Research team achieves critical step to opening elusive class of compounds to drug discovery

6 November 2011

The Scripps Research laboratory of Professor Phil Baran has created the largest amount of pure taxadiene isolated or prepared to date. Credit: Photo courtesy of the Scripps Research Institute

Taxanes are a family of compounds that includes one of the most important cancer drugs ever discovered, Taxol®, among other cancer treatments. But the difficulty producing these complex molecules in the lab has hampered or blocked exploration of the family for further drug leads. Now, a group of Scripps Research Institute scientists has successfully achieved a major step toward the goal of synthetically producing Taxol® and other complex taxanes on a quest to harness chemical reactions that could enable research on previously unavailable potential drugs.

Taxol®, the trade name for a chemical called paclitaxel first discovered in 1967 in the bark of a yew tree, is a highly successful drug used to treat ovarian, breast, lung, liver, and other cancer types. No less than seven different research groups have designed several ways to produce Taxol® synthetically, beginning in the 1990s with a team led by K.C. Nicolaou, chair of the Scripps Research Department of Chemistry.

While each synthesis was a significant accomplishment, each has also been exceedingly complex and inefficient. Using all these methods collectively, researchers have produced less than 30 milligrams of synthetic Taxol®. Producing other chemicals from the same promising taxanes chemical group is nearly as challenging, vastly limiting access to them for research.

Building Ferraris

Finding an efficient way to produce Taxol® in sizable quantity in the laboratory remains one of the most sought-after and elusive goals in organic chemistry. If accomplished, it would open the door to producing countless other taxanes that are not accessible from nature. Past methods were devised using conventional schemes where researchers plot a linear path of increasingly complex molecules leading to a target compound. Creating each increasingly complex molecule along that line is an inefficient process that often requires numerous extra steps to prevent unwanted reactions or to correct other chemical complications. "It's like trying to convert a Toyota Corolla into a Ferrari instead of just building a Ferrari," said Baran.

To build the Ferrari, Baran and his team are taking a different route. In 2009, the researchers showed that by using an unconventional scheme they could produce a simpler relative of Taxol® called eudesmane. They analyzed this target and then created what Baran calls a retrosynthesis pyramid. This is a diagram with the target compound at the top and lower levels filled with molecules that could theoretically be modified to reach the level above

them. Such a pyramid reveals not a set linear path, but a variety of path options open to chemical exploration.

With taxanes and related compounds there are two main phases in production, the cyclase phase and oxidase phase. Working up the bottom half of the pyramid involves mostly well-understood chemistry. During this cyclase phase, researchers construct a chemical scaffolding that Baran likens to a Christmas tree to which ornaments must then be attached. The ornaments are primarily reactive oxygen molecules and this "decoration," or oxidation, phase is the most challenging.

The eudesmane synthesis was something like decorating the Charlie Brown Christmas tree, while a completed Taxol® production could be compared to the lighting of the famous multi-story Rockefeller Center tree.

In the new paper, Baran's group reports erecting that Rockefeller tree and adding the first few ornaments -- a molecule called taxadiene. "It's a Herculean task," said Baran of Taxol® synthesis, "What we're doing here is merely part one."

A conventional taxadiene synthesis is inefficient and involves 26 steps to produce. The Baran group's method involves just 10 steps to produce many times what has been previously synthesized -- more than sufficient for planned research to find a way to efficiently produce Taxol®.

Innovation Leads to Access

The taxadiene synthesis is more than just a midway stop on the way to Taxol®. The researchers chose this molecule intentionally because, like a Christmas tree that can be decorated in any number of ways, this molecule can be modified to create a wide range of taxanes of varying complexities.

This is key, because at its heart the research isn't only about finding a better way to produce Taxol®, even though the group is working toward that goal. The current commercial Taxol® production method, which involves culturing cells from the yew tree, is more economical than any new synthesis is likely to be.

Instead, Baran and his team are aiming to understand the processes used in nature to produce the compound, which are many times more efficient than those used by scientists to date. "It's my opinion that when there's a huge discrepancy between the efficiency of nature and humans, in the space between, there's innovation."

More specifically, Baran believes that while developing an efficient synthesis for Taxol®, they will gain a fundamentally improved understanding of the chemistry involved and develop more widely applicable techniques. Such innovation could allow production of a whole range of taxanes currently inaccessible for drug discovery research either because the quantities researchers can produce are vanishingly small, or because they can't produce them at all. Control of the taxane oxidation process therefore offers the potential for discovering new and important drugs, perhaps even one or more that is better at fighting specific cancers than Taxol®.

Establishing the remaining steps between taxadiene and Taxol® or other more complex taxanes remains a challenging task that Baran estimates will take years. "Nature has a choreography in the way she decorates the tree," he said. "It's a precise dance she has worked out over millennia. We have to figure out a way to bring that efficiency to the laboratory setting."

The project, led by Scripps Research chemist Phil Baran, is described November 6, 2011 in an advance, online issue of the journal *Nature Chemistry*.

Provided by The Scripps Research Institute