Yuniarta et al./Pharmacoscript, Volume 5, No, 2, Agustus 2022, 157-171

Pharmacoscript

P-ISSN : 2622-4941 | E-ISSN : 2685-1121

MOLECULAR DOCKING STUDY OF 1‑ (PYRIDIN-4-YL)PYRROLIDINE-2-ONE DERIVATE AGAINST PROLYL-tRNA SYNTHETASE IN *PLASMODIUM FALCIPARUM*

Tegar Achsendo Yuniarta, Jesica Ersty Wawo, Dini Kesuma

Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia

*Email: tegar.achsendo@staff.ubaya.ac.id

Received: 05/07/2022 , Revised: 17/08/2022 , Accepted: 20/08/2022, Published: 31/08/2022

ABSTRAK

Enzim prolil-tRNA sintetase merupakan salah satu target baru untuk pengembangan obat antimalaria. Beberapa golongan senyawa telah berhasil diidentifikasi sebagai inhibitor enzim tersebut, salah satunya adalah derivat piridin-pirolidinon. Diketahui bahwa senyawa 4- [(3)- 3- siano- 3- (1- metilsiklopropil)- 2- oksopirolidin- 1- il]- N- {[3- fluoro- 5- (1- metil- 1H- pirazol- 4- il)fenil]metil}- 6 metilpiridin- 2- karboksamida merupakan salah satu senyawa yang cukup poten sebagai kandidat antimalaria, yang diprediksi melalui mekanisme inhibisi kerja enzim tersebut. Senyawa ini memiliki dua isomer dengan bioaktivitas yang berbeda cukup signifikan. Senyawa ini diduga menduduki situs ikatan ATP pada enzim tersebut, namun masih belum dapat dibuktikan dengan data kristalografi struktur kompleks ligan-protein. Penelitian ini bertujuan untuk memprediksi mode interaksi serta afinitas ikatan antara dua enantiomer dari 4- [(- 3- siano- 3- (1- metilsiklopropil)- 2- oksopirolidin- 1- il]- N- {[3- fluoro- 5- (1- metil- 1H- pirazol- 4- il)fenil]metil}- 6 metilpiridin- 2- karboksamida dengan pendekatan penambatan molekul menggunakan EasyDockVina 2.2. Metode ini bertujuan untuk melihat bagaimana nilai *docking score* serta interaksinya dengan enzim prolil-tRNA sintetase. Hasil penelitian yang diperoleh membuktikan bahwa senyawa enantiomer S memiliki afinitas yang lebih tinggi (-0.81±3.98) dibandingkan dengan enantiomer R (1.74±2.71). Hasil ini selaras dengan dengan data uji *in vitro* antimalaria yang menyatakan bahwa enantiomer S lebih poten dibandingkan dengan enantiomer R. Selain itu diprediksi bahwa interaksi dengan asam amino GLN475 dan THR478 memiliki peranan dalam interaksi ligan-enzim. Studi lebih lanjut perlu dilakukan untuk memastikan hasil ini dengan pendekatan yang lebih akurat secara in silico maupun verifikasi dengan uji enzimatik.

Kata kunci: antimalaria, penambatan molekul, piridin-pirolidinon, prolil-tRNA sintetase, stereokimia

ABSTRACT

Prolyl-tRNA synthetase is one of the novel targets to develop antimalarial drug candidate. Several class of inhibitors have been identified for the enzyme, one of which is pyridine-pyrrolidinone derivative. It is recently known that 4- [3- cyano- 3- (1- methylcyclopropyl)- 2- oxopyrrolidin- 1- yl]- N- {[3- fluoro- 5- (1- methyl- 1H- pyrazol- 4- yl)phenyl]methyl}- 6- methylpyridine- 2- carboxamide possess potent antimalarial activity, possibly via prolyl-tRNA synthetase inhibition. This compound possesses two enantiomeric form which yielded antimalarial bioactivity in different magnitude. It is argued that this compound occupies ATP binding site. However, 3D structure of ligand-protein complex has yet to be elucidated. This study aimed to predict binding mode and affinity of two enantiomers of 4- [3- cyano- 3- (1- methylcyclopropyl)- 2- oxopyrrolidin- 1- yl]- N- {[3- fluoro- 5- (1- methyl- 1H- pyrazol- 4- yl)phenyl]methyl}- 6- methylpyridine- 2- carboxamide using molecular docking approach with EasyDockVina 2.2. The results showed that S enantiomer possess better ligand affinity (-0.81±3.98) compared to R enantiomer (1.74±2.71). The result was in line with *in vitro* antimalarial assay, which stated the potency of S enantiomer more than R enantiomer. In addition, it is argued that residue GLN475 and THR478 plays important role in ligand-enzyme interaction. Further studies are needed to verify the result with more robust in silico method and enzymatic bioassay.

***Keywords**: antimalaria, molecular docking, pyridine-pyrrolidinone, prolyl-tRNA synthetase, stereochemistry*

INTRODUCTION

Malaria is one of the most life-threatening disease in the world, with an estimated mortality rate of 600,000 in the beginning of 2020 (WHO, 2021). Prolyl-tRNA synthetase is recently known as one of the viable targets in malaria treatment (Keller et al., 2012). This enzyme belongs to class II aminoacyl-tRNA synthetase whose task is to catalyze the conjugation of tRNA with their cognate amino acid, in this case L-proline (Yogavel et al., 2018) (Figure 1).

