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Beyond the SARs - Adding More Pizzazz to your Analysis

UGM 2019

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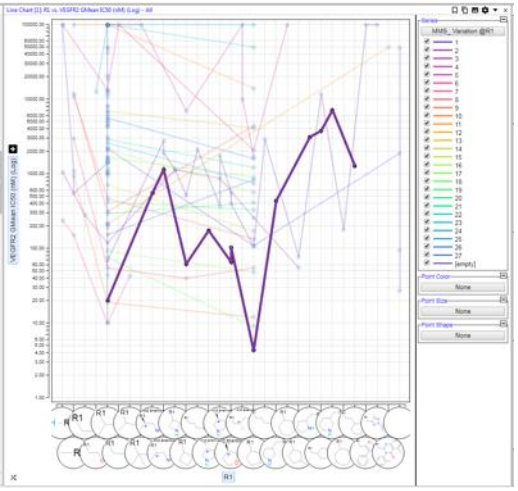
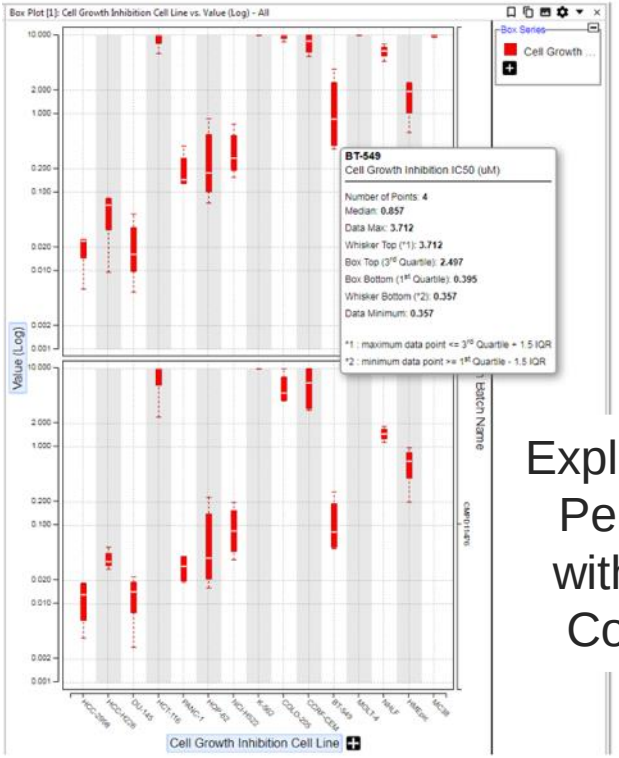
Senior Consultant

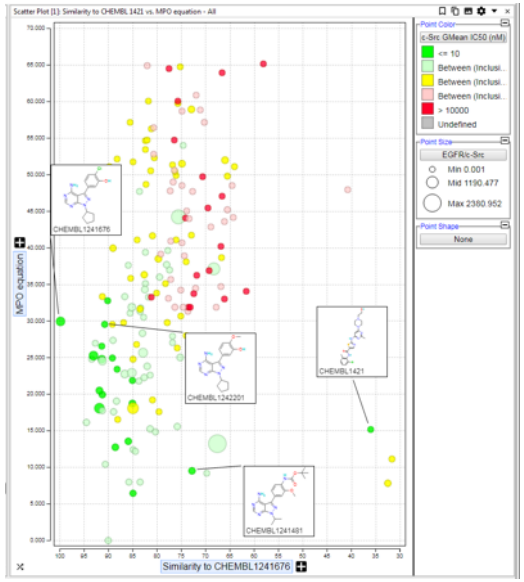
Beyond the SARs - Adding More Pizzazz to your Analysis



Exploring Activity Trends in Matched Molecular Series

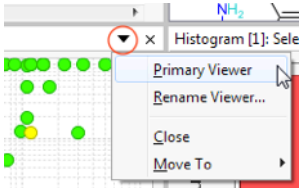


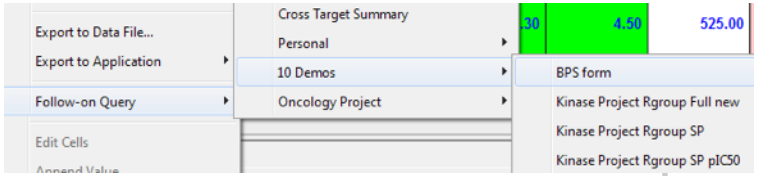
Exploring Assay Performance with Selected Compounds



Structure Similarity and MPO Scoring- Looking for Interesting Outliers

Revisiting Favorite Tools





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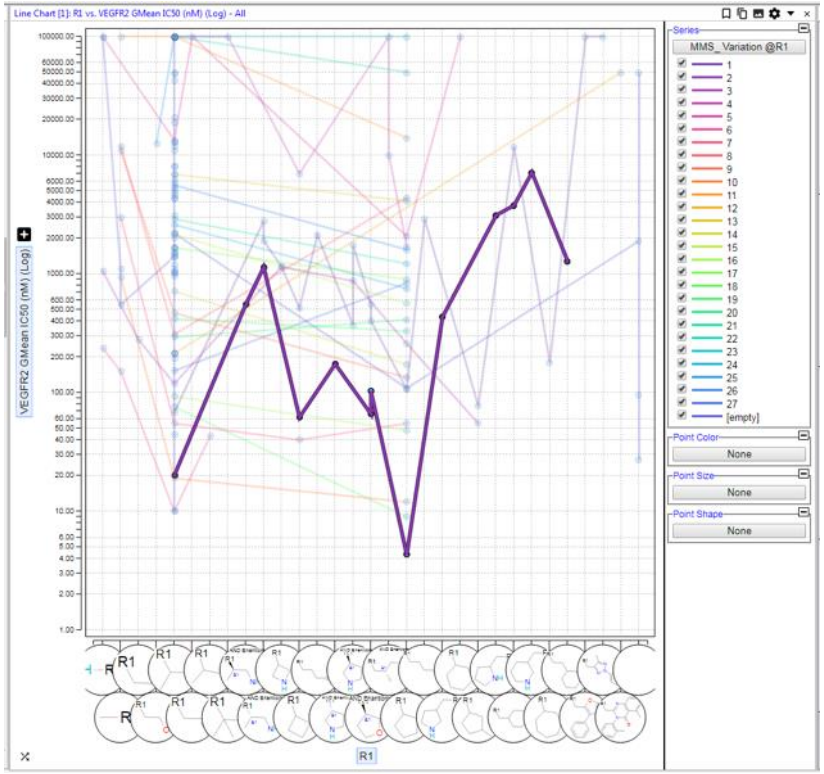
Exploring Activity Trends in Matched Molecular Series

- There are multiple D360 tools that enable the exploration of Structure Activity Relationships:
  - Chemical Series
  - Structure Similarity Maps
  - R-Group Analysis-RGM
  - Structure Comparison Viewer
  - Matched Molecular Series
- A combination of several of these tools will allow us to graphically examine the change in activity with variations in a specific portion of the structure



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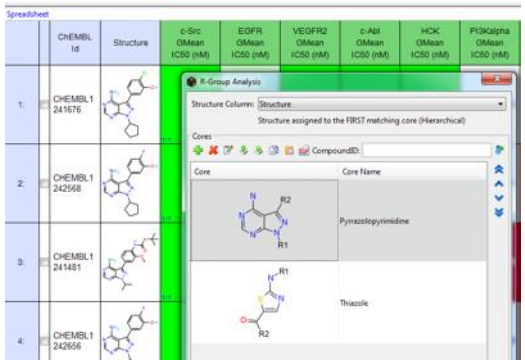
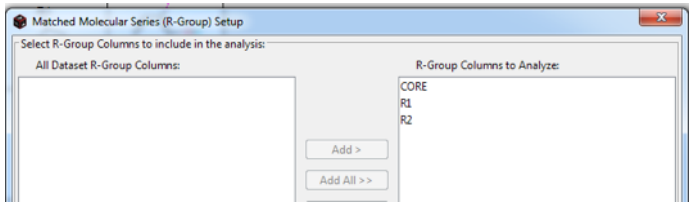
Exploring Activity Trends in Matched Molecular Series-Setup …

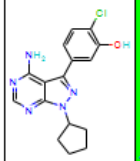
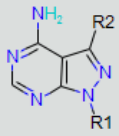
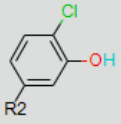
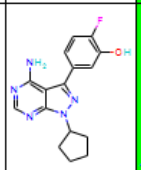
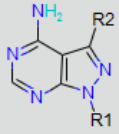
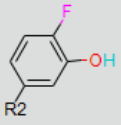
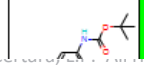
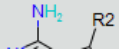
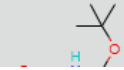


- **Do an R-Group Analysis**

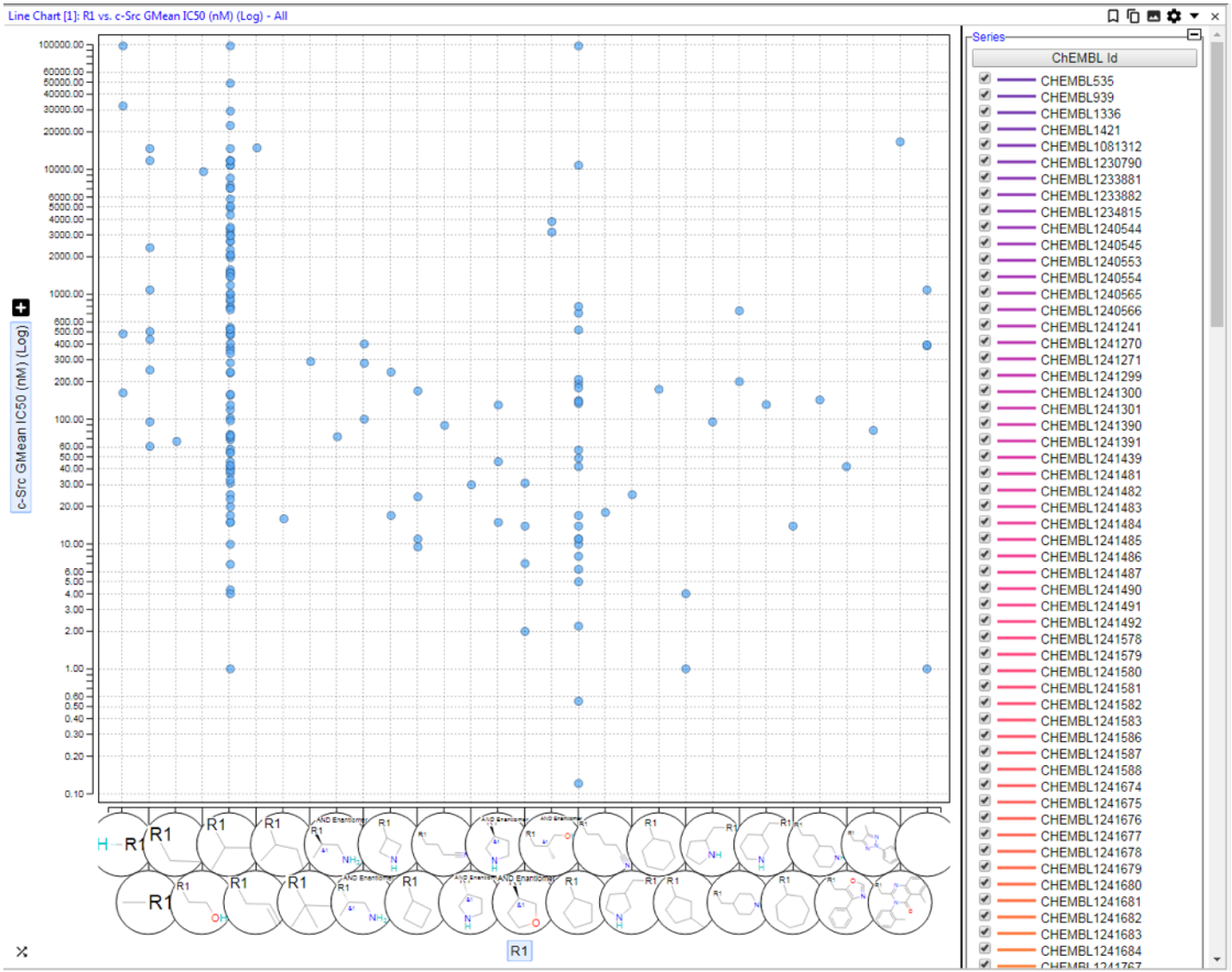


- **Do a Match Molecular Series Analysis**

Spreadsheet

		ChEMBL Id	Structure	c-Src GMean IC50 (nM)	EGFR GMean IC50 (nM)	VEGFR2 GMean IC50 (nM)	CORE	R1	R2	MMS_ Variation @CORE	MMS_ Variation @R1	MMS_ Variation @R2
1:		CHEMBL1 241676		0.12 1/1	67.00 1/1	4.30 1/1					2	2
2:		CHEMBL1 242568		0.55 1/1	318.00 1/1	106.00 1/1					1	2
												

Exploring Activity Trends in Matched Molecular Series-**Line Chart**



- **Create a Line Chart**
- **Set the X-Axis to R1**
- **Set the Y-Axis to Desired Property and Log Scaled**

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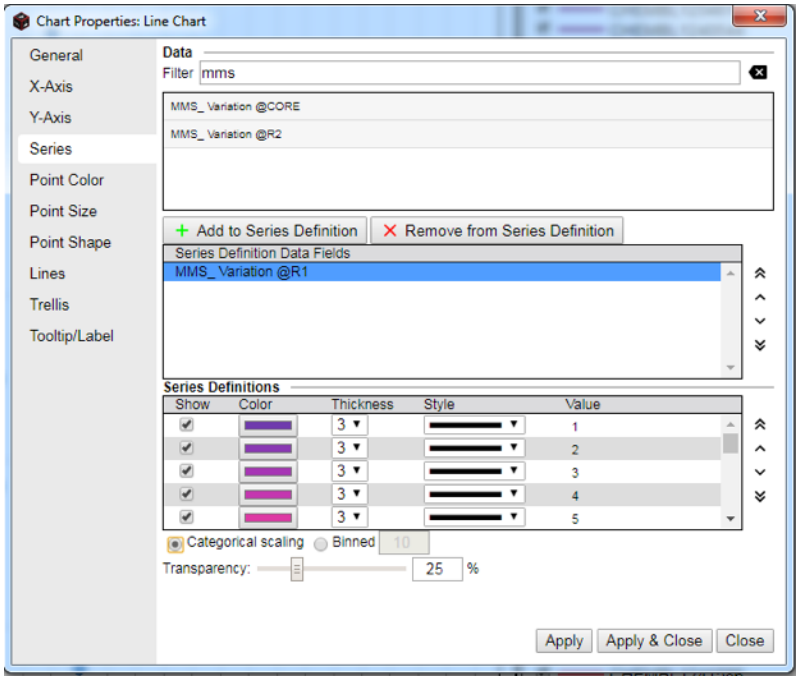
Exploring Activity Trends in Matched Molecular Series-**Setting up the Series**



