

Beyond Yew: Chemists Boost Taxol Yield

Several research groups have overcome significant barriers to produce a promising new anticancer drug now derived from the bark of the Pacific yew tree. The drug, taxol, has drawn great interest because of its success as an experimental treatment for ovarian tumors and, more recently, lung and breast cancers (SN: 2/22/92, p.124). It has also sparked controversy because it exists in minute quantities in the yew's bark, whose collection results in the death of the century-old trees.

But soon taxol may come, either directly or indirectly, from much less precious sources: cedar wood oil, the leaves of a yew common in Europe, the major ingredient of turpentine or even vats of living plant cells. Scientists reported on these developments last week at the American Chemical Society spring meeting in San Francisco.

"The key message is, we're ending the dependency on the Pacific yew," says Matthew Suffness, a medicinal chemist with the National Cancer Institute in Bethesda, Md. "We're moving to other areas in which other processes are viable."

Already, these advances have led to new, possibly better drugs based on taxol.

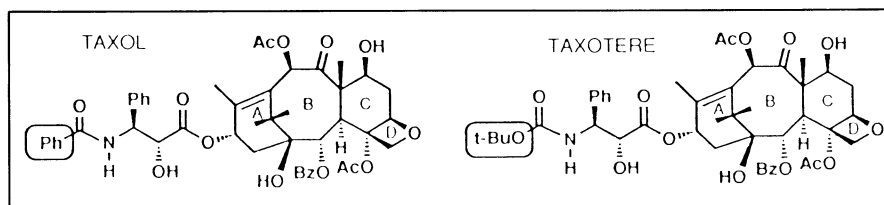
Years before taxol's supply became an issue, its synthesis intrigued chemists. This complex compound's core contains 20 carbon atoms arranged in three linked rings. In addition, a chain of atoms hangs off one ring, while other atoms make a square formation, or fourth ring, off another. "You're looking at a molecule that has tested the limits of synthetic chemistry," says Paul A. Wender, an organic chemist at Stanford University.

Three years ago, Wender upped the taxol-synthesis ante by deciding to develop a synthesis technique that companies could adapt easily for commercial production.

Wender starts with pinene, an inexpensive pine extract found in turpentine. In five steps, he turns pinene into the three-ring core; then, with eight more steps, he adds the right side groups to two of the rings. He expects to learn how to complete the third ring by the end of 1992.

Jeffrey D. Winkler, a chemist at the University of Pennsylvania in Philadelphia, also makes the taxol core, having independently devised a strategy similar to Wender's. But Winkler's team starts with an extract from cedar oil.

Eight years ago, Pierre Potier, an organic chemist with the Institute of the Chemistry of Natural Substances in Gif-sur-Yvette, France, found that the leaves of the European yew contain a compound



Chemical-structure diagrams show the similarity between taxol and Taxotere.

that closely resembles taxol's three-ring core. Potier came up with a series of chemical reactions for adding the side chain and converting this molecule to taxol.

Robert A. Holton, an organic chemist at Florida State University in Tallahassee, has also come up with an efficient way to join the leaf compound of the European yew with the side chain. Because the core molecule is bent like a cone around the place where the side chain attaches, the side chain has trouble getting close enough to attach. Holton and his group devised a rolled-up version of the side chain that fits easily into this cone. When it attaches, it opens up into the straight configuration needed to make the molecules active against tumors, says Holton. Moreover, he can easily modify the final molecule produced.

"He's improved that semisynthetic process tremendously," says Suffness. Bristol-Myers Squibb in New Brunswick, N.J., plans to produce taxol in this way, possibly for clinical use by next spring, Holton says.

Plant-cell cultures can also help improve the taxol supply and yield related compounds, reports Walter E. Goldstein, a chemical engineer with ESCAgenetics Corp. in San Carlos, Calif. "The taxol concentrations [from cultures] are many times the taxol concentrations one sees in the bark," he says. His company had begun producing vanilla through cell cultures but now has shifted its bioreactors to yew-cell cultures.

These scientists agree that taxol represents only a crude beginning for this new class of anticancer drugs. "Taxol is not the compound we want to use," Potier says. Aside from being hard to obtain, it does not dissolve easily, so it's difficult to inject into the body. Also, patients need high dosages.

