simulation on the Windows operating system. 2D representations of ligands and proteins was generated using ChemDraw Pro 16. The test ligands were subjected to energy minimization using Chem3D Pro 12. The process of separating the ligand and receptor and visualizing the results of molecular docking was carried out using Biovia Discovery Studio Visualizer 2020. The test ligand's structure from B. javanica was obtained from the ZINC database (http://zinc.docking.org/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/). Ligandscout was used to perform pharmacophore site interaction of test ligands and control drugs. Pre-ADMET (https://preadmet.bmdrc.kr/) was utilized to predict the pharmacokinetic profile and toxicity as well as Lipinski's rule of five.

2.3. Procedures

2.3.1. Molecular docking validation

Using Biovia Discovery Studio Visualizer, the downloaded NA protein structure was separated into ligands and receptor. Using Autodock Tools 1.5.6, the ligand was subjected to Gasteiger charges and receptors with Kollmann charges, and each ligand and receptor was saved in PDBQT format. The grid parameters were generated by creating a grid box with dimensions of 40x40x40 and grid coordinates of x = 0.324, y = 81.366, and z = 109.37 with grid space 0.375 Å, which was then centered on the ligand. Docking parameters were generated by selecting Genetic Algorithm parameters, with a GA runs value of 100. Lamarckian GA was used as the output. The docking procedure was then carried out using the command prompt.[8]

2.3.2. Molecular docking simulation

Chem3D was used to minimize energy in test ligands downloaded from ZINC and PubChem. Kollman charge was then added using Autodock tools 1.5.6. and the torque was adjusted. The test ligands were then saved in the form of PDBQT, and docking simulation was then carried out using the command prompt. Biovia Discovery Studio Visualizer was employed to visualize molecular docking results. Molecular docking and visualization results are ranked based on their free energy binding and intermolecular interactions with NA. Three test ligands were chosen for this study based on their free binding energy. Furthermore, two test ligands were chosen based on the most favorable intermolecular interactions.

2.3.3. Visualization of the interaction of test ligands with the NA enzyme

The interaction of test ligands and receptors is visualized by generating a complex between the ligand and NA enzyme using Autodock Tools 1.5.6. The interaction of the test ligand and NA enzyme complex was observed, and the 2D diagram was generated using the Biovia Discovery Studio Visualizer.

2.3.4. Pharmacophore interaction

Pharmacophore interaction of all test ligands was observed using LigandScout to obtain 2D and 3D models and bonds that constitute these ligands.

2.3.5. Pharmacokinetics and toxicity predictions

The structure of the test ligands was uploaded/drawn in the Mol file format (*.mol.) on the website https://preadmet.bmdrc.kr/ to predict ADME and toxicity parameters.

2.3.6. Lipinski's Rule of Five

Test ligands structures were uploaded in Mol file format (*.mol.) on the website http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp to automatically predict molecular mass, log P value, hydrogen bond donor, hydrogen bond acceptor, and molar refractivity.

3. Result

3.1. Method validation

The molecular docking method was validated by separating the control ligand from the target protein and then re-docking it again. The H5N1 NA enzyme (PDB ID: 2HU4) and the control ligand OTV were employed to verify this method. The RMSD value obtained from the validation results of the molecular docking method was 1.01 Å, indicating that the molecular docking parameters were acceptable and could be used for virtual screening experiments for compounds from B. javanica.

3.2. Molecular docking simulation

From the molecular docking simulation, clusters, free binding energy, inhibition constants and amino acid interactions are obtained. Table 1 shows that there are three compounds with the lowest binding energy, namely bruceoside C, bruceantinol, and bruceantine, each of which has a free binding energy of -10.53 kcal/mol, -8.93 kcal/mol, and -8.64 kcal/mol respectively.

