



Muse + TriposScore: A Ligand-Based Molecular Invention Approach

A Certara™ Company

Fabian Bös^{1*}, Brian B Masek², James R. Damewood³

¹Tripos International, Martin-Kollar-Straße 17, München, 81829, DE

²Tripos International, 1699 South Hanley Road, St. Louis, Missouri 63144, USA

³AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, Delaware 19850, USA

Introduction

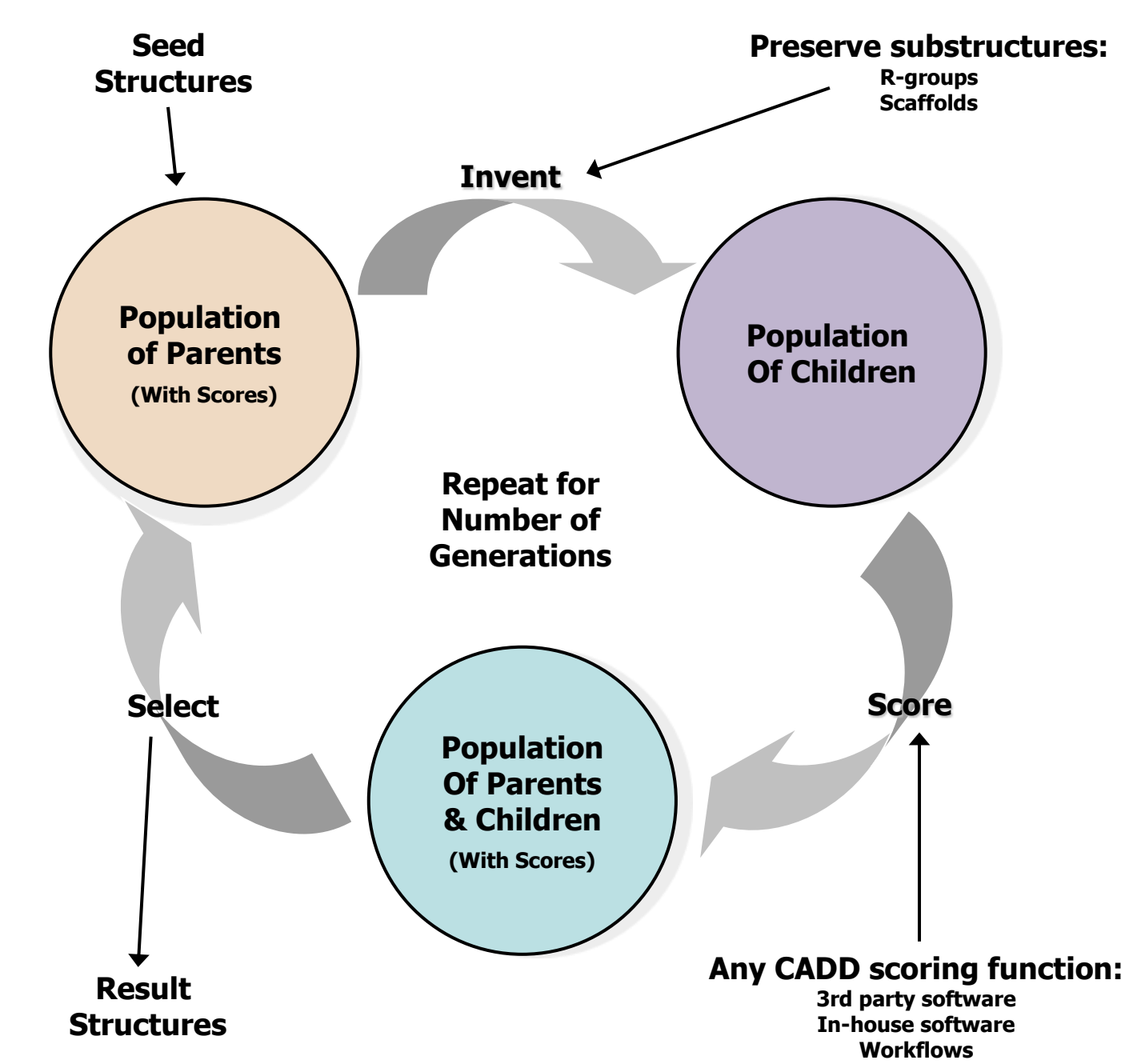
Successful drug discovery often requires optimization against a set of biological and physical properties. We describe our work on multi-parameter approaches to ligand-based molecular invention and studies that demonstrate its ability to successfully generate lead hops or scaffold hops between known classes of ligands.

