

CombiLibMaker™

GENERATE VIRTUAL COMBINATORIAL LIBRARIES



Combinatorial chemistry makes it theoretically possible to synthesize massive compound libraries. Because of the resources required, only a subset of all possible products from any given reaction can be synthesized and screened. Virtual combinatorial libraries are increasingly used to decide which compounds will be made or tested.^{1,2} CombiLibMaker creates these libraries and works with DiverseSolutions® or Selector™ for the design of diverse or focused libraries.

Applications

- Generate and name combinatorial products for registration in a corporate database
- Create combinatorial libraries for virtual high-throughput screening
- Build virtual products around lead compounds
- Enumerate candidates to select a subset for synthesis
- Enable diverse and focused library design

CombiLibMaker has two different modes of operation. The first mode corresponds to the perspective of combinatorial chemists and the second to that of traditional medicinal chemists.

In the first mode, reactants are combined to generate products. For each reactant type, a list of reactant molecules is required. This list could be a UNITY® hitlist resulting from a database search. Members of each list are reacted with members of every other list to form products in a combinatorial fashion. This mode is ideal for generating virtual libraries analogous to those produced in a combinatorial chemistry laboratory.

The second mode creates products by attaching side chains to specified sites on a core structure. Side chain groups can be selected from those provided by CombiLibMaker or imported from other sources. CombiLibMaker generates products for all permutations of the side chains at all

attachment sites on the core, excluding those permutations specified by the user.

This mode is appropriate for generating small libraries of analogs by strategic substitutions on a known lead compound.

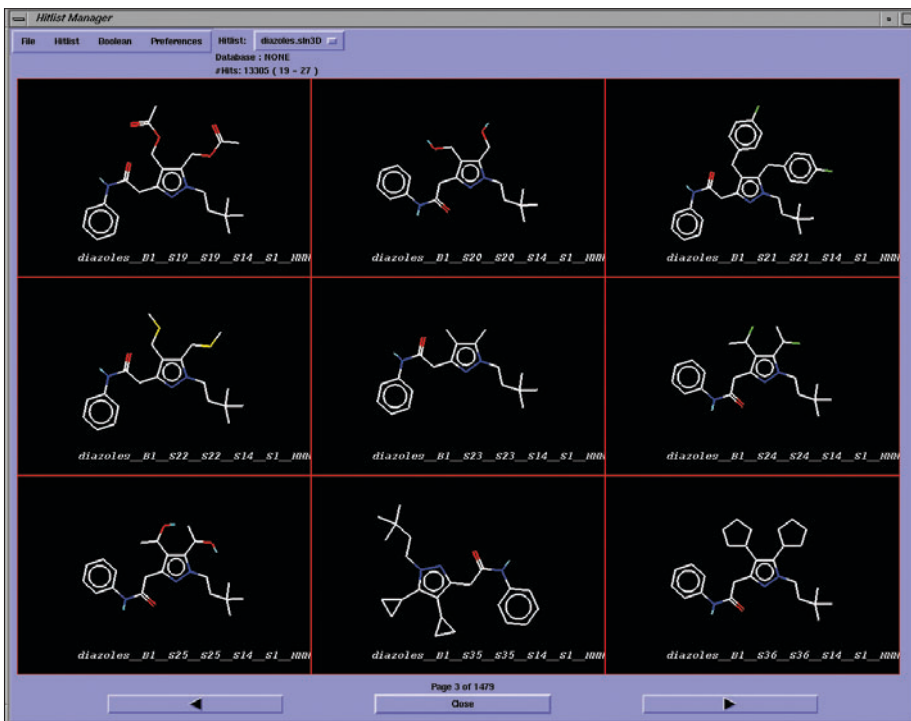
In either mode of operation, CombiLibMaker can suppress generation of products that fail user-specified filters such as molecular weight. Informative product names are created automatically, and reflect stereochemistry as well as specific reagents or side chains used in a product's formation.

With the CombiLibMaker 3D option, high quality 3D structures are generated using a

version of Concord® optimized for rapid library generation. CombiLibMaker can produce 3D structures that are core-aligned to simplify the prediction of activity by 3D QSAR methods such as CoMFA®, or to speed the docking and scoring of combinatorial products in virtual high-throughput screening.