- **Set up the Series to match the X-Axis R-Group**
- **Make the Axis Categorical**

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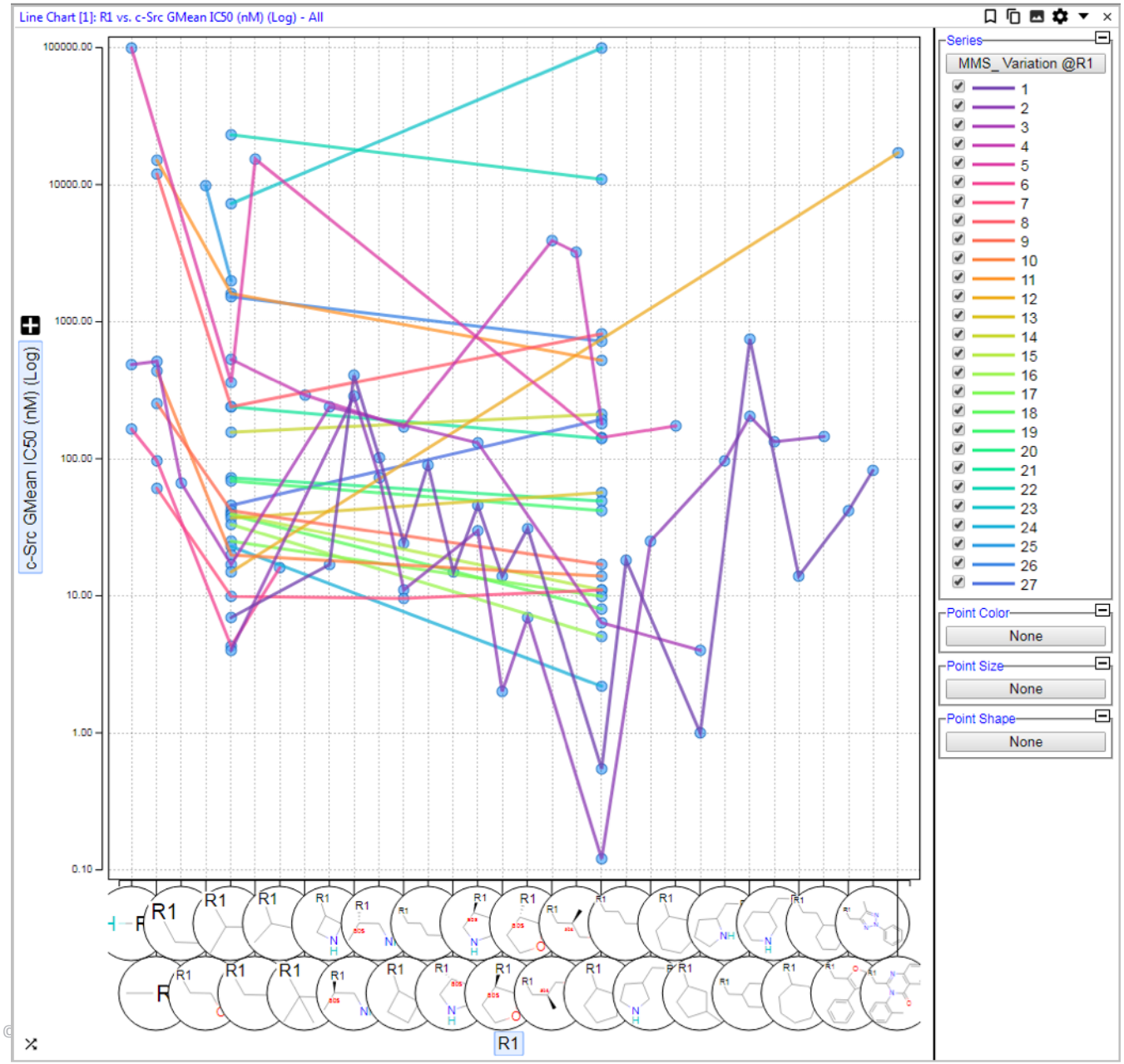
Exploring Activity Trends in Matched Molecular Series-**Connected Line Chart**



- **Select a line or a Series**

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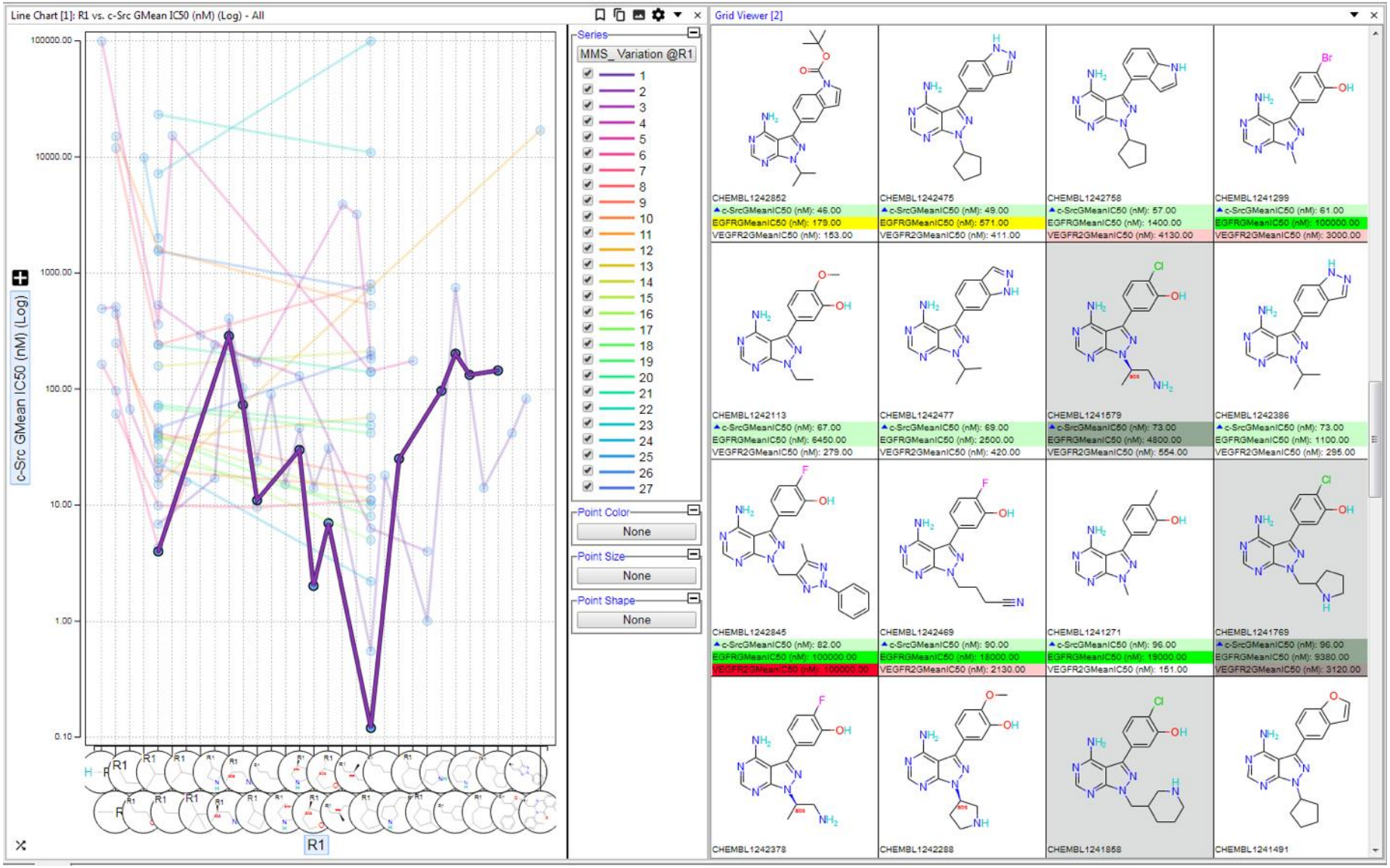
Exploring Activity Trends in Matched Molecular Series-**Add a Grid Viewer**



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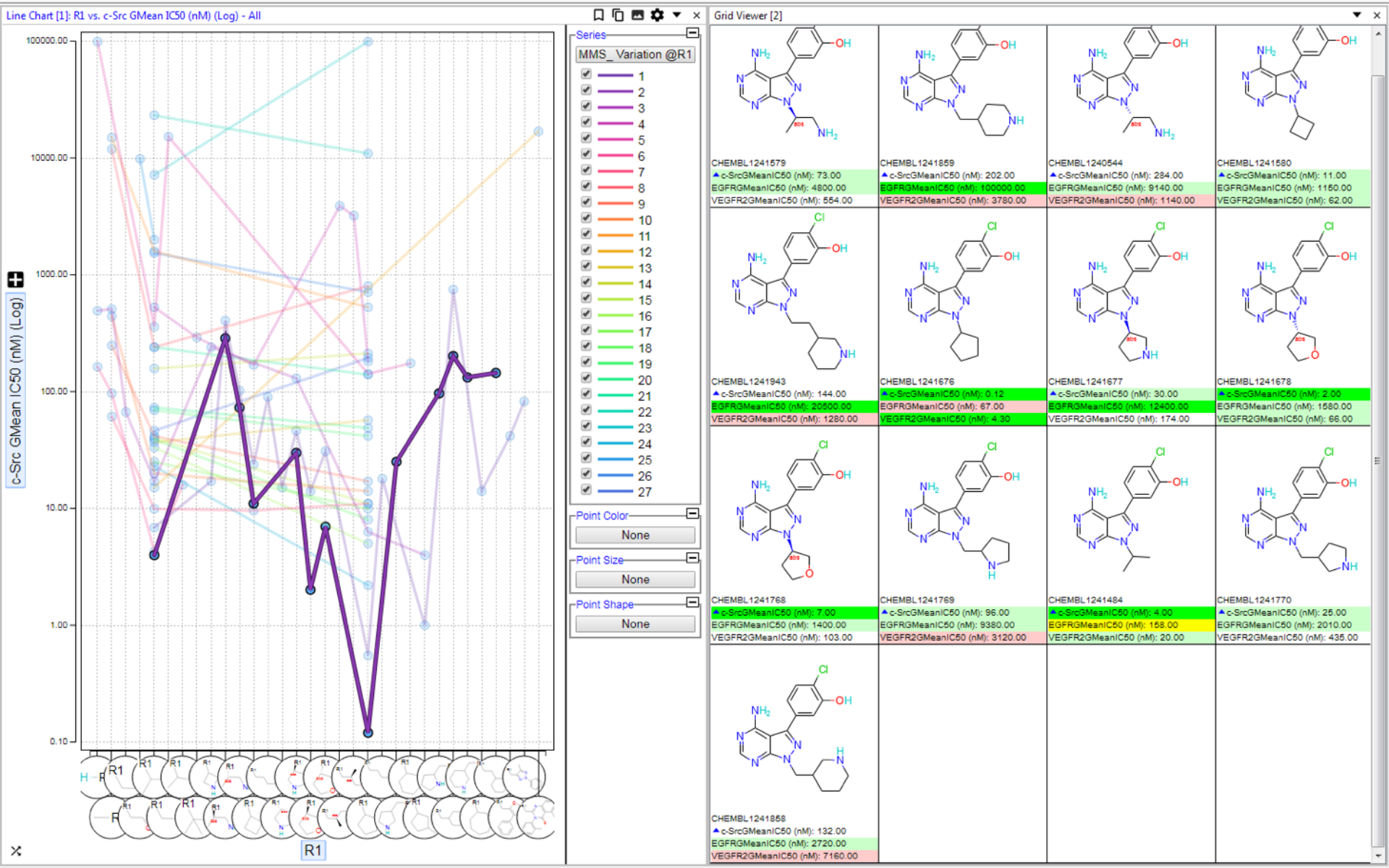
Exploring Activity Trends in Matched Molecular Series-**Primary Viewer mode**



