Design and Development of CNS Drugs

March 9, 2023

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Outline

- Neurological disorders
- The brain and blood brain barrier (BBB)
- Design strategies to get compounds into the brain
- Examples of implementation of strategies in disease states

Drug Discovery and the Central Nervous System

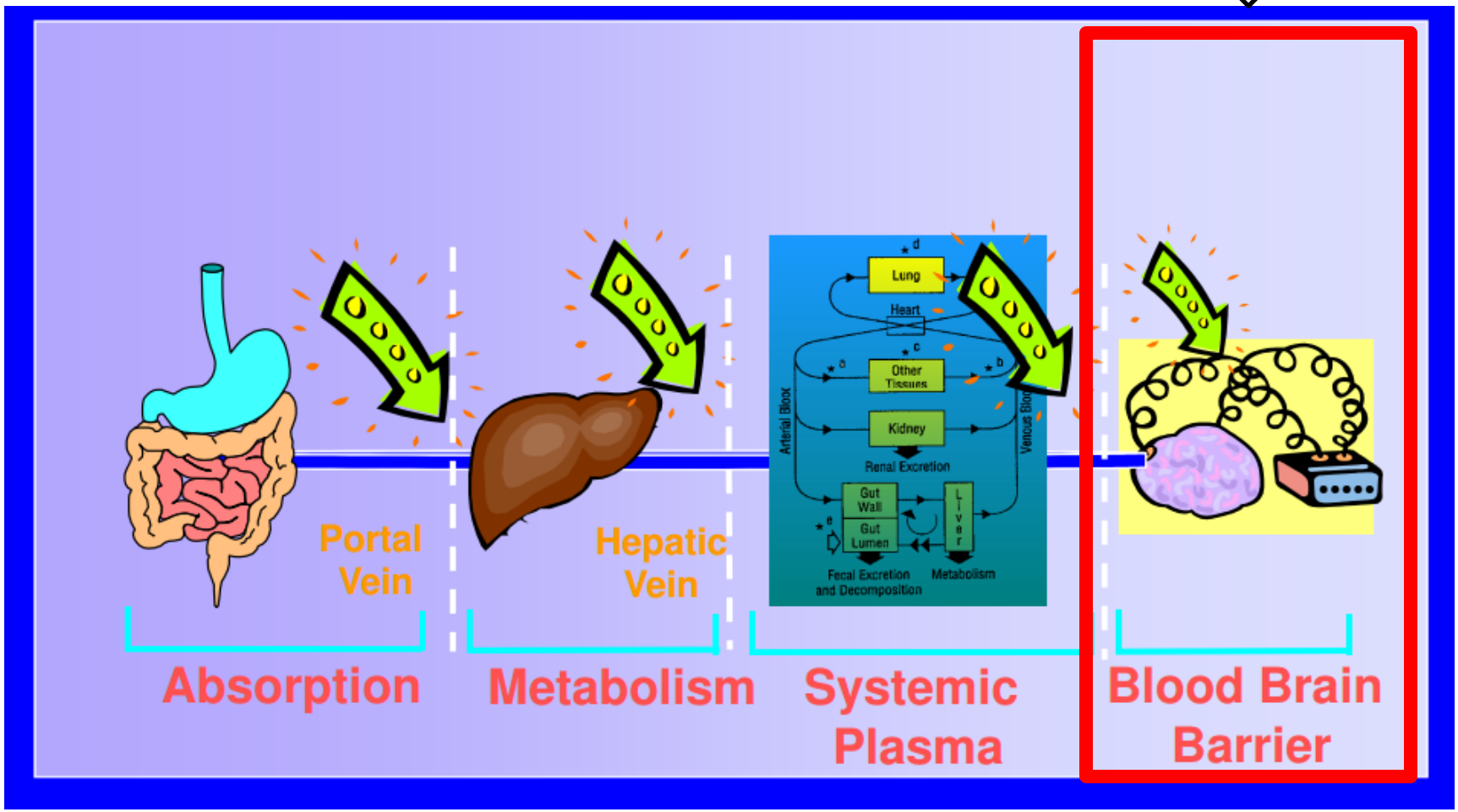
- Approximately 7000 drugs in the Comprehensive Medicinal Chemistry database
- Only 5% treat CNS disorders
- Physiological challenges for drug to get into the brain
- Failure rate of CNS drugs is higher than average
- Time from entry into FIH to approval is longer

Disorders Requiring Crossing the BBB
Centrally-acting drugs

Depression
Anxiety disorders
Seizure disorders
Schizophrenia
Bipolar disorder
Parkinson's disease
Alzheimer's disease
Stroke
Sleep disorders – Insomnia, Narcolepsy, Restless Leg Disorders

