

Chemistry/NIBR
Shanghai

A Practical View of Structure Activity Relationship (SAR) Analysis in Novartis Shanghai

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Symposium on Streamlining Drug Discovery,
Optibrium, The British Center, Shanghai

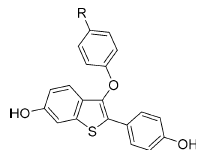
May 31 2018



NIBR in Shanghai, China

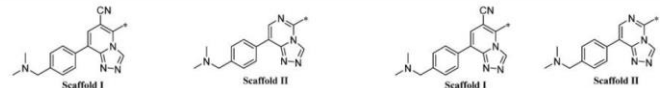
At the Forefront of Novartis Drug Discovery





cmpd.	R	solubility at pH 6.8 (mM)	ERα transcription IC ₅₀ (nM)	% ERα remaining	ERα degradation IC ₅₀ (nM)
16		0.34	748	41	26
17		> 1	457	58	31
35e		<0.005	40	48	n.d. ^a
35a		<0.005	53	40	58
35e		<0.005	10	45	1
35d		0.011	55		
37		0.19	219		
38		n.d. ^a	1	39	60
39		n.d. ^a	3	33	34
19		<0.005	53	39	11
18		0.009	125	47	17

cmpd.	Ar	ERα transcription IC ₅₀ (nM)	% ERα remaining
45		7,750	26
42a		1,270	27
42b		1,030	37
42c		5,020	35



R ₁	Cmpd	BioChem (IC ₅₀ , μM) ^a	Cmpd	BioChem (IC ₅₀ , μM) ^a	R ₁	Cmpd	BioChem (IC ₅₀ , μM) ^a	Cmpd	BioChem (IC ₅₀ , μM) ^a	
		10a	0.013	10b	0.013		35a	0.51	35b	0.15
		30b	0.093		36a	2.22	36b	12.4		
		31a	0.009	31b	0.019		37a	21.8	37b	0.049
		32a	0.15	32b	0.29		38a	2.34	38b	0.053
		33a	0.069	33b	0.77		39a	21.8	39b	0.049
		34a	0.069	34b	0.13		40a	14.9	40b	0.094

R-groups or Linkers

Analysis endpoints

- Enzymatic assay
- Cellular assay
- Selectivity
- Solubility
- Permeability
- H(M/R)LM
- TDI
- DDI
- hERG binding
- Off target panel

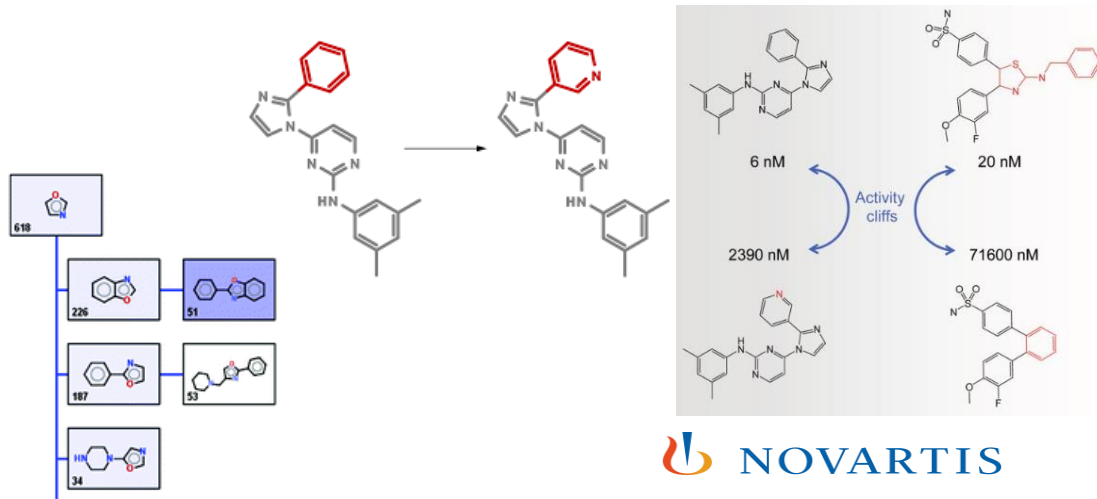
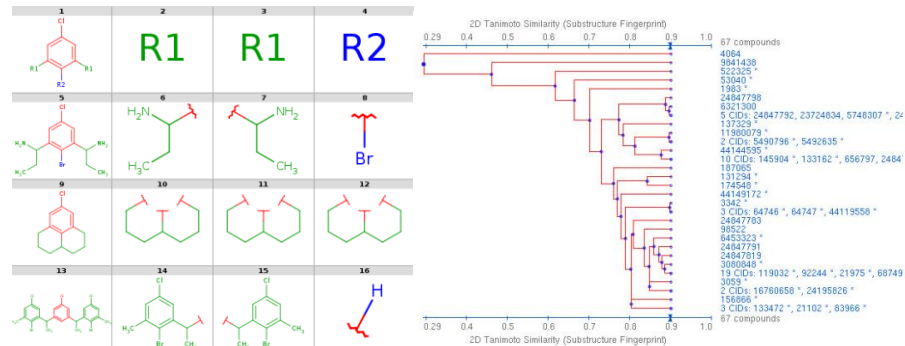
**Categorical/Numerical
value**

