optibrium

Closing the loop between synthesis and design: Helping chemists to use all the information in compound optimization

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Overview

- Visualising and understanding SAR
  - Card View™
  - Linking 2D and 3D SAR
    - Matched molecular pairs
    - Activity neighbourhood
- Design of new compound ideas with an improved balance of properties
  - Multi-Parameter Optimisation (MPO)
  - Glowing Molecule™
  - Medicinal chemistry idea generation
- Conclusions

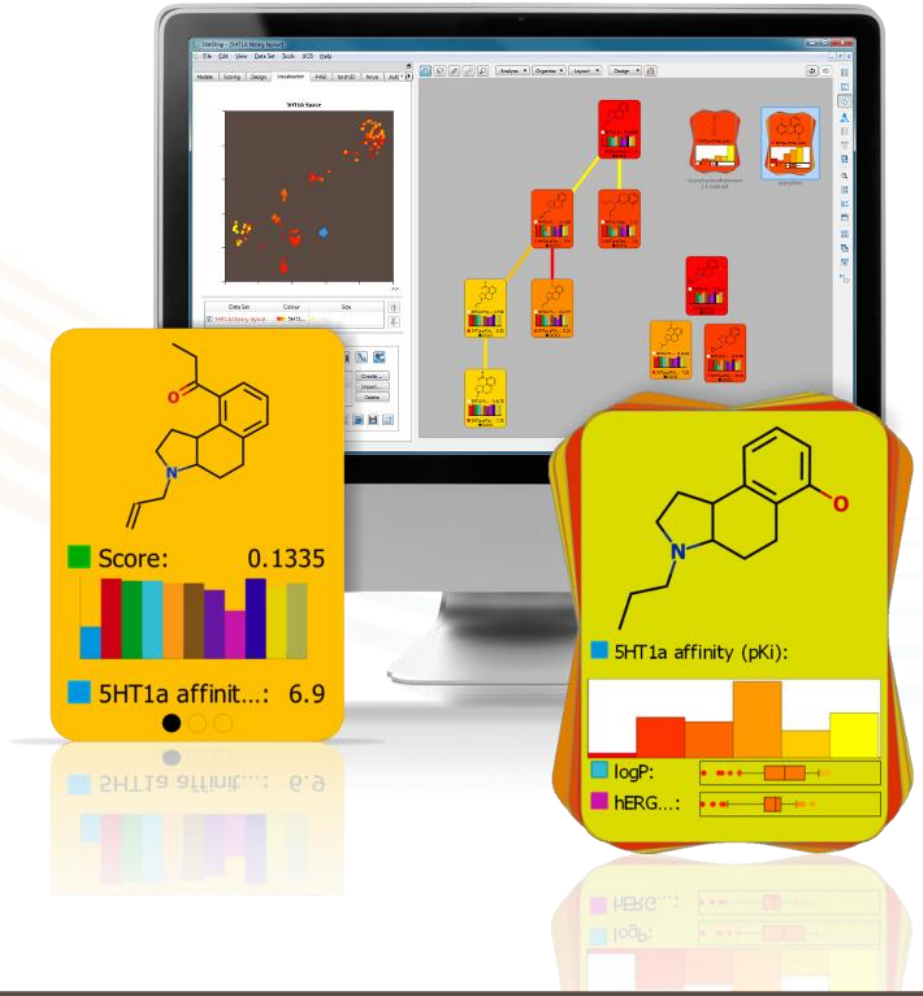
The Challenges

- More compounds
  - Synthesised in-house or at CRO
  - Purchased
  - *In silico* libraries
- More data and data types to understand
- Shorter project timelines
- Need to make intelligent decisions that guide selection and design of compounds with a balance of properties
  - Multi-Parameter Optimisation (MPO)

Visualising and Understanding SAR

Card View
Concepts

- Freedom from the constraints of ‘chemical spreadsheets’
  - Represent compound relationships
- Cards
  - Show relevant compound data
  - Complete freedom to move
- Stacks
  - Group compounds
  - Summarise and compare data
- Links
  - Highlight compound relationships
- Intuitive visualisation of SAR
  - Clustering, activity landscapes, matched molecular pairs…



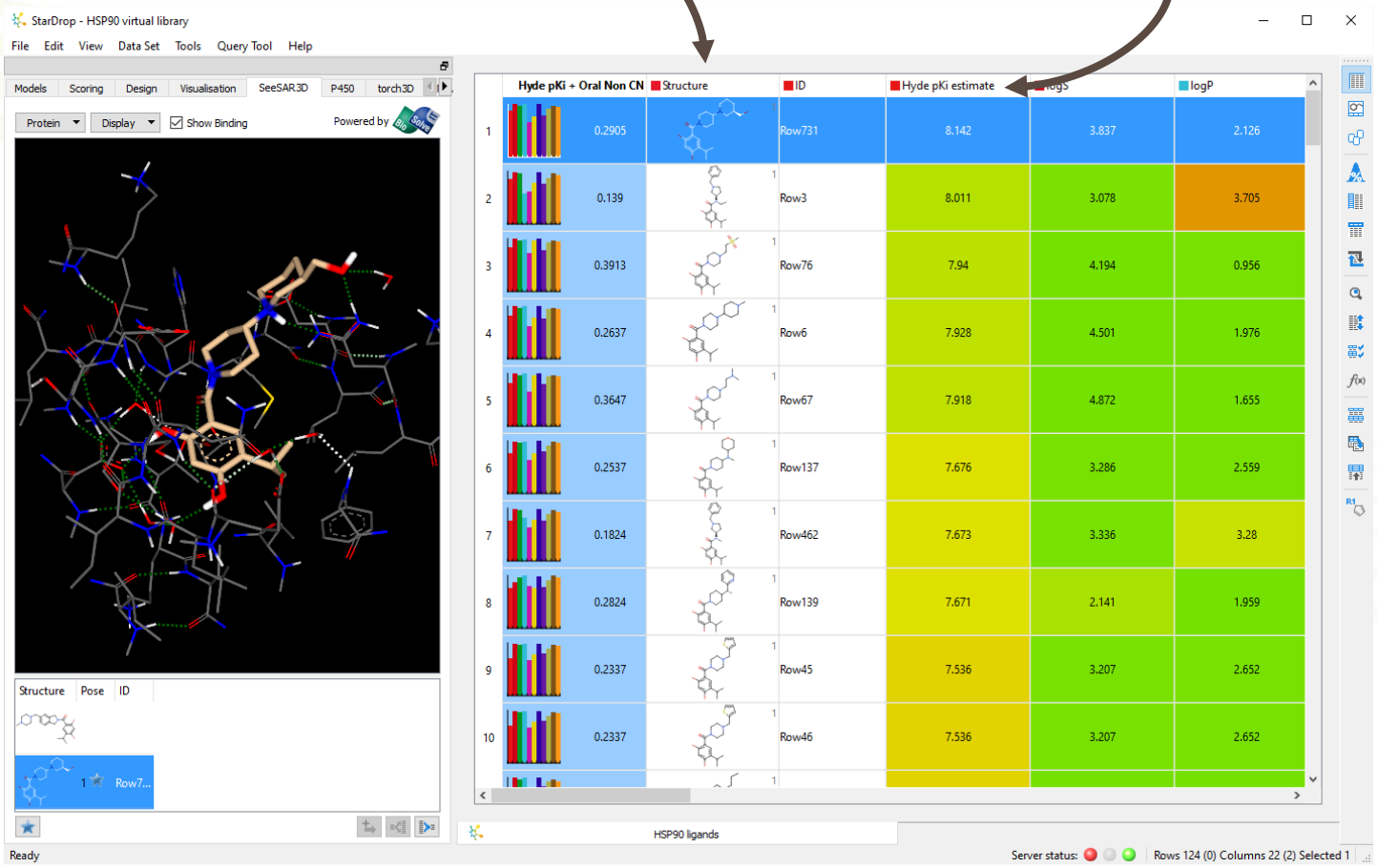
New SeeSAR 'Viewer' Module

Visualise 3D Structure Information

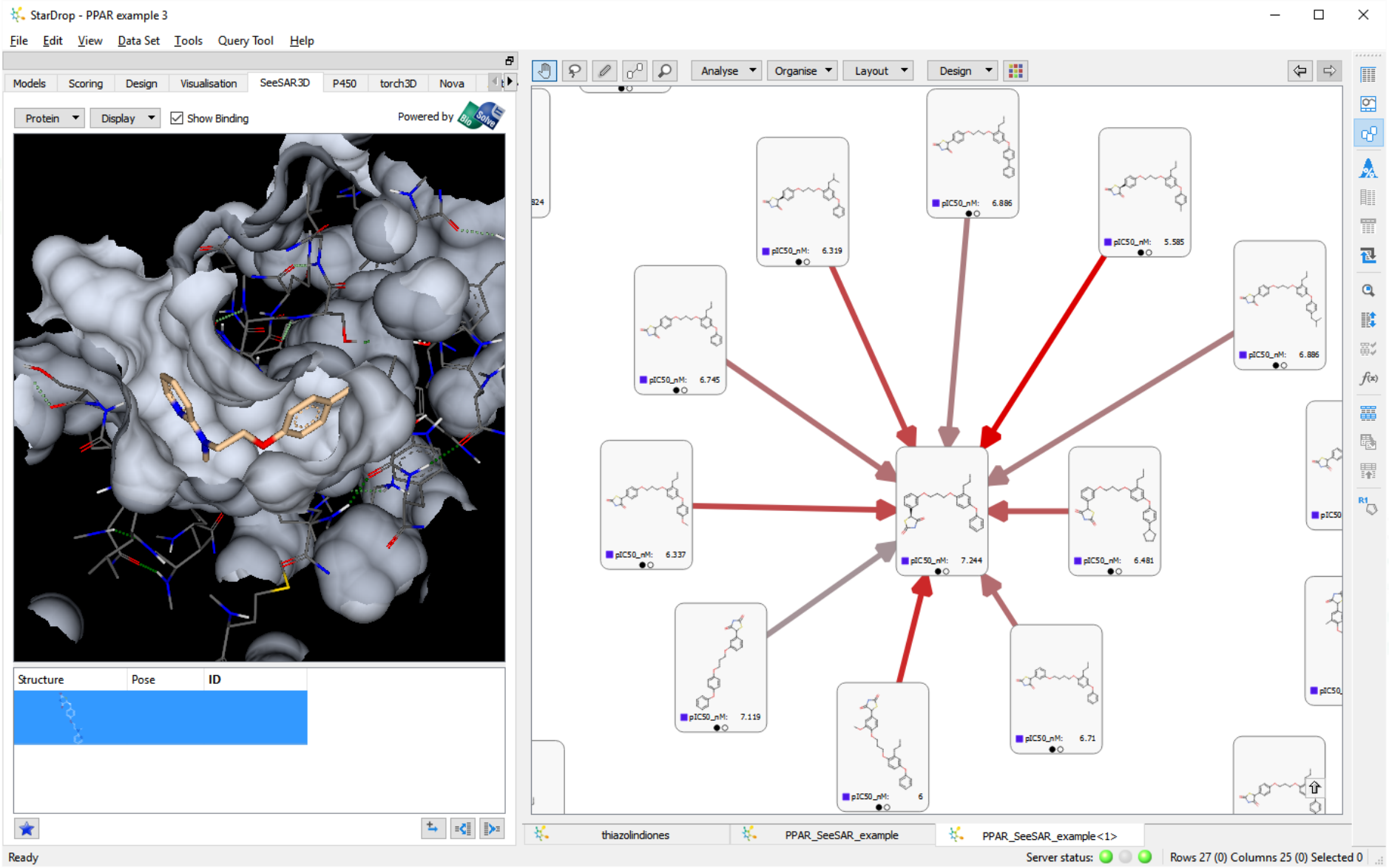
Import docking results or crystal structures, from SD/PDB files

