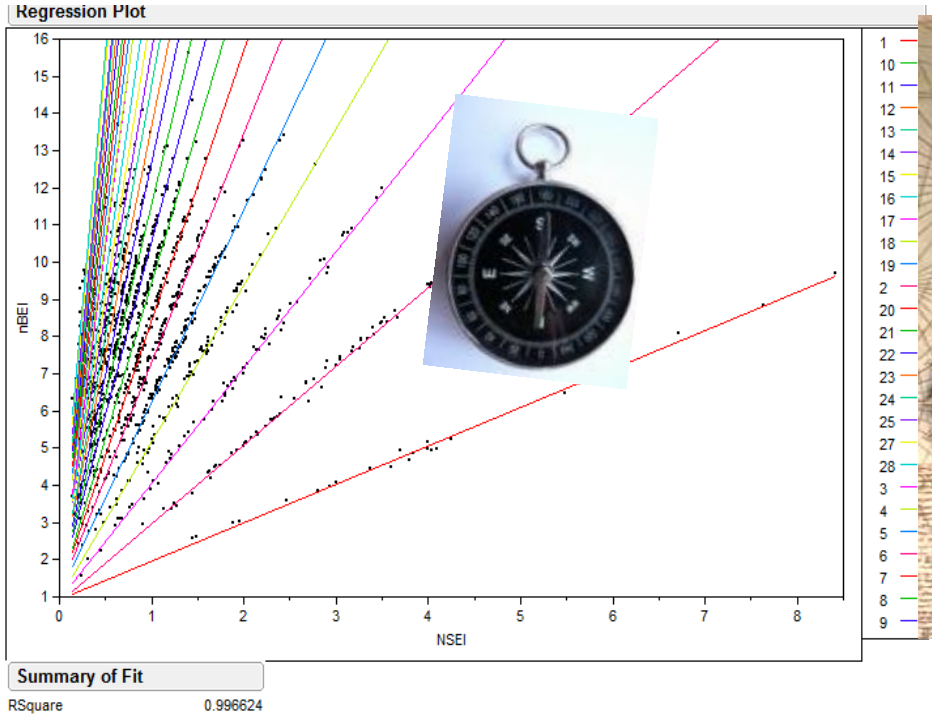
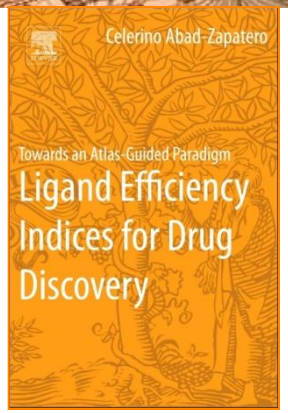
Ligand Efficiency Indices in Drug Discovery: Towards an Atlas-Guided Paradigm.





Introduction by Cele Abad-Zapatero

University of Illinois at Chicago.

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In science and technology:

Finding the right set of variables is quite often a major advance along the path to solve a problem.

Ex: Kepler's laws were formulated in terms of polar coordinates (r, θ) not in x, y, z. Critical for Newton's theory related to a central force.

What are Ligand Efficiency Indices (LEIs)? They are a new ‘set’ of variables intended to guide and direct drug discovery.

- They are numerical ways of combining the potency of ligands (K_i, IC_{50}, K_d) with their physicochemical properties: MW, PSA, NPOL(O,N), NHA and others.

- THEY PROVIDE A NATURAL LINK BETWEEN THE LIGAND (Chemistry) AND THE TARGET (Biology).

- THEY ATTEMPT TO PROVIDE AN ABSOLUTE SCALE TO COMPARE COMPOUNDS ON THE SAME BASIS OF SIZE AND POLARITY.

Initial Ligand Efficiency (LE*)

Initial equation connecting ligand-target (chemico-biological space)

$\Delta G = -RT\ln(K_i)$

Example values: K_i = 1.0 nM
ΔG = -12.4 kcal/mol at 300K

LE* = $\Delta g = \Delta G/NHAC$

NHAC= NHA no. of non-Hydrogen atoms.

Example:
1.0 nM comp. with 30 Non-H
LE of ligand: ~ -0.40

***Hopkins, Groom & Alex (2004) Drug Discovery Today 9, 430.**
Introduced to select most efficient ligands/fragments.

A Different Formulation: Ligand Efficiency Indices* (LEIs) based on physico-chemical properties.

Two complementary LIGAND EFFICIENCY INDICES were introduced soon after Hopkins' initial suggestion.

BINDING EFFICIENCY INDEX: BEI, relating affinity to size; MW (KDa)

SURFACE EFFICIENCY INDEX: SEI, relating affinity to polarity; PSA (A^2)

BEI= $-\log_{10}$ Ki/(MW/1000)= pKi/(MW(kD); MW in Kilo-Daltons

EXAMPLE: Ki = 1 nM(1.E-09), MW = 333 Da

BEI = 9/0.333= 27;

SEI = $-\log_{10}$ Ki/(PSA/100) = pKi/(PSA/100); PSA= Polar Surface Area;

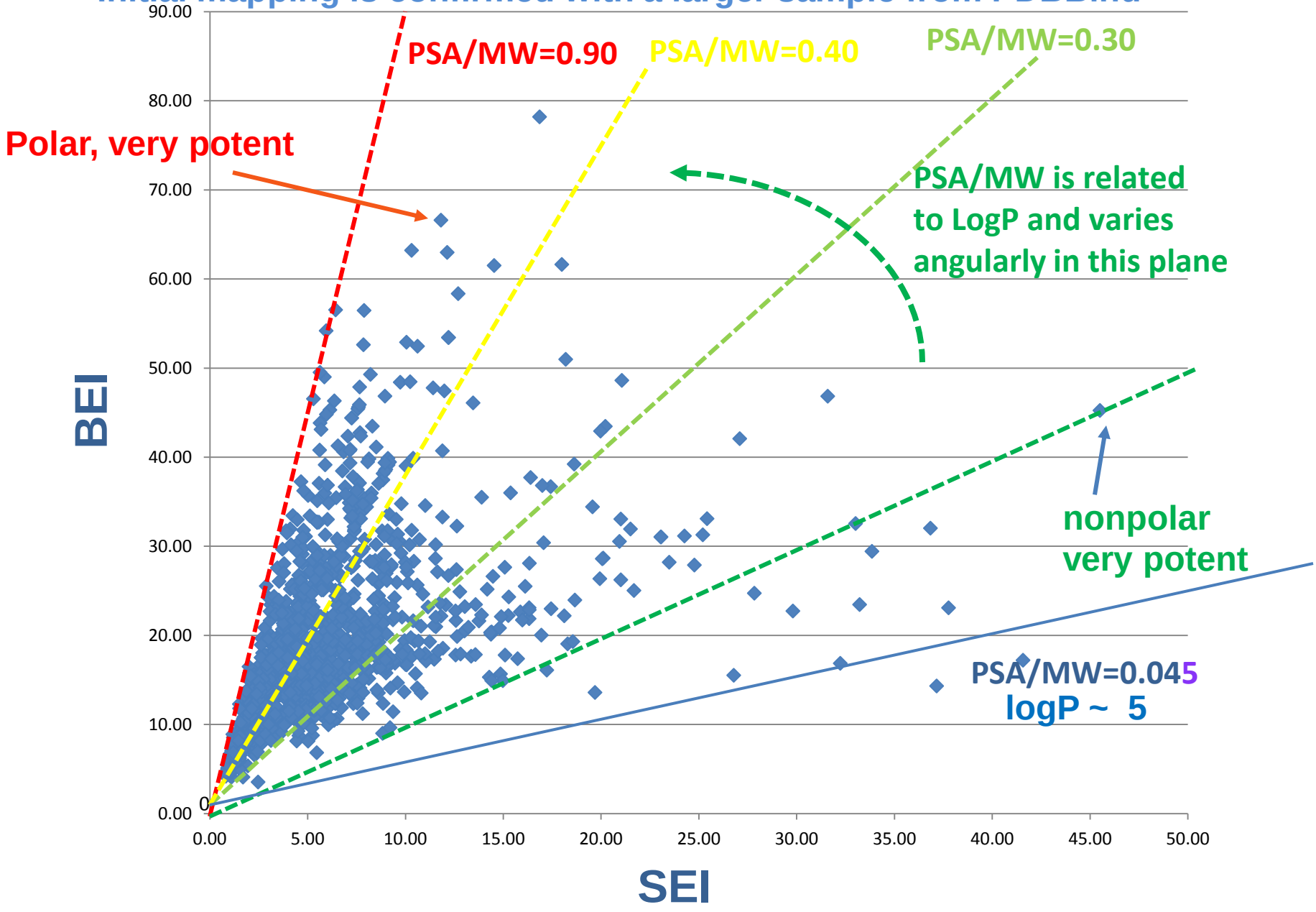
EXAMPLE: Ki = 1 nM (1.E-09); pKi = 9.0; PSA = 50 $Å^2$

SEI = 9/(50/100) = 9/0.5 = 18

NOTE : BEI/SEI = 10*PSA/MW; independent of target

*Abad-Zapatero, C. & J. Metz. (2005). *Drug Discovery Today* 10 (7) 464-469.

Overall distribution of SEI/BEI values for 1298 entries PDBBind, 2007
Initial mapping is confirmed with a larger sample from PDBBind



Another Definition of Ligand Efficiency Indices: Related to Number of Atoms (NPOL, NHA).

