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Preface

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Speech by the chairman of the committee

Ladies and gentlemen, welcome to the 15th Joint Conference on Chemistry (JCC) 2020.

1. The honorable, Rector of Universitas Kristen Satya Wacana.
2. The honorable, Dean of Faculty of Science and Mathematics, Universitas Kristen Satya Wacana.
3. The honorable, head of Department/Study Program, members of Chemistry Consortium (Univ. Diponegoro, Univ. Negeri Semarang, Univ. Sebelas Maret Surakarta, and Univ. Jend. Soedirman Purwokerto).
4. The honorable, Keynote Speakers.
5. The honorable, invited presenters, presenters, and all the conference participants.

First of all, we thank God for this extraordinary opportunity, so that we can hold the 15th JCC 2020, during pandemic COVID-19. At first, we were still confused and doubtful about the implementation of this conference. It also happened to be the first time we become the organizers of this prestigious Conference. But once again thanks to God's blessing and support from our colleagues, leaders, and support from the extraordinary Consortium, so that we can move forward with certainty.

At this moment, the challenge of a very bad situation due to the COVID-19 pandemic has spread to almost all countries, including Indonesia, so that we must face it together. Every component of this country must start moving according to its duties and portions. Likewise, with this consortium of five universities, the annual agenda in the form of an international conference must continue on time. Even though COVID-19 has not subsided yet, the 6 months that have just passed have educated us to be able to walk with Corona, which we don't know yet, when it will completely disappear. Although the plan has changed drastically due to the current condition, the 15th JCC will be held online and only for one day.

We invite four Keynote Speakers: Prof. Hadi Noor from Universitas Teknologi Malaysia, Prof. Hidetoshi Sato from Kwansei gakuin University, Japan, Prof. Ming -Kang Tsai from National Taiwan Normal University, Taiwan, and Dr. Tatas HP Brotosudarmo, Dipl. Chem., Ph.D from Indonesia, which also the previous Chief of HKI period 2018. Several invited speakers from members of the consortium also attend this 15th JCC. We also want to report that there are 60 papers that come from various places, for ex. Taiwan, Japan, Vietnam, Malaysia.



The 15th JCC activity would not have been possible without the help of many parties, therefore allow me as the chairman of the committee to say many thanks to all parties that we cannot mention one by one. Especially for my internal committee members, I would like to express my highest appreciation for the hard work and extraordinary cooperation for the implementation of the 15th JCC. We also thank all the 15th JCC participants who have joined online. Finally, we apologize if in the implementation there is something that is not pleasing to the hearts of all the participants. Thank you and have a good conference.

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- **Type of peer review:** Single-blind (Authors do not know who the reviewers are. The reviewers know who the authors are. The members of Reviewer Team reviewed papers by the relevance to the topics, paper format requirements, similarity, and English proofread.)
- **Conference submission management system:**
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- **Number of submissions received:** 39
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- **Number of submissions accepted:** 38
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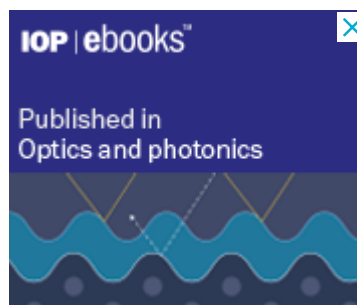
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Interaction of mutant PBP2a and bioactive compounds from *Streptomyces* with anti-MRSA activities

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Interaction of mutant PBP2a and bioactive compounds from *Streptomyces* with anti-MRSA activities

A Laksono, A Asnani* and P Iswanto

Chemistry Department, Faculty of Mathematics and Sciences,
Universitas Jenderal Soedirman, Purwokerto 53123

