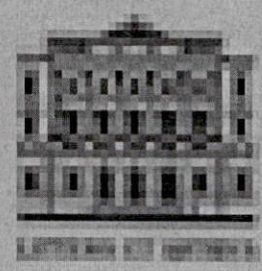


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


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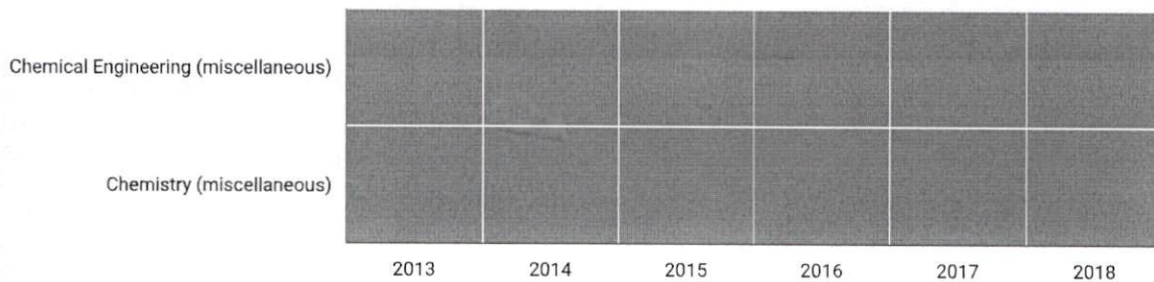
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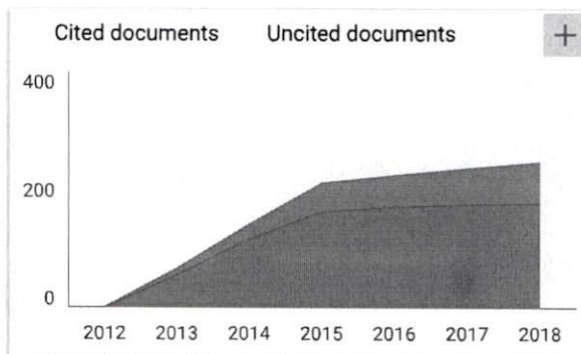
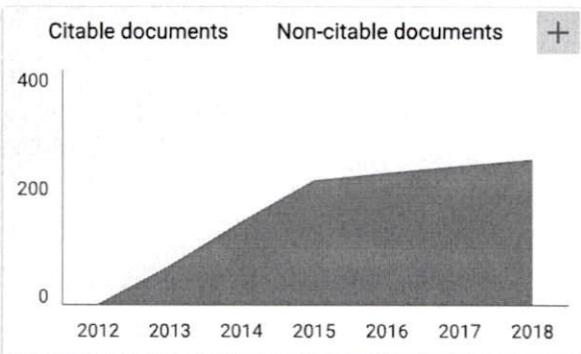
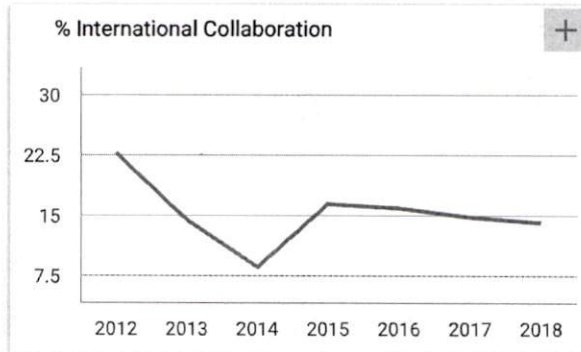
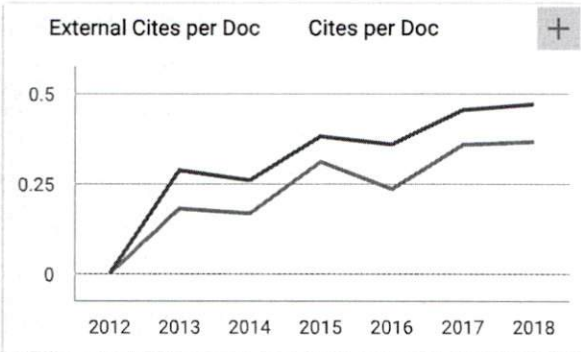
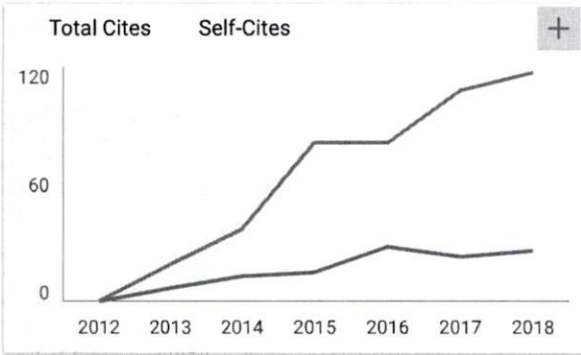
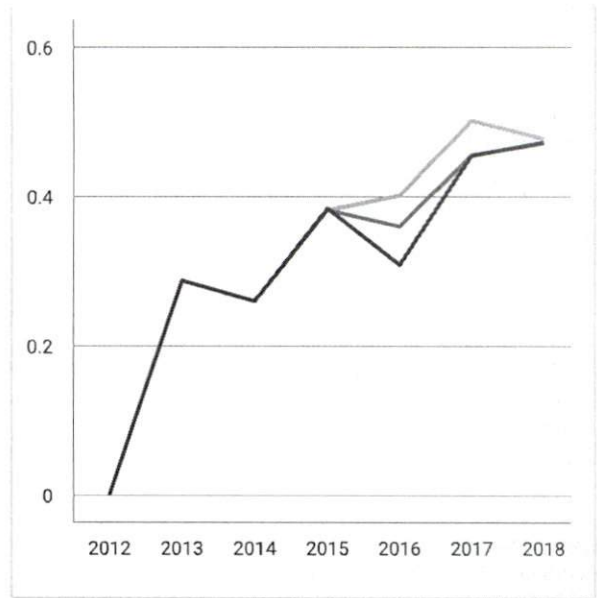


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SYNTHESIS AND ANTIPLATELET ACTIVITIES
OF SOME DERIVATIVES OF *p*-COUMARIC ACIDJuni Ekowati^{1,*}, Nuzul W. Diyah¹, Achmad Syahrani¹<https://doi.org/10.23939/chcht13.03.296>

Abstract. The synthesis of new derivatives of *p*-coumaric acid was carried out through serial reactions, *i.e.* alkylating, base hydrolysis, catalytic hydrogenation, and Fisher esterification. All reactions except catalytic hydrogenation were conducted by utilizing microwave irradiation from a household microwave oven. The antiplatelet tests using clotting time showed that *p*-coumaric acid and its derivatives have antiplatelet activity which is related to the lipophilic nature of the compounds and its affinity with the selected target molecule, *i.e.* COX-1 enzyme (PDB ID 1CQE).

