

Dudley, Gregory

Department of Chemistry and Biology
Florida State University

2005 Program
New Investigator (3-year project)

Project Title: Organic Synthesis and Methodology for Roseophilin, a Pharmacologically Active Natural Product

Project Summary: New treatments for cancer and other tobacco-related diseases come from myriad sources, with the drug discovery process of medicinal chemistry being one of the most successful and reliable. The strength of medicinal chemistry research derives from its systematic refinement of a lead compound into a powerful chemotherapy through painstaking optimization and testing.

Medicinal chemistry (biomedical research aimed at drug discovery and development) is an experimental science based on synthetic organic chemistry. New compounds may be chemically derived from the natural product, or they may be fully synthetic analogs prepared in the lab from bulk chemical ingredients. Either way, organic synthesis is the enabling technology for this type of biomedical research. Conversely, medicinal chemistry research is limited by limitations in organic synthesis.

This research project focuses on advancing the state of the art in organic synthesis. The desire to develop new drugs based on complex natural products like roseophilin, which is potently cytotoxic to a series of human cancer cell lines, drives this research. Several approaches for preparing the bridged multi-ring structure of roseophilin are under investigation, including novel ring-expansions and methods for incorporating key sub-structures within larger, pre-existing ring bridges. Devising new synthetic approaches to a molecule as challenging as roseophilin stimulates creativity and innovation. Several new methods for organic synthesis are also proposed herein, with important applications for biomedical research within and beyond the current project.

Cancer chemotherapy is by its very nature a daunting task: the goal is to kill human cancer cells selectively in the presence of a much larger system of non-cancerous human cells. At best, very subtle differences in highly complex biological systems are targeted for achieving this selectivity. Cytotoxic molecules of ever-increasing complexity are needed for precision targeting within a narrow chemotherapeutic window. Roseophilin is a particularly interesting target compound because of its intricate chemical structure and because its biochemical mechanism of action has not been linked to any known process. This hints at the possibility, pending further research, of a new approach to attacking cancer cells. Such research endeavors require efficient access to roseophilin and synthetic analogs, which would be made possible by successful realization of the ideas presented and explored within this research project.