* E-mail: ari.asnani@unsoed.ac.id

Abstract. Methicillin-Resistant *Staphylococcus aureus* (MRSA) is the leading cause of nosocomial infections in hospitals. Treatment of MRSA infection using ceftaroline has been reported to be resistant due to mutations in the Penicillin Binding Protein (PBP)2a. In silico's approach through virtual screening can analyze the bioactive compounds that can bind effectively to mutant PBP2a. The potential source of bioactive compounds with anti-MRSA activities is *Streptomyces*, which is the main antibiotic-producing bacteria. Thus, the study aimed to analyze the interactions of PBP2a/mutant PBP2a against ceftaroline and the interactions between mutant PBP2a against bioactive compounds from *Streptomyces*. The protein receptors were PBP2a (PDB 3ZG0) and mutant PBP2a (PDB 4CPK). The ligands used were ceftaroline (CID 9852981) as control and nine bioactive compounds produced by *Streptomyces*. Protein preparation and visualization used Discovery Studio, ligand preparation used Marvin, and molecular docking used Autodock4. The alignment results showed that mutant PBP2a has a more extended amino acid sequence (643 amino acids) than PBP2a (641 amino acids). The mutations that occurred in mutant PBP2a caused conformation changes in the active site of mutant PBP2a so that the interaction between ceftaroline and mutant PBP2a decreased. The virtual screening results indicated that 1-acetyl- β -carboline was the most potent compound as anti-MRSA with the lowest binding energy (-7.12 Kcal /mol) compared to ceftaroline (-6.32 Kcal/mol). The amino acids involved in the binding of 1-acetyl- β -carboline with PBP2a mutant were Ser403, Ser461, Asn464, Thr600; Ser462, Tyr446, and Ala642. This result suggests that 1-acetyl- β -carboline has better interaction with mutant PBP2a, hence might serve as a potential anti-MRSA compound.

1. Introduction

Methicillin-Resistant Staphylococcus aureus (MRSA) is *Staphylococcus aureus* bacteria resistant to β -lactam antibiotics such as penicillin and its derivatives, namely methicillin, oxacillin, dicloxacillin, nafcillin, and cephalosporin. Resistance to methicillin is caused by the *MecA* gene that produces Penicillin Binding Protein (PBP) 2a, which is insensitive to β -lactam antibiotics [1]. PBP has a significant role in the peptidoglycan biosynthetic reaction in the formation of bacterial cell walls [2]. There are four types of PBP, namely PBP1, PBP2, PBP3, and PBP4, which are complex proteins with glycosylase and transpeptidase activities. In MRSA, there is a fifth type of PBP, namely PBP2a, coded by the *MecA* gene [3]. This PBP2a causes MRSA to be insensitive to β -lactam class antibiotics and causes multiresistant strains.

One of the options for treating MRSA infection is the use of ceftaroline antibiotic, which serves as transpeptidase inhibitor in PBP2a [4]. However, Fishovitz et al. [5] have reported a mutation in PBP2a



so that MRSA becomes resistant to ceftaroline. Resistance occurs due to the mutation of two amino acids on the allosteric site of PBP2a, which causes changes in the conformation of the active site. These changes cause a decrease in the effectiveness of ceftaroline antibiotic binding and result in the ineffectiveness of ceftaroline for MRSA therapy [6]. The incidence of MRSA resistance to ceftaroline encourages the development of new bioactive compounds as anti-MRSA. WHO has even classified MRSA in the High-Risk category on the Priority Pathogen List for research and development of new antibiotics [7].

Exploring bioactive compounds that are antagonistic can be done through virtual screening of potentially bioactive compounds [8]. Molecular docking can be performed between the mutant PBP2a receptor and bioactive compounds as ligands to obtain bioactive compounds capable of interacting with mutant PBP2a. Molecular docking is an in-silico approach to pairing a protein molecule on the active side with other molecules with a specific purpose, for example, looking for potential new drugs [9]. It is known that ceftaroline antibiotic binds PBP2a on the active side at the Serin 403 position [10]. Therefore, the active site of PBP2a can be used as a reference for molecular docking to determine the interaction of PBP2a with other bioactive compounds to test the compound's potential as anti-MRSA. Lavanya et al. [11] conducted molecular docking to screen potential compounds from the ZINC database capable of interacting with MRSA that is resistant to ceftaroline. Mohamed et al. [12] reported that indigenous Sudanese natural ingredients, namely isoflavonoids-17, chalcon-21, diphyllin, and coumarin-29, were able to bind effectively with PBP2a in Ser404 using the molecular docking method.

One of the potential sources of bioactive compounds is actinomycetes, especially the genus *Streptomyces* which is the main antibiotic-producing bacteria. *Streptomyces* are known to produce antibiotic, anticancer, anti-inflammatory, anti-fungal, protein inhibitor, and other active compounds [13]. Indeed, the genus *Streptomyces* can produce potential compounds with anti-MRSA activity. Kemung et al. [14] have reviewed bioactive compounds with anti-MRSA activity produced by *Streptomyces*. Asnani et al. [15] have also reported that *Streptomyces* from mangrove sediment at Segara Anakan has potential as anti-MRSA. Hence, this study aimed to compare PBP2a protein interaction with mutant PBP2a against ceftaroline and screen bioactive compounds from *Streptomyces* as anti-MRSA candidates. The bioactive compounds with the most potential to bind to mutant PBP2a are expected to be the most potential anti-MRSA candidates.