Drug Distribution of Centrally-active Therapies

~2% of Small Molecules enter the brain



Maxmorpharma.com

The Blood Brain Barrier

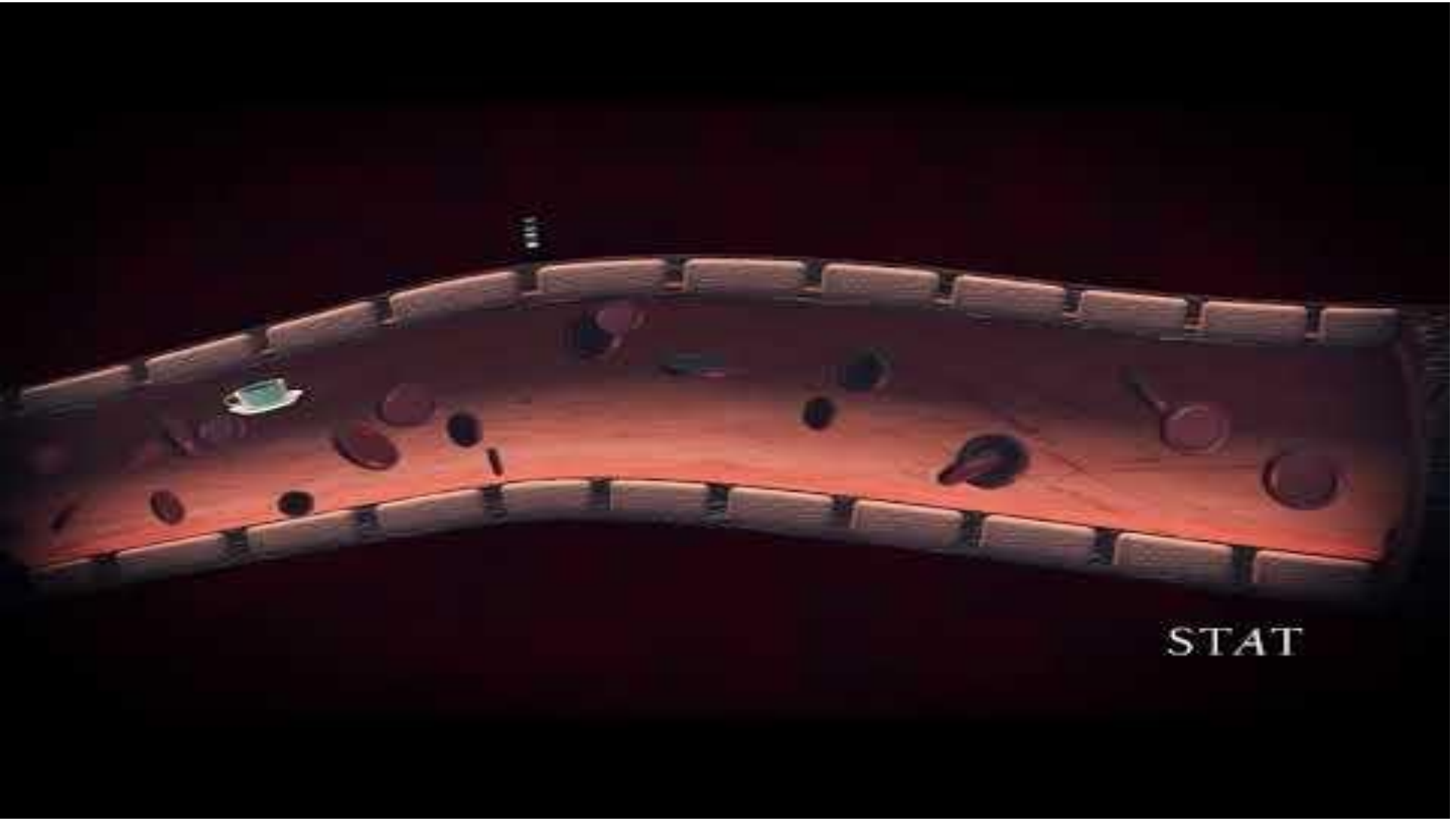
- 1695 – Ridley publishes “The Anatomy of the Brain.”
- 1885- Ehrlich reports that parental injection of dyes distribute to all organs except the brain and spinal cord.
- 1898- Bield and Kraus suggest that there is a barrier around the brain
- 1900- Lewandowsky shows that injection of cholic acids or sodium ferrocyanide had no CNS effects; coined the phrase “blood brain barrier” to explain the effects.
- 1967 – EM studies show the existence of a structural barrier around the brain.

The Blood Brain Barrier Function

- Controls the movement of molecules into and out of the CNS
  - Efflux Transporters such as P-gp
- Allows for control of the composition of the interstitial fluid
- Maintains synaptic functioning and neuronal connectivity
- Protects the CNS from toxins and inflammation
- Breakdown in the BBB is seen in several diseases including Parkinson's disease, Alzheimer's disease, and HIV-1 associated dementia
- Breakdown in the BBB may be an early indication of cognitive impairment

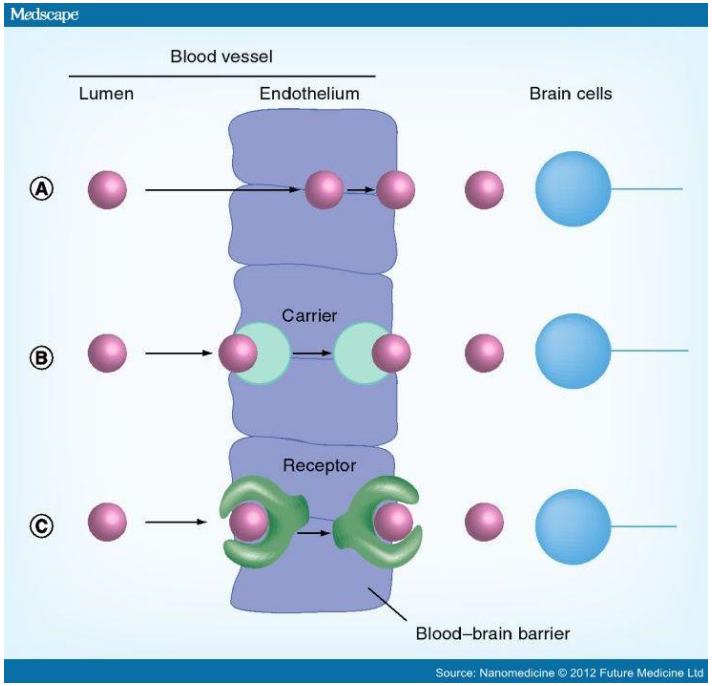
Journal of Drug Delivery Science and Tech. **2023**, 80, 104174
Pharm. & Therapeutics. **2022**, 234, 108119
Behav. Brain Res. **2021**, 402, 113125
Nature Medicine, **2019,** 270-276
Nature Reviews: Neurology, **2018**

Blood Brain Barrier



How Do Compounds Get into the Brain?

- Passive Diffusion
  - Low molecular weight and high lipophilicity
- Active transport
  - Utilizes transport proteins
- Endocytosis

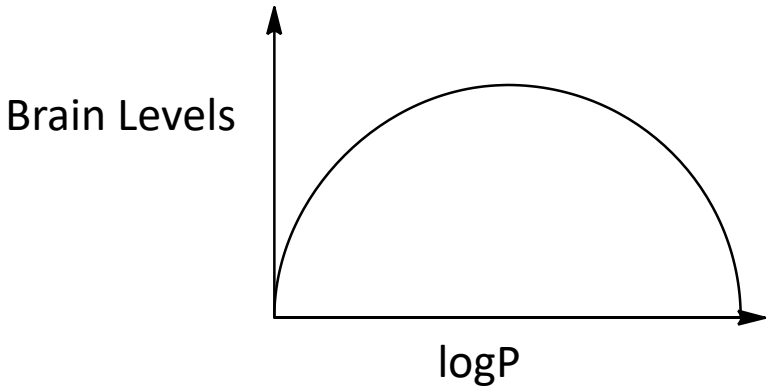


Nanomedicine. **2012**;7(8):1225-1233

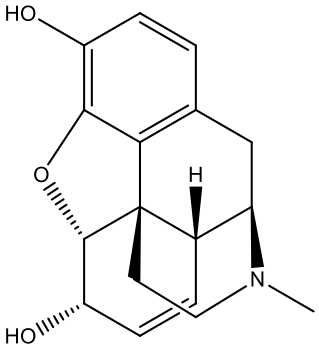
Passive Diffusion-
Chemical descriptors to design molecules targeting the brain

