Understanding and predicting brain penetration for CNS-targeted drugs

March 2018

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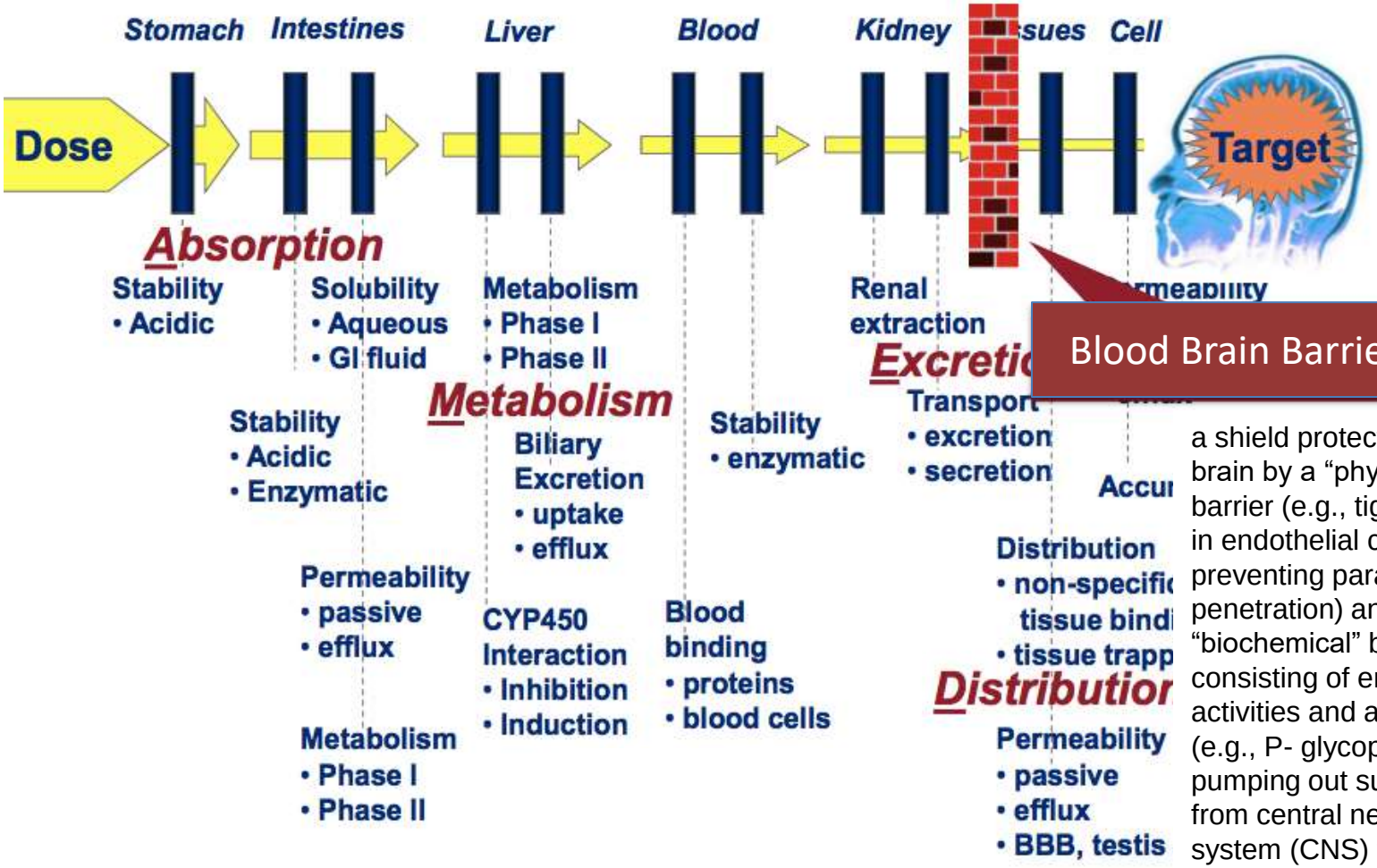
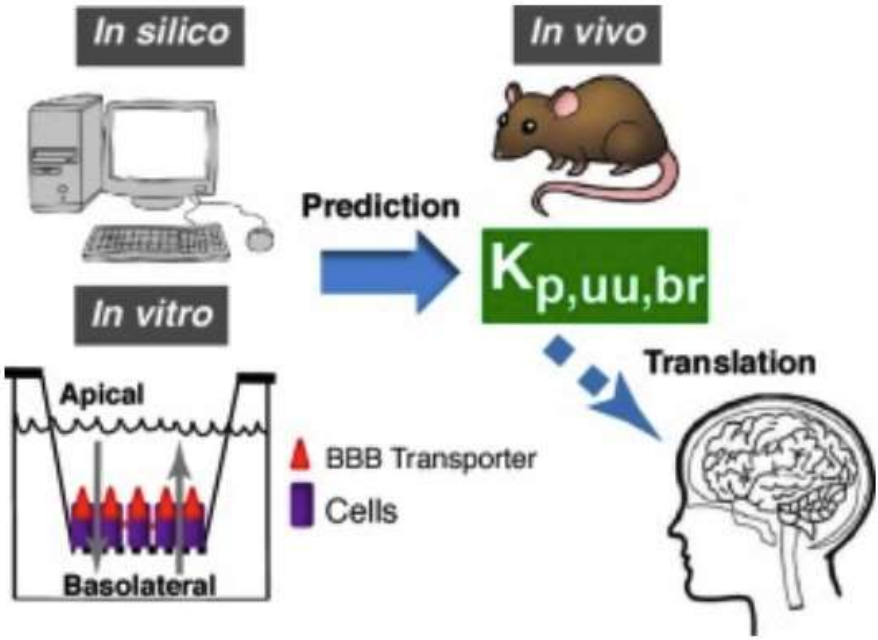
Increased hurdles for CNS targeted drugs



