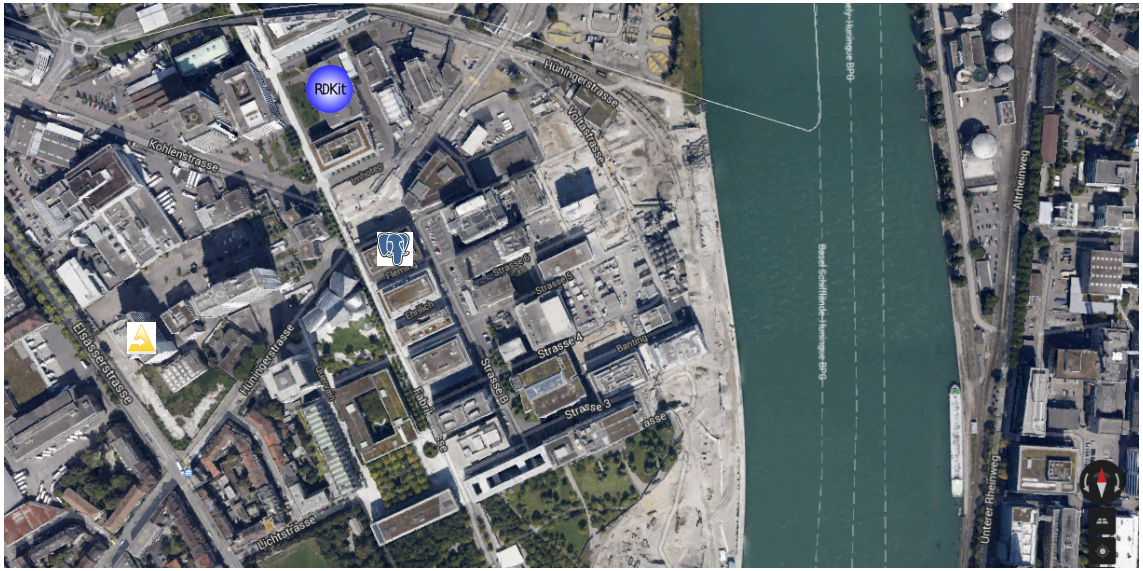


Open-source from/in the enterprise: the RDKit

Gregory Landrum

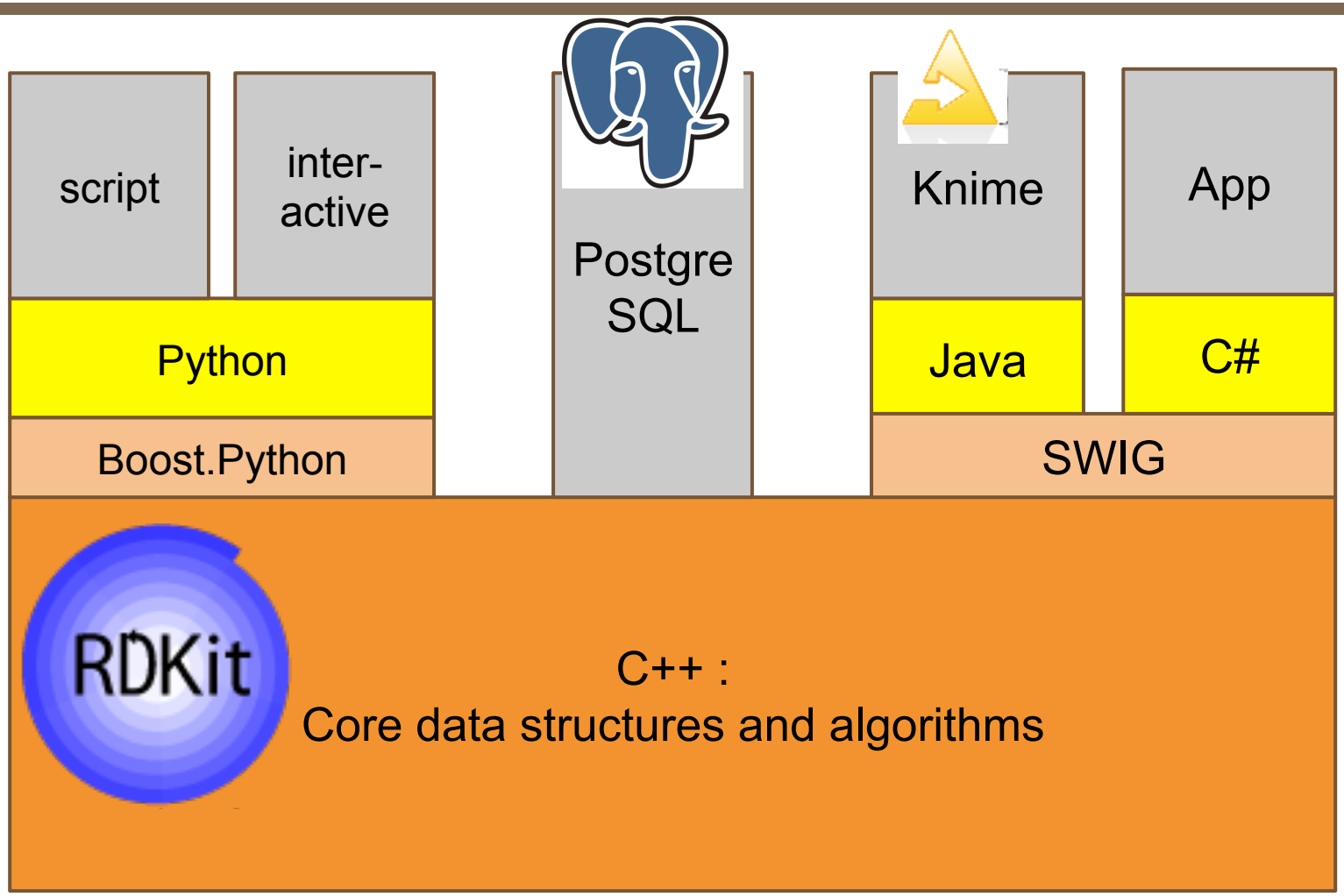
NIBR Informatics

Novartis Institutes for BioMedical Research, Basel, Switzerland

Outline

- RDKit integration with other open-source projects
  - Knime
  - PostgreSQL
  - IPython
  - Pandas
  - Lucene
- RDKit in NIBR, some case studies

What is this all about?