Key Physicochemical Descriptors

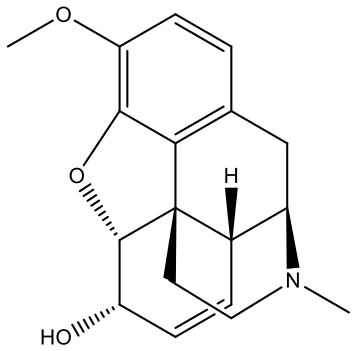
- ***logP***
  - Measure of lipophilicity; partion coefficient between an aqueous and lipophilic phase, usually water and octanol
  - Hansch – 1967- Parabolic relationship between logP and hypnotic activity
  - Optimal logP of approximately 2 for CNS activity
  - Refined to show the optimal value for a variety of CNS active molecules is 2.4



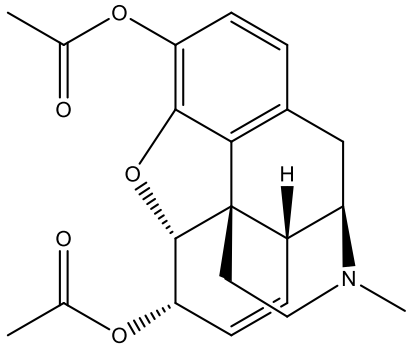
Example of logP and Brain Levels



logP = 0.84



log P = 1.2



logP = 1.84

Other Relevant Physicochemical Descriptors

- ***logD***
  - pH dependent; better descriptor since most CNS molecules have basic groups
  - **logD should be between 0 and 3**
- ***Hydrogen Bonding***
  - Increased H bonding capacity is associated with lower permeability
  - Also increases the risk of P-gp recognition
  - **Hydrogen bond donors < 3, Hydrogen bond acceptors < 7, total H-bonds <8**
- ***Polar Surface Area***
  - Measure of surface area over all polar atoms
  - Calculated as TPSA
  - **For a CNS compound it should be below 70**
- ***Molecular Flexibility and Rotational Bonds***
  - Increased molecular flexibility exerts a negative effect on brain penetration
  - **Rotatable bonds <8**

Physicochemical Parameters

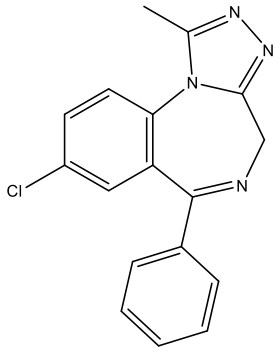
- ***pKa***
  - Most CNS compounds contain a charged group
  - **pKa around 8.4 is optimal**
- ***Molecular Weight***
  - Increased MW will lead to decreasing brain penetration
  - **MW < 450**

Multiparameter Optimization (MPO)

- CNS MPO (Pfizer, 2010)
- LogD and MW are better predictors than logD alone
- Developed scoring functions that combine multiple parameters into a single value
- Use clogP, clogD, MW, TPSA, HBD count, and pKa
- Assign a value of 0-1 for each property with 0 being undesirable and 1 being highly desirable
- 74% of CNS drugs are greater than or equal to 4
- Machine learning models

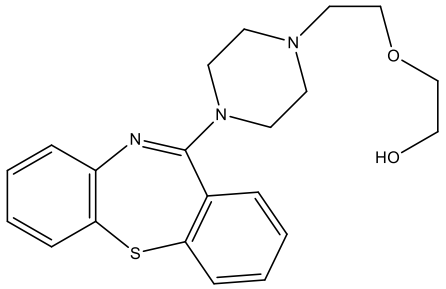
ACS Chem. Neurosci. **2021**, 12, 2247-2253
ACS Chem. Neurosci. **2020**, 11, 205-224 (Brain Exposure Efficiency Score)
Eur. J. Med. Chem. **2019**, 182, 111643
Drug Discovery Today **2017**, 22, 965-969
ACS Chem. Neurosci. **2010**, 1, 435-449

Representative CNS Drugs



Alprazolam

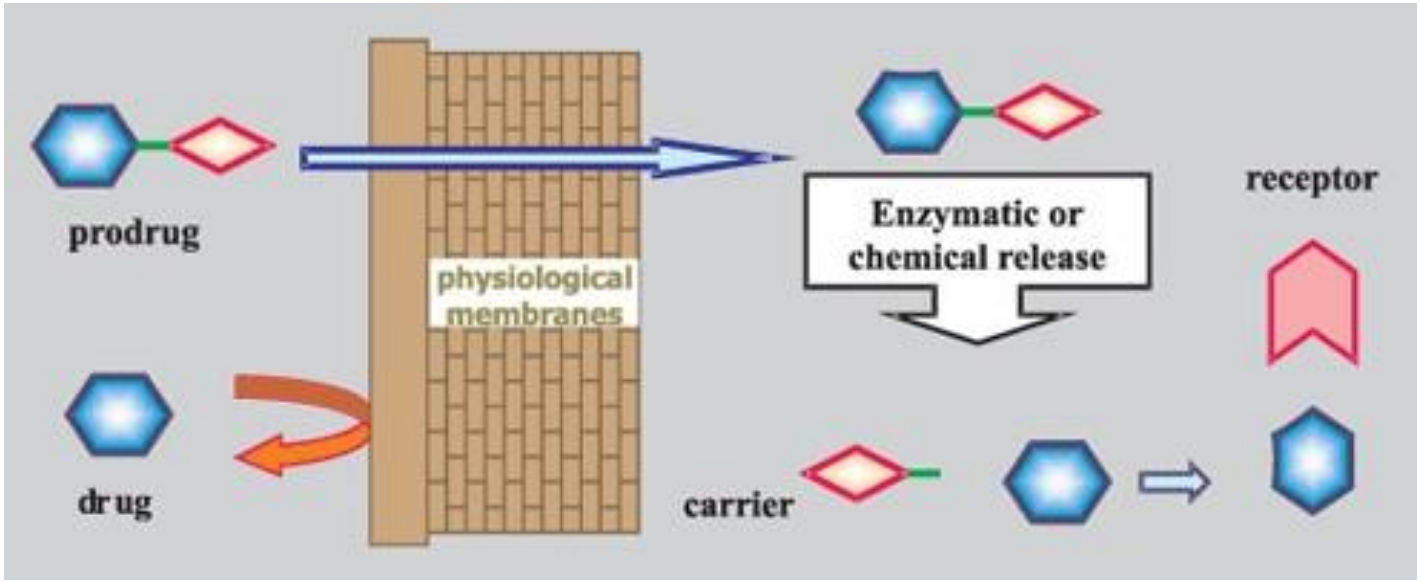
MW = 309
LogP = 3.1
HBA = 4
HBD = 0
PSA = 43
RB = 1
MPO = 5.8



