

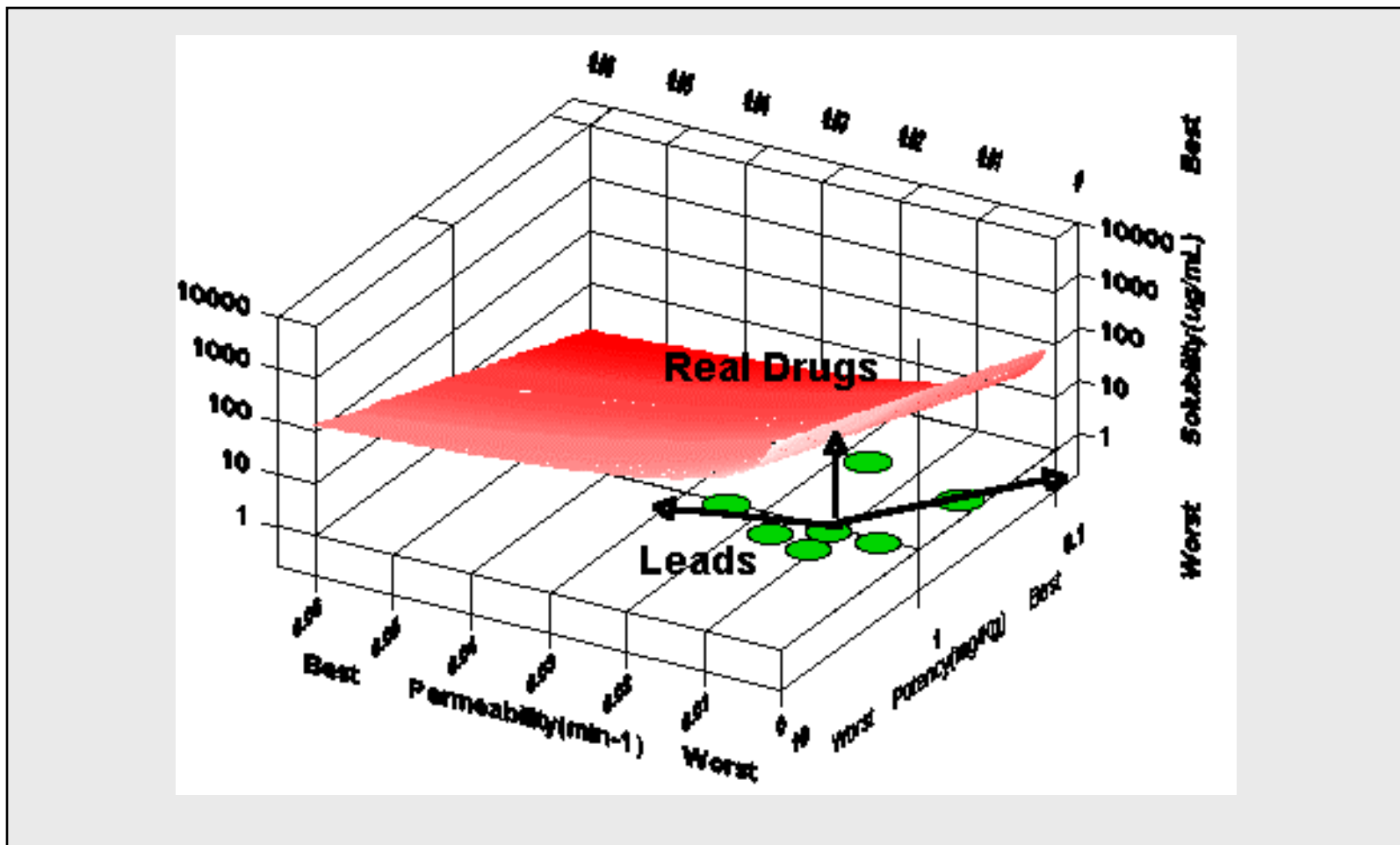
Will the Drugs of the Future Analyze like the Drugs of the Past?

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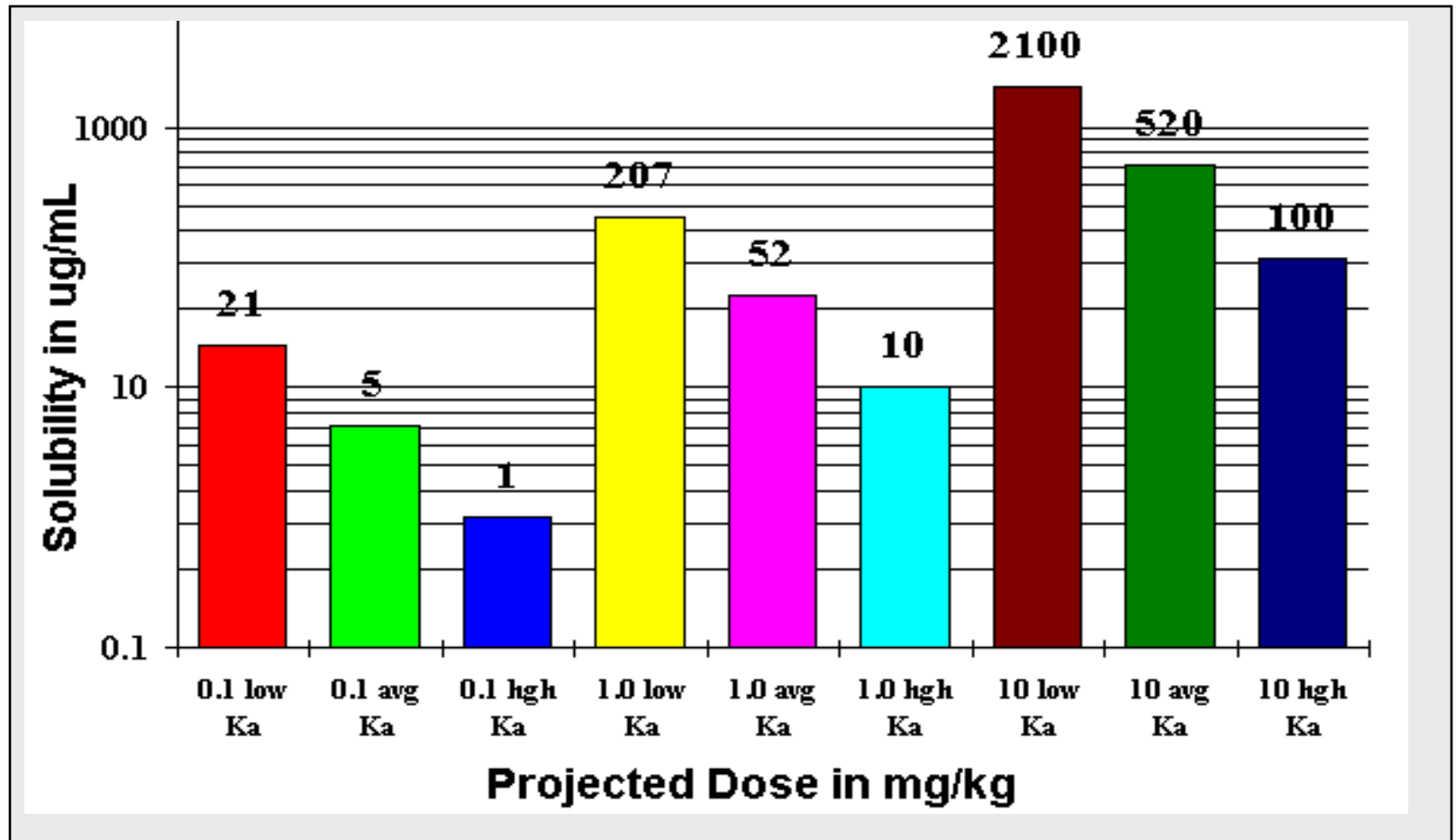
The bottom line message