Exact same algorithms/implementations accessible from many different endpoints

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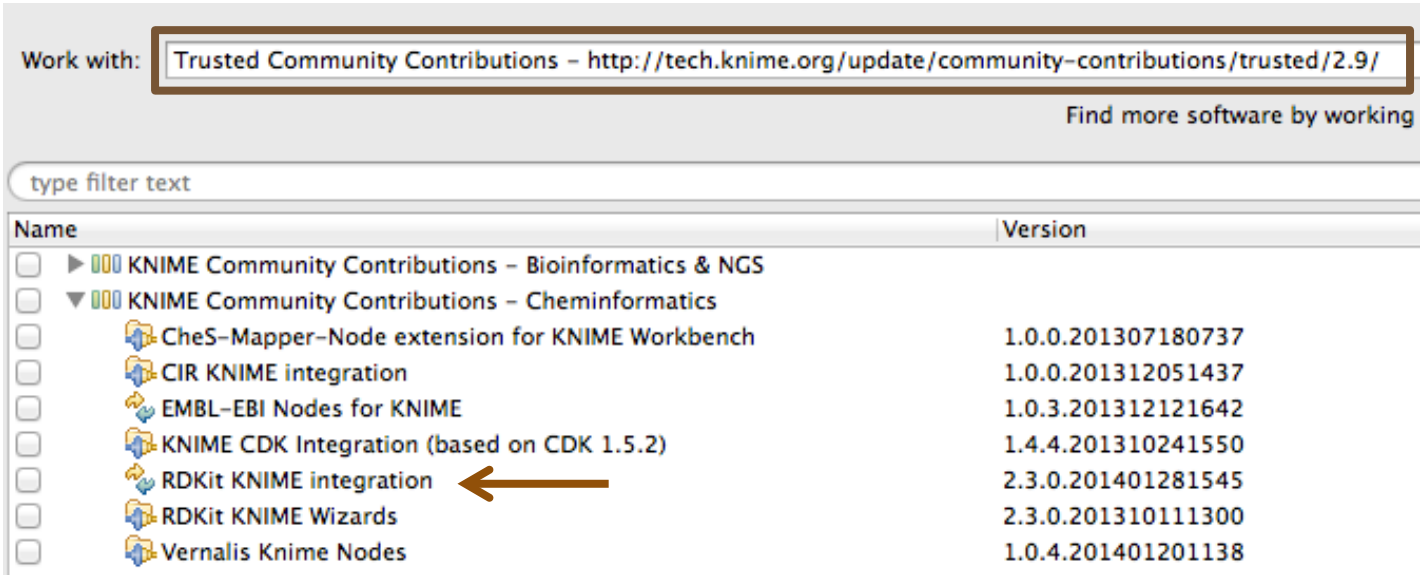
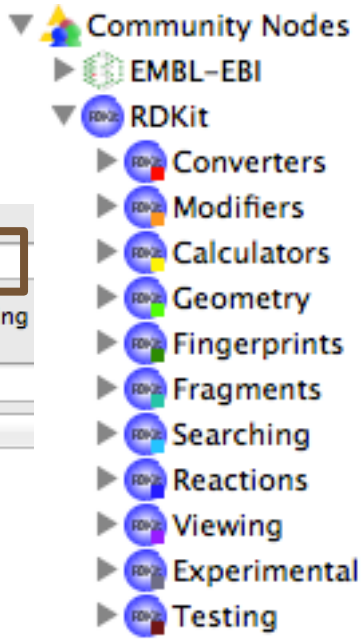
Knime integration

- *Open-source* RDKit-based nodes for Knime providing cheminformatics functionality
- Trusted nodes distributed from knime community site





- Work in progress: more nodes being added (new wizard makes it *easy*)

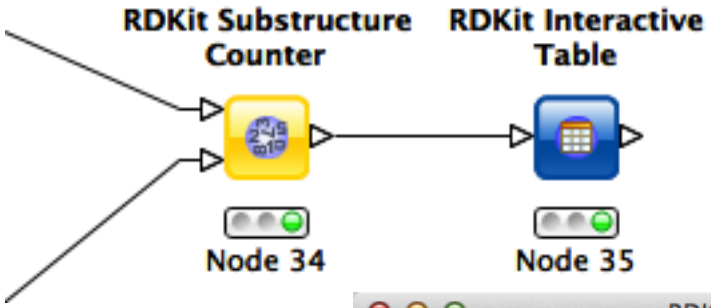
What's there?

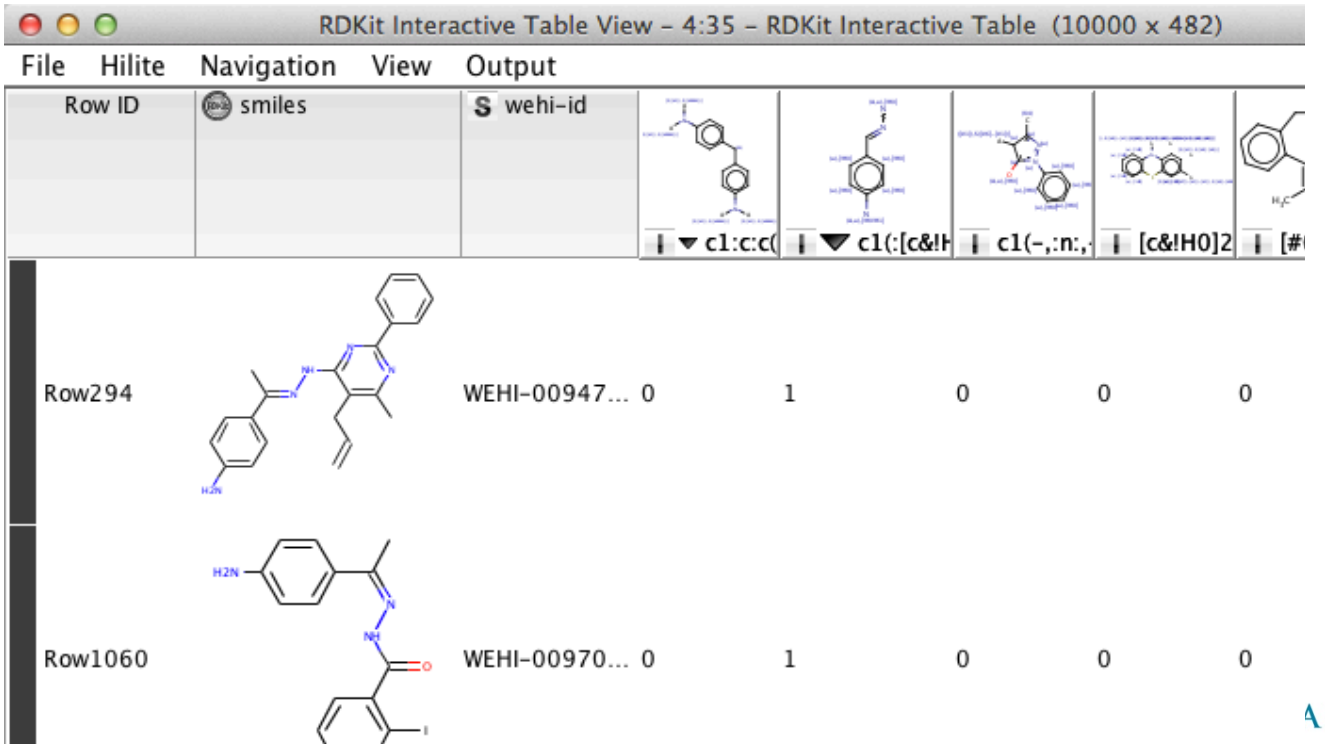
- Community Nodes
  - EMBL-EBI
  - RDKit
    - Converters
    - Modifiers
    - Calculators
    - Geometry
    - Fingerprints
    - Fragments
    - Searching
    - Reactions
    - Viewing
    - Experimental
    - Testing