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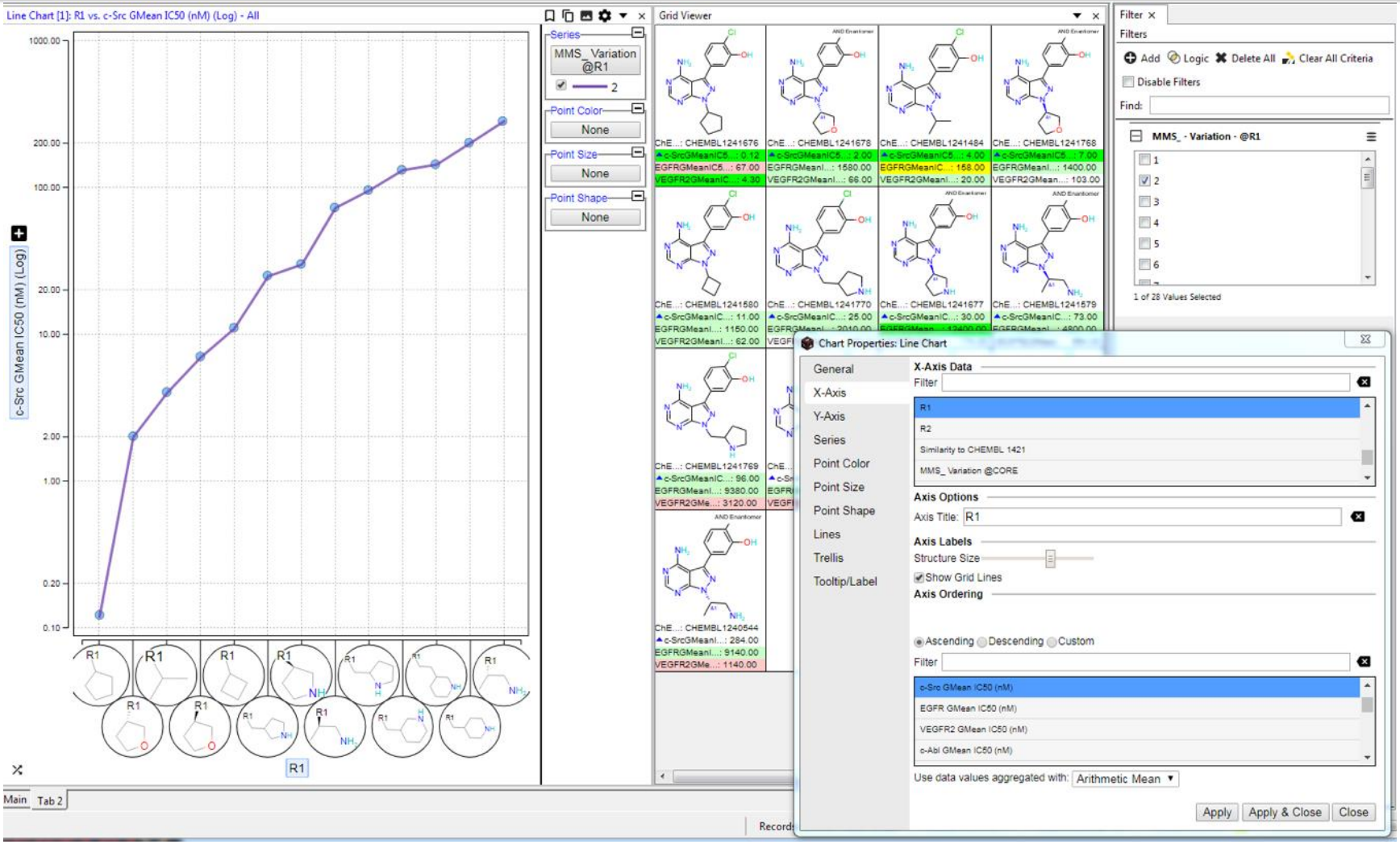
Exploring Activity Trends in Matched Molecular Series-**Focus on One Series**



- **Order R1 by activity**
- **You can easily pick other series from the filter dialog**
- **You can easily switch to other properties from the Y-Axis**

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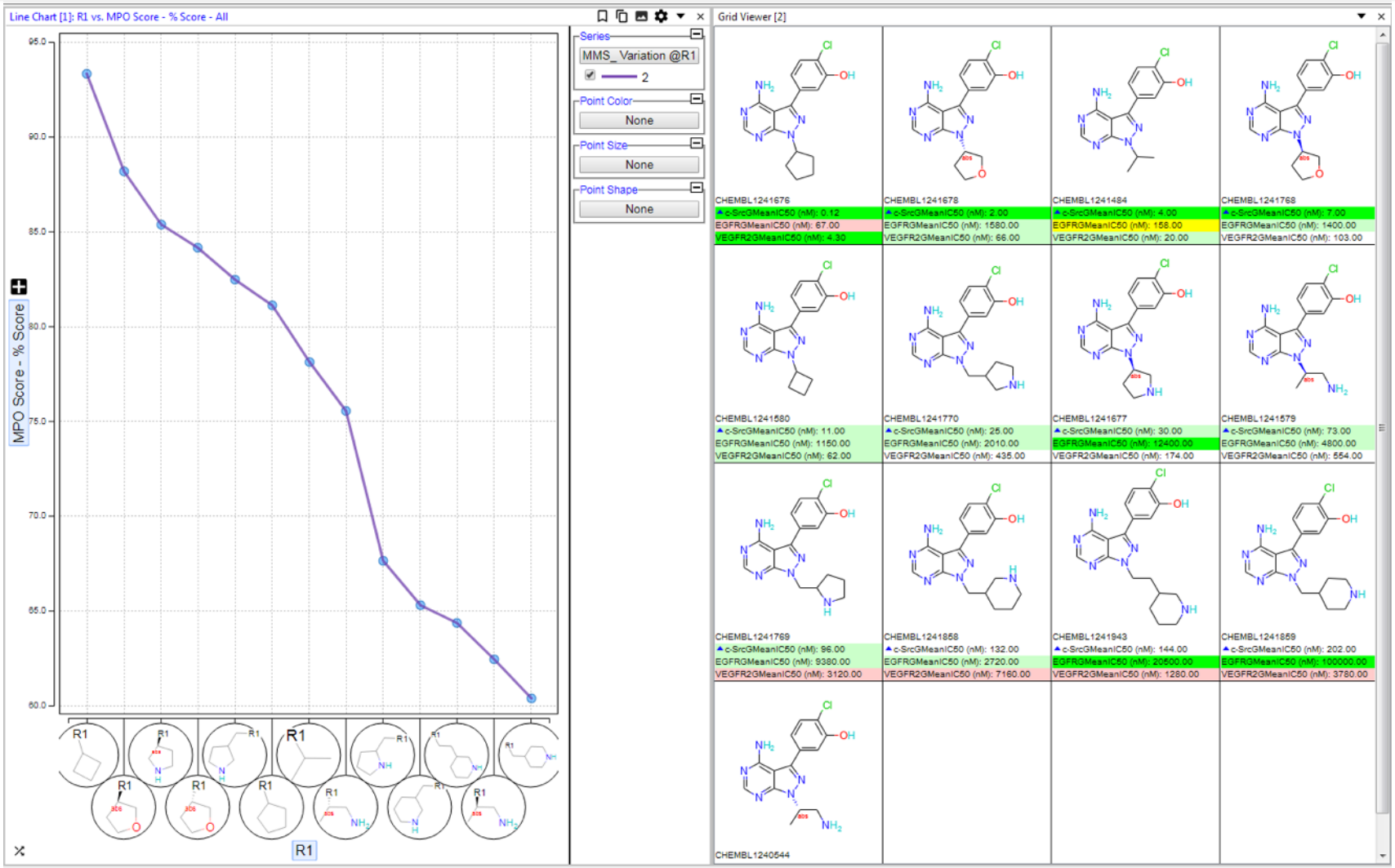
Exploring Activity Trends in Matched Molecular Series-**Focus on One Series-2**



- **Switched to MPO Score-Y-Axis**
- **Sorted R1 by MPO Score**

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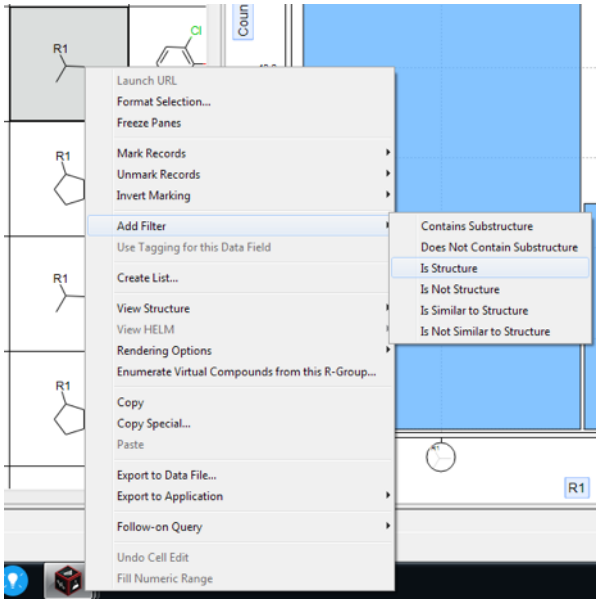
- **How does activity change when only one Fragment changes?**



- Right click on one of the desired R1 fragments and select Filter **Is Structure**
- Disable this Filter Gadget
- Right click on another one of the desired R1 fragments and select Filter **Is Structure**
- Re-enable the first structure gadget and set the logic for this section to be "**Any**". This will find all compounds in the dataset that have either of these R1 fragments

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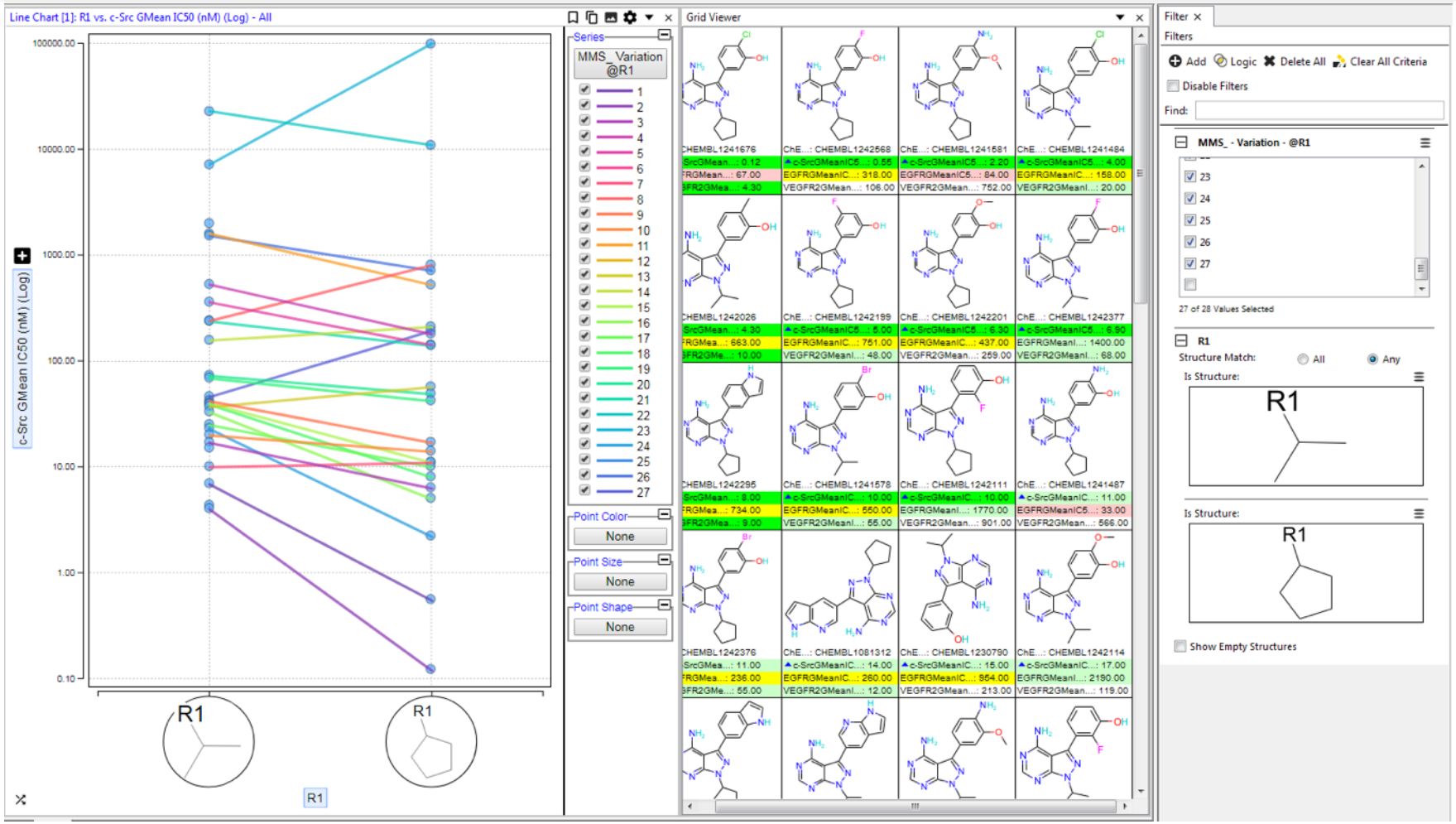
Exploring Activity Trends in Matched Molecular Series-Explore the Pairwise Results



- **Clear indications of the effect of pair-wise changes in activity**
- **Easy to change activity (Y-Axis) or individual R-Group pairs**

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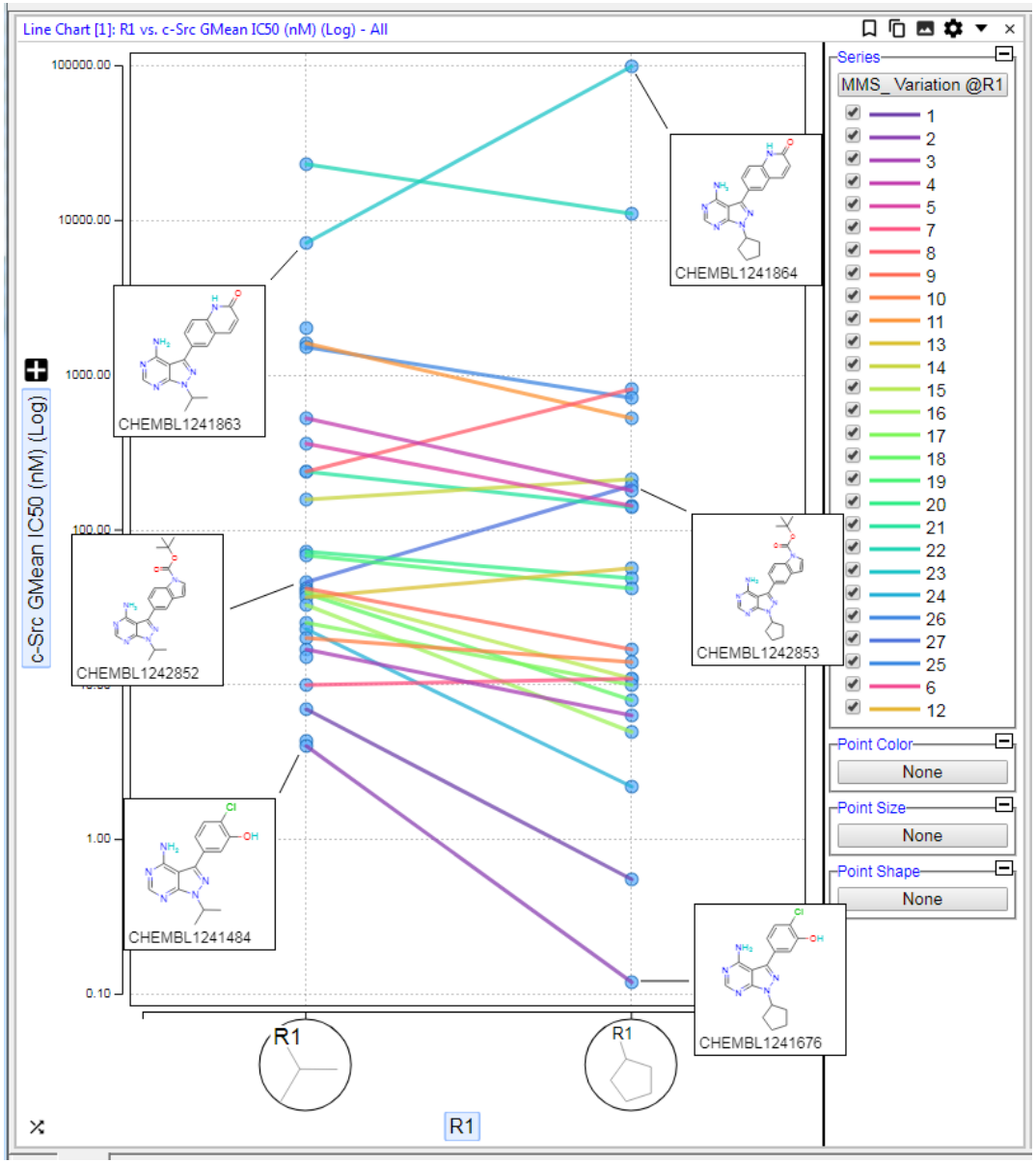
Exploring Activity Trends in Matched Molecular Series-**Explore the Pairwise Results**