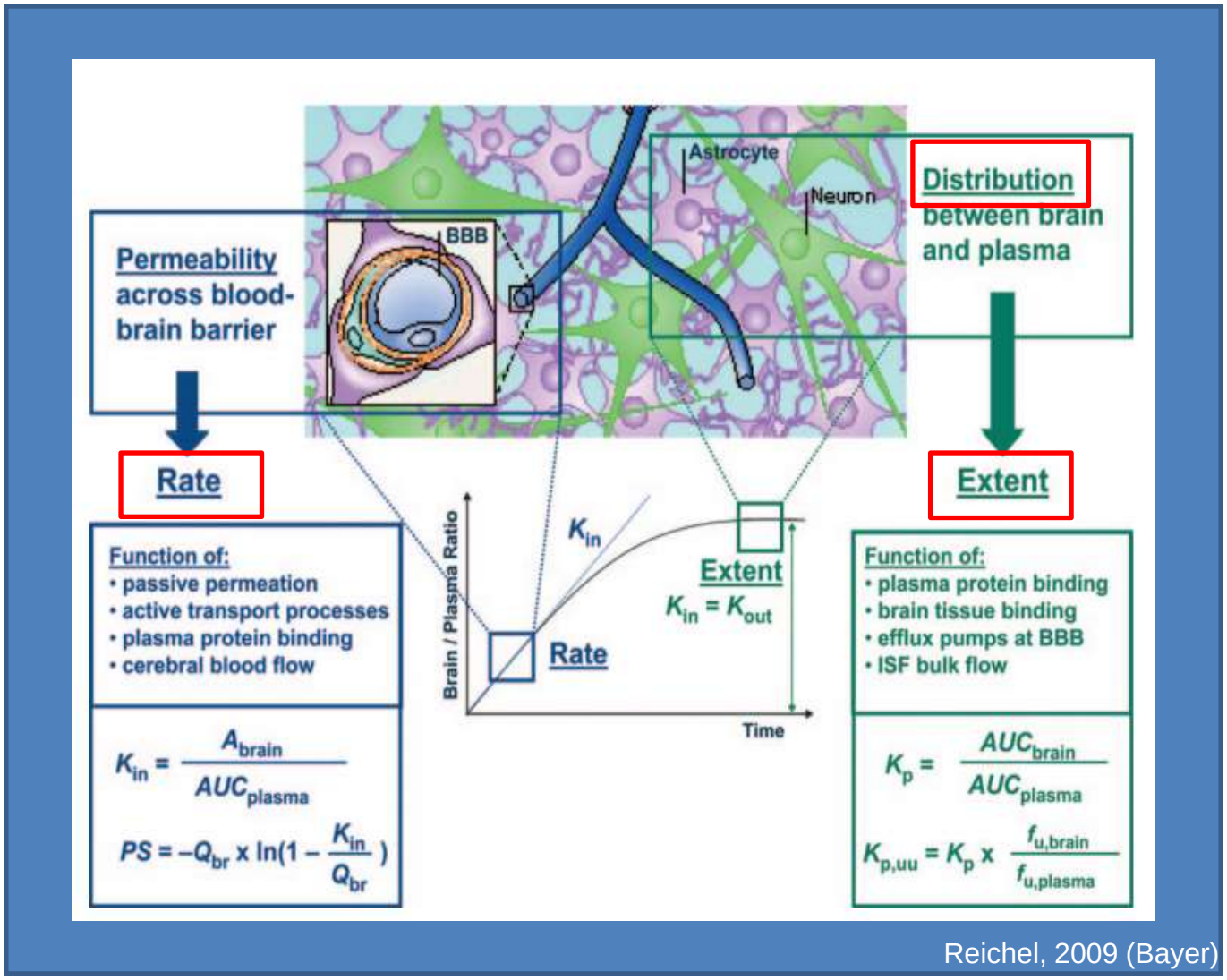
a shield protecting the brain by a “physical” barrier (e.g., tight junctions in endothelial cells preventing paracellular penetration) and a “biochemical” barrier consisting of enzymatic activities and active efflux (e.g., P- glycoprotein pumping out substrates from central nervous system (CNS) tissues)

CNS Paradigm

- Linking exposure/PK to efficacy/PD and to delineate key parameters is critical
- Challenge is to achieve a safe and efficacious concentration profile in the brain
- Past failures are due to underestimating the complexity of the brain, including pharmacokinetics (PK)
- Finding drug candidates with the right balance between free fraction in plasma and brain, and between rate and extent of CNS penetration and distribution in the CNS is key
  - all 3 have to be examined and integrated into one coherent concept

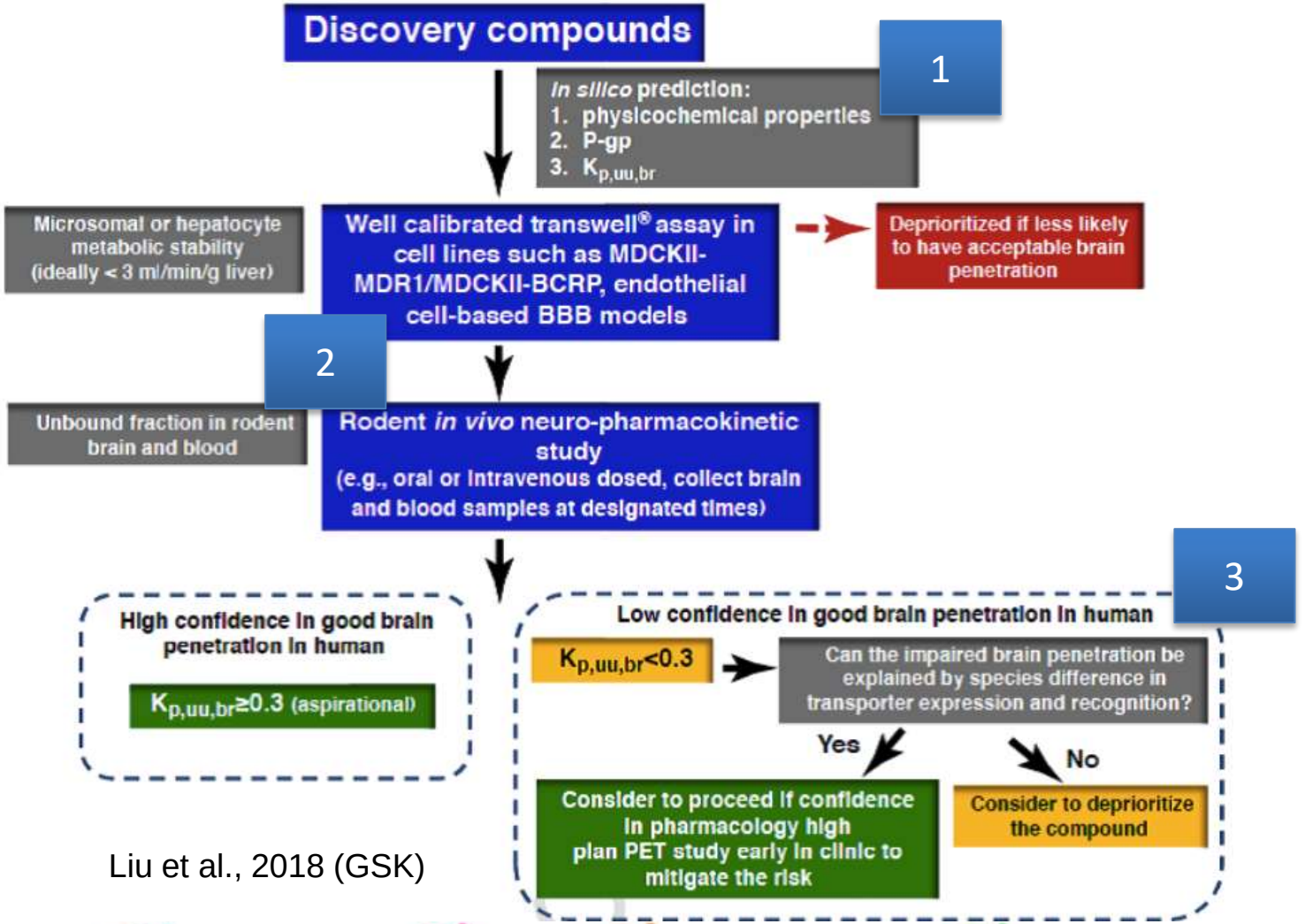


CNS Drug Discovery & the BBB



Reichel, 2009 (Bayer)