- Chemistry structures for oral drugs are constrained by fundamental principles
- Expect small molecule chemistry to be like the past
- Or maybe more topologically interesting and chiral

Aqueous Solubility and Permeability Data Must be Provided to Chemistry as Early as Possible to Avoid Oral Absorption Problems

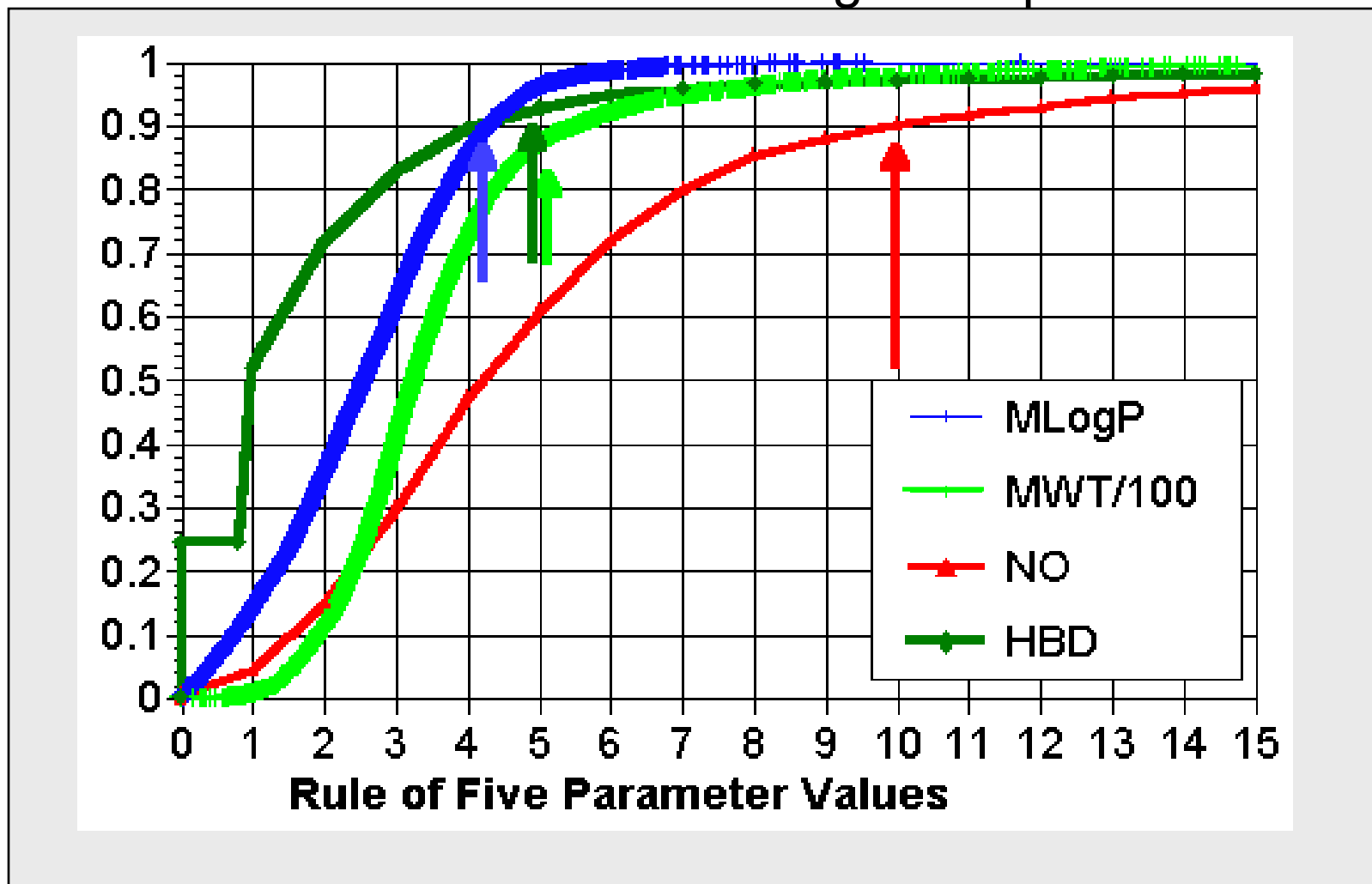


Minimum Acceptable Solubility in ug/mL Bars shows the minimum solubility for low, medium and high permeability (Ka) at a clinical dose.



Curatolo, William. **Physical chemical properties of oral drug candidates in the discovery and exploratory development settings.** Pharm. Sci. Technol. Today (1998), 1(9), 387-393.

Distribution Parameters for 7483 INN/USAN Drugs Define the 90% Limits Corresponding to Properties Unfavorable for Oral Drug Absorption.



The “rule of five” mnemonic

- Poor absorption or permeation are more likely when there are:
- More than 5 H-bond donors.
- The MWT is over 500.
- The CLog P is over 5 (or MLOGP is over 4.15).
- The sum of N's and O's is over 10.
- Substrates for transporters and natural products are exceptions.

Rules and common sense

- Rules play to the probability
- Exceptions will always exist
- For non orally active compounds
 - Michal Vieth et al. J. Med Chem, 2004, 47, 224-232The molecular properties and most commonly occurring structural elements are statistically analyzed to capture the differences between routes of administration.