**Better with smaller or
bigger value**

**Comparison with log
value**

Optional methods

- R-group decomposition
- Structure clustering
- Matched molecular pairs
- Activity cliffs
- Similarity matrix
- Scaffold tree



Available tools

1. ICM Molsoft (FOCUS)



2. Tibco Spotfire



3. StarDrop



4. Instant Jchem



5. Schrodinger



6. MOE



7. Cresset



8. KNIME



9. Various internal developed informatics tools & integrations

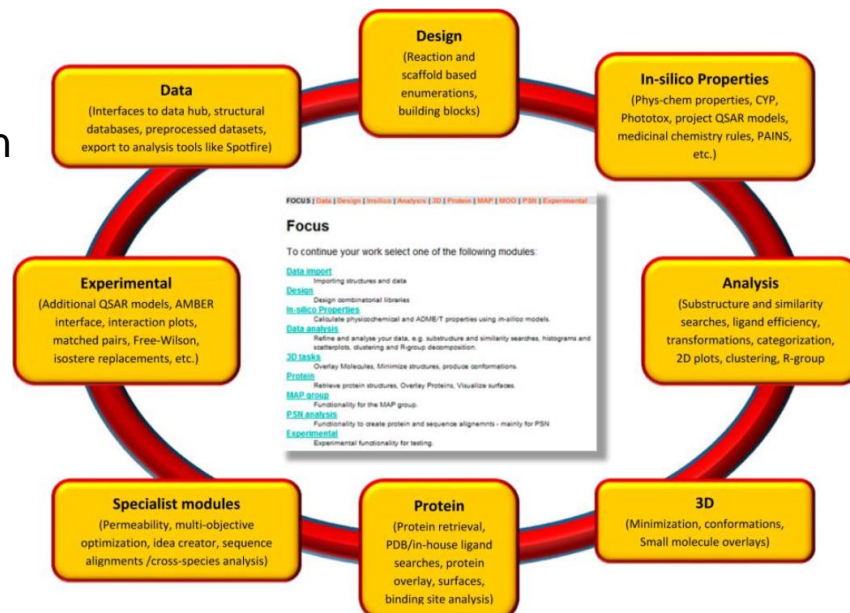
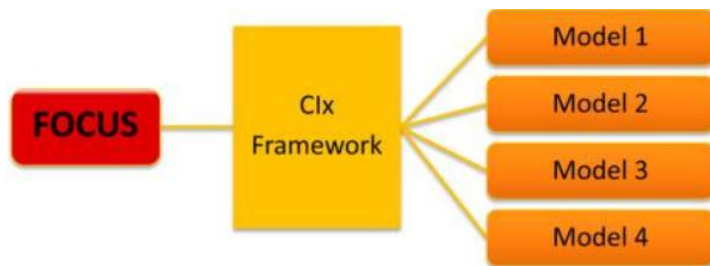


FOCUS Global Communication and Modeling Platform for Medicinal Chemists



FOCUS
Desktop app

- Customized based on MolSoft's ICM software
- An HTML page with set of scripts to:
 - Simplify internal ICM operations
 - Talk to internal data storage and calculation engines



Focus using scenarios

- Quick structure clustering (w/ 2D structure and/or properties)
- Similarity/substructure search (vendor and in-house structures)
- pKa, logD, hERG, PAMPA, solubility, clearance, TDI, Cyp predictions
- Synonym/structure convention (commercial, in-house identifiers)
- Structure annotation (PAINS, QED, Shape analysis, CNS MPO(multiparameter optimization) etc.)
- Library enumeration from reaction or scaffold (and reagent convention)
- R group decomposition

2D tasks

- LMW conformation and overlay
- Protein binding site analysis
- 3D ligand editors (quick molecule docking)

3D tasks

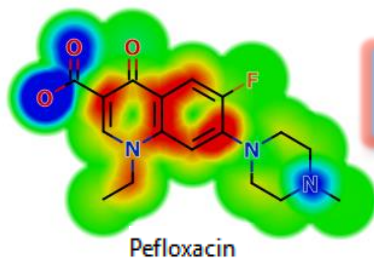
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<https://pubs.acs.org/doi/abs/10.1021/ci500598e>
<https://pubs.acs.org/doi/10.1021/cn100008c>

