# Optimizing Hits for Oral Activity and Dose

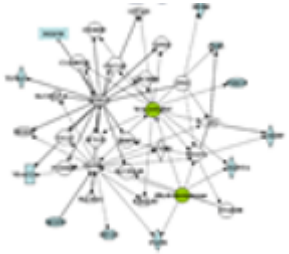
April 11, 2023

Kevin Cusack

# Todays Presentation: Optimizing Hits for Oral Activity and Dose

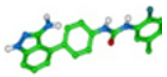
## - Where this work fits in versus drug discovery roadmap

Disease-Gene Relationship

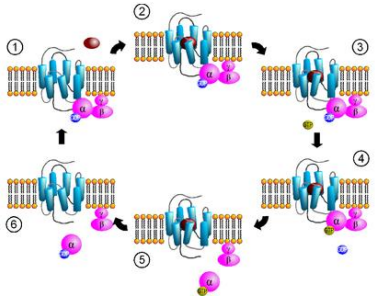


Protein to Modulate

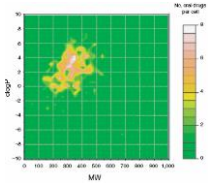
Ligand-protein binding



Functional response



Optimized properties, dose, safety, toxicology



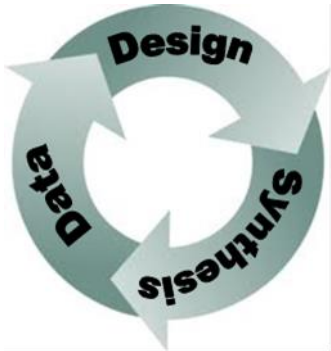
Formulation, scaleup, GLP safety, toxicology

Human dosing

Target Discovery & Validation → Hit Identification → Hit to Lead → Lead Optimization → Preclinical Development → Clinical Development

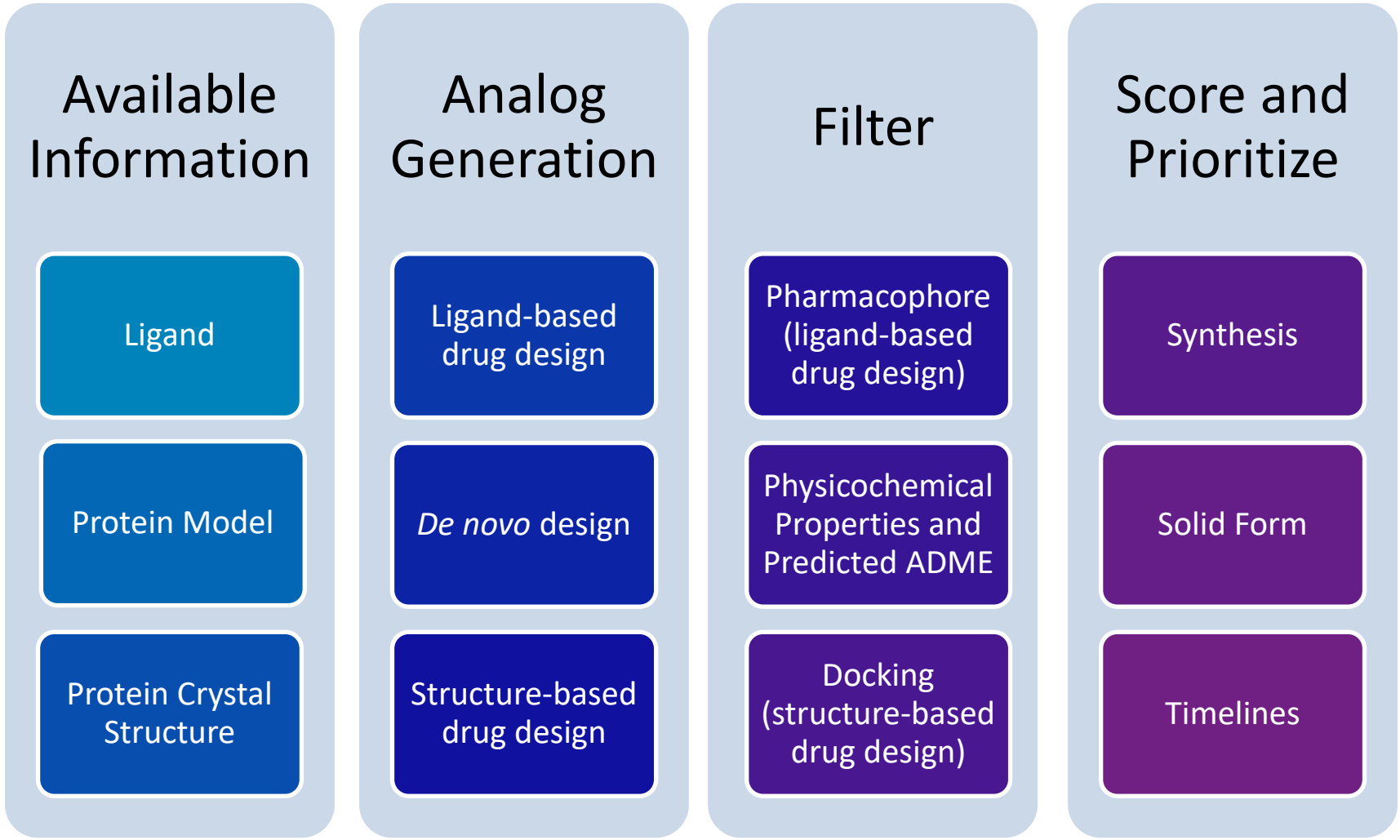
- Biochemical
- Biophysical

Iterative optimization of hit for oral activity and dose



# Strategy and Plans Vary Based on What Information is Available

- Design cycles are intentional and are focused on a hypothesis




Growing usage of in silico predicted properties and eADME pre-synthetically

# Role and Skills of Medicinal Chemist

## - Design safe & effective agents to treat disease (drugs) with optimum *in vivo* activity after oral administration

Designing drugs for optimum *in vivo* activity after oral administration is a balance of multiple parameters

- The term "multi-parameter optimization" (MPO) has been coined to capture the need to target a balanced profile between on target efficacy, off target efficacy and ADME properties
  - Efficacy – the ability to produce a desired result and involves potency (how tightly you interact with target protein) and effect (ability to elicit desired functional response)
  - ADME is the sum of absorption, distribution, metabolism and excretion for a given molecule

MPO avoids pursuit of potency alone ("$K_i$ is king")

- ✓ Deep knowledge of organic chemistry (e.g. conformers, energetics, P-chem)
- ✓ Knowledge of factors that influence ADME (absorption, distribution, metabolism and excretion) of drugs both *in vitro* and *in vivo*
- ✓ Knowledge of pharmacology, toxicology and safety for on-target and off-target effects
- ✓ Appreciation of patent and competitive intelligence, chemistry/biology information
- ✓ Basic understanding of clinical and regulatory requirements for disease target and for related drugs
- ✓ Familiarity with techniques and tools to assess biology and chemistry, and facility with a broad range of design and analysis tools
- ✓ *Knowledge of in silico techniques to ideate and predict small molecule properties and eADME endpoints*

*Drug design is making the best choices before synthesis—excellence in design can save you a lot of time, but it also demands a commitment to learning and a highly skilled synthetic team*

# Goal of Small Molecule Project Team is to Design Orally Efficacious Drugs

- Knowing some biology helps medicinal chemist better leverage the dose equation in optimization phase

*Key parameters determining efficacious dose*

**Unbound clearance:**
**How quickly does drug clear from the body?**

Physicochemical properties

Site of metabolism, route of elimination

Nature and fate of metabolites

***In vitro* and *in vivo* potency**

$$\text{Efficacious dose} \propto \frac{AUC_{eff,u} \times CL_{int,u} \times \text{target tissue impairment}}{f_a \times f_g}$$

Physicochemical properties

Permeability/transport models (QSAR)

Conformation, charge, donors

Solubility

**Unbound Efficacious AUC, how much free drug over time do you need at the target to have an effect?**

**Absorption:**
**How well is the drug absorbed after oral dosing? (permeability)**

$$\text{Target tissue exposure} = \frac{[\text{plasma}]_u}{[\text{target tissue}]_u}$$

**Tissue Exposure:**
**What is the free conc in the target tissue?**

**ADME**

**Assumptions:**

- Orally administered and hepatically cleared
- Pharmacology related to unbound concentration at site of action (AUCu or Css,u)