Muse [1] is a molecular invention tool that operates on an initial population of structures to invent new structures with improved scores. The ligand-based multi-criteria scoring function used in this work incorporates molecular shape and feature similarity, molecular fingerprint similarity, and a number of popular "Lipinski-like" molecular properties.

Retrospective studies on the targets Neurokinin 1, H1 receptor, and Angiotensin II demonstrate the ability of the above mentioned approach to generate novel ideas that are not only appealing to design scientists but are also validated by comparison to compounds known to demonstrate activity at the desired biological target.

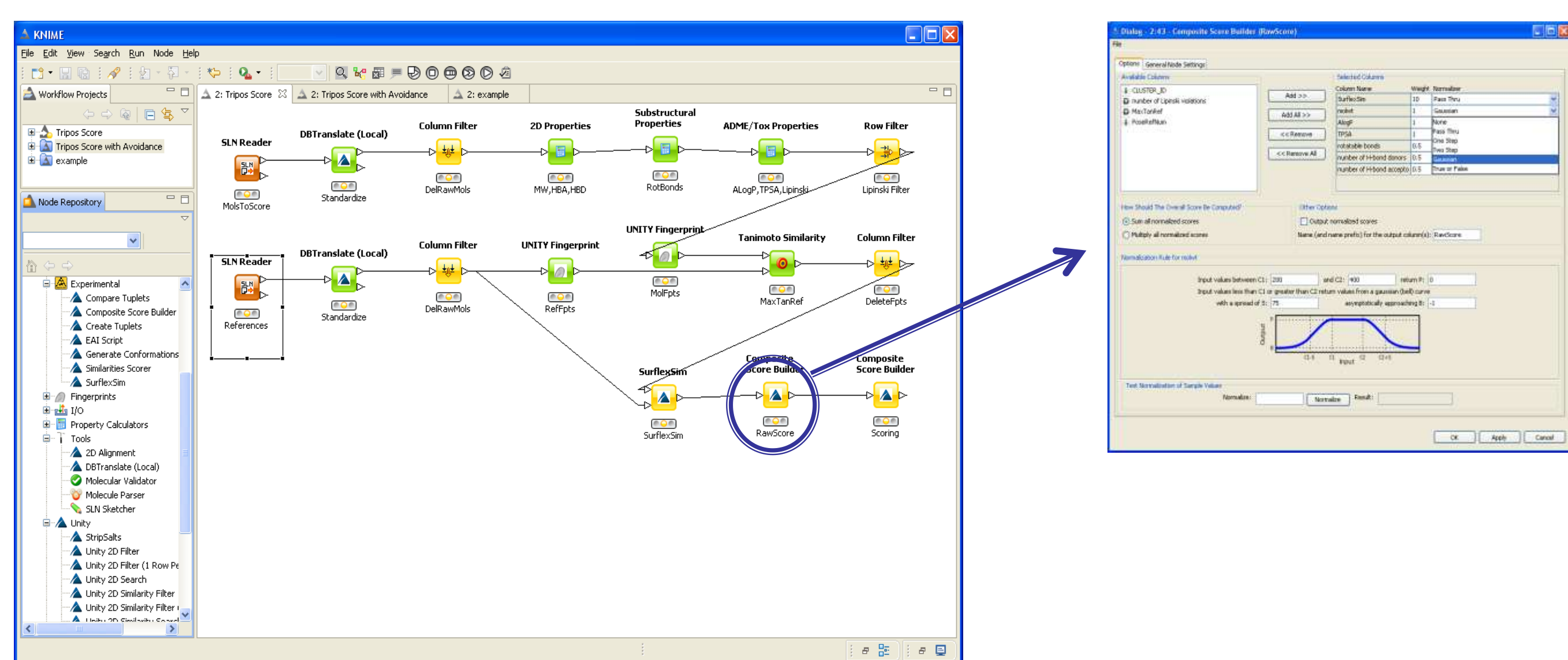
Molecular invention with Benchware Muse

- Based on an evolutionary algorithm, improves scores related to properties you wish to optimize
- User-defined scoring functions
- 33 chem-evolutionary operators only produce reasonable chemical structures and obey valence rules
- Contains fragment library extracted from the 2000 MDL Drug Data Report. Library can be modified or replaced by the user.
- Option to preserve substructures during invention.
- User editable filter list of unwanted and undesired substructures.

