Nontraditional Amine-Acid Coupling Reactions to Explore Structure-Function Relationships

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A molecule's properties are intimately linked to its medicinal function, yet there is a gap in our understanding of how properties are modulated by chemical synthesis. The most popular reaction in medicinal chemistry, the amide coupling, is an ideal arena to explore the relationship of reactions to properties, and ultimately function. Amines and carboxylic acids are some of the most abundant materials available for organic synthesis. They are traditionally coupled together using the amide coupling. This is due to the robustness of the reaction as well as challenges associated with generating reactive species from these stable functionalities. Theoretically there are many unique ways in which these two plentiful materials can be combined with each of them generating products diverse properties. Indeed, there has been a heavy focus recently on developing methodologies to use these pervasive molecules as partners for cross coupling reactions. Our lab is interested in further exploring and developing unique reactivities of amines and acids to complement the amide coupling and using them to explore the complex interplay between physicochemical properties and biological function. Using Katritzky Salt's to activate the amine, we have discovered a selective, de-aminative esterification that generates a molecule geometrically identical to the amide but contains one fewer hydrogen bond donor. Using robotics and high throughput experimentation, we have further developed a reaction that produces ethers from amines and acids. We have performed these reactions as well as several others on fluorescent dye scaffolds to generate matched molecular series. These series span a wide range of partition coefficient, charge, and polar surface area while maintaining bulk similarity (and molecular weight) to the "traditional" molecule one would synthesize from amine and acid. We are using these synthesized dyes to interrogate the effect of subtle changes to properties on cell level distribution.