StarDrop

- Default Scoring/Design/Visualization features
- Customized interface with in-house model and data warehouse

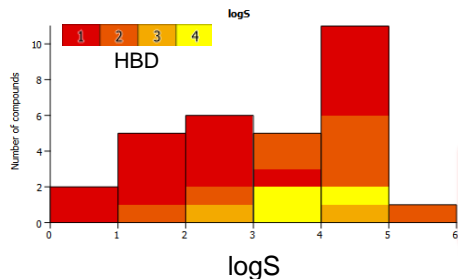
- StarDrop
 - logS
 - logS @ pH7.4
 - logP
 - logD
 - 2C9 pKi
 - hERG pIC50
 - BBB log([brain]:[blood])
 - BBB category
 - HIA category
 - P-gp category
 - 2D6 affinity category
 - PPB90 category
 - MW
 - HBD
 - HBA
 - TPSA
 - Flexibility
 - Rotatable Bonds
 - Legacy models

Quick model

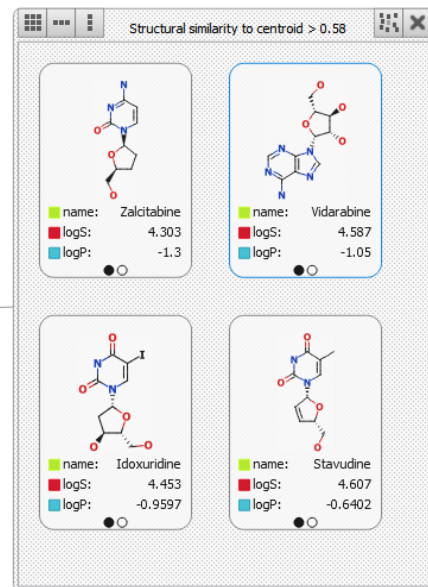
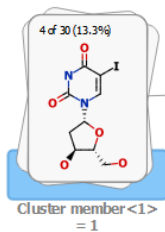


Mol glow

Cluster & card



visualizations



Structural similarity to centroid > 0.58. A window showing four chemical structures with their respective names and properties (logS, logP).

name	logS	logP
Zalcitabine	4.303	-1.3
Vidarabine	4.587	-1.05
Idoxuridine	4.453	-0.9597
Stavudine	4.607	-0.6402

StarDrop using scenarios

2D structure manipulation

- R group decomposition (or linker) !!!
- And different visualization after that
- Molecule clustering and card design for reporting
- Matched pair analysis (focused set with 2k cpds)
- Activity neighborhood (pros and cons of different groups)
- Molecule glowing with desired properties

- Scoring with customized requirements
- Quick model calculation (can be visualized in molecule glowing)
- Hit list triaging/selection

Cpd set operation

One quick example (patent analysis)

• Goals

- Identify the “key” compounds
- Propose possible “hole” of the chemical scaffold
- Example: WO2011142359 (targeting Adiponectin Receptor 2)

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局



(10) 国際公開番号

WO 2011/142359 A1

(43) 国際公開日

2011年11月17日(17.11.2011)

PCT

(54) Title: SPIRO COMPOUND AND DRUG FOR ACTIVATING ADIPONECTIN RECEPTOR

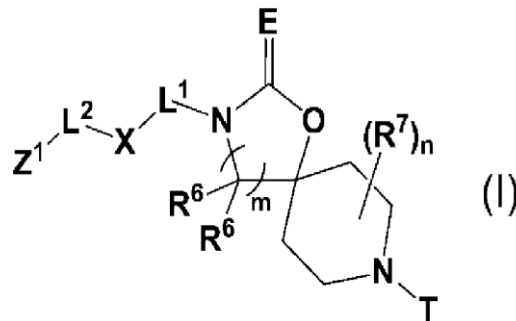
(54) 発明の名称: スピロ化合物及びアディポネクチン受容体活性化薬

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A61K 31/4545 (2006.01) A61P 3/04 (2006.01)
A61K 31/4725 (2006.01) A61P 3/10 (2006.01)
A61K 31/496 (2006.01) A61P 9/10 (2006.01)
A61K 31/497 (2006.01) A61P 35/00 (2006.01)
A61K 31/506 (2006.01) A61P 43/00 (2006.01)
A61K 31/5377 (2006.01) C07D 519/00 (2006.01)
A61K 31/541 (2006.01)

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Activities from PatBase and GOSTAR