Include docking scores or affinity predictions in MPO

Select between multiple poses



Linking 2D and 3D SAR
Understanding Activity Cliffs in 3D



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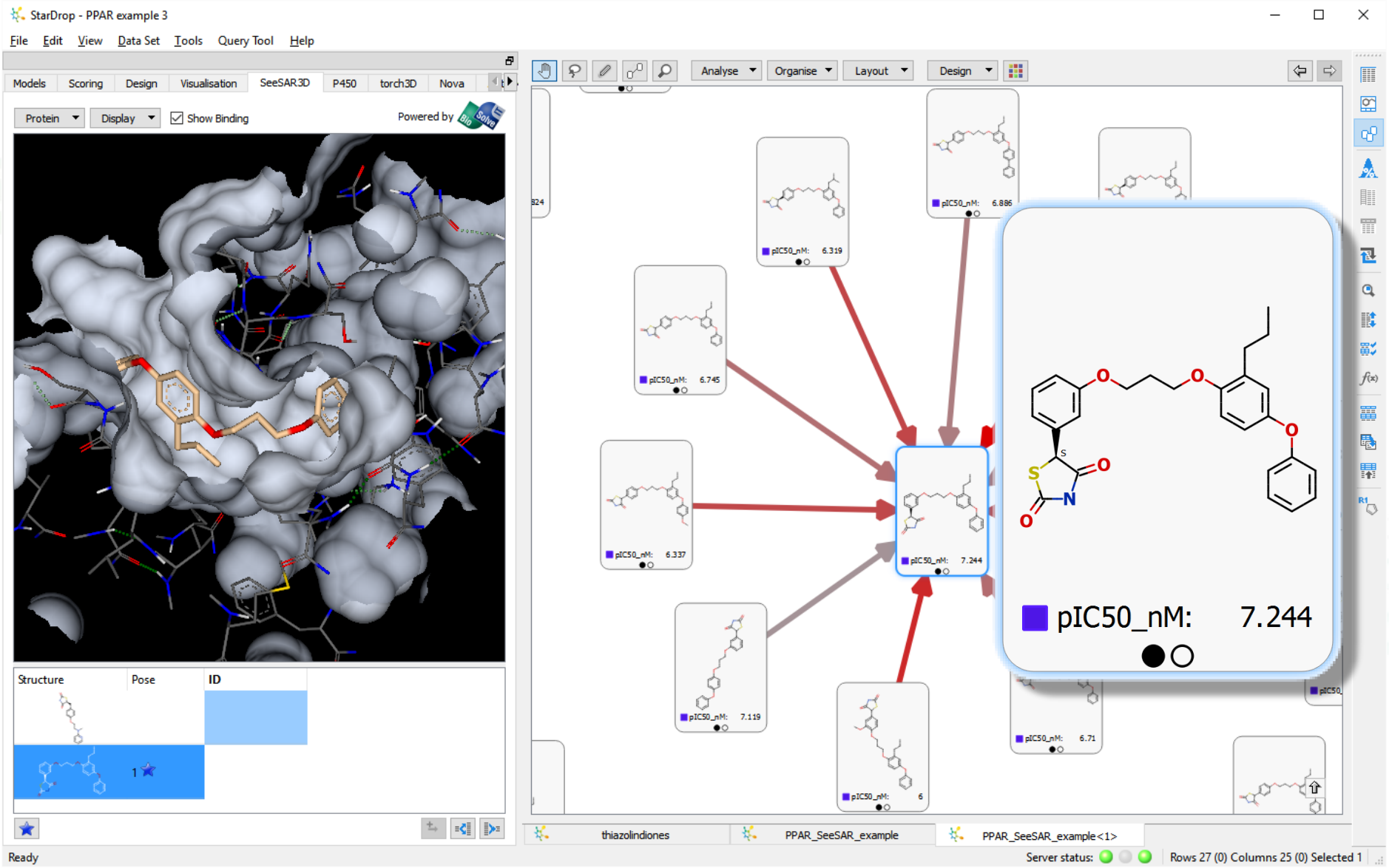

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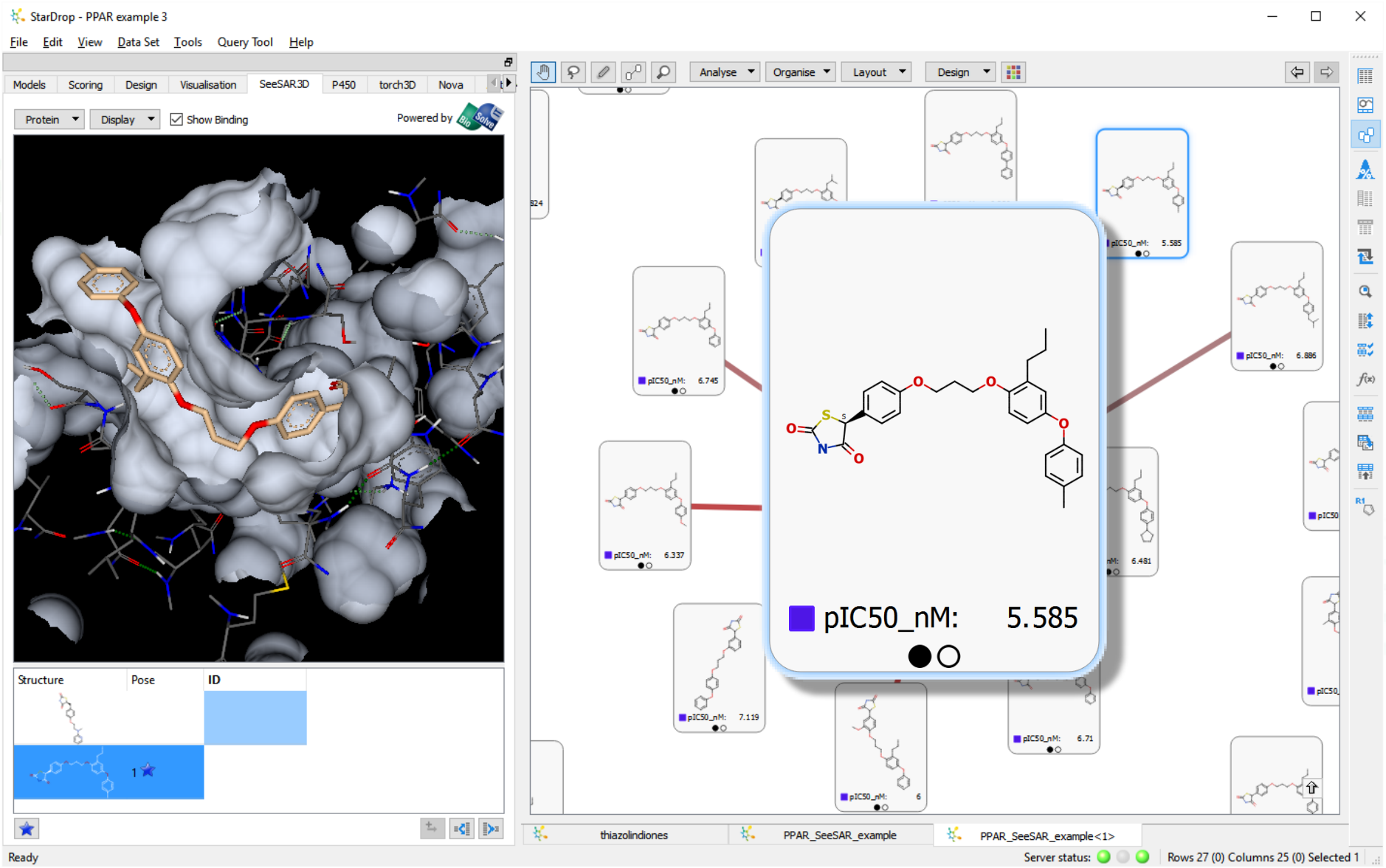

Linking 2D and 3D SAR

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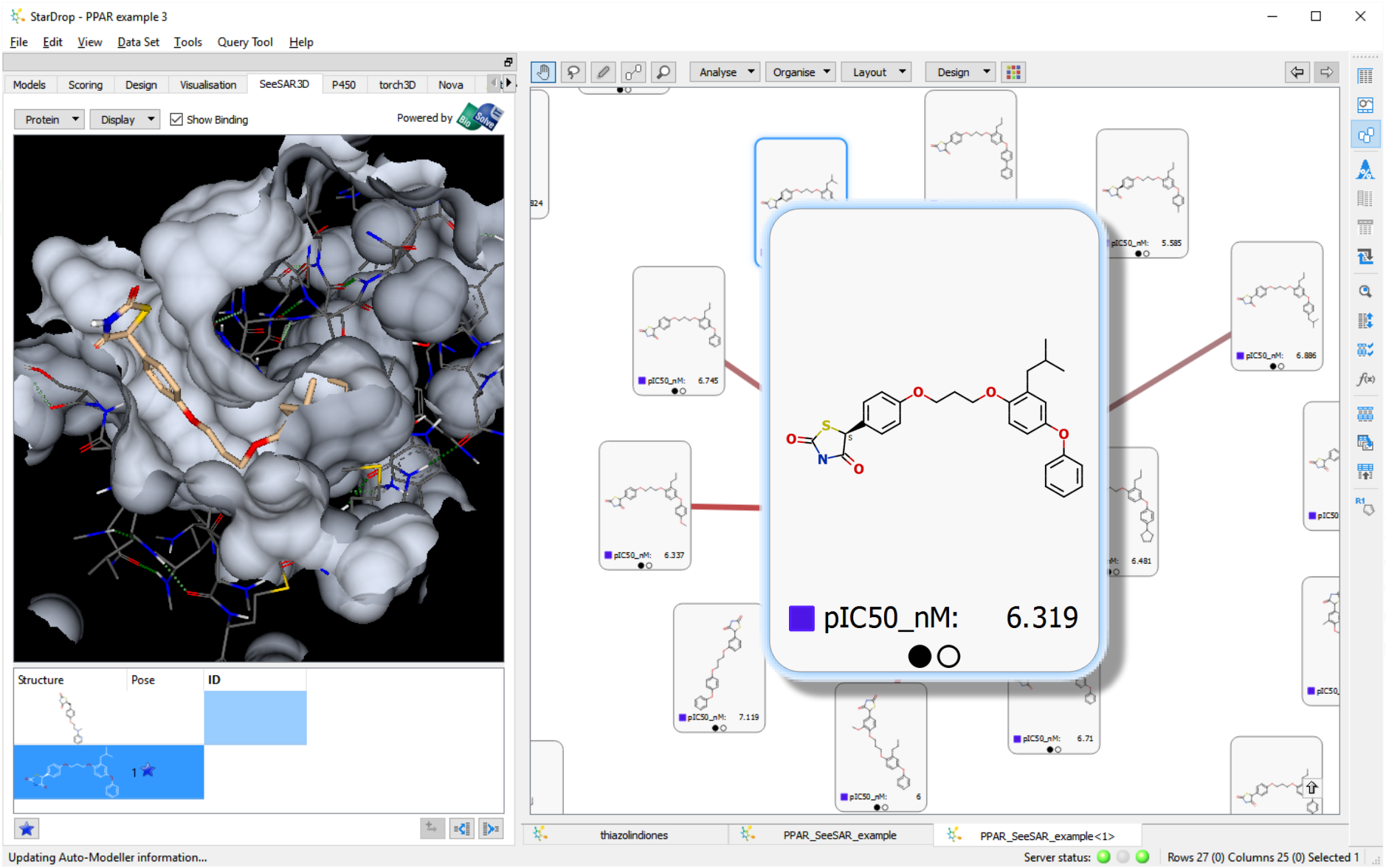
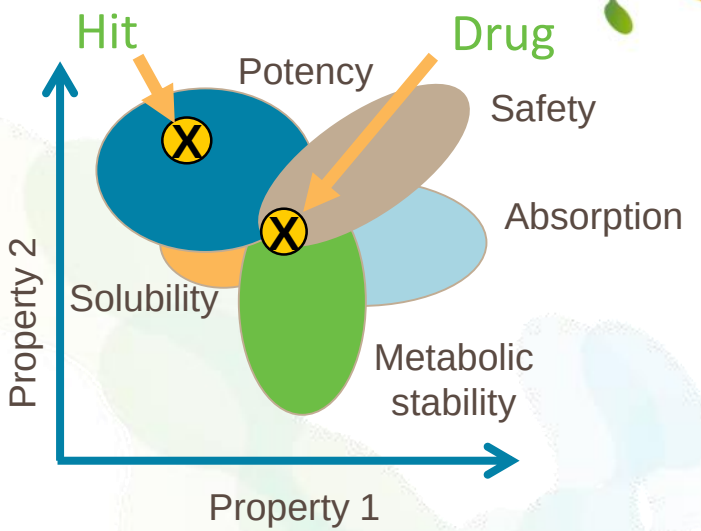


