QSAR for the characterization of drug resistance: Differential QSAR (DiffQSAR) using mathematical chemodescriptors

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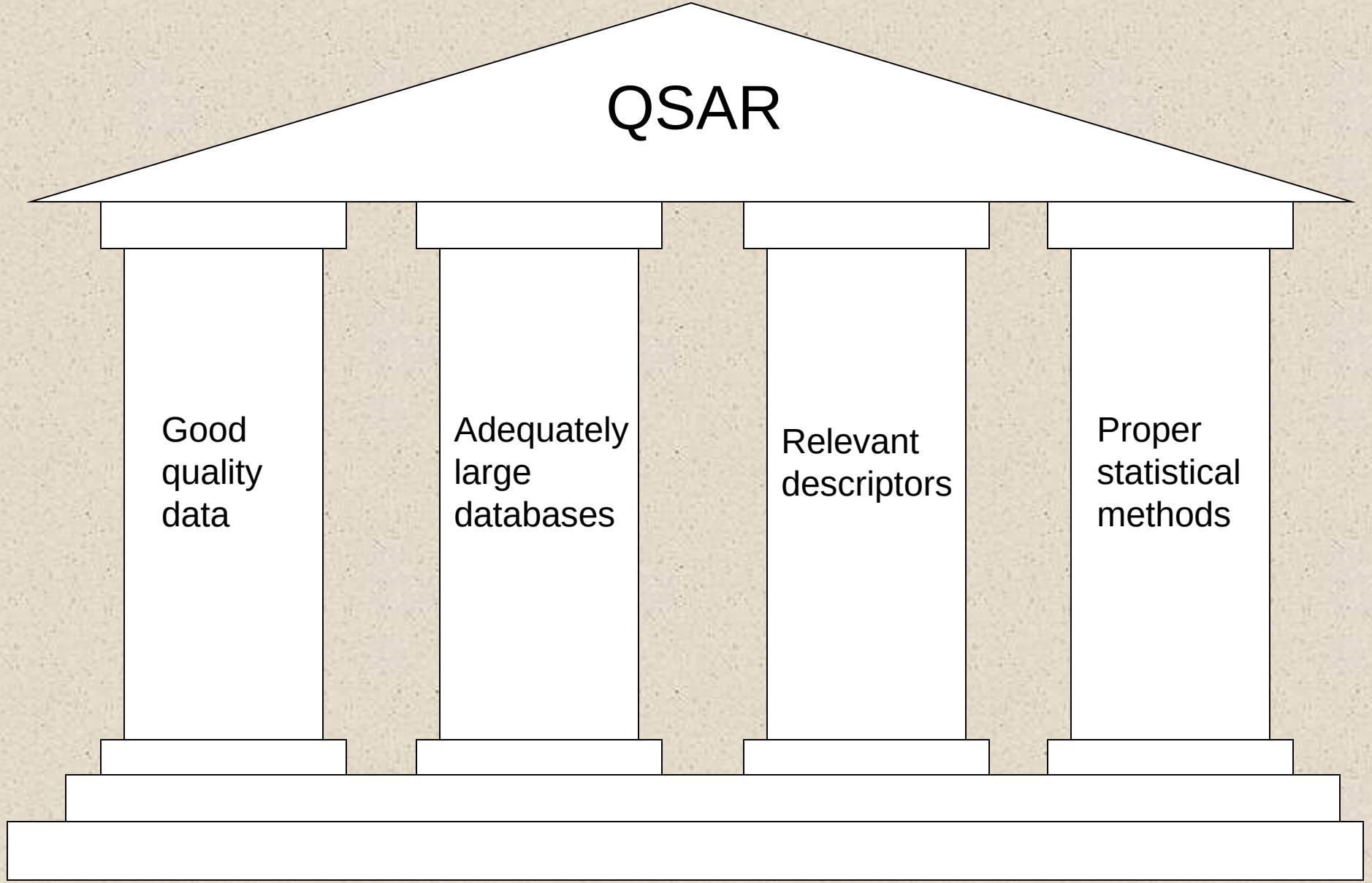
