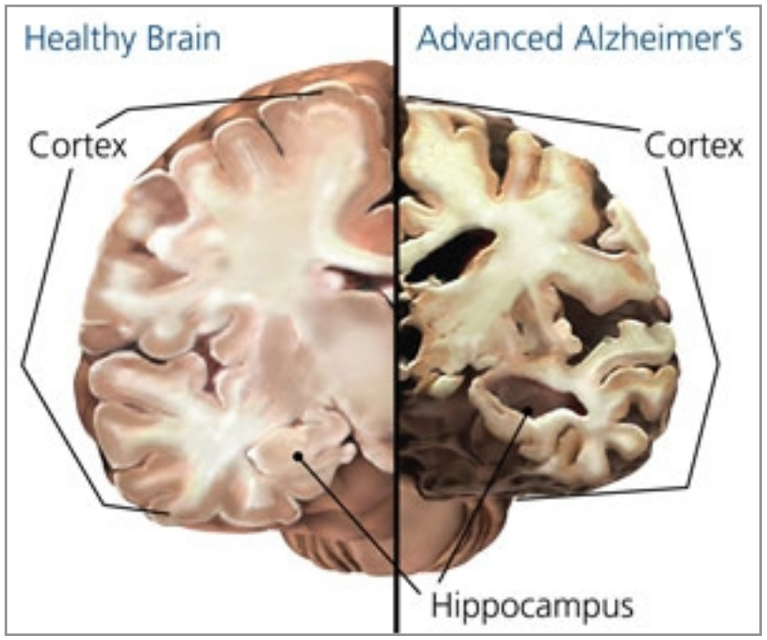
Central Nervous System Drug Design

MacMillan Group Meeting
Stefan McCarver
November 8th, 2017

Why is Central Nervous System Drug Discovery Important?

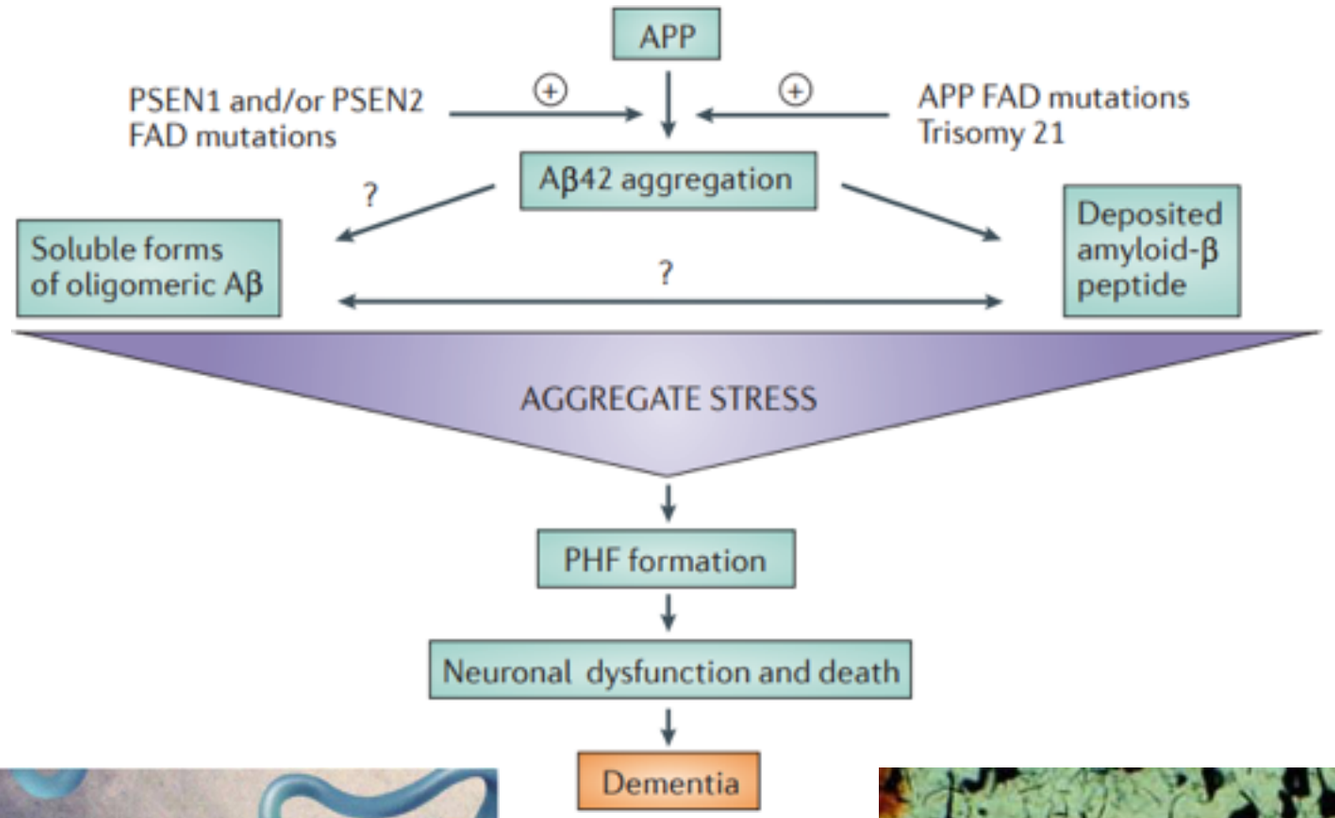
- Neurodegenerative Disease
  - Almost 6 million Americans suffer from either Alzheimer's or Parkinson's
  - There is a greater than 50% chance of dementia by age 90

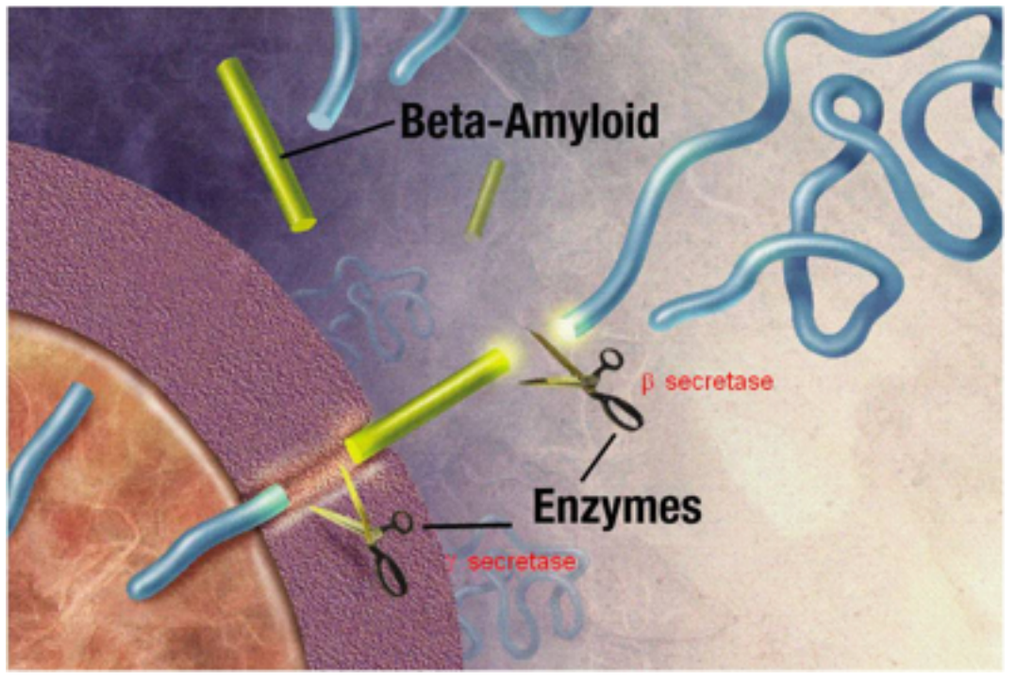


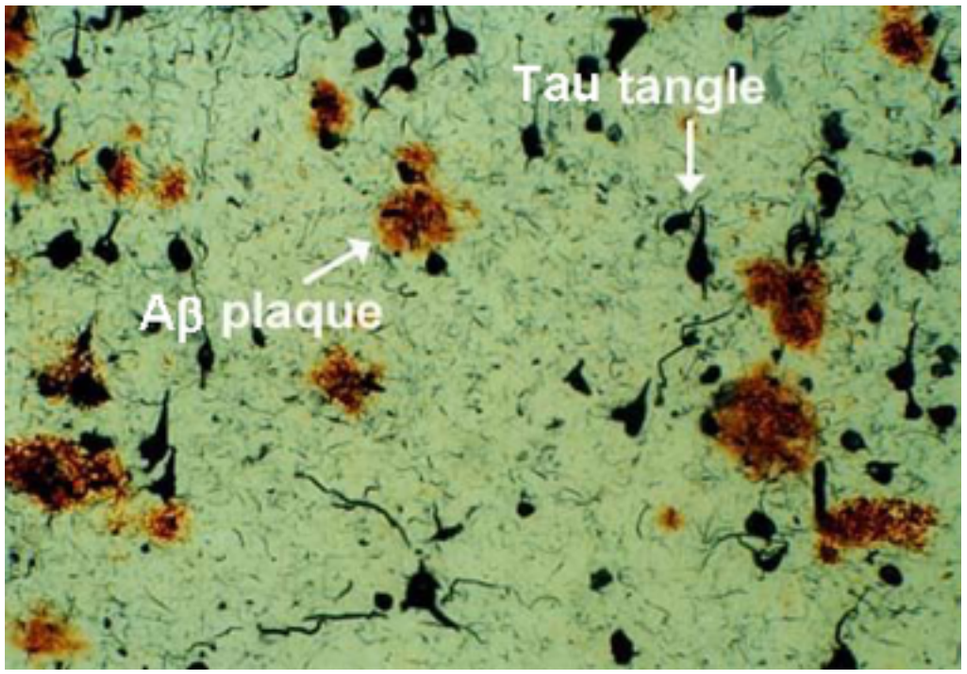
Despite the size of this societal burden, no effective treatments exist!

Cummings, J.; Lee, G.; Mortsdorf, T.; Ritter, A.; Zhong, K. *Alzheimer's & Dementia* **2017**, *3*, 367–384.

β-Amyloid Hypothesis in Alzheimer's Disease







Karran, E.; Mercken, M.; De Strooper, B. *Nat. Rev. Drug Discov.* **2011**, *10*, 698.
Shih, H-P.; Zhang, X.; Aronov, A. M. *Nat. Rev. Drug Discov.* **2017**

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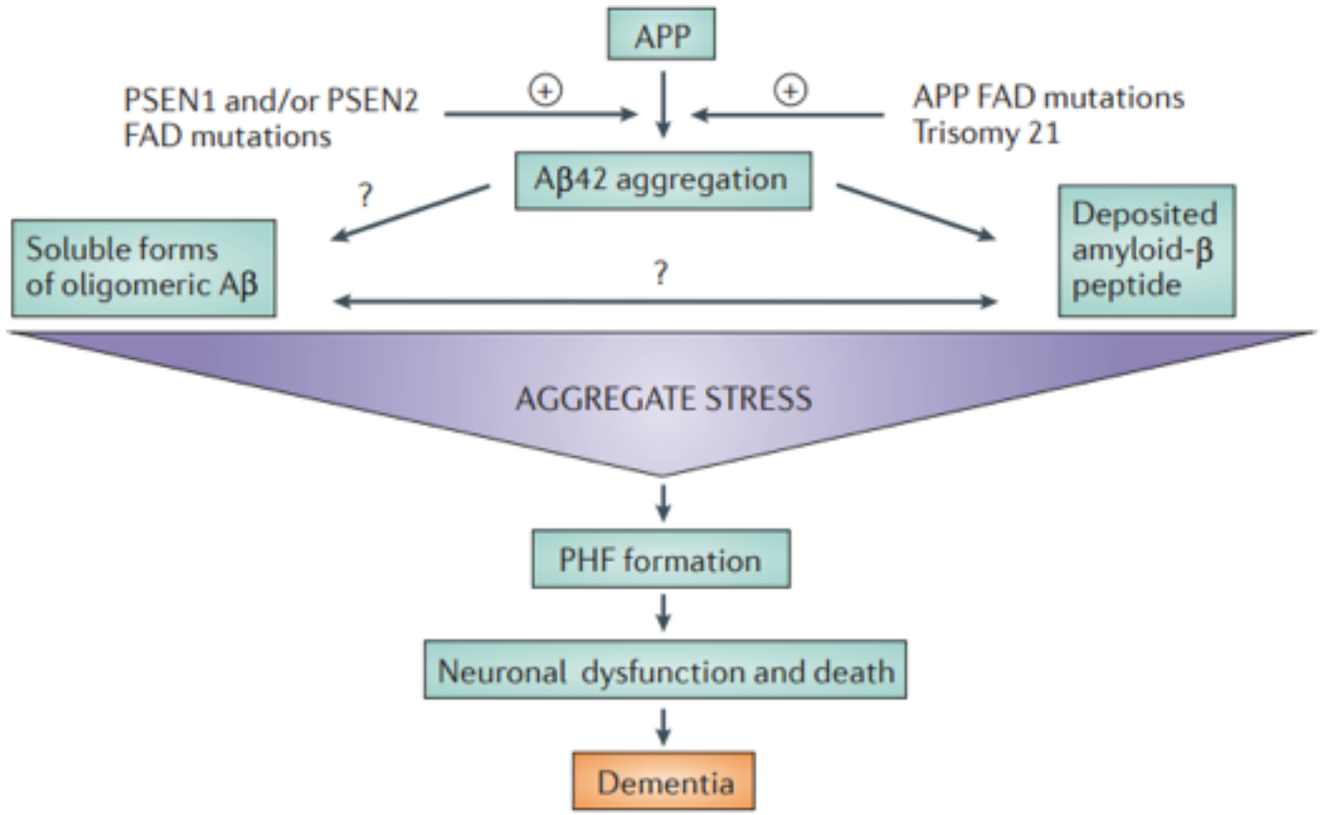

Indication	Mechanism	Number of discontinuations for pair	Example drug
Active unvalidated pairs with ongoing projects			
Alzheimer disease	Amyloid-β synthesis inhibitor	26	Semagacestat
Alzheimer disease	Amyloid-β deposition inhibitor	25	Tramiprosate
Alzheimer disease	Amyloid-β antagonist	24	Ponezumab
Non-insulin-dependent diabetes	PPAR α agonist	22	Aleglitazar
Alzheimer disease	Amyloid-β modulator	18	Lovastatin
Asthma	K^+ channel stimulator	15	Rilmakalim
Depression	5-HT_{1A} receptor agonist	14	Naluzotan
Breast cancer	EGFR inhibitor	12	Vandetanib
Non-insulin-dependent diabetes	Glucokinase stimulator	11	Piragliatin
Pain	TRPV1 antagonist	11	MK-2295

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Shih, H-P.; Zhang, X.; Aronov, A. M. *Nat. Rev. Drug Discov.* **2017**

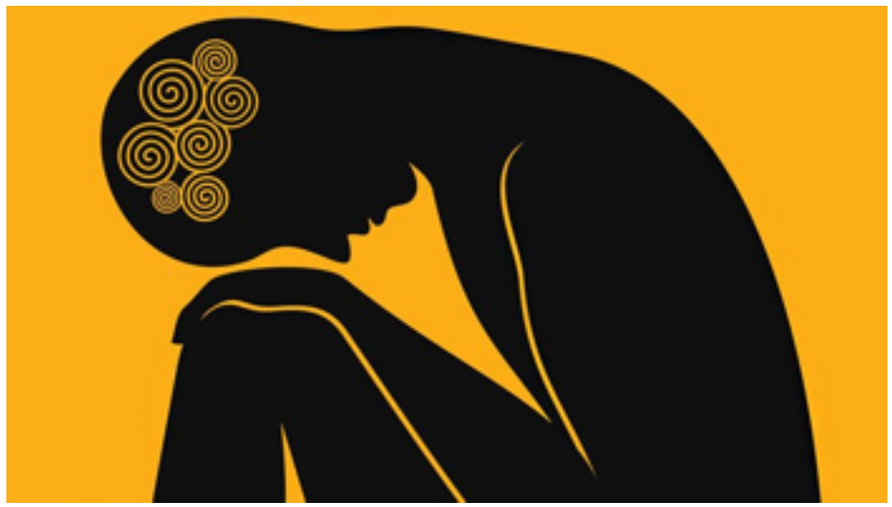
Why is Central Nervous System Drug Discovery Important?

- Mood Disorders - Depression

  - Overall lifetime prevalence rate of 17% (21% of women, 13% of men)

  - Depression is the second leading cause of disability worldwide

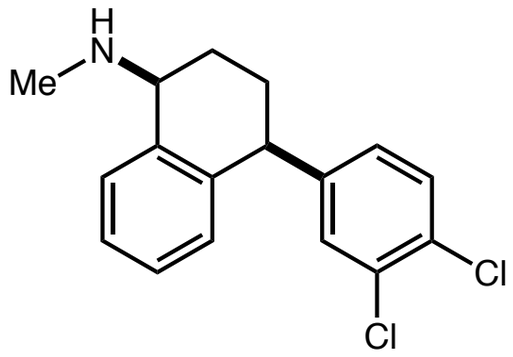
  - Responses are often delayed and many patients do not respond to treatment



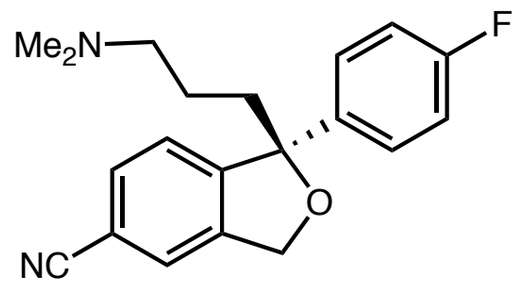
Nemeroff, C. B.; Owens, M. J. *Nature Neuroscience* **2002**, *5*, 1068–1070.