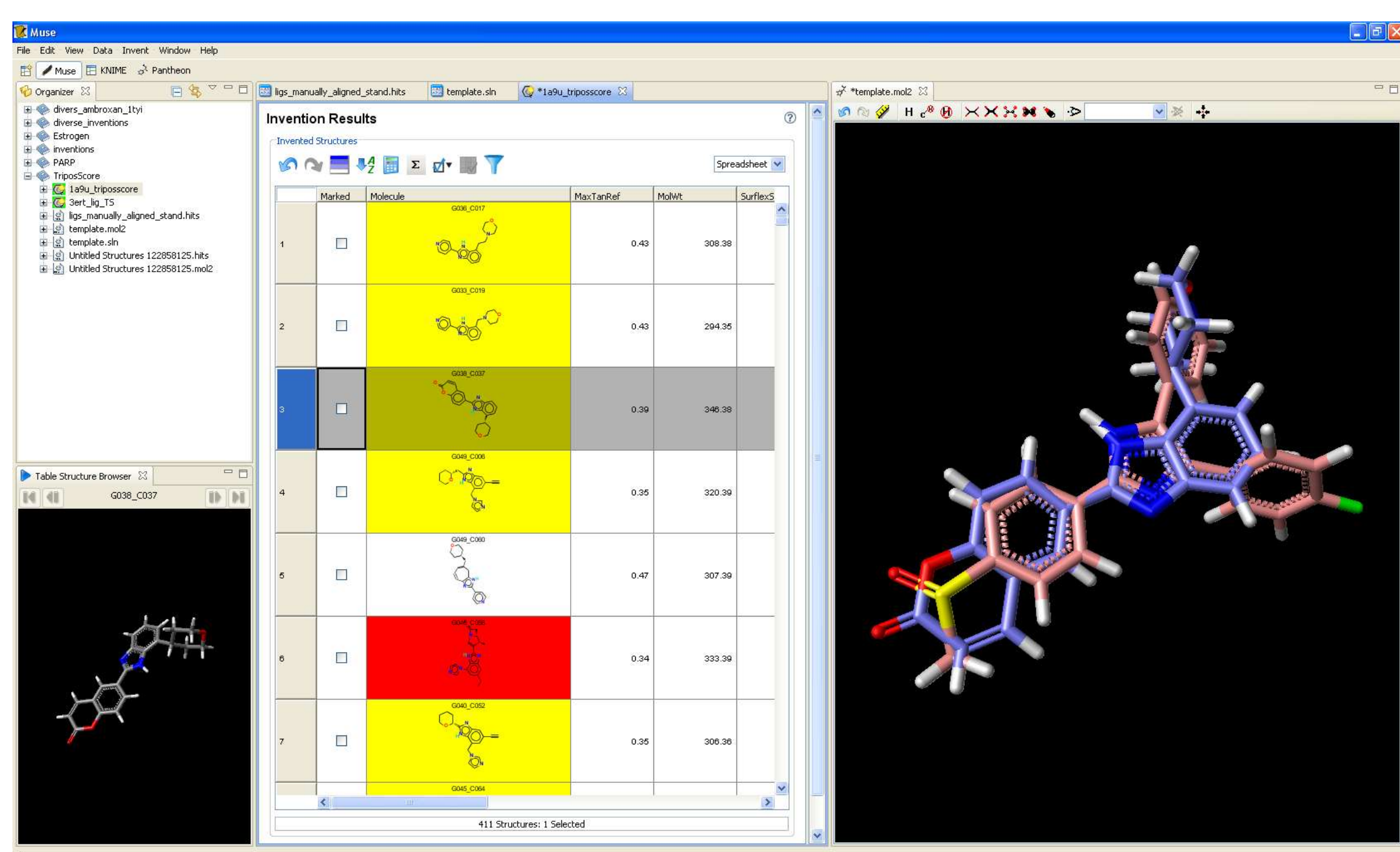


TriposScore

TriposScore is a ligand-based multi-criteria scoring function implemented as a KNIME [2] workflow, thus making it easy to modify and re-configure by the user. Structures invented by Benchware Muse are passed on to the KNIME workflow where they get their individual scores calculated in order to drive the evolutionary algorithm.