CNS Discovery Screening Cascade



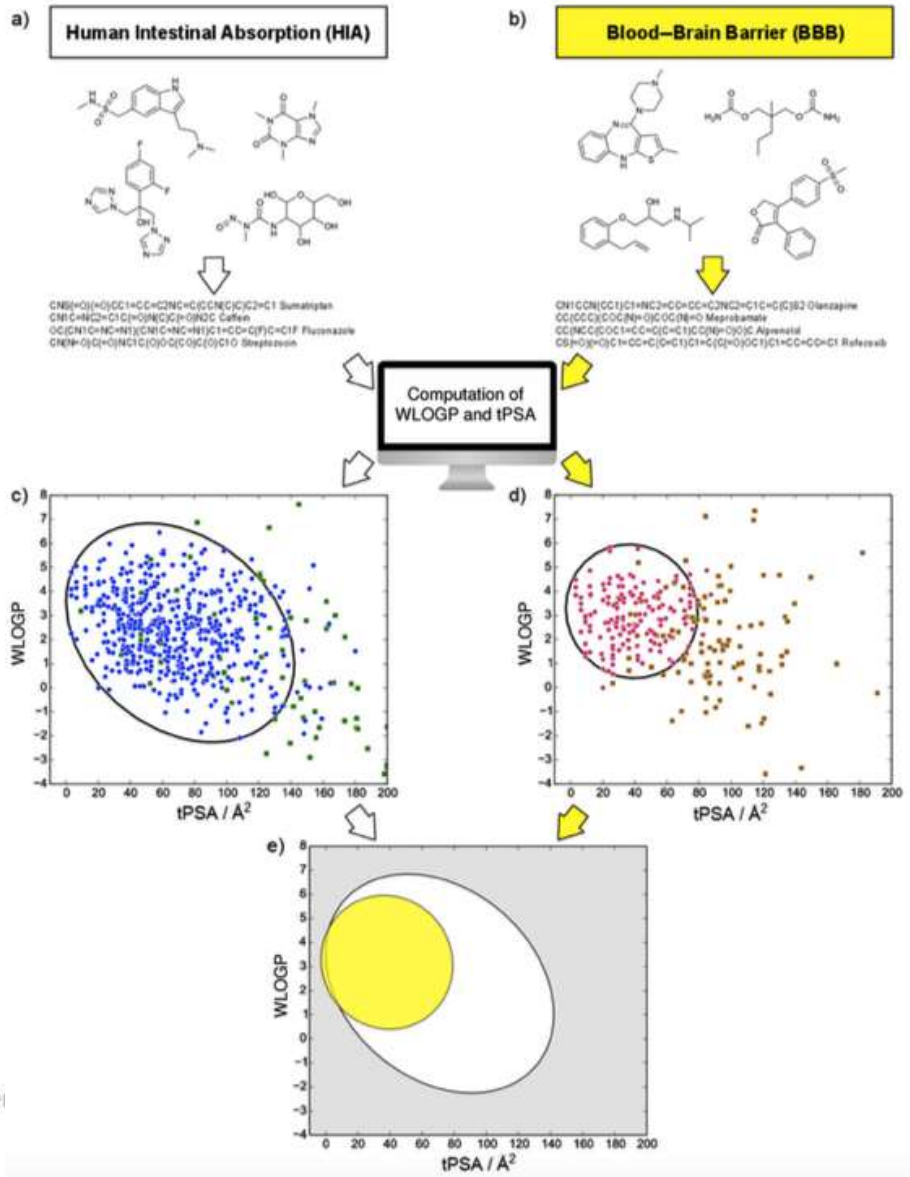
Liu et al., 2018 (GSK)

1

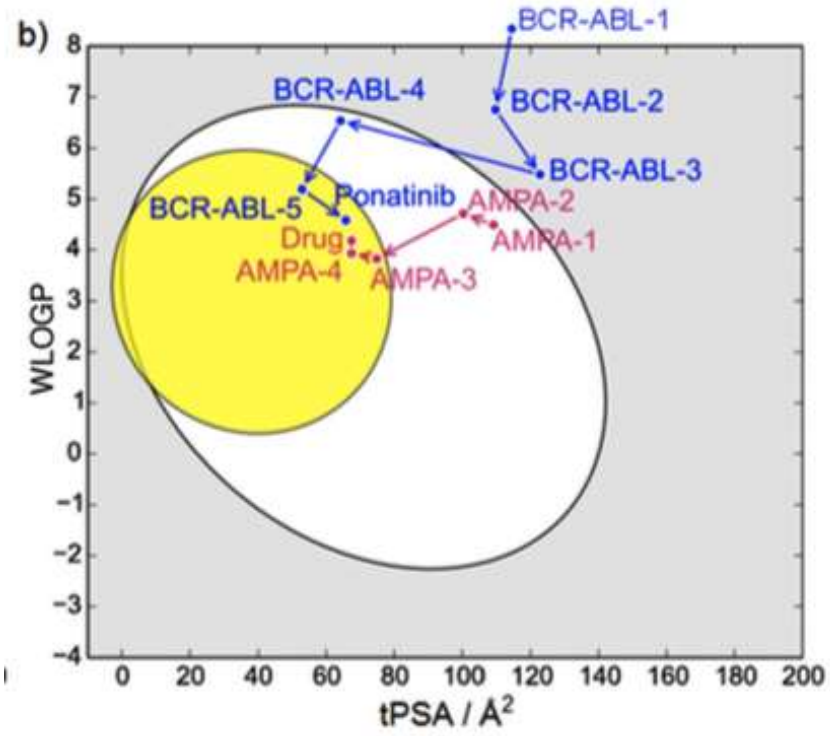
Predicting Brain Penetration

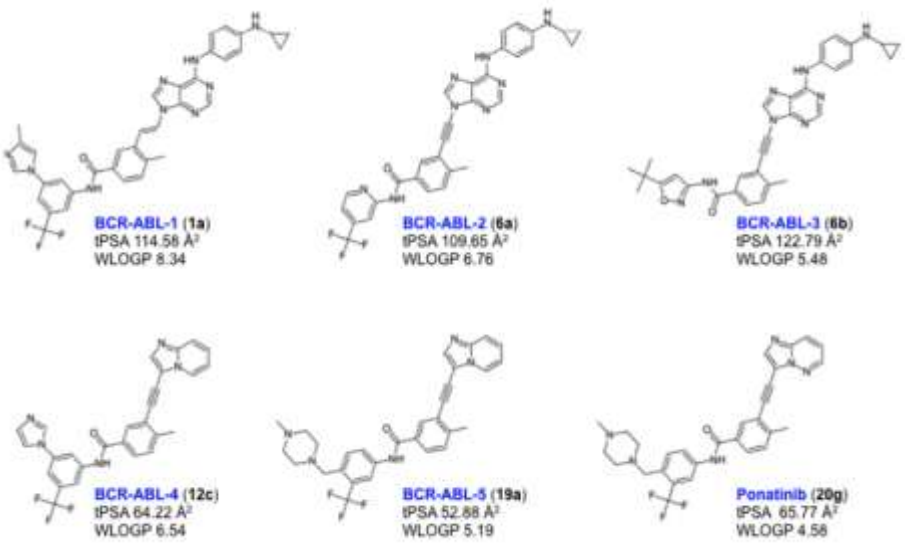
in silico – Physicochemical Properties

- Daina & Zoite, 2016
- BOILED-Egg
  - Brain Or IntestinaL EstimateD permeation
  - works by computing the lipophilicity and polarity of small molecules
  - Builds on Egan's et al *Egan* egg model