Keywords: *p*-coumaric acid, antiplatelet, COX-1, clotting time, catalytic hydrogenation.

1. Introduction

One of the leading causes of death from cardiovascular disease is thromboembolism. The accumulation of platelet formation plays an important role in the pathogenesis of thromboembolic disorders [1]. Many endogenous compounds, *e.g.* thromboxane A₂, thrombin, von Willebrand factor, and ADP increase platelet aggregation on different routes. Platelets maintain a balance between anti-aggregator and pro-aggregator behavior under normal physiological conditions [2]. The main treatment for this disease is antithrombotic, including antiplatelet. Aspirin is a widely used antiplatelet with the inhibiting mechanism of cyclooxygenase-1 (COX-1) enzyme [3]. However, about 15–25% of patients are known to be resistant to aspirin. In addition, there are side effects in the form of bleeding and neutropenia [4, 5].

One of the derivatives of the cinnamate compound, namely *p*-coumaric acid, [(*E*)-3-(4-hydroxyphenyl)acrylic acid] (**1**) has been reported to have antiplatelet activity [6, 7]. Zhao *et al.* [8] reported that compound **1** acts as an

anti-inflammatory agent by reducing the expression of inducible nitric oxide synthase (iNOS), COX-2, IL-1 β , and TNF- α at mRNA and/or protein levels in RAW264.7 cells stimulated by lipopolisaccharide (LPS). Molecule **1** also decreases cytokine levels to reduce MAPK pathway activation, NF- κ B, and decreases immune response [8].

One of the factors affecting antiplatelet activity is the drugs ability to penetrate cell membranes or lipophilicity of the compounds [7]. To improve the lipophilicity of **1**, methylation reaction was carried out with dimethyl sulphate in alkaline condition and Fisher esterification to modify carboxylic and OH-phenolic moieties of **1** thereby increasing the value of log P of its derivatives. The hydrogenation of vinyl double bond of **1** will also be performed to determine the effect of double bond against antiplatelet activity.

The antiplatelet test was implemented by the blood clotting time slide method. The prediction of antiplatelet mechanisms was studied in the *in silico* study with COX-1 enzyme [9]. The *in silico* study results were compared in terms of Rerank Score (RS) with aspirin.

2. Experimental

2.1. Materials

p-Coumaric acid (**1**) was bought from Aldrich; dimethyl sulphate, KOH, acetone, chloroform, potassium carbonate, HCl, H₂SO₄, NaOH, ether, ethanol, methanol, and Raney-Ni were purchased from Merck. Derivatives of compound **1** (*i.e.* **2-5**) were synthesized *via* several reactions (Fig. 1).

2.2. Methods

The synthesis reaction was monitored with TLC using UV lamp on $\lambda = 254$ nm to spot detection. Some synthesis reactions were conducted by household microwave oven SHARP model R-230R(S). Melting points were measured by Fischer-John melting point apparatus without correction. UV spectra were obtained by Shimadzu HP 8452 UV-vis spectrophotometer. IR spectra were performed using a Jasco FT-IR 5300

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spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained from the JEOL JNM-ECS 400 instrument (^1H NMR: 400 MHz, ^{13}C NMR: 100 MHz) using appropriate solvent (DMSO- d_6 for **2**, **3**, **5**; Pyr- d_5 for **4**). Physicochemical properties ($\log P$, MR, E_{total}) were obtained by Chem Bio Ultra program.

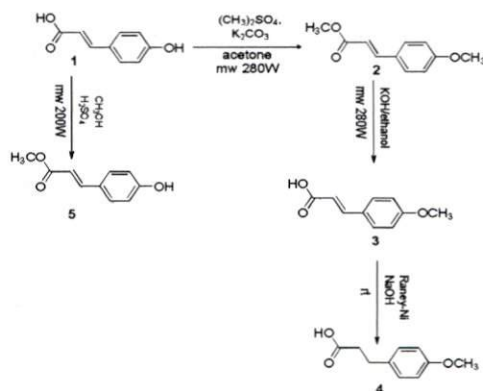


Fig. 1. Structure modification of *p*-coumaric acid (1)

2.2.1. (E)-Methyl 3-(4-methoxyphenyl)acrylate (2)

p-Coumaric acid (500 mg, 3.05 mmol) was dissolved in 10 ml of acetone. Potassium carbonate (1.25 g, 9.6 mmol) and dimethyl sulphate (2 ml, 21.9 mmol) were added to the mixture. The resulting mixture was irradiated in a microwave oven at 70 % power (280 W) for 10 min. (The mixture was tested by TLC, every 30 s). The crude product was poured into an Erlenmeyer flask containing distilled water and stirred at room temperature, after which it was washed several times and then recrystallized from ethanol.

Obtained product is white crystal; 75 % yield; m.p. 361 K. UV: λ_{max} (EtOH) 228 and 310 nm. IR (KBr; ν cm^{-1}): 2948, 1717, 1637, 1603, 1513, 1288, 1175, 823. ^1H NMR (DMSO- d_6 , δ ppm): 7.63 (2H, d, $J=8.4$ Hz, $-\text{CH}=\text{CH}-$), 7.57 (1H, d, $J = 15.8$ Hz, $\text{Ar}-\text{CH}=\text{CH}-\text{C}=\text{O}$), 6.93 (2H, d, $J = 8.4$ Hz, $-\text{CH}=\text{CH}-$), 6.44 (1H, d, $J = 15.8$ Hz, $\text{Ar}-\text{CH}=\text{CH}-\text{C}=\text{O}$), 3.76 (3H, s, $-\text{OCH}_3$), 3.66 (3H, s, $-\text{OCH}_3$). ^{13}C NMR (DMSO- d_6 , δ ppm): 167.5, 161.7, 144.9, 130.7, 130.7, 127.1, 115.6, 114.9, 114.9, 55.9, 51.8. All the spectral data are in agreement with the structure of the compound 2.