Already Potier has found that one compound derived from the European yew, called Taxotere, is more soluble and more efficient than taxol at killing lab-grown cancer cells. Physicians in Europe and the United States are now trying this compound in patients. "We believe that clinical use of taxol is no longer justified," Potier says. Holton, too, has produced several dozen taxol-like compounds for

evaluation.

And David G.I. Kingston at Virginia Polytechnic Institute and State University in Blacksburg has systematically altered side groups and the side chain of taxol. Kingston's data indicate that both the side chain and the box formation at the other end of the molecule are critical to taxol's anticancer effect. His work with some of these modified taxol molecules made him realize that he can make a soluble "prodrug," a compound that converts to taxol once in the body. A prodrug may make taxol easier to administer, he says.

"All of these technologies are going to play a role," says Suffness. — E. Pennisi

Infant memory shows the power of place

Six-month-olds rely on surprisingly specific aspects of their incidental surroundings — such as the color or design of a crib liner — to retrieve memories of a simple learned task, according to ongoing research by psychologists at Rutgers University in New Brunswick, N.J.

"Place information enjoys a privileged [mental] status much earlier in development than previously thought and seems to be the first level of retrieval for memories among infants and adults," asserts project director Carolyn Rovee-Collier.

The new findings, described in the March DEVELOPMENTAL PSYCHOLOGY, challenge current neuropsychological theories that consider basic language skills a prerequisite for memory development and assume that infants younger than around 9 months cannot store information about their surroundings in a systematic way.

Rovee-Collier's group conducted a series of experiments with a total of 85 infants. Each baby reclined in a seat placed in a playpen whose sides were draped by a yellow liner with green squares. A mobile featuring seven wooden figures and four jingling bells hung over the playpen. On two successive days, experimenters tied a satin ribbon attached to the mobile around an infant's ankle for 6 minutes and an experimenter

recorded the number of leg kicks as the infants learned to move the mobile. On the following day, an experimenter again charted kick rates for infants either in the original playpen or in one draped by a liner with a slightly different design.

Babies continued to kick at their previous rates if the liner displayed triangles instead of squares, but kicking dropped off drastically if circles or stripes adorned the liner. If the color of squares changed from green to red, or if the liner displayed no figures, infants continued to kick in response to the mobile. But if the color of the yellow background changed, or if colors on the liner were reversed (green background and yellow squares), infants showed no recognition of the mobile.

Kick rates also plummeted if experimenters removed the liner on the test day, leaving the familiar context of the infant's playpen and bedroom. This suggests that altered test contexts produce kick-rate declines not because of their novelty but because infants cannot locate the modified context in their original training memory, Rovee-Collier argues.

Previous experiments by her team showed that 6-month-olds remember how to move the mobile up to two weeks after training sessions, but only if the design of the crib liner remains the same. Even 3-month-olds learn that kicking sets the mobile in motion, and they retain this knowledge for three to five days, Rovee-Collier says. But a 3-month-old who trains in the bedroom and gets tested in the kitchen, or who goes from crib training to testing in a lower, portable crib, stares blankly at the previously encountered mobile.

"Young infants learn what happens in what place long before they are able to move from one place to another or learn the spatial relations between those places," Rovee-Collier contends. Although she declines to label an infant's reliance on specific features of a playpen liner as either conscious or unconscious, she adds that "the behavior of the babies we study is very deliberate."

She theorizes that context information serves as an "attention gate." When context during learning matches context at recall, recognition of basic perceptual cues — such as colors and some forms — permits attention to focus on memories for a learned task, such as moving a mobile with leg kicks. This theory holds that sensory receptors and the brain first break incoming information into "elementary perceptual units," which then get put back together to form a coherent perception.

Context's critical role in memory, which researchers have also observed among adults, suggests to Rovee-Collier that the brain harbors a single memory system rather than multiple types, as some researchers have proposed (SN: 11/17/90, p.312).

— B. Bower

Spying new quasar class, peering at M32

Two Earth-orbiting spacecraft have found new evidence for black holes lurking near the edge of the observable universe as well as in our own cosmological backyard.