Hydrogen bond interactions were observed between ligands, including oseltamivir, with important amino acid

residues in the active site of NA. There are eight important amino acid residues, namely GLU119, GLU227, ASP151, ARG292, ARG371, ARG118, ARG152, and TYR347. In Table 2 demonstrates that there are three compounds that have the greatest similarity to the natural ligand of oseltamivir: bruceantinol, bruceine B and bruceine C, each of which has a number of similar amino acid residues to oseltamivir of 6, 6 and 5 amino acids.

3.3. Visualization of the interaction of test ligands with receptors

The visualization technique enabled the identification of the amino acids and the nature of the bond formed as a result of the test ligands's interaction with the NA enzyme, as depicted in Figure 1.

3.4. Pharmacophore modeling

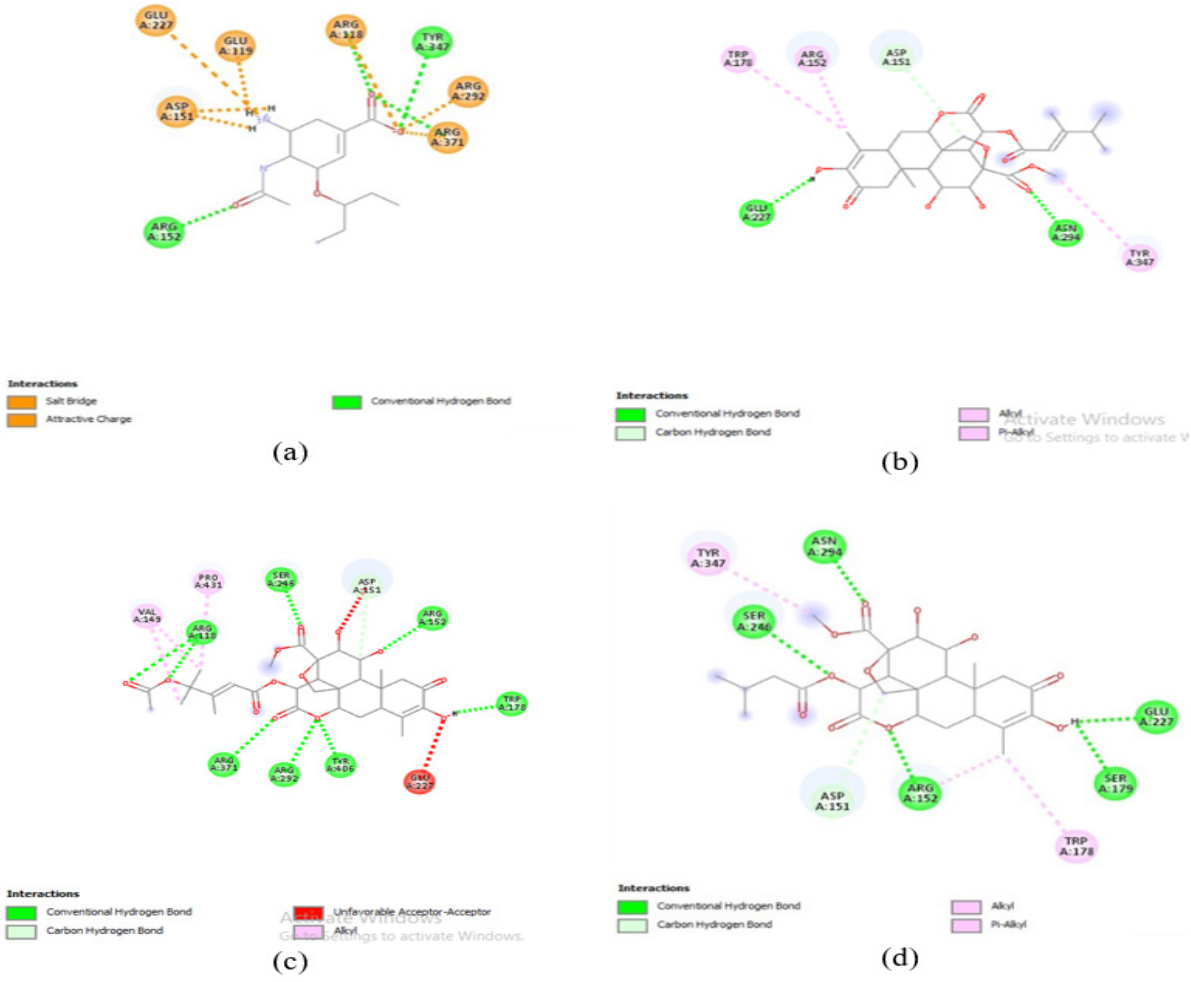
The control ligand OTV and ten B. javanica compounds were modeled using pharmacophores modeling. Visualization of the structure and arrangement of their 2D and 3D structure, which played a role in the compound's specific binding to the protein target is shown in Figure 2.