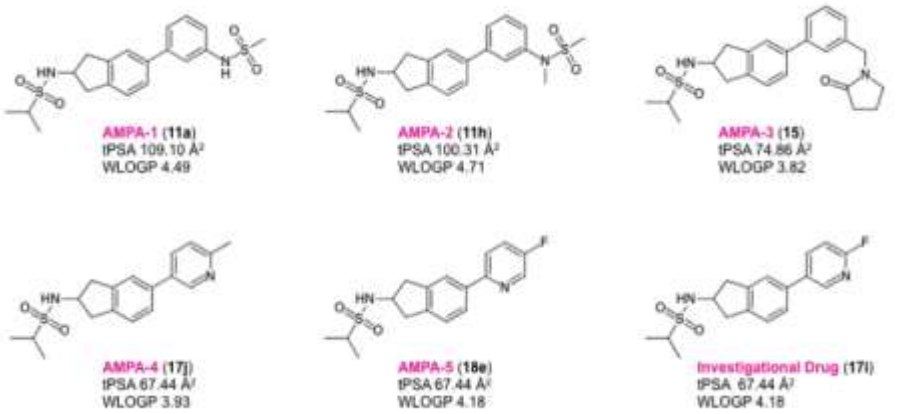


Optimisation of Drug Leads



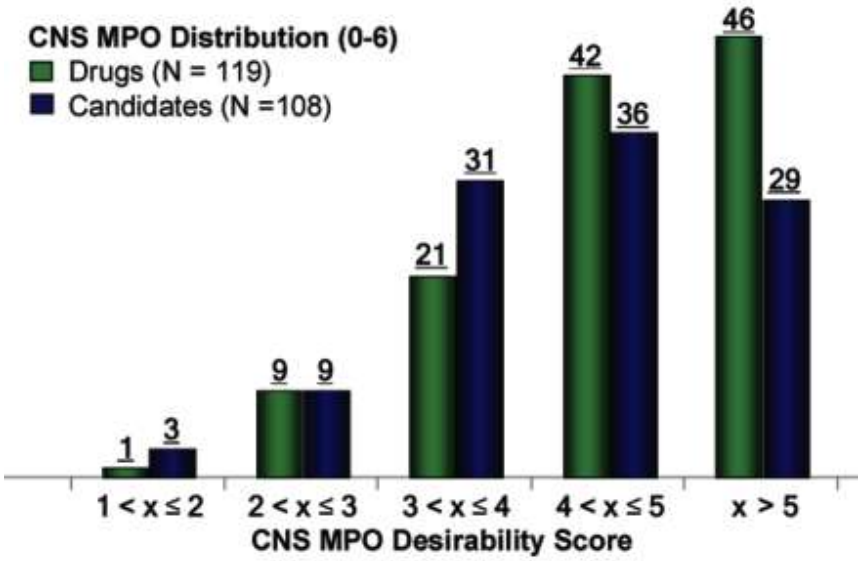


BCR-ABL - Huang et al., 2010 (Ariad)
AMPA – War et al., 2010 (GSK)

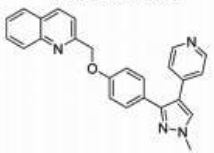


in silico – Physicochemical Properties

- Wager *et al.*, 2010; 2016
- CNS MPO
  - Multi-Parameter Optimisation
- Use of 6 parameters
  - cLogP, LogD, tPSA, MW, HBD and pKa
- Use of arbitrary selection of descriptors and calculations of score functions, search of thresholds of classification, and absence of any chemometric procedures



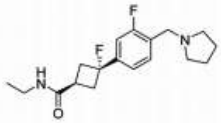
PDE10 inhibitor



PF-02545920

	Value	T0
ClogP	3.8	0.58
ClogD	3.5	0.24
TPSA	52.8	1.00
MW	392.5	0.77
HBD	0.0	1.00
pKa	4.3	1.00
CNS MPO		4.6

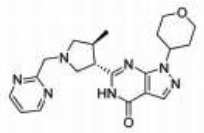
H3 antagonist



PF-03654746

	Value	T0
ClogP	2.4	1.00
ClogD	0.0	1.00
TPSA	32.3	0.62
MW	322.4	1.00
HBD	1.0	0.83
pKa	9.2	0.42
CNS MPO		4.9

PDE9 inhibitor

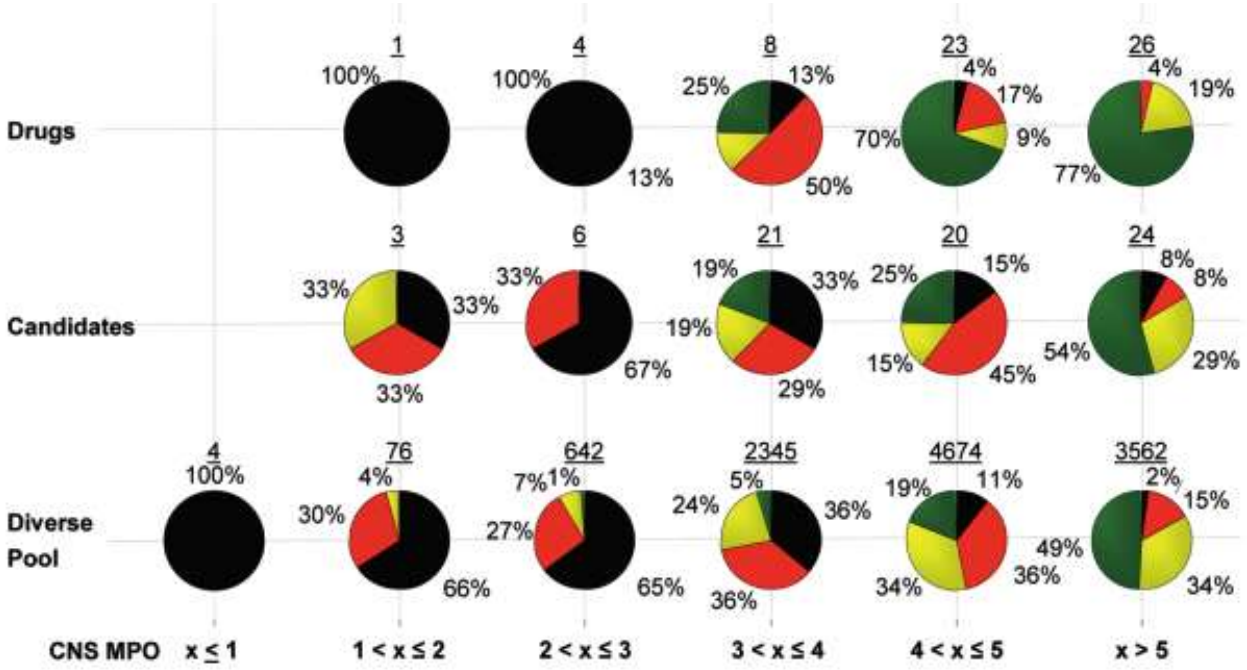


PF-04447943

	Value	T0
ClogP	-1.5	1.00
ClogD	-0.7	1.00
TPSA	101.9	0.60
MW	395.4	0.75
HBD	1.0	0.83
pKa	7.9	1.00
CNS MPO		5.2

in silico – Physicochemical Properties

- Alignment of MPO with desired ADME attributes such as high Papp, low P-gp, and low CLint,u is possible
  - ADME attributes: 3/3 (green), 2/3 (yellow), 1/3 (red), and no attributes (black)



