

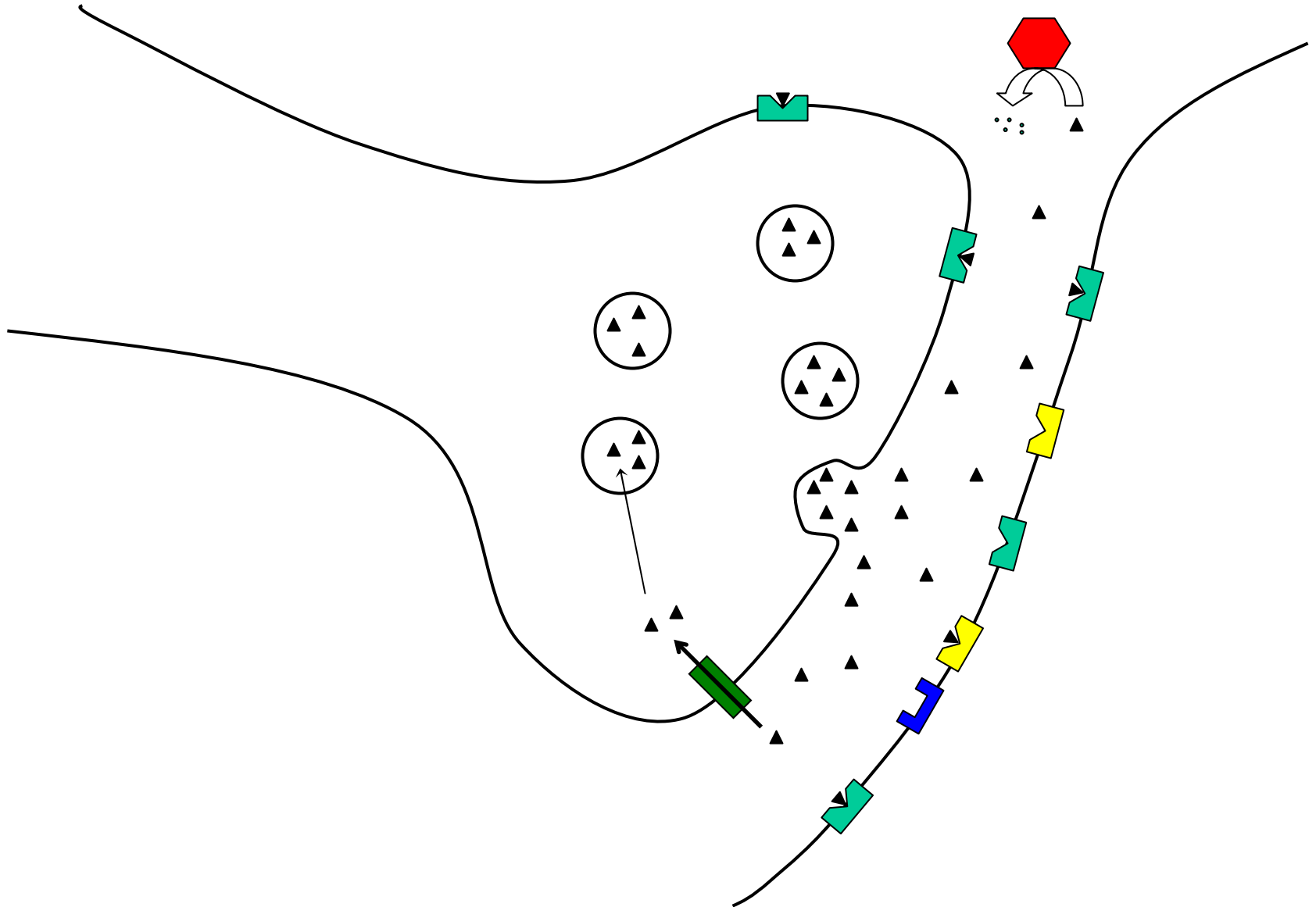
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<http://ocw.mit.edu>

SP.236 / ESG.SP236 Exploring Pharmacology  
Spring 2009

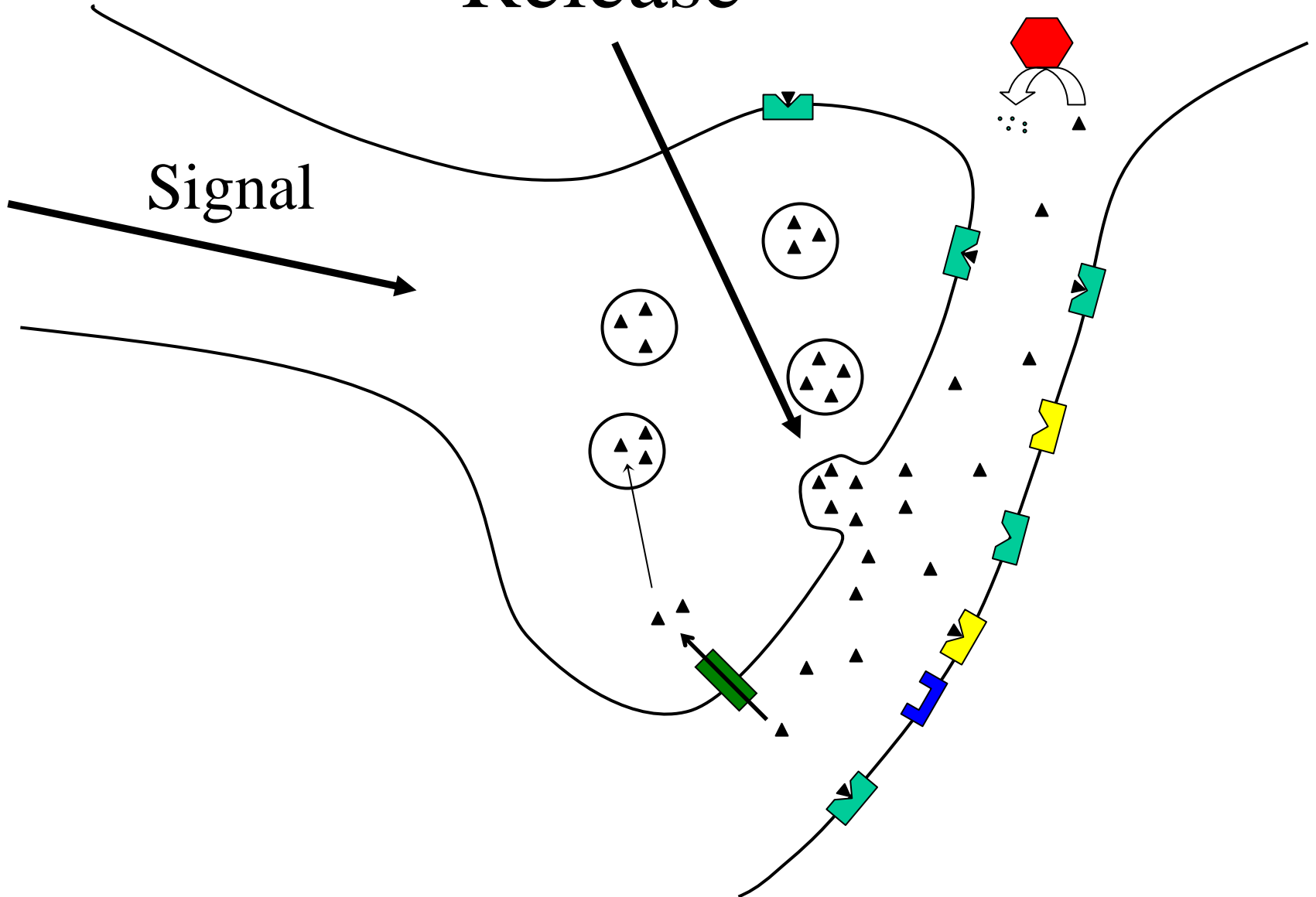
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# How the Brain Works

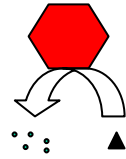
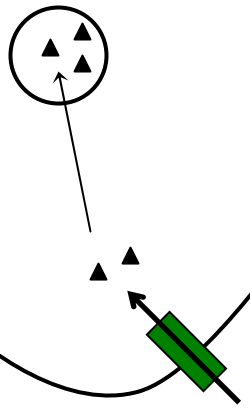
# Background: The Synapse

