Review Article

Computational Approaches for Drug Design and Discovery: An Overview

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ABSTRACT

The process of drug discovery is very complex and requires an interdisciplinary effort to design effective and commercially feasible drugs. The objective of drug design is to find a chemical compound that can fit to a specific cavity on a protein target both geometrically and chemically. After passing the animal tests and human clinical trials, this compound becomes a drug available to patients. The conventional drug design methods include random screening of chemicals found in nature or synthesized in laboratories. The problems with this method are long design cycle and high cost. Modern approach including structure-based drug design with the help of informatic technologies and computational methods has speeded up the drug discovery process in an efficient manner. Remarkable progress has been made during the past five years in almost all the areas concerned with drug design and discovery. An improved generation of softwares with easy operation and superior computational tools to generate chemically stable and worthy compounds with refinement capability has been developed. These tools can tap into cheminformation to shorten the cycle of drug discovery, and thus make drug discovery more cost-effective. A complete overview of drug discovery process with comparison of conventional approaches of drug discovery is discussed here. Special emphasis is given on computational approaches for drug discovery along with salient features and applications of the softwares used in *de novo* drug designing.

Introduction

Under the US law, a drug is any substance (other than a food or device), which is used in the diagnosis, cure, relief, treatment or prevention of disease, or intended to affect the structure or function of the body. This comprehensive definition is important for legal purposes, but simply a drug can be defined as any chemical that affects the body and its processes. The development of any potential drug begins with years of scientific study to determine the biochemistry behind a disease, for which pharmaceutical intervention is possible. The result is the determination of specific receptors (targets) that must be modulated to alter their activity by some means. After target identification, the goal then is to find compounds that interact with the receptor by mass screening (lead). From this point onward, a cycle of iterative refinement and testing continues until a drug is developed that undergoes clinical trials. The techniques used to refine drugs are combinatorial and structure-based design. After successful clinical phase, the drug is subjected to approval by regulatory authorities and then marketed. The modern-day drug discovery pipeline is shown in Figure 1.

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Factors affecting drug discovery

There are a number of factors that affect the drug discovery and development process. Important ones are as follows:

Medicinal objective: In general, more precise the medicinal objective, the less likely it is to develop a new drug; for example, it is easy to develop an antacid but much more difficult is to develop specific proton-pump inhibitor. Thus, the medicinal requirements affect the likelihood of success or failure in new drug discovery.

Ability of Medicinal chemist: The attributes of the chemist will influence the outcome of evolving new drugs on the basis of knowledge of chemistry of lead molecule and biology of diseased state.

Screening facilities: A successful and rapid mass screening mainly depends on the capacity to evaluate a large number of compounds and detect potentially clinically useful drugs in a very short span of time.

Drug development facility: Good facilities with interdisciplinary efforts by chemistry, biology, pharmacy and medical groups are necessary for drug development.

Cost of new drug: The following three factors affect the cost of drug development-

(i) *Number of compounds synthesized*: Of the about 5000-10,000 compounds studied, only one drug reaches the market.
(ii) *Nature of the lead molecule*: Cost of production will be high if the lead molecule is prepared by an expensive route.
(iii) *Standards required for new drugs*: The standards required by

