Cheminformatics and the Internet

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Paradigm Change in the Computer Age

Computer Access

- Then
  - Expert programmers via central mainframes
- Now
  - My two kids (ages 9 and 12) via personal computers

    (primarily for playing games)

Internet Access

- Then
  - Unix guru's through ARPANET
- Now
  - My two kids (ages 9 and 12) via World Wide Web

    (primarily for downloading game cheats)

Paradigm Change in Computational Chemistry

Quantum Chemistry calculations

- Then
  - Theoretical chemists developing new basis-sets, etc.
- Now
  - Organic chemists trying to figure out reaction mechanisms, etc.

Molecular Modeling tools

- Then
  - Computational chemists performing structure-based design, etc.
- Now
  - Medicinal chemists prioritizing “drug candidates,” etc.

What Sparked this Paradigm Change?

- E-mail, Telnet, FTP
  - Internet transport standards
  - Provided access to central information
- World Wide Web - 1993
  - “User-friendly” interface to the Internet via a Web-Browser
  - Information can be distributed to any machine with a Web-server
  - HTML, providing standard file exchange format

Impact on Chemistry

- **Virtual communities of chemists**
  - **e.g., ChemCenter, ChemSoc, ChemWeb**
    - **see Warr, W.** *J.Chem.Inf.Comput.Sci.*, **1998**, *38*, **966-975.**
- **Primary entry via text-based searches**
- **Non-text search components needed to support chemistry better**
  - **e.g., compound, spectrum, substructure, pharmacophore, shape**
- **Corporate intranets emerged with better structure and design for chemistry**

Chemistry Related Internet Standards

- **Chemical MIME types**
  - **see Rzepa, H.S.; Murray-Rust, P.; Whitaker, B.,** *J. Chem. Inf. Comput. Sci.* **1998**, *38*, **976-982**
- **Chemical Markup Language**
  - **http://www.xml-cml.org/**
- **VRML**
  - **See Casher, O.; Page, C.; Rzepa, H.** *Chem. Brit.*, **1988**, *34(9)*, **26-30.**
  - **See Dolata, D.P.; Wathen, S.P.** *J. Mol. Graph. Model.* **1998**, *16*, **37-46.**

Web-Enabled 3D “Free” Chemical Visualizers

- **RasMol - Roger Sayle**
  - http://www.umass.edu/microbio/rasmol/
- **ISIS/Draw - MDL**
  - http://www.mdli.com/download/idraw.html
- **WebLab Viewer - MSI**
  - http://www.msi.com/download/viewer/lite/

Various Web-based Cheminformatics Software

- **ChemFinder, (CambridgSoft)**
  - **index chemical information**
- **ChemSymphony**
  - **Java package, see Brecher** *Chimia*, **1998**, *52***(11), 668-672**
- **Spotfire Discovery Server**
  - **navigational aid for databases**
- **MineSet**
  - **3D visual navigation**
- **EyeChem**
  - **visualization toolkit, see Casher** *J.Mol.Graph.*, **1994**, *12***(3), 226-230**

Research Over the Internet

- **Data access - e.g., protein mass spectra**
  - **Fenyo et al.,** *Anal.Chem.*, **1996**, *68***(23),721A**
- **Data analysis - e.g., scanning probe microscopy data analysis system**
  - **http://pharm6.pharm.nottingham.ac.uk/processing/main.html**
- **Instrument operation - e.g., remote control of NMR systems**
  - **Buszko et al.,** *Appl.Mag.Reson.*, **1997**, *12***(95),101**
- **Simulation of spectra - e.g., IR spectra simulation and processing**
  - **http://www2.ccc.uni-erlangen.de/research/ir/english**

Examples for Web-Access to Chemical Information

- EPA rules and regulations
  - http://www.epa.gov/epahome/rules.html
- Database of G-protein coupled receptors
  - http://www-grap.fragmed.uit.no/GRAP/homepage.html
- Database of protein structures
  - http://pdb.pdb.bnl.gov
- Database of nucleic acids
  - http://ndbserver.rutgers.edu
- Biochemical compounds database
  - http://www.ibc.wustl.edu/klotho/#compounds

