CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

UTSA ROADRUNNERS

Importance of Small Molecule Physicochemical Properties in Drug Discovery

Foundations of Cancer Therapeutics Crash Course
Research Technology Workshops
August 18, 2021

Stanton F. McHardy, Ph.D.
Associate Professor
Director, CIDD Max and Minnie Tomerline Voelcker
Medicinal Chemistry Core Facility
Department of Chemistry, UTSA

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

Basic Physicochemical Properties (PCP)

➢ Lipophilicity

- LogP: partition coefficient between organic/aqueous media (octanol/water @ pH 7.4)
- LogD: distribution coefficient between organic/aqueous media across pH range
- More non-polar, lipophilic (“hydrophobic”) leads to higher LogD
- More polar, less lipophilic (“Hydrophilic”) leads to lower LogD

➢ Electrostatics

- pKa (-Log10Ka)
- Basicity/Acidity of a molecule
- Governs % of ionized species at different pH (gastric acid; 1.2, duodenum; 4.7-6.7, ileum; 6.1-7.3)

➢ Molecular Weight

➢ Topological Polar Surface Area (TPSA)

- Defined as the surface sum of all polar atoms within a molecule ($Å^2$)
- In general, TPSA > 140 suggests poor permeability
- TPSA < 90 favorable for BBB penetration and CNS targets

➢ Hydrogen Bond Donors and Acceptors

- # of each within a molecule can impact drug properties

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

What Key Drug Properties do PCP's Impact?

➢ *In Vitro* ADME and *in vivo* PK

- Microsomal and Hepatocyte Clearance (Cl_{int} or T1/2)
- CACO2 and MDR1/MDCK Permeability
- Route of drug clearance/excretion
- Oral Bioavailability
- Cyp450 Isozyme Inhibition

➢ Drug Solubility and Stability

- Aqueous solubility
- Salt formulations, etc.
- Crystallinity

➢ Drug Toxicity (Limited Applications)

- LogD and Phospholipidosis strongly related

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

General Physicochemical Property Trends

General Structure rules and trends for modifying LogD and tPSA

- More polar atoms (N, O, S) increase TPSA and decrease LogD
- Hydrophobic groups (alkyl, aryl, etc.) tend to increase LogD, however have no effect on TPSA.

General trends for ADME properties

Compounds with….

- Increases in LogD usually correlate with higher permeability, but lower metabolic stability.
- Increases in TPSA usually correlate with lower permeability, but higher metabolic stability.

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

Models: Lipinski RO5 and CNS MPO

Chris Lipinski's "Rule of 5"

- MW ≤ 500
- CLogP ≤ 5
- ≤ 5 HBD
- ≤ 10 HBA

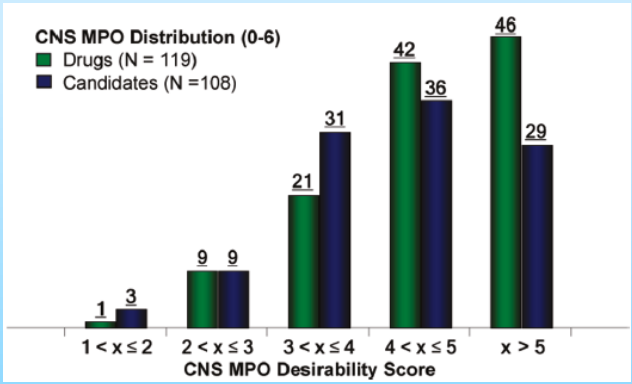
Optimized PCP values for oral bioavailability in marketed drugs

CNS Multi parameter Optimization (MPO)

- Analyzed 119 Marketed CNS drugs, 108 Pfizer CNS clinical candidates and 11,303 Pfizer proprietary CNS compounds.

- CLogP
- MW
- TPSA
- HBD
- pKa

Optimum range for all parameters set based on successful CNS clinical candidates. Combined CNS scoring function (>4 on 0-6 scale) predicts success….

