INHIBITION OF CYTOCHROME P450 BY ACETYLENE COMPOUNDS

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Description:

Cytochrome P450 (CYP) enzymes are an important super family of enzymes. These enzymes are involved in the production and destruction of steroid hormones, in the cytokine response, in the metabolism of foreign compounds and drugs, and in carcinogenesis. Our laboratory is studying possible inhibitors of several CYP enzymes.

The compounds we are studying have been synthesized by Dr. William Alworth's laboratory at Tulane and Dr. Maryam Foroozesh's laboratory at Xavier. These compounds are acetylene derivatives of known substrates of several important CYP enzymes. We are seeking to find compounds that inhibit by mechanism-based inhibition. In this type of inhibition, the enzyme metabolizes the inhibitor to its active form. The activated inhibitor then covalently binds to the enzyme and destroys it. Important implications of this research include developing anticarcinogens and developing cancer drugs.

Objectives:

The objects of this project include testing a group of recently synthesized adamantyl and naphthyl acetylenes to determine if they are inhibitors of CYP 1A1, 1A2 and 2B1 *in vitro*. We will be using commercial available human enzymes produced in culture in a fluorescence assay with a selective resorufin substrate. We will screen the compounds to determine which compounds are inhibitors. Using kinetic analysis methods we will determine the type of inhibition and the K_I and k_i kinetic inhibition parameters. This work will identify promising compounds to test further in cell culture or animal models and will give us insight to design better inhibitors.

Prerequisites:

Students who have completed organic chemistry and introductory biology will be able to carry out this work. Knowledge of cell biology and biochemistry are useful but not necessary.