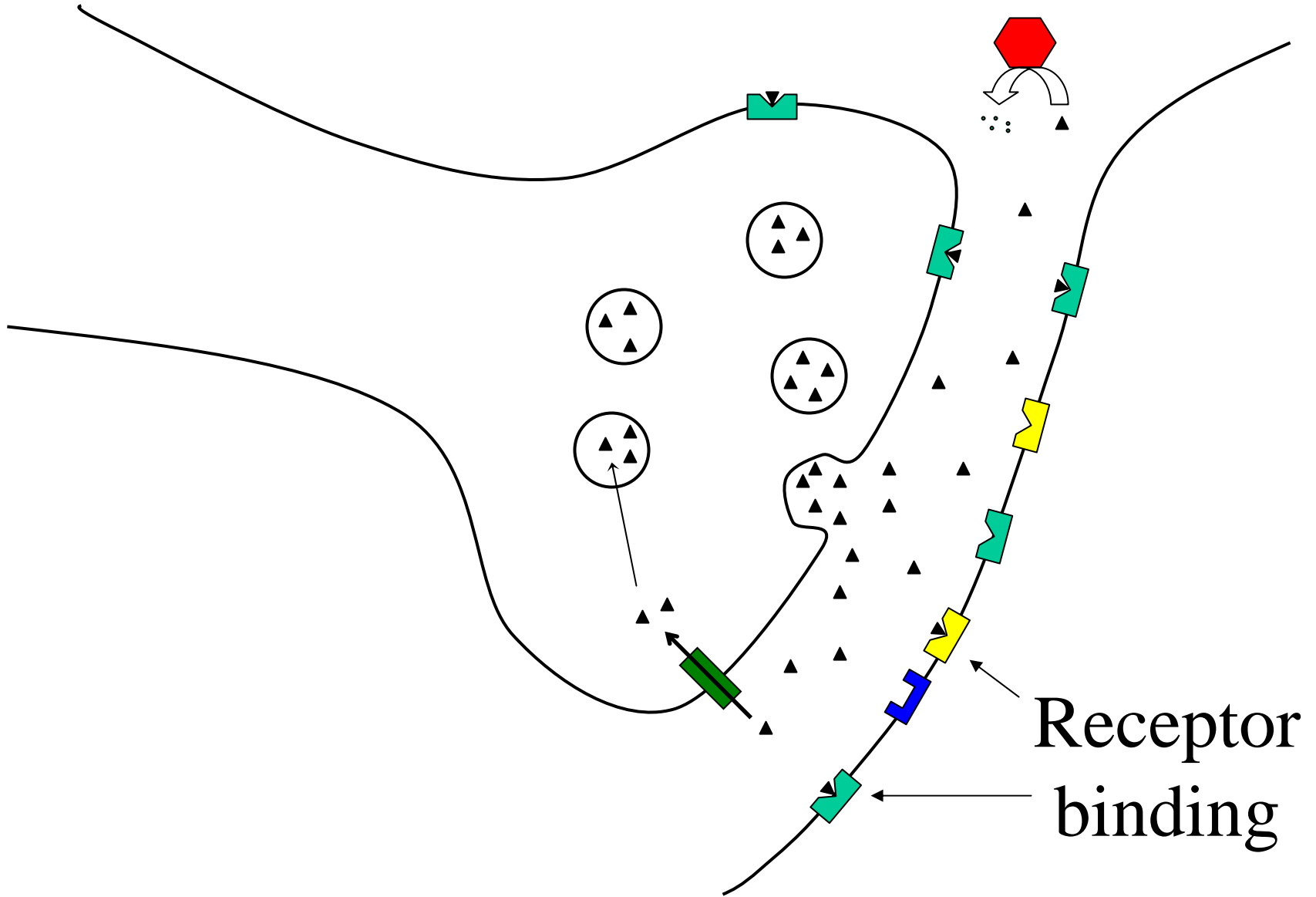


# Release



Signal





## Receptors:

Excitatory: Sends signals (action potentials)

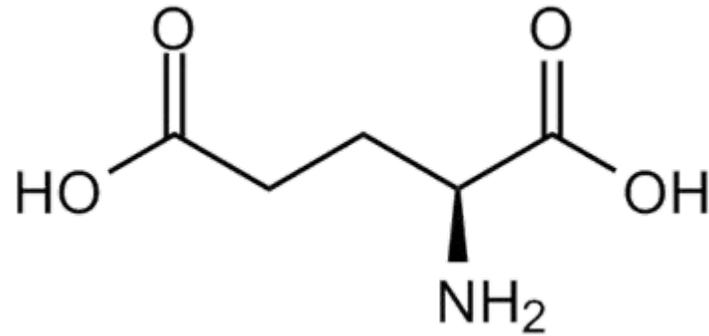
Inhibitory: Blocks signals

## Drugs, neurotransmitters, and other ligands:

Agonists: Stimulate receptors, mimic the neurotransmitter

Antagonists: Block receptors

# Glutamate

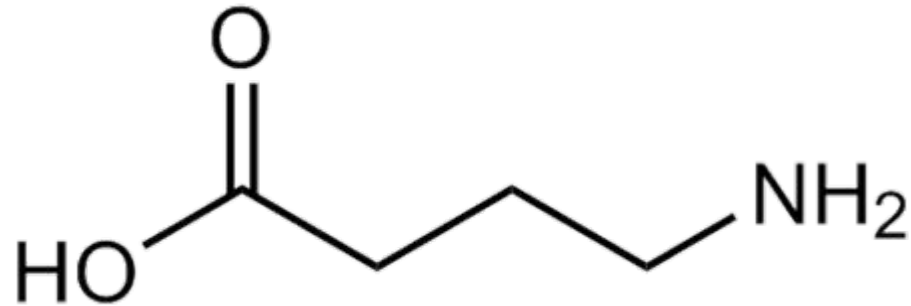


The most common excitatory neurotransmitter  
Glutamate is released by 80% of neurons

Learning

Memory

# GABA



The most common inhibitory neurotransmitter  
in the brain

Sleep

Muscle relaxation

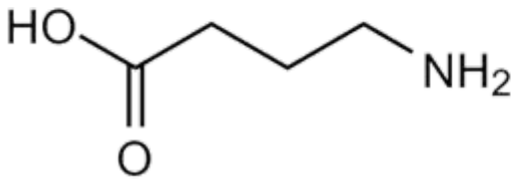
Anxiety relief

Impairs memory



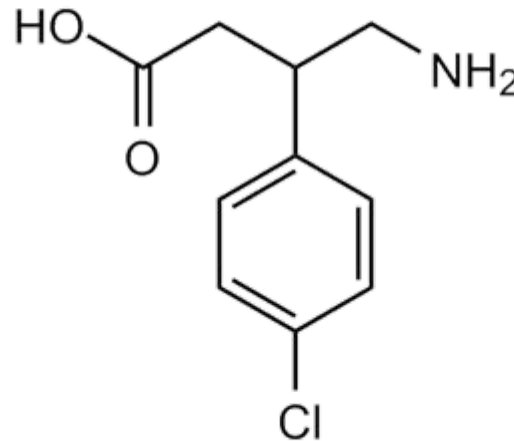
# How drugs mimic neurotransmitters: Drugs look like chemicals normally found in your body

GABA



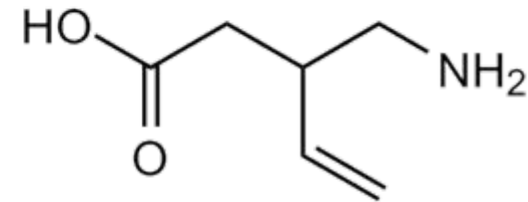
Neurotransmitter

Baclofen  
GABA Agonist  
(mimics GABA)



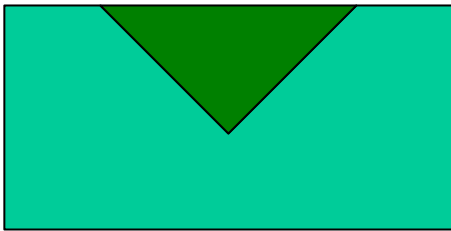
Drug

Vigabatrin  
Inhibits GABA  
breakdown

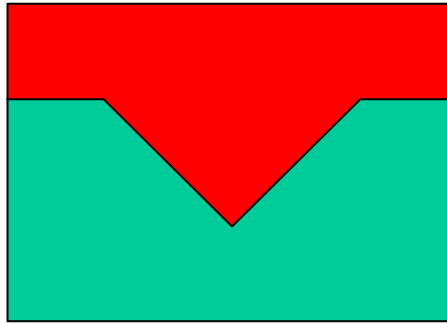


Drug

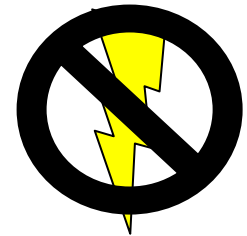
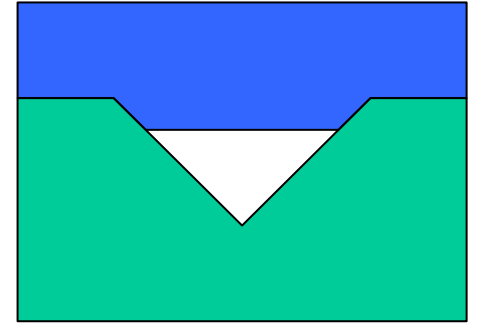
# Agonists and Antagonists



Neurotransmitter

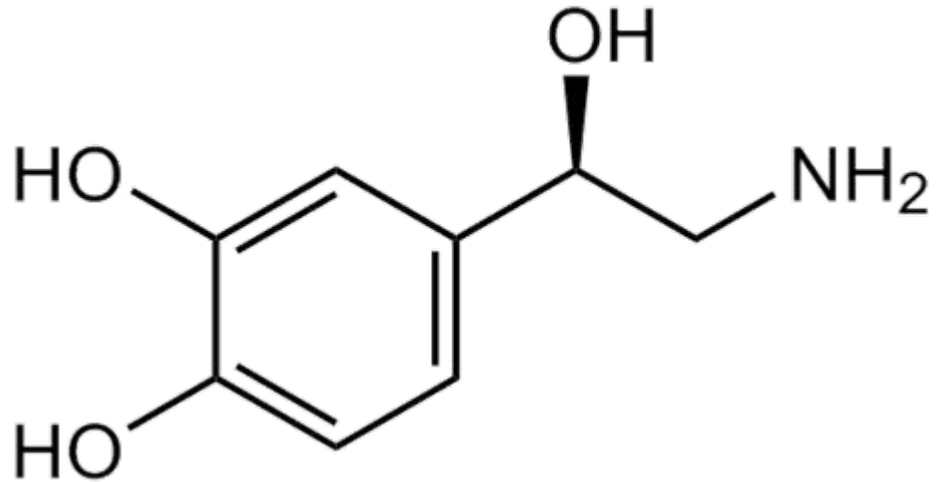


Agonist (drug)



Antagonist (drug)