2. Materials and methods

The PBP2a receptor protein was PDB 3ZGO, a PBP2a crystal structure that binds to ceftaroline [10]. The mutant PBP2a was PDB 4CPK, which is a crystal structure of PBP2a double clinical mutant N146K-E150K from MRSA [5]. The crystal structures of the two proteins were downloaded from the Protein Data Bank. The alignment of mutant PBP2a and PBP2a used Clustal Omega (1.2.4) multiple sequence alignment to analyze the differences caused by mutations. Protein preparation used Autodock4 [9] version 1.5.6.

The ligands were the antibiotic ceftaroline as control and nine bioactive compounds produced by *Streptomyces*, namely 1-acetyl- β -carboline, marinopyrrole A, cyslabdan, 4'-deacetyl griseucin A, griseucin A, polyketomycin, heliquinomycin, and chaxamycin D. All ligand structures were downloaded from PubChem and optimized with MarvinSketch 20.3.

Interaction of mutant PBP2a and bioactive compounds from *Streptomyces* was carried out based on the active side of mutant PBP2a, which is Serin 403 coordinates [10] using Autodock4 [9] version 1.5.6. Mutant PBP2a protein was not given a degree of freedom. In contrast, ligands were given a degree of freedom to predict the best position on the active site of the protein. The bond coordinates were x: -27.959; y: -19.845; and z: 6.711. The box's size to predict binding position was 50 on Autodock and docking parameters used LGA (Lamarckian Genetic Algorithm). Visualization of the amino acid bonds involved in the binding position and the interactions between the receptor protein and the ligand used the BIOVIA Discovery Studio Visualizer.

3. Results and discussion

3.1. Alignment of PBP2a and mutant PBP2a

Protein receptors alignment were performed by comparing the crystal structure of PBP2a (PDB 3ZG0), which binds to ceftaroline antibiotics with the crystal structure of mutant PBP2a (PDB 4CPK). Figure 1 shows the differences in the structures of PBP2a and mutant PBP2a. The mutations that occur in mutant PBP2a are on the allosteric site, which causes changes in the protein conformation so that ceftaroline cannot effectively bind to the active site [5]. This mutation causes MRSA to become resistant to ceftaroline.

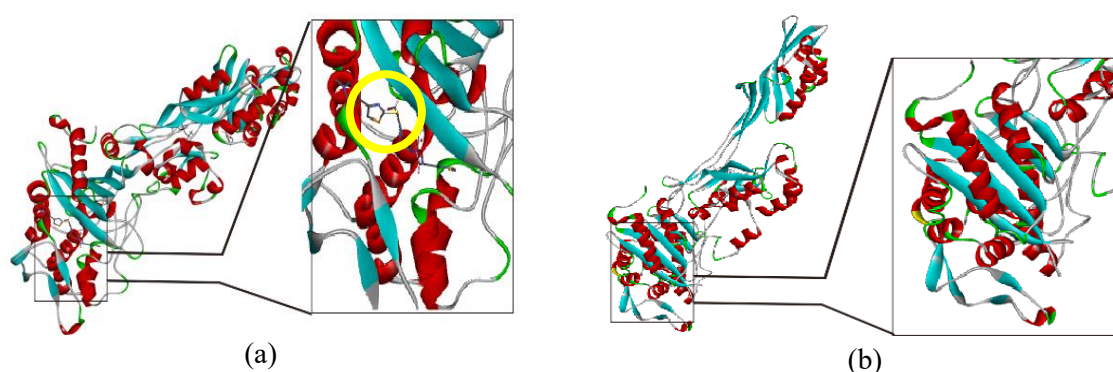


Figure 1. The crystal structure (a) PBP2a binds to the ceftaroline antibiotic on the active site of the A chain indicates by the yellow circle, (b) mutant PBP2a resistant to antibiotics does not bind to ligands on the active site of the A chain.

In addition to differences in the molecular structure of mutant PBP2a and PBP2a, there are also differences in the amino acid sequences of the two proteins. The results of the alignment analysis of the amino acid sequences of mutant PBP2a and PBP2a showed differences in the number of amino acids. The mutant PBP2a has a more extended amino acid sequence than PBP2a. The longer mutant PBP2a protein presumably is caused by a mutation on the allosteric site that changes the protein conformation. Table 1 shows the differences in amino acids of PBP2a (PDB 3ZG0) and mutant PBP2a (PDB 4CPK).