Global Online Structure Activity Relationship Database

Family: [Family Explorer](#)

Publication number	Publication date	Application number	Application date	Links
TW201211053 A	20120316	TW20110116426	20110510	<input type="checkbox"/>
WO11142359 A1	20111117	WO2011JP60769	20110510	<input type="checkbox"/>

Publication number WO2011142359 A1
Publication type Application
Application number PCT/JP2011/060769
Publication date Nov 17, 2011
Filing date May 10, 2011
Priority date May 10, 2010
Inventors [Satoshi Nakano, 25 More](#) »
Applicant [Nissan Chemical Industries, Ltd., 日産化学工業株式会社](#)
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[Legal Events](#) (5)

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


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from table_similar_patents
where similar_patents ilike '%142359%' )
select activity_type, activity_prefix,
activity_value, activity_uom, gvk_id
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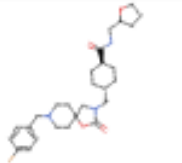
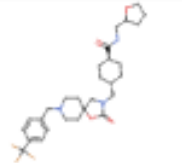
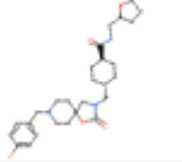
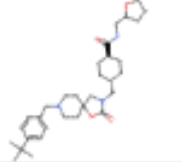
	ECR50	=	0.64	uM
	ECR50	=	0.76	uM

Quick view from StarDrop

- Matched pair and activity cliff

From	To	Count	Δ activity
		27	-1.635
		27	-0.94
	H	21	-0.5867
H		20	-0.538

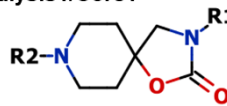
Four matched pairs were found with more than 20 occurrences

compound1	compound2	Transfo	Δ activity_value
		342	-9.68
		1084	-9.6

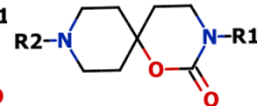
Most attractive activity change (activity cliffs)

Cores and R-groups

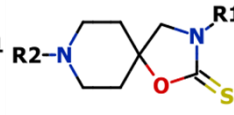
Analysis1/Core1



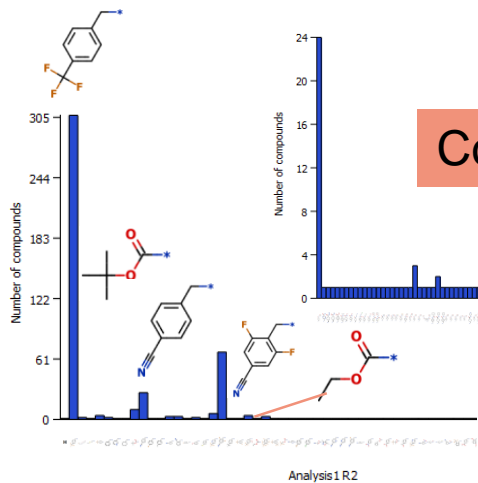
489 structures



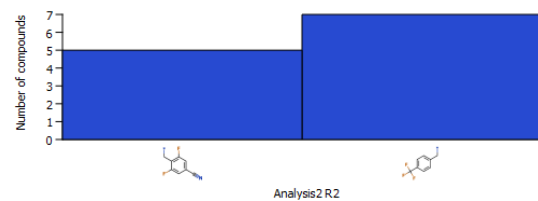
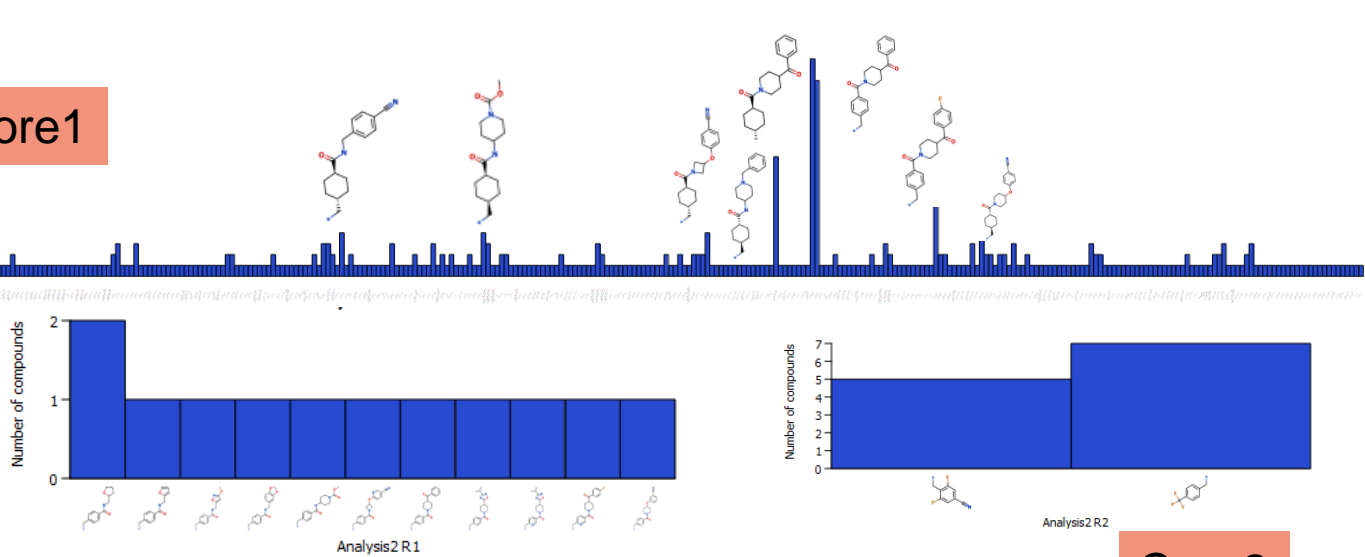
12 structures



