Reaction-based enumeration: Lessons learned in designing a workflow that chemists want to use

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Agenda

- Introduction to Optibrium
- Scaffold and Reaction-based Library Enumeration
- Reaction-based Library Enumeration
  - Reactions
  - Reagents
  - Products
  - Beyond Chemistry
- Conclusions

Introduction to Optibrium

www.optibrium.com

Augmented Chemistry®

Cerella™ an Augmented Chemistry® software product

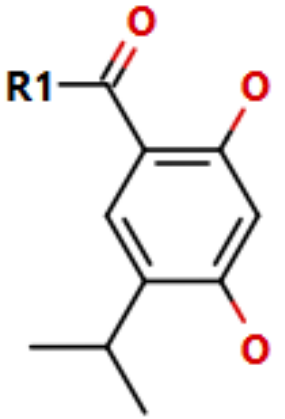
Inspyra™ an Augmented Chemistry® software product

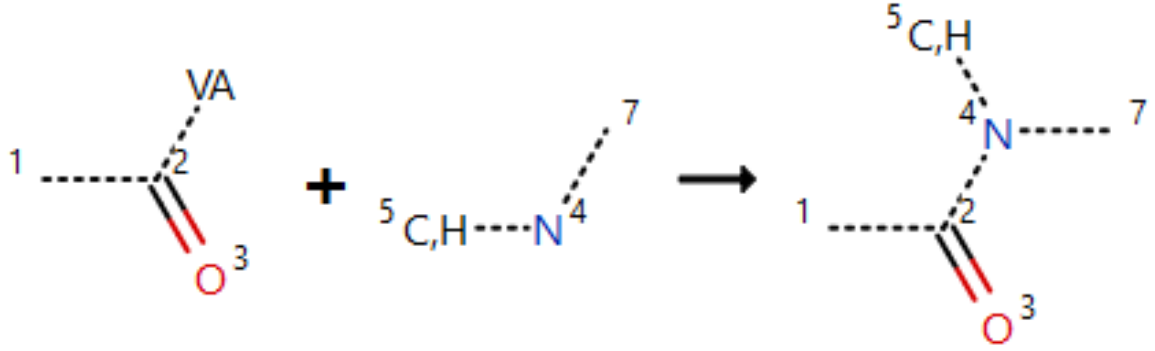
- Optibrium creates elegant software solutions for small molecule design, optimisation and data analysis
  - R&D of novel technologies to guide decisions and improve efficiency in drug discovery
- Two platforms forming an integrated ecosystem
  - StarDrop™
  - Augmented Chemistry®
- Global customer base from top-ten pharma to small biotech and academia
  - >180 customers worldwide
  - Adoption in other chemistry fields, e.g. animal health, agrochemicals, etc.

optibrium™

Types of Library Enumeration

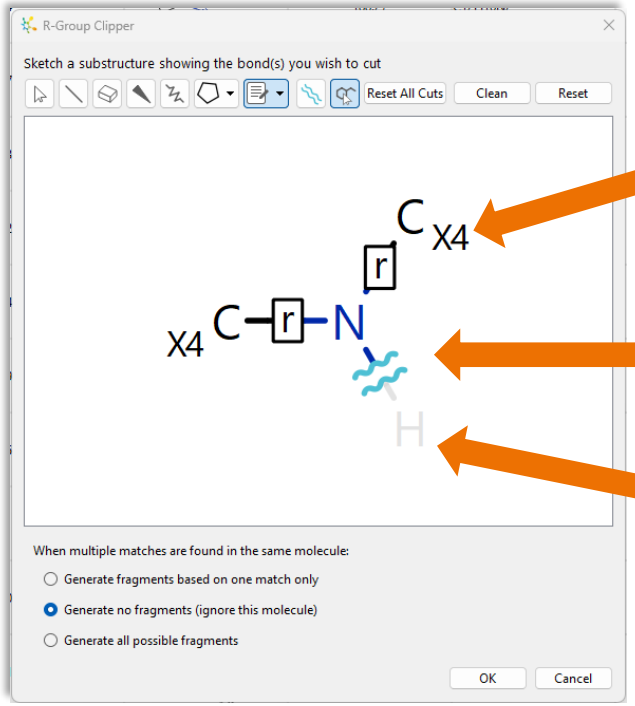
- Library enumeration involves joining fragments
  - R-groups, linkers and scaffolds
- Scaffold-based enumeration
  - Defined from the product
  - Uses pre-prepared lists of fragments
- Reaction-based enumeration
  - Defined from a reaction
  - Uses lists of reagents
  - Creates fragments on the fly





Reagent clipping

- Flexible fragment definition
  - From lists of reagents or building blocks
    - Metadata retained with fragment
  - Save and reuse fragment libraries