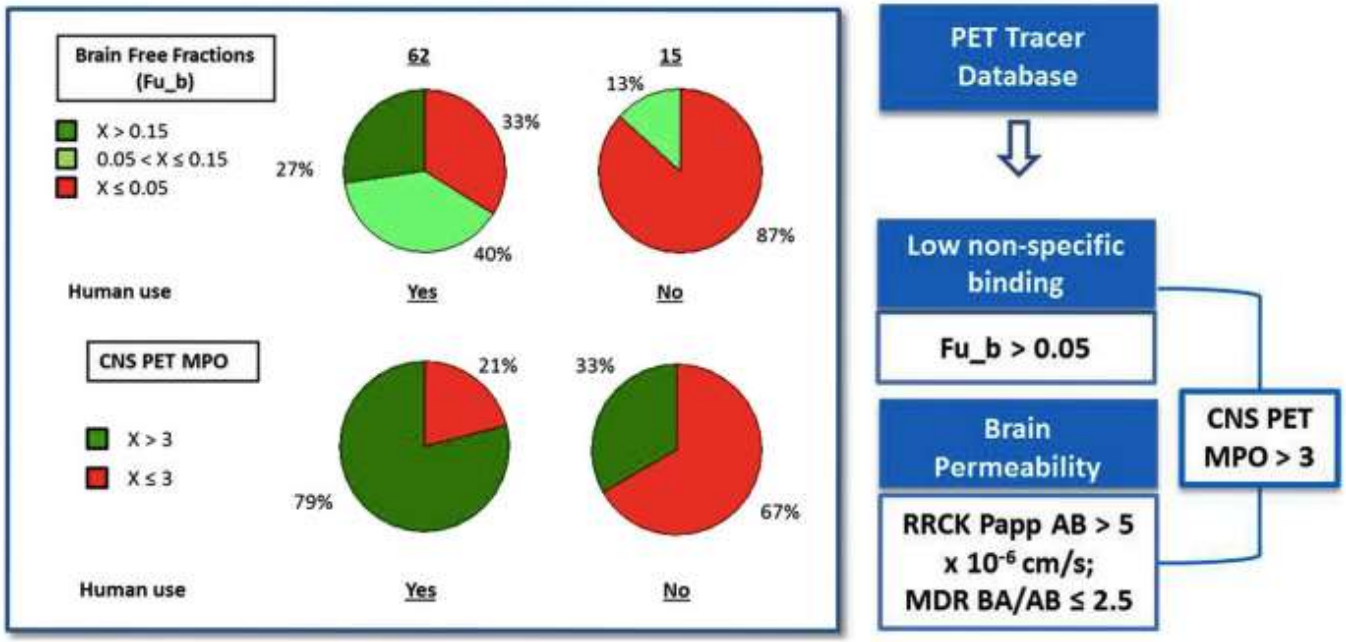
Wager et al., 2010 (Pfizer)

2

Enhancing PhysChem properties with *in vitro* ADME

Incorporating *in vitro* ADME data

- Use of ADME parameters to select PET ligands to enhance predictions
  - Zhang et al., 2013 compiled a PET ligand database consisting of 62 clinically validated CNS PET ligands and 15 unsuccessful radio-ligands as negative controls
    - key differences between the two categories in terms of physicochemical properties and *in vitro* ADME properties were identified



Application of *in vitro* ADME parameters

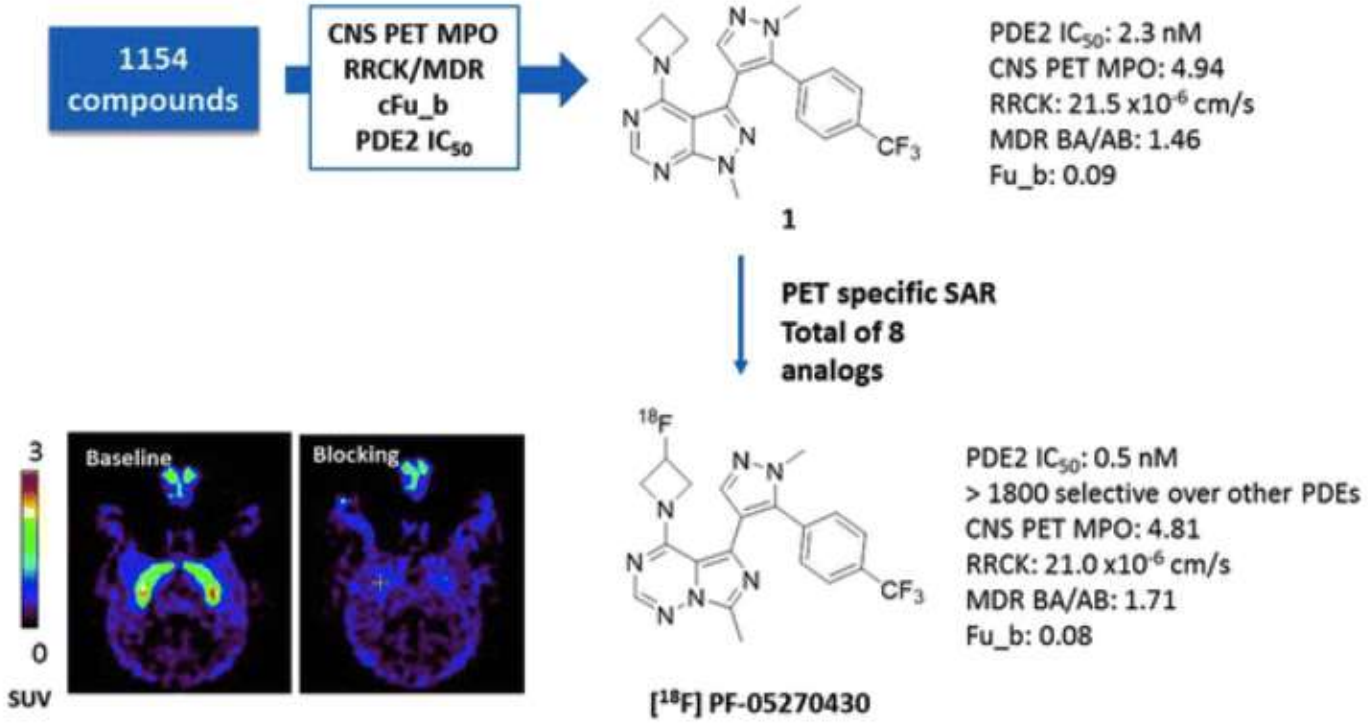
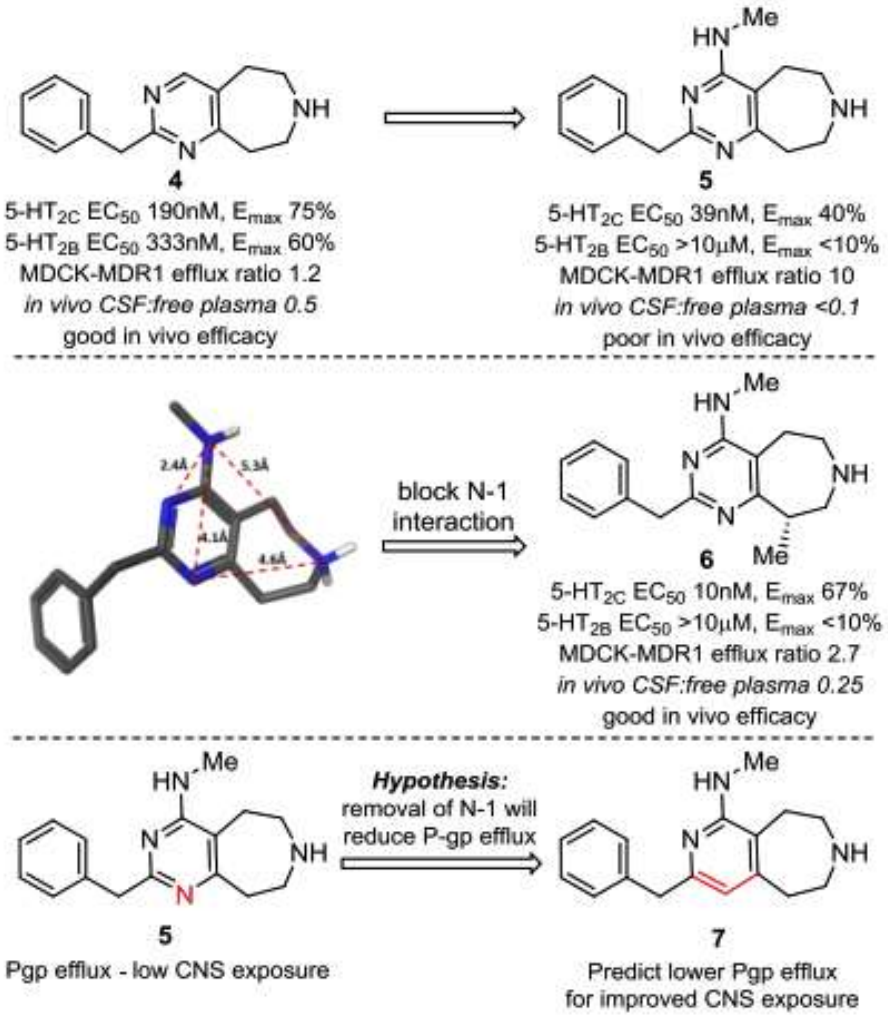


