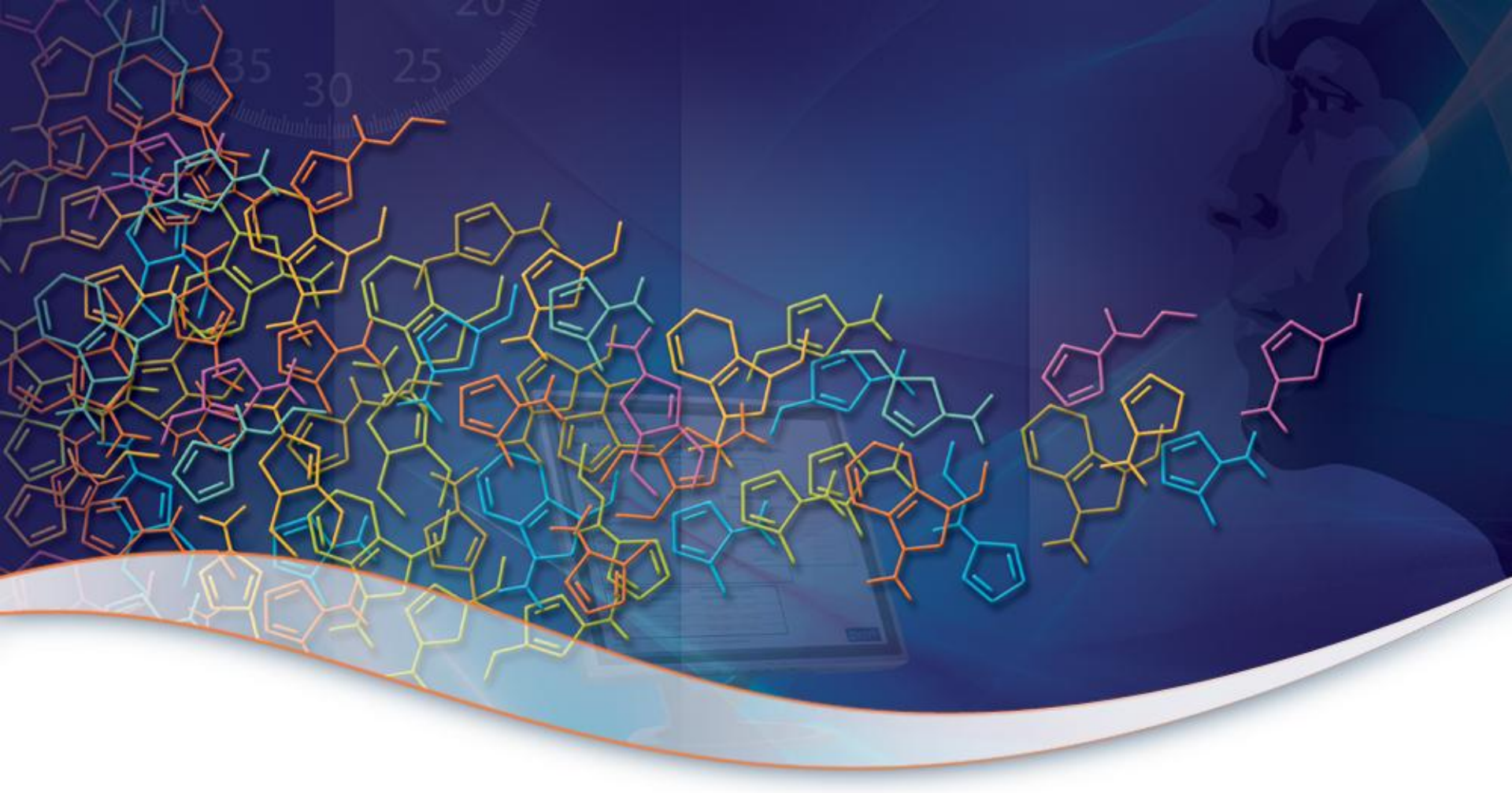

# Tripos Chemistry Extensions (TCE)

Dr. Fabian Bös, Application Scientist

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# Tripos Chemistry Extensions (TCE)

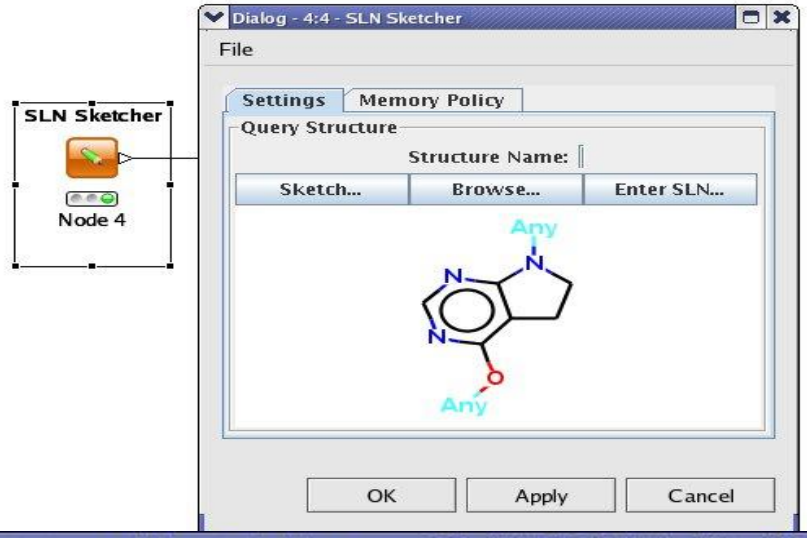
Introduces “chemical intelligence” to the KNIME platform