# The Drug Discovery Equation Has Not Changed, Still an MPO Problem

**DRUG** = *a*[potency] • *b*[efficacy] • *c*[selectivity] • *d*[absorption] • *e*[distribution] • *f*[metabolism] • *g*[excretion] • *h*[side effects] • *i*[acute/chronic toxicity] • *j*[mutagenicity] • *k*[solubility] • *l*[formulation] • *m*[taste] • *n*[smell] • *o*[stability] • *p*[cost] • *q*[patentability] • *r*[clinical efficacy] • *s*[idiosyncratic problem]

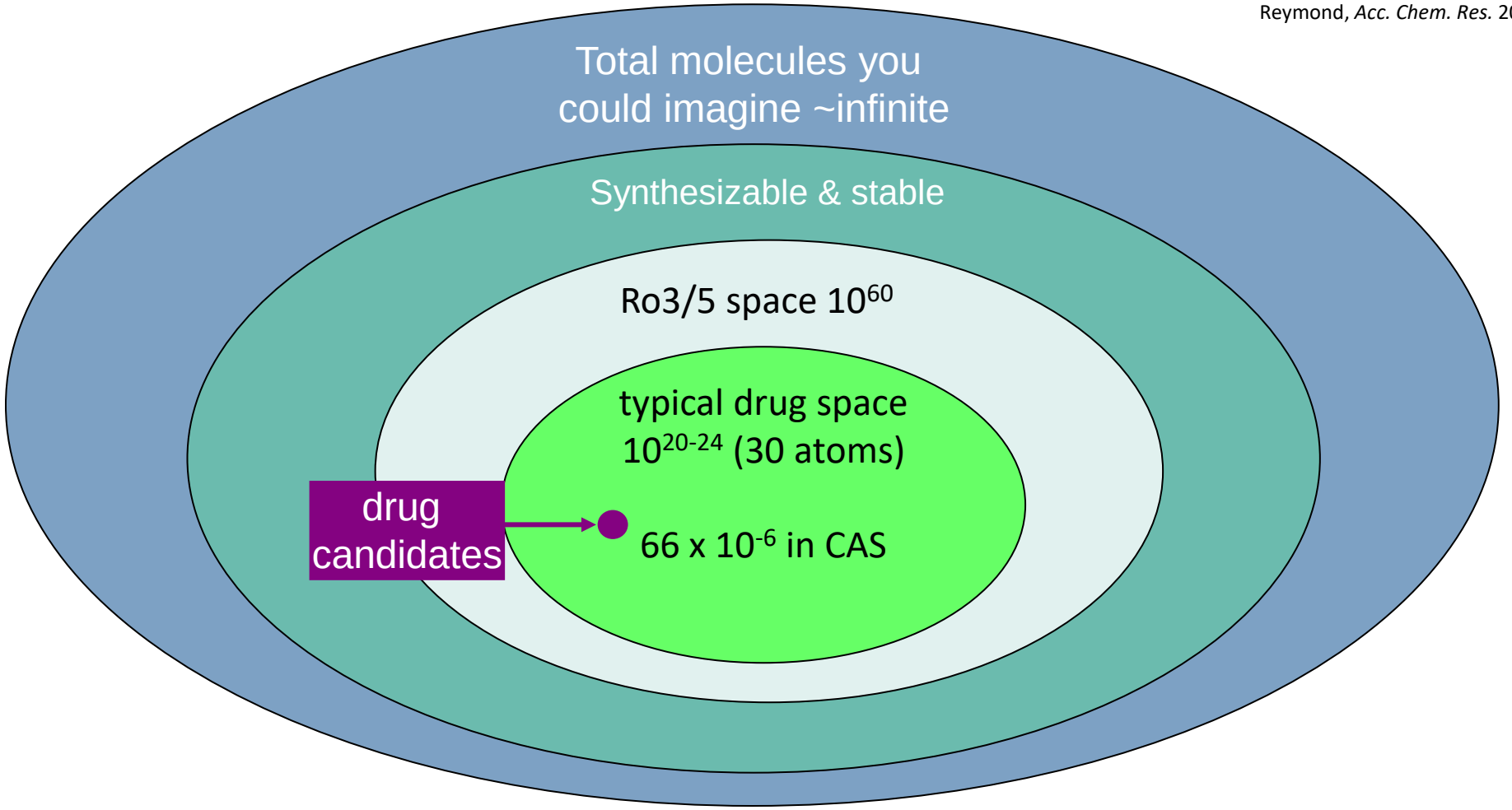
Target Product Profile (TPP)

- Overall likelihood of success a product of the individual probabilities
- Candidate drug deficiencies can be helped by chemical modification
  - Pharmacodynamic properties
  - Pharmacokinetic properties
  - Toxicological profile
  - Pharmaceutical properties
  - Other issues

- Best drug design balances optimization of these versus timely delivery

# Drugs Only Represent a Small Fraction of Synthesizable and Stable Molecules

Reymond, *Acc. Chem. Res.* 2015, 48, 3, 722–73




**Key principle: Design is about <u>making the right choices</u>.**

**Only a fraction of structures are in drug space; and only a tiny number of those can be superior and will become drugs**

# Physicochemical Properties of Oral Drugs On the Rise (1982-2004) but Still Acceptable

## - Multiple factors could be responsible including pursuit of potency, more diverse modalities and target classes

Hopkins et al., Nature Biotechnology (2006), 24(7), 805-815

| Parameter | 1980's | 1990's | 2000's | Total |
|---|---|---|---|---|
| **NAR** | 1.25 | 1.6 | 1.9 | 1.41 |
| **Fsp3** | 0.44 | 0.44 | 0.43 | 0.44 |
| **MWt** | 328 | 365 | 377 | 344 |
| **LogD** | 1.2 | 1.9 | 2.0 | 1.5 |
| **cLogP** | 2.0 | 2.5 | 2.6 | 2.2 |
| **tPSA** | 77.4 | 81.5 | 84.9 | 79.4 |

Lipinski Ro5 rule of fives for oral drugs

<500 mw, <5 ClogP, <5 HBD, <10 HBA

Space of highest concentration of drugs

cLogP 2-4, MW 250-400

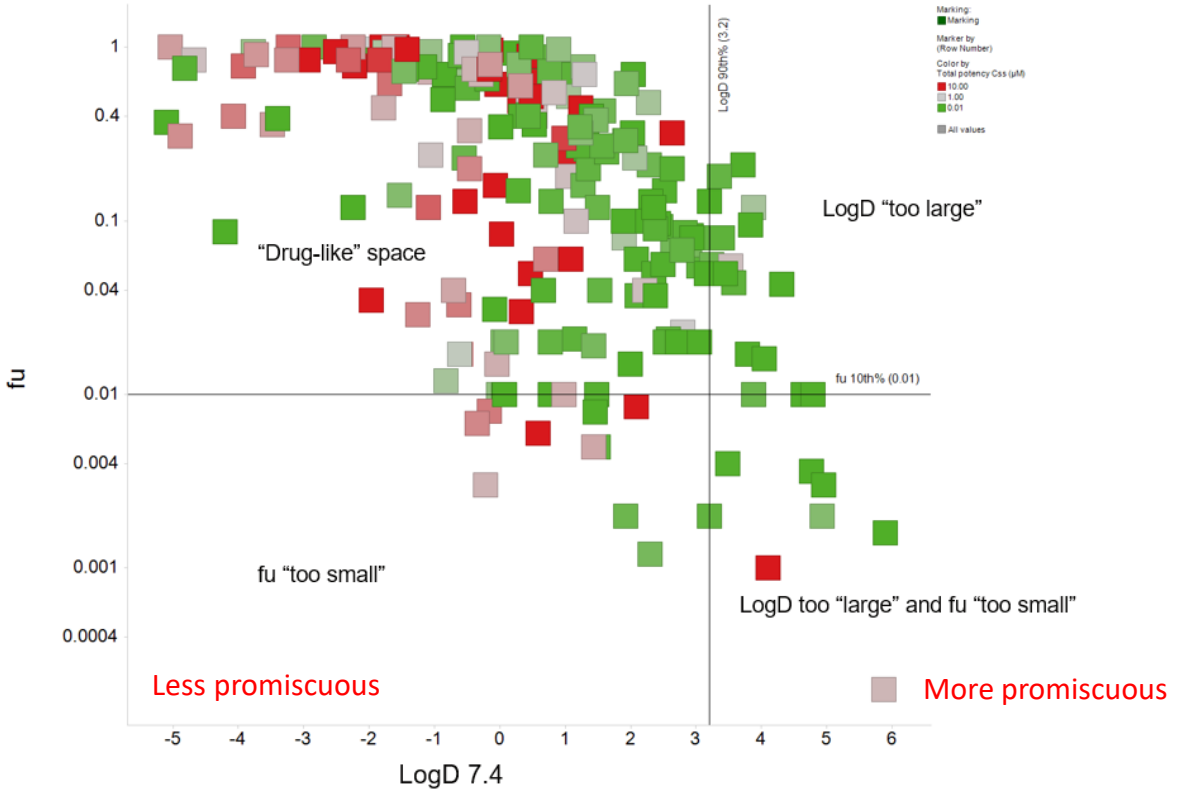
- On average in the last three decades drugs have become more lipophilic, more aromatic, have higher molecular weight, and more polar.
- In general though, drugs on average have low lipophilicity and molecular weight.
- Higher probability of oral efficacy around "drug like space"
  - *Know these properties the moment you conceive of a molecule*