Quetiapine

MW = 383
LogP = 2.1
HBA = 5
HBD = 1
PSA =73
RB = 6
MPO = 5.7

Prodrugs



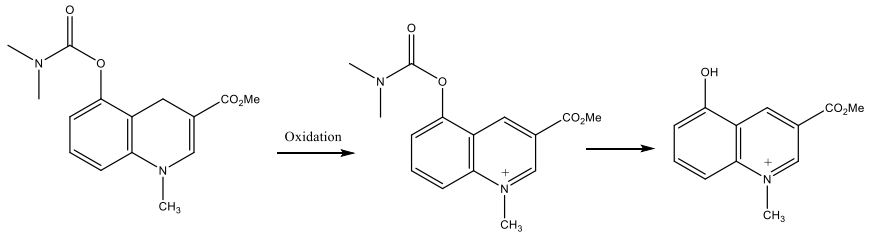
Efficient Delivery of RNAi Prodrugs, igtrcn.org

Prodrugs

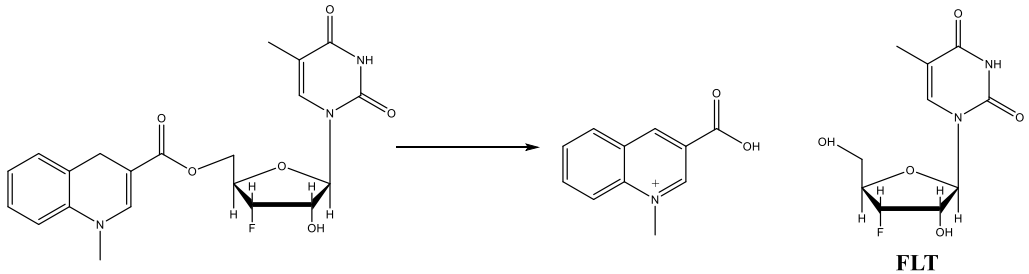
- Bioreversible derivatives of drug molecules that undergo a chemical or enzymatic biotransformation to the active forms within the body
- Overcomes pharmacokinetic limitations of parent drug
- Chemically modify a drug to become more lipophilic
- Specific type used in CNS research is a chemical delivery system (CDS)
- Increase lipophilicity and locks compound into brain preventing it from coming back out via efflux mechanism

Prodrugs

- Delivery of acetylcholinesterase inhibitor
  - Eliminate peripheral cholinergic activity



- Delivery of a brain imaging agent

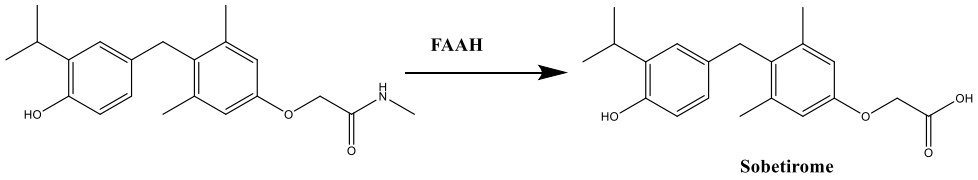


- Cell-penetrating peptides
  - Small peptides that cross the BBB
  - Transport small molecules, biologics

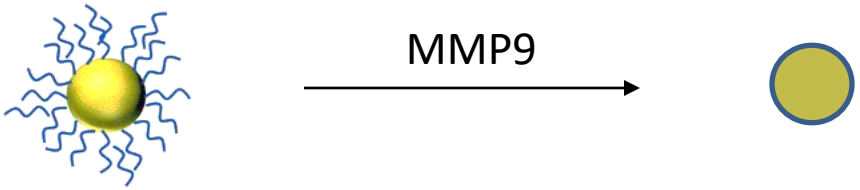
Eur. J. Pharm. Sci. **2022**, 168, 106054
ACS Chem. Neurosci. **2017**, 8, 2457-2467
ACS Chem. Neurosci. **2015**, 6, 737-744

Prodrugs

- Prodrug for delivery of thyromimetic sobetirome
  - Utilize fatty acid amide hydrolase (FAAH)
  - Eliminate peripheral thyroid activity; may be beneficial in MS