Chemistry Education Through the Internet

- **List of chemistry courses and tutorials**
  - **http://www-rohan.sdsu.edu/staff/drjackm/chemistry/chemlink/teach/teach1.html**
  - **http://www.utexas.edu/world/lecture/ch**
- **P-Chem course at University of Delaware**
  - **Noggle and Dybowski,** *J.Chem.Edu.*, **1998**, *75*(**11**), **1499.**
- **Drug Design chemistry course at University of Nebraska**
  - **Liu et al.,** *J.Chem.Edu.*, **1998**, *75*(**1**), **123-125.**

Chemistry Education Through the Internet

- **Web-based drug design course**
  - **http://www.netsci.org/Courseware**
- **Many examples of Web-based chemistry coursework (Henry Rzepa Home Page)**
  - **http://www.ch.ic.ac.uk/rzepa**
- **Degree courses over the Internet: Structure-Based Drug Design at University of Nottingham**
  - **Burt, C. et al., ACS 217th National Meeting, Anaheim 1999, CINF-68.**

Recent Reviews of Chemistry on Internet

- **Heller, S. R. "Chemistry on the Internet: the Road to Everywhere and Nowhere,"** *J. Chem. Inf. Comput. Sci.*, **1996**, *36*, **205-213.**
- **Boyd, D. B. "Compendium of Software and Internet Tools for Computational Chemistry,"** *Rev. Comput. Chem.* **1997**, *11*, **373-399.**
- **Wiggins, G. "Chemistry on the Internet: The Library on your Computer,"** *J. Chem. Inf. Comput. Sci.*, **1998**, *38*, **956-965.**
- **Güner, O.F. and Casher O. "Role of the Internet in Cheminformatics,"** *Curr. Opin. Drug Disc. & Dev.*, **1999**, *2*, **(3), 204-208.**

Some Examples for Commercial Intranet Informatics Software

- **MedChem and Diversity Explorer - MSI**
- **ChemScape Chime - MDL**
- **ChemEnlighten - Tripos**
- **Interactive Labs - ACD / Labs**

WebLab MedChem Explorer

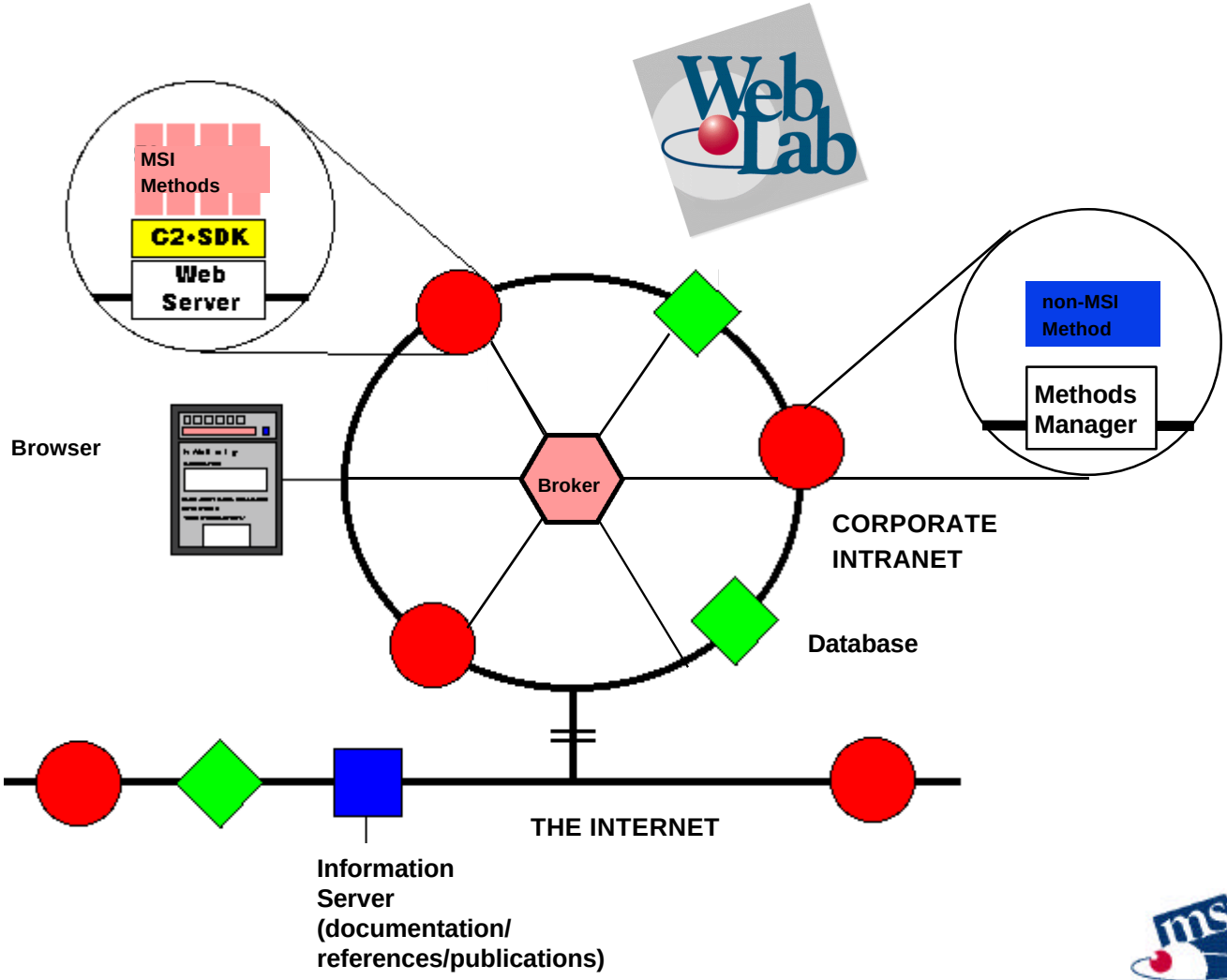
Utilizes the existing intranet infrastructure at your company