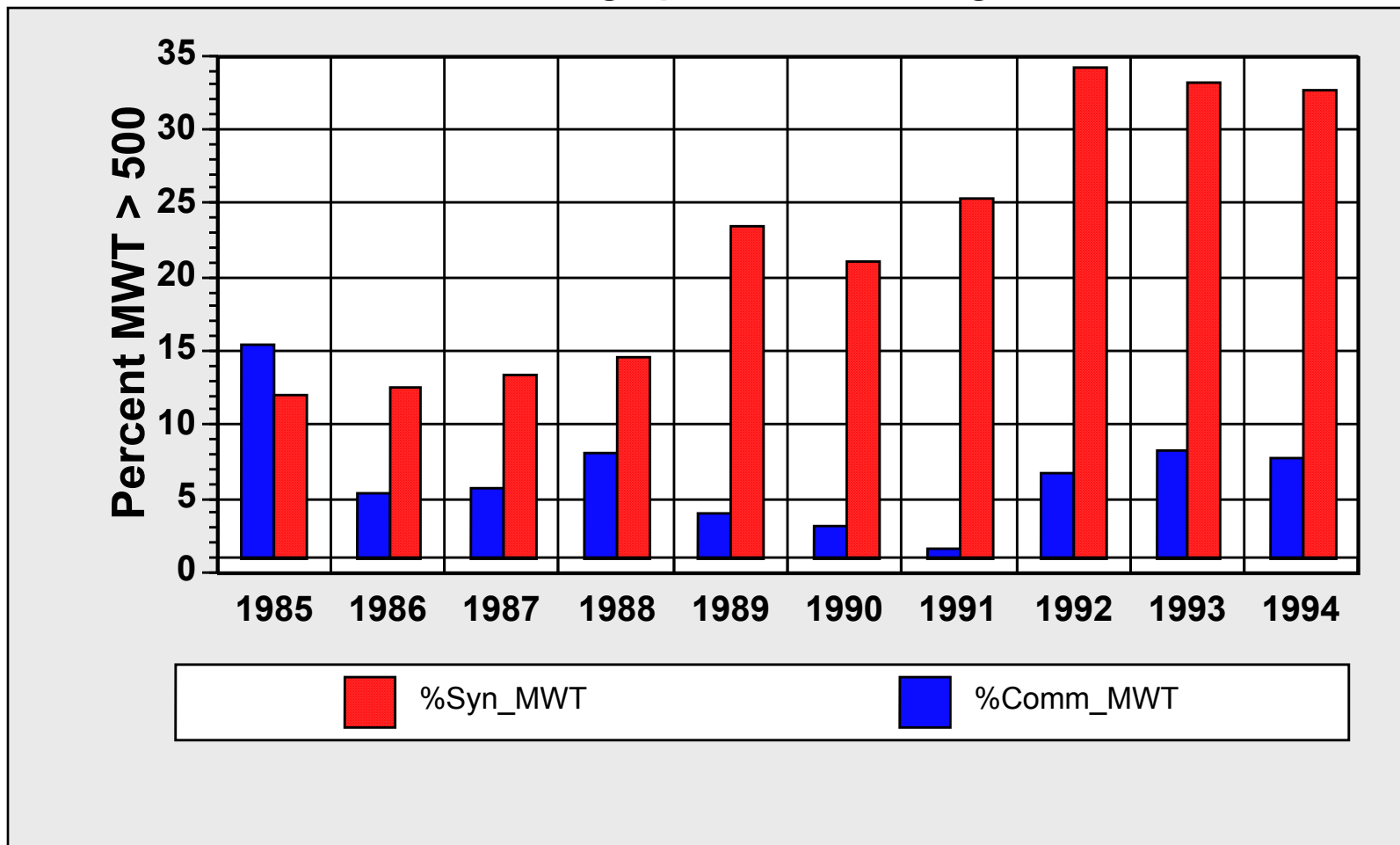
Today's reality in oral drugs

- Properties are worse in early discovery
- Approved drug properties are stable
- Properties improve through clinical
- Average MWT at approval is 350

Some targets are better than others

- Better
 - kinases
 - ion channels
 - aminergic GPCR's
- Worse
 - proteases
 - phosphatases
 - protein protein interactions

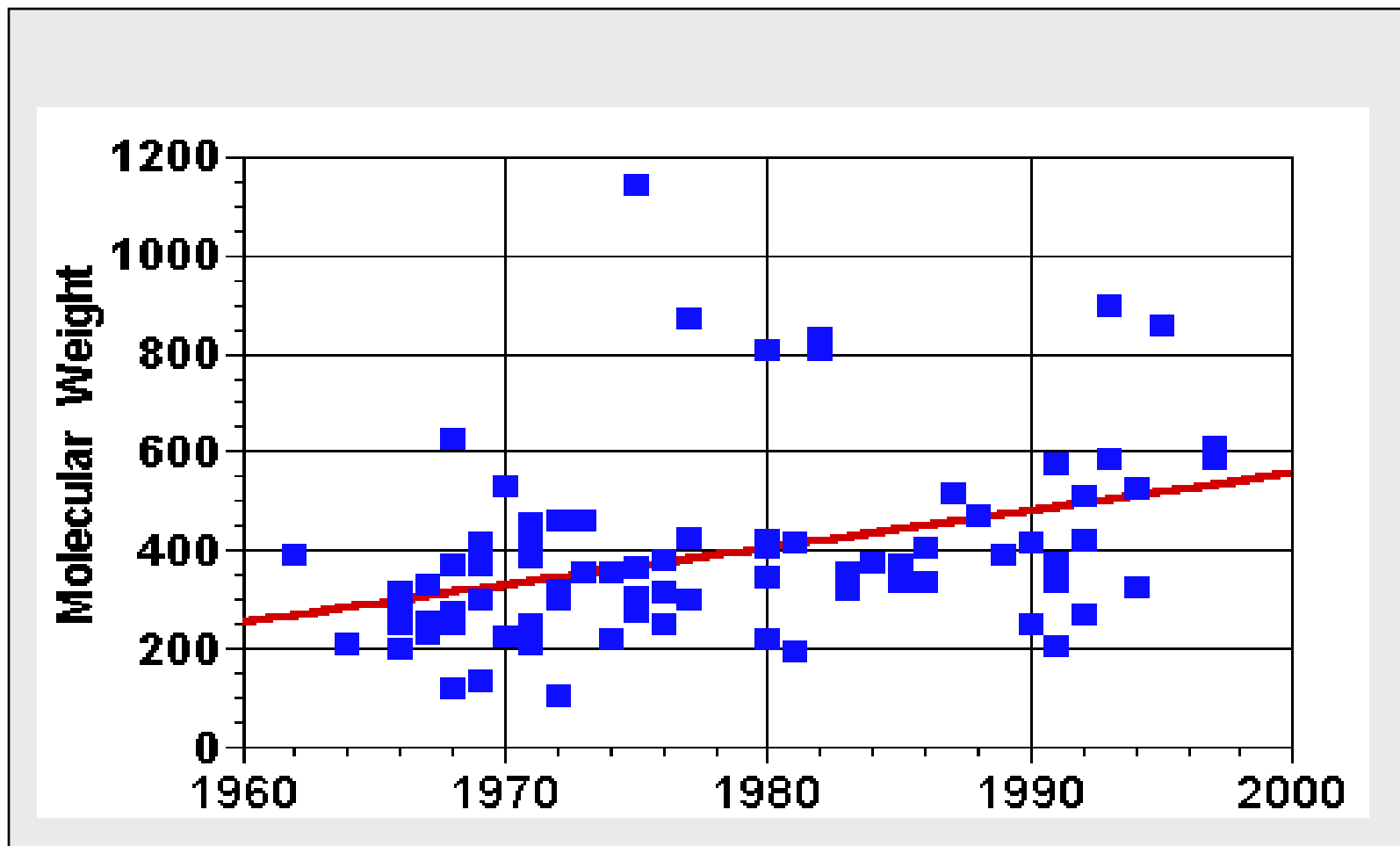
Leads at Pfizer changed towards higher molecular weight and lipophilicity with the advent of high throughput screening



