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REDISCOVERING NATURAL PRODUCTS

Cast aside for years, natural products drug discovery appears to be reclaiming attention and on the verge of a comeback

A. MAUREEN ROUHI, C&EN WASHINGTON

The pharmaceutical industry's productivity continues to be dismal. This state of affairs is due to many factors, and one may have been the diminished interest in natural products drug discovery as the industry embraced promising and exciting new technologies, particularly combinatorial chemistry.

However, the tide may be turning, for three reasons. First, combinatorial chemistry's promise to fill drug development pipelines with de novo synthetic small-molecule drug candidates is unfulfilled. Second, the practical difficulties of natural products drug discovery are being overcome by advances in separation technologies and in the speed and sensitivity of structure elucidation. And third, a compelling case is being made for the intrinsic utility of natural products as sources of drug leads.

For decades, natural products have been a wellspring of drugs and drug leads.



ESSENTIAL INGREDIENT A large natural product collection, including microbial cultures in fermentation flasks, is integrated into Albany Molecular Research's drug discovery program.
PHOTO BY ALPHONSE DEKLERK

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According to a recent survey by David J. Newman, Gordon M. Cragg, and Kenneth M. Snader of the [National Cancer Institute](#), 61% of the 877 small-molecule new chemical entities introduced as drugs worldwide during 1981–2002 can be traced to or were inspired by natural products [[J. Nat. Prod., 66, 1022 \(2003\)](#)]. These include natural products (6%), natural product derivatives (27%), synthetic compounds with natural-product-derived pharmacophores (5%), and synthetic compounds designed on the basis of knowledge gained from a natural product (that is, a natural product mimic; 23%).

In certain therapeutic areas, the productivity is higher: 78% of antibacterials and 74% of anticancer compounds are natural products or have been derived from, or inspired by, a natural product. These numbers are not surprising if it is assumed that natural products evolved for self-defense. But the influence of natural products is significant even in therapeutic areas for which they might not seem relevant, such as cholesterol management, diabetes, arthritis, and depression.

"Imagine if we eliminated natural products from drug discovery in the past," suggests Barry A. Berkowitz, a corporate vice president at [Albany Molecular Research](#). "We would not have the top-selling drug class today, the statins; the whole field of angiotensin antagonists and angiotensin-converting-enzyme inhibitors; the whole area of immunosuppressives; nor most of the anticancer and antibacterial drugs. Imagine all of those drugs not being available to physicians or patients today."

Despite that record of productivity, natural products drug discovery was de-emphasized in many big pharmaceutical companies in recent years. Newman says the trend began in the early 1990s, and the reasons were primarily practical. When automation, robotics, and personal computers came onto the drug discovery scene around the mid-1980s, chemistry became the rate-limiting step in drug discovery programs, he explains. The situation worsened in the early 1990s, with high-throughput screening, fast personal computers, and the breakneck pace at which molecular biology was identifying biological targets. Chemists couldn't supply the huge numbers of compounds required by screens that by this time were taking months instead of years.

At the same time, natural products drug discovery was still being done the traditional way: Drug targets were exposed to crude extracts, and in case of a hit--that is, evidence of activity--the extract was fractionated and the active compound isolated and identified. The process was slow, inefficient, and labor intensive, and it did not guarantee that a lead from screening would be chemically workable or even patentable.

In addition, natural products can get companies entangled in sticky intellectual property issues, according to Cornell University professor [Jerrold Meinwald](#). Negotiating agreements that are fair to all concerned parties to develop natural products collected in foreign countries has become "extremely difficult," he says.

Meanwhile, by the early 1990s, combinatorial chemistry was creating a buzz. It wasn't only faster and cheaper than natural products drug discovery, it also had the great advantage of clarity with respect to intellectual property. Drug companies paid attention.

At [Pfizer](#), for example, the number of compounds advancing from hits to leads from the screening of combinatorial libraries was much higher than from natural products, according to Christopher A. Lipinski, an adjunct senior research fellow at Pfizer Global R&D and author of the renowned rules for designing compounds with druglike properties. On this basis, natural products lost the competition for resources. "It was a no-brainer," he says.

But when productivity is measured by de novo synthetic small molecules advancing from hit to lead to approved drug, combinatorial chemistry offers zilch. For the period 1981–2002, "we have not been able to identify a de novo combinatorial compound approved as a drug in this time frame," Newman and coworkers write. "However, compounds that have been optimized by combinatorial chemistry are in all phases of drug development. Combinatorial chemistry may not currently be delivering as a discovery tool, but it is excellent for further development of active compounds," Newman adds.