But What About Designing New Compounds?

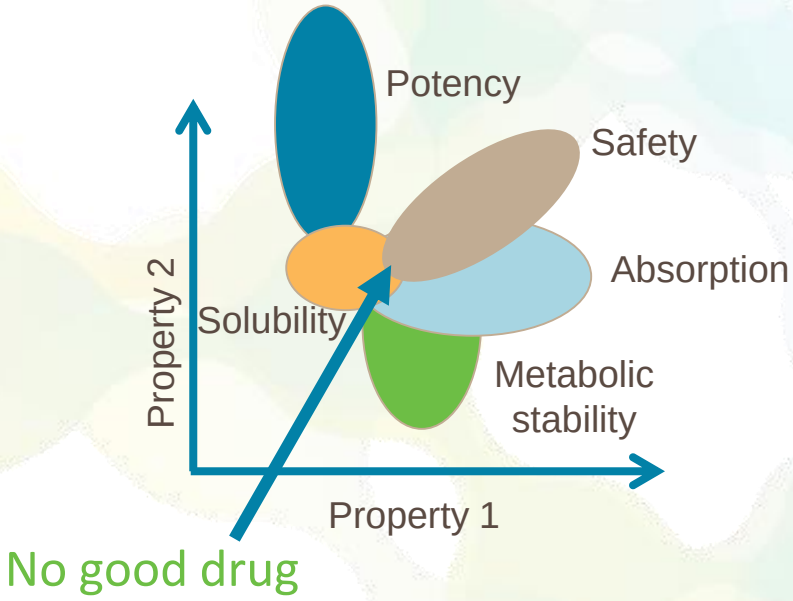
With an Improved Balance of Properties

The Objectives
Multi-Parameter Optimisation

- Identify chemistries with an optimal **balance** of properties



- Quickly identify situations when such a balance is not possible
  - –Fail fast, fail cheap
  - –Only when **confident**



StarDrop Prioritisation
Probabilistic Scoring

Integrated assessment of data against project criteria

Uniquely accounts for the uncertainties in all compound-related data (experimental or calculated)

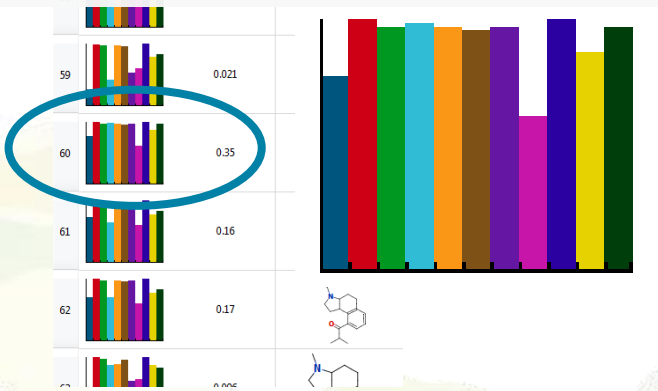
User-defined scoring profile

Profile: 5HT1a Scoring Profile *

Property	Desired Value	Importance
pKi 5HT1a affinity	8.00 -> inf	
logS	> 1	
HIA category	+	
logP	0.0 -> 3.5	
BBB category	+	
BBB log([brain]:[blood])	-0.20 -> 1.00	
P-gp category	no	
hERG pIC50	⩽ 5	
2C9 pKi	⩽ 6	
2D6 affinity category	low medium	
PPB category	low	

Compounds ranked by likelihood of success

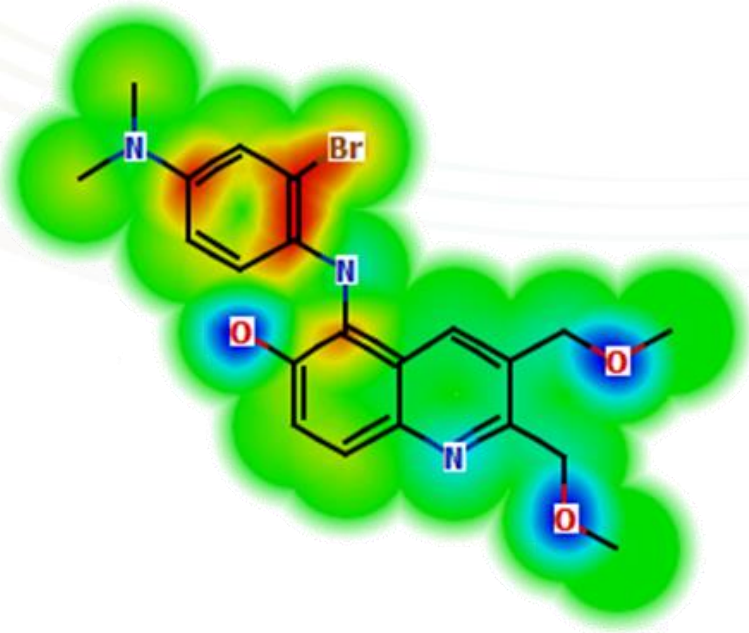
Histograms for quick visual guide to compound properties



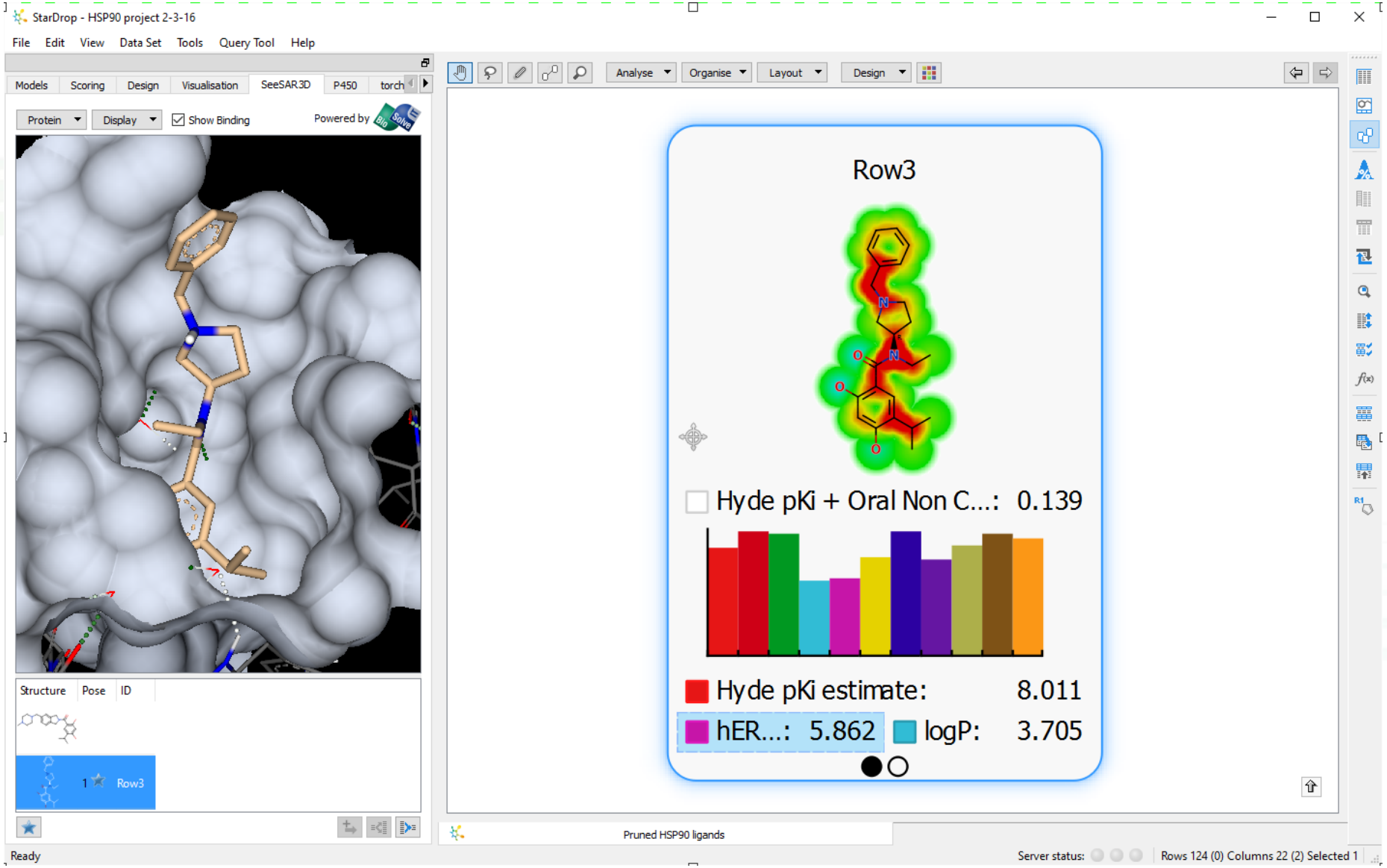
The Glowing Molecule

- Models provide estimates of compound's properties (if within the chemical space)
- However, StarDrop models also gives a visual indication of structural influences on predicted properties
  - "Why is a property value predicted?"
  - "Where can I change this property?"
- Glowing Molecule:

  Can be applied to:
  - StarDrop models
  - Scores
  - Auto-Modeller models

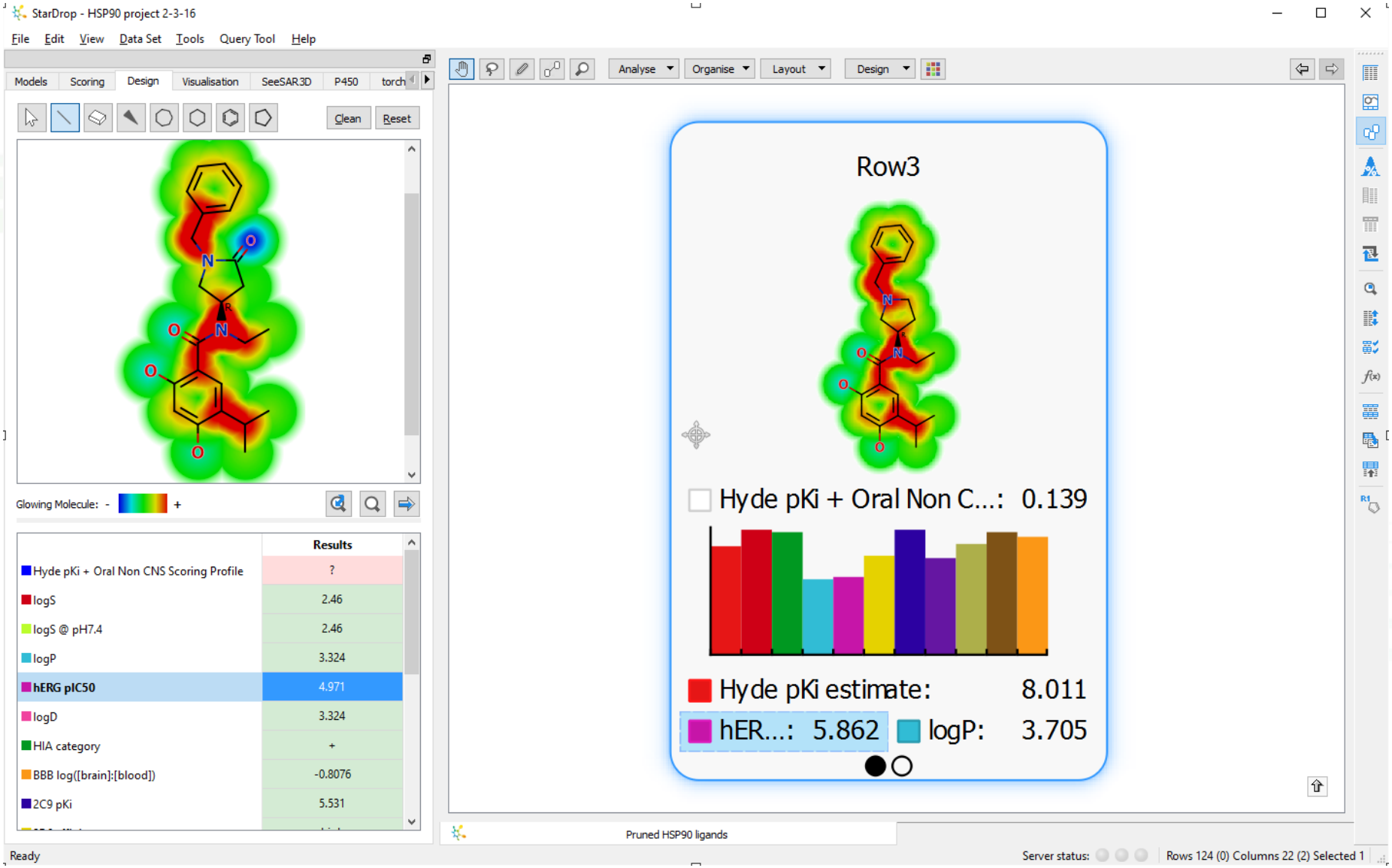


3D View… Optimisation Opportunities



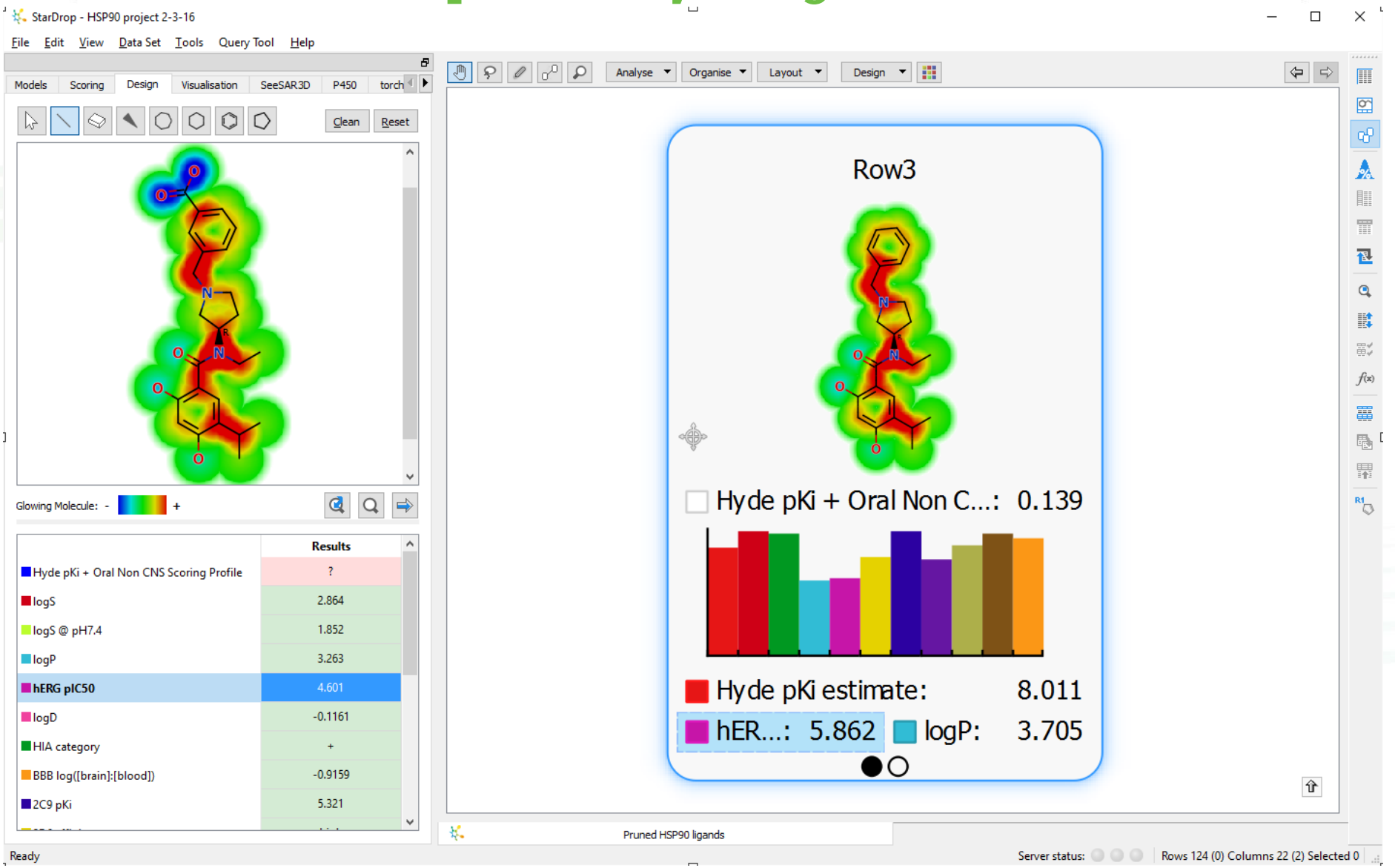
Optimisation Idea

Modify pKa of Nitrogen by Amide Substitution



Optimisation Idea

Add Polar Group to Phenyl Ring

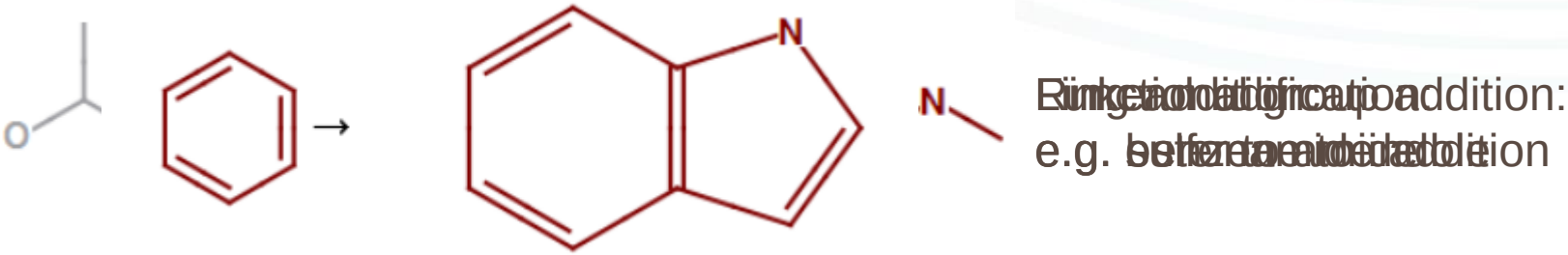


Automatic Generation of Compound Ideas
Objectives

- 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

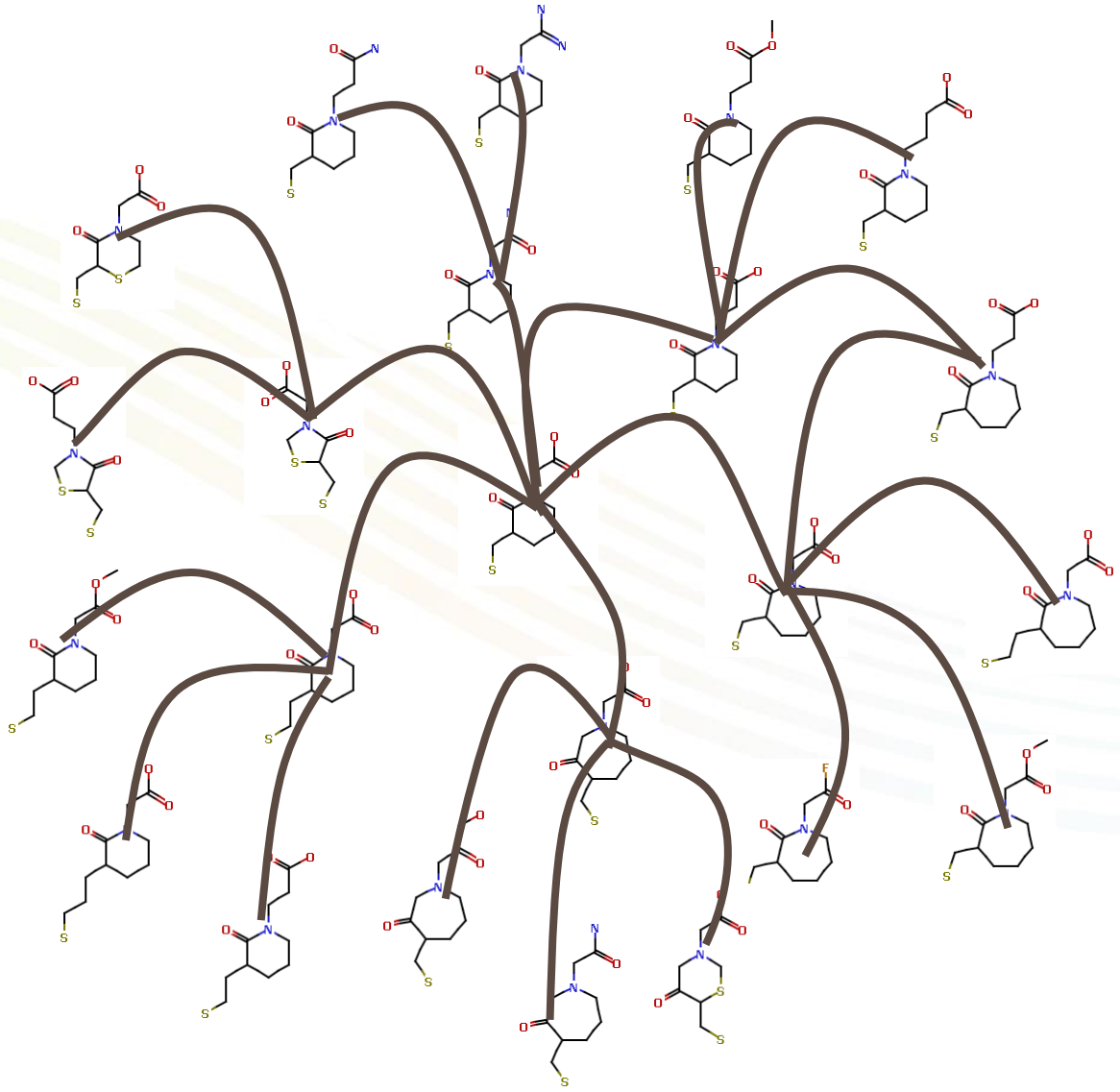
Generating Compound Ideas
Applying Med. Chem. 'Transformation Rules'

