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Chemists develop new method for making anti-cancer flavanones

Research helps set stage for development of new cancer therapeutics

By Megan Fellman

Flavonoids. You've heard of them — the good-for-your-health compounds found in plants that we enjoy in red wine, dark chocolate, green tea and citrus fruits. Mother Nature is an ace at making them, producing different ones by the thousands, but no chemist has figured out a good way to synthesize a special class of these chemicals in the laboratory. Until now.

Karl Scheidt, assistant professor of chemistry in the Weinberg College of Arts and Sciences, and his research team have synthesized 10 different flavanones, a type of flavonoid, using a new general method they developed that takes advantage of one simple catalyst.

The basic research gives chemists — for the first time — a method for making new molecules based on flavonoids, setting the stage for the development of new cancer therapeutics. The team's findings will be reported today in the April 4 issue of the Journal of the American Chemical Society (JACS).

Flavonoids, a broad family with more than 2,000 reported compounds, provides many different structures for chemists to investigate. In addition to those with anti-cancer activity, researchers could mimic flavonoids with beneficial properties such as anti-inflammatory, anti-viral or antibiotic.

The natural sources of the flavanones Scheidt chose to mimic? Milk thistle, soy, grapefruit and kosam, a root used in traditional Korean medicine, to name a few. All are known for their anti-cancer properties.

"I'm using nature as an inspiration for the development of new anti-tumor products," said Scheidt, who now will focus on using his method to develop molecules that will be effective against prostate cancer. "We have developed an enabling technology that opens up a new opportunity to make these flavanone compounds from scratch and to design them to do many things, including fight cancer. A better understanding of the flavanones' modes of action will help us improve their potential for use in medicine."

Scheidt says prostate cancer, second only to lung cancer as the leading cause of cancer-related deaths in men, is an important target. He is collaborating with Raymond Bergan, M.D., a clinical oncologist at the Feinberg School of Medicine who often treats prostate cancer patients who have run out of therapeutic options. The two were brought together through their involvement with the University's Center for Drug Discovery and Chemical Biology.

"Our goal is to keep cancer cells local, and some of the new molecules Karl already has made inhibit the motility of prostate cancer cells -- they stop the cells dead in their tracks," said Bergan, associate professor of hematology and oncology. "It is important for us to understand how these synthetic flavanones work because combination therapies are going to be the future in cancer treatment, much like we see with HIV. We need multiple compounds with different modes of action: one that stops cells from moving, another that kills cells where they are and a third that lets the body's immune system do its work. Karl and his team have opened this door."

"We are really excited to work on flavonoids with anti-cancer properties so we can selectively modify these natural products," said Scheidt. "We want to get selectivity and specificity using chemistry. A naturally occurring flavonoid may not have all the characteristics you want — it may not be potent enough, for example — but with chemistry you can go in and modify that structure, imbuing the molecule with more desirable traits, such as binding more effectively to a protein of interest or being less toxic to normal cells."

The biosynthesis of flavanones is not well understood; for years organic chemists have struggled to find a good way to make them in the lab. The difficulty was figuring out how to produce a desired molecule in one-handed form, as is found in nature.

In attacking this age-old problem, Scheidt and his team discovered a simple chiral catalyst, which comes from quinine, that successfully controls the chemical outcome and produces a left-handed molecule or a right-handed molecule, not a one-to-one mixture of both.

"Flavanones are chiral molecules, which come in two 'flavors,'" said Scheidt, who is left-handed and says he has been sensitive to handedness all his life. "We have a method to make just one 'flavor,' which no one has done before. Chiral molecules come in mirror images of the other, or two different 'hands.' Like your own hands, you can't superimpose one hand on the other. In both people and molecules, a left hand and a right hand are very similar but are not the same. In synthesizing flavonoids, you want to make one handedness over the other."

"Nature is the ultimate synthetic chemist and pharmacist," said Scheidt, who looks forward to synthesizing and evaluating new compounds with Bergan. "We may not be quite as sophisticated as nature, but our catalyst works beautifully. Small molecules can do really big things."



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