2.2.2. (E)-3-(4-Methoxyphenyl)acrylic acid (3)

Compound 2 (500 mg; 2.60 mmol) was dissolved in 20 ml of 5 % KOH/ethanol solution. The mixture was irradiated into a microwave oven at 70 % power (280 W) until the reaction was complete (6 min). Thereafter, the

resulting mixture was acidified with HCl to yield sediment of compound 3. This crude product was purified by recrystallization using methanol.

Obtained product is white crystal; 85 % yield; m.p. 443 K. UV: λ_{max} (EtOH) 228 and 308 nm. IR (KBr; ν cm^{-1}): 2936, 2844, 2561, 1685, 1623, 1598, 1255, 1173, 827 cm^{-1} . ^1H NMR (DMSO- d_6) 3.78 (3H, s, $-\text{OCH}_3$), 6.60 (1H, d, $J = 16$ Hz, $\text{Ar}-\text{CH}=\text{CH}-\text{C}=\text{O}$), 6.96 (2H, d, $J = 5.0$ Hz, $-\text{CH}=\text{CH}-$), 7.53 (1H, d, $J = 16$ Hz, $\text{Ar}-\text{CH}=\text{CH}-\text{C}=\text{O}$), 7.62 (2H, d, $J = 5.0$ Hz, $-\text{CH}=\text{CH}-$). ^{13}C NMR (DMSO- d_6 , δ ppm): 55.5, 114.5, 116.7, 127.0, 130.1, 143.9, 161.1, 168.0. All the spectral data are in agreement with the structure of the compound 3.

2.2.3. 3-(4-Methoxyphenyl)propanoic acid (4)

Compound 3 (500 mg; 2.77 mmol) was dissolved in 25 ml of 5 % NaOH solution. The mixture was heated until the MCA was dissolved and then cooled to room temperature again. A catalytic compound of Raney-Ni (565 mg; 5 mmol) was added to the mixture and stirred at room temperature for 1 h. When the rate of gas release decreased, the mixture was heated until the entire hydrogen gas was exhausted (if the volume of the mixture was reduced during heating, sufficient water was added to the initial volume) then the mixture was filtered. The black precipitate of Ni residue on the filter paper was washed with 2x5 ml of 5 % hot NaOH solution, followed by 2x5 ml of hot water. The filtrate was collected and cooled at room temperature. Then, 5 ml of HCl concentrate was dripped slowly and the temperature was maintained within 353–358 K. The precipitate was extracted using 3x10 ml of ether. The ether phase was evaporated and the forming crystals were dissolved in acetone to separate from the remaining Al mixed with the crystals. The acetone phase was evaporated, then white precipitate 4 was obtained. This crude product was purified by recrystallization using ethanol [10].

Obtained product is white crystal; 85 % yield; m.p. 369 K. UV: λ_{max} (EtOH) 202 and 223 nm. IR (KBr; ν cm^{-1}): 2930, 2835, 2596, 1703, 1612, 1512, 1302, 1246, 1215, 821. ^1H NMR (Pyr- d_5 ; TMS; δ ppm): 6.88 (2H, d, $J = 6.0$ Hz, $-\text{CH}=\text{CH}-$), 7.15 (2H, d, $J = 6.0$ Hz, $-\text{CH}=\text{CH}-$), 3.82 (3H, s, $-\text{OCH}_3$), 2.88 (2H, t, $J = 6.0$ Hz, $\text{Ar}-\text{CH}_2-\text{CH}_2-\text{C}=\text{O}$), 2.54 (2H, t, $J=9.0$ Hz, $\text{Ar}-\text{CH}_2-\text{CH}_2-$). ^{13}C NMR (Pyr- d_5 , TMS, δ ppm): 175.4, 158.7, 133.9, 130.3, 129.9, 114.9, 114.5, 55.3, 36.9, 30.9. All the spectral data are in agreement with the structure of the compound 4.

2.2.4. (E)-Methyl-3-(4-hydroxyphenyl)acrylate (5)

Compound 1 (500 mg; 3.05 mmol) was dissolved in 5 ml of methanol, then 2 drops of concentrated H_2SO_4

were slowly added to the mixture. The mixture was introduced into a microwave oven and irradiated at 50 % power (200 W) until the reaction was completed. The excess of methanol was evaporated, and then the residue was neutralized with 5 % potassium carbonate solution. The crude product **5** was washed with cold water and then purified by recrystallization using an appropriate solvent.

Obtained product is white crystal; 75 % yield; m.p. 419 K. UV: λ_{max} (EtOH) 230 and 314 nm. IR (KBr; ν cm^{-1}): 3378, 1687, 1268, 1177, 1617, 823. ^1H NMR (DMSO- d_6 ; TMS; δ ppm): 9.96 (1H, s, -OH), 6.75 (2H, d, $J = 8.2$ Hz, -CH=CH-), 7.50 (2H, d, $J = 8.2$ Hz, -CH=CH-), 3.65 (3H, s, -OCH₃), 7.52 (1H, d, $J = 15.8$ Hz, Ar-CH=CH-C=O), 6.35 (1H, d, $J = 15.8$ Hz, Ar-CH=CH-C=O). ^{13}C NMR (DMSO- d_6 , TMS, δ ppm): 167.6, 160.4, 145.3, 130.8, 130.8, 125.6, 116.3, 116.3, 114.4, 51.7. All the spectral data are in agreement with the structure of the compound **5**.

2.2.5. Clotting Time Assay

White male adult mice in good health of age 8-12 weeks and weight of 20-22 g were adapted and fed for one week and then randomly divided into 5 groups, each consisting of 6 mice. Each mouse was fed with their usual food every day and was given drink of water *ad libitum*. All mice were tested for blood clotting time (day 0) and were put into the mounting. The blood clotting time was calculated by putting mice on an observation desk. The mice's tail was cleaned by 70 % alcohol and then pierced with a surgical knife as far as 2 cm from the tail edge for 2 mm puncture depth. The dripping blood were then dripped into the object glass and observed for every 15 s to determine the onset of fibrin formation. Afterwards, the scarred mice were treated using betadine solution according to their groups. Low dose of ASP (80 mg) was used as a positive control and 0.5 % CMC-Na solution was used as negative control, both administered orally. The test solutions were given orally with the same dose of aspirin for 7 days. On the 8th day, blood clotting time on the test animals were analyzed according to the procedure outlined above [1]. Antiplatelet assay was approved by the Ethical Commission of Airlangga University.