Set atom and bond constraints

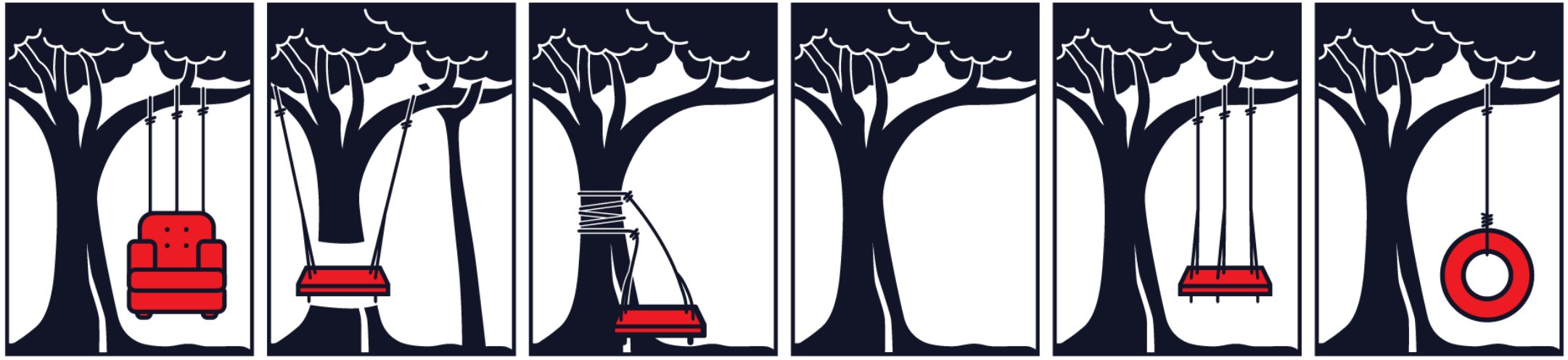
Define the bond to cut

Define the fragment to exclude

New column of fragments with metadata

	VID	SMILES	Fragment1_0	eMolecules URL	Quantity	MWT	Units
1	96276481			https://www.emolecules.c...	1	201.27	g
2	48572294			https://www.emolecules.c...	100	188.27	mg
3	44469267			https://www.emolecules.c...	1	202.29	g
4	36251563			https://www.emolecules.c...	0.25	202.29	g
5	26985702			https://www.emolecules.c...	1	188.27	g
6	17413314			https://www.emolecules.c...	5	190.29	g

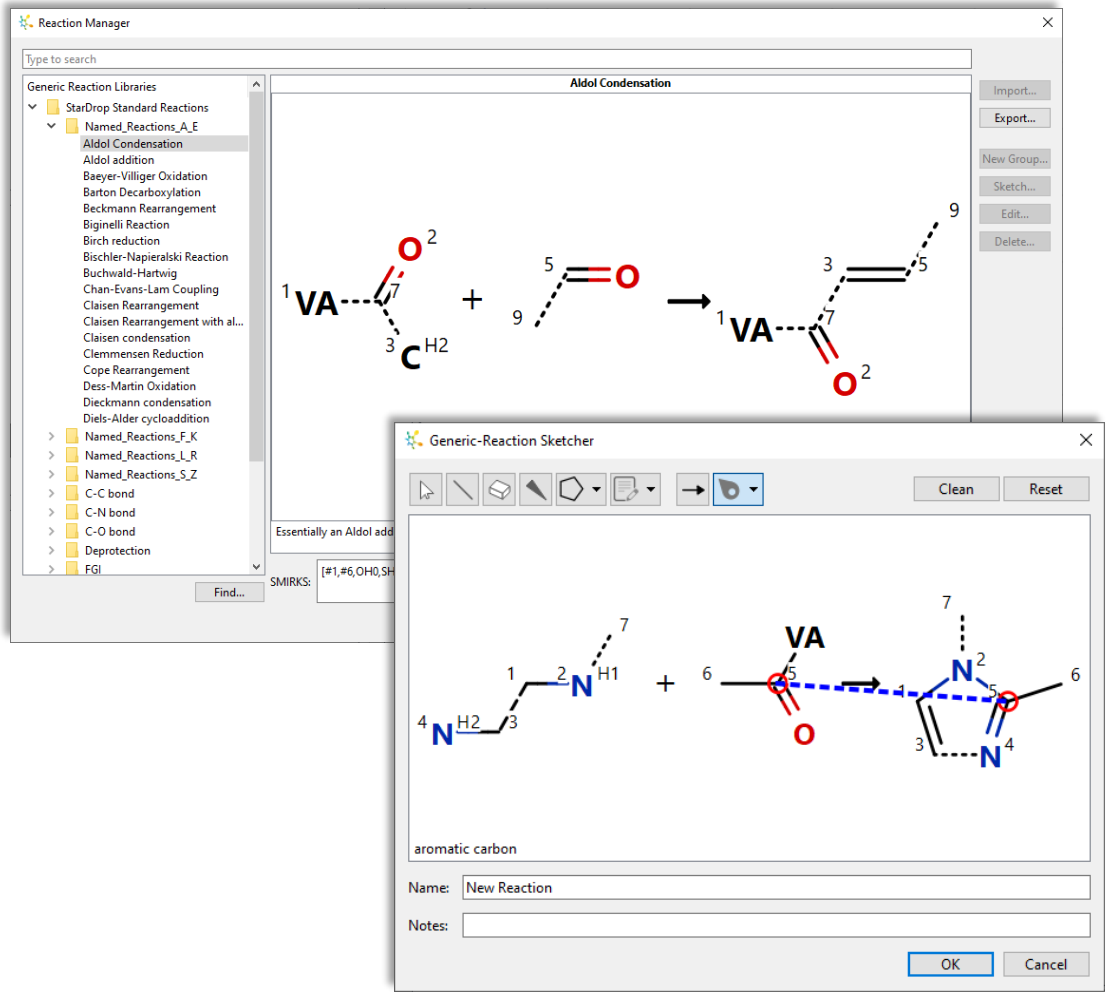
What a Scientist Really Wants



- Importance of working with users at every step
  - Scope, test and deliver
- User-friendly, flexible workflow that meets user requirements

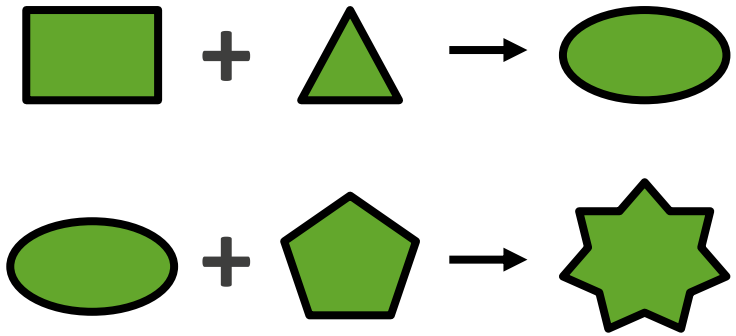
Reactions

- Approximately 100 pre-defined common reactions
  - Create centrally-managed and individual reaction libraries
- Import RXN files
- Edit existing reactions or define your own
  - On-the-fly
  - Save and share

