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2-Cinnamamido-4-Methylpentanamide and *N*-(2-Hydroxypropanoyl)Cinnamamide: Synthesis, Characterization, and Molecular Docking Studies Through PBP2a Protein

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ABSTRACT. Cinnamic acid has been found in several types of plants and has a diverse spectrum of bioactivity. Derivatization of cinnamic acid related to the improving bioactivity of a compound. Cinnamic acid can be found as an acid or in conjugated form with amides, esters, aldehydes. This research focus on the synthesis of amide derivatives of cinnamic acid to improve the bioactivity. Two compounds namely 2-cinnamamido-4-methylpentanamide (**1a**) and *N*-(2-hydroxypropanoyl)cinnamamide (**1b**) were carried out through amidation reaction using carbodiimide coupling reagent for 24 hours. The synthesized target compounds were characterized using FT-IR, GCMS-MS, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The compounds were evaluated their antibacterial activity by molecular docking simulation against PBP2a (PDB ID: 1MWT) using AutoDock4 and AutoDockTools software. PBP2a is one of the main proteins in MRSA that has evolved to resist *β*-lactam antibiotics and was proposed to be the most likely target of MRSA. The inhibitory process of this protein works through inhibition of the bacterial cell wall. The synthesis process of **1a** and **1b** produced yields of 22.13% and 25.20%. Molecular docking results showed that **1a** and **1b** had better energy ($\Delta G_{binding}$ -7.33 and -6.29 kcal/mol) than Streptomycin as the control positive. The compounds of **1a** and **1b** had interactions on PBP2a through hydrogen bond with Asn464, Thr600, and Tyr519. This present study showed that the synthesized compounds from cinnamic acid derivatives have a potential to be used as antibacterial agents.

Keywords: Amidation, antibacterial, 2-cinnamamido-4-methylpentanamide, molecular docking, *N*-(2-hydroxypropanoyl) cinnamamide.

INTRODUCTION

Cinnamic acid is one of the natural bioactive compounds found in almost all green plants as it has many medicinal uses. In general, cinnamic acid can be obtained from *cinnamon* (*Cinnamomum cassia*). Cinnamic acid and its derivatives such as caffeic acid, ferulic acid, coumaric acid, and *p*-hydroxycinnamic acid are widely found in foods such as fruits, vegetables, and grains (Adisakwattana, 2017). This compound can be obtained from natural materials although the quantity is very small, therefore researchers are trying to synthesize cinnamic acid (Kadidae et al., 2020).

Cinnamic acid is an aromatic carboxylic acid synthesized through the shikimate pathway with precursors phenylalanine and tyrosine (Kumar & Parle, 2019). Cinnamic acid can also be formed from the deamination process of phenylalanine by the enzyme *Phenylalanine Ammonia Lyase* (PAL) to produce cinnamic acid which undergoes enzymatic modification (Chandra et al., 2019). Cinnamic acid consists of active functional groups, substitutions on the phenyl ring, *α*,*β*-unsaturated double bonds, and carboxylic groups (Çalışkan et al., 2022).

Modifications of cinnamic acid can be made on both the *cis* and *trans* sides (Razzaghi-Asl et al., 2013. Cinnamic acid can be found as an acid or in conjugated form with amides, esters, aldehydes (Chochkova et al., 2017). Generally, ester derivatives are more reactive and easily decomposed than amides, but these compounds must first be converted to amides in order to be used as drugs (Firdaus et al., 2019). Amide derivatives of cinnamic acid are often synthesized because of their stable nature and not easily hydrolyzed (Lu & Ralph, 1998). Conjugation of cinnamic acid compounds with differences in structure and groups that substitute a compound has been known to provide different pharmacological effects (Silva et al., 2019).