4 structures



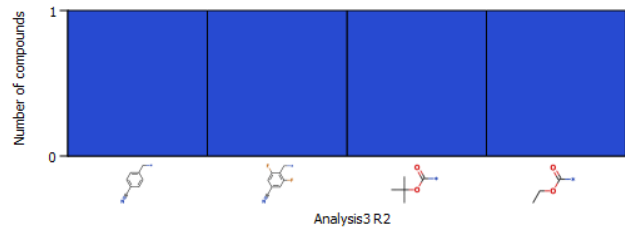
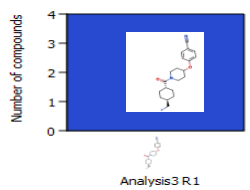
Core1



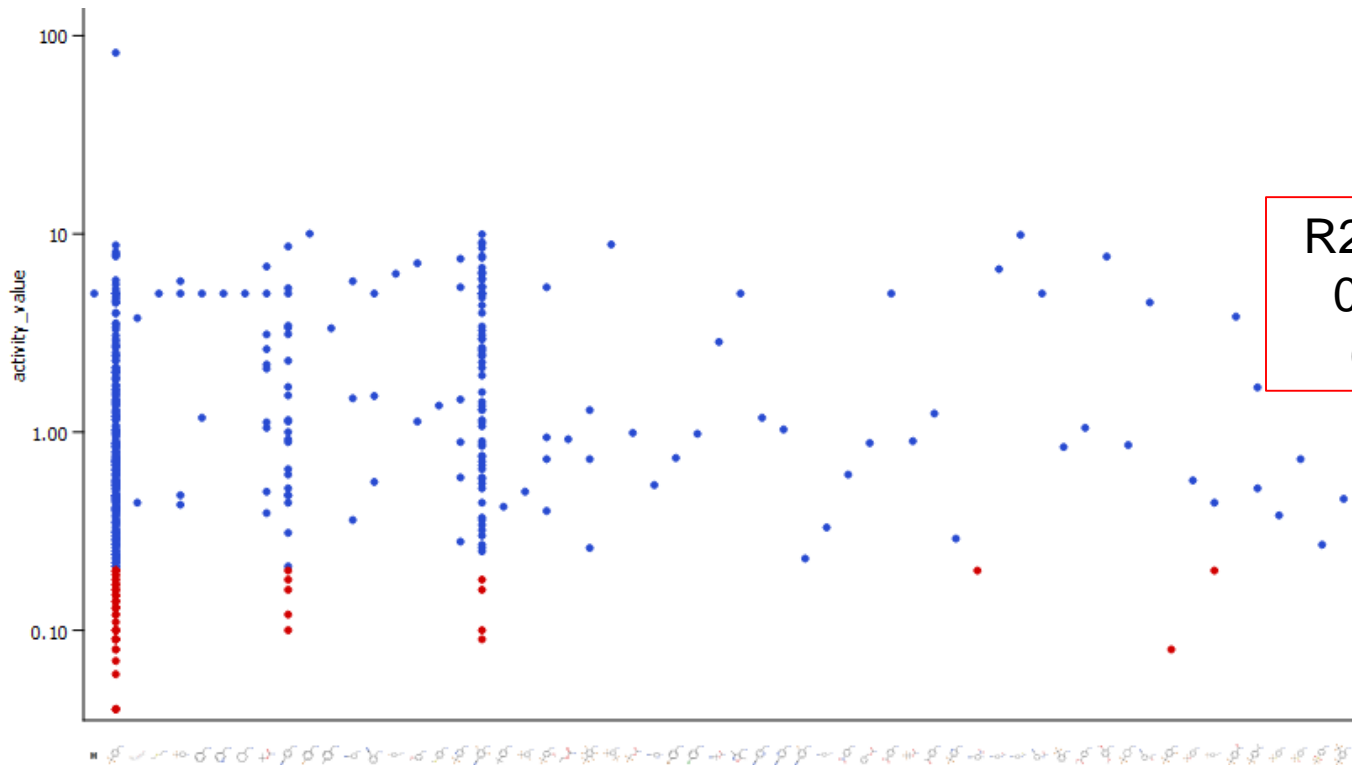
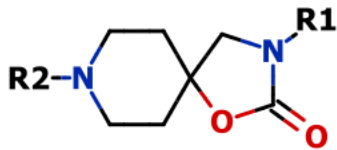
Core1 was focused

