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Automatic Generation of Compound Ideas to Guide Optimization

Innovative Lead Optimization and Candidate Selection by *in Silico* Synthesis and ADMET Prediction. December 3rd 2015

Matthew Segall, CEO, Optibrium Ltd.

Overview

- Automatic compound idea generation
  - *De novo* design
- Matched Series Analysis
  - SAR Transfer
  - Matsy™
- Medicinal chemistry transformation rules
- Conclusions

Automatic Generation of Compound Ideas
Objectives

- Traditionally have a scarcity of data
  - Time consuming and expensive to generate data
  - Easy to think of more ideas than can be synthesised and tested
  - Manually analyse all of the available data to select compounds
- With predictive models and MPO, it is easy to evaluate very large numbers of ideas
  - More ideas than one scientist can design and draw
- Generate new ideas to stimulate exploration of chemistry
  - *In silico* analysis helps to prioritise ideas for detailed consideration
- But… compound ideas must be **relevant and accessible**
  - First generation of *de novo* design methods tended to generate poor quality, non-synthesizeable structures

Matched Series Analysis

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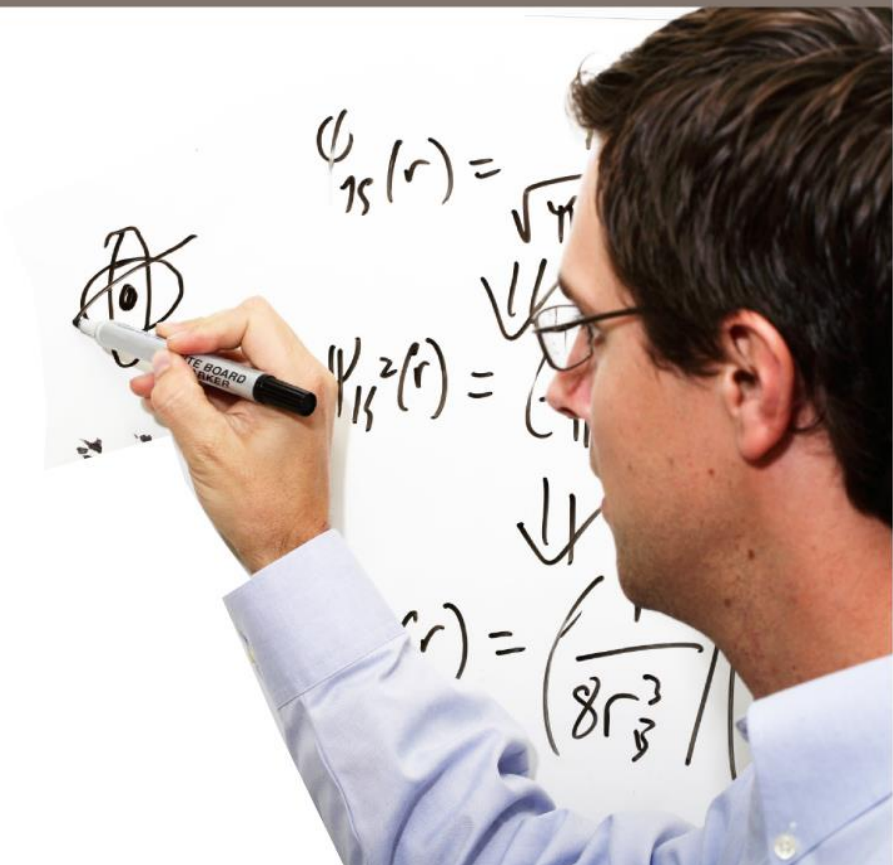
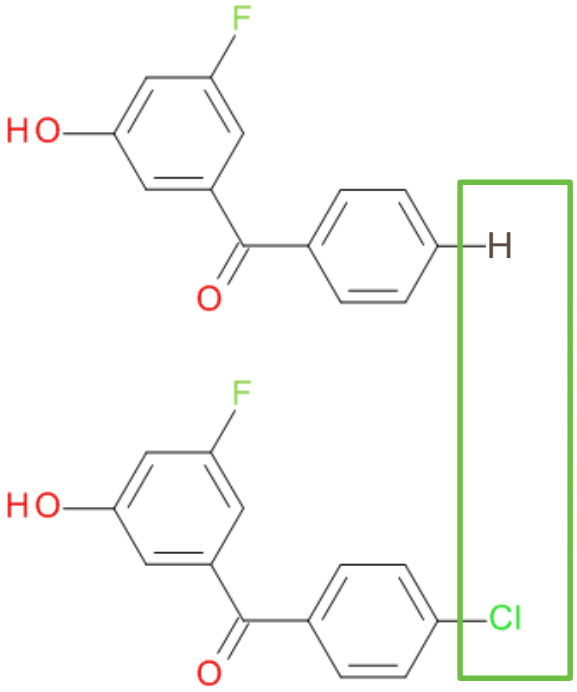