- For most of these pairs changing from isopropyl to cyclopentyl was beneficial, but for several pairs there was a dramatic decrease in activity

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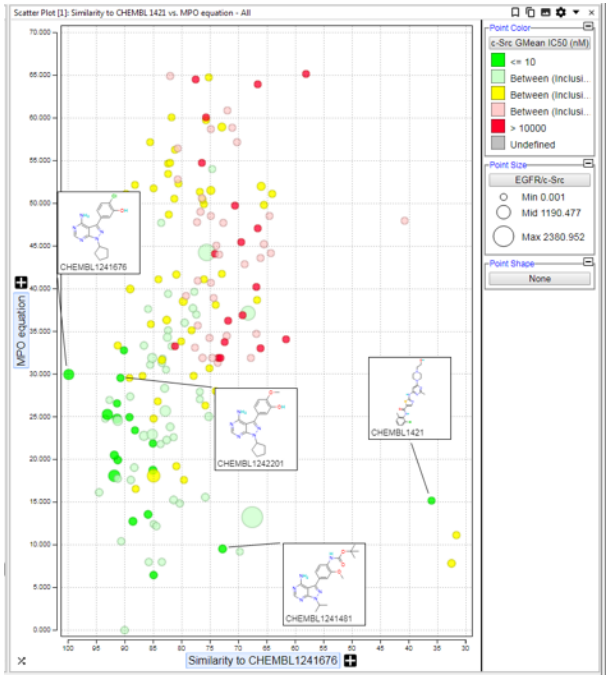
Structure Similarity and MPO Scoring-Looking for Interesting Outliers

- How do changes in the overall structure for a series of compounds affect activity?
  - Structure Similarity Maps give an overall view of all the structures along with activity data

- How does the activity vary with Similarity to a single compound?



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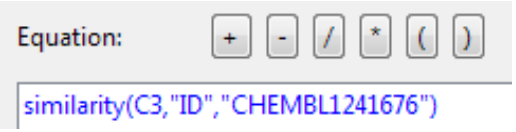
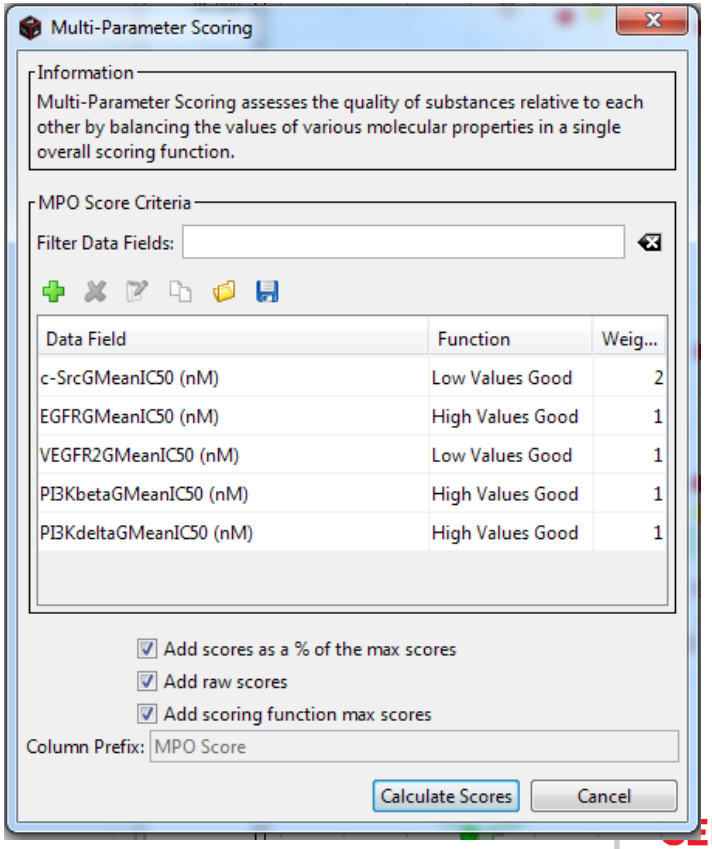
Structure Similarity and MPO Scoring-Looking for Interesting Outliers-Setup

- **Pick the Compound in your current dataset to focus on (e.g. CHEMBL 1241676)**
  - **This might be the most potent compound in your primary assay or the one with the best overall profile**
- **Create a Similarity equation**



- **Create a Multi-Parameter Score for your desired profile**



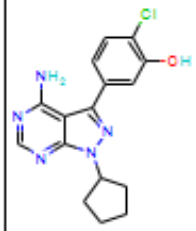
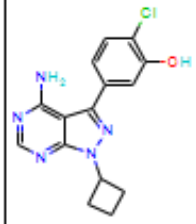
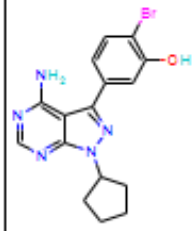
Structure Similarity and MPO Scoring-Looking for Interesting Outliers-Setup-2

- **Create an equation to show the MPO scores of all compounds relative to my reference compound**

Equation:

51.9-C28

Spreadsheet

		ChEMBL Id	Structure	Similarity to CHEMBL1241676	MPO Score - % Score	MPO relative to CHEMBL 1241676
1:	☐	CHEMBL1241676		100	51.9	-0.00
2:	☐	CHEMBL1241580		95	65.7	-13.84
3:	☐	CHEMBL1242376		93	57.0	-5.14
						

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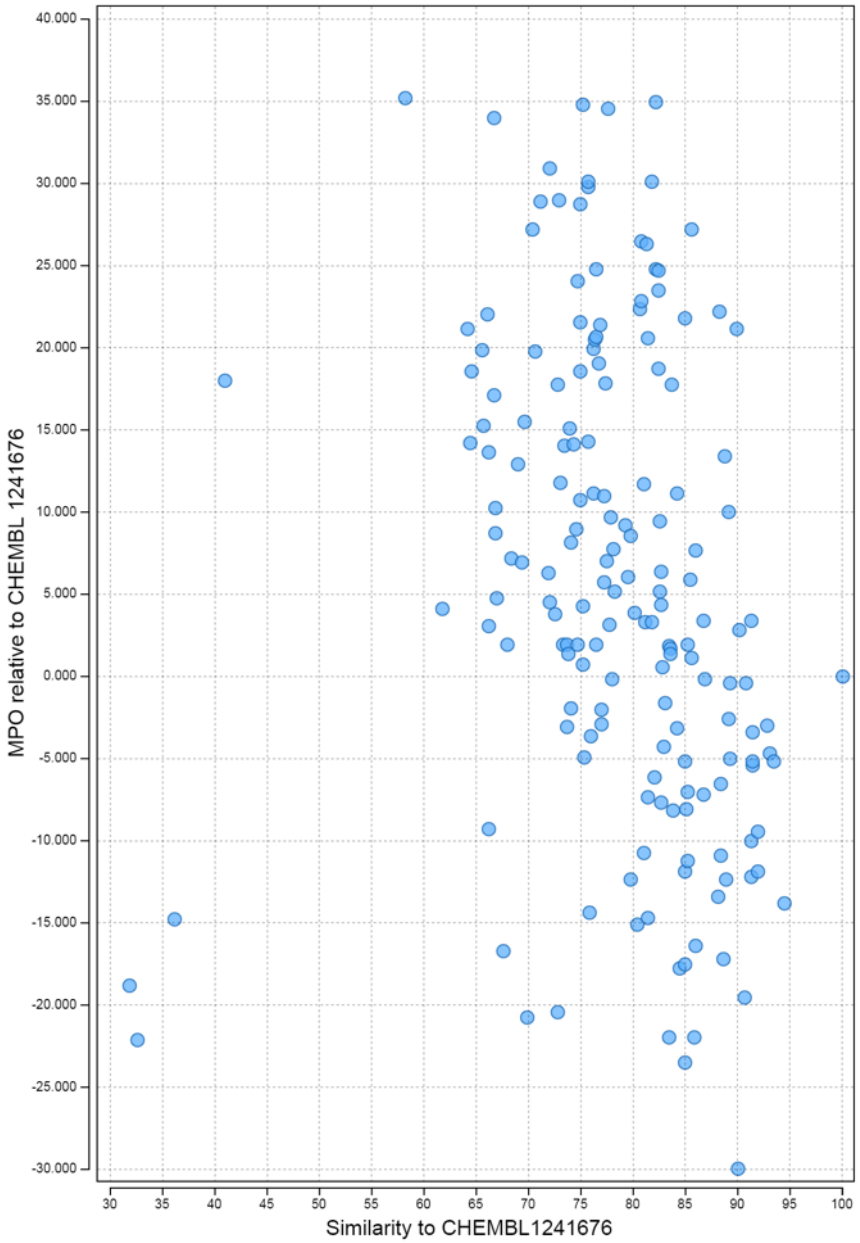
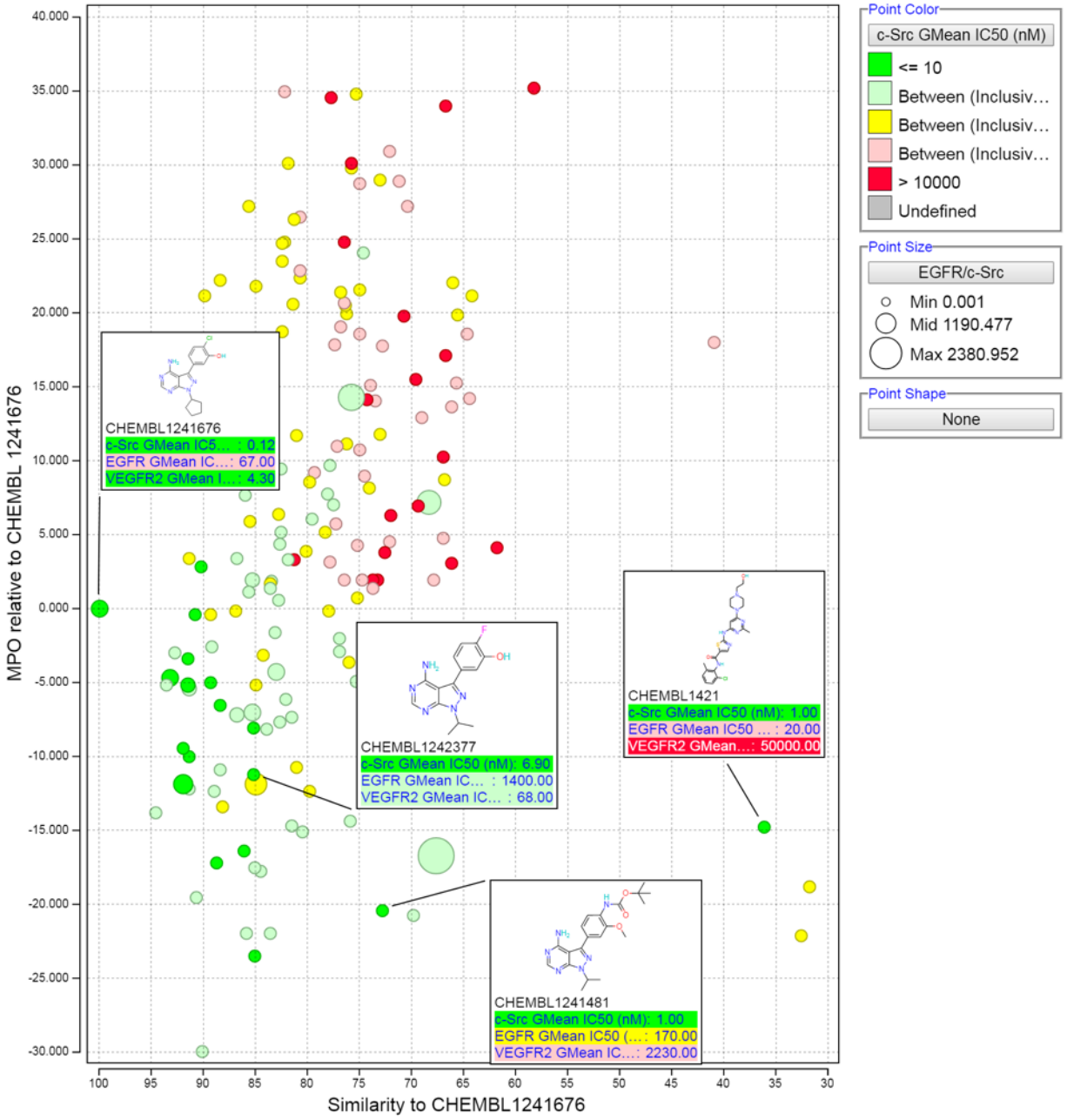
Structure Similarity and MPO Scoring-Looking for Interesting Outliers-Scatterplot



- Reverse the axis for the Similarity Score (X-Axis)
- Add in Point color for the primary assay
- Add in point size for a EGFR/c-Src selectivity value
- Add some assays to the tooltip
- Add in some sticky labels (v20.1!)