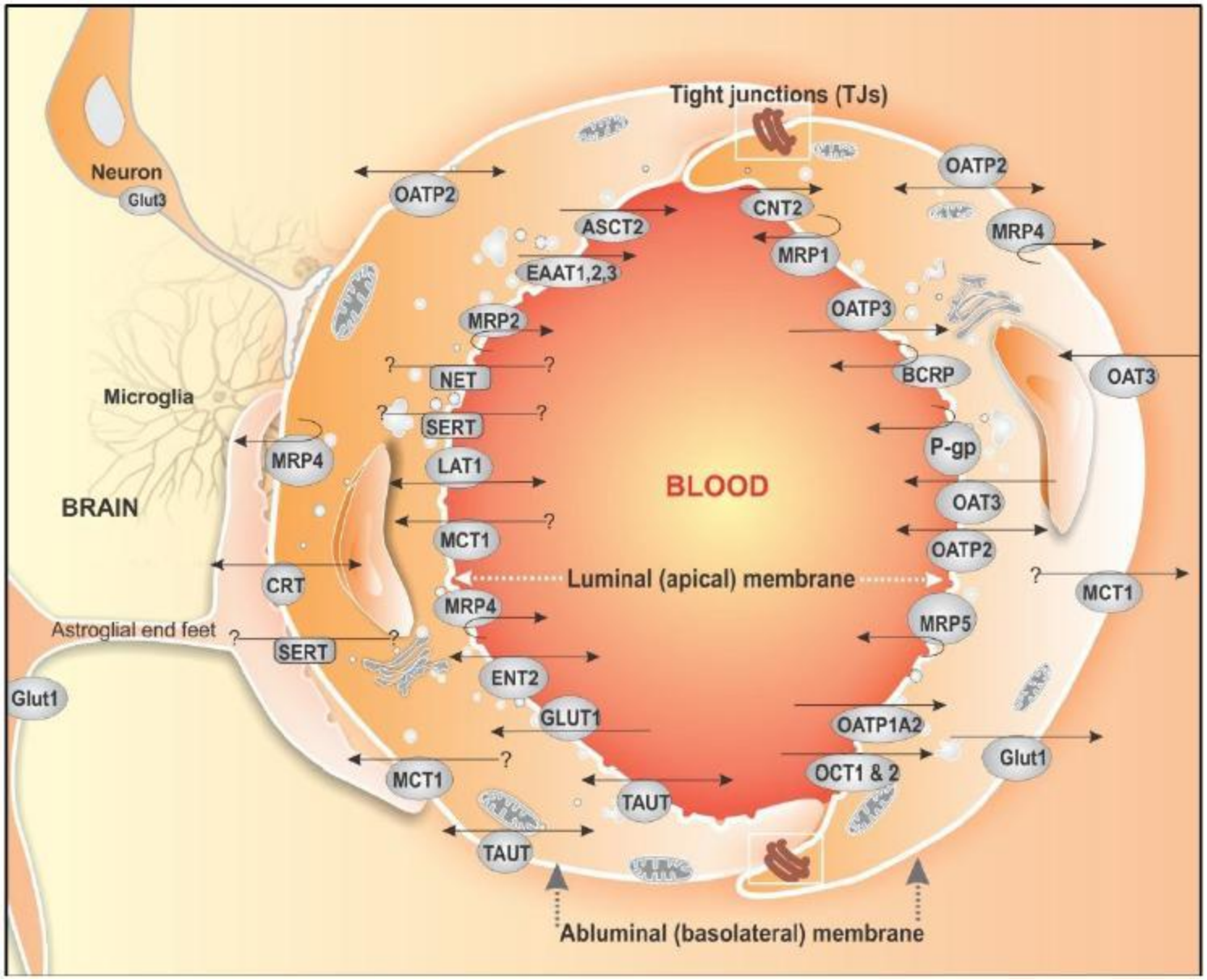


  - 50- fold increase in brain levels
- Brain targeting MMP9 responsive nanoparticles
  - MMP9 elevated in several neurological disorders



J Pharm. Sci. **2021**, 110, 1349-1364
ACS Chem. Neurosci. **2017**, 8, 2468-2476

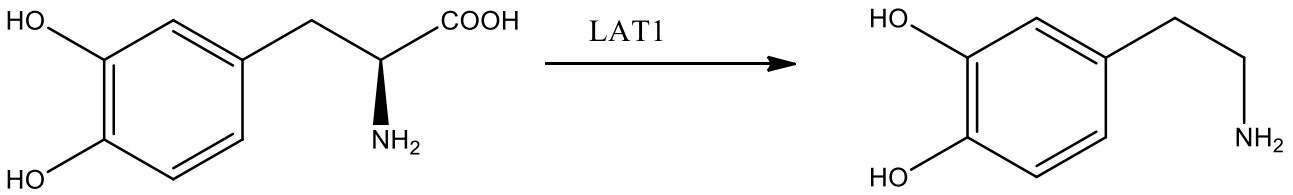
Active Transport-
How do medicinal chemists optimize molecules to get into the brain



BioImpacts, **2012**, 2, 5-22

Example of a Drug Using the Transporter LAT1

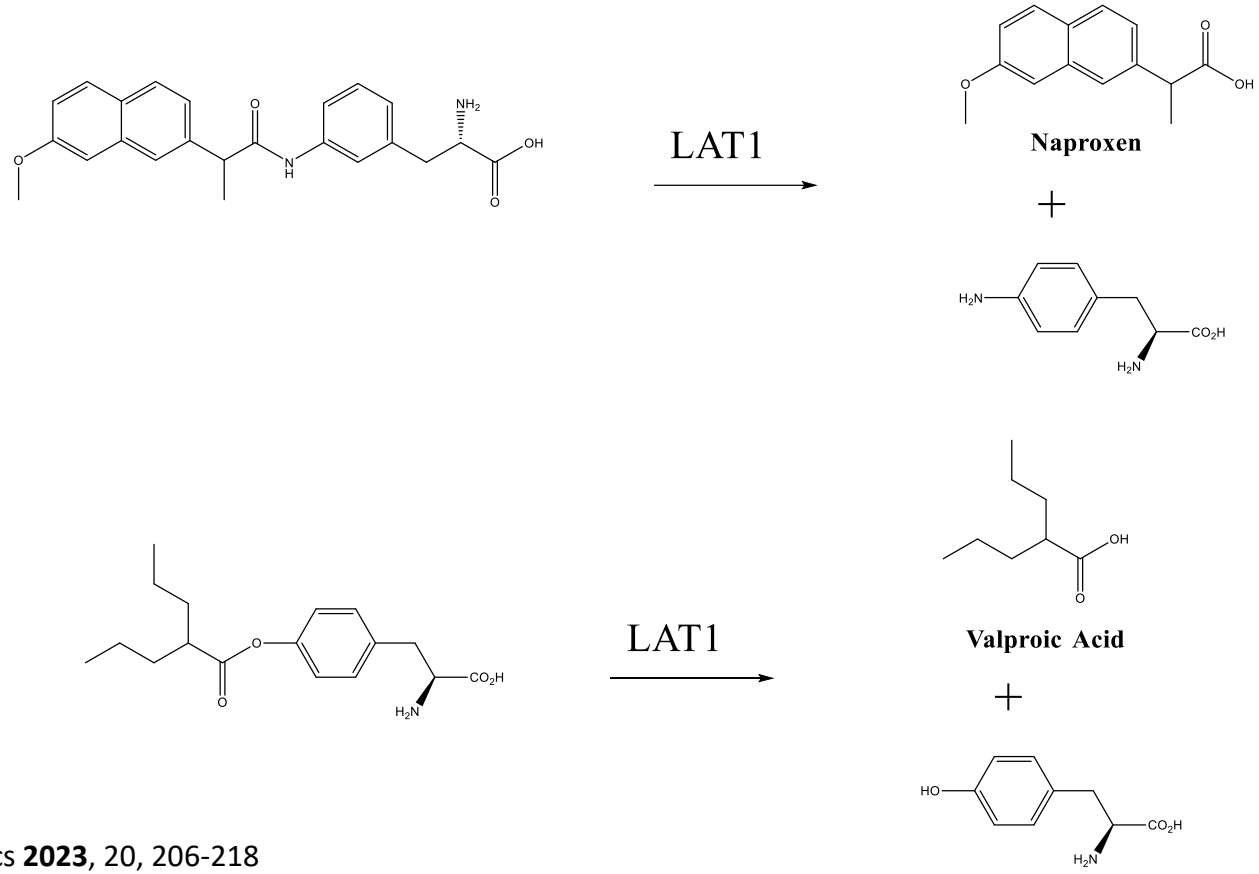
- Parkinson's disease is characterized by a low level of dopamine
- Dopamine will not cross the blood brain barrier
- 1967 L-Dopa is approved
- Arvid Carlson Nobel prize 2000; William Knowles Nobel Prize 2001