Matched Molecular Pairs



logS

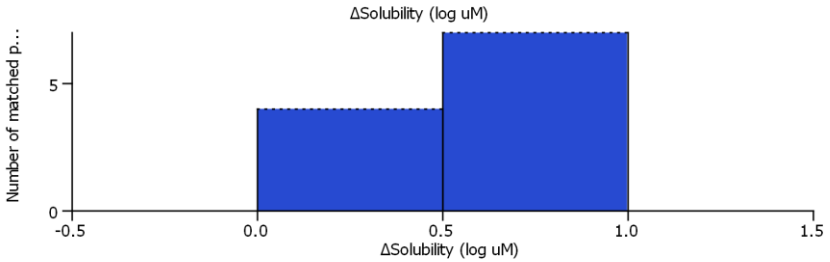
2.0

1.4

Matched Pair

Two compounds that differ only by a small replacement at a single position

From	To	Count	ΔSolubility (log uM)
		15	0.5927
		11	0.5642
		6	0.5443
		15	0.54

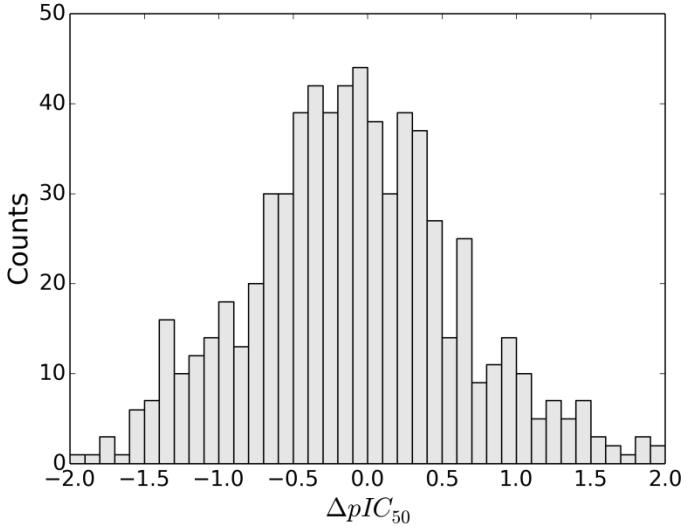


Limitations of Matched Molecular Pairs

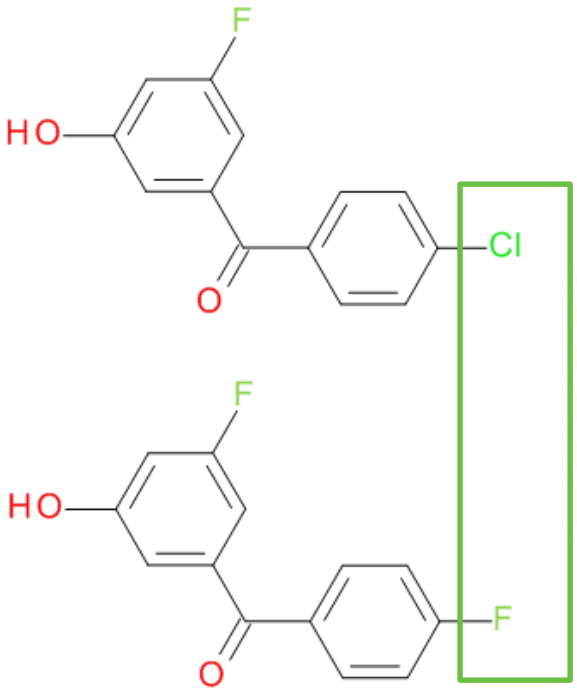
- If we look at all examples of a matched pair across diverse chemistry and target classes, they provide little information on target activity

Distribution of change in pIC_{50}

replacing  with 



Matched Series Principles



pIC_{50}

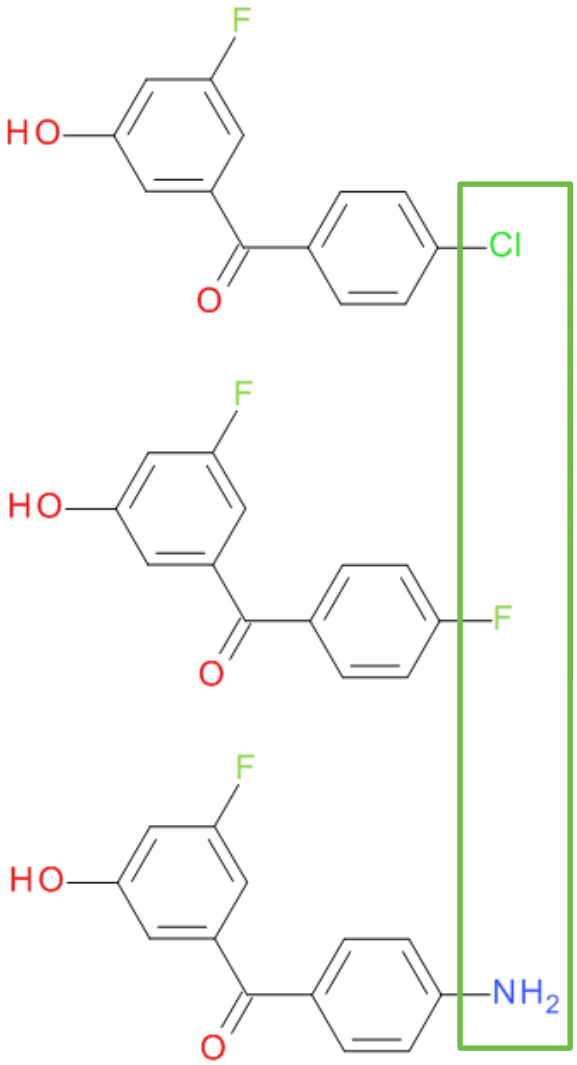
3.5

2.1

Matched Pair
(Matched Series of length 2)

[CL > F]

Matched Series Principles



pIC_{50}

3.5

2.1

1.6

Matched Series of length 3

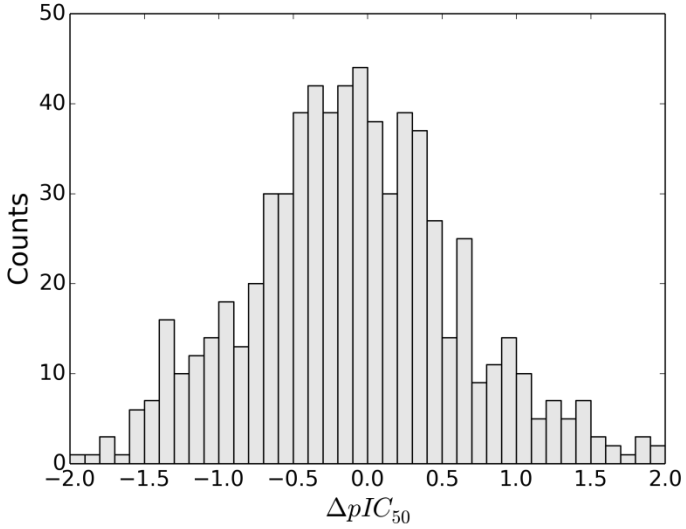
[CL > F > NH_2]

Matched Series Principles

- Longer series that match an observed order of activity improve our ability to make relevant predictions