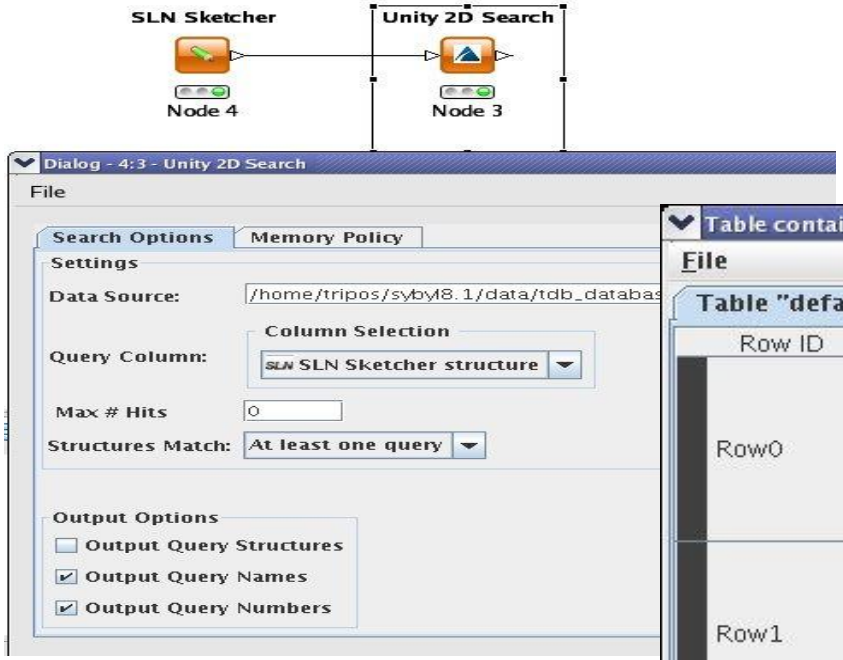
- read / write and process chemical structures
- perform cheminformatics tasks
- visualize & analyze molecular structures

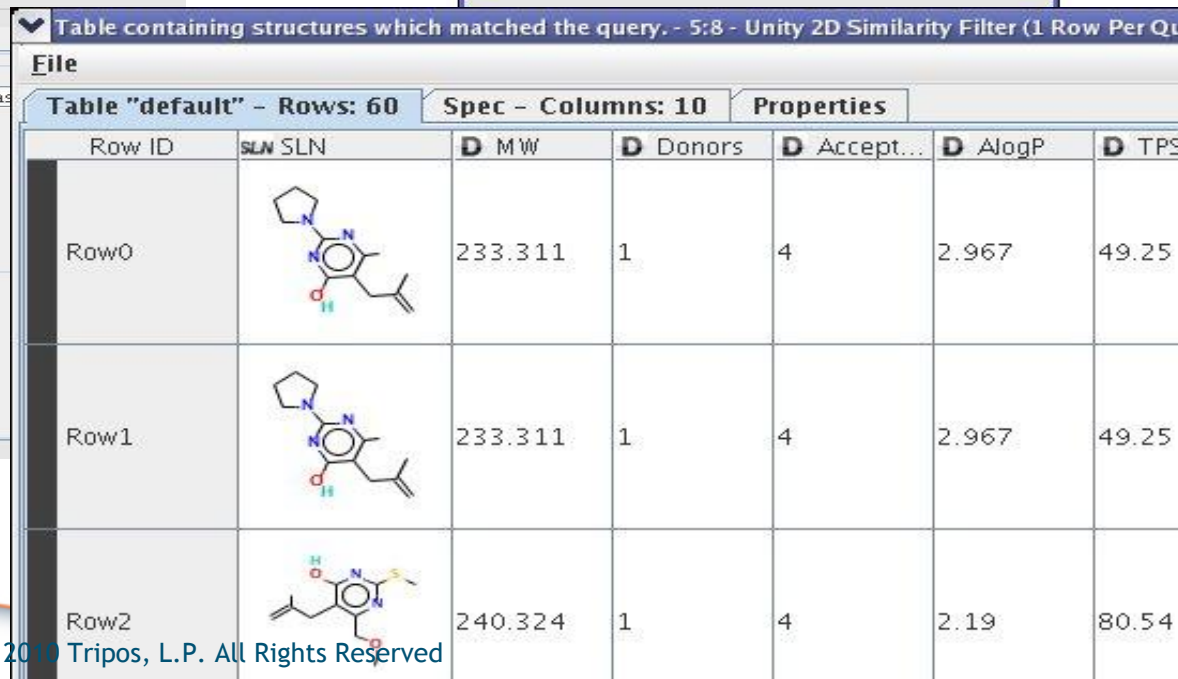
# Tripos Chemistry Extensions (TCE)

## Direct integration into KNIME

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

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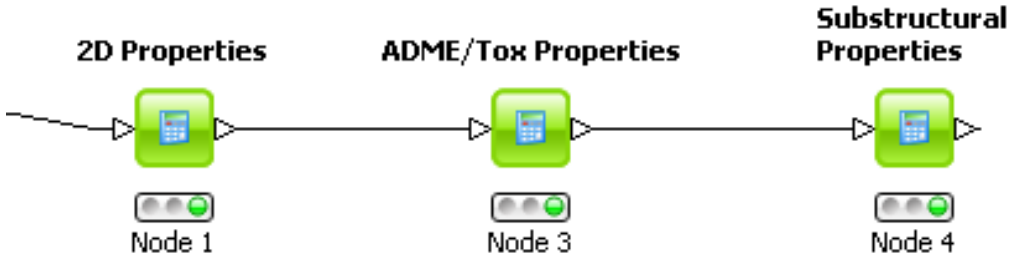
# Tripos Chemistry Extensions (TCE)