"The alarming decline in the number of new chemical entities in the past decade, from an average of 30 or so to as few as 17, has correlated with" decreased interest in natural products drug discovery, Berkowitz says. The trend is not surprising in as much as natural products have been proven sources of drugs, he adds.

"IN TOO MANY companies, in my view, management went all out to make combinatorial chemistry the way to get new leads, and it did not work because the need for structural complexity was restricted by the requirement for acceptable purity," says [Ralph F. Hirschmann](#), a professor of bioorganic chemistry at the University of Pennsylvania. For 37 years, he worked in various capacities at Merck, and during his tenure as head of basic research, [Merck](#) developed several blockbuster drugs.

Although combinatorial chemistry had not been proven as a drug discovery tool, many companies committed to it as the principal

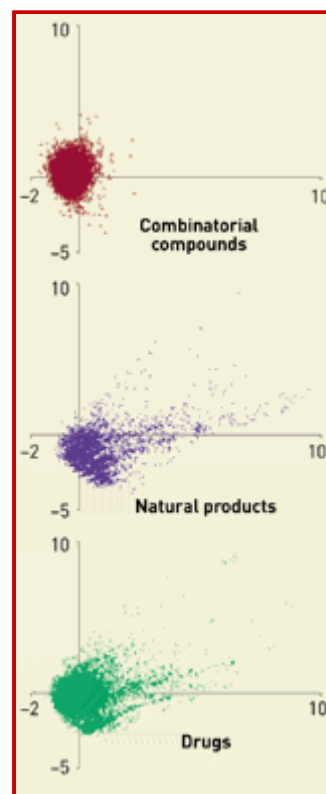
source of compounds for lead discovery, Hirschmann says. He suggests, in a foreword to the second edition of "[The Practice of Medicinal Chemistry](#)," edited by Camille G. Warmuth (Academic Press, 2003), that pharmaceutical companies should also try to validate new technologies--in the same way new biological targets are validated--"on a modest scale before they are extensively embraced."

Some say combinatorial chemistry technology has not had enough time to prove itself. Others say the early libraries were intrinsically useless for drug discovery because the compounds were too simple and too similar to each other. Screening works by exposing a target to as much chemical diversity as possible to find those rare compounds that will bind to the target. But the early combinatorial libraries offered only a narrow slice of chemical space--the multidimensional space in which individual molecules are points defined by their characteristics and descriptors.

"The combinatorial libraries in the early years were so flawed," Lipinski says, "that if you took the libraries across pharma from 1992 to 1997 and stored them in giant dumpsters you would have improved productivity."

A 1999 study by chemists at the German pharmaceutical company Bayer, comparing synthetic compounds and natural products, revealed striking differences in structural properties ([C&EN, March 29, 1999, page 28](#)). On average, natural products have higher molecular weights; incorporate fewer nitrogen, halogen, or sulfur atoms but more oxygen atoms; and are sterically more complex, with more bridgehead tetrahedral carbon atoms, rings, and chiral centers.

More recently, Miklos Feher and Jonathan M. Schmidt at SignalGene, Guelph, Ontario, analyzed and compared compounds from combinatorial libraries, natural products, and drugs in the market to evaluate how they occupy a statistically defined chemical space [[J. Chem. Inf. Comput. Sci., 43, 218 \(2003\)](#)]. (SignalGene no longer exists, and Feher is now director of



DISTINCTIVE In chemical diversity space, combinatorial compounds densely

computational chemistry at Neurocrine Biosciences, San Diego.)

The statistical plots show that combinatorial compounds cover a much smaller volume than natural products and that the volume

occupied by combinatorial compounds is only partly occupied by natural products. The plots show greater similarity in the distributions of drugs and natural products than in the distributions of combinatorial compounds and natural products. The authors suggest that combinatorial libraries that mimic the distribution properties of natural products might be more biologically relevant.

populate a small area, whereas natural products are more spread out [*J. Chem. Inf. Comput. Sci.*, **43**, 218 (2003)].

COURTESY OF HERBERT WALDMANN

MEANWHILE, the difficulties of natural products drug discovery are being overcome by technology and may now be a moot point. Indeed, in many smaller pharmaceutical companies, natural products are a significant, if not the only, source of compounds for screening. For major drug companies that cut back on natural products drug discovery, outsourcing may be the way to return to the game.

A more basic reason to have de-emphasized natural products drug discovery may be that natural products are not relevant to many human diseases. According to this view, natural products are logical starting points in the search for drugs against infectious diseases and cancer. But why should they be relevant to, say, schizophrenia?

"Natural products are highly evolved, highly specific, and can be highly effective toward the gene products with which they coevolved," explains [Stuart L. Schreiber](#), a chemistry professor at Harvard University and codirector of Harvard's Institute of Chemistry & Cell Biology and Center for Genomics & Proteomics. "However, it is unlikely that the true molecular target of a human disease will have been subjected to natural selection to yield a natural product counterpart. Natural products are simply not there to target the relevant proteins for human disease."

