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Structure-Based Strategies for Drug Design and Discovery

Irwin D. Kuntz

Most drugs have been discovered in random screens or by exploiting information about macromolecular receptors. One source of this information is in the structures of critical proteins and nucleic acids. The structure-based approach to design couples this information with specialized computer programs to propose novel enzyme inhibitors and other therapeutic agents. Iterated design cycles have produced compounds now in clinical trials. The combination of molecular structure determination and computation is emerging as an important tool for drug development. These ideas will be applied to acquired immunodeficiency syndrome (AIDS) and bacterial drug resistance.

Will the next generation of pharmaceuticals arise from a combination of crystallography and computational methods (*1–5*)? While I share the enthusiasm for structure-based drug design (*6–8*), it is the newest of several approaches to the lengthy process of finding and developing therapeutic agents (Table 1). One important discovery procedure is high-volume "random" screening of natural products, corporate databases of compounds, or peptides and oligonucleotides. Another method is the interception of specific biochemical mechanisms. Vaccine development is yet another route to anti-infectives. Finally, there are well-developed "active analog" approaches to improve upon initial discoveries. Any of these techniques, singly or in combination, can play a pivotal role in finding new drugs.

Can we design drugs from first principles, creating a molecule with a specific mode of action and acceptable biological properties? Today's answer is "no." What we can reliably expect is to design inhibitors, especially enzyme inhibitors, and to begin the long process of drug development from a sensible starting point.

Fifteen years ago, Seymour Cohen proposed a general paradigm for developing drugs for infectious diseases (*9*). Infectious agents, such as viruses, bacteria, fungi, or protozoa, encode or carry their own crucial enzymes and nucleic acids, which serve as obvious targets for intervention. In the succeeding decade and a half, the ability to identify, clone, express, and purify proteins and nucleic acids has increased enormously, making highly specific in vitro assay systems commonplace. These assays, in turn, lead to effective strategies for the discovery of a wide variety of inhibitors (*10*). Structural techniques have also advanced, and high-resolution molecular anatomies can be determined by crystallographic and magnetic resonance experiments. Thus the pieces are in place to extend Cohen's concept to structure-based design (*1, 3, 7, 11, 12*).

I will draw examples from AIDS and bacterial drug resistance. These two major health problems have three features in common: recent starting points as public health issues, known etiologies, and a large number of macromolecules as potential targets (Table 2).

Screening

The vast majority of drugs in the marketplace were derived from discoveries in large-scale screens or from analog development programs. Robotic systems can perform thousands of tests per day by means of radioactive labeling or spectroscopic detection, and further improvements can be expected (*13*). It is feasible to scan an entire corporate database (for example, 100,000 to 500,000 compounds) in less than a year's time. The coupling of cell metabolism to microsensors opens the door to rapid surveys of toxicity and function at the cellular level (*14*). The only current approved drugs against human immunodeficiency virus (HIV) were detected with screening techniques (*15*) and so were the original generation of antibiotics.

Understanding the biological or biochemical mechanism of a disease often suggests the types of molecules needed for new drugs (*16, 17*). Examples are substrate or cofactor analogs for thymidylate synthase as antitumor agents (*18, 19*) or the development of the captopril family of antihypertensives (*17*). In a similar manner, clavulinic acid acts as a β-lactamase inhibitor (*20*). Such efforts represent a proven route from test tube to pharmacy.

Substrate-Based Design of Protease Inhibitors

There are circumstances in which the "rational" design of inhibitors can be performed without a target structure. A good example is a two-step protocol for developing protease inhibitors: (i) characterize the substrate specificities of the protease; and (ii) synthesize peptides with similar features but with the hydrolyzable amide bond replaced by a nonreactive "isostere." The peptides can subsequently be optimized by modifications in the side chains or backbone. This approach has been used for renin inhibitors (*21*) and for inhibitors of the HIV-1 protease (*22*). One can proceed further by adding specific moieties such as chloromethyl ketones or phosphonates that are capable of forming transition-state analog complexes with the enzyme. Among the examples are inhibitors of the *Schistosoma mansoni* cercarial elastase (*23*) and carboxypeptidase A (*24*). It is reasonable to expect to obtain peptidelike inhibitors with nanomolar inhibitory constants in in vitro assays after 1 year of effort.