Manages the projects and experiments via Web browsers

Client-server Web environment together with a native application for the best distribution of resources

Integrates with your existing informatics environment to provide added value through modeling and analysis tools

WebLab Environment



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MedChem Explorer Applications

In 1998 - WebLab 1.5

[released]

- **Database Access**
- **Conformers**
- **Property Calculator**
- **Align/Pharmacophore**

In 1999 - WebLab 1.6

[to be released]

- **Molecular Overlay**
- **Activity Prediction**

MedChem Explorer DB Access

Direct access to third-party databases

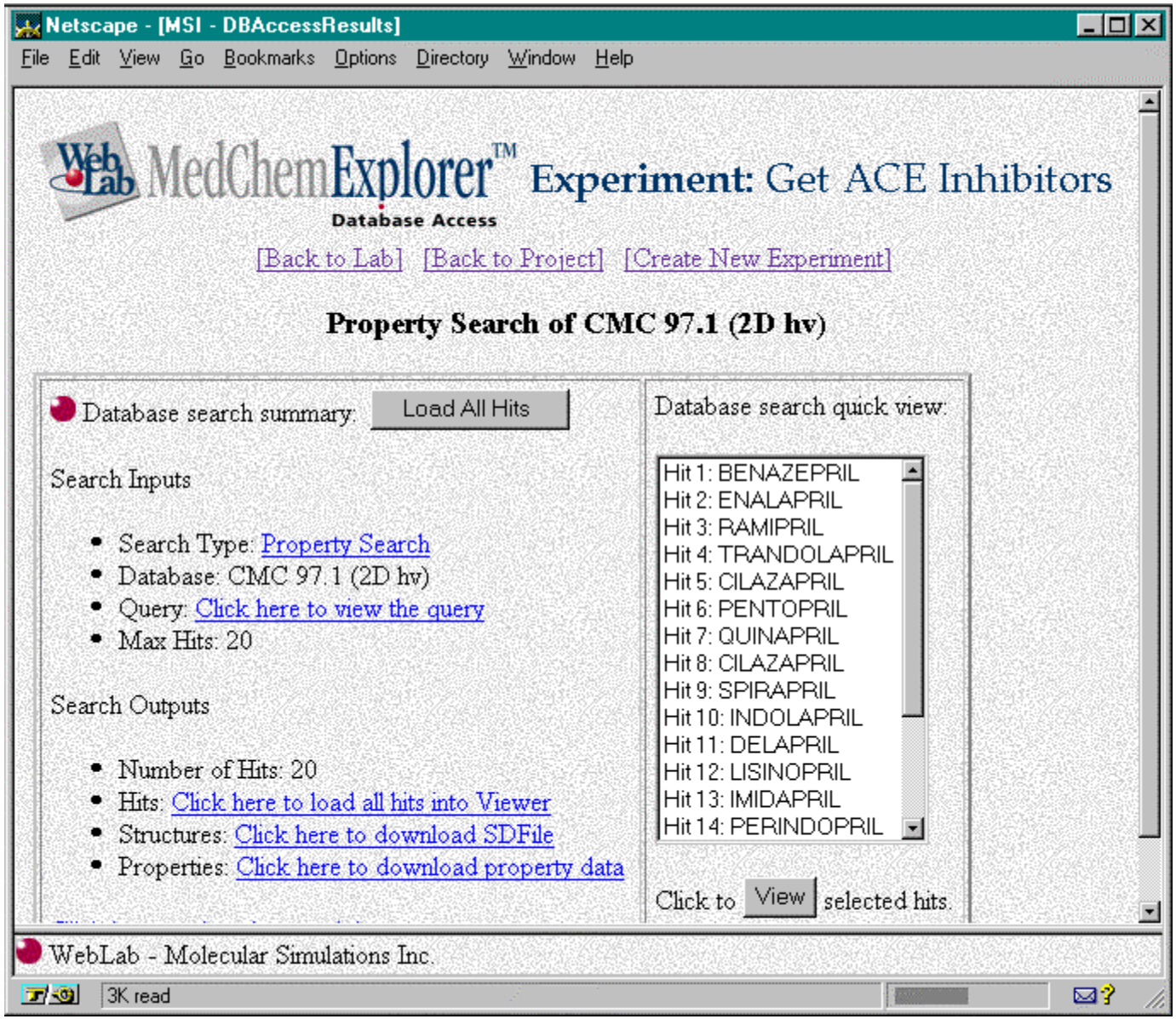
- **ISIS®**
- **Catalyst ®**
- **Daylight**