For infectious diseases, natural products are effective because most of these compounds evolved from microbial warfare, Schreiber says. For this reason, he advocates approaches to natural products research that will increase the rate of discovery and the affordability of natural products. An example he cites is the research of Jon Clardy, a professor of biological chemistry and molecular pharmacology at Harvard University Medical School. Clardy is trying to access directly from soil the DNA from nonculturable organisms that gives rise to natural products

and to put it in organisms that can be grown easily in the lab.

But when natural products are used as starting points to target proteins other than those with which they coevolved, "you have to confess that you've stepped away from the specialness of natural products, which is a billion years of natural selection," Schreiber says. Natural products therefore are no more special than well-designed, totally new, nonnatural compounds in binding to human disease targets.

Particularly for studying the biology of human diseases, natural products will not supply enough of the relevant tools, Schreiber argues. He and others have embarked on diversity-oriented synthesis programs to rapidly create natural-product-like libraries of compounds that nature may not have needed to make but could serve as chemical probes for human diseases. But other researchers maintain that natural products are intrinsically useful in drug discovery.

The view that natural products have limited relevance to human disease because the source organisms and humans did not coevolve is "a gross simplification," says Guy Miller, chief executive officer of Galileo Pharmaceuticals. The company, based in Santa Clara, Calif., focuses on developing drugs that target redox signaling pathways.

According to Miller, the fundamental reactions of energy metabolism are highly conserved; the energetic apparatus in a single-cell organism is very similar to that in humans. Therefore, how plants--or other natural-product-producing organisms--adapt to biochemical derangements can be instructive in finding treatments for related derangements in humans.

Even though natural products may not have coevolved with human proteins, they have emerged in nature to interact with biomolecules, points out Lynn H. Caporale, a New York City-based independent consultant to pharmaceutical and biotechnology companies. She is also the author of the recently published book "[Darwin in the Genome](#)" (McGraw-Hill, 2003), in which she writes: "Varied genomes, based on similar chemistry, have spread across the Earth. ... Indeed, we share with one another, no less than with the majesty of the redwoods and the doves, the fact that each of us is a unique creation of the barely tapped potential immanent in the first genomes on Earth."

"IF WE LOOK AT our own proteins, very few have evolved suddenly from nowhere," Caporale tells C&EN. "We share our gene families with other organisms. Whether

inside bacteria or inside us, there is a limited number of ways that the structural components of proteins, such as α -helices and β -sheets, can arrange themselves in space and interact with each other and with other molecular structures. Domain families of many human proteins already were on Earth back when we were relatives of the fungus," she points out.



"When you have no idea where to begin in a drug discovery program, nature is a good starting point. It would be unlikely that nature had not yet seen a structure similar to what you need, even if the compound isn't curing schizophrenia in a plant or fungus," Caporale says.

SUPERIMPOSABLE
Catalytic domains of leukotriene A4 hydrolase (blue), thermolysin (yellow), and angiotensin-converting enzyme (red) are similar even though they catalyze different reactions.
COURTESY OF HERBERT WALDMANN

Herbert Waldmann, a professor of chemical biology at Max Planck Institute for Molecular Physiology, Dortmund, and the University of Dortmund, Germany, offers a similar analysis, based on the premise that natural products evolved to perform a function that is achieved by binding to proteins. Therefore, natural products should be able to penetrate biological barriers and make their way to certain cells or organs in which they will exert the effect. Thus, natural products already are biologically validated to reach and bind specific proteins.

"If you look at all proteins and analyze them for structural features, you will find elements of conservatism and diversity," Waldmann says. The conservative elements are the domains--the parts that fold to compact secondary structures. Among the hundreds of thousands of human proteins, the number of distinct domains is only about 600 to 8,000. Thus, proteins that may seem altogether different are quite similar when viewed structurally. Diversity lies in the precise details. Similar domains may have very different amino acid sequences.

Waldmann says it is well known that similarities in protein domains have been exploited in drug discovery. An early example is provided by leukotriene A4 (LTA4) hydrolase and thermolysin, two proteins with different amino acid sequences and biological functions: LTA4 hydrolase triggers an inflammatory response by converting LTA4 to leukotriene B4; thermolysin is a protease. However, their catalytic domains are

similar, as revealed by X-ray structures [*Angew. Chem. Int. Ed.*, **41**, 2878 (2002)].