3.5. Pharmacokinetics and toxicity predictions

Predicted pharmacokinetic parameters include absorption (human intestinal absorption, HIA; and Caco-2); distribution (plasma protein binding, PPB; Blood Brain Barrier, BBB); metabolism (CYP2C19, CYP2C9, and CYP2D6); and toxicity parameters were predicated based on mutagenic and carcinogenic properties. The results of pre-ADMET predictions are detailed in Table 3.

3.6. Lipinski's Rule of Five

Compounds that meet the criteria outlined in Table 4 are potential active compounds for further pharmaceutical development, according to Lipinski's Rule of Five: donor hydrogen bonds must be no more than five, acceptor hydrogen bonds must



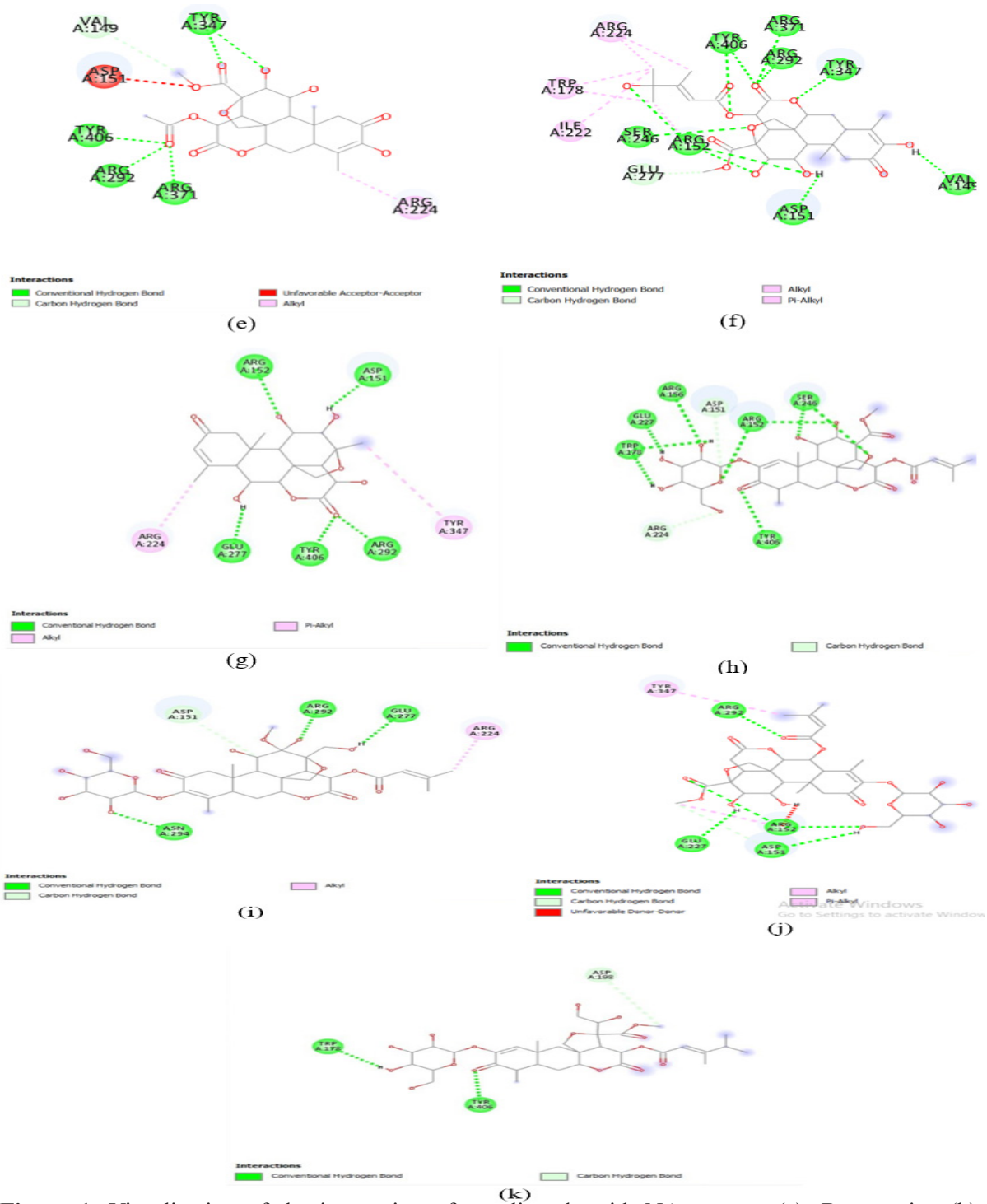


Figure 1. Visualization of the interaction of test ligands with NA enzyme (a), Bruceantine (b), Bruceantinol (c), Bruceine A (d), Bruceine B (e), Bruceine C (f), Bruceine G (g), Bruceoside A (h), Bruceoside B (i), Bruceoside C (j), Bruceantinoside A (k).

not exceed ten, the molecular weight cannot exceed 500 g/mol, and log P value cannot exceed 5 g/mol.[9]

4. Discussion

A total of ten compounds isolated from B. javanica have demonstrated inhibitory activity against the H5N1 NA. The compounds were subsequently optimized utilizing MM2 in Chem3D Pro 12.0 software. This energy optimization or minimization process aims to diminish the steric effect of a ligand, thereby producing a stable ligand form nearly identical to the ligand-receptor bond that exists in the human body.

The method is validated by removing the control ligand from the target protein and reattaching it to the induced-fit form of the protein. The crystal structure of H5N1 NA complexed with oseltamivir (PDB ID:

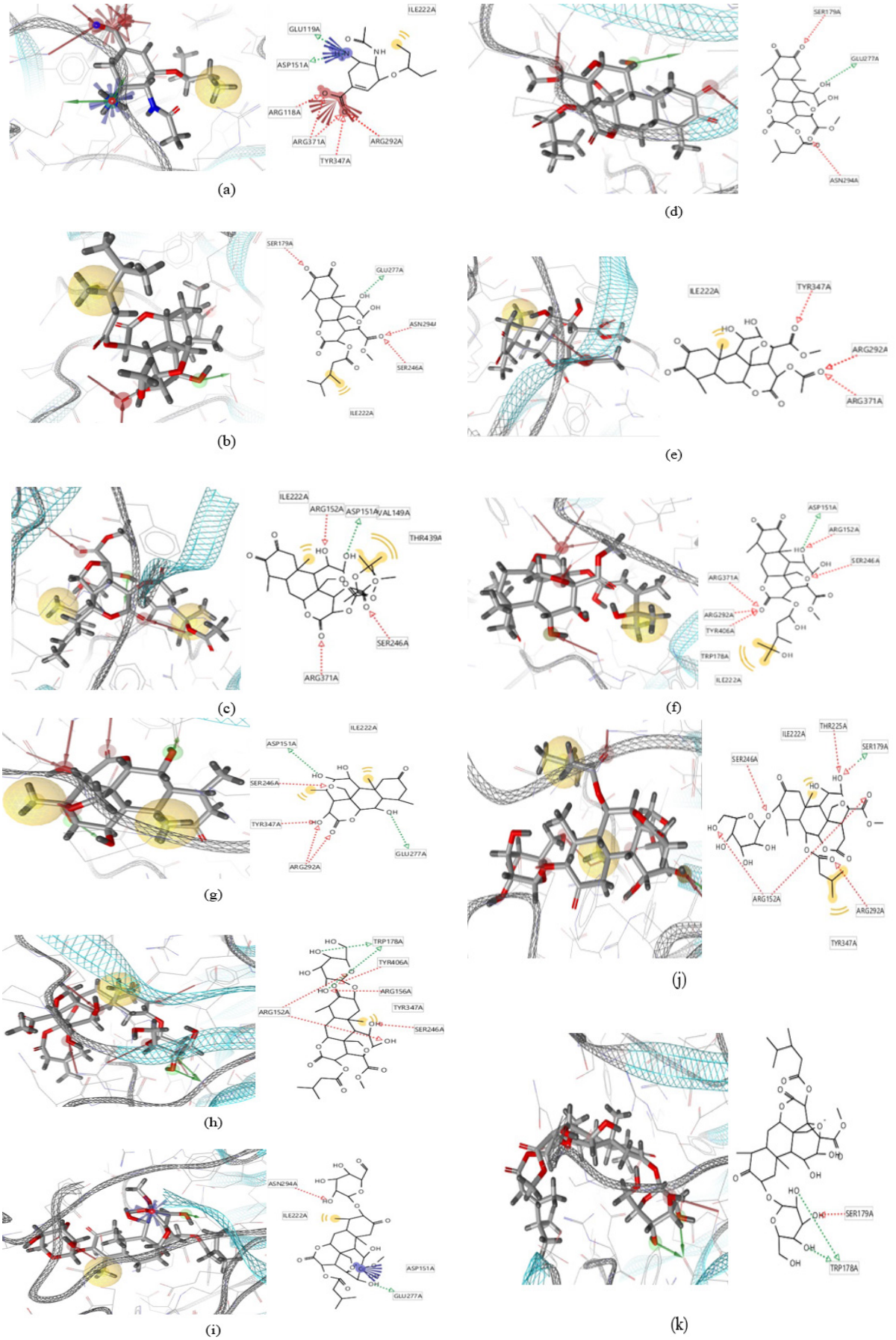


Figure 2. Visualization of the structure and arrangement of their 2D and 3D structure of ligands, which played a role in the compound's specific binding to the NA enzyme (a), Bruceantine (b), Bruceantinol (c), Bruceine A (d), Bruceine B (e), Bruceine C (f), Bruceine G (g), Bruceoside A (h), Bruceoside B (i), Bruceoside C (j), Bruceantinoside A (k).