The main element of the scoring function is the calculation of a similarity score to the reference structure by flexible molecular alignment technique Surfex-Sim [3]. UNITY fingerprints are used to calculate the structural similarity between the invented molecules and the reference structure in order to prevent the invented molecules from getting too close to the starting point. Several molecular properties such as molecular weight, hydrogen bond donor and acceptor count, polar surface area are calculated and compared to a user-defined range of values. The composite score builder node, which includes normalization functions such as linear or Gaussian normalization, is used to combine the multiple parameters calculated in the process of the workflow into one final score. It allows the usage of soft penalties instead of hard cutoffs that simply eliminate structures from the scoring process.

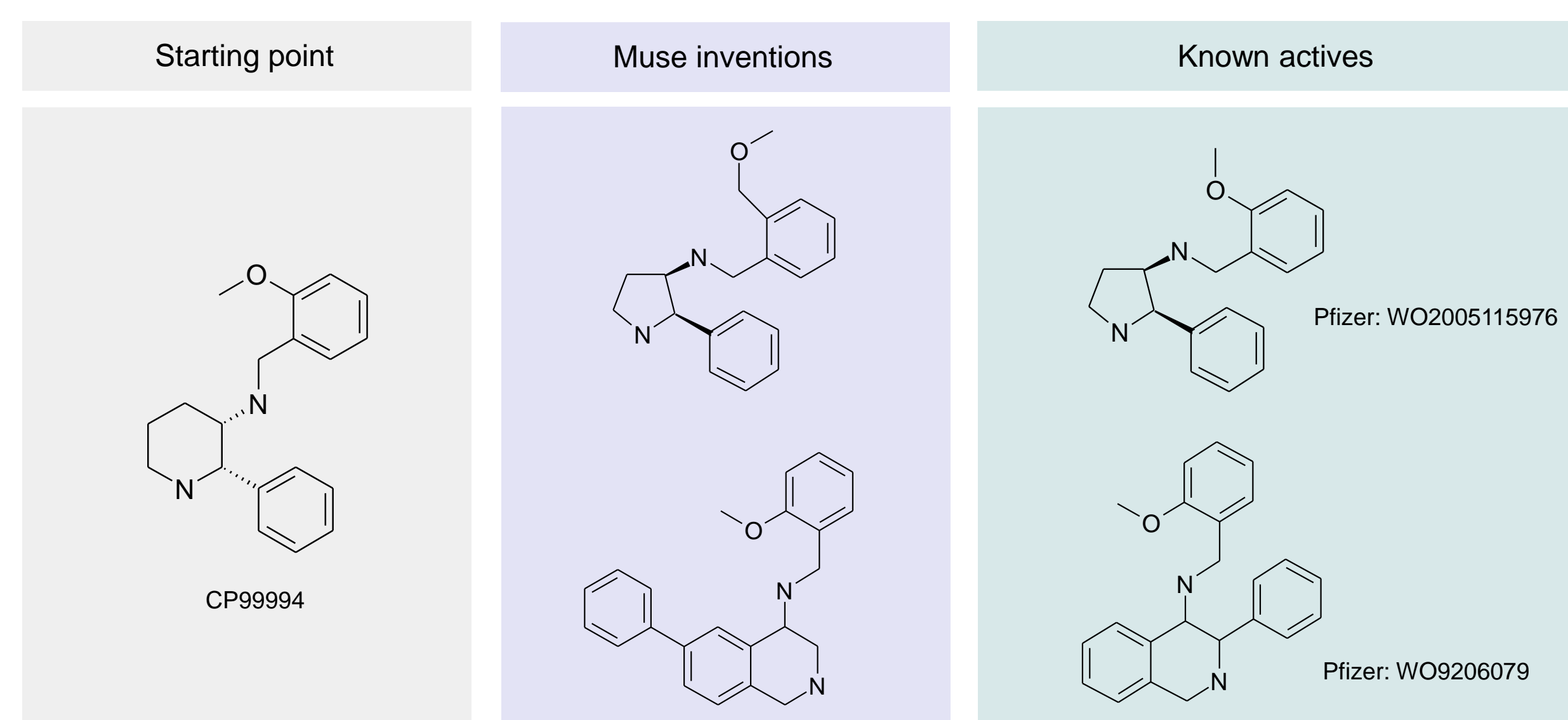


LITERATURE