Distribution of change in pIC_{50}

replacing  with 



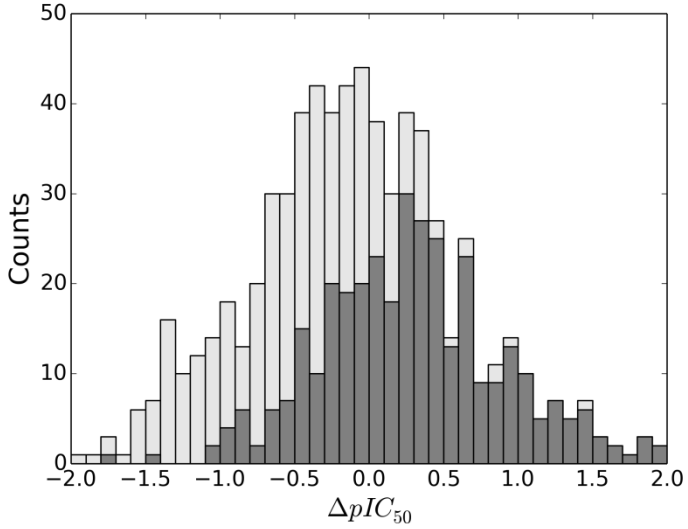
Matched Series Principles

- Longer series that match an observed order of activity improve our ability to make relevant predictions

Distribution of change in pIC_{50}

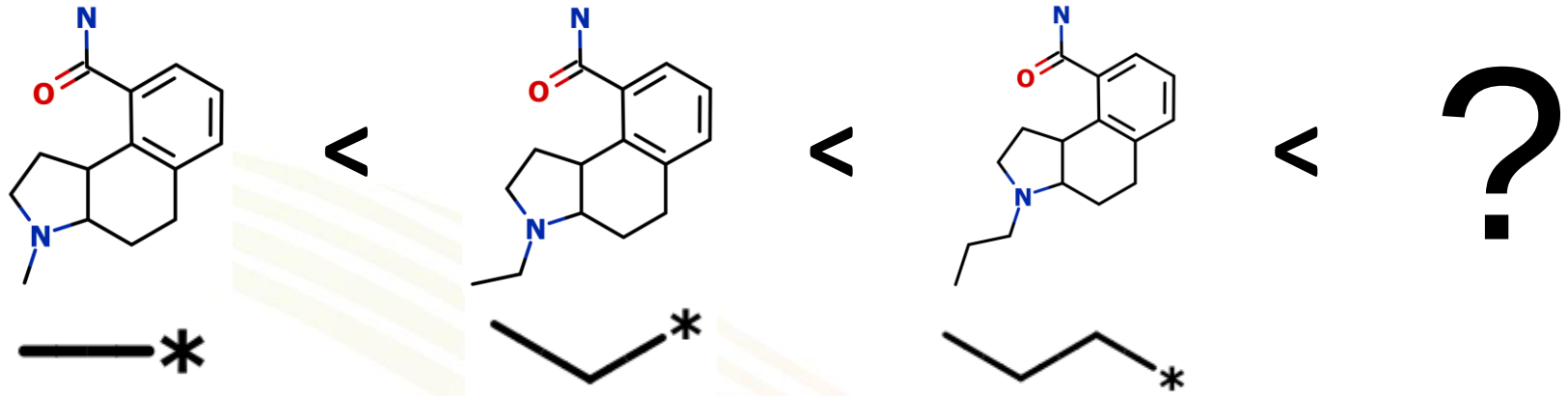
replacing  with 

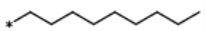
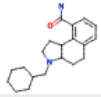
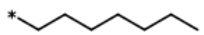
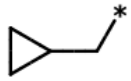
When we know  <  .



Matched Series Principles

Look up existing examples from a database

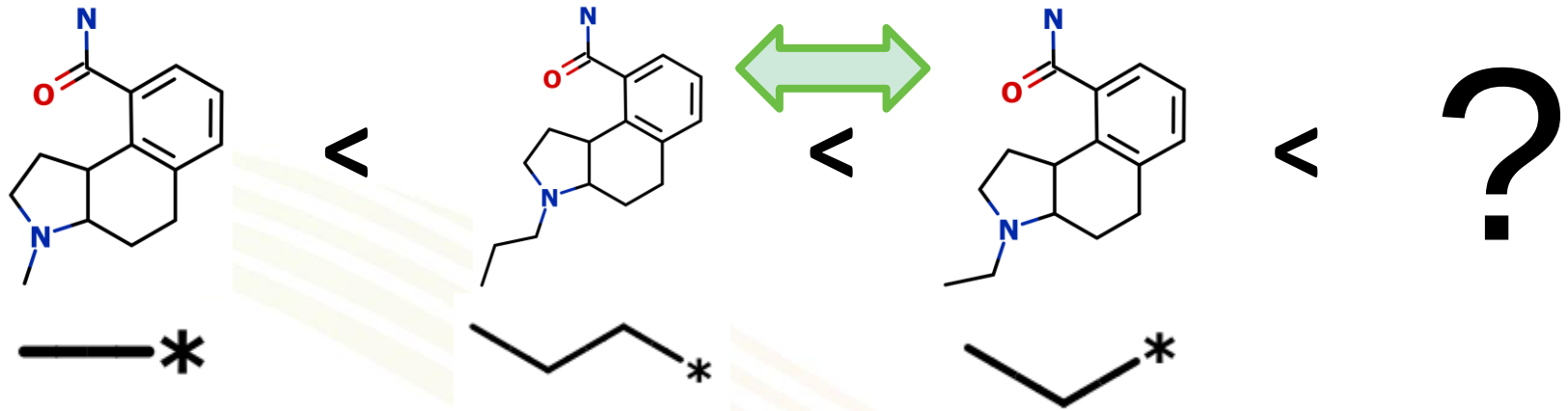


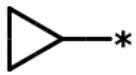
	Structure	RGroup	% that improve	Observations
1			90.5	21
2			72.9	59
3			68.8	32
4			61.5	26
5			59.1	44
6			59	39

Matched series suggest larger hydrophobes will be more active

Matched Series Principles

Look up existing examples from a database

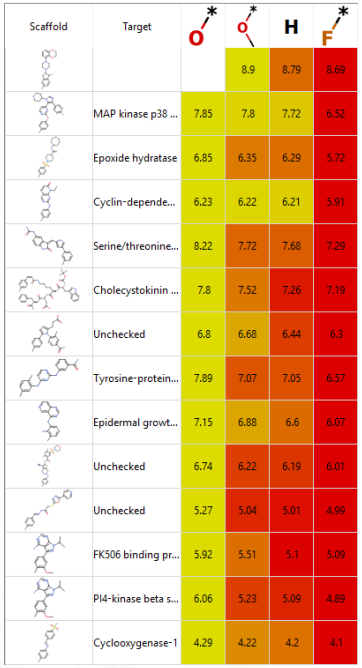


	Structure	RGroup	% that improve	Observations
1			39.1	23
2			35	20
3			34.6	26
4			32.7	107
5			28.1	32
6			27.3	22

