The Efficient Enumeration of Reaction Networks.

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Reaction Based Enumeration.

- Developed jointly with Evotec OAI.
- 'Reaction Based' - reactions are predefined.
- Choice of Reactant Classes, aids specificity.
- Flexible reagent selection.
- 'Reaction Network' GUI developed through discussions with Harvard Med. School.
- Integrated with Modgraph Registry and CSC (Chemical Supplier Catalogue).

Library Builder

- Exploits systematic nature of Daylight SMIRKS and SMARTS.
- SMIRKS generated on the fly.
- Many thousands of different SMIRKS. (Only one bug found).
- Selection from Inventory and selection of reaction centre are the same ‘thing’.
- Design of SMARTS is a compromise between trying to select only hits which are ‘useful’, (minimising list size) and excluding structures which are inappropriate.

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Enumeration Example

2 Step Reaction

$$A + B >> C$$
$$C + D >> E$$

2 A x 3 B = 6 C x 6 D = 36 E

A1 A2	+	B1 B2 B3	>	C1 (A1B1) C2 (A1B2) C3 (A1B3) C4 (A2B1) C5 (A2B2) C6 (A2B3)	+	D1 D2 D3 D4 D5 D6	>	E1 (A1 B1 D1) E2 (A2 B1 D1) E3 (A1 B2 D1) E4 (A2 B2 D1) E5 (A1 B3 D1) ...

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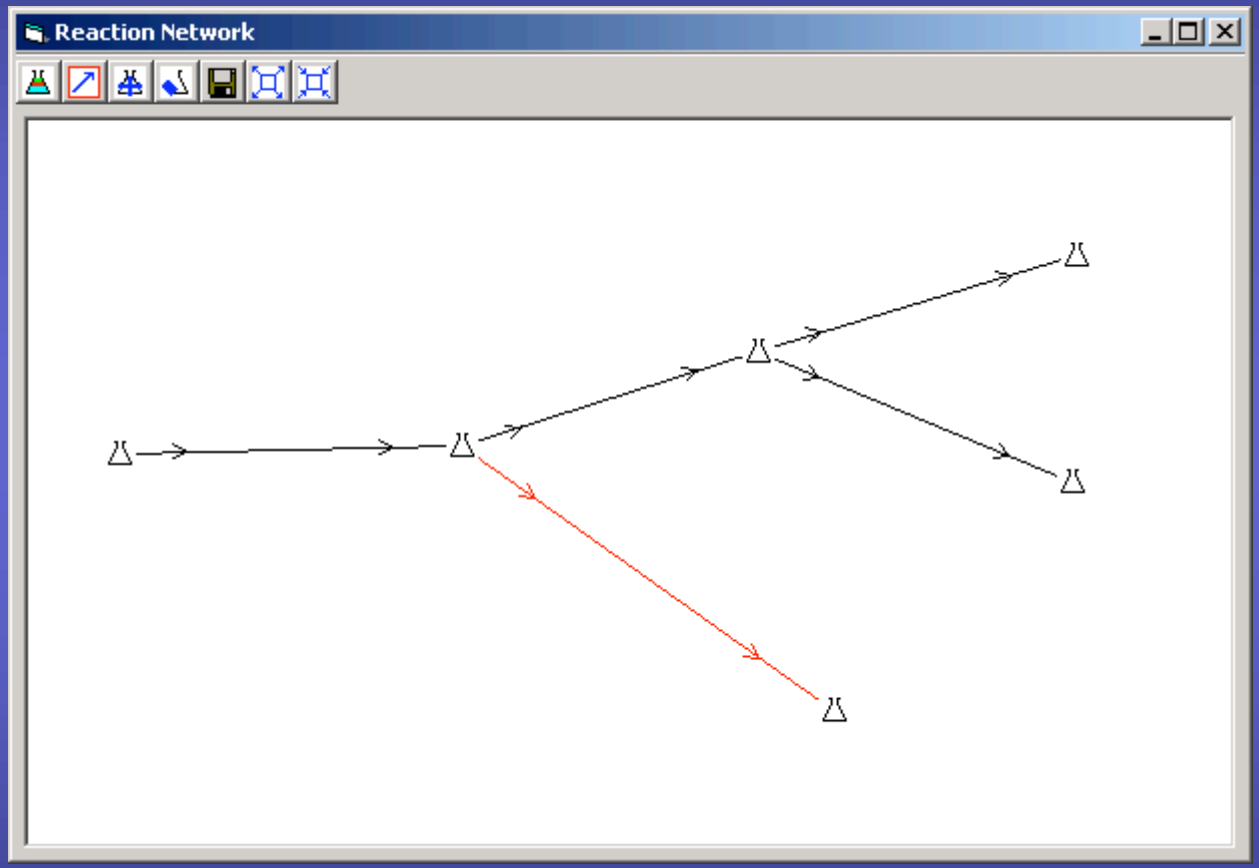
Network Design



First design the reaction network.

Nodes can be added, deleted and moved, zoom-in, zoom-out. Rules.