Advantages

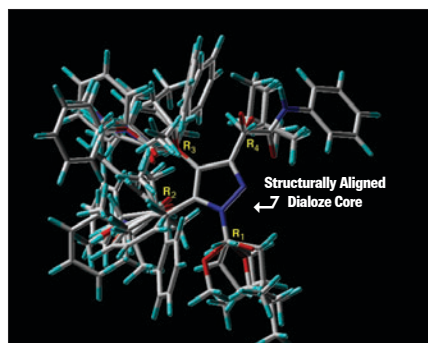
- CombiLibMaker builds 2D and 3D combinatorial libraries based on all types of chemistry, including dimerization and the formation of cyclic or bridged products.



Part of a virtual library of diazoles generated by CombiLibMaker in UNITY 3D hitlist format.

Features

- Reads and writes all common 2D and 3D file formats, including SDfiles, SMILES, SLN, cSLN, multi-MOL2, and UNITY hitlists and databases
- Step-by-step graphical interface arranged in a logical order that is intuitive to chemists
- Session files can be modified and reused
- Reactant cores can be equivalenced for dimerization-type reactions
- Side chain attachment points can be equivalenced to enable identical substitution at two or more sites
- Preview library and modify reaction definitions prior to enumeration
- Supports multi-product reactions



Diazoles generated by CombiLibMaker in UNITY 3D hitlist format with product cores aligned.

- 3D products can be output in core-aligned orientation to enable 3D-based approaches to virtual high-throughput screening, such as 3D searching with UNITY, 3D QSAR with CoMFA, and 3D docking with FlexX™.
- Reactant molecule lists can be edited manually or by using powerful, automated substructure searching capabilities.
- CombiLibMaker creates a session directory that stores all relevant information for later modification and reuse. Libraries can also be output in a compact format to reduce storage requirements, and enumerated when needed.
- Reactant molecules containing more than one occurrence of the reactant core can be automatically excluded to ensure one product per well.
- R-groups that are not preserved in the product, such as protecting groups, can be deleted automatically by CombiLibMaker, to avoid the need for manual clipping.
- Users control the extent to which reactant stereochemistry is preserved in products.
- CombiLibMaker works efficiently with DiverseSolutions for the design of diverse or focused combinatorial libraries that use complete synthetic arrays, minimizing the number of reactants required.

Complementary Software

- **ClogP/CMR** for including molar refractivity and logP in QSAR and ADME models.
- **Concord** for generating accurate 3D coordinates.
- **DiverseSolutions** for designing, comparing, or selecting compound libraries.
- **FlexX** for flexibly docking ligands into a binding site.
- **Legion™** for constructing virtual compound libraries.
- **OptDesign®** for designing and editing combinatorial libraries.
- **QSAR with CoMFA** for building predictive structure-activity and structure-property models.
- **Selector** for characterizing and sampling compound libraries.
- **StereoPlex®** for expanding the stereochemical diversity of a database.
- **UNITY** for locating compounds in databases that match a pharmacophore or fit a receptor site.

Hardware and Software Requirements

CombiLibMaker is accessible through the SYBYL® expert molecular modeling environment and requires a separate license. SYBYL and CombiLibMaker run on workstations operating under IRIX® (SGI®) or Linux® (x86). Additional CombiLibMaker licenses include CombiLibMaker3D for generating core-aligned 3D structures and PowerCombiLibMaker for parallel and distributed processing of 3D structures.

References

1. Cramer, R.D.; Patterson, D.E.; Clark, R.D.; Soltanshahi, F.; Lawless, M.S. "Virtual Compound Libraries: A New Approach To Decision Making In Molecular Discovery Research." *J. Chem. Inf. Comp. Sci.* **1998**, *33*, 1010.
2. Pearlman, R.S.; Smith, K.M. "Novel Software Tools For Chemical Diversity." *Perspectives In Drug Discovery and Design* **1998**, *9/10/11*, 339.



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