Table 1. Drug development steps (*71*).

Step	Years
Discovery and lead generation	1–2
Lead optimization	1–2
In vitro and in vivo assays	1–2
Toxicology trials	1–3
Human safety trials	1
Human efficacy trials	1–2
Total development time	6–12

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The design of protease inhibitors provides a directed and logical progression. This strategy is greatly assisted by the recent dramatic improvements in peptide synthesis and in screening by chemical or biological means (*25–28*). However, for many applications, there are problems with peptide-like agents as drugs (*29*). Frequently, they have short biological half-lives and poor bioavailability. Binding kinetics must also be considered (*30*). Hydrolysis can be reduced with D-amino acids or additional backbone modifications, but rapid clearance remains a general problem for molecular sizes above 800 to 1000 daltons. The prospects for oral delivery of peptides are uncertain, but injectable formulations are readily accessible, and other delivery modes—such as inhalation, nasal absorption, or electroporation—are under active study (*31*). The conversion of a peptide-based inhibitor into an orally active drug is an important challenge for the field of synthetic chemistry. There is no general solution to this "peptidomimetic" problem, but efforts include modification of the amide backbone (*32*), cyclization (*33*), β-turn mimics (*34*), and the use of unusual amino acids (*35*). Analogous issues arise in the use of oligonucleotides as therapeutic agents (*36, 37*).

Computational Strategies

Computer-based techniques can assist in both the discovery and the optimization of lead compounds. Macromolecular structures are useful in this effort, but they are not required if families of active compounds are available. In this seminal work, Hansch examined quantitative structure-activity relationships (QSAR) between biological activity and the underlying chemical properties such as atomic charges, oil-water partition coefficients, and molecular volumes (*38*). Extensions of the approach to three-dimensional (3-D) representations are available (*39, 40*). Alternatively, large databases of compounds can be searched for molecules with chemical or structural similarity to active leads. These methods have had relatively little impact on AIDS research to this point, but they have played a role in the development of sulfanilamide and cephalosporin antibodies (*41, 42*).

Structure-Based Design

The central assumption of structure-based design is that good inhibitors must possess significant structural and chemical complementarity to their target receptor (*43*). A four-step cycle for combining structural information and computational efforts is illustrated in Fig. 1. A structure of any form of the receptor provides a starting point for direct modeling activities. The structures of ligand-receptor complexes or of homologous receptors also contain valuable information. Repeated application of the cycle of Fig. 1 has led to compounds in clinical trials (*3, 4*). Structural insight is enhanced by a variety of computer programs, ranging from interactive designs with computer graphs to automated database searching (*44*) (Table 3). Several biotechnology companies have been formed primarily to carry out structure-based design, and most major pharmaceutical companies have structural and computational groups as part of their drug discovery effort.

Our own experience in the discovery of lead compounds illustrates this partnership of structure determination and computational efforts. We have developed a computer program called DOCK (*45*) that is used to solve the 3-D jigsaw puzzle of fitting putative "ligands" into appropriate sites on the receptor. A starting point is an x-ray crystallographic structure of the macromolecule. High-quality model-built structures, based on homologous proteins, are also proving useful (*23*). DOCK explores three important aspects of drug discovery: creation of a negative image of the target site, placement of the putative "ligands" into the site, and evaluation of the quality of fit (*12, 45–47*).