# Norepinephrine



Fight or Flight

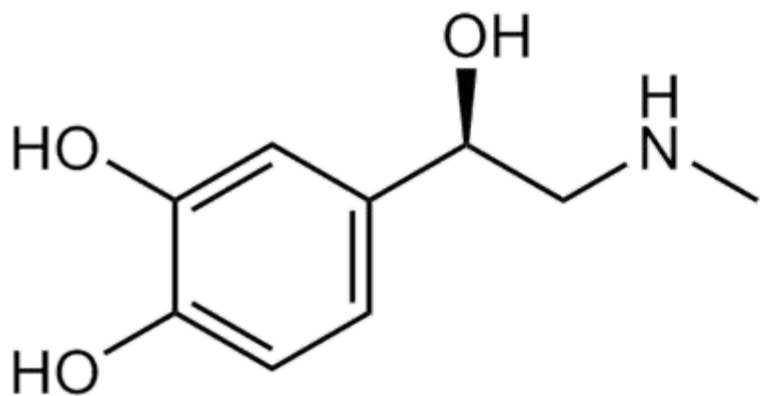
Increases heart rate

Excitement

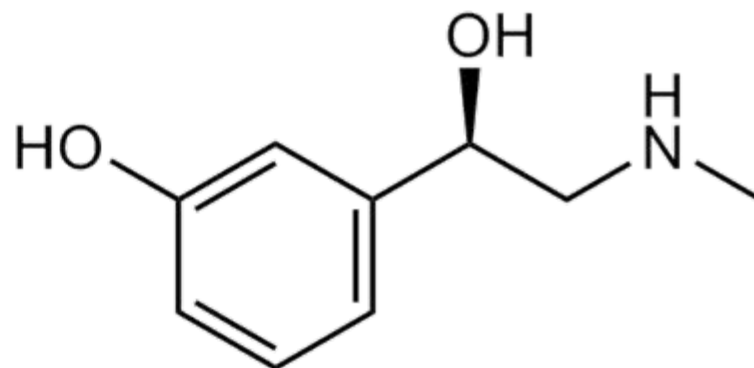
Fear

# Epinephrine and phenylephrine

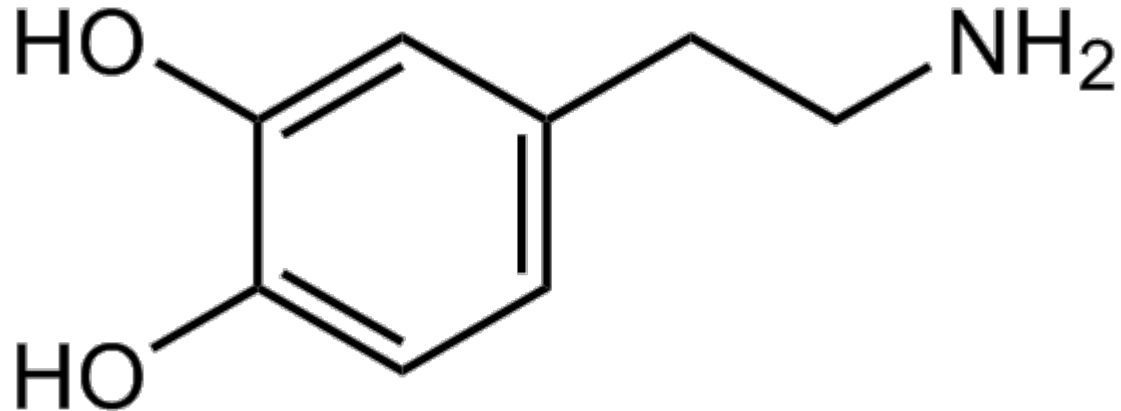
Epinephrine  
Adrenaline



Phenylephrine



# Dopamine

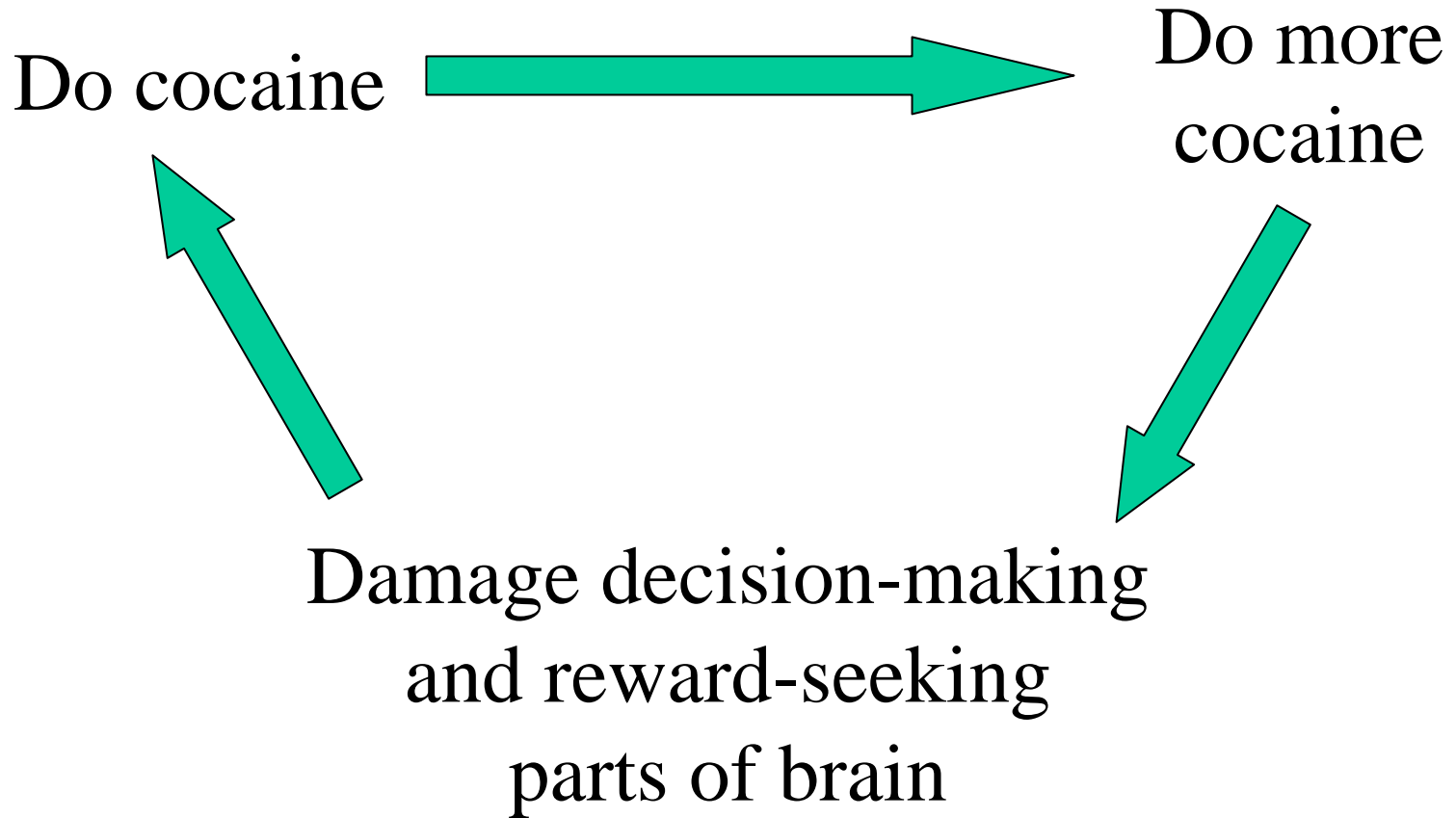


The Salience Neurotransmitter

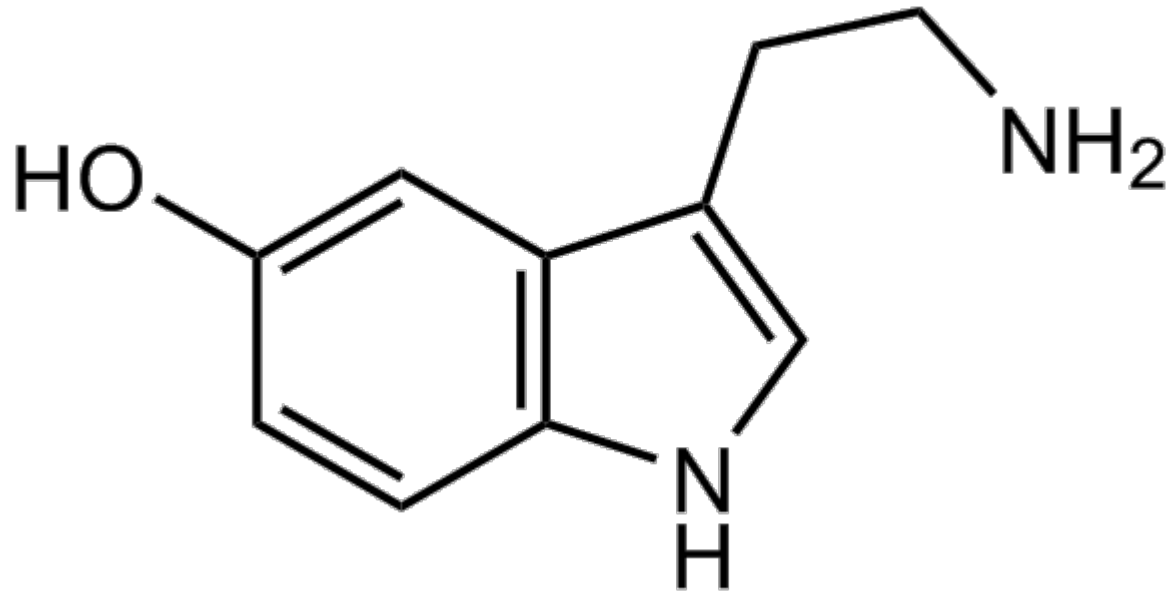
Rewards sex, eating

Increases alertness, happiness

# Addiction



# Serotonin (5-HT)



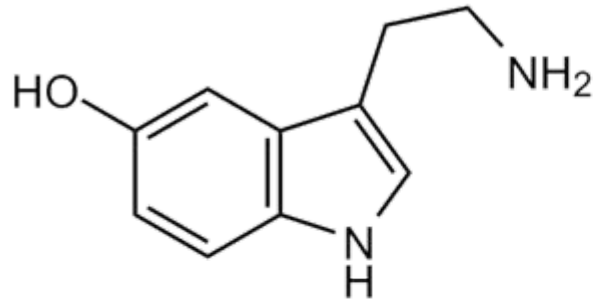
The Satiety Neurotransmitter

Feelings of fullness, contentment

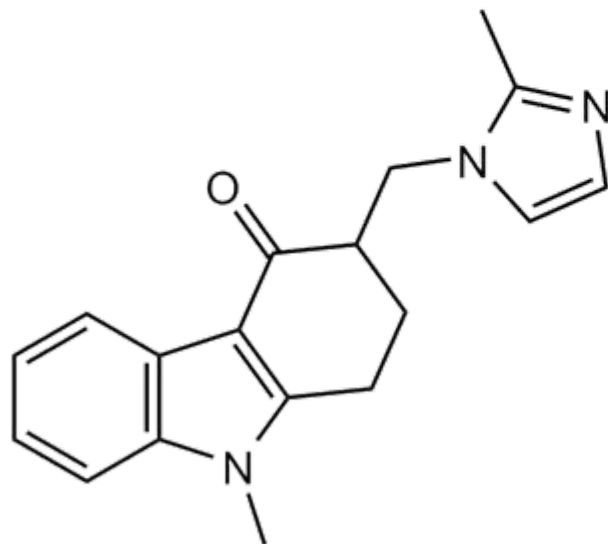
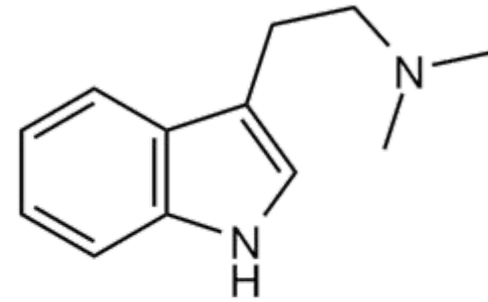