- 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 transformations

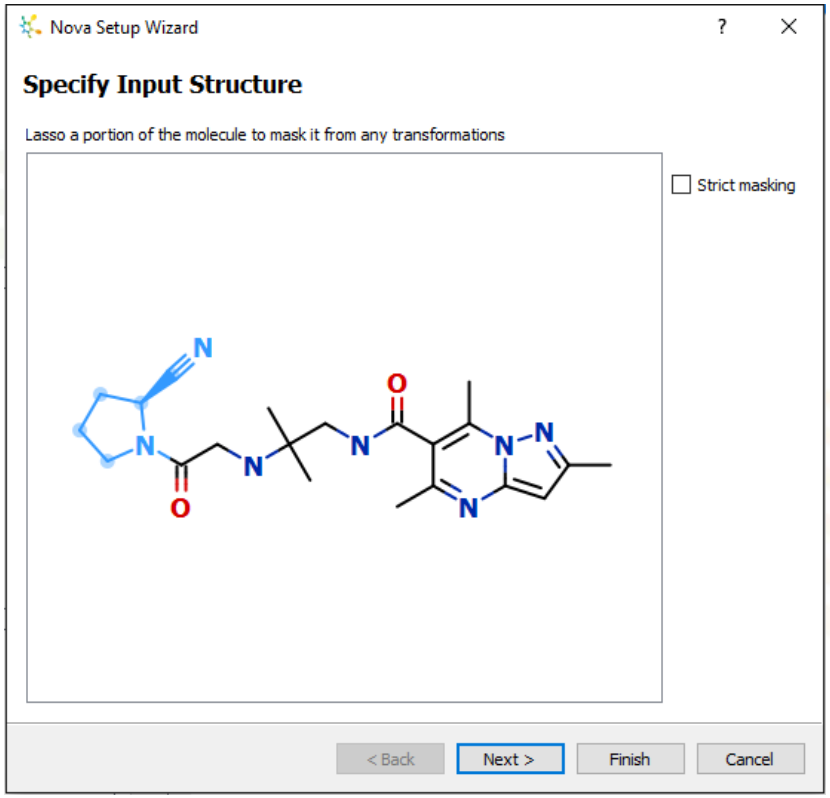


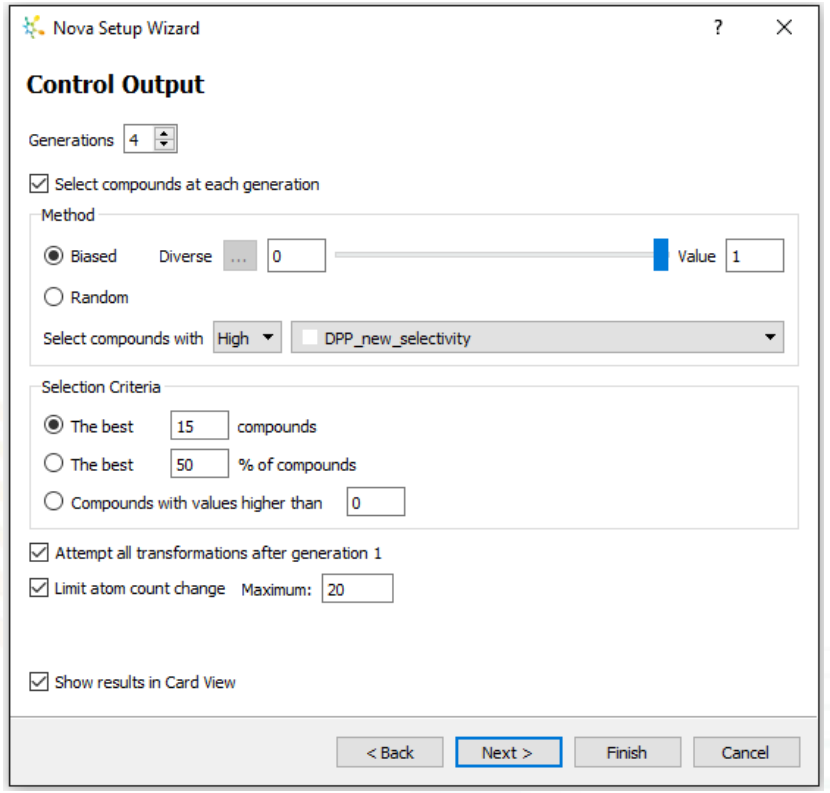
*Stewart *et. al.* Bioorg. Med. Chem. (2006) **14** p. 7011
*Segall *et al.* J. Chem. Inf. Model. (2011) **51** pp. 2967-2976

Exponential Growth!



Controlling the Process

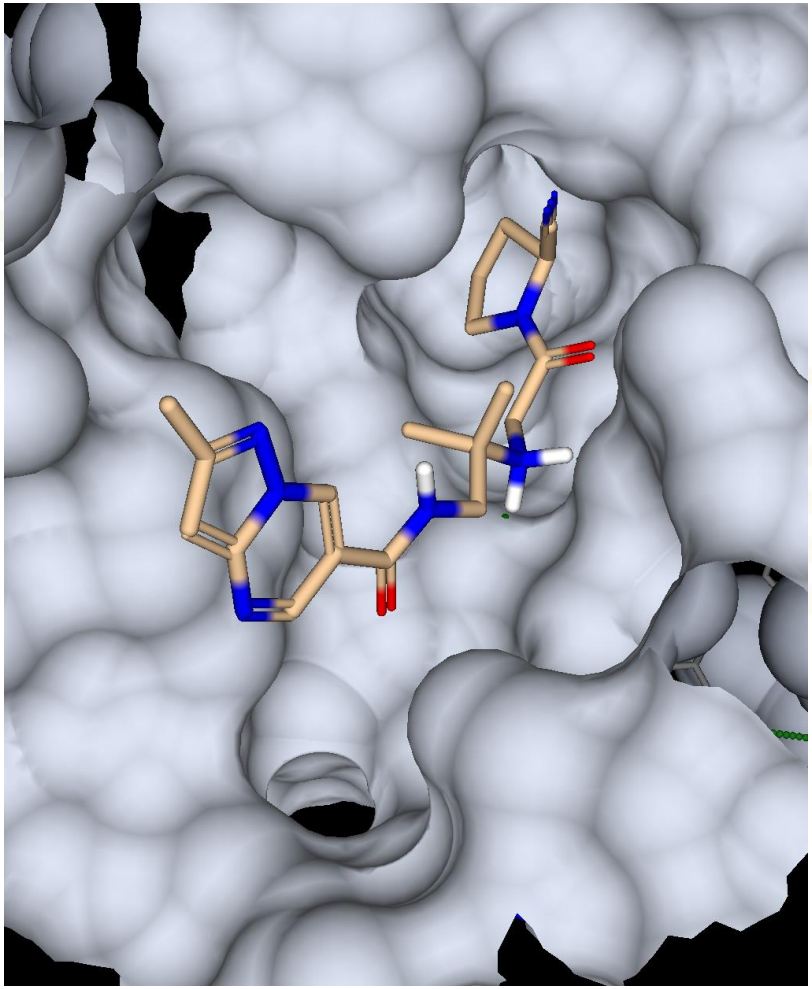


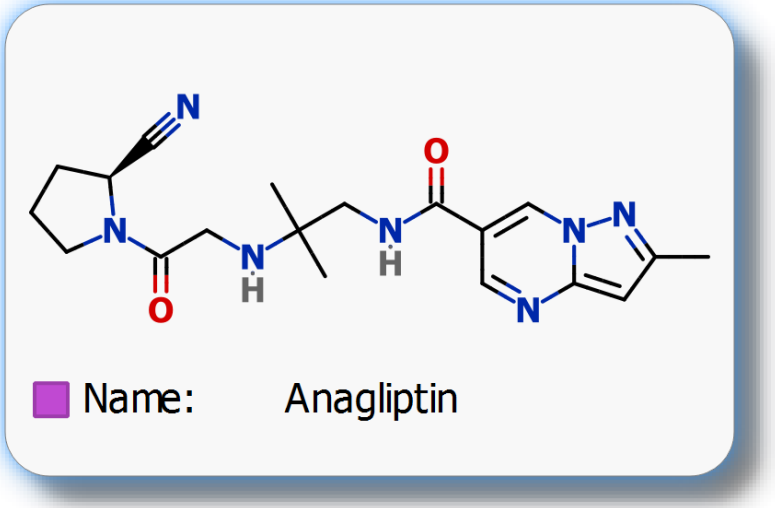


- Masked substructure is retained unchanged
- Apply multiple generations of transformations
- Bias selection in favour of property, score or diversity

