Guest Editorial

The "four color map theorem", posed in 1852, states that every map drawn on a sheet of paper can be colored with only four colors in such a way that countries sharing a common border have different colors. Proving this deceptively simple theorem has occupied the minds of some of the world's finest mathematicians. Nevertheless, the theorem did not succumb to proof until 1976. In their now famous paper, Appel and Haken described a computer algorithm that created all possible combinations of regions required to test a key provision of the proof. Their empirical observation was that no combinations disproved the provision, thus "proving" the theorem.[1]

The question was (and is), Did Appel and Haken's solution constitute a respectable proof? In his analysis of the proof, F. F. Bonsall concluded that if a computer is used to handle a large number of special cases, the understanding of the mathematician is imperfect, and that computer proofs of such theorems are "quasi-mathematics" and objectionable.[2] One reviewer of this analysis has countered that "...structuring a computer program to handle the complexity of a difficult problem represents a logical abstraction of the same nature as mathematics itself", and that "...understanding such a program structure is a form of mathematical understanding".[3]

In chemistry today, we have a similar (and healthy) rivalry between the elegant, intellectually satisfying approach to drug design of understanding the binding site in depth, in order to design its specific complement, and the brute-force, "try many reasonable possibilities and see what works" discovery approach aided by combinatorial chemistry. For us, the theorem that notivates both groups of discoverers may well be phrased as, *For any given molecular host, there is a single molecular guest that will demonstrate the strongest binding interaction under a given set of conditions*. If it were possible to synthesize and test all possible molecules that might serve as ligands, the identity of the tightest binder *would* be discovered. Clearly, this is not possible; it is estimated that 10^{200} organic molecules can be constructed of molecular weight less than 850. We are luckier than mathematicians in that we need only find an approximation to the tightest binding molecule to make a contribution of technological and economic importance. In our more pragmatic attitude to discovery, the empirical approach need not be thought of as a last resort. And, like computer analysis of mathematical theorems, the empirical approach offers substantial chemically based challenges and rewards. Structure a synthesis program to explore the set of all possible molecules to its fullest represents a logical abstraction of the same nature as synthetic strategy itself.

Where we lose is in our relative lack of "computing power". Although the libraries of oligonucleotides and of oligopeptides (billions and up) that have been created are enormous (some of these are discussed in the overview by Schultz and co-workers in this issue), it is currently not possible to generate all possible molecules, either experimentally or computationally. We cannot, therefore, use combinatorial chemistry to find the best possible ligand for a given receptor (or, at least, to known that we have found it). Thus, we need to limit the set of ligands, somehow, to the set of molecules that is most likely to give the best results. How can we do this?

One way is to pattern the libraries after the molecules that are currently effective pharmaceuticals. The structures of the top 20 ethical pharmaceuticals prescribed in 1994 are shown in Figure 1. This set of molecules can be characterized by low molecular weight, the presence of at least one ring, neither extreme polar nor nonpolar character, at most one ionizable group (most often ammonium), and the absence of highly reactive functionality. Such molecules are often said to be "drug-like". The combinatorial synthesis of libraries of drug-like molecules is currently more difficult than that of oligonucleotide or oligopeptide libraries, but this is a kinetic barrier and not a thermodynamic barrier. The fact that some groups have been engaged successfully in this pursuit for several years now has provided the basis for this dedicated issue of *Accounts*.

We have learned that multistep organic synthesis can be carried out on a solid support; that the development of such reactions is often slower than that for reactions accomplished in solution; that sometimes solid-supported reactions are superior to those conducted in solution. We see clearly that there is a distinction to be made between making small amounts of large numbers of compounds and making larger amounts of smaller numbers of compounds, and that the useful tools may be different for each goal. I, at least, have concluded that combinatorial chemistry is as much about discovering the right reactions and conditions as about aiming for libraries of specific target molecules. It is also clear that combinatorial synthesis is *useful* only when the products can be tested in an efficient manner; this integration of synthetic method with biological testing method is not second nature to either chemists or biologists. Finally, I am convinced that the only limitation to the kinds of chemistry we can accomplish combinatorially is our willingness to view the development of high-volume synthesis as an activity worthy of study. In 10 years, most organic chemists in industry will be using both combinatorial and automated chemistry methods on a routine basis.

Combinatorial chemistry is not going to solve all problems, even in medicinal chemistry. Combinatorial chemistry does afford a tool with which we may solve some important (and, yes, even practical) problems. Like using a computer to prove a theorem, combinatorial chemistry is currently foreign and even distasteful to some; in reality, it represents a new thought process for chemists and, therefore, a new set of challenges. To quote a colleague,[4] "The utility of

(1) For reviews, see: (a) Gardner, M. *Sci. Am.* **1960**, *203*, 218. (b) Appel, K.; Haken, W. *Sci. Am.* **1977**, *237*, 108.
(2) Bonsall, F. F. *Am. Math. Monthly* **1982**, *89*, 8.
(3) Murray, F. J. *Math. Rev.* **1983**, *83d*, 1335.
(4) Quoted with permission of Prof. David Lynn, University of Chicago.