Relieves depression

Serotonergic drugs I

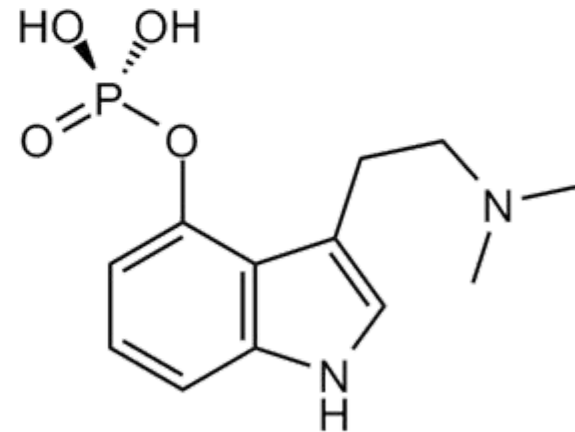
Serotonin



Dimethyltryptamine  
DMT



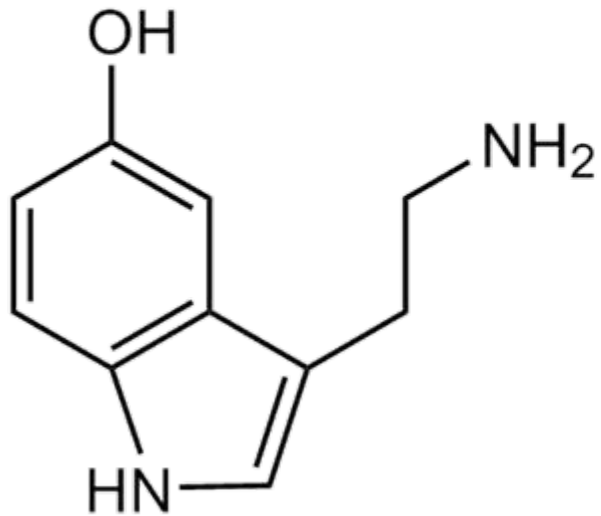
Ondansetron  
Zofran



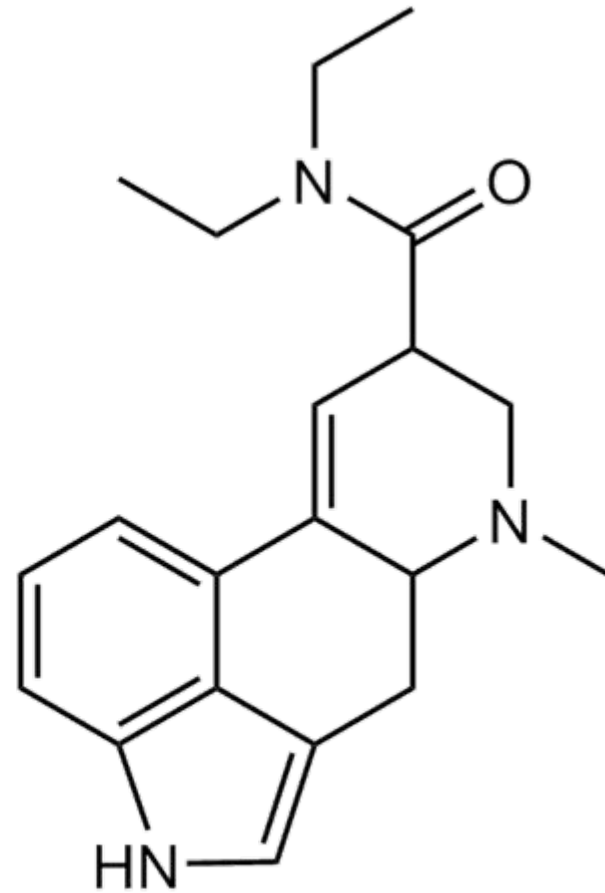
Psilocybin



Serotonergic drugs II



Serotonin



Lysergic Acid Diethylamide

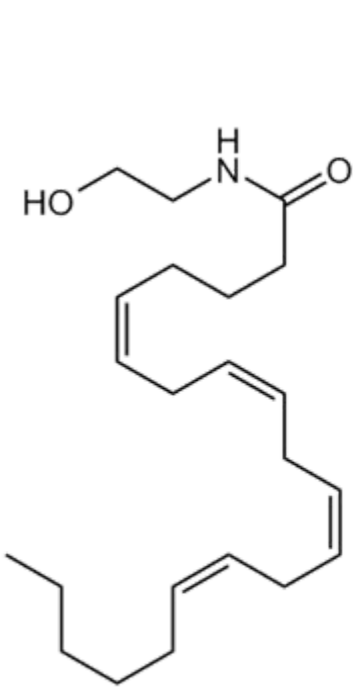
# Sedatives

- Examples: Alcohol, Valium
- Relieve anxiety, induce sleep
- Antipunishment effect:

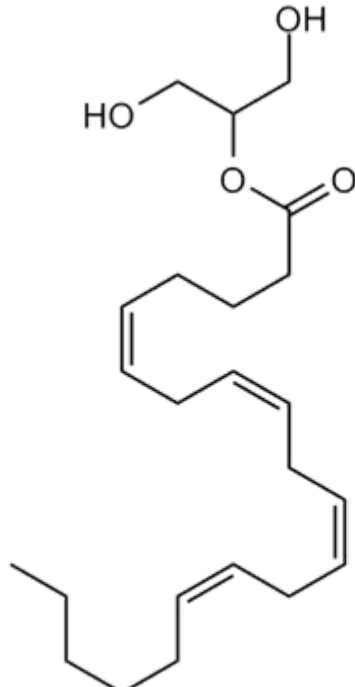
Enables fearful people to board airplanes, speak in public, ride in elevators

Causes normal people to have unprotected sex, drive drunk, do dangerous and stupid things