Structure Similarity and MPO Scoring-Looking for Interesting Outliers-Scatterplot tuned



- **Compounds that are similar in structure to the target that have a much lower MPO?**
- **Compounds that are not similar to the target compound that have good, if not better MPO?**

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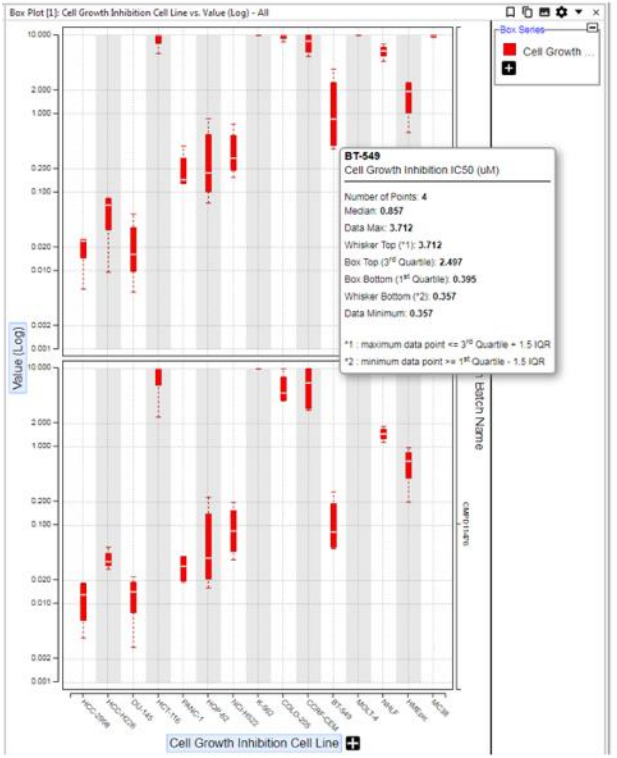
Exploring Assay Performance with Selected Compounds

- There are several ways to see how your compounds are behaving in assays:
  - Dose Response Curves
  - Statistical aggregation types like standard deviation and confidence intervals as columns to your dataset
  - Looking at the in cell indicators for the clues about the underlying unaggregated data

- Several other assay performance analyses you might want to do:
  - How standards perform in assays over time
  - Reproducibility of compounds across assays



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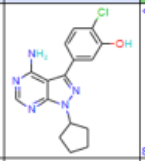
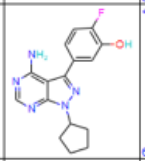
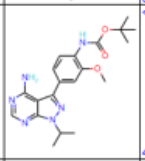
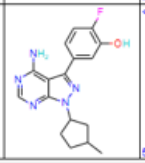
Exploring Assay Performance with Selected Compounds-Standards-setup

- **Compound ID (constrained by 4 compound IDs)**
- **Structure (if desired)**
- **Assay that is under review (e.g. c-Src Kinase)**
  - **Include the summarized value (e.g. IC50) with the aggregation functions GMean and Concatenate LF and Standard Deviation.**
  - **Include the date the experiment was run with the aggregation function of Concatenate LF.**

Spreadsheet

	Compound ID	Structure	c-Src Kinase GMean IC50 (uM)	c-Src Kinase Std Dev IC50 (uM)	c-Src Kinase Concat IC50 (uM)	c-Src Kinase Concat Assay Date
1:	CMPD821		0.00263 (81/91)	0.004 (81/91)	0.002 0.003 0.002 0.002 0.001 0.002 0.001 0.002 0.005 (82/91)	10-Sep-2015 15-Sep-2015 10-Sep-2015 15-Oct-2015 15-Oct-2015 17-Nov-2015 15-Sep-2015 01-Dec-2015 03-Feb-2016 (91/91)
2:	CMPD10912		0.148 (66/70)	0.048 (66/70)	0.146 0.121 0.136 0.114 0.242 0.170 0.146 0.176 0.165 (66/70)	15-Oct-2015 10-Sep-2015 15-Oct-2015 15-Sep-2015 06-May-2015 06-May-2015 01-Dec-2015 03-Feb-2016 27-Jan-2016 (70/70)
3:	CMPD18965		6.74 (4/67)	8.363 (4/67)	>25.000 >25.000 >25.000 12.200 >2.500 >25.000 >25.000 >25.000 >25.000 (67/67)	21-Jul-2008 25-Jul-2008 14-Jul-2008 14-Jul-2008 09-Jun-2008 09-Jun-2008 19-May-2008 12-May-2008 27-May-2008 (67/67)
4:	CMPD188761		0.0379 (52/57)	0.047 (52/57)	0.043 0.049 0.054 0.034 0.061 0.071 0.031 0.043 0.044 (52/57)	15-Oct-2015 10-Sep-2015 15-Oct-2015 15-Sep-2015 17-Nov-2015 18-Aug-2015 01-Dec-2015 06-Jan-2016 13-Jan-2016 (57/57)

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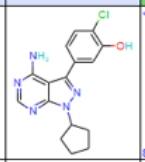
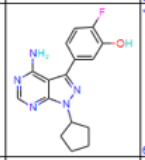
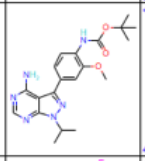
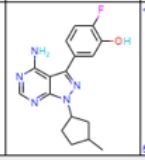
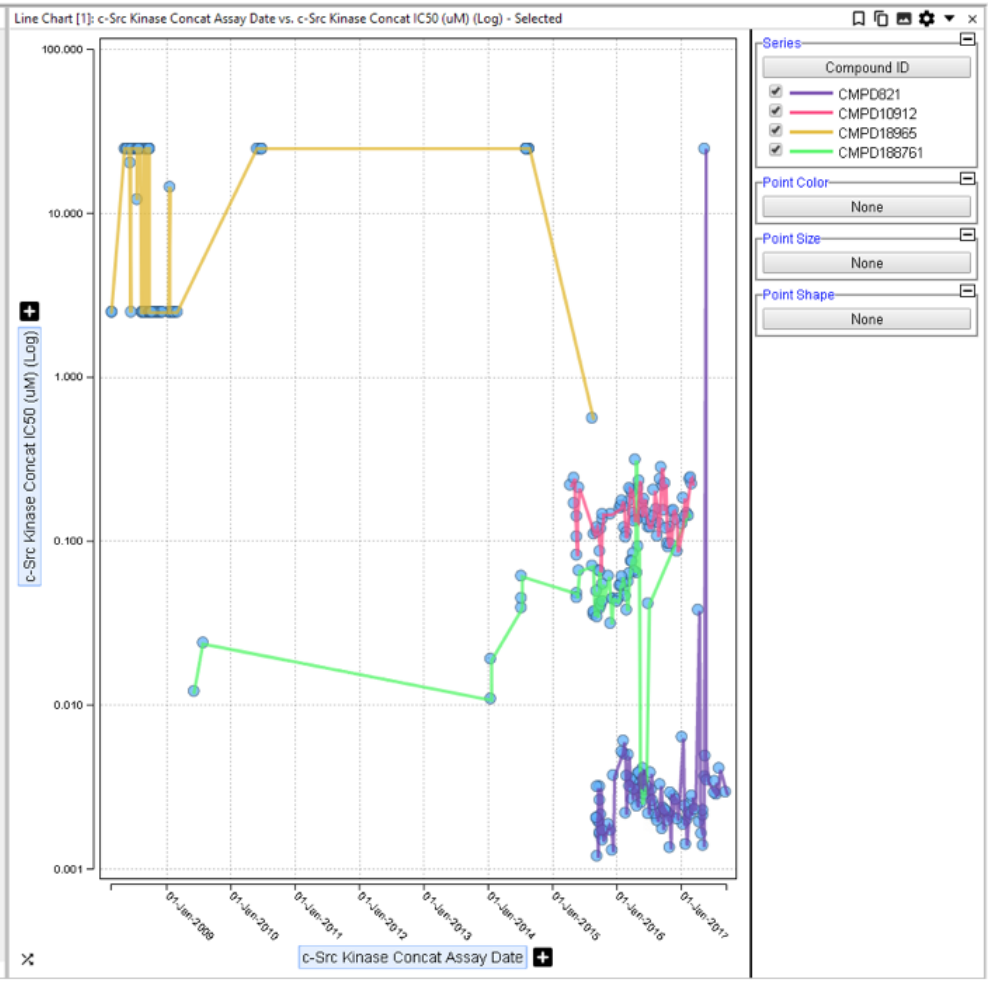
Exploring Assay Performance with Selected Compounds-Standards-Line Chart

- **Add a Line Chart**
  - **X-Axis is date the experiment was run (concat LF)**
  - **Y-Axis is Assay IC60 (concat LF). Set this axis to be log scaled**
  - **Set the Line Series up to use the Compound ID column**

Spreadsheet

	Compound ID	Structure	c-Src Kinase GMean IC50 (uM)	c-Src Kinase Std Dev IC50 (uM)	c-Src Kinase Concat IC50 (uM)	c-Src Kinase Concat Assay Date
1:	CMPD821		0.00263 (81/91)	0.004 (81/91)	0.002 0.003 0.002 0.002 0.001 0.002 0.001 0.002 0.005 (82/91)	10-Sep-2015 15-Sep-2015 10-Sep-2015 15-Oct-2015 15-Oct-2015 17-Nov-2015 15-Sep-2015 01-Dec-2015 03-Feb-2016 (91/91)
2:	CMPD10912		0.148 (66/70)	0.048 (66/70)	0.146 0.121 0.136 0.114 0.242 0.170 0.146 0.176 0.165 (66/70)	15-Oct-2015 10-Sep-2015 15-Oct-2015 15-Sep-2015 06-May-2015 06-May-2015 01-Dec-2015 03-Feb-2016 27-Jan-2016 (70/70)
3:	CMPD18965		6.74 (4/67)	8.363 (4/67)	>25.000 >25.000 >25.000 12.200 >2.500 >25.000 >25.000 >25.000 >25.000 (67/67)	21-Jul-2008 25-Jul-2008 14-Jul-2008 14-Jul-2008 09-Jun-2008 09-Jun-2008 19-May-2008 12-May-2008 27-May-2008 (67/67)
4:	CMPD188761		0.0379 (52/67)	0.047 (52/67)	0.043 0.049 0.054 0.034 0.061 0.071 0.031 0.043 0.044 (52/67)	15-Oct-2015 10-Sep-2015 15-Oct-2015 15-Sep-2015 17-Nov-2015 18-Aug-2015 01-Dec-2015 06-Jan-2016 13-Jan-2016 (57/67)



Exploring Assay Performance with Selected Compounds-Reproducibility

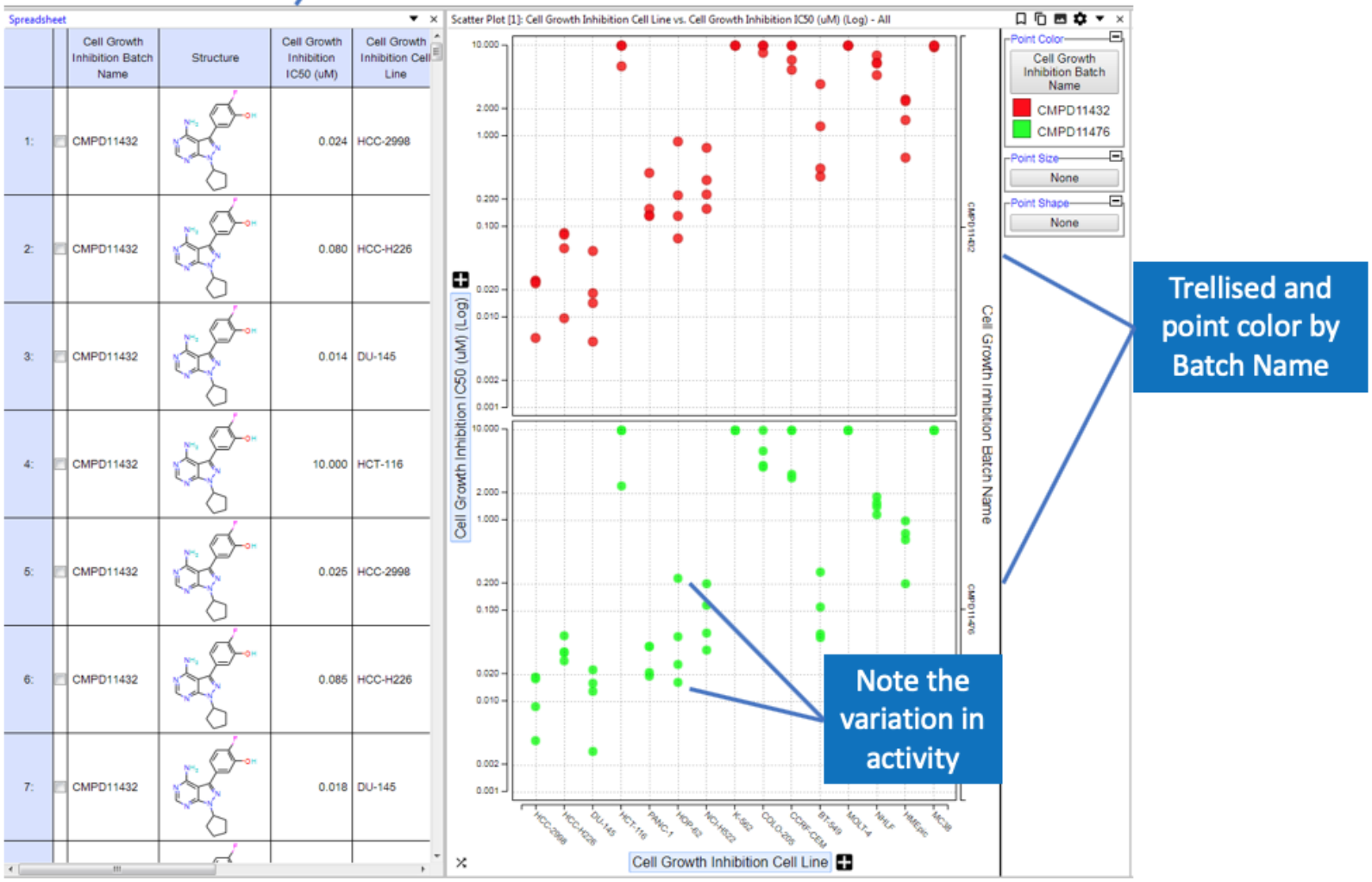
- **In assay development or quality control you might want to see how multiple measurements during the same run look for your compounds**
- **While it is easy to add in statistical fields like Standard Deviation, Min, Max… it is sometimes easier to just visualize it**

