

ISSUES IN DRUG DISCOVERY



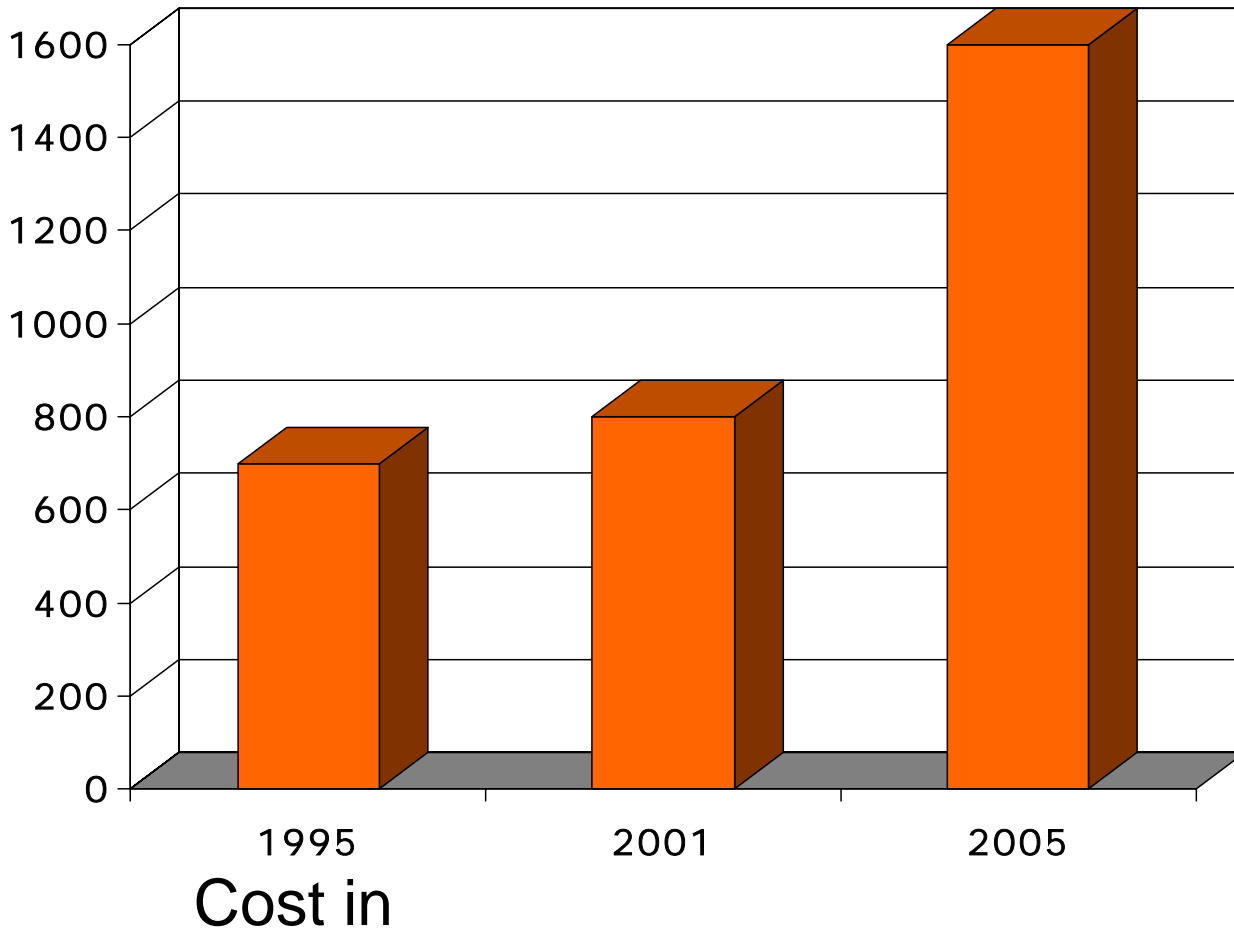
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Drug Discover Cost Escalate