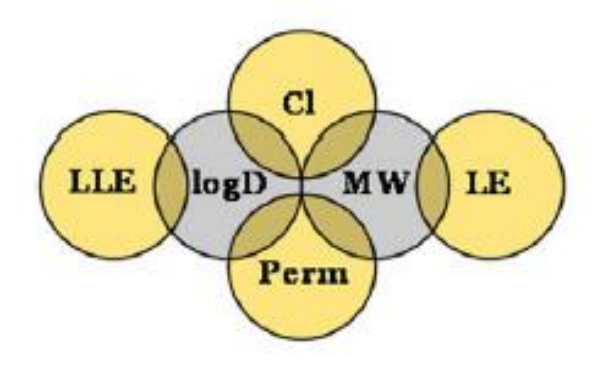


a) Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (March 2001). "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings". *Adv. Drug Deliv. Rev.* **46** (1-3): 3–26.

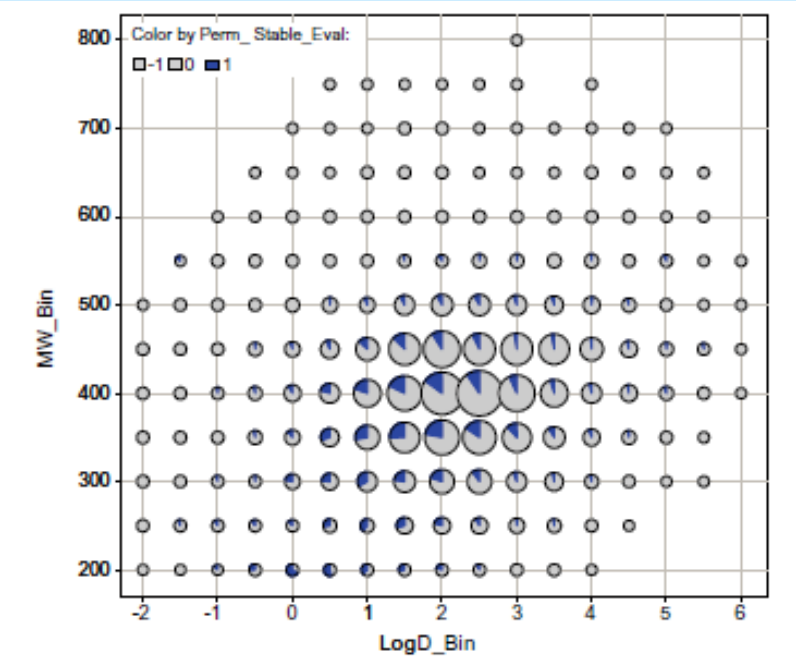
b) Travis Wager, Xinjun Hou, Patrick R. Verhoest and Anabella Villalobos,"Moving beyond Rules: The Development of a Central Nervous System Multi-parameter Optimization (CNS MPO) Approach To Enable Alignment of Drug like Properties", ACS Chem. Neurosci., **2010**, 1 (6), pp 435–449

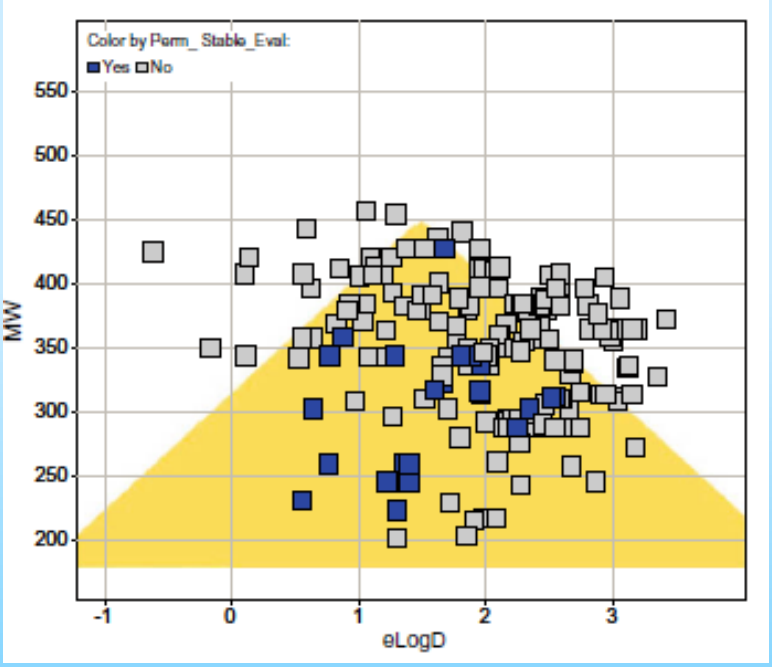
CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