Setup

- Compound ID (constrained by two compound IDs)
- Structure
- Assay that is under review (e.g. Cell growth Inhibition)
  - Desired result type (e.g. **IC50**) and set the cell line condition to be **unpivoted**
  - Include the Analysis fields **Batch Name** and **Experiment Date**
  - Constrain the Experiment date to a date or set of dates to review
  - Set the query to run as **Unaggregated**

Exploring Assay Performance with Selected Compounds-Scatter Graph

Unaggregated, not pivoted dataset



Trellised and point color by Batch Name

Note the variation in activity

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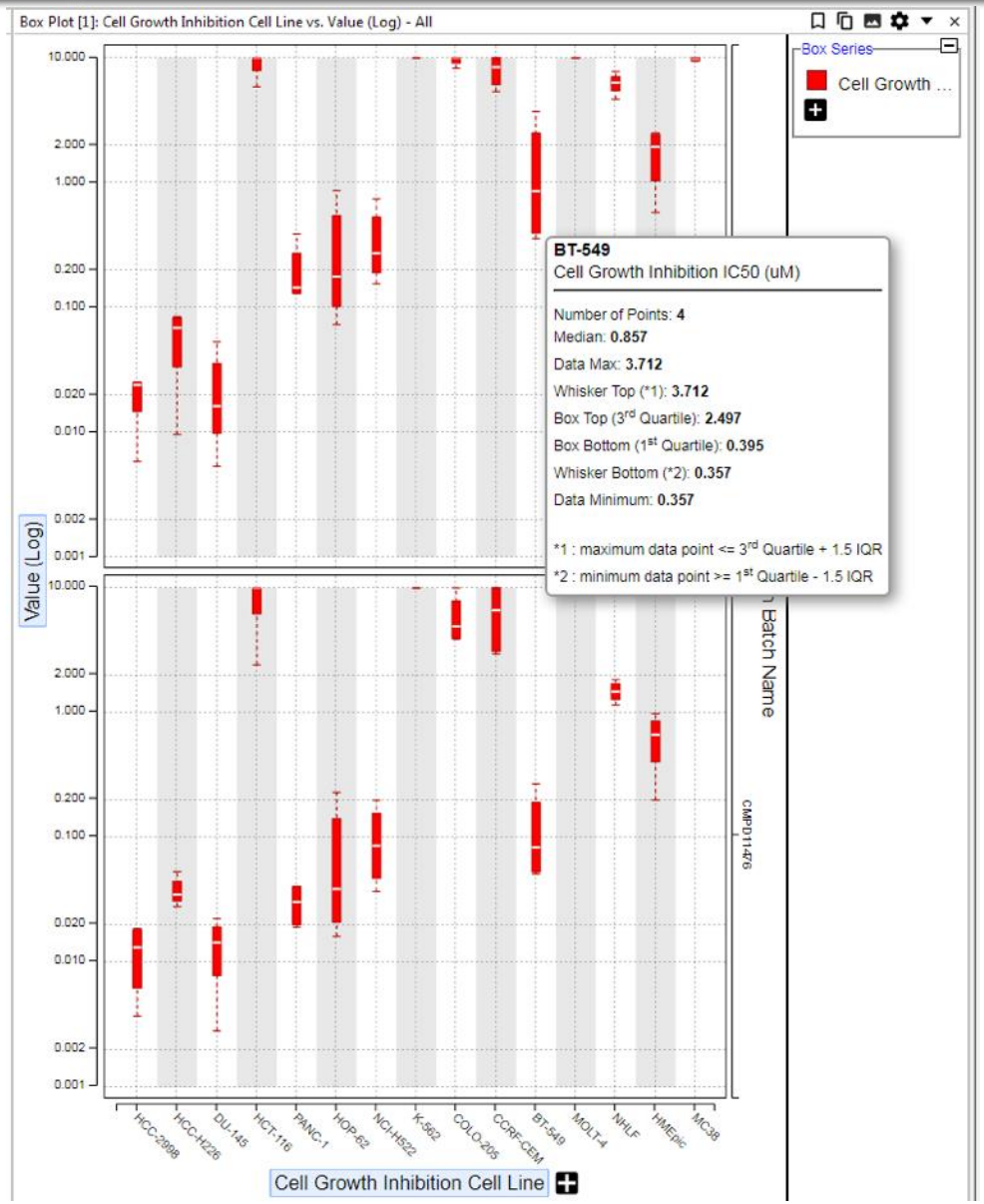
Exploring Assay Performance with Selected Compounds-Box Plot



- **Box Plots give a quick visual indication of data range**
- **Tooltips afford all the detailed statistics for the Box (and Whisker)**

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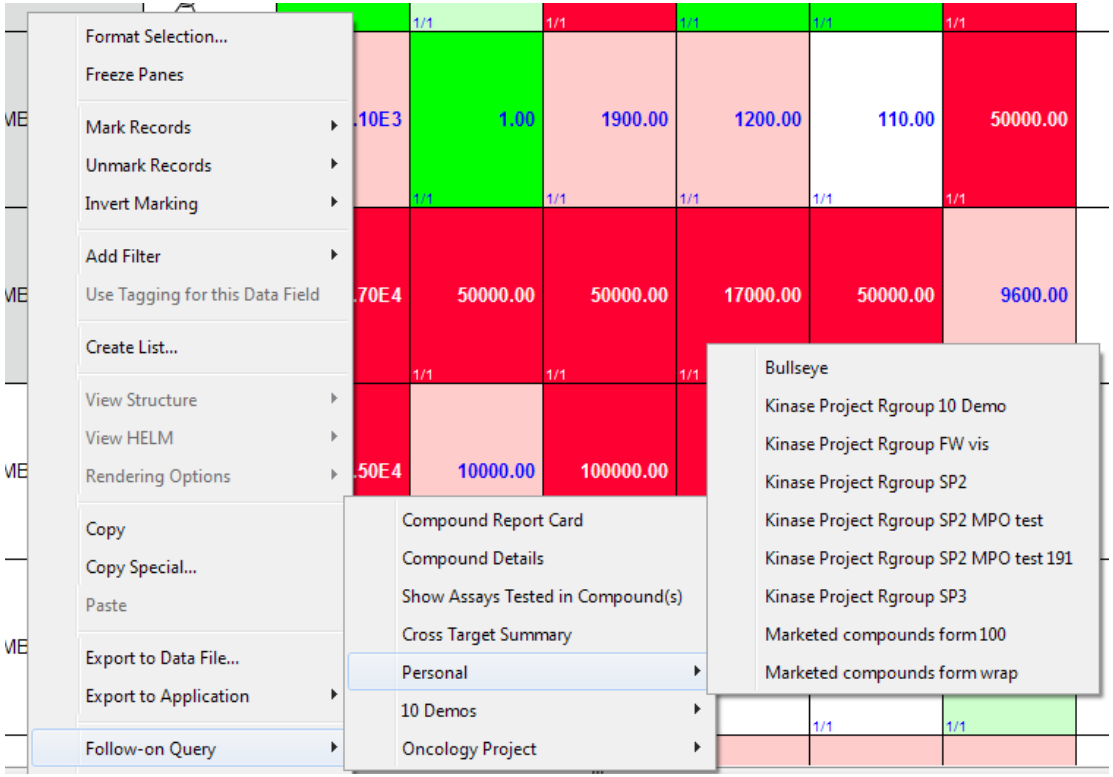
Follow On Queries-not just for Administrators

- **Most organizations have Follow On Queries (FOQ) as standard templates for common workflows**
- **Often overlooked is the ability for any user to create FOQs for personal or project use**



Any query can be an FOQ that

- **Has a Domain-able field (e.g. Compound ID) or a structure field exposed in the widget**
- **Is saved as a widget**
- **Is visible on the Dashboard**

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KnowledgeBase Articles-where to find these workflows!

- An Overview of Virtual Compounds
- Adding Virtual Compounds to a D360 Dataset
- Enumerating Virtual Compounds from R-groups and Cores
- Deleting Virtual Compounds from a D360 Dataset
- Creating a D360 Dataset from a Chemical Structure File or Sketch
- Capturing Virtual Compounds

- **Exporting Data**
  - Exporting Data to Excel
  - Exporting Data to Data Files - csv, tsv, sdf, xls, xlsx, json
  - Exporting Data to PowerPoint
  - Copying Data to the Clipboard

- **Miscellaneous**
  - D360 URL execution of query templates
  - Installing D360 on a Windows PC
  - Installing D360 on a Mac
  - How to Specify Chiral Information in Commonly used Chemical Sketchers
  - Test Automation Tool

- **Tips and Tricks for Small Molecule Discovery**
  - Exploring Activity Trends in Matched Molecular Series
  - Structure Similarity and Multi-Parameter Scoring - Looking for Interesting Outliers
  - Exploring Assay Performance with Selected Compounds
  - Bioprofile Summary Results

- **D360 Partner - A D360 Client for External Research Partners**
  - D360 Partner - An Overview of Sharing Data with External Research Partners
  - D360 Partner setup for Administrators
  - D360 Partner Query setup
  - D360 Partner Use

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Acknowledgements

- Exploring Activity Trends in Matched Molecular Series
  - John Cummings (Roche), Lars Burgdorf (Merck KGaA), Dietrich Boese (Merck KGaA)

- Exploring Assay Performance with Selected Compounds
  - Beverley Smith (Medimmune)

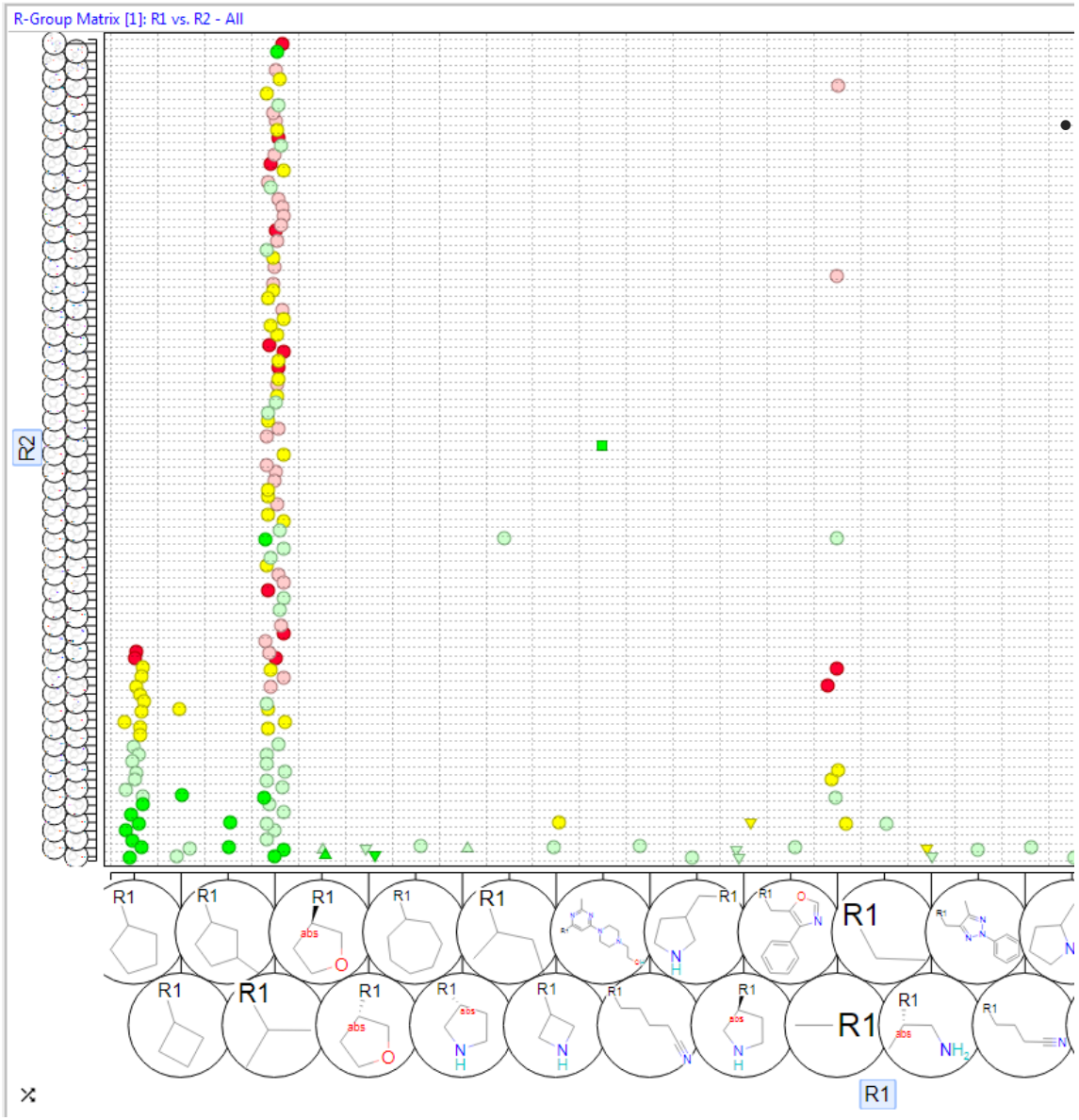
- Favorite tools
  - Justin Montgomery (Pfizer)

- Certara Folks
  - David Lowis, and the Development Team for giving me all the tools…

One More Thing…R-Group Activity Contribution Analysis

- Modeling the contribution of each R-Group fragment to any activity could lead to a better understanding of the SAR for the series
- With a good model in hand, you should be able to Predict the activity of Virtual compounds
- This would augment the services that several companies have with virtual assays.