Amide derivatives of cinnamic acid compounds are among the most widely used derivatives in the field of medicinal chemistry. Formation of the amide bond

occurs through condensation of a carboxylic acid with an amine. Some large-scale studies use acid chloride coupling to activate the acid to form amides. Common reagents that are often used include thionyl chloride ($SOCl_2$), phosphorus oxychloride ($POCl_3$), and oxalyl chloride ($C_2O_2Cl_2$) (Dunetz et al., 2016). However, currently carbodiimide coupling reagents such as *N,N*-dicyclohexyl carbodiimide (DCC), *N,N'*-diisopropylcarbodiimide, and *N*-ethyl-*N*-(3-dimethylaminopropyl)carbodiimide (EDC) are the most widely used coupling reagents (Dabhi et al., 2023).

Research related to cinnamic acid as antibacterial, can be an effort to support the steps of the World Health Organization (WHO) in terms of treatment due to MDR bacterial resistance which is growing in a short time (Shankar, 2016). Multidrug-resistant (MDR) bacteria, known as bacteria that are resistant to more than three classes of antibiotics, continue to grow without the development of antibiotics (De Oliveira et al., 2020). The Center for Disease Control and Prevention (CDC) reports that by 2025 it is predicted that around 23,000 people will die from infectious diseases with antibiotic resistance (Bintari & Risandiansyah, 2019).

The rapid increase in bacterial resistance and the lack of new antibiotics to kill bacteria require ongoing efforts that focus on the development of antibacterial agents (Benítez-Chao et al., 2021) and the search for new methods to treat resistance. Deng and Song, (2020), wrote in their research that new antibacterial drugs are needed to combat infections due to antibiotic-resistant strains. Moreover, the approaches applied in drug development today are very expensive and slow regardless of the development of technological advances (Coumar, 2021). In addition, to conduct laboratory-scale experiments in vitro, it is also necessary to perform computational studies. Molecular docking is used to model the dominant binding of a ligand to a three-dimensional structure protein, rank the results according to their binding affinity, and propose a structural hypothesis of how a ligand may inhibit the target (Mourad & Alahmad, 2022). This research use PBP2a as a target protein because this enzyme plays an important role in the biosynthesis of the core component of cell walls (Ambade et al., 2023). PBP2a is a type of PBP encoded by the mecA gene which causes resistance of *Staphylococcus aureus* bacteria to the antibiotic methicillin (MRSA) (Gondokesumo & Kurniawan, 2019). The presence of the PBP2a protein makes MRSA insensitive to *β*-lactam antibiotics and causes resistance (Laksono et al., 2020). Through molecular docking studies, the target drug compound will bind to PBP2a protein and inhibit transpeptidase so as to inhibit cell wall peptidoglycan biosynthesis (Ambade et al., 2023).

Based on this description, cinnamic acid compound derivatives have high potential so that further research needs to be carried out through structural modification. This research will synthesize through amidation process using *L*-leucinamide and lactamide as reagents. The results of the synthesis were then tested for their potential as antibacterial in molecular docking study against PBP2a protein.

EXPERIMENTAL SECTION

Materials

The materials methanol, aquadest, chloroform, ethyl acetate, acetone, n-hexane, acid chloride, pyridine was obtained from Merck. Additionally, *L*-leucinamide and lactamide were purchased from Sigma-Aldrich (Saint Louis, USA). The progress of the reactions was monitored by analytical thin layer chromatography (TLC). Flash chromatography columns ware performed using silica gel.

Instrumentation

The instruments used in this study were FT-IR from Shimadzu 8501, Gas Chromatography-Mass Spectrometry was obtained from Shimadzu GC-MS Agilent instrument, and ^{1}H- and ^{13}C-NMR were recorded on JEOL ECZ500R instrument at 500 MHz and 125 MHz. For the acquisition of the spectra, TMS, $CDCl_3$, and dimethyl sulfoxide were used as solvents.

The molecular docking was performed using i3 4GB RAM; 64-bit system type. The programs used in molecular docking were AutoDock4 with the help of AutoDockTools (Morris et al., 2009), Chimera (Pettersen et al., 2004), and Discovery Studio Visualizer.

