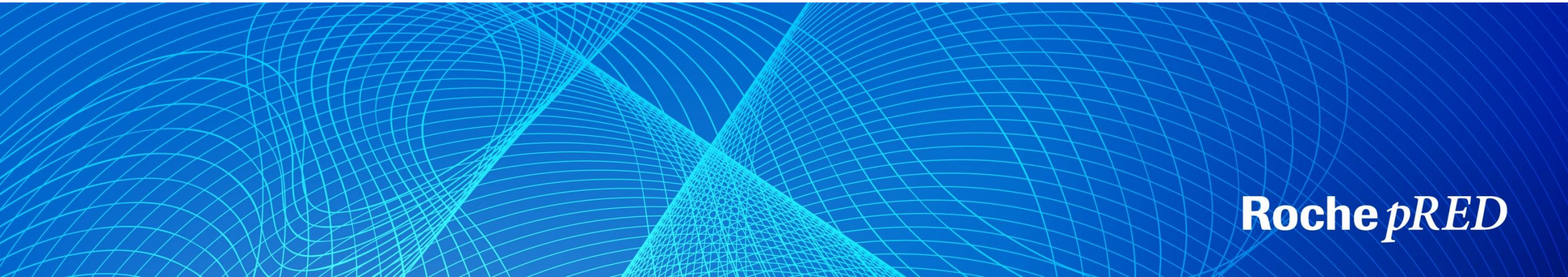
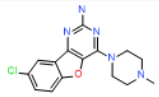
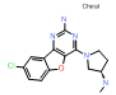
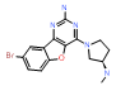
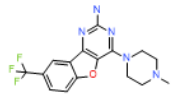
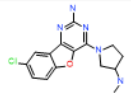
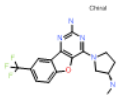
Are You Additive?
SAR Approaches for Small Molecule Drug Discovery

Christian Kramer, F. Hoffmann-La Roche Ltd., Basel



SAR analysis: At the heart of Medicinal Chemistry

Structure <MOLFILE>	CHEMBLID	Histamine H4 Ki (nM)
	CHEMBL1914541	0.10
	CHEMBL1091874	0.40
	CHEMBL1914781	0.70
	CHEMBL1914755	0.80
	CHEMBL1914750	0.90
	CHEMBL1914783	1.00
	CHEMBL1914542	1.10
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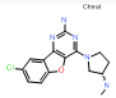
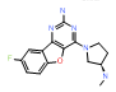
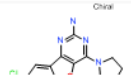
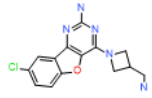
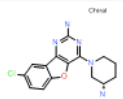
	CHEMBL1091875	2.00
	CHEMBL1914782	2.00
	CHEMBL1914543	2.40

Structure <MOLFILE>	CHEMBLID	Histamine H4 Ki (nM)
	CHEMBL1914547	3.40
	CHEMBL1914745	3.60
	CHEMBL1914746	4.70
	CHEMBL1914548	5.70
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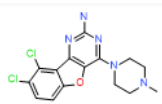
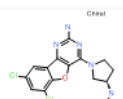
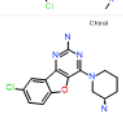
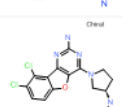
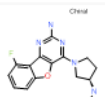
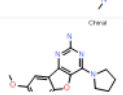
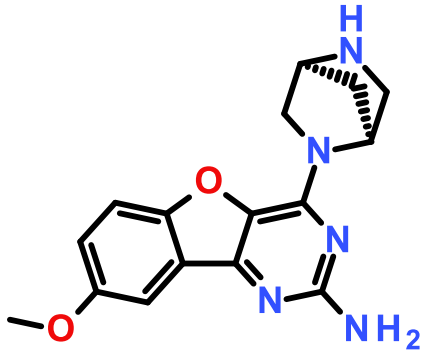
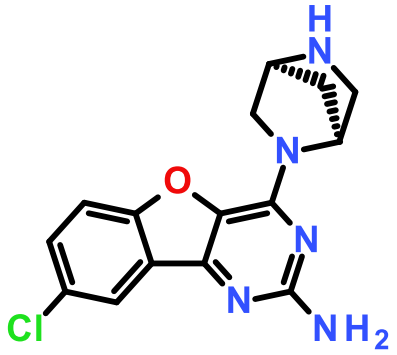
	CHEMBL1914757	7.70
	CHEMBL1914785	8.00
	CHEMBL1914549	9.10
	CHEMBL1914786	10.00
	CHEMBL1914778	10.00
	CHEMBL1914784	11.00

B. M. Savall et al. / Bioorg. Med. Chem. Lett. 21 (2011) 6577–6581

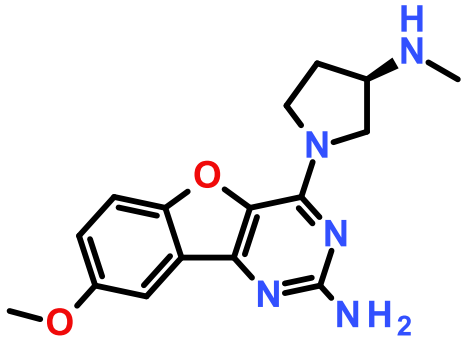
Additivity



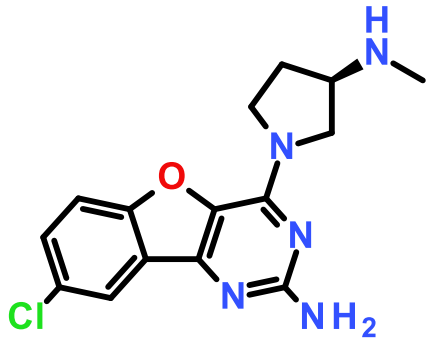
CHEMBL1915035
H4 K_i (nM): 416



CHEMBL1914748
H4 K_i (nM): 26



CHEMBL1914784
H4 K_i (nM): 11



CHEMBL1091874
H4 K_i (nM): 0.4

What is Additivity?

For the same functional group in the same position, you expect the same contribution to binding affinity

Mathematics:

The value of a magnitude corresponding to a whole object is equal to the sum of the values of the magnitudes corresponding to its parts for any division of the object into parts.

$$\mu(A \cup B) = \mu(A) + \mu(B)$$

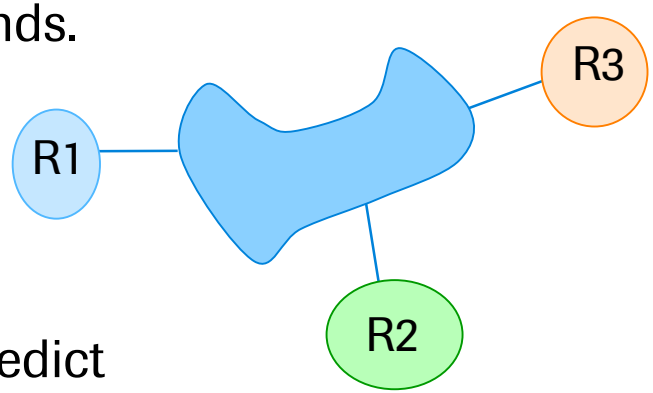
Why do we care about Additivity?

MedChem projects have a **limited number of shots** on goal (1000 – 5000 compounds).