DRUG Facts

- 10-15 years from conception → market for drug
- First-year sales > \$1B/drug
- Increase in late Stage Failures
Fail in final clinical Trials
Drug Recalls:
e.g. Seldane, Hismanal, Propulsid, Posicor,

Drug recalls since 1997

2005	Vioxx	Pain Relief
	Bextra	Pain Relief
	Paladone	Pain Relief
2004	Baycol	Cholesterol
	Raplon	Anesthesia
2000	Lotronex	Irritable Bowel Syndrome
	Propulsid	Nighttime Heartburn
	Resulin	Type 2 Diabetes

RECALLED DUE TO SERIOUS SIDE EFFECTS

1999	Hismanal	Antihistamine
	Raxar	Antibiotic
1998	Posicar	High Blood Pressure Angina
	Duract	Pain Reliever reliever
	Seldane and Seldane-D	Antihistamine
1997	Pondimin	Obesity
	Redux	Obesity

VIOXX



- **WHAT IT DOES:** anti-inflammatory drug designed to fight acute pain and disabling inflammation of arthritis without the stomach problems that can accompany aspirin or other non-steroidal anti-inflammatory drugs.
- **CLASS:** Vioxx is part of a drug class called COX-2 inhibitors. The drugs block the COX-2 enzyme that has been linked with inflammation.
- **HEART RISK:** Since 2000, studies show a link between Vioxx and risk of blood clots leading to heart attack and stroke.
- **2003 SALES:** \$2.55 billion
- **COMPETITORS:** Pfizer's Celebrex and Bextra; Novartis' Prexige, a COX-2 inhibitor approved in 17 countries and seeking U.S. FDA approval; Merck's Arcoxia, a newer COX-2 inhibitor sold in 47 countries. Not yet approved by U.S. regulators due to concerns about possible heart and stroke risk. Decision expected in late October.
- **PATIENTS:** 84 million people have used Vioxx since 1999.

Effects



A study comparing Vioxx with a placebo in 2,600 patients found a twofold increase in heart attacks and strokes, but only after 18 months of continuous use.

COX-2 inhibitor

Doctors say older drugs, such as ibuprofen, available over the counter or by prescription, can be effective, especially when taken with stomach-protecting medicines.

In Charleston, W.Va., Faye Ewing, 75, says Vioxx is the only thing that worked for him.

EFFECT onMERCK



Lower stock price

Lower debt rating

CLASS Action law suit

Loss of \$2.5 billion product

Bright side – MERCK has

\$6.2 Billion Cash 6/04

Cardotoxicity hERG

- Several drugs, e.g. Seldane, Raxar, Propulsid fail due to hERG inhibition
- Inhibits ion-channels
- Caused prolonged QT-interval which can cause cardiac arrhythmia and possible death (called torsades du point)
- Incidence probably depends on patients' predisposition
 - Seldane 1/28,500 prescriptions
 - Raxar seven cardiac-related deaths and three cases of TdP out of 2.7 million prescriptions
 - Others withdrawn prior to marketing
 - Serlect, Zeldox, Lidoflazine

Pharma headache



- More extensive/expensive testing in clinical trials required by FDA using QT interval surrogate for Tdp
- Low incidence difficult to detect in clinical trials, and QP imperfect indicator for TDP
- Try to develop high-throughput screens for hERG interference
 - Path Clamping to measure potential difference
very expensive, labor intensive
 - Need good in-silico predictor