2.2.6. In silico study

The *in silico* study was performed on the crystal structure of the enzyme COX-1 (PDB ID 1CQE) with 2.90 Å resolution, which was downloaded from the RCSB Protein Data Bank (www.rcsb.org), in the form of binding ligand crystal COX-1 with FLP_1650 [A]. The complex 1CQE-FLP_1650 [A] crystal structure was downloaded to the active site and determined for its binding sites. The 3D molecular structure of test compounds was imported into the active site and placed in a cavity in accordance with FLP_1650 [A]. The *in silico* assay was conducted into an

appropriate cavity of the SE algorithm using MolDock with the maximum of 1500 iterations. The affinity of the ligand was determined and the score expressed as Rerank Score (RS). The complex enzyme ligand with pose with the highest score showed the best interaction. The best docking result must fulfill the requirements, namely the lowest energy and the position of the molecule that is in the same bond with FLP_1650 [A], observed visually. Observation of enzyme-ligand interactions included hydrogen bonding, steric interactions (Van der Waals), as well as electrostatic performed to pose with the highest score of RS [10].

3. Results and Discussion

The structure modification of the *p*-coumaric acid (**1**) used the Fisher esterification reaction, alkylation, and catalytic dehydrogenation mentioned above, yielded the desired compounds, namely **2**, **3**, **4**, **5** (Fig. 1).

In this research, syntheses of **2**, **3**, and **5** were successfully conducted by microwave irradiation. The basic mechanism of microwave irradiation is caused by the agitation of polar or ionic molecules that move because of magnetic field movement. The occurrence of these magnetic movements causes the particles to try to orientate or parallelize with the field, limiting the movement of particles due to the interaction between particles and dielectric resistance. This will cause heat that centers on the magnetic plate. Microwave irradiation is different from the conventional heating method since in the conventional heating, oil bath or heating mantle is heated first followed by its solvent. This kind of heat distribution will cause heat differences between the mantle and the solvent [11, 12].

The alkylation reaction between the phenolic group of **1** with dimethyl sulfate was conducted, according to the principle of Williamson ether synthesis [13], to produce compound **2**. It was indicated by the loss of sharp peak the phenolic group of compound **1** at wavenumber of 3383 cm^{-1} and the appearance of a new peak of methoxy ether moiety of compound **2** at wavenumber of 1288 cm^{-1} . These changes were supported by three protons addition of the methoxy group (s, 3H) at 3.76 ppm of ^1H NMR spectrum. This methoxy group could also be observed in the ^{13}C NMR spectrum of compound **2** at a chemical shift of 51.8 ppm. The loss of phenolic groups had been confirmed by FeCl_3 reagent addition, which gave a positive purple color for the compound **1** as the result of complex formation between Fe^{3+} and the ligand, *i.e.* phenolic group. On the other hand, the compound **2** showed no purple color indicating that it had no phenolic groups. During process reaction, there should be no presence water that may affect hydrolysis of the dimethyl sulfate. Therefore, acetone was used as a solvent. The

methylation reaction using dimethyl sulfate on cynamate derivate, namely Azragel, that has activities as antiplatelet which inhibited thromboxane formation, was also reported by Baytas *et al.* [14].

Besides being able to alkylating the phenolic moiety of **1**, dimethyl sulfate can also be used for the alkylation of carboxylate moiety. Potassium carbonate was used to form the carboxylic ion of **1** so that its nucleophilic property increased to react with methyl group of dimethyl sulfate [15]. The alteration of carboxylic acid group of **1** into an ester group of **2** was shown by the loss peak at the wavenumber of 2836 cm^{-1} , which appears as a broadened peak because of the presence of the hydrogen bonds between $-\text{OH}$ of carboxylic acid moiety of **1**. In addition, the $\text{C}=\text{O}$ carbonyl group of **1** at wavenumber of 1672 cm^{-1} was replaced by the peak of $\text{C}=\text{O}$ ester of **2** at wavenumber of 1717 cm^{-1} . The presence of methyl ester and methyl ether could be observed in the chemical shift of 3.76 and 3.66 ppm (s, 3H) of ^1H NMR spectra as well as at 55.9 and 51.8 ppm of ^{13}C NMR spectra of **2**. Interpretation of spectral data from structural characterization of **2** concludes that its chemical structure is identical to the structure of same compound that was reported by Sun *et al.* [16].

The hydrolysis of **2** into **3** was performed in the base condition using KOH as reagent with ethanol as a solvent according to our previous research [17]. This method was selected because it is an irreversible reaction with the formation of potassium *p*-methoxycoumarate salt, and that salt was reacted easily with HCl to obtain compound **3**. The alteration of ester moiety of **2** into carboxylic acid group of **3** was displayed by the loss of $-\text{C}=\text{O}$ carbonyl ester peak at wavenumber of 1717 cm^{-1} and the presence of $-\text{C}=\text{O}$ carbonyl acid at 1685 cm^{-1} . The hydrogen bonding of $-\text{OH}$ carboxylic acid of **3** also showed at wave number 2844 cm^{-1} . This change was also clarified by the loss of three protons of the methyl ester group of **2** at the chemical shift 3.66 ppm (3H,s) of ^1H -NMR spectra and the loss of one carbon atom at 51.8 ppm of ^{13}C -NMR spectra. Hydrolysis of ethyl *p*-methoxycinnamate in alkaline condition, which employs conventional heating, may also produce compound **3** [17], but it will take a longer time than the microwave irradiation method that was used in this study.

The structure modification from **3** to **4** was conducted through the catalytic hydrogenation reaction with Raney-Ni as the metal catalyst. Raney-Ni metal works to reduce the double bond of **3** by these mechanisms: (i) adsorption of vinylic double bond of compound **3** on the surface of the hydrogenated metal catalyst, (ii) attachment of hydrogen by the β -carbon of compound **3** to form a σ -bond between the metal and α -C, and finally (iii) reductive elimination of the free alkane,

compound **4** [10, 18]. The transformation of structure **3** to **4**, was characterized by the loss of proton vinylic double bond, which was visible on the chemical shift 6.60 ppm (1H,d, $J = 16\text{ Hz}$) and 7.53 ppm (1H,d, $J = 16\text{ Hz}$). This double bond was transformed into a single bond which was characterized by two triplet peaks at chemical shift 2.88 and 2.54 ppm of ^1H NMR spectra.

