Synthesis of natural molecule could lead to better anti-cancer drugs

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In early 2007, Northwestern University chemist Karl Scheidt's interest was piqued when marine chemist Amy Wright reported in the *Journal of Natural Products* that a new natural compound derived from an uncommon deep-sea sponge was extremely effective at inhibiting cancer cell growth.

As a synthetic chemist fascinated by natural products and their potential in medicine, Scheidt knew what he had to do: Make that molecule.

After six months of intense effort, Scheidt, graduate student Daniel Custar and postdoctoral fellow Thomas Zabawa successfully built the molecular structure reported in the paper. That's when they discovered something strange and unexpected when they compared the spectra, or unique molecular fingerprints, of their structure and that of the natural compound: The spectra did not match, which meant that the structures did not match. Something was wrong.

This story and how the Northwestern team solved the mystery and determined the real structure of neopeltolide, the natural compound derived from the marine sponge, is reported in a paper published in the Jan. 23 issue of the *Journal of the American Chemical Society* (JACS). Knowing neopeltolide's structure will help researchers learn how the new compound works, which could lead to new, more-effective anti-cancer drugs.

"The reported biological activity of this new natural compound was

fantastic -- two to three orders of magnitude more potent for some cancer cells than Taxol®, a common chemotherapy drug," said Scheidt, assistant professor of chemistry in the Weinberg College of Arts and Sciences at Northwestern. (Taxol® also has its origins in nature, having been extracted from the Pacific yew tree.) "Synthetic chemists are inspired by such structures. Because of the potential benefits to human health, these are the compounds you want to go after."

Marine sponges can't move and escape predators, and they don't have claws, teeth or quills, so they have developed a different kind of defense mechanism: chemical protection. The sponge and/or bacteria hosted by the sponge produce poisonous compounds to ward off enemies. This chemical factory makes sponges rich sources of interesting natural products, many with cell-killing abilities.

After discovering the spectrum of their first built molecule did not match the natural compound's spectrum, Scheidt and his team faced two possibilities -- either they had done something wrong while building the molecule or the structure was reported incorrectly.

The researchers double checked their methods, found they were "spot on" and concluded the structure was reported incorrectly. Which meant the right structure still needed to be determined. Custar and Zabawa decided to set up a cot in the lab's computer room to cut down on their commute to the lab and set to work.

Again, using simple starting materials and complex chemical synthesis, the team built a new molecule, just slightly different from the first one. This time they perturbed just two carbon atoms, making them "down" instead of "up," in chemist speak. The researchers compared the spectrum of this new structure with that of the natural compound, and this time the spectra matched perfectly. These results are those published in the JACS article.

To construct the compound, Scheidt, Custar and Zabawa used an efficient, convergent synthesis, a bit akin to how a car is put together on an assembly line -- with major parts, like the engine, built separately and then put together in the final piece. “Our approach brings three equal fragments together to form the whole, which is better than building in a linear sequence,” said Scheidt. “We pushed the envelope of what can be done with organic chemistry to do it.”

Unbeknownst to the Northwestern researchers, a group led by James S. Panek, an organic chemist at Boston University, was working on the neopeltolide structure at the same time as Scheidt and his team. In their work, Panek’s group also discovered the original published structure to be incorrect and determined the correct structure, using steps different from Scheidt’s to get there. Panek’s results were published a few weeks after the time Scheidt submitted his paper to JACS.

“The synthetic chemists have done an amazing job in such a short time,” said Wright, who works at the Harbor Branch Oceanographic Institution. Wright isolated neopeltolide from a sponge she collected near Jamaica in 1993; she and her team reported its biological activity and structure in the 2007 article that inspired Scheidt’s work.

“I was impressed with the molecular modeling work that Karl’s group did to propose a variety of structures,” said Wright. “The beauty is that we can find a compound in nature, and synthetic chemists can then build the structure in the lab. That structure and related compounds can then be tested for drug discovery.”

“Nature is the biggest pharmacy around,” said Scheidt. “Sixty to seventy percent of pharmaceuticals are inspired by natural products. We learn from nature, but we want to improve on nature, too.”

Neopeltolide stops cell division in an unusual place, and this activity is

different from that of other commonly known and utilized chemotherapies. “We know there is something different going on with this new molecule, and we want to start figuring out if this behavior is the beginning of a new way to treat cancer,” said Scheidt.

In addition to the original structure, Scheidt and his team currently have six or seven other synthetic compounds to test. The researchers want to see if they can make a smaller, simpler molecule that is just as effective against cancer cells but also more selective, leaving healthy cells alone. A few small chemical tweaks may be all that is needed.

With the new compound’s correct structure in hand, the real journey can begin, says Scheidt. He plans to work with Wright and Professor Craig Crews, a molecular biologist at Yale University, to screen the tweaked molecules against different cancer cell lines and to discover how they work so new pathways for treating cancer can be identified.

Source: Northwestern University