3WQH

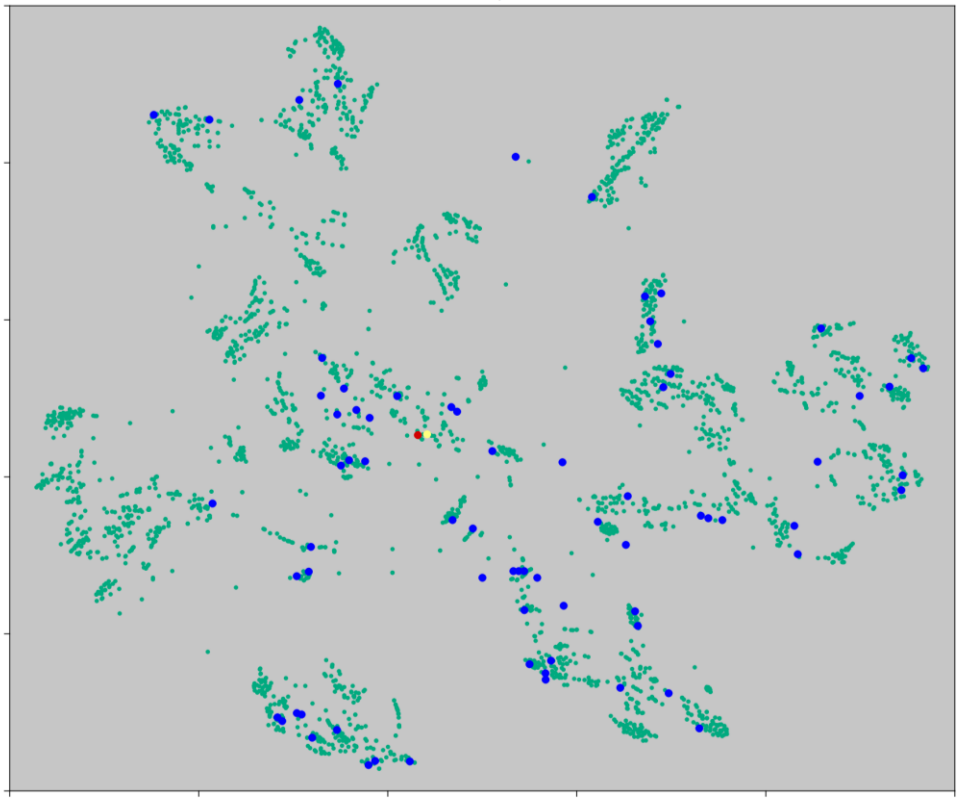
Crystal Structure of Human DPP-4 in Complex with Anagliptin





Watanabe, Y.S. *et al.*
J. Enzyme Inhib. Med. Chem. (2015) pp 1-8

DPP-4 Chemical Space

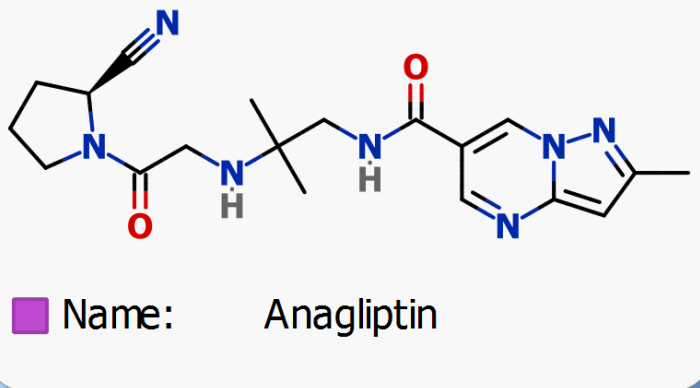


Key

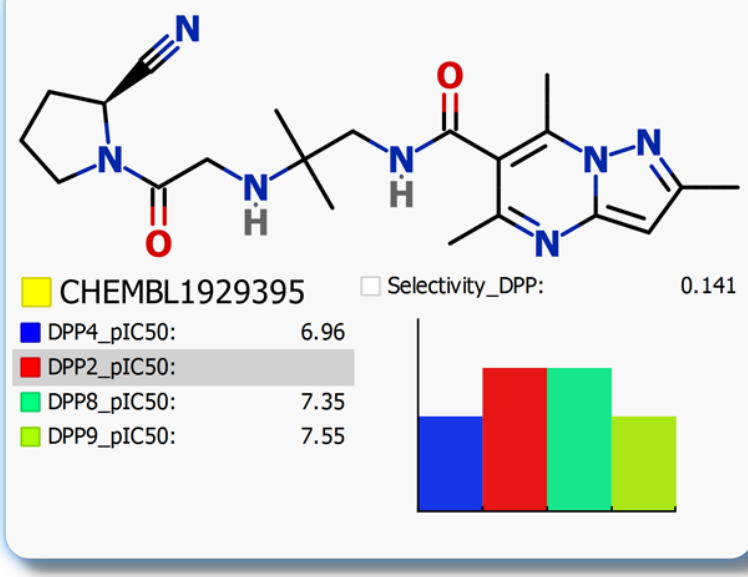
CHEMBL1929395

DPP4 ligands

DPP-IV multi_assay

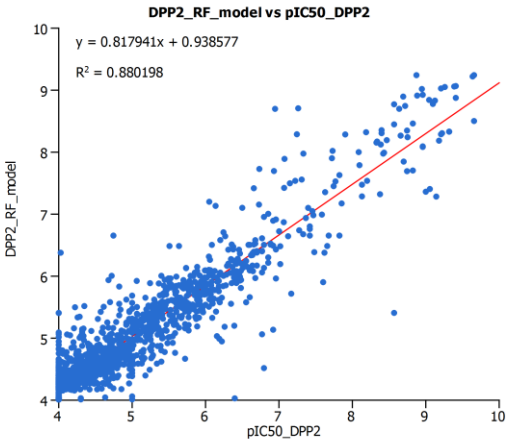


Name: Anagliptin

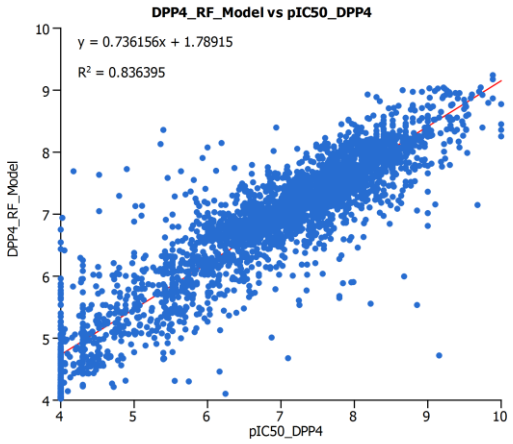


DPP Models

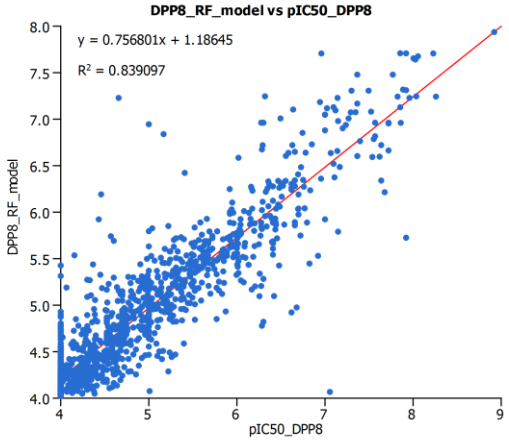
- DPP-2



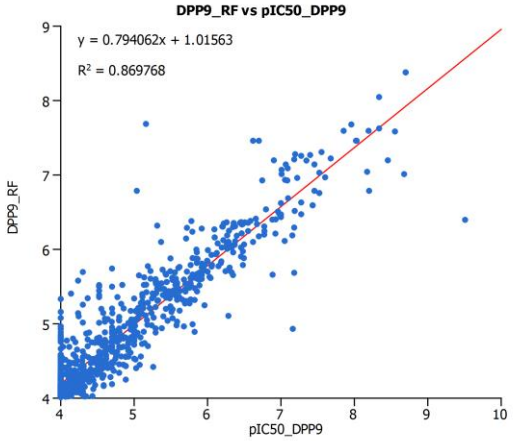
- DPP-4



- DPP-8

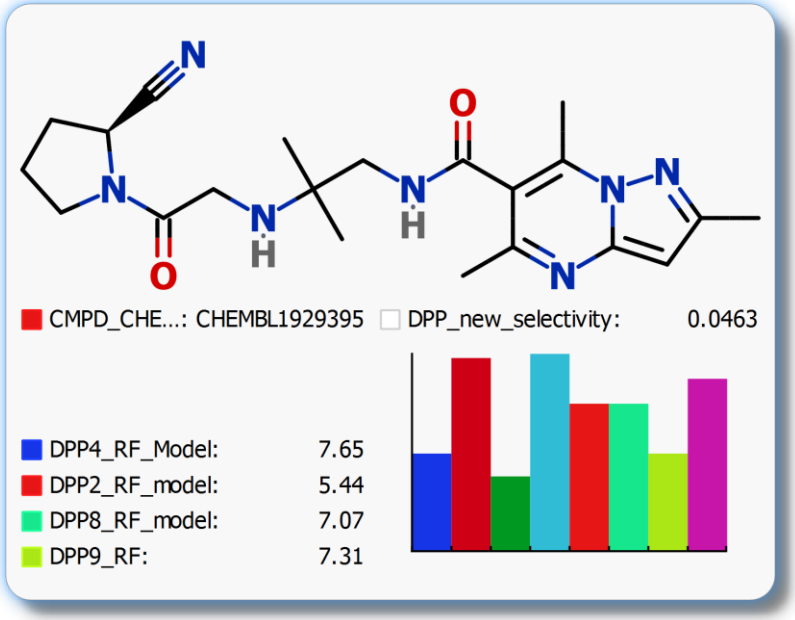


- DPP-9



Probabilistic Scoring

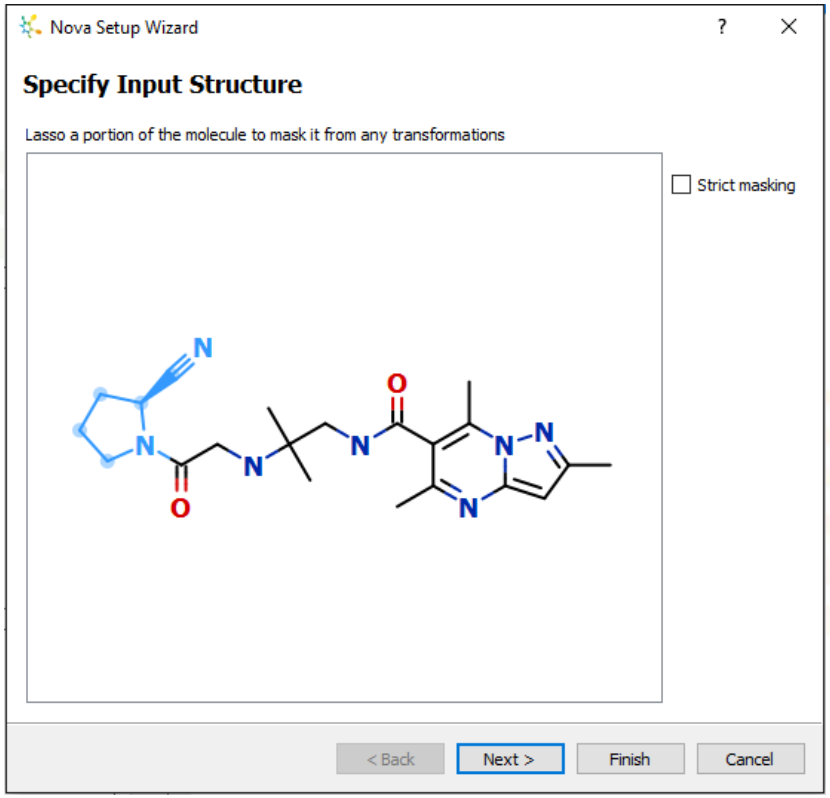
Designing to Achieve a Balance of Properties