Synthesis 2-cinnamamido-4-methylpentanamide

Cinnamic acid (1000 mg, 6.73 mmol, 1 equiv) was added with *L*-leucinamide (2243.1 mg, 13.46 mmol, 2 equiv), and reagent *N,N*-dicyclohexylcarbodiimide (DCC) 1388.6009 mg (1 equiv), and 4-dimethylaminopyridine (DMAP) 411.102 mg (3.365 mmol, 0.5 equiv). The solution was dissolved with 5 mL of pyridine and then refluxed at 100 °C for 24 hours. The reaction results obtained were then extracted using ethyl acetate solvent as the organic phase and distilled water as the inorganic phase. The organic phase was added with anhydrous $MgSO_4$ to attract water, then evaporated and fractionated by gravity column chromatography. Fractions that have the same Rf value are then combined, then evaporated until a solid is obtained. Furthermore, purity tests were carried out by TLC analysis and melting point. The pure crystals obtained were analyzed by FT-IR, GCMS-MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopy to determine the structure of the synthesized compounds.

2-cinnamamido-4-methylpentanamide (1a)

Molecular formula $C_{15}H_{20}N_2O_2$, m/z 260.2 $[M+H]^+$, yield 22.12%, m.p. 170 °C, FT-IR (KBr disc): 3273.01 cm^{-1} (N-H), 2924.03 cm^{-1} (C-H sp^2), 2851.59 cm^{-1} (C-H sp^3), 1705.86 cm^{-1} (C=O), 1652.44 cm^{-1} (C=C olefin), 1615.47 cm^{-1} (C=C aromatic), 1370.50 cm^{-1} (CH_3), 1444.64 cm^{-1} (CH_2),

and 1341.04 cm^{-1} (C-N). ^{1}H-NMR (500 MHz, chloroform-*d*) δ, ppm: 7.631 (1H, 16 Hz, *d*), 7.474 (2H, 1.5 Hz, *m*), 7.340 (1H, 1.5 Hz, *m*), 7.340 (2H, 1.5 Hz, *m*), 6.474 (1H, 15.5 Hz, *d*), 1.791 (2H, 7 Hz, *d*), 1.761 (1H, 6 Hz, *d*), 1.677 (1H, 3.5 Hz, *m*), 0.975 (3H, 4.5 Hz, *m*), and 0.975 (3H, 4.5 Hz, *m*). ^{13}C-NMR (125 MHz, chloroform-*d*) δ, ppm: 177.799 (C-1), 168.604 (C-17), 142.371 (C-3), 136.352 (C-4), 131.015 (C-7), 130.056 (C-5 and C-9), 129.009 (C-6 and C-8), 121.580 (C-2), 53.141 (C-12), 42.381 (C-13), 26.841 (C-14), 23.596 (C-15), and 22.003 (C-16).

Synthesis *N*-(2-hydroxypropanoyl) cinnamamide

Cinnamic acid (1000 mg, 6.73 mmol, 1 equiv) was added with lactamide (1210.05 mg, 13.46 mmol, 2 equiv), and reagent *N,N*-dicyclohexylcarbodiimide (DCC) 1388.6009 mg (1 equiv), and 4-dimethylaminopyridine (DMAP) 411.102 mg (3.365 mmol, 0.5 equiv). The solution was dissolved with 5 mL of pyridine and then refluxed at 100 °C for 24 hours. The reaction results obtained were then extracted using ethyl acetate solvent as the organic phase and distilled water as the inorganic phase. The organic phase was added with anhydrous $MgSO_4$ to attract water, then evaporated and fractionated by gravity column chromatography. Fractions that have the same Rf value are then combined, then evaporated until a solid is obtained. Furthermore, purity tests were carried out by TLC analysis and melting point. The pure crystals obtained were analyzed by FT-IR, GCMS-MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopy to determine the structure of the synthesized compounds.

