

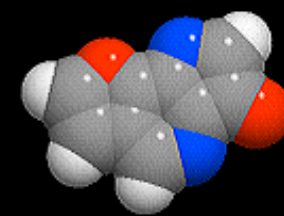
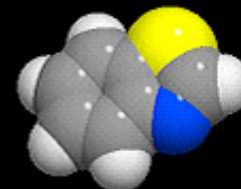
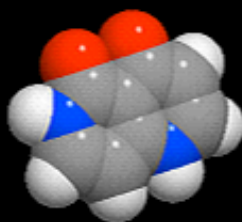
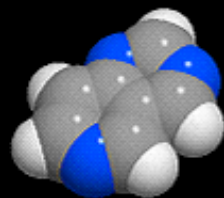
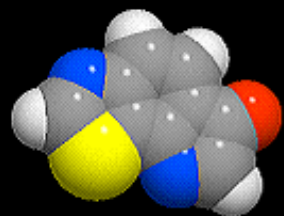
QUEST FOR THE RINGS

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with contributions from

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Basel, Switzerland**



Rings in Organic Molecules

Ring in molecules determine:

- shape of the molecule, molecule flexibility
- 3D position of substituents
- interaction with receptor (ring heteroatoms, as well as hydrophobic interactions)
- global molecular properties

Electronic ring properties determine molecule reactivity

- metabolic stability
- toxicity

Rings (scaffolds) play a central role in Combinatorial Chemistry

Rings in Various Molecular Collections

% Molecules with	Bioactives ~150'000	PubChem ~5.1 million	Nat. prods. ~120'000
any ring	96.8	98.4	91.3
aliphatic rings	65.2	42.2	73.2
aromatic rings	75.6	93.3	37.9
simple aromatic r.	73.3	91.9	36.3

**73.3% of drugs contain simple aromatic rings,
but their diversity is very limited.**





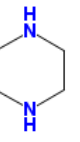
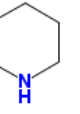





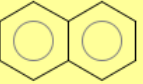


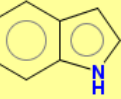
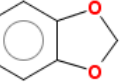
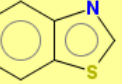
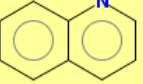





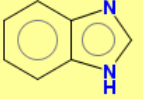



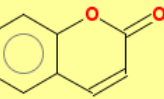
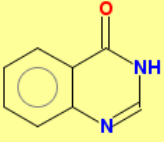
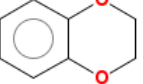
Source of data

Bioactives: WDI (Thomson Derwent) + MDDR (Elsevier MDL)

PubChem: <http://pubchem.ncbi.nlm.nih.gov/> (Sep 2006, normalized structures)

Natural Products: Dictionary of Natural Products (Chapman & Hall / CRC)

Most Common Rings in PubChem

 80.13	 4.96	 4.70	 4.62	 4.58	 4.09
 3.22	 2.93	 2.65	 2.56	 2.47	 2.47
 2.16	 1.70	 1.69	 1.66	 1.65	 1.61
 1.59	 1.30	 1.18	 1.16	 1.07	 1.01
 0.95	 0.95	 0.91	 0.89	 0.88	 0.86

20 of 30 most common rings (marked yellow) belong to simple aromatic subset.

Poor Scaffold Diversity

Scaffold type	PubChem ~5.1 million	Bioactives ~150,000
5	50	36
6	69	34
55	107	30
65	590	229
66	305	107
555	10	1
565	118	18
655	100	20
656	239	56
665	505	142
666	383	107
All	2'476	780

The number of unique simple aromatic scaffold types identified is relatively small.

Intuitively, one would expect much higher scaffold diversity.

Quest to Identify Novel Bioactive Rings

Question

Can we identify novel scaffolds with good chance of bioactivity ?

