Automated lead discovery

The automatic generation of new lead compounds by using computer-controlled, iterative robotic synthesis and analysis of chemical libraries is the subject of a new US patent (no. 5,463,564) granted to 3-Dimensional Pharmaceuticals, Inc. of Exton, PA, USA. The company has termed the new technology DirectedDiversity™.

The new technology is a computer-driven, iterative process of generating chemical compounds with a prescribed set of physical and/or biological properties. According to Dr F. Raymond Salemme, President and CEO of the Company, "the technology controls the process of discovering chemical compounds in much the same way that a computer's operating system controls the computer".

The first step in the process is the generation of a synthetically manageable chemical template with the desired physical, biological and/or synthetic properties. Then the template is exploded into a "virtual chemical library" by accessing the potential chemical reaction of the template with the 145,000 commercially available chemicals in the *Available Chemical Directory*. The virtual library is then computationally screened by the computer program and ranked by the ability of each compound to fit the target receptor and the desired physical properties. Based upon this ranking, a set of compounds are synthesized and tested in the bioassay followed by iterations of additional synthesis and testing.

During each iteration, a chemical library is robotically synthesized, the compounds are evaluated in a bioassay, and the structure and activity of individual molecules in the library are analyzed to determine how closely they match the desired set of properties. A database records all observed structural data and activity for each compound and generates a structure–activity model. Using the information generated during each cycle of iteration, the computer program designs the synthesis of the next set of compounds. The process continues through multiple steps until a new drug lead with the desired properties has been generated.

"We believe that the DirectedDiversity™ technology has the potential to have a profound effect on the future of drug discovery," said Salemme. "Our process captures and uses vast amounts of information to develop libraries of novel, small molecule drugs by selectively combining a particular set of chemical building blocks. DirectedDiversity™ is an operating system that is capable of harnessing the potential of combinatorial chemistry."

According to company spokesperson Jerry Parrott, the new technology has already been used to discover novel thrombin inhibitors and is being used to generate new lead compounds for cardiovascular disease, cancer and autoimmune diseases. 3-Dimensional Pharmaceuticals hopes to license the new technology to major pharmaceutical companies.

Robert W. Wallace

Book review

Cancer Chemotherapeutic Agents edited by W.O. Foye, American Chemical Society, 1995. US$149.95 (xx + 698 pages) ISBN 0 8412 2920 1

Thirty-six authors have contributed to an overview text on cancer chemotherapeutic agents that is remarkably thorough and up-to-date. The intention of the text is to describe in detail the prominent and determinant role that chemistry has played in the discovery and development of current and promising new antitumor agents. Although a complete or comprehensive coverage of cancer chemotherapeutic agents is beyond the scope of any single volume, this book succeeds in including the major classes of antitumor agents, essentially all clinically useful drugs, and many of the more promising candidates.

It is inspirational to read the succinct and accurate accounts of the efforts that were responsible for the clinical introduction of many of the agents, the time that elapsed between discovery of a lead and the clinical introduction of a drug, and the role that chemistry played in shaping that success.

Seventeen chapters cover the breadth of cancer chemotherapeutic agents. Remarkably, not only are the history, biological properties, clinical activity, current status, mechanism of action, metabolism, resistance, new directions and potential limitations of the agents presented, but even the highlights of many of the natural products total syntheses are covered.

The text is a pleasure to read and it is destined to become an indispensable aid to those working in the field and a primary resource of information to those unfamiliar with the area. All libraries and most medicinal chemists will want their own copy of this text.

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