

Triplos Chemistry Extensions (TCE)

Dr. Fabian Bös, Application Scientist



Tripos Chemistry Extensions (TCE)

Introduces “chemical intelligence” to the KNIME platform

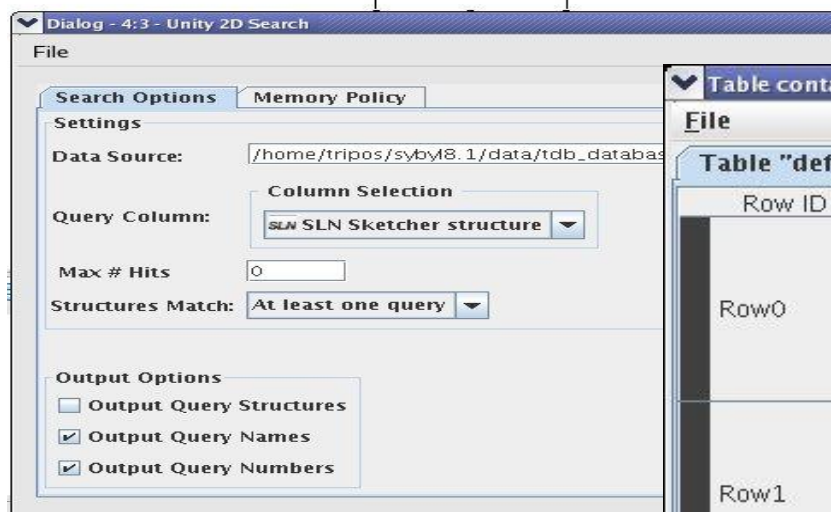
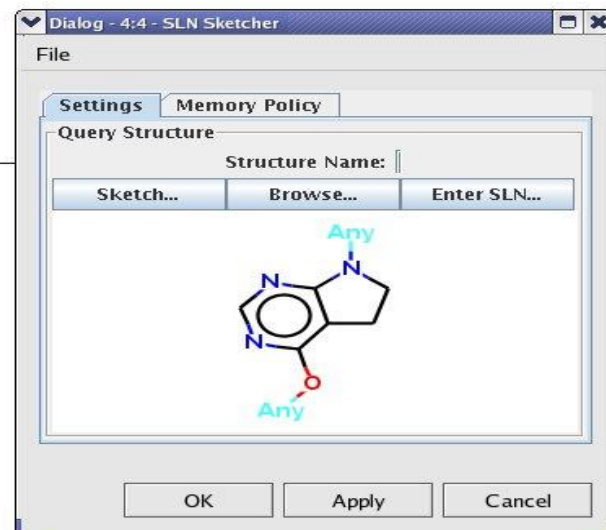
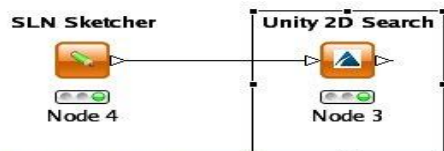
- read / write and process chemical structures
- perform cheminformatics tasks
- visualize & analyze molecular structures



Tripos Chemistry Extensions (TCE)

Direct integration into KNIME

- Right mouse click to configure
- 2D rendering in KNIME table



Row ID	SLN SLN	D MW	D Donors	D Accept...	D AlogP	D TPS
Row0		233.311	1	4	2.967	49.25
Row1		233.311	1	4	2.967	49.25
Row2		240.324	1	4	2.19	80.54



Tripos Chemistry Extensions (TCE)

Read / write the following chemical file formats:

MOL2 Reader



Node 1

SD Reader



Node 2

SLN Reader



Node 3

SMILES Reader



Node 4

UNITY DB Reader



Node 5

MOL2 Writer



Node 6

SD Writer



Node 7

SLN Writer



Node 8

SMILES Writer



Node 9

Unity DB Writer

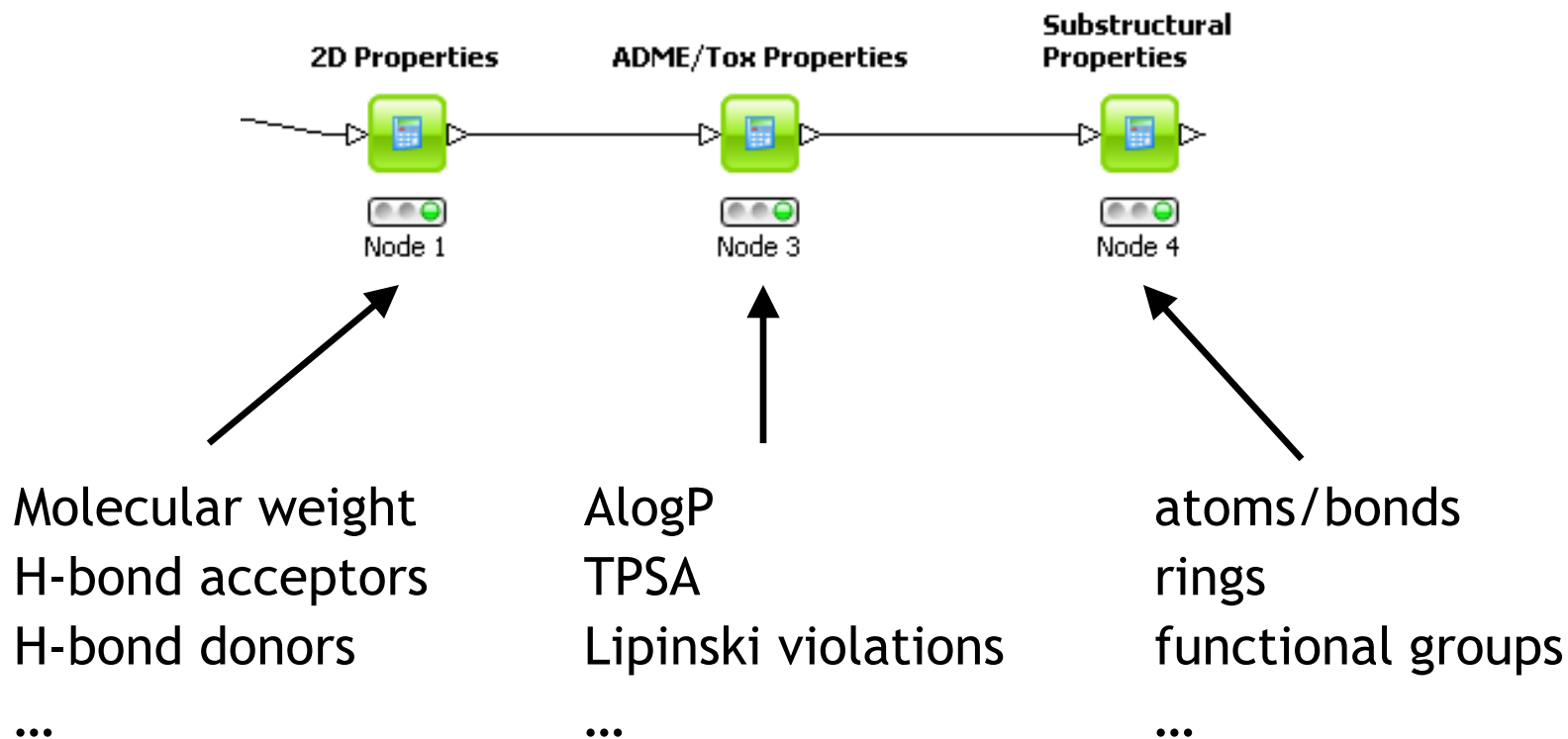


Node 10



Tripos Chemistry Extensions (TCE)

Compute molecular properties





Tripos Chemistry Extensions (TCE)

Compare molecules:

UNITY Fingerprint



Node 1

Tanimoto Similarity



Node 2

Create Tuplets



Node 9

Compare Tuplets



Node 4

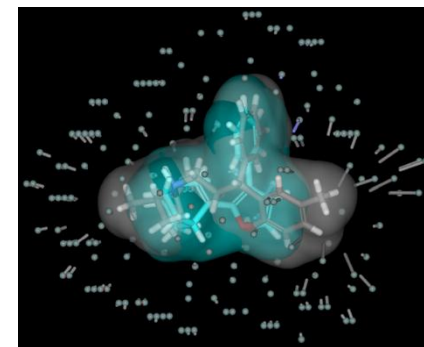
SurflexSim



Node 5

using

- Fingerprints
- Steric & Pharmacophore Tuplets¹
- Molecular shape, hydrogen bonding and electrostatic properties²



[1] Abrahamian et. al., J. Chem. Inf. Comput. Sci., 43, 458-468, (2003). [2] Jain, J. Med. Chem., 47, 947-961 (2004) & Cleves, J. Med. Chem., 49, 2921-2938 (2006).



Tripos Chemistry Extensions (TCE)

Useful Tools:

Molecule Parser



Node 6

Molecular Validator



Node 1

2D Alignment



Node 3

DBTranslate (Local)



Node 2

Concord (local)



Node 4

SLN Sketcher



Node 5

HQSAR:

HQSAR Learner



Node 1

HQSAR Predictor



Node 2

Model Writer



Node 3

HQSAR: QSAR method based on molecular hologram fingerprints.



Tripos Chemistry Extensions (TCE)

2D & 3D UNITY database searching:

Unity 2D Search



Node 9

Unity 2D Filter



Node 14

**Unity 2D
Similarity Filter**



Node 16

**Unity Exact
Match Filter**



Node 19

**Unity 2D
Similarity Search**



Node 10

**Unity 3D
Query Reader**



Node 21

Unity 3D Filter



Node 18

Unity Flex Filter



Node 20

Search nodes act on (existing) UNITY database directly
Filter nodes act on the structures in a KNIME table

Triplos Chemistry Extensions (TCE)

Visualization:



Untitled - KNIME workflow: Fri Sep 25 15:10

File Edit View Display Select Calculate Align Window Help

SYBYL-X 1.0 (linux_os2x), Created Aug 31, 2009

File Edit View Compute Applications Biopolymer UNITY Options Help

Screen Shot

Grab

○ a Single Window

SLNFromKNIME5913158395222133354 (/tmp/SLNFromKNIME5913158395222133354.h

File Edit View Compute Info Graph Options QSAR

AutoFill Pick Points Show RowSel Select Rows Select Cols

25 of 25 rows 0 of 0 columns No Analysis

1:

<input type="checkbox"/>	1: cefazolin
<input checked="" type="checkbox"/>	2: salicylic_acid
<input checked="" type="checkbox"/>	3: phenylbutazone
<input checked="" type="checkbox"/>	4: sulfisoxazole
<input checked="" type="checkbox"/>	5: hydrocortisone
<input checked="" type="checkbox"/>	6: pyridostigmine_bromide
<input checked="" type="checkbox"/>	7: dextromethorphan
<input checked="" type="checkbox"/>	8: estazolam
<input checked="" type="checkbox"/>	9: ganciclovir
<input checked="" type="checkbox"/>	10: iodoquinol

Show Selected Rows

Current Row Id: 1 (1 of 25)
cefazolin

Previous Next

Mark Current

Jump to Row of 25

Copy Molecule to M2

Help Close

Using customized SYBYL settings contained in

```
SYBYL> TABLE OPRI /tmp/SLNFromKNIME5913158395222133354.h
SYBYL>
ROW 1 cefazolin
```

Default Molecule: M1 :: Default Directory: /home/ulrike/

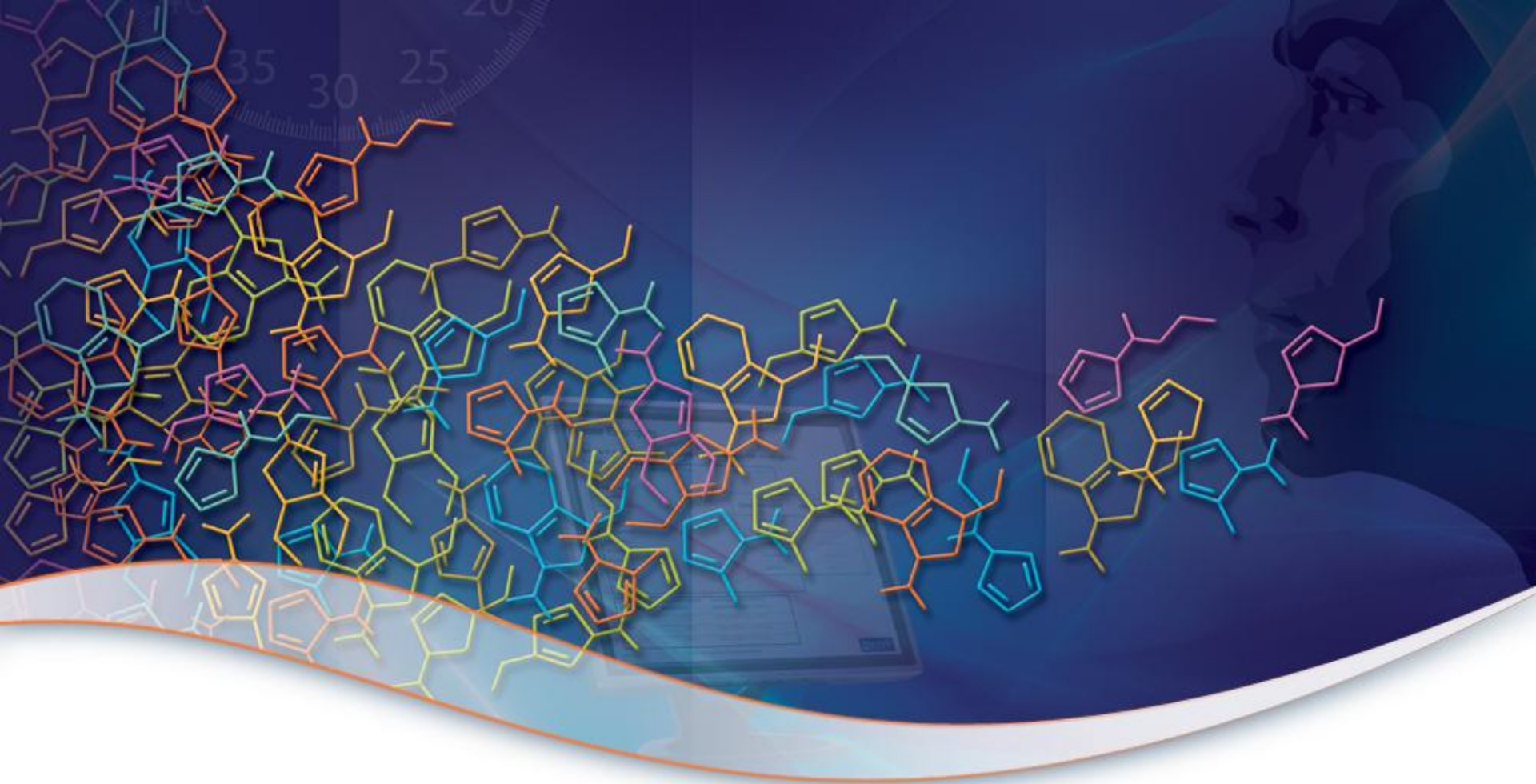
Slide 1 - OpenOffice.org 1.1.5

KNIME

Ready Deselected All.