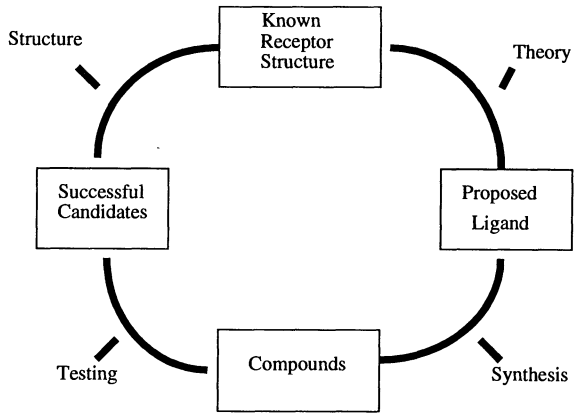

Fig. 1. General approach to the structure-based design of biological inhibitors. Begin with the determination of the structure of the target receptor. Theoretical principles and experimental data are used to propose a series of putative ligands. These compounds are synthesized and tested. The final step is the determination of the structure of the receptor-ligand complex. The figure emphasizes the cyclic and multidisciplinary aspects of this type of project.

Table 2. Macromolecular targets (**A**) for inhibition of HIV (*72, 73*) and (**B**) for drug-resistant bacteria.

	Target	Function	Intervention	Structures
A	CD4	Human cell recognition site	Vaccines, soluble CD4	X-ray (*74, 75*)
	gp120	Viral protein that recognizes CD4	Vaccines, soluble CD4	
	p24	Capsid stability		
	Reverse transcriptase	Converts viral RNA into DNA	AZT, ddC, ddI	X-ray (*76, 77*)
	RNA-DNA	Transcription intermediate	RNA, DNA ligands	Model
	RNase H	Removes viral RNA	RNase inhibitors	X-ray (*78–81*) NMR (*82, 83*)
	Integrase	Incorporates DNA into host genome		
	tat	Regulates viral transcription	Benzodiazepines, nucleosides	NMR (*84*)
	TAR	tat binding region	Antisense oligonucleotides	
	rev	Trans-activating factor		
	Protease	Processes viral polyprotein	Protease inhibitors	X-ray (*85–92*)
B	Dihyropteroate synthase	Folate pathway	Sulphonamides	
	Dihydrolfolate reductase	Folate pathway	Trimethoprim	X-ray (*93, 94*)
	β-lactamase	Hydrolyzes lactams	Clavulinic acid	X-ray (*95, 96*)
	DNA gyrase	DNA supercoiling	4-Quinolones	X-ray (*97*)
	Aminoglycoside modifying enzymes	Chemical model of antibiotics		

As a first step, DOCK characterizes the entire surface of the macromolecule, seeking the grooves and invaginations in the surface that form the target sites. These sites are filled with sets of overlapping spheres. A set of sphere centers serves as the negative image of a specific site (Fig. 2). Typically, the sites found by the program include the active regions of enzymes, recognition and allosteric features, and other small pockets that have no known function (*45*). The program is not restricted to examining enzymes. It has been applied to nucleic acid structures (*48, 49*), viral coat proteins (*50*), and the study of protein-protein binding interactions (*51*). Automatic characterization of potential binding sites is especially useful in examining complex viral surface proteins such as hemagglutinin (*50*). We can also use a "positive image" of a macromolecular surface by reversing the mathematical procedure and producing spheres inside the "receptor" (*51*).

The second step in the DOCK algorithm matches x-ray or computer-derived structures of putative ligands (*52*) to the image of the receptor on the basis of a comparison of internal distances. Matching algorithms come from a well-studied area in combinatorial mathematics called the "isomorphic subgraph" problem (*53*). Although a systematic search of all ways to fit two objects together is not feasible, rapid heuristic approximations are available (*45, 46, 51*) that examine thousands of alternative geometric matches per second. Each of these orientations must be evaluated to measure the goodness of fit of the "ligand" to the site. At first, we used a simple proximity scoring method (*12, 45, 54*) as a measure of steric complementarity. Recently, we have expanded the scoring functions to include a full intermolecular force field (*47*).