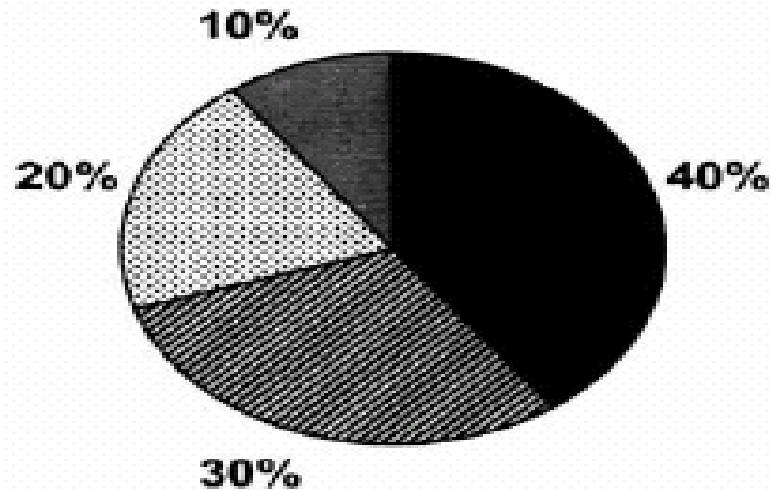
REFERENCE



Most of the pictures and descriptions of ADME-Tox taken from

T. Thompson, "Early ADME in Support of Drug Discovery: The Role of Metabolic Stability studies, Current Drug Metabolism, 2000, I 215-241

Cause of Late Stage Failures in Clinical Trials



- Poor Pharmacokinetic Properties
- ▨ Lack of clinical efficacy
- ▩ Toxicity (animals or human)
- Other

Properties of a good drug



- Desired Activity
- Desired Potency
- Available in desired form
(solubility, bioavailability)
- Targets desired tissue
- Desired duration of action (metabolized and excreted)
- No side effects