Fig. 4
Discovery of a PDF_{2A}-selective PET ligand [^{8}F]PF-05270430 guided by CNS PET ligand design parameters

Zhang & Villalobos, 2016 (Pfizer)

Reducing the impact of P-glycoprotein



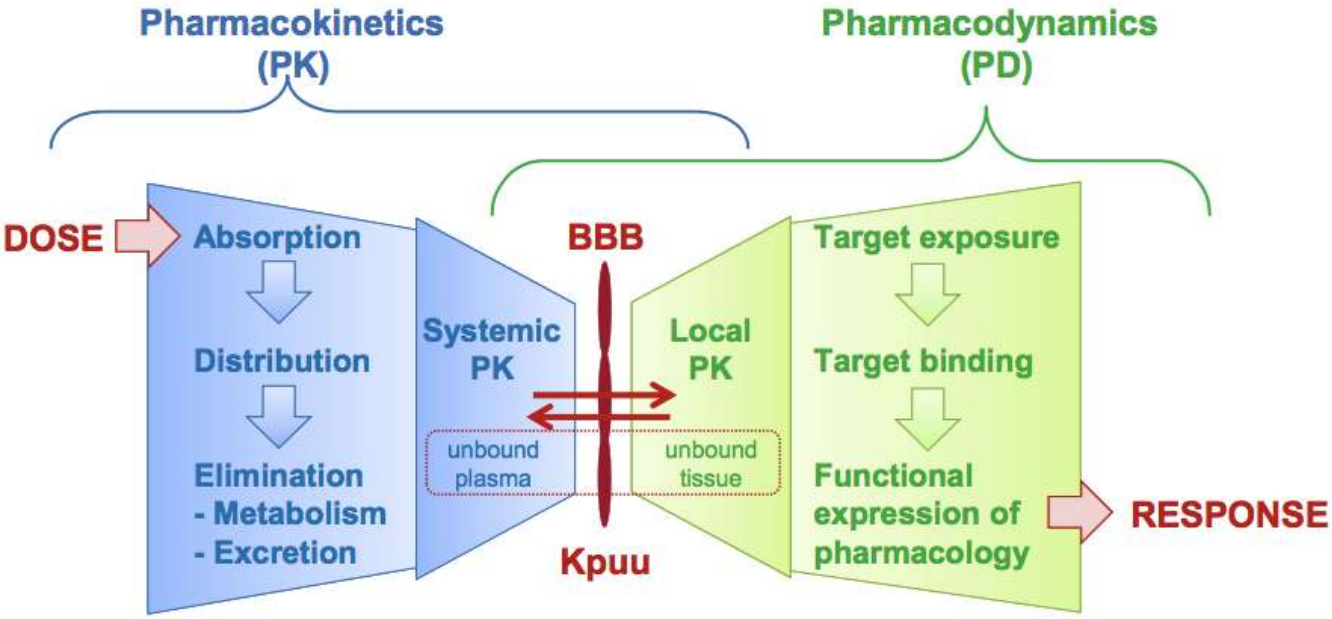
Rouquet et al, 2015 (Pfizer)

- Design of $5HT_{2C}$ agonists for the treatment of obesity, urinary incontinence, psychiatric disorders and sexual dysfunction
- Pharmacophore models (e.g. Seelig et al., 2004) for P-gp have highlighted the role of aromatic hydrophobic interactions and intramolecular hydrogen bond Acc-Acc distances of ~2.5 Å and ~4.6 Å as P-gp recognition features

3

Brain Penetration and Kp,uu Values

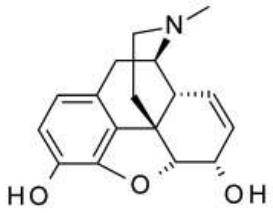
Unbound drug concentrations



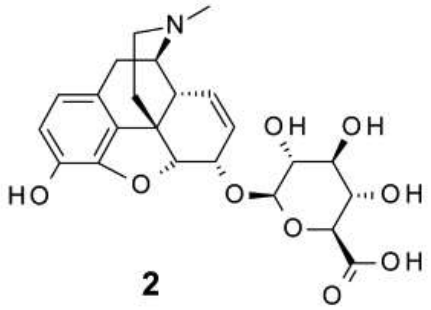
- Unbound brain concentrations is a key determinant of brain occupancy for GPCR targets
- 3 Pillars of drug survival (Morgan et al., 2012)
  - Exposure at site of action
  - Target binding
  - Expression of functional pharmacological activity

PK/PD driven by unbound concentrations

Table 1. Morphine and Morphine-6-glucuronide Paradox Explained by Considering Drug $C_{u,b}$ Data[27,28]