# Serum Protein Binding Carries Potential Benefits and Potential Risks

## - Can prolong duration of action but high log P/D tracks with compound promiscuity and low free drug concentration

Kratochwil, N. et al, *Biochem. Pharmacol.* **2002**, *64*, 1355
Leeson and Springthorpe, Nature Reviews, Drug Discovery, 2007, 881

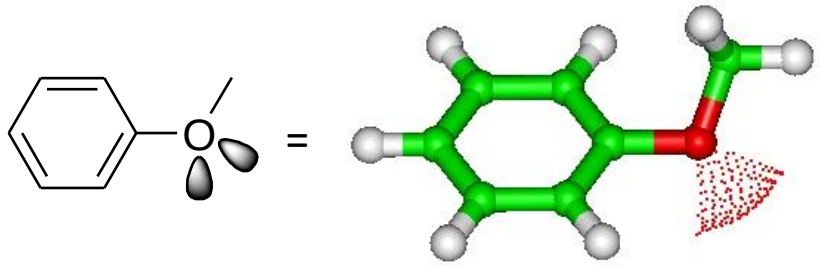
- Binding of a drug to plasma proteins…
  - *Benefits*: prolongs duration of action ("drug reservoir"), limits metabolic clearance of poorly extracted drugs, *may* increase distribution ($V_D$) of insoluble compounds
  - *Risks*: concentration of "free" (i.e. active) drug reduced, may limit distribution into tissues, increased promiscuity




Protein binding in plasma and accumulation in blood cells in suspension increases with increasing lipophilicity

# If Polarity Dominates Profile, Risk of Poor Absorption Increases

## - Role of PSA and Number of N+O, balance is best



Anisole: TSA=145; PSA=9

Excessive molecule polarity can inhibit dissolution in and transport through non-polar CNS and intestinal membranes

- Rule-of-thumb: PSA= 13 x (N+O atoms)
  Norinder, U. et al. *Adv. Drug Del. Rev.* **2002**, *54*, 291
- PSA <90 Å$^2$ good BBB penetration
  Ertl, P. et al. *J. Med. Chem.* **2000**, *43*, 3714
  Clark, D. et al. *J. Pharm. Sci.* **1999**, *88*, 815
- PSA <140 Å$^2$ good oral bioavailability
  Veber, D. et al. *J. Med. Chem.* **2002**, *45*, 2615
- PSA 200-250 Å$^2$ is upper limit for any minimally useful bioavailability
  Norinder, U. et al. *J. Med. Chem.* **2001**, *44*, 1927
- Odds of toxicity
  - High-clogP/low-TPSA compounds are approximately 2.5 times more likely to be toxic as to be clean with a 6X odds ratio
- Tox data from 245 pre-clinical candidates, BMCL 2008, 4872

# Impact of Common Pharmacophoric Units on clogP

| Compound | ClogP |
|---|---|
| Ar-Ar | 4.0 |
| Ar-$CH_2CH_3$ | 3.2 |
| Ar-Cl | 2.9 |
| Ar-$CH_3$ | 2.6 |
| Ar-$OCH_3$ | 2.1 |
| Ar-H | 2.1 |
| Ar-CN | 1.6 |
| Ar-OH | 1.5 |
| Ar-NH-CO-$CH_3$ | 1.3 |
| Ar-$NH_2$ | 0.9 |
| Ar-$SO_2$-$CH_3$ | 0.5 |

+2 for phenyl unit

+0.5 for $CH_2$ unit

neutral for $OCH_3$

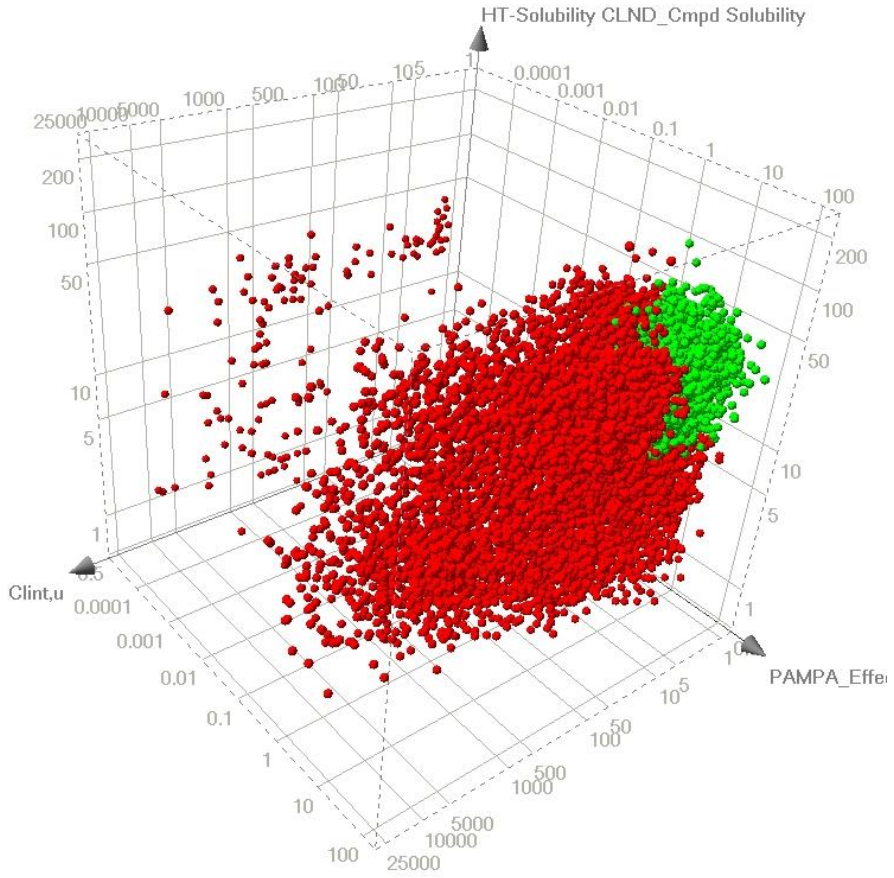
-0.5 for OH

-1 for aniline $NH_2$

-1.5 for sulfone

# Optimal ADME Space Matches Oral Drug Space

## - Very similar Physicochemical Properties




Color by Clint,u <10, PAMPA >1.5, CLND >10:

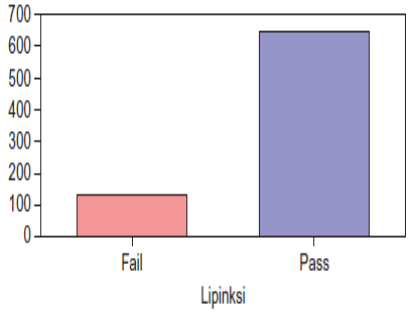
Yes No

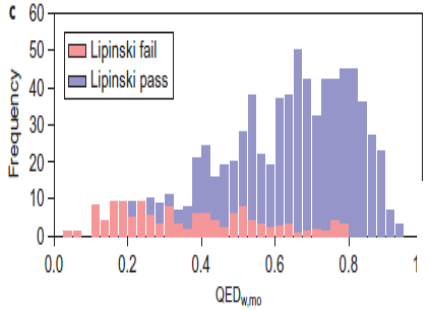
| Parameter | Average Green | Average Drugs |
|---|---|---|
| clogP | 2.3 | 2.2 |
| LogD | 1.91 | 1.5 |
| MWt | 351 | 344 |
| TPSA | 66.7 | 79.4 |
| FSp3 | 0.35 | 0.44 |
| NAR | 2.25 | 1.41 |