The program searches 3-D databases of small molecules and ranks each candidate on the basis of the best orientations that can be found for a particular molecular conformation (*12, 46, 47*). Each molecule can be evaluated either on its own merits or as a template. The template concept encourages chemists to look beyond the literal database entries to the design of new chemical species. The ability of DOCK to propose specific molecules in specific orientations in the active site is one of its strongest features. Although some of these molecules are related to substrates, cofactors, or known inhibitors, others can be of novel structures (*12*).

Computer programs such as DOCK can provide a rapid and controlled exploration of the geometric intricacies of target sites. Ligands can be examined at a rate of 10 to 100 per minute, making it possible to examine databases of 100,000 compounds in less than a week with a workstation. Implementing the program on a supercomputer or parallel-processing device makes it possible to search a corporate database of 500,000 compounds in a day.

Databases of interest for drug design include the Cambridge Structural Database (CSD), a compendium of approximately 100,000 molecules whose crystal structures have been determined (*55*), the Fine Chemicals Directory (FCD) distributed by Molecular Design Limited (San Leandro, California), and, in prototype form, portions of the Chemical Abstracts registry. The latter two databases have been generated in 3-D form by means of a rule-based conformation generator called CONCORD, developed by R. Pearlman at the University of Texas (*52*). Most corporate databases have been converted into 3-D coordinates by CONCORD.

Using DOCK and the CSD and FCD databases, my colleagues have found or designed inhibitors for a wide variety of enzymatic and receptor systems (Table 4). Typically, the 100 to 200 best-scoring compounds are examined with computer graphics (Table 3). Of these, 10 to 50 are selected for testing on the basis of chemical and toxicological properties. We find that between 2 and 20% of the compounds tested show inhibition in the micromolar range. In every case we have tried, DOCK has proven extremely valuable as a computer screening procedure and as a method of generating structural hypotheses about ligand-receptor interactions.

The use of DOCK to optimize leads has been more problematic. The two major difficulties are obtaining the proper ligand

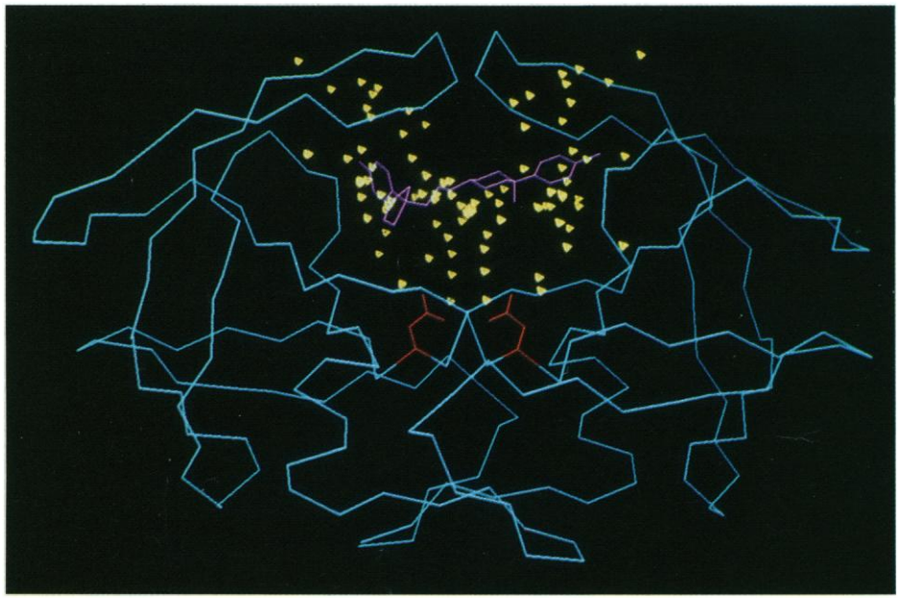

Fig. 2. New structure of HIV-protease (cyan), complexed with a nonpeptide protease inhibitor, UCSF8 (magenta) (*120*). The negative image of the enzyme active site created by DOCK is shown in yellow. At the bottom of the figure, in red, are the active aspartic acids.

Table 3. Examples of available computer programs (*44*).