Table 1. The results of the alignment analysis of 3ZG0 and 4CPK.

PBP2a	Amino acids		Position	
	PDB 3ZG0	PDB 4CPK	PDB 3ZG0	PDB 4CPK
A chain	-	Lysine	-	1
	Asparagine	Lysine	120	121
	Glutamic acid	Lysine	124	125
	-	Glutamic acid	-	643
	-	Lysine	-	1
B chain	Asparagine	Lysine	120	121
	Glutamic acid	Lysine	124	125

3.2. Ligand optimization

The ligands used in this study were ceftaroline antibiotics as control and nine bioactive compounds with potency as anti-MRSA from *Streptomyces*. Structure optimization of ligands used MarvinSketch. Structure optimization aims to ensure the correct structure of the ligands. It minimizes the energy to

stabilize the structures before the ligands are used in molecular docking. The ligand optimization generated structure with energies ranges from 46.47 to 227.48 Kcal/mol (table 2). The compounds that have been minimized were then used as ligands in molecular docking.

Table 2. The Energy minimization from ligands optimization

No	Compounds	CID	Energy (Kcal/mol)
1	Ceftaroline	138756682	127.30
2	1-Acetyl- β -carboline	638667	46.47
3	Frigocyclinone	11476774	109.56
4	Marinopyrrol A	24797083	85.86
5	Cyslabdan	24778014	113.11
6	4'-deacetyl griseusin A	56834145	90.09
7	Grieusin A	16102131	89.14
8	Polyketomycin	10395823	227.48
9	Heliquinomycin	101714016	127.30
10	Chaxamycin D	53344649	164.45

3.3. Interaction of mutant PBP2a and ligands

Molecular docking was performed 20 times from the LGA calculation to produce the best position with the lowest binding energy. The smaller binding energy with the receptor protein indicates good results in which the binding is more stable than that with the higher binding energy. The results of the molecular docking of nine bioactive compounds from *Streptomyces* based on binding energy are presented in table 3. The 1-acetyl- β -carboline compound has the lowest binding energy (-7.12 Kcal/mol) compared to other bioactive compounds, including the control ceftaroline (-6.32 Kcal/mol). This result suggests that the interaction between 1-acetyl- β -carboline and mutant PBP2a is the most effective so that 1-acetyl- β -carboline has the potential as anti-MRSA. The best interactions between ligands and receptor proteins were further visualized using Discovery Studio to analyze the amino acid bonds.

Table 3. The binding energy from the interaction of protein and ligand.

No	Compounds	Binding Energy (Kcal/mol)
1	Ceftaroline	-6.32
2	1-acetyl- β -carboline	-7.12
3	Frigocyclinone	-6.66
4	Marinopyrrol A	-6.27
5	Cyslabdan	-5.67
6	4'-deacetyl-griseusin A	-5.10
7	Grieusin A	-4.55
8	Polyketomycin	-4.49
9	Heliquinomycin	-3.55
10	Chaxamycin D	-1.41

The docking result of ceftaroline on the active site of the mutant PBP2a has a binding energy of -6.32 Kcal/mol. The amino acid involved in the binding of ceftaroline with mutant PBP2a are lysine at a

position of 430 (Lys430) with hydrogen bonding (figure 2). Amino acids involved in the binding interactions of ceftaroline and mutant PBP2a through hydrogen bonds are Lys430, Tyr446, Asn464, Gln521, Thr600, Ala601, and Gln613 in the A chain.

Ceftaroline is known to have a high affinity for PBP2a. It binds to the active site of the PBP2a on the amino acid Ser403 [10]. The results of visualization of ceftaroline binding with mutant PBP2a showed different binding to PBP2a. This difference in binding is probably the cause of the different responses of MRSA containing mutant PBP2a to ceftaroline therapy. Allosteric site changes that occur in mutant PBP2a has changed the conformation on the active site of mutant PBP2a [5]. Apparently, the binding affinity of the receptor to ceftaroline decreases due to conformation changes of the active site of the protein, thus resulting in resistance to ceftaroline.