- RDKit
  - Converters
    - RDKit From Molecule
    - RDKit To Molecule
    - RDKit From InChI
    - RDKit To InChI
    - RDKit From IUPAC
    - RDKit Canon SMILES
  - Modifiers
    - RDKit Add Hs
    - RDKit Remove Hs
    - RDKit Aromatizer
    - RDKit Kekulizer
    - RDKit Salt Stripper
  - Calculators
    - RDKit Descriptor Calculation
    - RDKit Calculate Charges
  - Geometry
    - RDKit Generate Coords
    - RDKit Optimize Geometry
    - RDKit Add Conformers
    - RDKit Open 3D Alignment
    - RDKit RMSD Filter
  - Geometry
  - Fingerprints
    - RDKit Fingerprint
    - RDKit Fingerprint Reader
    - RDKit Fingerprint Writer
    - RDKit Diversity Picker
  - Fragments
    - RDKit Molecule Fragmenter
    - RDKit Find Murcko Scaffolds
  - Searching
    - RDKit Substructure Filter
    - RDKit Molecule Substructure Filter
    - RDKit Dictionary Substructure Filter
    - RDKit Functional Group Filter
    - RDKit Substructure Counter
  - Reactions
    - RDKit One Component Reaction
    - RDKit Two Component Reaction
  - Viewing
    - RDKit Interactive Table
    - RDKit SMILES Headers
    - RDKit Highlighting Atoms
  - Experimental
    - RDKit R Group Decomposition

RDKit Interactive Table

- KNIME interactive table with molecules as column headers

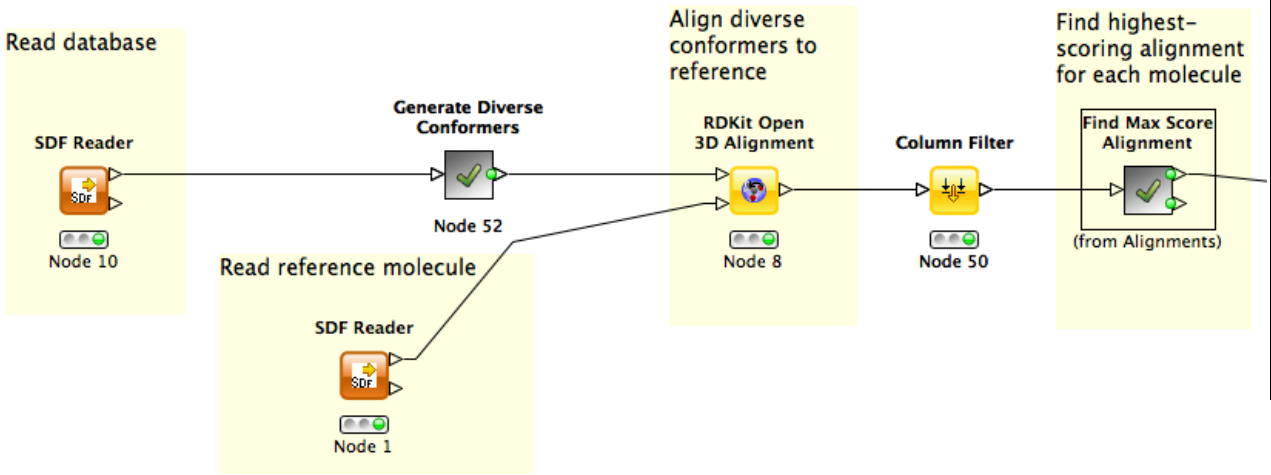


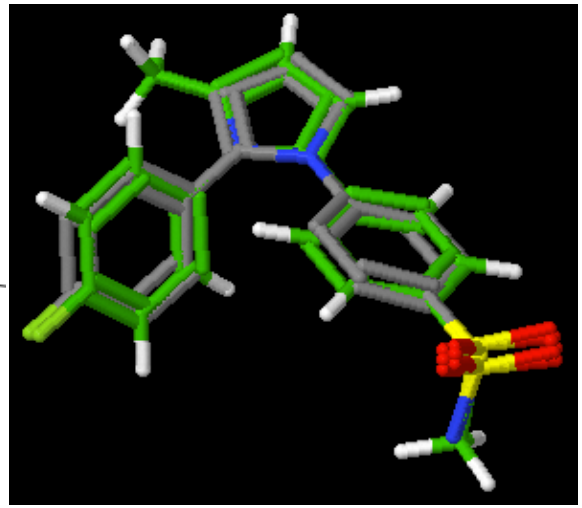


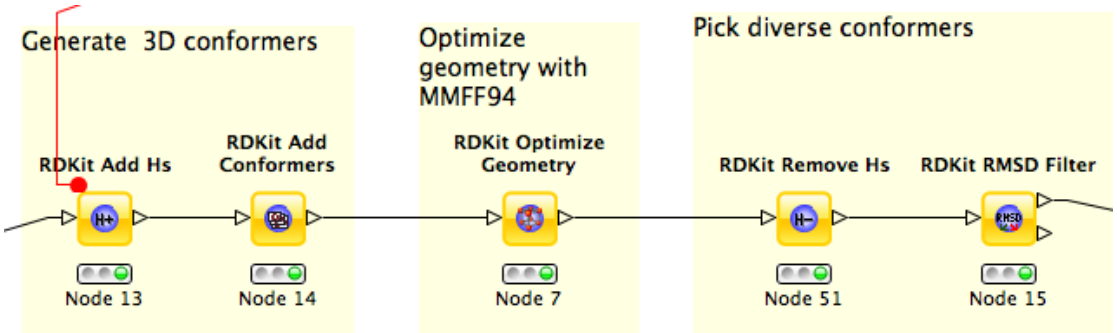
ARTIS

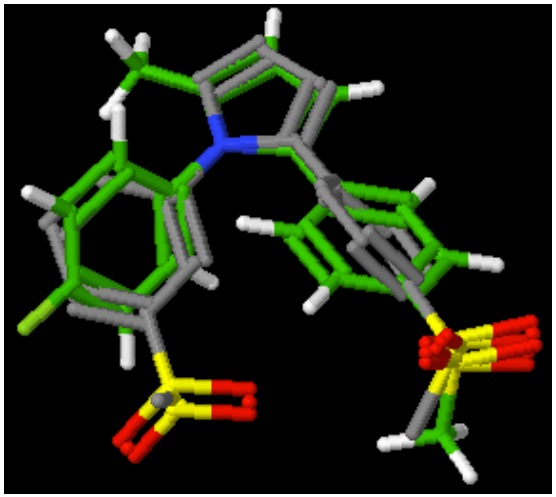
Functionality for working with 3D molecules

- Example: flexible molecule-molecule alignment









PostgreSQL integration

- PostgreSQL (http://www.postgresql.org): a robust, flexible, and extensible relational open-source database. Rich collection of extensions available
- RDKit “cartridge”:
  - Fast substructure and similarity search
  - Fingerprints (count-based and bit-vector):

    Morgan (ECFP-like), FeatMorgan (FCFP-like), RDKit (Daylight like), atom pair, topological torsion, MACCS
  - Standard molecule properties and descriptors
- Basis for myChEMBL (http://chembl.blogspot.co.uk/2013/10/chembl-virtual-machine-aka-mychembl.html) Ochoa, R., Davies, M., Papadatos, G., Atkinson, F., & Overington, J. P. (2014). myChEMBL: a virtual machine implementation of open data and cheminformatics tools. *Bioinformatics*, *30*(2), 298–300.