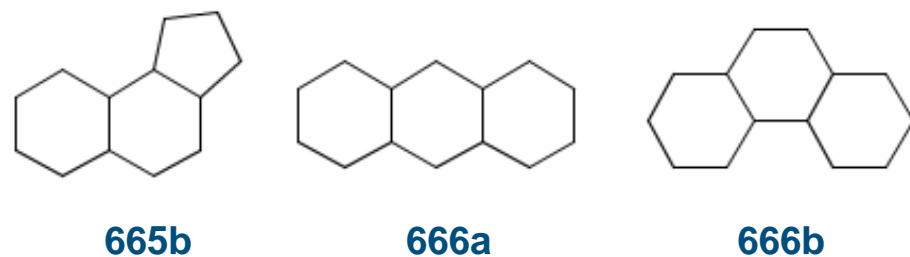
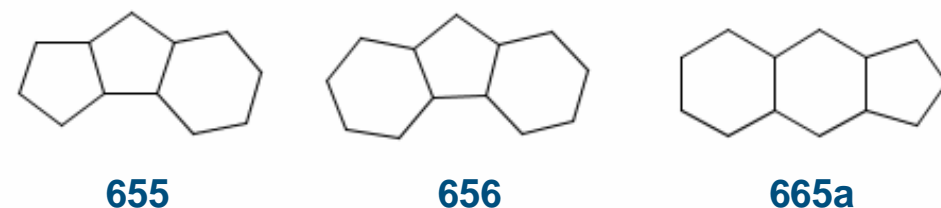
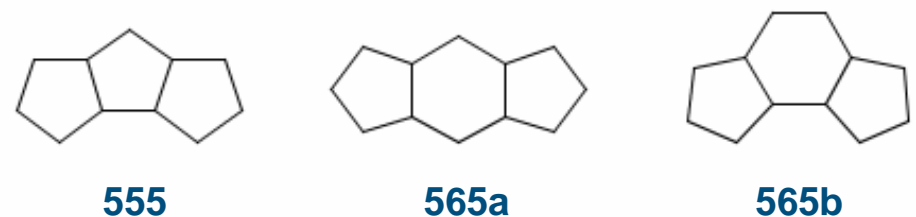
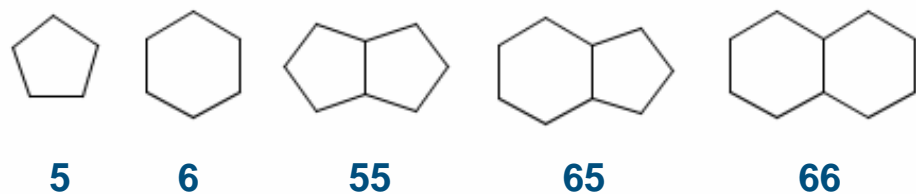
Data

- 1) scaffolds found in bioactive molecules
- 2) complete enumeration of scaffolds up to certain complexity level

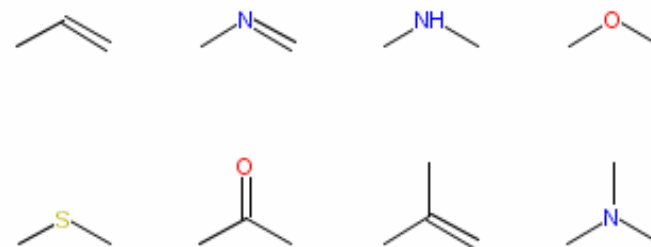
Method

Characterization of scaffolds by various calculated properties and classification of dataset by self-organizing neural networks. Identification of “active areas” in the scaffold space.

Constructing Rings



Building Blocks



Basic “chemistry” rules:

- max 4 heteroatoms
- max 2 exocyclic bonds
- no unstable bonds (O-O ...)

Only conjugated scaffolds were created. The 14 simple frames shown above form simple aromatic ring subset.

Virtual Library of Aromatic Rings

Scaffold type	Virtual set	PubChem ~5.1 million	Bioactives ~150,000
5	66	50	36
6	134	69	34
55	1'672	107	30
65	7'793	590	229
66	8'300	305	107
555	17'244	10	1
565	54'781	118	18
655	68'633	100	20
656	63'395	239	56
665	196'404	505	142
666	161'743	383	107
All	580'165	2'476	780

Number of scaffold types generated and found in existing collections.

580'165 scaffolds generated *in silico*, versus 780 found in drugs

Calculation of Ring Properties

Property calculation should be fast, properties should be easy to interpret.

Structural properties

atom counts, exocyclic atom counts, hetero / C ratio ...

Global molecular properties

MW, logP, PSA ...

Quantum chemical properties

Energy, DM, atomic charges ...

