# Drug Informatics for Chemical Genomics

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## *An Overview*

First Annual

ChemGen IGERT Retreat

Sept 2005

# Topics

- ChemGen Informatics
- The ChemMine Project
- Library Comparison

# ChemGen Informatics

A Multidisciplinary Symbiosis

- Cheminformatics
- Drug Informatics
- Network Analysis & Modeling
- Structural Informatics
- Bioinformatics

# Cheminformatics

- Structure formats & format rendering
- Property descriptor generation
- Similarity searching
  - Substructure & similarity
  - Property searches
  - Model-based searches
    - Pharmacophore & QSAR
- 3D conformer calculation
- Library design & analysis
  - Library comparison
  - Structure & descriptor clustering
  - Diversity analysis
- Data management: databases

# Drug Informatics

- Screening database
- Bioactivity data
- Lead prioritization
  - QSAR analyses
  - Pharmacophore modeling
- Structural informatics
  - Docking
  - Rational drug design
  - Virtual screening

# Bioinformatics and Network Analysis

- Bioinformatics
  - Sequences & mRNA/protein profiling
  - Protein-protein interaction data
  - Pathways & Ontologies
  - Mutant analysis
- Network Analysis
  - Clustering (HC, KM, PCA, MDS, NN, etc )
  - Systems modeling
- Statistics for everything

# Dilemma for Academic Institutions

**Current infrastructure**

- Very limited open-source resources
- Dominance of commercial software

**Decision: commercial vs. public**

- Black boxes for a lot of $
- Focus on public resources with internal development time

**Advantage of Public Resource Approach**

- Higher educational value
- Transparent, modifiable and shareable
- Higher public impact

# ChemMine: Chemical Genomics DB

Compound mining and screening database for drug and chemical genomics discovery

- Current functionality
  - Activity- & property-based searching
  - Structure-based searching
  - Online clustering
  - Upload and retrieval of screening data
- Long term goals
  - Central depository of internal and external screening data
  - Online service for mining of drug-like compounds
  - Ontologies for bioactives and screening data
- *In silico* discovery
  - Training set for predictive approaches
    - Property-focused libraries
  - Systems approaches
    - Predictive process modeling

Publication: *Plant Physiol* (2005) **138**, 573-577

# Functionality Overview

URL: http://bioweb.ucr.edu/ChemMine/

Over 2.5 million structures

- Screening libraries
- Bioactives & natural CMPs
- Metabolic compounds

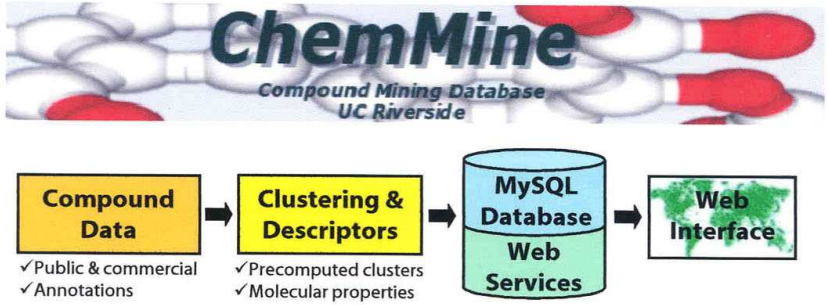
Activity information

- Screening data
- Target proteins
- Literature

Web services

- Clustering
- Chemical descriptors
- Structure formats

(A)

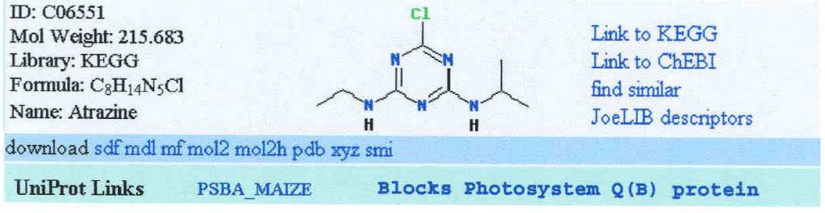



(B)

Descriptor Table (partial view)

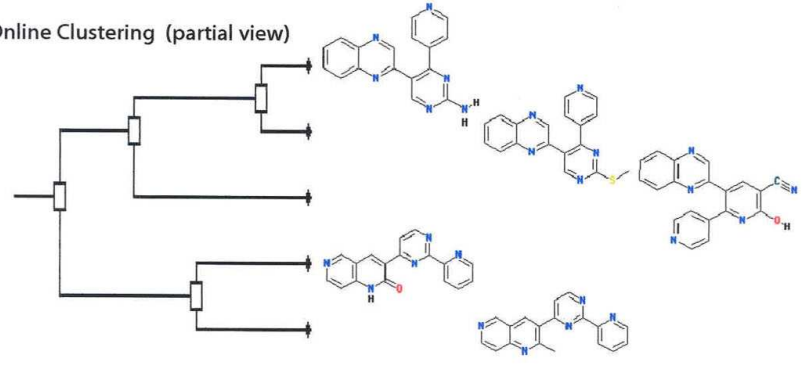
| | ID | Mol Weight | FOR | LGP | HA1 | HA2 | HD1 |
|---|---|---|---|---|---|---|---|
| ☑ | 1234 | 193.244 | $C_{14}H_{11}N$ | 5.1797 | 12 | 1 | 0 |
| ☑ | 12340 | 612.505 | $C_{32}H_{16}O_8N_6$ | 9.5864 | 22 | 2 | 0 |
| ☑ | 123400 | 409.432 | $C_{23}H_{23}O_6N$ | 8.2873 | 29 | 6 | 1 |
| ☑ | 123401 | 372.458 | $C_{21}H_{28}O_4N_2$ | 10.3585 | 33 | 5 | 2 |

Annotation Page (partial view)