PostgreSQL integration

Substructure search

```
chembl_17=# select molregno,m from rdk.mols where
m@>'c1ccc2c(c1)C(=NN(C2=O)Cc3nc4cc(ccc4s3)C)CC(=O)O';
 molregno |                                m
----------+-------------------------------------------------------------
     7502 | O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)ccc3s2)c(=O)c2ccccc12
    23364 | O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)cc(C(F)(F)F)c3s2)c(=O)c2ccccc12
    23439 | O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)cc(Cl)c3s2)c(=O)c2ccccc12
    23462 | O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)cc(F)c3s2)c(=O)c2ccccc12
    24192 | Cc1cc2nc(Cn3nc(CC(=O)O)c4ccccc4c3=O)sc2c(C)c1
    24190 | COc1cc2sc(Cn3nc(CC(=O)O)c4ccccc4c3=O)nc2cc1C(F)(F)F
    24194 | Cc1ccc2sc(Cn3nc(CC(=O)O)c4ccccc4c3=O)nc2c1
    24237 | O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)c(O)cc3s2)c(=O)c2ccccc12
    24331 | CC(c1nc2cc(C(F)(F)F)ccc2s1)n1nc(CC(=O)O)c2ccccc2c1=O
(9 rows)

Time: 112.325 ms
```

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PostgreSQL integration

Similarity search

```
chembl_17=# select * from get_mfp2_neighbors('O=C(O)Cc1nn(Cc2nc3cc(C(F)
(F)F)ccc3s2)c(=O)c2ccccc12') limit 5;
 molregno |                          m                          |    similarity
----------+-----------------------------------------------------+--------------------
     7502 | O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)ccc3s2)c(=O)c2ccccc12  |                  1
    24184 | O=C(O)Cc1nn(Cc2nc3ccc(C(F)(F)F)cc3s2)c(=O)c2ccccc12  | 0.859649122807018
    24153 | O=C(O)Cc1nn(CCc2nc3cc(C(F)(F)F)ccc3s2)c(=O)c2ccccc12 | 0.830508474576271
    24152 | O=C(O)Cc1nn(Cc2nc3ccccc3s2)c(=O)c2cc(C(F)(F)F)ccc12  | 0.813559322033898
    24150 | O=C(O)Cc1nn(Cc2nc3ccccc3s2)c(=O)c2ccc(C(F)(F)F)cc12  | 0.813559322033898
(5 rows)

Time: 1222.426 ms
```

Notice that results come back in sorted order

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PostgreSQL integration

Other functionality

```
chembl_17=# select mol_formula('O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)ccc3s2)c(=O)c2ccccc12');
  mol_formula
---------------
 C19H12F3N3O3S
(1 row)
chembl_17=# select mol_logp('O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)ccc3s2)c(=O)c2ccccc12');
 mol_logp
----------
   3.7004
(1 row)
chembl_17=# select mol_inchi('O=C(O)Cc1nn(Cc2nc3cc(C(F)(F)F)ccc3s2)c(=O)c2ccccc12');
mol_inchi
------------------------------------------------------------------------------------------
-----------------------------------------------
 InChI=1S/C19H12F3N3O3S/
c20-19(21,22)10-5-6-15-14(7-10)23-16(29-15)9-25-18(28)12-4-2-1-3-11(12)13(24-25)8-17(26)27
/h1-7H,8-9H2,(H,26,27)
(1 row)
```

PostgreSQL integration

Other functionality

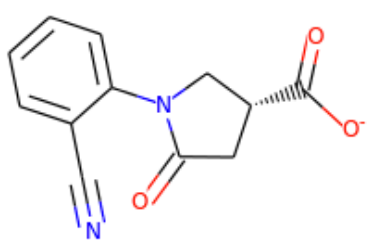
```
chembl_17=# select mol_to_ctab('CC'::mol);
                              mol_to_ctab
-----------------------------------------------------------------------
                                                                      +
      RDKit          2D                                               +
                                                                      +
   2  1  0  0  0  0  0  0  0  0999 V2000                              +
     0.0000    0.0000    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0+
     1.2990    0.7500    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0+
   1  2  1  0                                                         +
 M  END                                                               +

(1 row)
```

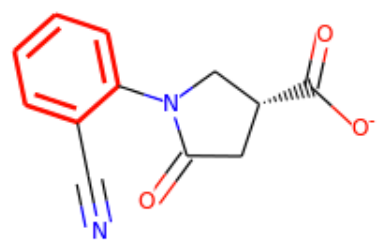
IPython notebok integration

- IPython: a very powerful interactive shell for python
  http://www.ipython.org
- IPython notebook: IPython in the browser, with graphics
  - combines code and output in one place
  - great tool for reproducible research
  - Example notebook with graphics.
- RDKit integration:
  - Display molecules, substructure matches, reactions, graphics from PyMOL

```
In [3]: Chem.SetHybridization(m)
        m
Out[3]:
```



```
In [4]: tmp=m.GetSubstructMatch(Chem.MolFromSmarts('c1cccccl'))
        m
Out[4]:
```