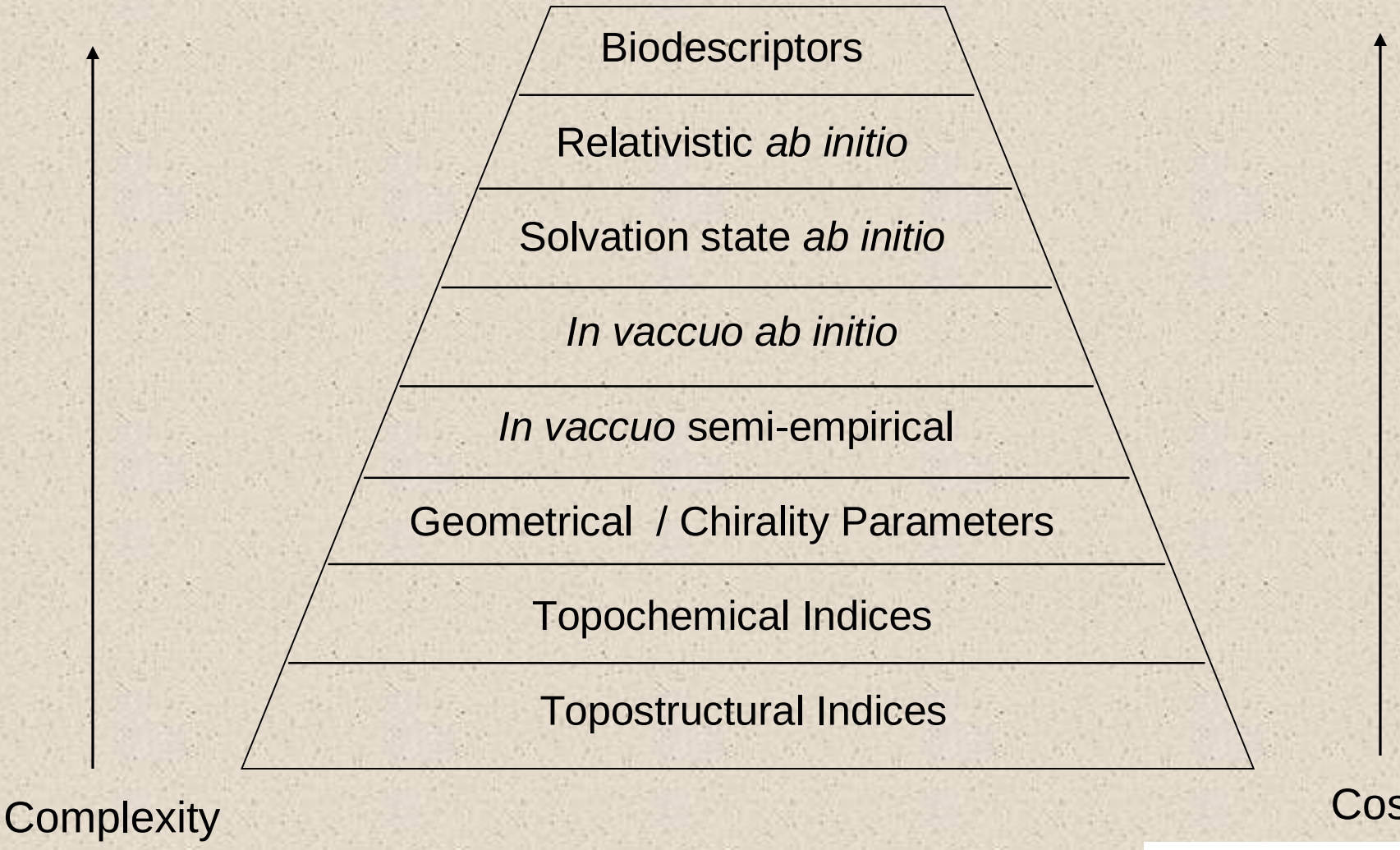
The most fundamental and lasting objective of synthesis is not production of new compounds, but **production of properties.**