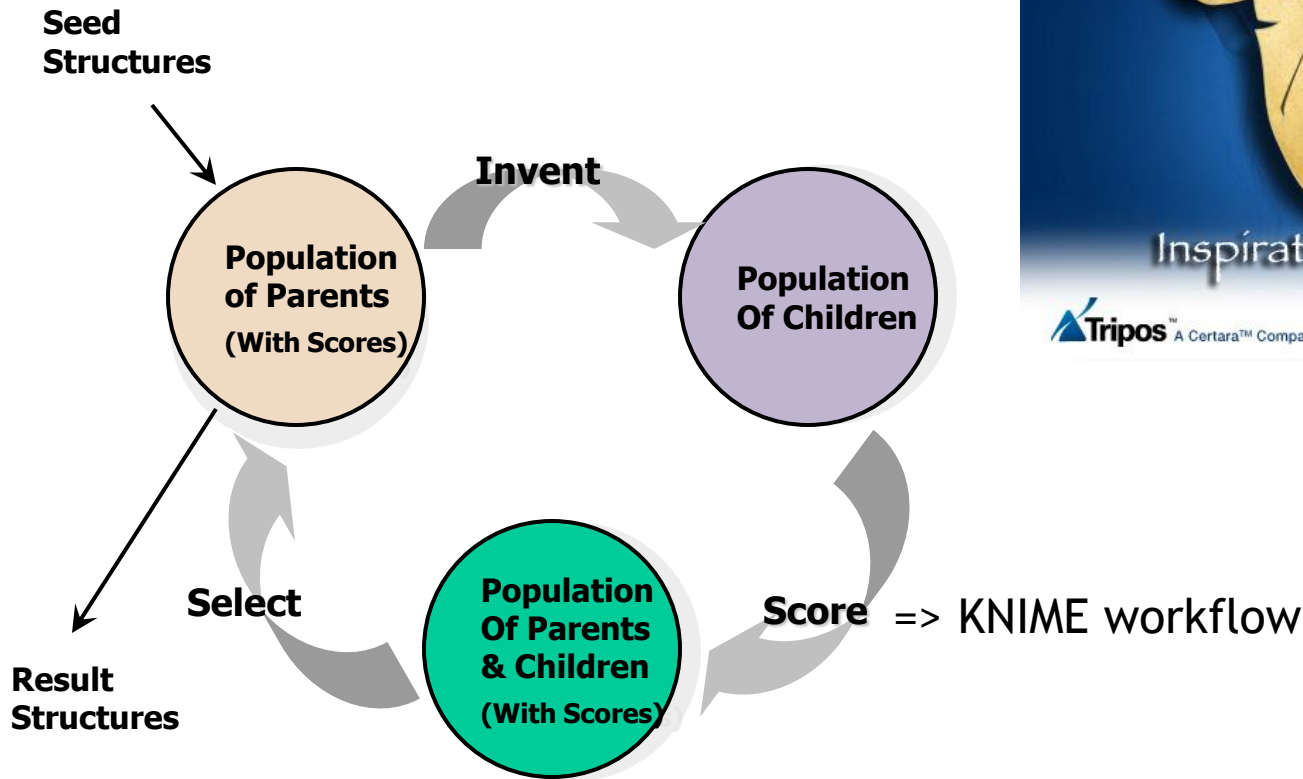
SLN Reader
Node 16

Sybyl Spreadsheet
Node 10



TripoSTMScore, a KNIME-based multi-criteria scoring function for molecular invention

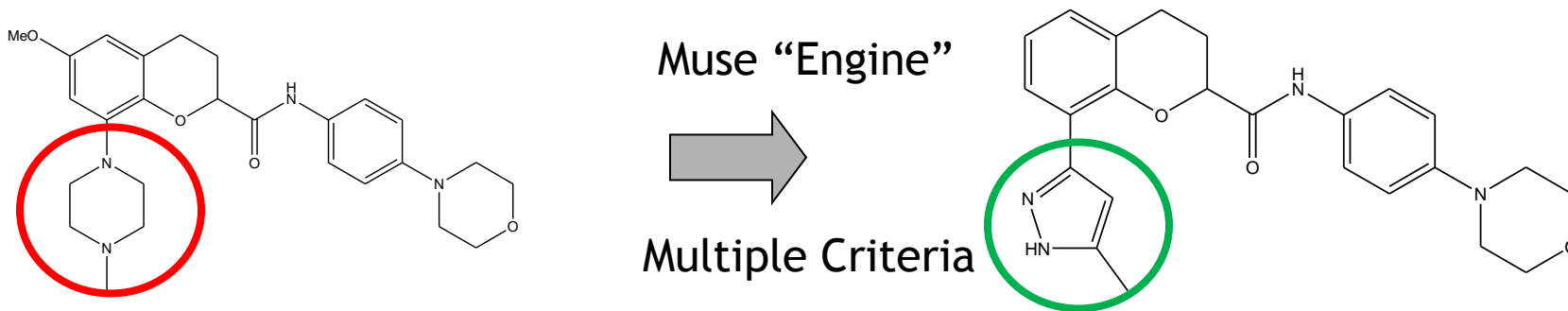
Multi-Criteria Composable Scoring Via KNIME