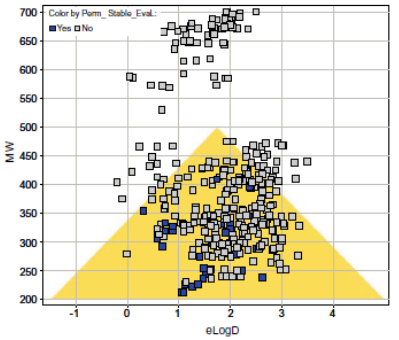
# Structural Mnemonics Help Increase Probability of Success During MPO-Design Phase

## - Mostly physicochemical and structure based (for favorable profiles, and away from risky profiles)

- Lipinski Ro5 rule of fives for oral drugs
  <500 mw, <5 ClogP, <5 HBD, <10 HBA
- Pfizer 3/75
  <3 LogD, >75 $A^2$ TPSA total polar surface area
- ‘Golden Triangle’
- and many others . . . QED, rot bonds Veber, Ro4, Ro3 phospholipidosis index, BCS, CNS MPO
- Efficiency measures (potency vs. properties, i.e. LLE, LipE, BEI)
- Toxicophores (e.g. FDA/yellow/red/orange structure alerts)
- PAINS, promiscuous aggregators, ‘red herrings’



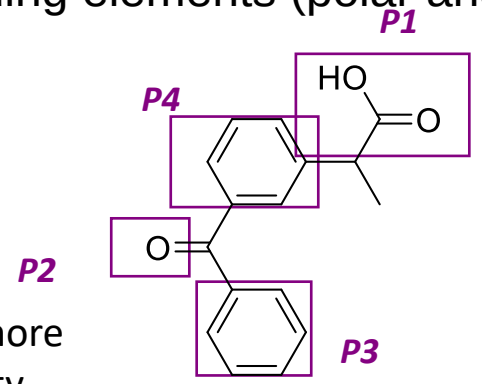

Probabilistic yes, but traverse at risk: "Cost-efficient modern drug discovery has a substantial statistical component to it: Envelope pushers need to have the resources to take on the higher risks" (Jorgensen, *Science* **2004**, 1813)

# Drugs are Composed of Pharmacophoric Units

Kratochwil, N. et al. *Biochem. Pharmacol.* **2002**, *64*, 1355
Bemis, G.; Murcko, M. *J. Med. Chem.* **1996**, *39*, 2887
Cereto-Massague, A. et. Al. *Methods* **2015**, *71*, 58
A. M. Davis and S. J. Teague, Angew. Chem. Int. Ed. 38, 736-749 (1999)

A drug drives its effect through a ***molecular target*** (Paul Ehrlich, 1854-1915)

- A ***pharmacophore*** is a representation of the minimal essential ligand elements needed to drive that interaction
- 90% of drugs have 3-9 binding elements (polar and non-polar groups)
  - 1-5 H-bond donors
  - 0-10 H-bond acceptors
  - 5-30 hydrophobic atoms




*ketoprofen*

Why? These define the pharmacophore
- Control binding strength, specificity
- Control physicochemical properties

- Reflects range needed for potent binding to target

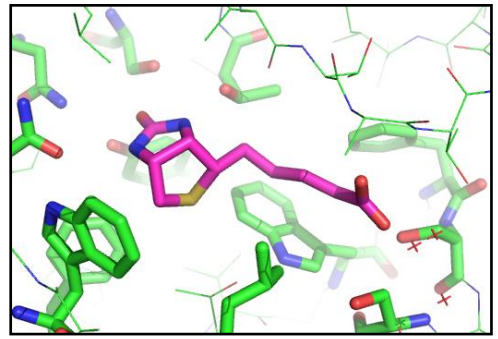
Methyl can be a pharmacophoric unit or it can participate in shielding of the acid (or both)

- High polarity of acid may limit passive absorption and alpha methyl group may shield the acid and thus increase passive permeability
- Binding to protein target is a combination of electrostatics, conformation/shape and hydration

# Each Pharmacophoric Unit Contributes to Affinity and Selectivity
## - Magnitude of Different Molecular Interactions

| | |
|---|---|
| Electrostatic | 0-4 kcal/mol (per interaction) |
| H-bonds (one partner charged) | 0-3 kcal/mol (per interaction) |
| H-bonds (both partners neutral) | 0-1.5 kcal/mol (per interaction) |
| Hydrophobic | 0-0.8 kcal/mol (per -$CH_2$-) |
| Hydrophobic | 0-3 kcal/mol (per benzene ring) |
| Cation-$\pi$ | 0-1 kcal/mol (per aryl ring) |
| $\pi$-stack | 0-1.5 kcal/mol (per aryl ring) |
| Halogen bond | 0-0.5 kcal/mol (per halogen) |
| Dipole-Dipole | really weak (a few tenths of kcal/mol) |
| Induced Dipole-Dipole | even weaker |
| Electrostatic (Repulsive) | 0 to –4 kcal/mol (per interaction) |

Biotin - Avidin, $K_d$ = 1 fM (PDB 1AVD)



- 7 H-bonds
- 8 hydrophobic interactions
- 4 Rotors
- 0 Electrostatic interactions
- 0 bound waters

- 1.4 kcal/mole = 10x change in potency = 1 log unit
  - The above values refer to physiological conditions
- Does not account for water interactions

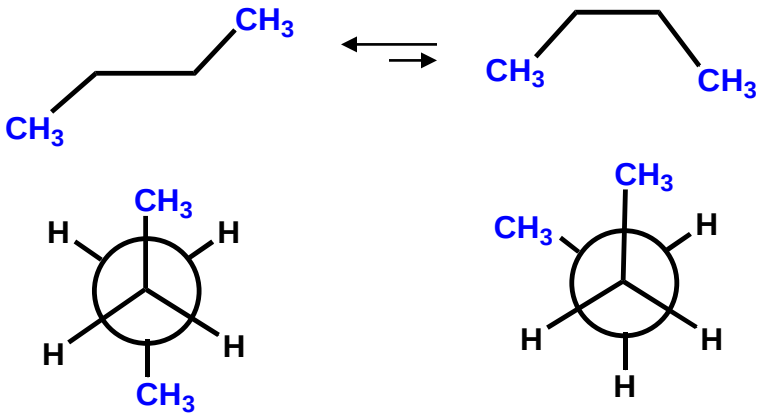
# Conformation Matters to On and Off Target Binding

## - Increasing number of rotatable bonds to allow fit in a pocket comes with a penalty

Every rotatable bond you have in your molecule could cost you about 0.5 log units in potency. Note: this number is never zero--there is always some penalty.

There is an entropic penalty that must be paid when a molecule has to go from multiple conformations in solution to a single conformation in a target site, e.g.

<u>The simplest case of a rotatable bond: Butane</u>




trans (anti)
(low energy)

gauche
(high energy)

At equilibrium, there is
66% trans and 34% gauche.
$K_{eq}$ = 1.9

corresponds to
$\Delta G$ = 0.4 kcal/mole energy difference.
0.3 of a log-unit energy difference.

