Name(s)

Maanasi Kademani

Project Number

S0512

Project Title

Anacardic Acid Analogs for the Inhibition of Matrix Metalloproteinase-2

Abstract

Objectives

According to the American Cancer Society, cancer is the cause of death for over two million individuals worldwide every year. As of 2016, over 15.5 million people are living with cancer in the United States. Cancer not only takes a large toll on the afflicted individual and their families, but it has significant economic impacts as well, costing over eighty-billion dollars a year in the US in direct medical fees. Cancer metastasis, the spread of cancer cells throughout the body, is the key driver of mortality in cancer patients. The dysregulation of the Matrix Metalloproteinase-2 enzyme (MMP-2) has been previously identified to play a critical role in the development of cancer cell metastases, particularly in breast cancer. Recent studies have shown inhibition of the MMP-2 enzyme by anacardic acid, a natural compound found in cashew nut shell extract. Therefore, it is hypothesized that structurally similar compounds (analogs) of anacardic acid that provide increased inhibition of Matrix Metalloproteinase-2 (MMP2) can be identified and developed into potential drug-like lead compounds for future drug discovery studies for the possible prevention of cancer metastasis.

Methods

In this study, computational docking studies and enzymatic inhibition studies were utilized to determine analogs of anacardic acid and the strength and stability of their inhibitory qualities. To generate the docking model for MMP-2, the 3D structure was downloaded from the Protein Data Bank using the code 1QIB.pdb. Anacardic acid s binding energy to MMP-2 (-9.0 kcal/mol) was used as a standard of comparison for the binding energies of the analogs of anacardic acid tested when docked computationally into MMP-2. Fourteen analogs, labeled (A-N), were derived from anacardic acid to be tested. All analogs were drawn using Marvin Sketch, docked into MMP-2 using AutoDock Tools 1.5.6, and their binding energies were compared to that of anacardic acid. Of the fourteen derivatives tested, Analog H was found to have the lowest binding energy at -9.9 kcal/mol.

To demonstrate the success of the analogs in binding to MMP-2, an enzymatic inhibition study was performed. Our computer-generated Analog H was synthesized by Dr. Dave Martin s Synthetic Chemistry lab at UCR and its binding stability was analyzed.

Results

Inhibition of the enzyme was observed at higher concentrations of the compound with calculated IC50 values of 15.1 ?M and 75.1 ?M for anacardic acid and Analog H, respectively, indicating that Analog H was a weaker inhibitor of MMP-2.

Summary Statement

In this study, computational docking studies and enzymatic inhibition studies were utilized to identify and confirm potential inhibitors of Matrix Metalloproteinase-2 for the possible prevention of cancer metastasis.

Help Received

Project guidance was provided by Dr. Jeff Perry and Taylor Dennis at the Perry Lab at the University of California, Riverside.