Read / write the following chemical file formats:

# Tripos Chemistry Extensions (TCE)

## Compute molecular properties



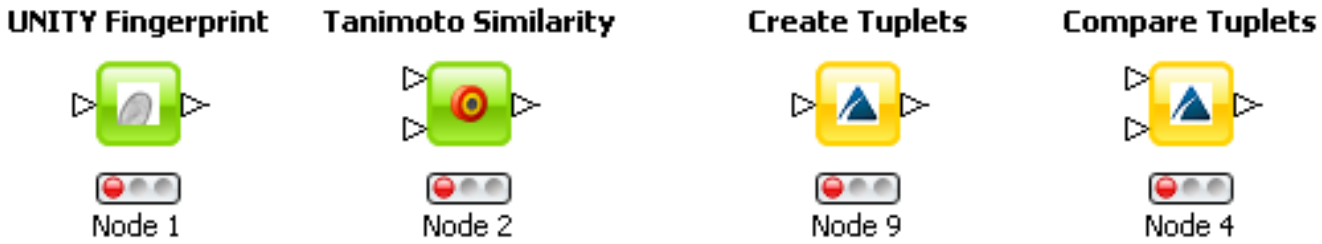

Molecular weight
H-bond acceptors
H-bond donors
…

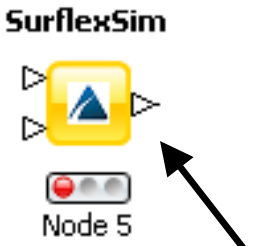
AlogP
TPSA
Lipinski violations
…

atoms/bonds
rings
functional groups
…

# Tripos Chemistry Extensions (TCE)

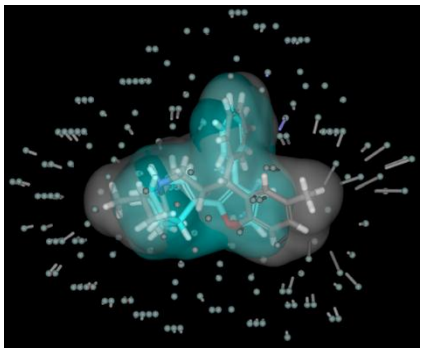
Compare molecules:




using

- Fingerprints
- Steric & Pharmacophore Tuplets[1]
- Molecular shape, hydrogen bonding and electrostatic properties[2]



[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).

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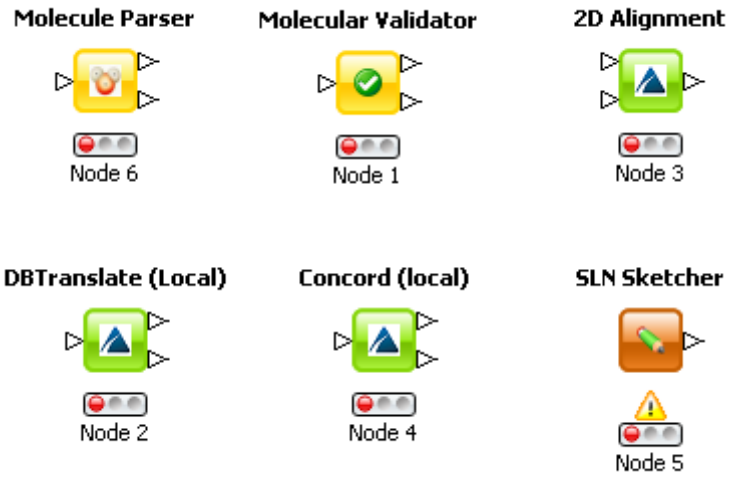
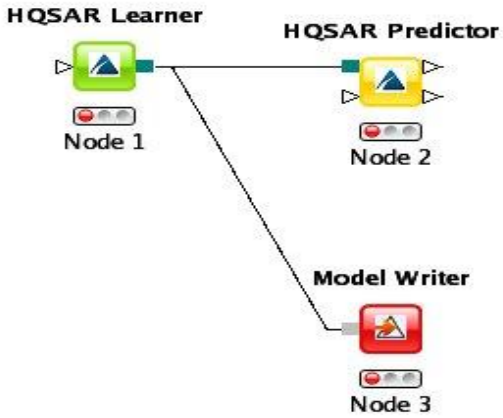
# Tripos Chemistry Extensions (TCE)