Thought experiment:
Scaffold with three R-groups and n =100 substituents each:

$$N_{combinations} = n_{R1} * n_{R1} * n_{R1} = 100 * 100 * 100 = 1\,000\,000\ compounds$$

Without additivity, one would need to synthesize and test all 1 Mio. compounds.



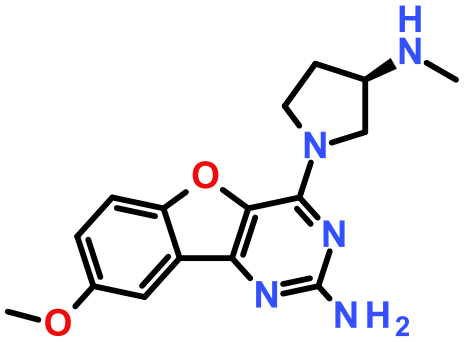
→ Need to understand when SAR is additive and when not

→ Use Additivity to our advantage

This talk is about **MedChem Design Tools** that help understanding and predict SAR based on the Additivity principle.

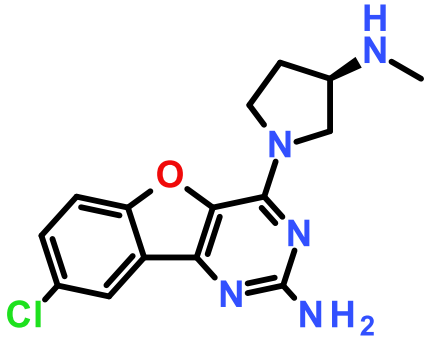
MATCHED MOLECULAR PAIR ANALYSIS

MMP Analysis: Most basic manifestation of Additivity principle



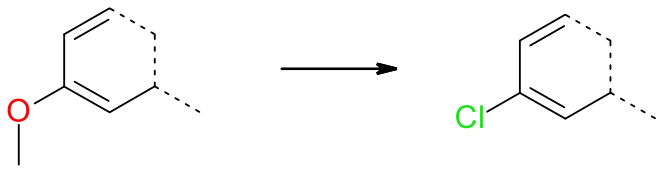
CHEMBL1914784
logD = 0.5

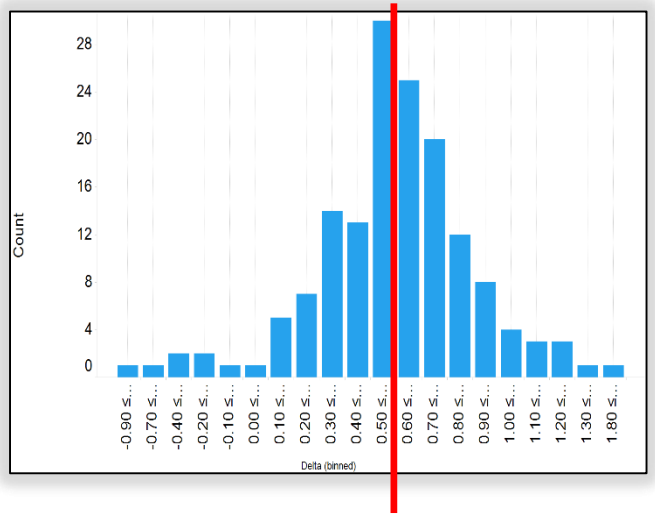
Δ logD = ?