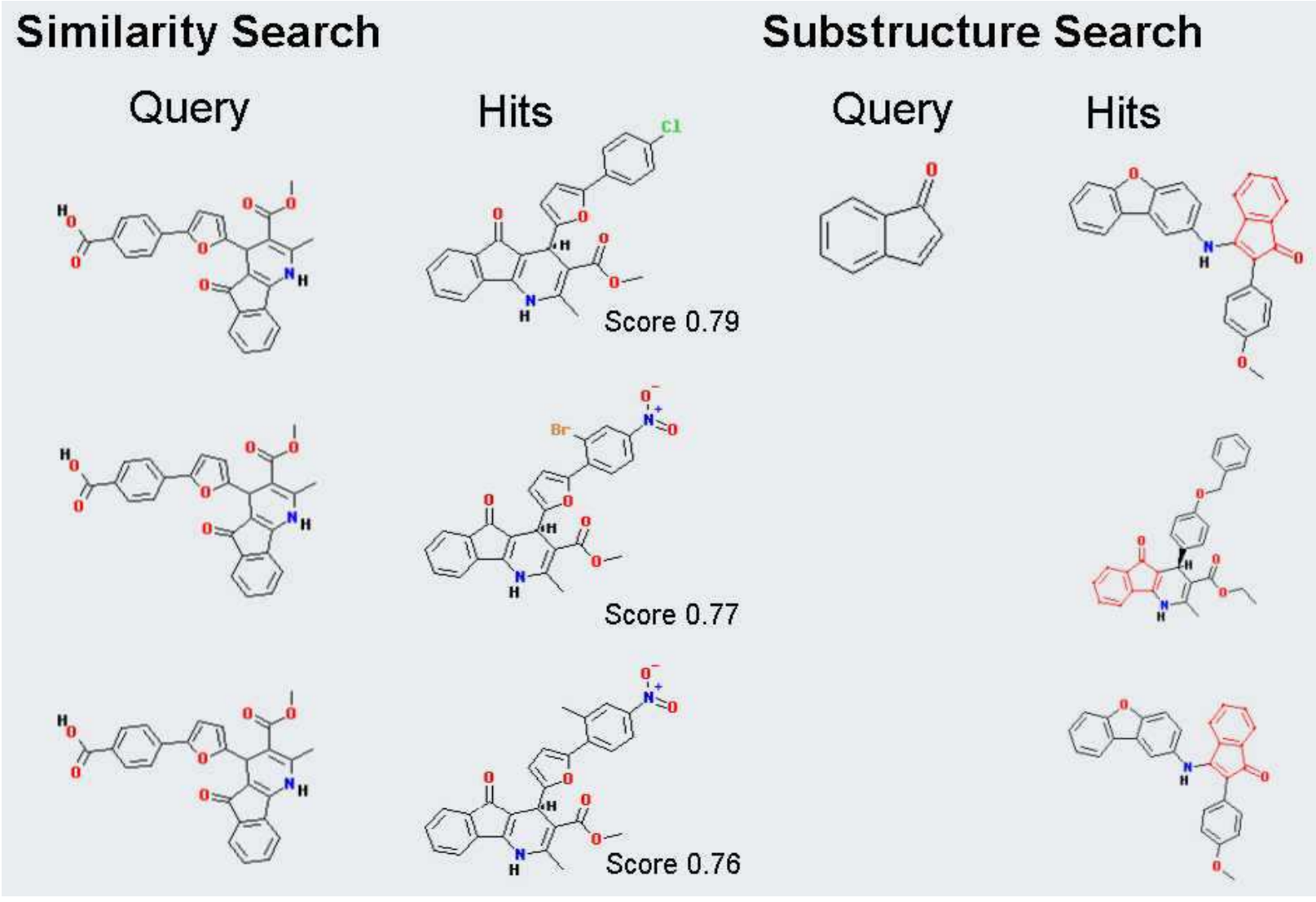



(C)

Online Clustering (partial view)



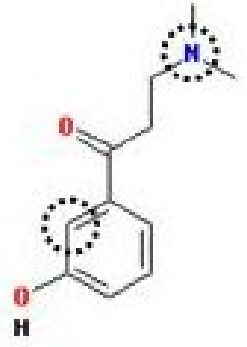
# Similarity Searching



# 2D Fragment Similarity Searching

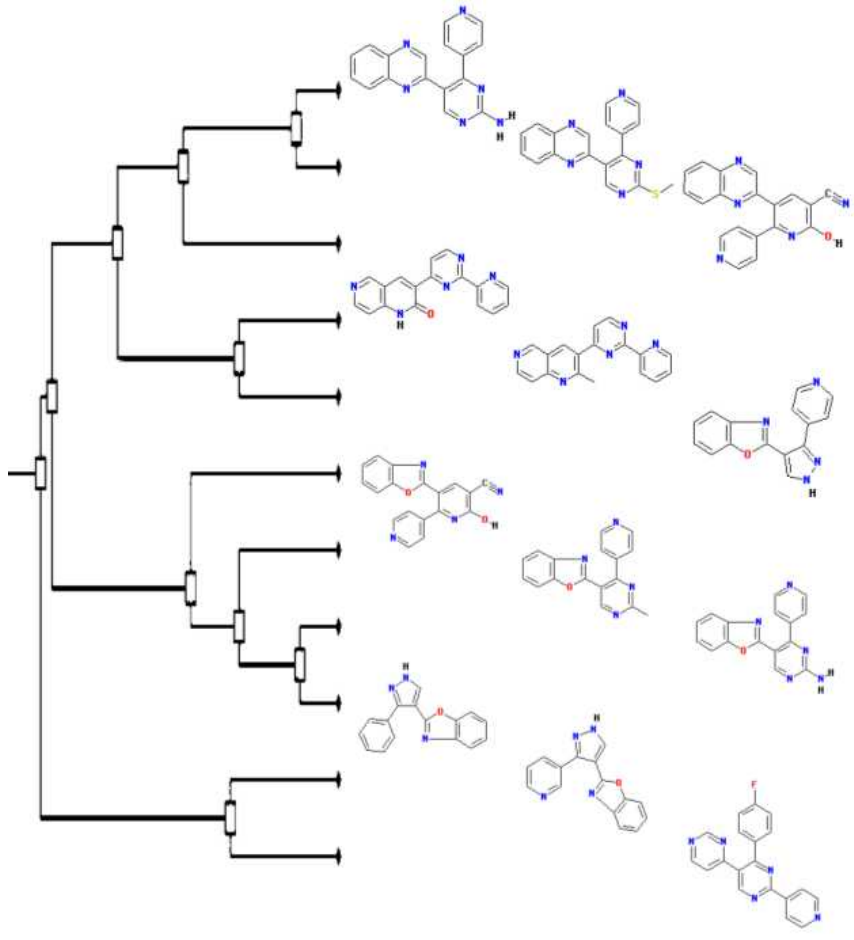
- Most commonly used for large database searching.
- 3D approaches used in pharmacophore searching.
- Advantages
  - Fast and accurate
- Involves 2 major steps
  - Structural descriptors
  - Similarity coefficients/measures
- Structural descriptors in similarity searching
  - Atom pairs: C12N03_06
  - Atom sequences: C12C13C13C02C02N03
  - Fingerprints: rules to enumerate all fragments in common structures
- Substructure searching
  - Similar to atom sequences

