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Original Article

Molecular modelling studies of Histone Deacetylase inhibitors as anticancer agents

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ABSTRACT

Background: Cancer causes death to over 7.6 million people every year. The disease can be classified as cells' uncontrolled division. This uncontrolled division of cells or uncontrolled growth is caused by DNA damage. This eventually results in genes mutations, which encodes cell division controlling proteins. Histone deacetylase (HDAC) is one among the principal targets for the anticancer drugs.

Methods: Molecular docking studies of nearly 60 Trichostatin A, SuberoylAnilide Hydroxamic Acid and Sulfonamide anilides which show good inhibitory activity against HDAC were carried out using GLIDE program of Schrödinger Suite 2009. Comparison of docking scores of the compounds with their respective QSAR IC_{50} have also been made.

Results: From Trichostatin A and SuberoylAnilide Hydroxamic Acid analogues binding results, it was found that HDAC conformational changes are based on the ligand binding. C/N/O atoms present in the aliphatic chains of the analogues interacted well with the Zn^{2+} metal ion and active site amino acid residues to disrupt the enzymatic activity of target protein HDAC.

Conclusion: Analogue inhibition taken into study with the target protein HDAC assures to be an advantageous therapeutic approach in cancer treatment.

1. Introduction

Cancer is the fundamental cause of death in developed countries. Cancer affects people at all ages and is classified as uncontrolled division of cells.[1] Cancer is spread either by direct growth invading the adjacent tissue or by metastasis. Severity in symptoms depends on the site, character of malignancy and metastasis.[2] This unregulated growth may be caused by DNA damage, which may result in gene mutation that is responsible for cell division controlling proteins.[3,4] Cell

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proliferation or division exists in relatively all tissues. The equilibrium between cell proliferation and programmed cell death is habitually monitored by uprightness of organs and tissues. This unsuppressed cell proliferation guides to either a benign or malignant tumour.[5] Cancer can be treated by many therapies and the choice of therapy eternally depends on the location, tumour grade and disease stage depends on patients' natural stage.[6] Histones acetylation state modulation plays a substantial role in administration of gene expression.[7,8] Histone Acetyl Transferases (HATs) and Histone Deacetylases (HDACs) are two enzymes that modulate histone acetylation and deacetylation. They are also popular as protein switch.[9] HDACs disruption has been related to a broad range of human cancers. HDAC inhibitors are effective inducers of growth arrest, cell differentiation and cell apoptosis. Hence they also arise as powerful anticancer agents.[10] Literature review also shows that HDAC inhibitors are apparent in the neurodegenerative and genetic disorder treatment.[11] Some of the substantial HDAC inhibitors are Trichostatin A (TSA) and SuberoylAnilide Hydroxamic Acid (SAHA) analogues.[12] They have the capability to induce diversified effects present within the cell like cell differentiation, initiation of cell cycle arrest and elimination of tumour growth.[13]

TSA analogues claim customary features as

(i) A large hydrophobic region binding to the hydrophobic portion of the enzyme adjoining the active site.
(ii) An aliphatic chain consisting of 5 or 6 carbons connected to hydrophobic region.

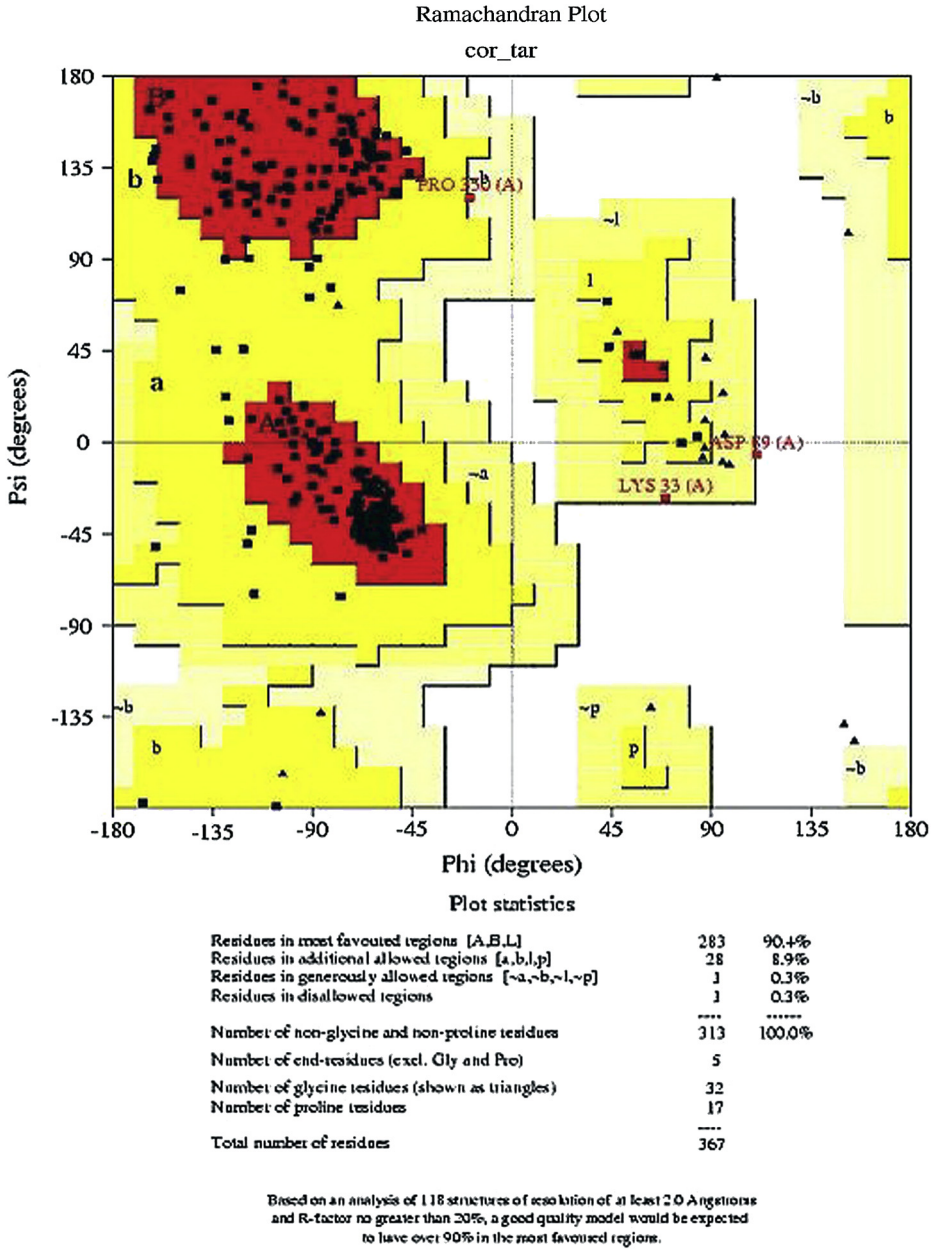

Fig. 1 – Ramachandran plot for the modelled target HDAC using PROCHEK.