Quantum Chemical Calculations

SMILES



3D structure (CORINA)



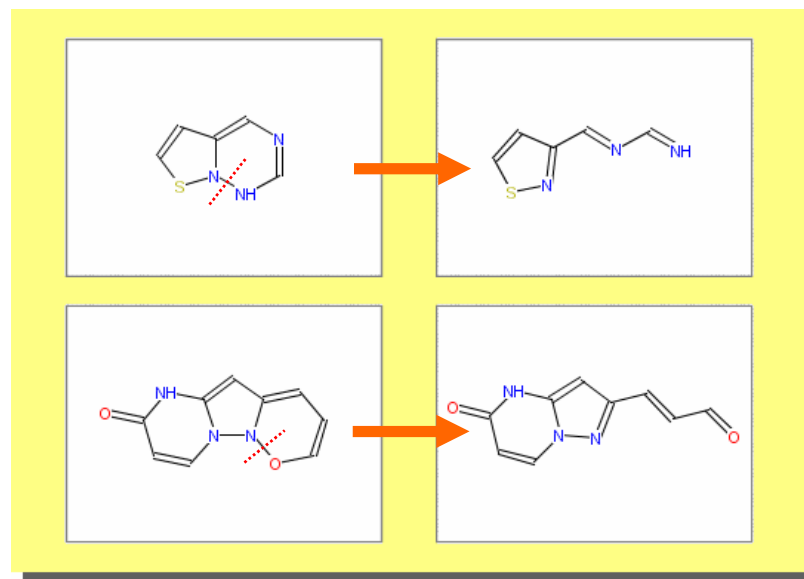
Full geometry optimization (AM1)



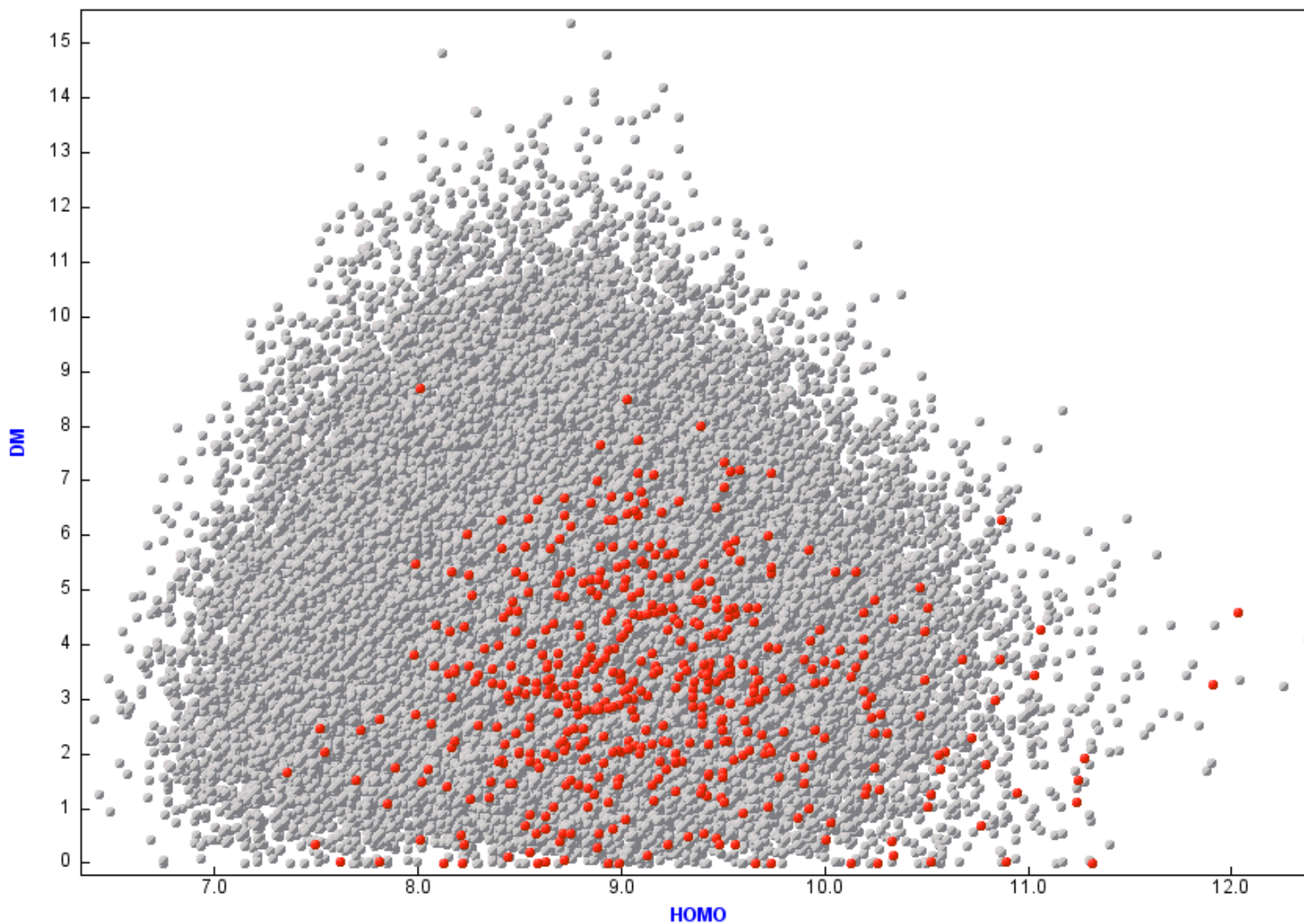
Consistency check (generation of unique SMILES from optimized geometry, comparison with the original SMILES), the check removed cases when ring opened during the optimization (see the figure)



