

DISCOtech™

AUTOMATICALLY ELUCIDATE PHARMACOPHORE MODELS
USING PRECALCULATED CONFORMERS



In the absence of a receptor structure, the identification or optimization of a lead depends on discovering the pharmacophore – the shared molecular features and their spatial relationship essential for biological activity. Starting from a set of precomputed conformers for a set of ligands, DISCOtech uses clique detection¹ methods to generate multiple pharmacophore hypotheses that can be compared and refined.

Applications

- Generate and refine pharmacophore hypotheses for a set of ligands that bind to the same receptor
- Build pharmacophore queries for use in 3D database searches
- Predict the binding mode of a set of ligands
- Identify functional group correspondences for molecules bound to the same receptor
- Determine an alignment rule to enable 3D QSAR studies of a set of ligands

features (nodes) and interfeature distances (connections).

DISCOtech's models are returned to a Molecular Spreadsheet™ that lists each model with its score, number of features, and distance tolerances. The scoring function assesses the quality of pharmacophore models by taking into consideration the number of molecules, the number of features, and interfeature distances.

Models are easily browsed and analyzed using displays that show features as color-coded spheres as well as interfeature distances. Conformers can be superimposed on the models and distances recorded

in the spreadsheet for further analysis.

An automated model refinement procedure selects conformers based on their similarity to a model and then performs clique detection over the focused set of conformers.

DISCOtech is integrated within the SYBYL® molecular modeling environment, enabling a seamless transfer of data to other applications.

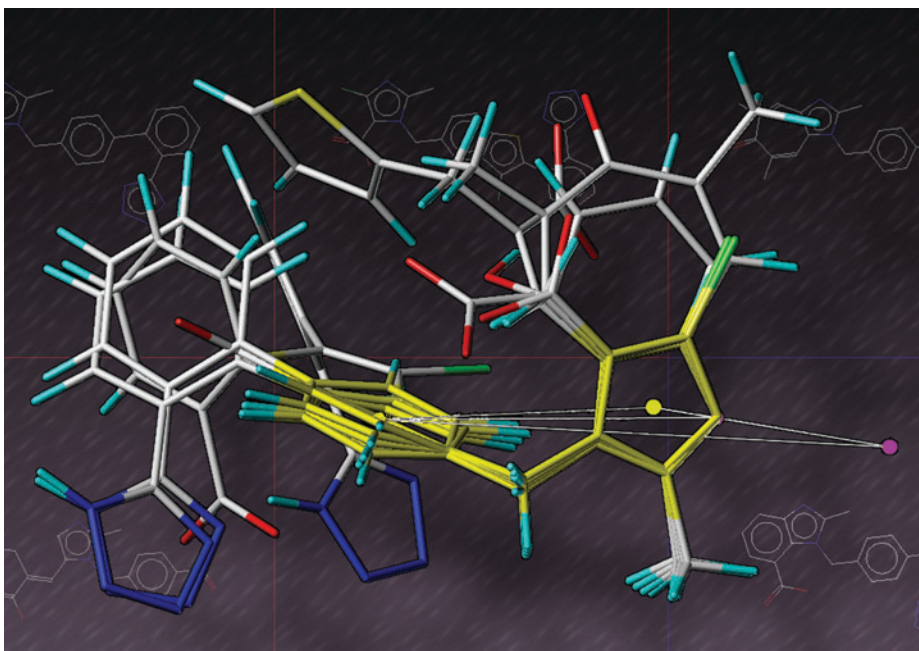
Advantages

- A streamlined, easy-to-use interface minimizes the need for user intervention while still allowing full control of parameters

Pharmacophore models serve as alignment rules in QSAR with CoMFA® for lead optimization, as queries for a UNITY® 3D flexible database search to identify potential lead compounds, and as queries for shape-based screening of databases using FlexS™

From an initial pool of conformers that are imported or automatically generated using a variety of search methods, DISCOtech selects a diverse set of conformers for each ligand. The diversity is based on interfeature distances, ensuring high quality, information-rich input.

These diverse conformers are used in DISCOtech's clique detection routine to find 3D alignments of the pharmacophore features in different molecules. A clique is a subgraph in which every node is connected to every other node. DISCOtech reduces the conformers to sets of pharmacophore



Angiotensin II receptor antagonists and their pharmacophore determined by DISCOtech. The model is displayed as a UNITY query using lines to represent interfeature distances and spheres color-coded by type to represent features. Atoms that hit the UNITY query based on the model are shown in yellow.

Features

- Generate conformers using Confort™, stochastic methods, or import conformers generated by other methods
- Automatic recognition of hydrogen bond donors/acceptors, hydrophobic sites, and other potential pharmacophore elements
- Pharmacophore model scoring function based on the number of features, the number of molecules that fit the model, and the interfeature distances
- Optional user editing to remove uninteresting features from molecules
- Diverse conformer selection based on maximal diversity or using the OptiSim®² algorithm
- Flexible displays that are easily managed, including spherical representation of features, interfeature distances with tolerances, and conformer overlay onto pharmacophore models

- DISCOtech requires no advance knowledge of key functional groups or predefined correspondences between functional groups in different ligands
- Donor/acceptor sites are represented as UNITY features, allowing DISCOtech models to be used directly in UNITY searches to locate compounds in databases that satisfy pharmacophore models.
- Novel tools that evaluate interfeature distances ensure diversity in the conformers selected for model generation.
- DISCOtech's clique detection algorithm produces the highest quality models possible by automatically iterating through the adjustable parameters (distance tolerance, number of features and molecules used) until the default or user-specified limits are reached.
- A straightforward mechanism for model refinement enables easy selection of new input conformers based on similarity to a particular model.

Hardware and Software Requirements

DISCOtech requires a separate license and is accessible through the SYBYL expert molecular modeling environment. Conformer generation using Confort requires a separate license. If 2D structures are used as input for Confort, a Concord® license or Confort 2D to 3D option is required. SYBYL/Base and DISCOtech run on workstations operating under IRIX® (SGI®) or Linux® (x86).

Validation

DISCOtech has been used to generate pharmacophore models for dopaminergic and benzodiazepine agonists,¹² muscarinic antagonists,³ and melatonin agonists⁴ that have been used in QSAR with CoMFA studies and UNITY searches to develop new molecules with increased activity.

Complementary Products

- **Confort and Advanced Computation** for generating sets of conformers
- **UNITY** for rapid, flexible 3D searching of databases to identify lead compounds based on a pharmacophore hypothesis
- **QSAR with CoMFA** for constructing predictive structure-activity models from sets of aligned molecules
- **FlexS** for testing binding mode hypotheses using shape-based screening and automatic structural alignment of drug-like molecules
- **GASP™** for automatic pharmacophore elucidation with full conformational flexibility
- **Concord** for rapidly converting 2D chemical structures into high quality 3D structures

References

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