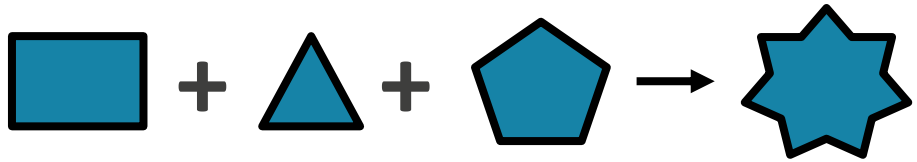


Flexible Reaction Definition

- No requirement to mimic the real life lab process
- Combine multiple steps in a single enumeration



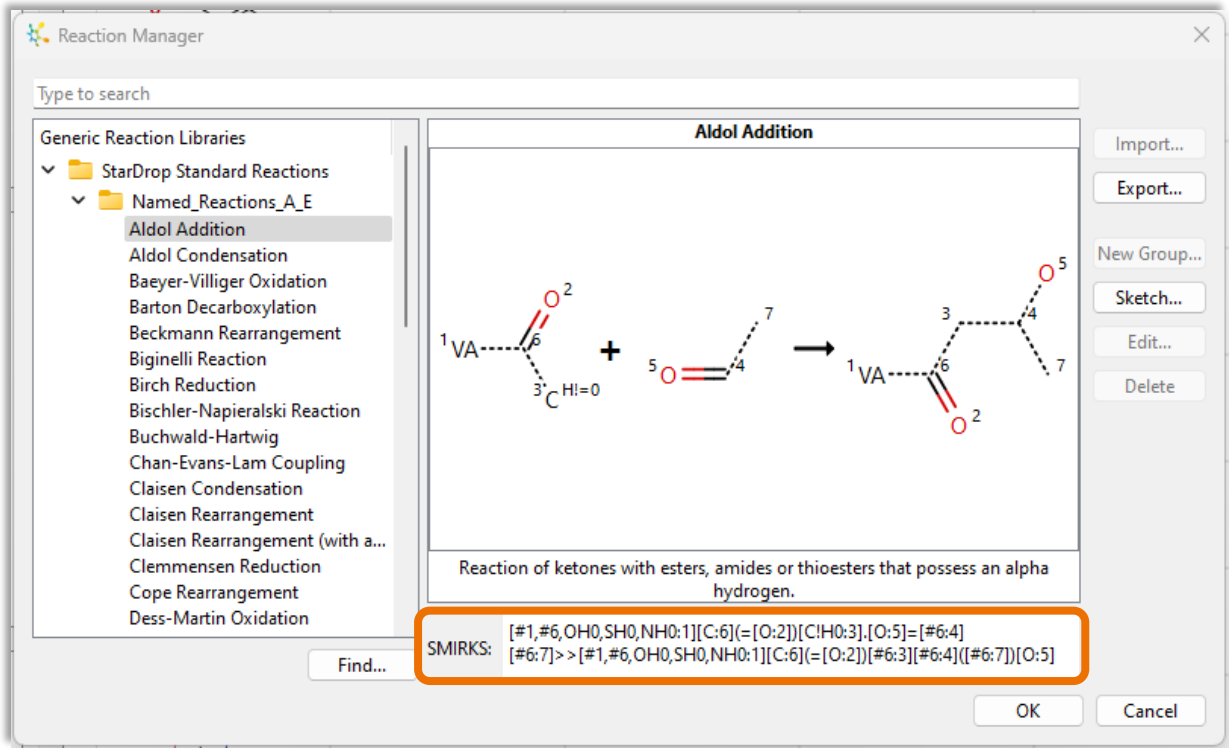
vs



- For example, BOC-deprotection followed by amide formation

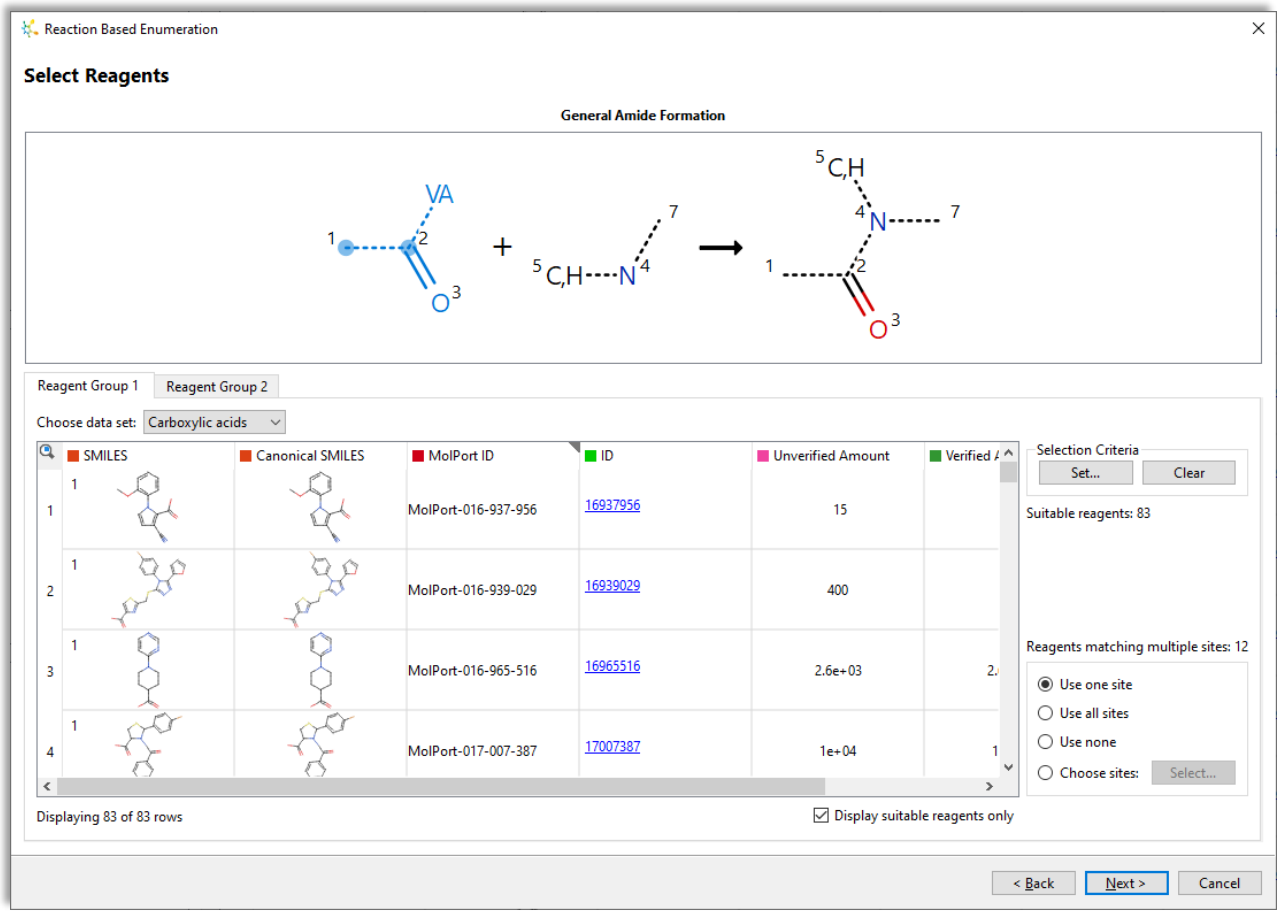
SMIRKS

- SMIRKS is the language the computer uses to define a reaction
  - [#1,#6,OH0,SH0,NH0:1][C:6](=[O:2])[C!H0:3].[O:5]=[#6:4][#6:7]>>[#1,#6,OH0,SH0,NH0:1][C:6](=[O:2])[#6:3][#6:4]([#6:7])[O:5]