NSEI = $-\log_{10}$ Ki/(NPOL) = pKi/NPOL(N,O);
EXAMPLE: 1 nM, Ki = 1.0E-09, with 3 (N+O)

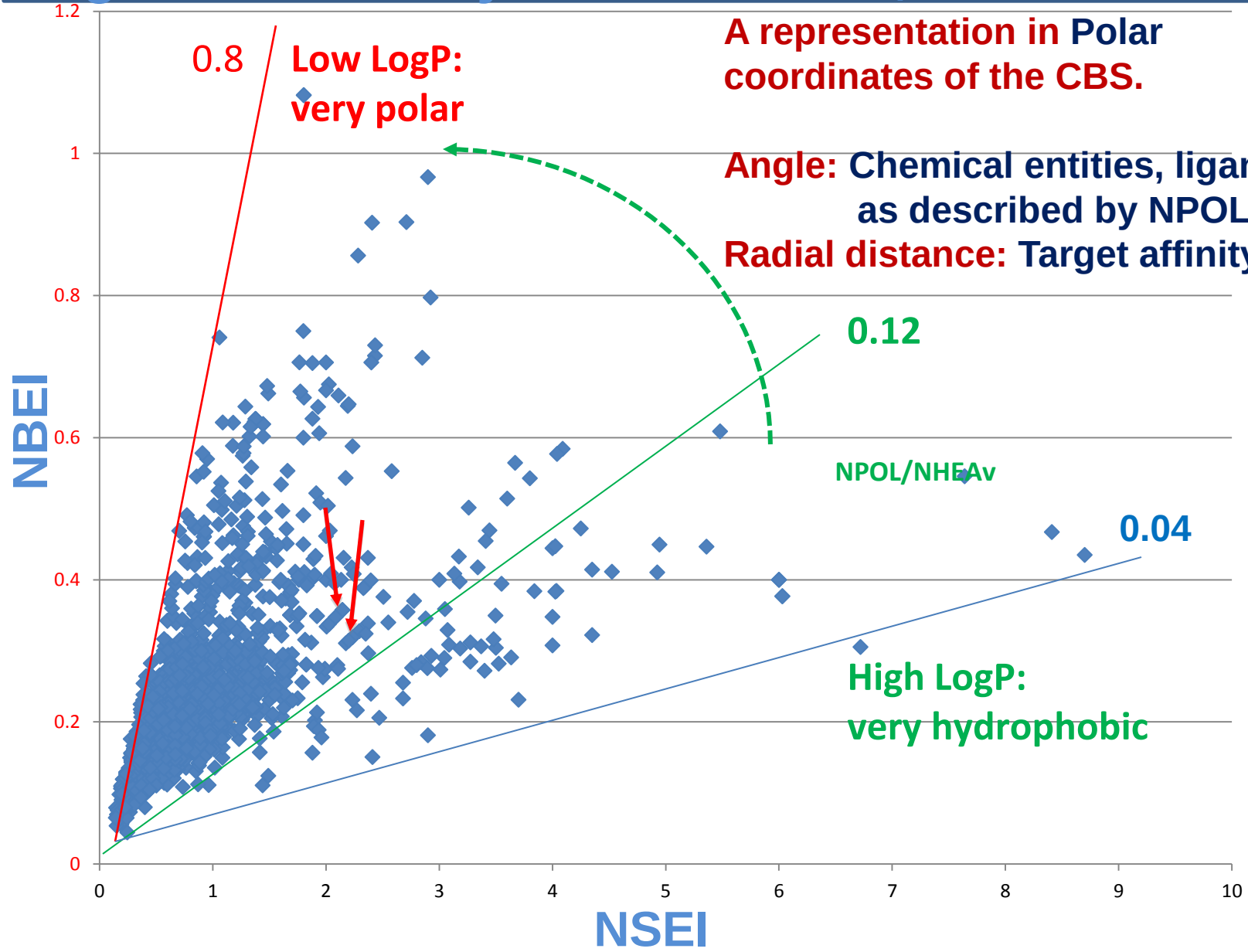
NSEI = 3

NBEI= $-\log_{10}$ Ki/(NHA)= pKi/(NHA);
EXAMPLE: 1 nM, with 18 (NHA)

NBEI = 0.5

NOTE:
NBEI/NSEI = NPOL(N,O)/NHA (non-H)= 0.5/3 = **0.167**
Ratio of polar/non-polar atoms (non-H): 3/18 = 1/6 = **0.167**

PDBBind as a function of Number-related Ligand Efficiency Indices: NSEI, NBEI



OBJECTIVE: Mapping the content of Target-Ligand Databases in 'Efficiency Planes', using variables related to LEIs.

✓Retain the template of angular (chemistry) vs. radial (biology) separation.

but:

✓Achieve a better separation of the ligands in terms of their polarity or NPOL(N+O) content.

A slightly' different pair of atom-related variables: nBEI, NSEI: better separation.

change to

$NBEI = -\log_{10}(Ki)/NHA$ →

$nBEI = -\log_{10}[(Ki/NHA)]$ [1]

$NSEI = -\log_{10}(Ki)/NPOL$ [2]

from [2]: $-\log_{10} Ki = NPOL*NSEI$ [3]

Eliminating –log Ki, between equations [1] and [2] (eliminating target dependence):

From [1]: $nBEI = -(\log_{10}Ki - \log_{10}NHA)$;

→ $nBEI = -\log_{10}Ki + \log_{10}(NHA)$;

Substituting the value of $-\log_{10}Ki$ from [3]:

→ $nBEI = NPOL*NSEI + \log_{10}(NHA)$

$y = a * x + b$

linear relationship between nBEI, NSEI

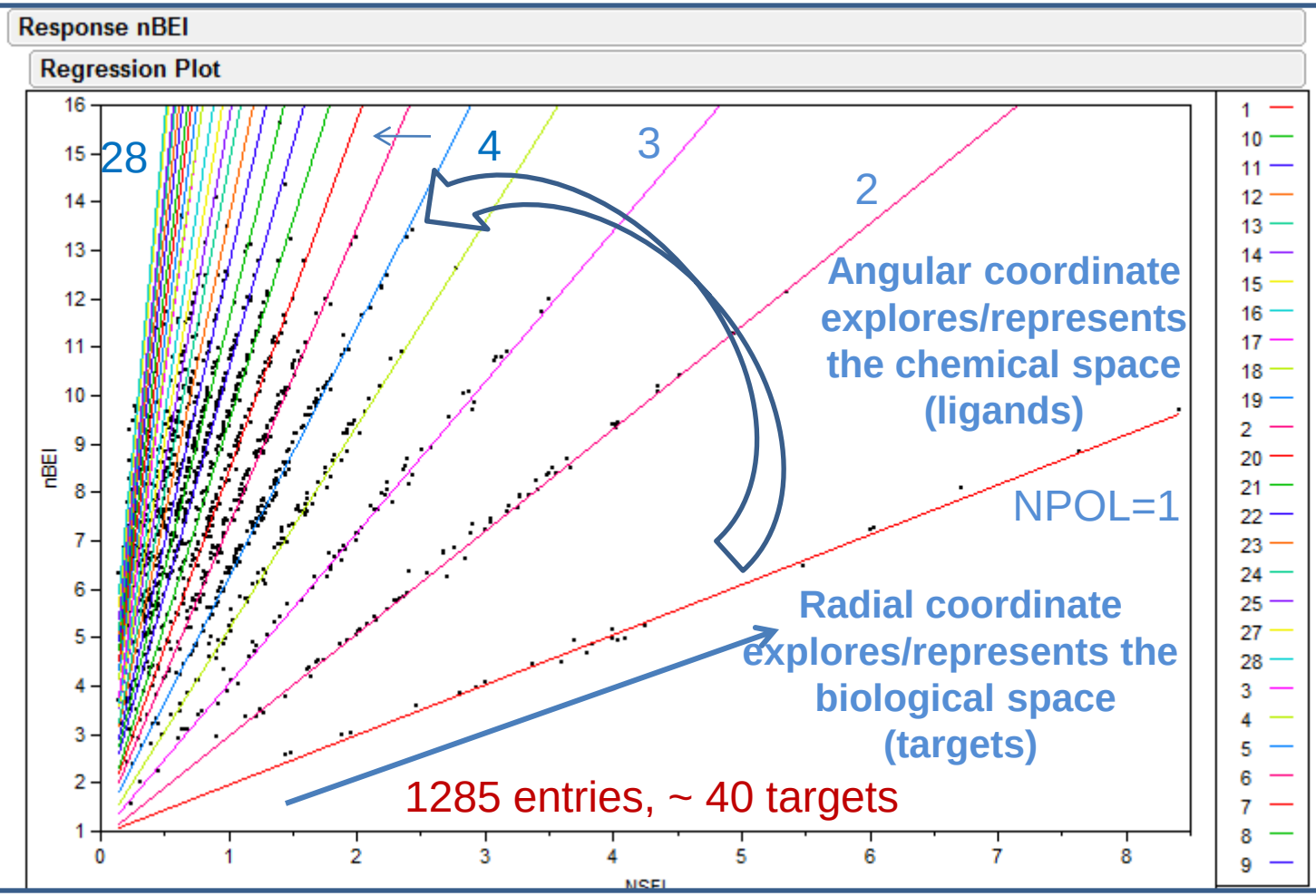
or

NOTE: if $mBEI = -\log_{10}[(Ki/MW)]$;

→ $mBEI = NPOL*NSEI + \log_{10}(MW)$

between mBEI, NSEI

Cartesian mapping of Chemico-Biological Space: PDBBind



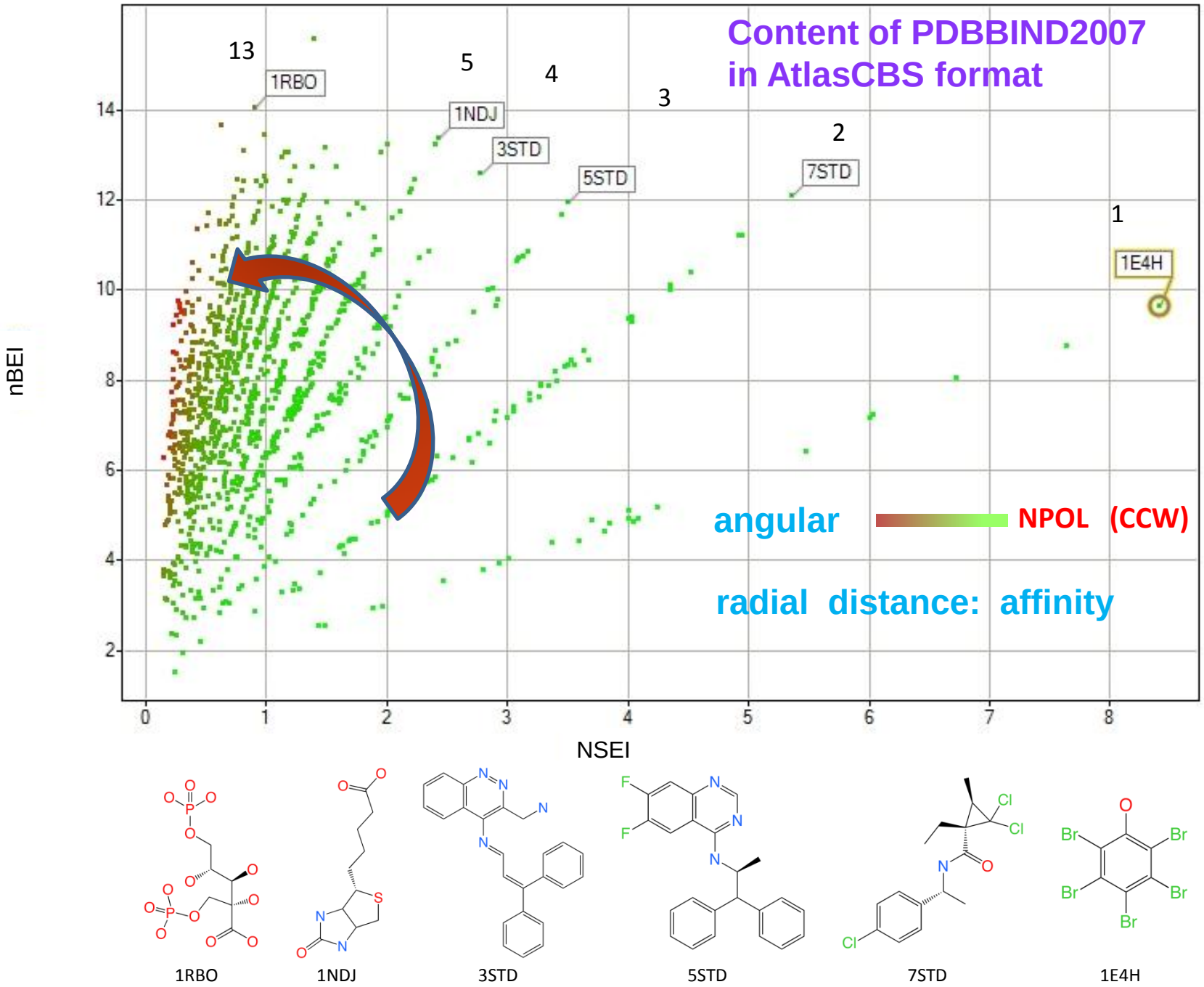
Family of lines expressed by: $nBEI = NPOL*NSEI + \log_{10}(NHA)$