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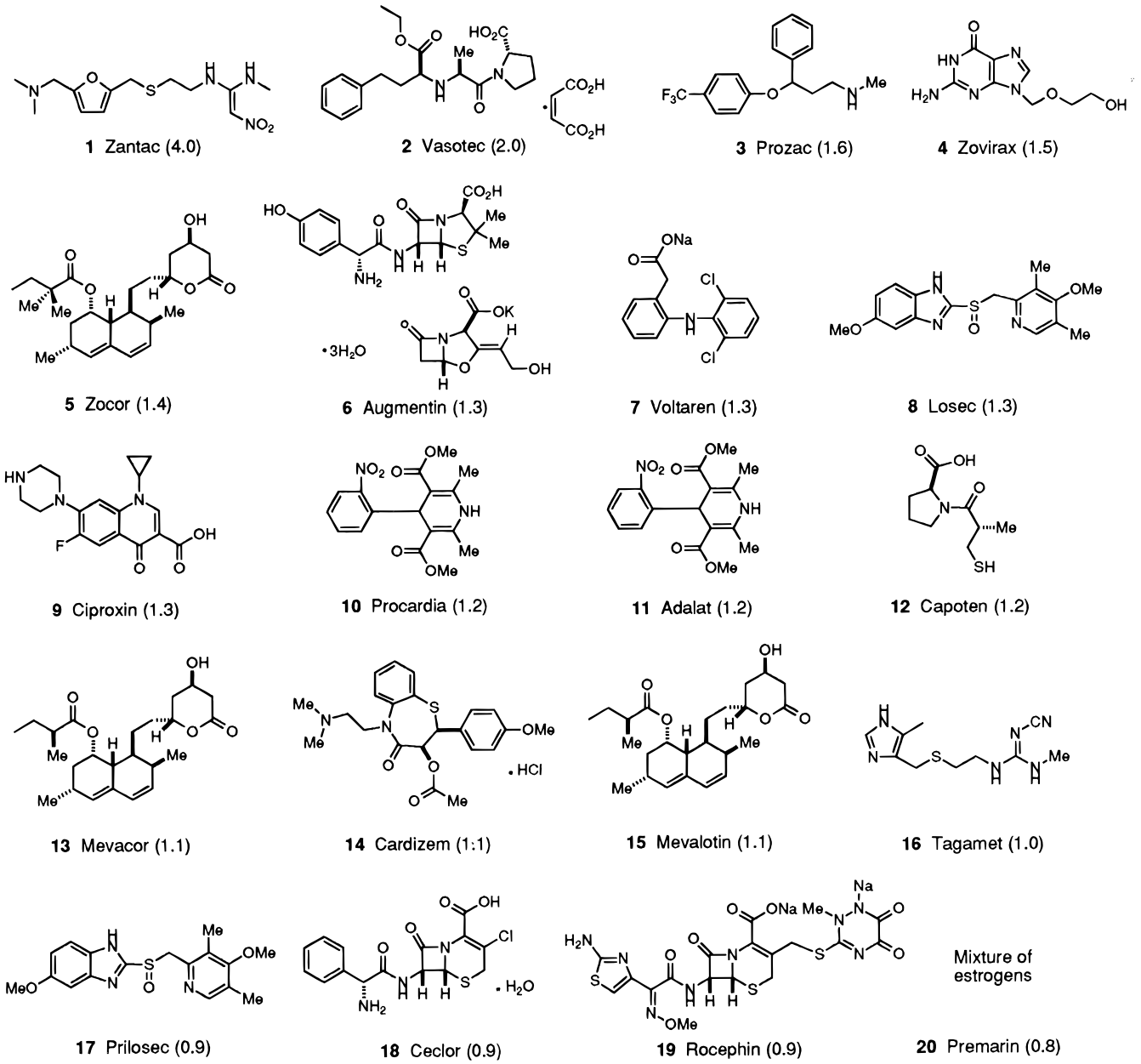

Figure 1. Top 20 ethical pharmaceuticals prescribed in 1994 (numbers in parentheses represent sales in billions, U.S.$). Source: SCRIP, No. 2040, July 7, 1995, p 23.

thinking about alternate routes to a solution is certainly a take-home message of science; we call it creativity." The reality is that no one route to discovery has a lock on success yet, and that alternate routes are to be welcomed. Recent application of combinatorial methods to more "organic" syntheses, as described in this issue, provides a new and potentially powerful way to solve important problems. Our urge to discover and to understand will ultimately compel us to reach for enlightenment in whatever form it takes.[5]

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