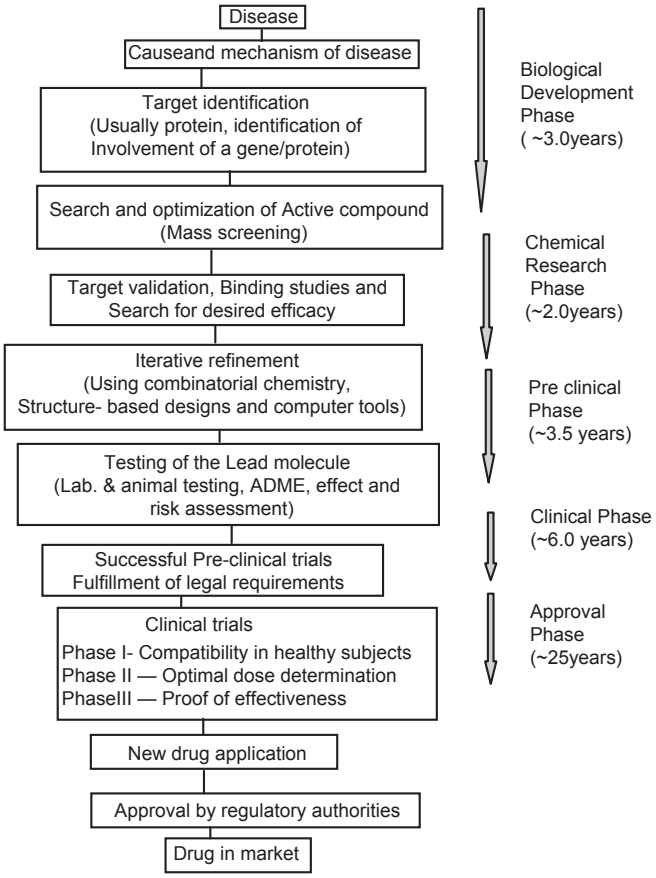

Figure 1: Different phases of drug discovery process

regulatory authorities prior to release of a drug into the market have increased dramatically. In the discovery phase, each drug cost about $350 million. The Food and Drug Association processes I, II and III cost another $150 million. This brings the total to about $500 million for each drug put on to the market for consumers.

Due to these factors, the process of drug discovery is undergoing a complete overhaul to be cost-effective and to meet the supply and demand fundamentals.

Approaches for drug discovery

Evidence of the use of medicines and drugs can be found as far back in time as 3100 BC. The current scenario of development of new drugs needs no emphasis in light of the current global situation of health and disease. For the majority of time, drug discovery has been a trial-and-error process. Conventionally, the process of drug development has revolved around an almost blind screening approach, which was very time-consuming and laborious. The disadvantages of conventional drug discovery as well as the allure of a more deterministic approach to combat disease have led to the concept of "Rational drug design" in the 1960's. New understanding of the quantitative relationship between structure and biological activity ushered in the beginning of computer-aided drug design (CADD). A comparison of conventional and modern drug discovery approach is given in Table 1. With the introduction of integration and knowledge management solutions with the help of computers, a new era is beginning in drug discovery. The development cost will be cut by almost a third. The development times are reduced from 10-16 years to only 6-8 years.

How to design a drug?

At the onset, it is important to know what features an "ideal" drug should have. The drug

i) must be safe and effective
ii) should be well absorbed orally and bioavailable
iii) metabolically stable and with a long half-life
iv) nontoxic with minimal or no side effects
v) should have selective distribution to target tissues

Now a days, after knowing the detail information of the target and lead molecule, a drug is designed with the help of computer tools. This can potentially save pharmaceutical companies, government and academic laboratories alike from pursuing the "wrong" leads. Design process of a drug is given in Figure 2.

Structure-based drug design

Structure-based drug design (SBDD) is considered as one of the most innovative and powerful approaches in drug design. SBDD is an iterative approach. It requires three-dimensional (3D) structure of the target protein, preferentially complexed with a ligand, where binding mode, affinity and confirmation of a ligand binding can be discerned. Subsequently, various methods are used to design a high-affinity inhibitor either via virtual computer screening of large compound libraries or through design and synthesis of novel ligands. Designed compounds are then tested in appropriate assays and the information is further used to guide the SBDD. Recent advances in computational methods for lead discovery include various commercially available softwares for *de novo* drug design, iterative design, selectivity discrimination, and estimation of ligand-binding affinities.

SBDD and emergence of structural genomics are paving the way to develop designer drugs. Two approaches to SBDD, the docking of known compounds into a target protein and *de novo* drug design has been merging as a single robust and powerful tool. In addition, dynamics simulation of multiple copies of molecular building blocks

Table 1: Comparison of conventional and modern drug discovery approach

Parameter	Conventional approach	Modern approach
Process	Trial and error	More logical
Basis	Blind screening	Specific and target based
Execution of steps involved	Sequential	Parallel
Disciplines involved	May be incompatible	Compatible
Cost of drug development	Very high	About one-third
Drug development time	~10-16 years	~6-8 years
Interdisciplines of drug development	Strictly separate	Coordinated
Transparency of process	Less	More
Management of process	Difficult	Easy
Redundancy	Exists	Can be avoided
Communication between disciplines	Complicated	Uncomplicated