Smaller branched hydrophobes suggested by this series

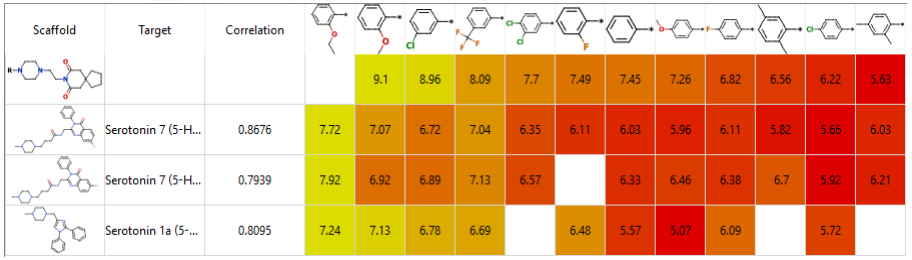
Matched Series Principles

- Matsy™
  - Shorter matched series (≥3)
  - High number of observations (≥20)
  - Key metric: % of observed series that improve activity



Scaffold	Target	O*	O*	H	F*
			8.9	8.79	8.69
	MAP kinase p38 ...	7.85	7.8	7.72	6.52
	Epoxide hydratase	6.85	6.35	6.29	5.72
	Cyclin-depende...	6.23	6.22	6.21	5.91
	Serine/threonine...	8.22	7.72	7.68	7.29
	Cholecystokinin ...	7.8	7.52	7.26	7.19
	Unchecked	6.8	6.68	6.44	6.3
	Tyrosine-protein...	7.89	7.07	7.05	6.57
	Epidermal growt...	7.15	6.88	6.6	6.07
	Unchecked	6.74	6.22	6.19	6.01
	Unchecked	5.27	5.04	5.01	4.99
	FK506 binding pr...	5.92	5.51	5.1	5.09
	PI4-kinase beta s...	6.06	5.23	5.09	4.89
	Cyclooxygenase-1	4.29	4.22	4.2	4.1

- SAR Transfer
  - Longer matched series (≥8)
  - Few observations
  - Key metric: Correlation (R^2) between observed series



Scaffold	Target	Correlation											
				9.1	8.96	8.09	7.7	7.49	7.45	7.26	6.82	6.56	6.22	5.63
	Serotonin 7 (5-H...	0.8676	7.72	7.07	6.72	7.04	6.35	6.11	6.03	5.96	6.11	5.82	5.66	6.03
	Serotonin 7 (5-H...	0.7939	7.92	6.92	6.89	7.13	6.57		6.33	6.46	6.38	6.7	5.92	6.21
	Serotonin 1a (5-...	0.8095	7.24	7.13	6.78	6.69		6.48	5.57	5.07	6.09		5.72	

Medicinal Chemistry Transformation Rules

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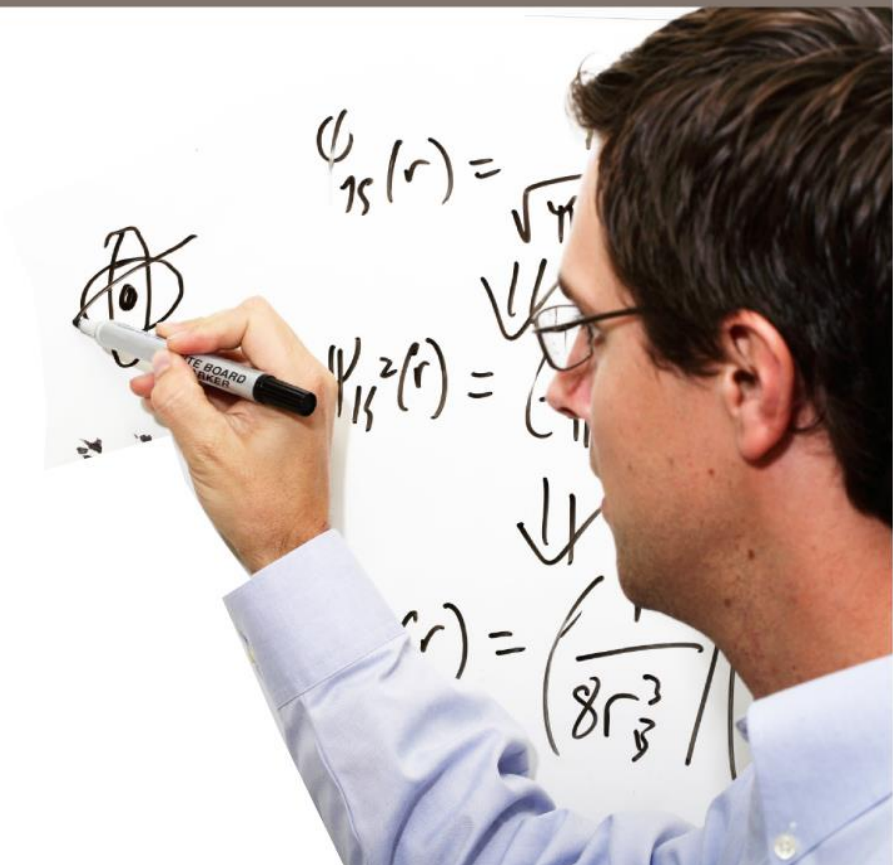