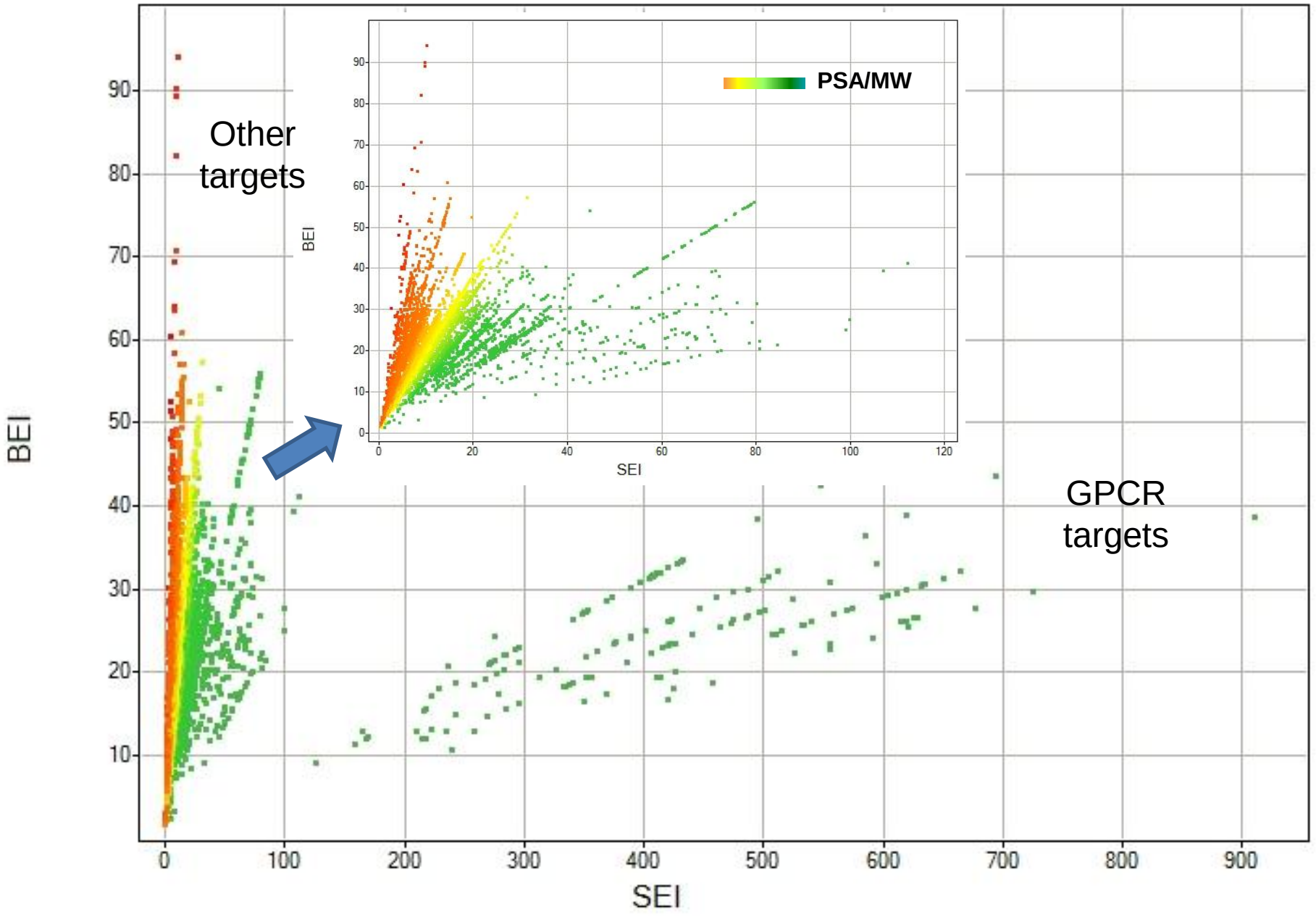
Analysis of Variance

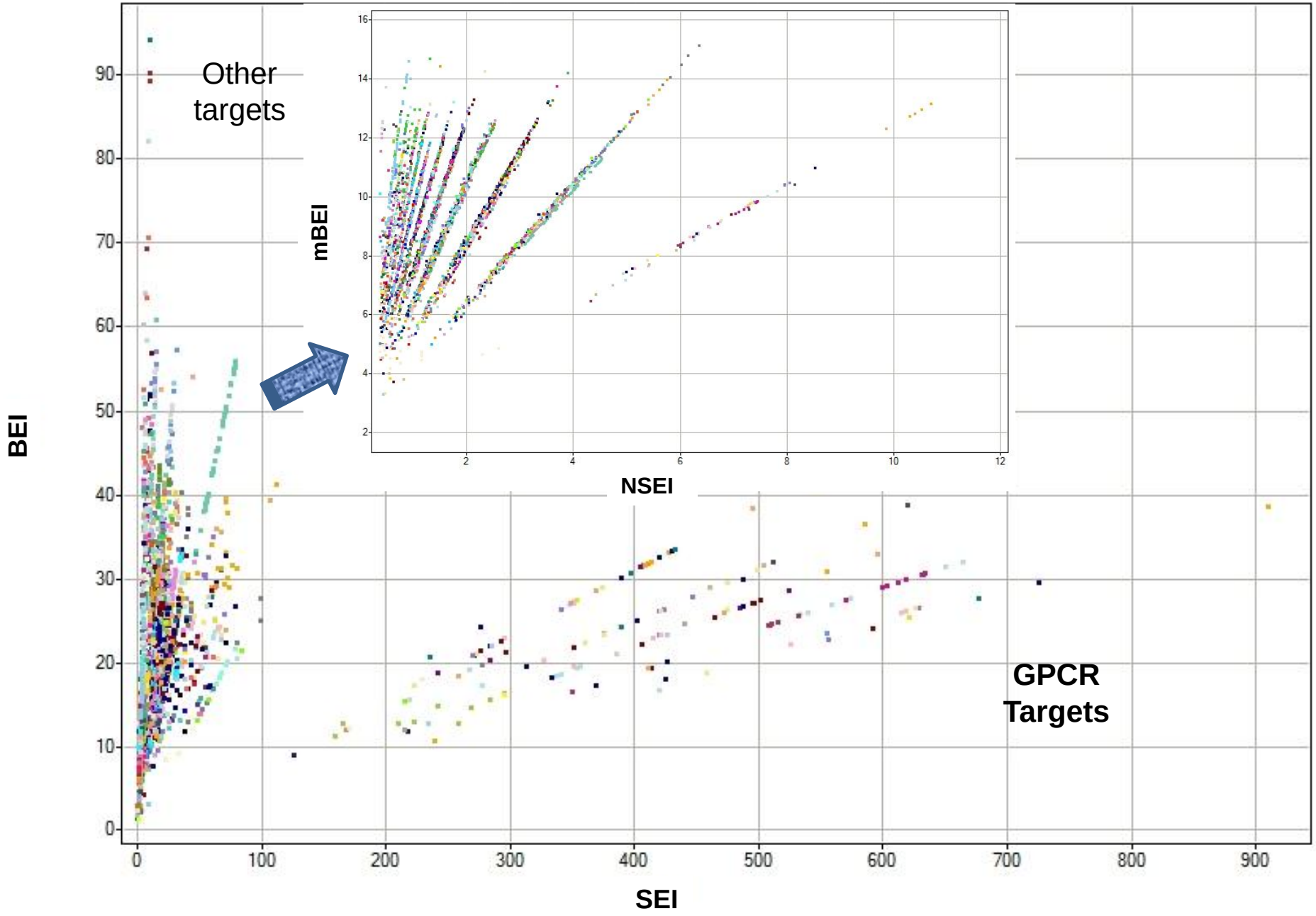
Source	DF	Sum of Squares	Mean Square	F Ratio
Model	53	6439.1525	121.493	6856.427
Error	1231	21.8129	0.018	Prob > F
C. Total	1284	6460.9654		0.0000*

Effect Tests

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
ON_number	26	26	4186.8965	9087.907	0.0000*
NSEI	1	1	36.9240	2083.790	<.0001*
ON_number*NSEI	26	26	2360.1317	5122.806	0.0000*