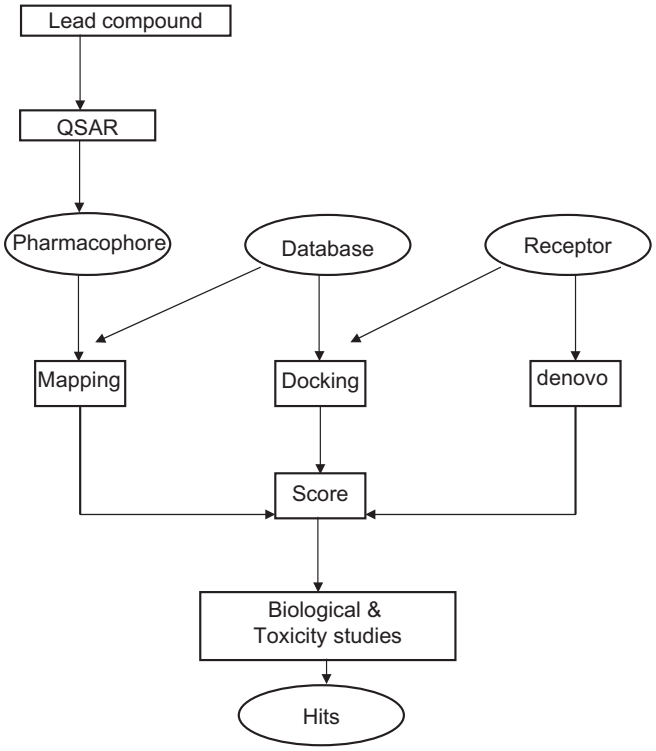

Figure 2: Schematic representation of drug design with the help of computer tools

in the presence of a receptor molecule is also a useful strategy for drug design, In the future, SBDD will merge with high throughput and informatic technologies such as bioinformatics to design drugs with multiple homologous targets simultaneously.

Dynamic combinatorial chemistry is a recently introduced supramolecular approach that uses self-assembly processes to generate libraries of chemical compounds. In contrast to the stepwise methodology of classical combinatorial techniques, dynamic combinatorial chemistry allows for the generation of libraries based on the continuous interconversion between the library constituents. Spontaneous assembly of the building blocks through reversible chemical reactions virtually encompasses all possible combinations, and allows the establishment of adaptive processes owing to the dynamic interchange of the library constituents. Addition of the target ligand or receptor creates a driving force that favors the formation of the best-binding constituent– a self-screening process that is capable, in principle, of accelerating the identification of lead compounds for drug discovery.

Drug design based on bioinformatics tools

The processes of designing a new drug using bioinformatics tools have opened a new area of research. However, computational techniques assist one in searching drug target and designing drug *in silico*, but it is time-consuming and expensive. Bioinformatics tools can provide information about potential targets that include nucleotide and protein sequencing information, homologs, mapping information, gene and protein expression data, function prediction, pathway information, disease associations, variants, structural information and taxonomic distribution among others. This means that time, effort and money can be saved in characterization of different targets. The field of bioinformatics has become a major part of the drug discovery pipeline, playing a key role for validating drug targets. By integrating data from many inter-related yet heterogeneous resources, bioinformatics can help in our understanding of complex biological processes and help improve drug discovery.

Computer-aded drug design

Role of computers

Computational tools have become increasingly important in drug discovery and design processes. Methods from computational chemistry are used routinely to study drug-receptor complexes in atomic detail and to calculate properties of small-molecule drug candidates. Tools from information sciences and statistics are increasingly essential to organize and manage the huge chemical and biological activity databases that all pharmaceutical companies now possess, and to make optimal use of these databases.

In addition, the act of generating chemical derivatives is highly amenable to computerized automation. Libraries of derivative compounds are assembled by application of targeted structure-based combinatorial chemistry from the analysis of active sites. Because of the combinatorial nature of this method, a large number of candidate structures may be possible. A computer can rapidly generate and predict the binding of all potential derivatives, creating a list of best potential candidates. In essence, computer filters all weak binding compounds, allowing the chemist to focus, synthesize, and test only the most promising ligands. Thus, using the CADD software to aid in the refinement of lead molecules is the most effective manner in which these tools can be employed. The use of computer modeling to refine structures has become standard practice in modern drug design.