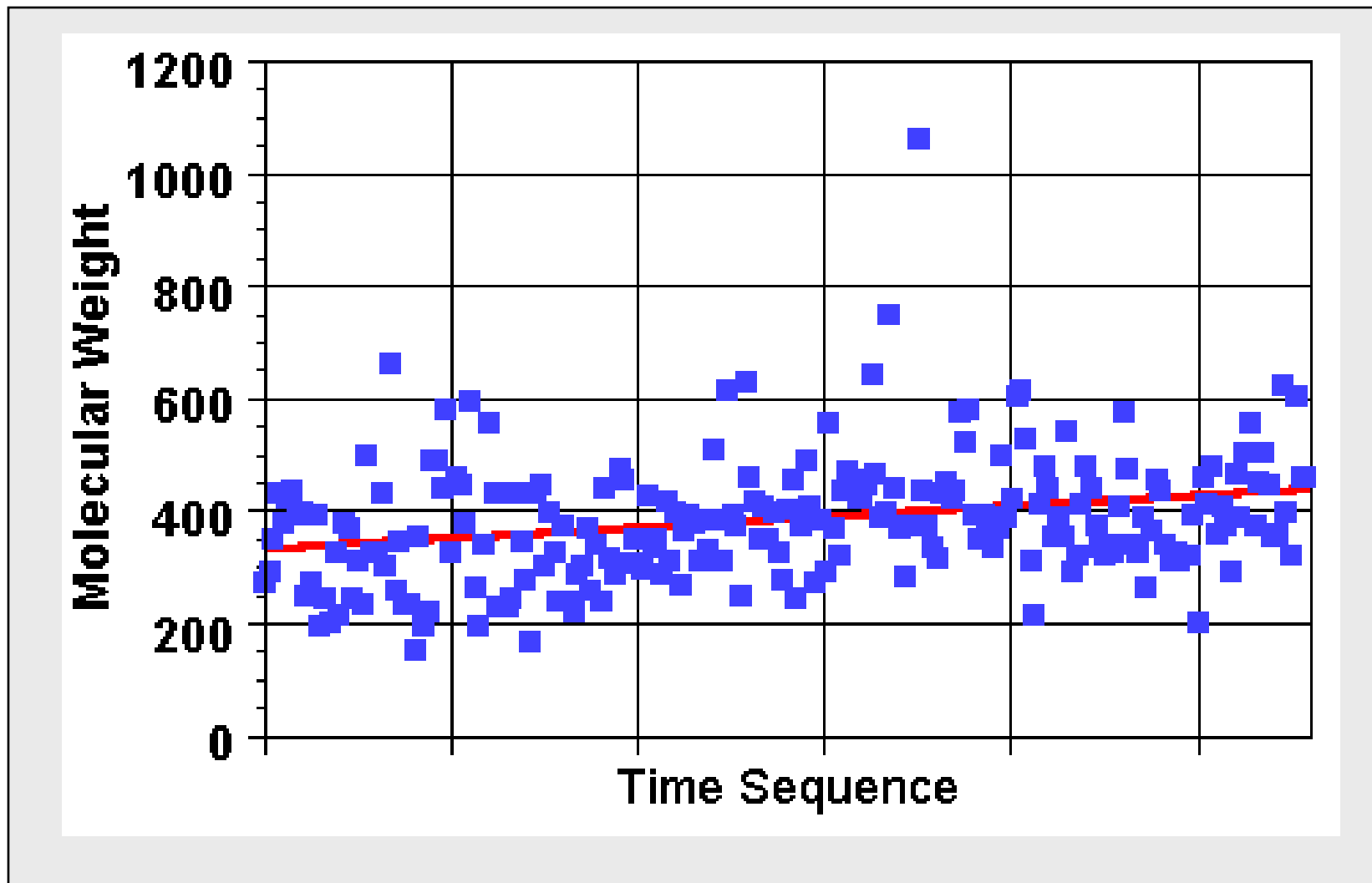
What is new in screening

- Fragment screening
- MWT 175 – 225
- Optimizable by medicinal chemistry
- Rule of 3
- Screen at 100 μ m – 5 mM
- NMR, x-ray, MS
- Bottom line - no trend to poor properties

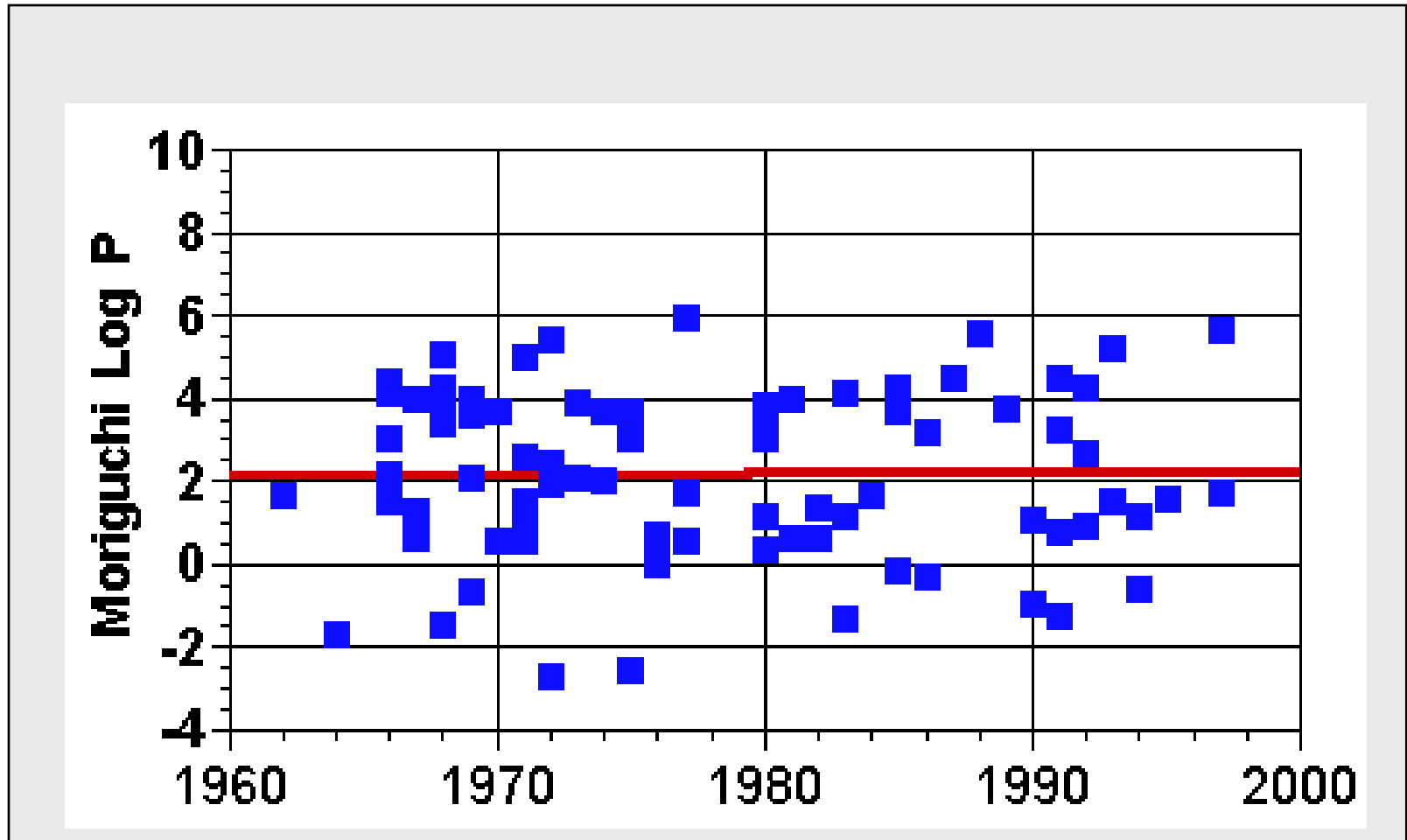
Upwards molecular weight trend in Merck advanced candidates