CHEMBL1091874
logD = 0.5 + 0.59 = 1.09

Roche MMP DB



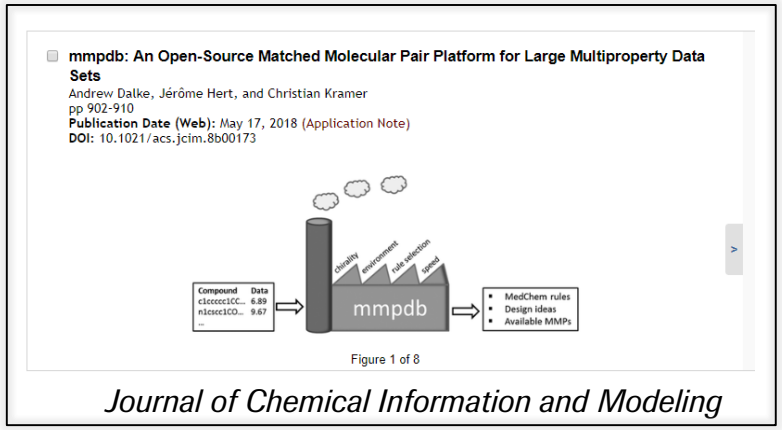


Median = 0.59

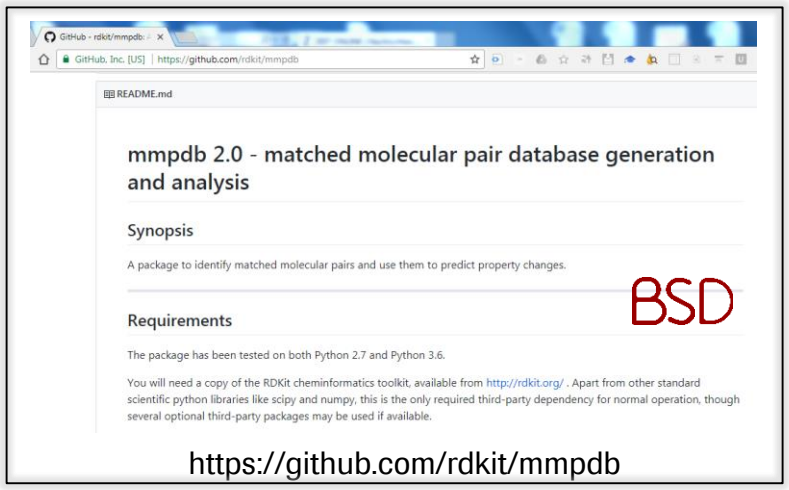
Access to MMP analysis @ Roche

MMP engine MMPDB

public Open-Source MMP toolkit
under active development



Journal of Chemical Information and Modeling



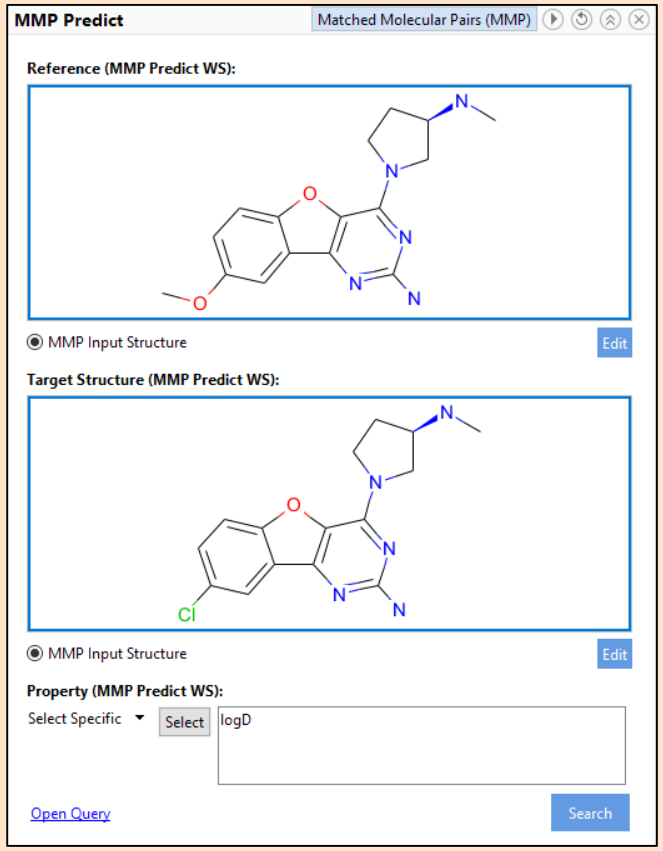
https://github.com/rdkit/mmpdb

MMP GUI

implemented into D360 to give non-Experts easy access

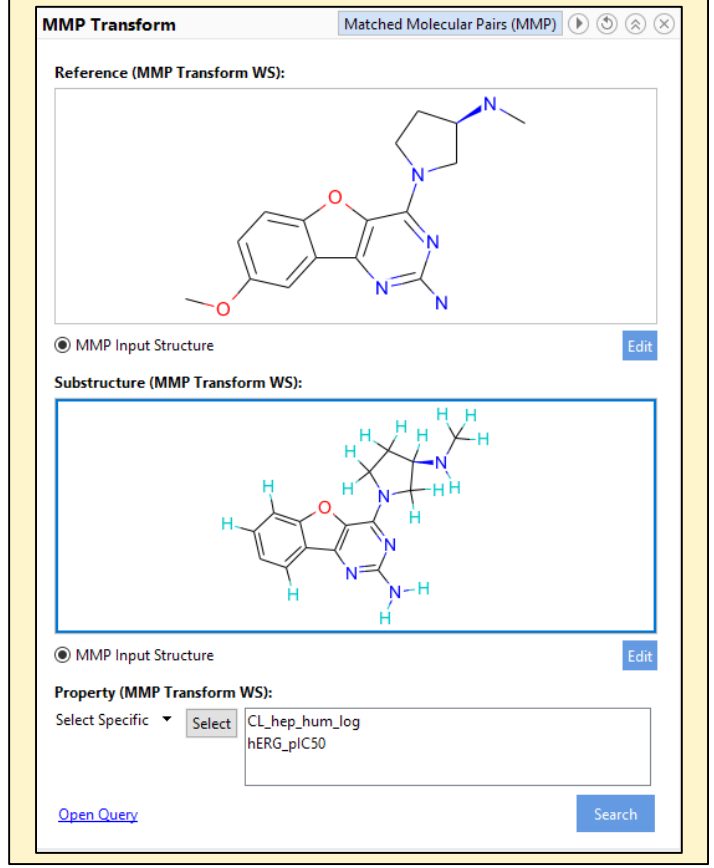
MMP Predict

Analyze pairs for specific transformations



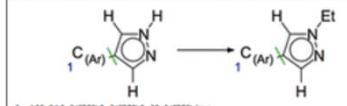
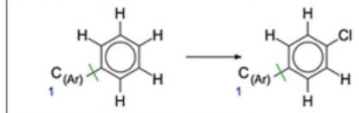
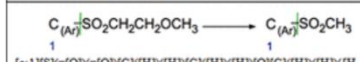
MMP Transform

MMP-Suggestions to solve specific problems

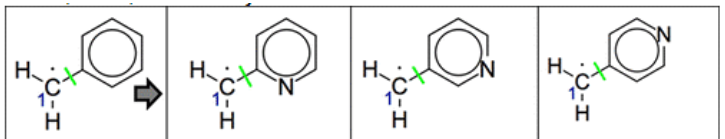


Application of Matched Pairs: PhysChem and ADMET data

Individual rules

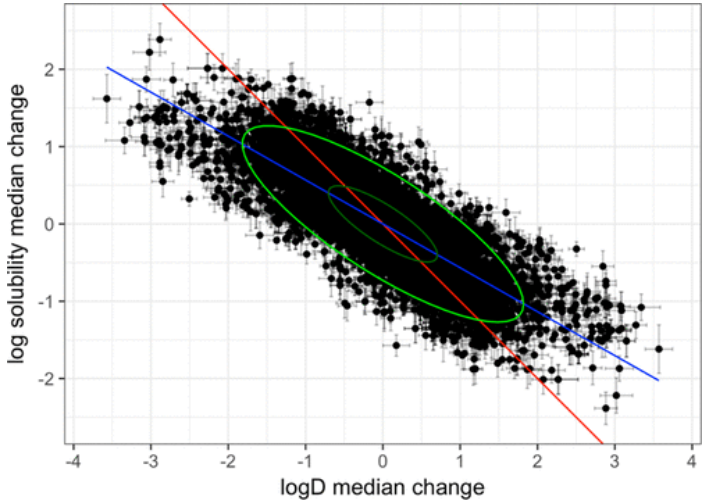
Transformation	Human microsomal Clearance median change ± std (nPairs)	logD median change ± std (nPairs)
 [c:1][c]1[c][H][n][H][n][c][H]1>> [c:1][c]1[c][H][n][n][c][H]1)[C][H][H][C][H][H][H]	-0.34±0.71 (13)	0.35±0.45 (15)
 [c:1][c]1[c][H][c][H][c][H][c][H][c][H]1>> [c:1][c]1[c][H][c][H][c][c][H][c][H]1)[Cl]	-0.32±0.51 (53)	0.7±0.74 (117)
 [c:1][S](=[O])(=[O])[C][H][H][C][H][H][O][C][H][H][H][H]>> [c:1][S](=[O])(=[O])[C][H][H][H]	-0.59±0.38 (14)	0.0±0.11 (19)

Characterize Fragments



Property	Δ ± std (nPairs)	Δ ± std (nPairs)	Δ ± std (nPairs)
logD*	-0.64 ± 0.70 (75)	-0.92 ± 0.72 (70)	-0.87 ± 0.79 (54)
Solubility	1.00 ± 0.75 (98)	0.84 ± 0.80 (98)	0.79 ± 0.81 (77)
hERG	-0.39 ± 0.47 (57)	-0.36 ± 0.44 (24)	0.12 ± 0.54 (37)
PPB human*	0.31 ± 0.42 (32)	0.73 ± 0.42 (37)	0.79 ± 0.38 (17)
human Mic Clearance	-0.11 ± 0.46 (43)*	-0.07 ± 0.57 (90)	Insufficient examples
human Hep Clearance	-0.28 ± 0.30 (8)	-0.14 ± 0.13 (5)	-0.04 ± 0.30 (7)
CYP3A4 inhibition	-0.31 ± 0.49 (22)	0.65 ± 0.54 (20)	0.96 ±0.67 (21)
CYP2D6 inhibition	-0.41 ± 0.51 (8)	0.49 ± 0.52 (7)	1.08 ± 0.66 (8)
CYP2C19 inhibition	-0.69 ± 0.74 (3)	0.01 ± 1.11 (8)	0.74 ± 0.91 (6)

General correlations



+ suggest compounds to solve problems, clean-up data, identify outliers etc.