Norris Award Lecture, 1968
George S. Hammond

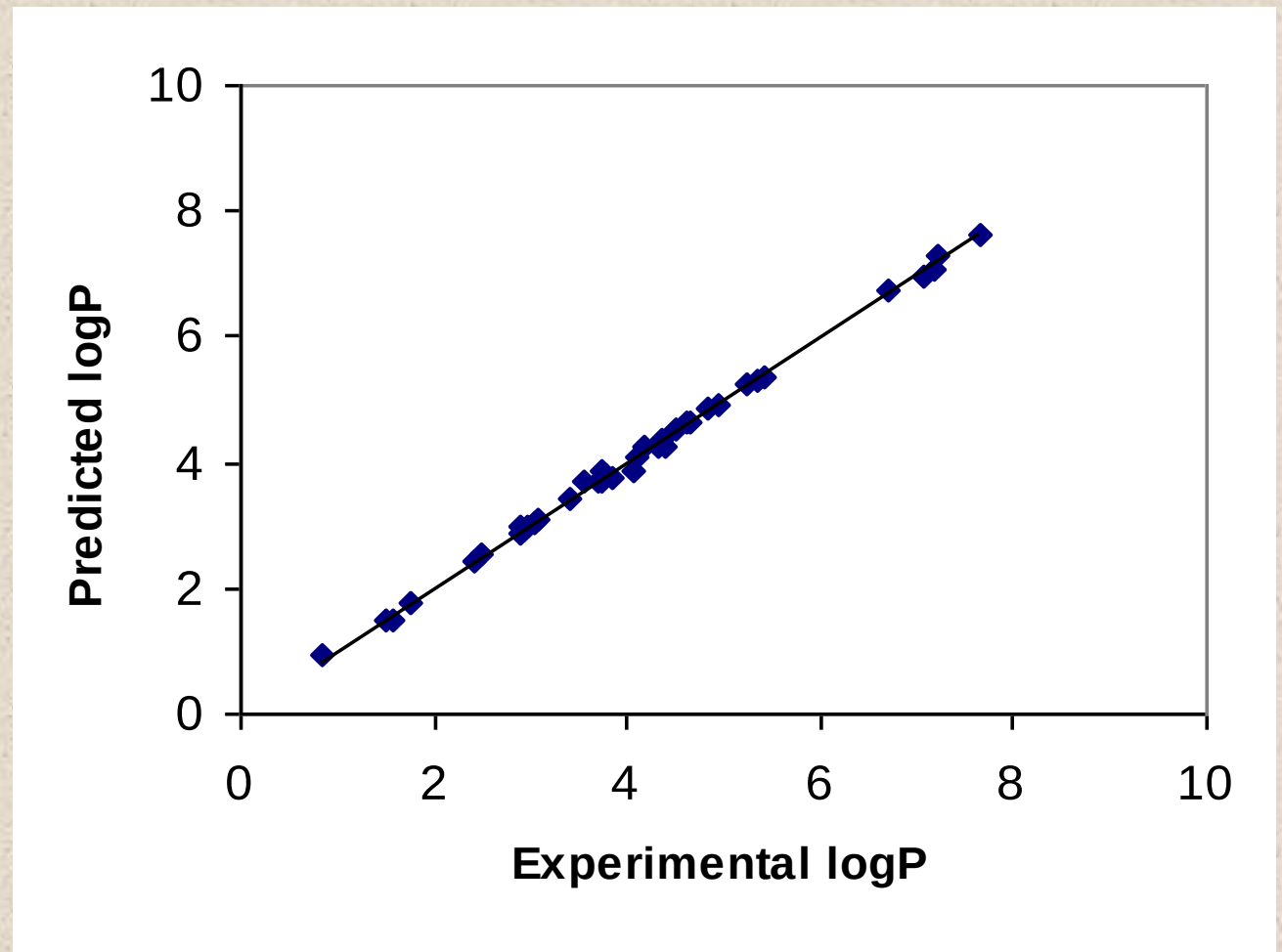
MAJOR PILLARS OF QSAR



Hierarchical QSAR



Blood: Air Partition Coefficient Model (TC) Developed on 39 Diverse Chemicals