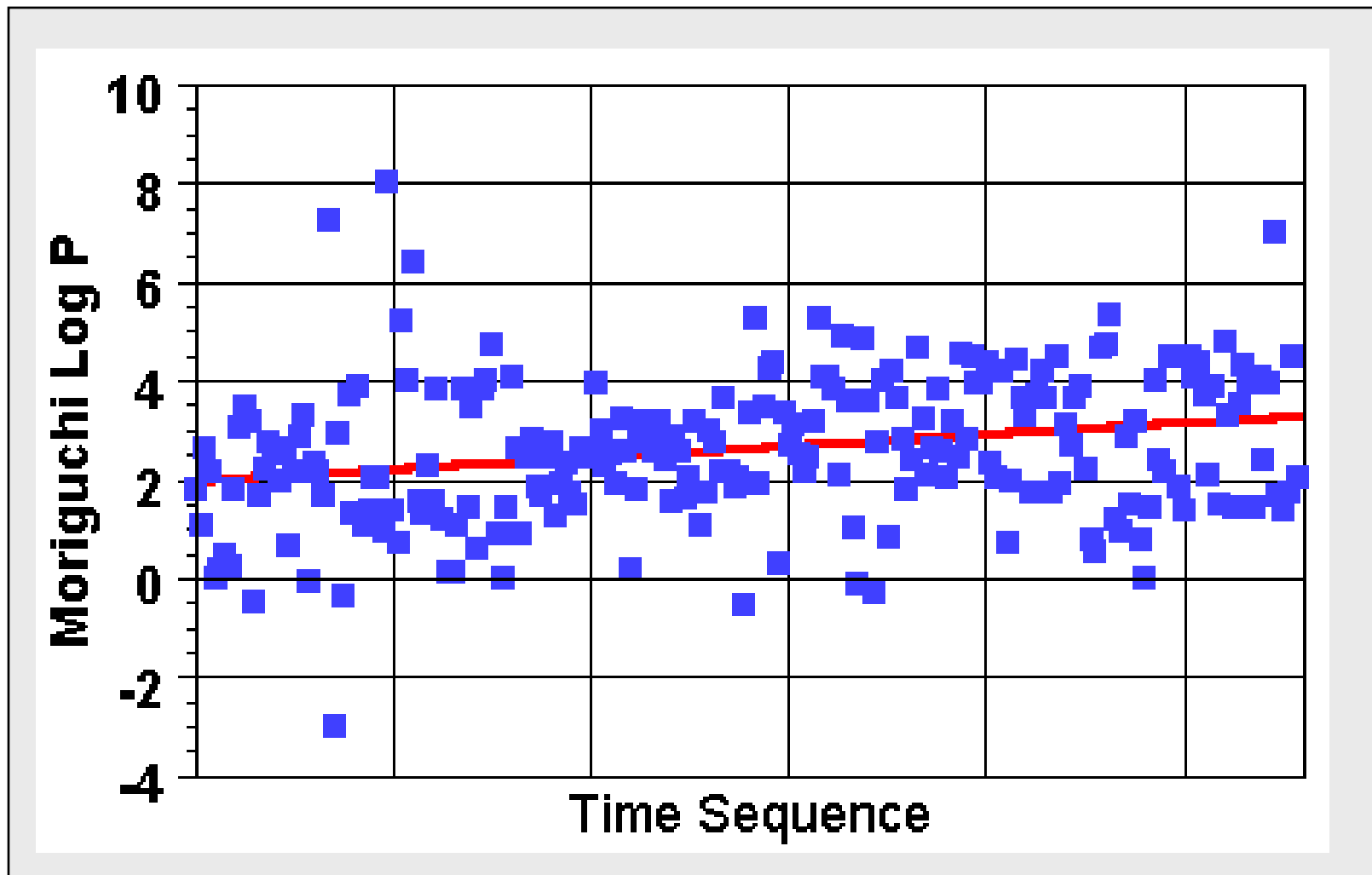
Upwards molecular weight trend in Pfizer, Groton early candidates