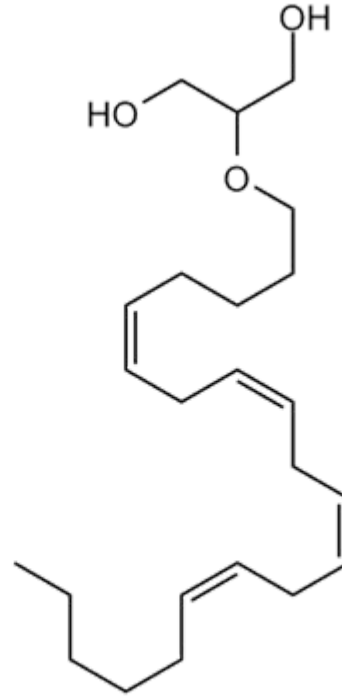
# Cannabinoids



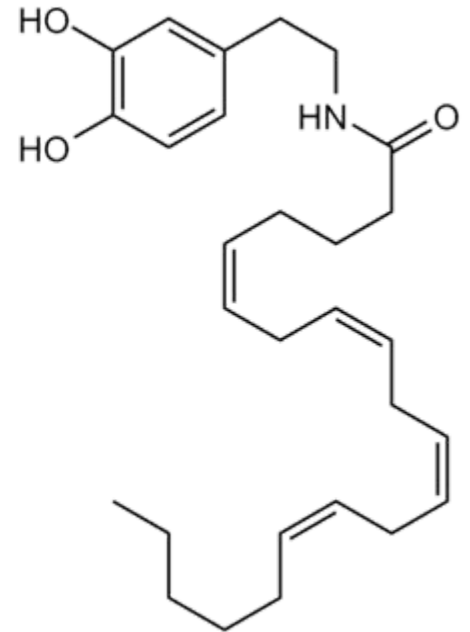
Anandamide



2-AG



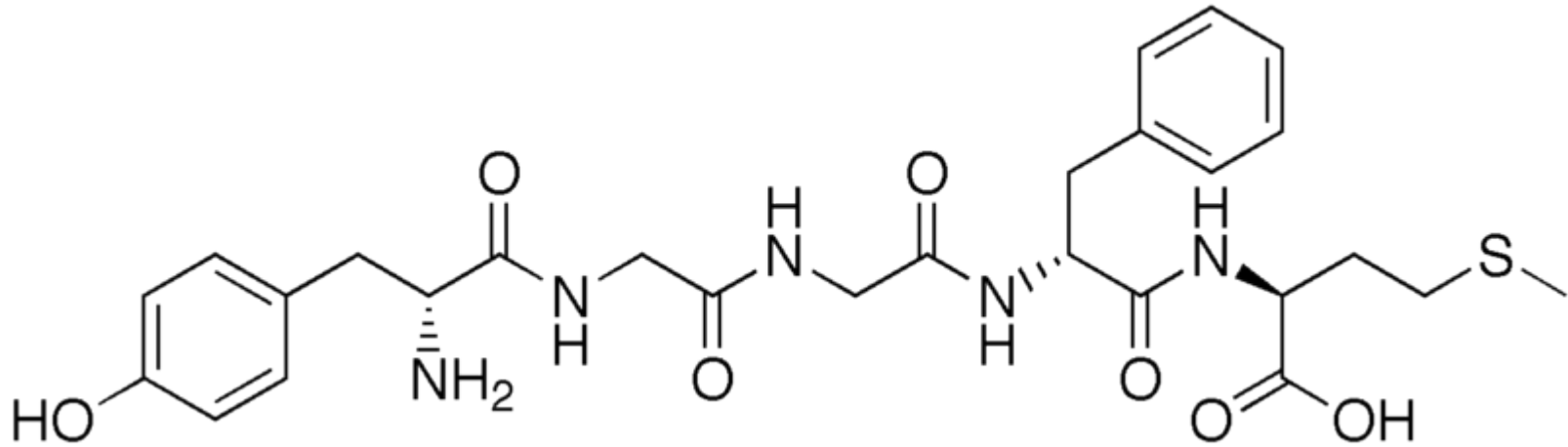
2-AGE



NADA

Marijuana mimics these molecules in the brain

# Opioids



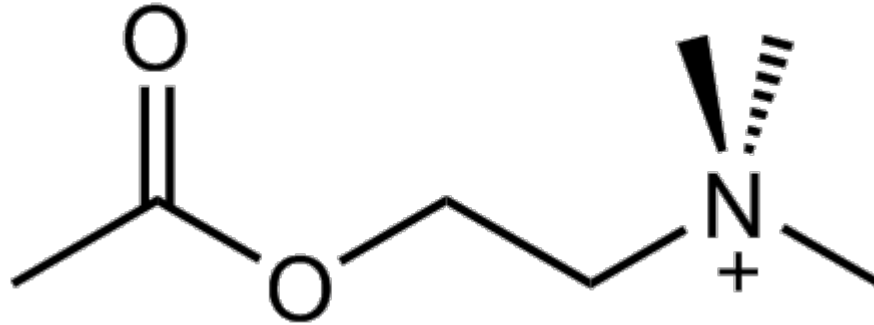
Morphine mimics these

Relieve pain and worry

Induce sleep

Slow digestive tract

# Acetylcholine (ACh)



Nicotine mimics this

Alertness

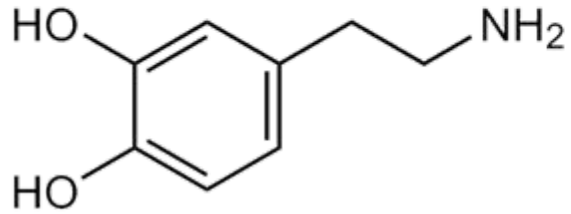
Memory

Moves muscles

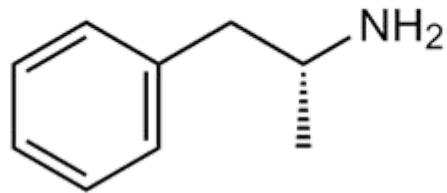
Causes secretions (saliva, sweat)

# Dopaminergic and cholinergic drugs

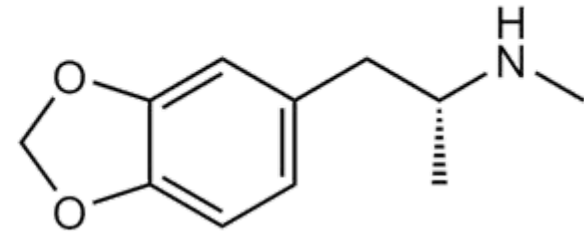
## Dopamine



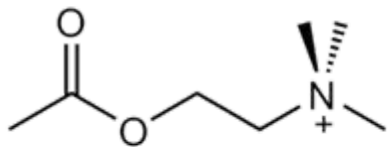
## Amphetamine



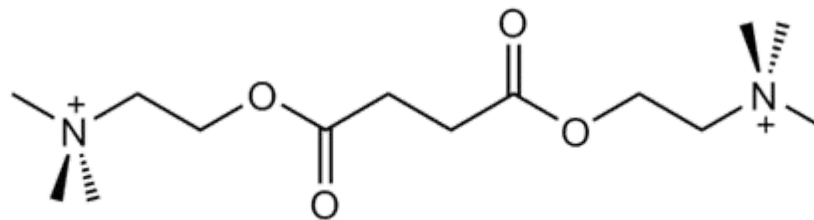
## MDMA (Ecstasy)