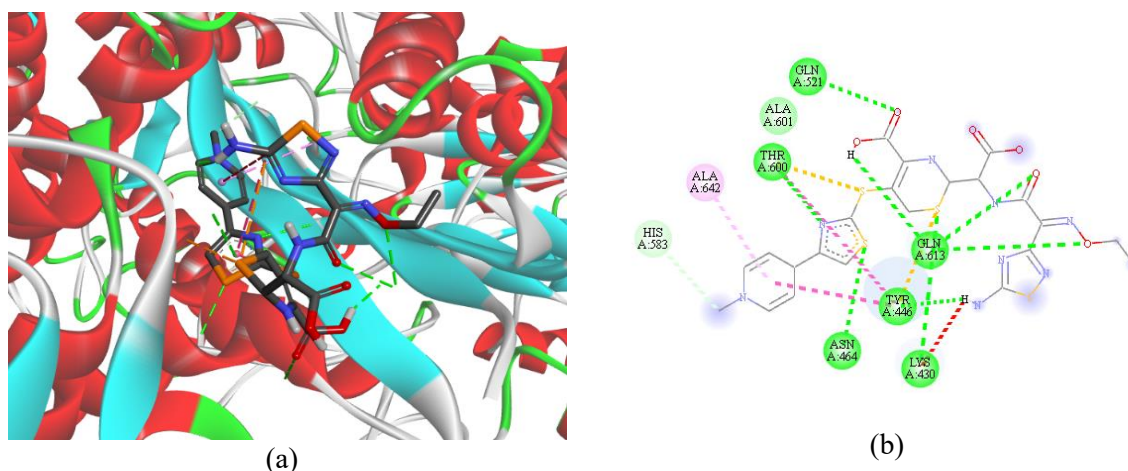


Figure 2. (a) 3D visualization of ceftaroline-protein receptor binding interactions; (b) 2D visualization of the amino acids involved.

Nine bioactive compounds from *Streptomyces* were successfully docking on the active site of mutant PBP2a with the same active site as PBP2a. Based on the docking results, 1-acetyl- β -carboline and frigocyclinone compounds are potential anti-MRSA compounds with bond energies of -7.12 and 6.62 Kcal/mol. The affinity binding of the 1-acetyl- β -carboline and frigocyclinone to mutant PBP2a are stronger than that of ceftaroline.

1-Acetyl- β -carboline is a compound of the alkaloid indole group isolated from *Streptomyces sp.* 04DH52 [16]. This molecule could enter and bind to the active site of mutant PBP2a with the least bond energy compared to other ligands. The small binding energy shows the bond's strength in which the smaller the value, the stronger the bonds formed. Docking of the 1-acetyl- β -carboline with the mutant PBP2a receptor protein gave binding energy of -7.12 Kcal/mol. Amino acids involved in the binding of 1-acetyl- β -carboline with receptor proteins through hydrogen bonding are Ser403, Ser461, Asn464, Thr600; and through the pi-sigma bonds are Ser462, Tyr446, and Ala642 in the A chain (figure 3A). Frigocyclinone is a bioactive compound isolated from *Streptomyces griseus* strain NTK 97 [17]. Frigocyclinone has good inhibitory activity against Gram-positive bacteria *Bacillus subtilis* DSM 10 and *S. aureus* DSM 20231. Docking of the frigocyclinone molecule with the mutant PBP2a receptor protein gave binding energy of -6.66 Kcal/mol. Amino acids involved in the binding of frigocyclinone with receptor through hydrogen bonds are Lys430, Gln521, Gln613, Glu602; and through phi-sigma bonds is Met641 on the A chain (figure 3B).

