Title: Development and Optimization of Lead Scaffolds for the Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD)

Abstract: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. NAFLD is defined as hepatic steatosis with more than 5% of liver weight attributed to fat. This metabolic disease develops in the absence of other causes, such as excessive alcohol use, and is associated with obesity and diabetes. Therapies to combat NAFLD, such as exercise, proper nutrition, and weight loss have been insufficient for most patients. Currently, there are no small molecule therapeutics specifically approved for NAFLD, representing a largely unmet medical need. Few validated targets for NAFLD exist. Stimulating hepatocyte lipolysis to reduce excess fat in the liver is one proposed strategy to treat NAFLD. We hypothesize that identification of small molecules that stimulate hepatocyte lipolysis will offer key chemical probes for drug development and serve as a therapeutic for NAFLD. Preliminary screening has identified four scaffolds with substantial both in vitro and in vivo efficacy for NAFLD. Medicinal chemistry will be used to expand these lead scaffolds through structure-activity relationships (SAR) with the goal of optimizing in vivo efficacy and drug-likeness. Each compound will be evaluated by its ability to reduce hepatocellular lipid content and activate AMPK, a metabolic switch that reprograms lipid metabolism and induces lipolysis. Through this work, we hope to develop chemical probes for target identification and discover leads for further preclinical development for NAFLD.