- Encodes reaction, variable atoms and atom/bond constraints
- Also represent SMIRKS graphically
  - Enables graphical editing
  - Support multiple levels of understanding
- Export SMIRKS to other platforms



Reagents

- Reagent lists as StarDrop data sets
  - Minimal preparation
  - Can be reused flexibly
- Configure and filter on the fly
  - Detection of unsuitable reagents
  - Selection criteria (filters)
  - Define regioselectivity



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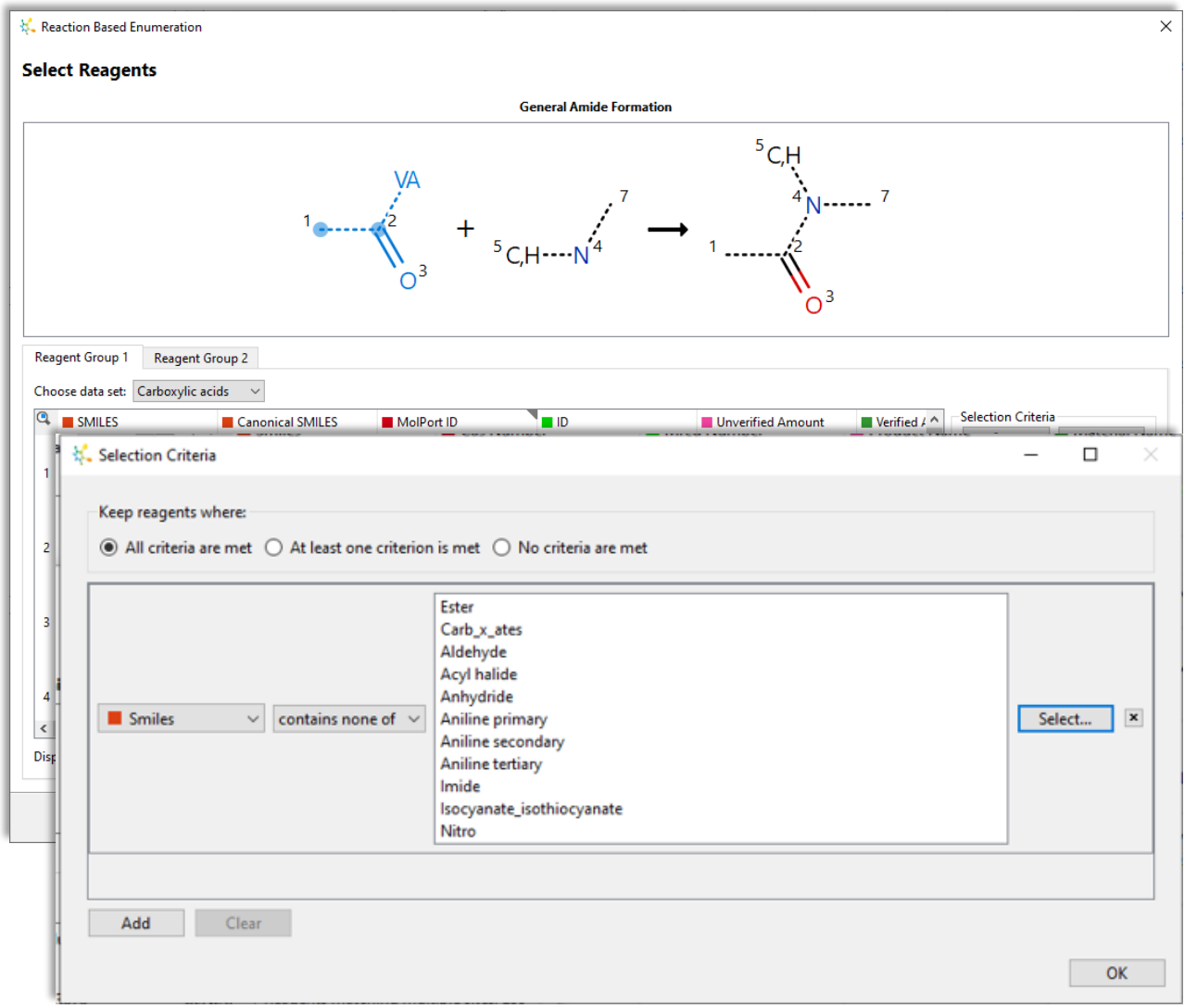

