Abstract

The Tousled-like Kinases (TLKs) belongs to a family of serine/threonine Kinases, which have a pivotal role in the DNA damage response and repair, chromosomal stability, DNA replication, and transcription. Cancerous cells require a rapid, effective, robust DNA repair mechanism which TLKs would provide in greater extent. TLK1B upregulation in several cancers is because of the genotoxic stress. Cancer cells gain radioprotection through the overexpression of TLK1B. Inhibiting these specific kinases would starve the cancer cells of its requirement to survive DNA damage and repair. TLKs involvement in cancer gives a solid reason to use as drug targets, and there are not enough inhibitors for TLKs in the current market. Presently, the crystal structure of the TLK1B is not solved, and the active sites are not known, so the synthesis of inhibitors is a tough task. Because of this TLK1B Kinase domain is cloned, expressed, and purified to study the biochemical and biophysical characteristics of the protein. A set of in-house synthesized novel inhibitors and its activity are studied using ADP Glo assay among which the molecules J3-57, TA-93, TA-83, and TA-78 given better results. *In-silico* study shows the predicted structure and similarity of it with the solved crystal structure of TLK2-KD. The interacting residues in the active site also correspond to the crystal structure. The Induced fit docking results agree with the in-vitro results. The best-docked complex was J3-57 concluded based on docking score, and TA-83 has a higher number of interacting residues in the ATP binding pocket.

Keywords: TLK1B-KD, Purification, Phenothiazine scaffold, Michaelis-Menten kinetics, Induced fit docking.