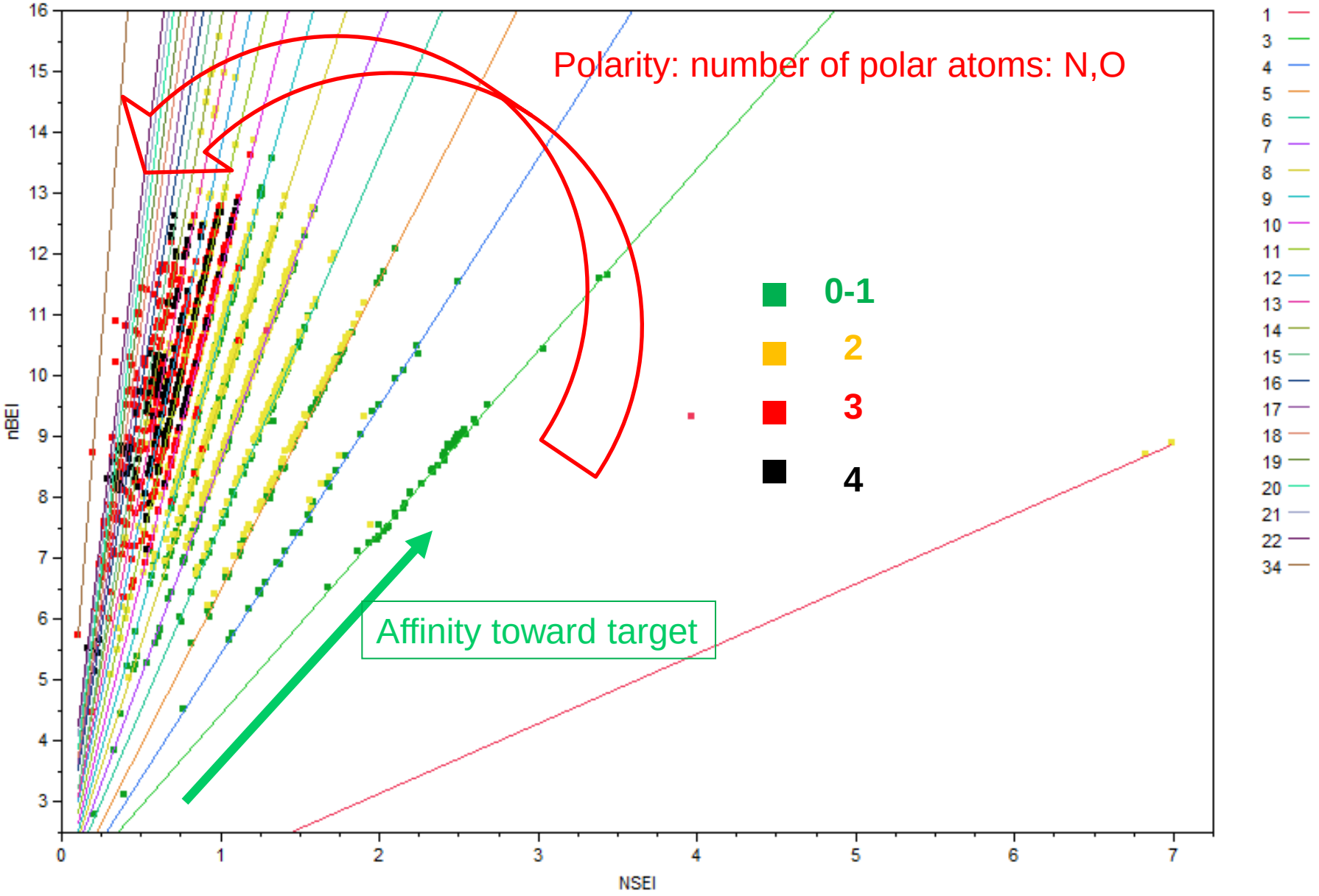

Content of PDBBIND2007
in AtlasCBS format
13
5
4
3
2
1
1RBO
1NDJ
3STD
5STD
7STD
1E4H
nBEI
NSEI
angular
NPOL (CCW)
radial distance: affinity
1RBO
1NDJ
3STD
5STD
7STD
1E4H


Other targets
GPCR targets
PSA/MW
BEI
SEI
0
100
200
300
400
500
600
700
800
900
10
20
30
40
50
60
70
80
90
0
20
40
60
80
100
120


Other targets
mBEI
NSEI
BEI
SEI
GPCR Targets

The following slides show some illustrative examples

LEIs and Ro5:Number of Ro5 violations vs. nBEI-NSEI plane for HIV inhibitors*



*Starlite database from the ChEMBL-EBI group: 2523 entries.
Data from P. Bento and C.A-Z.

Atlas-like representation of Chemico-Biological Space (CBS)

Permits:

✓Analyze/compare the content of databases: inhibitors vs. drugs.

✓Drug-Discovery Trajectories
(internal and external, competition)

✓Chemical series for different or similar targets.

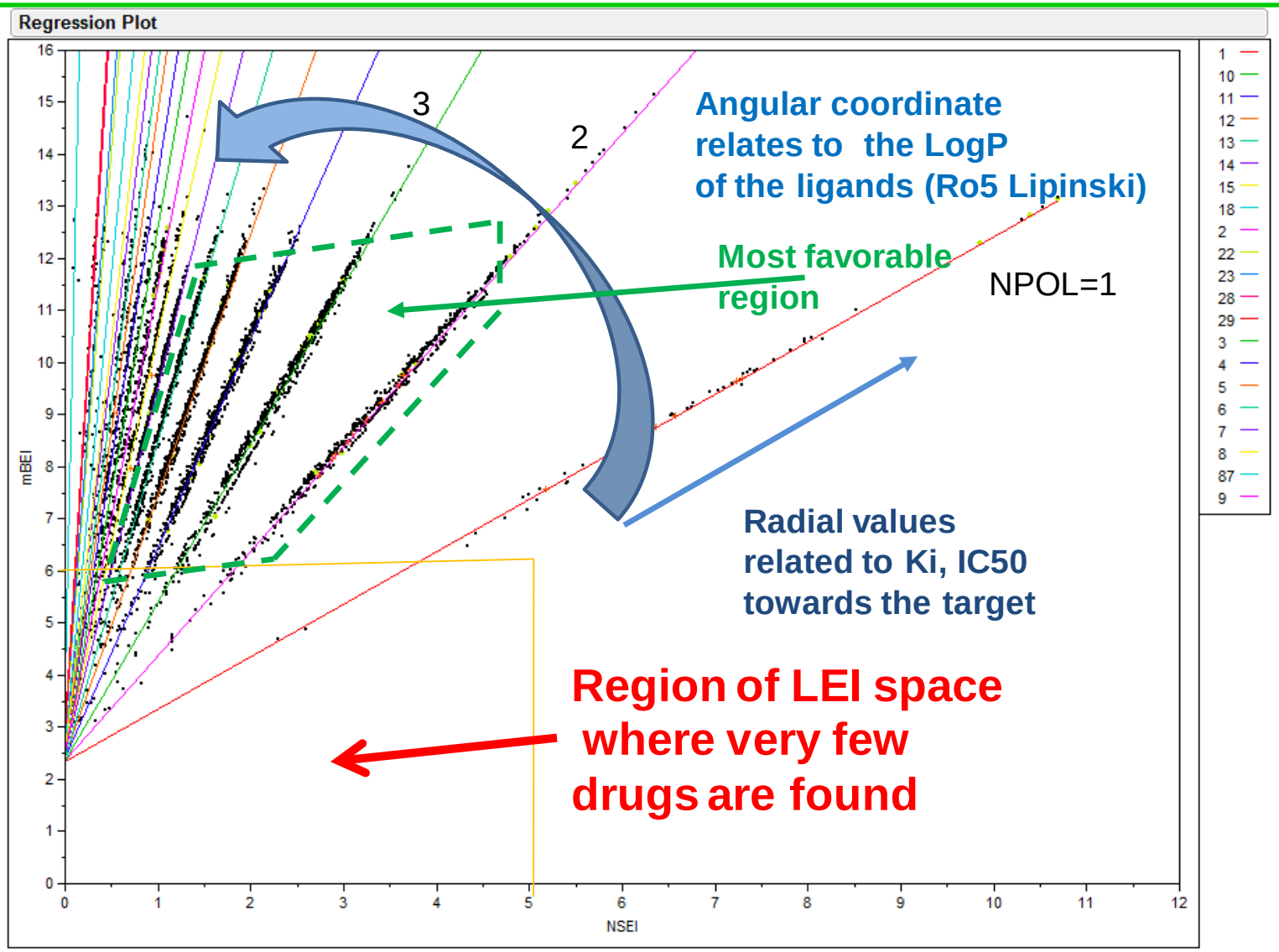
✓Analyses of Fragment-Based Strategies.

✓Optimization variables in a more objective way.

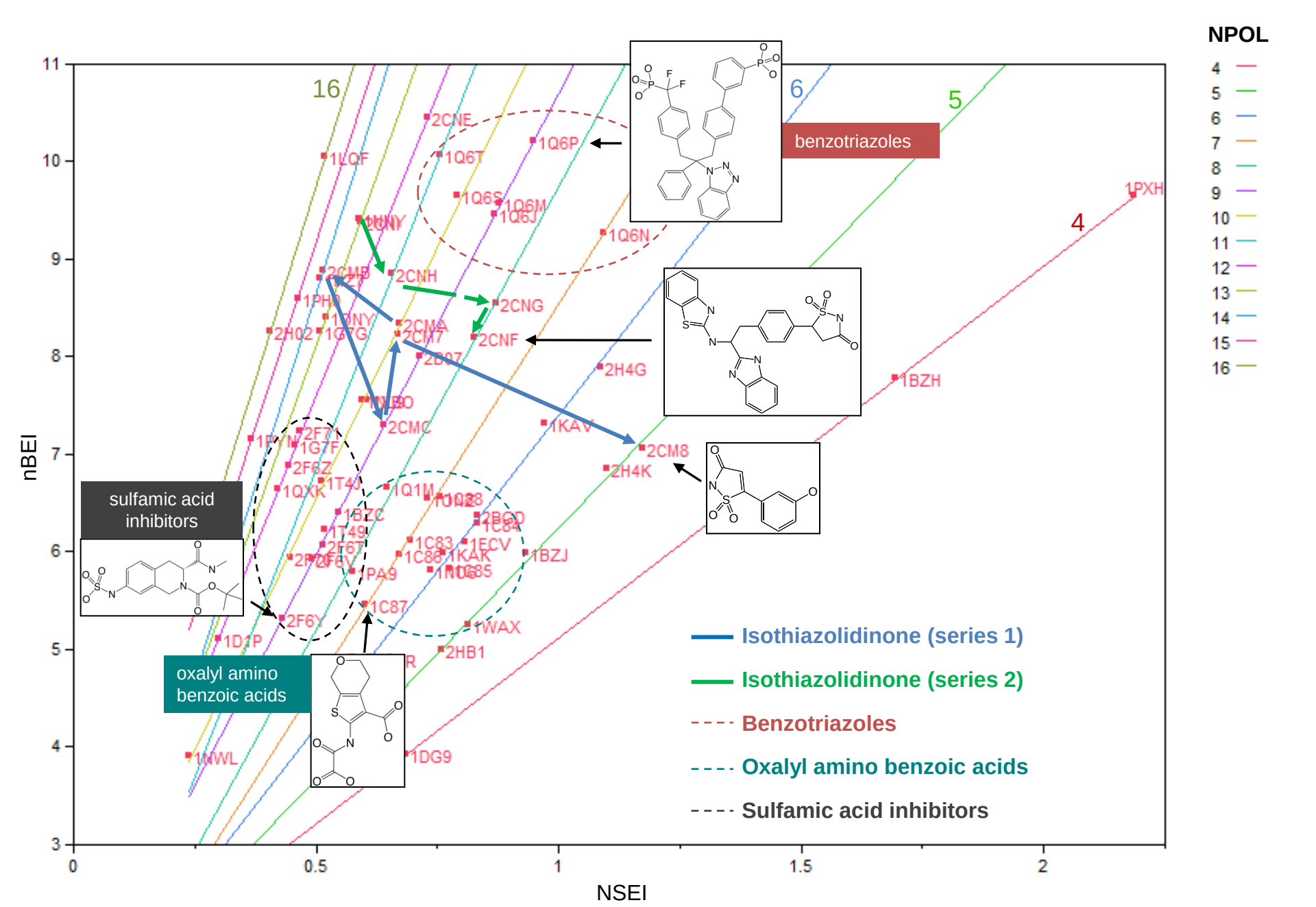
- Efficiency-Based (Driven) Drug Discovery.