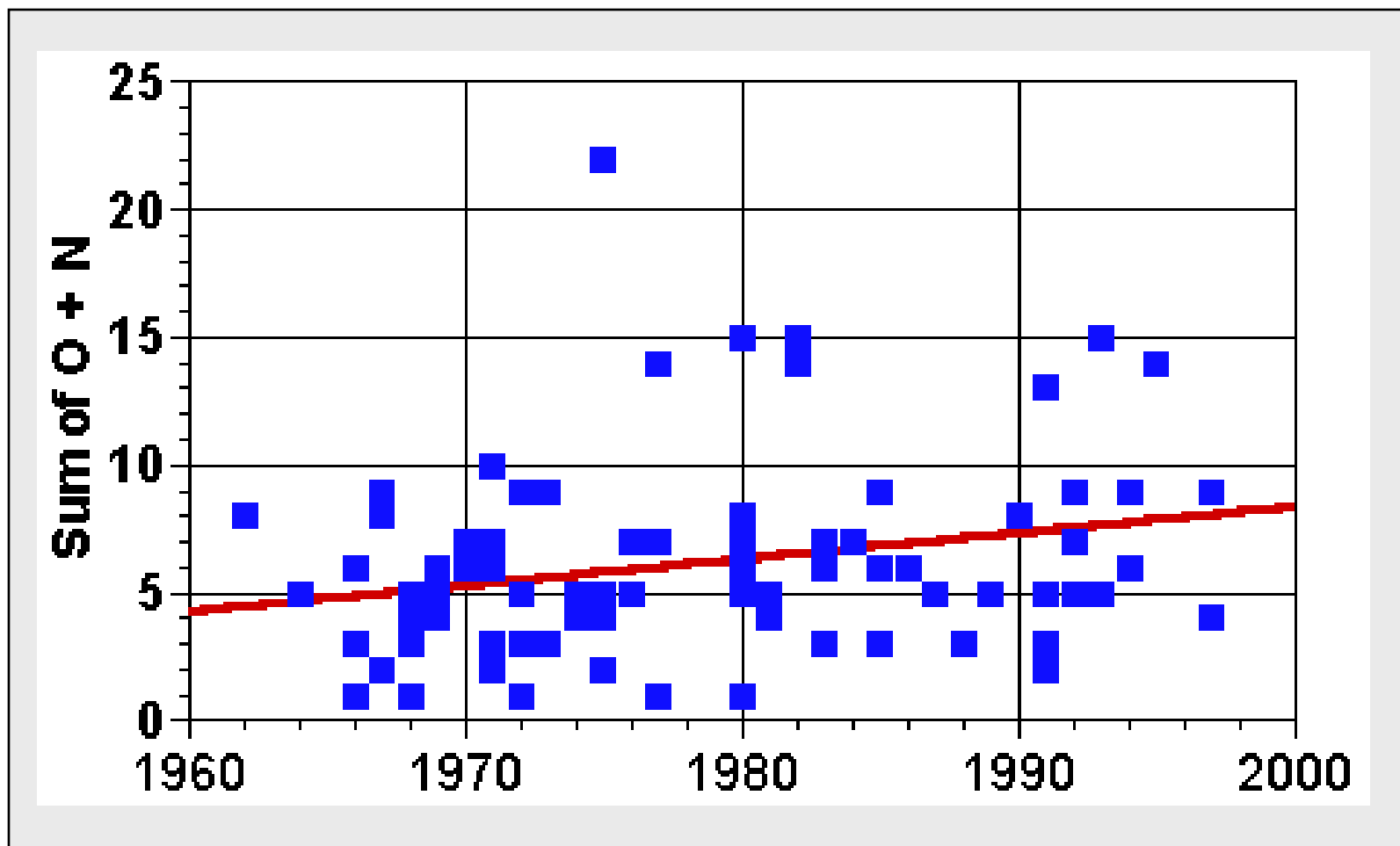
No increase in lipophilicity with time in Merck advanced candidates



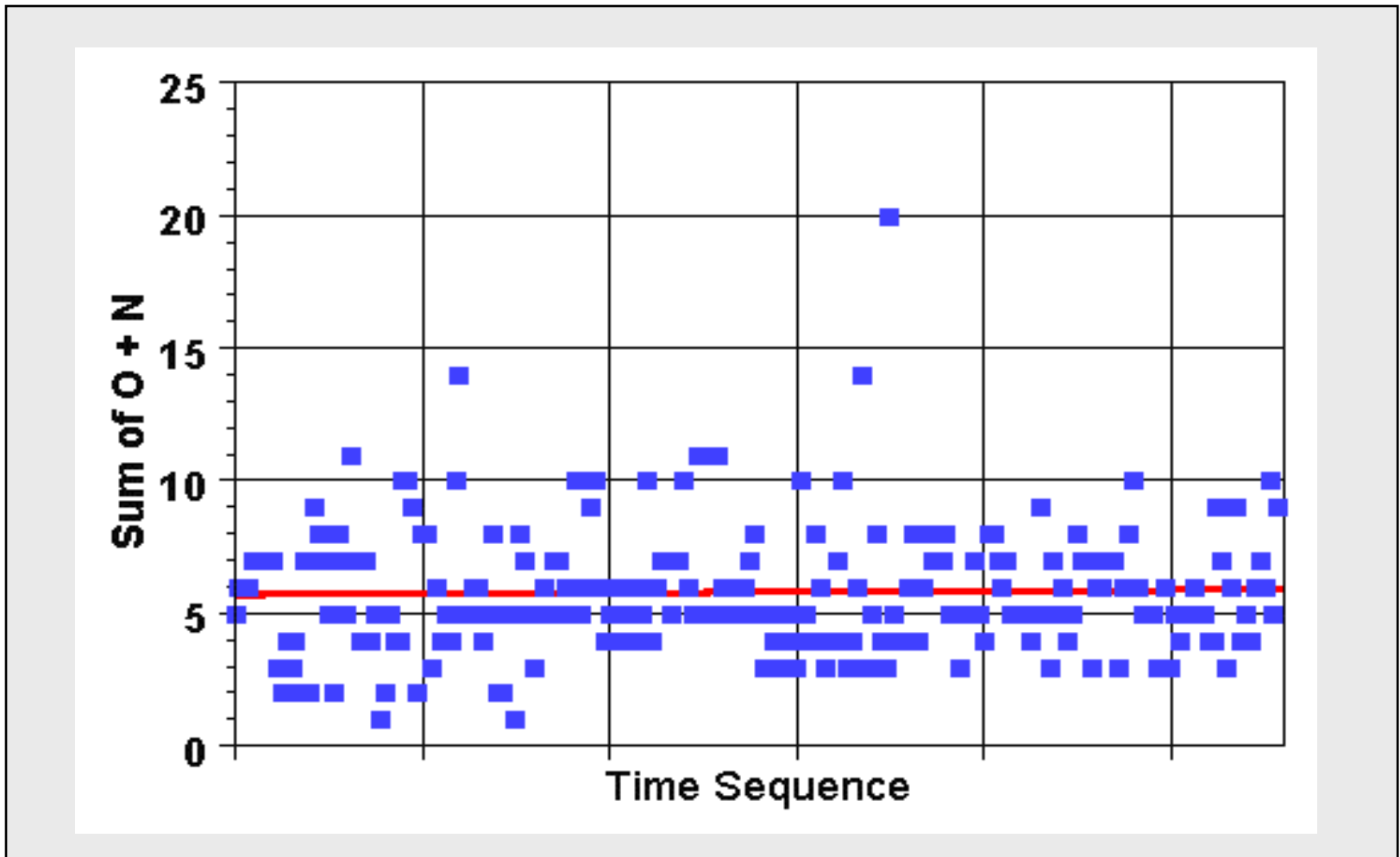
Upwards lipophilicity trend with time in Pfizer, Groton early candidates



Increasing hydrogen bond acceptor trend with time in Merck candidates



No hydrogen bond acceptor trend with time in Pfizer, Groton candidates



Potency and delivery options

- 80% of oral IND's are 1 mg/kg potency
- 10% of oral IND's are 0.1 mg/kg potency
- Dose is the key factor
- 20 mg dose allows delivery options
 - pulmonary
 - dermal
 - sublingual
 - oral via low capacity transporters

