BAB 5
KESIMPULAN DAN SARAN

5.1 Kesimpulan Penelitian

Berdasarkan hasil penelitian ini dapat disimpulkan bahwa:

1. Simulasi dinamika molekul, yang dilakukan selama 200 ns, menghasilkan perhitungan rata-rata RMSD untuk semua atom protein 0,26 nm dan untuk atom penyusun tulang belakang 0,18 nm.
2. Hasil perhitungan RMSF menunjukkan bahwa pada bagian 6 dan 13 memiliki fleksibilitas tertinggi. Sub bagian 6 tidak memiliki residu yang berinteraksi dengan Rapamycin, tetapi sub bagian 13 memiliki residu A108, Y109, G110, R112, F114, I118. Residu tetap berinteraksi dengan ligan turunan sikloheksimida adalah Y109
3. Interaksi antara MIP dan ligan turunan sikloheksimida terjadi melalui interaksi ikatan hidrogen (Y55, D66, Q78, A108, dan Y109) dan interaksi hidrofobik (T50, Y55, F65, D66, F77, Q78, S80, Q81, V82, I83, T86, D106, Y109, G110, R112, F114, I 118, dan F126).
4. Selama membentuk kompleks, ligan turunan sikloheksimida mengalami perubahan konformasi.

5.2 Saran Penelitian

Berdasarkan hasil yang diperoleh maka dapat disarankan untuk mengetahui afinitas ligan turunan sikloheksimida 2(4-((2*R*)-2-((1*S*,3*S*,5*S*)-3-5-dimetil-2-oksosikloheksil)-2-hidroksietil-2,6 dioksopiperidin-1-il)-N-((1*R*,5*S*,7*R*)-1-hidroksitrisiklo [3.3.1.1^{3,7}] dekan-3-il) asetamida dengan perhitungan energi bebas.

DAFTAR PUSTAKA

Abraham, M.J., van der Spoel, D., Lindahl, E., and Hess, B. 2018, GROMACS User Manual version 2018.2. https://www.gromacs.org/

Allen, M.P., and Tildesley, D.J. 1989, Computer Simulation of Liquids. *Britania Raya*: Clarendon Press.

BIOVIA, 2020, Discovery Studio Visualizer. Dassault Systèmes. https://3ds.com/products-services/biovia/products.

Bussi, G., Donadio, D. and Parrinello, M. 2008, Canonical Sampling through Velocity-Rescaling, *The Journal of Chemical Physics*, **126(1)**: 014101-1– 014101-7.

Case, D.A., Ben-Shalom, I.Y., Brozell, S.R., Cerutti, D.S., Cheatham, T.E., Cruzeiro, V.W.D., Darden, T.A., Duke, R.E., Ghoreishi, D., Gilson, M.K., Gohlke, H., Goetz, A.W., Greene, D., Harris, R., Homeyer, N., Huang, Y., Izadi, S., Kovalenko, A., Kurtzman, T., Lee, T.S., LeGrand, S., Li, P., Lin, C., Liu, J., Luchko, T., Luo, R., Mermelstein, D.J., Merz, K.M., Miao, Y., Monard, G., Nguyen, C., Nguyen, H., Omelyan, I., Onufriev, A., Pan, F., Qi, R., Roe, D. R., Roitberg, A., Sagui, C., Schott-Verdugo, S., Shen, J., Simmerling, C.L., Smith, J., Salomon-Ferrer, R., Swails, J., Walker, R.C., Wang, J., Wei, H., Wolf, R.M., Wu, X., Xiao, L., York, D. M. and Kollman, P.A. 2018, AMBER 2018 Reference Manual (Covers Amber18 and AmberTools18), University of California, San Francisco.

Ceymann, A., Horstmann, M., Ehses, P., Schweimer, K., Paschke, A-K., Steinert, M., and Faber, C. 2008, Solution structure of the *Legionella pneumophila* Mip-rapamycin complex, *BMC structural biology*, **8**:1-12.

Childers, M. and Daggett, V. 2018, Validating Molecular Dynamics Simulations Against Experimental Observables in Light of Underlying Conformational Ensembles, *The Journal of Physical Chemistry B*, **122(26)**: 6673-6689.

Cunha, B.A., Burillo, A. and Bouza, E. 2016, *Legionnaire*' Disease, *Lancet*, **387(10016):** 376-385.

Darden, T., York, D. and Pedersen, L. 1993, Particle Mesh Ewald: An N - log(N) Method for Ewald Sums in Large Systems, *The Journal of Chemical Physics*, **98(12)**: 10089-10092.

Freitas, R.F, & Schapira, M. 2017, A systematic analysis of atomic protein-ligand interactions in the PDB, *MedChemComm*, **8(10)**: 1970–1981

Grubmüller, H. 1995, Predicting slow structural transitions in macromolecular systems: conformational flooding, *Physical Review E*, **52(3):** 2893-2906.