The more distant finding comes from an ongoing sky survey of gamma rays, radiation more energetic than X-rays. Last week in Washington, D.C., scientists reported that the Compton Gamma Ray Observatory (GRO) had detected strong gamma-ray emissions from three quasar-like objects that lie billions of light-years from Earth. The intensity of gamma radiation from each source — quasar relatives called BL Lac objects — represents 10 trillion times the output of the sun at all wavelengths.

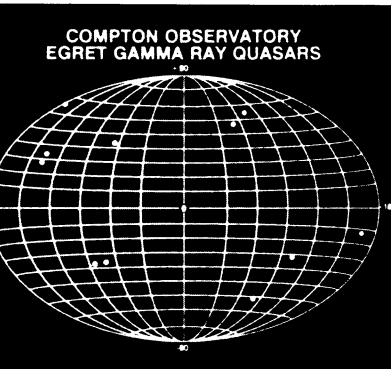
GRO had previously identified eight quasars with similarly high-intensity gammas (SN: 1/25/92, p.60). Those findings, combined with the new observations, may represent a new class of quasars that radiate predominantly at gamma-ray wavelengths, says GRO scientist Neil Gehrels of NASA's Goddard Space Flight Center in Greenbelt, Md.

While the mechanism to produce such emissions remains a mystery, the underlying powerhouses must be supermassive black holes, Gehrels asserts. No other known phenomenon could account for such intense radiation spewed from such small volumes of space, he contends. The new findings point to a surprising similarity between certain types of quasars and quasar-like objects. They also solve a key puzzle about the gamma-ray radiation from the quasars, Gehrels says.

When GRO first began detecting gamma rays from quasars, researchers had trouble believing the results. If some quasars beamed that much radiation toward Earth, they likely radiated a total of 10 to 100 times that amount in all directions — and that was impossible, since the concentration of gammas needed to produce such intense radiation would cause the gammas to collide and annihilate each other, leaving pairs of oppositely charged subatomic particles in their stead.

Enter the BL Lacs. Researchers already had evidence suggesting that BL Lacs radiate light in a single beam. Since certain quasars, called blazars, share several other features with BL Lacs, scientists reasoned that blazars, too, might emit a single beam. Thus, the total gamma-ray energy emitted by these quasars wouldn't far exceed the intensity recorded and would match that permitted by theory, Gehrels says.

Rapid fluctuations in gamma rays



Sky map, centered on Milky Way, shows gamma-ray-emitting quasars and BL Lacs.

emitted by the blazars and BL Lacs support this model. It's as if each object beams its energy like a flashlight that sometimes strikes the GRO detector dead on and sometimes all but misses it.

Another finding announced last week involves visible-light emissions from an object much closer to home. The Hubble Space Telescope's planetary camera has detected unusually intense starlight from the center of a tiny galaxy called M32, a satellite to the Andromeda galaxy, the Milky Way's nearest spiral neighbor. The intensity indicates that M32 packs 100 million times more stars near its core than the distribution of stars in the vicinity of the sun, reports Tod R. Lauer of the National Optical Astronomy Observatories in Tucson, Ariz. He and his colleagues suggest that the high density stems from a small black hole at M32's center, with a mass about 3 million times that of the sun.

Lauer adds that researchers had suspected that M32 harbors a black hole ever since ground-based observations in the 1980s showed that the orbital velocities of stars rose toward its center, as if they were circling a massive object.

But caveats abound, Lauer notes. Hubble's blurred vision (SN: 7/7/90, p.4) can resolve only the very beginning of a rise in star density; the density might level off farther into the core. And unlike other recently reported black hole candidates (SN: 1/25/92, p.52), M32 has no central jet, nor does its core radiate intensely at any wavelength. Lauer suggests that smaller black holes, like the one proposed for M32, may "eat" surrounding gas less frequently, spewing out less energy.

Jeremy Goodman of Princeton (N.J.) University notes that other nearby galaxies suspected of harboring black holes also radiate relatively little. The final verdict, he says, awaits high-resolution observations of star velocities at M32's core, a feat that researchers can't perform until Hubble gets corrective optics in 1994.

— R. Cowen

NASA/GRO