Retrieval of calculated data from the result file

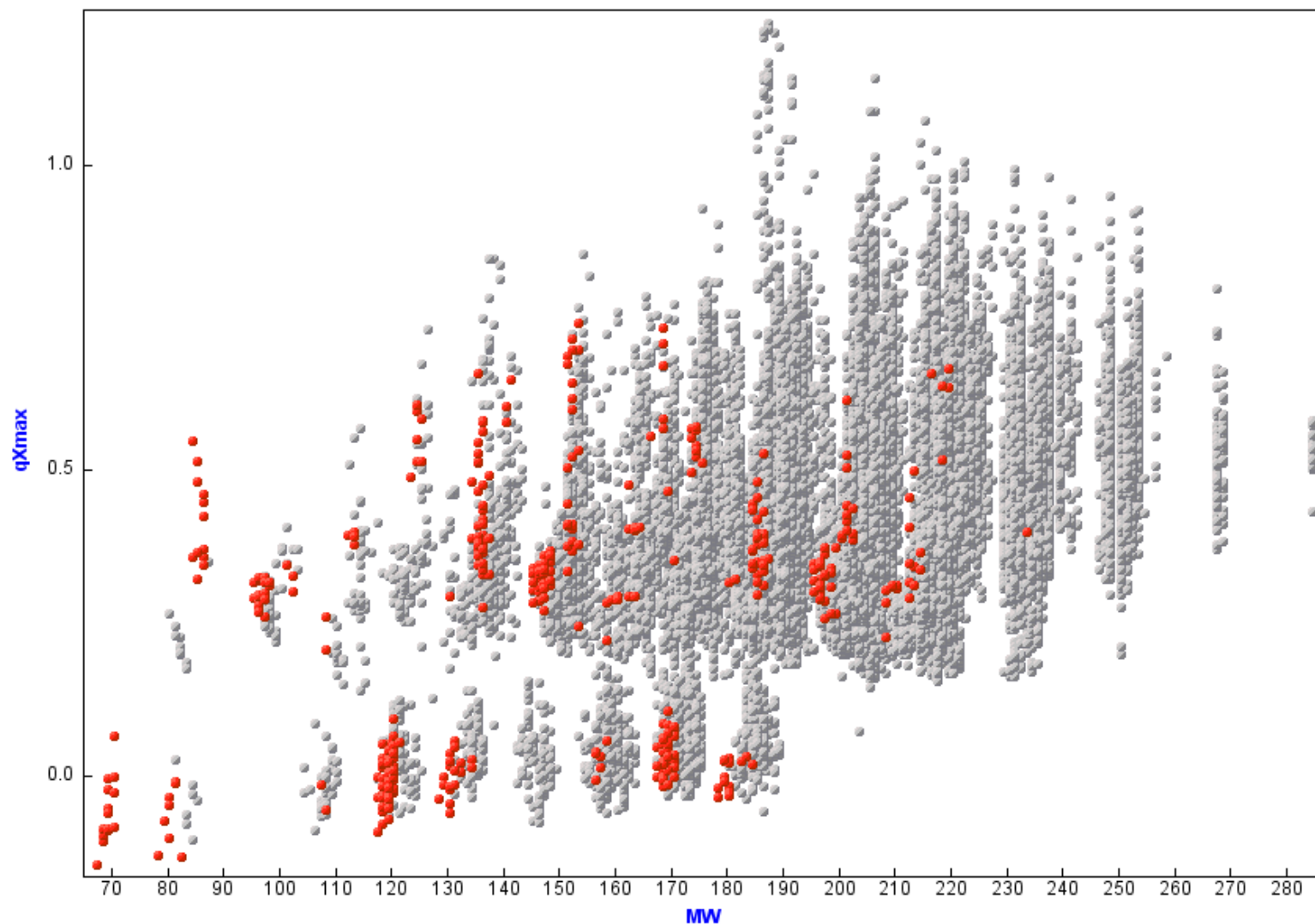


Analysis of Ring Properties



Some properties show no difference in distribution between active subset (red) and the whole virtual collection.