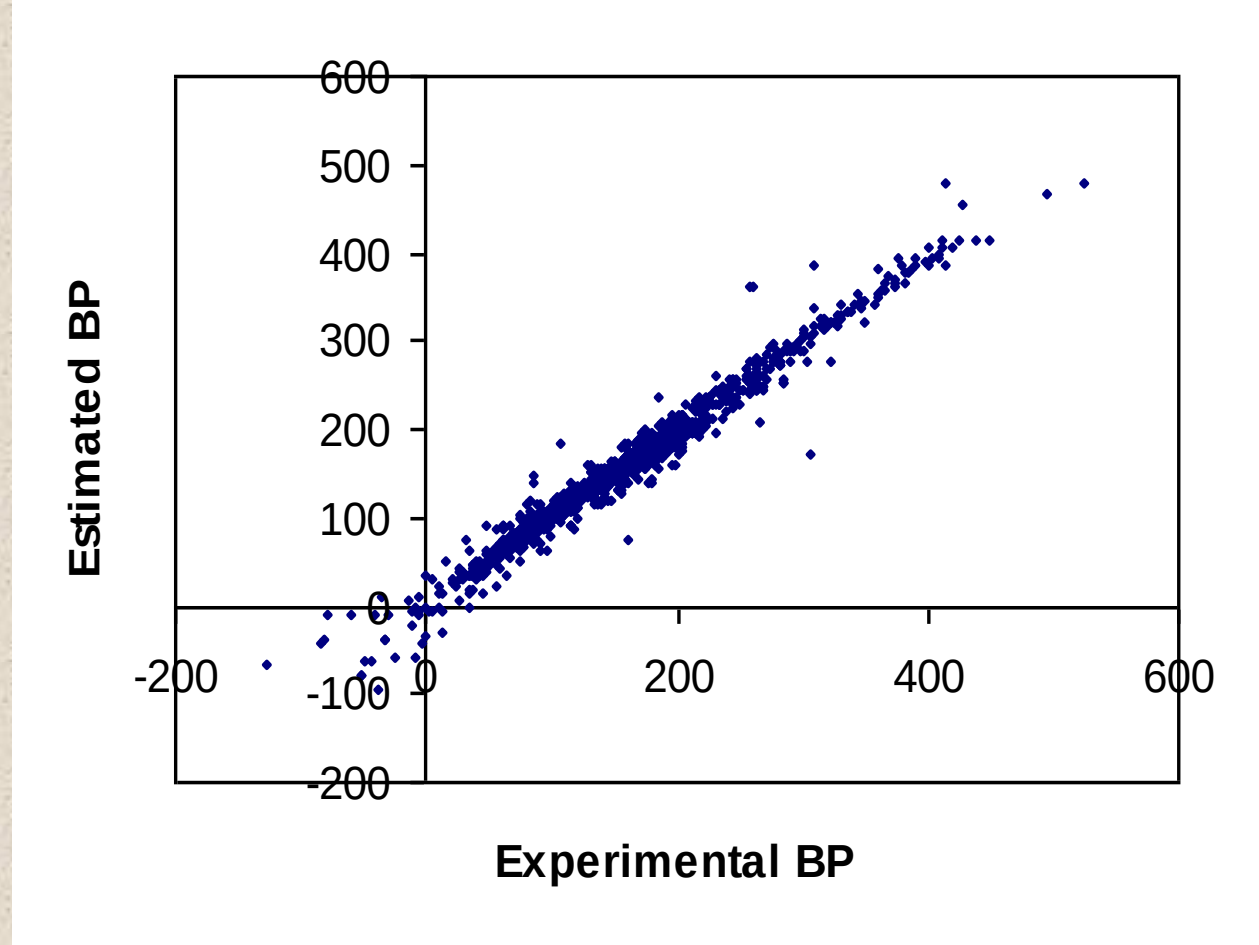


S. C. Basak, D. Mills, H. A. El-Masri, M. M. Mumtaz, and D. M. Hawkins, *Environ. Toxicol. Pharmacol.*, 16, 45–55 (2004).