Sample Structure



# Online Clustering

- Similarity-based
- Descriptor-based
- Hierarchical or binning clustering
  - All-against-all similarity
  - Distance matrix
  - Clustering



# Preclustered Libraries

| PubChem: 711,361 compounds | | | | | | | |
|---|---|---|---|---|---|---|---|
| Similarity | Number of Clusters | Cluster Size >100 | >50 | >20 | >10 | >2 | Singlets |
| 90% | 110969 | 27 | 54 | 280 | 1199 | 109409 | 389901 |
| 80% | 116707 | 77 | 173 | 805 | 2579 | 113073 | 299187 |
| 70% | 88050 | 198 | 329 | 1520 | 3530 | 82473 | 169431 |
| 60% | 43730 | 95 | 148 | 667 | 1844 | 40976 | 80526 |

# Descriptor Clustering

| | ID | Mol Weight | FOR | LGP | HA1 | HA2 | HD1 | HD2 | ACG | AOH | BAG | FRB | ROT | AB | HCY | HPG | MOR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ☑ | 6000002 | 299.326 | $C_{19}H_{13}ON_3$ | 4.4841 | 4 | 4 | 0 | 0 | 0 | 0 | 0 | 0.115 | 3 | 26 | 2 | 0 | 89.285 |
| ☑ | 6000047 | 297.435 | $C_{20}H_{27}ON$ | 5.0786 | 1 | 2 | 1 | 1 | 0 | 1 | 0 | 0.08 | 2 | 25 | 1 | 3 | 91.3358 |
| ☑ | 6000086 | 290.362 | $C_{18}H_{18}N_4$ | 3.7471 | 4 | 4 | 0 | 0 | 0 | 0 | 0 | 0.08 | 2 | 25 | 3 | 1 | 85.6332 |
| ☑ | 6000087 | 267.329 | $C_{15}H_{17}N_5$ | 2.5788 | 4 | 5 | 0 | 0 | 0 | 0 | 0 | 0.043 | 1 | 23 | 3 | 2 | 75.6992 |
| ☑ | 6000107 | 265.353 | $C_{17}H_{19}N_3$ | 3.6399 | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0.086 | 2 | 23 | 2 | 1 | 80.5079 |
| ☑ | 6000133 | 292.335 | $C_{17}H_{16}ON_4$ | 2.5934 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0.08 | 2 | 25 | 3 | 0 | 82.6012 |
| ☑ | 6000139 | 366.339 | $C_{20}H_{13}N_4F_3$ | 5.4542 | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 0.133 | 4 | 30 | 2 | 0 | 97.4957 |
| ☑ | 6000175 | 267.326 | $C_{16}H_{17}ON_3$ | 2.4862 | 3 | 2 | 1 | 1 | 0 | 0 | 1 | 0.086 | 2 | 23 | 2 | 0 | 77.4759 |
| ☑ | 6000256 | 332.786 | $C_{19}H_{13}N_4Cl$ | 5.0888 | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 0.111 | 3 | 27 | 2 | 0 | 97.5037 |
| ☑ | 6000296 | 420.509 | $C_{26}H_{24}N_6$ | 4.192 | 4 | 5 | 1 | 1 | 0 | 0 | 1 | 0.108 | 4 | 37 | 3 | 0 | 122.344 |
| ☑ | 6000298 | 342.348 | $C_{21}H_{14}O_3N_2$ | 5.5734 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0.137 | 4 | 29 | 2 | 0 | 101.469 |
| ☑ | 6000309 | 334.322 | $C_{19}H_{12}N_4F_2$ | 4.7136 | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 0.107 | 3 | 28 | 2 | 0 | 92.4097 |
| ☑ | 6000372 | 292.289 | $C_{17}H_{12}O_3N_2$ | 4.4202 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0.166 | 4 | 24 | 2 | 0 | 83.9634 |
| ☑ | 6000433 | 342.348 | $C_{21}H_{14}O_3N_2$ | 5.5734 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0.137 | 4 | 29 | 2 | 0 | 101.469 |
| ☑ | 6000440 | 338.362 | $C_{21}H_{14}ON_4$ | 4.7368 | 4 | 5 | 0 | 0 | 0 | 0 | 0 | 0.1 | 3 | 30 | 2 | 0 | 100.24 |
| ☑ | 6000441 | 316.332 | $C_{19}H_{13}N_4F$ | 4.5745 | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 0.111 | 3 | 27 | 2 | 0 | 92.4517 |
| ☑ | 6000452 | 255.275 | $C_{13}H_{13}ON_5$ | 1.1791 | 5 | 6 | 0 | 0 | 0 | 0 | 0 | 0.045 | 1 | 22 | 3 | 0 | 68.1202 |
| ☑ | 6000480 | 258.402 | $C_{17}H_{26}N_2$ | 3.8445 | 0 | 0 | 2 | 1 | 0 | 0 | 2 | 0.047 | 1 | 21 | 2 | 0 | 78.2375 |
| ☑ | 6000792 | 442.592 | $C_{15}H_8O_4N_2ClI$ | 3.5978 | 5 | 6 | 1 | 1 | 0 | 0 | 0 | 0.08 | 2 | 25 | 2 | 0 | 86.1251 |
| ☑ | 6000815 | 455.462 | $C_{26}H_{21}O_5N_3$ | 5.9762 | 5 | 5 | 2 | 2 | 0 | 0 | 0 | 0.216 | 8 | 37 | 1 | 0 | 129.063 |
| ☑ | 6000887 | 350.325 | $C_{19}H_{14}O_5N_2$ | 4.3097 | 4 | 4 | 1 | 1 | 0 | 0 | 0 | 0.214 | 6 | 28 | 1 | 0 | 95.1981 |
| ☑ | 6000956 | 420.523 | $C_{21}H_{28}O_5N_2S$ | 4.203 | 7 | 7 | 1 | 1 | 0 | 0 | 0 | 0.3 | 9 | 30 | 0 | 0 | 113.197 |