Analysis of Ring Properties



Some parameters show distinct clustering of active scaffolds (red) in the certain regions of physicochemical space.

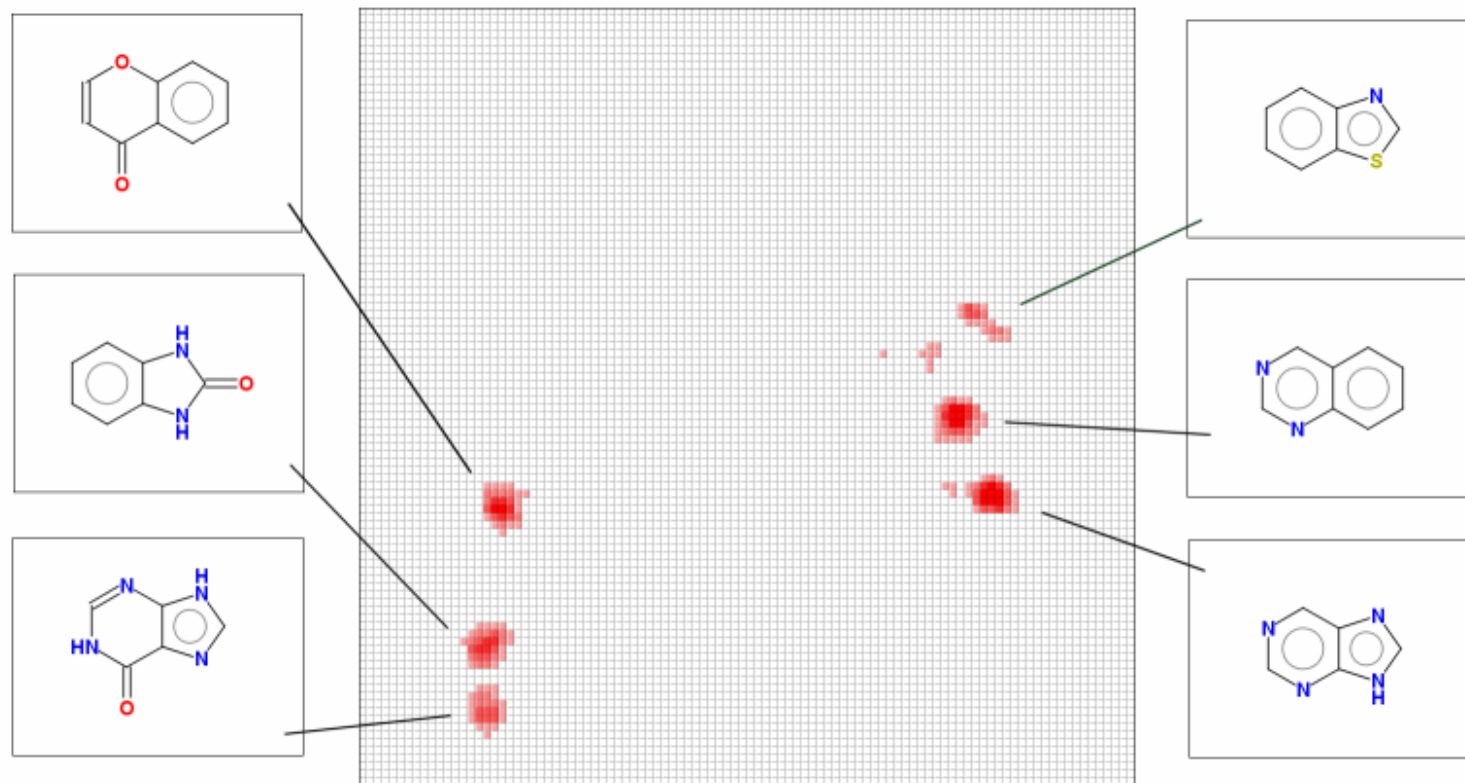
Self-Organizing Neural Networks

A SOM (Kohonen) neural network is a powerful tool to simplify and classify complex multidimensional data.