So the current role of computer in drug design lies in:

a) Storing and retrieving information
   i) Structures determined experimentally by X-ray cryst allography for biological targets (enzymes) and drug molecules
   ii) Molecules and activities to test the affect of small structural changes on biological activity
b) Information about toxicity and its relationship to structure
c) Visualization of molecules
   i) Similarities/differences between drugs and receptors
   ii) Interaction between drugs and receptors
d) Calculations
   i) Interaction strengths
   ii) Motion (dynamics)

Challenges in computer-aided drug design

Highly intellectual professionals with interdisciplinary knowledge of various facets of science, most importantly, biology, chemistry and computation are required for CADD and this is a major challenge for this field. In scientific computing, accuracy and processing time are always important. Thus, in order to make the calculations in a finite period of time, a plethora of assumptions, significant approximations, and numerous algorithmic shortcuts has to be used. This, in turn, greatly diminishes the calculated accuracy of any ligand receptor interaction. This remains the most significant challenge in CADD. Another problem is generation of a vast number of undesired

chemical structures as there are a nearly infinite number of potential combinations of atoms and most of them are either chemically unstable, synthetically unfeasible or have higher toxicity.

Keeping in mind these shortcomings of CADD, improved generation of softwares with more user-friendly programs, superior and fast computational facilities, and creation of synthetic feasible and stable chemical compounds and with refinement feature has been developed in the last decade.

Drug design softwares

General approach

The development of a new drug starts with the design of suitable candidate compounds, so-called "Ligands," which are selected on the basis of how these compounds are recognized by the target protein and binds to it. "Ligbuild" is a powerful tool to build a legend just based on a protein structure in Brookheaven format. Performing experiments to know protein dynamics is expensive as well as time-consuming. The only alternative, computer simulation of the dynamics of molecule (MD simulation), becoming increasingly important to identify which molecular properties are important and what are the molecular interactions responsible for binding. Evaluation of binding agent is done by scoring approach. "Score" is a tool to evaluate the binding affinity of protein-ligand complex with known 3D structure. Candidate molecules are further screened out on several criteria. Permeability across the biomembrane is an important characteristic. XLOGP can calculate logP (logarithm of the partition coefficient of a solute between octanol and water) of the common organic compounds, Furthermore, XLOGP can provide detailed hydrophobicity distribution information of the molecule. PLOGP can calculate log*P* values of peptides along with Molecular Lipophilicity Potential (MLP) profile of a protein with known structure. A database-based predictive system is also developed to assess the risk and toxicity of the chemicals in the early stage of drug design.

The activity prediction studies on the basis of shape of the molecule include

i) Fast and efficient clustering of molecules based on molecular shape
ii) Field-based similarity computation of molecular structure
iii) Flexible Quantitative Structure Activity Relationships (QSAR) analysis of molecules based on shape cluster

Comparative Molecular Field Analysis (CoMFA) has been widely used as a type of 3D QSAR method during the last 10 years.

Rational programs used

Drug design programs fall in one of three main categories: scanners, builders, or hybrids.

Scanners-These types of programs are used for screening of lead compounds. All database search programs fall into this category.

Strengths

i) Complete control of user on query specifications
ii) Established synthetic feasibility of compounds tested
iii) Rapid determination of potential binding ligands
iv) No scoring function required

Weaknesses:

i) Requirement of a wide database of structures
ii) Diversity of potential hits is limited as there is no recombination or derivatization of retrieved structures

Builders and Hybrids-These programs are mainly used for *de novo* generation of lead compounds. In these, database contains fragments or chemical building blocks instead of complete compounds and requires the attachment point of the weak binding protein. It creates a population of derivatives with improved receptor complementarity by recombination or derivatization from fragments by making incremental changes iteratively.

Strengths

i) No database of structures required
ii) Offers a vast number of potential derivative structures
iii) Creates truly novel ligands

Weaknesses

i) Questionable synthetic feasibility of compounds
ii) Generation of chemically unstable structures
iii) Depends mainly on ability of developer

Software used

Some of the frequently used software for drug design and their salient features are as follows:

Affinity

- Automated, flexible docking
- Uses the energy of the ligand/receptor complex to automatically find the best binding modes of the ligand to the receptor (energy-driven method)

AutoDock (Automated Docking of Flexible Ligands to Receptors)

