2013 REU Poster: Small Molecule Evolution: A Biomimetic Approach to Small Molecule Lead Generation and Optimization

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Small Molecule Evolution: A biomimetic approach to small molecule lead generation and optimization

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Abstract

The goal of my project was to determine the standard calibration curves of compounds in the small molecule evolution library. Solutions of several small molecules were prepared at various concentrations and analyzed using the nanoAcquity UPLC instrument. Diode array traces were collected for each solution, in which UV-active compounds showed up as a single peak in the chromatogram. These peaks were extracted at a single wavelength (usually λ_{max}) to produce new traces, and peak area was determined. Plots of peak area against concentration were obtained for each small molecule, and the results showed a linear relationship between concentration and peak area at a single wavelength. Equations of the line were found and this data will be used to determine unknown concentrations of small molecules in solution after chemical reactions are performed. This information will be vital for the biological assessment of new compounds formed by chemical modification.

Introduction

The small molecule evolution (SME) project is an innovative approach to the discovery of new drug leads. Inspired by nature, SME begins with already complex molecules, both natural and unnatural, and utilizes chemical reactions to modify their core structures in an unbiased yet systematic manner. This method of synthesis allows for rapid generation of new natural product-like compounds, and gives us access to new chemical spaces not covered in traditional drug screening libraries. An integral component to the success of SME is the ability to efficiently process and analyze micro-scale reaction mixtures and identify new compounds that would be submitted for biological assessment. New compounds identified by instrumental analysis are tested for bioactivity in a variety of biological assays, and active compounds are characterized and further optimized, while inactive compounds are re-subjected to reaction conditions.

Data and Results

Standard calibration curves

- Substrate solutions of known concentrations prepared in DMSO (or water)
- Concentrations = 0.10, 0.20, 0.25, 0.50, 1.00 mM
- Solutions run using analytical method developed for analysis of reaction mixtures
- Spectra extracted at a specific wavelength (ideally \( \lambda_{max} \))
- Peak area determined
- Peak area plotted against concentration
- Linear relationship obtained between peak area and concentration

Future Work

- Data was not obtained for some small molecules; this will be revisited
- Calibration curve data will be used to determine sample concentrations for biological assays
- Standard calibration curves will be obtained for all new compounds introduced into the small molecule library

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