Why high in-vivo potency is difficult

- In-vitro and in-vivo activity
 - do not scale linearly
- Low dose in-vivo
 - transporters are not saturated
 - compounds clear rapidly
- So excellent in-vitro
 - but not so good in-vivo

High in-vivo potency is luck

- Planning high in-vivo potency is impossible
- Transporters are not understood
- Technically difficult screening
 - double transfectants
 - 10 years in the future
- No chemistry guidance
- Assays needed to solve a problem

Funky strange compounds

- Don't expect many strange structures that deviate from the "rule of 5"
- Unless a miracle happens and the transporter problem is solved soon
- Unless something happens to make discovery of high in-vivo potency possible

Poor intestinal permeability

- Unsolvable in formulation
 - “academic” science 10 years from reality
- Solvable in chemistry with pro-drugs
 - technically difficult
- Solvable in chemistry by structure changes
 - intramolecular H-bond
 - often limited by target biology limitations

Peptidomimetics increasing?

- Pro -
 - more protease targets in the human proteome than we expected
- Con
 - proteases are at the fringes of druggability
 - permeability issues are unsolvable in formulation

Historically few “innovator” targets / year

CHEMISTRY	CAS	NAME	YEAR	MWT	TARGET
Glucophage	657-24-9	Glucophage	1994	67.09115	perhaps acetylCoA carboxylase 2
Precose	56180-94-0	Precose	1995	645.6174	a-glucosidase
Cozaar	124750-99-8	Cozaar	1995	422.9212	Angiotensin receptor AT1
Fosamax	66376-36-1	Fosamax	1995	249.0983	perhaps farnesyl diphosphatase dehydrogenase
CellCept	116680-01-4	CellCept	1995	433.506	Inosine monophosphatase dehydrogenase
Accolate	107753-78-6	Accolate	1996	575.6892	Leukotriene receptor
Rezulin	97322-87-7	Rezulin	1997	441.5505	Peroxisome proliferator activated receptor
Plavix	120202-66-6	Plavix	1997	321.8284	Platelet P2Y12 receptor
Integrilin	188627-80-7	Integrilin	1998	831.9771	Platelet glycoprotein lib/IIIa receptor
Aggrastat	142373-60-2	Aggrastat	1998	440.6066	Platelet glycoprotein lib/IIIa receptor
Celebrex	169590-42-5	Celebrex	1998	381.3792	Cyclooxygenase 2
Viagra	139755-83-2	Viagra	1998	474.5862	Phosphodiesterase type 5
	180288-69-1	Herceptin	1998		ERBB2 (aka HER2/neu)
	185243-69-0	Enbrel	1998		Recombinant receptor for TNF
	170277-31-3	Remicade	1998		antibody for TNF
Rapamune	53123-88-9	Rapamune	1999	914.1972	FK-binding protein & target of rapamycin TOR kinase
Targretin	153559-49-0	Targretin	1999	348.4896	Retinoid X receptors
Xenical	96829-58-2	Xenical	1999	495.7495	Gastrointestinal lipase
	220578-59-6	Mylotarg	2000		Antibody to CD33
Tracleer	147536-97-8	Tracleer	2001	551.6261	Endothelin receptor
Gleevec	152459-95-5	Gleevec	2001	493.6167	BCR-ABL
	189032-40-4	Natrecor	2001		Recombinant B-type natriuretic peptide
	143090-92-0	Kineret	2001		Recombinant interleukin 1 receptor antagonist
	98530-76-8	Xigris	2001		Recombinant activated protein C

24 New Ligands in 8 Years Across Everybody

Decline of natural products

- Similar decision across most of Pharma
 - pragmatic, based on results
 - chemistry complexity is no advantage unless needed
- Decline coincident with:
 - rise of automated chemistry
 - demise of phenotypic screening
 - decline of infectious disease research
- Resurrection:
 - watch for reversal of the above three trends

Nucleotide targets?

- Protein targets:
 - hydrophobic binding
- Nucleotide targets
 - ionic, H-bonding binding
- Where would you find a library for screening against nucleotide targets?

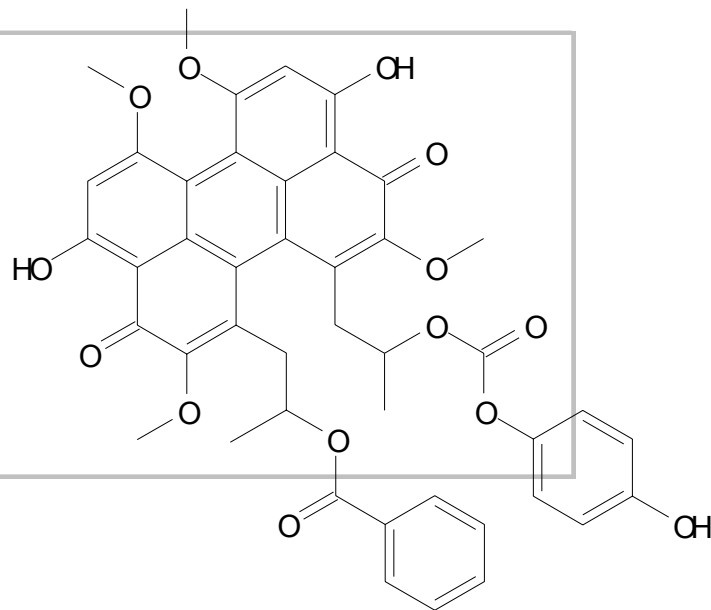
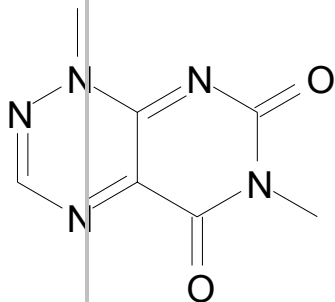
Space in screening and ligands

- Mechanistic screening
 - narrow target opportunity space
- Phenotypic screening
 - broad target opportunity space
- Typical medicinal chemistry compounds
 - broad chemistry space
- Natural products and diversity oriented synthesis
 - narrow chemistry space

Matching targets and ligand space

- Natural products and DOS
 - phenotypic targets - good
 - mechanistic targets – poor
- Typical medicinal chemistry
 - phenotypic targets – excellent: BUT
 - mechanism deciphering is tough
 - Mechanistic targets – good
 - mechanism is known so not an issue