## Useful Tools:



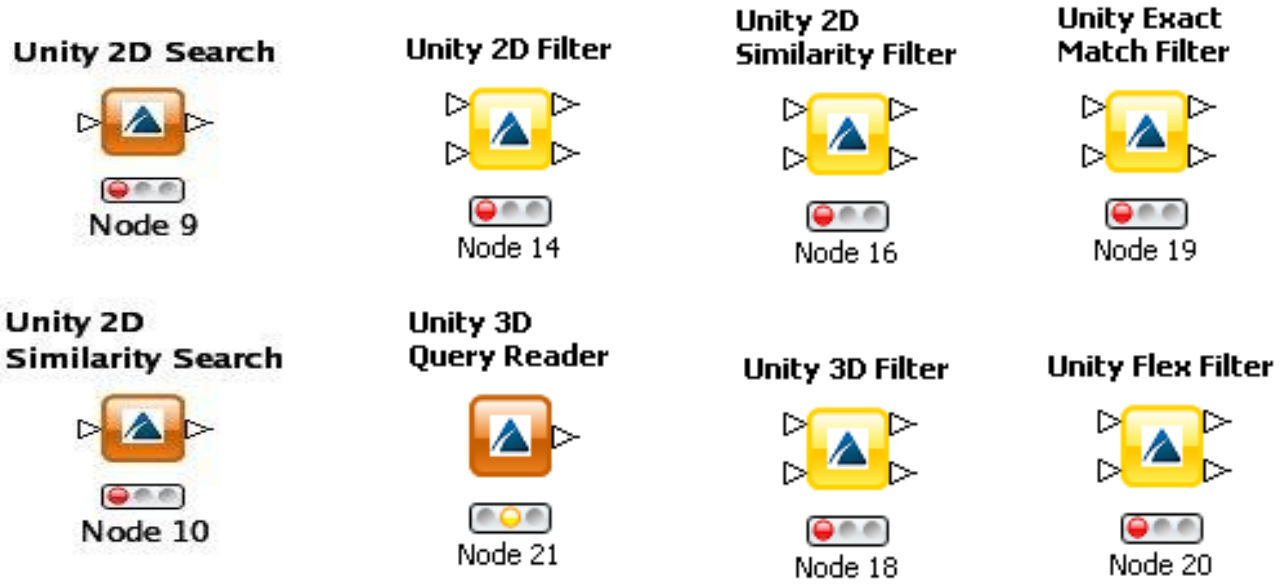

## HQSAR:




HQSAR: QSAR method based on molecular hologram fingerprints.

# Tripos Chemistry Extensions (TCE)

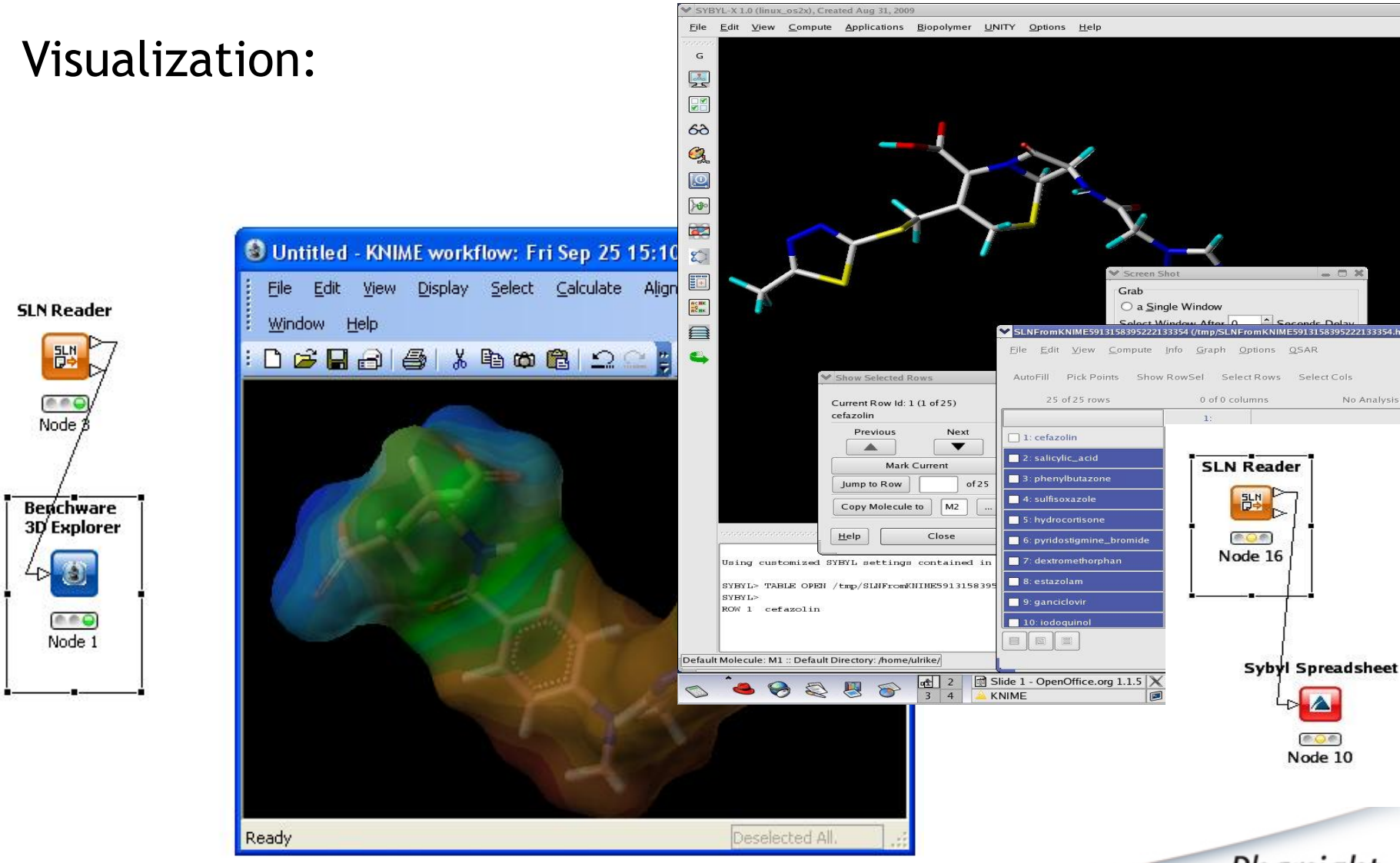
2D & 3D UNITY database searching:

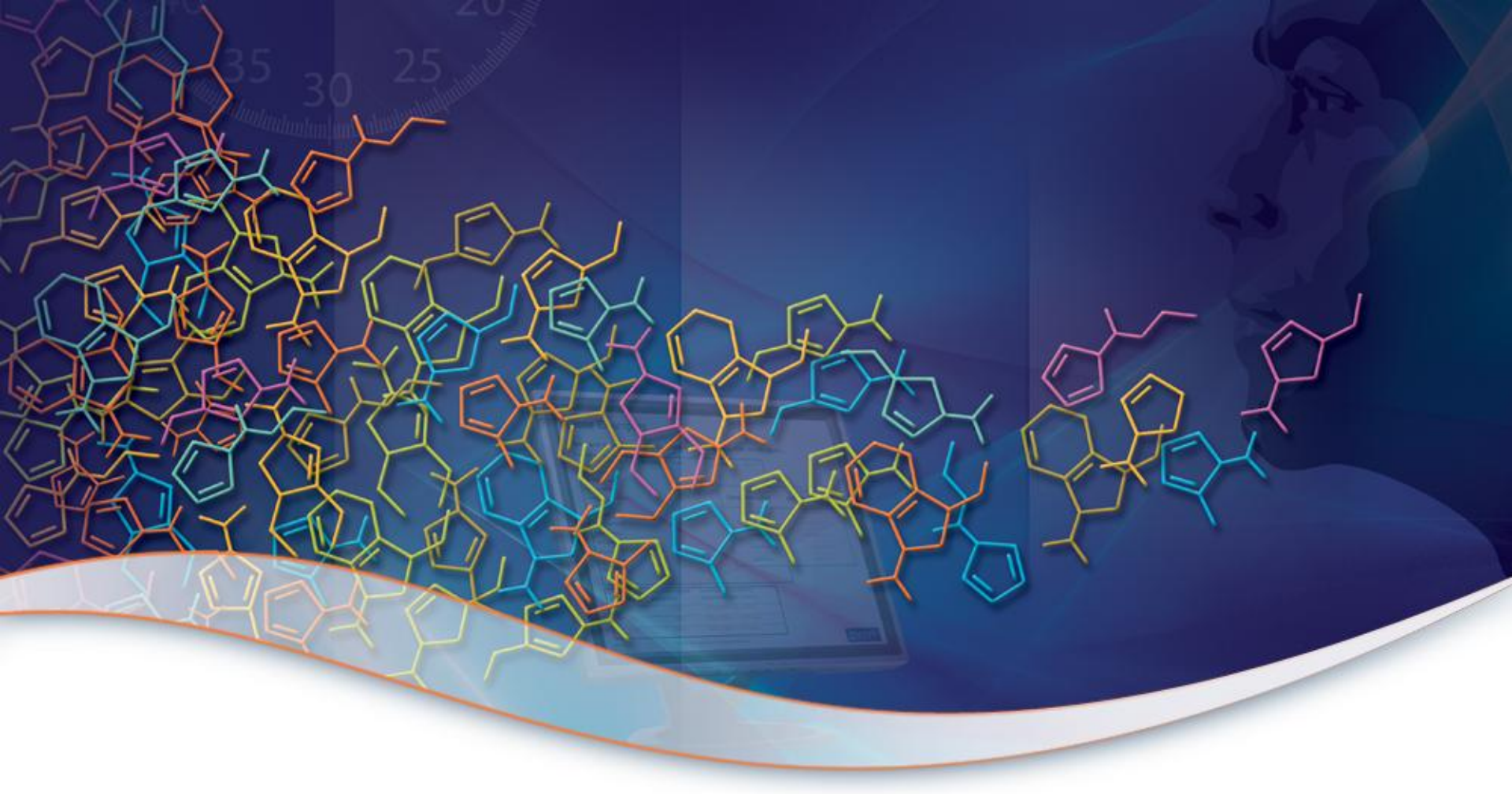



Search nodes act on (existing) UNITY database directly
Filter nodes act on the structures in a KNIME table

# Tripos Chemistry Extensions (TCE)

Visualization:





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

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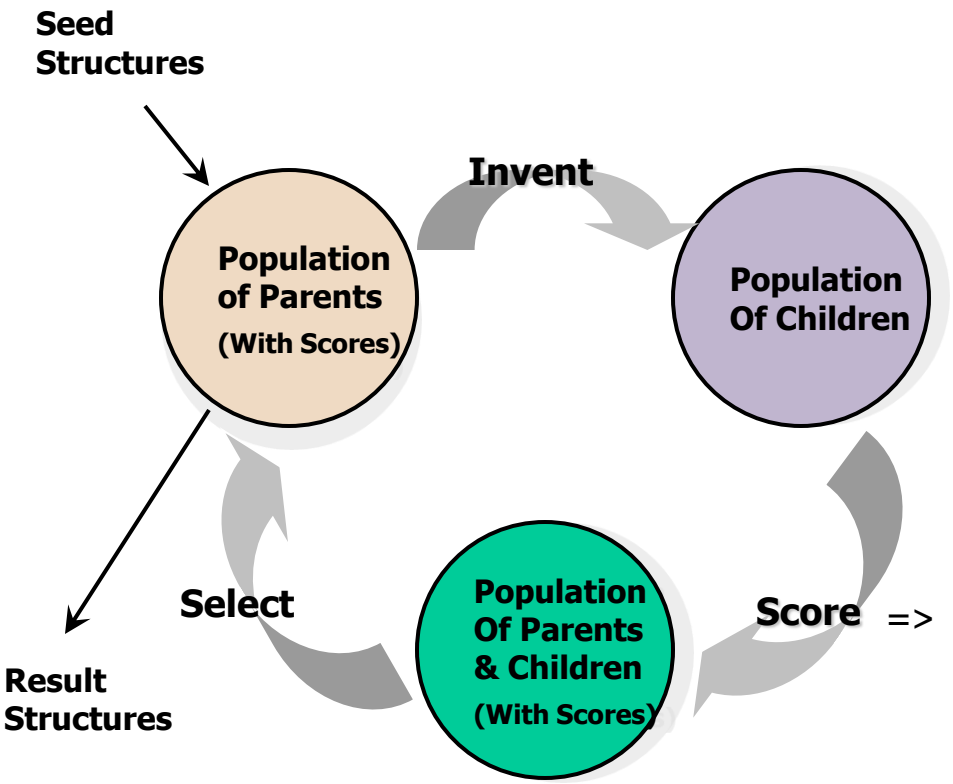
# Multi-Criteria Composable Scoring Via KNIME

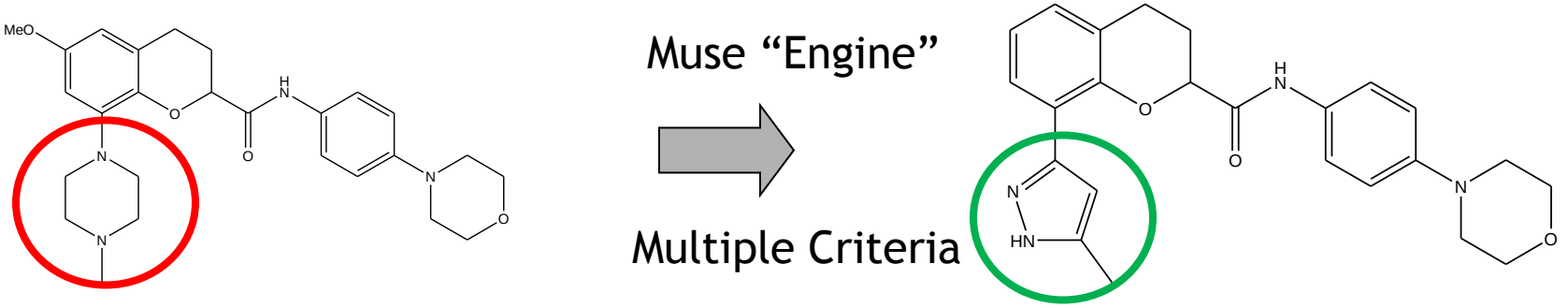



=> KNIME workflow

# Multi-Criteria Composable 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-HT1b 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.

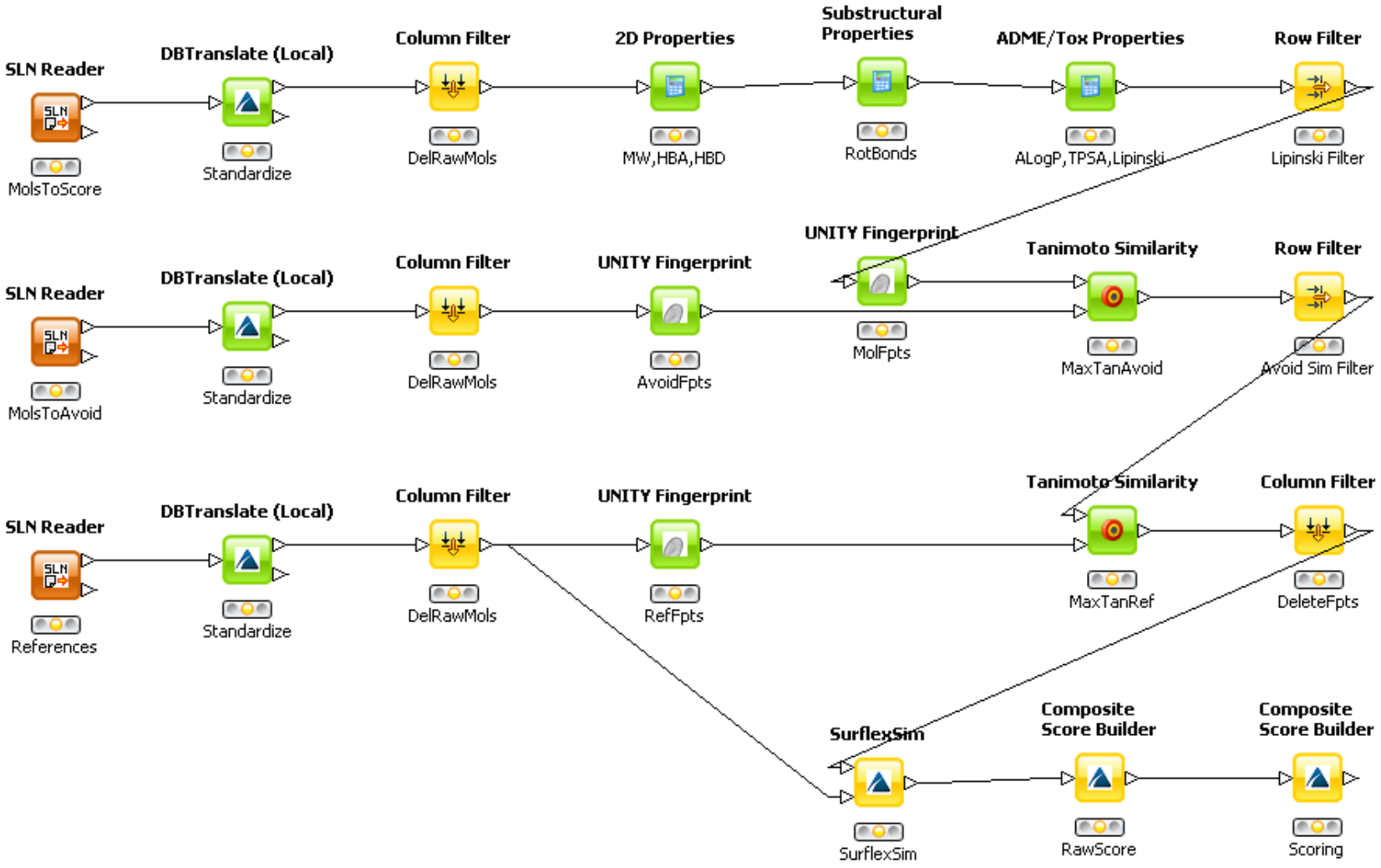
The centerpiece of the collaboration effort will be the development of Tripos' new Muse™ *de novo* design product, which is targeted for commercial release in the fourth quarter of 2008. Muse, which will be designed to accelerate the identification and optimization of lead candidates, will combine *de 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

