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AREA: ORGANIC (Synthetic, Bioorganic, Medicinal Chemistry)

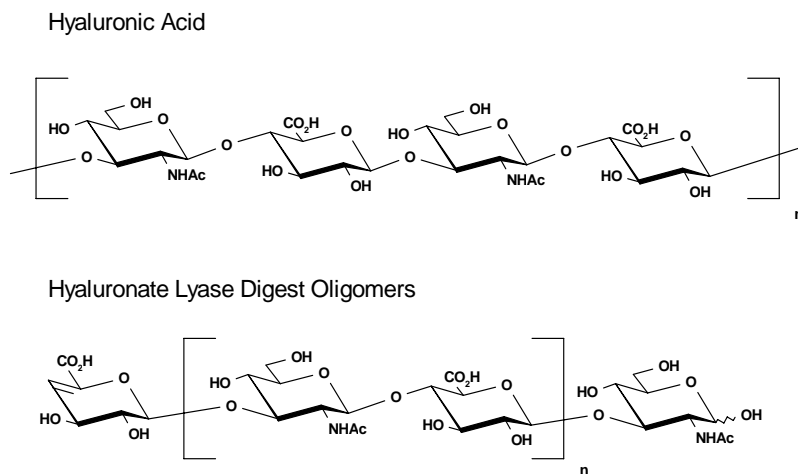
Our research program is centered around the bioorganic chemistry of carbohydrates and heterocyclic compounds as these relate to medicinal chemistry, principally in the fields of chemotherapy of cancer and viral diseases. We are primarily organic chemists who are engaged in the design, synthesis, and evaluation of compounds of medicinal interest. We work in the development of synthetic procedures for complex organic compounds. More recently, we have embarked on a project in nanoscience, making use of carbohydrate structures to impart cell-like properties to nanostructures. 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 computational chemistry.

Please refer to our WEB page for updated information:  
<http://www.chem.utk.edu/faculty/baker.html>

Four currently active projects are the following:

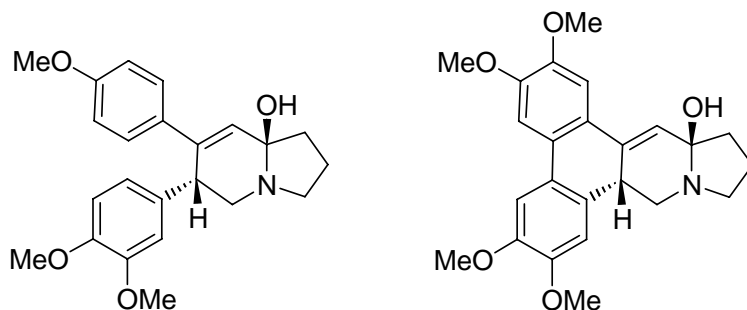
1. *Antimetastatic Oligosaccharides from Hyaluronic Acid*

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.



## 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. A very active compound, DCB-3503, is a product of our research.

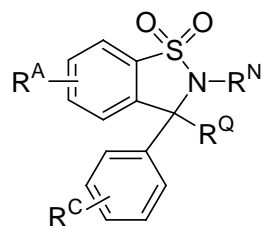


Tyloindicine F (NSC-650393)

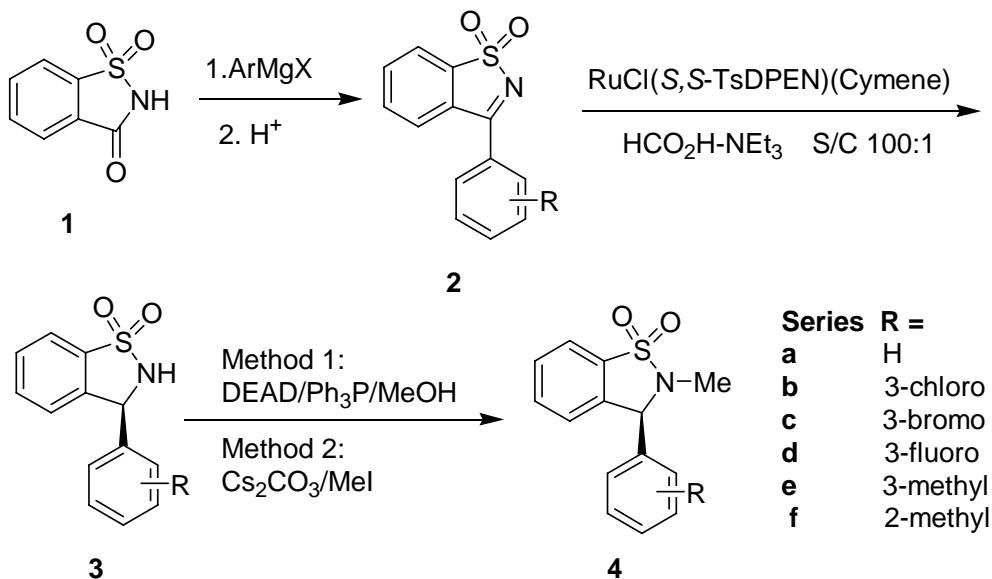
Tyloindicine G (NSC-650394)