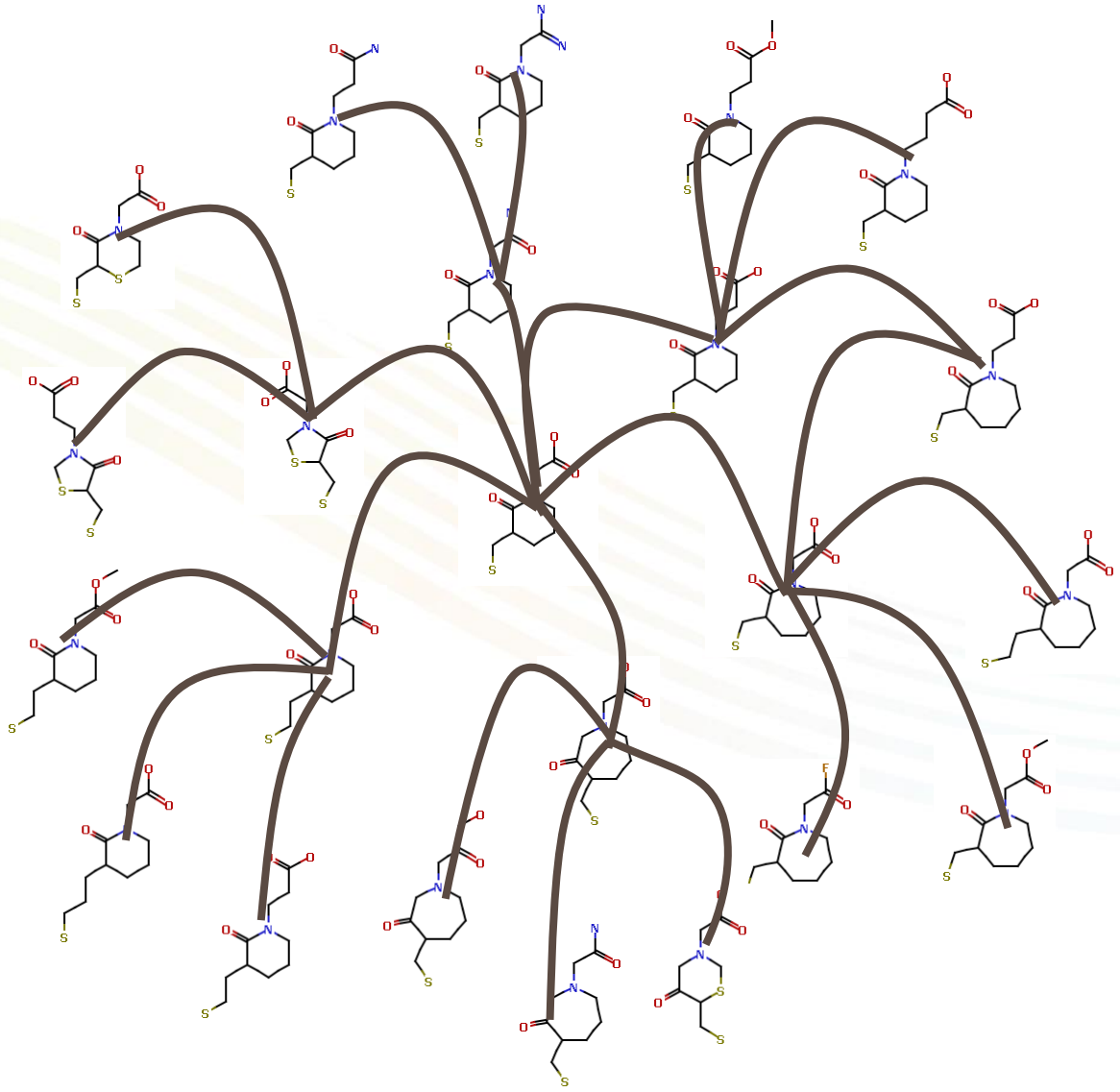
Generating Compound Ideas
Applying Med. Chem. 'Transformation Rules'

- Compounds generated must 'make sense' from a medicinal chemistry perspective
- Apply 'transformation rules', derived from medicinal chemistry experience, to initial compound(s)*
  - Library of >200 transformations, generate ~180 new compounds per input
  - >94% of structures generated acceptable to med. chemists
  - Not only functional group replacement but also framework

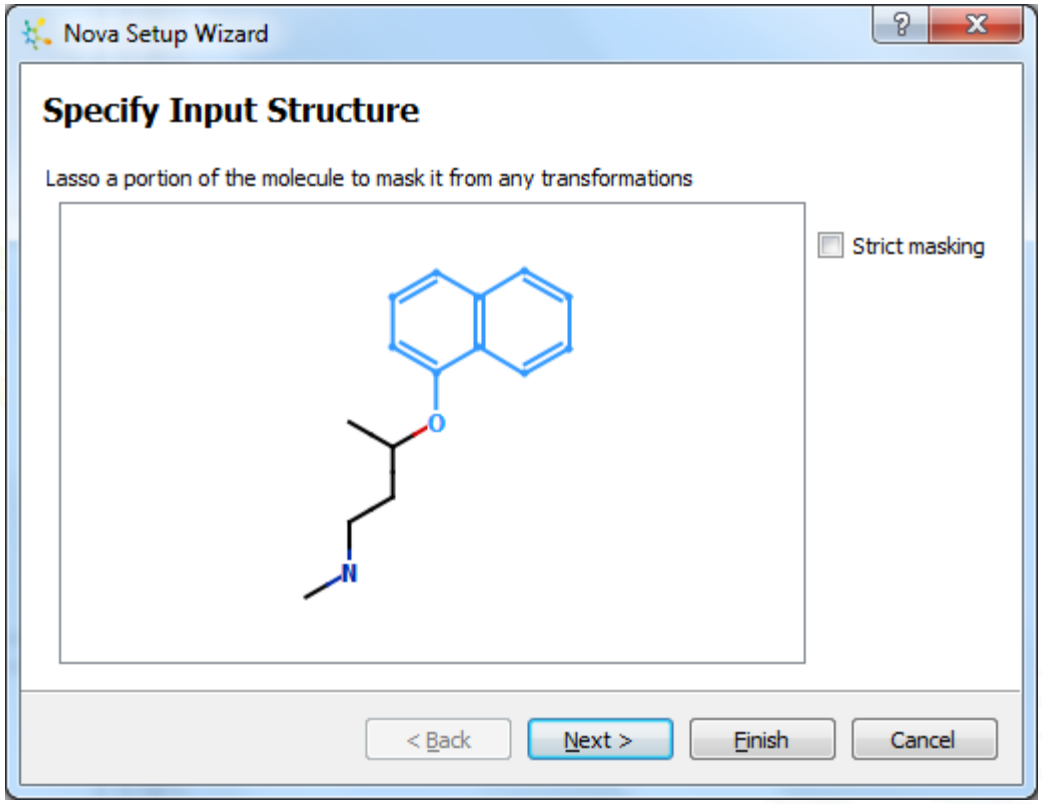
Ring addition: e.g. benzene addition

*Stewart *et. al.* Bioorg. Med. Chem. (2006) **14** p. 7011
*Segall *et al.* J. Chem. Inf. Model. (2011) **51** pp. 2967-2976

Exponential Growth!