ADME-TOX causes more late-stage Failures



A-Absorption

D-Distribution

M-Metabolism

E-Excretion

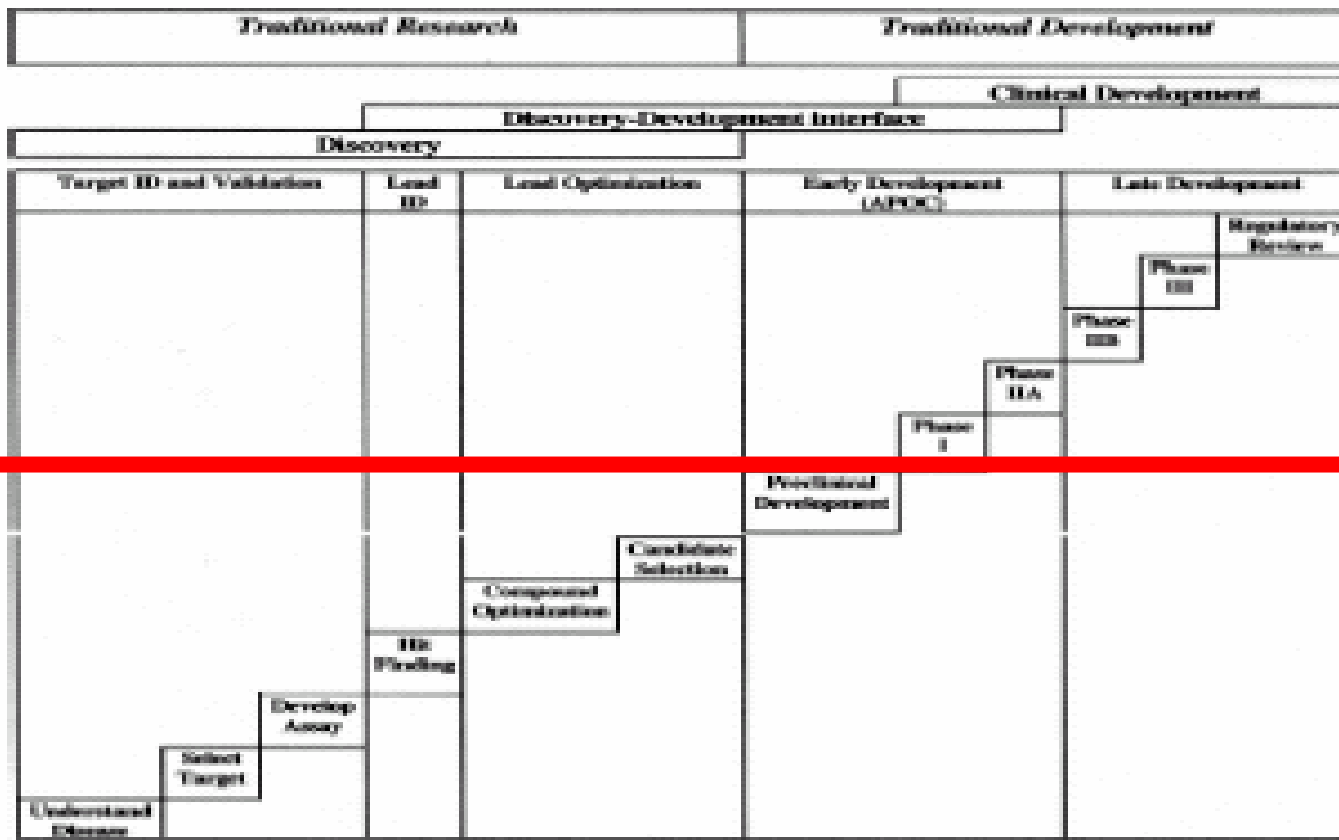
Tox – Toxicity

ADME-Tox



- Solubility
 - Absorption
 - Mutagenicity
 - Bioavailability
 - Metabolic Stability
 - Blood Brain Barrier Permeability
 - Cardiac Toxicity (hERG)
 - Plasma Protein Binding
- QSAR/QSPR tries to predict this in-silico

Rational Drug Design



Steps



- Target ID and Validation
- Lead Identification
- Lead Optimization and Validation
- Early Development
 - Preclinical Development
 - Phase 1 and IIa clinical trials
- Late Development
 - Phase IIb and Phase 3 clinical trials

DRUG DISCOVERY PROCESS



- Identify Target

Identify cellular and genetic factors playing a role in disease

- Validate/Prioritize Target

Be sure interactions with drug target do effect disease

LEAD IDENTIFICATION



- SCREEN large libraries of compounds for potential use against target.

Ideally develop assay that can be used for High Throughput Screening (HTS)

Assay roughly approximates desired property

LEAD OPTIMIZATION



- Found set of active compounds
- Assay in more detail
- Tweak to improve
- Examine further properties

PRECLINICAL



- **Preclinical technology.** During the preclinical development of a drug, laboratory tests document the effect of the investigational drug in living organisms (*in vivo*) and in cells in the test tube (*in vitro*).
- **Chemistry manufacturing and controls (CMC)/Pharmaceutics.** The results of preclinical testing are used by experts in pharmaceutical methods to determine how to best formulate the drug for its intended clinical use. For example, a drug that is intended to act on the sinuses may be formulated as a time-release capsule or as a nasal spray. Regulatory agencies require testing that documents the characteristics -- chemical composition, purity, quality and potency -- of the drug's active ingredient and of the formulated drug.
- **Pharmacology/Toxicology.** about the pharmaceutical composition of the drug, its safety, how the drug will be formulated and manufactured, and how it will be administered to the first human subjects.

CLINICAL TRIALS: Phase 1



- Small studies of safety and tolerability in humans.
- Testing includes observation and careful documentation of how the drug acts in the body -- how it is absorbed, distributed, metabolized and excreted.

Phase II



- Determine effectiveness and further study the safety of the candidate drug in humans.
- 6 months to three years.
- Treat patients with conditions.
- Randomized; drug versus placebo/current standard in double blind studies.

Phase III



Expanded testing of effectiveness and safety of an investigational drug, usually in randomized and blinded clinical trials.

One to four years.

Safety and efficacy testing is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats.