1



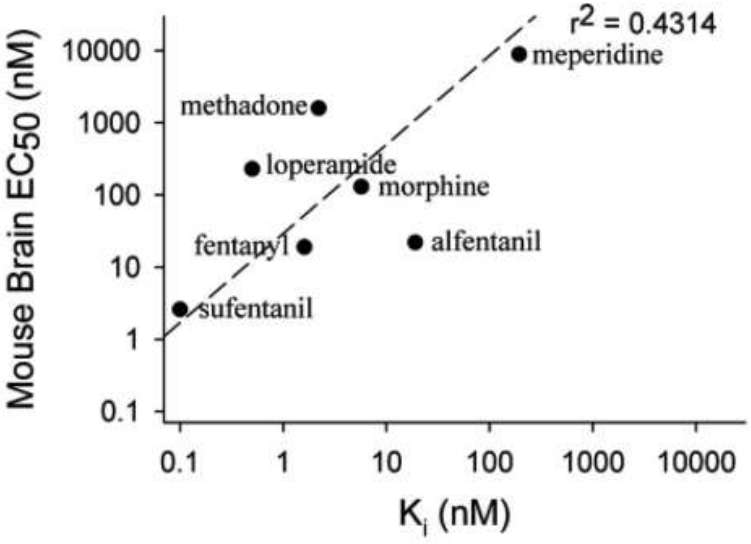
2

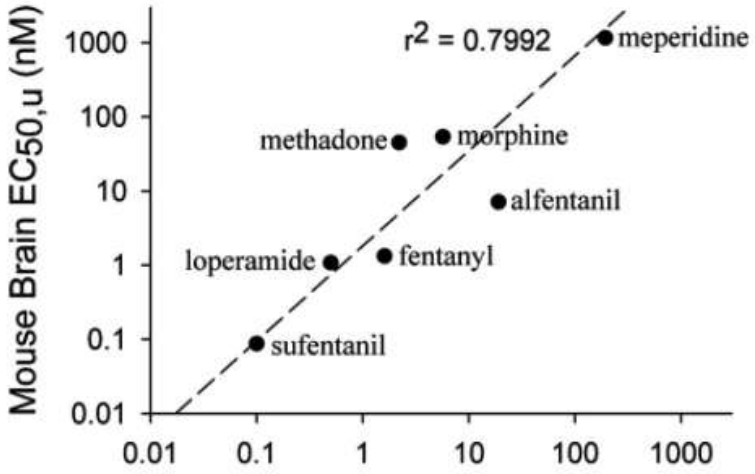
compd	MOR[a] K_i (nM)	AUC_b[b] (μM/min)	K_p	ISF AUC[c] (μM/min)	$K_{p,uu}$
1	22	186	0.74	79	0.51
2	63	42	0.05	336	0.56

[a][^{3}H]-Naloxone displacement binding assay in MOR-expressing cell membranes.[25] [b]Total brain AUC concentration in rat, 10 mg/kg (s.c.). [c]Measured by *in vivo* transcortical microdialysis.[28]

What is driving the brain penetration of the unbound morphine glucuronide considering that its more polar?

Rankovic et al., 2014 (Lilly)





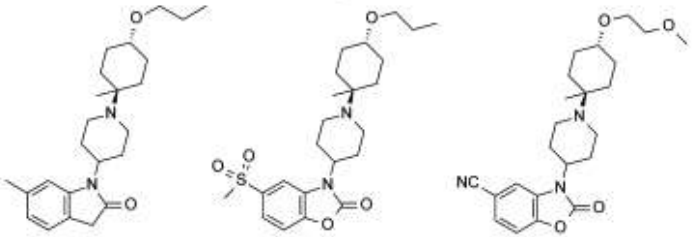
Kalvass et al., 2007

Impact of Lipophilicity and HBD

Table 3. M1 Agonists: Reducing Lipophilicity To Improve $C_{u,b}$[96]

Lipophilicity

Johnson et al., 2010 (GSK)

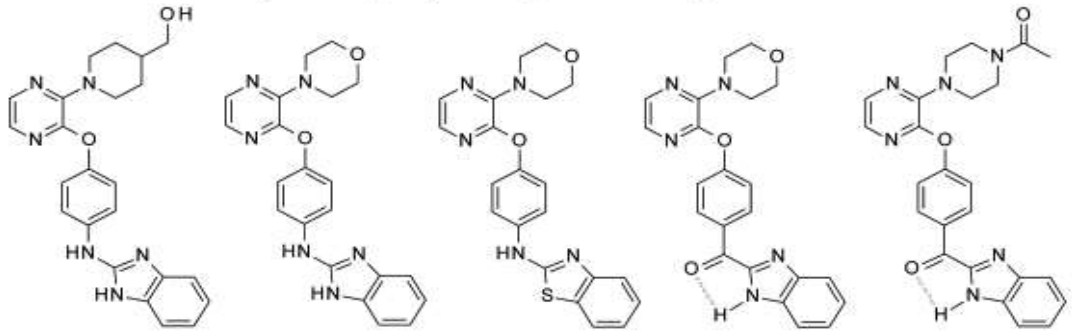


3 4 5

compd	M_1 pEC_{50}	cLogP	Cl[a] (mL/min/kg)	K_p	$f_{u,b}$ (%)	$f_{u,p}$ (%)	$C_{u,b}$[a] (nM)	$C_{u,p}$[a] (nM)	$K_{p,uu}$
3	9.3	3.5	85	5.7	6	20	2.5	2.6	0.96
4	8.6	1.5	11	0.8	36	40	168	378	0.44
5	8.0	1.5	23	1.7	39	38	261	265	0.98

[a]3 mg/kg p.o. (rat).

Table 6. PDE10A Inhibitors: Reducing HBD Capacity To Improve Brain Exposure[101]



12 13 14 15 16

compd	PDE10A IC_{50} (nM)	HBD	ER[a]	Cl[b] (L/h/kg)	F[b] (%)	RO[c] (%)
12	92	3	76.7			
13	1.1	2	11.1			
14	4.3	1	2.4			
15	4.5	1	0.9	0.53	10	21.3
16	5.1	1		0.07	56	57.1

[a]MDR1-MDCK. [b]Fed male Sprague–Dawley rats; dose: 5 mg/kg p.o. [c]Dose: 10 mg/kg.

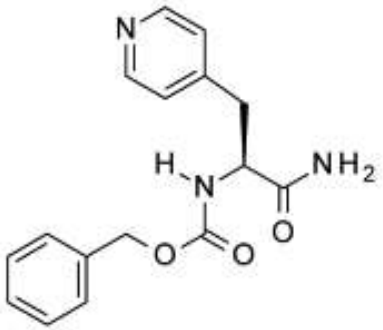
HBD

Hu et al., 2013 - Amgen

YGNATURE discovery

IMHB

- The formation of an intramolecular hydrogen bond (IMHB) may increase lipophilicity, which, in turn, may improve passive permeability as well as impair P-gp recognition



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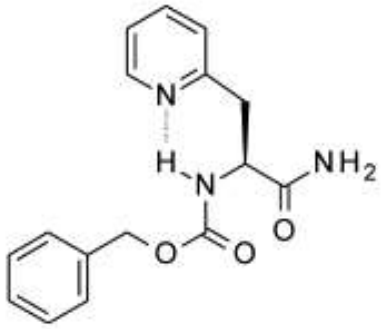


