Identification of novel inhibitor of MAPKs from Leishmania donovani: Comparative in-silico analysis

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Leishmaniasis is a group of vector borne zoonotic infection caused by homoflagellate obligate intra macrophage protozoan parasite from the genus Leishmania. Alternating between flagellated promastigotes in sand-fly and non-flagellated amastigotes in mammals, the parasite infects 10 million to 12 million people in 88 countries. Current therapeutics are limited to availability, efficacy, cost and drug resistance. Therefore, new strategic target enzymes and drugs are of major priority for health researchers. Among the several enzymes secreted by Leishmania, mitogen activated protein kinase 4 (MPK4) is a crucial stress related enzyme reported to be essential for the survival of both forms of Leishmania. Hence, a computational approach to model the protein and discover a novel inhibitor of MAPK4 was performed in this study. The MPK4 protein was modelled using MODELLER v9.17. Ligand based modeling approach was chosen using PDB ID: 4QNY as template and the best generated model quality analysis indicated 92.5% of residues in favored region of Ramachandran plot, 57.5% Errat quality, 79.34% Verify 3D%, -39,971 DOPE score and -6.46 Z-Score. The model was submitted to PMDB and accession ID: PM0080988 was provided. Virtual ligand based Screening was conducted using ATP as template in iStar server. Top 100 molecules were chosen based on USR and USRCAT scores and docked against PM0080988 using Autodock v4.2. GA based docking was performed using 0.37A^{o} grid spacing, number of energy evaluations was 2,500,000, maximum number of generation was set to 27,000 and 50 runs were computed. Zinc ID: 80020341 and 12526770 showed lowest binding energy of -7.77 kcal/mol and -7.48 kcal/mol showing potentiality as drug candidates. The molecules were also found to obey Lipinski’s rule of five. The docked poses of ATP and the two zinc molecules were further studied by molecular dynamic simulation using GROMACS v5.0 to understand the fine atomic details of molecular interaction. The simulation computation gave better understanding of the ligand molecules.