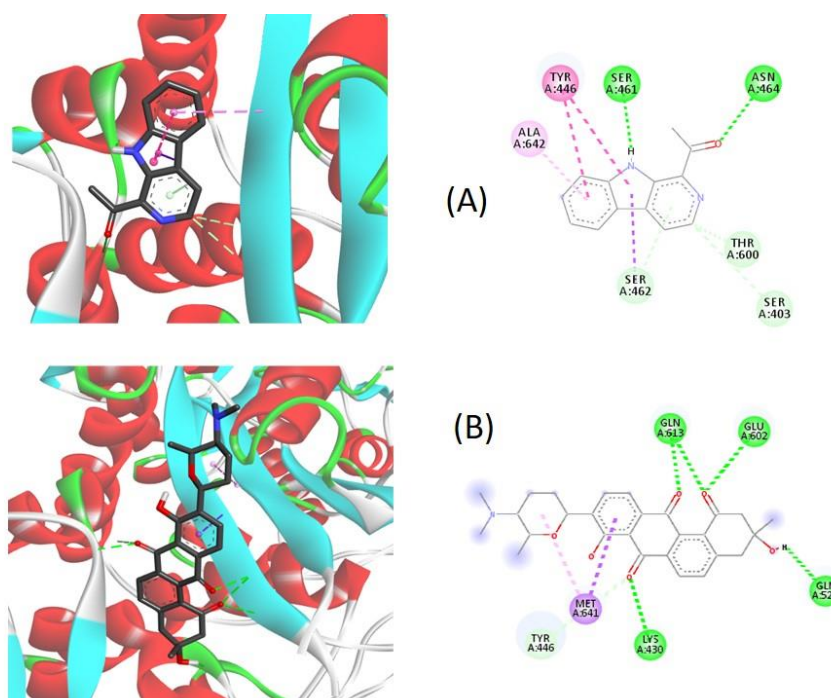


Figure 3. 3D visualization and 2D visualization of the amino acids involved in the interaction of (a) 1-acetyl- β -carboline and mutant PBP2a protein receptor, and (b) frigocyclinone and mutant PBP2a.

4. Conclusion

A virtual screening approach can be used to analyze the potential of bioactive compounds as anti-MRSA. Virtual screening of nine bioactive compounds from *Streptomyces* using molecular docking showed that 1-acetyl- β -carboline and frigocyclinone are potential compounds as anti-MRSA compared to ceftaroline control based on binding energy. This approach is expected to save time, effort, and cost before drug design and development is carried out for production.

Acknowledgment

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Ari Asnani Unsoed <ari.asnani@unsoed.ac.id>

[The 15th JCC] Editor Decision

1 message

The 15th Joint Conference on Chemistry 2020 UKSW <jcc@uksw.edu>

Sun, Aug 30, 2020 at 4:09 PM

To: ari.asnani@unsoed.ac.id

Dear Authors,

We have reached a decision regarding your submission to the 15th JCC 2020 with publication to the IOP-MSE (Material Science and Engineering).










Please find the attached files.

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No : 72/JCC-15/FSM/UKSW/VIII/2020
Re : The 15th JCC Scopus-indexed IOP-MSE Acceptance

August 30, 2020

Dear : Agung Laksono, Ari Asnani, Ponco Iswanto

Congratulations, We are pleased to inform that your paper entitled

Interaction of Mutant PBP2a and Bioactive Compounds from Streptomyces with Anti-MRSA Activities has been recommended for publication in The 15th JCC Scopus-indexed IOP-MSE (Material Science and Engineering). You are requested to send your **camera-ready** version in **word document and PDF**. We would like to remind you that it is mandatory for your paper to be revised as per reviewers' comments, according to IOP template, and pass Turnitin (equivalent alternatives) **less than 25%**. Please find the attached files.

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Ari Asnani Unsoed <ari.asnani@unsoed.ac.id>

[The 15th JCC] Reminder: Final Proofs

2 messages

The 15th Joint Conference on Chemistry 2020 UKSW <jcc@uksw.edu>

Thu, Sep 24, 2020 at 2:09 PM

To: Adi Purnomo <adi.spurnomo@yahoo.com>, amirawaluddin01@gmail.com, ari.asnani@unsoed.ac.id, Cholid Junaidi <cholidjunaidi@live.undip.ac.id>, eka_suprihatin@unud.ac.id, "Ferdy S. Rondonuwu" <ferdy.rondonuwu@uksw.edu>, giyanto081578663380@gmail.com, Gunawan Gunawan <gunawan@live.undip.ac.id>, Hartati Sucipto <hartati.sucipto@uksw.edu>, ibnsudria@gmail.com, iman.abdullah@sci.ui.ac.id, leny.yulianti@machung.ac.id, marinakartika@gmail.com, nurul.ismillayli@unram.ac.id, pak_pran@yahoo.com, poncoiswanto@gmail.com, Riniati riniati <riniati@polban.ac.id>, siahaan.parsaoran@live.undip.ac.id, syahidanaulia123@gmail.com, teguh@mipa.uns.ac.id, MARIA ULFA FAMILY <ulfa.maria2015@gmail.com>, usman01@pertamina.com, wahyu_hidayat@udb.ac.id, Yohanes Martono <yohanes.martono@uksw.edu>, Yosie Andriani <yosie.hs@umt.edu.my>

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Yes, everything is correct.

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