Multi-Criteria Composible Scoring Via KNIME

Described several examples of successful “retrospective leadhopping” using molecular invention based on multiple criteria (see Webinar at www.tripos.com)

Described design of novel non-basic side chain to solve DMPK/Tox problem



Shape and Pharmacophore Similarity to different targets

Polypharmacology (e.g. D1 and D2 dopamine receptors)

Range of Predicted Physical/ADME Properties

E.g cLopP,

E.g. BBB, Solubility, hERG, etc..

Inverse QSAR

Shape and Pharmacophore avoidance of other targets

Selectivity for anti-targets

2D fingerprint distance to “undesirables”

Competitors compounds

Toxicophores

D.A. Nugiel, et. al. “Denovo Design of a Picomolar Nonbasic 5-HT_{1b} Receptor Antagonist”
J Med Chem 53 (4), 2010, 1876-1880



Multi-Criteria Composable Scoring Via KNIME

October 8, 2008 9:00 AM Eastern Daylight Time

Tripos International Enters into Agreement to Collaborate on a Molecular Invention Workflow for Drug Discovery with AstraZeneca

ST. LOUIS--([BUSINESS WIRE](#))-- Tripos International, a leading provider of drug discovery informatics products and services, today announced a collaboration agreement with AstraZeneca to develop a new drug discovery workflow solution.

The centerpiece of the collaboration effort will be the development of Tripos' new Muse™ *de novo* design product, which is targeted for commercial release in the fourth quarter of 2008. Muse, which will be designed to accelerate the identification and optimization of lead candidates, will combine *de novo* design with multi-criteria optimization to deliver the first of many solutions being prepared for release on Tripos' highly flexible, adaptable and extensible Pantheon™ platform.



Multi-Criteria Composable Scoring Via KNIME

TriposScore

Shape and Pharmacophore

Surflex-Sim

Molecular Properties

AlogP

MW

TPSA

H-Bond Don and Acc Counts

Rot Bonds Count

Lipinski Violations

Avoid Anti-Targets

2D Fingerprint Similarity

Score “Normalizers” and
“Combiner”

Square, Pass/Fail, Bell Curve,
Trapazoid

Weighted sums (or products)