L-DOPA

Dopamine

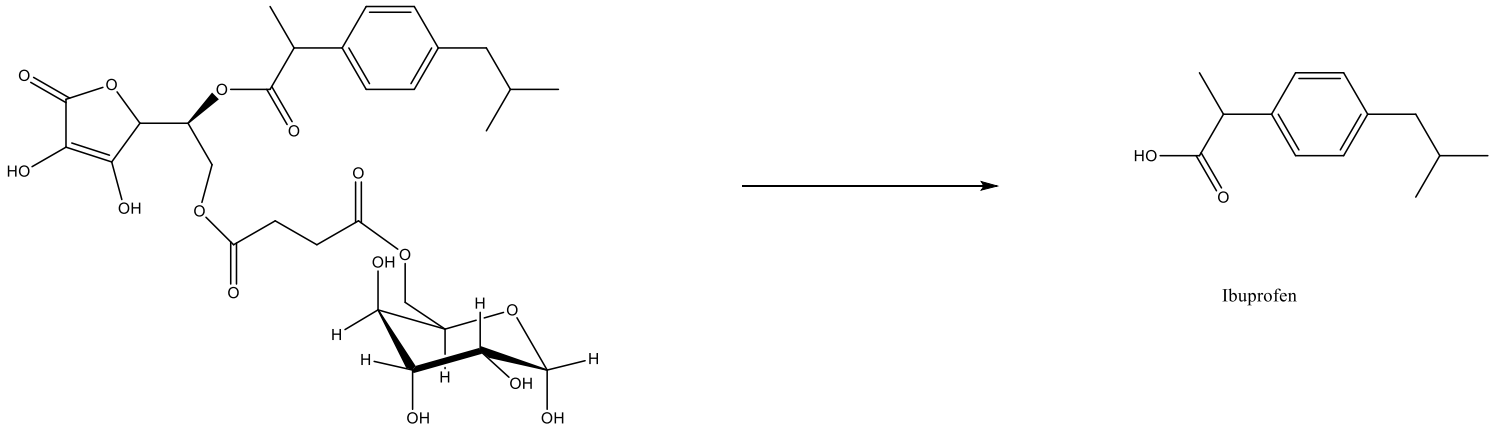
Example of Conjugating a Drug to a LAT1 Substrate



Mol. Pharmaceutics **2023**, 20, 206-218
ACS Chem. Neurosci. **2020**,11, 4301- 4315
European J Pharm. Sci. **2019,** 129, 99-109
J. Contr. Rel., **2017**, 261, 93-104
Mol. Pharmaceutics, **2011**, 8, 1857-1866

Example of Conjugating a Drug to Glucose and Vitamin C transporters

- Utilize transporters for glucose and transporter for vitamin C
- Release ibuprofen in the brain
- Dual targeting prodrug showed neuroprotective effect compared with control



Drug Delivery, **2018,** 25, 426-434

Receptor Mediated Transport

- Viruses can be transported into the brain
  - Zika
  - Japanese encephalitis
  - SARS-CoV-2 - ?
  - Chakravarty, N. et al. *FEBS Letters ,* **2021,** 595, 2854-2871
    - S1 spike protein is transported across mouse brain
    - Utilize the ACE2 receptor on the BBB
    - Inflammatory response

- Certain large molecule peptides in the blood undergo receptor mediated transport across the BBB via endogenous peptide receptors
  - Insulin uses the BBB insulin receptor
  - Transferrin is transported across the BBB using the endogenous transferrin receptor

Nat. Neurosci. **2021,** 24, 368 - 371

Receptor Mediated Transport

- Parkinson's Disease
  - Glial-derived neurotrophic factor (GDNF) is a protein that promotes the survival of dopaminergic neurons
  - Does not get into the brain
  - Fusion protein of GDNF coupled with the transferrin recognition antibody
  - Significant improvement in three models of PD

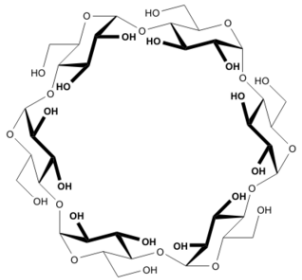
- Epilepsy, Pain
  - Metabotropic glutamate receptor-1
  - Antibody antagonist of mGluR1 coupled to a single-domain antibody
  - 20-fold increase in brain levels

The FASEB Journal **2017**, 30, 1927-1940
Clinical Pharm. and Therap. **2015**, 97, 347-361

Using Drug Delivery to Target the Brain

Alternative Approaches

- Nose to brain
  - Potential way to bypass the blood brain barrier
  - Recent work on intranasal steroids for glioma and seizure disorders
- Cyclodextrins
  - Consist of cyclic oligosaccharides

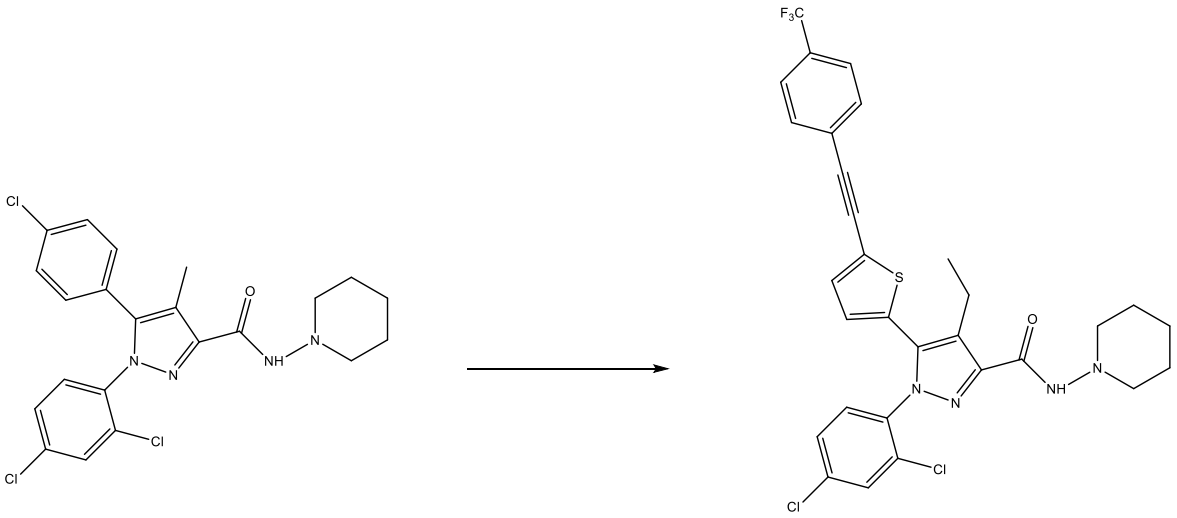


  - Modify efflux of drugs
- P-glycoprotein inhibitors
- Disruption of the blood brain barrier
  - Delivery of nanoparticles

Appl. Mater. Interfaces. **2023,** 15, 120
Neurotherapeutics, **2021** 18, 544-555
International Journal of Therapeutics, **2021**, 120250
Scientific Reports, **2018,** 2218