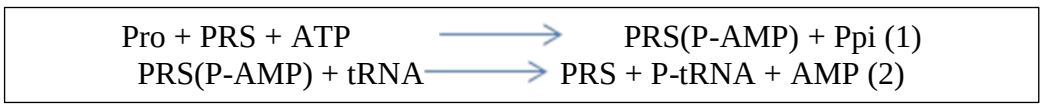


Figure 1. Prolyl-tRNA synthetase mechanism of action (Pro = proline; PRS = prolyl-tRNA synthetase enzyme; ATP = adenosine triphosphate; AMP = adenosine monophosphate; Ppi = inorganic pyrophosphate)

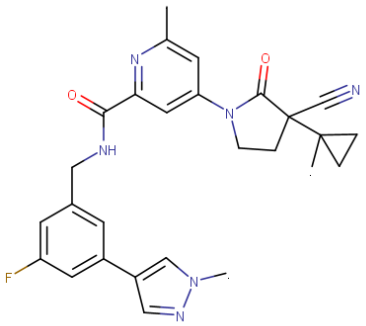
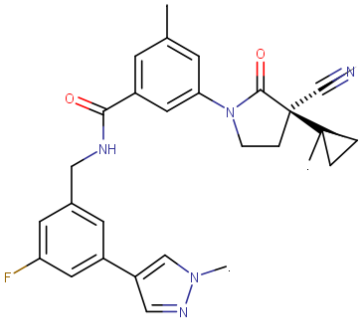
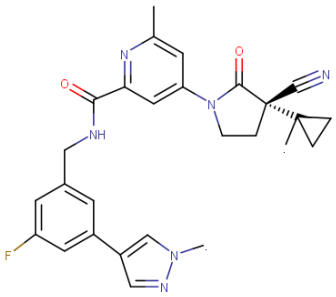
There are three orthosteric binding sites (L-proline, ATP, 3' end of tRNA) and an allosteric pocket which has been elucidated as potentially druggable (Jain et al., 2015; Hewitt et al., 2017; Adachi et al., 2017). However, it bears some similarity with its human orthologue (Zhou et al., 2013; Jain et al., 2014), which makes some inhibitors are not only active against *Plasmodium falciparum*, but also towards *Homo sapiens* (Jain et al., 2015). This finding leads to further exploration in order to find more selective inhibitor against prolyl-tRNA synthetase in *Plasmodium falciparum* (Mai

et al., 2014; Herman et al., 2015; Hewitt et al., 2017; Jain et al., 2017).

Recently, it was found that a series of compounds with pyridine-pyrrolidinone scaffold possess antimalarial activity. It is argued that these compounds act as ATP site binder in *P. falciparum* Prolyl-tRNA synthetase (Adachi et al., 2017). Furthermore, these compounds also showed high selectivity index towards *Plasmodium falciparum*, suggesting their suitability to be developed as potential novel antimalarial candidates (Table 1) (Okaniwa et al., 2021). Interestingly, it can be observed a distinctive result for compound (1-3). Upon observing the structures, it is instantly known that those compounds differ from each other in terms of stereochemistry. While compound 1 refers to the racemic form, compound 2 and 3 is the R and S enantiomer, respectively. Antiparasitic activity of those conformers showed significant difference, notably the S enantiomer exhibits inhibitory activity around 400 times better than its R enantiomer. This is one of the obvious examples of how stereoselectivity impacts ligand-receptor interaction (Triggle, 1997).

Molecular docking is a major computational technique which can be employed to evaluate ligand-protein interaction. Owing to the advancement of computer technologies, molecular docking is becoming more computationally affordable and can be performed using personal computer, even on laptop (Prieto-Martínez et al., 2018). This method is applicable in both retrospective and prospective manner, *i.e.* predicting a possible binding mode of a known ligand and evaluating a potential ligand prior to *in vitro* assay (Pinzi & Rastelli, 2019). However, care must be taken before taking conclusions regarding its results, since molecular docking also prone to some limitations. Some of the challenges are regarding the correct pose prediction and binding affinity. Up to this date, there are no single perfect molecular docking tools nor algorithms which yields outstanding reliability for any ligands or proteins (Wang et al., 2014; Bolcato et al., 2019). Therefore, it is necessary to validate the docking protocol before it can be used (Jain & Nicholls, 2008).

Table 1. Antimalarial activity of compounds with 1-(Pyridin-4-yl)Pyrrolidine-2-one scaffold (Okaniwa et al., 2021).

Compounds	Structure	IC_{50} (µM) (*P. falciparum* strain 3D7)
1		0.01
2 (R)		4.00
3 (S)		0.01

* Compound in red was used in this study

This study aimed to predict the possible binding mode of pyridine-pyrrolidinone enantiomeric compound in prolyl-tRNA synthetase of *P.falciparum* using molecular docking. Here, we focused on compound 2 (R) and 3 (S) which is an enantiomer which possess contrasting antimalarial potency (Okaniwa et al., 2021).