"Bestatin is a natural product that inhibits proteases of the class to which thermolysin belongs," Waldmann says. "The similarity in structures between those proteases and LTA4 hydrolase prompted people to prepare a series of bestatin analogs to find more potent inhibitors of LTA4 hydrolase, and several were found."

Waldmann notes that angiotensin-converting enzyme (ACE) also has structural similarities with thermolysin and LTA4 hydrolase. ACE inhibitors are important drugs for regulating hypertension. Both ACE and LTA4 hydrolase are inhibited by captopril, a blockbuster ACE inhibitor. "The train of thought is clear," he says. "The similarity in protein domain structure can be exploited to develop inhibitors of enzymes with different functions based on the guiding structure of a natural product."

ON THE OTHER HAND, because of the similarity of domains, scientists have believed that inhibitors developed based on domains would be promiscuous. The development of tyrosine kinase inhibitors is illustrative. "The argument 10 years ago was that if nature is so conservative, you won't find selective inhibitors of tyrosine kinases," Waldmann says. "But if you look at the fine structure of the domain, nature has created biological diversity. If you now find a natural product that binds to a domain, it can serve as a starting point for a compound library. Analogs of that natural product will be the basis of chemical diversity that matches the biological diversity."

A recent demonstration comes from Waldmann's own lab. He and coworkers prepared a 74-compound library based on the natural product called nakijiquinone C. This compound inhibits a particular receptor tyrosine kinase (RTK) involved in breast cancer. Waldmann's team was searching for inhibitors of other RTKs. When tested against six RTKs, including three involved in tumor angiogenesis, seven of the compounds showed low-micromolar inhibitory activity against four RTKs. Of those, two were selective for a specific RTK [*J. Med. Chem.*, **46**, 2917 (2003)].

Synthetic chemists must decide what is sensible to prepare. Waldmann says it makes a lot of sense to be guided by natural products, as well as nonnatural compounds with validated biological relevance.

Waldmann's thesis reminds Meinwald of the story about a drunken man looking for his car keys under a lamppost. When asked if he dropped the keys around the lamppost, he replies,

"No, but the light is better here."

"You can ignore the fact that natural products have not evolved to interact with humans specifically," Meinwald tells C&EN.

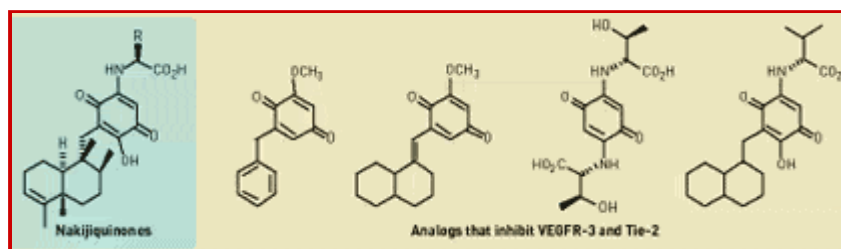
"The point is natural products have evolved to interact with something, and that something may not be so different from human proteins. By looking for natural products and building libraries around them, you would have increased your chances of finding compounds that do something versus compounds that are just out there but have not evolved in relation to proteins. If you looked under enough lampposts, you may find something sooner or later, but there's less going for you with that random approach than there is if you look in the biological world."

"If you want to address a biological question with a chemical probe--whether the question is related to basic biology or to an effort to develop a drug, one has to consider first the biological relevance of the chemical structure, ahead of how to make it," Waldmann says. "The chemistry has to be adapted to the biology, even if the effort is high. It will take longer to develop the right compound, but what you get at the end is of superior quality."

To date, one small molecule from de novo combinatorial chemistry is in Phase II clinical trial, according to Newman's search of publicly available sources. BAY 43-9006, a 3-thienyl urea, was identified from high-throughput screening of 200,000 compounds [*Curr. Pharma. Design*, **8**, 2269 (2002)]. [Bayer](#) is developing it as an anticancer agent.

Meanwhile, among the 10 small-molecule new chemical entities introduced in 2003 as of June 30, eight were derived from or inspired by natural products, Newman says. And among 137 new small molecules in Phase II or Phase III clinical trials for cancer as of June 30, 59% are natural products or compounds derived from or inspired by natural products, he adds.

"It is important to revisit decisions in light of new information," Caporale says. "Right now is a frustrating and challenging time in the pharmaceutical industry. As they decide how to allocate limited resources, decisionmakers have to view natural products in a new light. You can waste a lot of resources making a lot of molecules that don't work. It is important to be aware that natural products drug discovery isn't like what it used to be."



GUIDED BY NATURE A compound library developed around nakijiquinones, which are natural inhibitors of the receptor tyrosine kinase called Her-2/Neu, produced analogs that inhibit two other receptor tyrosine kinases, VEGFR-3 and Tie-2.

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