Structure-activity relationships	(*38, 98–100*)
Graphics	
Interactive graphics	(*101*)
Molecular surfaces	(*102*)
Volume rendering	(*103*)
Molecular calculations	
Quantum mechanics	(*104*)
Conformation generation	
Systematic	(*105–107*)
Heuristic	(*52*)
Distance geometry	(*108*)
Molecular mechanics	(*109, 110*)
Molecular dynamics	(*111*)
Free energy perturbation	(*64, 65*)
Docking	(*45, 112–117*)
Similarity	(*118, 119*)

Table 4. DOCK leads developed at the University of California, San Francisco.

System	Affinities		Reference
	1st lead	2nd generation	
HIV protease	100 μM	5 μM	(*54, 120*)
B-form DNA	10 μM		(*49*)
RNase H	500 μM		(*121*)
Thymidylate synthase	900 μM	3 μM	(*56*)
Hemagglutinin	100 μM	5 μM	(*50*)
CD4-gp120*	5 μM		(*122*)
Malaria protease†	10 μM		(*123*)

*Developed in collaboration with Procept, Inc., Cambridge, Massachusetts. †Structure obtained from homology model-building.

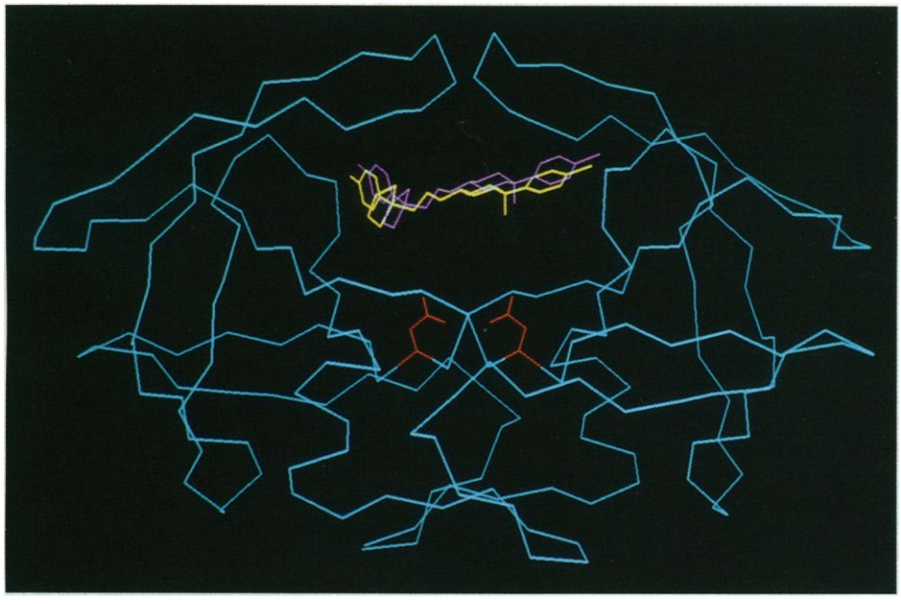

Fig. 3. Observed position (magenta) (*120*) and calculated position (yellow) (*124*) of UCSF 8 with the intermolecular force field scoring procedure (*47*).

conformation and discriminating among several proposed interaction modes of similar energy (*47, 51*). Many assumptions are required to scan large databases in a reasonable amount of time. These include: rigid ligands and rigid receptors, neglect of bound water molecules and counterions, and simplified evaluations of interaction energies. Some of these limitations are being removed as computational power increases. In recent work, with improved force fields and an experimental ligand conformation, the highest scoring orientations produced by DOCK correspond to the crystallographic binding mode within 1 to 2 Å (Fig. 3). In a project to design thymidylate synthase inhibitors, we have proceeded rapidly to affinities of 3 to 5 μM by combining the consensus results from DOCK with crystal structures of a weak inhibitor and a similarity search of the FCD with MACCS software (Molecular Design Limited, San Leandro, California) (*56, 57*).

