Scientists find long-sought method to efficiently make complex anticancer compound

August 1 2013

Scientists at the Scripps Research Institute have achieved the first efficient

chemical synthesis of ingenol, a highly complex, anticancer substance found in the *Euphorbia* genus of plant, whose milky sap has long been used in traditional medicine. Credit: Photo courtesy of The Scripps Research Institute.

Scientists at The Scripps Research Institute (TSRI) have achieved the first efficient chemical synthesis of ingenol, a highly complex, plant-derived compound that has long been of interest to drug developers for its anticancer potential. The achievement will enable scientists to synthesize a wide variety of ingenol derivatives and investigate their therapeutic properties. The achievement also sets the stage for the efficient commercial production of ingenol mebutate, a treatment for actinic keratosis (a common precursor to non-melanoma skin cancer), that at present must be extracted and refined inefficiently from plants.

"I think that most organic chemists had considered ingenol beyond the reach of scalable chemical synthesis," said TSRI Professor Phil S. Baran.

Baran and his laboratory report their achievement in this week's issue of *Science Express*, the early online edition of the journal *Science*.

An Anticancer Substance from Nature

Ingenol and its derivatives are found in the widely distributed *Euphorbia* genus of plant, whose milky sap has long been used in traditional medicine to treat skin lesions. Ingenol mebutate, extracted from the common "petty spurge" plant (*E. peplus*), was recently approved by the U.S. FDA, European Medicines Agency, Medicines Australia and Health Canada to treat actinic keratosis, a common type of precancerous lesion associated with cumulative sun exposure. Formulated and marketed as Picato®, the drug has also shown effects in models and in early trials of non-melanoma skin cancers.

In late 2011, the drug's manufacturer, Denmark-based LEO Pharma, collaborated with Baran's laboratory to find an efficient way to synthesize ingenol mebutate using organic chemistry—the usual method for producing modern drugs. "At the time, the only way to get the product was by a relatively lengthy extraction process from the *E. peplus* plant," said Michael Sierra, LEO Pharma's director of external discovery. "We were hoping to get a more efficient synthetic route for production, as well as a method that would allow us to make new derivatives."

Studies have shown that ingenol mebutate, which is applied topically, can treat precancerous skin cells with unusual swiftness, while sparing healthy skin cells. The treatment has a direct cancer-cell-killing effect, and also induces an inflammatory reaction. Researchers suspect that derivatives of ingenol mebutate may be useful in treating other types of cancer, if they can be delivered properly.

Until now, it was debatable whether such derivatives could ever be synthesized. Some prominent researchers have suggested recently that the efficient chemical synthesis of structurally unusual "terpenoid" compounds such as ingenol is an unreachable goal—and that drug developers should seek biotechnology solutions instead. Even leading scientists of LEO Pharma initially had their doubts. "It was initially hard for me to sell this project to the company," said Sierra. "But I knew Phil, and I knew that his lab could do this."

Achieving the 'Unreachable' Goal

Baran and his team started by examining what is known about ingenol's natural synthesis in plant cells. "A key feature of the natural synthesis is that the basic framework of the molecule is built first, and then in a second phase the important oxygenated functional groups are added," said Steven J. McKerrall, a graduate student in the laboratory who was

one of the two first authors of the study.

Following that basic strategy of mimicking nature, McKerrall, Baran and their colleagues began designing the synthesis. They were eventually able to hone the process to 14 steps, starting from a common and inexpensive chemical, carene, and ending with long-sought ingenol. "Syntheses of ingenol have been described in the past, but they all require more than 37 steps," said co-lead author Lars Jørgensen, a postdoctoral fellow in the Baran Laboratory.

The new and concise synthesis turned out to yield relatively large quantities of ingenol, making it an efficient approach to the production of ingenol mebutate and other ingenol derivatives. The two-phase design also provides a significant amount of a key intermediate compound, which enables the efficient preparation of various ingenol derivatives. "We won't have to go through the entire synthesis every time we need to make a new ingenol derivative; we can start synthesizing from this intermediate compound," said Jørgensen.

Sierra and others at LEO Pharma were pleased with the project's outcome. "It's a pretty amazing feat: the total synthesis of ingenol within a year and a half of starting our collaboration," he said. "It's great to work with a research group like this."

To Baran, the achievement serves also as an emphatic rejoinder to those who had declared chemical synthesis a dead-end technique for making such complex natural compounds. "With this study we rebut that argument conclusively," he said. "And there are many other complex natural compounds waiting to be synthesized using a strategy like ours—this is really just a glimpse of the future of chemical synthesis."

More information: "14-step synthesis of (+)-ingenol from (+)-3-carene," *Science*, 2013.

Provided by The Scripps Research Institute