

David C. Baker: Research Program

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Area: Organic (Synthetic, Bioorganic, Medicinal Chemistry)

Our research program is centered around the bioorganic chemistry of carbohydrates and heterocyclic compounds as these relate to medicinal chemistry, principally in the fields of chemotherapy of cancer and viral diseases. We are primarily organic chemists who are engaged in the design, synthesis, and evaluation of compounds of medicinal interest. We work in the development of synthetic procedures for complex organic compounds. Considerable time is spent with structural elucidation by NMR, MS, and X-ray methods, as well as with chromatographic separation methods, including HPLC. Our design strategies include use of molecular modeling and calculational chemistry.

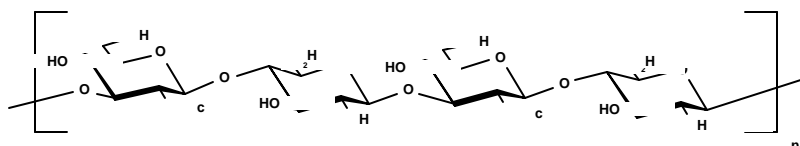
Please refer to our WEB page for updated information:
<http://sugar.chem.utk.edu/~bakergp/baker.htm>

Four currently active projects are the following:

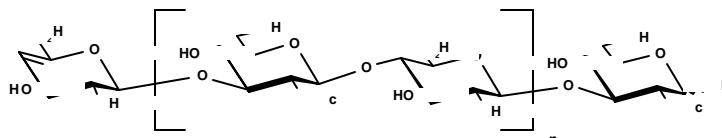
1. *Antimetastatic Oligosaccharides from Hyaluronic Acid*

This project involves the isolation of oligosaccharides derived from hyaluronic acid (HA), a large polymer that occurs in living systems, including humans. HA is involved as an attractant for roaming cancer cells in the process of translocation and the development new tumor foci (a process termed metastasis). We have developed a line of short oligosaccharides (hyaluronate lyase digest oligomers, below) that, when given to mice in a murine model of metastatic melanoma, halt the metastasis. Our work is on the isolation and structural elucidation of these compounds, plus developing a set of mimetic compounds that are resistant to enzymatic breakdown in the body. Herein lies our major challenge: synthesis of these mimetics.

Hyaluronic Acid

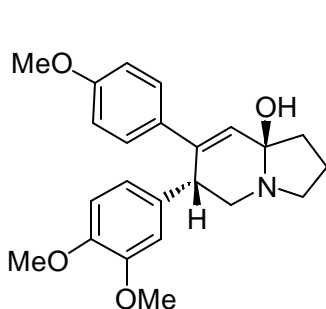


Hyaluronate Lyase Digest Oligomers

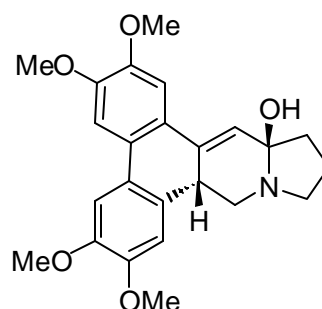


2. Studies of Tyloindicines: Extremely Potent Antitumor Agents with an Unknown Mechanism of Action.

We have as lead compounds two of the most potent anticancer compounds ever screened at the National Cancer Institute: tyloindicines F and G (below). These compounds, first discovered from a plant in India, are now being synthesized in our lab. We have already encountered activity among synthetic analogues. We plan combinatorial strategies to develop a viable anticancer drug. As the mechanism of action of these compounds is totally unknown, we are collaborating with cancer biologists to work on these aspects.



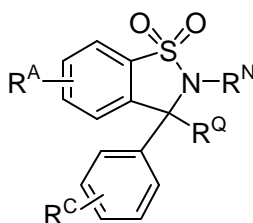
Tyloindicine F (NSC-650393)