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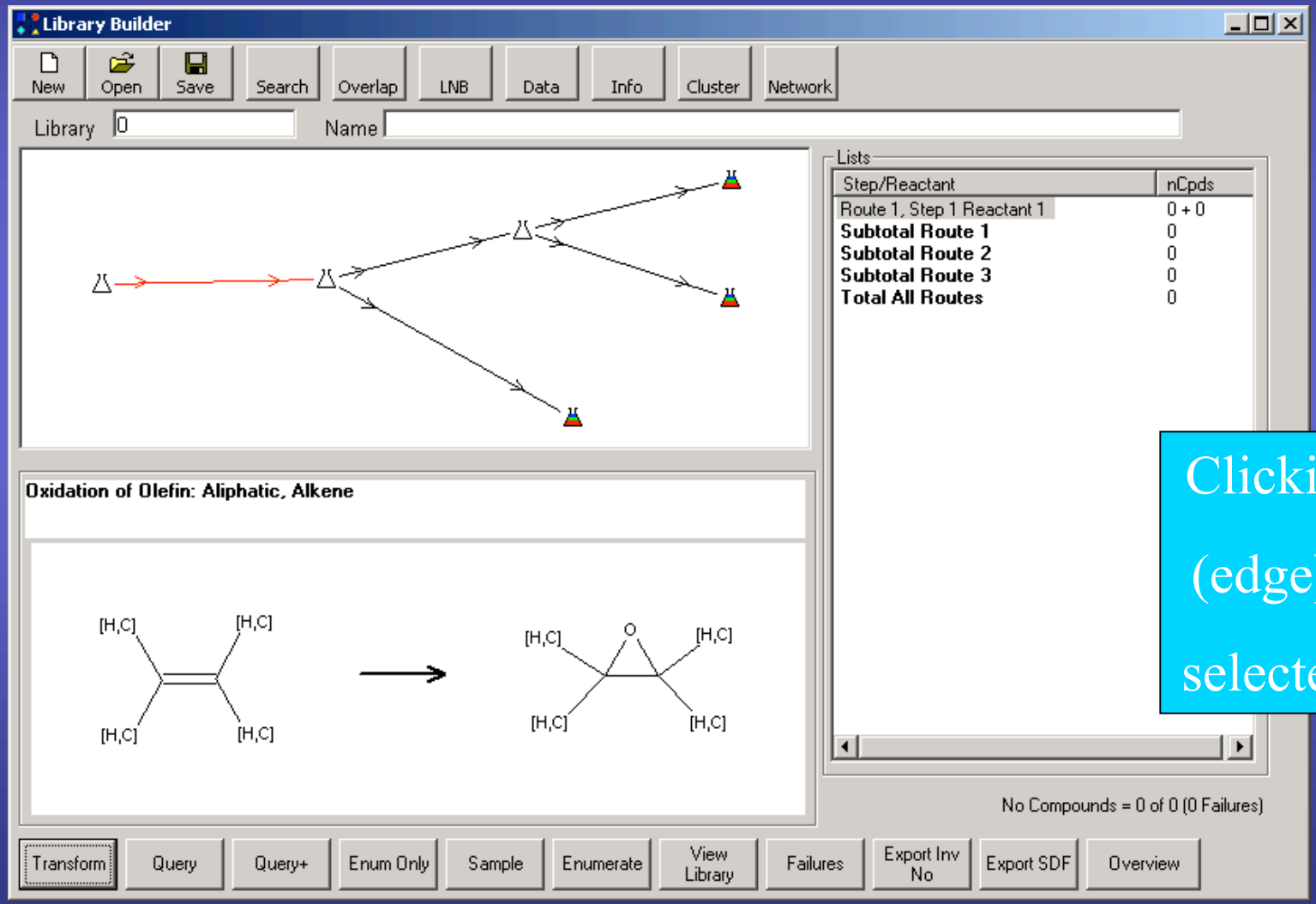
Template Approval



Clicking on step (edge) displays selected reaction

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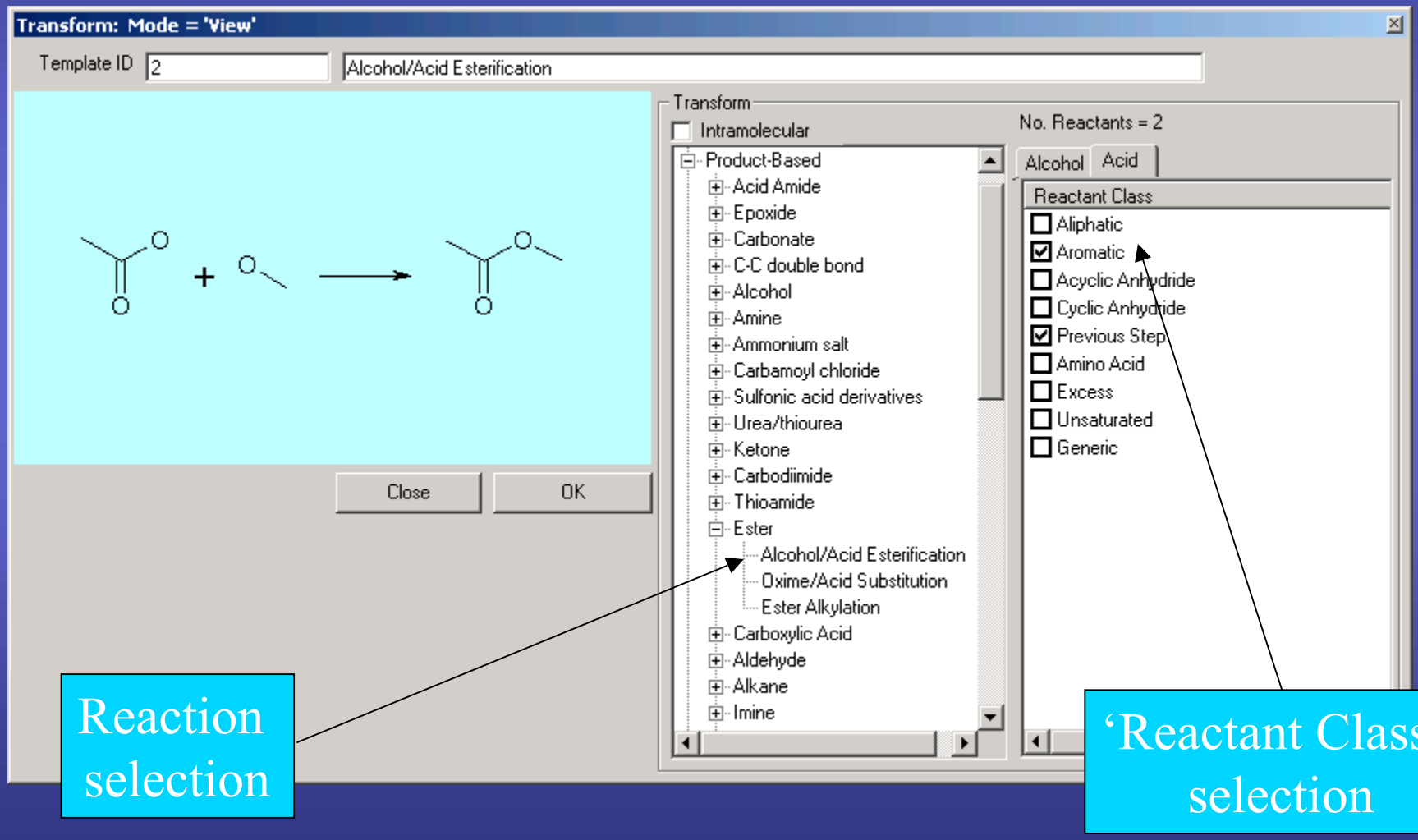
Reaction Selection