MATERIALS AND METHODS

Materials

3D structure of *P.falciparum* prolyl-tRNA synthetase was obtained from Protein Data Bank (https://www.rcsb.org/). PDB ID 4YDQ was selected among several available crystal structure due to the availability of AMPPNP ligand, which was used as native

ligand in this study (Jain et al., 2015). Compound 2 (R) (4 - [(3R) - 3 - cyano - 3 - (1 - methylcyclopropyl) - 2 - oxopyrrolidin - 1 - yl] - N - {[3 - fluoro - 5 - (1 - methyl - 1H - pyrazol - 4 - yl)phenyl]methyl} - 6 methylpyridine - 2 - carboxamide) and 3 (S) (4 - [(3S) - 3 - cyano - 3 - (1 - methylcyclopropyl) - 2 - oxopyrrolidin - 1 - yl] - N - {[3 - fluoro - 5 - (1 - methyl - 1H - pyrazol - 4 - yl)phenyl]methyl} - 6 - methylpyridine - 2 - carboxamide) was used as ligand. MarvinSketch 20.4 was used to build the ligand structure (available from http://www.chemaxon.com). MGLTools 1.5.7 (https://ccsb.scripps.edu/mgltools/) was used to prepare the ligand and protein. Molecular docking was performed using EasyDockVina 2.2 (ElTijani et al., 2019), a graphical interface for Vina (Trott & Olson, 2010). Ligand-protein interaction was checked using BIOVIA Discovery Studio Visualizer 2020 (BIOVIA, Dassault Système, 2021). Standard personal computer hardware was used in this study.

Methods

Compound 2 (R) and 3 (S) was drawn in 3D structure using DREIDING forcefield (Mayo et al., 1990) and then added by Gasteiger charge (Gasteiger & Marsili, 1980). Meanwhile, 3D structure of the protein was also prepared by adding hydrogen atom and Kollman charge (Singh & Kollman, 1984). Afterwards, grid box area was set on the position of AMPPNP ligand, based on assumption that these ligands occupy the ATP-binding region (Adachi et al., 2017; Okaniwa et al., 2021). Molecular docking was performed using EasyDockVina 2.2 (ElTijani et al., 2019). Firstly, re-docking was done using AMPPNP ligand to ensure that the protocol will yield correct binding pose. Afterwards, the ligands were docked on the ATP-binding region. Furthermore, ligand-protein complex with best score was evaluated of its interaction with surrounding amino acid residues. Those procedures were replicated 10-fold in order to get more detailed result.

RESULTS AND DISCUSSION

Stereochemistry aspect has always played important role for chiral organic compounds, especially in terms of how they interact with biological system. Numerous drugs can be put forward as an example, namely β-adrenergic inhibitors (Vashishta & Kumar, 2020), quinine-quinidine (White, 2007), and the infamous case of thalidomide (Vargesson, 2015). One of the principal

causes for this phenomenon is the specificity of ligand interaction with receptor, which obey the Fischer lock-key theory (Koshland Jr., 1995). It means that a binding site could be occupied perfectly by one enantiomer, but possibly not the other. Therefore, it is necessary to evaluate the impact of enantiomer towards its biological target in order to ensure the optimal pharmacologic action attained while avoiding any undesirable effect. In this study, we have tried to elucidate the possible molecular interaction between stereoisomers of 4 - [3 - cyano - 3 - (1 - methylcyclopropyl) - 2 - oxopyrrolidin - 1 - yl] - N - {[3 - fluoro - 5 - (1 - methyl - 1H - pyrazol - 4 - yl)phenyl]methyl} - 6 - methylpyridine - 2 - carboxamide and *P. falciparum* prolyl-tRNA synthetase *in silico*.

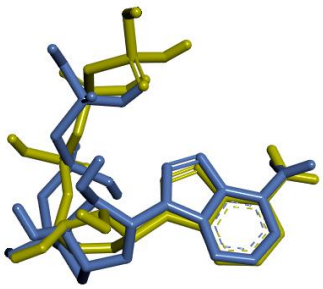


Figure 2. Re-docking result of native ligand ANPP. Yellow color indicates co-crystallized ligand, Blue color indicates re-docked pose

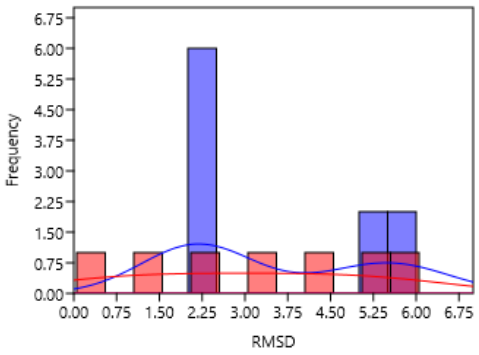


Figure 3. KDE plot of RMSD distribution over 10 re-docking simulation of AMPPNP

Molecular docking was performed against enzyme complexed with AMPPNP (PDB ID: 4YDQ) (Jain et al., 2015), a non-hydrolyzable analogue of ATP (Penningroth et al., 1980; Jain et al., 2017). According to previous study, the binding site which it occupies is predicted to be the site of action of test compounds (Okaniwa et al.,2021). First, re-docking step was done in a grid box size of 10 x 10 x 10 $Å^3$. The RMSD value obtained from this step was 2.04 Å, which is slightly above the commonly implemented threshold (2.0 Å) (Figure 2) (Kramer et al., 1999). Another way to evaluate pose prediction is by observing RMSD distribution profile over 10 re-docking replicates (Jain & Nicholls, 2008; Prieto-Martínez et al., 2018). Using Kernel Density Estimator plot (Hammer et al., 2001; Maldonado-Rojas et al., 2021), it can be seen that most of the resulting poses were found around 2.0-2.5 Å (Figure 3). This

result was caused by the large amount of rotatable bond in AMPPNP (n = 8), which makes it slightly difficult for VINA placement algorithm to reproduce correct binding pose.

