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De-Novo Design of Hits Against New Delhi Metallo-β-Lactamase Enzyme

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ABSTRACT

The New Delhi Metallo-β-lactamase 1 (NDM-1) is a class of Metallo-β lactamase enzyme. It is responsible for hydrolyzing almost all β-lactam antibiotics, leading to multi-drug resistance in bacteria. The lack of specific therapeutic options against this target creates an emerging need to develop new molecules against it. The multistep fragment- and knowledge-based de-novo design methods were considered for this study to design small molecules. The designed molecules were evaluated by molecular docking and dynamics simulation, followed by drug-likeness prediction. This study reports that a new drug-like chemical entity exhibits good binding behavior against the MDM-1 enzyme. Nonetheless, in-depth biological evaluation is required to determine the efficacy of the designed binders to develop new therapeutics against NDM-1.

KEYWORDS

De-Novo Design, Molecular Docking, Molecular Dynamics, NDM-1

1. INTRODUCTION

The suppression of pathogenic bacterial infection has plays an important role for human health in all over the world. Out of all the β-lactam antibiotics play an important role for the treatment of pathogenic bacterial infections by inhibiting bacterial cell wall synthesis by imitate transpeptidase and avert cross-linking of peptidoglycon stands. (Sauvage et al., 2008) But extensive uses of β-lactam and other antibiotics leads to rapid increase in antibiotic resistance, creating the health crisis in the world with reduce effectiveness of antibiotics. (Khan et al., 2017b) This is due to class B β-lactamase also known as metallo-β lactamase (MBL) which hydrolysis most of the β-lactam antibiotics by one or two zinc ions present at its active site and does not follow the covalent catalytic mechanism. This event makes it resistant to almost all β-lactum-based antibiotics. (Crowder et al., 2006) The MBL family has been mainly classified in three subclasses B1, B2, B3. (Wang et al., 1999) The subclass B1 metallo-β-lactamases use either one or two equivalent zinc unit. Subclass B2 metallo-β-lactamases

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are use any one equivalent zinc but at separate binding site other than subclass B1 enzymes. Subclass B3 metallo-β-lactamases are bind with both zinc ions but coordination happened at different position than of other subclasses. (Heinz & Adolph, 2004)

Since its discovery, MBL plays a major role for its resistance threat towards all antibiotics, which increase interest more towards its biochemical interaction rather than clinical concern. (Sabath & Abraham, 1966) Since then MBLs is responsible towards increase in antibiotic resistance threat with a spread of new superbugs New Delhi metallo-β-lactamase 1 (NDM-1). NDM-1 first reported in Klebsiella pneumonia and Escherichia coli infections from New Delhi, India in 2008. (Yong et al., 2009) After that it was found rapidly widespread in a lot of different bacteria around the world. (Heinz et al., 2019) NDM-1 is an N-terminal single peptide contain plasmid-encoded single chain protein forms a β-lactamase fold of α/β/β/α sandwich having two zinc ions (at the active site Zn1 and Zn2), where Zn1 binds to three histidine residues (H120, H122 and H189) and Zn2 is coordinated to histidine (H250), aspartate (D124) and cysteine (C208) residues. The irrational use of antibiotics will help the enzyme muted itself rapidly and developed new super bugs in the NDM family with more resistance towards antibiotics.

Amongst all MBLs only NDM-1 can able to hydrolyzed all marketed β-lactam antibiotics and showed as wide spectrum of β-lactamase activity. Limited therapeutics against NDM-1 available in the market creates a necessity to develop suitable agents in order to inhibit NDM-1 activity (Chiou et al., 2015; Crowder et al., 2006). Fragment based *de*novo design (Todorov et al., 2006) (Katiyar et al., 2018) approach is a powerful structure based drug design (Batool et al., 2019) tool. In the present study, inhibitor type ligand bound X-ray crystallographic information of NDM-1 structural coordinates was considered and subjected for designing hits on the basis of fragment based drug design approach. The designed hit was further analyzed by molecular docking and molecular dynamics simulations respectively followed by theoretical drug likeness property calculations.

2. MATERIAL AND METHODS

All computational work was conducted using the computer consisting intel i9 9900k processor integrated with RTX 2070 NVIDIA GPU, running over Linuxmint 19.3 operating system. Opensource PyMOL™ 1.8.4.0, Free Maestro virtualizer was used to virtualize the 3D structures. The Openbabel software (O'Boyle et al., 2011) was used to generate requires ligand file format. Charm-Gui ligand designer (Lee & Im, 2019) (www.charmm-gui.org/?doc=input/ligdesigner), LigDream (www.playmolecule.com/LigDream) (Ghosh et al., 2021) online server based tools were used to perform denovo design. Autodock GPU (Santos-Martins et al., 2021) and Autodock Vina (Trott & Olson, 2009)þ was used to perform molecular docking. Desmond 6.5 (Shaw, 2006) software was used to perform molecular dynamics. The Mprop (https://molsoft.com/mprop/) online server software was used to perform drug-likeness property prediction respectively.

2.1 Protein Preparation

The crystal structure of New Delhi metallo-β-lactamase was retrieved from ProteinDatabank (www.rcsbpdb.org, PDB ID:6LIP). After importing the 3D coordinated of New Delhi metallo-β-lactamase enzyme the protein preparation wizard of Schrödinger LLC software (Madhavi Sastry et al., 2013) available with Desmond 6.5 interface was used to optimize the structure followed by removal of inbound crystallographic water and ions. The optimized protein coordinates was saved in pdb file format. The inbound ligand coordinate was extracted and saves separately in pdb file format. The zinc ions were retained in the protein structure. The AurodockTools software (www.autodock.scripps.edu/resources/adt) was used to convert pdb files into pdbqt file format after adding kollman charge. The confined ligand binding site (X=13.5, Y=13.00, Z=3.25) was used as a search space.