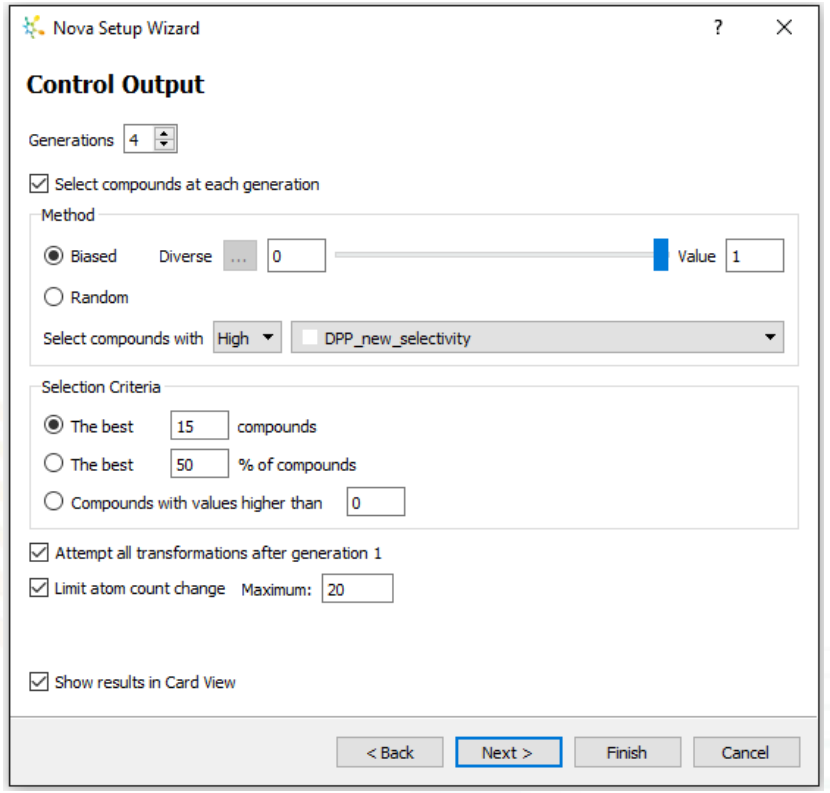


Profile: DPP_new_selectivity

Property	Desired Value	Importance
DPP4_RF_Model	6 -> inf	
logS	> 1	
HIA category	+	
logP	0 -> 3.5	
DPP2_RF_model	⩽ 6	
DPP8_RF_model	⩽ 6	
DPP9_RF	⩽ 6	
hERG pIC50	⩽ 5	

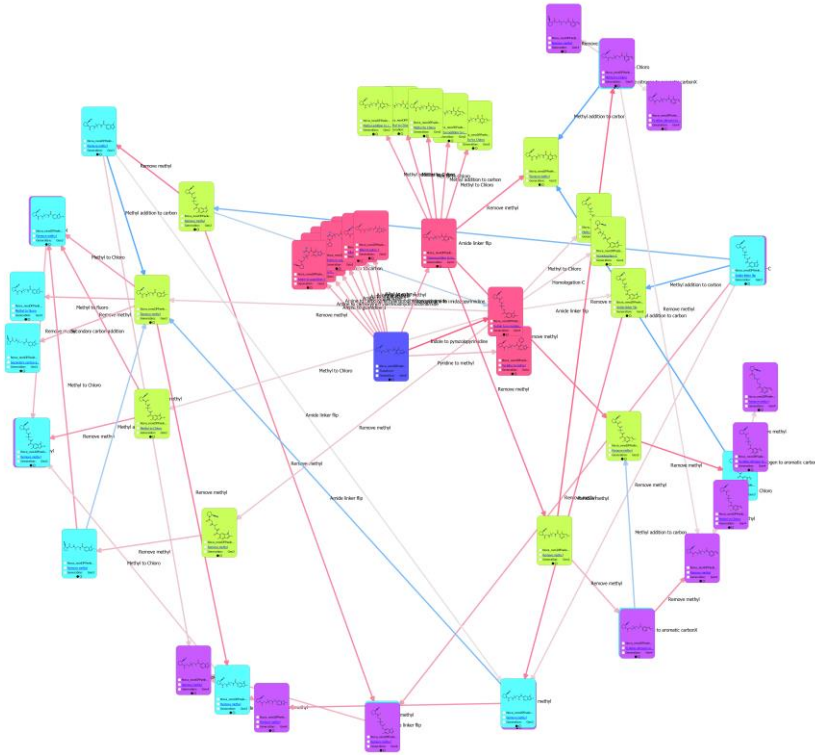
Nova Set-up





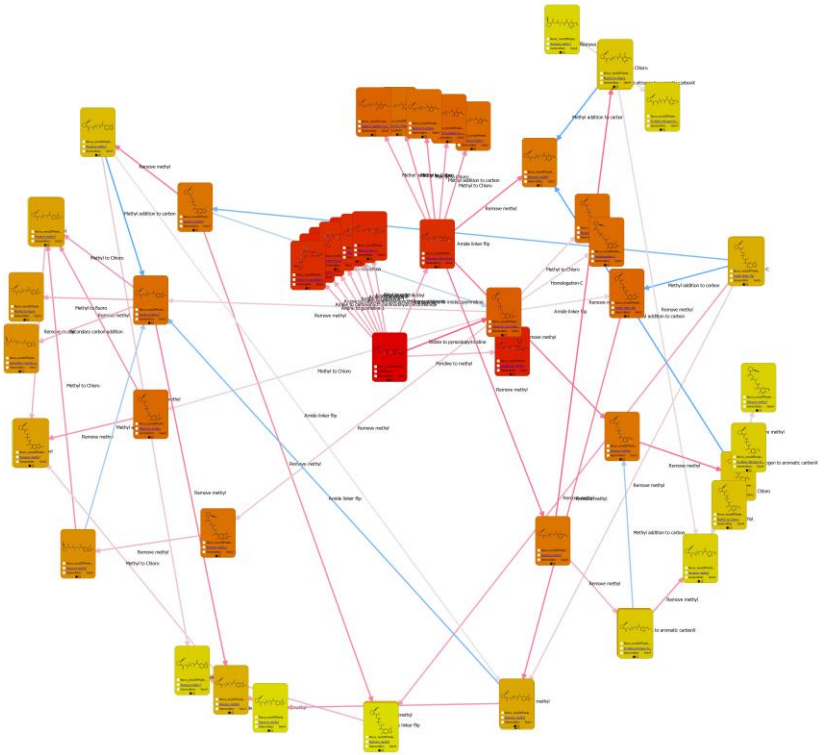
Card View

Visualising Nova Results



Colour by: Generation

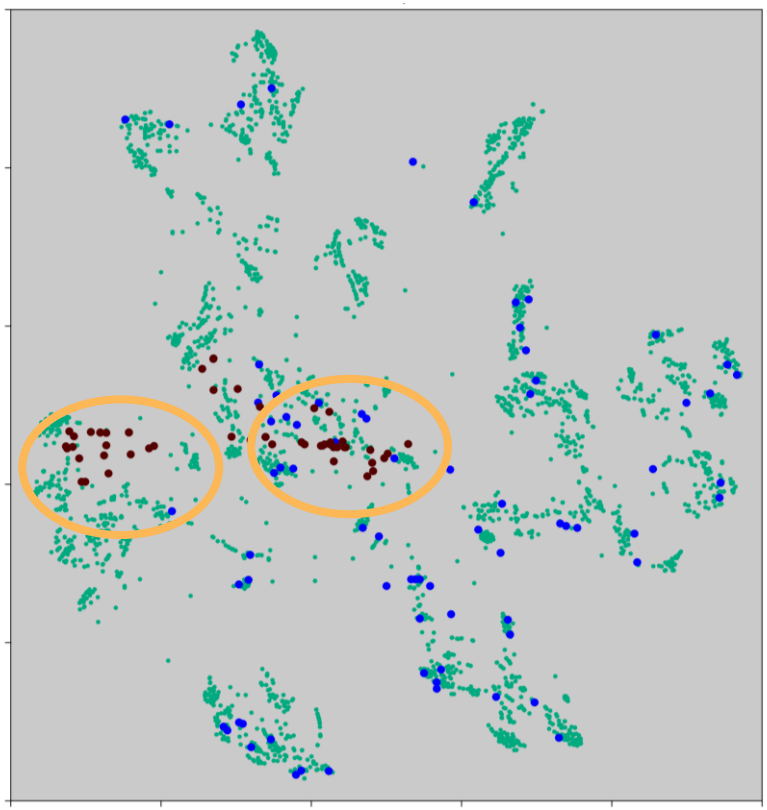
	Name	Colour
1	Gen0	
2	Gen1	
3	Gen2	
4	Gen3	
5	Gen4	