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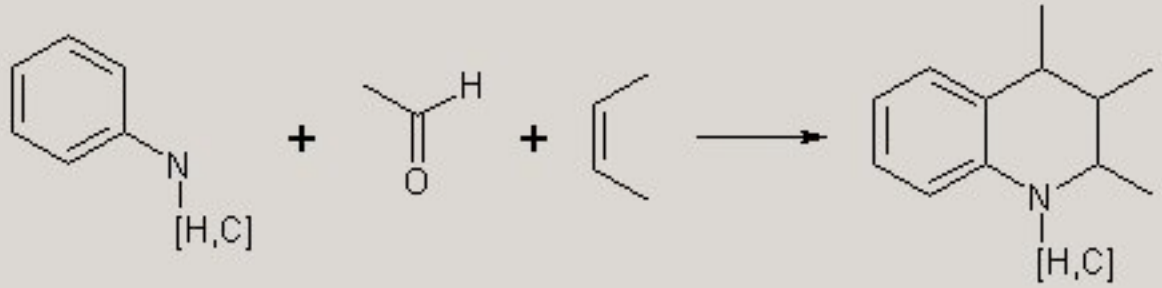
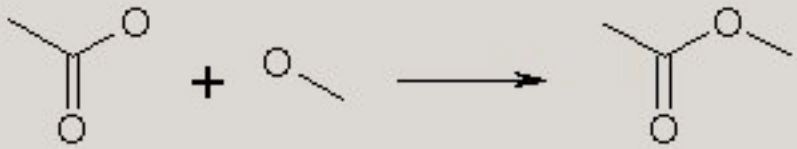
Reaction Overview

Overview: template = WX24V

Quinoline: Aliphatic, Aldehyde + Primary, Aromatic Amine + Aliphatic, Alkene



Alcohol/Acid Esterification: Primary, Alcohol + Aromatic, Previous Step, Acid



Overview can be printed

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Reactant Selection

Search for reactants is based on either:

- Inventory number
- Exact structure
- Any Combination of
    1. Default SMARTS - the SMARTS based on reactant class selection.
    2. Sub-structure
    3. Filter - applies additional SMARTS based on reactant classes
    4. Molecular weight range.
- Two Stage Selection. Select list and select from list.

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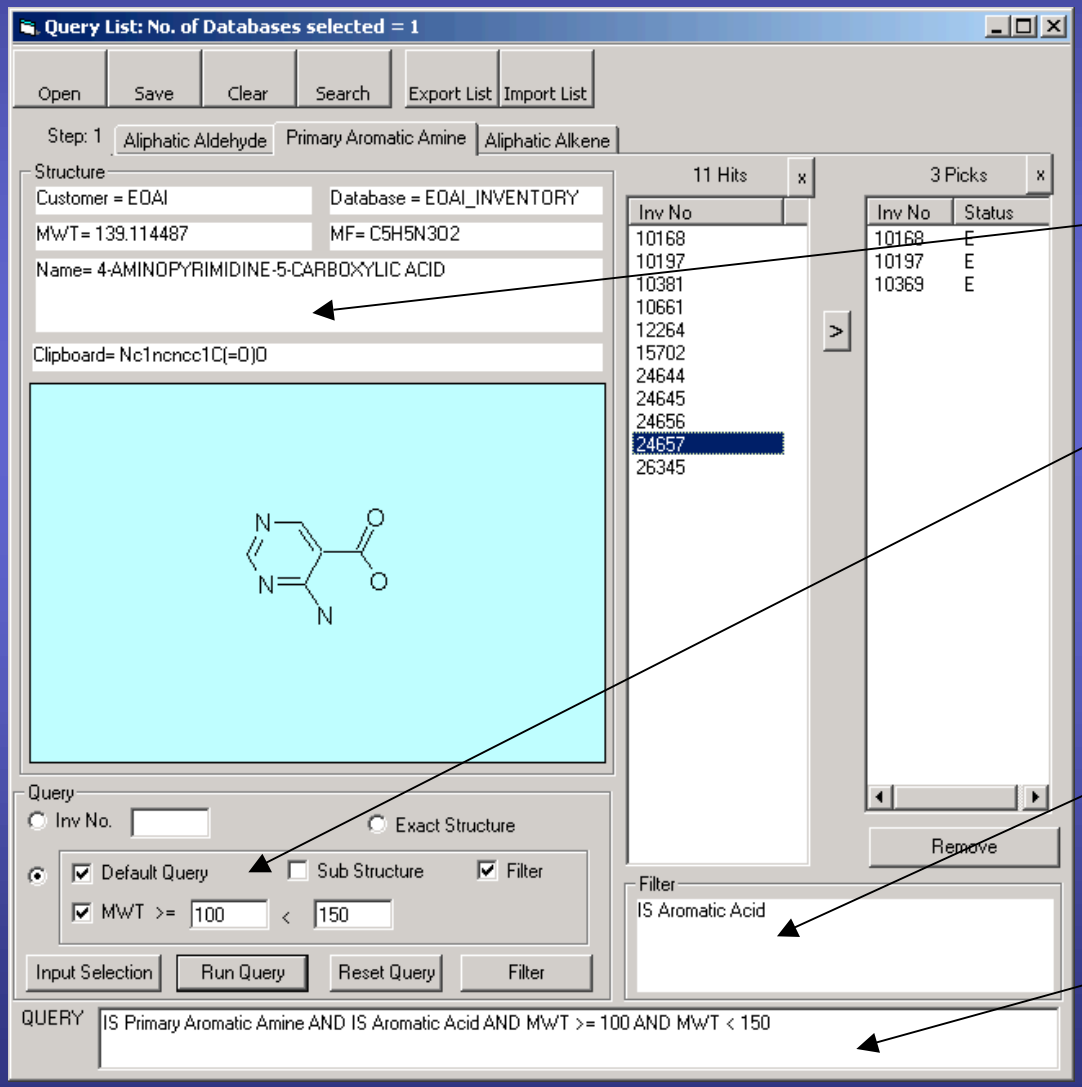
Reagent Selection - Stage 1.



Multiple, customer specific databases.

Reactant Structure and details.

Default Query

+ Filter

+ MW range

Filter selected by name/class.

English description of Query.