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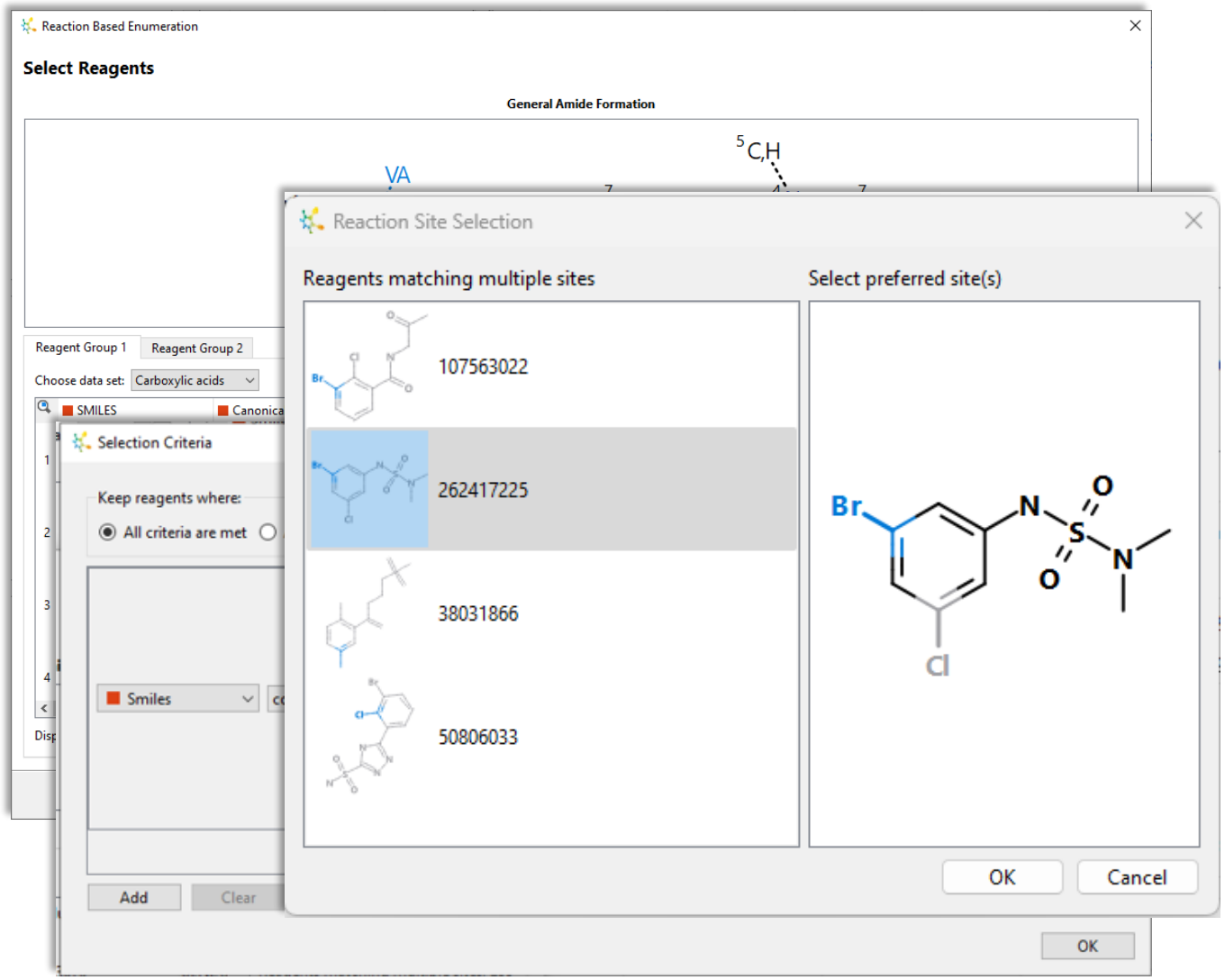
