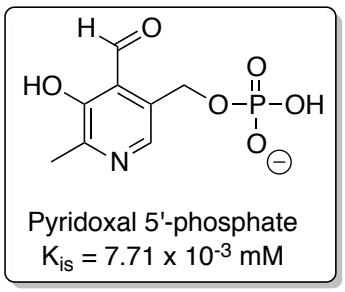
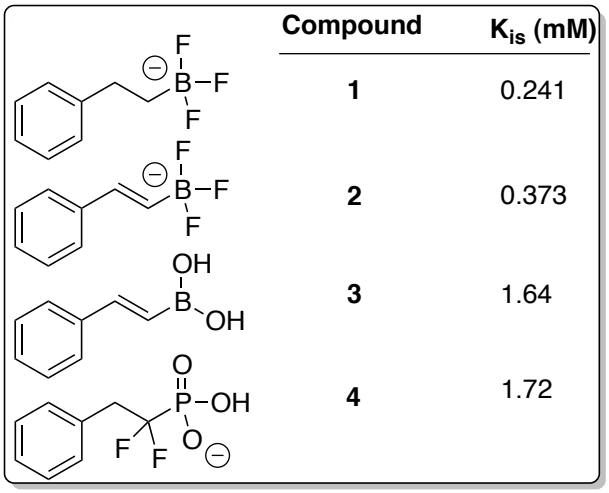
TITLE:
Making, modeling and biological testing of potential anticancer agents

RESEARCH DESCRIPTION:
The intent of this project will be to make, model and test compounds that could act as potential inhibitors of low molecular weight protein tyrosine phosphatase (LMW PTP). Inhibitors of LMW PTP may possess potential anti-cancer properties by inhibiting dephosphorylation (removal a phosphate group from a protein) of certain receptors.

Phosphatases are enzymes that are involved in the cell signal transduction process. When information is not properly conveyed in the cell, problems in the generation of signals necessary for different cellular events such as growth, migration, metabolism, gene transcription, cell-cell communication, ion channel activity, immune response and apoptosis/survival decisions occur. When these events are not controlled, cancer and other disease states such as diabetes occur. Recent studies have assessed the role of LMW PTPs in cell transformation (conversion to cancerous cells). In theses studies, it was shown that the expression of LWM PTP mRNA and protein is significantly increased in human breast, colon, bladder and kidney tumor samples. Moreover, its enhanced expression was generally prognostic of a more aggressive cancer. It has been suggested that LMW PTP may contribute to cancer invasivity (attacking adjacent tissues) by stabilizing cell-cell contacts. *Inhibitors of LMW PTP hence may possess potential anti-cancer properties.*

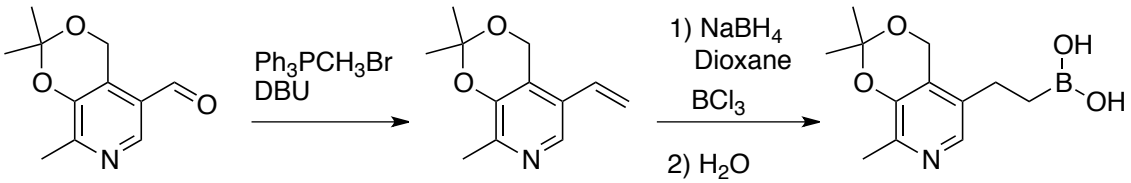
We are tying to make, model and test compounds that resemble pyridoxal 5'-phosphate (PLP). PLP is a known inhibitor of LMW PTP, but it is also used in many enzymatic processes so we need to develop something that is specific for just LMW PTP. One area of focus is altering the polar phosphate head into something different. For instance a boronic acid, phosphonate or carboxylic acid:



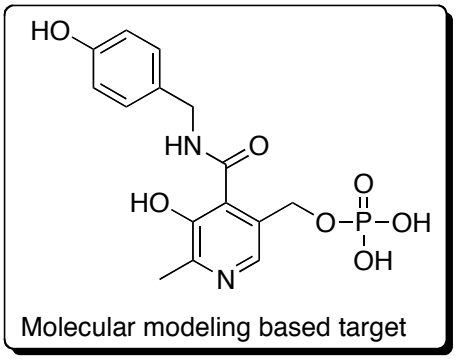


Compound	K_{is} (mM)
1	0.241
2	0.373
3	1.64
4	1.72

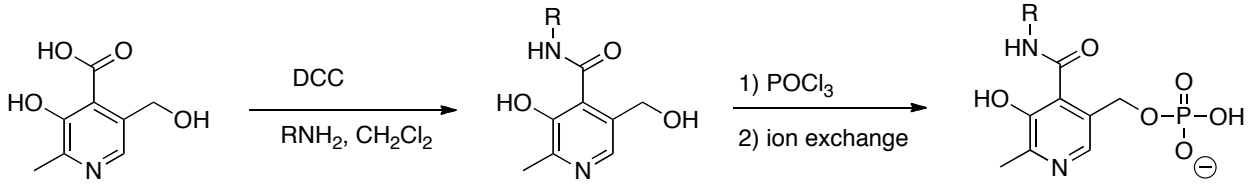
Proposed Synthesis of Boronic Acid Derivatives of PLP



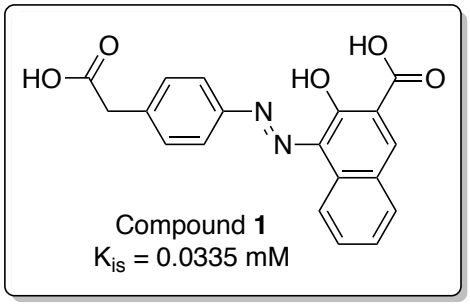
Another area is to build specificity by branching and filling an ancillary pocket in the enzyme:



Proposed Synthesis of Amide Derivatives of PLP



And finally, we are looking at inhibitors that do not resemble PLP at all. Currently, we are focusing on making derivatives of Compound **1**. Compound **1** was found by *in silico* and *in vitro* screening the National Cancer Institute's Diversity Set II.



Proposed Synthesis of Derivatives of Compound 1