Colour by: DPP_new_selectivity

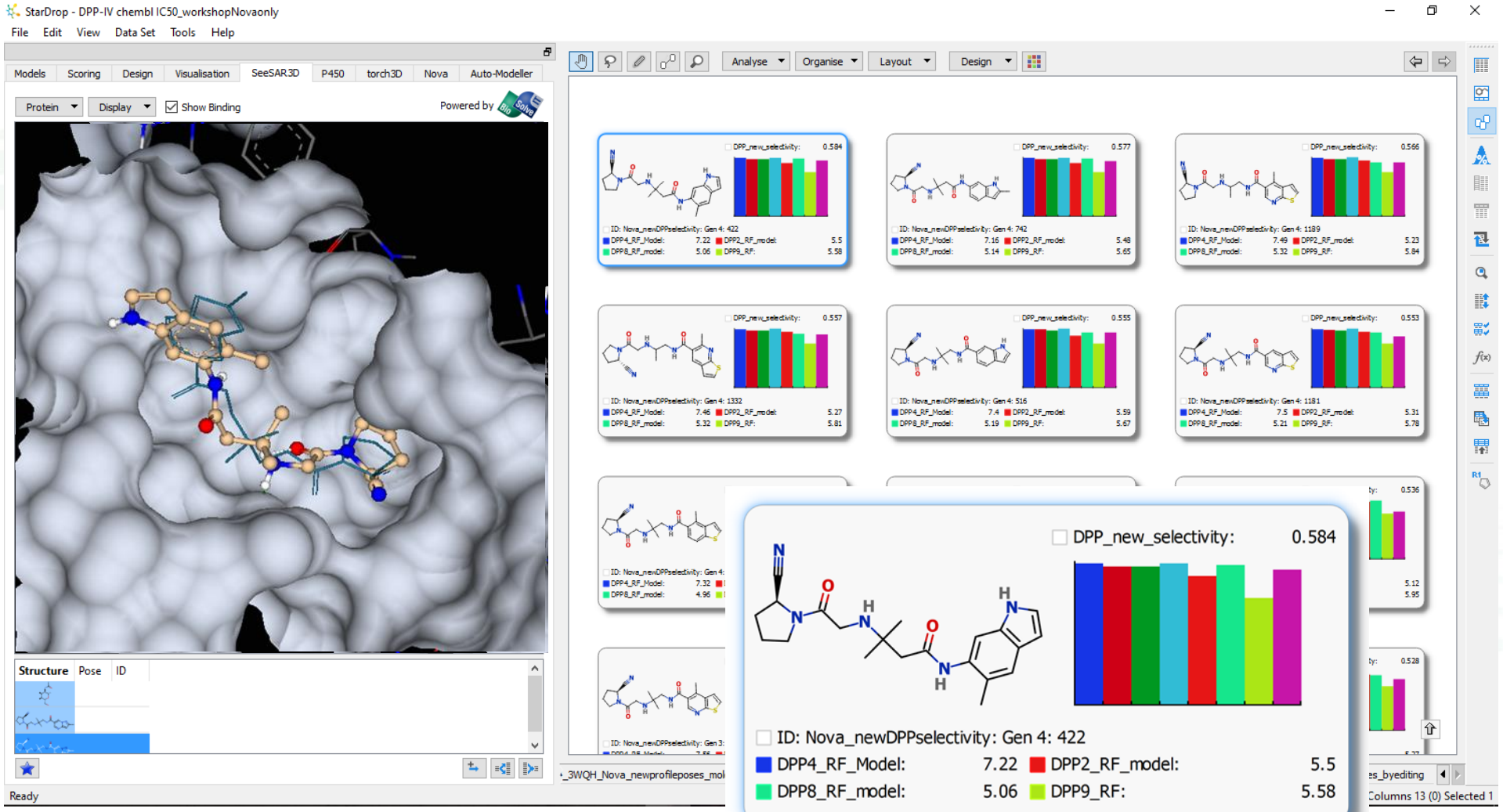
	Name	Colour
1	High	
2	Low	

New Selective DPP-4 Ideas
Explore Novel Chemistry Space

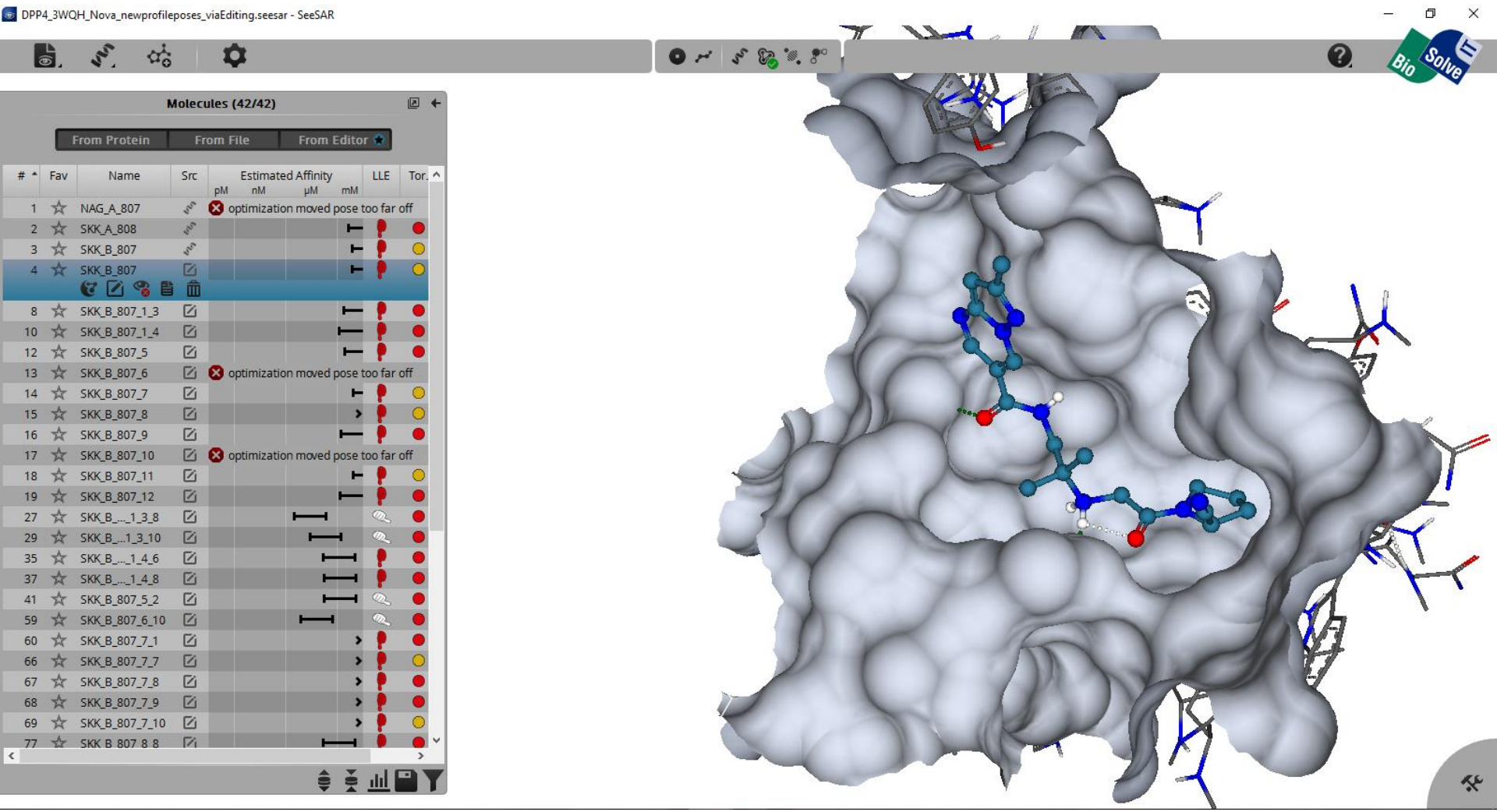


- New compound ideas sample multiple areas of chemistry space
  - Close to the known DPP-4 ligands
  - Areas of greater diversity

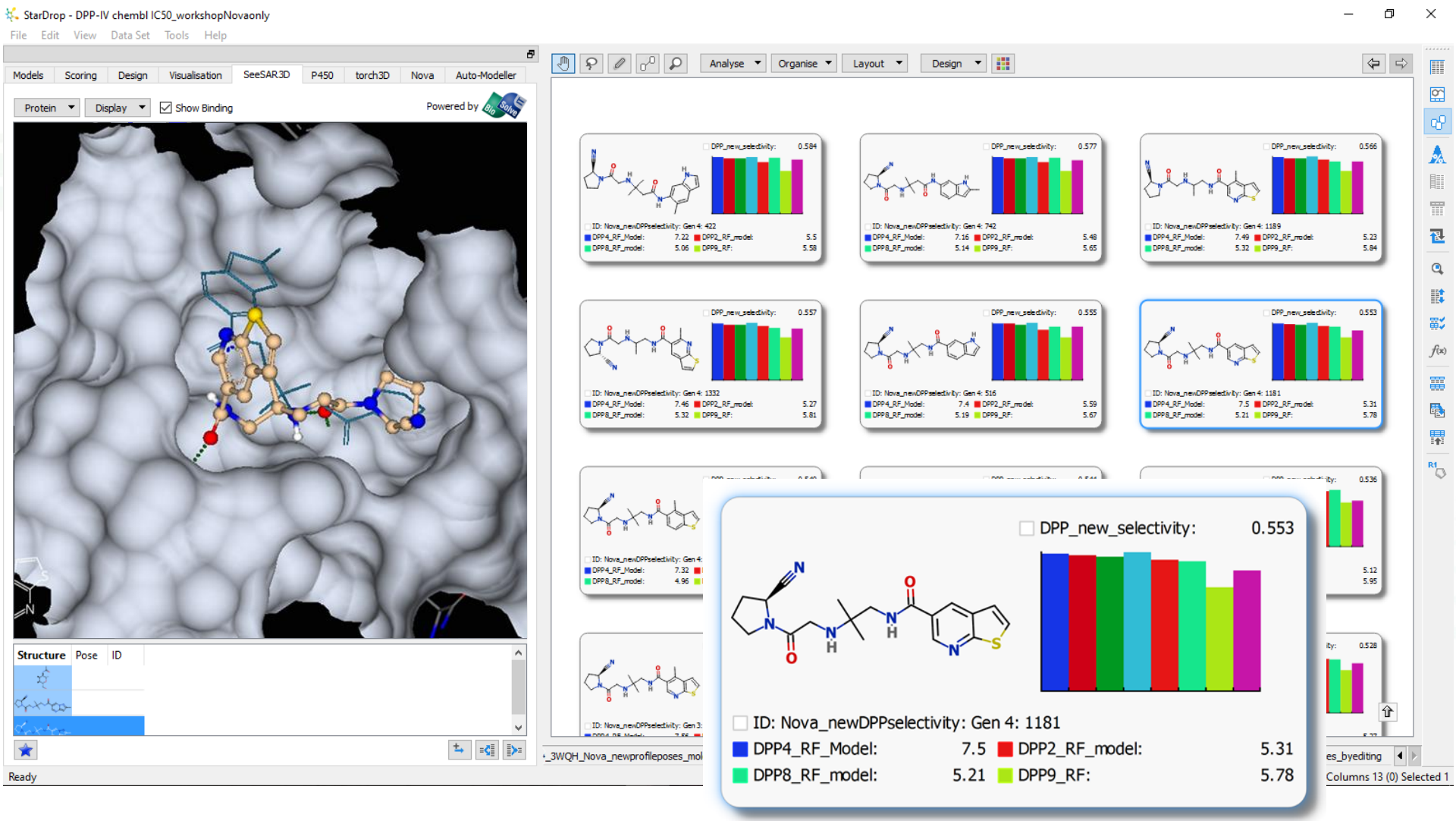
Selective DPP-4 Ideas



Hyde Scores in SeeSAR



Selective DPP-4 Ideas



Conclusions

- Seamless integration of 2D and 3D information aids interpretation of SAR
  - Intuitive visualisations identify patterns
  - Understanding of interactions (3D) and relationships (2D)
- Using all the available information guides selection and design of compounds
  - Understand and rationalise structural modifications
  - Improved balance of properties
  - Avoid missing opportunities
- For more information:
  - www.optibrium.com/stardrop and www.biosolveit.com/SeeSAR
  - Optibrium: Booth 1227 or outside of room 6E (MEDI)

Acknowledgements

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