Rich Search Options

- **Text-based (ISIS, Catalyst)**
- **2D Similarity (ISIS, Daylight)**
- **2D Substructure (ISIS, Daylight, Catalyst)**
- **3D Pharmacophore (ISIS, Catalyst)**
- **3D Shape (Catalyst)**

Tabulated results

- **option to present results in MS Excel**
- **option to export SDFile**



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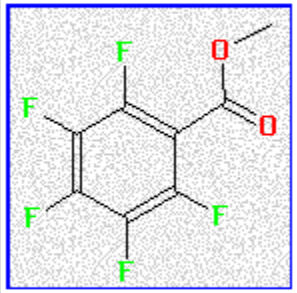
Netscape - [MSI - DBAccessResults]

File Edit View Go Bookmarks Options Directory Window Help



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ALDRICH                9502
METHYL PENTAFLUOROBENZOATE
36629-42-2
.
_F    30,307-0                 5 G            USD         24.60
.........................
FLROCHEM               9402
METHYL PENTAFLUOROBENZOATE
36629-42-2
.
PURE
_F    F05123                   5 G            UKL         16.00
.........................
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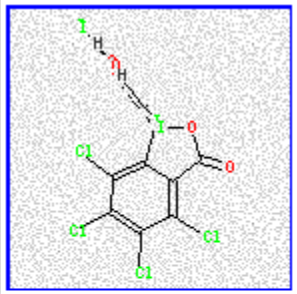