UMD Natural Resources Research Institute

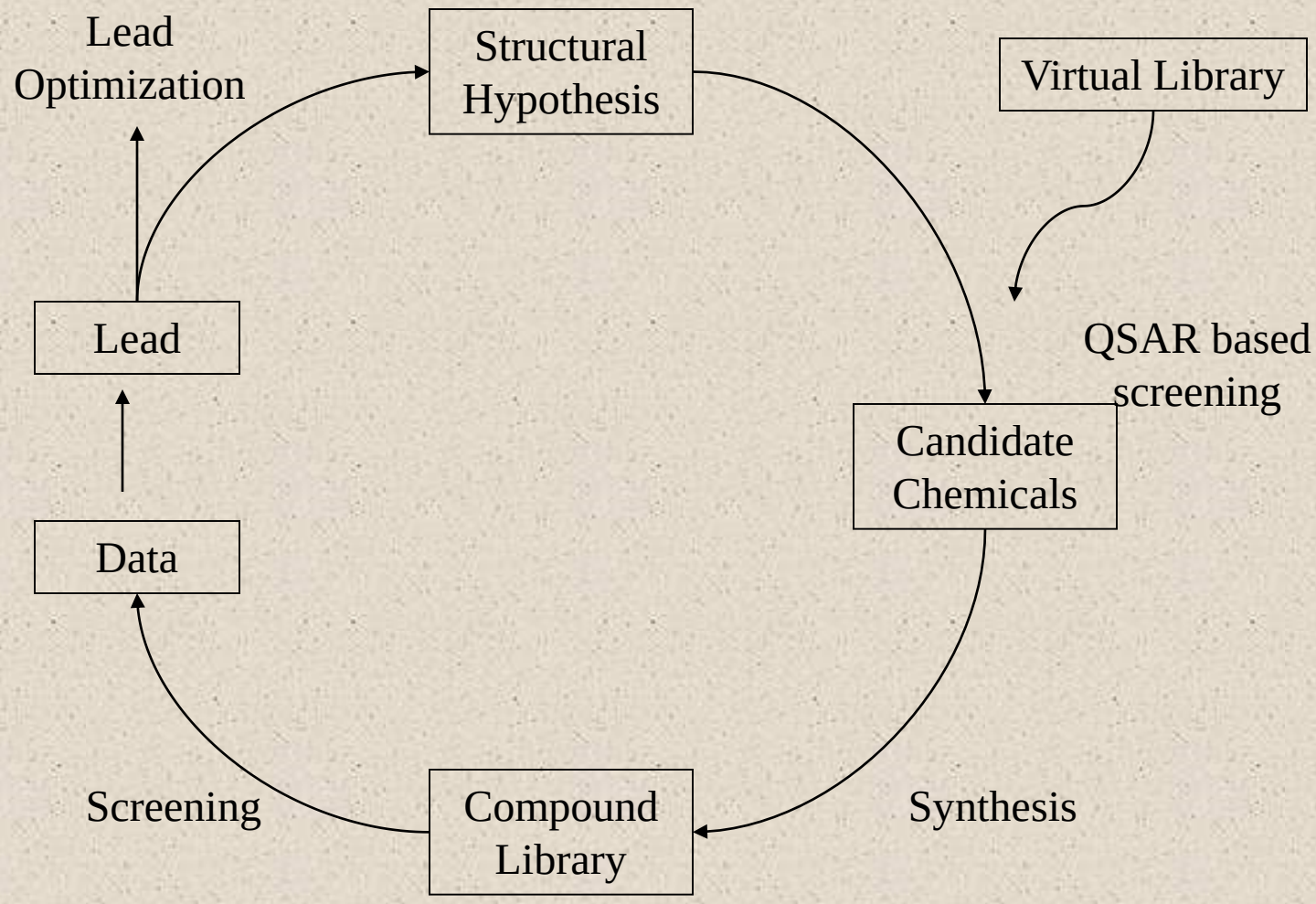
Normal Boiling Point for 1015 Diverse Chemicals

$n = 1015$, $R^2 = 0.97$, $s = 15.7$, $F = 4014$



Basak, S. C. and Mills, D. *MATCH*, 2001, 44, 15-30.