The alteration of compound **1** into **5** was characterized by the appearance of peaks at 3378 and 1687 cm^{-1} of ester moiety, replaced peaks at 2836 and 1672 cm^{-1} of carboxylic acid moiety. The methyl ester group also was observed at chemical shift 3.65 ppm (s, 3H) in ^1H NMR spectra and 51.7 ppm in ^{13}C NMR spectra. Vo *et al.* [19] reported anti-inflammatory activity of **5** by stimulation Akt signaling pathway on macrophage cells. This anti-inflammatory mechanism compound **5** is same as compound **1** [8].

Structural modification of **1** into **2-5** will cause changes in physicochemical properties of the molecules, including $\log P$, MR and E_{total} . The change in molecular properties result in the difference in nature of their interactions with target molecules (receptors), that can be expressed in rerank score (RS). The physicochemical properties of the compound are shown in Table 2. $\log P$ describes the ratio of molecular affinity of nonpolar solvents versus polar solvents representing lipophilic character of QSAR study [20]. MR is a molecular size influenced by its polarizability that classified as steric property, E_{total} is molecular free energy in the most stable conformation that is one of the electronic properties of a molecule, whereas RS is a free energy of ligand-protein binding that exhibits the affinity of the compound against a selected target molecule [21], *i.e.* COX-1 enzyme (PDB ID 1CQE).

3.5. Antiplatelet Activities Test Conducted with the Clotting Time Slide Method

Low dose of aspirin can be used as an antiplatelet and inhibitor of COX-1 [3, 21]. Based on this fact, the antiplatelet test was performed using mice with corresponding aspirin doses (20 mg/kg BW). The results of antiplatelet of each compound group with slide clotting time method are: CMC-Na (129.7 ± 6.39); **1** (253.5 ± 11.61); **2** (355.6 ± 8.79); **3** (301.8 ± 11.66); **4** (211.8 ± 11.66), **5** (263.7 ± 12.89); ASP (339.2 ± 9.9) seconds as shown in Fig. 2.

Based on the ANOVA statistical test (Fig. 2) it can be seen that the blood clotting time of compound **1** and its derivatives (**2-5**) have significant differences with the negative control group, namely the CMC-Na test group ($P < 0.05$). This suggests that compound **1** and its derivatives have antiplatelet effects. The clotting times of

compounds **2**, **3**, and **5** show significant improvements compared to the compound **1**. While compound **4** has significantly different clotting time compared to all test groups ($P < 0.05$), it has a lower antiplatelet effect than other derivatives. All synthesized compounds give greater effect than negative control. Compounds **2** and **3** have clotting times that are not significantly different from the positive control of aspirin (ASP), which shows its potential as the same antiplatelet.

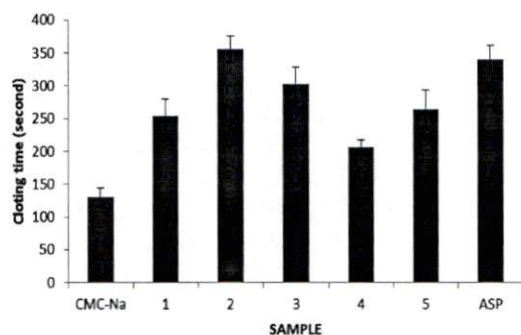


Fig. 2. Histogram of antiplatelet activity (mean \pm SE) by slide clotting time method of compounds **1–5**, CMC-Na (control negative), and ASP (control positive)

This can be explained with the *in silico* study of COX-1, where the docking score in the form of rerank scores (RS) according to the MVD 5.5 program is shown in the Table. The RS of ASP is -287.4 kJ/mol. The RS value of *p*-coumaric acid is higher than those of its derivatives. It means that its derivatives are capable to construct more stable interactions with the receptor than

p-coumaric acid. Meanwhile, the RS of **4** show similarly low interactions with COX-1 and thromboxane. The best docking poses of ASP and *p*-coumaric acid derivatives (**2–5**) are shown in Fig. 3. The interactions of the functional groups of each test compound with the COX-1 amino acid residue are shown in Fig. 4.

The COX-1 enzyme was constitutively expressed in most tissues, in which it controlled the synthesis of prostaglandins. COX-1 is the only form of enzyme present in mature thrombocyte and is also present in the blood vessels of endothelium, gastrointestinal epithelium, brain, spinal cord, and kidney [22].

In Fig. 4 it can be seen that all molecules of the test compound are in the same bonding place as FLP_1650 [A], namely cavity-5. RS FLP is -372.1964 kJ/mol. The RS data in the Table, which is free energy of enzyme-ligand interaction (ΔG , kJ/mol), shows the amount of energy of Van der Waals, electrostatic and hydrogen bonding interactions, and it can be used to predict how strong the ligand-enzyme bonds. The presence of methoxy groups in compounds **2** and **3** increases the strength of interaction with amino acid residues in compound **1** and all derivatives having carboxylate groups form the hydrogen bond on the $-\text{COOH}$ moiety with the amino acid residues of Arg 120 of COX-1 enzyme as in the ligand reference, namely flubiprofen (FLP_1650 [A]), as reported by Fauchier *et al.* [7]. The double bond change of vinylic in **3** into single bond in **4** converts the hybridization of the rigid sp^2 bond into freely rotating sp^3 , resulting in weaker interactions with the residue.