N-(2-hydroxypropanoyl) cinnamamide (1b)

Molecular formula $C_{12}H_{13}NO_3$, m/z 219.09 $[M+H]^+$, yield 25.20%, m.p. 180 °C, FT-IR (KBr disc): 1691.00 cm^{-1} (C=O); 3282.19 cm^{-1} (N-H); 1450.36 cm^{-1} (C-N); 1204.42 cm^{-1} (C-O), 1516.60 cm^{-1} (C=C aromatic), 1612.41 cm^{-1} (C=C olefin), 2955.69 cm^{-1} (C-H sp^2), 3365.97 cm^{-1} (OH), and 1337.83 cm^{-1} (CH_3); ^{1}H-NMR (500 MHz, chloroform-*d*) δ, ppm: 7.783 (1H, 16 Hz, *d*), 6.505 (1H, 16 Hz, *d*), 7.418 (2H, 1.5 Hz, *m*), 7.260 (2H, 1.5 Hz, *m*), 7.260 (1H, 1.5 Hz, *m*), 1.633 (7 Hz, *d*), and 1.571 (3H, 7 Hz, *d*); ^{13}C-NMR (125 MHz, chloroform-*d*) δ, ppm: 173.187 (C-1), 117.015 (C-2), 146.675 (C-3), 129.206 (C-5 and C-9), 128.438 (C-6 and C-8), 130.991 (C-7), 165.690 (C-12), 70.500 (C-13), and 17.957 (C-14).

Molecular Docking

The molecular docking process was performed using Auto Dock 4.2 program with the help of AutoDock Tools (Morris et al., 2009). Each ligand was tethered to the active side of the bacterial protein. The protein structure used in this research was PBP2a (PDB ID: 1MWT) since this protein is considered to be potent against MRSA bacteria (Masumi et al., 2022). Each ligand and protein substrate were prepared to dock using Chimera software by adding hydrogen and optimizing the structure (Pettersen et al., 2004). The grid box size used is 60 x 66 x 60 Å with X-center, −34.264; Y-center, 44.65; Z-center, 66.778, and spacing 0.375 Å. The docking protocol was set to give the 10 best conformations and run at a maximum evaluation energy of 2,500,000 using the Lamarckian Genetic Algorithm that was implemented in the AutoDock4 package (Masumi et al., 2022). The best conformation was chosen based on the lowest binding energy value and the visualization of 2D interaction was depicted using Discovery Studio Visualizer program (BIOVIA, 2019).

RESULTS AND DISCUSSION

Synthesis of 2-cinnamamido-4-methylpentanamide

In this study, 2-cinnamamido-4-methyl pentanamide has been successfully synthesized by one-pot reaction method reported by (Vale et al., 2022) using *N,N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). The IR spectra showed peak 1705.86 cm^{-1} (C=O) as carbonyl, 3273.01 cm^{-1} N-H, and 1341.04 cm^{-1} C-N as amine group. It is indicated that 2-cinnamamido-4-methylpentanamide has been synthesized. The mass spectrum of 2-cinnamamido-4-methylpentanamide at m/z 260.

^{1}H and ^{13}C-NMR spectral data revealed supporting evidence to identify the structures of the compound. According to the target compound, the product that is successfully formed has 12 different types of protons. The methyl group was highlighted by the appearance of a *multiplet* peak at 0.975 ppm. The ^{13}C-NMR data showed that compound **1a** has 15 carbon atoms consisting of 6 carbon atoms in the aromatic ring, 2 carbon atoms on the *cis-trans* side, one carbon atom in the carbonyl group, and 6 carbon atoms according to the structure of the reacted reagent. The carbons in the **1a** compound resulting from the synthesis reaction of cinnamic acid and *L*-leucinamide reagent are indicated by 5 signals at δ 53.141 ppm, δ 42.381 ppm, δ 26.169 ppm, δ 23.596 ppm, and δ 22.003 ppm. The spectra of IR and NMR was presented in **Table 1**.

Based on IR, ^{1}H- and ^{13}C-NMR spectra, it was showed that amidation cinnamic acid with *L*-leucinamide using DCC and DMAP has produced 2-cinnamamido-4-methylpentanamide (**1a**) compound. The synthesized compound has a yield of 22.13%, white solid, and melting point of 170 °C. The others research reported a variation of yield. The difference in yield can be caused by the difference of reaction time that are not yet optimal.