C. Kramer, A. Ting, H. Zheng, J. Hert, T. Schindler, M. Stahl, G. Robb, J. J. Crawford, J. Blaney, S. Montague, A. G. Leach, A. G. Dossetter, E. J. Griffen. Learning Medicinal Chemistry Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Rules from Cross-Company Matched Molecular Pairs Analysis (MMPA) *J. Med. Chem.*, **2018**, *61*, 3277–3292. DOI: 10.1021/acs.jmedchem.7b00935

FREE-WILSON ANALYSIS

Free-Wilson analysis

Journal of Medicinal Chemistry

VOLUME 7, NUMBER 4 JULY 6, 1964

A Mathematical Contribution to Structure–Activity Studies

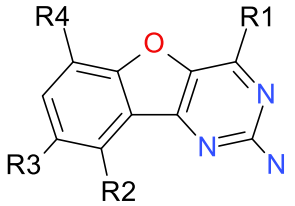
SPENCER M. FREE, JR., AND JAMES W. WILSON

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

Received February 4, 1964

A mathematical technique is suggested as a means of describing structure–activity relationships of a series of chemical analogs. The data requirements included specific side chain arrangements and performance characteristics of all analogs tested. Two examples illustrate the use of the additive mathematical model where the performance characteristics are measures of biological activity. The results rank the structural changes per position by estimating the amount of biological response attributed to each change. The estimates are both positive and negative. Several uses for the mathematical solution are suggested.

Approach

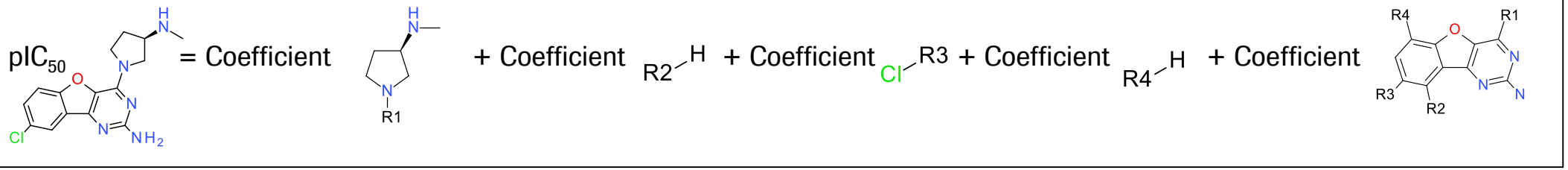


1.) Fragment Dataset:

2.) Fit linear equation system with R-groups as independent factors

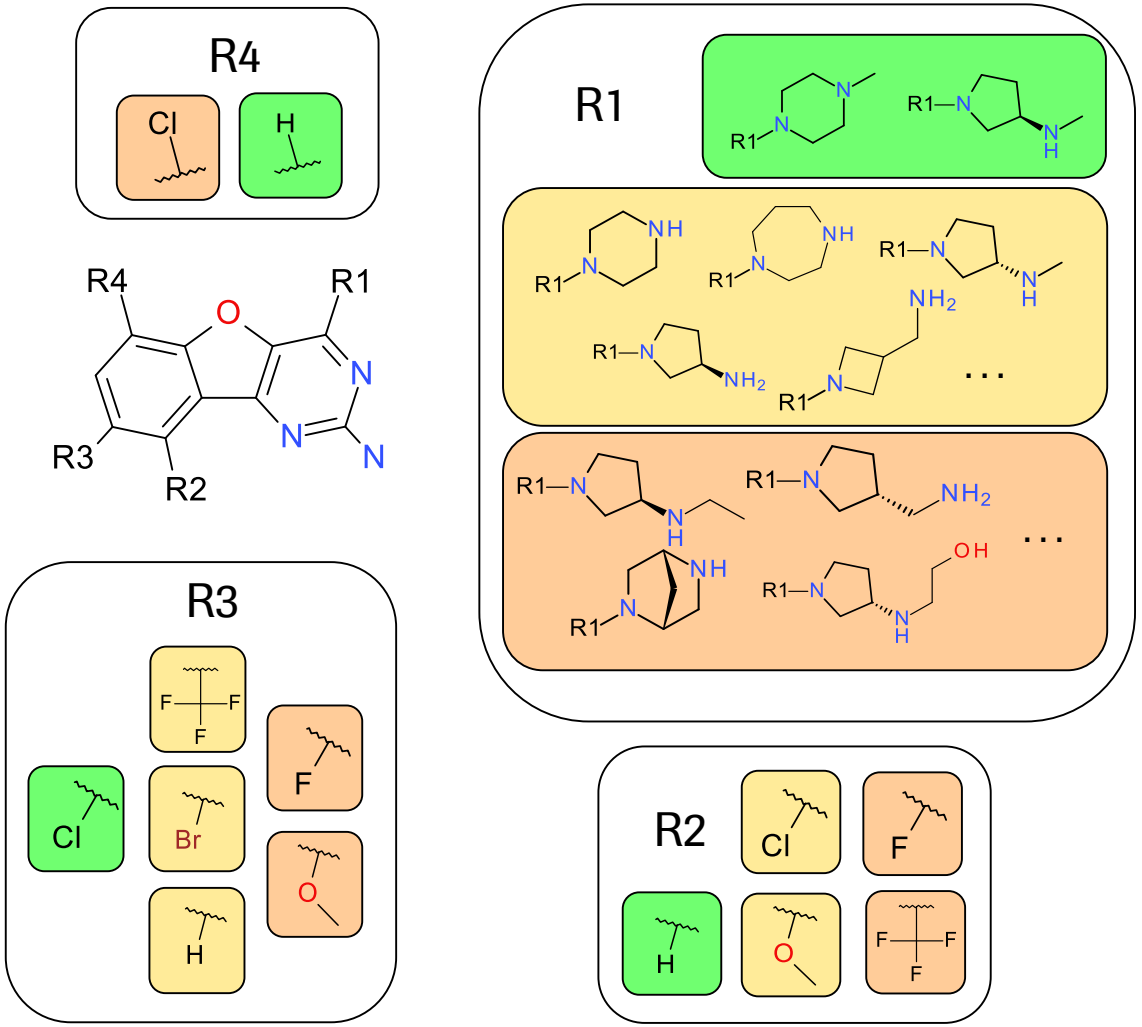
3.) Interpret Coefficients as functional group contributions at specific location on scaffold (solves localization problem for on-target MMP)

Advanced Free-Wilson for SAR analysis
Fit different scaffold with overlapping R-group assignments in one model to test for SAR transferability.