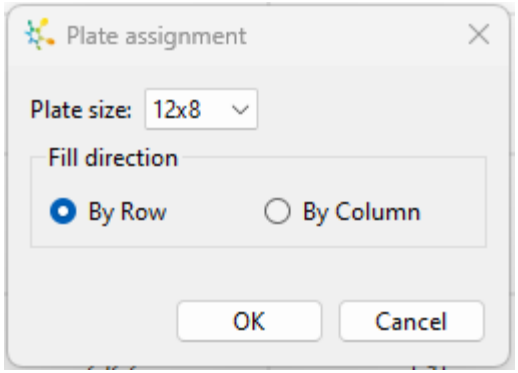
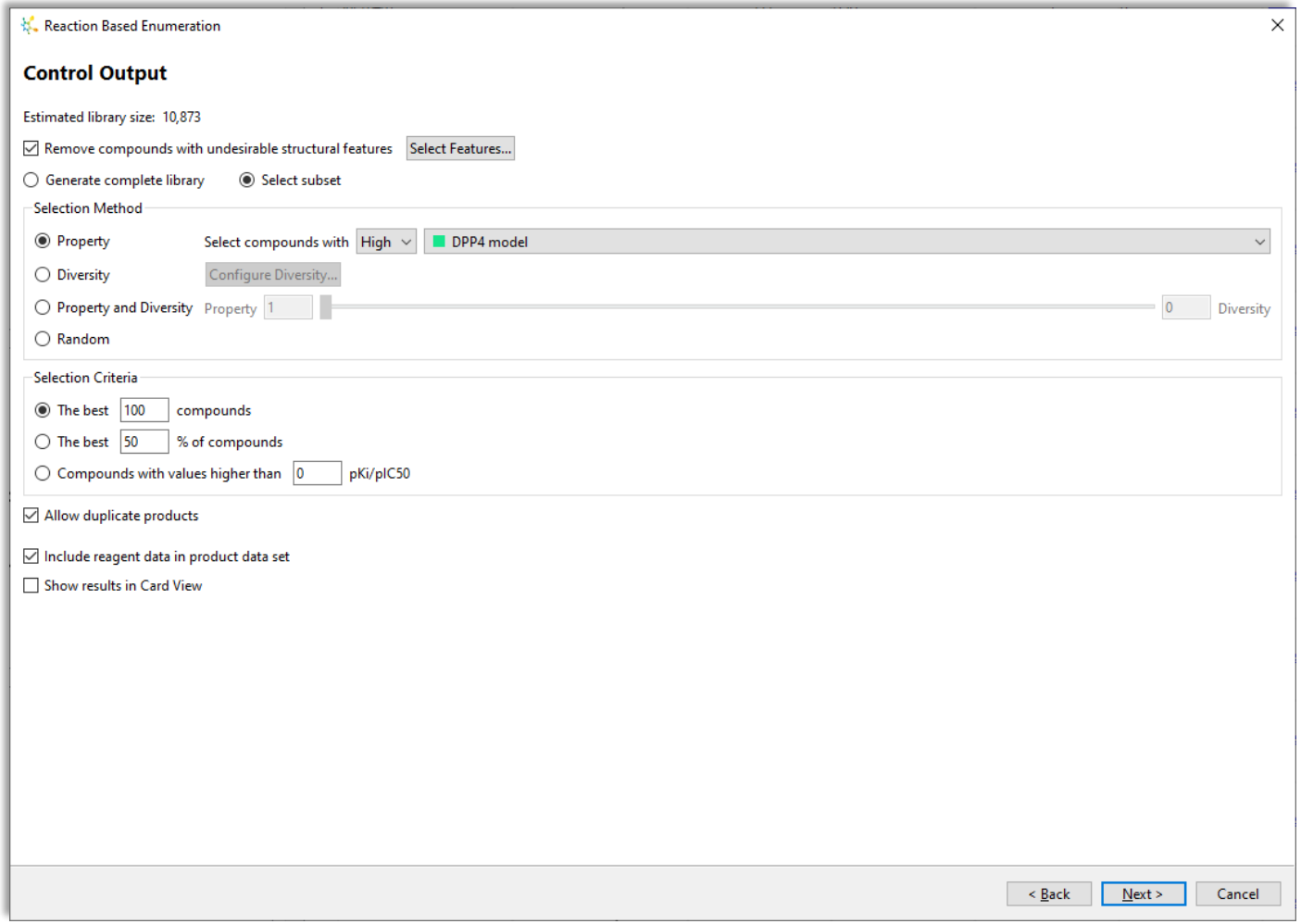