Existing Antidepressant Treatments

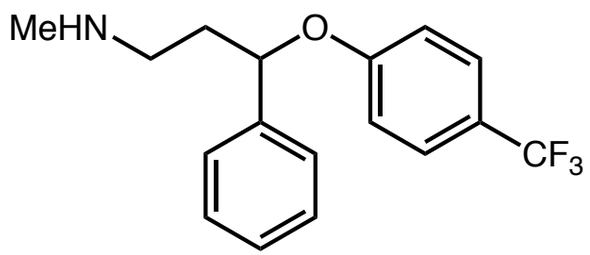
most best-selling antidepressants have identical biological targets



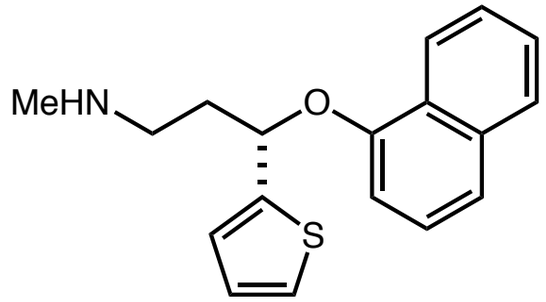
sertraline (Zoloft®)
selective serotonin reuptake inhibitor



escitalopram (Lexapro®)
selective serotonin reuptake inhibitor



fluoxetine (Prozac®)
selective serotonin reuptake inhibitor



duloxetine (Cymbalta®)
serotonin-norepinephrine reuptake inhibitor

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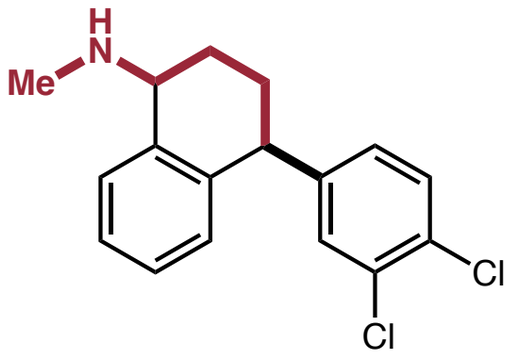

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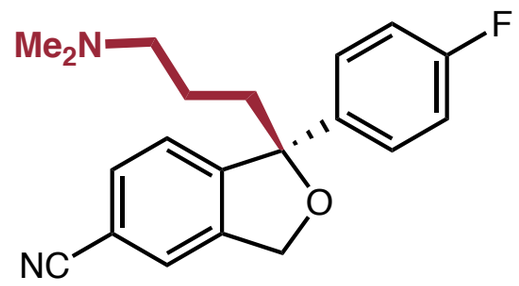

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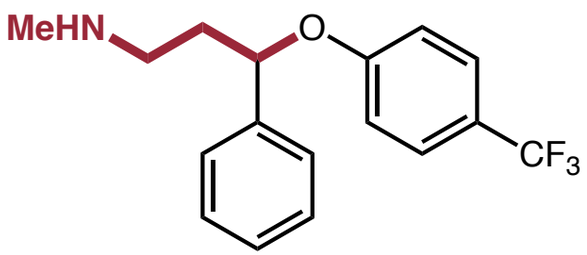

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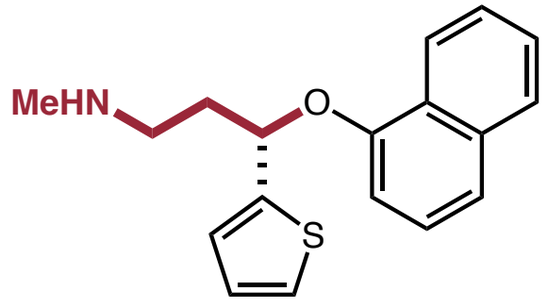

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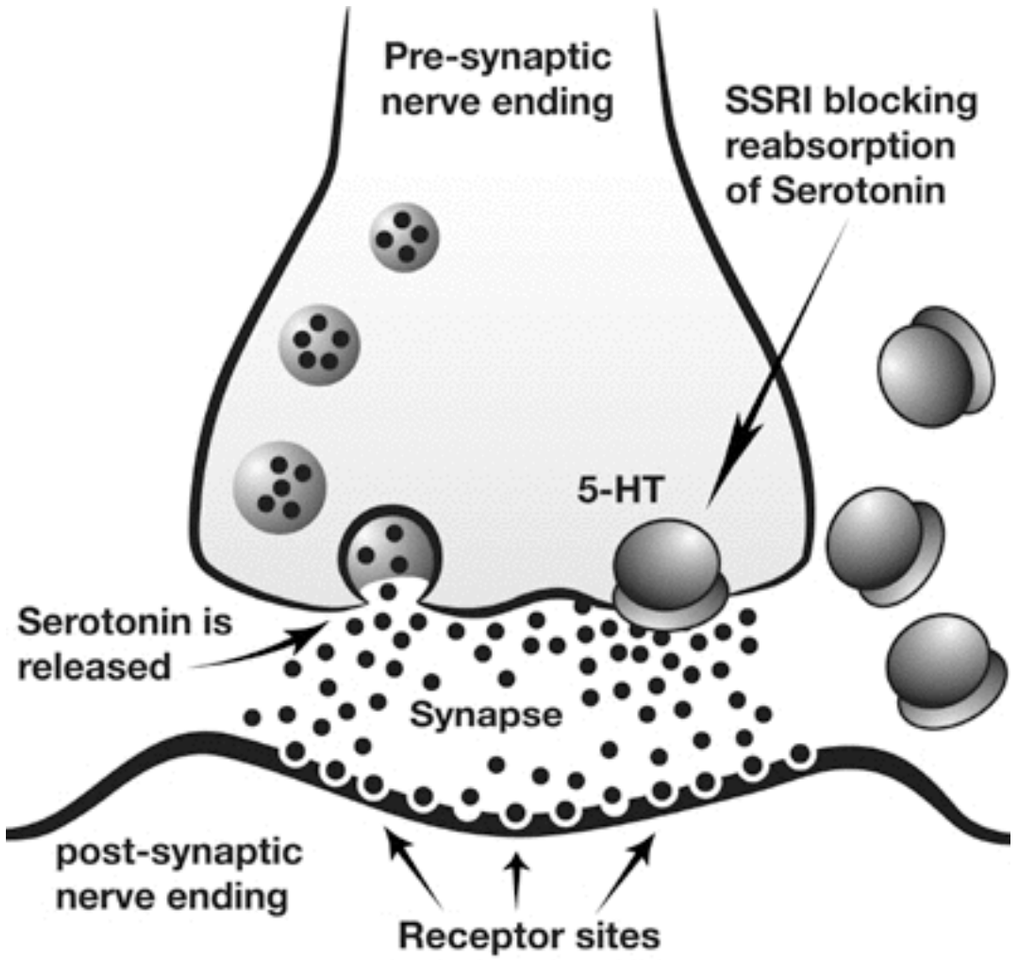
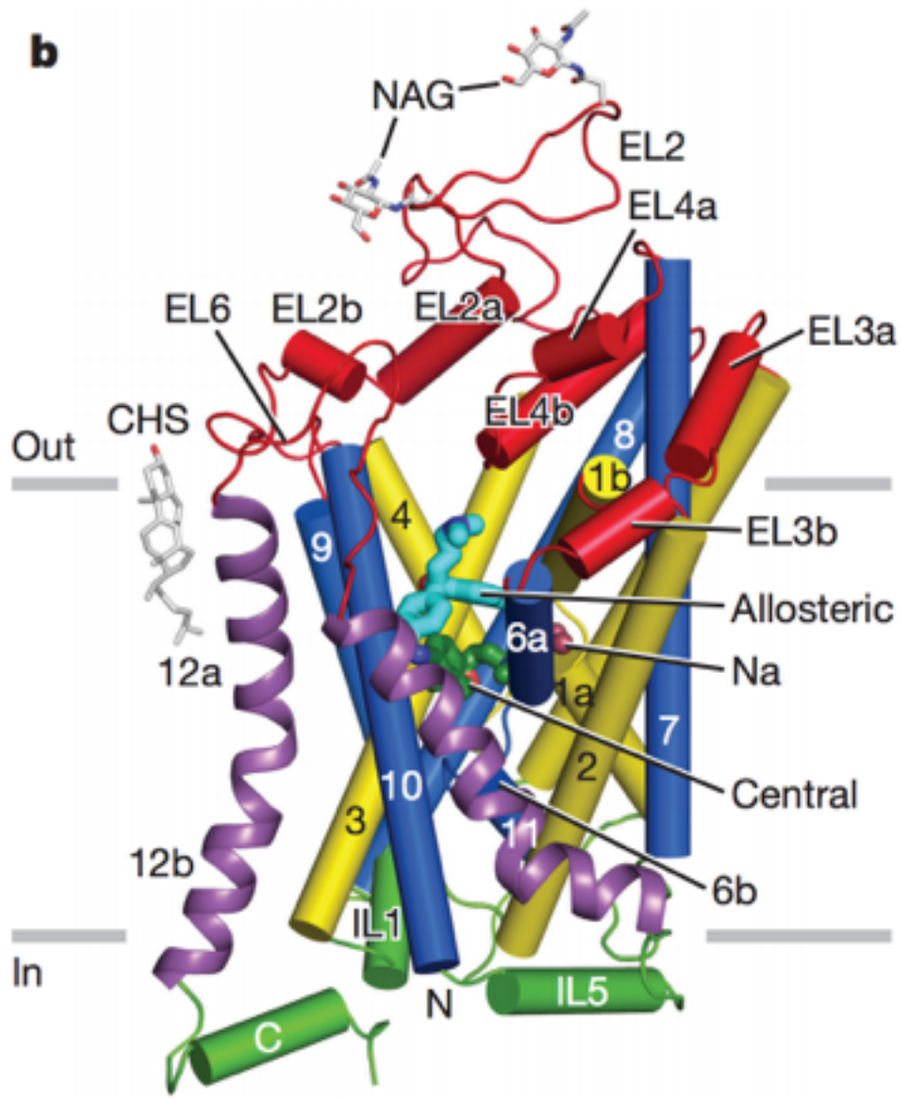
Existing Antidepressant Treatments

serotonin reuptake inhibitor target

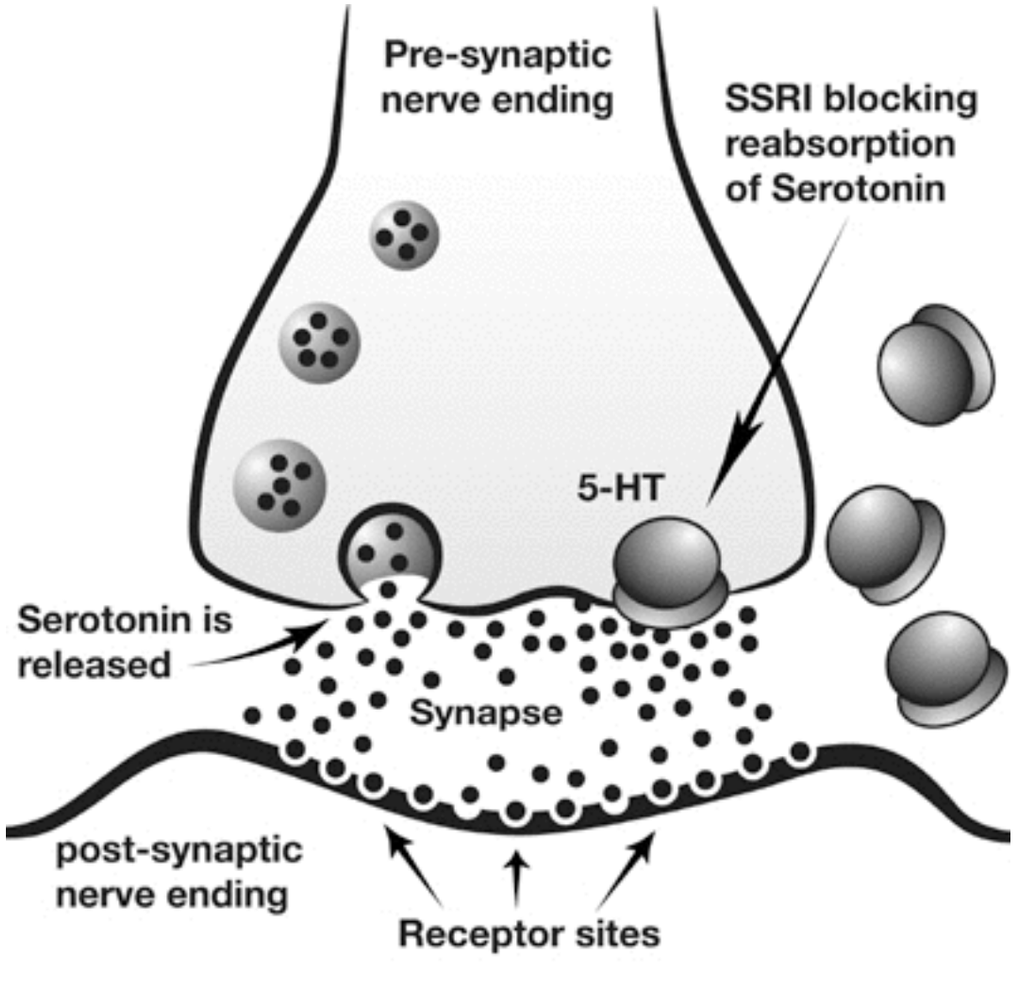


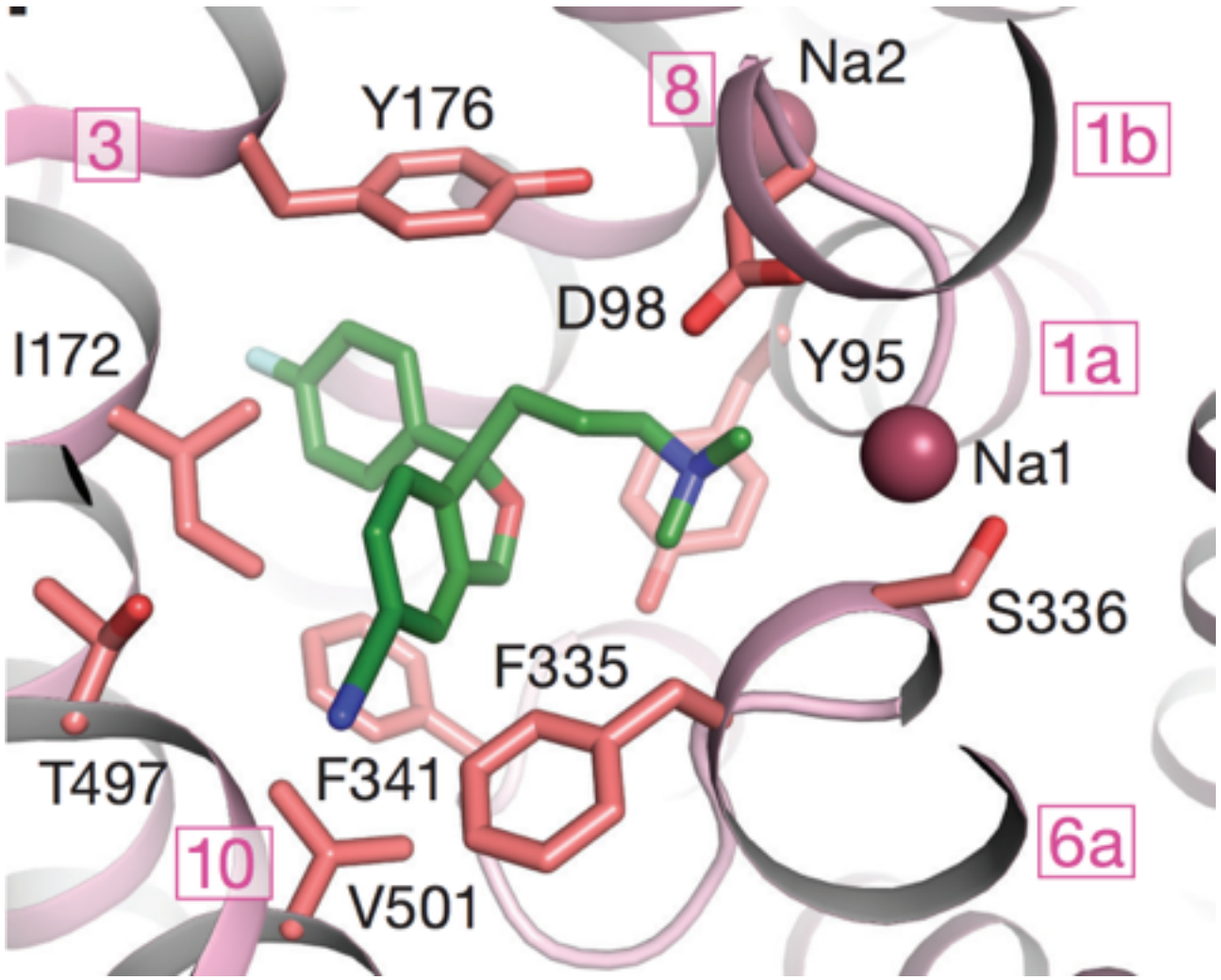


Coleman, J. A.; Green, E. M.; Gouaux, E. *Nature* **2016**, *532*, 334.

Existing Antidepressant Treatments

serotonin reuptake inhibitor target





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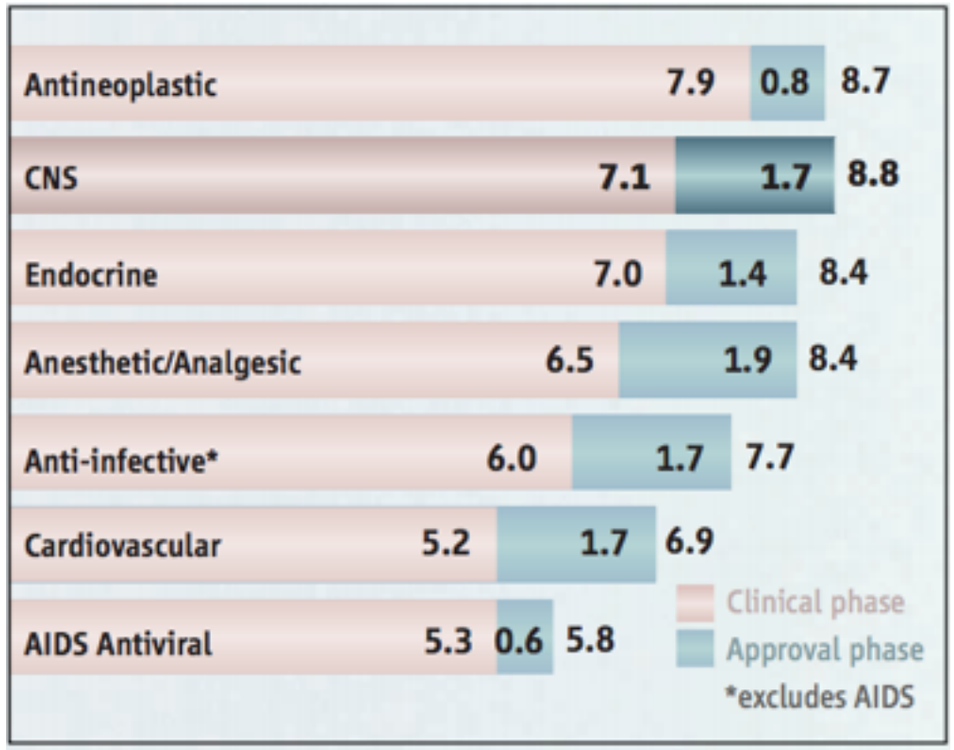
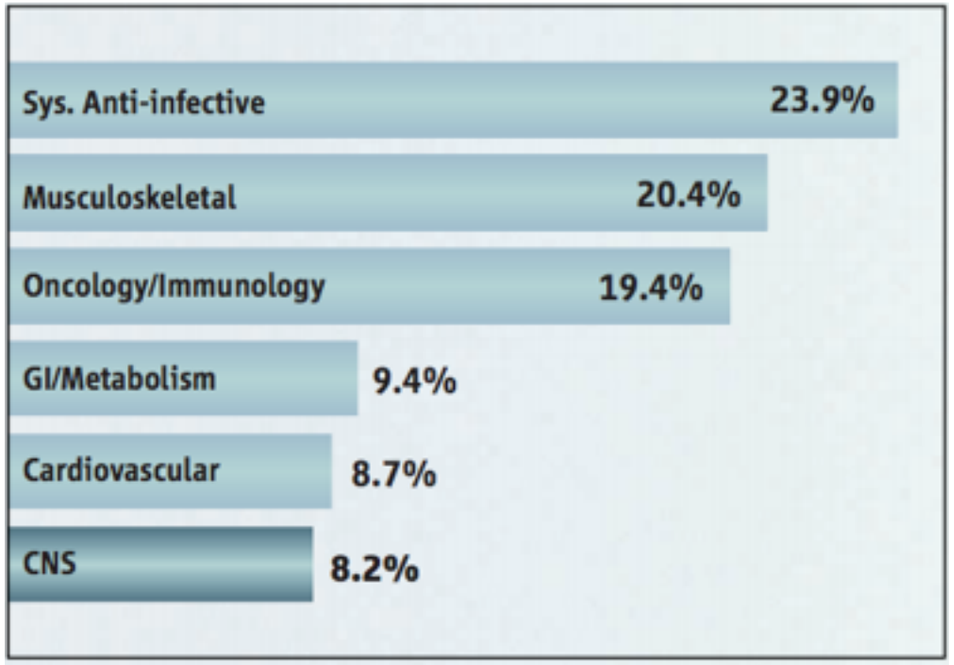
Innovation Gap in CNS Drug Development

investment in CNS drug design has decreased rapidly in recent years

- CNS drugs cost more and take longer to bring to market than most other therapies
- Only 8% of clinical compounds are approved, about half the average success rate



Clinical development and approval time (years)



Clinical approval success rate

Innovation Gap in CNS Drug Development

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Halted drug discovery in
pain, depression, and anxiety

Halted drug discovery in bipolar disorder,
depression, schizophrenia, and anxiety