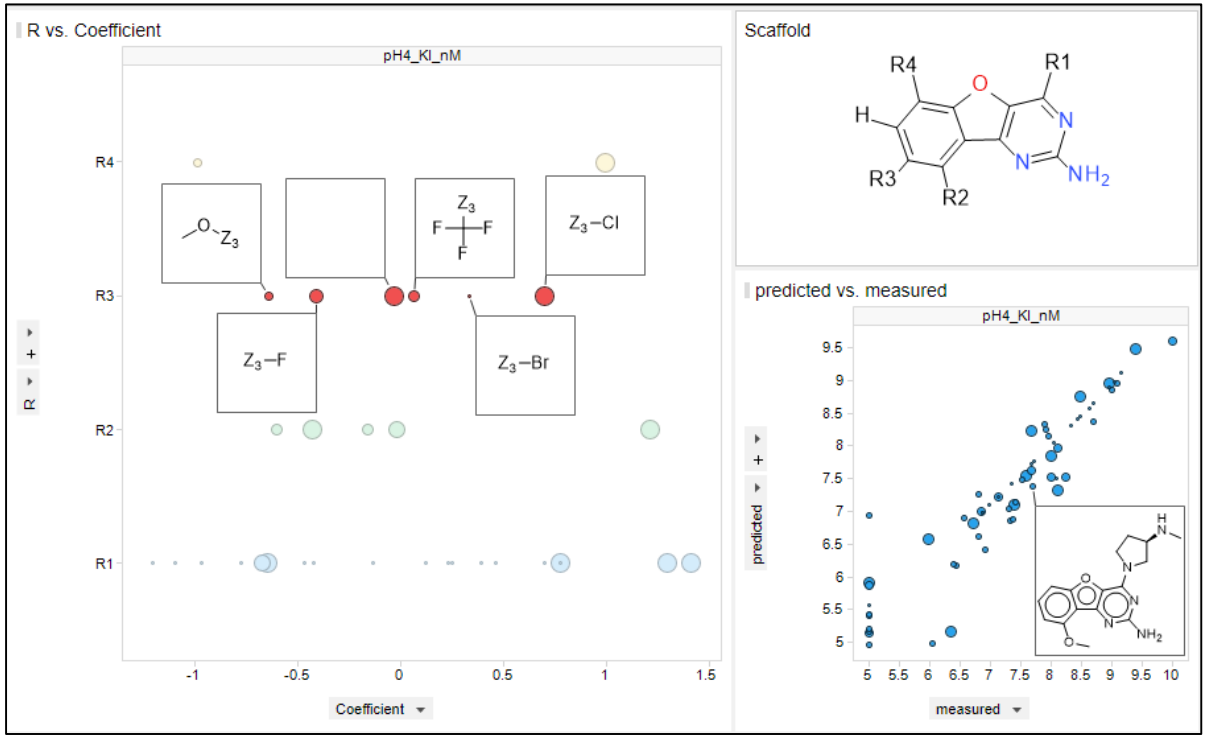


MedChem SAR slides vs Free-Wilson analysis

Classic MedChem SAR analysis

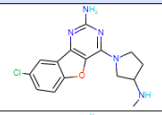
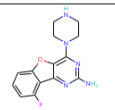
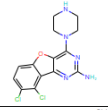
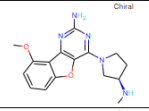
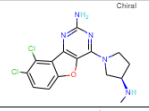
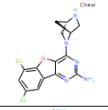
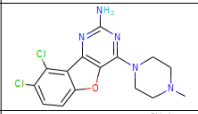
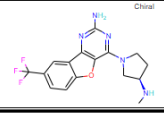


Free Wilson Analysis



Roche Free-Wilson Implementation

D360 Activity Dataset

		SRN	Structure	H4_KI_nM
1:	☐	CHEMBL1914750		0.900
2:	☐	CHEMBL1914769		145.000
3:	☐	CHEMBL1914774		7.700
4:	☐	CHEMBL1914780		20.000
5:	☐	CHEMBL1914786		10.000
6:	☐	CHEMBL1915036		10000.000
7:	☐	CHEMBL1914757		7.700
8:	☐	CHEMBL1914783		1.000

Dataset Split

Fit Free-Wilson

Visualize

one core
one series

D360

D360/ SpotFire

Basic Free-Wilson

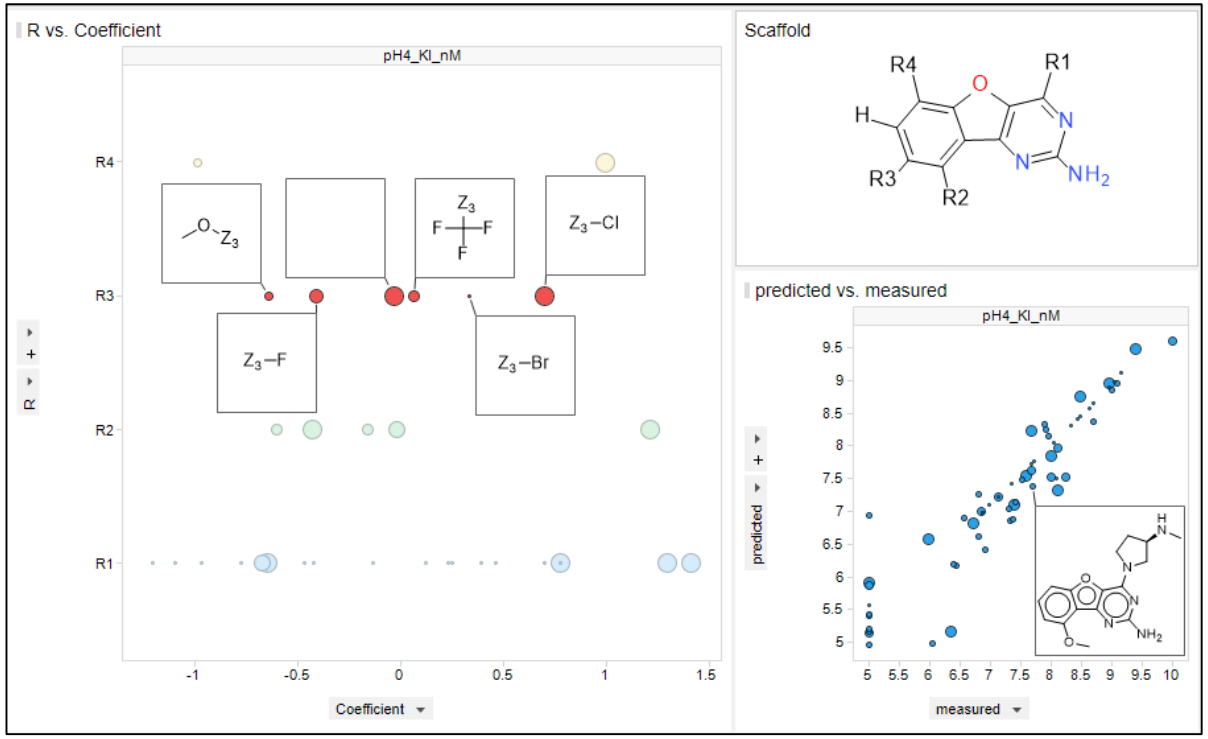
several cores
and/or several series

Python script

SpotFire

CADD Expert Free-Wilson

Usage example



Automated SAR analysis within seconds

Extension1: Test transferability of SAR on specific Rgroups between Series and Cores

Extension2: Enable extrapolation by R-group specific QSAR models (on Free-Wilson coefficients)

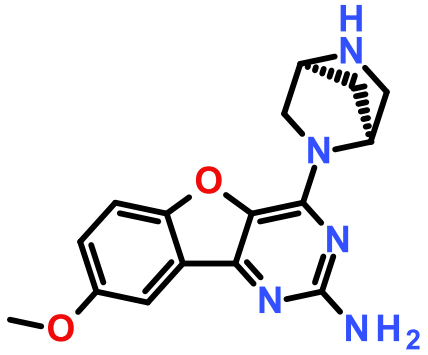
8 columns from H4-ChEMBL1919838_suggestions

Structure	Property	Predicte…	CORE	R1	R2	R3	R4
	pH4_KI_nM	9.24				Z_3–Br	[Z4]H
	pH4_KI_nM	8.86					[Z4]H
	pH4_KI_nM	8.60				Z_3–Br	[Z4]H
	pH4_KI_nM	8.60				Z_3–Br	[Z4]H
	pH4_KI_nM	8.52				Z_3–Br	[Z4]H