Synthesis of *N*-(2-hydroxypropanoyl) cinnamamide

N-(2-hydroxypropanoyl) cinnamamide has been synthesized from cinnamic acid and lactamide by carbodiimide coupling reagent. *N,N*-dicyclohexylcarbodiimide (DCC) reagent acts as an acid activator and *N,N*-4-dimethyl amino pyridine (DMAP) as catalyst. In the reaction process, DCC

acts as a carboxylic acid activator that forms carboxylic anions, carboxylic anions attack the imidate carbon of DCC, then DMAP activates its carbonyl carbon to attack the hydroxyl group of alcohol. After deprotonation, the precipitation of dicyclohexylurea (DCU) and the formation of amides occur. The synthesis process was assisted with reflux for 24 hours.

The IR spectra showed the presence of -OH group shown at 3365.97 cm^{-1} and the carbonyl group also shifted from 1691.00 cm^{-1}, which indicated the characteristic peak for conjugated carbonyl vibration. Based on IR spectra, the compound also showed new peak appeared at 3282.19 cm^{-1}, 1450 cm^{-1} and 1204,42 cm^{-1} that was identified as lactamide group. The spectra of IR and NMR of compound **1b** were presented in **Table 2**. The mass spectrum of *N*-(2-hydroxypropanoyl) cinnamamide showed the same molecular mass as the theoretical at m/z 219. ^{1}H-NMR spectra helped to clarify the synthesis of *cis-trans* alkene by showing double peaks at 7.783 and 6.505 ppm (J=16 Hz). The ^{13}C-NMR spectra showed highly deshielded carbonyl carbon (C-1) at 173.187 ppm and (C-12) at 165.690 ppm. The position of proton and carbon showed that the synthesized compound was cinnamic acid derivative.

Table 1. FT-IR and NMR data of 2-cinnamamido-4-methylpentanamide (**1a**)

FT-IR (cm^{-1})	^{1}H-NMR (ppm)	^{13}C-NMR (ppm)
1615.47 (C=C aromatic)	-	177.799
1652.44 (C=C olefin)	7.631 (1 H, 16 Hz, *d*)	121.580
2924.03 (C-H sp^2)	6.474 (1 H, 15.5 Hz, *d*)	142.371
1705.86 (C=O)	-	136.352
3273.01 (N-H)	7.474 (2 H, 1.5 Hz, *m*)	130.056
1341.04 (C-N)	7.340 (2 H, 1.5 Hz, *m*)	129.009
1370.50 (CH_3)	7.340 (1 H, 1.5 Hz, *m*)	131.015
2851.59 (C-H sp^3)	1.761 (1 H, 6 Hz, *d*)	53.141
1444.64 (CH_2)	1.791 (2 H, 7 Hz, *d*)	42.381
	1.677 (1 H, 3.5 Hz, *m*)	26.841
	0.975 (3 H, 4.5 Hz, *m*)	23.596
	0.975 (3 H, 4.5 Hz, *m*)	22.003
	-	168.604

Table 2. FT-IR and NMR data of *N*-(2-hydroxypropanoyl) cinnamamide (**1b**)

FT-IR (cm^{-1})	^{1}H-NMR (ppm)	^{13}C-NMR (ppm)
1516.60 (C=C aromatic)	-	173.187
1612.41 (C=C olefin)	7.783 (1 H, 16 Hz, *d*)	117.015
2955.69 (C-H sp^2)	6.505 (1 H, 16 Hz, *d*)	146.675
1691.00 (C=O)	7.418 (2 H, 1.5 Hz, m)	129.206
3282.19 (N-H)	7.260 (2 H, 1.5 Hz, *m*)	128.438
1450.36 (C-N)	7.260 (1 H, 1.5 Hz, *m*)	130.991
1337.83 (CH_3)	-	165.690
1204.42 (C-O)	1.633 (7 Hz, *d*)	70.500
3365.97 (-OH)	1.571 (3 H, 7 Hz, *d*)	17.957