"Golden Triangle" Optimizing Clearance and Oral Absorption



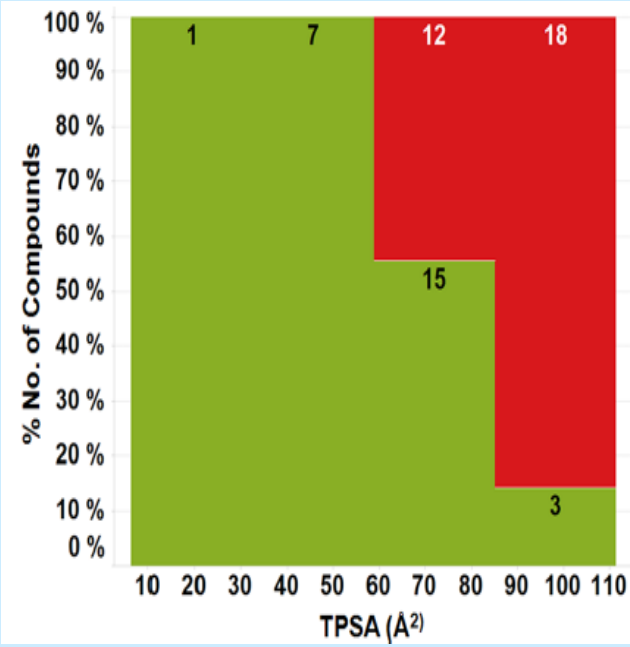
- Impact of MW and LogD on clearance, permeability (oral absorption), ligand efficiency and ligand-lipophilicity index.
- Authors analyzed a structurally diverse set of 47,018 compounds with in vitro clearance and permeability data, as well as both experimental and calculated LogD.

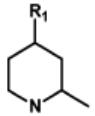
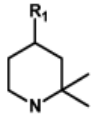
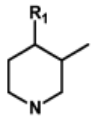
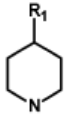
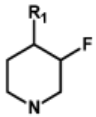
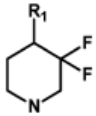




Johnson, T.W., K.R. Dress, and M. Edwards, Using the Golden Triangle to optimize clearance and oral absorption. *Bioorg Med Chem Lett,* **2009**. *19*, 5560-4.

PCP and P-Glycoprotein Efflux



Compound	Structure	NER[a]	Calculated HBA strength for piperidine N[b]	Calculated basic pka for piperidine N[c]	TPSA (Å^2)
1		162	2.9	10.1	67
2		45	2.7	10.2	67
3		39	2.7	10.2	67
4		12	2.4	10	67
5		1.7	2	8.45	67
6		1.1	1.5	6.8	67

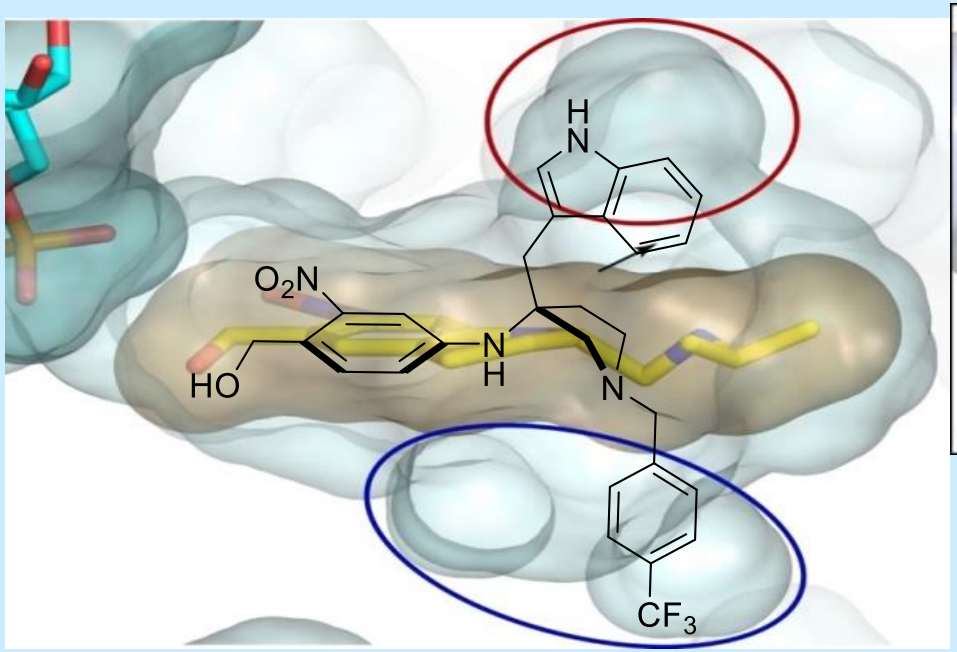
2000 Lilly compounds analyzed:

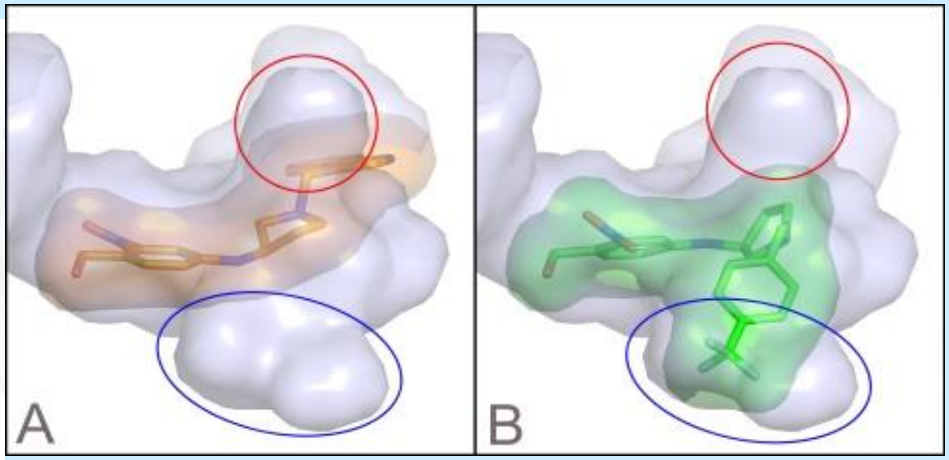
- Highest probability (75%) of being a PGP substrate with TPSA >60 and pKa >8.
- Lowest probably (10%) of being PGP substrate with TPSA <60 and pKa <8.

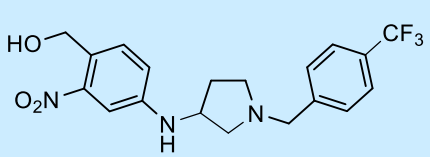
Desai, P.V., Sawada, G.A., Watson, I.A. and Raub, T.J., Integration of in Silico and in Vitro Tools for Scaffold Optimization during Drug Discovery: Predicting P-Glycoprotein Efflux. *Mol. Pharmaceutics,* **2013**, *10,* 1249−1261.