Best combinations missing

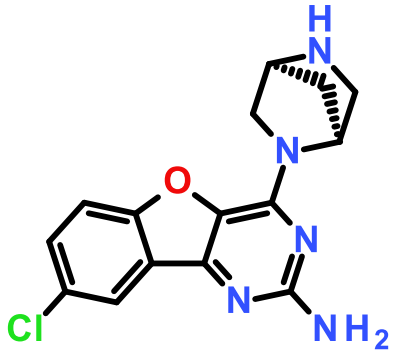
NONADDITIVITY ANALYSIS

How to quantify Nonadditivity



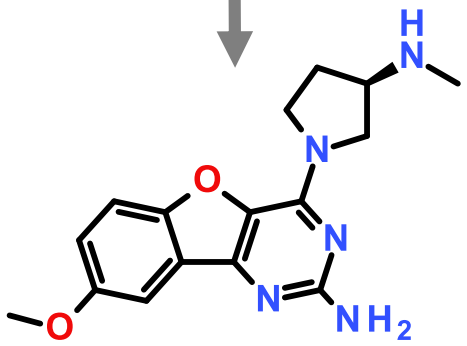
CHEMBL1915035
H4 K_i (nM): 416
pK_i = 6.38

ΔpK_i = 1.21



CHEMBL1914748
H4 K_i (nM): 26
pK_i = 7.59

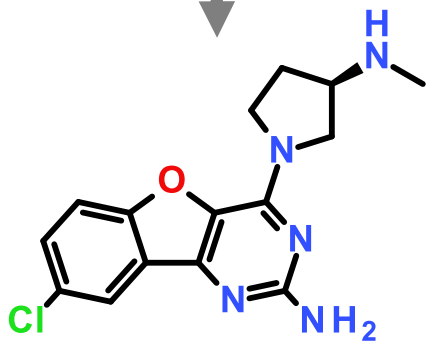
ΔpK_i = 1.58



CHEMBL1914784
H4 K_i (nM): 11
pK_i = 7.96

ΔpK_i = 1.44

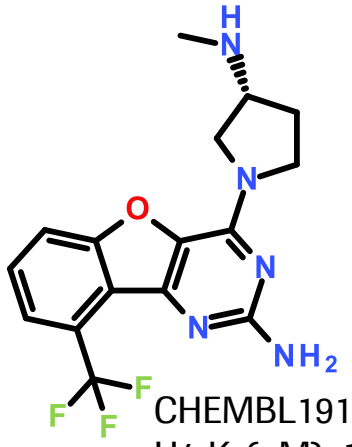
ΔpK_i = 1.81



CHEMBL1091874
H4 K_i (nM): 0.4
pK_i = 9.40

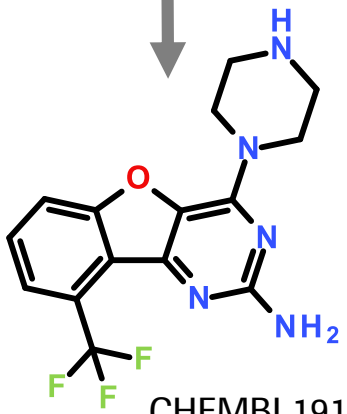
Nonadditivity
$= \Delta\Delta pK_i$
= 1.44 – 1.21
= 1.81 – 1.58
= 0.23

How to quantify Nonadditivity



CHEMBL1914779
H4 K_i (nM): 10 000
pK_i = 5

ΔpK_i = 1.92

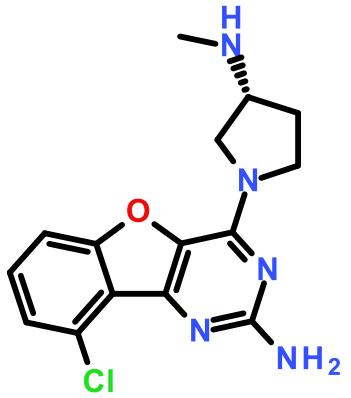


CHEMBL1914770
H4 K_i (nM): 121
pK_i = 6.92

ΔpK_i = 2.4

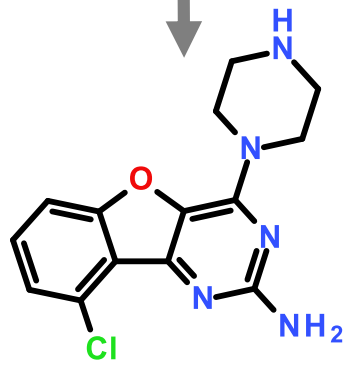
ΔpK_i = -0.94

Nonadditivity
= $\Delta\Delta pK_i$
= 2.4 – (-0.94)
= 1.92 – (-1.42)
= 3.34



CHEMBL1914777
H4 K_i (nM): 40
pK_i = 7.4

ΔpK_i = -1.42



CHEMBL1914768
H4 K_i (nM): 1049
pK_i = 5.98

Reasons for Nonadditivity

Conformational changes

Intramolecular H-bonds,[1]
protein side-chain movements[2]

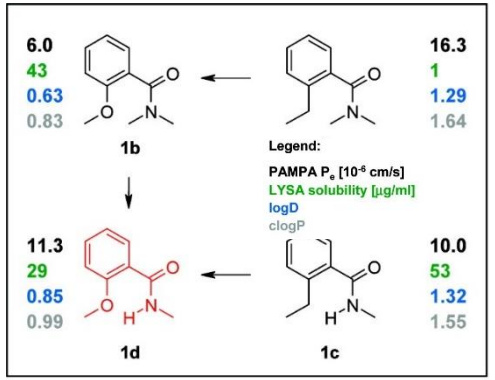
Ligand flips in binding site[3]

Substituent competition[3]

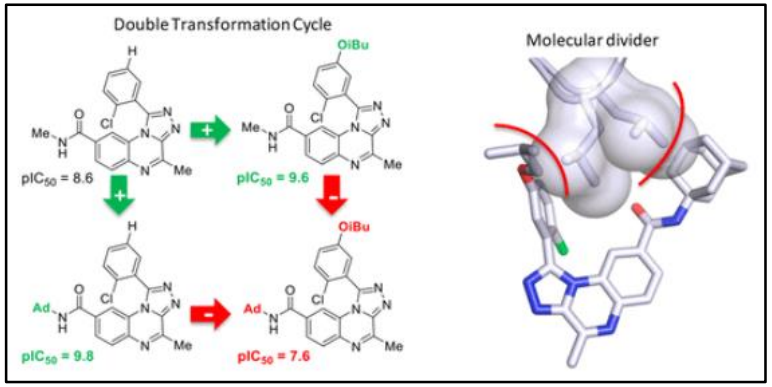
Uneven Enthalpy-Entropy compensation

Fixation of side chains[4]
Adaptive Water Networks
(see work from Klebe group)