Reduce Drug Costs



Increase quantity:

Automation

Computation In-silico

Improve Efficiency

Improve ADME/Tox profiles

Minimize failed leads

Example of ADME failures



Inadequate bioavailability by route of administration

Failure to distribution to tissue/cellular site of interaction

Rapid metabolism

Rapid Elimination

New ERA



Combinatorial Chemistry

High Throughput Screening

Screen large libraries of candidates

Screen directed or designed libraries of
newly prepared candidates

Try to screen ADME-Tox early

Better to Fail Early/Fail Cheaply

Value of models for metabolic stability

Model	Physiological relevance	Compound throughput	Time needed	Cost	Comment
Human in vivo	most ↓ ↓ ↓ ↓ ↓ ↓ least	lowest ↓ ↓ ↓ ↓ ↓ ↓ highest	most ↓ ↓ ↓ ↓ ↓ ↓ least	most ↓ ↓ ↓ ↓ ↓ ↓ least	Need regulatory approval, toxicology, formulation and bulk drug
Animal in vivo					Still considered best predictor, yet expensive and increasingly controversial
Isolated whole organ					Time consuming, requires animal or human donor
Cellular					Generally considered reliable, in vitro-in vivo correlations are improving, immortal cell lines available
Subcellular					Generally considered reliable, in vitro-in vivo correlations are improving, immortal cell lines available
Isolated enzyme/receptor					Requires, animal or human donor, but enables higher throughput
Recombinant enzyme/receptor					Now readily available, necessary for today's high throughput assays