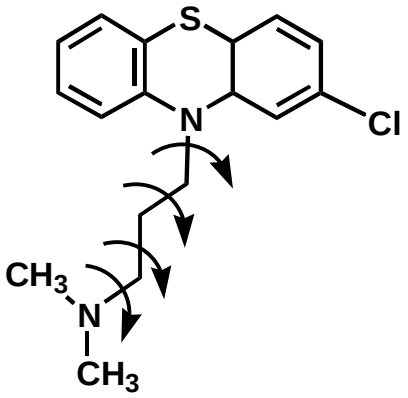
- 7 rotatable bonds could be a 3 log <u>penalty</u> in potency.
- With this many conformations, the molecule is likely spending very little time in a conformation appropriate for receptor binding

# Relationship of Rotatable Bonds to Bioavailability and Safety

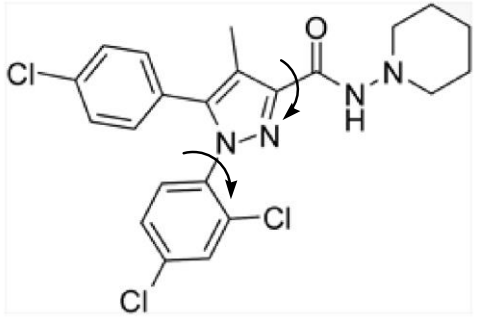
- Rigidification is a strategy used to decrease off target activity

Veber, et. al., J. Med. Chem. 2002, 45, 2615

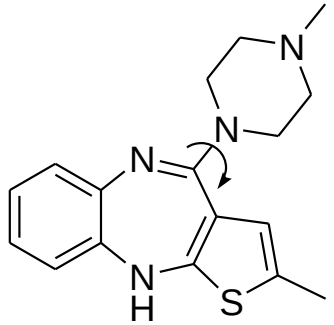
**Known drugs have on average about 4 rotatable bonds**



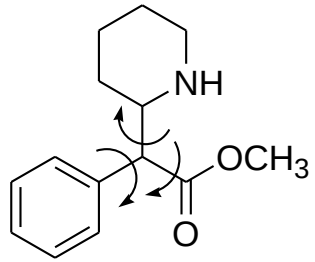

Chlorpromazine



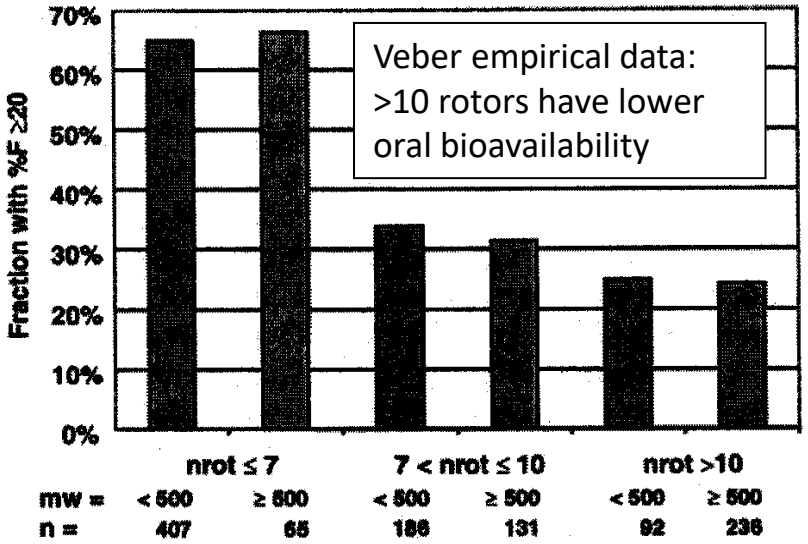

Rimonabant




Olanzapine




Methylphenidate




More rotatable bonds correlated w ↓F%

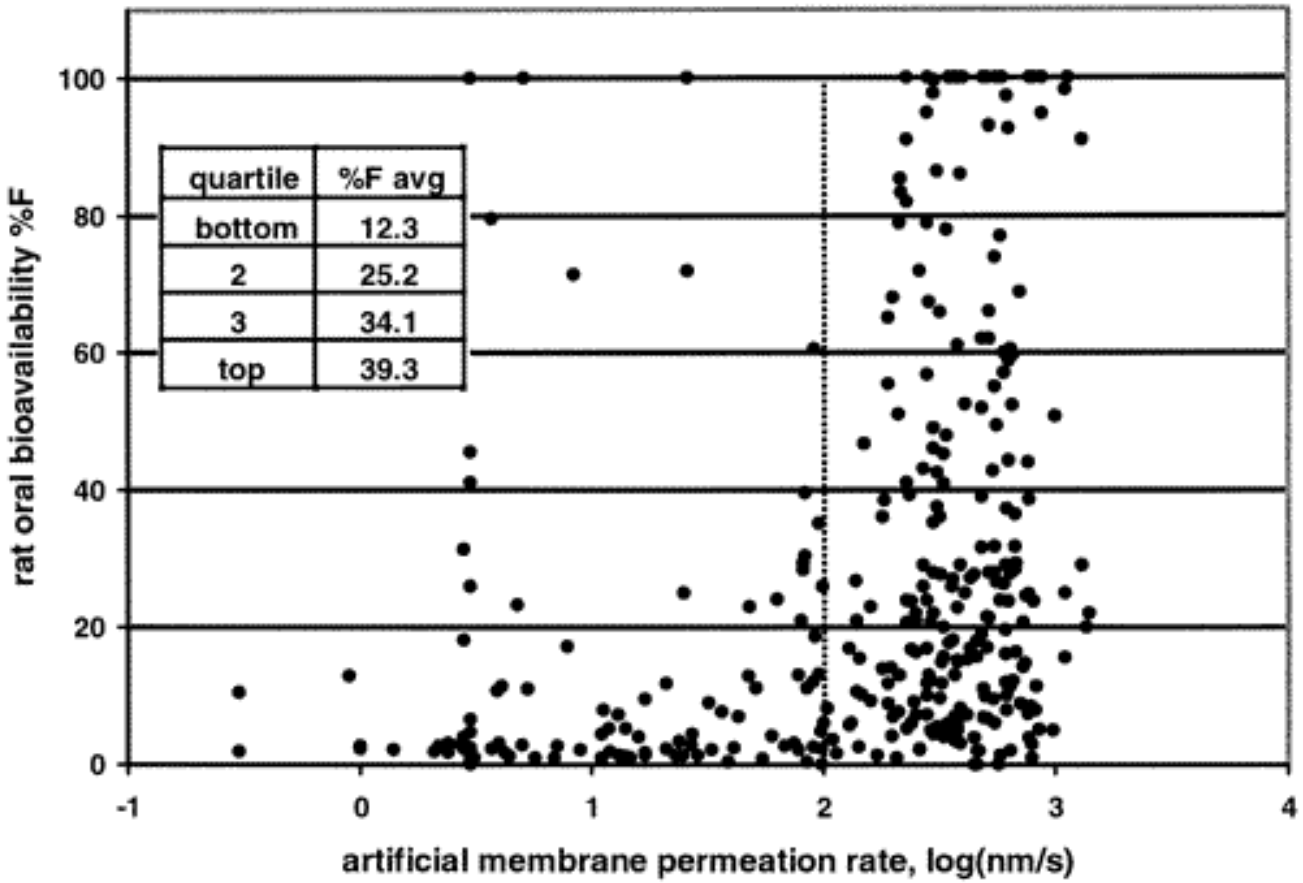
More rotatable bonds = more opportunities for conformations that bind to off target sites, and thus reduce specificity (safety issue)

Rigidification can be used effectively to address selectivity issues including CYP's

# Poor Membrane Permeability Can Also Contribute to Poor Bioavailability (F)

- Correlated to Poor Absorption, Poor F%

Veber, D. et al. *J. Med. Chem.* **2002**, *45*, 2615

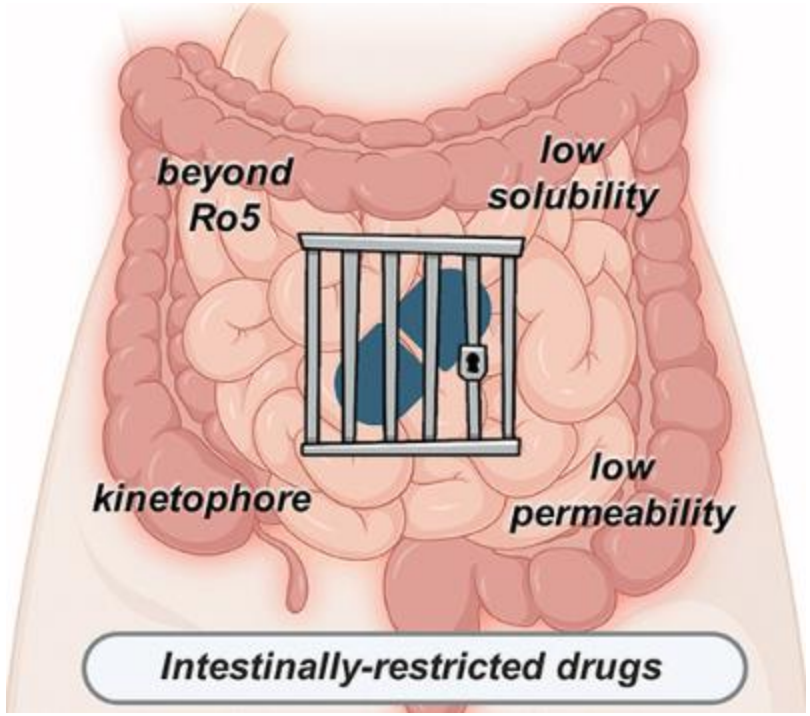


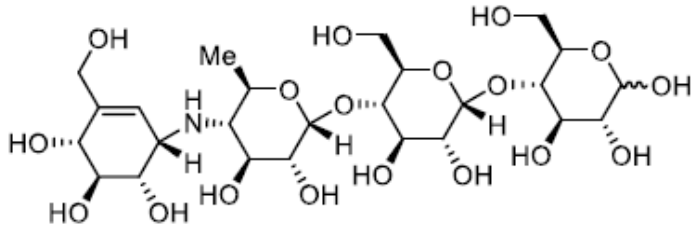

- Highly polar molecules can have poor permeability
- Highly flexible molecules can have poor permeability