- It consists of three separate programs:
  AutoDock performs the docking of the ligand to a set of grids describing the target protein
  AutoGrid precalculates these grids
  AutoTors sets up which bonds will be treated as rotatable in the ligand
- Provide an automated procedure for predicting the interaction of ligands with biomolecular targets and help to narrow the conformational possibilities and in identification of the most suitable structure
- Uses a Monte Carlo (MC) simulated annealing (SA) technique for configurational exploration with a rapid energy evaluation using grid-based molecular affinity potentials
- A powerful approach to the problem of docking a flexible substrate into the binding site of a static protein
- It has application in X-ray crystallography, SBDD, lead optimization, virtual screening, combinatorial library design, protein-protein docking and chemical mechanism studies

Combibuild

- Structure-based drug design program created to aid the design of combinatorial libraries
- Screens a library possible reactants on the computer, and predicts which ones will be the most potent
- Successfully applied to find nanomolar inhibitors of Cathepsin D

DockVision

- A docking package created by scientists for scientists by including Monte Carlo, Genetic Algorithm and database screening docking algorithms

FRED

- Accurate and extremely fast, multiconformer docking program
- Examines all possible poses within a protein active site, filtering

for shape complementarity and optional pharmacaphoric features before scoring with more conventional functions

FlexiDock

- Simple, flexible docking of ligands into binding sites on proteins
- Fast genetic algorithm for generation of configurations
- Rigid, partially flexible, or fully flexible receptor side chains provide optimal control of ligand binding characteristics
- Conformationally flexible ligands
- Tunable energy evaluation function with special H-bond treatment
- Very fast run times

FlexX

- Fast computer program for predicting protein-ligand interactions
- Two main applications:
  Complex prediction (create and rank a series of possible protein-ligand complexes)
  Virtual screening (selecting a set of compounds for experimental testing)
- Conformational flexibility of the ligand; rigid protein
- Placement algorithm based on the interactions occurring between the molecules (limited to low-energy structures)
- MIMUMBA torsion angle database used for the creation of conformers; interaction geometry database used to exactly describe intermolecular interaction patterns
- Boehm function (with minor adaptations necessary for docking) applied for scoring

Glide

- High-throughput ligand-receptor docking for fast library screening
- Fast and accurate docking program
- Identifies the best binding mode through Monte Carlo sampling
- Provides an accurate scoring function for ranking of binding affinities
- Can enrich the fraction of suitable lead candidates in a chemical database-by predicting binding affinity rapidly and with a reasonable level of accuracy-will greatly enhance the probability of success in a drug discovery program

Gold

- Calculates docking modes of small molecules into protein binding sites
- Based on genetic algorithm for protein-ligand docking
- Studies full ligand and partial protein flexibility
- Predicts energy functions partly based on conformational and non-bonded contact information from the CSD
- Choice of scoring functions: GoldScore, ChemScore and User defined score
- Has virtual library screening

Hint

- Hydropathic Interactions
- Empirical molecular modeling system with new methods for *de novo* drug design and protein or nucleic acid structural analysis
- Translates the well-developed Medicinal Chemistry and QSAR formalism of LogP and hydrophobicity into a free energy interaction model for all biomolecular systems based on the experimental data from solvent partitioning
- Calculates 3D hydropathy fields and 3D hydropathic interaction maps
- Estimates LogP for modeled molecules or data files
- Numerically and graphically evaluates binding of drugs or inhibitors into protein structures and scores DOCK orientations
- Constructs hydropathic (LOCK and KEY) complementarity maps (can be used to predict an ideal substrate from a known receptor or protein structure or to propose the hydropathic structure from known agonists or antagonists)
- Evaluates/predicts effects of site-directed mutagenesis on protein structure and stability

Ligplot

- Program for automatically plotting protein-ligand interactions
- Generates schematic diagrams of protein-ligand interactions for a given PDB file
- Interactions shown are those mediated by hydrogen bonds (dashed lines between the atoms involved) and by hydrophobic contacts (represented by an arc with spokes radiating toward the ligand atoms they contact)

Situs

- Program package for modeling of atomic resolution structures into low-resolution density maps
- Software supports both rigid-body and flexible docking using a variety of fitting strategies

Vega

- Calculates ligand-receptor interaction energy

Dock

- Generates many possible orientations (and more recently, conformations) of a putative ligand within a user-selected region of a receptor structure
- Orientations may be scored using several schemes designed to measure steric and/or chemical complementarity of the receptor-ligand complex
- Evaluates likely orientations of a single ligand, or to rank molecules from a database
- Searches databases for DNA-binding compounds
- Examines possible binding orientations of protein-protein and protein-DNA complexes
- Designs combinatorial libraries