In sum, DOCK works well as a computer screening procedure for generating leads. To improve the program, we are examining ways to search the conformational space of ligands (*58*) and to correct for desolvation of the ligand and receptor surfaces on binding (*59, 60*). We are also developing a program for interactive docking and design (*61*) and a program to focus on the subtle structural and chemical differences among closely related enzymes (*62*). Docking methods are being explored in several other laboratories (Table 3).

Prediction of accurate free energies of interaction and accurate binding geometries remains an important goal for all structure-based efforts. A promising technique is the free energy perturbation calculation. Surprisingly accurate free energy differences (with 1 to 2 kcal/mol) can be obtained in favorable cases (*63–65*). The method can also include the effects of desolvation. The difficulties with this approach are similar to those described above—it requires good sampling of the conformational and configurational states available to both ligand and receptor. For any computational method, relative accuracies within 1 kcal/mol are required if one seeks quantitative predictions of binding affinities for a series of related compounds. Experiment plays a decisive role in calibrating such efforts.

Response Time of the Drug Design Cycle

The AIDS epidemic and the spread of drug-resistant bacteria illustrate the continued danger posed by infectious diseases. What can be done to shorten the response time of the drug development system? Because the process involves a series of steps, each of approximately the same duration (Table 1), fundamental improvements are needed at every level. Lead discovery can certainly proceed more rapidly with a combination of computer screening, high-volume assays, and more rapid structural determinations. Computer programs can now examine substantial databases in a few days. With improved hardware, 3-D searches of the entire Chemical Abstracts Registry would be feasible. In selected cases, quantitative estimates of binding constants are now on the scientific horizon. The next generation of computers should make such calculations applicable to a wider range of problems. Technical advances continue in the realm of structure determination. High-speed area detectors and the use of synchrotron sources mean that new structures can be completed in a week, and that a turnaround of a structure per day can sometimes be achieved. The least controlled step in crystallography is the growth of crystals. This remains unpredictable and is a serious bottleneck for structure determination for membrane-bound proteins.

Lead optimization and the development of active analogs can move more rapidly in the future if it is possible to adapt the modular chemistry approach that has been so successful in peptide and oligonucleotide synthesis to a wider range of compounds. It should be possible to exploit a core of thoroughly researched general reactions for organic synthesis. It is also crucial to improve toxicological assays by increasing reliance on specially adapted bacterial systems, cell culture, and the use of transgenic animals. Most of the time and money required to develop a drug is spent at the end of the development cycle. The loss of a promising candidate during clinical trials is an expensive and disheartening event. Any procedure that can detect serious obstacles at an early stage is much to be desired.

The immense efforts to find anti-AIDS drugs and to provide effective agents for drug-resistant microorganisms will test the various strategies of drug development. The only drugs useful for HIV available through 1991 were generated by screening known pharmaceuticals. However, several HIV protease inhibitors are moving through clinical trials. These were developed with the substrate-based approach outlined earlier. Nonpeptide inhibitors derived from structure-based efforts are also being reported (*54*). The status of the structure determinations for a number of AIDS-related macromolecules is summarized in Table 2A.

Of specific interest in this issue are the prospects for countering the drug-resistant mechanisms of prokaryotes. The fundamental routes for evasion include enzymatic degradation of drugs, mutation of bacterial target proteins, changes in membrane permeability, and overproduction of key enzymes. Each of these can be attacked through structural efforts. Some targets for bacterial systems are given in Table 2B. The most straightforward efforts involve enzymes such as the β-lactamases or differential inhibition of enzymes on the folate pathway. Other exciting targets deal with drug transport mechanisms (*66, 67*).

Future Prospects

Looking ahead, areas for new work include antiviral, antifungal, and antiparasitic drugs and the problems of general drug resistance

in eukaryotes. Each of these areas has important targets for structure-based design, for example: the viral coating-uncoating phenomena (68), the mating factor systems in yeast, specific enzymes in parasitic organisms (23, 69), and the multidrug-resistance apparatus in human cells (70). There are encouraging signs that structure-based collaborative projects can have a large impact on these important problems.

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