Core2

Core3



Core1(C1)

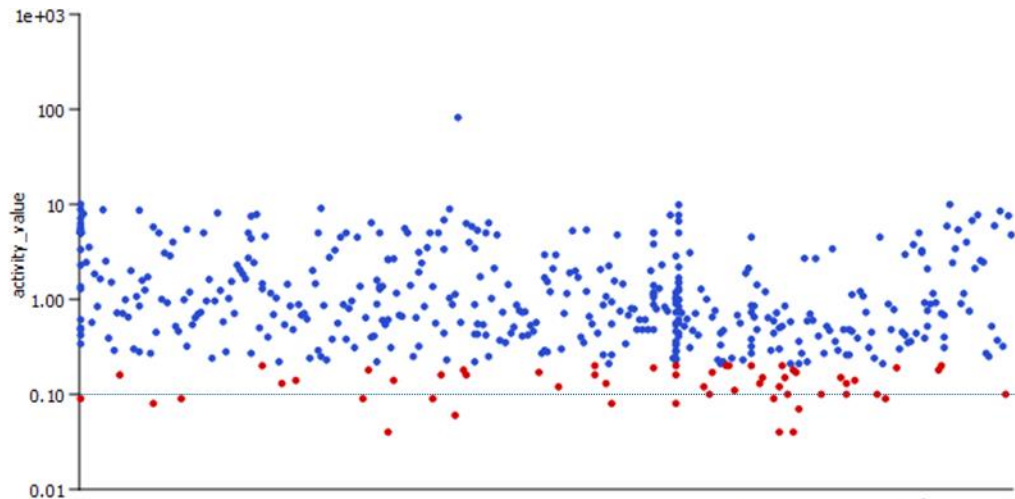
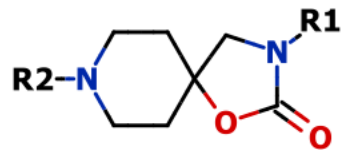


R2 with less than
0.2 uM activity
(few options)