A few brief illustrations are given

The mBEI-NSEI plot for a larger sample of marketed drugs *

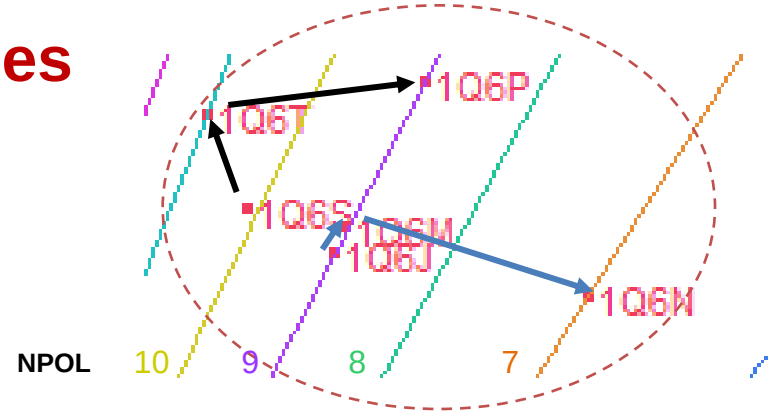


*WOMBAT database (~7,000 entries) courtesy of T. Oprea

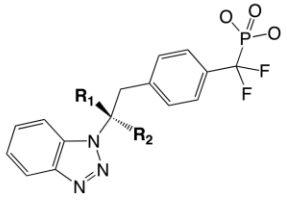


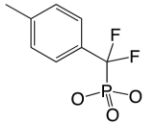
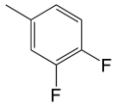
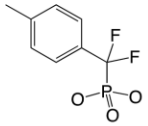
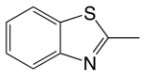
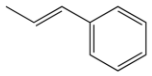
Different chemical series for PTP1B (Protein Tyrosine Phosphatase 1B) (PDBBind)

Benzotriazoles

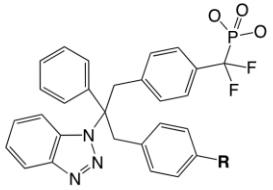


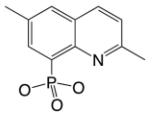
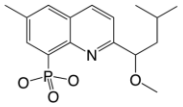
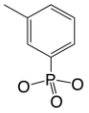
nBEI, NSEI and IC50 (nM) Values for the First Generation Aryldifluoromethyl-Phosphonic Acid Inhibitors



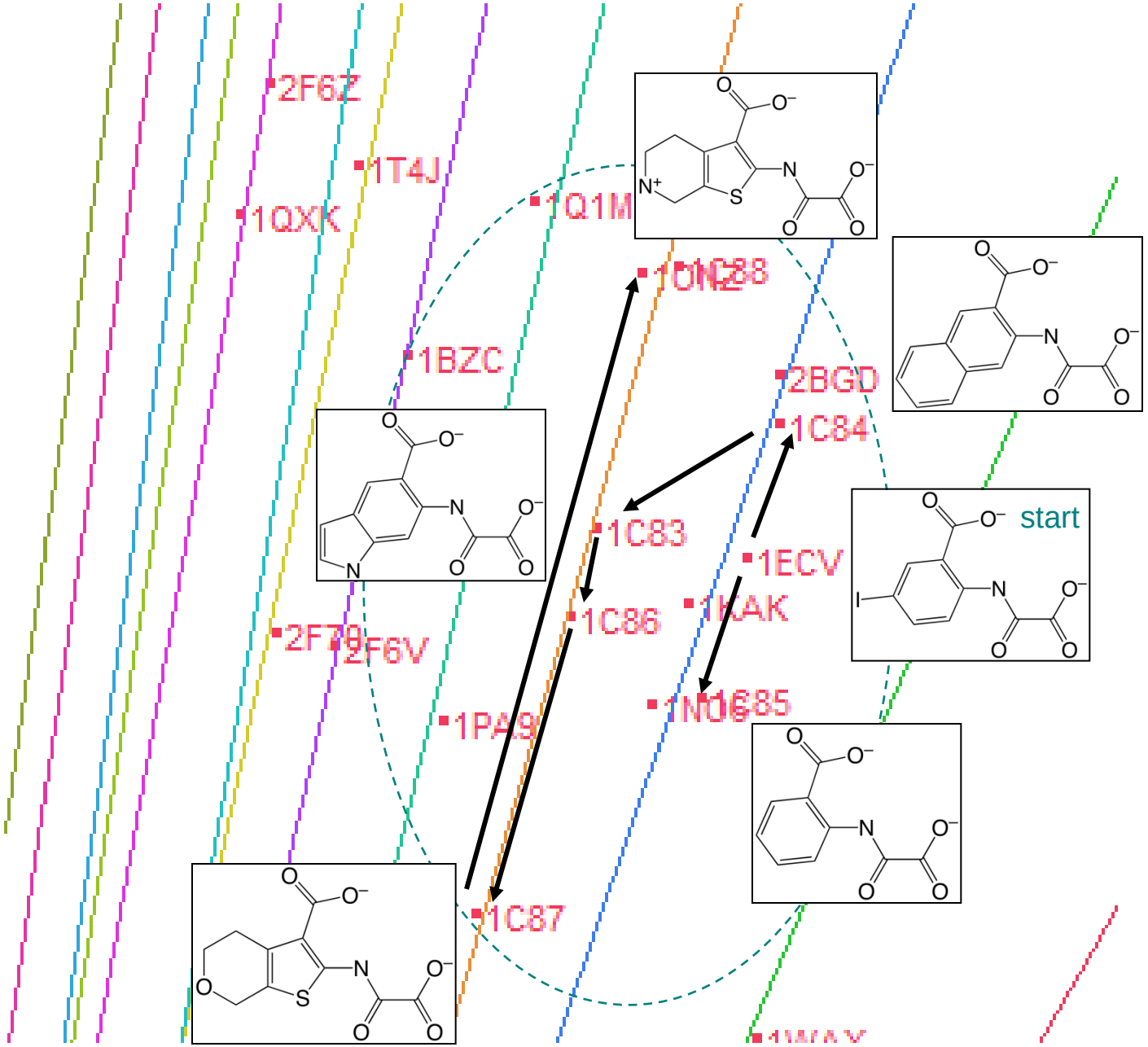
Compound	R1	R2	nBEI	NSEI	IC50
1Q6J			9.45	0.87	16
1Q6M			9.56	0.88	13
1Q6N			9.26	1.09	23

nBEI, NSEI and IC50 (nM) Values for Some Compounds Designed to Interact with F52 and A27



Compound	R	nBEI	NSEI	IC50
1Q6S		9.64	0.79	12
1Q6T		10.06	0.75	5
1Q6P		10.20	0.95	3