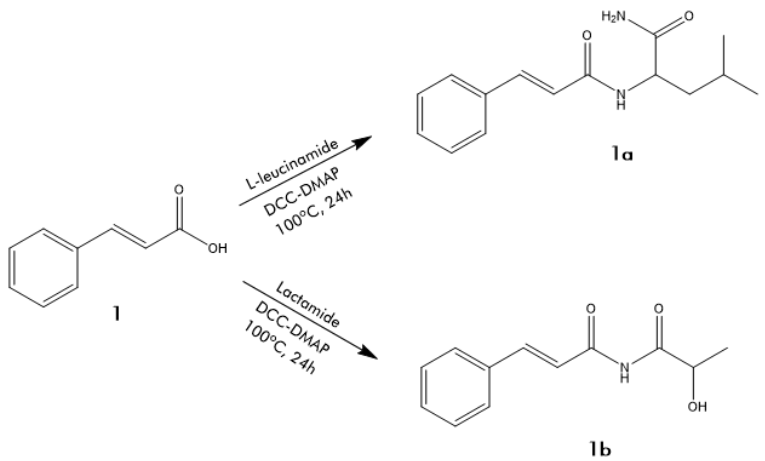

Figure 1. Synthesis pathways of **1a** and **1b**

The presence of resonating alkene carbon (*α* and *β*-carbon) is indicated at 117.015 and 146.675 ppm. The electron density in the double bond is very strong and makes the molecule is more stable attracted by carbonyl through resonance. The delocalization of electrons was reduced from *β* carbon to *α*-carbon and resulted in the *β*-carbon resonance being more deshielded than *α*-carbon. From this characterization showed that compound *N*-(2-hydroxypropanoyl) cinnamamide has been formed. The synthesized product yield 25.20% in a yellow solid with melting point of 170 °C. The synthetic pathways of 2-cinnamamido-4-methylpentanamide (**1a**) and *N*-(2-hydroxypropanoyl) cinnamamide (**1b**) was presented in **Figure 1.**

Molecular Docking

Molecular docking was performed to identify its potential binding modes. The synthesized compounds were docked to penicillin binding protein 2a (PBP2a) (PDB ID: 1MWT). The selection of PBP2a protein from methicillin-resistant *Staphylococcus aureus* (MRSA) is because PBP2a is responsible for catalyzing the production of peptidoglycan within the bacterial cell wall and has lower *β*-lactam-containing binding energy than other PBPs (Masumi et al., 2022). Docking results of **1a** and **1b** compounds showed that all the compounds have lower docking score compared to streptomycin (**Table 3**). This means that **1a** and **1b** complexes are more stable and have stronger inhibitory potential against the target protein than the antibiotic streptomycin.

In general, optimal interaction in molecular docking study can be demonstrated by binding energy values which is lower than -5 kcal/mol (Bahrun and Soekamto, 2021). The smaller the binding energy produced by a ligand and protein complex, the better inhibitory ability of a drug compound. This is also consistent with study by Kalalo et al. (2020), explained that binding energy lower than -6 kcal/mol has good binding to protein target and can be considered as a potential compound for designing new antibacterial drugs targeting MRSA.

Table 3. Molecular docking results of synthesized compounds against PBP2a protein

Ligand	Binding Energy (kcal/mol)	Inhibition Constant (mM)	Interaction of Hydrogen Bond
1a	-7.33	4.25	Asn(B):464; Thr(B):600; Ser(B):403; and Tyr(B):519
1b	-6.29	24.58	Asn(B):464 and Thr(B):600
Streptomycin	-6.14	2.00	Asn(B):464 and Arg(B):445