Analysis1R2

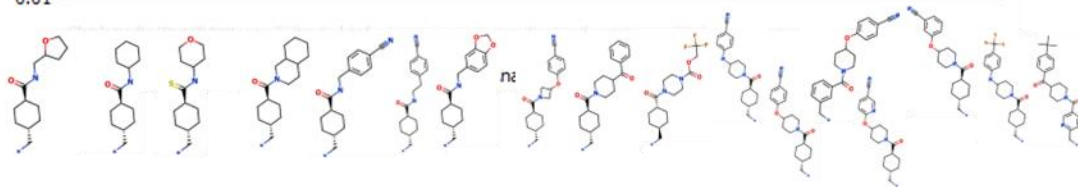
NOVARTIS

R1 from C1

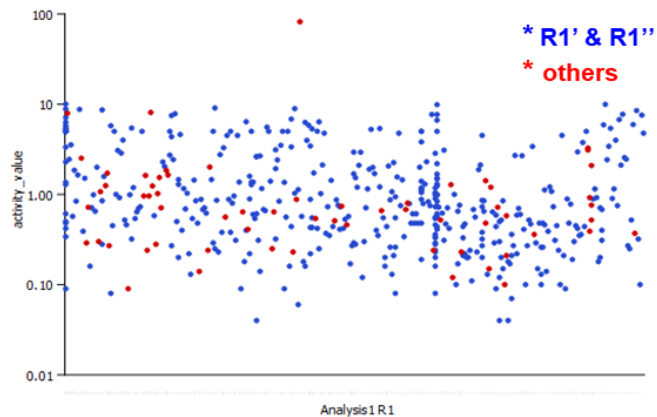


R1 with less than
0.2 uM activity

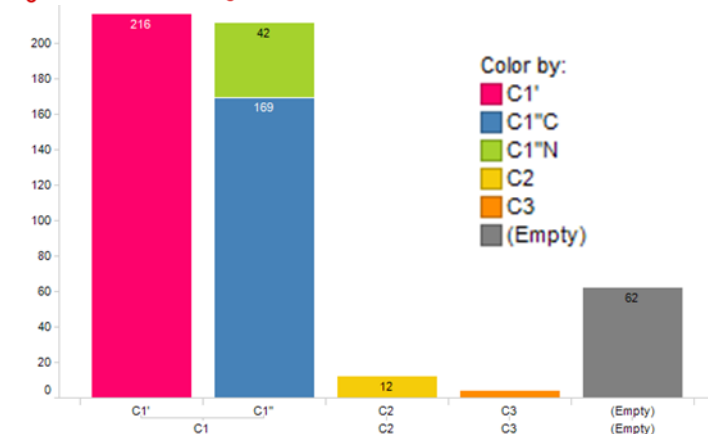
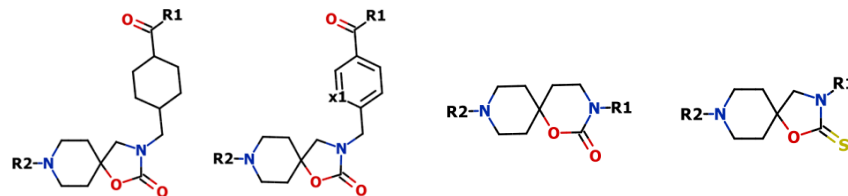
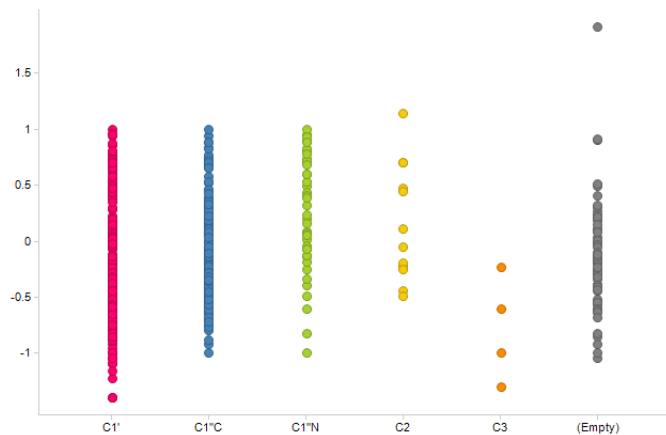
Needs to break down
to smaller pieces



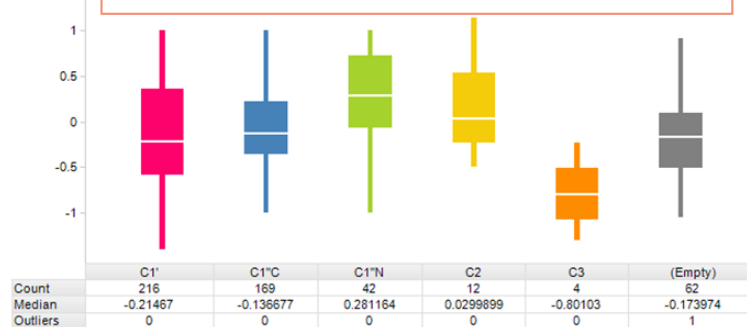
C1' & C1''



No attractive structures was found with <0.1 activity

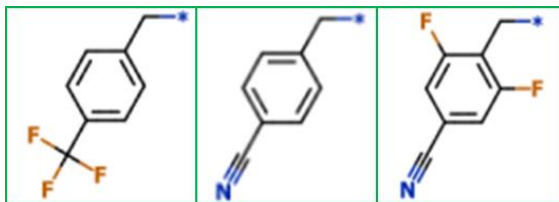


C2 -> C1''N -> C1''C -> C1' -> C3 ??

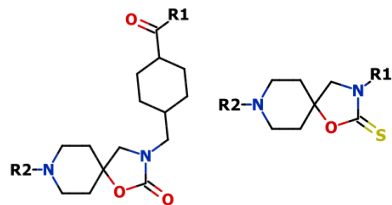
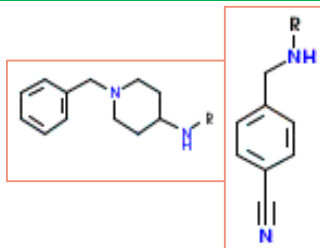
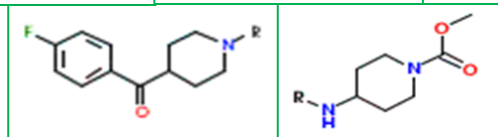
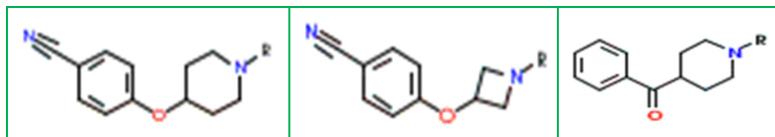