Combinatorial Chemistry & QSAR

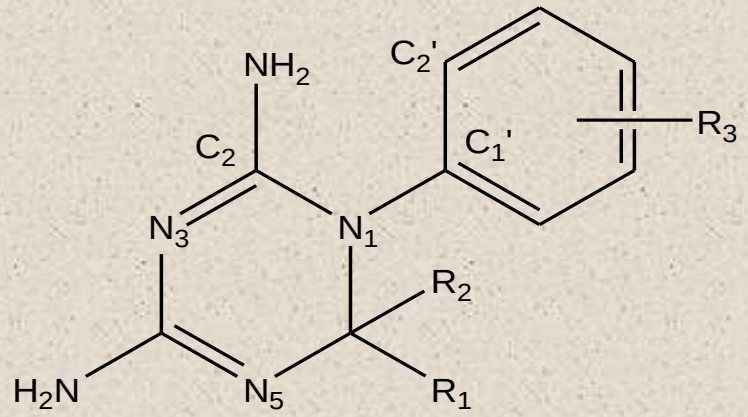


Differential QSAR

QSAR of molecules acting on related bio targets to illuminate the differences in chemical-biological interactions.

Differential QSAR

Cycloguanil analogs as PfDHFR inhibitors



- Wild type
  vs
- Mutant type

- TIs and APs
- RR, PCR, PLS
- Low overlap of significant descriptors

Regression Results

Dependent variable = binding affinity

Model	N	Descriptors	q^2, wild type			q^2, mutant type		
			RR	PCR	PLS	RR	PCR	PLS
1a 1b	58	TI	-0.617	0.123	-0.077	0.785	0.712	0.788
2a 2b	58	TI + AP	0.631	0.212	0.391	0.857	0.684	0.787
3a 3b	57[a]	TI	0.674	0.231	0.511	0.795	0.695	0.750
4a 4b	57[a]	TI + AP	0.790	0.292	0.726	0.874	0.691	0.836

[a] Compound #22 excluded

Of the 20 descriptors with the highest [t] values **only two are common between the wild and resistant strains** of plasmodium DHFR

QSAR to gauge biology

Characterization of Dihydrofolate Reductases from Multiple Strains of *Plasmodium falciparum* using Mathematical Descriptors of their Inhibitors

Subhash C. Basak, Denise Mills, and Douglas M. Hawkins, **Chemistry and Biodiversity, , 8, 440-453, 2011**

Five strains of DHFR

Wild, mut 1, mut 2, mut 3,and mut 4

Quantify their pairwise differences based on the set of significant descriptors needed for QSARs of inhibitors

Conclusions

The subsets of influential descriptors needed for the various strains may be looked upon as **high-dimensional pharmacophores** based on a set of calculated descriptors which capture the **distinct, but essential, chemical-biological interactions** involving the inhibitors and various DHFR enzymes, one from the wild type *Pf* and the others from resistant varieties of the organism.

Conclusions

Alterations in the genetic makeup of organisms, including the malaria parasite *Pf*, various multi-drug resistant bacteria such as mycobacterium tuberculosis (MTb), viruses such as Hepatitis C virus [46], human immunodeficiency virus influenza virus are occurring continuously in nature because of their exposure to drugs, adverse conditions, and other evolutionary pressures

Conclusions

The pair-wise kappa values in conjunction with macromolecules (enzyme or receptors) and structurally broad set of ligands for the respective biotarget(s) may be a **useful tool in gauging the evolving mutual similarities/ dissimilarities of mutating organisms from a computational chemistry point of view.**