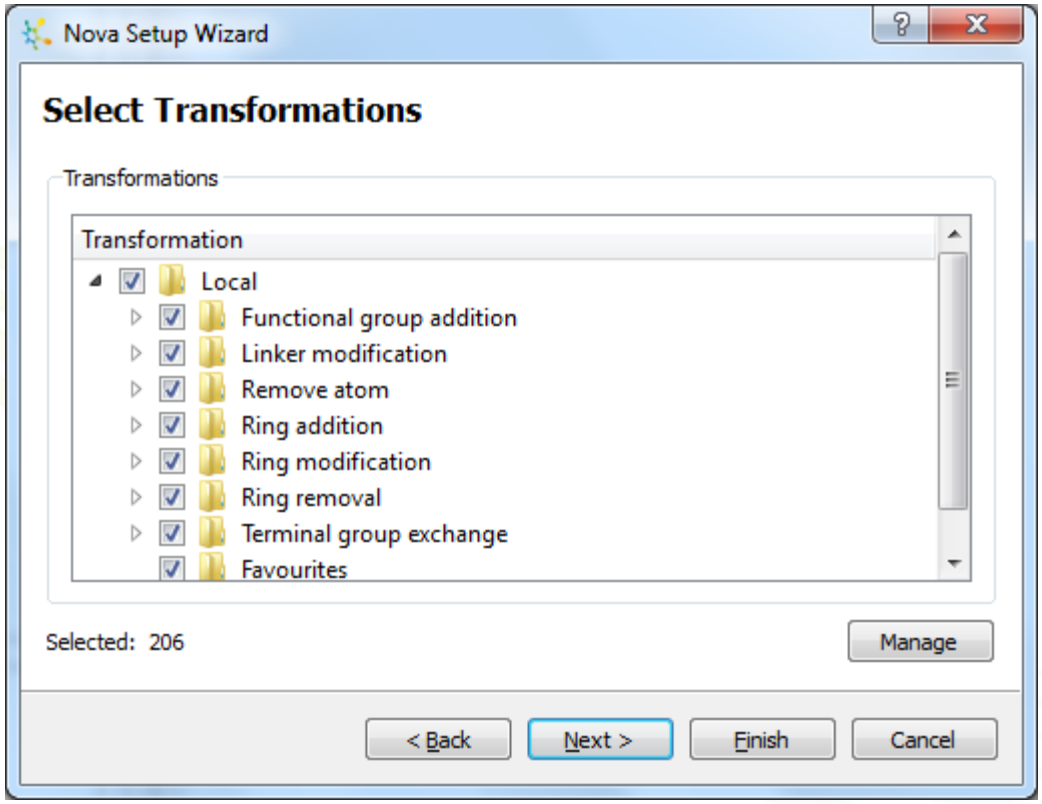


Controlling the Process



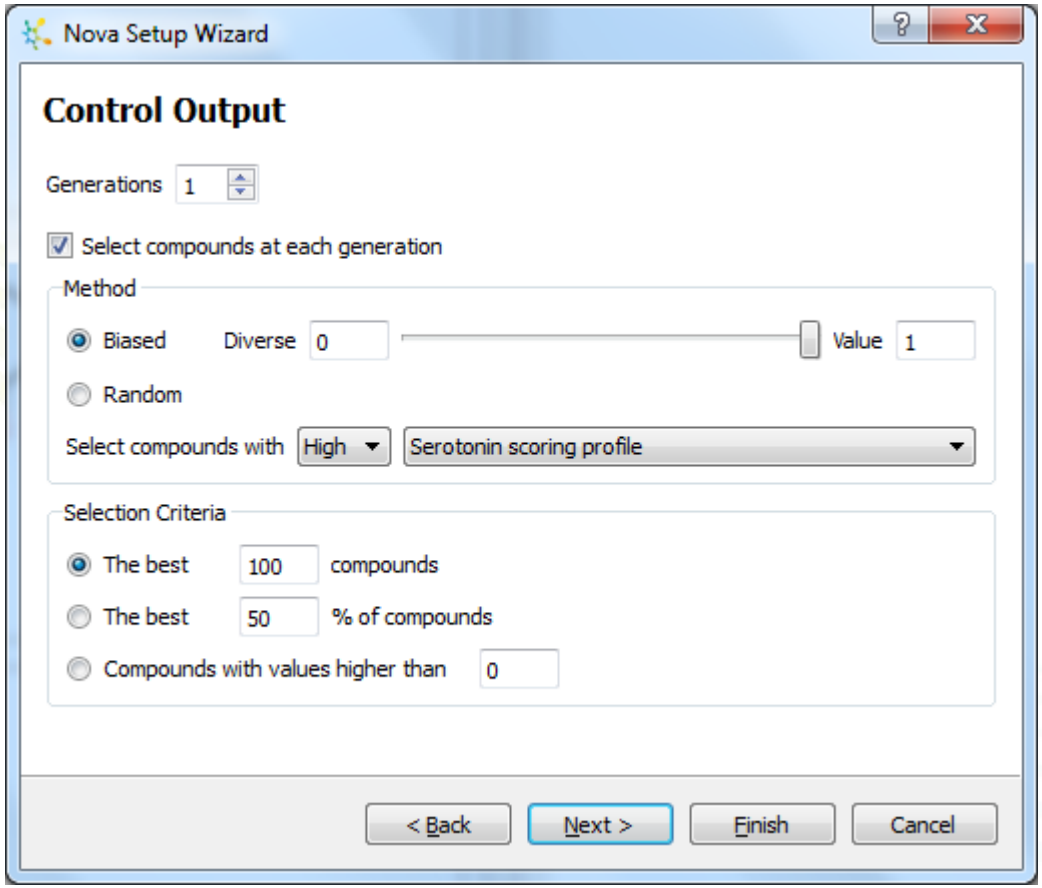
- Specify initial structure
- A region can be selected to be fixed (no changes allowed)