Afterwards, molecular docking was conducted using the previously validated method. Upon evaluating the lowest docking score for each run, it can be observed that 6 out of 10 docking replicate yielded docking scores in accordance with the *in vitro* study (Okaniwa et al., 2021). The mean score obtained for each ligand also confirmed the same result (Compound 2 (R) = 1.74±2.71; Compound 3 (S) = -0.81±3.98) (Table 2). However, each docking replicate tends to yield fluctuate result among each other as can be seen in the high standard deviation value. We argued that the implementation of short exhaustiveness parameter (n = 8) in this study affects the inability of docking scores to reach convergence, since the nature of stochastic algorithm implemented in Vina (Torres et al., 2019; Nguyen et al., 2020).

Table 2. Docking score results of compound 2 and 3

Compound	Docking Score										Mean
	1st run	2nd run	3rd run	4th run	5th run	6th run	7th run	8th run	9th run	10th run	
2 (R)	-4.7	0.8	2.7	1.8	6.1	2.6	2.5	0.7	3.0	1.9	1.74±2.71
3 (S)	1.3	0.0	5.1	-2.6	1.2	-3.9	-4.6	-5.0	-4.9	5.3	-0.81±3.98

* Data in red conforms to *in vitro* antimalarial activity (Okaniwa et al., 2021)

Observation of ligand interaction with amino acid residues in those six replicates showed two significant hydrogen bondings formed by the S-enantiomer (GLN475 & THR478), which is observed less in its R counterpart. It is possible that these interactions play important role in the ligand binding process. These amino acid residues have been shown to participate in ligand-receptor interaction for AMPPNP (Figure 4) and a potent prolyl-tRNA synthetase inhibitor, halofuginone (Jain et al., 2015). Ligand-metal interaction with Mg is more observable in docking poses for compound 2 (R) than compound 3 (S). The type of interaction observed is pi-cation and metal-lone pair. This is different with ATP and its analogue, which needs to make coordination bond with pyrophosphate oxygen atoms (Figure 3). This step is important for the formation of amino acyl-adenylate complex (Kalervo Airas, 2007) (Zhou et al., 2013). Ligand-residue clash is also observed in most of docking pose, both in R and S

enantiomer. This unfavorable interaction causes higher energy, which weaken ligand binding to protein. Especially it is noticeable in ligand-metal than ligand-amino acid interaction. For example in 5th docking run (Table 3), compound 2 (R) yields several unfavorable interaction between Mg with pyrrolidinone ring and cyano group, while compound 3 (S) yields clash with amino acid residues. We argued that metal-ligand repulsive interaction is stronger than clash caused by hydrogen-bond interaction mismatch.