Suggestions

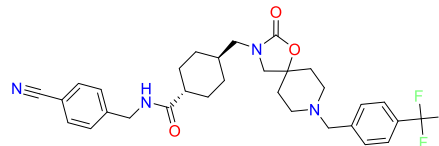
R2-group



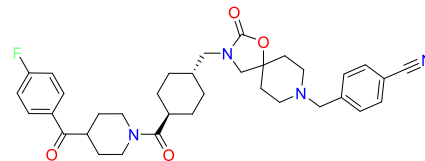
R1-group



Key cpds



Potentials

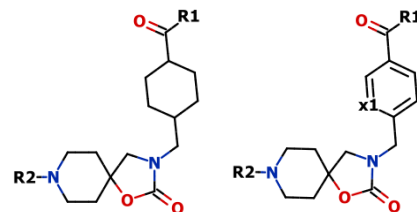


Acknowledgement

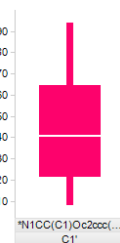
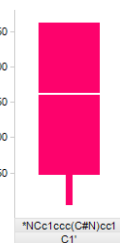
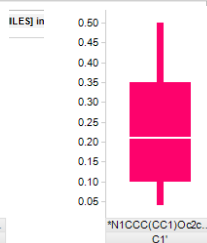
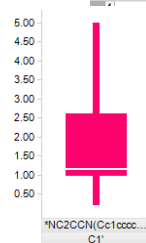
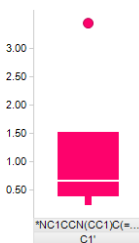
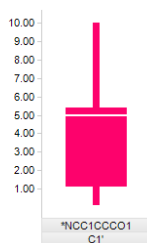
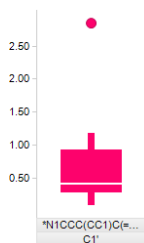
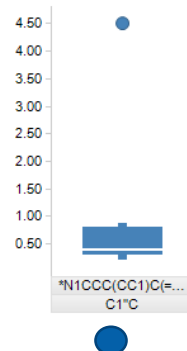
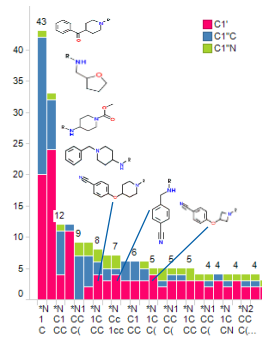
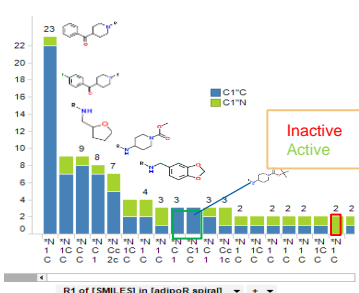
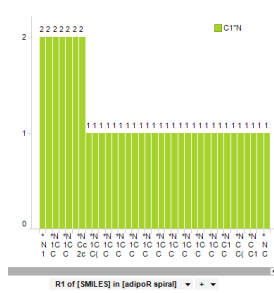
- Chemists @ NIBR Shanghai
- Informatics colleagues from other NIBR site
- Yi Liu @ Shanghai Tech University
- Our vendors who provide those fantastic tools

backup

R1 from C1' & C1''



- C2 -> C1''N -> C1''C -> C1' -> C3



Software	StarDrop	Focus	Schrodinger 2017-2	MOE 2016.08	Data Warrior	Insatant JChem	SpotFire
Analysis Method							
R-Group Decomposition	✓♥	✓	✓	✓♥	✓♥	✓	✓
Automatic Core Scaffold Determination	✗	✗	✓	✓♥	✓♥	✗	✗
Clustering	✓	✓♥	✗	✗	✓	✓	✓
Scaffold Tree	✗	✓♥	✓ Scaffold Decomposition	✓♥	✓ Analysis Scaffold	✓ No tree	✓☹
Matched Molecular Pairs	✓♥	✗	✗	✓♥	✓	✗	✗
Activity Cliff	✗	✗	✓♥	✓♥	✓♥	✓ No License	✓
Structure Activity Landscape Index	✓	✗	✗	✗	✓	✗	✗
Principle Component Analysis	✗	✓	✓	✓	✓	✗	✓