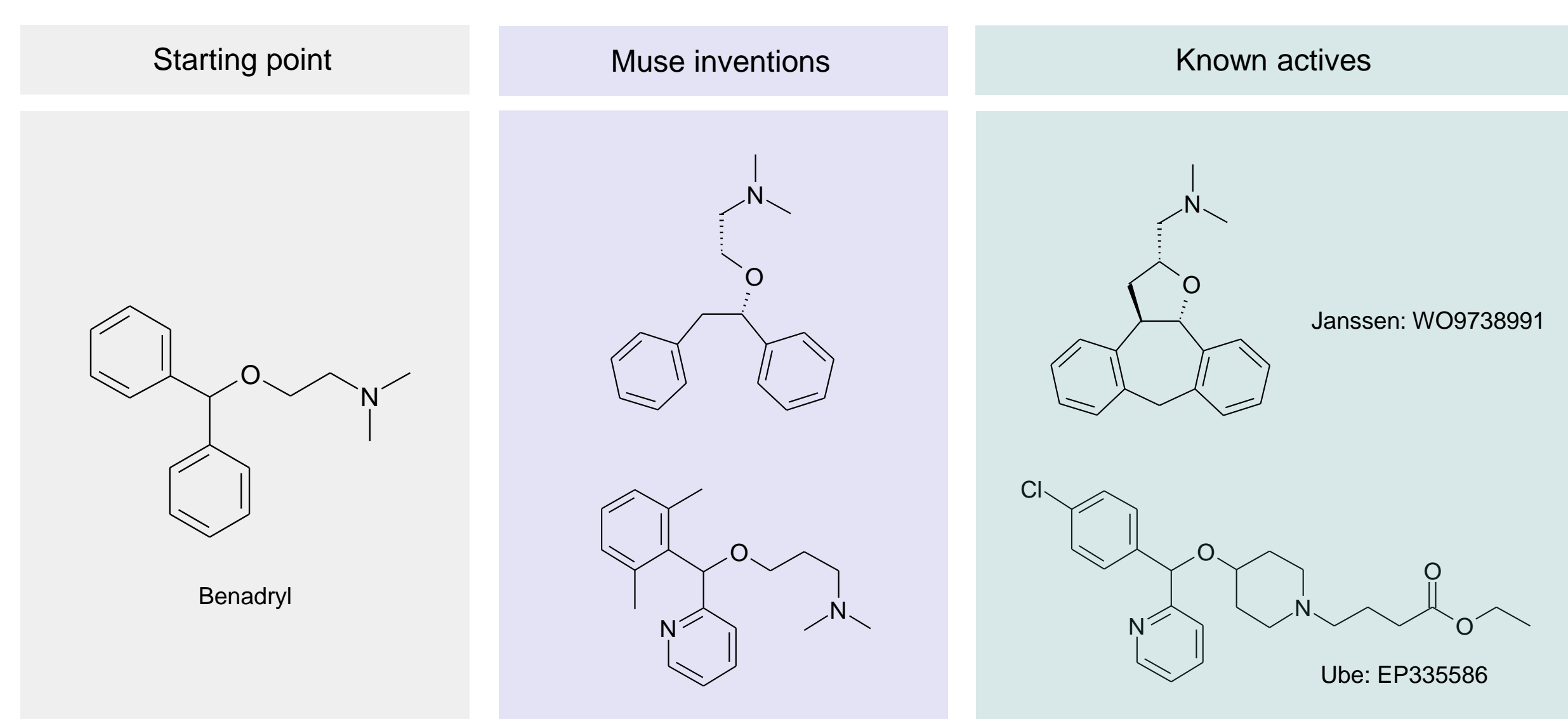
- A 30 day free trial of Benchware Muse including TriposScore is available at <http://www.tripos.com/download>
- Berthold M.R. et al., KNIME: The Konstanz Information Miner, www.knime.org (version 2.0.3).
- Jain, A. N. "Morphological similarity: A 3D molecular similarity method correlated with protein-ligand recognition." *J. Comp.-Aided Mol. Des.*, **14**, 199-213 (2000).
- MacLeod, A. et al., Synthesis and Biological Evaluation of NK1 Antagonists Derived from L-Tryptophan, *J. Med. Chem.*, **38**, 934-941 (1995).
- Anthes, J.C. et al. Biochemical Characterization of Desloratadine, A Potent Antagonist of the Human Histamine H1 Receptor, *Eur. J. Pharmacol.*, **449**, 229-237 (2002)
- Bradbury, R.H. et al., New Nonpeptide Angiotensin II Receptor Antagonists. 2. Synthesis, Biological Properties, and Structure-Activity Relationships of 2-alkyl-4-(biphenylmethoxy)quinoline Derivatives. *J. Med. Chem.* **35**, 4027-4038 (1992).