Table 1. Molecular docking simulation results

Ligand	Cluster	Binding energy (kcal/ mol)	Ki (µM)	Amino acid interaction		
				Hydrogen bonds	van der Waals	Others
Bruceantine	100	-8.64	4.86	GLU227, ASN294, ASP151	-	Alkyl & Pi-Alkyl : TRP178, ARG152, TYR347
Bruceantinol	43	-8.93	0.28	ARG118, SER246, ARG152, TRP178, ARG371, ARG292, TYR406, ASP151, PRO431, VAL149	-	Unfavorable acceptor-acceptor : GLU227
Bruceine A	87	-7.16	5.65	SER246, ASN294, ARG152, SER179, GLU227, ASP151	-	Alkyl & Pi-Alkyl : TYR347, TRP178
Bruceine B	54	-7.90	0.55	ARG371, TYR406, ARG292, TYR347, SER246, ARG152, ASP151, VAI149, GLU277	-	Alkyl & Pi-Alkyl : ARG224, TRP178, ILE222
Bruceine C	36	-8.54	0.55	SER246, ARG152, ASP151, TYR406, ARG371, ARG292, TYR347, VAL145, GLU277	-	Alkyl & Pi-Alkyl : ARG224, TRP178, ILE222
Bruceine G	100	-7.20	5.29	ARG152, ASP151, GLU277, TYR406, ARG292	-	Alkyl & Pi-Alkyl : ARG244, TYR347
Bruceoside A	52	-6.35	21.98	ARG156, GLU227, TRP178, TYR406, ARG152, SER246, ASP151,ARG224	-	-
Bruceoside B	20	-4.92	247.26	ARG292, ARG277, ASN294, ASP151	-	Alkyl : ARG224
Bruceoside C	15	-10.53	0.02	ASN294, SER246, GLU277, ALA346	-	Pi-Alkyl : TYR347 Unfavorable Donor-Donor Acceptor-Acceptor : TRP178
Bruceantinoside A	30	- 5,03	206.62	TRP178, TYR406, ASP198	-	-

2HU4) was used to validate this method. The validation of this molecular docking method reveals the magnitude of the calculation error. The results of molecular docking were considered valid if the value of the Root Mean Square Deviation (RMSD) is less than or equal to 2 Å, indicating that the position of the test ligand after visualization will be more similar to the natural (control) ligand, making the method used more precise. If the RMSD value is greater than two (>2 Å), the error in the calculation results is greater[10]. The RMSD value obtained from method validation, molecular docking, is 1.01 Å, indicating that the molecular docking parameters are acceptable and can be used for virtual screening experiments for compounds from *B. javanica.*

Ten ligands were then subjected to molecular docking simulations utilizing Autodock Tools 1.5.6. The outcomes derived from the process of molecular docking encompass the quantification of the binding energy, determination of the inhibition

Table 2. Similarity of amino acid residues between test ligands and control ligands

Ligands	Residue								Similarity with
	GLU 119	GLU 227	ASP 151	ARG 292	ARG 371	ARG 118	ARG 152	TYR 347	OTV
Oseltamivir	√	√	√	√	√	√	√	√	8
Bruceantine		√	√				√	√	4
Bruceantinol		√	√	√	√	√	√		6
Bruceine A		√	√				√	√	4
Bruceine B		√	√	√	√		√	√	6
Bruceine C		√		√	√		√	√	5
Bruceine G		√		√			√	√	4
Bruceoside A		√	√				√		3
Bruceoside B				√					1
Bruceoside C	√		√	√		√		√	5
Bruceantinoside A									0

constant, and elucidation of the molecular interactions exhibited by the test compound with the specific amino acid residues that engage in binding interactions within the active site of the H5N1 NA receptor. The free binding energy value denotes the energy that a compound expends in order to interact with a receptor. A lower value of free binding energy indicates that a ligand can compete better against other ligands to bind with its target receptor.[11]

Table 1 shows the free binding energy values for *B. javanica* compounds which vary, ranging from -10.53 to -4.92 kcal/mol. Subsequently, the three best compounds were selected which had the lowest binding energy: bruceoside C, bruceantinol, and bruceantine, each of which had a free binding energy of -10.53 kcal/mol, -8.93 kcal/mol, and -8.64 kcal/mol, respectively. The low free binding energy indicates that the ligand has good molecular interactions with the receptor.

Apart from free binding energy, amino acid residues with hydrogen bonds also need to be considered. In Table 2, the bruceoside C compound, which has the lowest free bond energy, has 5 hydrogen bonds with important amino acid residues; the brucenatinol compound has 6 hydrogen bonds with important amino acid residues, while the bruceantine compound, which has a fairly low free binding energy only has 4 hydrogen bonds. with amino acid residues. Interactions are seen based on the similarity of the amino acid residues of the ligands of the compounds. These amino acid residues are GLU119, GLU227, ASP151, ARG292, ARG371, ARG118, ARG152, TYR347.