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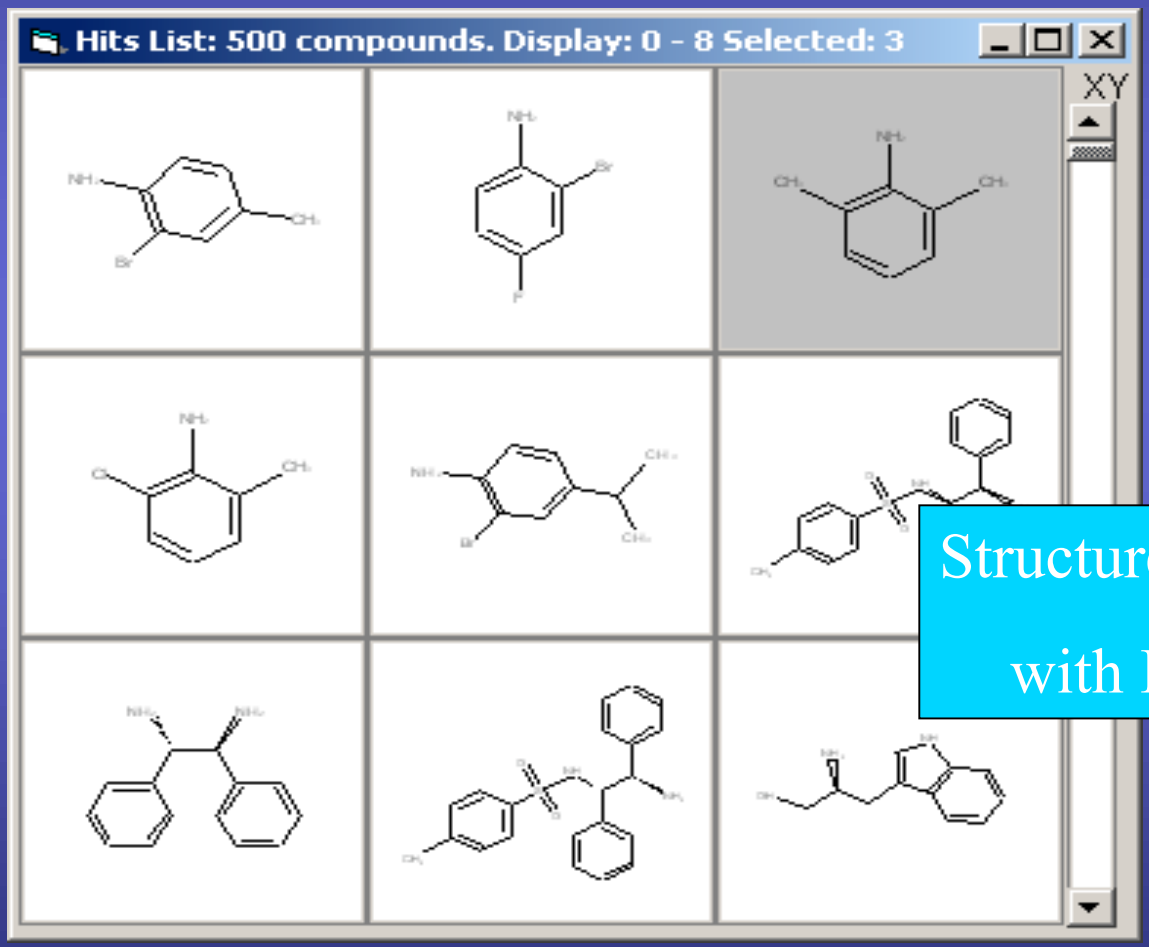
Reagent Selection - Stage 2



Structures are displayed with Inventory No.

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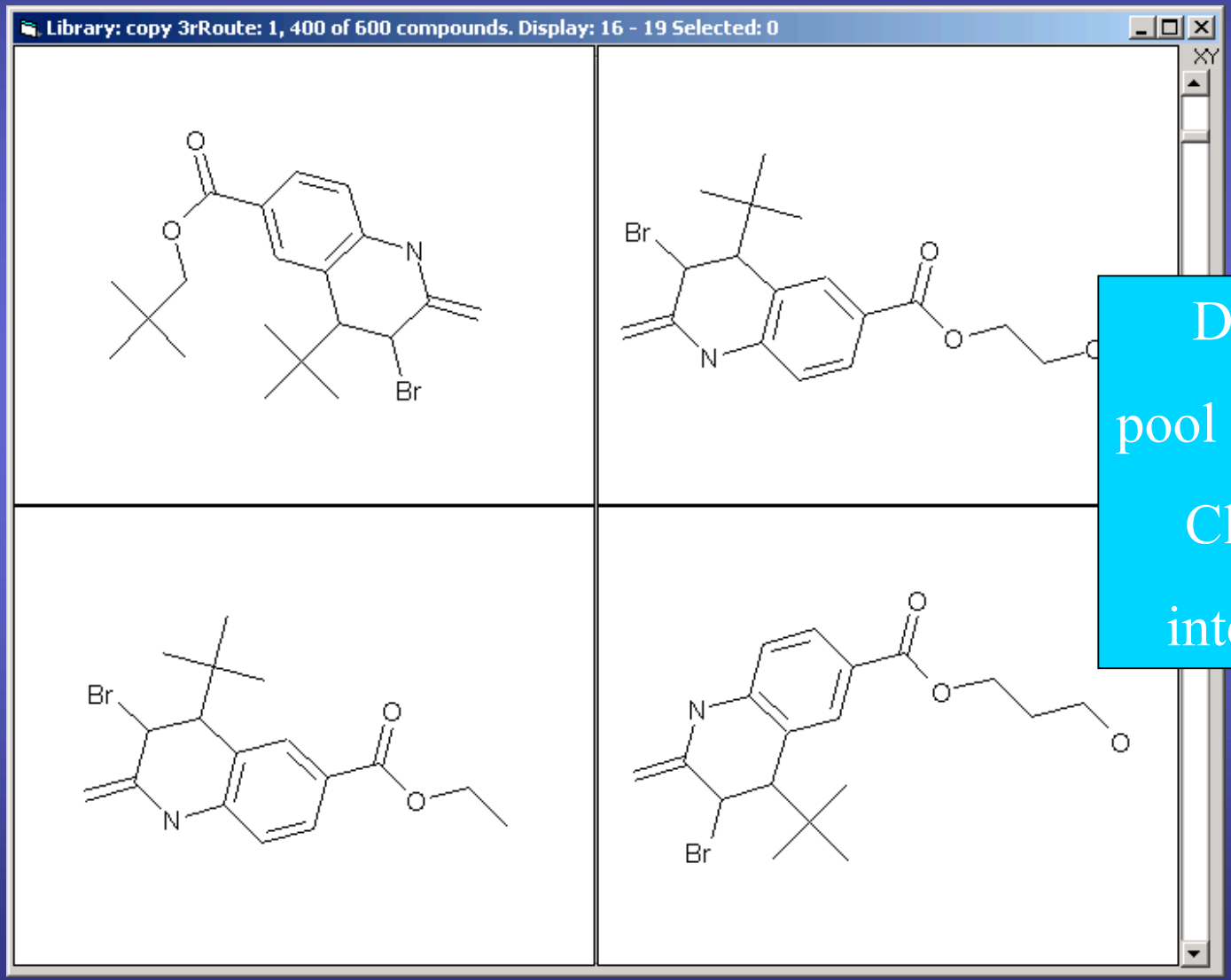
Library View