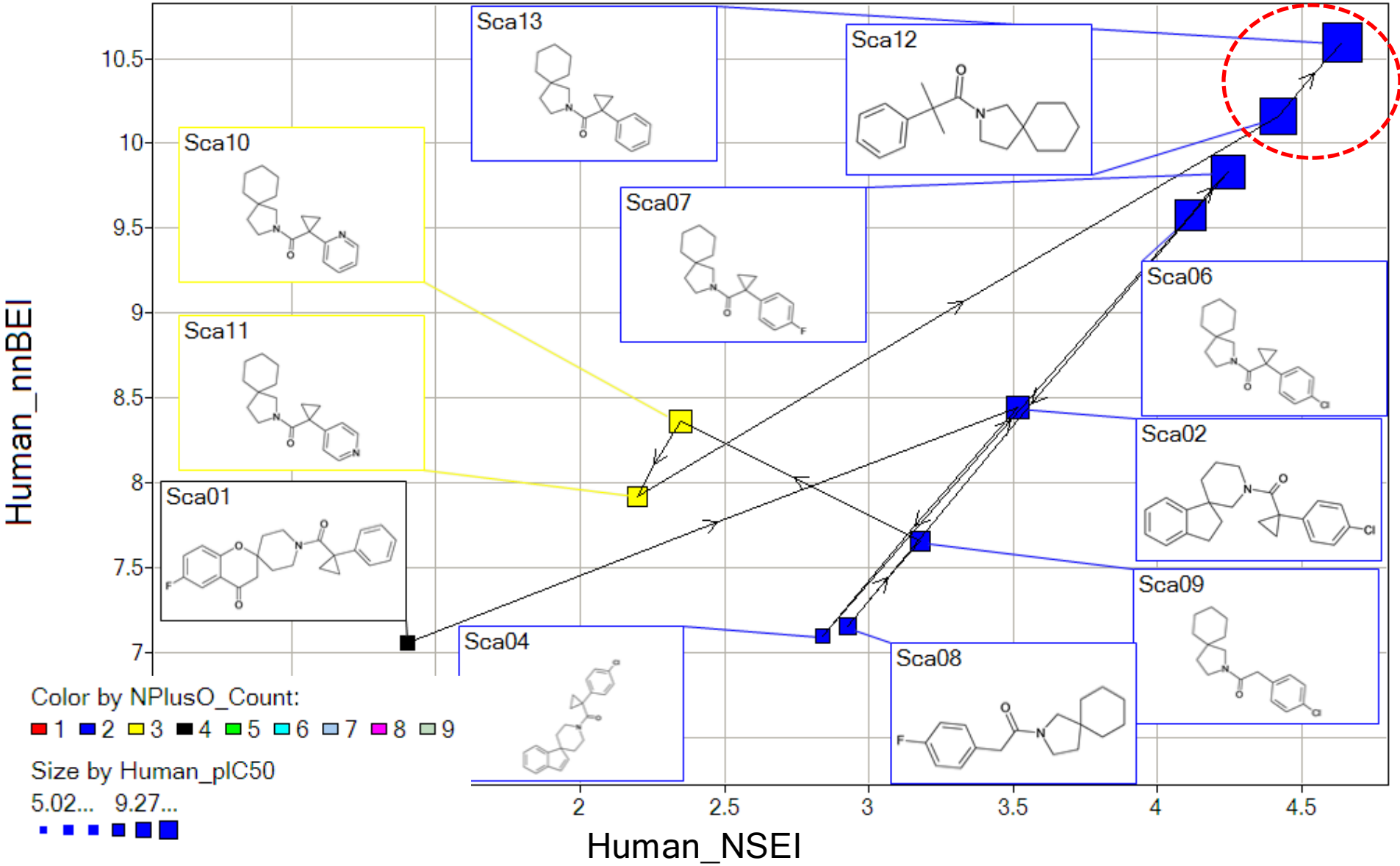
Oxalylamino benzoic acids



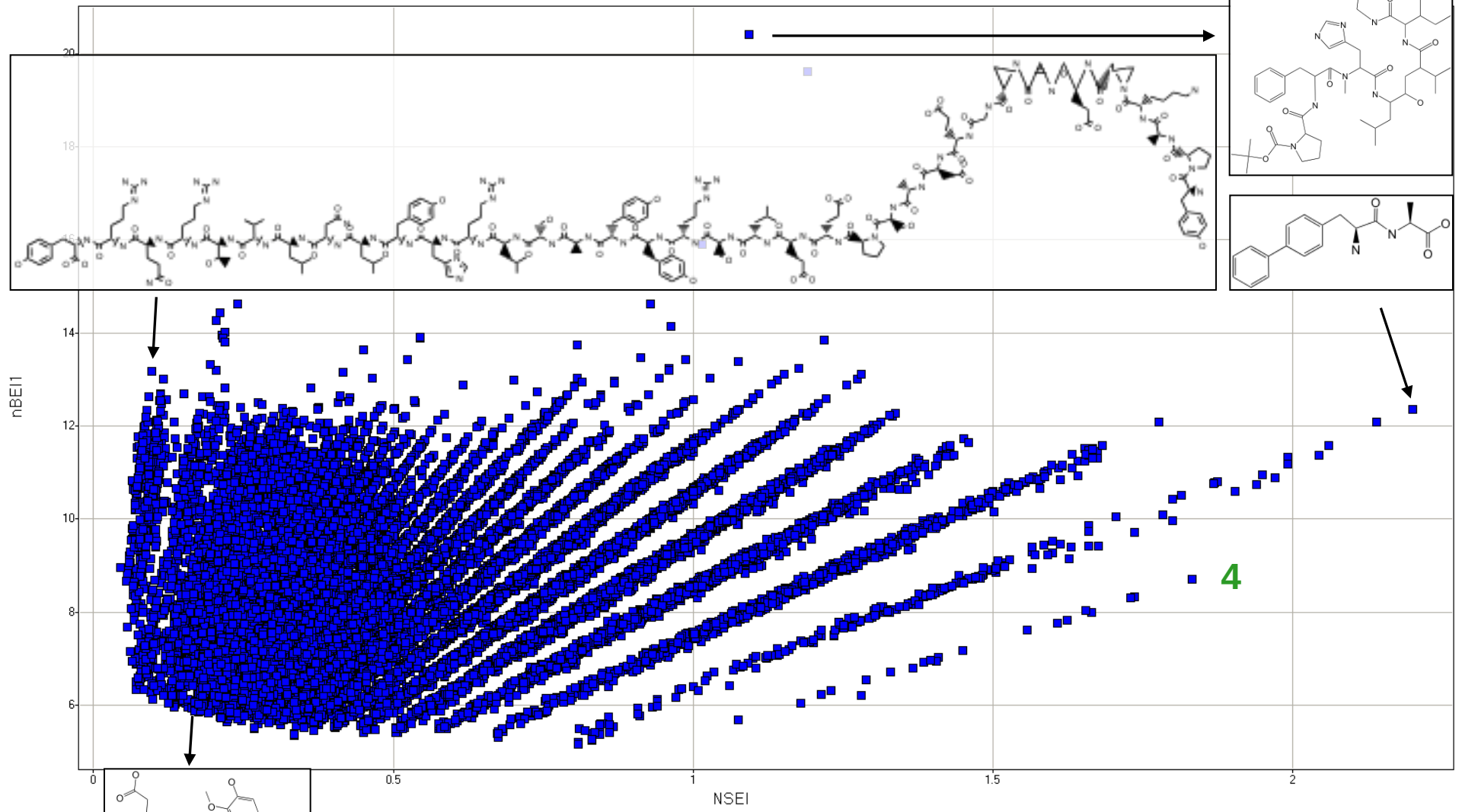
11βHSD1- Human_NSEI vs. nBEI-Spiro Carboxy Amide

Christmann-Frank et al. Molecular Informatics. (2011). 30 (2-3), 137-144.

Best compounds!