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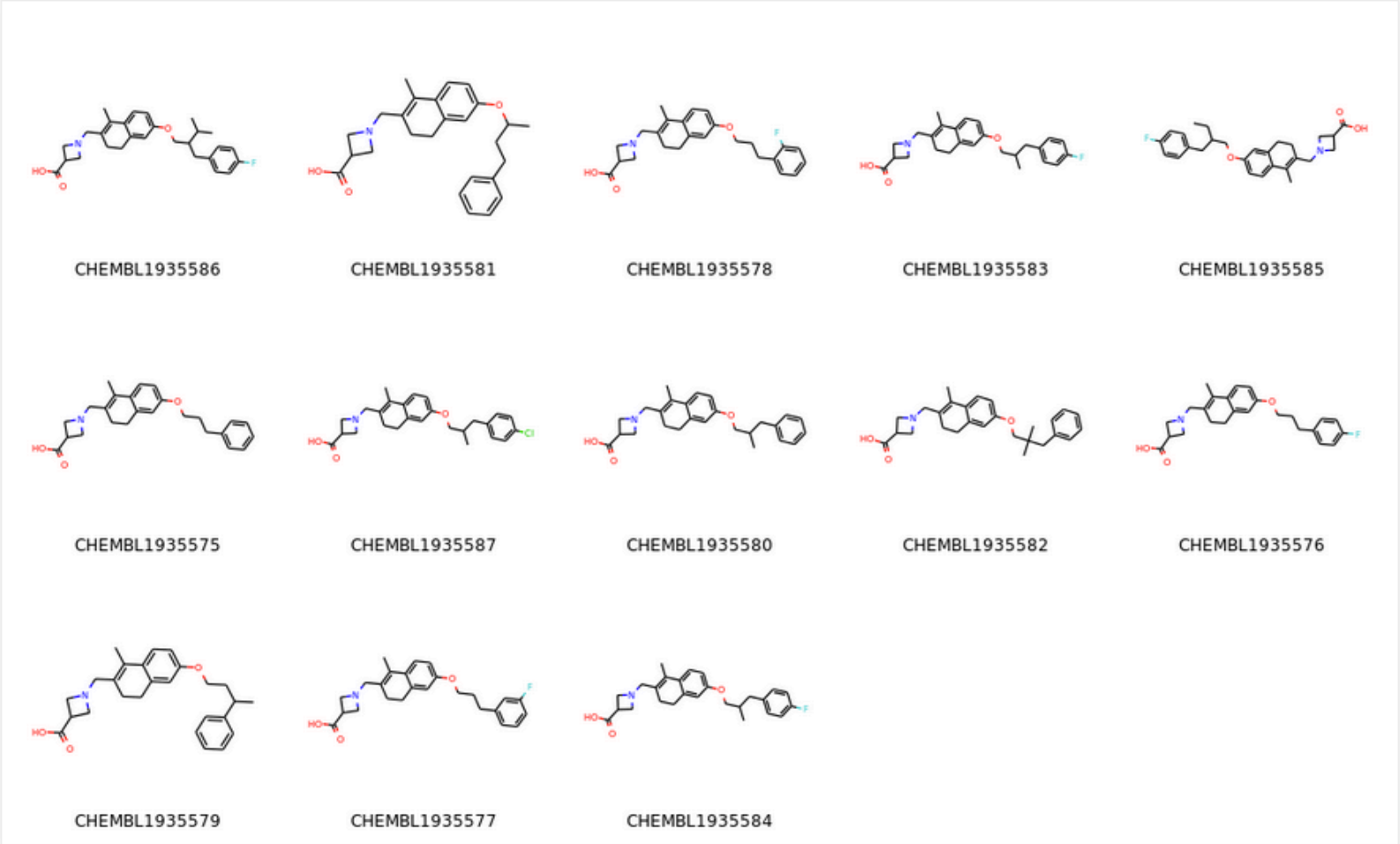
IPython notebook integration:
Molecule tables

IP[y]: + RDKit

In [8]:
```
ids,smis= zip(*cmpds)
mols = [Chem.MolFromSmiles(x) for x in smis]
Draw.MolsToGridImage(mols,molsPerRow=5,legends=ids)
```

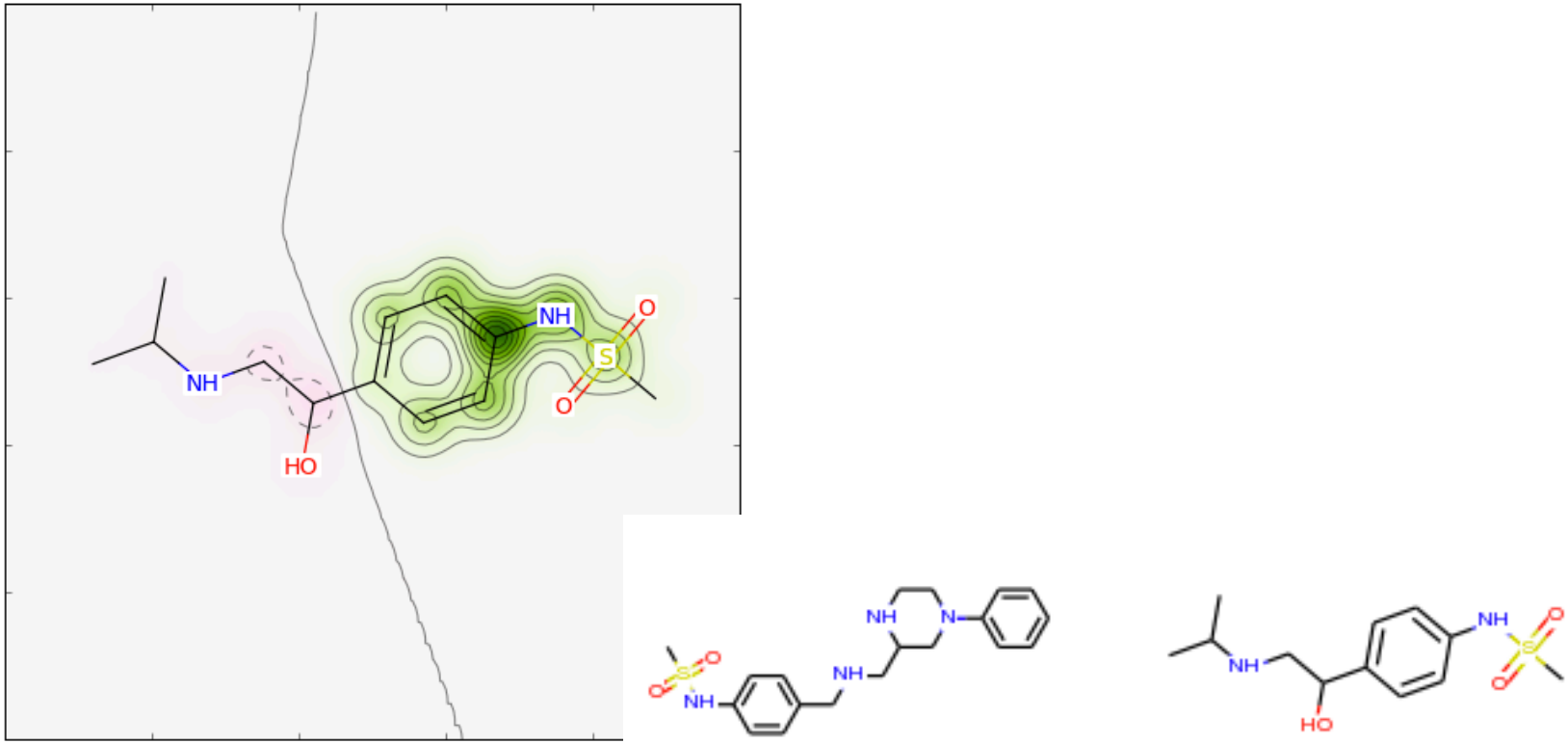
Out[8]:



http://rdkit.blogspot.ch/2014/02/more-on-datasets-ii.html

IPython notebook integration:
Similarity Maps

```
In [56]: SimilarityMaps.GetSimilarityMapForFingerprint(ms[0],ms[16],SimilarityMaps.GetTTFingerprint)
Out[56]: (<matplotlib.figure.Figure at 0x109786850>, 0.31663113006396593)
```



Riniker, S. & Landrum, G. A. J Cheminf (2013). http://www.jcheminf.com/content/5/1/43