Pharmokinetics



Increase reliance on in-vitro testing

faster

cheaper

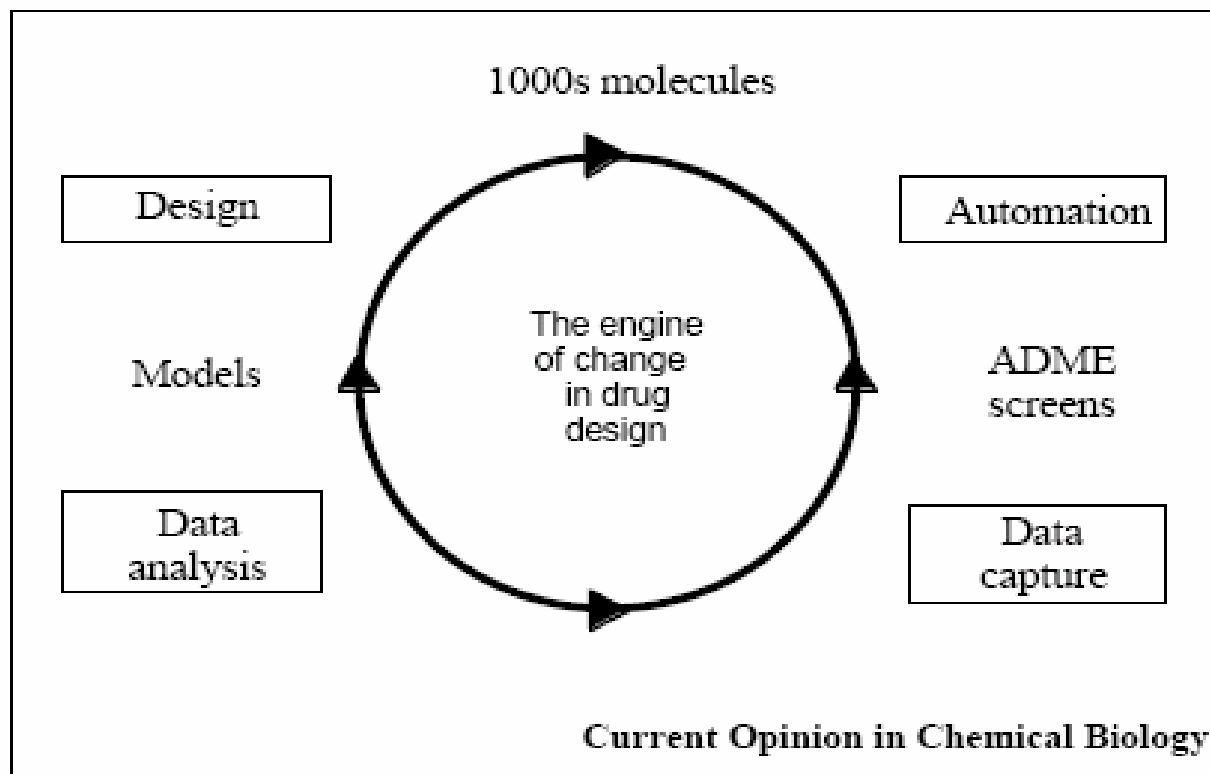
high throughput

more ADME problems/more late stage failures

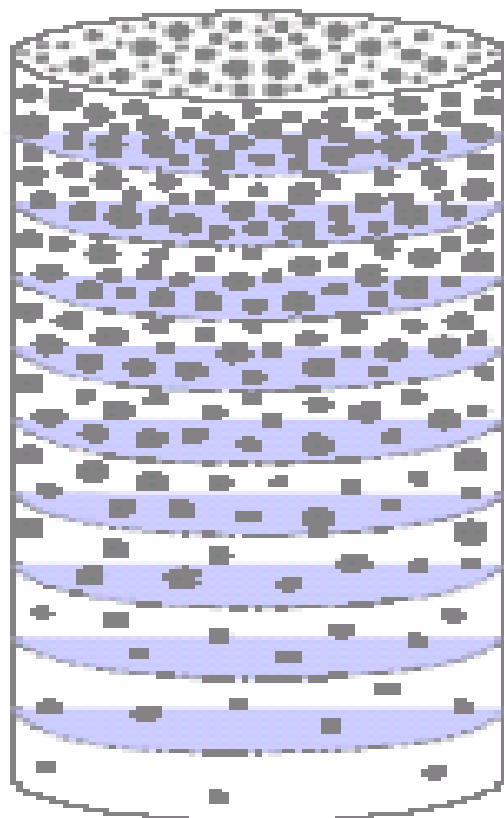
in vitro different from in vivo

By definition if it works in animal model must at least have some reasonable drug-like properties.

PUT ADME earlier in cycle



ADME-TOX FILTERS



Chemistry

Biology

Microsomal Stability Screen

IV Clearance Screen

Metabolite Screening

Rapid Rat PO/PK Screen

Rat IV / PO PK

**Dog / Monkey IV / PO PK +
Metabolite ID**

Pre-Development Checks

Drugs into Development

In-Silico Screening

- Gather Training Data Pairs
(Molecule, Response) (in-vitro, in vivo)
- “Learn” function using Training Data
 $f(\text{Molecule}) \approx \text{Result}$
- Use function to screen new molecules
 $f(\text{new molecule}) = \text{predicted result}$

