Thesis Title: Rational Design, Synthesis and Biological Activity of Some Glutamine-Based Anticancer Hydroxamates as Promising Matrix Metalloproteinase-2 Inhibitors.

Abstract

Matrix metalloproteinase-2 (MMP-2) plays crucial roles in cancer progression, metastasis and invasion. Thus, it is an attractive target for anticancer drug development. This study explores the design, synthesis, and evaluation of novel glutamine-based hydroxamate-based potential MMP-2 inhibitors as effective anticancer agents. This study also combines QSAR modeling (regression and classification-based analysis), molecular docking, and molecular dynamics (MD) simulation analyses to provide insights into the structural features and molecular interactions essential for MMP-2 inhibition. Molecular docking-based analyses revealed the significance of specific amino acid residues as well as highlighted the importance of steric and hydrophobic properties critical for effective MMP-2 inhibition. MD simulations further validated these findings, showing stable binding interactions between these compounds and the MMP-2 enzyme. Again, four novel molecules with highly potent MMP-2 inhibitory efficacy (IC_{50} in nM) demonstrated promising cytotoxicity against several cancer cell lines especially against chronic myeloid leukemia (CML) cell line K562 selective over normal cell line HEK-293. Also, these compounds induced apoptosis, arrested cell cycle phases, and reduced MMP-2 expression, suggesting potential antileukemic activity. Therefore, these novel MMP-2 inhibitors can be effective for targeted anticancer therapy, especially for CML to open up new avenues in the future.