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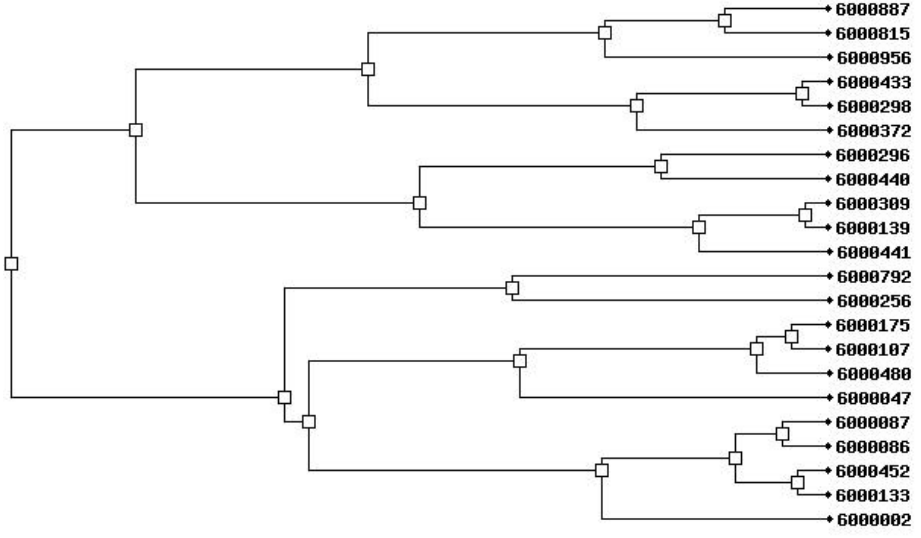


# Future Updates

- Management of screening data
  - Upload of bioactivity information from external and internal screens
  - Diverse data types
    - Compound upload
    - Quantitative data forms
    - Image data
    - User-specific data?
  - Development of ontology for bioactives, screening data and phenotypes
  - Routines for publishing user data including mandatory curation system
  - Interoperability with other screeing projects: ChemBank, PubChem, etc.

- Chem/drug informatics utilities
  - QSAR analysis tools
  - Expansion of drug-likeness and descriptor predictions
  - Drug informatics R/BioConductor libraries
  - Size-insensitive similarity searching
  - Combinatorial searches, e.g. similarity plus descriptors
  - IUPAC/InChI names
  - 3D conformer generation

# Library Comparisons

Assemble collection of 50-100K diverse drug-like compounds

**Selection Criteria**

- Screening compounds, bioactives and natural products
- Minimum overlap within and between libraries
- Vendor diversity (J Chem Inf Comput Sci 44: 643-651)
- Majority drug-like: 'plant Lipinski rules' (Pest Manag Sci 58: 219-233)
- Elimination of undesirable side groups (filters)
- Recommendations (ICCB, etc.)
- Literature (e.g. Tudor Oprea: Curr Drug Disc Technol 1: 211-220)
- Resupply situation
- Price

# Analyzed Libraries

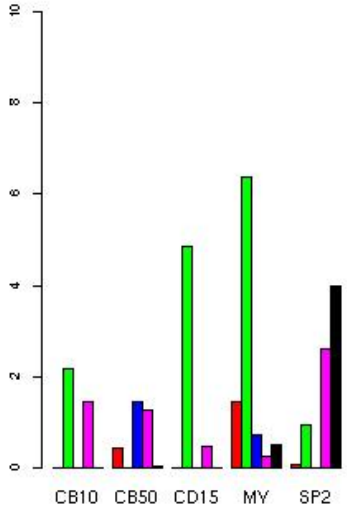
- Quantity conversions
  - First library: 0.1mg [20$\mu$l], 5$\mu$g/$\mu$l [10-20mM]
  - Final assay conc: 5-10ng/$\mu$l [10-40$\mu$M]
  - Number of screens: 100 screens with 100$\mu$l end volume
- Analyzed collections
  - ChemBridge: Microformat, 10,000 CMPs (0.1mg)
  - ChemBridge: DIVERSet, 50,000 CMPs (0.25mg)
  - Chemical Diversity: ICCB set, 15,000 CMPs (0.5mg)
  - Sigma/TimTec: MyriaScreen, 10,000 CMPs (0.25mg)
  - Microsource: Spectrum, 2,000 CMPs (0.25mg)
- On waiting list
  - ChemBridge: NOVACore (parallel DOS), 40,000 CMPs, 0.25mg
  - Biomol/TimTec: MaxiVerse, 9,600 CMPs, 0.25mg
  - World Molecules/MDD Inc: x CMPs
  - Enamine: 10,000-20,000 CMPs, 0.25mg
  - Analyticon Discovery: MEGAbolite & NatDiverse, 3000 CMPs, 0.25mg