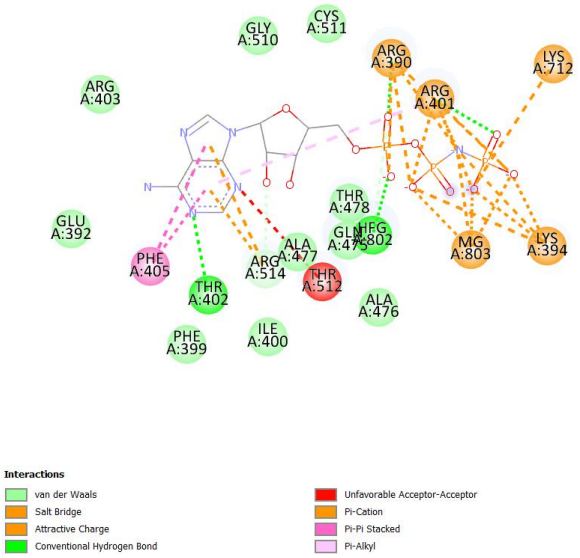
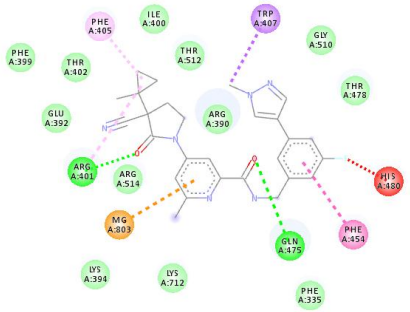
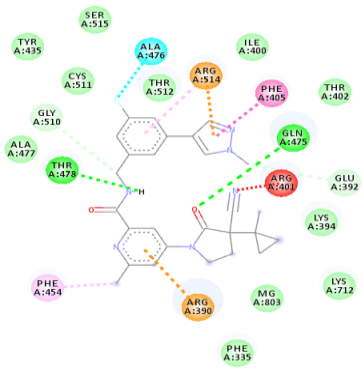
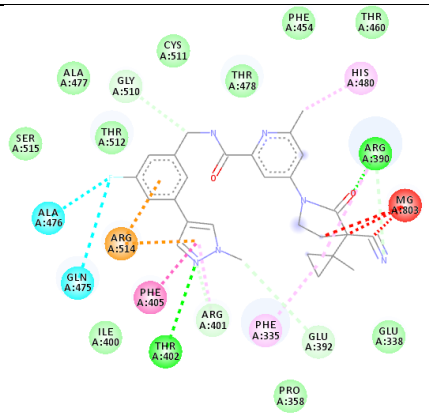
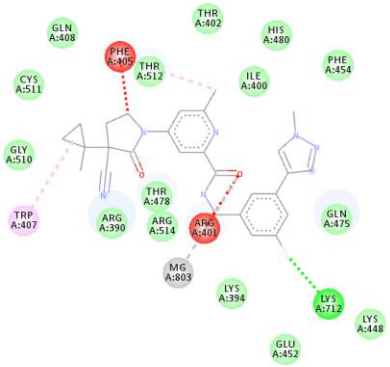
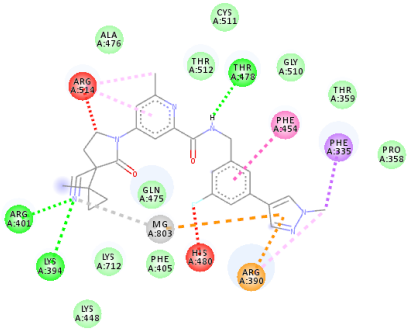
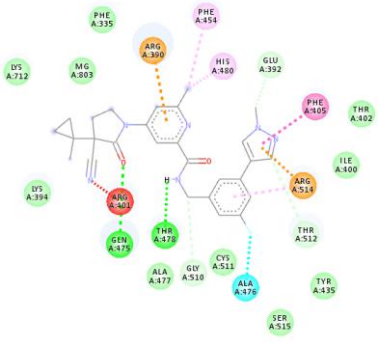
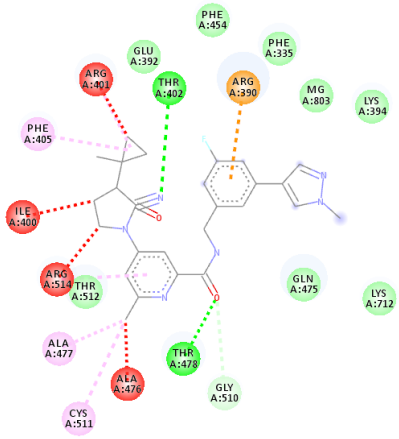
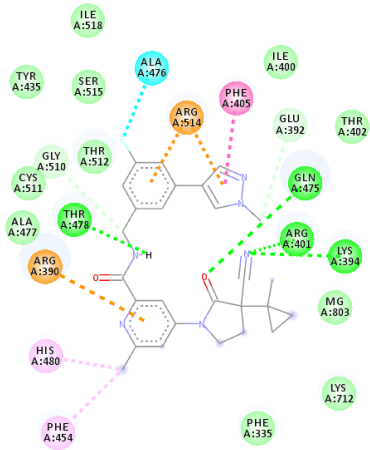
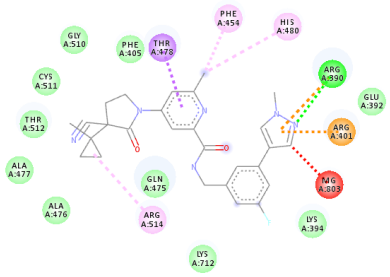
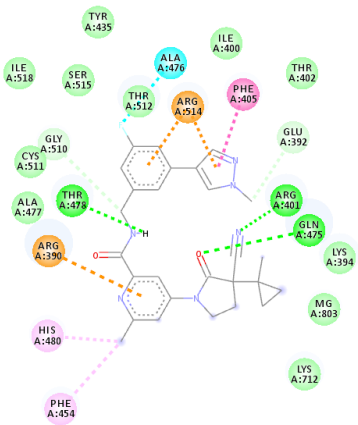


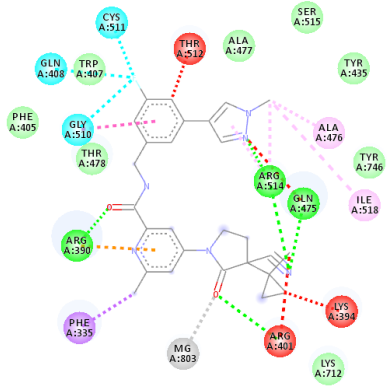
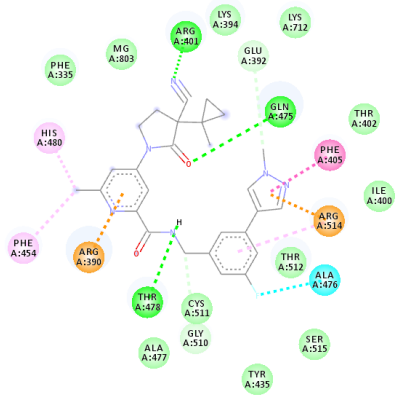
Figure 4. 2D diagram of AMPPNP interaction with amino acid residues and Mg^{2+} ion

Table 3. Ligand-Amino Acid interactions of compound 2 and 3

Docking Run	Compound	Essential Interaction
4	2 (R) 	Hydrogen Bond = ARG401,GLN475 Unfavorable Interaction = HIS480 Metal Interaction = Cation-π with pyrridine ring
	3 (S) 	Hydrogen Bond = GLN475,THR478 Unfavorable Interaction = ARG401 Metal Interaction = N/A

5	2 (R)		Hydrogen Bond = ARG390,THR402 Unfavorable Interaction = Mg Metal Interaction = Unfavorable Interaction with pyrrolidinone ring & cyano group
	3 (S)		Hydrogen Bond = LYS712 Unfavorable Interaction = ARG401,PHE405 Metal Interaction = with oxygen of amide group
6	2 (R)		Hydrogen Bond = LYS394,ARG401 Unfavorable Interaction = HIS480,ARG514 Metal Interaction = with nitrogen of cyano group
	3 (S)		Hydrogen Bond = GLN475,THR478 Unfavorable Interaction = ARG401 Metal Interaction = N/A