Table

Physicochemical properties of *p*-coumaric acid (1) and its derivatives (2-5)

Compound	Chemical structure	RS, kJ/mol PDB 1CQE	logP	MR, cm^3/mol	E_{total} kJ/mol
1		-289.8067	1.54	44.67	44.096
2		-318.2710	2.07	55.54	58.279
3		-301.9787	1.81	50.10	73.370
4		-275.7909	1.56	48.25	26.888
5		-308.7899	1.81	50.10	28.350

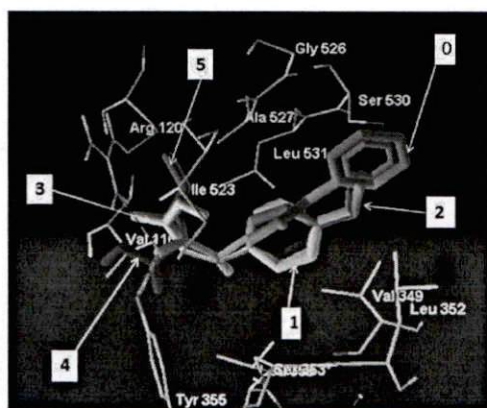


Fig. 3. Docking pose of FLP_1650 [A] (0), 1, 2, 3, 4, 5 on cavity 5 (Vol 54.272) of COX-1 (PDB 1CQE)

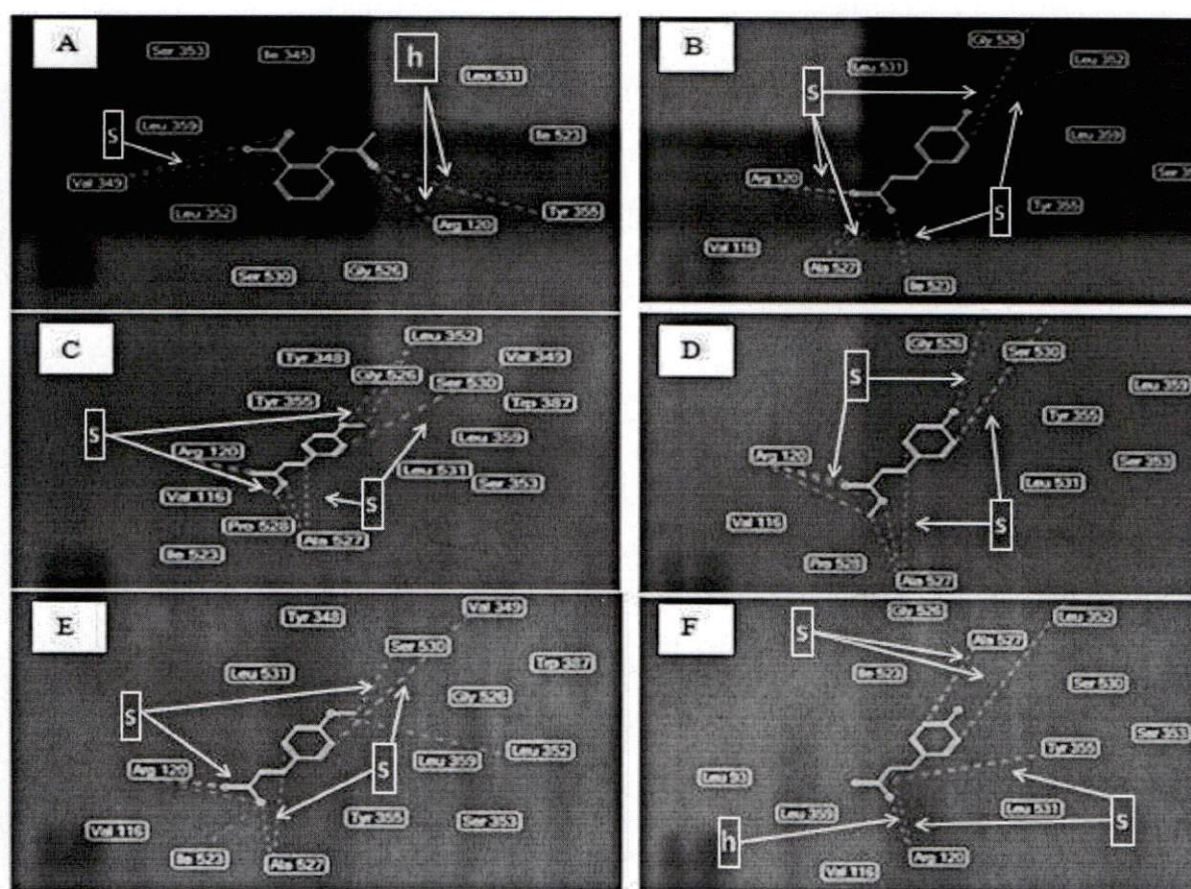


Fig. 4. 2D pictures showed interaction of ASP (4A), 1 (B), 2 (C), 5 (D), 3 (E), and 4 (F) with amino acid residues in cavity 5 of enzyme COX-1 (PDB 1CQE). Hydrogen bonding interaction marked as h; steric interaction marked as S

As *in silico* study results, it appears that the molecule 1 and its derivatives inhibit COX-1 enzyme. COX-1 binding of compound 1 and its derivatives in

blood platelets will prevent COX-1 pathway to produce thromboxane-A2 (TXA2) and afterward restrain platelet aggregation for the period of platelets lifecycle [20, 21].

3.6. The Relationship between Physico-Chemical Properties and Biological Activity

The statistical analysis was carried out by regression method between each dependent variable against antiplatelet activity, with one independent variable of physicochemical property. The result showed a linear relationship between physicochemical properties and antiplatelet activity among 5 tested compounds. The result is supported by the physicochemical properties, especially lipophilic ($\log P$) and RS properties. It may occur because in the determination of antiplatelet activity, the tested compound is administered through oral route to experimental animals. By this route, the compound capability in penetrating membrane barrier directly to the site of action depends on their lipophilic character. In this case the lipophilic nature ($\log P$) appears to indicate a significant role. There is a significant linear relationship ($P < 0.05$) between $\log P$ (partition coefficient) and antiplatelet activity (blood clotting time). The significant linear relationship ($P < 0.05$) also occurs between docking score (RS) and blood clotting time (CT) as indicated by the equations:

- (1) $CT = 227.749 \log P - 123.102$
($n = 5$, adjust $R^2 = 0.785$, $F = 15.163$, $P = 0.030$)
- (2) $CT = -13.228 RS - 666.662$
($n = 5$, adjust $R^2 = 0.713$, $F = 10.927$, $P = 0.046$)

Based on these equations it is known that antiplatelet activity is related to the lipophilic nature of the compound ($\log P$) and its affinity (RS) with the selected target molecule, *i.e.* COX-1 enzyme (PDB ID 1CQE). With the higher $\log P$ value, the antiplatelet activity will increase according to the coefficient of variable having a positive value. In terms of RS, with more negative free energy of the interaction between the compound and COX-1 the antiplatelet activity increases.