IPython notebook integration:
PyMol

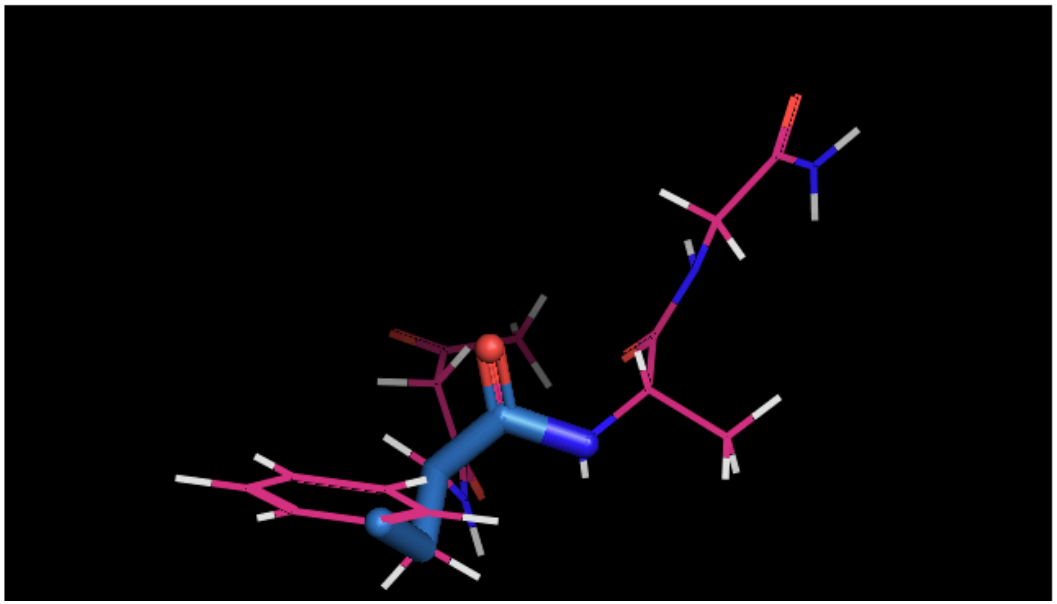
IP[y]: + RDKit

In [12]:
```
nm = Chem.Mol(matchingMols[3])
GetFF=lambda x,confId=-1:AllChem.MMFFGetMoleculeForceField(x,AllChem.MMFFGetMoleculeProperties(x),confId=conf
Id)
AllChem.ConstrainedEmbed(nm,core1,getForceField=GetFF)
rms = float(nm.GetProp('EmbedRMS'))
print 'RMS:',rms


v.ShowMol(core1,molB=Chem.MolToMolBlock(core1,kekulize=False),name='core')
v.SetDisplayStyle('core','sticks')
v.ShowMol(nm,'constrained embed',showOnly=False)
v.GetPNG(preDelay=2)
```

```
RMS: 0.0407469103071
```

Out[12]:



http://rdkit.blogspot.ch/2013/12/using-allchemconstrainedembed.html

Pandas integration

pandas + RDKit

- Pandas: library for working with data tables in Python. Integrates well with matplotlib and ipython

  http://pandas.pydata.org/
- RDKit integration:
  - Load smiles tables or SD files into Pandas data tables
  - Adds molecule columns to existing tables with smiles/SD columns
  - Enables substructure filters on tables
  - Integration with IPython notebook to render molecules

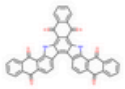
Pandas integration

pandas + RDKit

Molecules in tables

```
In [6]: PandasTools.AddMoleculeColumnToFrame(data,smilesCol='smiles',molCol='molecule',includeFingerprints=False)
        data.head(2)
```

Out[6]:

	smiles	mutagenic	molecule
cas			
2475-33-4	O=C1c2ccccc2C(=O)c3c1ccc4c3[nH]c5c6C(=O)c7ccccc7C(=O)c6c8[nH]c9c%10C(=O)c%11ccccc%11C(=O)c%10ccc9c8c45	0	
820-75-7	NNC(=O)CNC(=O)\C=N\#N	1	None

Substructure filters

```
In [11]: data.groupby(data['molecule'] >= nitroso).describe().unstack()
```

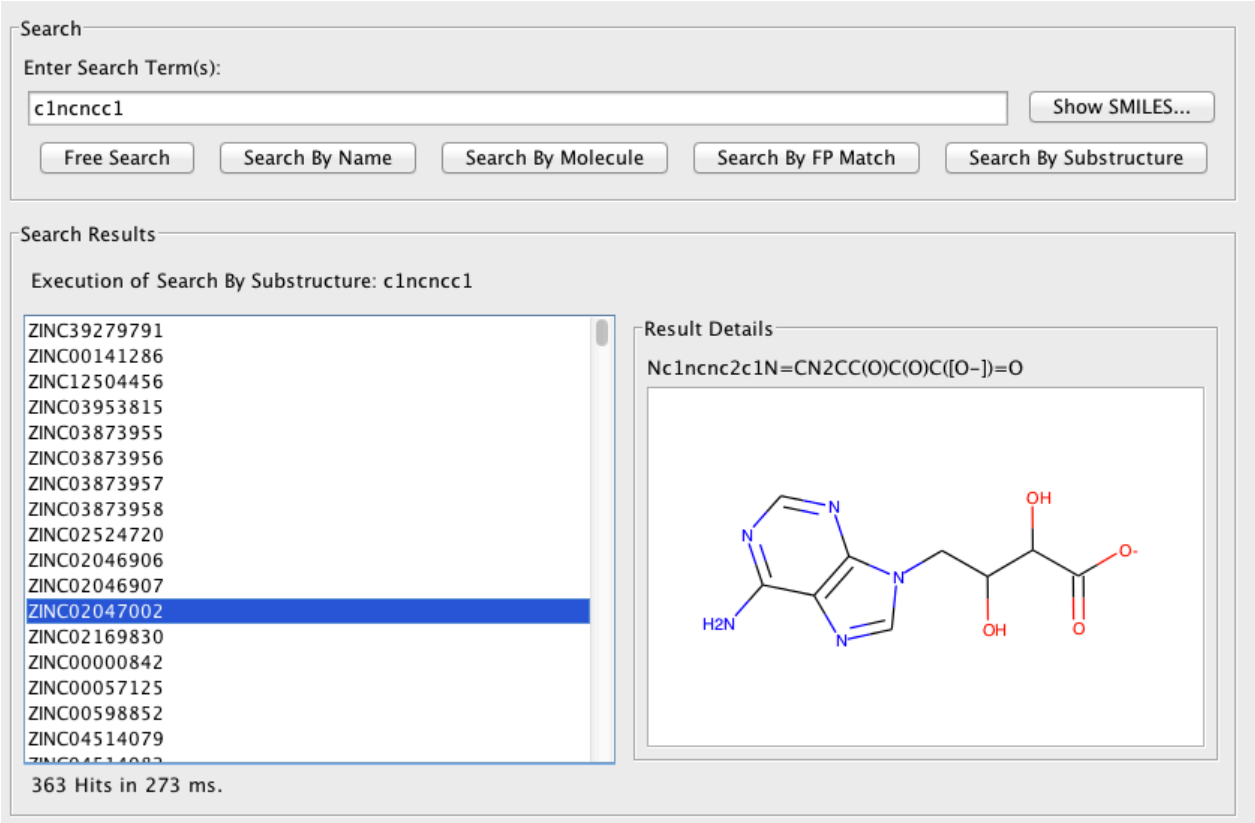
Out[11]:

	mutagenic							
	count	**mean**	**std**	**min**	**25%**	**50%**	**75%**	**max**
molecule								
False	5217	0.461760	0.498583	0	0	0	1	1
True	1233	0.838605	0.368044	0	1	1	1	1

http://nbviewer.ipython.org/github/rdkit/UGM_2013/blob/master/Tutorials/pandastools/Pandas_RDKit_UGM.ipynb