7	2 (R)		Hydrogen Bond = THR402,THR478 Unfavorable Interaction = ILE400,ARG401,ALA476,ARG514 Metal Interaction = N/A
	3 (S)		Hydrogen Bond = LYS394,ARG401,GLN475,THR478 Unfavorable Interaction = N/A Metal Interaction = N/A
8	2 (R)		Hydrogen Bond = ARG390 Unfavorable Interaction = Mg Metal Interaction = Unfavorable Interaction with pyrrazole ring
	3 (S)		Hydrogen Bond = ARG401,GLN475,THR478 Unfavorable Interaction = N/A Metal Interaction = N/A

9	2 (R)		Hydrogen Bond = ARG390,ARG401,GLN475, ARG514 Unfavorable Interaction = LYS394,ARG401,THR512 Metal Interaction = with oxygen of pyrrolidinone ring
	3 (S)		Hydrogen Bond = ARG401,GLN475,THR478 Unfavorable Interaction = N/A Metal Interaction = N/A

CONCLUSION

Overall, from the current molecular docking studies it can be seen that both stereoisomer of 4-[3-cyano-3-(1-methylcyclopropyl)-2-oxopyrrolidin-1-yl]-N-{[3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-6-methylpyridine-2-carboxamide possess identical results to *in vitro* studies, where S isomer interacts better than R isomer. However, further studies still needed to be carried out both *in silico* (flexible docking or molecular dynamics simulation) and *in vitro* enzymatic assay to ensure the correct binding mode of 1-(Pyridin-4-yl)167yrrolidine-2-one derivate can be elucidated.

REFERENCES

Adachi, R., Okada, K., Skene, R., Ogawa, K., Miwa, M., Tsuchinaga, K., Ohkubo, S., Henta, T. & Kawamoto, T. (2017). Discovery of a novel prolyl-tRNA synthetase inhibitor and elucidation of its binding mode to the ATP site in complex with L-proline. *Biochemical and Biophysical Research Communications*; *488(2)*; 393-99.

Biovia, Dassault Système, Discovery Studio Visualizer 2020, San Diego: Dassault

Système, 2021.

Bolcato, G., Cuzzolin, A., Bissaro, M., Moro, S. & Sturlese, M. (2019). Can We Still Trust Docking Results? An Extension of the Applicability of DockBench on PDBbind Database. *International Journal of Molecular Sciences*; *20(14)*; 3558.

ElTijani, A., Alsafi, M.Y. & Ahmed, A.F. (2019). EasyDockVina: Graphical Interface for Ligand Optimization and High Throughput Virtual Screening with Vina. *Zenodo*.

Gasteiger J., Marsili M. (1980). Iterative partial equalization of orbital electronegativity—a rapid access to atomic charges. Tetrahedron. 36(22): 3219-28.

Hammer, Ø., Harper, D.A.T. & Ryan, P.D. (2001). PAST: PALEONTOLOGICAL STATISTICS SOFTWARE PACKAGE FOR EDUCATION AND DATA ANALYSIS. *Palaeontologica Electronica*. 4(9).

Herman, J.D., Pepper, L.R., Cortese, J.F., Estiu, G., Galinsky, K., Zuzarte-Luis, V., Derbyshire, E.R., Ribacke, U., Lukens, A.K., Santos, S.A., Patel, V., Clish, C.B., Sullivan Jr., W.J., Zhou, H., Bopp, S.E., Schimmel, P., Lindquist, S., Clardy, J., Mota, M.M., Keller, T.L., Whitman, M., Wiest, O., Wirth, D.F. & Mazitschek, R. (2015). The cytoplasmic prolyl-tRNA synthetase of the malaria parasite is a dual-stage target of febrifugine and its analogs. *Science Translational Medicine*; *7(288)*; 288ra77.

Hewitt, S.N., Dranow, D.M., Horst, B.G., Abendroth, J.A., Forte, B., Hallyburton, I., Jansen, C., Baragaña, B., Choi, R., Rivas, K.L., Hulverson, M.A., Dumais, M., Edwards, T.E., Lorimer, D.D., Fairlamb, A.H., Gray, D.W., Read, K.D., Lehane, A.M., Kirk, K., Myler, P.J., Wernimont, A., Walpole, C., Stacy, R., Barrett, L.K., Gilbert, I.H. & Van Voorhis, W.C. (2017). Biochemical and Structural Characterization of Selective Allosteric Inhibitors of the Plasmodium falciparum Drug Target, Prolyl-tRNA Synthetase. *ACS Infectious Diseases*; *3(1)*; 34-44.

Jain, A.N. & Nicholls, A. (2008). Recommendations for evaluation of computational methods. *Journal of Computer-Aided Molecular Design*; *22(3-4)*; 133-9.

Jain, V., Kikuchi, H., Oshima, Y., Sharma, A. & Yogavel, M. (2014). Structural

and functional analysis of the anti-malarial drug target prolyl-tRNA synthetase. *Journal of Structural and Functional Genomics*; *15(4)*; 181-90.

Jain, V., Yogavel, M., Oshima, Y., Kikuchi, H., Touquet, B., Hakimi, M-A. & Sharma, A. (2015). Structure of Prolyl-tRNA Synthetase-Halofuginone Complex Provides Basis for Development of Drugs against Malaria and Toxoplasmosis. *Structure*; *23(5)*; 819-29.