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

In Silico Docking Guiding Novel Core Design

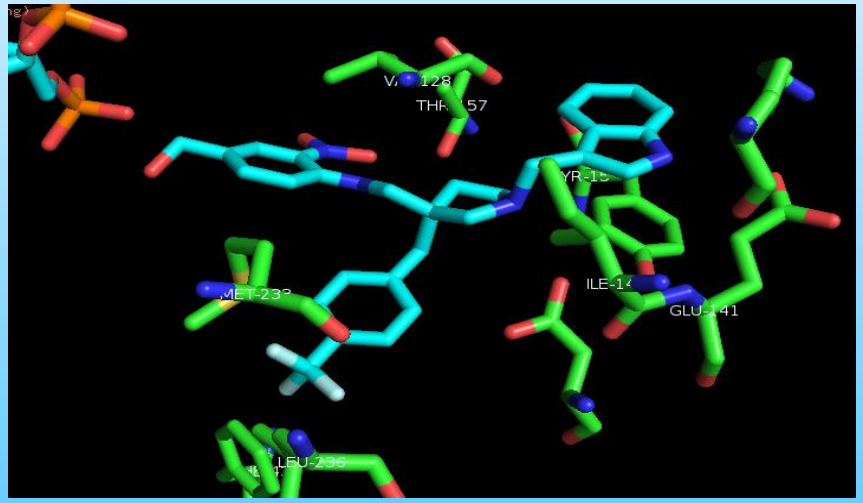


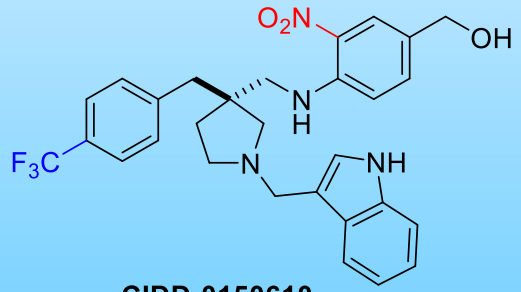




CIDD-0000204

CIDD-0072229



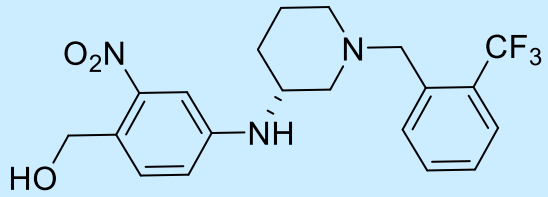


CIDD-0150610

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

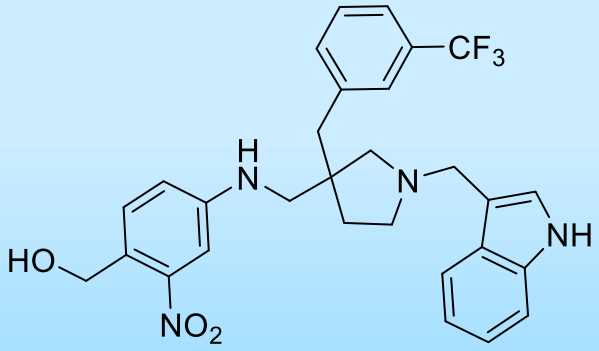
In Vitro ADME Data and PCP's

Compound	CIDD-0072229	CIDD-0149830
Cl_{int} Human hepatocytes (µL/min/million cells)	59.8	26.7
Cl_{int} Human microsomes (µL/min/mg protein)	92.8	77.2
CYP1A2 IC_{50}	20.7 µM	>50 µM
CYP2C9 IC_{50}	3.5 µM	5.6 µM
CYP2C19 IC_{50}	13 µM	9.3 µM
CYP2D6 IC_{50}	7.5 µM	215 nM
CYP3A4 IC_{50}	3.1 µM	7.9 µM
MDCK Papp, A-B ($x10^{-6}$ cm/s)	9.9	0.2
MDCK/MDR1 Ratio B-A/A-B	0.7	18.5
CACO2 Papp, A-B ($x10^{-6}$ cm/s)	3.3	<0.1
CACO2 Efflux ratio	.9	>62
AMES mutenigicity (+/-)-S9	Negative	Negative
HERG IC50	10 µM	5 µM
Human % protein binding	99%	99%
Rat % protein binding	99%	99%



CIDD-0072229

MW: 409.4
TPSA: 78.4
LogD: 3.3
pKa: 7.6



(+/-)-CIDD-0149830

MW: 538.6
TPSA: 94.4
LogD: 3.6
pKa: 9.3

CENTER FOR INNOVATIVE DRUG DISCOVERY
utcidd.org

Summary and Final Thoughts….

- Physicochemical properties (PCP) have an enormous impact on drug properties and impact the ability to develop a successful compound for clinical applications.
- PCP analysis should be incorporated at the very beginning of a drug discovery program and used as a key decision tool for lead advancement.
- Calculated PCP values are a great starting point, but when available, experimentally determined values (LogD) are extremely valuable.
- Although PCP's are a great guide to optimizing drug properties, routine screening of in vitro ADME/PK in an iterative SAR process is absolutely critical for optimizing drug ADME and correlating data to PCP's for future design cycles.