Lucene integration

- Still in the experimental stage
- Adds substructure search functionality with fingerprint screenout to Lucene
- Includes demo app for testing



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RDKit in NIBR

- Extensive use by CADD, informaticians, and IT
- Lots of convenience code/wrappers for accessing internal data sources and tools
- Combined with the Avalon toolkit (another NIBR-supported open-source project), provides the underpinning for many of our global chemistry-based applications

The Avalon toolkit

- C/Java cheminformatics toolkit
- Primary author: Bernd Rohde (NIBR Informatics Basel)
- http://sourceforge.net/projects/avalontoolkit/
- Functionality:
  - Canonical SMILES
  - Avalon fingerprint (highly optimized substructure fingerprint)
  - Molecular standardization (STRUCHK)
  - 2D Coordinate generation
  - Tomcat webapp for 2D rendering

- The RDKit has (optional) Python bindings for much of the functionality

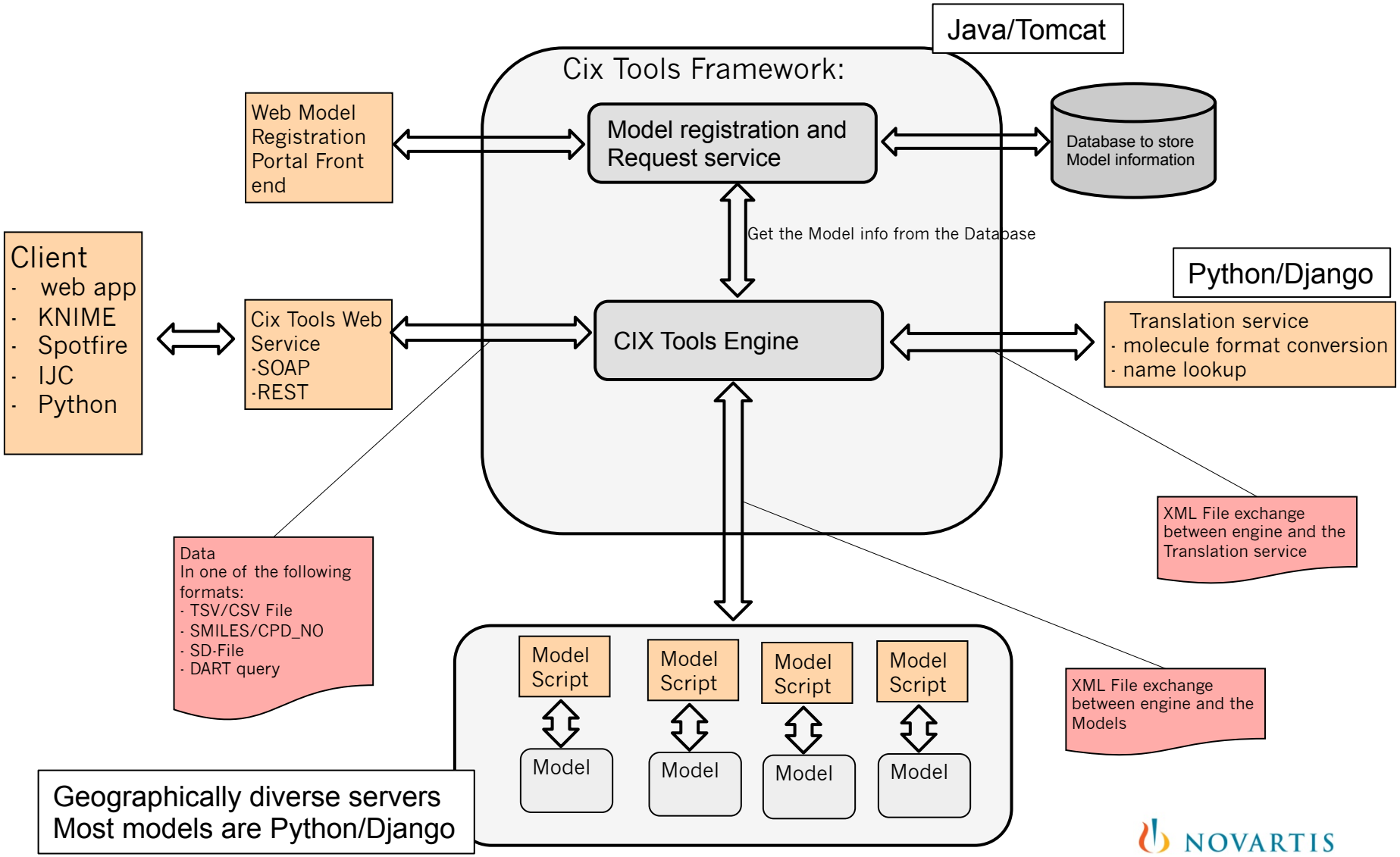
RDKit in NIBR

Case study 1: CIx Framework

- "Service bus" for cheminformatics/CADD services
- Handles format conversions for input/output automatically

  i.e. callers can provide SMILES input to a service/model wants CTABs with 3D coordinates
- Supports versioning of models/services
- Tight integration with scientific tools (e.g. Tibco Spotfire, Knime, Instant JChem, etc.)
- Enables trivial addition of "chemical intelligence" to web apps
- Makes it easy to globally deploy models: once a new model/service (or new version of a model/service) is registered with the Framework, it is instantly globally accessible

CIx Framework architecture



RDKit in NIBR

Case study 2: Small-Molecule Registration

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- Internally developed web application for compound registration
- C#-based web services writing to Oracle
- RDKit + Avalon toolkit for structure standardization
- RDKit + InChI used for structure-key calculation
- Calls out to CIx Framework for standard computed properties

- Independent (but validated) Python implementation of standardization and structure-key calculation for standalone use

RDKit in NIBR

Case study 3: QSAR Toolkit

- Descriptor calculator providing access to all available internal descriptors
- Tools for pulling assay data from our data warehouse
- Standardized model-building
- Standardized reporting for evaluation and peer review
- Packaging for deployment via CIx Framework
- Model Watchdog:

  Pulls most recent data, generates predictions, creates report showing evolution of model accuracy over time

RDKit in NIBR

Case study 4: Similarity Server

- Central PostgreSQL database with easily available compounds
  - in-house available
  - available from reliable vendors
- Kept up-to-date
- Substructure search
- Similarity search with various fingerprints:
  - Avalon
  - Morgan2, Morgan3, FeatMorgan2
  - Atom Pairs, Topological Torsions
- Web services interface
- Available to chemists via one of their standard desktop tools