Scaffold data were normalized and pre-processed to remove non-informative descriptors and resultant data matrix (~580'000 structures, ~40 descriptors) was analyzed by NN.

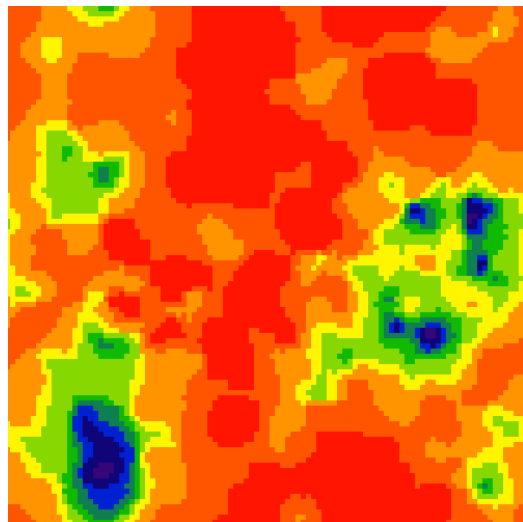
A net size with 100 x 100 cells was used, with the Kohonen network implemented in-house using Java.

Neural Network Analysis of Ring Properties

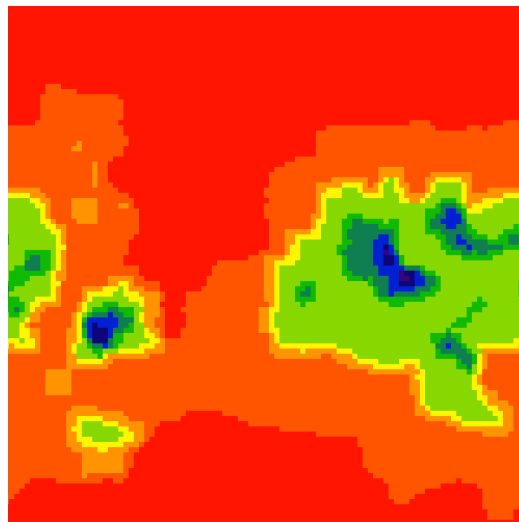


The bioactivity is sparsely distributed in several small “activity islands”. Novel scaffolds from these areas have a good chance of showing biological activity.

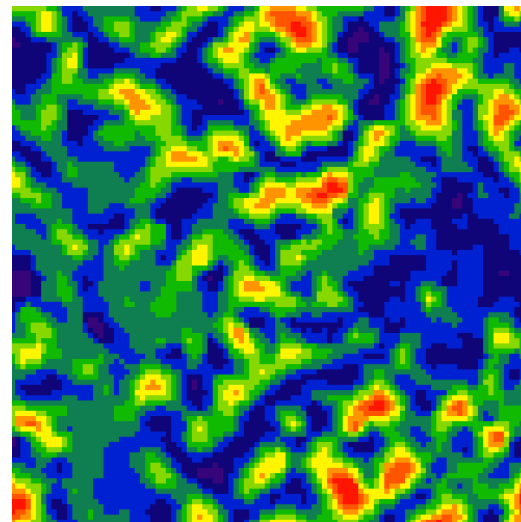
Neural Network Analysis of Ring Properties



natoms



nNOS



DM

Although some properties show rough correlation with bioactivity, the overall relationship of bioactivity on properties is complex and non-linear.

The most important features are size, heteroaromatic composition of scaffolds and their stability.

Application of Ring Database in Drug Design

Purchase of samples for screening

identification of molecules containing rings having good bioactivity score, novel for company collection

Prioritization of scaffolds for combinatorial chemistry

design of combichem libraries around novel scaffolds with putative bioactivity

Bioisosteric replacement / scaffold hopping

identification of (known) rings having the same physicochemical properties as target ring

Synthesis of novel bioactive heterocycles

invention of synthetic methods leading to novel ring systems

More Information

Quest for the Rings - In Silico Exploration of Ring Universe to Identify Novel Bioactive Heteroaromatic Scaffolds

Peter Ertl, Stephen Jelfs, Jörg Mühlbacher, Ansgar Schuffenhauer, and Paul Selzer

J. Med. Chem. 49, 4568 - 4573 (2006)