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4159-77-7
.
_F    32,896-0                 1 G            USD         18.55
_F    32,896-0                 5 G            USD         59.75
.........................
```

WebLab - Molecular Simulations Inc.

Document: Done

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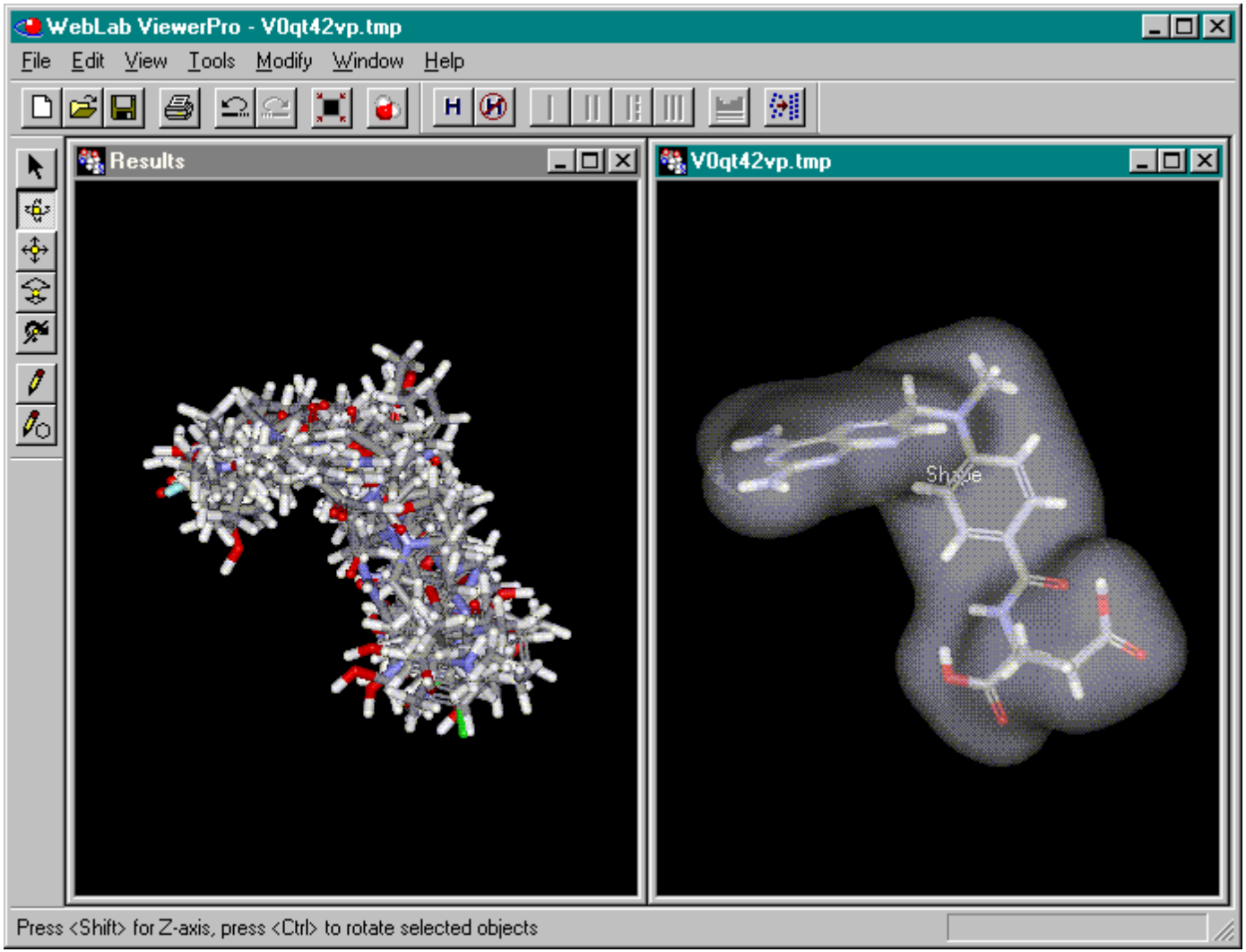

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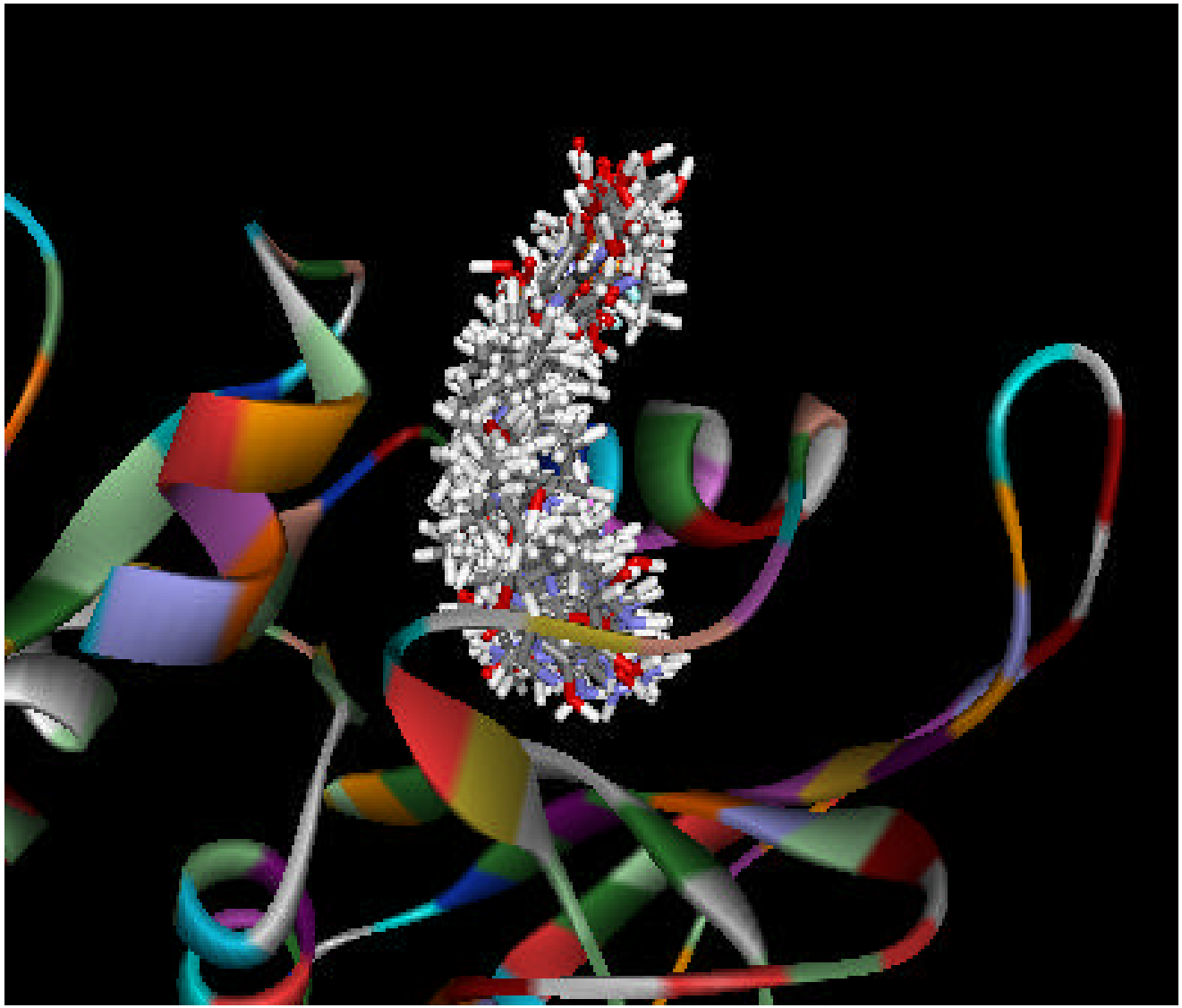

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MedChem Explorer Conformers

Energy minimization

- **options for setting default for using different forcefields (Dreiding and CFF97)**

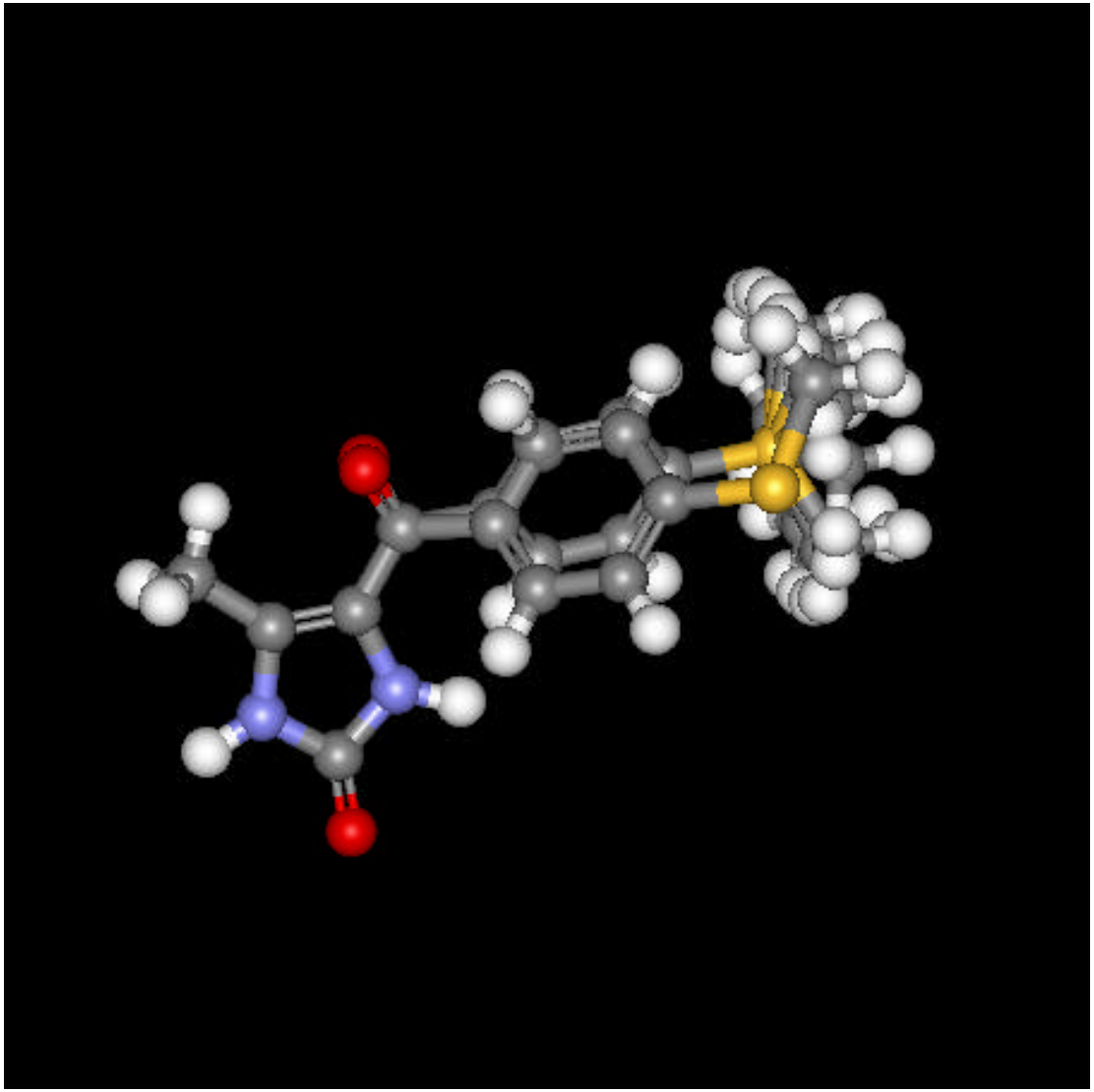
Conformation generation

- **Systematic conformation analysis**
  - **lowest energy conformations**