# Clustering Methods

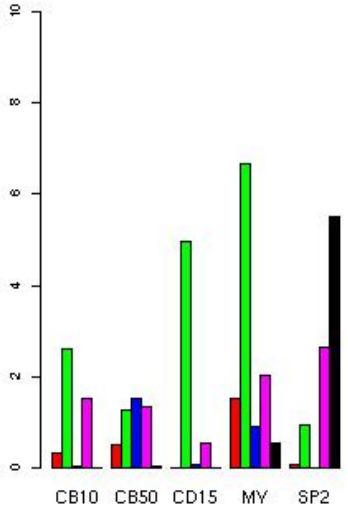
- Principal component analysis
  - Reduction technique of multivariate data to principal compoments to identify hidden variances
- Multidimensional scaling
  - Displays distance matrix of objects in spacial plot
- Single linkage binning
  - Uses provided similarity cutoff for grouping of items

# Similarity Clustering

100% Ident APs




90% Ident APs

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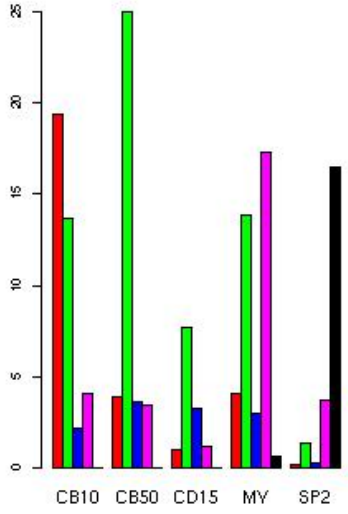
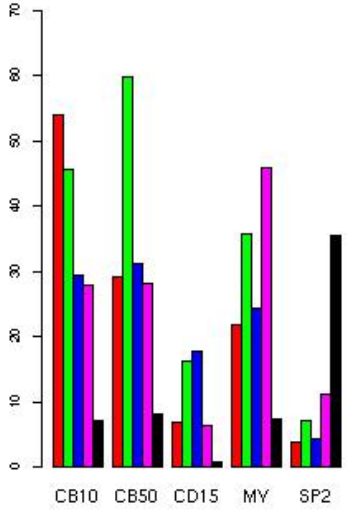
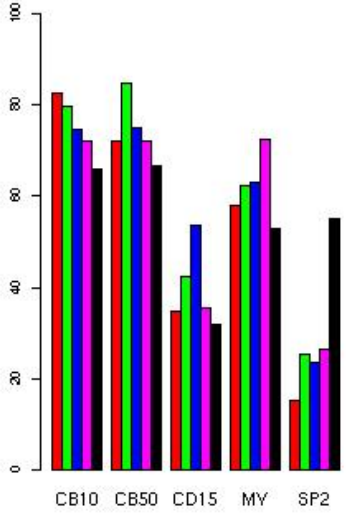



70% Ident APs



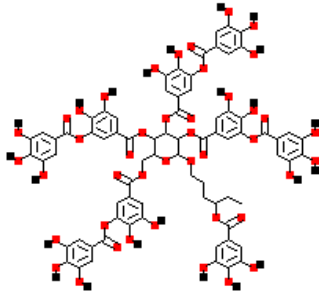

60% Ident APs



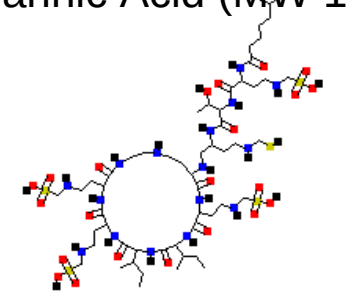

CB10 CB50 CD15 MY10 SP2

# Property PCA

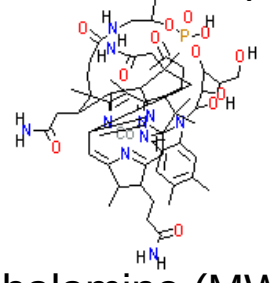
Diversity relative to 80 complex bioactives in MS Spec



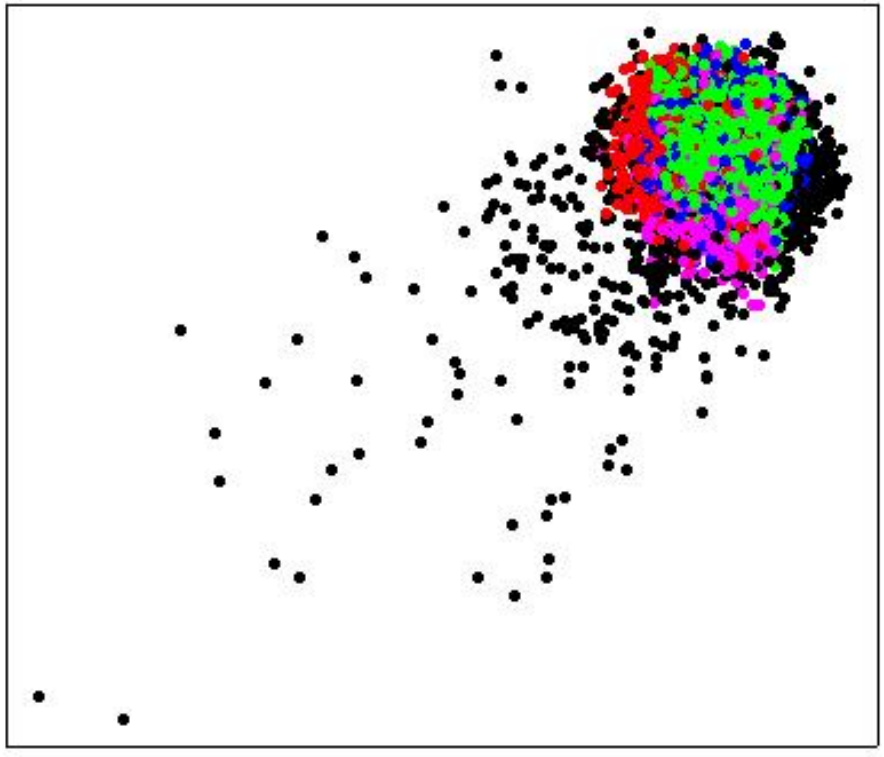
Tannic Acid (MW 1600)



Colistimethate (MW 1400)



Cobalamine (MW 1100)