4. Conclusions

Four derivatives of *p*-coumaric acid (2-5) have been obtained through some reactions, *i.e.* alkylation, hydrolysis, catalytic hydrogenation, and Fisher esterification. All of the derivatives have anti-platelet activities. The presence of methyl group increases the activity, whereas the change of double bond of vinylic into single bond in 4 decreases the interaction with COX-1, hence decreasing its antiplatelet potentials compared to those of other derivatives.

Acknowledgments

This research was funded by Research Publication Acceleration Grant of Faculty of Pharmacy Airlangga University in year 2016-2017.

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<https://doi.org/10.1161/01.HYP.0000258106.74139.25>

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Accepted: August 29, 2018

СИНТЕЗ І АНТИТРОМБОЦИТАРНА ДІЯ ДЕЯКИХ ПОХІДНИХ *p*-КУМАРОВОЇ КИСЛОТИ

Анотація. Синтезовано нові похідні *p*-кумарової кислоти за участю реакцій алкілювання, основного гідролізу, каталітичного гідрування та естерифікації Фішера. Всі реакції, за винятком каталітичного гідрування, проводились за допомогою мікрохвильового опромінення побутової мікрохвильової печі. За результати аналізів на тромбоцити, враховуючи час згортання крові, показано, що *p*-кумарова кислота та її похідні мають антитромбоцитарну активність, яка пов'язана з ліпофільною природою сполук та їх спорідненістю з вибраною цільовою молекулою, тобто ферментом COX-1 (PDB ID 1CQE).

Ключові слова: *p*-кумарова кислота, антитромбоцитарний, COX-1, час згортання крові, каталітичне гідрування.

submission of your paper to Ch&ChT

4 messages

Olena Shyshchak <oshyshchak@gmail.com>
To: juni-e@ff.unair.ac.id

Mon, Mar 5, 2018 at 7:52 PM

Dear authors,
We received your manuscript, thanks.

We will send it for the review *only* after receiving *a statement (any form convenience for you) that the article was not either published or submitted for publication in any other domestic and abroad journals.* Please, notice also that the period of time from submitting paper to its publication is approximately 6-10 months.

Best regards,
Dr. Olena Shyshchak
Executive secretary
journal Ch&ChT

juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Wed, Mar 7, 2018 at 10:15 AM

Dear Dr. Olena Shyshchak,
Executive secretary
journal Ch&ChT


Following our submission 2 days ago, herewith we send the manuscript again and the copyright form of statement letter requested.

Thank you for your attention.

Best regards
Dr. Juni Ekowati, MSi., Apt.
Faculty of Pharmacy
Airlangga University
Surabaya Indonesia

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2 attachments

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Olena Shyshchak <oshyshchak@gmail.com>
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Wed, Mar 7, 2018 at 2:03 PM

Dear authors,

We received your statement, thanks, and sent the article for the review (registration number is 155/05.03.18). After receiving referee report I'll send it to you for comments. Please, notice that the period of time from submitting paper to its publication is approximately 6-10 months.

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journal Ch&ChT



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juni ekowati <juni-e@ff.unair.ac.id>
To: Achmad Syahrani <achmad-syahrani@ff.unair.ac.id>

Tue, Mar 20, 2018 at 11:40 AM

[Quoted text hidden]

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9 messages

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Mon, Mar 12, 2018 at 4:18 PM

Dear authors,

In attach there is referee report for your article. Please make necessary corrections and send us revised version and/or your answers to the referee.

Best regards,

Dr. Olena Shyshchak

Executive secretary

journal Chemistry & Chemical Technology

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juni ekowati <juni-e@ff.unair.ac.id>
To: Achmad Syahrani <achmad-syahrani@ff.unair.ac.id>

Tue, Mar 20, 2018 at 11:38 AM

[Quoted text hidden]

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juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Tue, Mar 27, 2018 at 4:33 PM

Dear Dr. Olena Shyshchak,
Executive secretary
journal Ch&ChT

Thank you for referee comments to our manuscript.
Herewith we send again our manuscript after reviewed.

Thank you for your attention.

Best regards
Dr. Juni Ekowati, MSi., Apt.
Faculty of Pharmacy
Airlangga University
Surabaya Indonesia

[Quoted text hidden]

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Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Tue, Mar 27, 2018 at 5:10 PM

Dear authors,

We received your revised version, thanks, and sent it again to the reviewer (according to his requirement). After receiving the answer I'll inform you

Best regards,
Dr. Olena Shyshchak
Executive secretary
journal Ch&ChT

[Quoted text hidden]

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Thu, Mar 29, 2018 at 12:53 PM

Dear authors,

Please see re-reviewed version. The reviewer ask you to correct everything he marked with red color

Best regards,
Olena Shyshchak



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juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Mon, Apr 2, 2018 at 12:29 PM

Dear Dr. Olena,

Herewith we send a second revision of our manuscript, especially words marked with red color from the reviewer.

Thank you.

Best regards
Juni Ekowati

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Olena Shyshchak <oshyshchak@gmail.com>
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Mon, Apr 2, 2018 at 1:05 PM

Thank you, I sent the revised version again to the referee

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Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Mon, Apr 2, 2018 at 6:27 PM

Dear authors,
Your revised version is accepted for publication. Now I am sending it for Grammar checking and copy-editing.
Before the issue printing (approximately 8-10 months from the date of submission) I'll send you proofs.

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Dr. Olena Shyshchak
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journal Ch&ChT

2018-04-02 8:29 GMT+03:00 juni ekowati <juni-e@ff.unair.ac.id>:
[Quoted text hidden]

juni ekowati <juni-e@ff.unair.ac.id>
Draft

Tue, Apr 3, 2018 at 10:40 AM

----- Forwarded message -----
From: **Olena Shyshchak** <oshyshchak@gmail.com>
Date: Mon, Mar 12, 2018 at 4:18 PM
Subject: referee report for your paper in Ch&ChT
To: juni ekowati <juni-e@ff.unair.ac.id>

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8 messages

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Wed, Jun 12, 2019 at 2:30 PM

Dear authors,

See in attach proofs of your article and send me your corrections **in 5 days**. Please, pay attention to your names and symbols, especially in equations or reactions, because they may be changed during paper was formed by the publishing house. After the mentioned term no changes will be possible.

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Executive secretary

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juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Sat, Jun 15, 2019 at 2:13 AM

Dear Dr. Olena

I have proofread our article. No correction from us.
Thank you

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Juni Ekowati
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juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>


Mon, Jun 17, 2019 at 3:02 PM

Dear Olena,
If it is possible, I need a correction in the **Title** part of our article. Please change **P-COUMARIC ACID** into **p-COUMARIC ACID** (sticky note).
Thank you.

