COMPUTATIONAL STUDIES ON INHIBITION OF EPIGENETIC MODIFICATIONS OF CANCER CODES

Thesis Submitted to

The Open University of Sri Lanka

for the award of degree of

Doctor of Philosophy in Chemistry

August 2022

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Ph.D / NAT. Sc /2018 / 02

ABSTRACT

Genetic make - up dictates the future in which genes and fate are closely related. When the cells divide, the genes can pick up mistakes called mutations. DNA is considered the ultimate hereditary molecule, while epigenetic factors are considered the ultimate controllers. Epigenetics is the study of how people's behaviors and environment can cause changes that affect genes' regularity. Epigenetic modifications such as DNA methylation and histone deacetylation are well-studied examples of semi-reversible covalent chemical modifications that influence the gene on-off event without changing the DNA sequence. The histone deacetylase (HDAC) enzyme deacetylates the histone protein by removing the acetyl group from the lysine residues, whereas the DNA methyltransferase (DNMT) enzyme methylates the fifth cytosine carbon located near guanine in the DNA strand. The over-expressions of these enzymes have been shown to silence the expression of tumor suppressor genes, allowing the abnormal cells to progress through the cell cycle unimpeded while dividing uncontrollably, leading to cancer. Therefore, the research on the inhibition of HDAC and DNMT enzymes has shown an increase in the research interest among the researchers. In this study, the inhibitory efficacies of fifteen HDAC inhibitors such as SAHA (vorinostat), LBH589 (panobinostat), PCI24781 (abexinostat), PXD101 (belinostat), LAQ824 (dacinostat), SB939 (pracinostat), RAS2410 (resminostat), TSA (trichostatin A), ITF2357 (givinostat), CBHA (m-Carboxycinnamic acid bis-hydroxamide), GCK1026 (scriptatid), TFMK (trifluoromethylketone-9,9,9-trifluoro-8-oxo-N-phenylnonanamide), AKA (alpha-ketoamide-N-cyclohexyl-N-methyl-2-oxononanediamide), MS275 (entinostat), CI994 (tacedinaline) and three DNMT inhibitors such as azacitidine, decitabine, and zebularine were studied by in-silico approach. In addition to the DNMT inhibitors, two hundred natural product compounds from the Sri Lankan Flora database, a web-based information system, were selected in DNMT studies. SAHA and azacitidine, the respective approved HDAC and DNMT inhibitors (approved by the US Food and Drug

Administration), were considered reference inhibitors. The crystal structures of the receptors (HDLP (PDB ID: 1ZZ1.pdb) and DNMT (PDB ID: 3WSR.pdb)) were obtained from the Protein Data Bank, and the HDAC inhibitor structures were optimized using the G09W. The docking between HDLP and HDAC inhibitors was carried out by AutoDock-Vina software. For DNMT studies, initially, MM-GBSA-assisted structure-based virtual screening against DNMT enzyme was performed for the natural products imported from the Sri Lankan Flora database. The high-throughput virtual screening, standard precision docking, and extra precision docking are the tools used in the virtual screening process. The hits obtained were checked for their potency by considering sinefungin, which is the bound inhibitor in the DNMT crystal structure; as a result, seven molecules were identified as potent DNMT inhibitors. These docked HDLP and DNMT complexes were then employed for 100 ns molecular dynamics simulation. The inhibitory efficacies of the above-studied compounds were estimated by computing the enzyme's backbone stability, positional stability of the individual amino acids, interaction and binding energies between enzyme and inhibitors, number of intermolecular hydrogen bonds, principal component analysis, cavity analysis, etc. This investigation improves the understanding of the atomic-level description of the inhibitor binding site and how the inhibitors change the environment of the enzyme's active site; it also helps to examine the impact of the amino acids' conformational changes on gene accessibility. The results of this in-silico study revealed that LBH589 and PCI24781 are potential lead compounds for inhibiting HDLP. Therefore, it is possible to use these compounds as HDAC inhibitors in clinical practices. Also, the inhibitory potential of the compounds derived from natural products NP#0003 (Petchicine) and NP#0011 (Ouregidione) are almost similar to that of reference inhibitor azacitidine against the DNMT enzyme. From this study, the above compounds can be recommended for clinical trials for cancer treatments. Further, this theoretically derived model would minimize the cost, time, energy, and resources being invested in the drug discovery process.