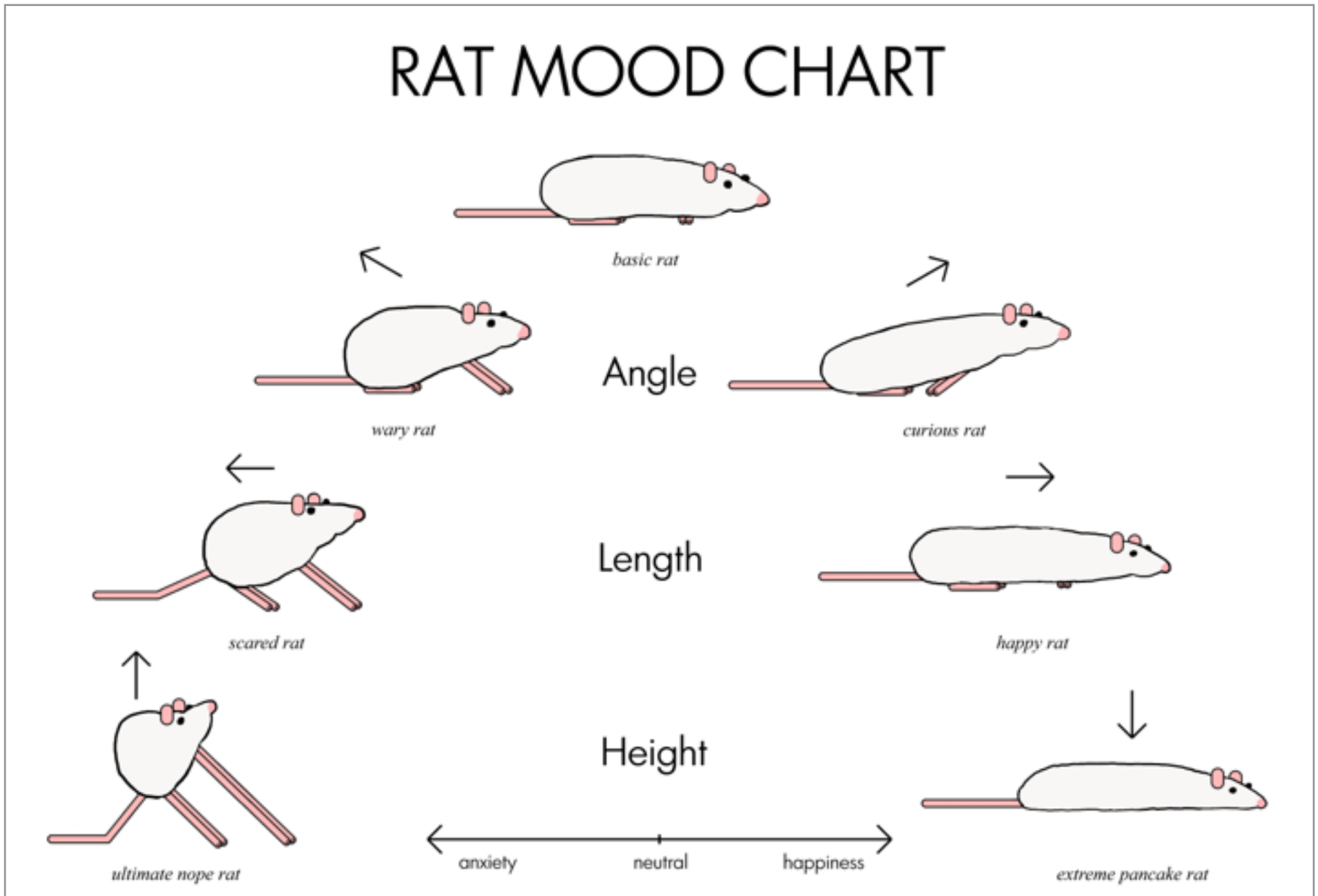
Designing Therapies for Neuropsychiatric Diseases is Challenging

Inadequate Pre-Clinical Models

Challenging Target Validation

Mechanisms Poorly Understood

Pre-Clinical Models Possess Limited Predictive Value



"There is growing agreement that there are no animal models of psychiatric disorders such as depression that capture the relevant pathophysiology"

Pankevich, D. E.; Altevogt, B. M.; Dunlop, J.; Gage, F. H.; Hyman, S. E. *Neuron* **2014**, *84*, 546–553.

Pre-Clinical Models Possess Limited Predictive Value

“Forced Swim Test”

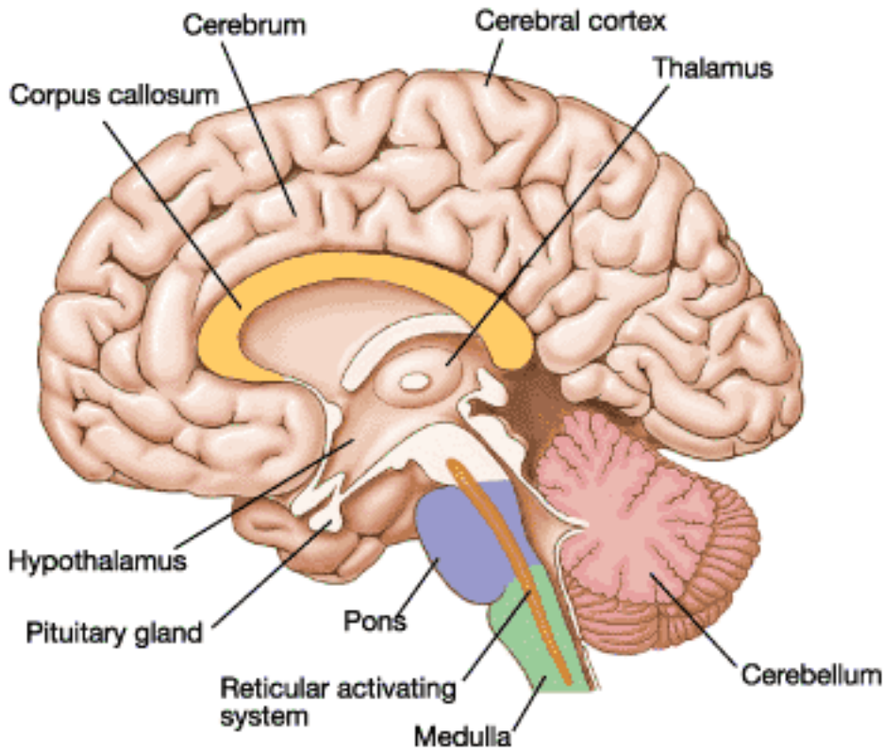
Mobile rat = “happy rat”

Immobile rat = “depressed rat”

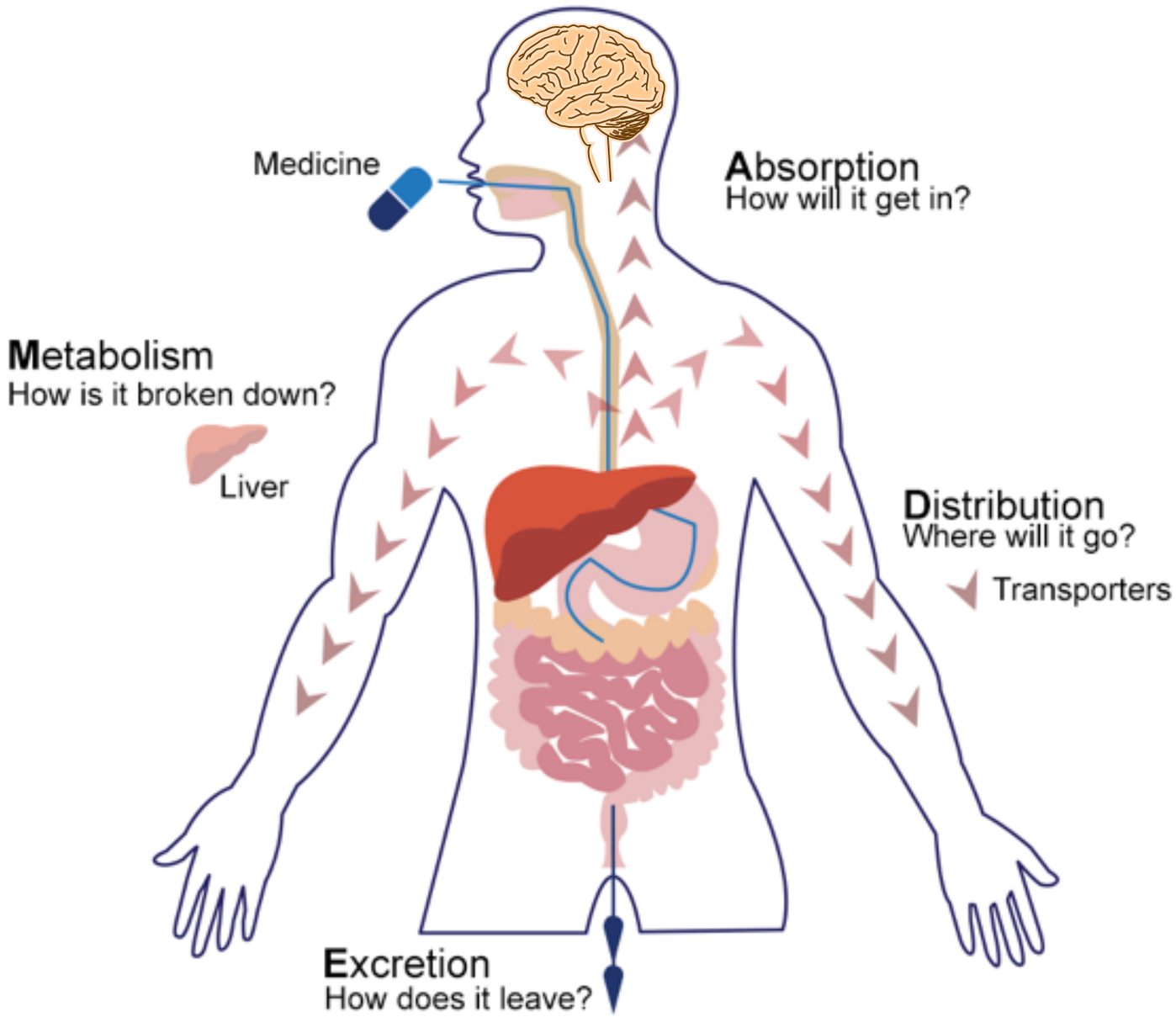
CNS Disease Mechanisms are Not Well Understood

Deep understanding of disease mechanism is difficult to achieve.

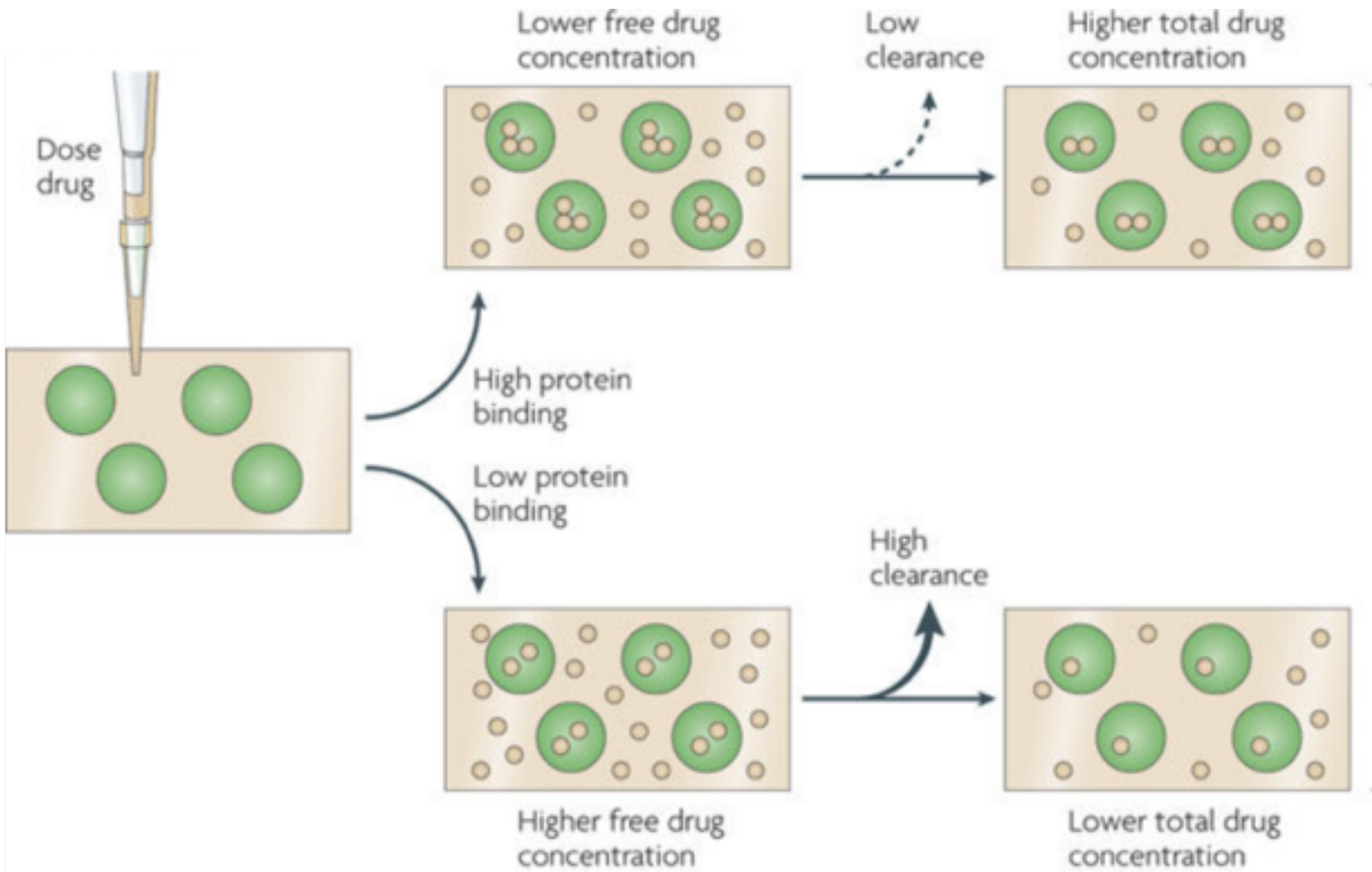
- Human brain biology is incredibly complex
- Significant differences from animal models
- Surgical procedures are impossible in most cases
- *Brain disorders are not cell autonomous*



How Do Molecules Enter and Exit the Brain?



The Free Drug Hypothesis

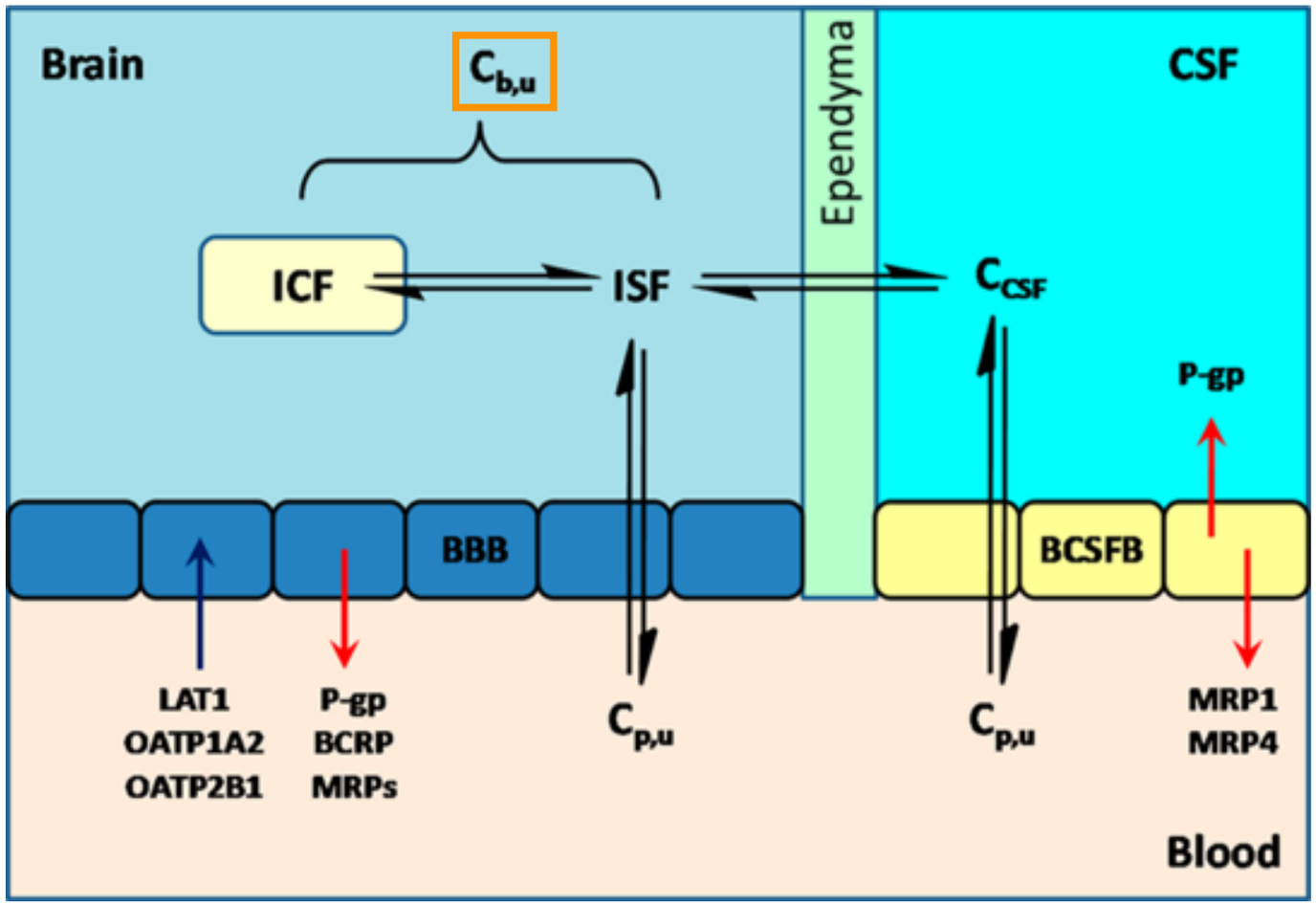


I. The free drug concentration at the site of action is responsible for pharmacological activity *in vivo*

II. At steady state in the absence of active transport, free drug concentration is the same on both sides of any biomembrane

How Do Molecules Enter and Exit the Brain?

Blood-Brain Barrier: Endothelial cells with very tight intracellular junctions

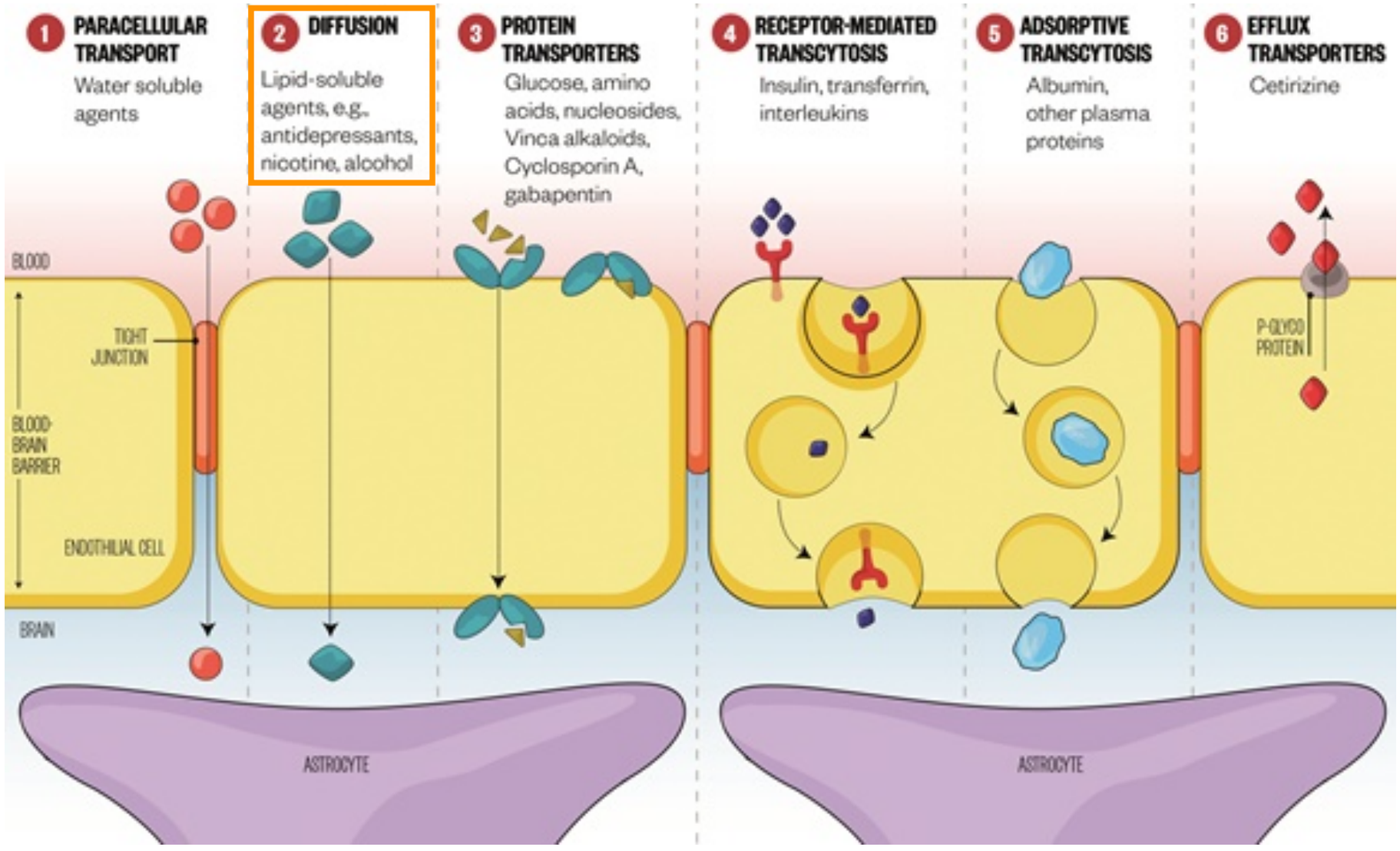


- $C_{b,u}$: unbound brain concentration
- ISF : interstitial fluid
- ICF : intracellular fluid

- A number of transport proteins regulate drug or other molecule concentration in the brain via active transport mechanisms

Di, L.; Rong, H.; Feng, B. *J. Med. Chem.* **2013**, *56*, 2–12.