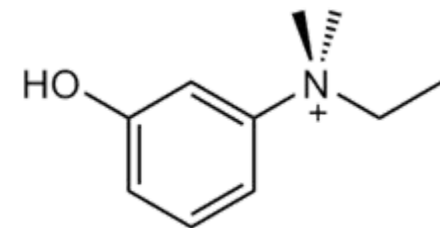
## Acetylcholine



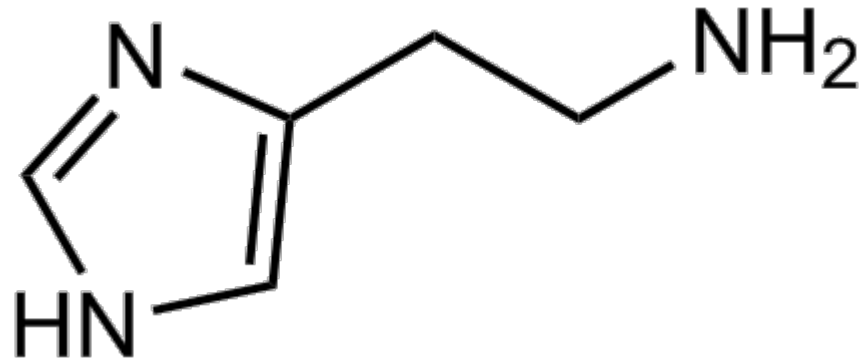
## Succinylcholine



## Edrophonium



# Histamine



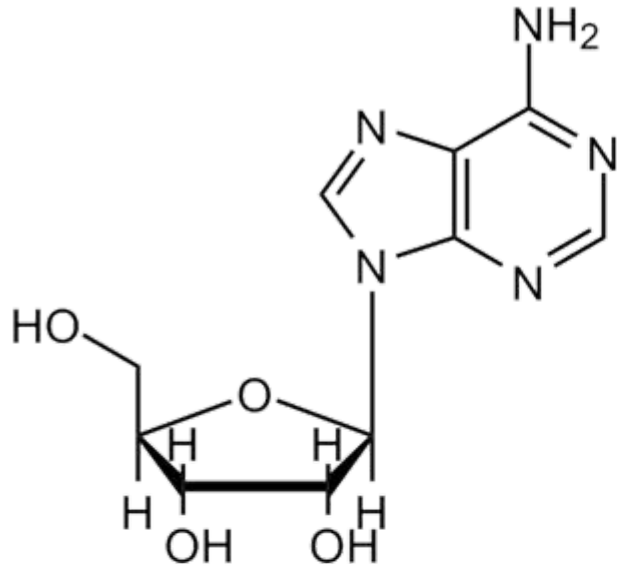
Alertness

Itchiness

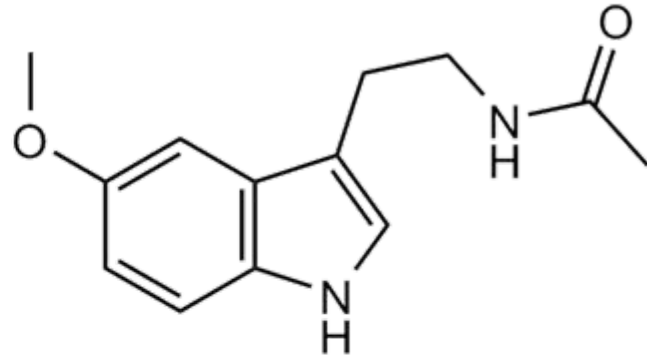
Rashes

Causes stomach acid secretion

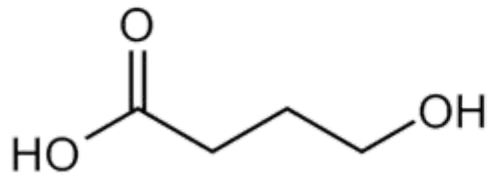
# Other small neurotransmitters



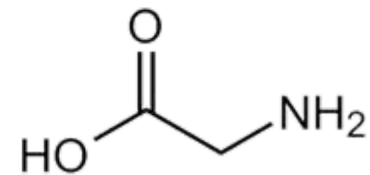
Adenosine



Melatonin