Configurable and Extendable

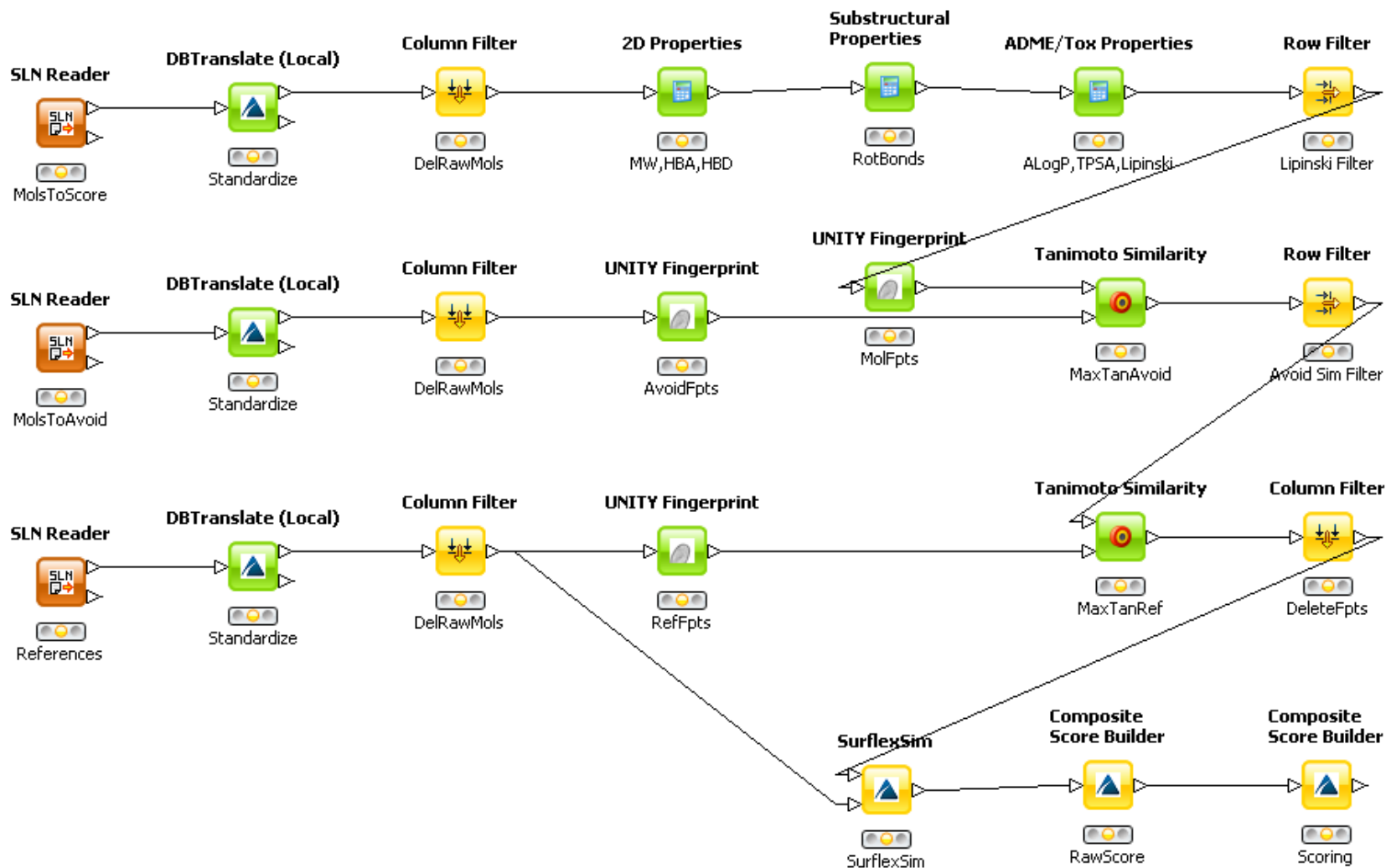
Integrate in-house tools

Use your own ADME models

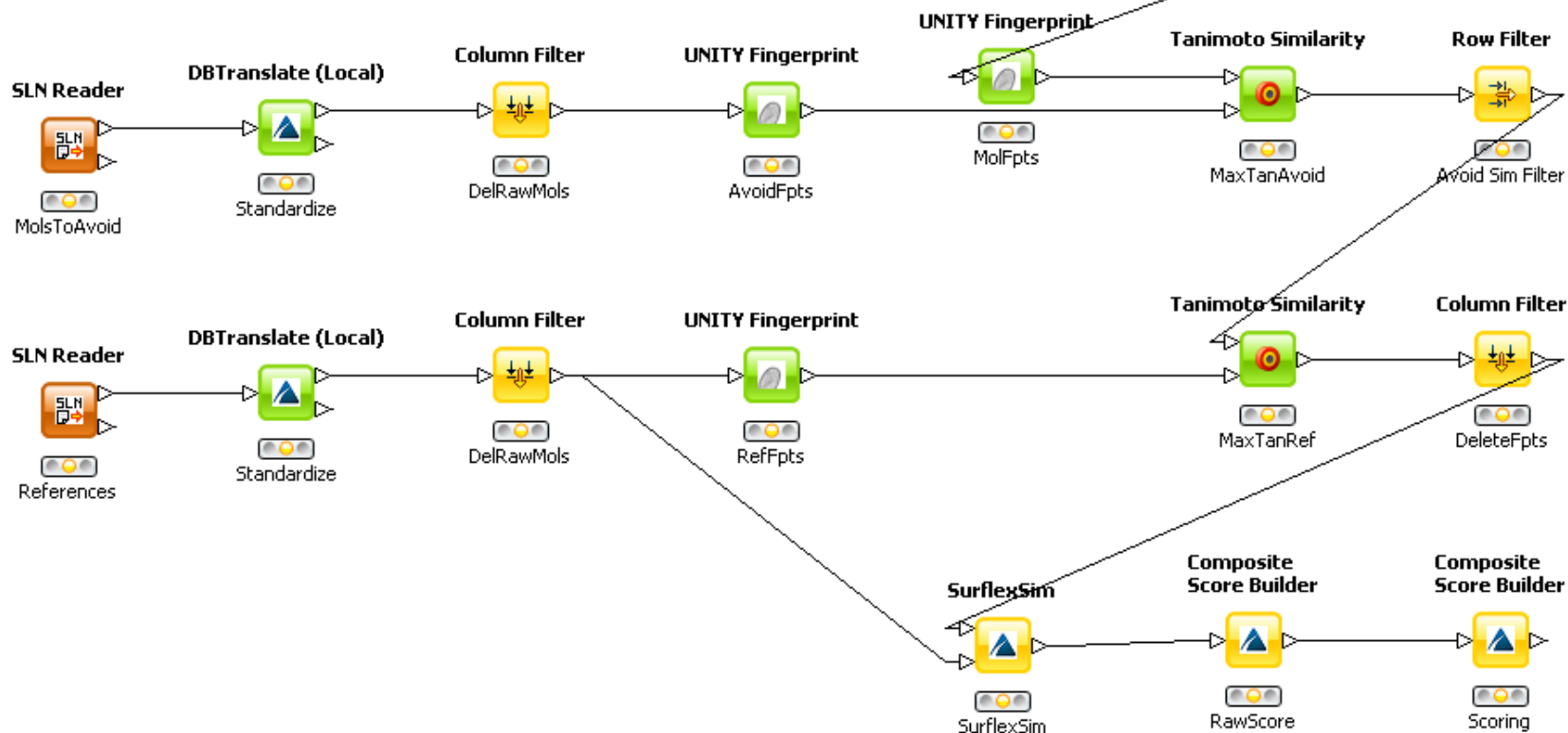