Crossing the Blood-Brain Barrier

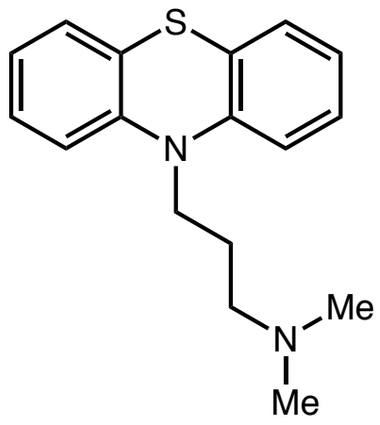


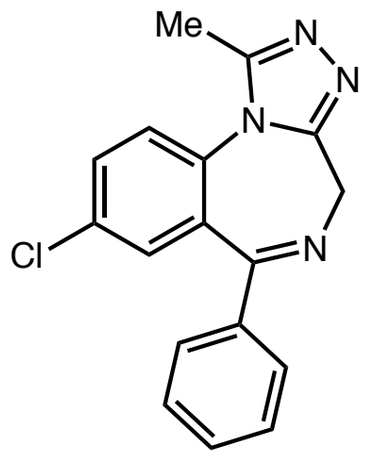
Most common route: Passive permeation

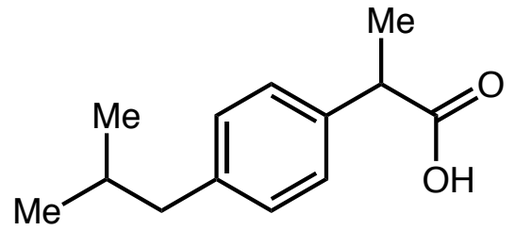
Abbott, N. J.; Rönnbäck, L.; Hansson, E. *Nature Reviews Neuroscience*

Crossing the Blood-Brain Barrier

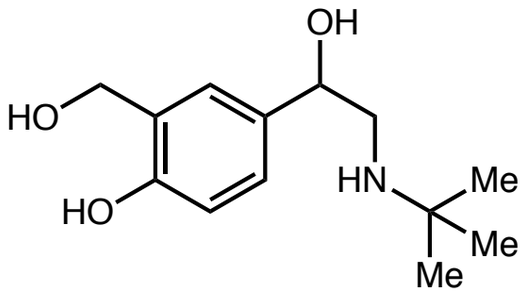
Blood-brain barrier permeable

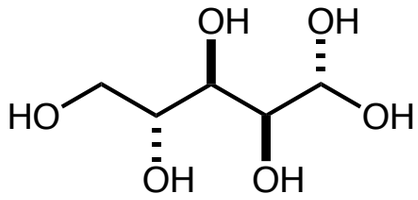


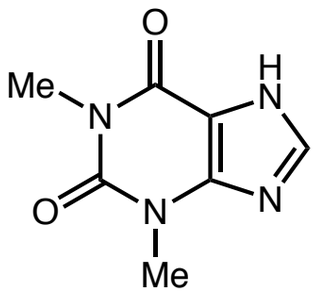




Do not diffuse across BBB

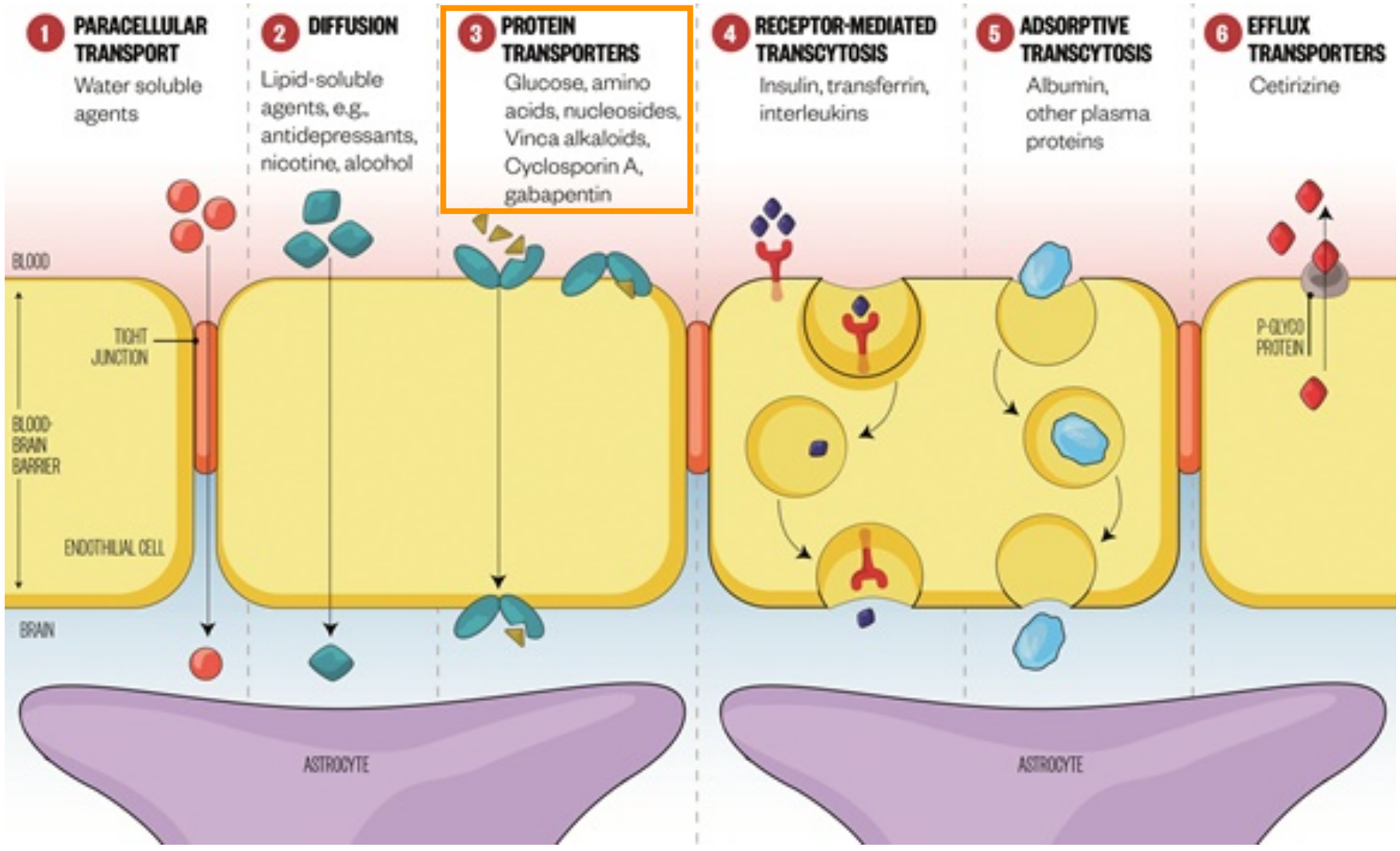






Carpenter, T. S.; Kirshner, D. A.; Lau, E. Y.; Wong, S. E.; Nilmeter, J. P.; Lightstone, F. C. *Biophysical Journal* **2014**, *107*, 630–641.

Crossing the Blood-Brain Barrier



Active Transport

Abbott, N. J.; Rönnbäck, L.; Hansson, E. *Nature Reviews Neuroscience*

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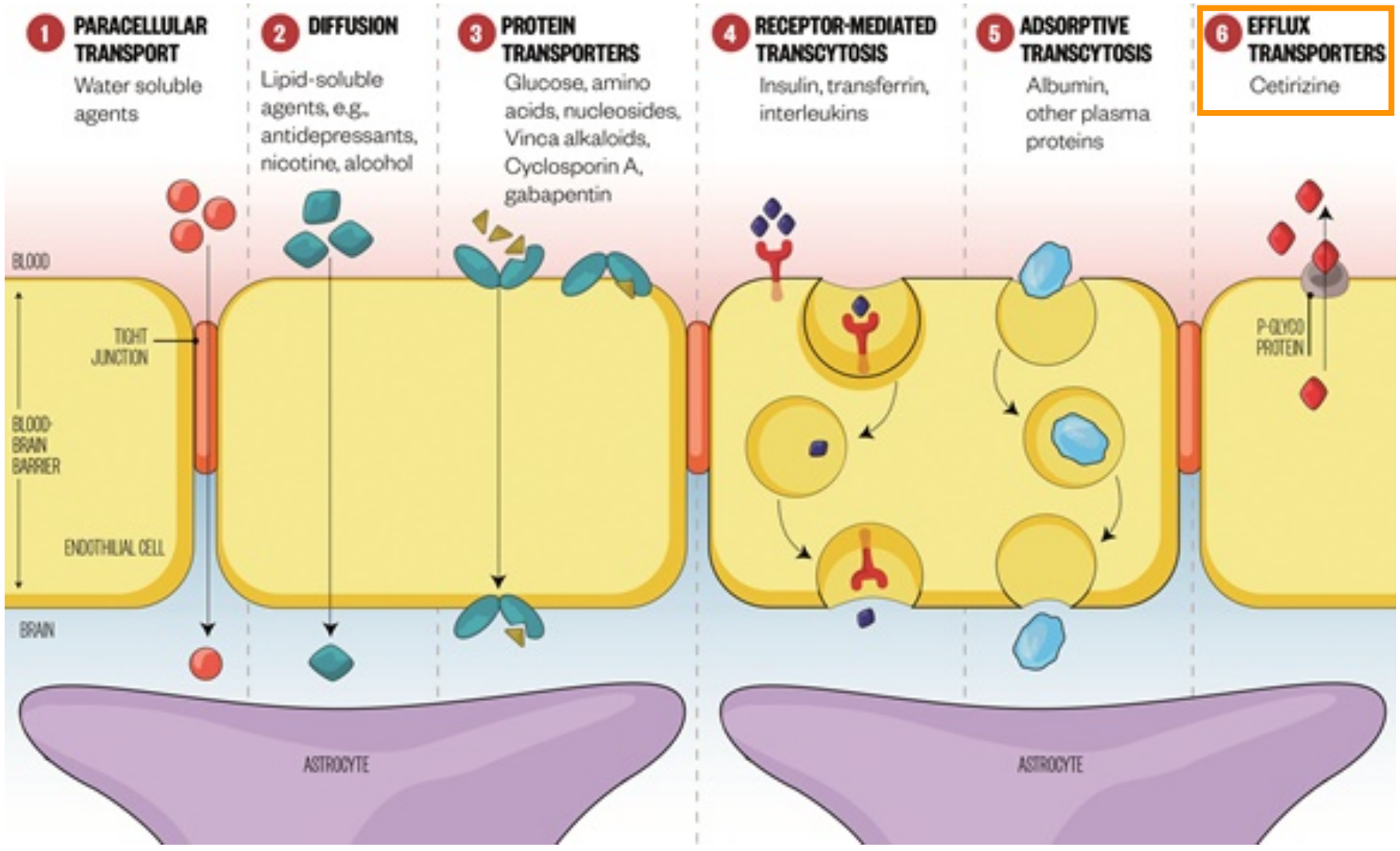
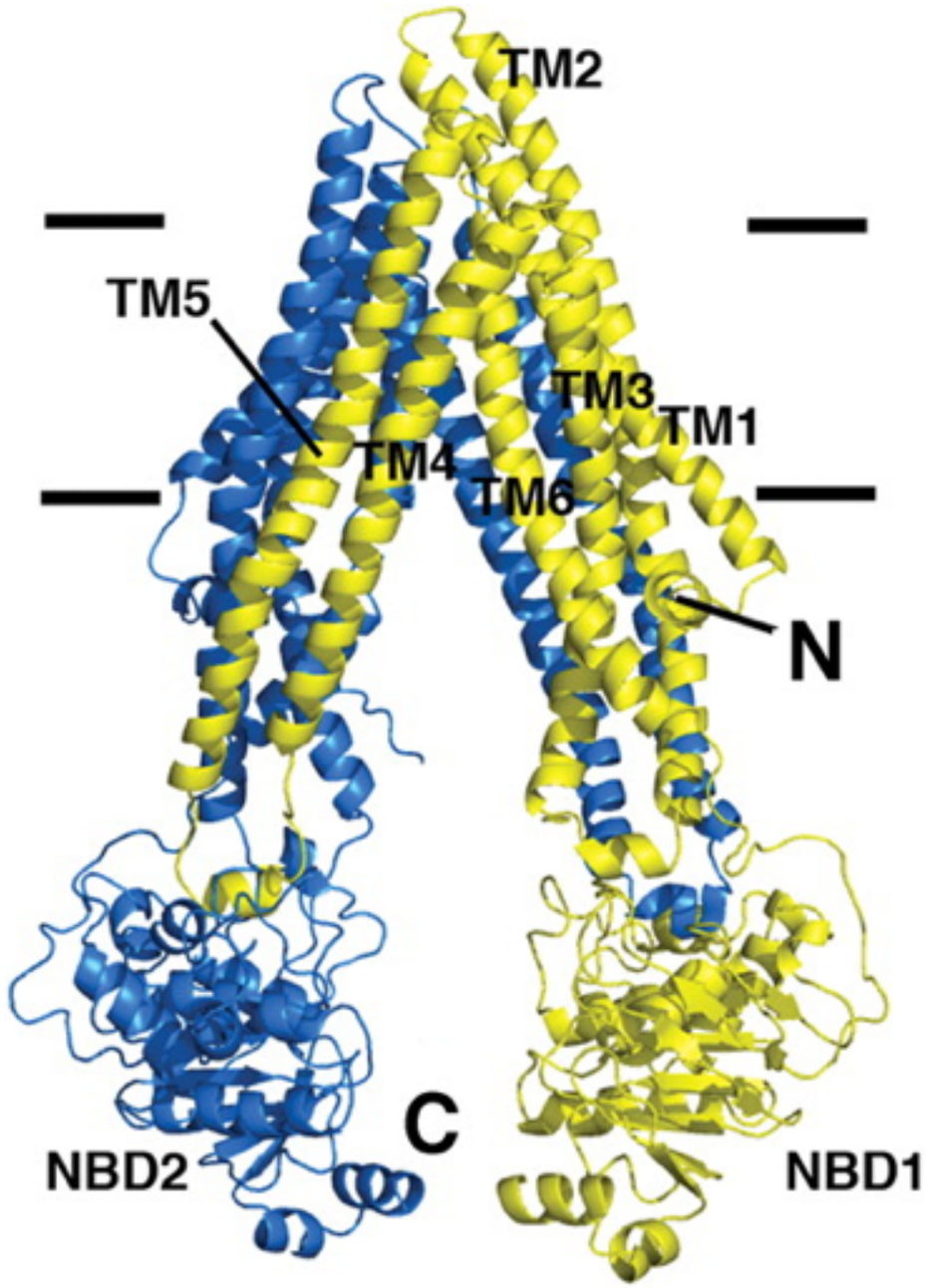


Efflux mechanisms need to be avoided!

Abbott, N. J.; Rönnbäck, L.; Hansson, E. *Nature Reviews Neuroscience*

P-Glycoprotein Mediated Efflux



P-Glycoprotein

Highly expressed at the blood-brain barrier

Serves as a molecular “pump”

Very broad substrate specificity

Aller, S. G.; Yu, J.; Ward, A.; Weng, Y.; Chittaboina, S.; Zhuo, R.; Harrell, P. M.; Trinh, Y. T.; Zhang, Q.; Urbatsch, I. L.; Chang, G. *Science* **2009**, *323*, 1718–1722.

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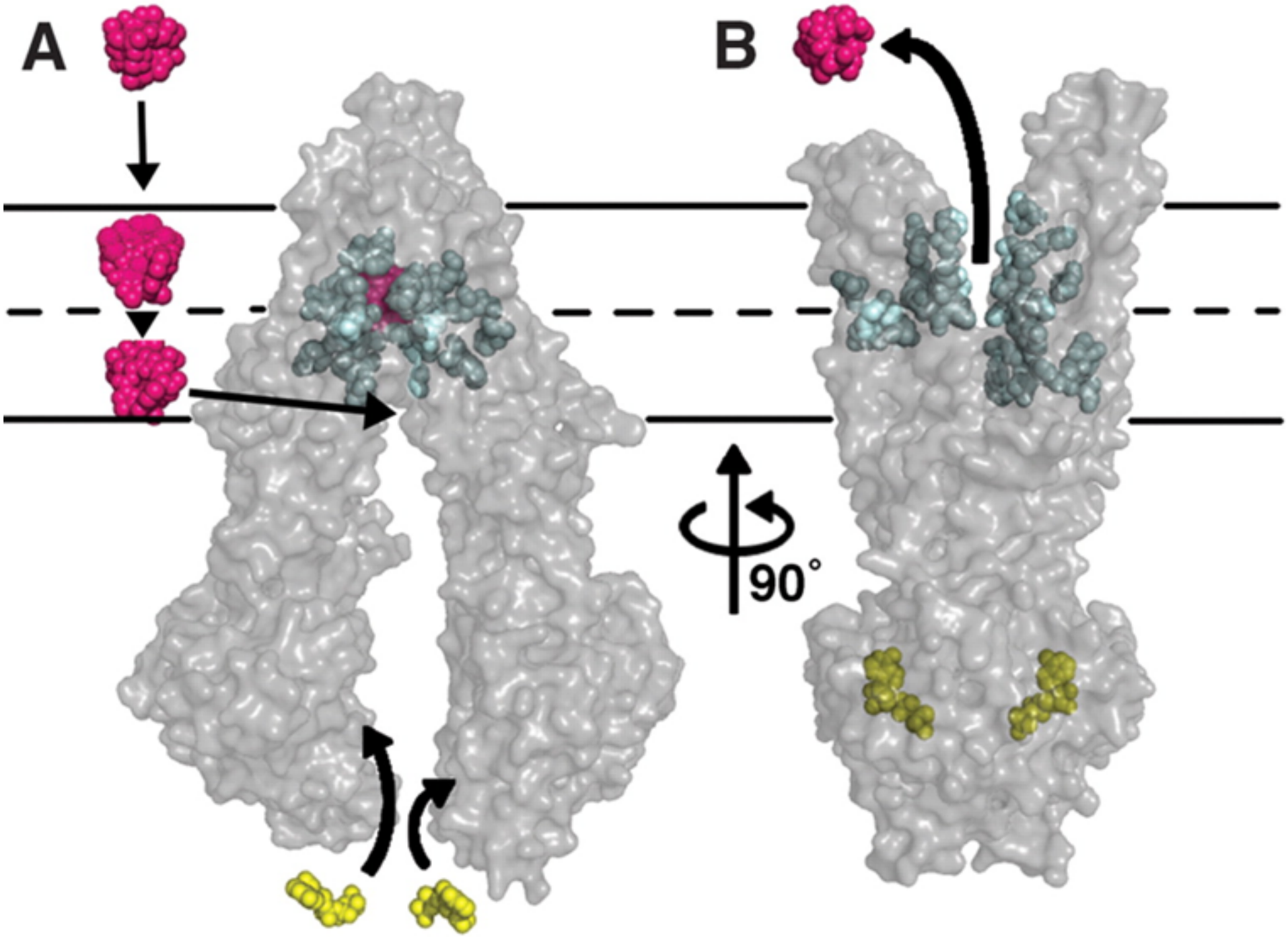

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Critical Parameters and How They Are Measured

1. $C_{b,u}$: unbound brain concentration

2. $K_{p,uu}$: unbound brain to plasma ratio

3. P_{app} : rate of brain permeability

4. ER : efflux ratio

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Measurement of Unbound Drug Concentration in the Brain

Total Brain Concentration
C_b

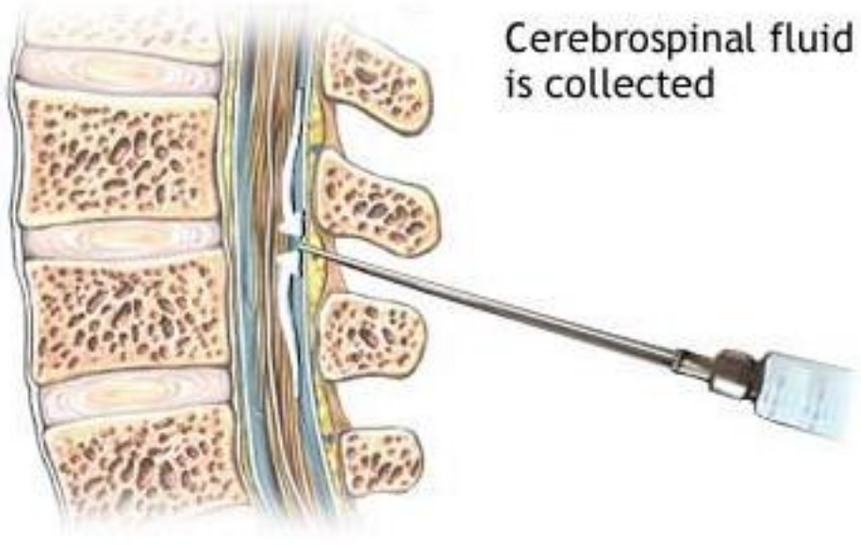
Brain Fraction Unbound
$f_{u,b}$

$C_b \times f_{u,b} = C_{u,b}$

Unbound drug concentration is the most important parameter for CNS pharmacokinetics.