Juni Ekowati

On Wed, Jun 12, 2019 at 2:31 PM Olena Shyshchak <oshyshchak@gmail.com> wrote:

[Quoted text hidden]

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Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Tue, Jun 18, 2019 at 12:42 PM

Thank you

пт, 14 черв. 2019 о 22:13 juni ekowati <juni-e@ff.unair.ac.id> пише:

[Quoted text hidden]

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Tue, Jun 18, 2019 at 12:43 PM

It's done already

пн, 17 черв. 2019 о 11:03 juni ekowati <juni-e@ff.unair.ac.id> пише:

[Quoted text hidden]

juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Mon, Jul 22, 2019 at 5:58 AM

Dear Dr Olena,
Whether our article has a DOI number? If so, could you send our article with DOI number to me.

Thank you
Regards
Juni Ekowati

On Wed, Jun 12, 2019 at 2:31 PM Olena Shyshchak <oshyshchak@gmail.com> wrote:

[Quoted text hidden]

Olena Shyshchak <oshyshchak@gmail.com>
To: juni-e@ff.unair.ac.id

Mon, Jul 22, 2019 at 5:59 AM

Sorry, I am out of the office now.
I will contact with you after August 26, 2019

Best regards,
Olena Shyshchak

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Tue, Aug 27, 2019 at 3:40 PM

DOI number is 10.23939/chcht13.03.296 The article will be available in the journal's site approximately in two-three weeks

Regards,
Olena

пн, 22 лип. 2019 о 01:59 juni ekowati <juni-e@ff.unair.ac.id> пише:

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final acceptance of your paper to Ch&ChT

7 messages

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Fri, Aug 31, 2018 at 7:10 PM

Dear authors,

I am preparing now your article for the final acceptance and need some corrections. All my questions or incomprehensible places I marked with yellow or green (see attach). Please correct them in the same file and send me back also marked with the color.

Best regards,
Olena Shyshchak
Executive secretary
journal Chemistry & Chemical Technology

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juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Sat, Sep 8, 2018 at 3:29 PM


Dear Dr. Olena Shyshchak
Executive secretary
Journal Chemistry & Chemical Technology

Thank you for notification of receiving our manuscript. Herewith we send manuscript correction results in yellow colour.

Best regards

Juni Ekowati
Department of Pharmaceutical Chemistry
Faculty of Pharmacy
Airlangga University

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Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Tue, Sep 11, 2018 at 3:57 PM

Dear Juni Ekowati,
The changes were accepted except Figs. 3 and 4. See comments in the text

Regards,
Olena Shyshchak

сб, 8 вер. 2018 о 11:29 juni ekowati <juni-e@ff.unair.ac.id> пише:
[Quoted text hidden]

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juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Thu, Sep 13, 2018 at 4:42 PM

Dear Dr. Olena Shyshchak,

Herewith we send the corrected article on Fig. 3 and Fig. 4.
Thank you

Regard
Juni Ekowati
[Quoted text hidden]

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Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Thu, Sep 13, 2018 at 5:43 PM

Dear Juni Ekowati,
The article is accepted, thank you

Regards,
Olena Shyshchak

ЧТ, 13 вер. 2018 о 12:42 juni ekowati <juni-e@ff.unair.ac.id> пише:
[Quoted text hidden]

juni ekowati <juni-e@ff.unair.ac.id>
To: Olena Shyshchak <oshyshchak@gmail.com>

Wed, Dec 12, 2018 at 8:58 PM

Dear Dr. Olena Shyshchak

I need an information about time schedule for our paper will be published.

Thank you
Regards,
Juni Ekowati

[Quoted text hidden]

Olena Shyshchak <oshyshchak@gmail.com>
To: juni ekowati <juni-e@ff.unair.ac.id>

Thu, Dec 13, 2018 at 2:02 PM

Dear authors,
The number of submitted papers is huge. Unfortunately the number of issues of the journal and the volume of every issue is limited, so the actual period from submission to publication is approximately 10-12 months. I gave notice about this in every message. Your article was received on March 05, 2018 and will be published according to its turn in the general list

Best regards,
Olena Shyshchak
Executive secretary
journal Chemistry&Chemical Technology

7/19/2020

Airlangga University Mail - final acceptance of your paper to Ch&ChT

ср, 12 груд. 2018 о 15:58 juni ekowati <juni-e@ff.unair.ac.id> пише:

[Quoted text hidden]

doi number

2 messages

Olena Shyshchak <oshyshchak@gmail.com>

Wed, Aug 28, 2019 at 5:48 PM

To: Остап Івашків <ivostpet@gmail.com>, Олена Астахова <olena.brat@gmail.com>, Amrita srivastava <amritasri2019@gmail.com>, Володимир Моравський <vmoravsky@gmail.com>, SBAI SALAH EDDINE <salaheddinechimie@gmail.com>, "Тетяна Михайлівна, Деркач" <derkach.tm@knutd.edu.ua>, Kovo Godfrey Akpomie <kovoakpmusic@yahoo.com>, Abhishek srivastava <aabhichem@gla.ac.in>, Alena Kulish <onlyalena@mail.ru>, juni ekowati <juni-e@ff.unair.ac.id>, Володимир Дутка <vdutka@ukr.net>, Ирина Цихановская <cikhanovskaja@gmail.com>, Department of Physical and Colloid Chemistry <phys.chem.lp@gmail.com>, "Elizabete F. Lucas" <elucas@ima.ufrj.br>, Вікторія Воробйова <vorobyovavika1988@gmail.com>, Dyah Hesti Wardhani <dwardhani@che.undip.ac.id>, OMAN <zuas.oman@gmail.com>, Myroslav Malovanyy <myroslav.mal@gmail.com>, ibtisseem kahoul <ibtisseemkahoul@yahoo.com>

Dear authors,

Here you can see doi numbers assigned for your articles in the journal Chemistry&Chemical Technology (V.13, No3, 2019). Full texts will be available on the journal's site in approximately two weeks

Best regards,

Olena Shyshchak

Executive secretary

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juni ekowati <juni-e@ff.unair.ac.id>

Wed, Aug 28, 2019 at 6:05 PM

To: Olena Shyshchak <oshyshchak@gmail.com>

Thank you very much for your information.

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