Using the BBB to prevent a molecule from exerting its CNS side effects

- Receptors for certain drugs may not be restricted to the brain
- What do you do if you want to keep a molecule ***out*** of the brain?
- Rimonabant – selective CB1 Antagonist for weight loss
- Serious CNS side effects



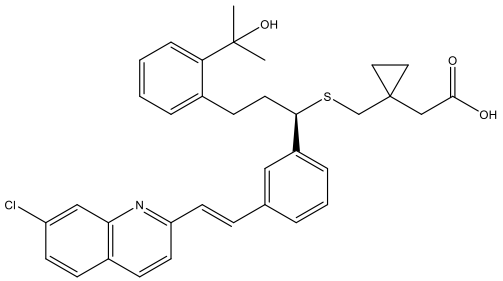
Rimonabant **TM38837**

Frontiers in Pharmacology, **2019**, 10, 207

Repairing the BBB

MMP Inhibitors

- Approximately 50 million cases of epilepsy in the world
- Blood brain barrier leakage may contribute to seizures
- Matrix metalloprotease inhibitors may be useful for repairing the BBB



Montelukast

Wnt ligands

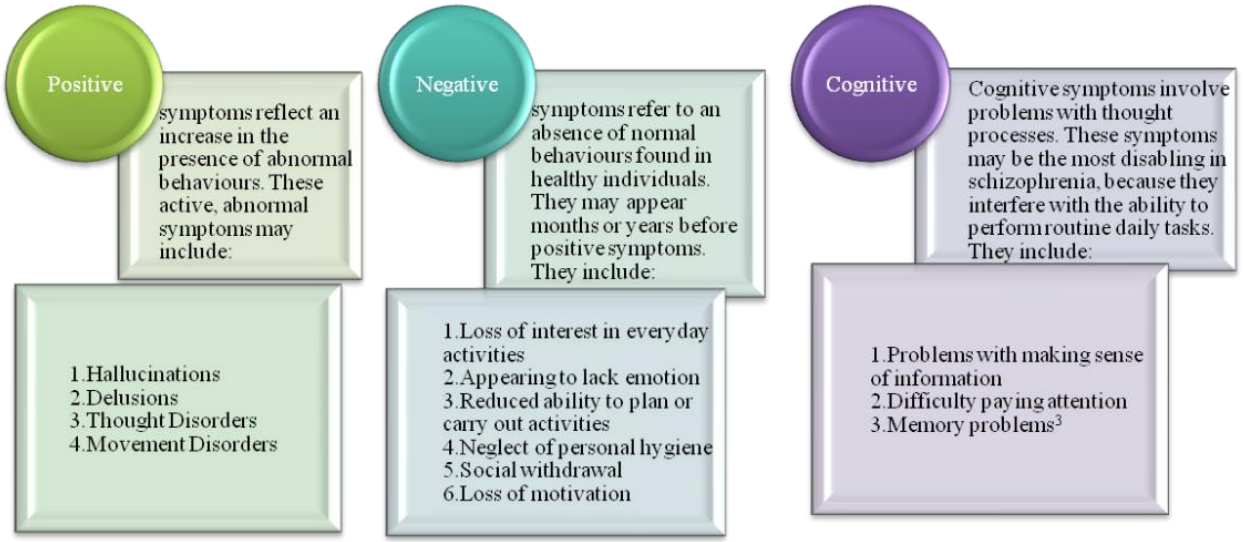
- Repair the BBB in models of ischemia

Science, **2022,** 375, 6852
Journal of Exp. Pharmacology, **2021**, 13, 23-31
.J Neurosci., **2018**, 4301-4315

Examples of Designing Compounds That Get into the Brain

Schizophrenia

- Chronic mental illness that effects 0.5 – 1.0 % of the population
- Symptoms are classified as positive, negative, or cognitive
  - Positive
  - Negative
  - Cognitive

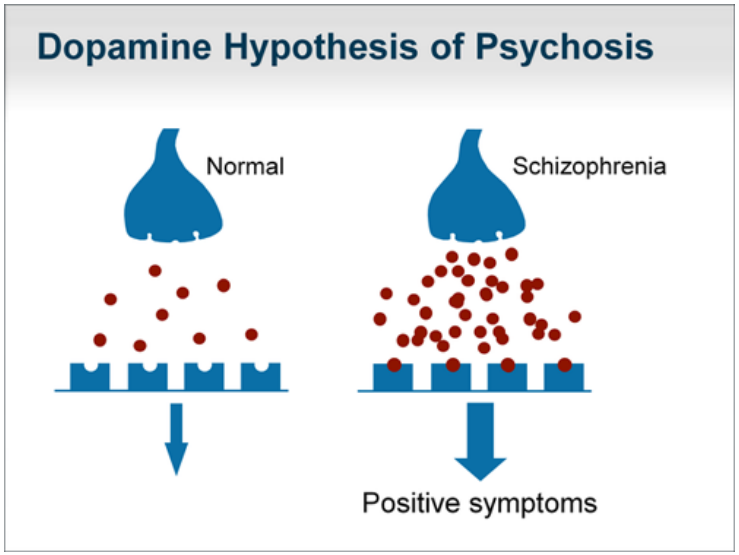


Bipolar Disorders, 2015 http://bipolarsymptoms.com/schizophrenia-symptoms/

Examples of Designing Compounds That Get into the Brain

Schizophrenia

- Majority of drugs focus on dopaminergic receptors such as D2 and serotonin receptor 5-HT2a.



- Approaches have emerged that involve non-dopaminergic receptors

Research Directions in Schizophrenia Treatment: Mechanisms of Action for Next-Generation Agents
https://www.medscape.org

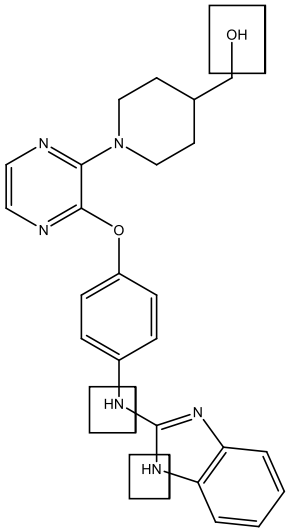
First generation vs second generation antipsychotics

- First generation (typical) medications
  - Focused on dopamine antagonism
  - Effective against the positive effects of schizophrenia
  - Due to involvement of dopamine in movement may have motor side effects
- Second generation (atypical) medications
  - Focus on non-dopaminergic pathways
  - Have effects on negative symptoms
  - Side effect profile is more favorable