  - **diverse set of conformations**
- **Diverse sampling of conformational space**

Tabulated results

- **option to present results in MS Excel**
- **option to export SDFiles**

Conformations Overlaid



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MedChem Explorer Property Calculator

Calculate hundreds of properties/descriptors

- **Conformational**
  - **conf. energy penalty, lowest energy, etc.**
- **Electronic**
  - **dipole moment, sum of charges, etc.**
- **Structural**
  - **MW, No. of Hbond donors/acceptors, etc.**
- **Thermodynamic**
  - **logP, molar refractivity, heat of formation, etc.**
- **Spatial**
  - **area, molecular volume, PMI, etc.**
- **Quantum Mechanical (MOPAC)**
  - **HOMO, LUMO, heat of formation, etc.**

Calculate Lipinski properties

Netscape - [MSI - Release day testing/Props]

File Edit View Go Bookmarks Options Directory Window Help

WebLab MedChemExplorer™

Property Calculator

Experiment: Props

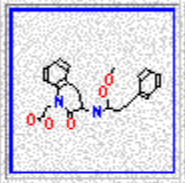
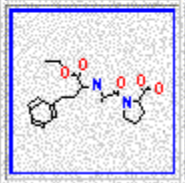
[Back to Lab] [Back to Project] [Create New Experiment]

Property Calculator Results

Load All Molecules Into Viewer

These molecules have missing data:
CILAZAPRIL

Click here to view log files: | c2.log | com.log |

Name		Area	Vm	Hbond acceptor	AlogP	Hf
BENAZEPRIL		485.3399	391.7695	6	3.297601	-82.5369
ENALAPRIL		456.0659	357.2125	6	2.101001	-159.069

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MedChem Explorer
Align/Pharmacophore

Molecular alignment based on common chemical features

- **Hbond acceptor/donor**
- **Lipophilic**