Bruceoside C and bruceantinol have the largest number of hydrogen bond interactions with the NA active site among the three compounds with lowest free binding energy.

Table 3. Pre-ADMET simulation results

Ligands	Absorption		Distribution		Metabolism			Toxicity	
	HIA (%)	CaCO2 (%)	PPB (%)	BBB (%)	CYP 2C19	CYP 2C9	CYP 2D6	Mutagenic	Carcinogenic
Bruceantine	65.338	30.155	53.174	0.063	Non	Inhibitor	Non	-	+
Bruceantinol	47.935	19.871	39.591	0.049	Non	Inhibitor	Non	-	+
Bruceine A	52.577	20.277	43.210	0.062	Non	Inhibitor	Non	-	+
Bruceine B	40.529	20.019	36.139	0.047	Non	Inhibitor	Non	-	+
Bruceine C	40.871	20.015	38.500	0.076	Non	Inhibitor	Non	-	+
Bruceine G	56.638	17.981	33.991	0.536	Non	Inhibitor	Non	-	+
Bruceoside A	8.733	18.855	34.193	0.065	Non	Inhibitor	Non	-	+
Bruceoside B	8.738	19.101	33.755	0.136	Non	Inhibitor	Non	-	+
Bruceoside C	8.738	19.267	33.447	0.156	Non	Inhibitor	Non	-	+
Bruceantinoside A	11.225	18.781	36.009	0.049	Non	Inhibitor	Non	-	+

Table 4. Lipinski simulation results

Ligands	Molecular mass (dalton)	Log P	H-Donor	H-Acceptor	Molar Refractivity	Note
Oseltamivir (Ligan alami)	312	-0.053	5	6	77.146	Comply
Bruceantine	548	1.153	3	11	131.647	Not Comply
Bruceantinol	606	0.839	3	13	142.655	Not Comply
Bruceine A	522	0.597	3	11	122.507	Not Comply
Bruceine B	480	-0.429	3	11	108.726	Not Comply
Bruceine C	564	0.268	4	12	133.107	Not Comply
Bruceine G	394	-1.068	4	8	92.655	Comply
Bruceoside A	682	-2.369	6	16	154.636	Not Comply
Bruceoside B	682	-2.224	6	16	154.707	Not Comply
Bruceoside C	682	-2.225	6	16	154.707	Not Comply
Bruceantinoside A	710	-1.664	6	16	163.551	Not Comply

The inhibition constants (Ki) of bruceoside C and bruceantinol are also commendable. The Ki value serves as an indicator of the degree to which a compound inhibits its receptor. As the Ki value decreases, the inhibitory force becomes stronger.[12] Bruceantinol has Ki value of 0.28 µM, whereas bruceoside C has Ki value of 0.02 µM.

Pharmacophore ligand interaction aimed to determine the position and arrangement of a 2D and 3D ligand structure that influences its specific binding to the protein target. The process by which ligands with varied structures can bind to similar receptor sites is elucidated by pharmacophore. In addition, it can also be employed to detect new ligands that bind to the same receptor via virtual screening.

A preliminary analysis of ADMET (absorption, distribution, metabolism, and excretion), as well as the toxicity of compounds derived from *B. javanica* and the control ligand OTV, was carried out. Absorption (specifically, Caco-2 and HIA) and distribution (BBB; PPB) were evaluated. The parameters of the compound's toxicity were predicted by examining its mutagenic and carcinogenic characteristics.

HIA categorizes substances according to their degree of intestinal absorption: good (70-100%), moderate (20-70%), or poor (0%-20%). By utilizing Caco-2 as an in-vitro model, the prediction of drugs' effects on humans via the intestinal epithelial cell barrier was performed. Three categories were used to determine the quality of Caco-2 cell uptake: low (4), medium (4–70), and high (> 70).[13] The HIA and Caco-2 values for bruceantinol are 47.93% and 19.87%, respectively. Comparatively, the Caco-2 value of bruceoside C is 19.26% and the HIA value is 8.78%. Thus, its quality of cell absorption and intestinal absorption of bruceantinol are both deemed to be moderate. In contrast, cellular absorption of bruceoside C is of moderate quality and is poorly absorbed in the intestine.