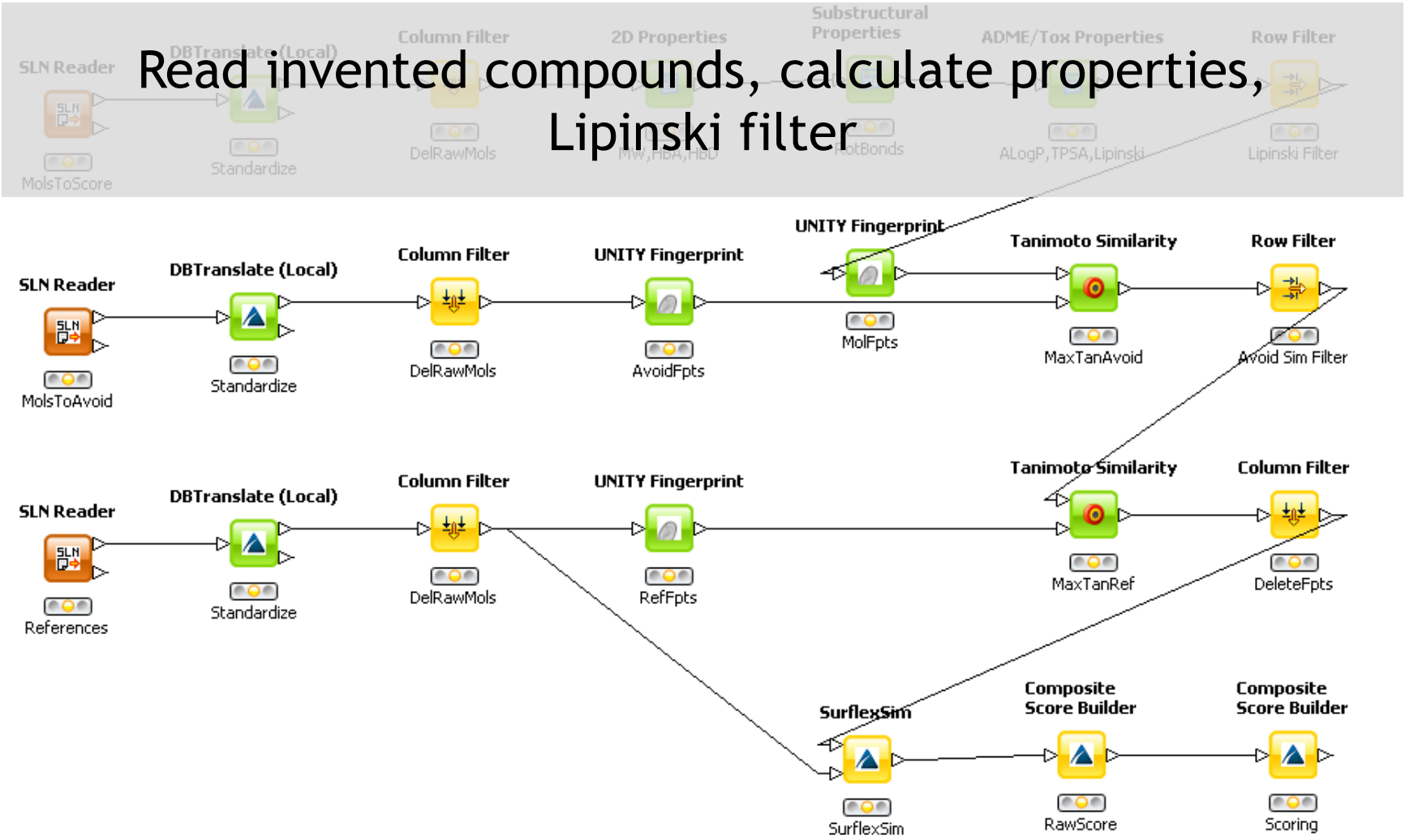
- Shape and Pharmacophore
  - Surflex-Sim
- Molecular Properties
  - AlogP
  - MW
  - TPSA
  - H-Bond Don and Acc Counts
  - Rot Bonds Count
  - Lipinski Violations
- Avoid Anti-Targets
  - 2D Fingerprint Similarity
- Score "Normalizers" and "Combiner"
  - Square, Pass/Fail, Bell Curve, Trapazoid
  - 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