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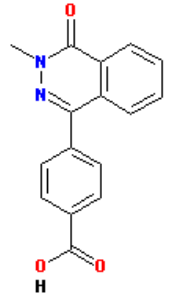
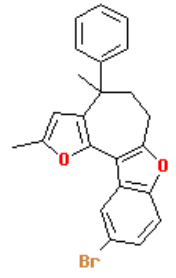


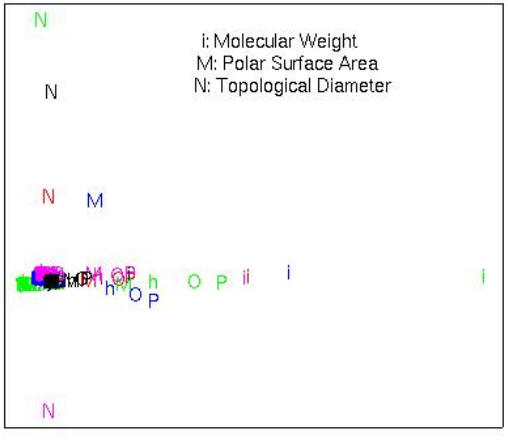
56421 (MW 270)



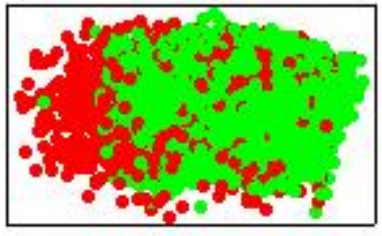
19737 (MW 390)

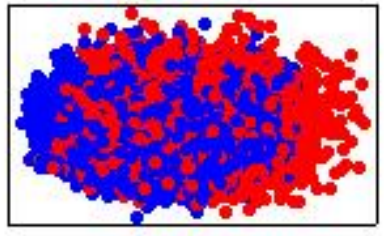
# Property Differences

Property Plot




Compound Plots





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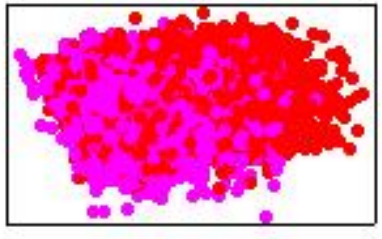
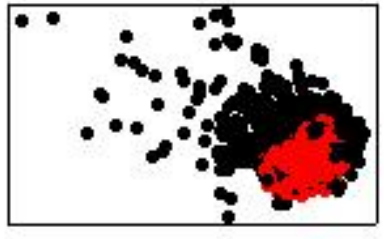
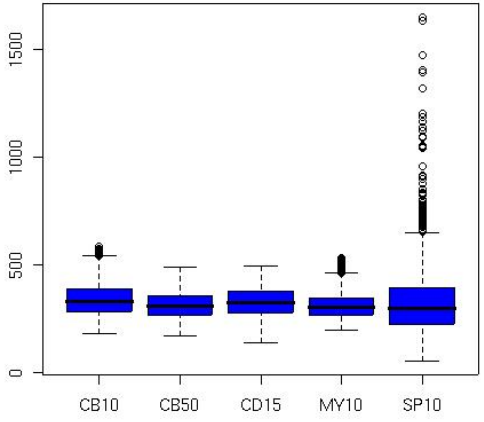