Controlling the Process



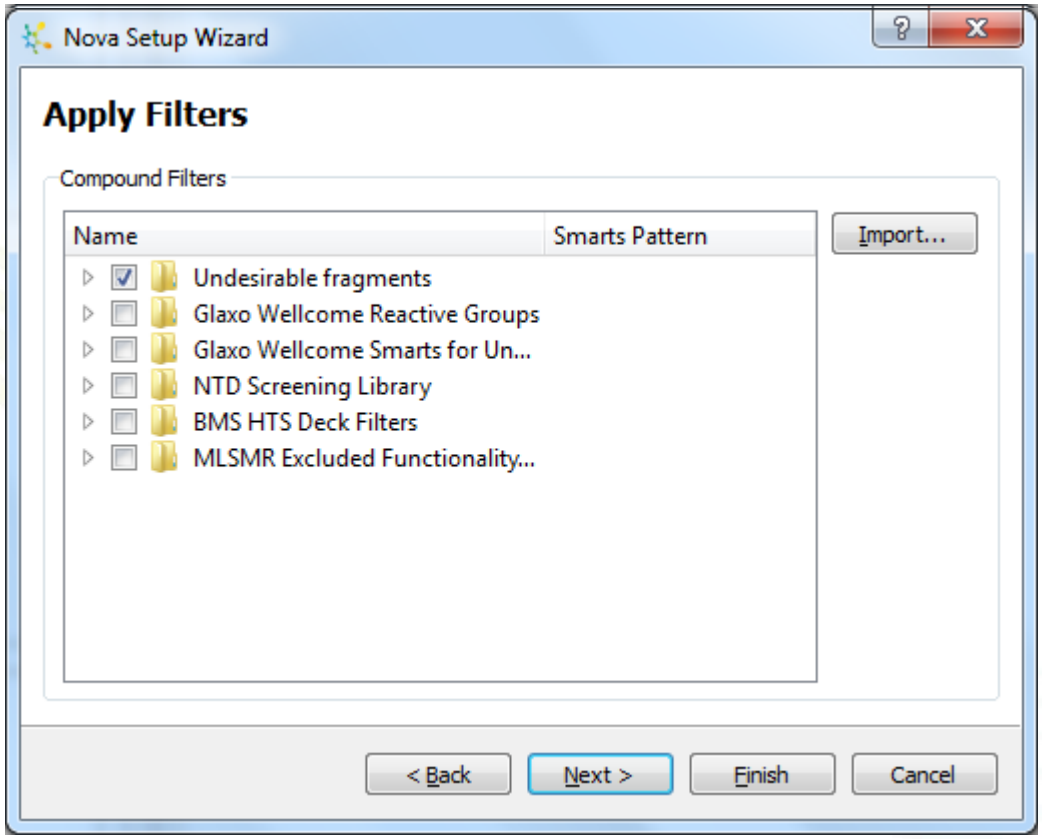
- Select transformations to apply
- Transformations can be managed for specific objectives

Controlling the Process



- Apply multiple generations of transformations
- Bias selection in favour of property, score or diversity

Controlling the Process



- Apply substructure filters to results

Extending the Database of Transformations

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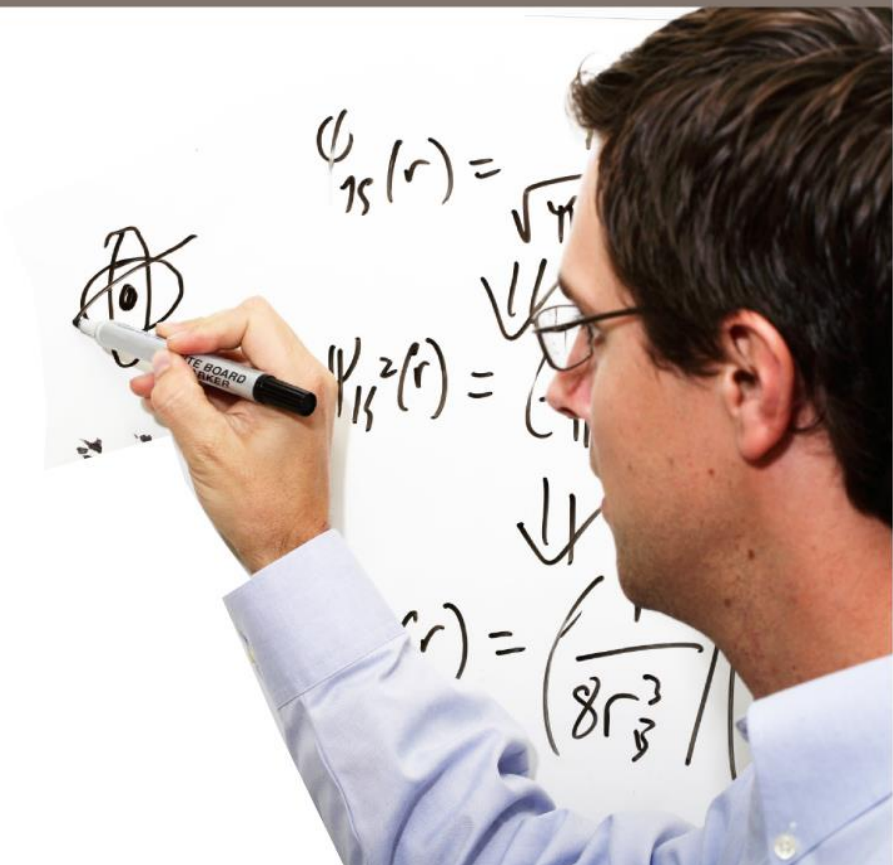