Products

- Define selection criteria for products using a property, MPO score or diversity
- Include reagent metadata with products for easy ordering
- Apply to plate well locations



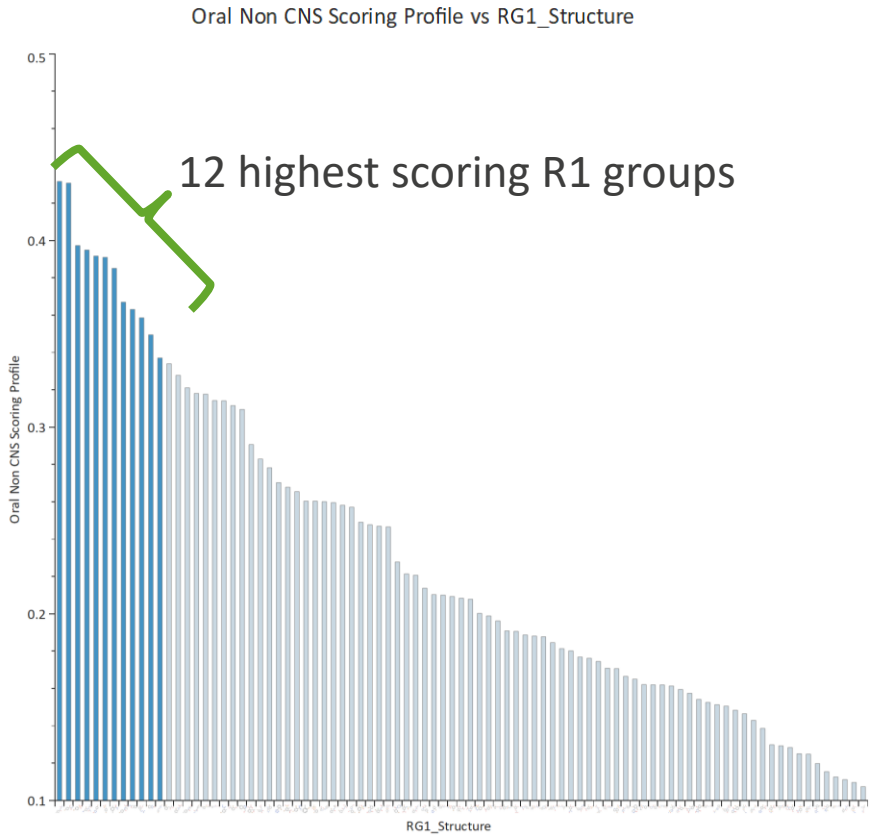


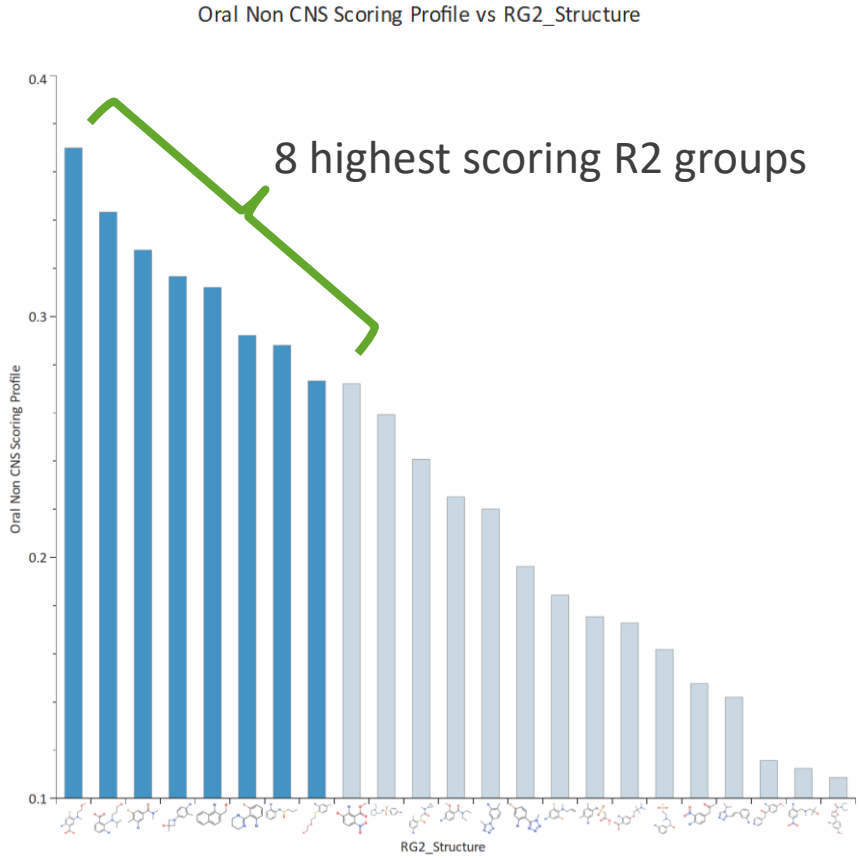
Above and Beyond Chemistry

- Speed of enumeration
- Considering the process a chemist goes through
- Metadata and reagent IDs carry through
- Methods for reagent selection to fit plate dimensions or optimize a property
  - Ability to sample library using fewest reagents.

Prioritising Reagents Using Product Properties

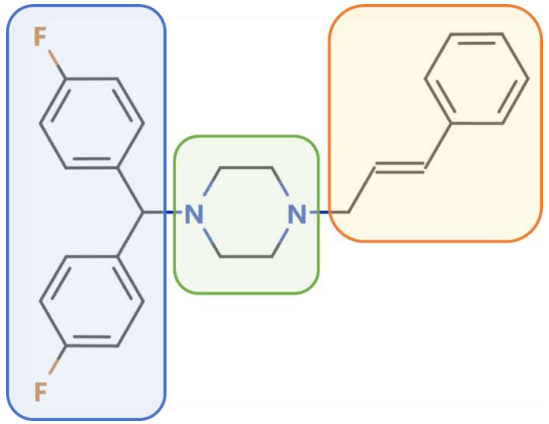
- Select the R-groups generating the highest scores
  - e.g 12 x R1 and 8 x R2 for a 96-well plate