Di, L.; Rong, H.; Feng, B. *J. Med. Chem.* **2013**, *56*, 2–12.

Measurement of Unbound Drug Concentration in the Brain



In humans, CSF concentration approximates brain concentration when transporters are not involved.

$C_b \times f_{u,b} = C_{u,b}$

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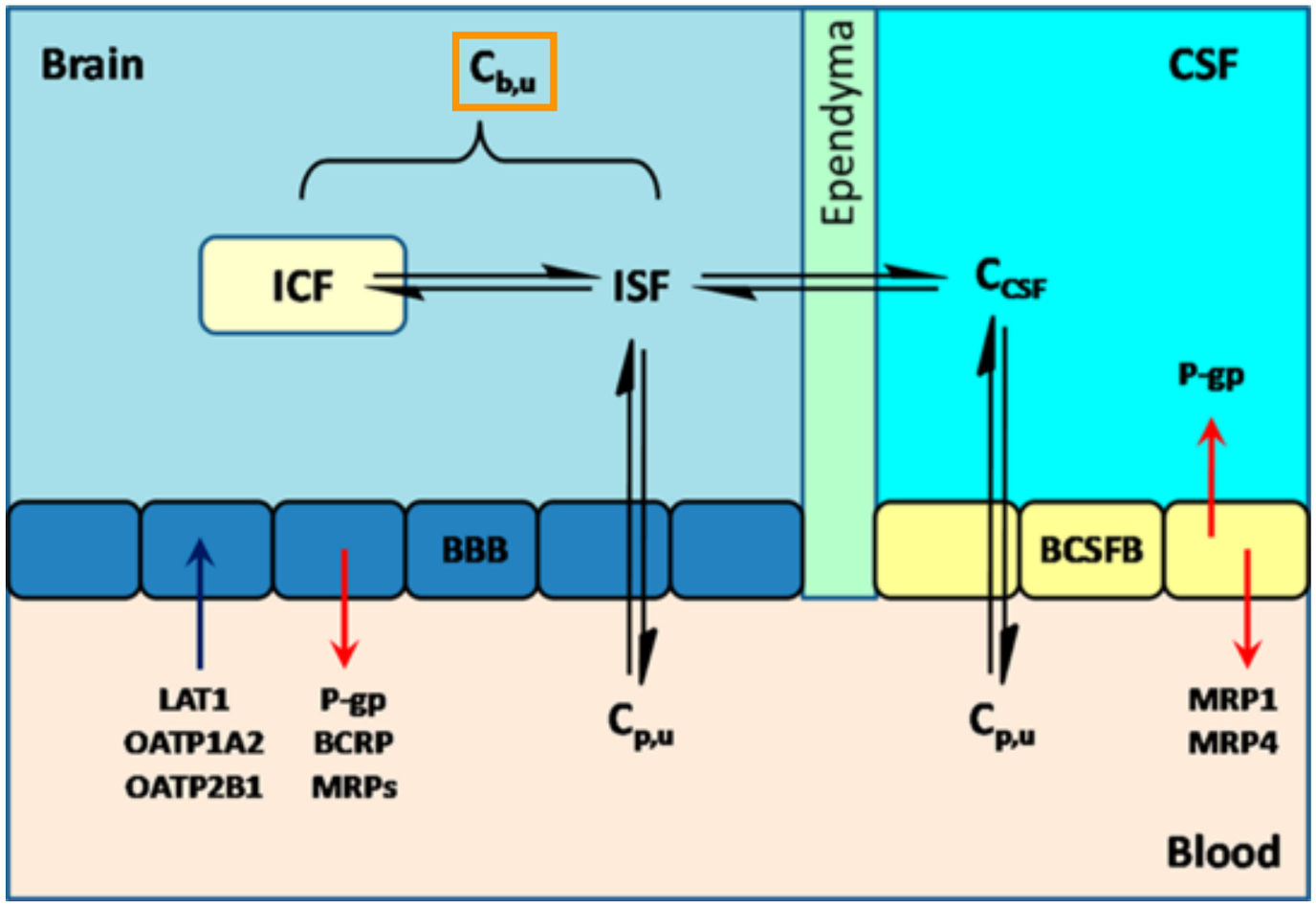
How Do Molecules Enter and Exit the Brain?

Blood-Brain Barrier: Endothelial cells with very tight intracellular junctions



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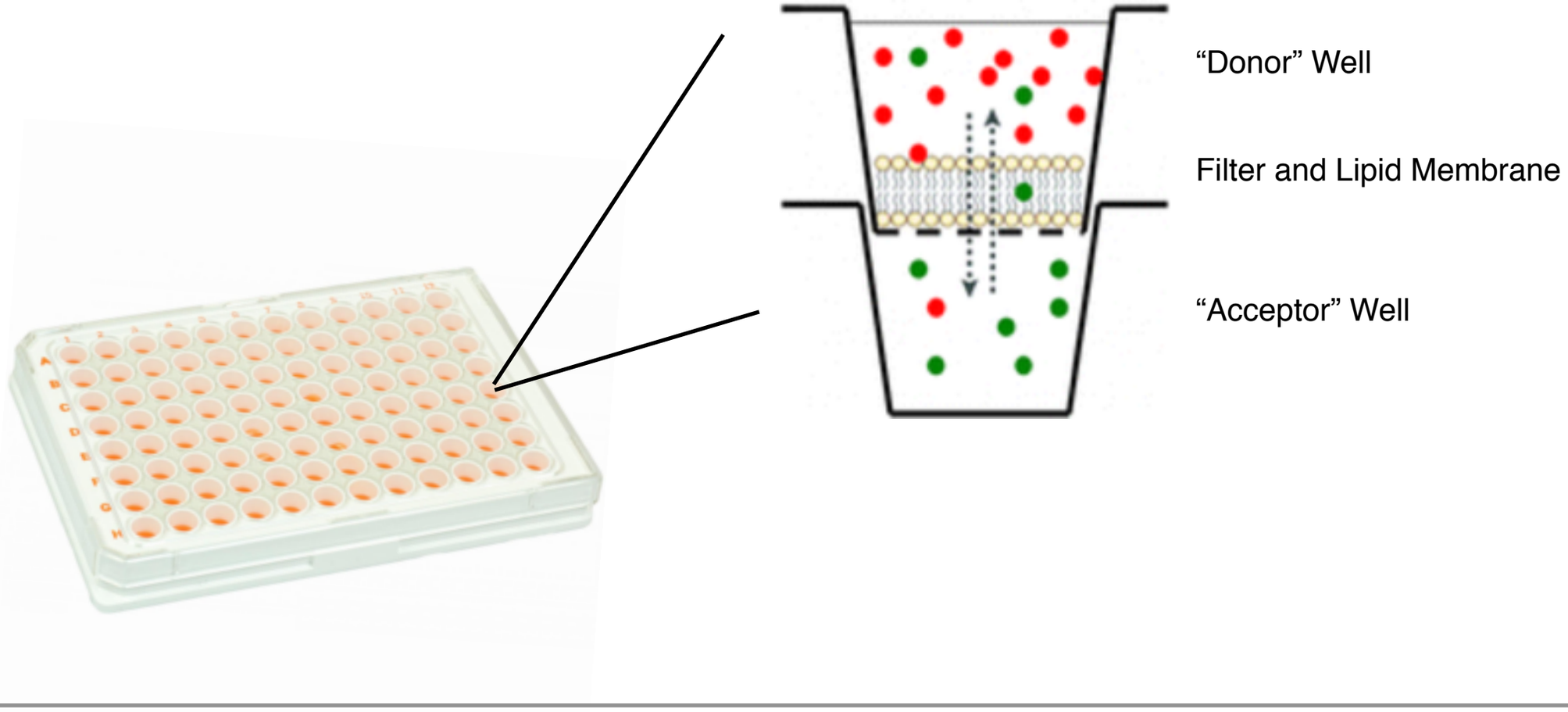
Blood-Brain Barrier Passive Permeability



Parallel Artificial Membrane Permeability Assay

The amount of drug in each compartment is measured following an incubation period.

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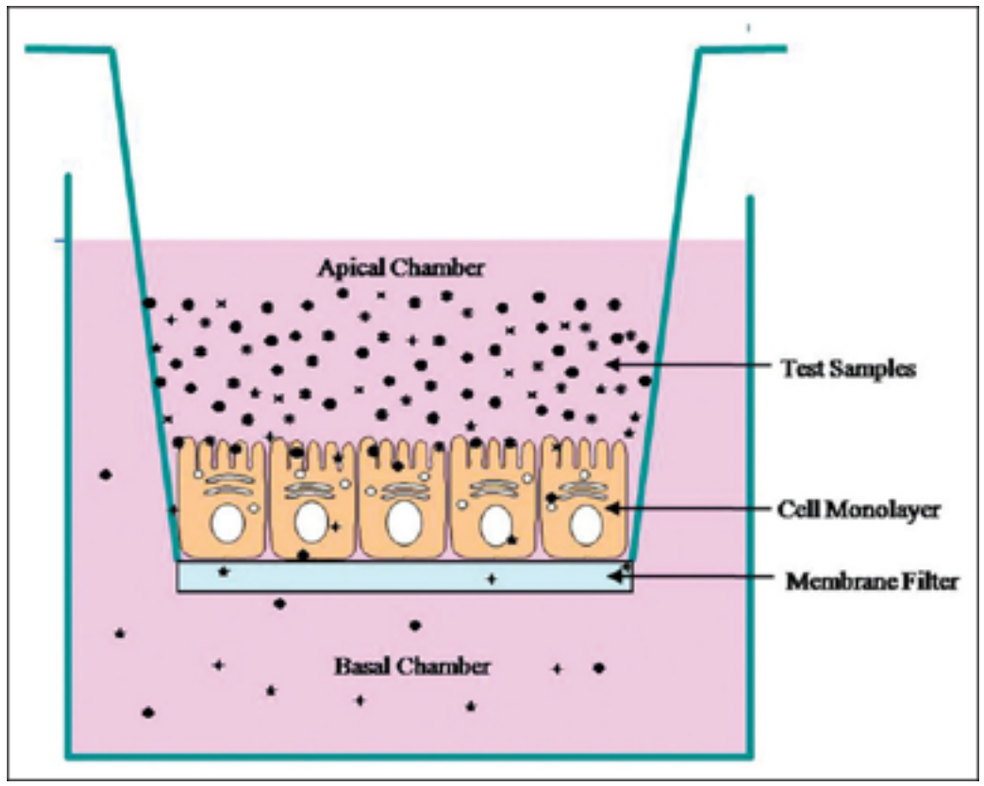
Measuring Efflux Ratio with MDR1-MDCK

Culture Cells

Madin Darby canine kidney

transfection with MDR1



Measure Concentration

Efflux Ratio (ER) = (compound in apical chamber)/(compound in basal chamber)

highly effluxed compounds are prevented from diffusing to the basal chamber

Devkar, S. T.; Kandhare, A. D.; Sloley, B. D.; Jagtap, S. D.; Lin, J.; Tam, Y. K.; Katyare, S. S.; Bodhankar, S. L.; Hegde, M. V. *J. Adv. Pharm. Technol. Res.* **2015**, *6*, 159–164.
Feng, B.; Mills, J. B.; Davidson, R. E.; Mireles, R. J.; Janiszewski, J. S.; Troutman, M. D.; de Morais, S. M. *Drug Metab. Dispos.* **2008**, *36*, 268–275.

Measuring Receptor Occupancy

How can you tell if a drug is reaching its target?

Measuring Receptor Occupancy

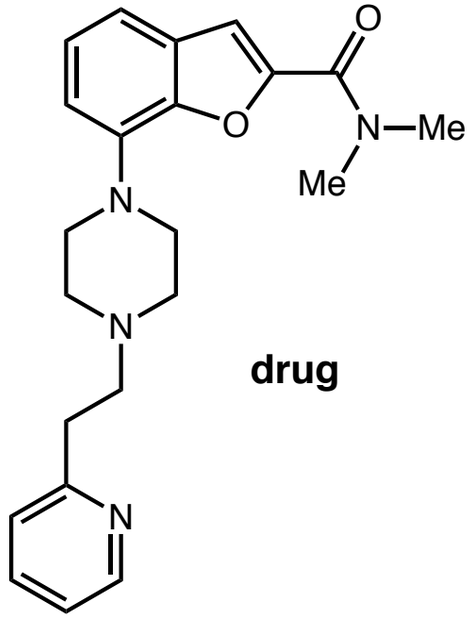
vehicle administration

tracer administration

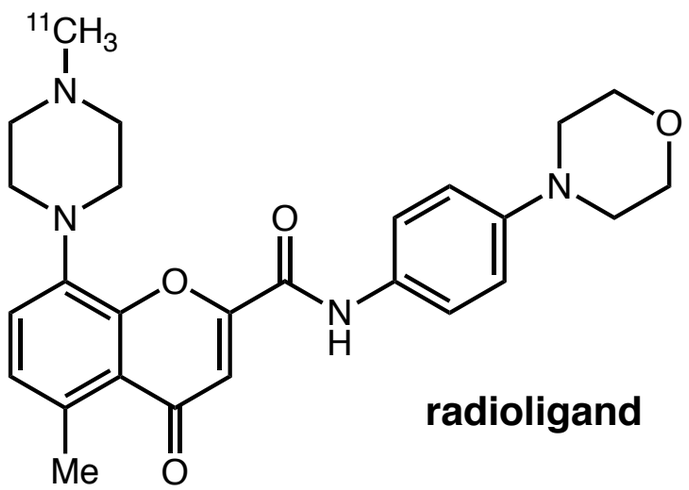
drug administration

ınistration

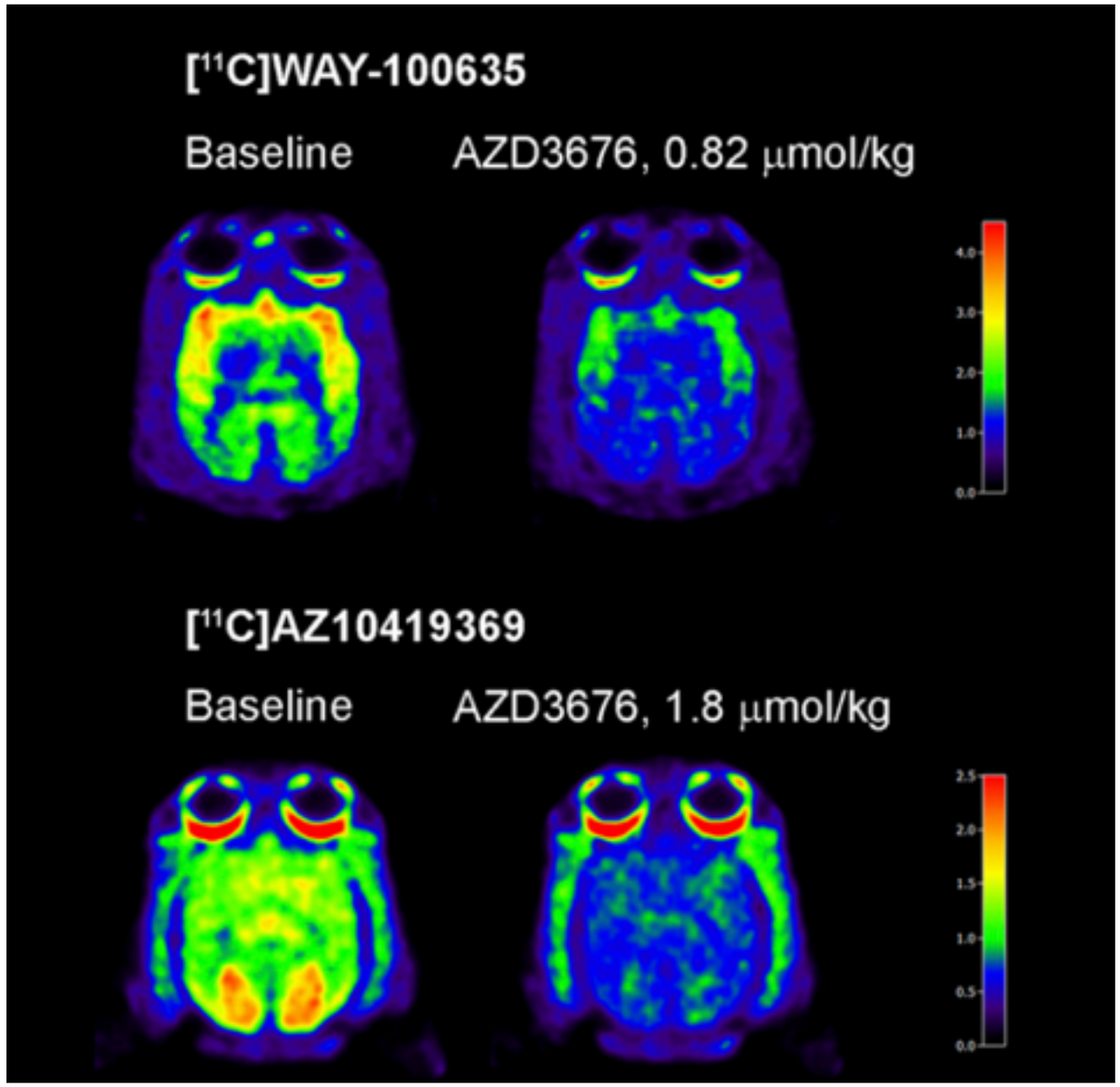
Measuring Receptor Occupancy



drug



radioligand

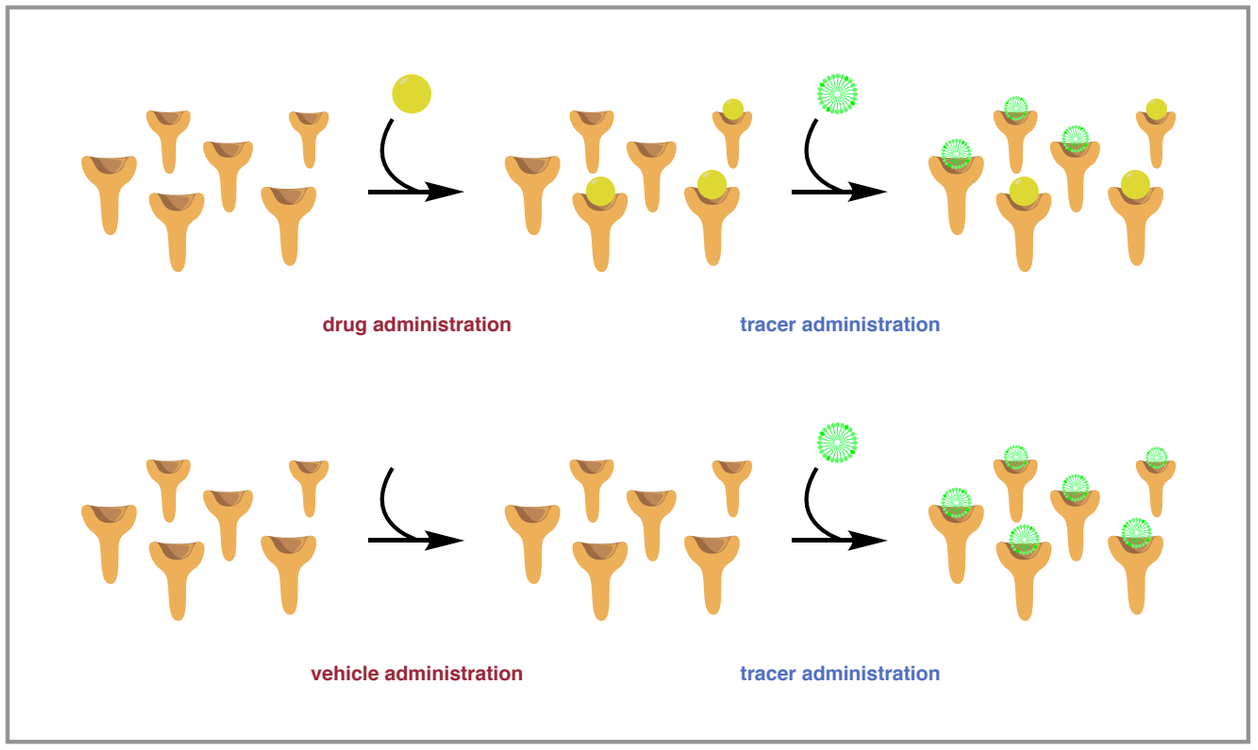


5-HT$_{1A}$ receptor occupancy

Varnas, K. *et. al. J. Pharmacol. Exp. Ther.* **2016**, *358*, 464–471.

