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Design and Synthesis of Small-Molecule Inhibitors of Cathepsin L as Potential Anti-Metastatic Agents

The spreading of cancer from a primary tumor to separate and distinct locations in the body is known as metastasis. This metastatic process can be a major challenge in the successful treatment of cancer. Cathepsin L is a cysteine protease that plays a major role in the degradation of extracellular matrix thus providing a mechanism by which cancer cells can invade and migrate into surrounding tissue and vasculature. A long-standing collaboration between the Pinney Research Group and the Trawick Research Group at Baylor University has resulted in the discovery of a privileged library of small-molecule inhibitors of cathepsin L. The most promising compounds demonstrate potent (nanomolar range) inhibition of cathepsin L and are highly selective for cathepsin L in comparison to other structurally similar enzymes (cathepsin B and cathepsin K). A benzophenone-based thiosemicarbazone analogue known as KGP94 is one of the best cathepsin L inhibitors that we have discovered to date. KGP94 is undergoing further biochemical and biological evaluation in three separate research collaborations and sufficient quantities of KGP94 are necessary to complete these studies. One major goal of this proposal is a re-synthesis of KGP94. Through our structure activity relationship studies and chemical characterization analysis, it has become apparent that a symmetrical thiosemicarbazone would be highly desirable as opposed to the unsymmetrical nature of KGP94. Therefore, a second major goal of this study is to design and synthesize such a molecule. Finally, it is intriguing to consider the impact that replacing the thiosemicarbazone molecular functionality with a different electrophilic moiety, such as the selenosemicarbazone group, might have in terms of the ability of such a compound to inhibit cathepsin L. Thus, molecules containing such functionality will be synthesized. Collectively, these studies will enhance our understanding of the molecular characteristics necessary to achieve highly selective small-molecule inhibitors of cathepsin L.