CALIFORNIA SCIENCE & ENGINEERING FAIR
2018 PROJECT SUMMARY

Name(s)

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Project Number

38481

Project Title

Synthesizing Inhibitors of Isocitrate Dehydrogenase 1 to Inhibit Glutamine-Dependent Reductive Carboxylation in Tumors

Abstract

Objectives/Goals

Metabolic reprogramming is a hallmark of cancer, and tumor cells with defective mitochondria use alternative, efficient metabolic pathways to produce ATP energy when the electron transport chain is impaired. The purpose of this project is to synthesize a variety of small molecule inhibitors for the enzyme isocitrate dehydrogenase 1 (IDH1), in order to inhibit the alternative metabolic pathway glutamine-dependent reductive carboxylation in brain tumors.

Methods/Materials

Two classes of inhibitors were synthesized, one with a rhodanine ring core structure and the other with a thiazolidinedione ring core structure. The rhodanine inhibitor synthetic method was modified from the paper #Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases by 2-Thiohydantoin Compounds" by Fangrui Wu, et al. I changed some of the intermediate reactants to use more cost effective chemicals. This meant my workup (filtration and washing) and analysis of my products varied greatly from the literature, due to products with different chemical properties. The thiazolidindione inhibitor synthetic method was taken directly from #Thiazolidinoneâ€“Peptide Hybrids as Dengue Virus Protease Inhibitors with Antiviral Activity in Cell Culture" by Christoph Nitsche, et al. I simply changed one of the side chains to make the resulting compound slightly larger.

Results

Thin-layer chromatography (TLC) was performed using the starting materials and products of the various reactions to analyze whether a chemical reaction occurred or not. The TLC analysis was performed in a 1:1 ethyl acetate and hexane solvent because after testing multiple solvents, this was the one that produced the clearest results. My TLCs indicate that my two inhibitors were synthesized, and all reactions have occurred.

Conclusions/Discussion

Inhibitors with rhodanine and thiazolidinedione ring cores have been synthesized; further research includes performing R group substitutions and analyzing the activity and efficacy of the small molecule inhibitors using an Instant Isocitrate Dehydrogenase I ELISA Kit. This research delves into the possibility of treating cancer from the metabolic aspect, specifically, this research can indicate which structures and which core rings (rhodanine or thiazolidinedione) are effective inhibitors of IDH1.

Summary Statement

Two classes of small molecule inhibitors of the enzyme isocitrate dehydrogenase 1 were chemically synthesized; one class with a rhodanine ring core structure and the other with a thiazolidinedione ring core structure.

Help Received

My teacher, Mr. Darren Dressen, taught me useful lab techniques, like rotary evaporation and vacuum filtration. Dr. Steven Richards, BioElectron Corporation, helped me understand some chemical properties that must be considered when synthesizing inhibitors to treat human patients.