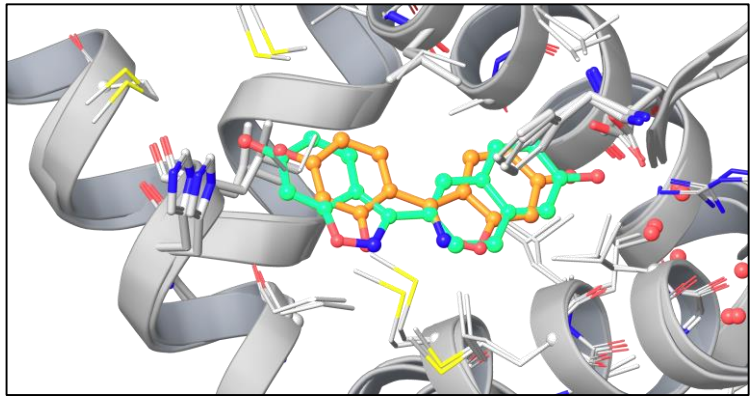
Experimental errors and assay noise

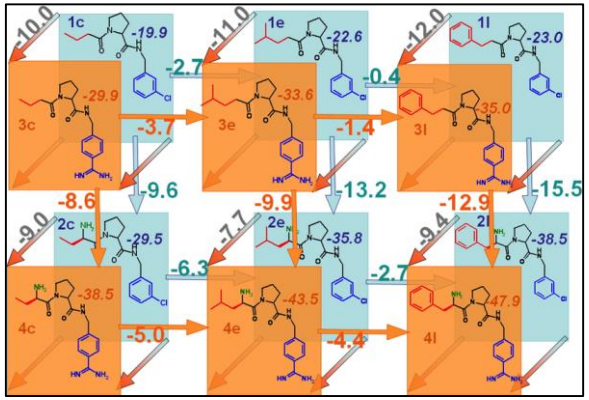


[1]



[2]


[3]



[4]

[1] B. Kuhn, P. Mohr, M. Stahl. Intramolecular Hydrogen Bonding in Medicinal Chemistry. *J. Med. Chem.*, **2010**, *53*, 2601–2611.
[2] L. Gomex et al. Mathematical and Structural Characterization of Strong Nonadditive Structure–Activity Relationship Caused by Protein Conformational Changes. *J. Med. Chem.*, **2018**, *61*, 7754–7766.
[3] C. Kramer, J.E. Fuchs, K.R. Liedl. Strong Nonadditivity as a Key Structure–Activity Relationship Feature: Distinguishing Structural Changes from Assay Artifacts. *J. Chem. Inf. Model.*, **2015**, *55,* 483–494.
[4] Baum, B.; Muley, L.; Smolinski, M.; Heine, A.; Hangauer, D.; Klebe, G. Non-additivity of Functional Group Contributions in Protein–Ligand Binding: A Comprehensive Study by Crystallography and Isothermal Titration Calorimetry. *J. Mol. Biol.* **2010**, *397*, 1042–1054.

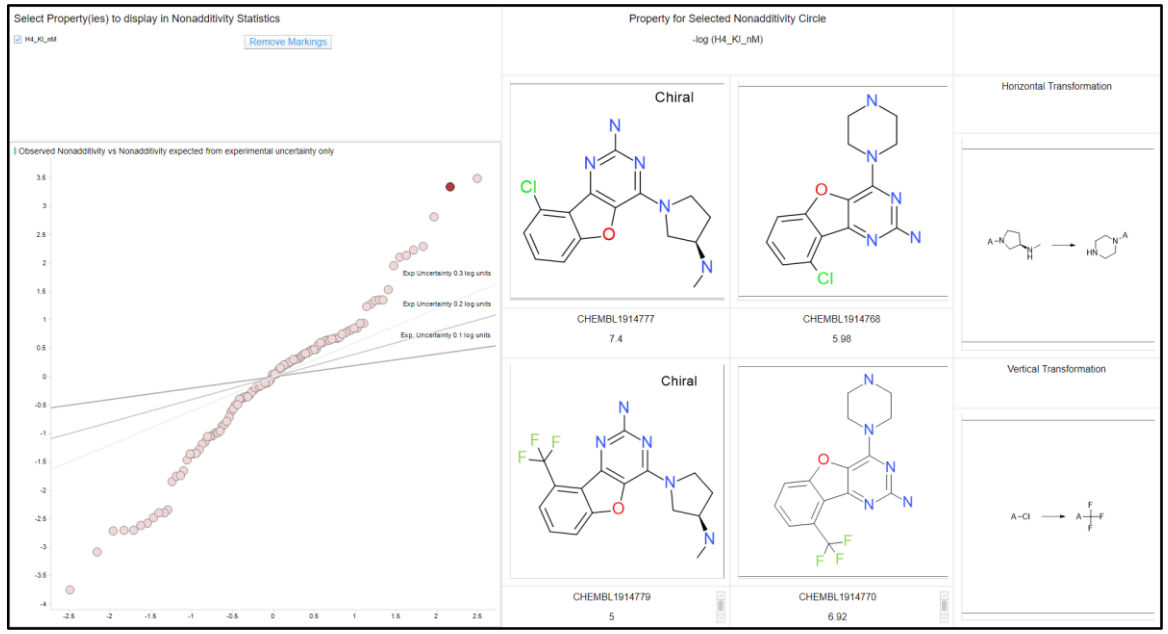
Statistical Nonadditivity analysis

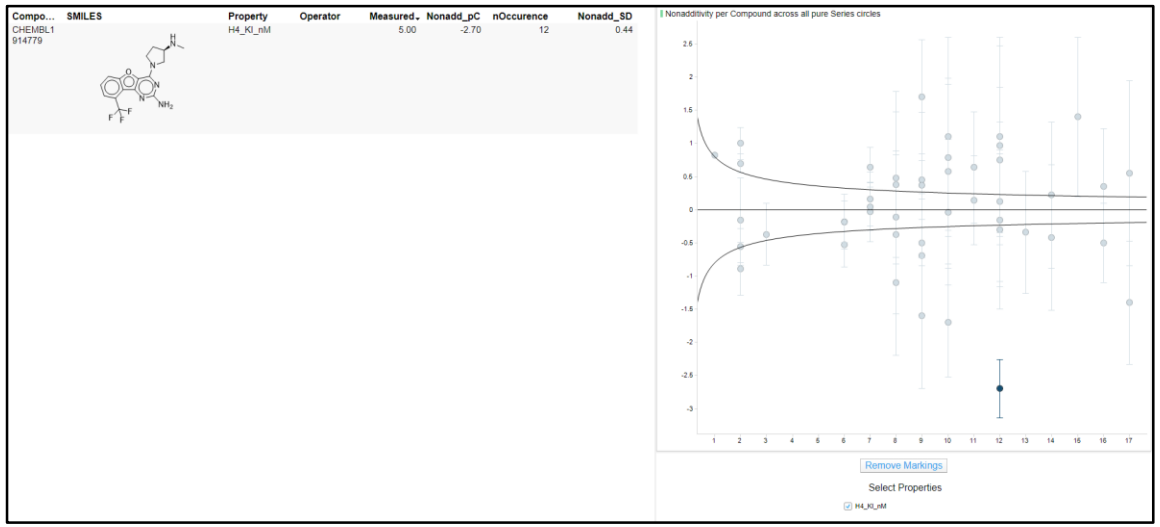
Process

- Compute all NonAdd cycles for given on-target dataset (based on mmpdb)
- Visualize distribution using QQplot and per-Compound Nonadditivity distribution