Hess, B., Bekker, H., Berendsen, H.J.C. and Fraaije, J.G.E.M. 1997, LINCS: A Linear Constraint Solver for Molecular Simulations, *Journal of Computational Chemistry*, **18**: 1463–1472.

Hollingsworth, S.A. and Dror, R.O. 2018, Molecular Dynamics Simulation for All, Neuron, **99(6):** 1129-1143.

Holtje, H. D., Sippl, W., Rognan, D. and Folkers, G. 2008, *Molecular Modeling: Basic Principle and Applications*, ed.3rd, WILEY-VCH Verlag GmbH & Co. KgaA, Germany, 16-18.

Humphrey, W., Dalke, A., and Schulten, K. 1996, VMD: visual molecular dynamics, *Journal of Molecular Graphics*, **14**:33-38.

Hünenberger, P. H., Mark, A. E. and Van Gunsteren, W. F. 1995, Fluctuation and cross-correlation analysis of protein motions observed in nanosecond molecular dynamics simulations, *Journal of Molecular Biology*, **252(4):**492-503.

Iliadi, V., Staykova, J., Iliadis, S., Konstantinidou, I., Sivykh, P., Romanidou, G., Vardikov. F. D., Cassimos. and D., Konstantinidis, T. G. 2022, *Legionella pneumophila*: The Journey from the Environment to the Blood. *Journal of Clinical Medicine*, **11(20),** 6126.

Jorgensen W.L., Chandrasekhar J., Madura J.D., Impey R.W., and Klein, M.L. 1983, Comparison of simple potential functions for simulating liquid water, *Journal of Chemical Physics*, **79**:926-935.

Juli, C., Sippel, M., Jager, J., Thiele, A., Weiwad, M., Schweimer, K., Rosch, P., Steinert, M., Sotriffer, C.A. and Holzgrabe, U. 2011, Pipecolic Acid Derivatives as Small-Molecule Inhibitors of The Legionella MIP Protein, *Journal of Medicinal Chemistry*, **54(1)**: 277–283.

Leach, A.R. 2001, *Molecular Modelling: Principles and Applications* 2nd edition, Pearson Education, London.

Lindorff-Larsen, K., Piana, S., Palmo, K., Maragakis, P., Klepeis, J. L., Dror, R. O., and Shaw, D. E. 2010, Improved side-chain torsion

potentials for the Amber ff99SB protein force field, *Proteins: Structure, Function and Bioinformatics.* **78**:1950-1958.

Maiorov, V. N. and Crippen, G. M. 1995, Size-independent comparison of protein three-dimensional structures, *Proteins: Structure, Function, and Bioinformatics*, **22(3):**273-283.

Miyamoto, S and Kollman P.A. 1992, SETTLE: An Analytical Version of the SHAKE and RATTLE Algorithm for Rigid Water Models. *Journal of Computational Chemistry*, **13(8):** 952-962

Mobley, D. L., Bayly, C. I., Cooper, M. D., Shirts, M. R. and Dill, K. A. 2009, Small molecule hydration free energies in explicit solvent: An extensive test of fixed-charge atomistic simulations. *Journal of Chemistry Theory Computation*, **5**:350–358.

Parrinello, M., dan Rahman, A. 1981, Polymorphic transitions in single crystals: A new molecular dynamics method, *Journal of Applied Physics*, **52**:7182-7190.

Patodia, S., Bagaria, A., and Chopra, D. 2014, Molecular dynamics simulation of proteins: A brief overview. *Journal of Physical Chemistry & Biophysics*, **4(6)**: 1

Phin, N., Parry-Ford, F., Harrison, T., Stagg, H.R., Zhang, N., Kumar, K., Lortholary, O., Zumla, A. and Abubakar, I. 2014, Epidemiology and clinical management of *Legionnaire*' *disease, The Lancet Infectious Disease*, **14(10):** 1011-1021.

Rasch, J., Theuerkorn, M., Unal, C., Heinsohn, N., Tran, S., Fischer, G., Weiwad, M. and Steinert, M. 2015, Novel Cycloheximide Derivatives Targeting the Moonlighting Protein Mip Exhibit Specific Antimicrobial Activity Against *Legionella pneumophila*, *Bioengineering and Biotechnology*, **3**: 1-8.

Sousa da Silva, A.W. and Vranken, W.F. 2012, ACPYPE-AnteChamber PYthon Parser interfacE. *BMC Research Notes*, **5**: 367.

Tong, M. and Jiang, Y. 2015, FK506-Binding Proteins and Their Diverse Functions, *Current Molecular Pharmacology*, **9(1)**: 48–65.

Wang, J., Wolf, R.M., Caldwell, J.W., Kollman, P.A. and Case, D.A. 2004, Development and Testing of a General Amber Force Field, *Journal of Computational Chemistry*, **25(9):** 1158-1174.