Jain, V., Yogavel, M., Kikuchi, H., Oshima, Y., Hariguchi, N., Matsumoto, M., Goel, P., Touquet, B., Jumani, R.S., Tacchini-Cottier, F., Harlos, K., Huston, C.D., Hakimi, M-A. & Sharma, A. (2017). Targeting Prolyl-tRNA Synthetase to Accelerate Drug Discovery against Malaria, Leishmaniasis, Toxoplasmosis, Cryptosporidiosis, and Coccidiosis. *Structure*; *25(10)*; 1495-505.

Kalervo Airas R. (2007). Magnesium dependence of the measured equilibrium constants of aminoacyl-tRNA synthetases. *Biophysical Chemistry*; *131*; 29-35.

Keller, T.L., Zocco, D., Sundrud, M.S., Hendrick, M., Edenius, M., Yum, J., Kim, Y-J., Lee, H-K., Cortese, J.F., Wirth, D.F., Dignam, J.D., Rao, A., Yeo, C-Y., Mazitschek, R. & Whitman, M. (2002). Halofuginone and other febrifugine derivatives inhibit prolyl-tRNA synthetase. *Nature Chemical Biology*; *8*; 311-17.

Koshland Jr., D.E. (1995). The Key-Lock Theory and the Induced Fit Theory. *Angewandte Chemie International Edition in English*; *33(2324)*; 2375-8.

Kramer, B., Rarey, M. & Lengauer, T. (1999). Evaluation of the FLEXX Incremental Construction Algorithm for Protein–Ligand Docking. *Proteins*; *37*; 228-41.

Mai, H.D.T., Thanh, G.V., Tran, V.H., Vu, V.N., Vu, V.L., Truong, B.N., Phi, T.D., Chau, V.M. & Pham, V.C. (2014). Synthesis of febrifuginol analogues and evaluation of their biological activities. *Tetrahedron Letters*; *55(52)*; 7226-8.

Maldonado-Rojas, W. Salinas-Torres, J. & Olivero-Verbel, J. (2021). Identification of Potential Human Protein Targets for Soybean Isoflavones. *Journal of Brazilian Chemical Society*; *32(4)*;767-76.

Mayo, S.L., Olafson, B.D. & Goddard, W.A. (1990). DREIDING: a generic force field for molecular simulations.

Journal of Physical Chemistry; *94*; 8897-909.

Nguyen, N.T., Nguyen, T.H., Pham, T.N.H., Huy, N.T., Bay, M.V., Pham, M.Q., Nam, P.C., Vu, V.V. & Ngo, S.T. (2020). Autodock Vina Adopts More Accurate Binding Poses but Autodock4 Forms Better Binding Affinity. *Journal of Chemical Information and Modelling*; *60*; 204-11.

Okaniwa, M., Shibata, A., Ochida, A., Akao, Y., White, K.L., Shackleford, D.M., Duffy, S., Lucantoni, L., Dey, S., Striepen, J., Yeo, T., Mok, S., Aguiar, A.C.C., Sturm, A., Crespo, B., Sanz, L.M., Churchyard, A., Baum, J., Pereira, D.B., R.V.C., Guido, Dechering, K., J., Wittlin, S., Uhlemann, A-C., Fidock, D.A., Niles, J.C., Avery, V.M., Charman, S.A. & Laleu, B. (2021). Repositioning and Characterization of 1-(Pyridin-4-yl)170yrrolidine-2-one Derivatives as Plasmodium Cytoplasmic Prolyl-tRNA Synthetase Inhibitors. *ACS Infectious Disease*; *7(6)*; 1680-9.

Penningroth, SM., Olehnik, K. & Cheung, A. (1980). ATP Formation from Adenyl-5”yl Imidodiphosphate, a Nonhydrolyzable ATP Analog. *Journal of Biological Chemistry*; *255(20)*; 9545-8.

Pinzi, L. & Rastelli, G. (2019). Molecular Docking: Shifting Paradigms in Drug Discovery. *International Journal of Molecular Sciences*; *20*; 4331.

Prieto-Martínez, F.D., Arciniega, M. & Medina-Franco, J.L. (2018). Molecular docking: current advances and challenges. *TIP Revista Especializada en Ciencias Químico-Biólogicas*; *21(Supl.1)*; 65-87.

Singh, U.C. & Kollman, P.A. (1984). An approach to computing electrostatic charges for molecules. *Journal of Computational Chemistry*; *5(2)*; 129-45.

Torres, P.H.M., Sodero, A.C.R., Jofily, P. & Silva Jr, F.P. (2019). Key Topics in Molecular Docking for Drug Design. *International Journal of Molecular Sciences*; *20(18)*; 4574.

Triggle, D.J. (1997). Stereoselectivity of drug action. *Drug Discovery Today*; *2(4)*; 138-47.

Trott, O. & Olson, A.J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*;

31(2); 455-61.

Vargesson, N. (2015). Thalidomide-induced teratogenesis: History and mechanisms. *Birth Defects Research Part C: Embryo Today: Reviews*; *105(2)*; 140-56.

Vashishta, V.K. & Kumar, A. (2020). Stereochemical facets of clinical β-blockers: An overview. *Chirality*; *32(5)*; 722-35.

Wang, Z., Sun, H., Yao, X., Li, D., Xu, L., Li, Y., Tian, S. & Hou, T. (2014). Comprehensive evaluation of ten docking programs on a diverse set of protein–ligand complexes: the prediction accuracy of sampling power and scoring power. *Physical Chemistry Chemical Physics*; *18*; 12964-75.