Chemistry Terra Incognita

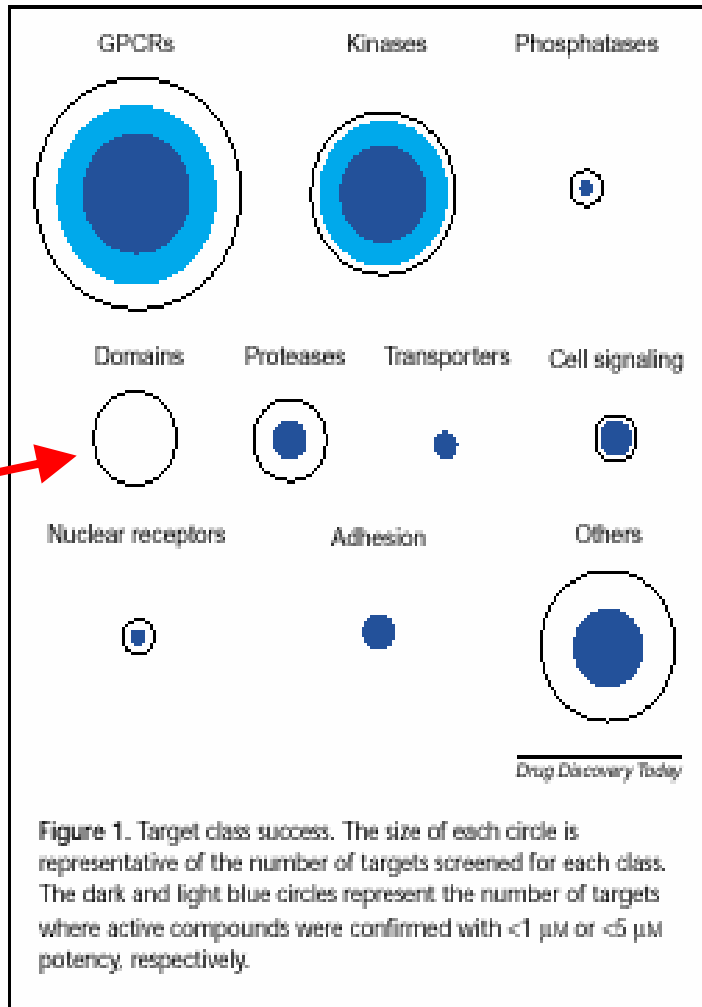


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Lepourcelet, Maina; Chen, Ying-Nan P.; France, Dennis S.; Wang, Huisheng; Crews, Phillip; Petersen, Frank; Bruseo, Charles; Wood, Alexander W.; Shivdasani, Ramesh A. Small-molecule antagonists of the oncogenic Tcf/ β -catenin protein complex. *Cancer Cell* (2004), 5(1), 91-102.

Success rate in protein-protein interactions



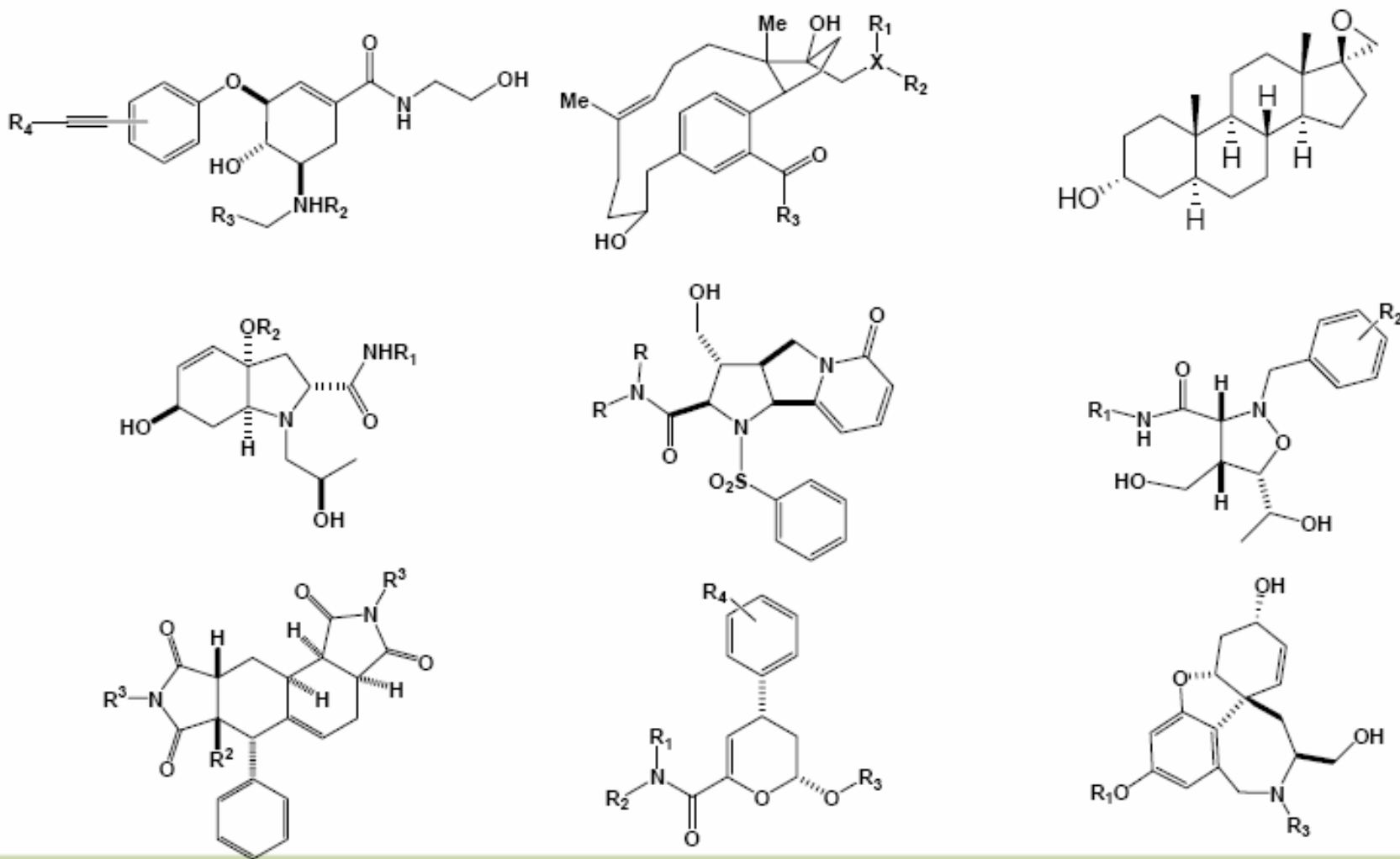
**Size of colored graphic
= screening success at
Pharmacopeia**

**Reproduced with permission from
“Targeting signal transduction with
large combinatorial collections”, D.
S. Auld, D. Diller, K. Ho, Drug
Discovery Today, 2002, 7(24) 1206-
13.**

Protein protein interactions

- Normal combichem does not work
- Natural products or DOS?
- Fragment screening on allosteric sites??

Skeletal diversity in DOS Infinity libraries



DOS, the big experiment

- DOS works on protein protein interactions
 - big change in chemistry
 - topologically complex, chiral compounds
- DOS fails on protein protein interactions
 - business as usual in analytical chemistry