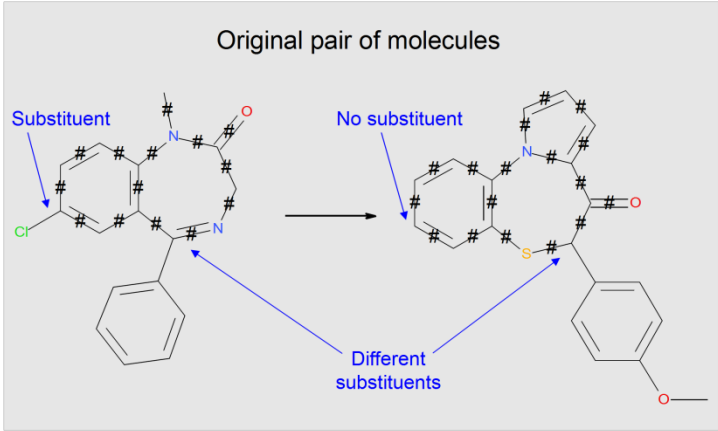
BIOSTER

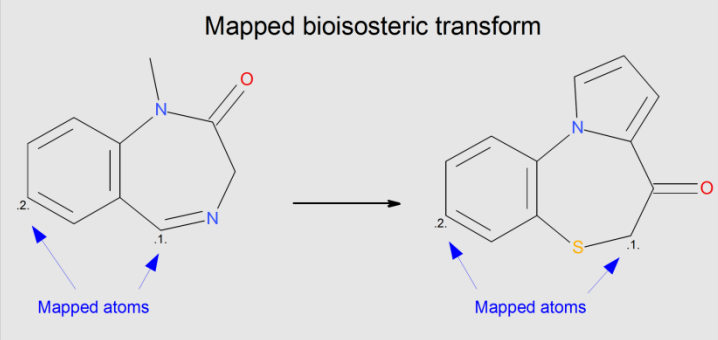
- Database of >32,000 pairs of compounds representing optimisation steps in chemistry projects*
  - Manually curated from the literature by Dr István Ujváry
- Library of transformations defined from pairs of molecules
- Addresses additional questions, e.g.
  - What modifications have been successfully applied to similar compounds?
  - Identify potential lead-hopping strategies
  - Search for patent protection/busting strategies

* Ujváry and Hayward, in Methods and Principles in Med. Chem. (Vol. 54), N. Brown (ed)

Generating Transformations

- Substructure replacement manually defined
- Handle different substitutions
  - Matched using heuristics
- Avoid promiscuity
  - Constraints on application
- 25,351 transformations generated (~80% success)

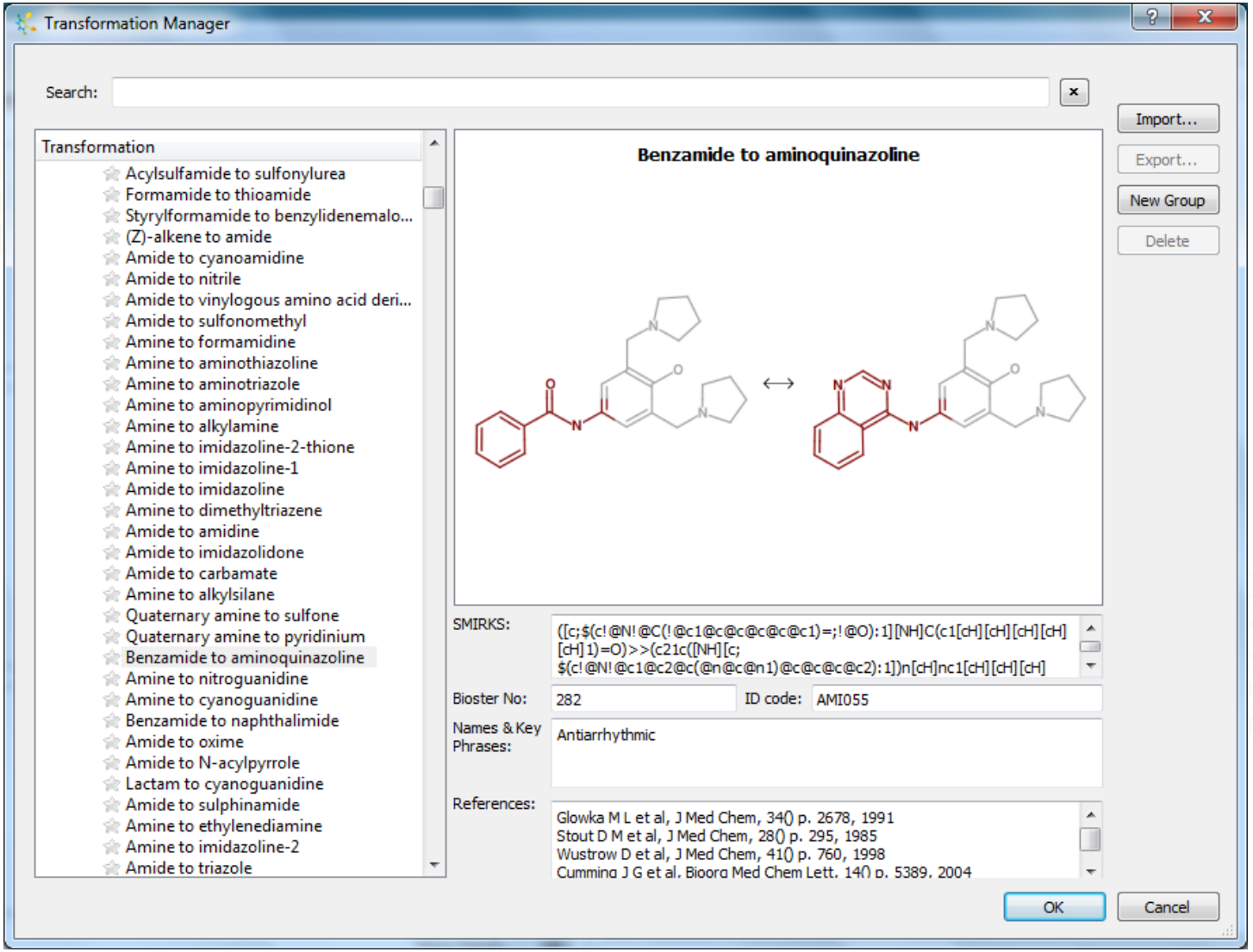




SMIRKS generated

```
([C;$(C1@c2@c(@N(!@C)@C(=;!@O)@C@N=1)@c@c@c@c2):1]1c2c
(N([CH3])C(=O)[CH2]N=1)[cH][cH][c:2][cH]2)>>(n21-c3c
(S[C;$(C1(@S@c3@c(-;@n2@c(@C1=;!@O)@c@c@c2)@c@c@c@c3)
!@[H]):1](C(c1[cH][cH][cH]2)=O)[H])[cH][c:2][cH][cH]3)
```

Transformation Library



Conclusions

- Matched Series Analysis
  - Improves on matched molecular pair analysis to generate more relevant suggestions to improve target activity
- Medicinal Chemistry Transformation Rules
  - Based on medicinal chemistry experience to generate relevant and accessible compounds ideas
- Combine with predictive models and MPO to improve *balance* of properties
- Please see:
  - M.D. Segall Expert Opin. Drug. Discov. (2014) 9(7), pp. 803-817
  - O'Boyle *et al.* Drug Discovery World, Fall 2015, pp. 55-59