## 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.



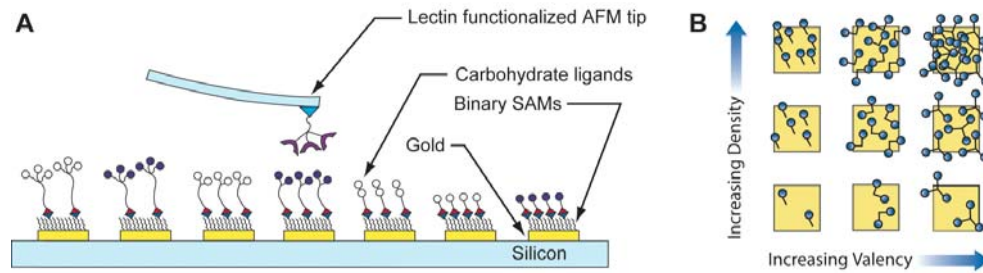
#### 4. Sculpting the Surface of Nanoparticles: Constructing a Cell-like Surface

Cell surfaces are coated with a complex layer of carbohydrates linked to proteins and lipids (glycoconjugates) that forms the surface landscape of the cell. This landscape is rich in chemical and structural features that vary among cell types, providing the basis for cell recognition, adhesion, and communication. Cells are recognized via their displayed carbohydrate features (epitopes) by proteins termed lectins, which may be free in solution or anchored to the surfaces of other cells. One important theme is that recognition of cell surfaces by lectins involves *hierarchical patterns* of carbohydrate features (epitopes). That is, recognition depends not just on the molecular structure of a carbohydrate, but on distinct, nanometer-scale spatial arrangements of carbohydrate epitopes embedded within the complex surface landscape.

In the present proposal, we seek to explore the structure of conserved carbohydrate patterns on bacteria and their recognition by collectins, which are  $Ca^{2+}$ -dependent, pathogen-detecting lectins of the mammalian innate immune system. Our effort consists of two parts: (1) emulation of hierarchically structured patterns of carbohydrates from the bacterial surface in synthetic model surfaces and (2) molecular-level examination of the interaction between collectins with both the synthetic surfaces and natural bacterial surfaces using single-molecule atomic force microscopy (AFM) techniques. Together, these efforts will provide both fundamental insight into the distinctive chemical features of pathogens and will lay the foundation for future development of new analytical technologies for detection, identification, and characterization of microbial or viral pathogens. By making use of precisely tailored chemical surfaces, prepared through chemical synthesis coupled with nanofabrication techniques, it will be possible to mimic the hierarchical carbohydrate patterns of the bacterial cell surface with a level of fidelity heretofore unrealized.

The core of our effort will be re-creating bacterial surface carbohydrate patterns, allowing us to decipher a critical part of the code embedded in the bacterial surface landscape

and provide fresh insight into how bacteria and other pathogens interact with the human innate immune system, how they are distinguished, and how some escape detection. As a starting point, we will prepare surfaces functionalized with different patterns of a monosaccharide, mannose, and assess their recognition by a model collectin protein, the mannose-binding lectin (MBL). As we progress, we will make the surface more diverse and cell-like through the use of mannose-capped oligosaccharides (MCOs) while exploring other collectins, such as the lung surfactant protein D (SP-D), and appropriate carbohydrate epitopes for them. *The unique concept of our work is the combination of surface density with molecular valency to create hierarchical patterns* (Fig. 1).



**Figure 1.** *A:* AFM interrogation of glycocluster arrays for collectin affinity. The lectin is chemically bonded to the AFM tip. *B:* Top view of a model array illustrating the interplay of glycocluster valency (1, 2 or 3 sugars) and surface density to create patterns of sugars.