The classification of PPB values was based on their affinity for protein: those that bind strongly to plasma protein (above 90%) and those that bind weakly to plasma protein (below 90%).[14] Bruceoside C possesses a PPB value of 33.44%, whereas bruceantinol exhibits a PPB value of 39.59%. It can be concluded that both compounds poorly bind to plasma proteins.

The BBB parameter (Cbrain/Cblood) represents the partition value of substances between the brain and blood. A BBB value exceeding 2.0 signifies high compound absorption across the blood-brain barrier; values between 0.1 and 2.0 indicate moderate compound absorption, and values below 0.1 indicate low compound absorption across the blood-brain barrier.[15,16] Bruceoside C possesses a BBB value of 0.156523%, whereas bruceantinol has a BBB value of 0.0492711%. Based on the findings, it can be inferred that bruceantinol exhibits limited absorption across the blood-brain barrier, whereas bruceoside C demonstrates moderate absorption. Attributable to their metabolic

processes, bruceantinol and bruceoside C inhibit CYP2C9.

The Ames test was utilized to conduct the toxicity evaluation. A positive result indicates that the compound is mutagenic and potentially carcinogenic.[17] Bruceoside C and bruceantinol are not mutagenic, but there might be a possibility that they may cause cancer. A carcinogenic test was performed to collect information regarding the carcinogenic potential of a compound on experimental animals and to ascertain the toxicity of a substance that may or may not induce cancer with prolonged use.[18,19]

In addition, the physicochemical properties of the test compound are crucial for determining its drug-likeness. Permeability and solubility are crucial considerations in drug development when evaluating a compound. The objective is to avoid drug failure caused by insufficient permeation or absorption.[20]

Lipinski's rules dictate that a potential drug intended for oral administration must satisfy five criteria: its molecular weight should not exceed 500 Daltons, it should possess significant lipophilicity (measured by a log P value not exceeding 5), it should have no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and its molar refractivity should fall within the range of 40 to 130. The conditions referred to as the "Rule of Five" and are displayed in Table 4.[21] Bruceantinol and bruceoside C fail to comply with Lipinski's rule due to their molecular weight, number of acceptor hydrogen bonds, and molar refractivity not satisfying the criteria outlined in the Rule of Five.

Compounds with a molecular weight greater than or equal to 500 Daltons will encounter challenges in penetrating through digestion or the skin membrane. The log P value is correlated with the compound's polarity, which is directly proportional to the molecule's hydrophobicity. Nevertheless, when a compound exhibits excessive hydrophobicity, its toxicity is likely to increase due to its ability to disperse extensively throughout the body, resulting in reduced binding selectivity towards target proteins. The quantity of hydrogen bond donors and acceptors indicates that an increase in hydrogen bond capacity will result in a corresponding increase in the energy needed for absorption.[9,22]

5. Conclusion

The study concluded that among the ten compounds, bruceantinol stands out as the most promising. It exhibits a binding free energy value of -8.93 kcal/mol, an inhibition constant of 0.28 μM, and forms six intermolecular interactions with the NA binding site. Based on the pre-ADMET test results, it has been determined that bruceantinol might have the potential to cause cancer, but it does not possess mutagenic properties. According to Lipinski's test results, bruceantinol fails to comply with Lipinski's rules, thus rendering it unsuitable for use as an oral preparation. Hence, it is imperative to alter the structure of bruceantinol in order to achieve pre-ADMET and Lipinski outcomes that fulfill the specified criteria. Further in vitro and in vivo experiments is essential to validate the efficacy of bruceantinol in inhibiting the NA enzyme for avian influenza treatment.

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