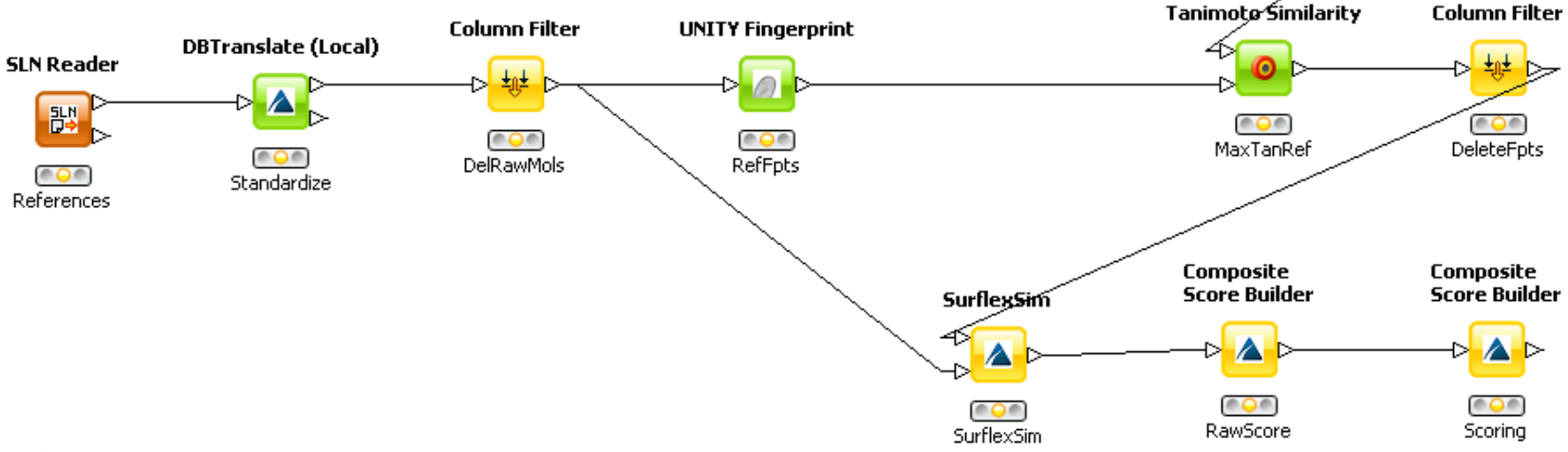
Read invented compounds, calculate properties, Lipinski filter



# 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

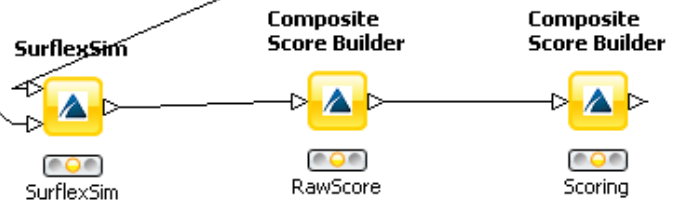


# Multi-Criteria Composable Scoring Via KNIME

Read invented compounds, calculate properties, Lipinski filter

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

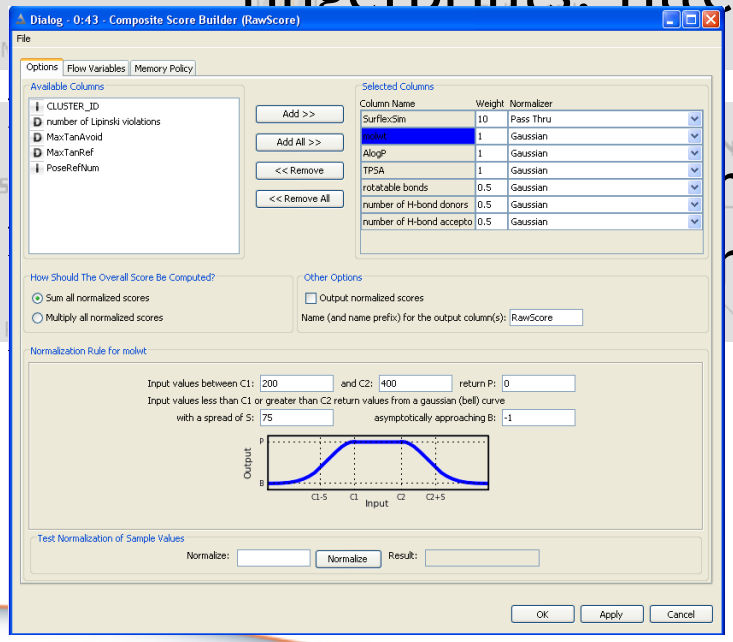
Read reference structures, calculate & compare UNITY fingerprints



# 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




Flexible 3D shape & pharmacophore similarity, final score building

Tripos Chemistry Extensions:

# www.tripos.com/knime

Multi-Criteria Composable Scoring Via KNIME:

# www.tripos.com/muse

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