Display of pool compounds. Click to see intermediates

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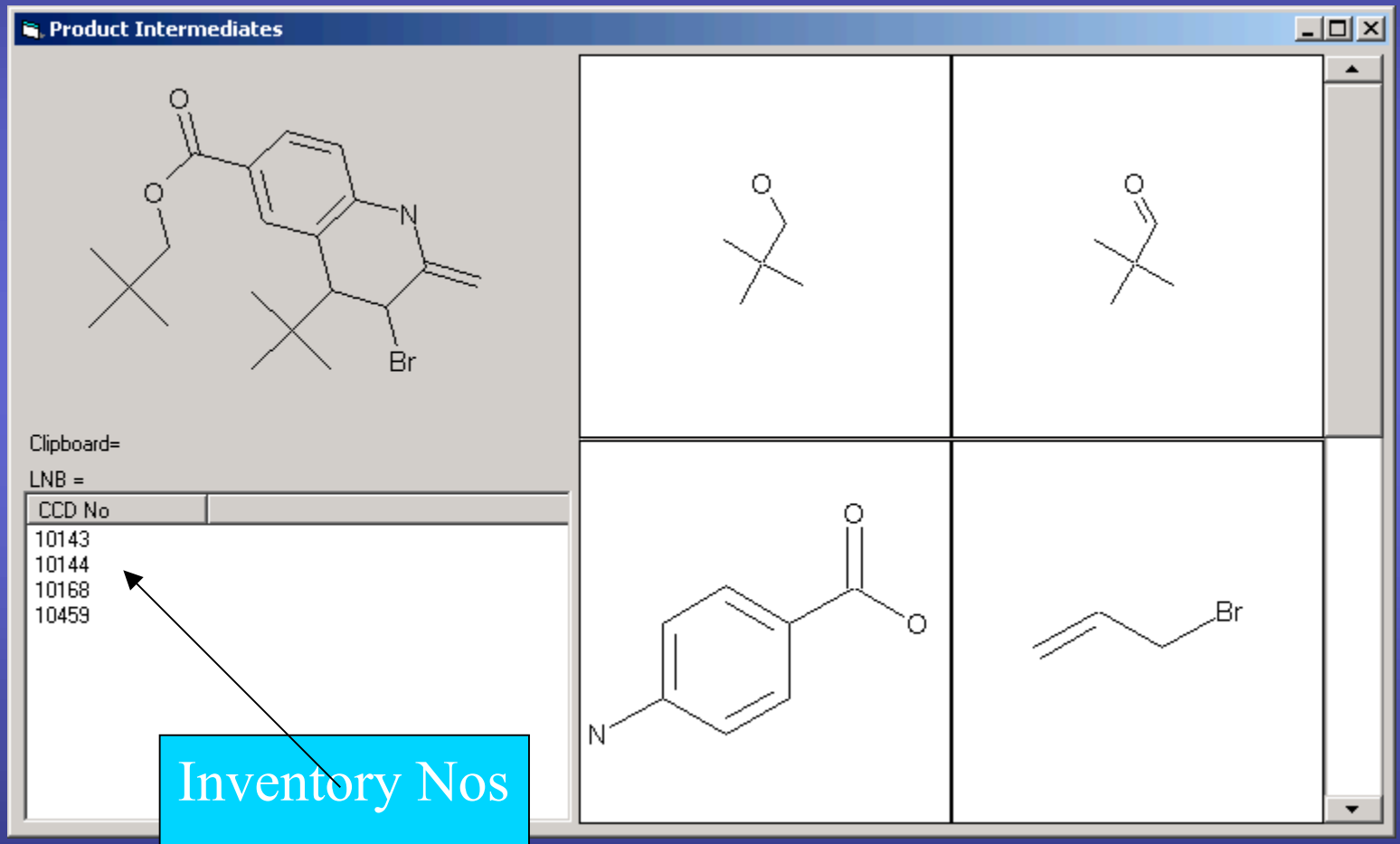
Product Intermediates



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Enumeration Algorithm

- Fast and efficient enumeration of very large libraries.
- The library is split into a number of ‘experiments’, such that the number of compounds in one experiment is minimized, subject to no intermediate being synthesized more than once. **Minimum memory usage; maximum speed**.
- Minimising memory usage is more important, since writing to a db is likely to be RDS.
- Library Sample Algorithm - minimum library size consistent with every reactant being used at least once.