Measuring Receptor Occupancy

- Receptor occupancy studies provide the most direct information on drug exposure
- Cost and time concerns preclude their use for all but the most advanced compounds

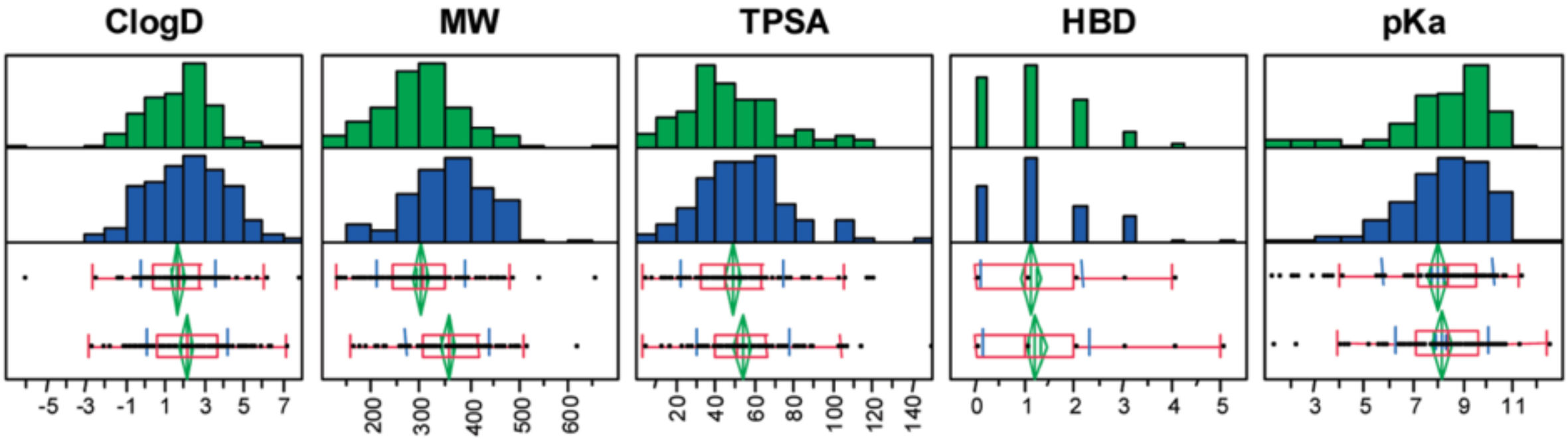


Optimization of Compounds for CNS Penetration

Lipophilicity	■ Often leads to increased potency ■ Increased off-target activity
Polar Surface Area	■ Surrogate measure of hydrogen-bonding and polarity ■ Strong correlation with membrane permeability
Hydrogen Bonding	■ Leads to lower passive permeability ■ Increases risk of P-gp efflux
pK_a	■ Most CNS drugs contain at least one basic center ■ High pK_a can lead to increased efflux
Molecular Flexibility	■ High flexibility can decrease passive permeation ■ Can be improved by IMHB and cyclization

Wager, T. T.; Chandrasekaran, R. Y.; Hou, X.; Troutman, M. D.; Verhoest, P. R.; Villalobos, A.; Will, Y. *ACS Chem. Neurosci.* **2010**, *1*, 420–434.

Optimization of Compounds for CNS Penetration



analysis of 119 marketed CNS drugs and 108 Pfizer CNS candidates

Wager, T. T.; Chandrasekaran, R. Y.; Hou, X.; Troutman, M. D.; Verhoest, P. R.; Villalobos, A.; Will, Y. *ACS Chem. Neurosci.* **2010**, *1*, 420–434.

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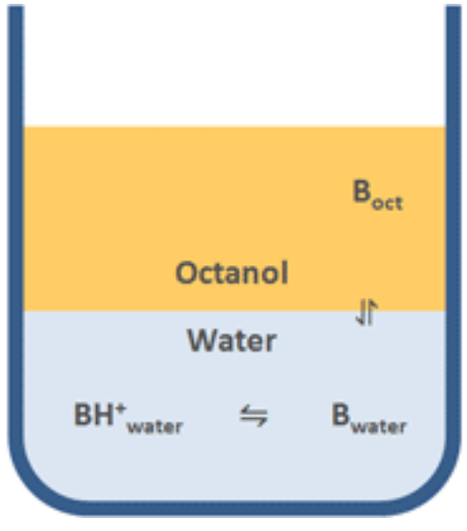
Optimization of Compounds for CNS Penetration

LogP = a determination of lipophilicity based on partitioning between octanol and water

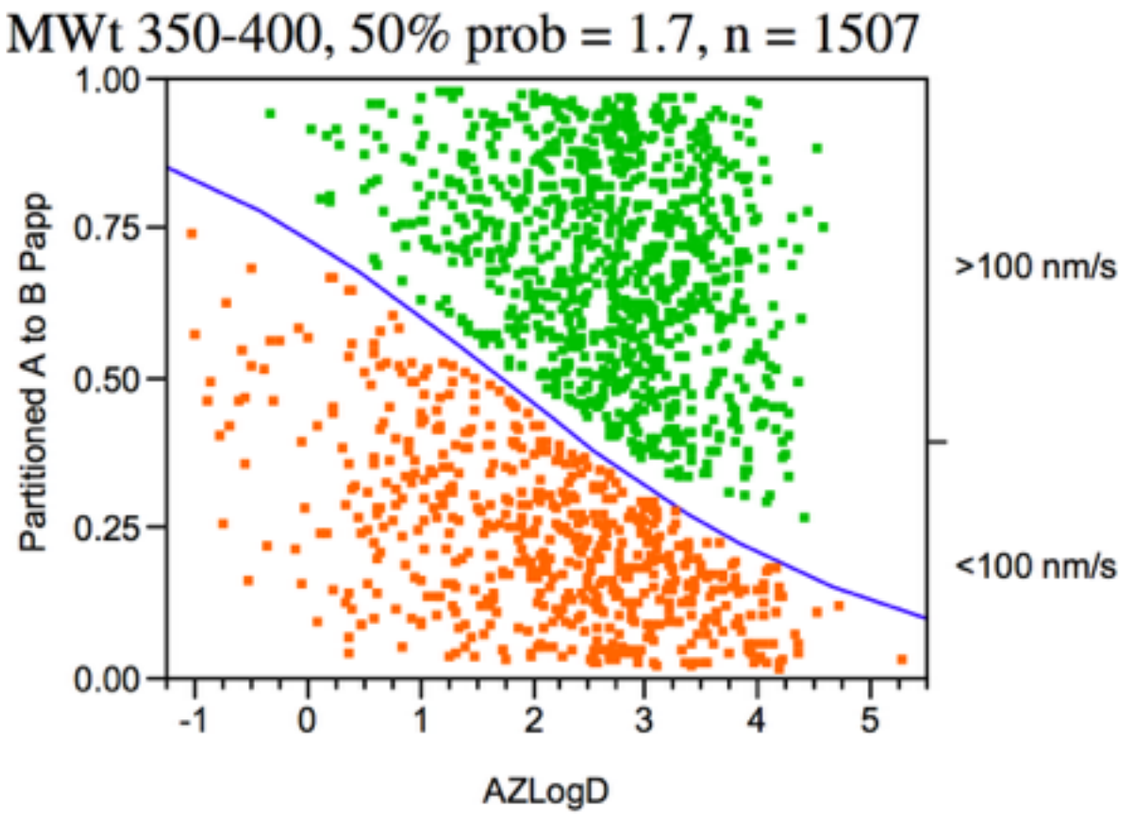
LogD = a pH dependent counterpart to logP, measured at a specific pH using a buffer

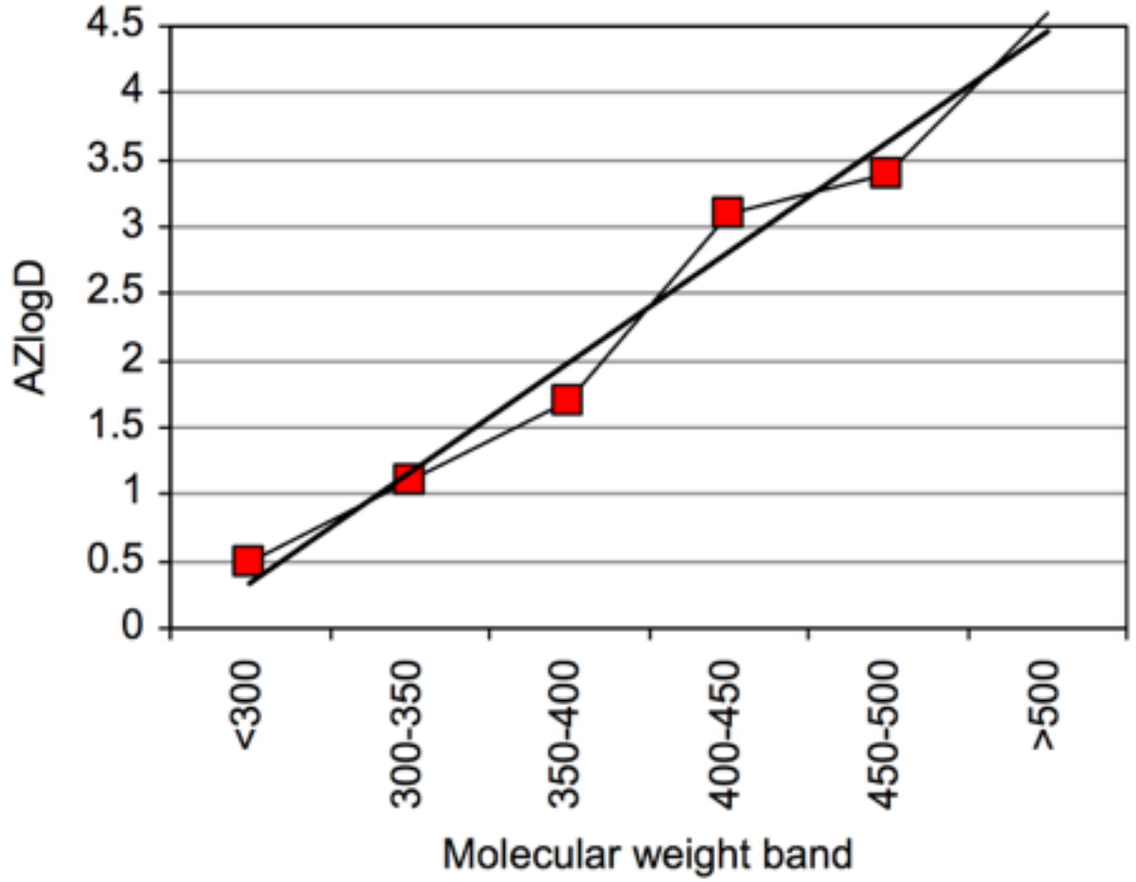


$$log\ P_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right)$$

Wager, T. T.; Chandrasekaran, R. Y.; Hou, X.; Troutman, M. D.; Verhoest, P. R.; Villalobos, A.; Will, Y. *ACS Chem. Neurosci.* **2010**, *1*, 420–434.

Increased Lipophilicity Leads to Higher Permeability

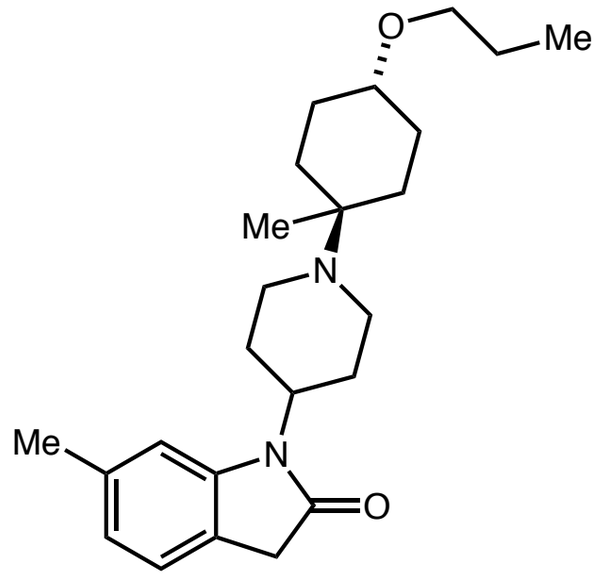




Passive permeability (P_{app}) as a function of pH - dependent partition coefficient

Waring, M. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2844–2851.

Reducing Lipophilicity to Improve Unbound Brain Concentration



selective muscarinic M_1 agonist from a GSK high throughput screen

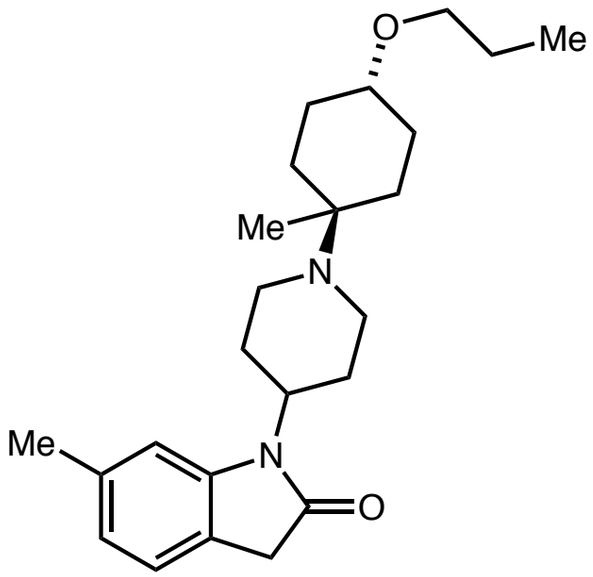
receptor is highly expressed in the hippocampus and cerebral cortex

potential targets for treatment of cognitive deficits including in Alzheimer's and schizophrenia

previous compounds showed some clinical efficacy, discontinued due to side effects

Johnson, D. J. *et. al. Bioorg. Med. Chem. Lett.* **2010**, *20*, 5434–5438.

Reducing Lipophilicity to Improve Unbound Brain Concentration



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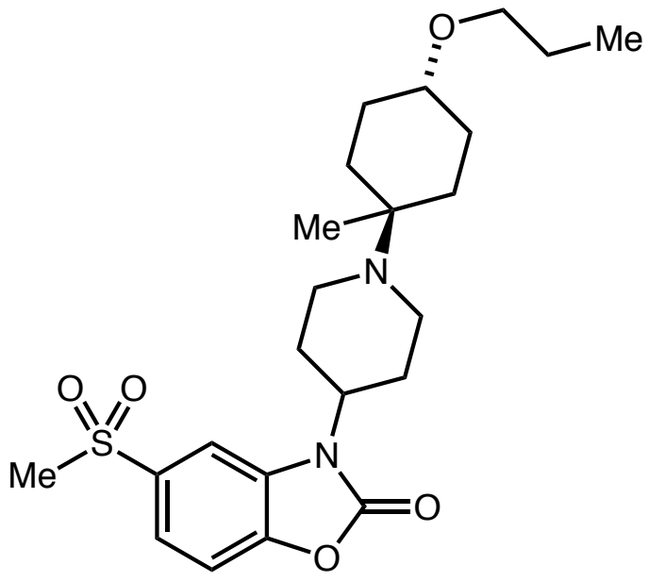

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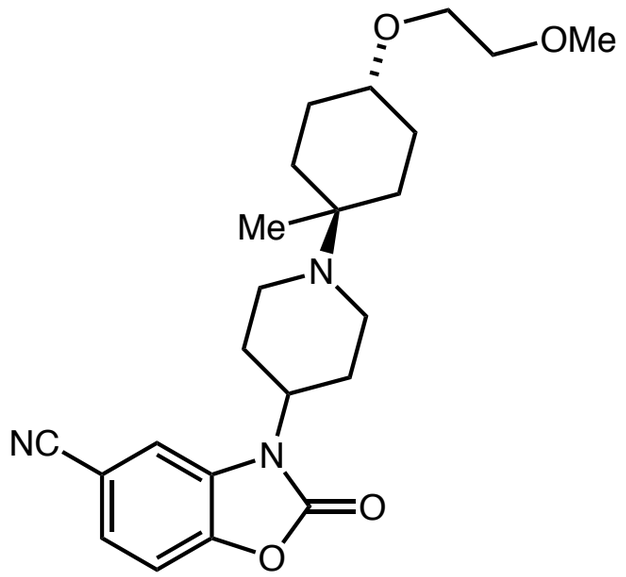

3

#	cLogP	K_p	$f_{u,b}$	$f_{u,p}$	$C_{u,b}$ (nM)	$C_{u,p}$ (nM)	$K_{p,uu}$
1	3.5	5.7	6%	20%	2.5	2.6	0.96
2	1.5	0.8	36%	40%	168	378	0.44
3	1.5	1.7	39%	38%	261	265	0.98

Johnson, D. J. *et. al. Bioorg. Med. Chem. Lett.* **2010**, *20*, 5434–5438.

