ABSTRAK

Penghambatan protein *3C-like protease* (3CLpro) oleh senyawa inhibitor dapat menghambat maturasi protein nonstruktural yang berperan pada proses replikasi, translasi, dan transkripsi virus SARS-CoV-2. Senyawa 2-(2-klorofenil)-7-(isokuinolin-4-il)-5,7-diazaspiro[3.4]oktana-6,8-diona, atau yang disebut SLL-0197800, memiliki potensi penghambatan yang sangat tinggi secara *in vitro* terhadap protein 3CLpro SARS-CoV-2 dengan nilai EC_{50} sebesar 77 hingga 110 nM. Selain itu, senyawa ini memiliki kelebihan, seperti: potensi sebagai antivirus berspektrum luas, hasil pengujian farmakokinetik yang baik secara *in vitro*, dan spesifitas yang baik secara *in vitro*. Tujuan penelitian ini untuk mengkaji interaksi senyawa 2-(2-klorofenil)-7-(isokuinolin-4-il)-5,7-diazaspiro [3.4]oktana-6,8-diona dengan protein 3CLpro SARS-CoV-2 secara *in silico* menggunakan metode penambatan molekuler dan simulasi dinamika molekuler pada kondisi fisiologis manusia selama rentang waktu 50 nanosekon. Penelitian ini merupakan penelitian deskriptif eksploratif menggunakan perangkat lunak YASARA-*Structure* untuk menganalisis parameter *root mean square deviation* (RMSD) penambatan ulang, energi ikatan, jarak ikatan, mode interaksi, RMSD atom *backbone*, dan RMSD *ligand movement.* Seluruh nilai RMSD yang diperoleh dari penambatan ulang ≤ 2 Å. Nilai ΔRMSD atom *backbone* dan *ligand movement* yang diperoleh pada 5 ns terakhir penelitian ini ≤ 2 Å. Oleh karena itu, stabilitas kompleks senyawa SLL-0197800 dengan protein 3CLpro telah tercapai dalam simulasi dinamika molekuler pada kondisi fisiologis manusia selama 50 nanosekon. Interaksi hidrogen dengan residu Gln189 dan interaksi dengan residu penting His41 diduga memiliki peran penting dalam pose interaksi senyawa SLL-0197800 dengan protein 3CLpro berdasarkan inspeksi visual pada akhir simulasi. Interaksi hidrofobik dengan Met49, Asn142, Met165, Val186, Arg188, Thr190 dan Gln192 juga hadir pada akhir simulasi.

Kata Kunci: SARS-CoV-2, *3C-like protease* (3CLpro), SLL-0197800, Penambatan Molekuler, Dinamika Molekuler

ABSTRACT

Inhibition of the 3C-like protease (3CLpro) protein by inhibitor compounds can block the maturation of nonstructural proteins involved in the replication, translation, and transcription processes of the SARS-CoV-2 virus. The compound 2-(2-chlorophenyl)-7-(isoquinolin-4-yl)-5,7-diazaspiro[3.4]octane-6,8-dione, referred to as SLL-0197800, has shown very high inhibition potential in vitro against the 3CLpro protein of SARS-CoV-2, with an EC50 value ranging from 77 to 110 nM. In addition, this compound has advantages such as broad-spectrum antiviral potential, favorable pharmacokinetic testing results in vitro, and good specificity in vitro. This study aimed to examine the interaction of the compound 2-(2-chlorophenyl)-7-(isoquinoline-4-yl)-5,7-diazaspiro[3.4]octane-6,8-dione with the 3CLpro protein of SARS-CoV-2 using molecular docking and molecular dynamics simulations under human physiological conditions for a duration of 50 nanoseconds. This research is descriptive-exploratory, utilizing the YASARA-Structure software to analyze parameters such as root mean square deviation (RMSD) of redocking, binding energy, binding distance, interaction modes, RMSD of the backbone atoms, and RMSD of ligand movement. All RMSD values obtained from redocking were ≤ 2 Å. The ΔRMSD values of the backbone atoms and ligand movement obtained during the last 5 ns of the study were ≤ 2 Å. Therefore, the stability of the SLL-0197800-protein 3CLpro complex was achieved in molecular dynamics simulations under human physiological conditions for 50 nanoseconds. Hydrogen bonding interactions with residue Gln189 and interactions with the important His41 residue are believed to play a crucial role in the interaction pose of the SLL-0197800 compound with the 3CLpro protein, based on visual inspections at the end of the simulation. Hydrophobic interactions with Met49, Asn142, Met165, Val186, Arg188, Thr190, and Gln192 were also present at the end of the simulation.

Keywords: SARS-CoV-2, 3C-like protease (3CLpro), SLL-0197800, Molecular Docking, Molecular Dynamics