- PSA <140 $Å^2$ good oral bioavailability

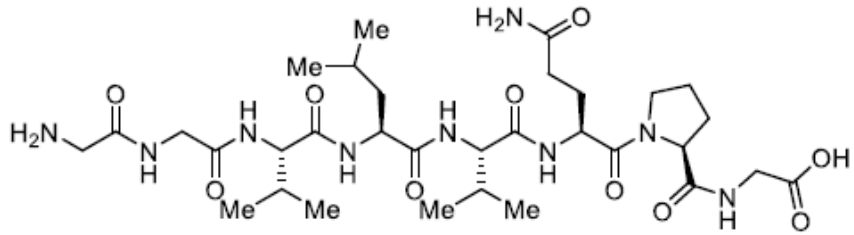
# Polarity and Flexibility Can be Leveraged for Tissue Restriction

Dorel, et. al. ACS Med. Chem. Lett. 2023, asap

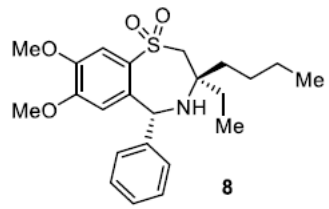


**1**
**Acarbose (Precose)**
α-glucosidase and
α-amylase inhibitor
TPSA = 321 Å$^2$
cLogP = –9
HBD = 14; HBA = 19

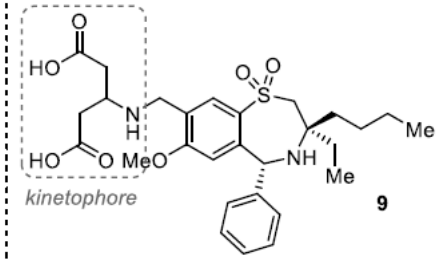


**4**
**Larazotide acetate**
**(AT-1001)**
zonulin antagonist
TPSA = 301 Å$^2$
cLogP = –2.2
HBD = 11; HBA = 19



**8**

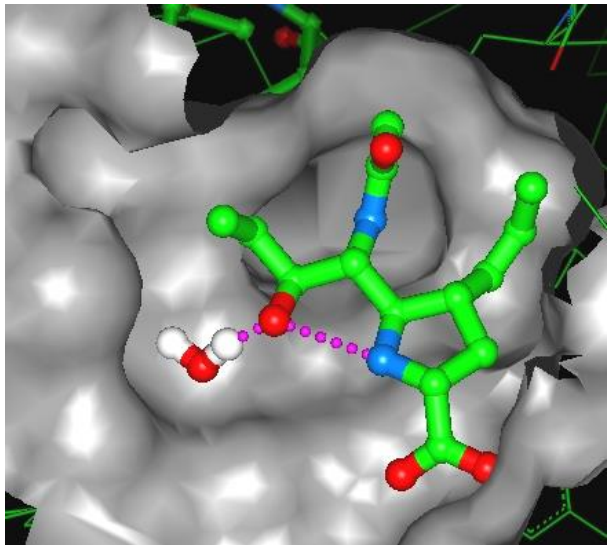
**264W94**
hIBAT $IC_{50}$ = 180 nM
MDCK $P_{app}$ = 107 nm/s

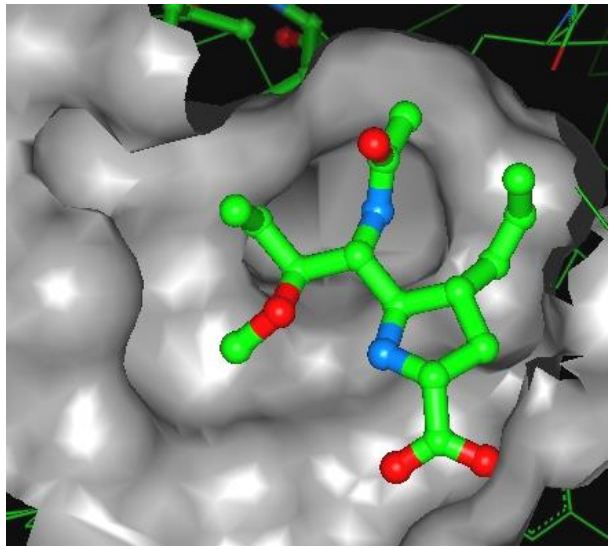



**9**

**linerixibat (GSK2330672)**
hIBAT $IC_{50}$ = 42 nM
MDCK $P_{app}$ = 7 nm/s

# Role of Water in Design and Selection of Analogs for Synthesis



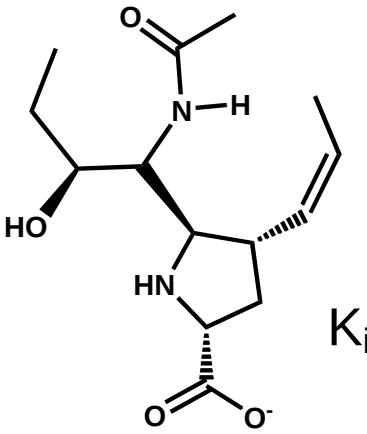


**1-Log gain in affinity from water displacement**

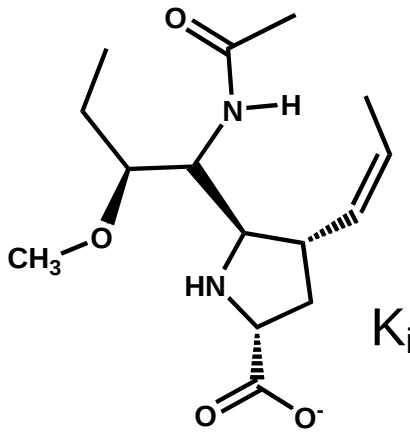
Need to understand the energy of the water
$\Delta G=\Delta H-T\Delta S$

- Disordered (high entropy) vs. ordered
- Stable in protein vs. stable in water network

