ABSTRACT

SARS-CoV-2 has ravaged the health of millions of people globally and affected almost every sphere of life. Many efforts are being made to combat the COVID-19 pandemic's emerging and recurrent waves caused by its evolving and more infectious variants. As a result, novel and unexpected targets for SARS CoV-2 have been considered for drug discovery. 2-O-Methyltransferase (nsp10/nsp16) is a significant and appealing target in the SARS-CoV-2 life cycle because it protects viral RNA from the host degradative enzymes via a cap formation process. In this work, we propose prospective allosteric inhibitors that target the allosteric site SARS-CoV-2 Mtase. Four drug libraries containing ~119,483 compounds were screened against the allosteric site of SARS-CoV-2 Mtase identified in our research. The identified active compounds exhibited robust molecular interactions and alloscore-score rankings with the allosteric site of SARS-CoV-2 Mtase. Moreover, to further assess the dynamic stability of these compounds (CHEMBL2229121, ZINC000009464451, SPECS AK-91811684151, NCI-ID=715319) a 100 ns MD simulation along with its apo-form were performed that provided insights on the dynamic nature of these allosteric inhibitors at the allosteric site of the SARS-CoV-2 Mtase. Additionally, in investigations of MM/GBSA relative binding free energies revealed a good perspective for these allosteric inhibitor/enzyme complexes, indicating their robust antagonistic action on SARS-CoV-2 (nsp10/nsp16) methyltransferase. We conclude that these allosteric repressive agents should be further evaluated through investigative assessments in order to combat the recurring spread of COVID-19.

AIMS AND OBJECTIVES

The main objectives of this research are:

1. Use of computational approaches for the identification of Allosteric site of SARS-CoV-2 Methyltransferase enzyme and its potent selective inhibitors.
2. Utilization of Molecular dynamics Simulations techniques for evaluating the stability of these identified lead inhibitory compounds in this viral protein's allosteric site.
3. And calculation of its relative free binding energies (MM-GBSA) of these ligands in complex with the SARS-CoV-2 Mtase.

METHODOLOGY

Structure of the Main protease were retrieved from the RCSB-Protein Databank. Allosteric site of Methyltransferase of SARS-CoV-2 were identified via the Allosite-Pro online server. The AlloFinder [1] computational allosteric drug discovery platform was utilized for the identification of allosteric drugs against the SARS-CoV-2 Mtase. AlloFinder has built-in four drug libraries (ZINC diversity, CHEMBL diversity, SPECS diversity, and NCI diversity drug libraries) and for screening all these compounds it integrates the genetic algorithm from AutoDock-Vina [2] which will provide docked conformations for each of these screened compounds against our target protein. Finally, the Alloscore algorithm [3] of AlloFinder will then identify the optimal binding energy from each compound's conformational ensemble which will result in the potential allosteric drug-like compounds specifically targeting the SARS-CoV-2 NSP10/NSP16 Mtase allosteric site. For validation of the stable compound's binding and its relative binding free energy calculations, Molecular dynamics simulations and the MM/GBSA approach will be used respectively.

RESULTS AND DISCUSSION

2-MD-Simulations Stability Studies

CONCLUSION

We employed the AlloFinder allosteric drug discovery platform and its integrated multiple algorithms and identified robust allosteric inhibitors against SARS-CoV-2 Mtase. These allosteric inhibitors (CHEMBL2229121, ZINC000009464451, SPECS AK-91811684151, NCI-ID=715319) exhibited robust molecular contacts and associations with the allosteric site of SARS-CoV-2 Mtase. These compounds exhibited superior Allo-score rankings and showed multiple multiplets interactions i.e. Hydrophobic, Van der Waals, H-bonding, etc. with the allosteric site residues. Additionally, the Mol-Dynamics studies showed that these compounds have constant, sustained, and stable interactions with the allosteric site of SARS-CoV-2 Mtase, while the MM-GBSA energy calculations also showed strong binding of these compounds to this allosteric site. The results of the MM/GBSA analysis and molecular dynamics simulations suggest the potential in vitro inhibitory effect of these allosteric repressive drugs against SARS-CoV-2 Methyltransferase.

REFERENCES