- Currently deploying a new version based on chemfp

RDKit in NIBR

Case study 5: Compound Series and Favorites

- Central system to store definitions of the chemical series that project teams are working on
- Captures annotations and relationships
- Searchable, including Markush search (using ChemAxon cartridge)
- Accessible via web services
- RDKit used for scaffold validation

RDKit in NIBR

Case study 5: Compound Series and Favorites

Scaffold

Compound

RDKit in NIBR

Case study 5: Compound Series and Favorites

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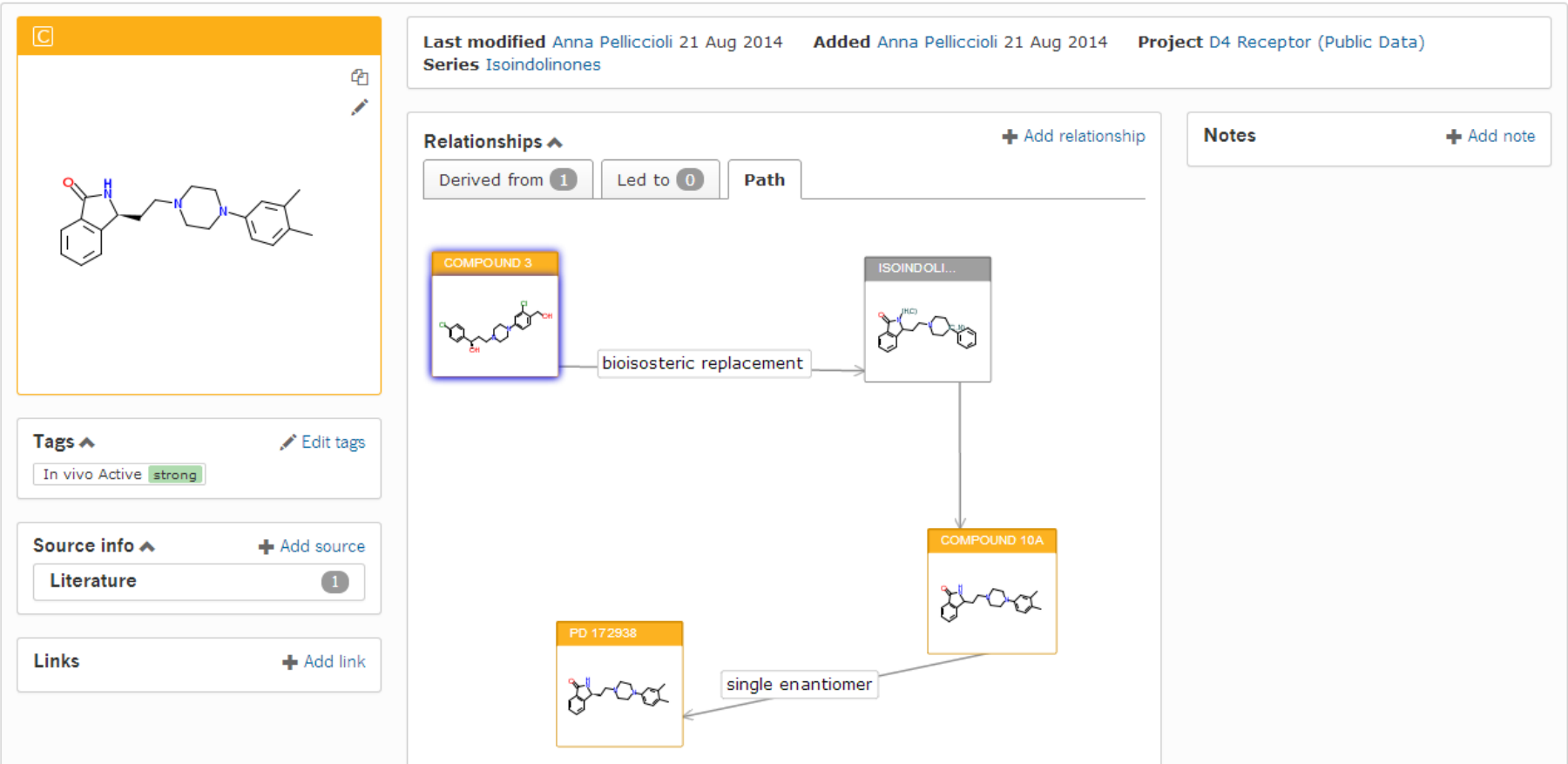
PD 172938



NIBR Open Source

Something new

opensource.nibr.com

Apps | Boost | DART-stage | DART | STL | Open in Papers | Other

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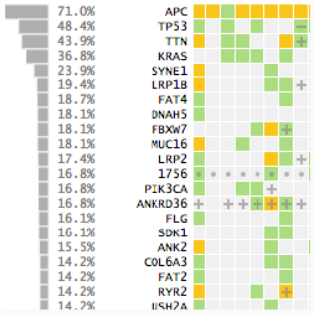
GridVar



GridVar is a jQuery plugin that visualizes multi-dimensional datasets

RDKit

RDKit

A collection of cheminformatics and machine-learning software written in

GitHub, Inc. [US] https://github.com/novartis

Boost | DART-stage | DART | STL | Open in Papers

Search or type a command | Explore | Gist | Blog | Help

Novartis

Find a repository...

gridvar JavaScript ★4 ⑂2

GridVar is a jQuery plugin that visualizes multi-dimensional datasets as layers organized in a row-column format.

Updated a month ago

Acknowledgements

http://www.rdkit.org

- General:
  - Remy Evard (NIBR/Informatics)
  - Richard Lewis (NIBR/GDC)
  - Tom Digby (NIBR/Legal)
  - Peter Gedeck (NIBR/GDC)
  - Nik Stiefl (NIBR/GDC)
- RDKit Community
  - Roger Sayle (NextMove): PDB Parser
  - Andrew Dalke (Dalke Scientific): FMCS
  - Paolo Tosco (University of Turin, now Cresset): MMFF94, Open3DAlign
  - Jameed Hussain (GSK, now CCG): Fraggle, mmpa
- Pandas, scikit-learn:
  - Sereina Riniker (NIBR/Informatics, now ETH)
  - Nikolas Fechner (NIBR/Informatics)
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  - Thorsten Meinl (knime.com)
  - Bernd Wiswedel (knime.com)
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  - Nikolas Fechner (NIBR/Informatics)
- CIx Framework
  - Sandra Mueller (NIBR/Informatics)
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  - Riccardo Vianello (NIBR/Informatics)
- Compound Series & Favorites
  - Anna Pelliccioli (NIBR/Informatics)
  - Manuel Schwarze (NIBR/Informatics)
  - Recca Chatterjee (NIBR/Informatics)
  - Mikhail Rybalkin (NIBR/Informatics)
  - Roman Bolshev (NIBR/Informatics)
- NIBR Open Source
  - Ken Robbins (NIBR/Informatics)
  - Dennis Jen (NIBR/Informatics)
  - Mark Schreiber (NIBR/Informatics)

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