Use 3rd party nodes

Webservices

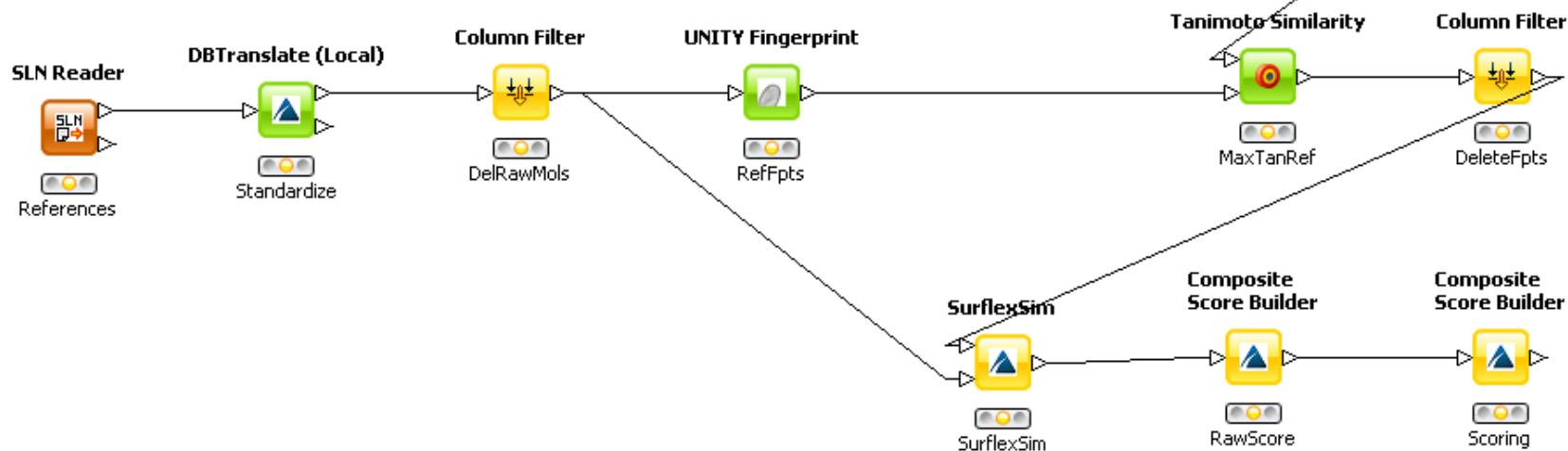
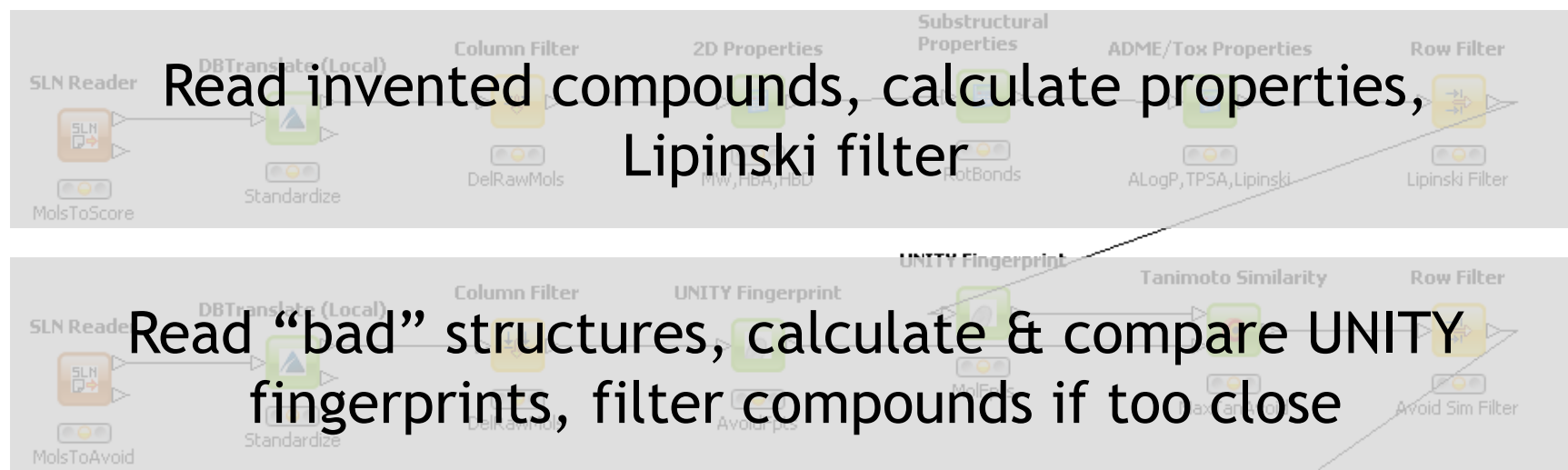
Multi-Criteria Composable Scoring Via KNIME