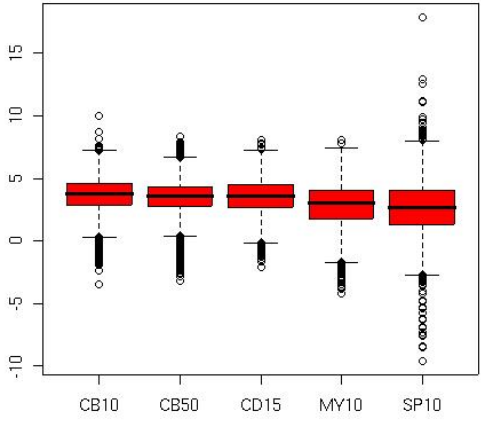


# Lipinski Descriptors

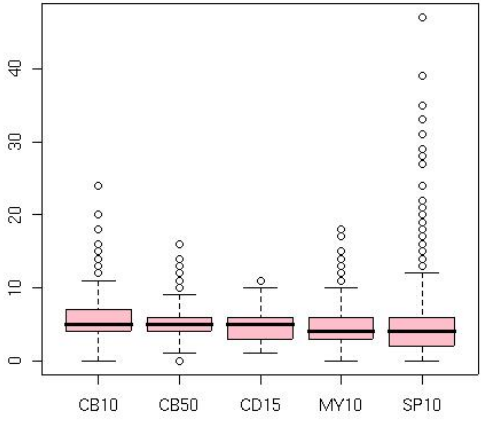
Molecular Weight



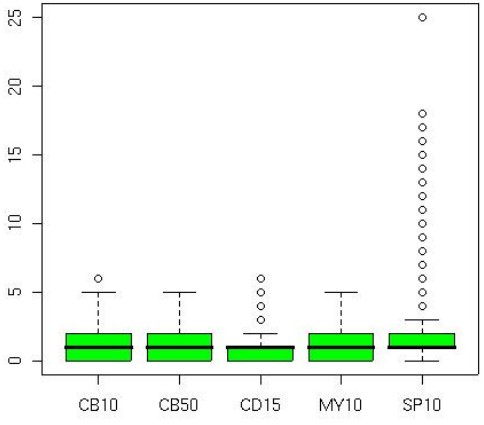

LogP



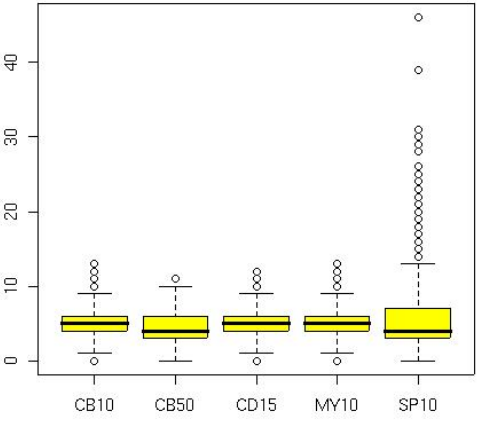

Rotatable Bonds




Hydrogen Bond Donors




Hydrogen Bond Acceptors



# Similarity Clustering #2

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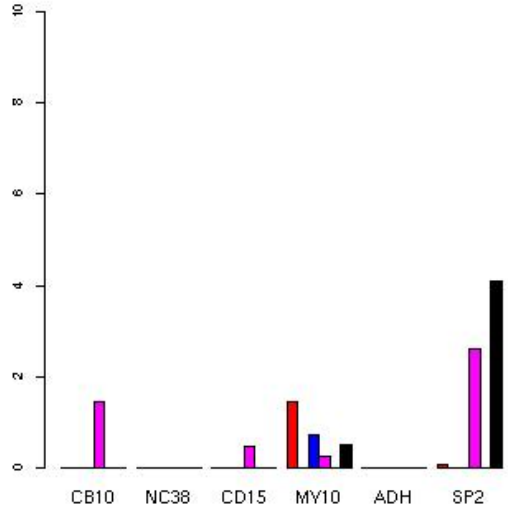


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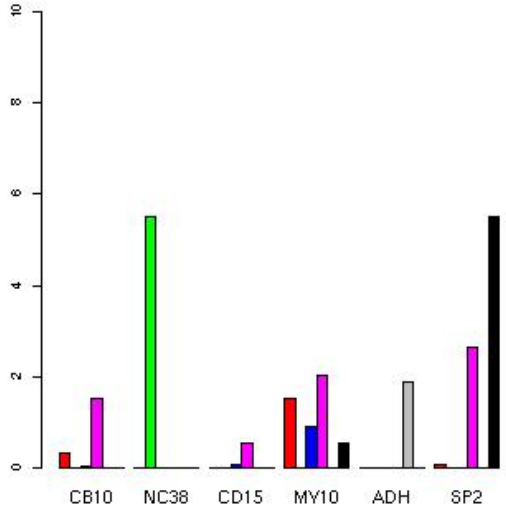
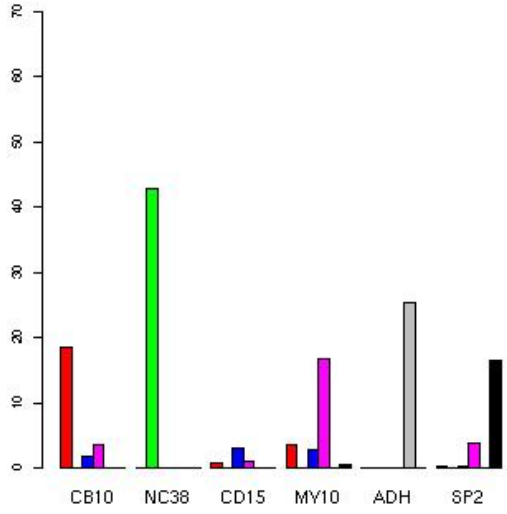
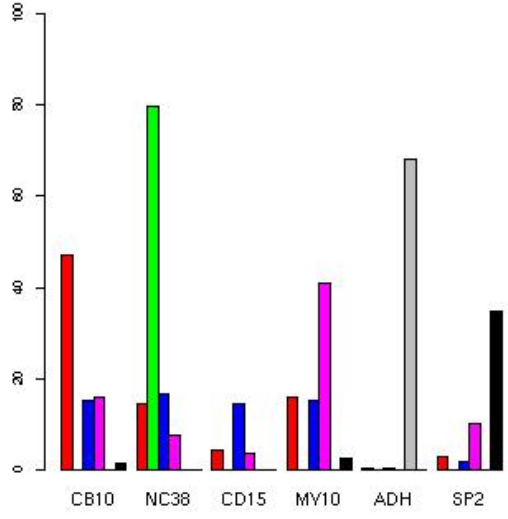