Mathematical Model

- Have data $(x_1, y_1), \dots, (x_m, y_m)$

- Construct predictive function

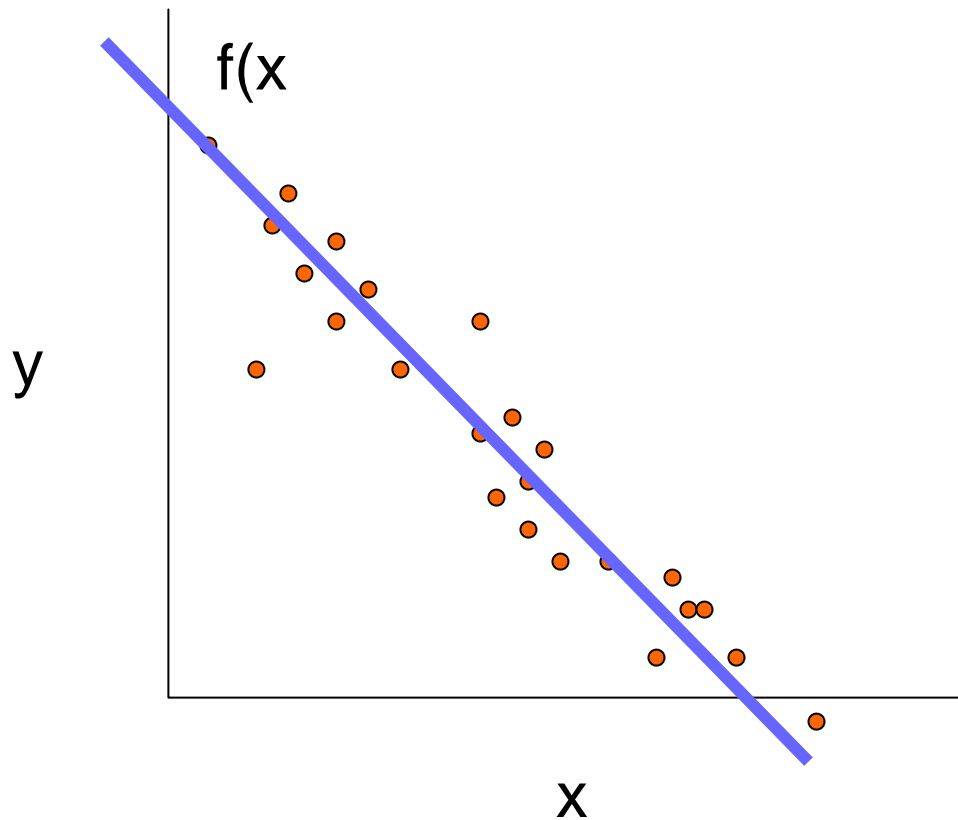
$$f(x) \approx y$$

- Solve mathematical model to find f

$$\min_f \sum_{i=1}^m (f(x_i) - y_i)^2$$

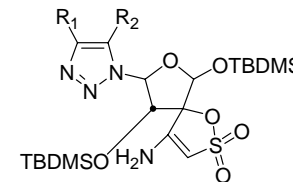
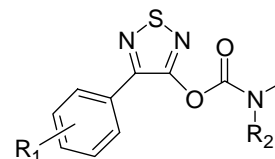
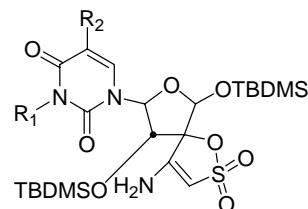
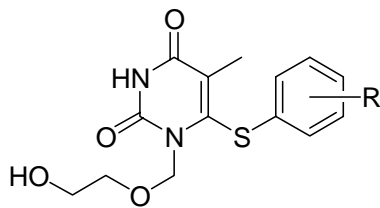
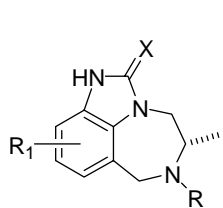
- Want f to generalize well on future data

Regression Picture



HIV Reverse-Transcriptase Inhibition modeling

- Have a few Molecules that have been tested



- First question: What is x?

X needs to represent the qualities of the molecule important for bioactivity

- From chemistry/biology know important properties of molecules

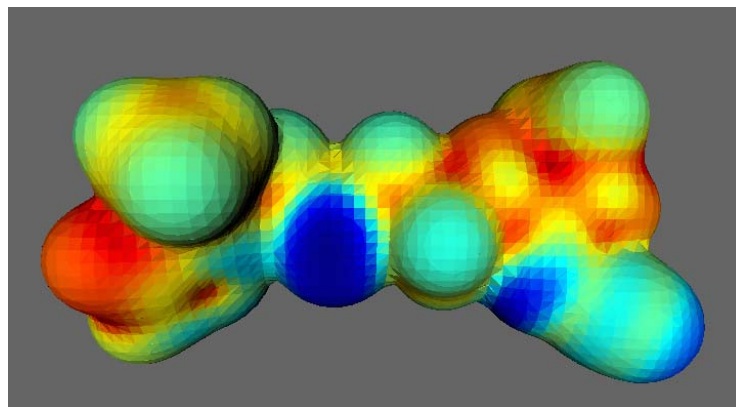
Molecular Weight

Electrostatic Potential

Ionization Potential

- Molecule Shape/Size

- Need to map this to numeric properties, X



Thursday



Guest Lecturer: Dr. Sukumar

How do you represent a molecule for
QSPR/QSAR?

Note additional reading