- Schrodinger WaterMap
  - Displace, replace, interact, avoid




$K_i$ = 1.3 nM

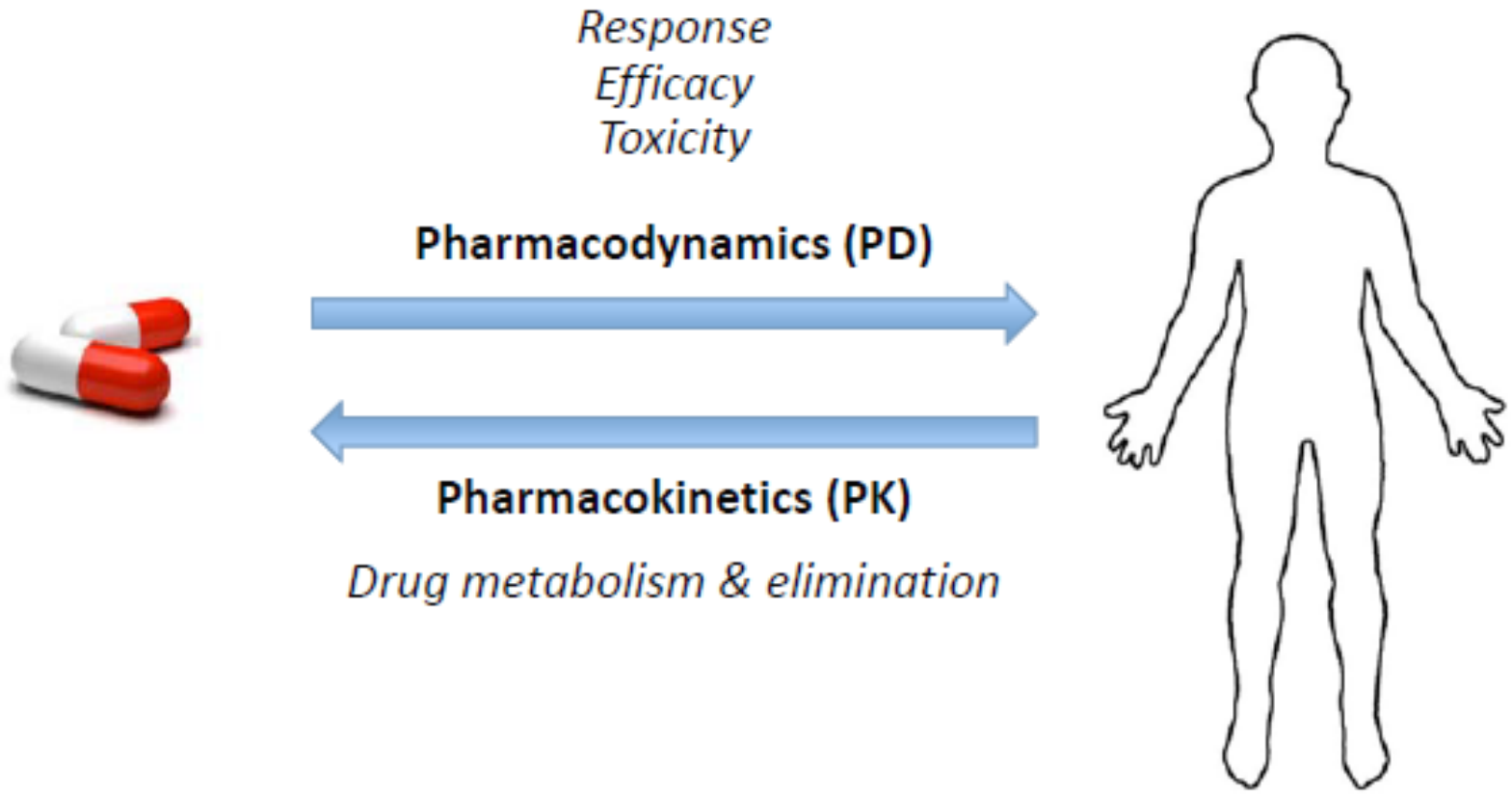



$K_i$ = 0.16 nM

"Structure-Based Characterization and Optimization of Novel Hydrophobic Binding Interaction in a Series of Pyrrolidine Influenza Neuraminidase Inhibitors," Maring, C. J. et al., *J. Med. Chem.* **2005**, 48, 3980-3990.

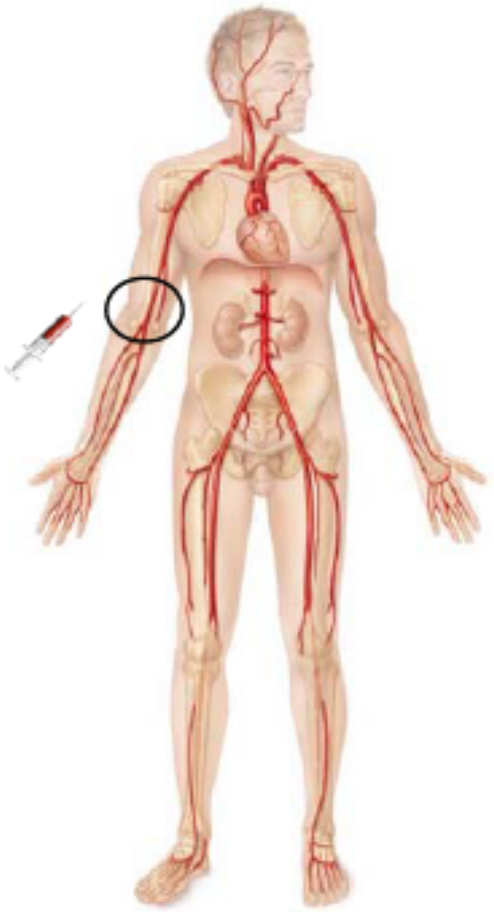
# Drug & Human Body

*Interaction goes both ways…*

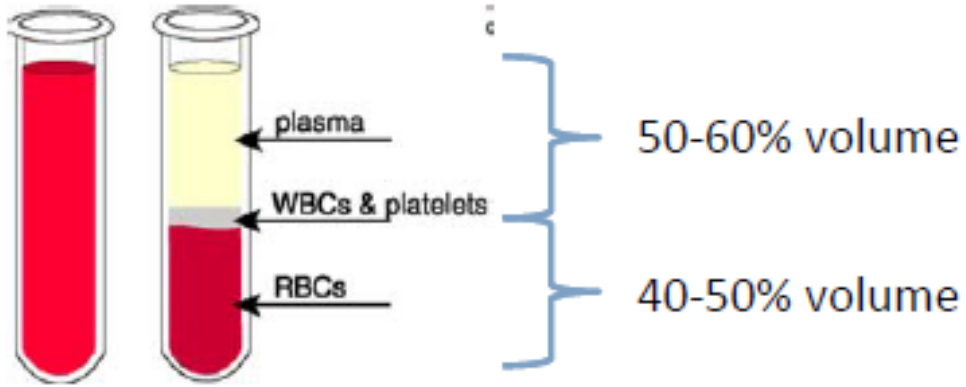


# Blood/Plasma Exposure

*Blood is the most readily accessible body fluid*



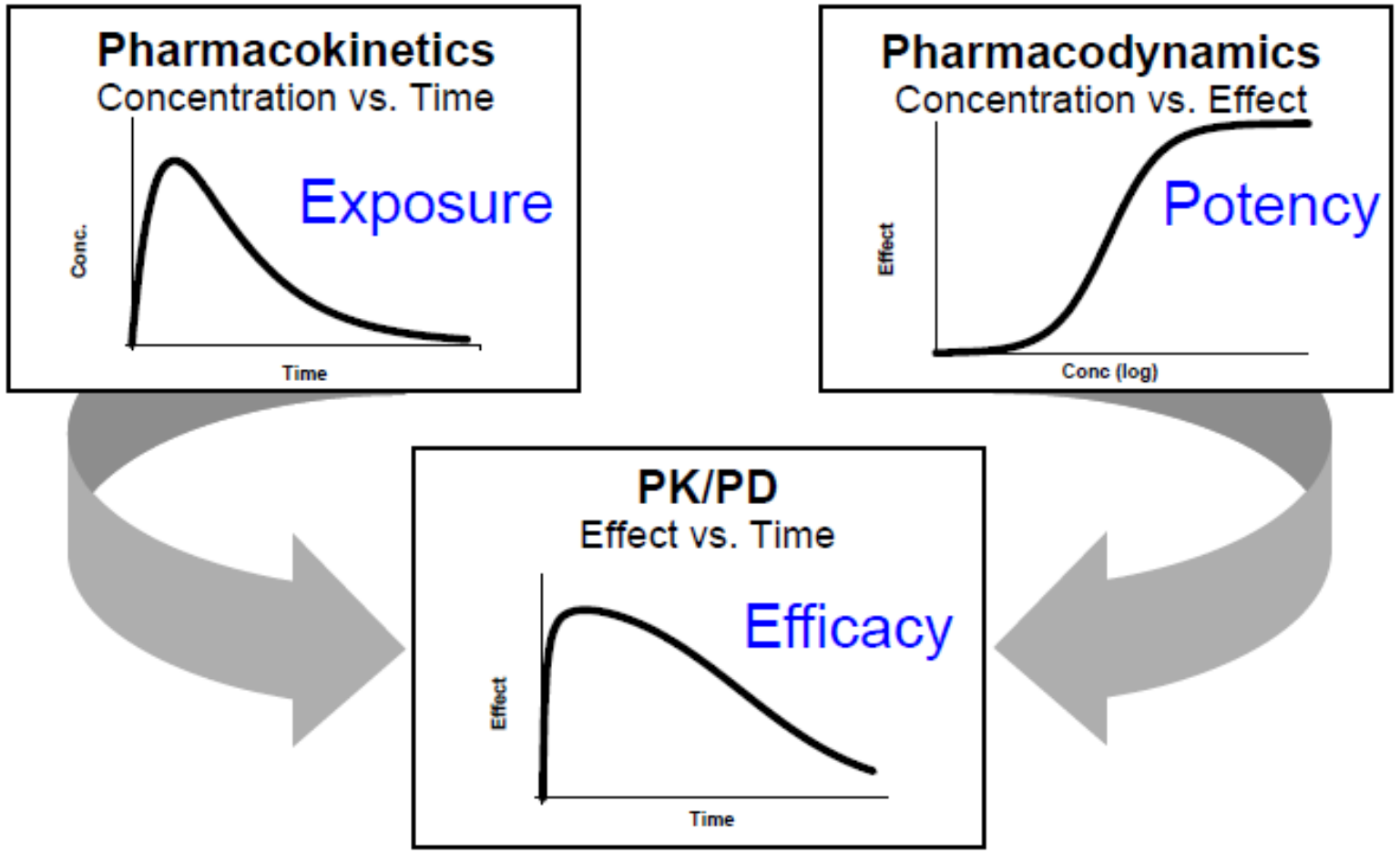
**Systemic Circulation**




- Blood/plasma concentration ratio
- Plasma contains many vital proteins (e.g. fibrinogen, globulins, albumin)
  - Plasma protein binding