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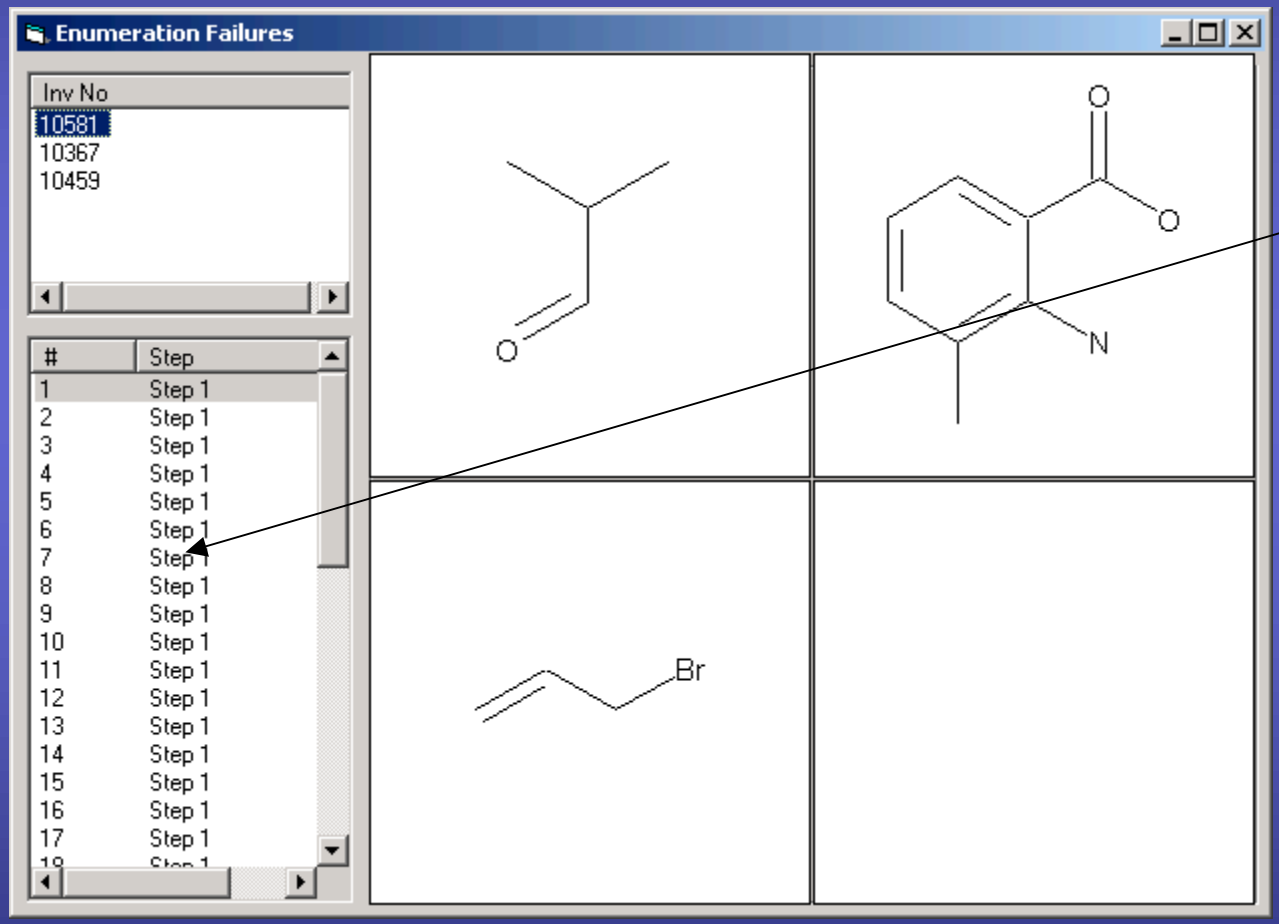
Failures List



Shows the step no. which failed and reagents up to that step.

Here the failure is due to absence of aromatic H ortho to NH2

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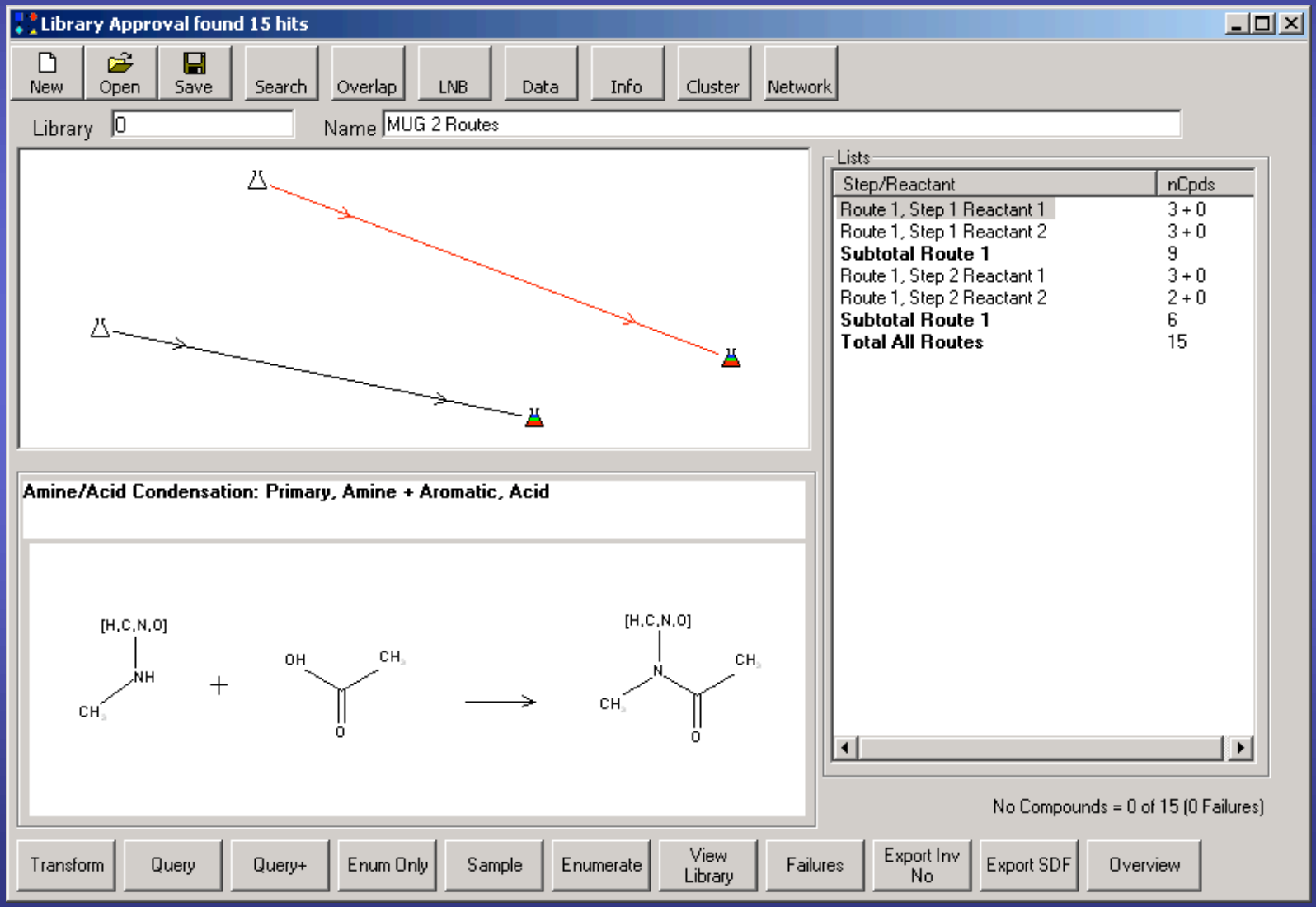
Routes can be Disjoint.