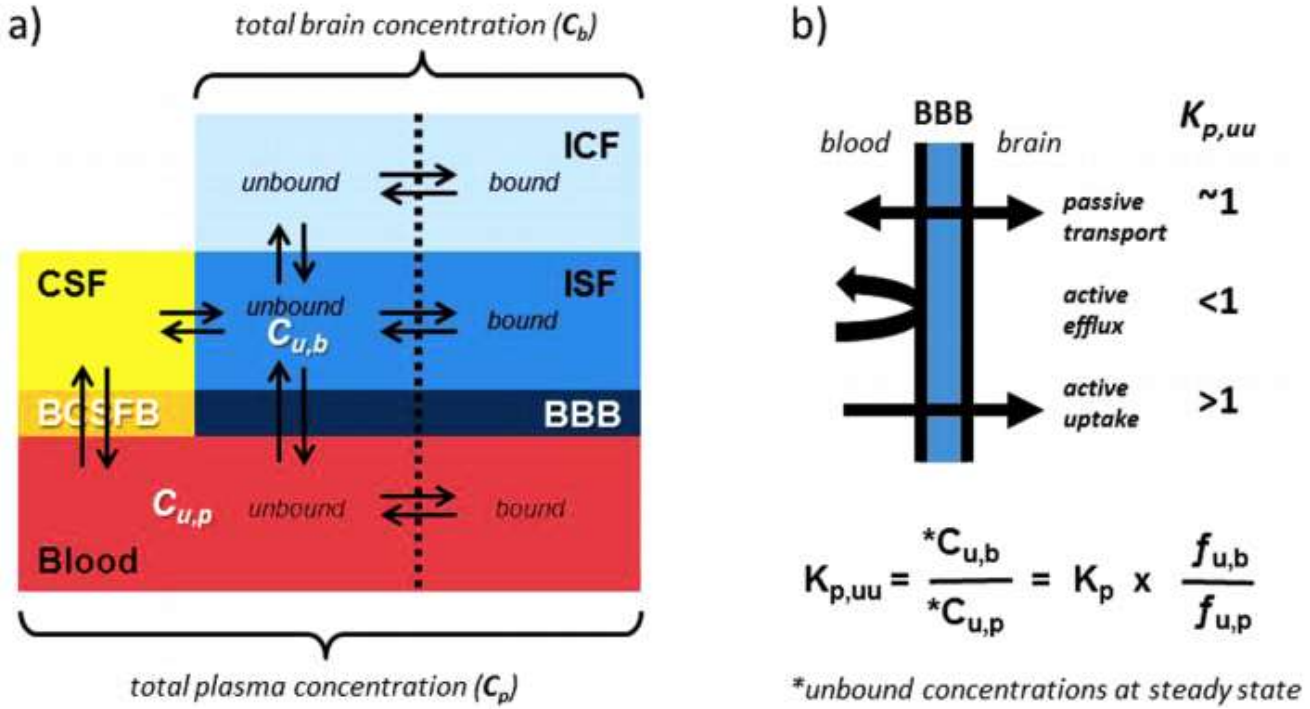
18

compd	HBD	P_{app} [b]	ER[c]
17	2	43	3.1
18	2[a]	177	1.1

[a]Includes one intramolecular H-bond. [b]Apparent AB permeability in the MDR1-MDCK assay. [c]BA/AB permeability ratio in the MDR1-MDCK assay.

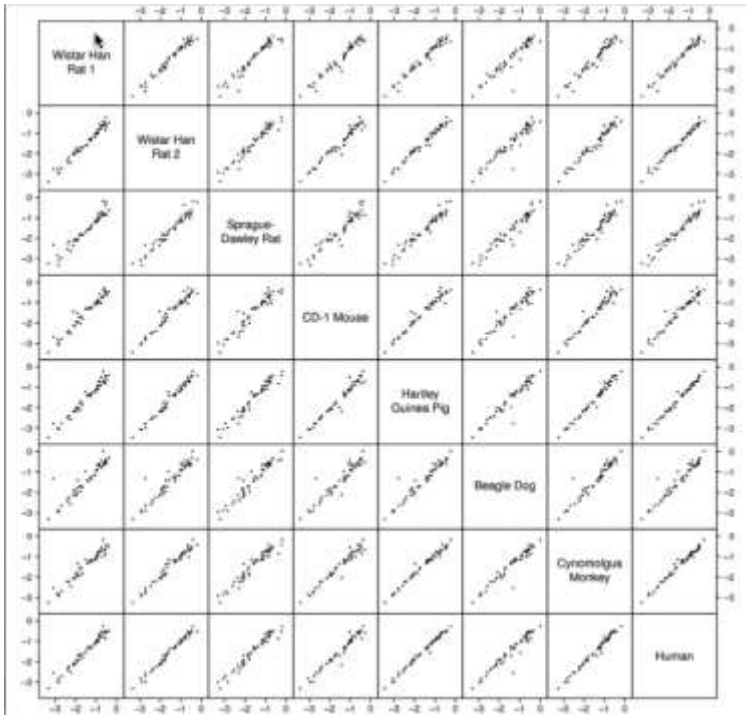
Rafi et al., 2012

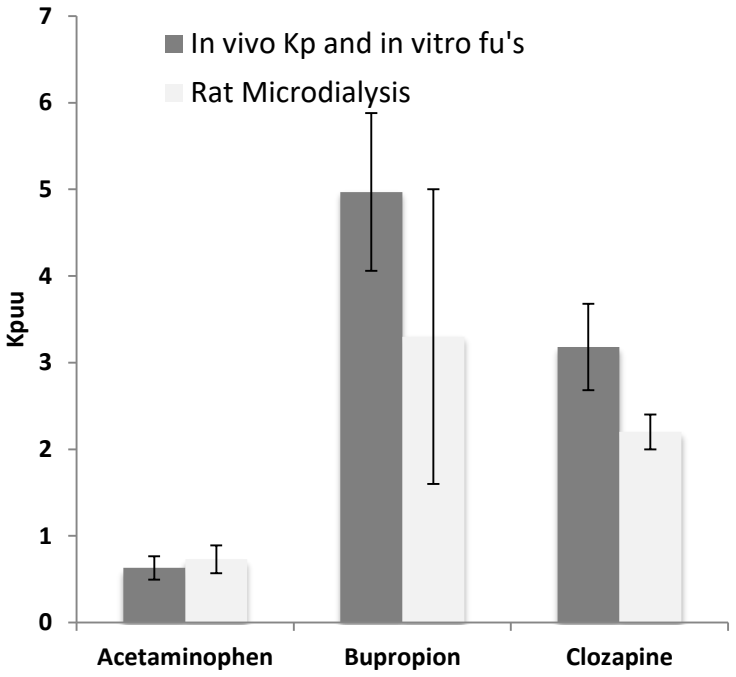
Principle CNS PK Parameters and Concepts



Rankovic et al., 2014

Kp,uu – Comparison with Microdialysis





- Species independence in brain tissue binding (Di et al., 2011)
- Good relationship (Summerfield et al., 2016)

Translating between rat and human Kp,uu

- In general, compounds are characterized by reasonably good brain penetration in humans if they have good brain penetration in rats
- However, compounds can show either good or limited brain penetration in humans if they have restriction of brain penetration in rats

Compound	Species (Male)	Oral Dose (mg/kg)	Brain $AUC_{(0\text{-last})}$ (ng*h/mL)	Blood $AUC_{(0\text{-last})}$ (ng*h/mL)	Brain:Blood Ratio	$K_{b\,u,u}$
18	CD1 Mouse	10	1800	963	1.9	0.98
	SD Rat	5	2390	2010	1.2	0.62
	Cyno Monkey	2.5 (Brain) 5 (Blood)	1968	1721	2.3	3.39

Unpublished data

Summary

- in silico tools are available for predicting brain penetration
- The concept of free drug concentrations as the central PK parameter for PK/PD has now also entered the CNS arena (which has long been the case for peripheral indications)
- Kp,uu allows for the simulation of unbound brain concentrations on the basis of the unbound plasma concentration-time profile
  - Kp,uu is therefore complementing Kp as a more useful PK parameter of CNS penetration

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