White NJ. (2007). Cardiotoxicity of antimalarial drugs. *The Lancet infectious diseases*; *7(8)*; 549-58.

World Health Organization (2021). World Malaria Report. World Health Organization, Geneva.

Yogavel, M., R. Chaturvedi, P., Babbar, Malhotra, N., Jain, V. & Sharma, A. (2018). Drug targeting of one or more aminoacyl-tRNA synthetase in the malarial parasite Plasmodium falciparum. *Drug Discovery Today*; *23(6)*; 1233-40.

Zhou, H., Sun, L., Yang, X-L. & Schimmel, P. (2013). ATP-directed capture of bioactive herbal-based medicine on human tRNA synthetase. *Nature*; *494*; 121-4.

Pharmacoscript

Vol. 5
No. 2
Agustus
2022

P-ISSN: 2622-4941
E-ISSN: 2685-1121

LEMBAGA PENELITIAN DAN PENGABDIAN KEPADA MASYARAKAT (LPPM)
UNIVERSITAS PERJUANGAN TASIKMALAYA

Editorial Team

Editorial Board

TEMPLATE

Article template

Vol. 5 No. 2 (2022): Pharmacoscript

DOI: https://doi.org/10.36423/pharmacoscript.v5i2

Published: 2022-08-31

Articles

ADDITIONAL MENU

TEMPLATE

TOOLS

VISITORS

View My Stats

Indexed By:

Editorial Office

Lembaga Penelitian dan Pengabdian Masyarakat Universitas Perjuangan Tasikmalaya
Website: https://www.e-journal.unper.ac.id/index.php/PHARMACOSCRIPT
E-mail : pharmacoscript@unper.ac.id

23191 View MyStat

PHARMACOSCRIPT

UNIVERSITAS PERJUANGAN TASIKMALAYA
P-ISSN : 26224941 E-ISSN : 26851121

0
Impact Factor

31
Google Citations

Sinta 4
Current Acreditation

Google Scholar Garuda Website Editor URL

History Accreditation

2018 2019 2020 2021

Garuda Google Scholar

3D-PHARMACOPHORE MODELING AND MOLECULAR DOCKING TO STUDY THE POTENTIAL ANTI-CANCER AGENT FROM Ficus septica Burm. L
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 24-37
2022 DOI: 10.36423/pharmacoscript.v5i1.756 Accred : Unknown

IDENTIFIKASI PEMBENTUKAN KO-KRISTAL TRIKLABENDAZOL-ASAM OKSALAT DAN UJI KELARUTANNYA
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 1-13
2022 DOI: 10.36423/pharmacoscript.v5i1.758 Accred : Unknown

OPTIMASI HYDROXYPROPYL METHYL CELLULOSE K15M DAN NATRIUM CARBOXYMETHYL CELLULOSE SEDIAAN BUCCAL FILM
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 14-23
2022 DOI: 10.36423/pharmacoscript.v5i1.786 Accred : Unknown

POTENSI INTERAKSI OBAT PASIEN HIPERTENSI DAN DIABETESMELITUS TIPE2 DI INSTALASI RAWAT JALAN RSUD TOTO KABILA
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 56-61
2022 DOI: 10.36423/pharmacoscript.v5i1.792 Accred : Unknown

FORMULASI DAN UJI STABILITAS FISIK ESSENCE MASKER SHEET DARI EKSTRAK KULIT BUAH DELIMA (Punica granatum L.)
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 93-104
2022 DOI: 10.36423/pharmacoscript.v5i1.846 Accred : Unknown

AKTIVITAS ANTIOKSIDAN DAN INHIBISI ENZIM TIROSINASE EKSTRAK ETANOL BUAH GANDARIA (Bouea macrophylla Griff.) SECARA IN VITRO
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 62-70
2022 DOI: 10.36423/pharmacoscript.v5i1.856 Accred : Unknown

POTENSI INTERAKSI OBAT ANTIHIPERTENSI PADA PASIEN GERIATRI RAWAT INAP DI SALAH SATU RUMAH SAKIT KOTA BANDUNG
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 71-92
2022 DOI: 10.36423/pharmacoscript.v5i1.890 Accred : Unknown

MOLECULAR DOCKING DAN UJI TOKSISITAS REMDESIVIR, LOPINAVIR, RITONAVIR DAN FAVIPIRAVIR TERHADAP M-PROTEASE SARS-CoV-2
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 5 No. 1 (2022): Pharmacoscript 38-55
2022 DOI: 10.36423/pharmacoscript.v5i1.893 Accred : Unknown

PENGARUH METODE MASERASI DAN REFLUKS TERHADAP TOTAL FENOL DAN FLAVONOID DARI DUA VARIETAS UMBI UBI JALAR (Ipomoea batatas L.)
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 4 No. 1 (2021): Pharmacoscript 98-108
2021 DOI: 10.36423/pharmacoscript.v4i1.592 Accred : Sinta 4

EFEKTIVITAS GEL DAUN PANDAN WANGI SEBAGAI OBAT LUKA BAKAR PADA TIKUS PUTIH JANTAN
Lembaga Penelitian dan Pengabdian Masyarakat, Universitas Perjuangan Tasikmalaya Pharmacoscript Vol. 4 No. 2 (2021): Pharmacoscript 131-140
2021 DOI: 10.36423/pharmacoscript.v4i2.595 Accred : Sinta 4

View more ...