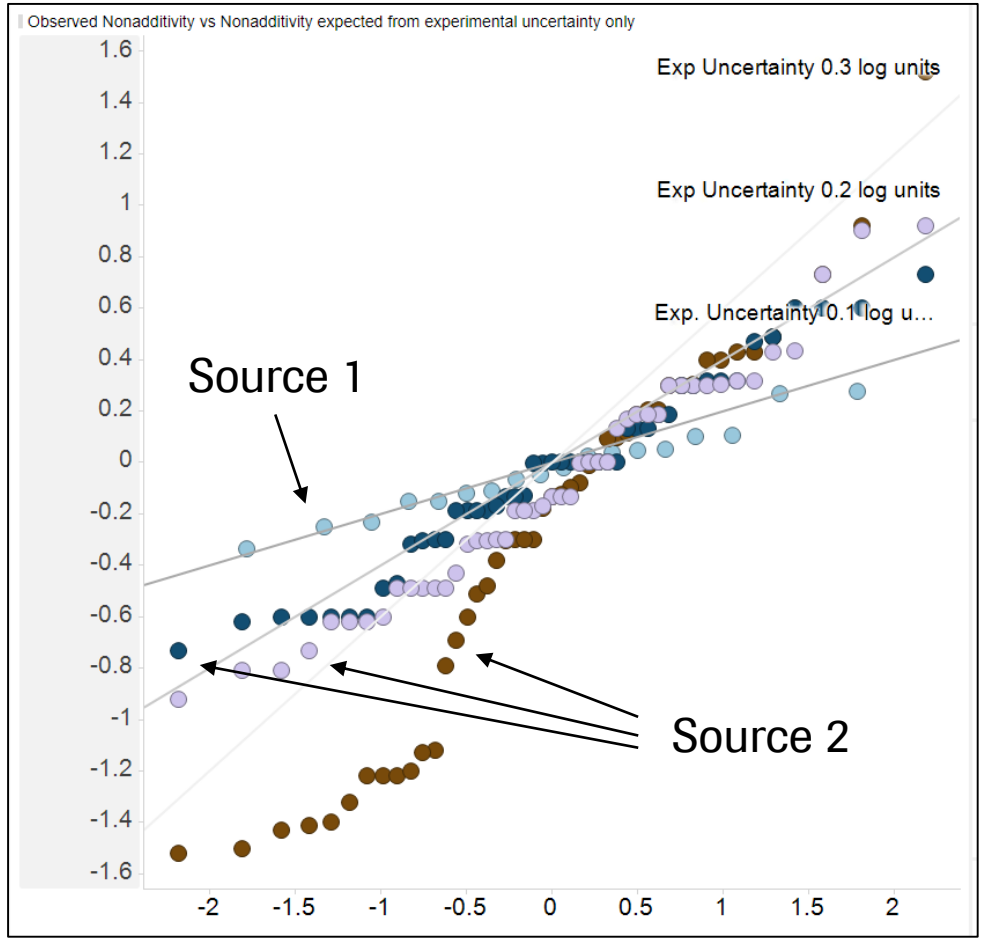
Applications

- Find outliers, experimental uncertainty, and real nonadditivity
- Individually analyze single compounds (remeasure) and cycles with extreme nonadditivity (conformational effects) to understand and use Nonadditivity
- Nonadditivity analysis can be automatically calculated for a given dataset. Scientific work is then to analyze data and draw appropriate conclusions.



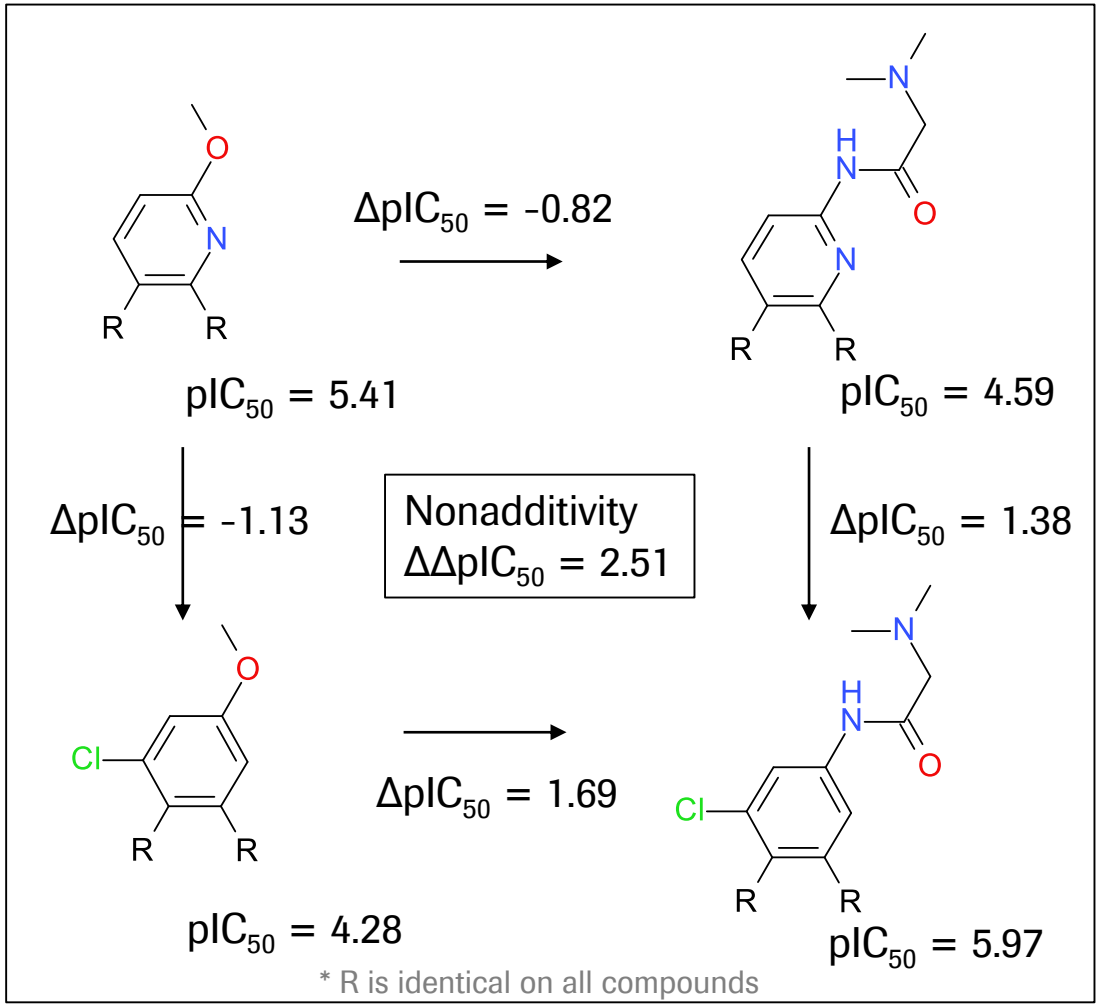


Usage



Same compounds, similar assays from different sources:

Nonadditivity helps identifying better assay with lower noise



Strong Nonadditivity, overlooked by project team

Chemical Reason: N directs substituents in opposite directions

Summary
SAR analysis at the heart of medicinal chemistry

Automating SAR analysis helps drug design to get more

- Comprehensive: Avoid missing trends
- Fast: SAR in seconds rather than hours/days
- Rational: Quantify trends

Additivity is

- Important: one of the few key principles in MedChem
- Crucial: MedChem optimization would not be possible otherwise
- Frequent: Nonadditivity exists but strong Nonadditivity is rather rare. Yet understanding Nonadditivity is crucial for driving MedChem exploration.

Additivity-based SAR analysis Tools in practice

- **Additivity-based SAR analysis tools**
  - MMP analysis
  - Free-Wilson analysis
  - Nonadditivity analysis …

  resonate with chemists since it resembles their way of thinking
- **Good integration** is very important for regular usage.
- **Strong impact** on experimental procedures, design, and prioritization of compounds can be made with proper SAR analysis tools.

Doing now what patients need next