GHB

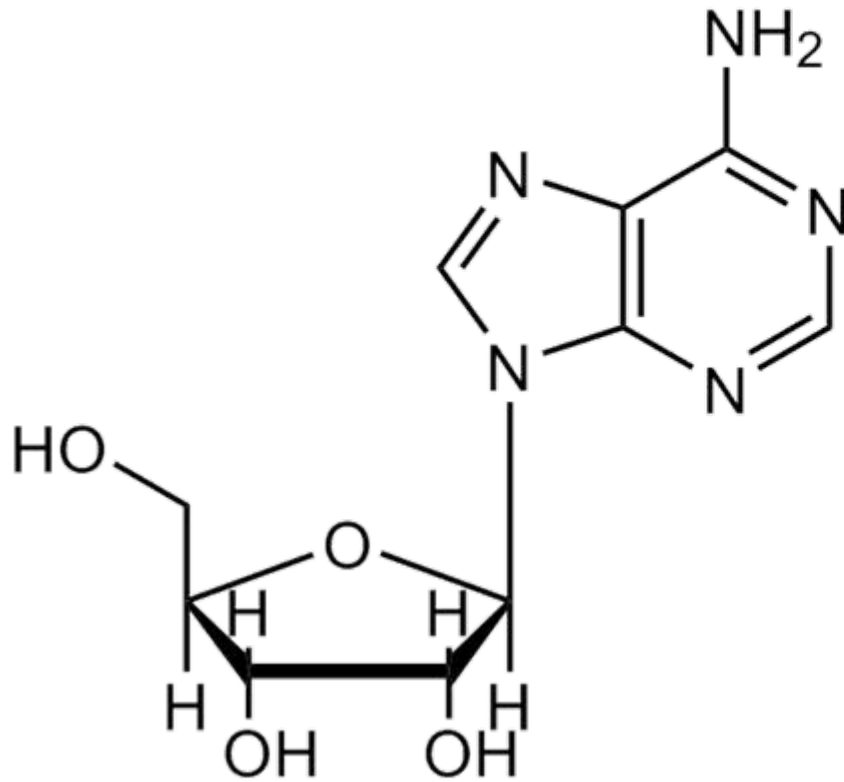


Glycine

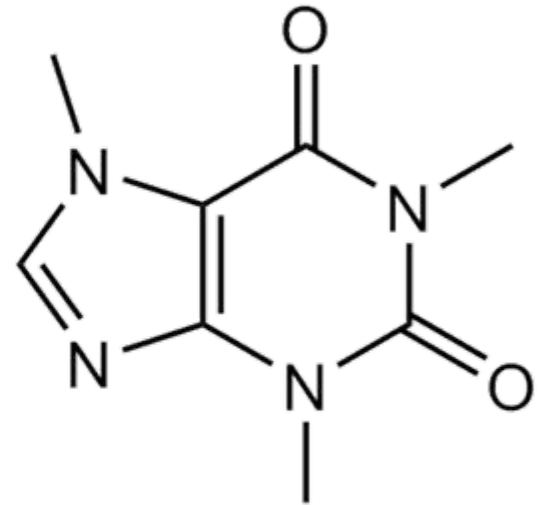


# Adenosine and caffeine

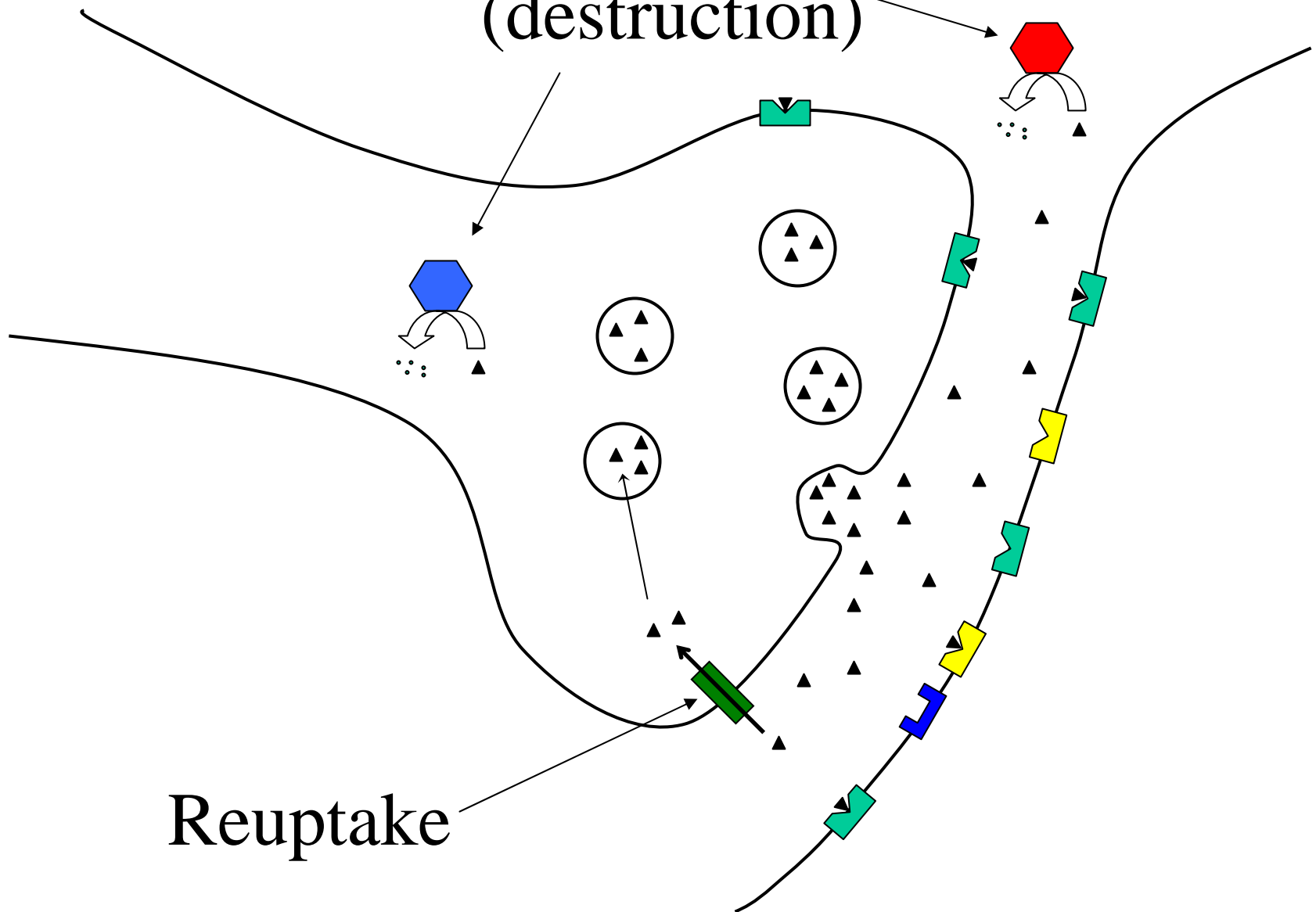
## Adenosine



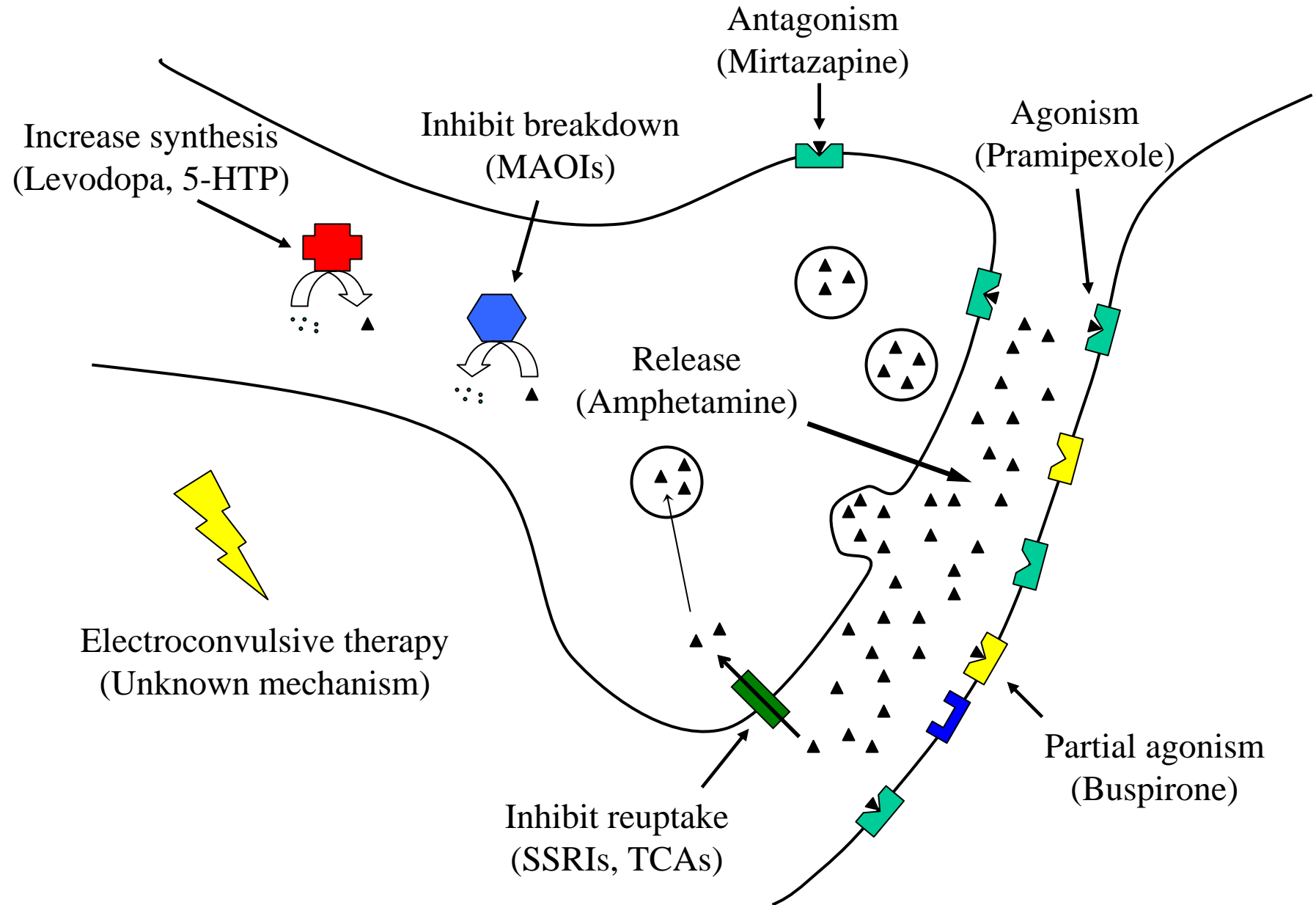
## Caffeine



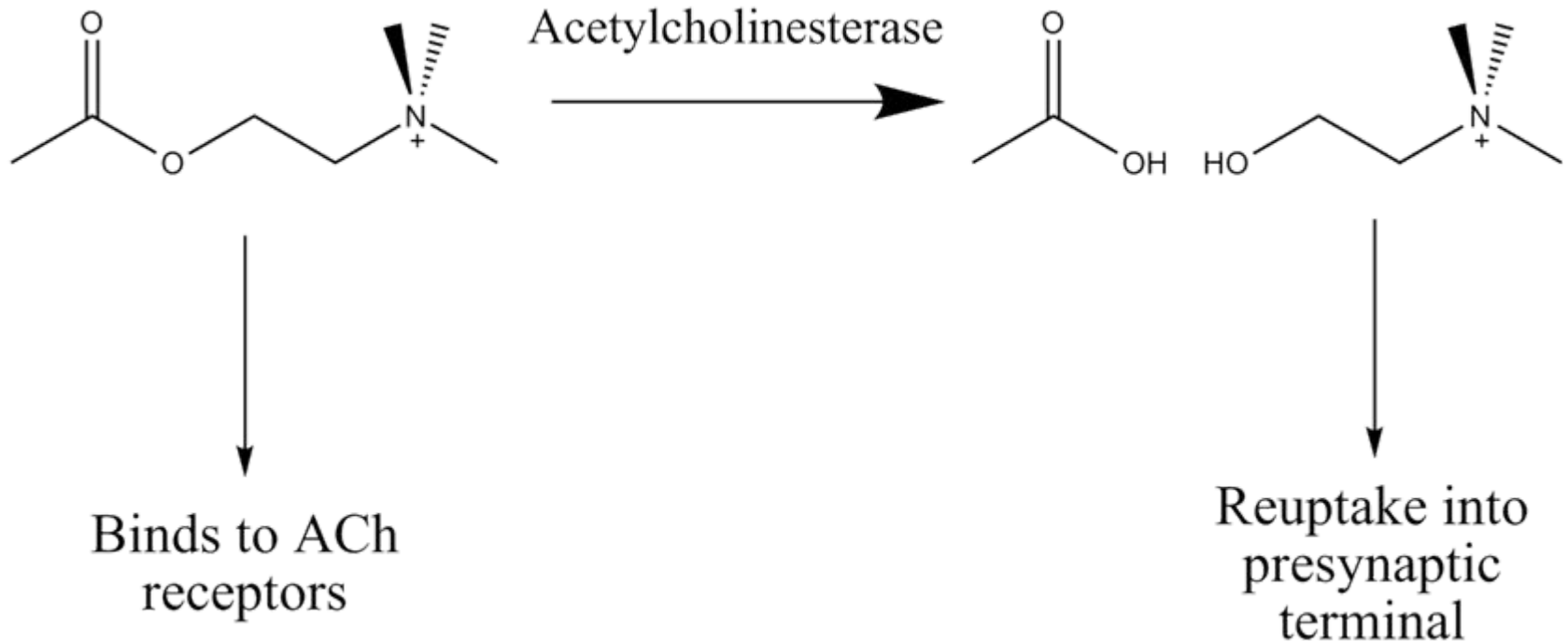
Metabolism  
(destruction)



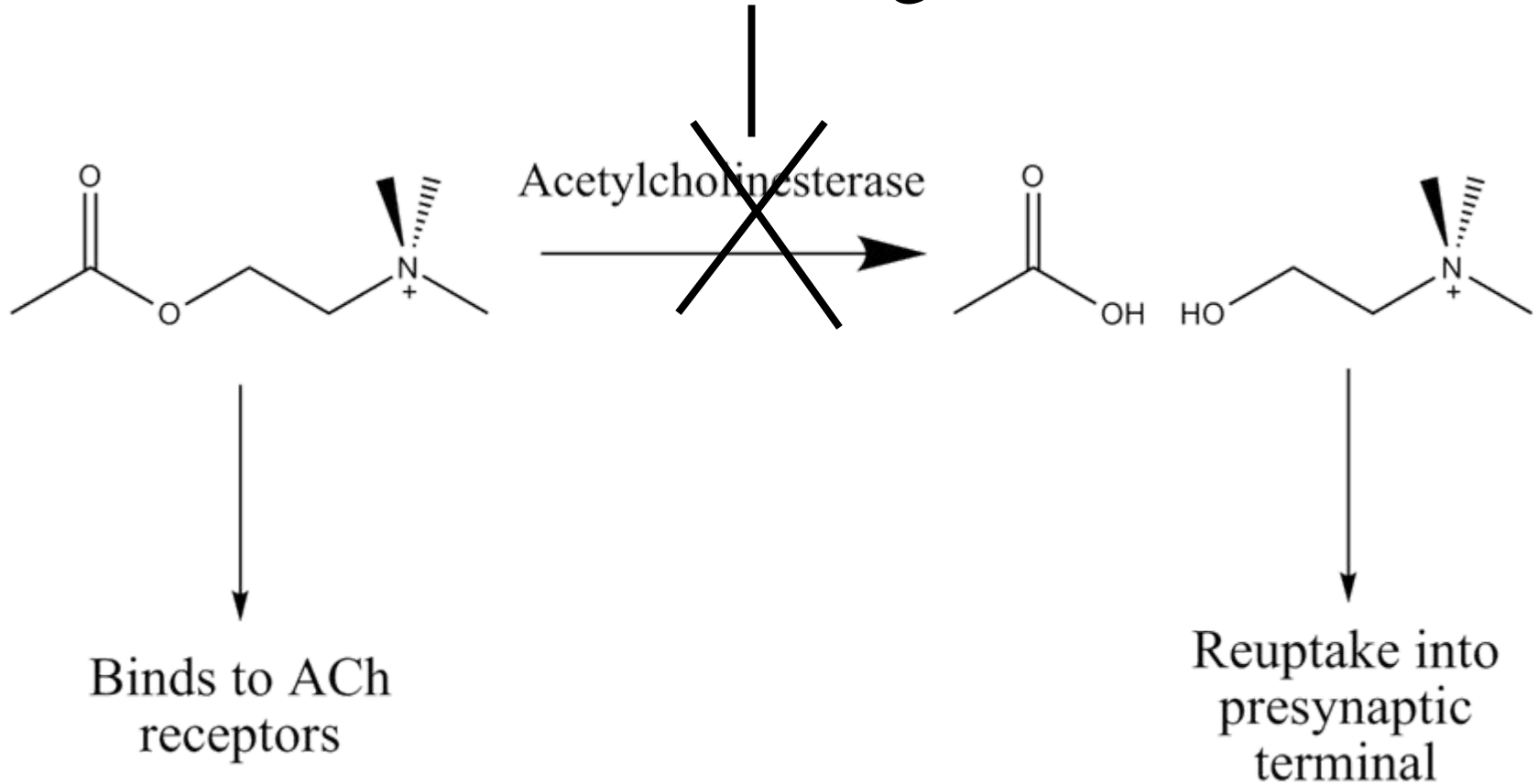
# Antidepressant Mechanisms



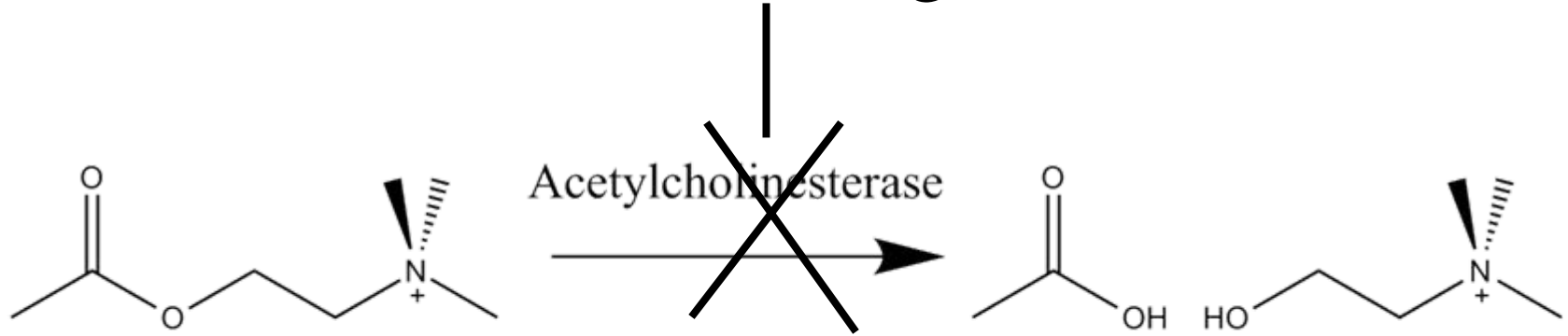
# Acetylcholine (ACh)