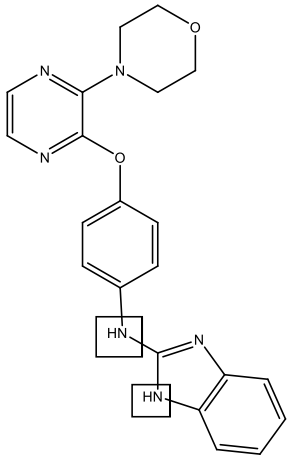
Phosphodiesterase 10 Inhibitors

- PDE10A highly expressed in the medium neuron of the striatum which is the region most associated with schizophrenia
- PDE10 inhibitors may be useful treating all three major symptoms of schizophrenia
- Targets cAMP and cGMP and not dopamine
- Potentially devoid of some of the side effects associated with agents directly acting on dopaminergic receptors

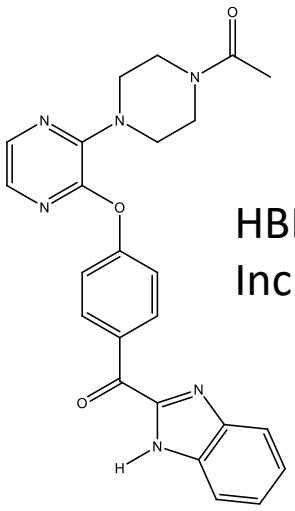
PDE10 Inhibitors -Reducing HBD



HBD = 3
Poor brain exposure



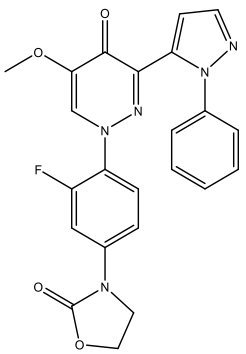
HBD = 2



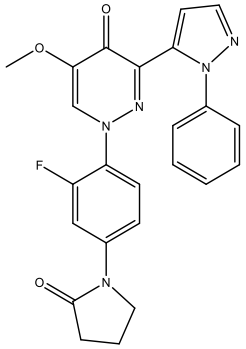
HBD = 1
Increase brain levels

Eur. J. Med. Chem. **2021**, 214, 113155
J. Med. Chem. **2013**, 56, 8781-8792

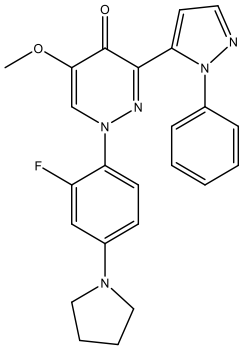
PDE10 Inhibitors – PSA, LogD, and P-gp



TPSA = 91
ER = 6.2

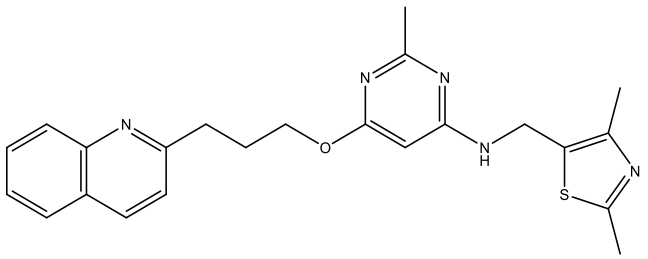


TPSA = 82
ER = 2.0



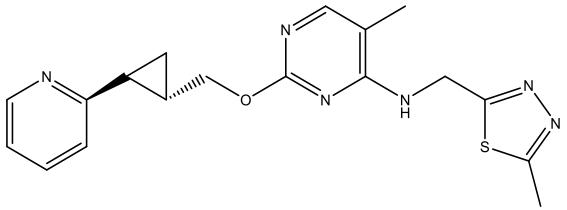
TPSA = 65
ER = 0.56

Biorg. Med. Chem. **2015**, 23, 7138-7149



LogD = 3.3

Improve lipophilicity and
P-gp affinity



LogD = 2.1

Currently in Phase 2b clinical trials

J. Med. Chem. **2023**, 66, 1157 - 1171

Intranasal Delivery and the Blood Brain Barrier

- Intranasal Route
  - Decreased levels of brain-derived neurotrophic factor (BDNF) has been implicated in schizophrenia
  - Intranasal administration of BDNF improves symptoms in *in vivo* models
- Blood brain barrier integrity
  - Breakdown of the blood brain barrier may be involved in the development of schizophrenia
  - 22q11.2 deletion syndrome – compromised BBB and increased incidence of developing the disease
  - Imatinib (Abl kinase inhibitor) restores function of BBB

Cells, **2023**, 12, 422
J.Psych.Res. **2022,** 156, 538

Summary

- The blood brain barrier prevents most small molecules from entering the brain
- Chemists have a variety of predictive tools that they employ to design compounds that can get into the brain
- Transporters can be utilized to shuttle drugs into the brain
- New methods involving fusion of antibodies, nose to brain technologies, and nanotechnology will aid in the future delivery of drugs

References

Blood brain barrier-on-a-chip to model neurological diseases. J. Drug Del. Sci. Tech. **2023**, 80, 104174

Nanotechnology Approaches for Enhanced CNS Drug Delivery in the Management of Schizophrenia. Adv. Pharm. Bull. **2022**, 490-508

Strategies for Structural Modification of Small Molecules to Improve Blood-Brain Barrier Penetration: A Recent Perspective J. Med. Chem. **2021**, 64, 13152 – 13173.

Prodrug Strategy for enhanced therapy of central nervous system disease. Chem. Comm. **2021,** 57, 8842.

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Computational modeling in glioblastoma: from the prediction of blood-brain barrier permeability to the simulation of tumor behavior. Miranda, Ana; Cova, Tania; Sousa, Joao; Vitorino, Carla; Pais, Alberto Future Medicinal Chemistry **2018**, 10, 121-131.

Demonstration of Direct Nose-to-Brain Transport of Unbound HIV-1 Replication Inhibitor DB213 Via Intranasal Administration by Pharmacokinetic Modeling. Wang, Qianwen; Zhang, Yufeng; Wong, Chun-Ho; Edwin Chan, H. Y.; Zuo, Zhong AAPS Journal **2018**, 20, 1-11.

The Blood Brain Barrier and its Role in Alzheimer's Therapy: An Overview. Current drug targets **2018**, 19, 155-169.

Current State and Future Perspectives in QSAR Models to Predict Blood-Brain Barrier penetration in Central Nervous System Drug R&D. Mini-Rev. in Med. Chem. **2017**, 17, 247-257.

CNS Drug Design: Balancing Physicochemical properties for Optimal Brain Exposure. J. Med. Chem, 2015, **58**, 2584-2609

Recent Advances in Delivery Through the Blood-Brain Barrier. Curr. Topics in Med. Chem. **2014**, 14, 1148-1160.

Demystifying Brain Penetration in Central Nervous System Drug Discovery. J. Med. Chem. **2013**, 56, 2-12.

Questions

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