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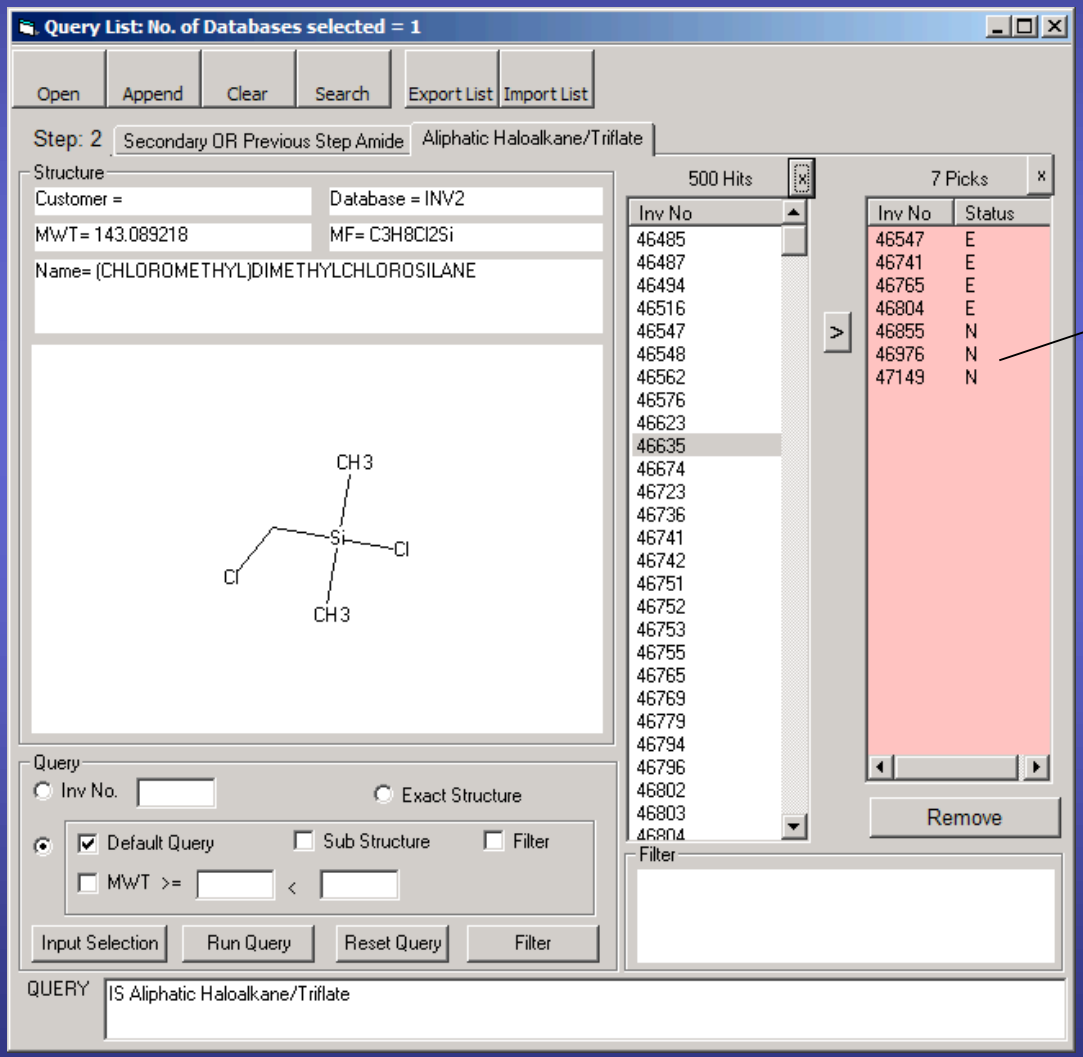
Query +



Three extra compounds added.

Avoid re-enumerating whole library. (Time, Data).