R-Group Activity Contribution Analysis – Setup



- **R-Group Matrix**
  - R1 sorted by Min c-Src activity
  - R2 sorted by first fragment c-Src activity

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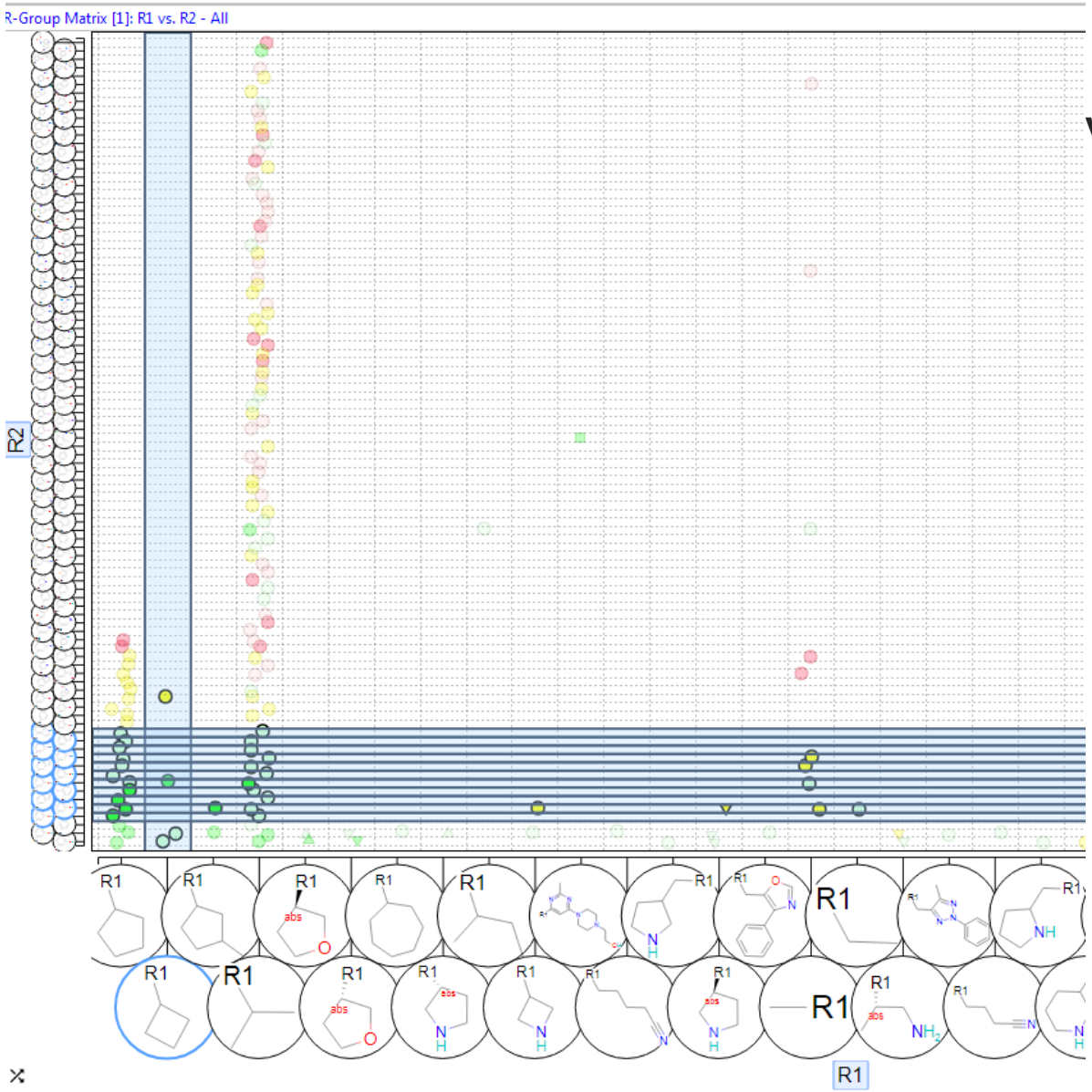
R-Group Activity Contribution Analysis – Virtual Compounds 1



Virtual Compounds

- Selected the section where expected activity might be found

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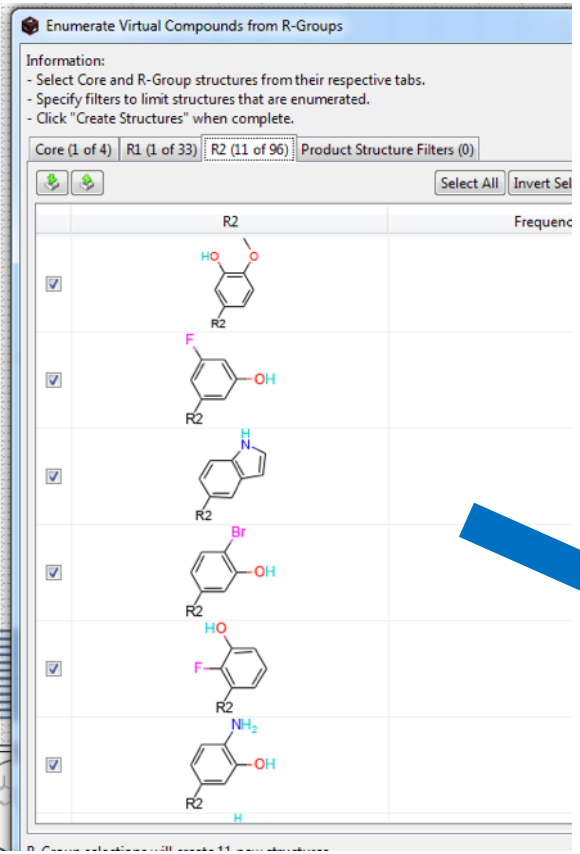
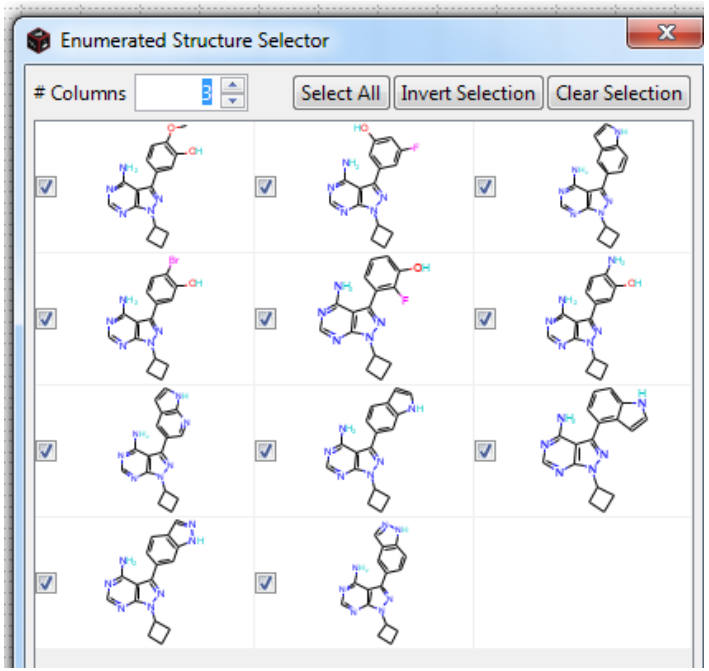
R-Group Activity Contribution Analysis – Virtual Compounds 2





- **Virtual Compounds**
  - Enumerated the Compounds

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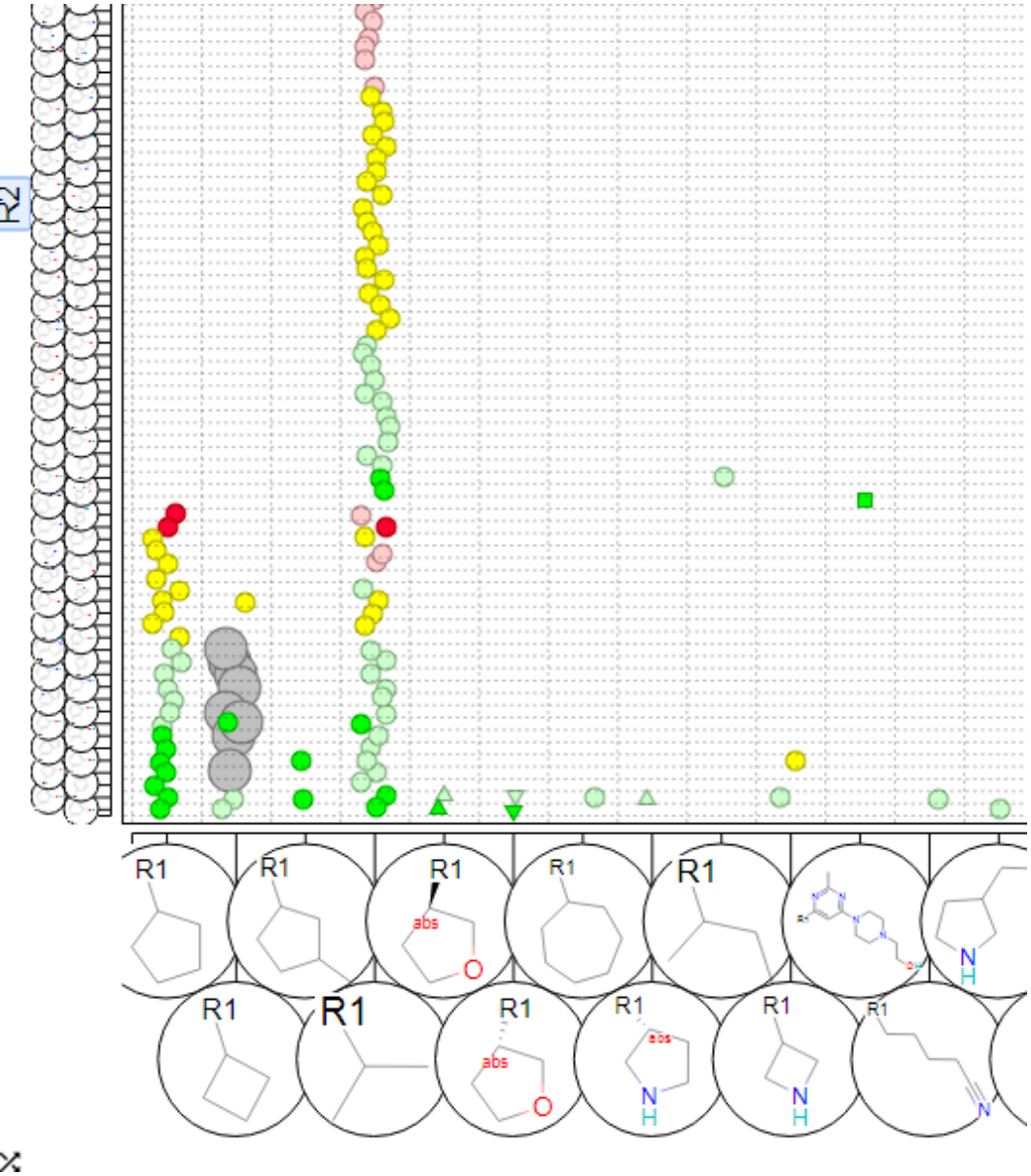
R-Group Activity Contribution Analysis – Virtual Compounds 3



- **R-Group Matrix**
  - **New Virtual Compounds are highlighted with larger size and no activity**

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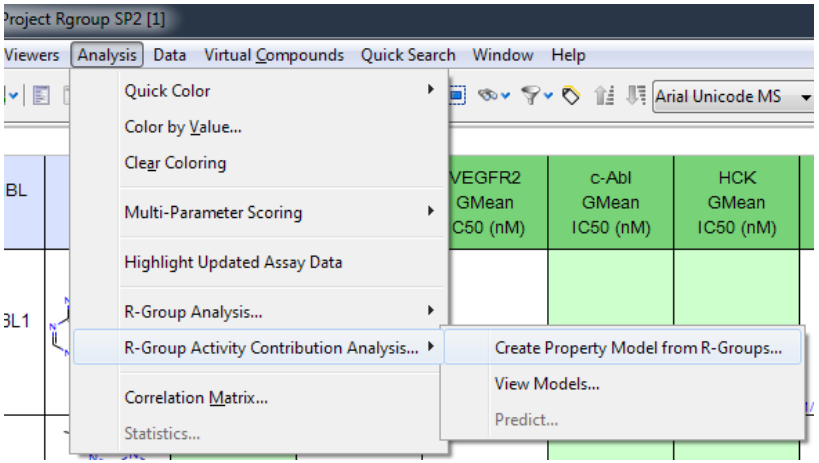
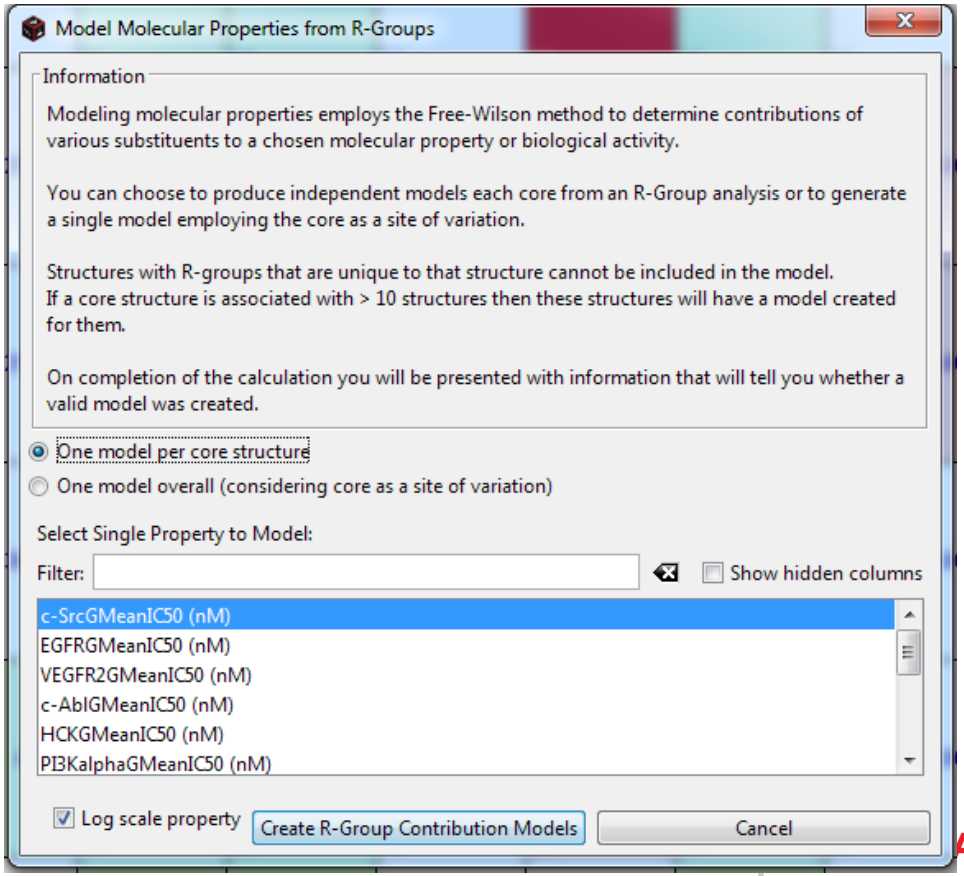
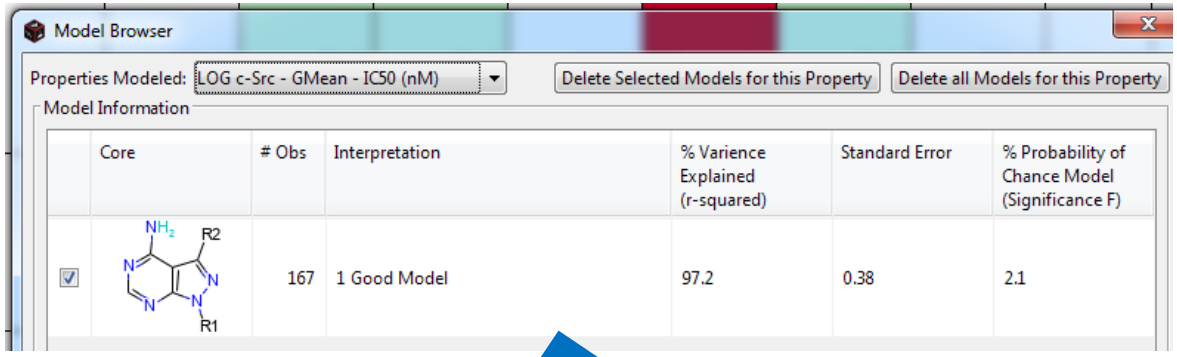
R-Group Activity Contribution Analysis – Analysis Setup