Retrospective Studies

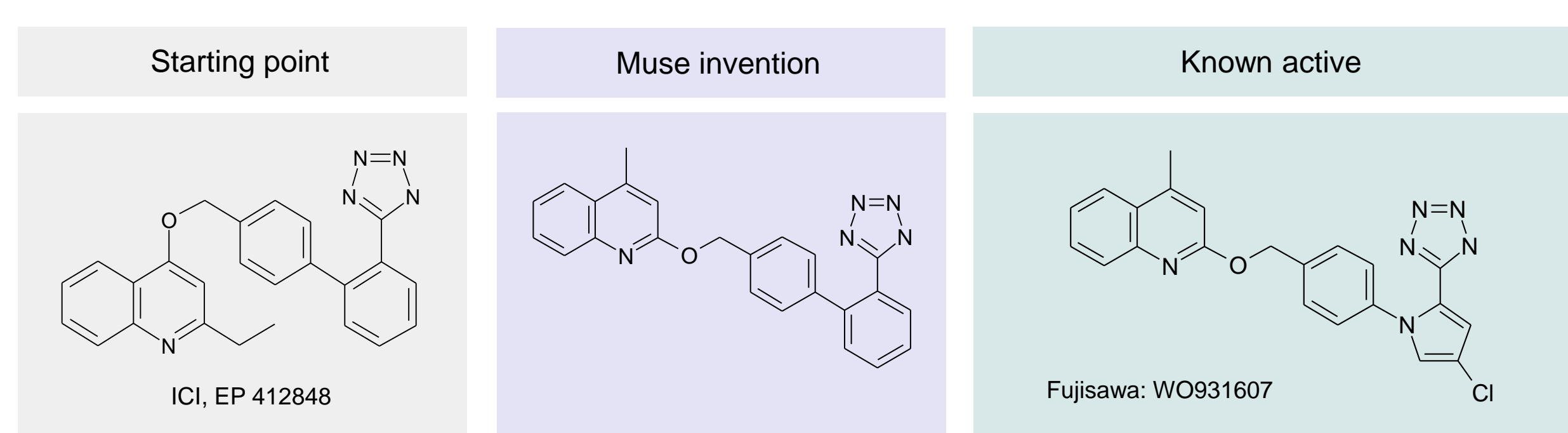
Search for Neurokinin 1 (NK1) antagonists has been active in the pharmaceutical industry for some time with therapeutic targets that have included depression, asthma, nausea, and analgesia. The well know NK1 antagonist, CP99994 [4] (IC₅₀ ~ 0.5 nM) was used as a starting point for *de novo* design experiments.



Antihistamines are widely used for the treatment of allergies, in particular, in response to the seasonal release of pollen, resulting in allergic rhinitis. Classical antihistamines are H1 antagonists. Beginning with Benadryl [5] (K_i ~ 2.5 nM), a variety of compounds were designed by Benchware Muse that are very similar to compounds known to have activity at the H1 receptor.



The development of potent Angiotensin II (All) antagonists as antihypertensive agents has been the focus of considerable effort in the pharmaceutical industry. Beginning with a compound reported by ICI [6] (IC₅₀ ~ 31 nM), several *de novo* design experiments were conducted with Benchware Muse.



In the above examples, Benchware Muse has generated either significant modifications of existing molecular frameworks or structurally new molecular templates relative to the design starting points, demonstrating the power of this new *de novo* design method.