Optimization of Compounds for CNS Penetration

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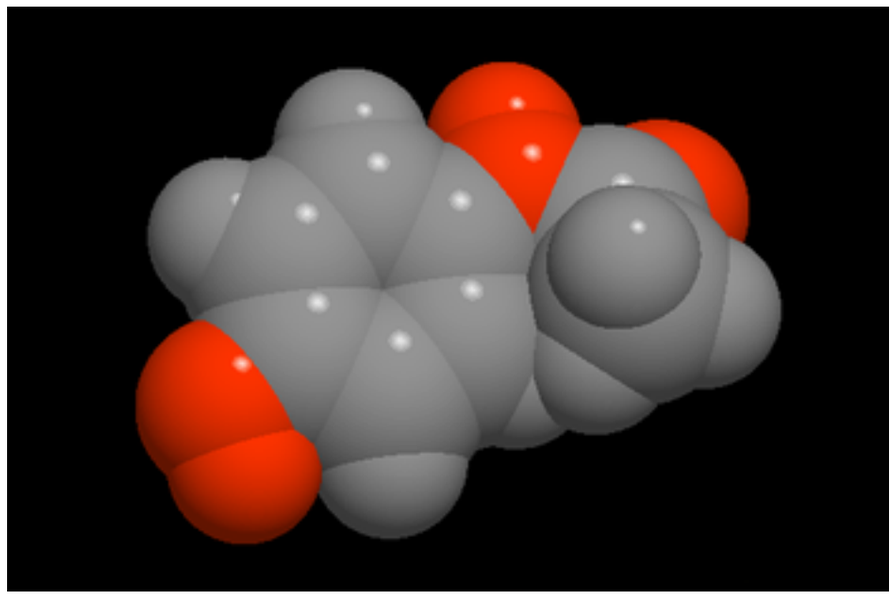
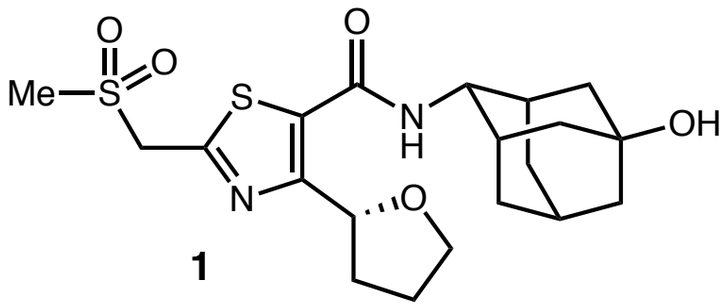
Optimization of Compounds for CNS Penetration

Polar surface area: surface sum over all polar atoms (O, N, etc.) including attached hydrogens

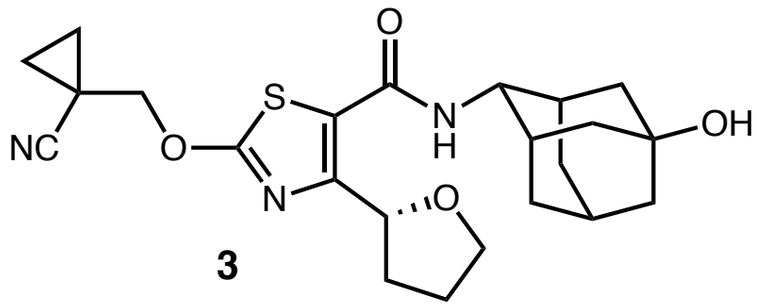
Typically < 140 $Å^2$ for cell membrane permeability and < 90 $Å^2$ for BBB permeability



Higher Polar Surface Area Reduces CNS Exposure



1



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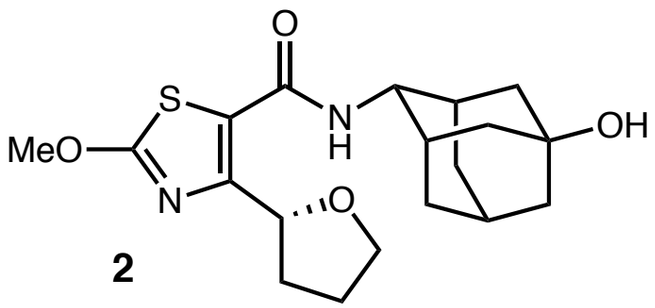
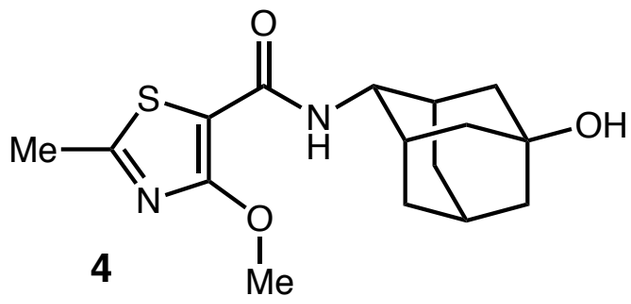


2



4

#	LogD	PSA (Å^2)	$K_{p,uu}$
1	0.4	111	0.03
2	2.6	93	0.4
3	2.3	84	0.7
4	2.0	75	0.9

Goldberg, F. W. *et. al. J. Med. Chem.* **2014**, *57*, 970–986.

Optimization of Compounds for CNS Penetration

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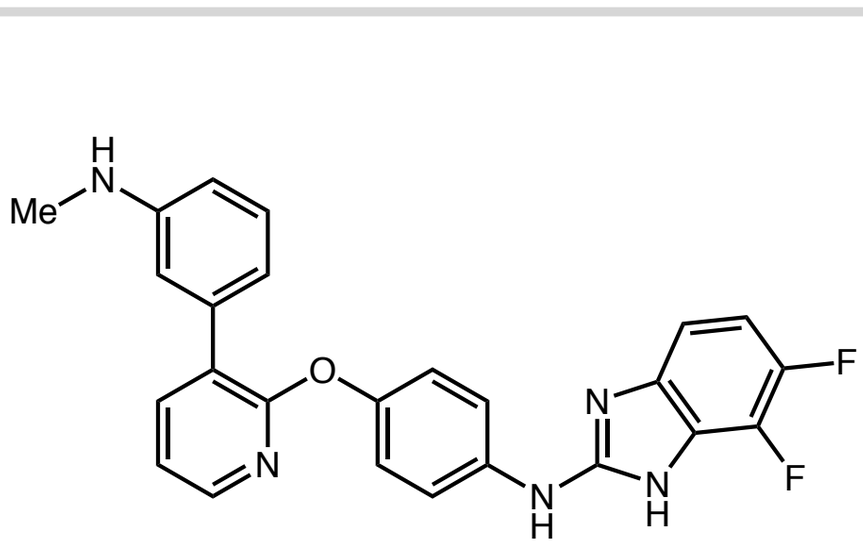
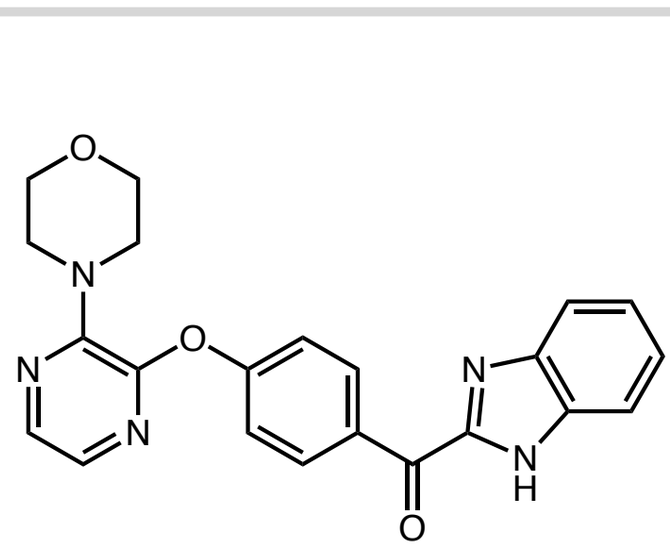
Optimization of Compounds for CNS Penetration

- PDE10A inhibitors for the treatment of schizophrenia (Amgen)
- regulates cAMP and cGMP in signaling pathway downstream from dopamine receptors



initial HTE hit (IC_{50} = 10 nM)



after optimization (IC_{50} = 5 nM)

Optimization of Compounds for CNS Penetration

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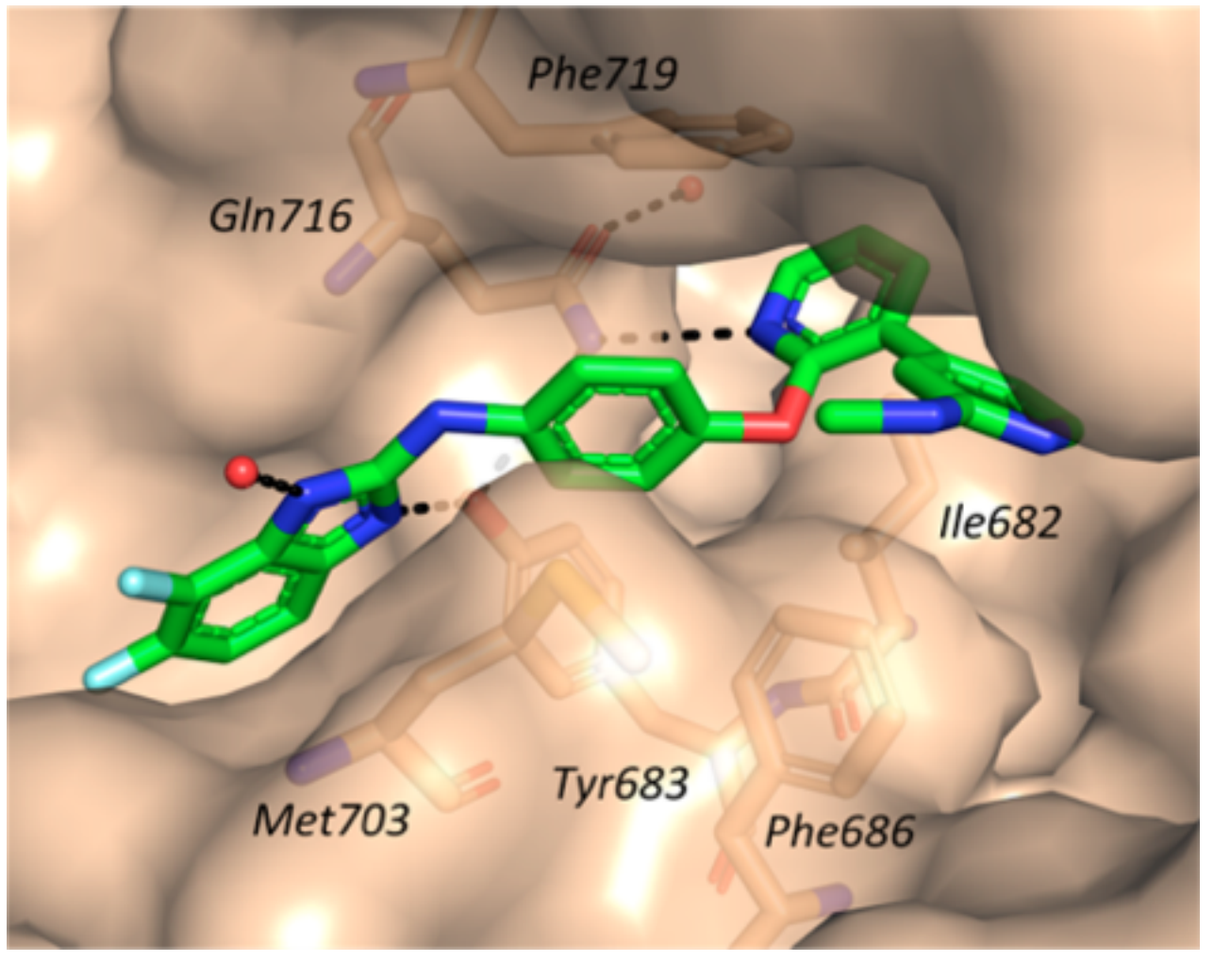
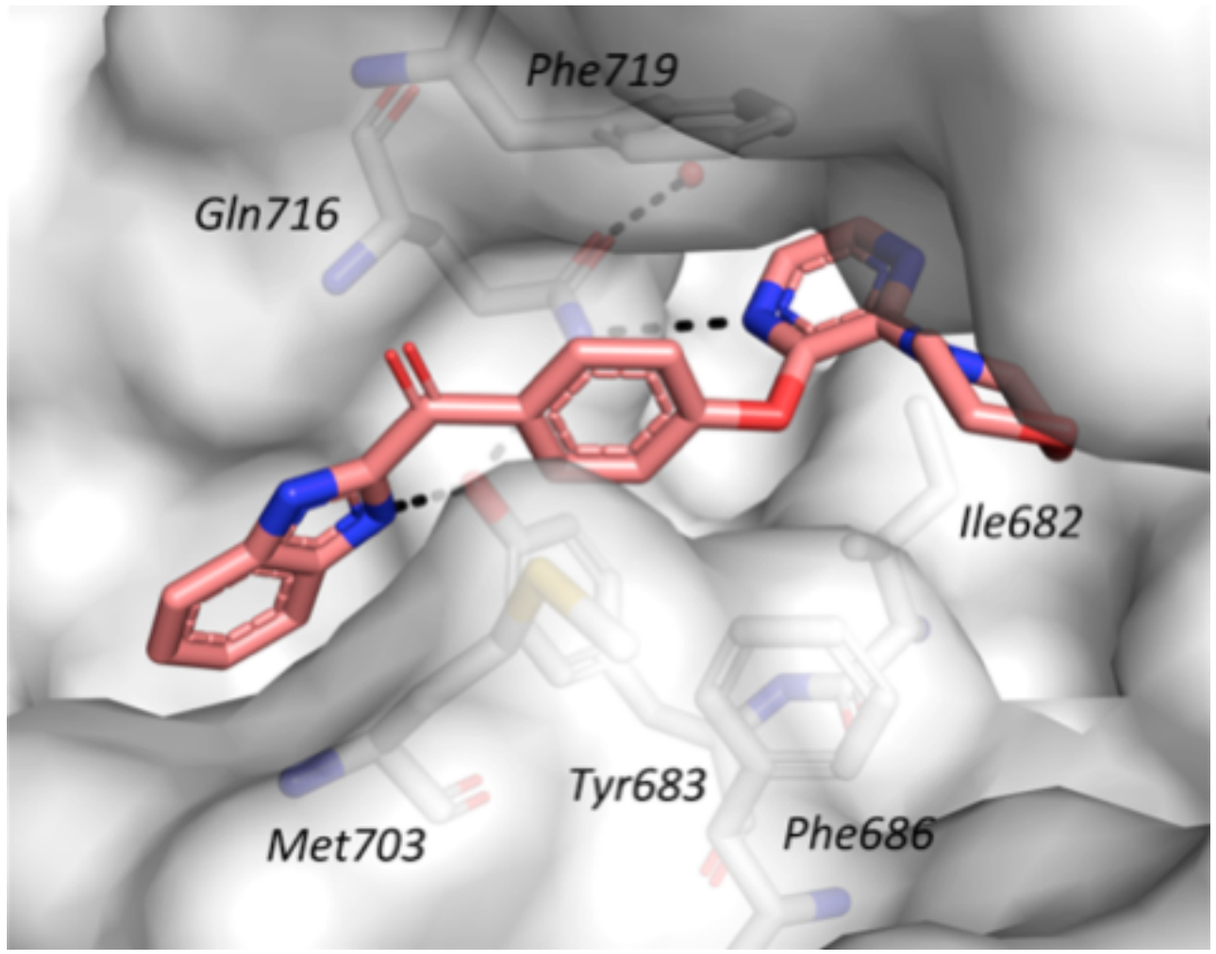
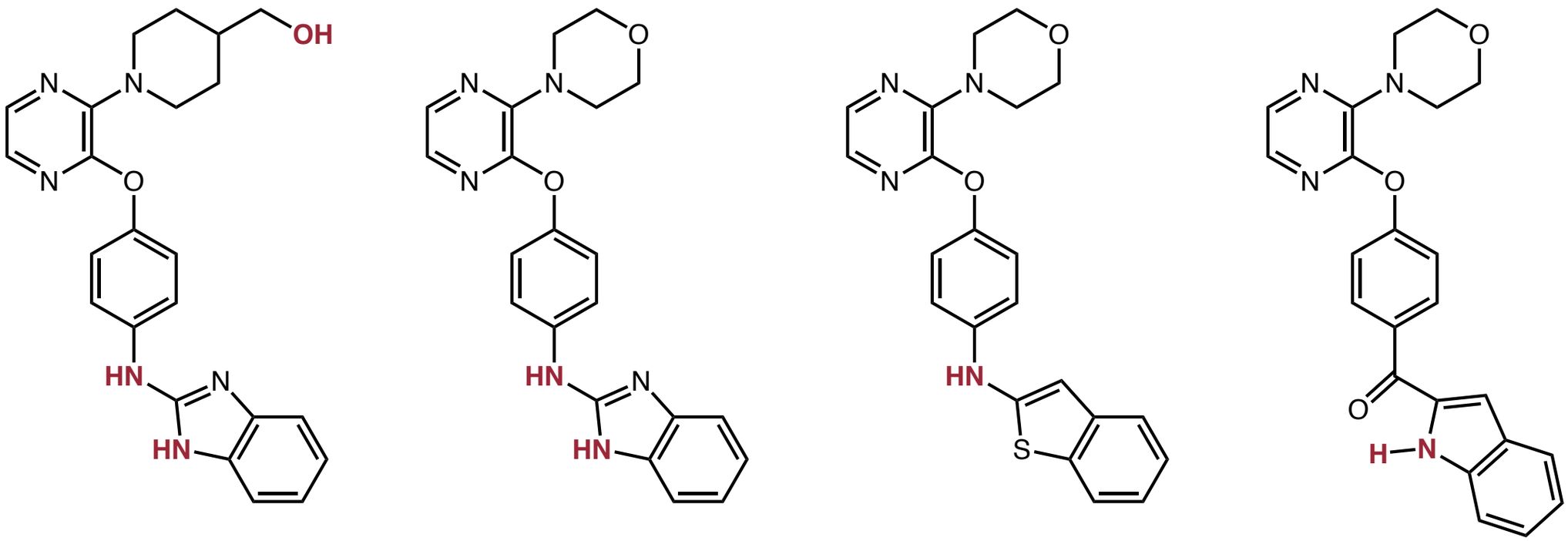
- regulates cAMP and cGMP in signaling pathway downstream from dopamine receptors





Hydrogen Bond Donors Can Lead to P-gp Efflux

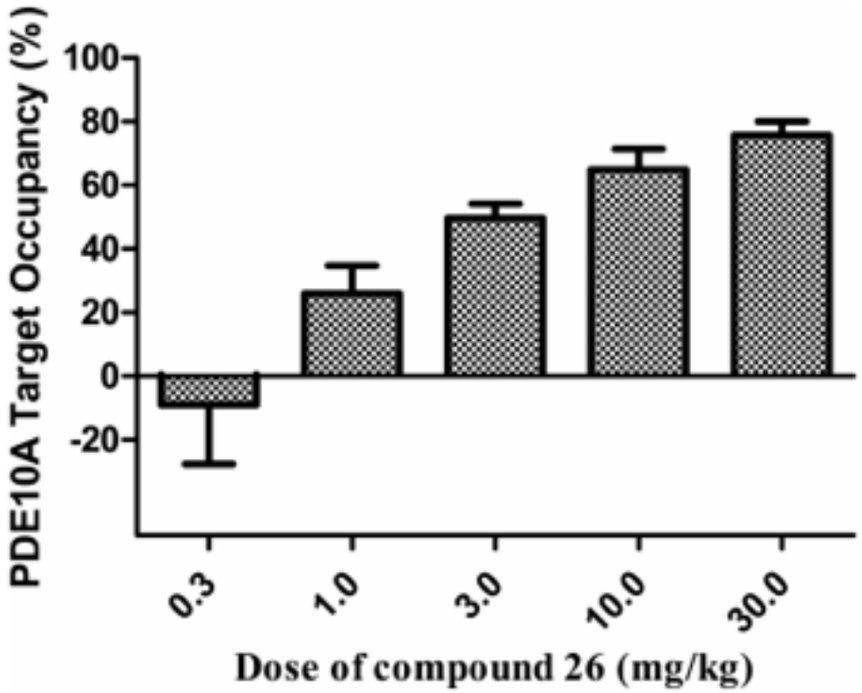


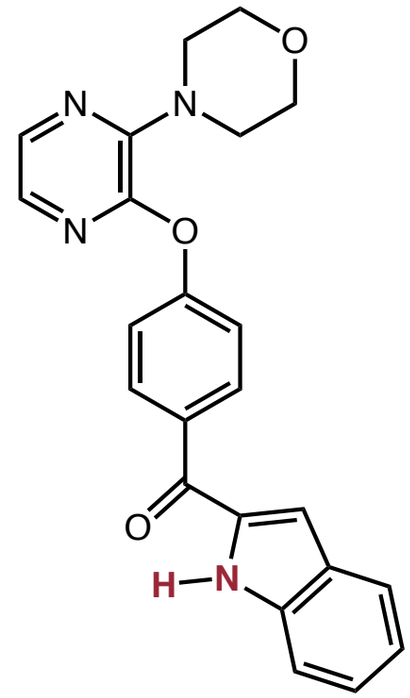
1 **2** **3** **4**

#	IC_{50} (nM)	HBD	efflux ratio
1	92	3	76.7
2	1.1	2	11.1
3	4.3	1	2.4
4	4.5	“1”	0.9

Hu, E. *et. al. J. Med. Chem.* **2013**, *56*, 8781–8792.