- **Negative or positive ionizable**

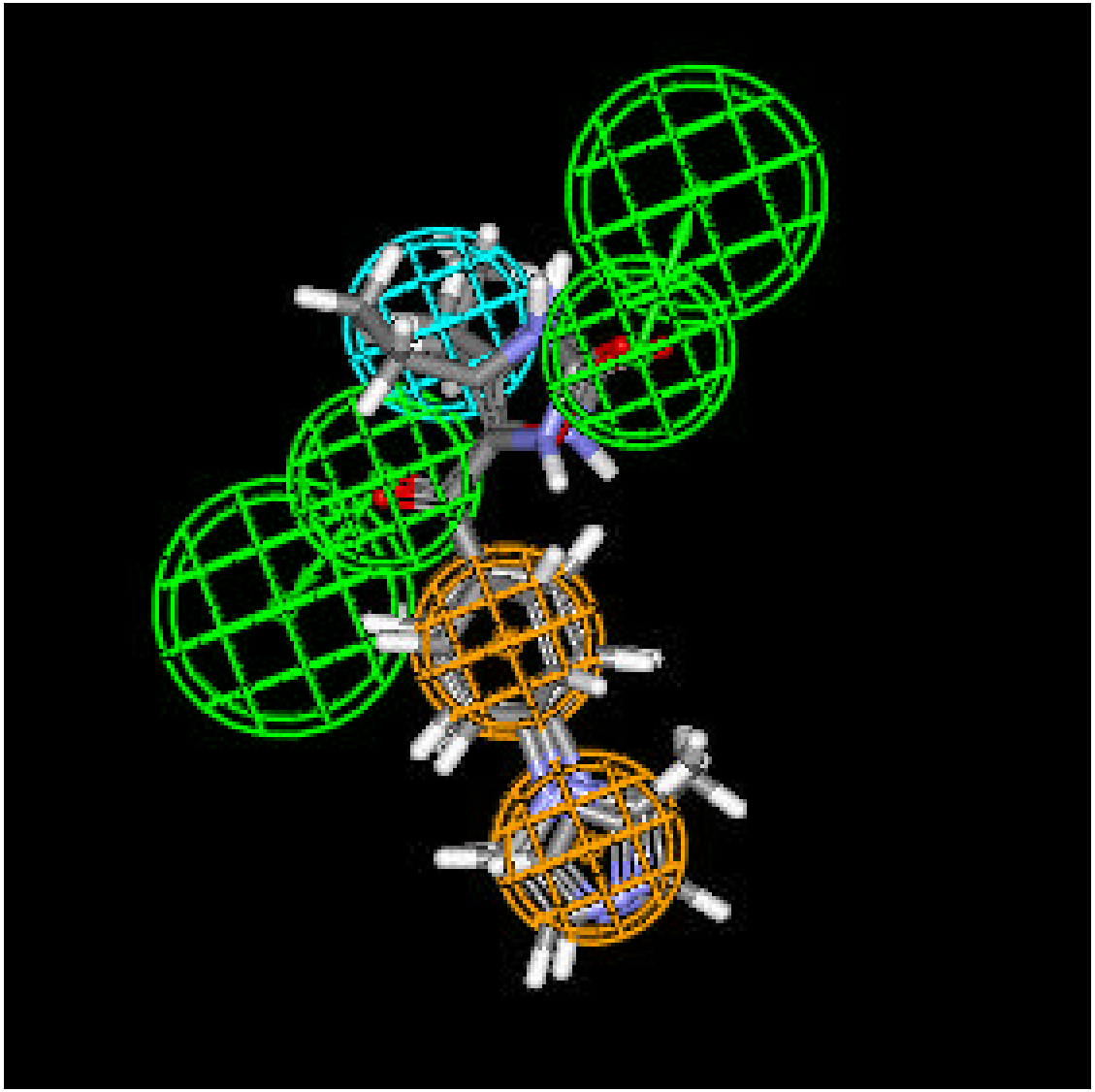
Development of pharmacophore models based on alignment

- **pharmacophore models can be used to search catalyst databases via ME.DBAccess**

Tabulated results

- **option to present results in MS Excel**
- **exports aligned hits and/or pharmacophores**

A Pharmacophore Model



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WebLab 1.6

To be released in 1999

Two new applications:

- **Molecular Overlay**
- **Activity Prediction**

Enhancements to DBAccess

- **Property search with Daylight databases**

MedChem and Diversity Explorer getting closer

Improved stability

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Acknowledgements

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