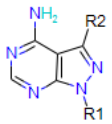
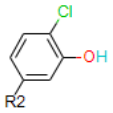
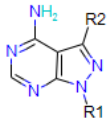
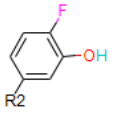
- **R-Group Activity Contribution Analysis (v20.1)**

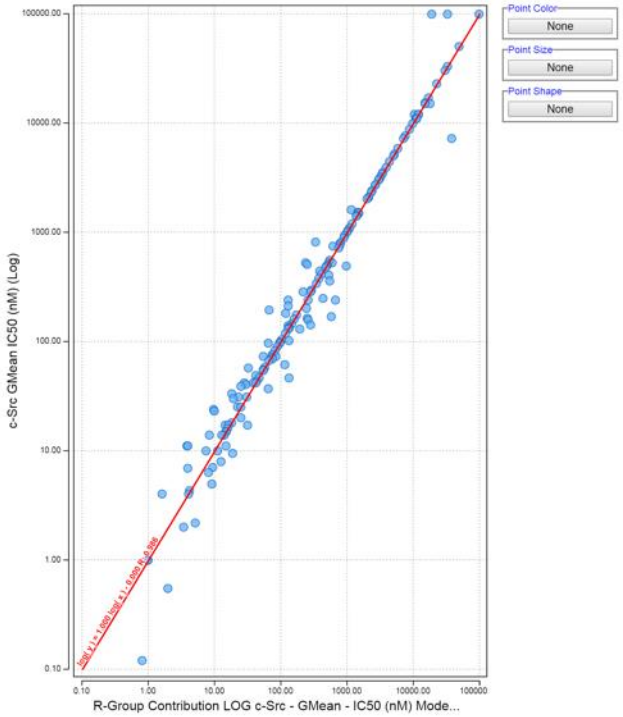


R-Group Activity Contribution Analysis – Analysis Setup - 2



- **Good Model with low standard error**

CORE	R1	R2	R-Group Contribution LOG c-Src - GMean - IC50 (nM) CORE Contribution	R-Group Contribution LOG c-Src - GMean - IC50 (nM) R1 Contribution	R-Group Contribution LOG c-Src - GMean - IC50 (nM) R2 Contribution	R-Group Contribution LOG c-Src - GMean - IC50 (nM) Modeled Value
			1.78	-2.07	0.20	0.81
			1.78	-2.07	0.59	1.99



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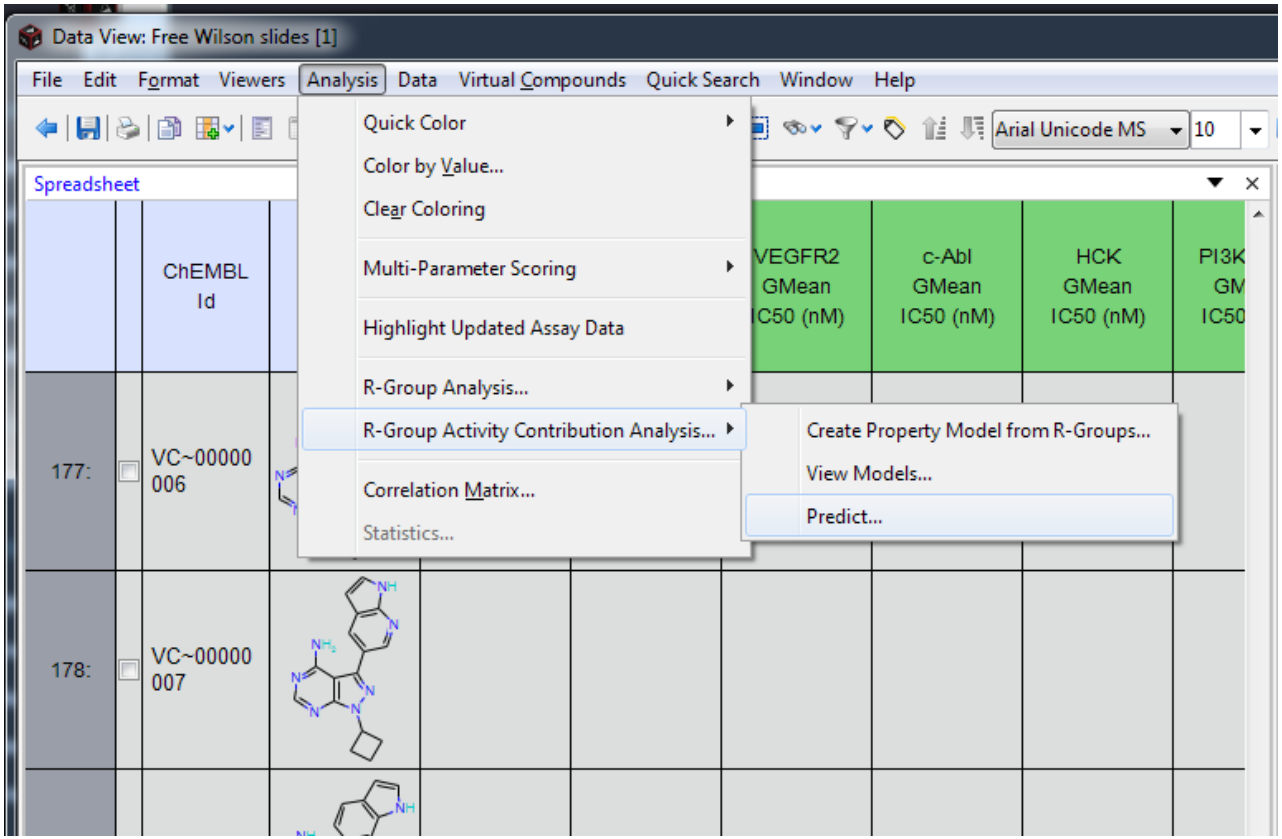
R-Group Activity Contribution Analysis – Predict!

- **With a good model in place lets predict the activity of the Virtual Compounds**



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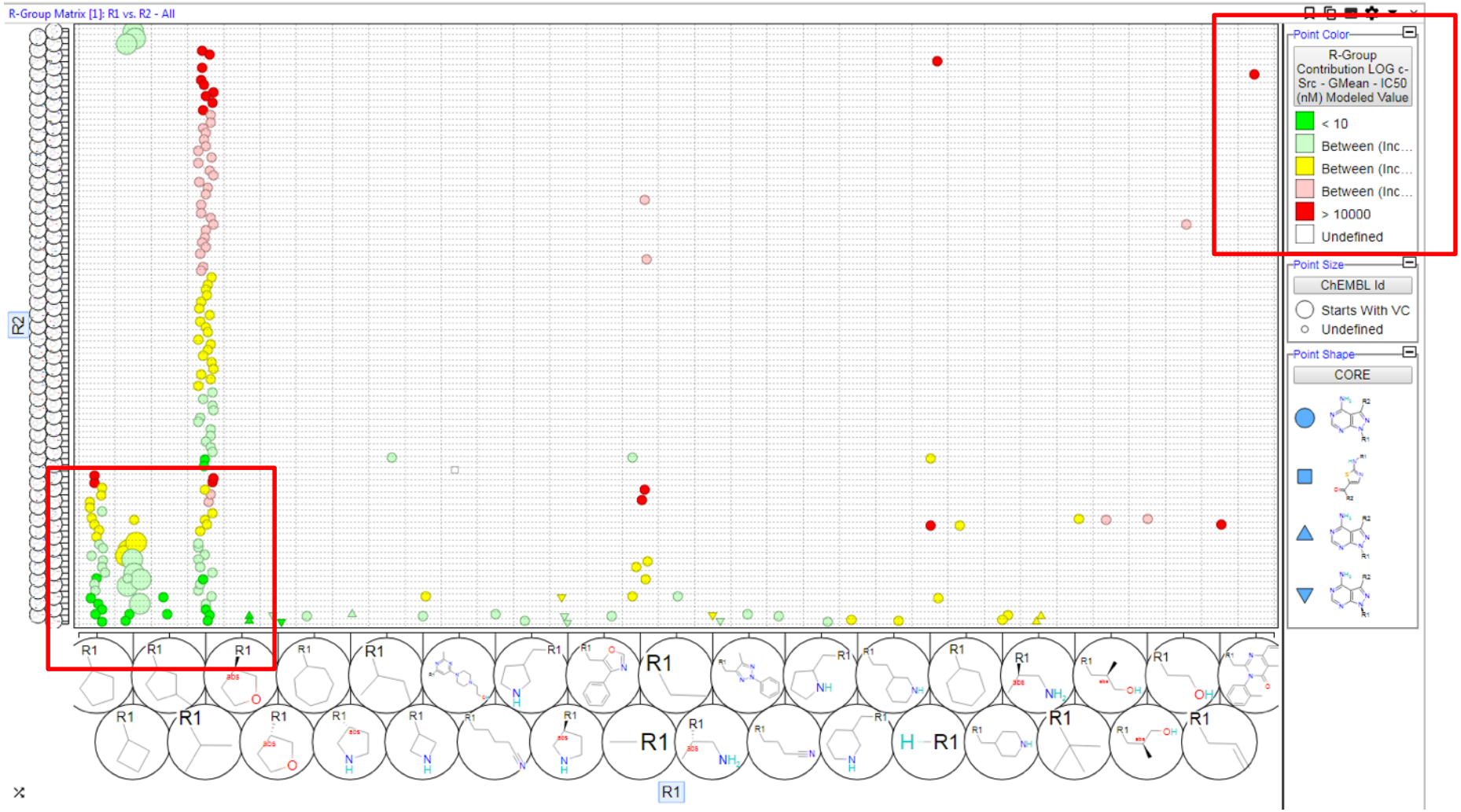
R-Group Activity Contribution Analysis – New RGM

- **R-Group Matrix with the Point Color by Model Predicted Activity**



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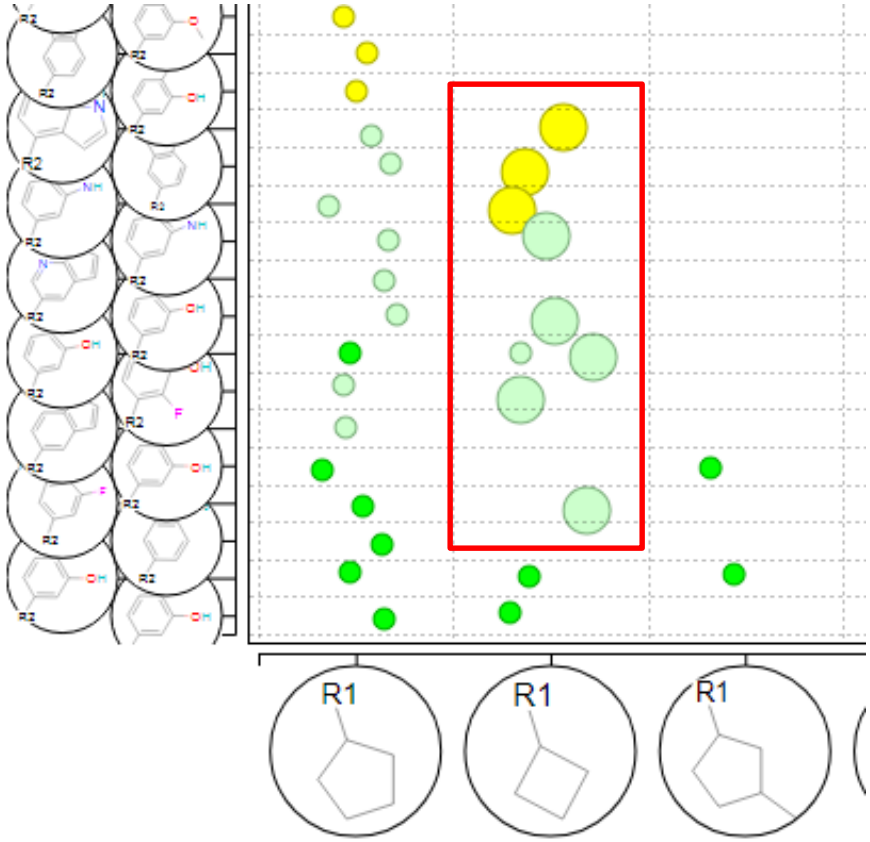
R-Group Activity Contribution Analysis – New Targets for Synthesis

- **Virtual Compounds with Modeled Predicted Activity…**
- **Filtering by this predicted activity for the Virtual Compounds affords good candidates for Synthesis**



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