Hydrogen Bond Donors Can Lead to P-gp Efflux





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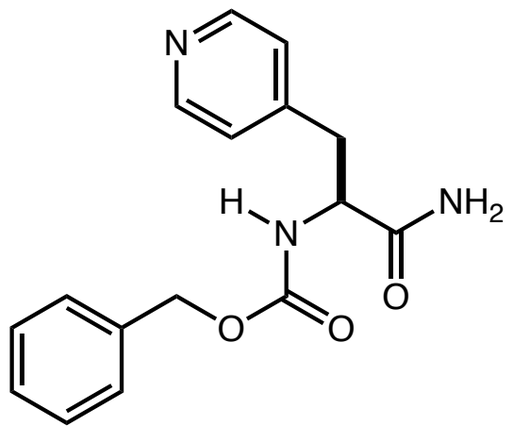
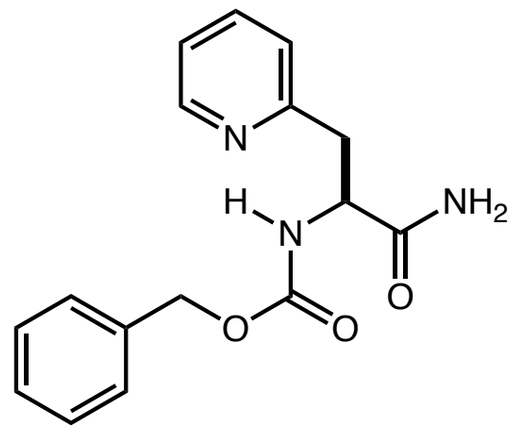
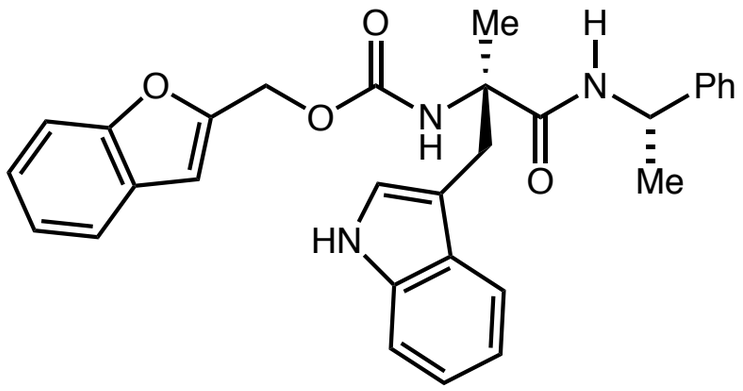
Intramolecular Hydrogen Bonding Generally Improves PK



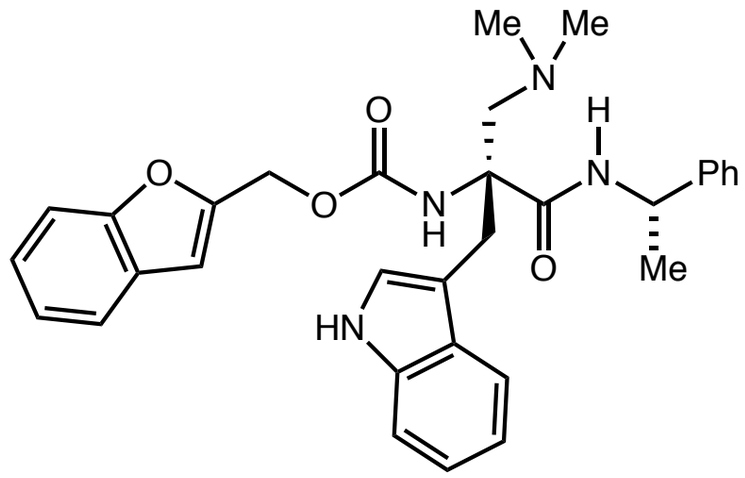
ER = 3.1



ER = 1.1



K_p = 0.4, MED = 30 mg/kg



K_p = 6.0, MED = 1 mg/kg

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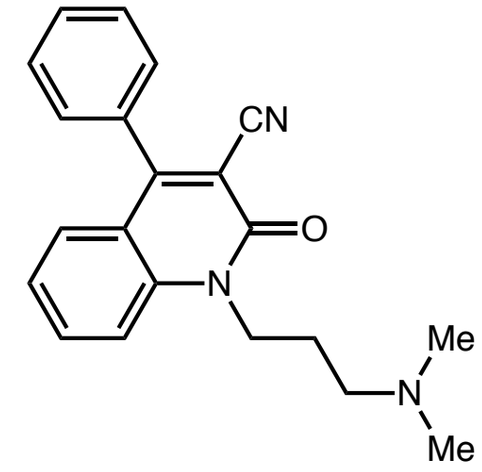
α7 Nicotinic Acetylcholine Receptor Agonists

- Target of growing interest for cognitive deficits and negative symptoms in schizophrenia
- Several α7 nAChR agonists have demonstrated efficacy in preclinical models

High Throughput Evaluation

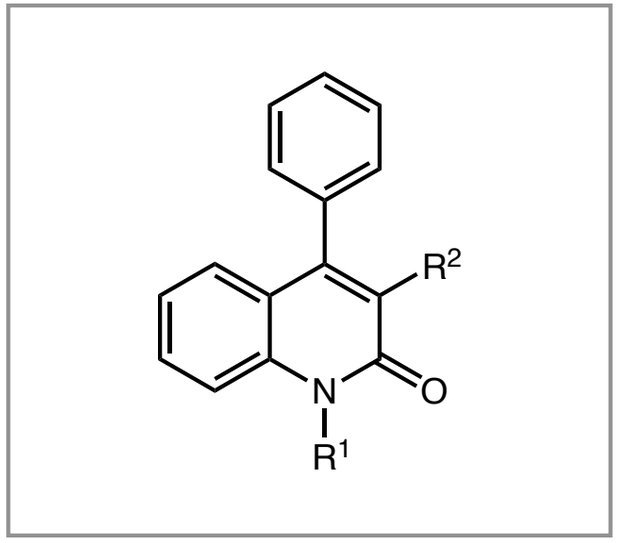


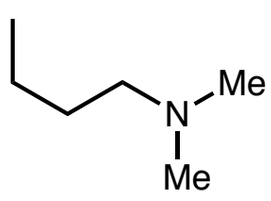
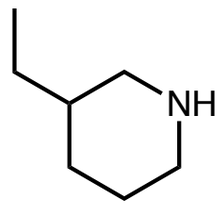
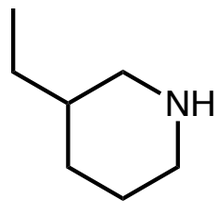
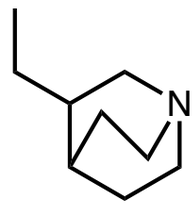
Lead Compound

α7 EC_{50} = 1.3 μM
good selectivity over $5HT_3$ receptor

McDonald, I. M. *et. al. Bioorg. Med. Chem. Lett.* **2013**, *23*, 1684–1688.

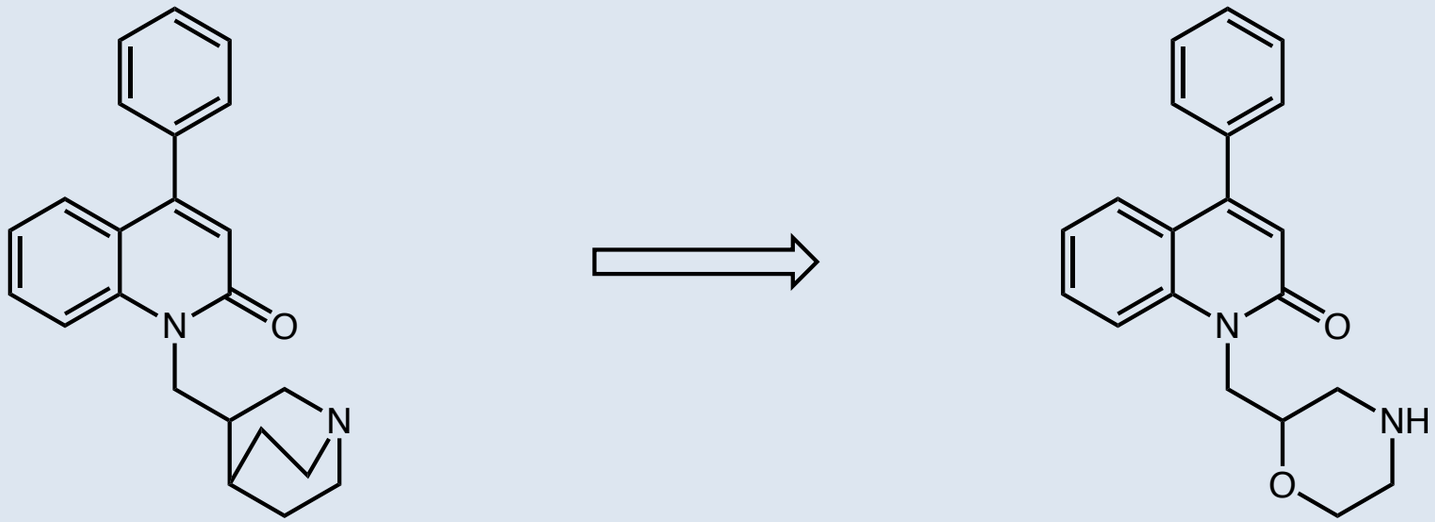
α7 Nicotinic Acetylcholine Receptor Agonists



R^1	CN	CN	H	H
R^2				
EC_{50} (μM)	1.3	0.9	0.46	0.15

McDonald, I. M. *et. al. Bioorg. Med. Chem. Lett.* **2013**, *23*, 1684–1688.

High pK_a Can Lead to Reduced CNS Exposure



pK_a = 10.1
ER = 6.9
K_p = <0.02

pK_a = 8.1
ER = 1.0
K_p = 0.9

Attenuated basicity leads to significantly reduced efflux and good brain/plasma distribution

McDonald, I. M. *et. al. Bioorg. Med. Chem. Lett.* **2013**, *23*, 1684–1688.

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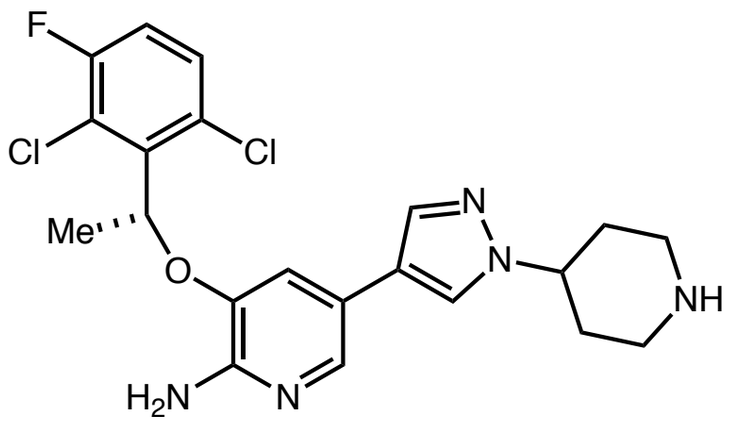
Rigid Structures are Often More Membrane Permeable



crizotinib

anaplastic lymphoma kinase inhibitor

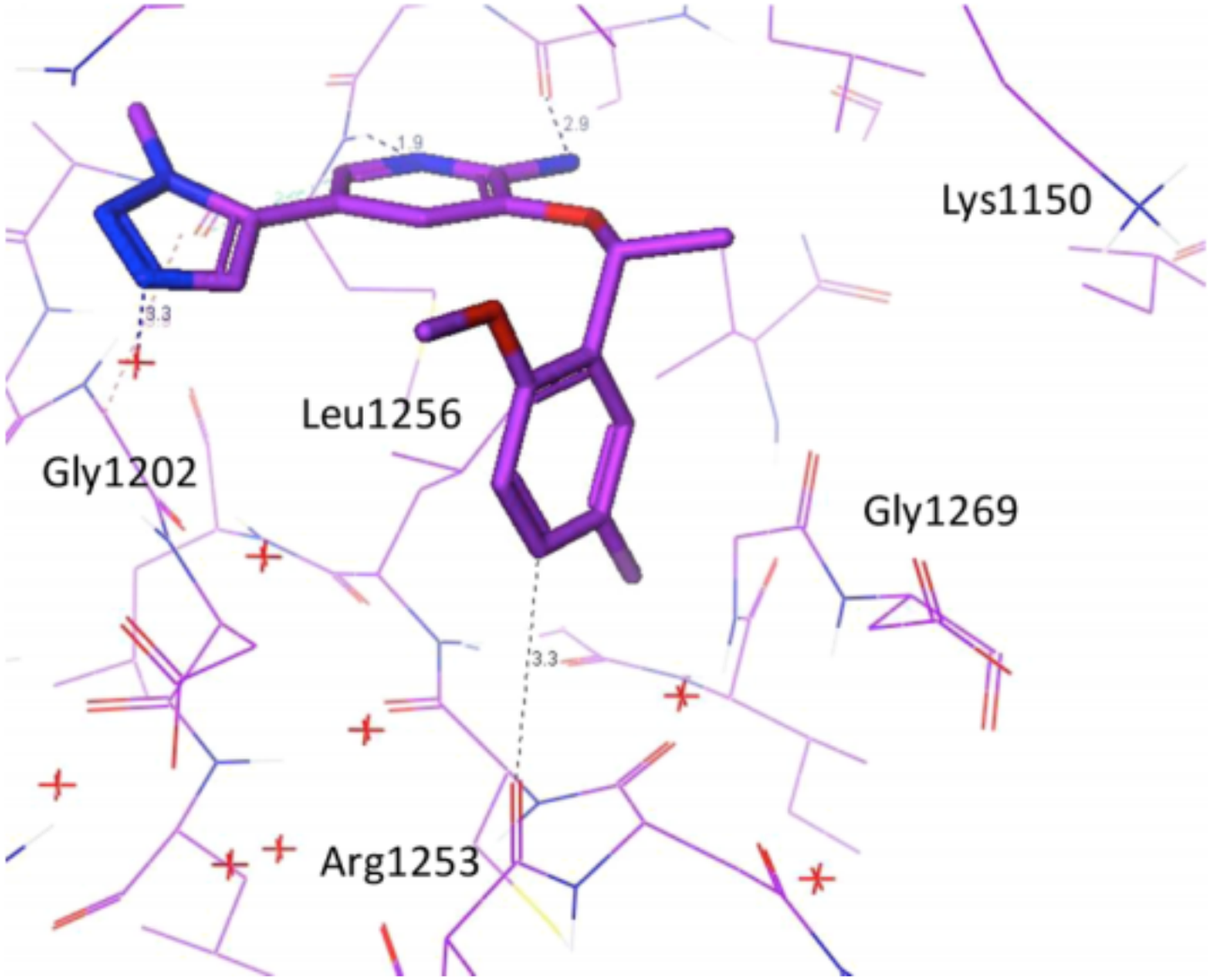
non-small cell lung carcinoma

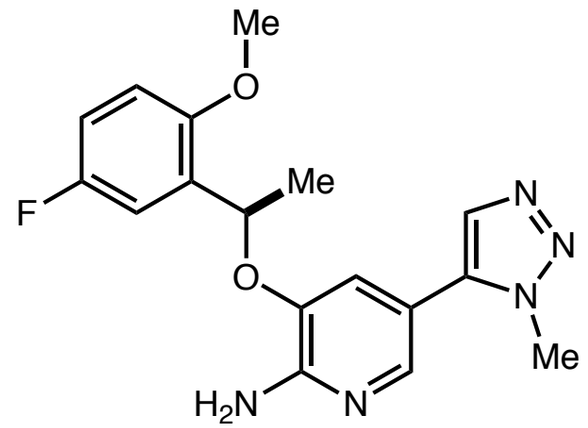
in some patients, point mutations and cancer metastasis into the brain is observed

a compound effective against mutant ALK and CNS penetrant was needed

Johnson, T. W. *et. al. J. Med. Chem.* **2014**, *57*, 4720–4744.

Rigid Structures are Often More Membrane Permeable





Johnson, T. W. *et. al. J. Med. Chem.* **2014**, *57*, 4720–4744.

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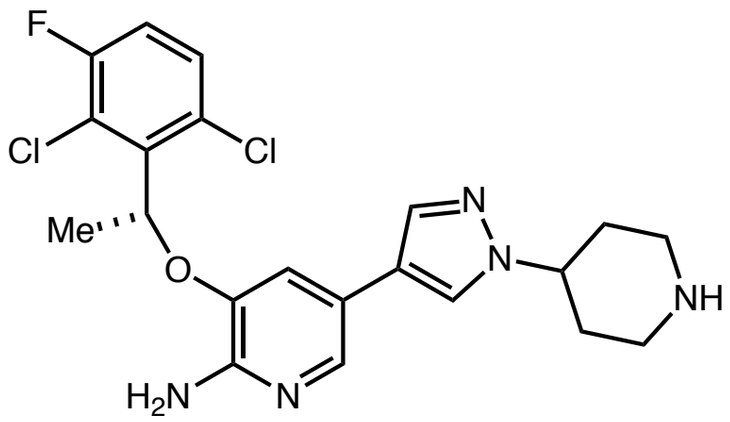
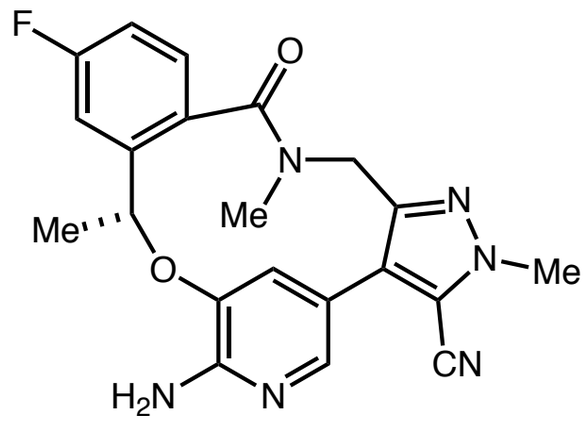


crizotinib

anaplastic lymphoma kinase inhibitor

non-small cell lung carcinoma

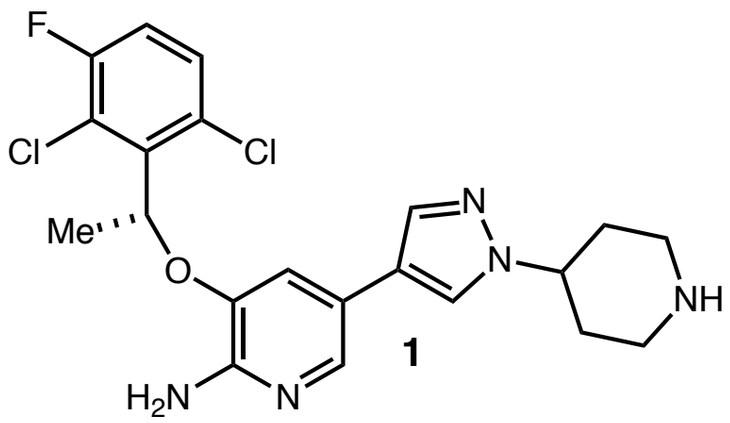


in some patients, point mutations and cancer metastasis into the brain is observed

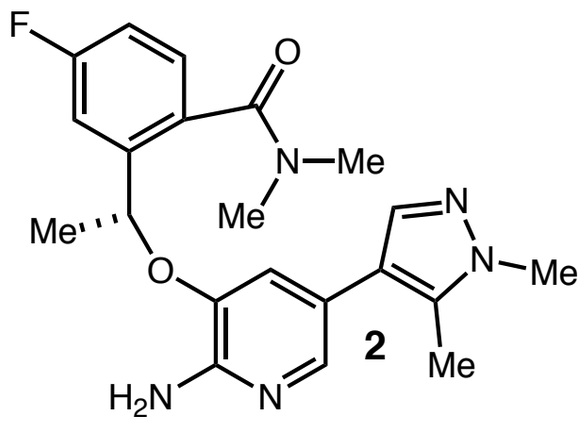
a compound effective against mutant ALK and CNS penetrant was needed

Johnson, T. W. *et. al. J. Med. Chem.* **2014**, *57*, 4720–4744.

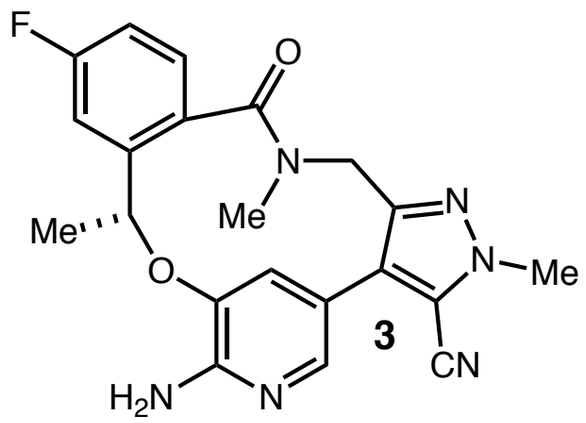
Rigid Structures are Often More Membrane Permeable



1



2



3

#	K_i (nM)	RB #	PSA (Å^2)	cLogP	P_{app}	ER	CSF/$C_{u,p}$
1	0.74	5	78	3.6	12.5	44.5	0.03
2	22	6	86	2.2	18.8	7.6	–
3	0.70	0	110	1.6	28.8	1.5	0.31

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Questions?