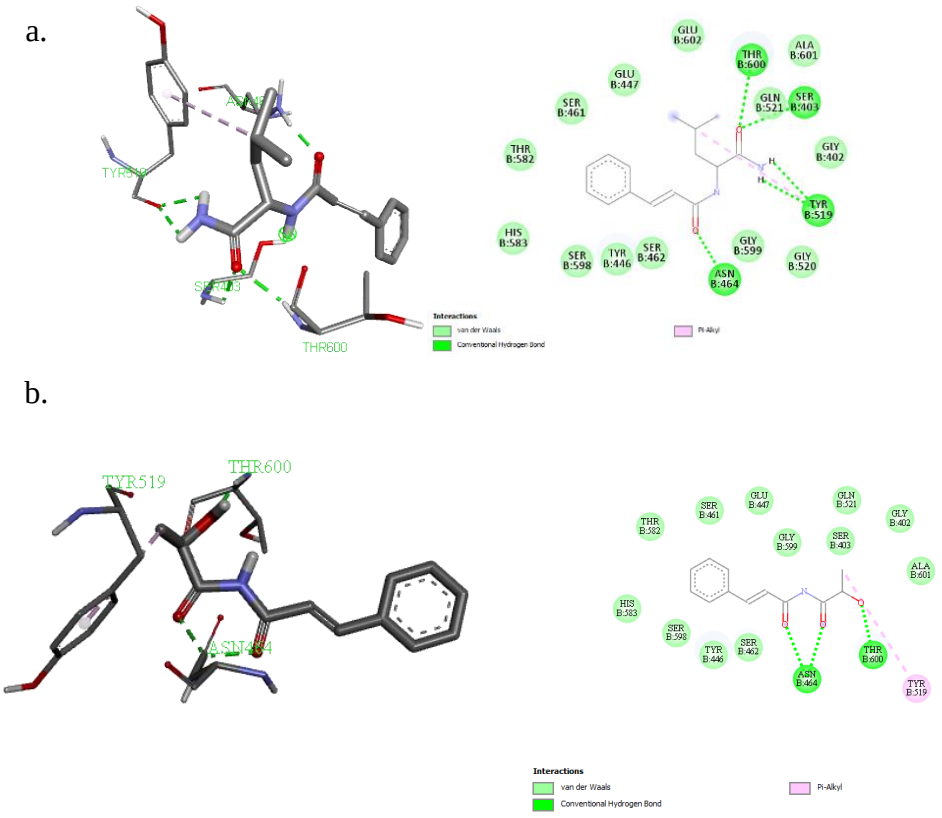

Figure 2. Visualization of the interaction between PBP2a protein receptor with (a) 2-cinnamamido-4-methylpentanamide (**1a**) and *N*-(2-hydroxypropanoyl)cinnamamide (**1b**)

The inhibition constant (Ki) is an additional parameter to consider the molecular docking results. According to Arulanandam, (2021), a good interaction between ligands and target proteins is indicated by a decreased Ki value. There is a correlation between the binding energy data and inhibition constants; low binding energy values provides low inhibition constants as well. Not only that, the effectiveness of a compound also depends on the type of residue protein that interacts with ligand, because interactions with different protein residues provide different mechanisms of action (Ferreira et al., 2015).

The stability of the ligand interaction is indicated by binding energy value and the inhibition constant determined by the type of bond and the number of ligand interactions with amino acids residue on the active side of the protein target (Masumi et al., 2022). Visualization of docking results between **1a** and **1b** compound with PBP2a target protein can be seen in **Figure 2**.

The docking results obtained that **1a** form hydrogen bonds interaction with amino acid residues tyrosine (Tyr519), asparagine (Asn464), glutamine (Gln521), and threonine (Thr600). While **1b** interact as hydrogen bond with amino acid residues asparagine (Asn464) and threonine (Thr600). The existence of bonding interactions contributes to the stability of a compound interaction with the target protein. Thus, it was predicted that **1a** and **1b** compounds have potential as antibacterial activity based on molecular docking results.

CONCLUSIONS

Synthesis of two cinnamic acid derivatives has been conducted using DCC/DMAP reagents and obtained yields of 22.12% (**1a**) and 25.20% (**1b**). The results of molecular docking analysis through molecular docking against PBP2a protein show that both compounds have potential as antibacterial in terms of binding energy values, inhibition constants, and amino acid residue interactions.

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