# Efficacy = Potency + Exposure

*Translation of efficacy requires translation of both potency and exposure*



# Physicochemical Properties, ADME and Physical Properties are All Important to Dose

- Dose limiting absorption can kill otherwise good compounds

Yee, S. *Pharm Res.* **1997**, *14*, 763 (adapted from R. Sawchuk, U. of Minn (2001), "Pharmacokinetics & Drug Development")

**What's Good?**

| Property | *Low Risk* | *Medium Risk* | *High Risk* |
|---|---|---|---|
| **Log P** | 1-3 | 3-4 | <0 or >5 |
| **$P_{app}$ ($x10^6$ cm/s)** | >20 | 2-20 | <2 |
| **Solubility (μg/mL)** | >1000 | 10-1000 | <10 |
| **HLM, $t_{1/2}$ (min)** | >200 | 50-200 | <50 |

Additional confounds in the DMPK/formulation profile (for animal tox, or human clinical form):

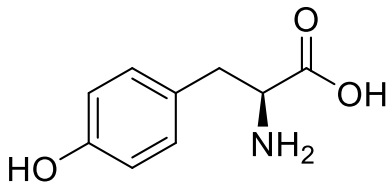
- Instability (chemical or enzymatic) in lumen, metabolism (especially first-pass metabolism), efflux transport (e.g. P-glycoprotein), high crystallinity, high melting point, slow intrinsic dissolution rate, hydrolytic, thermal, or photoinstability, incompatibility with excipients, multiple polymorphs, emergence of low solubility polymorphs

# Recent Progress in Drug Design Focused Around Pre-synthetic Modeling

## - No method currently captures shape, electrostatics and conformation

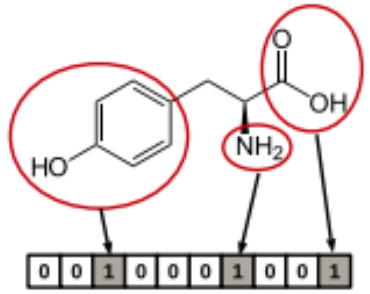
Muegge et. al. (2016) Expert Opin. Drug Disc., 11:2, 137-148
Rogers, et. al., J. Chem. Inf. Model. 2010, 50, 742-754
You, et. al. Signal Transduction and Targeted Therapy (2022) 7:156

It is possible to describe a drug in a way that a computer can understand and manipulate it



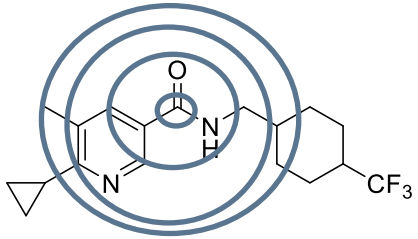

Tyrosine

Topological Fingerprints

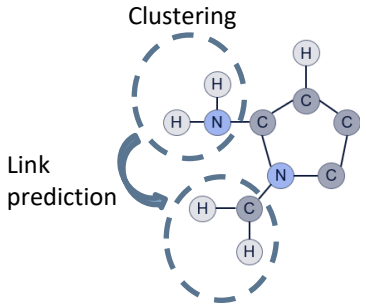



2-D Fingerprint
Of Tyrosine

Circular Fingerprints (ECFP)




Graph Based




Language based

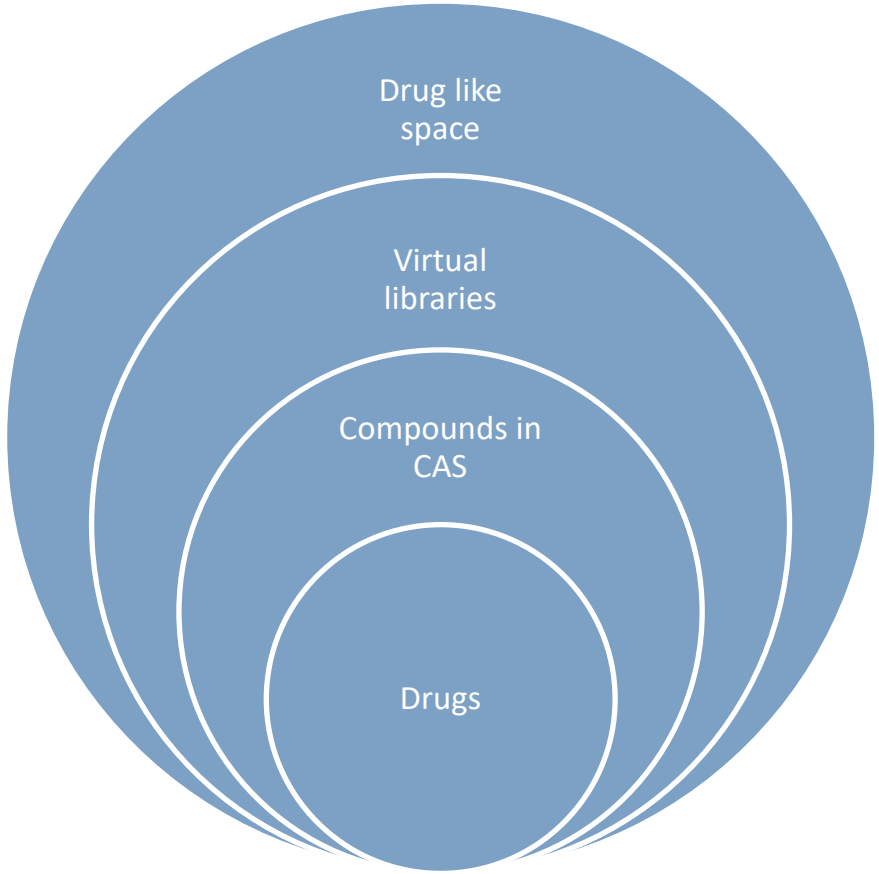
OC1=CC=C(C[C@H](N)C(O)=O)C=C1 (SMILES)

- Computationally useful for screening but does not capture conformation, shape or other three-dimensional characteristics and tautomers (current limitation of how a model is defined including some graph networks)

# It is Also Possible to Enumerate Billions to Trillions of Potential Structures

## -37 billion compounds that are able to be purchased

Tingle, et. al., J. Chem. Info. Model. 2023, 63, 1166




Significant expansion of virtually enumerated chemical space to billions of virtual compounds

- Cannot enumerate forever however

Companies taking a fragment/reaction approach to library design and screening

- a X b X c library reactions similar to a DEL (DNA encoded library)
- Chooses reaction based on need
  - Feature Trees (F-Trees)
  - Tanimoto similarity
  - Substructure…

# Role of Medicinal Chemist Has Evolved

Expert Medicinal Chemist
- Synthetic Expert

Hit

- "Magic methyl"
- What a drug looks like
- Design as an art

Lead

- "I think this looks like a drug vs. ummm . . . this looks ugly'
- Chemists use pattern recognition to develop opinions based on specific experiences
- Computers are great at pattern recognition

Drug

Expert Medicinal Chemist
- Synthetic Expert
- Computationally savvy
- Team approach

- Methyl displaces a high energy water
- Selectivity within protein family is attainable due to conformational differences in the proteins
- Can predict affinity and solubility with physics-based methods like FEP
- Drug like space can be identified and probability of compounds outside this space becoming drugs can be better understood
- *Design is intentional and is built around a hypothesis in each design cycle*
- *In silico techniques are leveraged pre-synthetically*

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