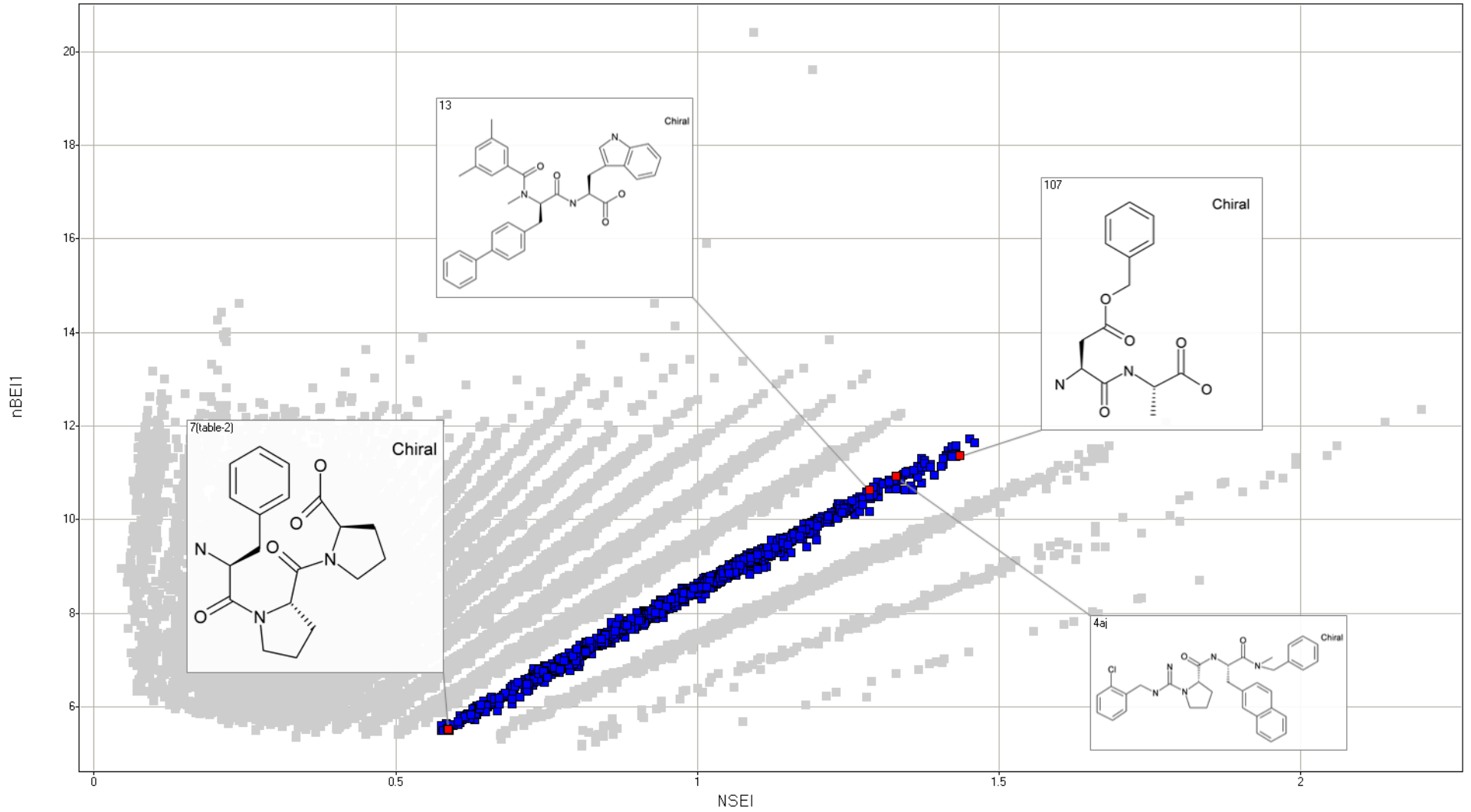


Mapping peptides in Chemico-Biological-Space



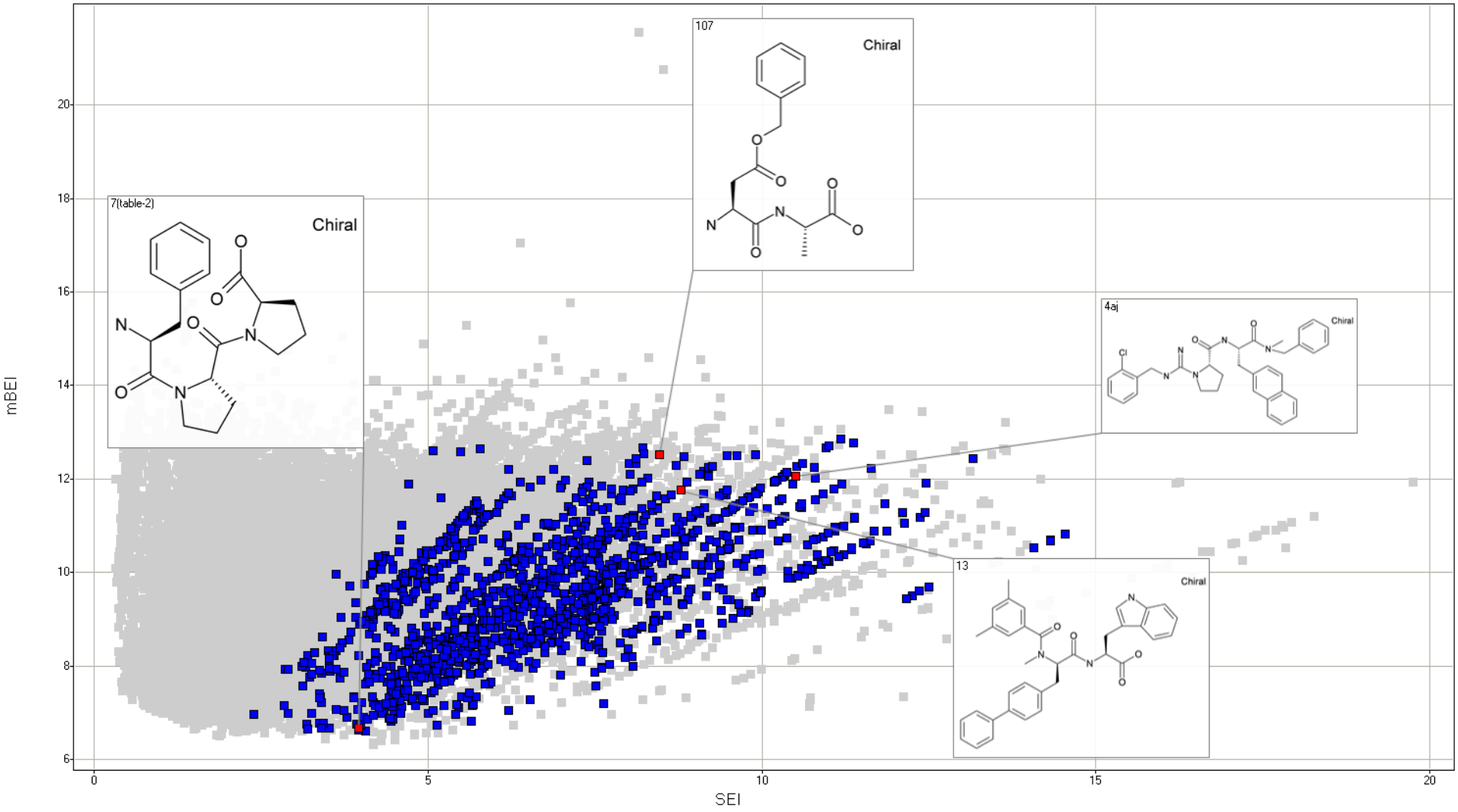
$nBEI = NPOL*NSEI + \log_{10}(NHA)$.
Range of NPOL: 4-138. Illustrated from 5-101.
Peptide sample from ChEMBL. N ~22,000.

Selecting one line of chemical space: NPOL=7



$$nBEI = NPOL*NSEI + \log_{10}(NHA)$$

Selecting one line of chemical space: NPOL=7. Change of coordinates



$$mBEI = (PSA/100)*SEI + \log_{10}(MW)$$

POSTCARD No.2a HIV-P and HIV-RT

Firefox File Edit View History Bookmarks Tools Window Help (100%) Thu Oct 4 11:37 AM

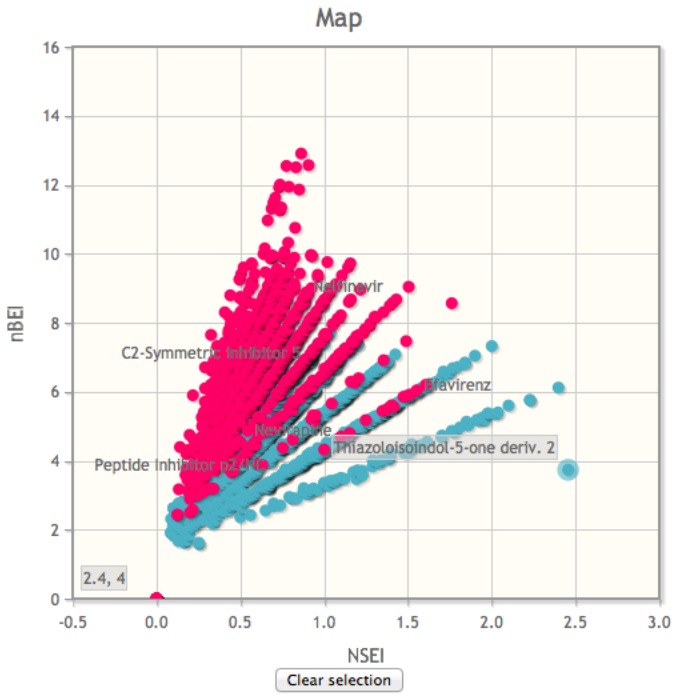
AtlasCBS server

AtlasCBS server | AOL Mail (2492) | UIC WebMail 1.4.20

ebi.ac.uk https://www.ebi.ac.uk/chembl/atlascbs/viewer.jsp

Google

Map viewer



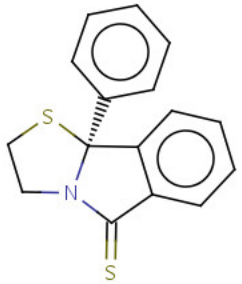
Name	Definition
BEI	p(Ki), p(Kd), or $p(IC_{50})$/MW(kiloDa)
SEI	$p(K_i)$, $p(K_d)$, or $p(IC_{50})$/(PSA/100 Å^2)
NSEI	NSEI = $-\log_{10}$ Ki/(NPOL) = pKi/NPOL(N,O)
NBEI	NBEI= $-\log_{10}$ Ki/(NHEA)= pKi/(NHEA)
nBEI	nBEI= $-\log_{10}$[(Ki/NHEA)]
mBEI	mBEI=$-\log_{10}$[(Ki/MW)]

Selection | Viewer | Data | Filters | Exports

Current Selection

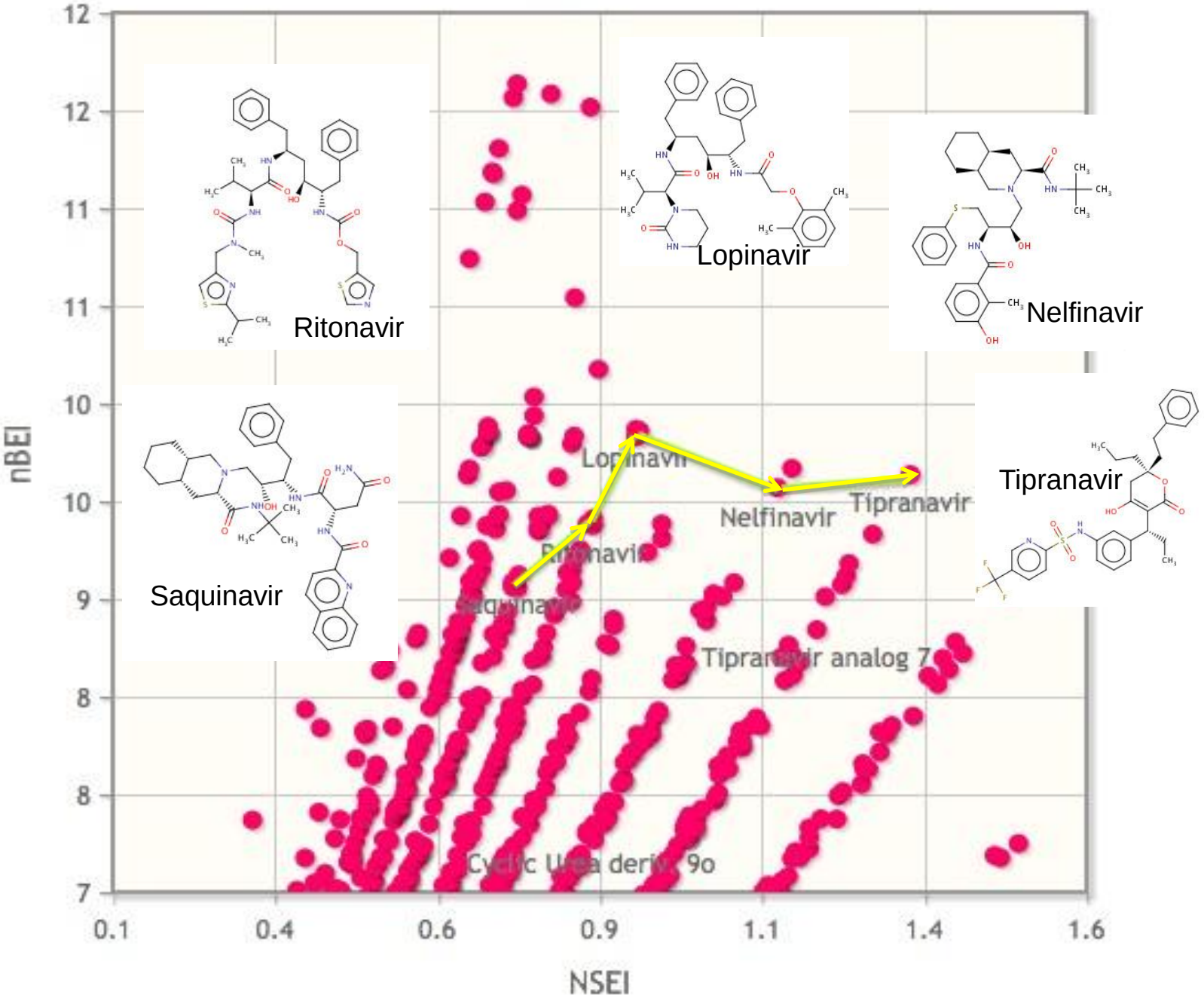
Name	SMILES	X	Y
Efavirenz	c1c(ccc2c1[C@](OC(=O)N2)(C(F)(F)F)C#CC1CC1)Cl	PDB	PDB
Nelfinavir	c1(c(cccc1C(=O)N[C@@H](CSc1ccccc1)[C@@H](CN1[C@@H](C[C@H]2[C@@H]	PDB	PDB

Selected molecule



Name	Thiazoloisoindol-5-one deriv. 2
Mass	283.41
Polar atoms	1
TPSA	60.63
Heavy Atoms	19
pIC_{50}	2.455932
Link	BindingDB

POSTCARD No.2b HIV-P



Atlas-like representation of Chemico-Biological Space (CBS)

Permits:

✓Analyze/compare the content of databases

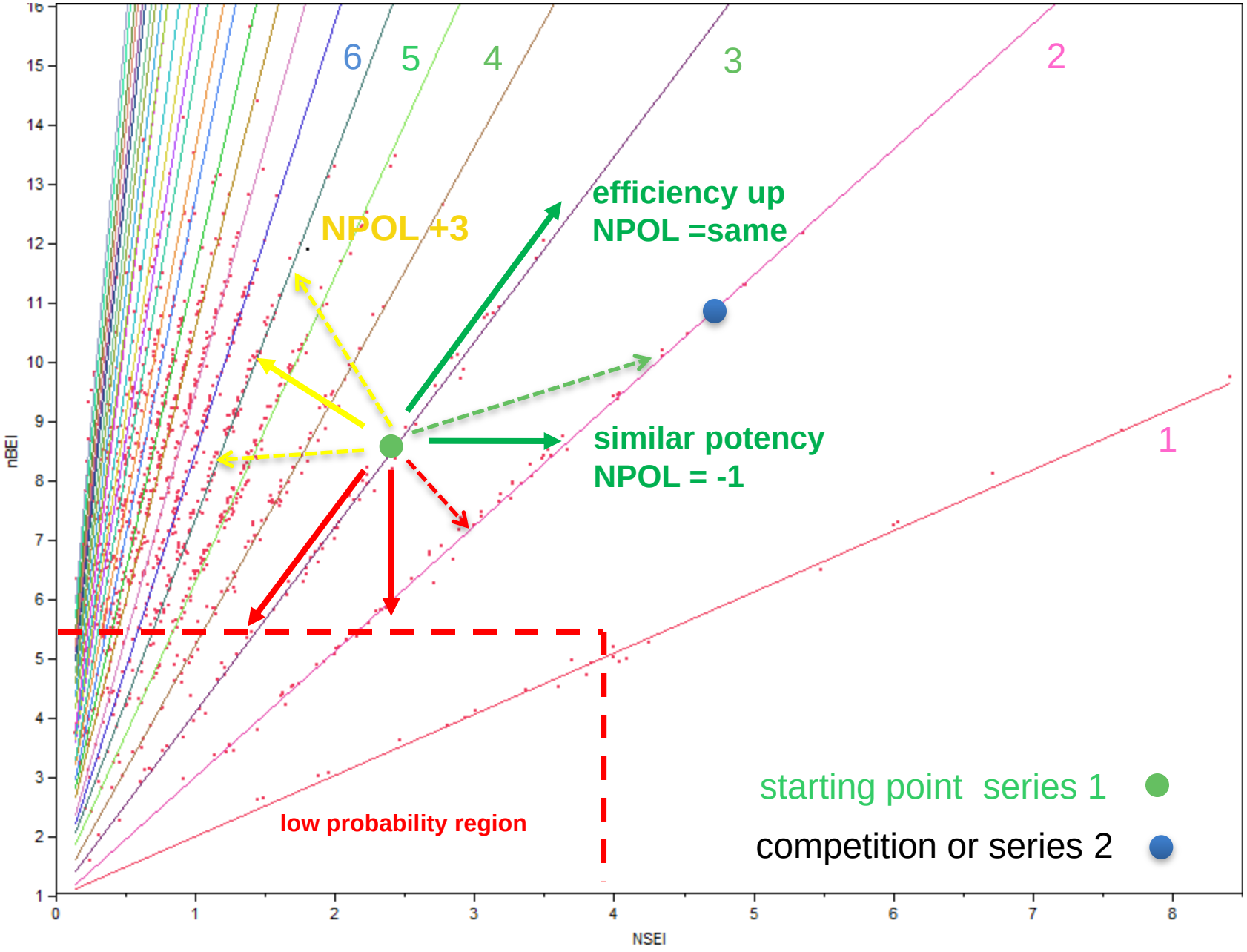
✓Drug-Discovery Trajectories
(internal and external, competition)

✓Chemical/Drugs series for different or similar targets.

Analyses of Fragment-Based Strategies:
fragment libraries, nat. products, optimal paths.

✓Optimization of variables in a more objective way
(Equivalence of Ligand Efficiency Indices)

- Efficiency-Based (Driven) Drug Discovery.


6
5
4
3
2
1
NPOL +3
efficiency up
NPOL =same
similar potency
NPOL = -1
low probability region
starting point series 1
competition or series 2
nBEI
NSEI
0
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16

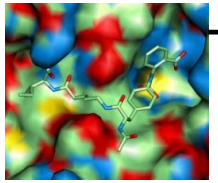
Efficient Structure-Based Drug Design Cycle

1 Individual input, idea generators, libraries, screens

include affinity data if known

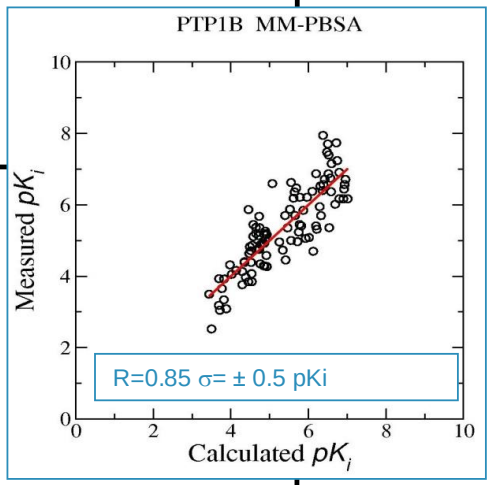
Predicted or known

Generate 3-D structure 2



3 Structure of target:inhibitor complexes from project or public domain: PDB, PDBBind, MOA, model (1 example or an entire series binding in a similar mode/pose)

Img. 1

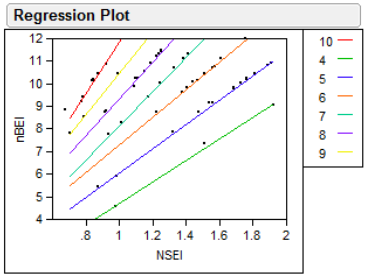


4 use experimental data to 'scale' to theoretical K_i, IC_{50} values: 'Parameterize' (potencials, MD, various docking algorithms)

5 measure, extract or estimate Ki, IC50 from known poses

6 compute efficiency indices: SEI, BEI, nBEI, NSEI and others.

Img. 2



7 select most efficient (filter or statistics)

Compounds with most favorable binding efficiency indices: SEI/BEI; NSEI/nBEI;, LEP/LEH or others.

*C. Abad-Zapatero. Expert Opinion in Drug Discovery. 2007, 2(4), 469-488.

Summary

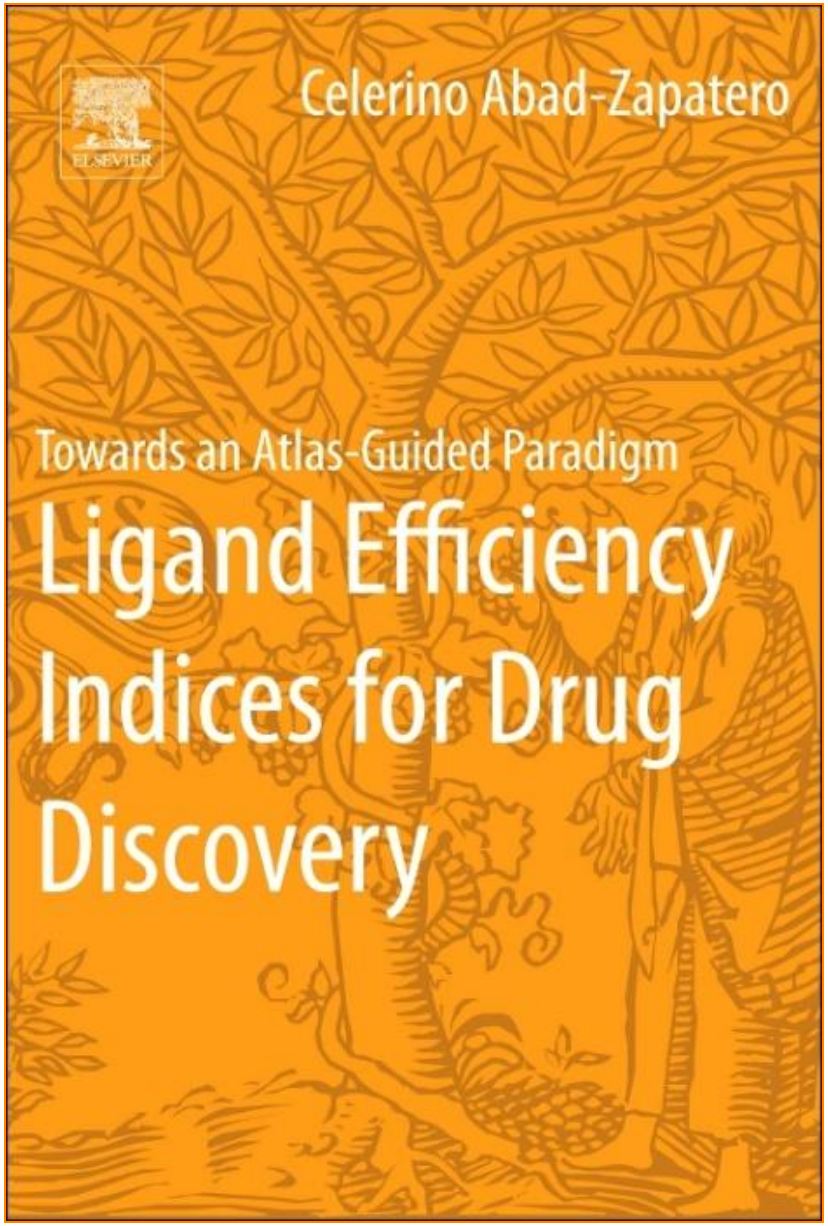
- Ligand Efficiency Indices (LEIs) can be used as variables to map ligand-target complexes into Cartesian planes (BEI/SEI; nBEI/NSEI, mBEI/NSEI and others).

- This representation provides an 'Atlas-like' map of CBS that can be used to analyze:

  - ✓Content/Comparison of Databases.
  - ✓The mapping of 'drug-like' regions in CBS.
  - ✓Drug-Discovery Trajectories for individual targets.
  - ✓Chemical/Drug series for similar or identical targets.
  - ✓Optimization of series/compounds.
    Fragment-Based Strategies/libraries.

- LEIs can be used as superior optimization variables, rather than potency alone.

- In the future, LEIs could provide a robust analytical/statistical framework to direct and optimize Drug Discovery: Efficiency-Based Drug Discovery within the AtlasCBS paradigm.



- **If you wish to continue exploring these ideas you can consult the AtlasCBS web server at:**

https://www.ebi.ac.uk/chembl/atlascbs

- **For further reading, you can study the papers published on this topic that are mentioned in the documentation of the AtlasCBS site. In addition, all these concepts have been summarized and illustrated in a small book published in 2013.**

More importantly, this variable framework has been implemented in a AtlasCBS module in StarDrop that will permit the incorporation of LEIs into their MPO profiles in the near future.

Thank you for your attention.

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