Icm-Dock

- Provides access to the chemical information and a unique set of tools for accurate ligand-protein docking, peptide-protein docking and protein-protein docking
- Functions:
  Automatic preparation of a molecule for a flexible docking
  Automatic identification of rotatable bonds
  Procedure for protein-protein and peptide-receptor docking
  2D representations and automatic 2D to 3D conversion
  Refinement of docking solutions
  Assessment of fast grid potential and partial charges

GRAMM (Global RAnge Molecular Matching)

- Empirical approach to smoothing the intermolecular energy functions by changing the range of the atom-atom potentials
- Performs an exhaustive six-dimensional search through the relative translations and rotations of the molecules
- Used for protein-protein and protein-ligand docking

Bielefeld Protein Docking

- Detects geometrical and chemical complementarities between surfaces of proteins and estimates docking positions

Bigger

- Biomolecular complex Generation with Global Evaluation and Ranking

- Efficient protein-docking algorithm
- Predicts the structure of binary protein complexes from the unbound structures
- Search the complete binding space and select a set of candidate complexes
- Evaluates and rank each candidate according to the estimated probability of being an accurate model of the native complex
- Intergrated in CHEMERA, a molecular graphics and modeling program for studying protein structures and interactions

ClusPro

- Integrated approach to protein-protein docking
- Docking algorithm includes the following steps:
  Rigid body docking based on the Fourier correlation approach (used DOT and ZDOCK docking programs)
  Selection of structures with favorable desolvation and electrostatic properties
  Clustering the retained complexes using a pairwise RMSD criterion
- Refinement of the 25 largest clusters by the flexible docking algorithm SmoothDock

Ludi

- Fits molecules into the active site of a receptor by matching complementary polar and hydrophobic groups
- Suggests modifications to increase the binding affinity of ligand
- Suggests a ligand candidate by inference from a set of active analogs
- Uses Scoring function to prioritize the hits

Ludi/CAP

- Ensures synthetic feasibility of compounds proposed by Ludi
- Has 3D Ludi library prepared from two databases of compounds available for purchase (CAP) and commercially available compounds
- Calculates molecular interaction sites on a receptor to search suitable ligands
- Offers ease and speed in testing working models and hypotheses
- Eliminates redundant hits
- Saves time and money in drug design

Dot

- Daughter Of TURNIP
- Used for computation of the electrostatic potential energy between two proteins or other charged molecules

Haddock

- High-Ambiguity Driven protein-protein Docking
- Generates biochemical and/or biophysical interaction data such as chemical shift perturbation data resulting from nuclear magnetic resonance titration experiments or mutagenesis data introduced as *ambiguous interaction restraints* to drive the docking process

Hex

- Protein docking and molecular superposition program
- Uses spherical polar Fourier correlations to accelerate docking calculations

Rachel

- Real-Time Automated Combinatorial Heuristic Enhancement of Lead compounds
- Builder-type drug-refinement program
- Designed to optimize weak binding lead compounds in an automated, combinatorial fashion
- Incorporates a *heuristic active site mapping algorithm* to determine the optimal chemical characteristics of the receptor
- Has a massive *diversity index* for search of compounds
- Can cross-reference other database components by chemical composition
- Component specification language permits the removal of undesired structures
- Allows the user to easily generate focused scoring functions to estimate ligand binding to a specific target receptor

Conclusions

The development of new drugs with potential therapeutic applications is one of the most complex and difficult process in the pharmaceutical industry. Millions of dollars and man-hours are devoted to the discovery of new therapeutic agents. As the activity of a drug is the result of a multitude of factors such as bioavailability, toxicity and metabolism, rational drug design has been utopias for centuries. Very recently, impressive technological advances in areas such as structural characterization of biomacromolecules, computer sciences and molecular biology have made rational drug design feasible. CADD is no longer merely a promising technique. It is a practical and realistic way of helping the medicinal chemist. On its own it is unlikely to lead to pharmaceutical novelties but it has become a significant tool, an aid to thought and a guide to synthesis. Still, drugs that are synthesized and tested by the computational techniques, can contribute a clear molecular rationale and above all provide a spur to the imagination.

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