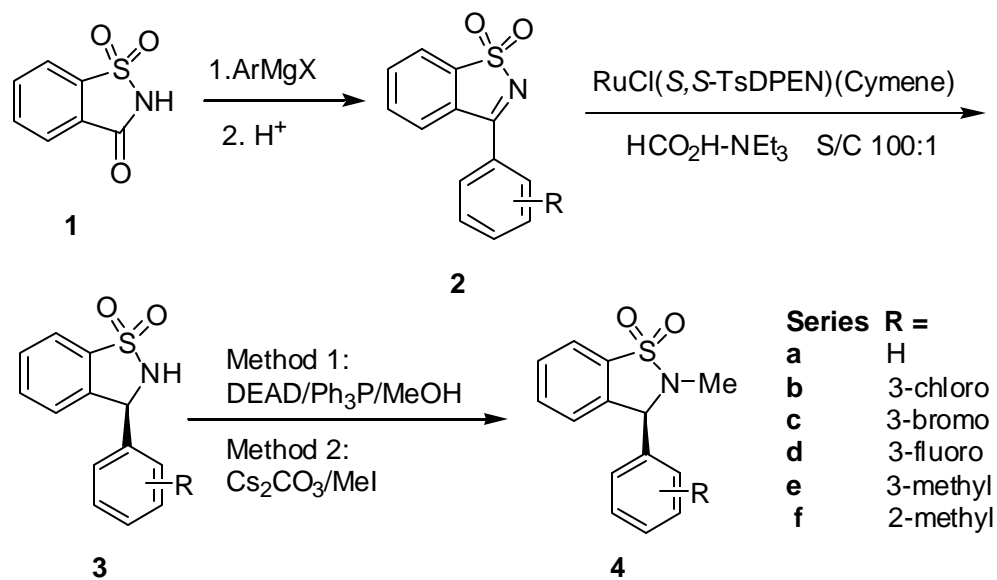
Tyloindicine G (NSC-650394)

3. Sultams: A New Type of Anti-HIV Reverse Transcriptase Inhibitor.

This project has uncovered a new type of reverse transcriptase (RT) inhibitor for the HIV virus. We have to date compounds that are as active as many nonnucleoside RT inhibitors in clinical use. Work is in progress to improve activity towards resistant strains of HIV by making use of molecular modeling. We have a cloned RT enzyme on which we are beginning NMR studies and X-ray crystallography with one of the inhibitors to determine precisely the mode of binding of our compound to the RT.

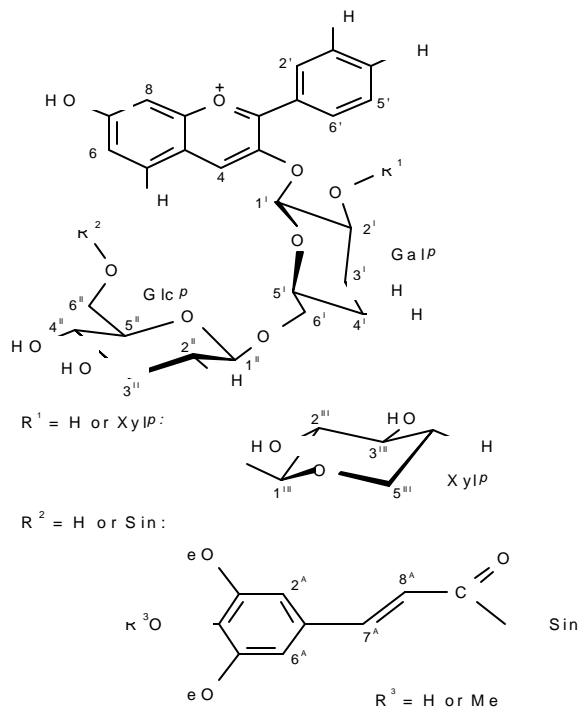


A route to several of these sultams is shown below. Note that in step 2 we have developed a catalyst that selectively reduces the C=N bond to the desired (+)-S-isomer.



4. Rational Design of Anthocyanins with Increased Color Stability.

This project, carried out in collaboration with Dr. Donald Dougall in the Botany Department, involves the biosemisynthetic synthesis of modified anthocyanins that have potential as food colorants. The compounds are produced by addition of functionalized carboxylic acids to a tissue culture of the wild carrot (*Daucus carota*), which esterifies a terminal OH on a glucose residue. Our input is structural (NMR, MS) to determine why certain carboxylic acids impart color stability to these molecules. We are applying principles of medicinal chemistry to rationally develop a colorant that will give a stabilized compound as a candidate food colorant.



1. $R^1 = \text{xylP}$, $R^2 = \text{H}$
2. $R^1 = \text{xylP}$, $R^2 = \text{Sin}$, $R^3 = \text{H}$
3. $R^1 = \text{xylP}$, $R^2 = \text{Sin}$, $R^3 = \text{Me}$
4. $R^1 = \text{H}$, $R^2 = \text{Sin}$, $R^3 = \text{H}$
5. $R^1 = \text{H}$, $R^2 = \text{Sin}$, $R^3 = \text{Me}$

