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In-silico Studies on Development of Potential Drug Target of Novel NEDD8 Activating Enzyme Inhibitor with MLN4924 for Cancers †

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Abstract: Fragment-based drug design is one of the methods for designing new drug molecules. This work designs the inhibitors for Neural Precursor Cell Expressed Developmentally Down-regulated Protein 8-activating enzyme (NEDD8-AE), which is the most commonly studied UBLs and has more amino acid similarity to ubiquitin. NEDD8-AE leads to DNA replication, resulting in DNA damage and cell death. NEED8, a precursor processed by deadenylating enzymes through its hydrolase activity at conserved C-terminal Gly6 residue. The deadenylating enzymes expose a glycine-glycine motif, which provides the attachment site for target substrates. NEDD8-AE is an essential component of the NEDD8 conjugation pathway, controlling the activity of the cullin ring subtype of ubiquitin ligases, which has been done with the already reported small molecule such as MLN4924, that has a potential antineoplastic activity suppressing the outgrowth of liver cancer cell *in-vitro* and *in-vivo*. In the first phase of this work, the hotspot Lys103, Asp81, Arg90, Asp12, and Asp79 was identified in 1R4N, 1R4M, 1TT5 through the interaction study. The target protein has been subjected to structural analysis, sequence analysis, and simulation studies. In the next phase, the fragment-based drug design has been performed for generating ligands, which uses the structural properties of the target protein and screens the affinity for ligand binding in the active sites. This method will search the receptor binding site to elucidate the ligand interacting regions. The fragments are developed by using the De-novo receptor, and evolution was carried out by the De-novo evolution protocol in the Discovery studio. Finally, new leads of about 200 ligand molecules were generated, and those ligands were subjected to screening processes like ADME-Tox prediction analysis, after which one optimal lead has been selected. The screened ligand molecules have been analyzed for their pharmacophoric properties using Discovery studio and compared with the marketed anti-cancer drugs available in Drug Bank. Thus, 18 potential ligand molecules were selected, and their structures and IUPAC names were generated using Chem draw software.

Keywords: NEDD8; fragment-based drug design; ubiquitin; Schrodinger; discovery studio; chem draw.

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Conflicts of Interest

The authors declare no conflict of interest.