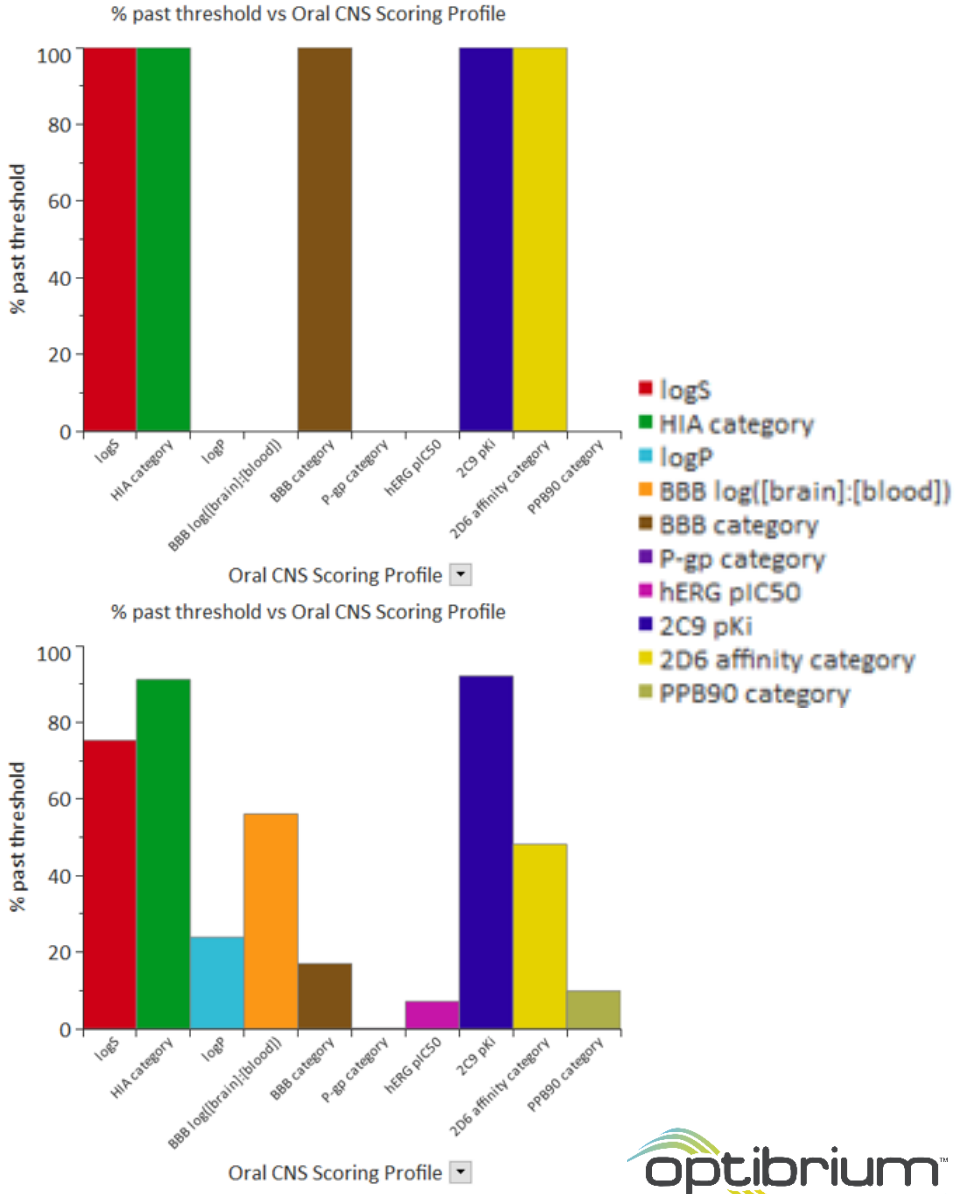
Flunarizine Library

- 10,530 product library based on flunarizine



Profile: Oral CNS Scoring Profile

Property	Desired Value	Importance
logS	> 1	
HIA category	+	
logP	0 -> 3.5	
BBB log([brain]:[blood])	-0.2 -> 1	
BBB category	+	
P-gp category	no	
hERG pIC50	⩽ 5	
2C9 pKi	⩽ 6	
2D6 affinity category	low medium	
PPB90 category	low	

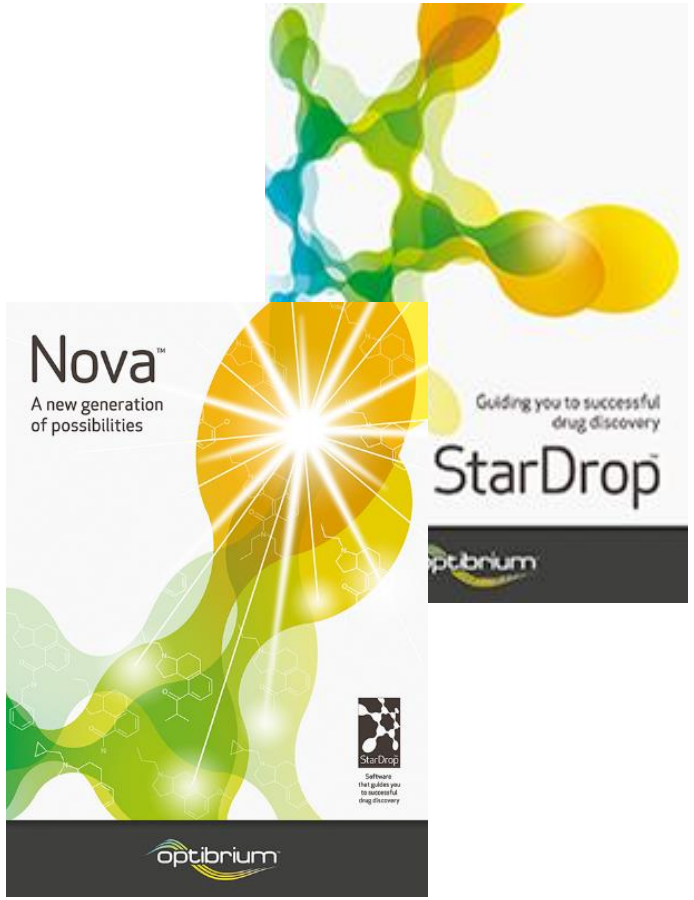


- Score for oral bioavailability and CNS penetration

- Some library compounds meet threshold for logP, BBB log([brain]:[blood]), hERG pIC50 or PPB90

Conclusions

- Reaction-based enumeration in StarDrop's Nova™ module is:
  - User friendly
    - Easy to interpret
    - Supports different levels of experience
  - Flexible
    - Prepared reaction libraries and filters support major use cases
    - Ability to add and customise for in-house chemistry and expertise
  - Fast
    - Combine reactions in a single enumeration
    - Metadata for easy inventory and building block requests
    - Select an optimal subset of compounds for synthesis
- User feedback at every step of development is critical



Acknowledgements

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Celgene

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For more information and a demo visit optibrium.com/project/nova/