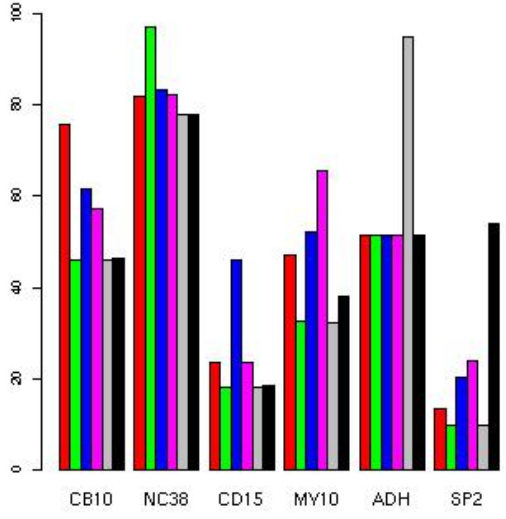

80% Ident APs




70% Ident APs




60% Ident APs

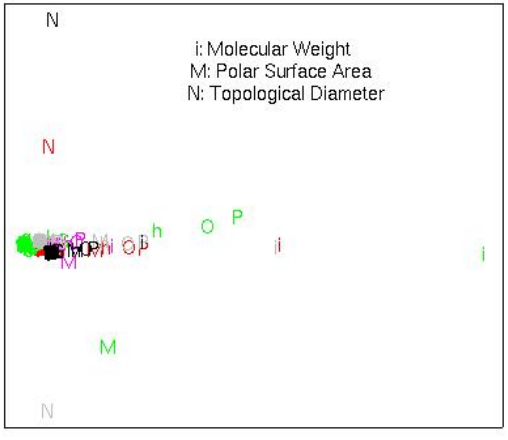



CB10 NC38 CD15

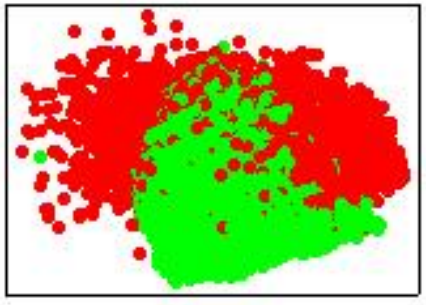
MY10 ADH1 SP2

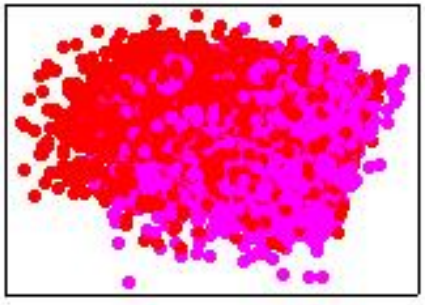
# Property Differences #2

Property Plot




Compound Plots





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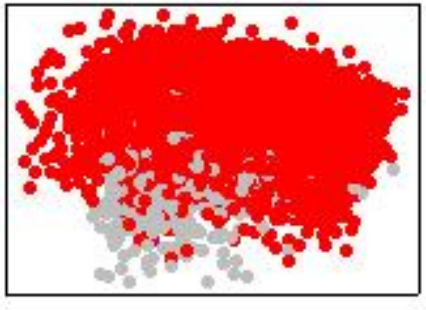
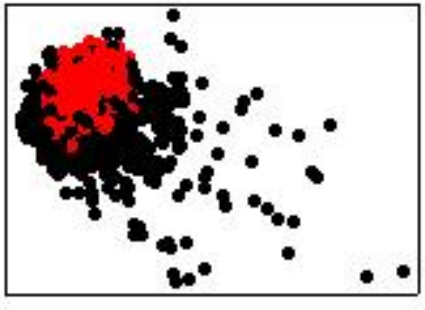
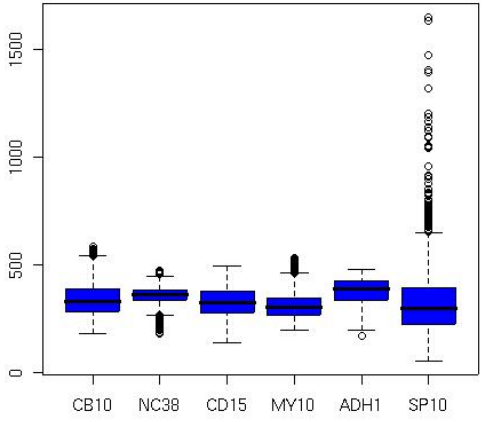


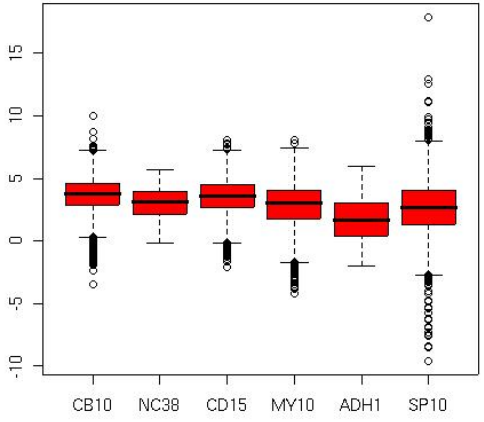


# Lipinski Descriptors #2

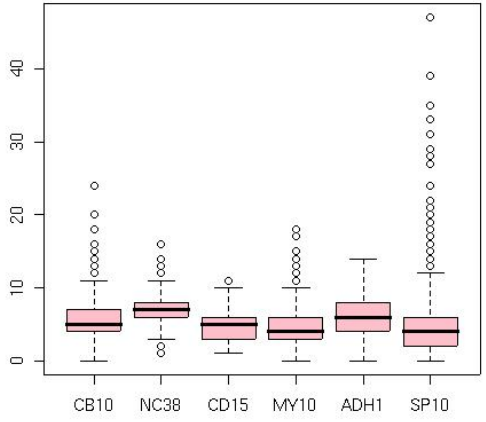
Molecular Weight



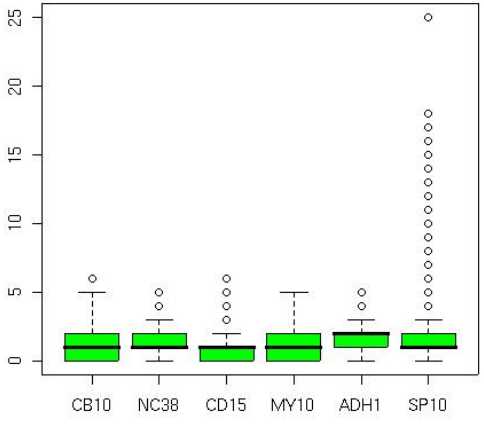

LogP



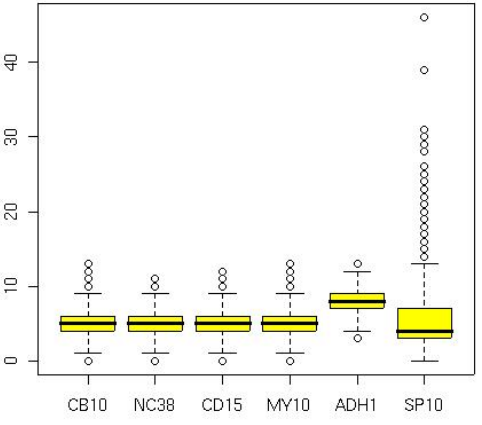

Rotatable Bonds




Hydrogen Bond Donors




Hydrogen Bond Acceptors



# Conclusions

- Low overlap in high similarity ranges (>80%)
- Strong overlap in low similarity ranges (<70%)
- Small differences in property spectrum
- Property spectrum clusters around known drugs
- Base decision on:
  - Price
  - Resupply
  - Vendor diversity

# Lab Members

**Center for Plant Cell Biology, UCR**

- Julian Krause, Undergraduate S. (CS)
- Josh Lauricha, Systems Admin (CS)
- Kevin Horan, Programmer (Math/CS)
- Li-Chang Cheng, Undergraduate (CS)
- Charles Jang, Graduate S. (CG)
- Colleen Knoth, Graduate S. (CG)
- Jack Cui, Temp (BCH/CS)
- Thomas Girke, AC & PR (BCH/MolB/BI)

# Questions

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