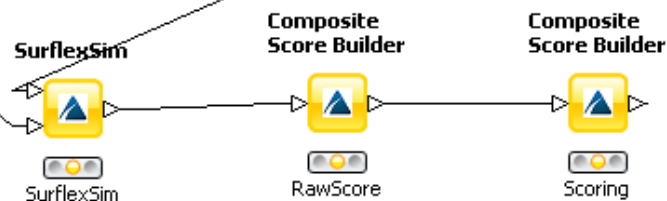
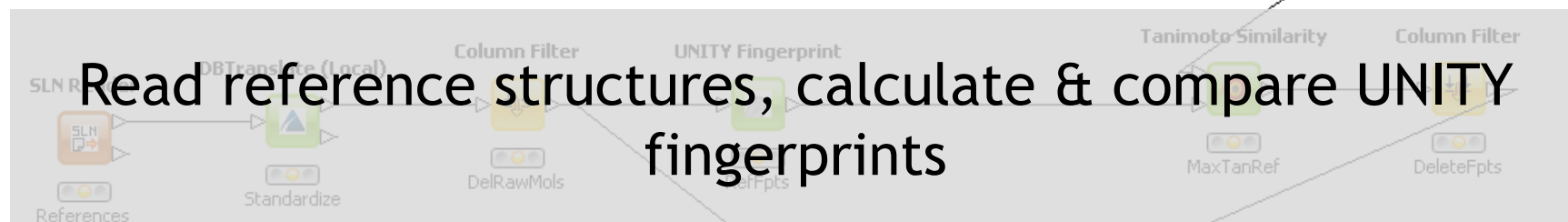
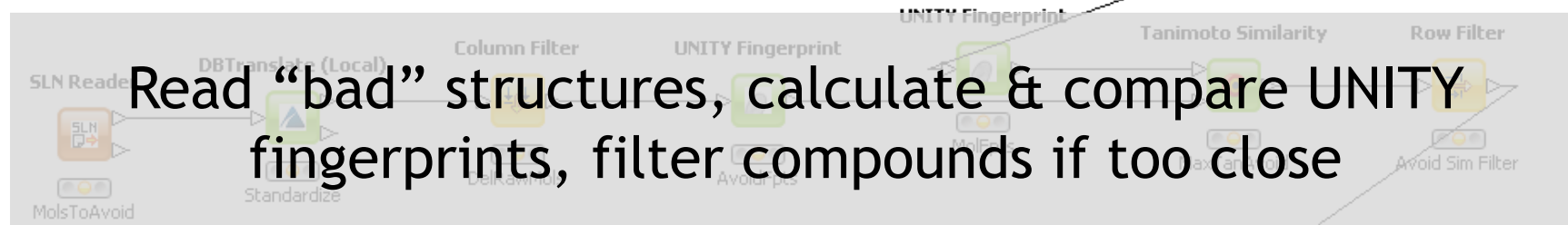
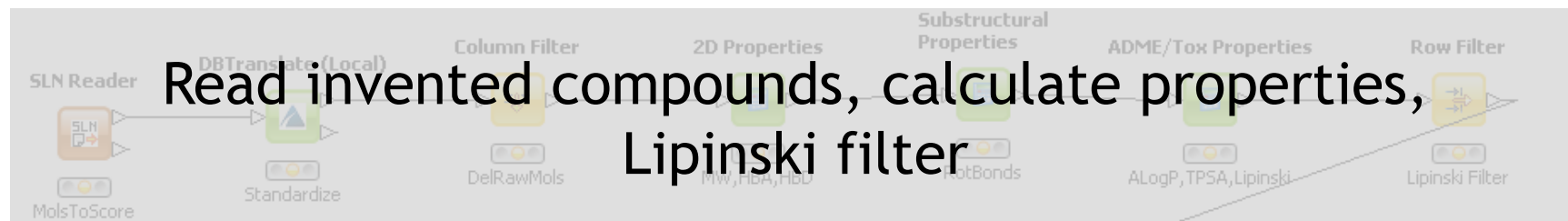
Multi-Criteria Composable Scoring Via KNIME



Multi-Criteria Composable Scoring Via KNIME



Multi-Criteria Composable Scoring Via KNIME



Multi-Criteria Composable Scoring Via KNIME

Read invented compounds, calculate properties, Lipinski filter

Read "bad" structures, calculate & compare UNITY fingerprints, filter compounds if too close

Calculate & compare UNITY fingerprints

Flexible 3D shape & pharmacophore similarity, final score building

Column Name	Weight	Normalizer
SurflexSim	10	Pass Thru
molwt	1	Gaussian
AlogP	1	Gaussian
TPSA	1	Gaussian
rotatable bonds	0.5	Gaussian
number of H-bond donors	0.5	Gaussian
number of H-bond acceptors	0.5	Gaussian



Tripos Chemistry Extensions:
www.tripos.com/knime

Multi-Criteria Composable Scoring Via KNIME:
www.tripos.com/muse

fboes@tripos.com
+49 89 451030 24