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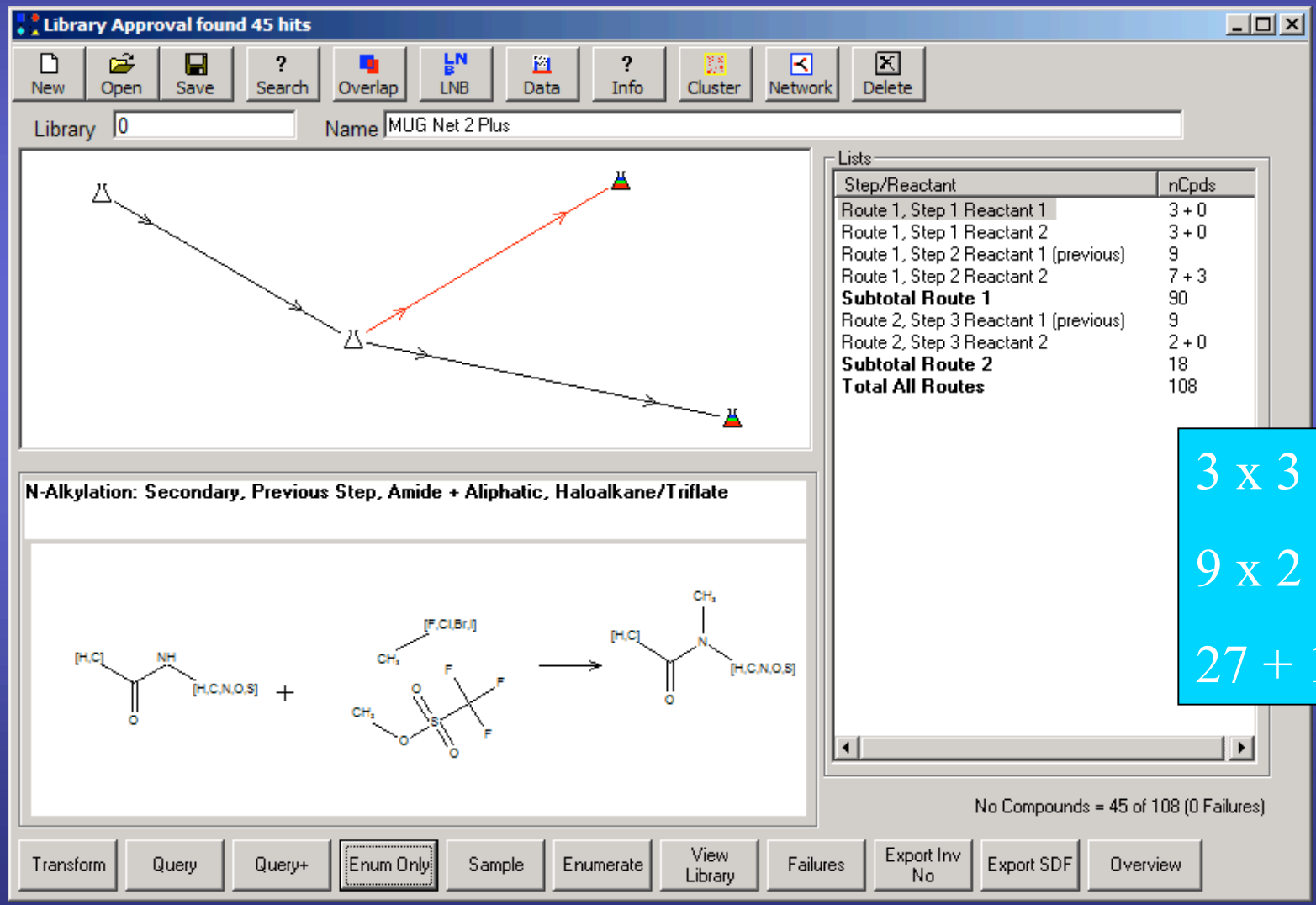
Query +



3 x 3 x 3 = 27

9 x 2 = 18

27 + 18 =45

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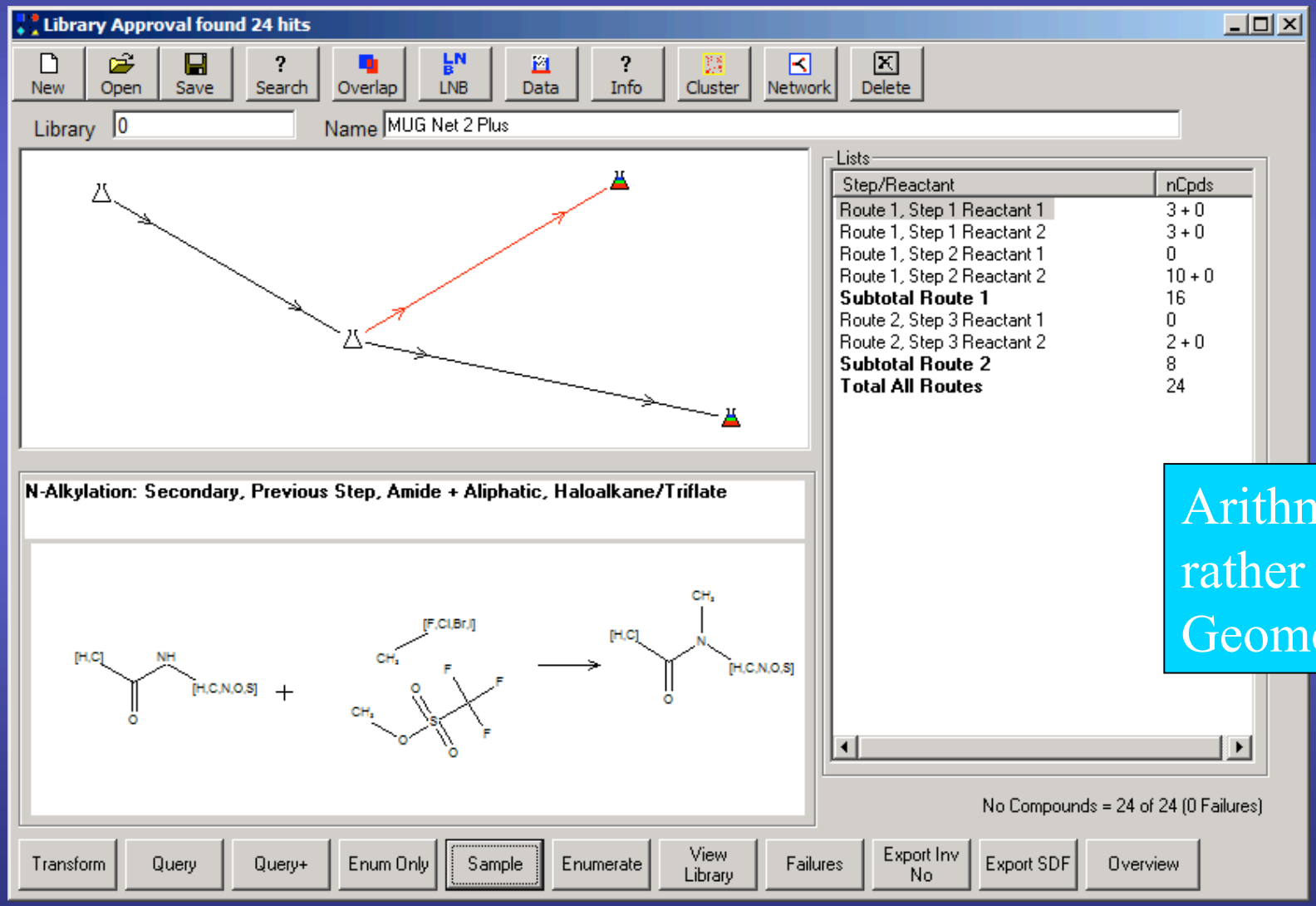
Sampling



Arithmetic rather than Geometric.

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Futures and Options

- Customisation. Integration with other applications/business process. Plate layout, library filtering, LNB assignment etc.
- Variable Sample size.
- Improvements to Reagent selection.
- Specification of Reaction Centre per reactant.

Acknowledgements

- John Bradshaw
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