# VX nerve gas



# VX nerve gas

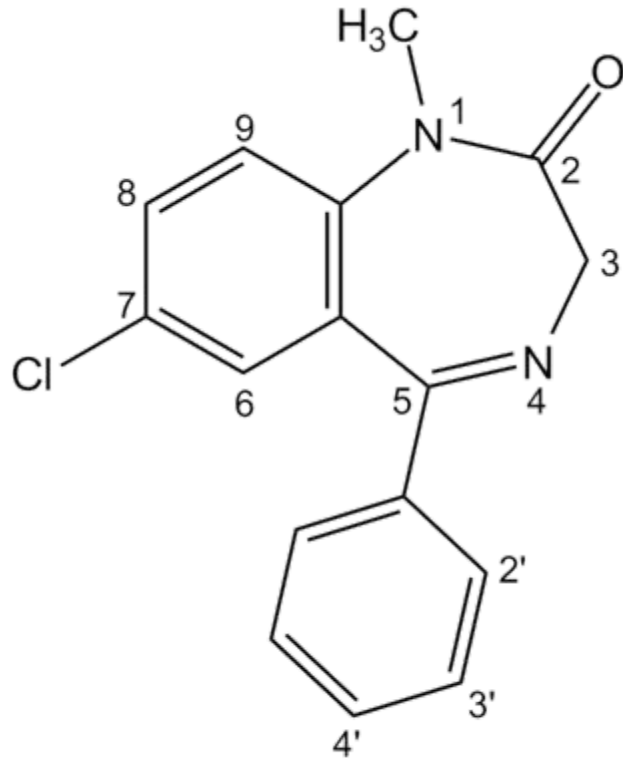


~~Binds to ACh receptors~~

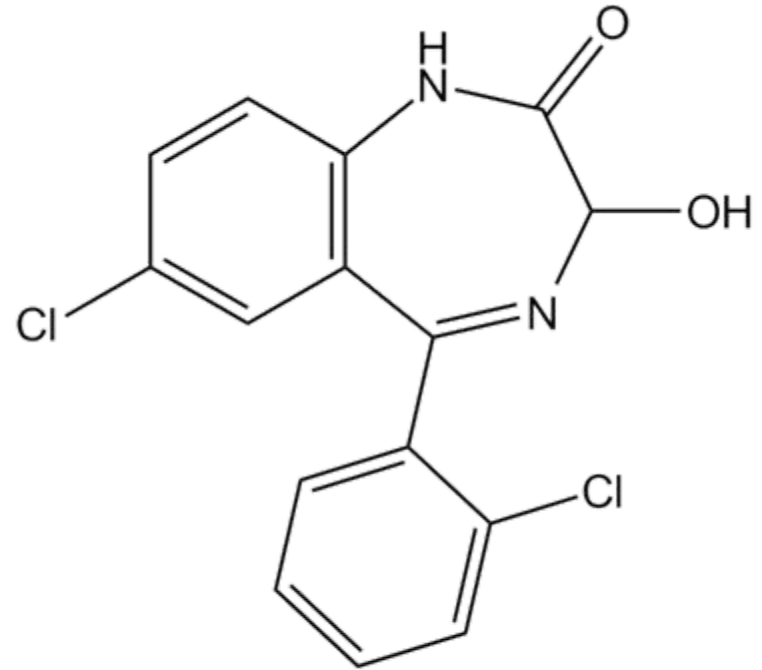
BZ (anticholinergic)

Reuptake into presynaptic terminal

# Benzodiazepine receptor ligands



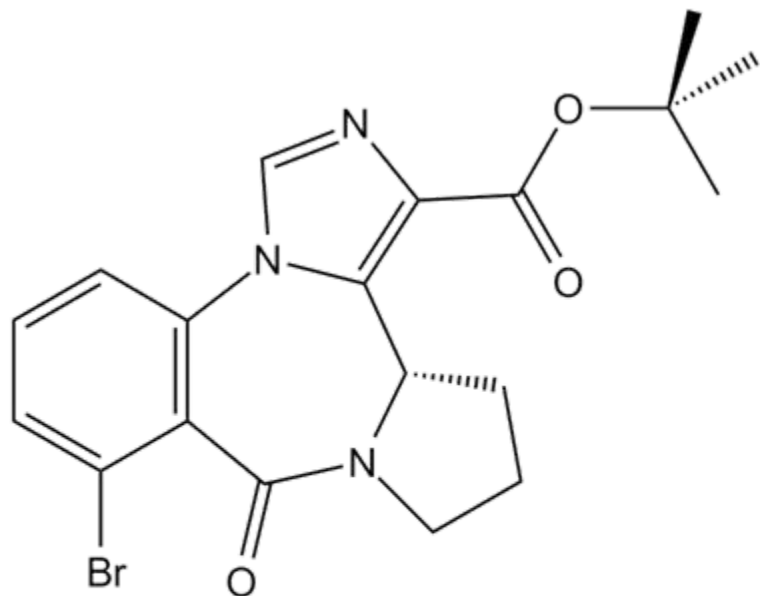
Diazepam



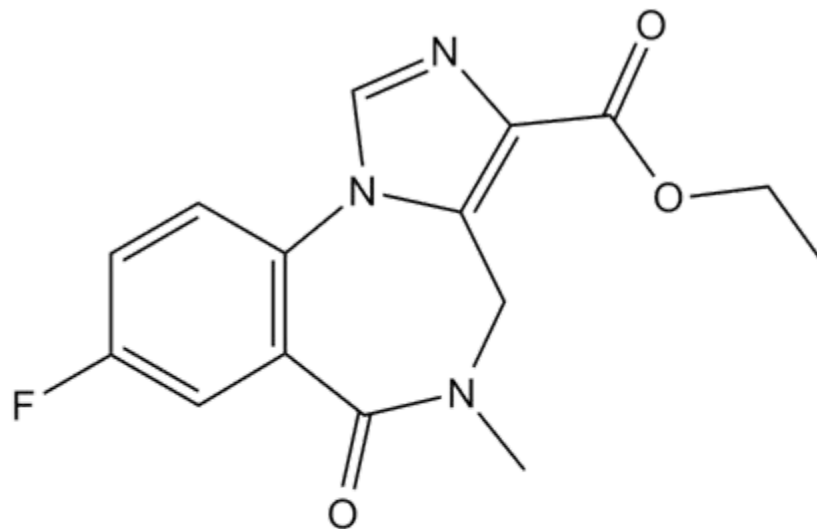
Lorazepam

Full agonists

# Benzodiazepine receptor ligands



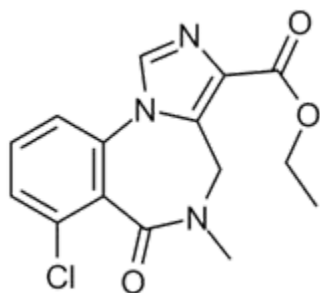
**Figure 5:** Bretazenil,  
a partial agonist



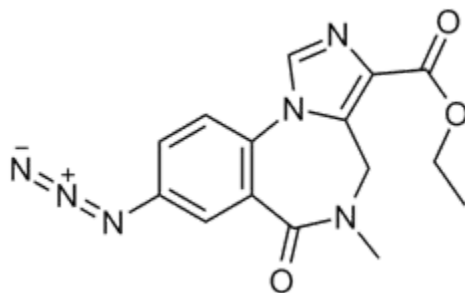
**Figure 6:** Flumazenil,  
an antagonist



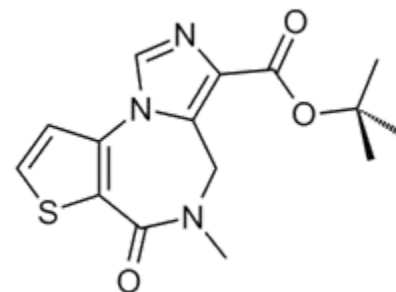
# Benzodiazepine receptor ligands



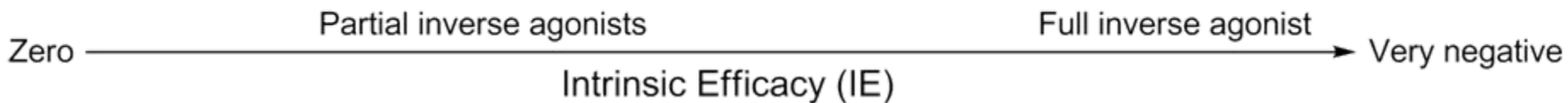
**Figure 7:** Sarmazenil,  
Ro 15-3505



**Figure 8:** Ro 15-4513

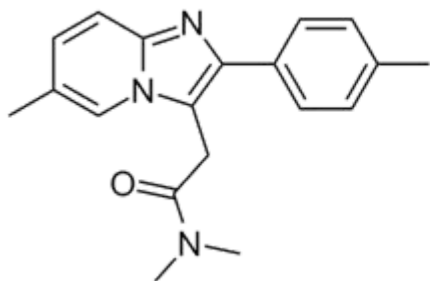


**Figure 9:** Ro 19-4603



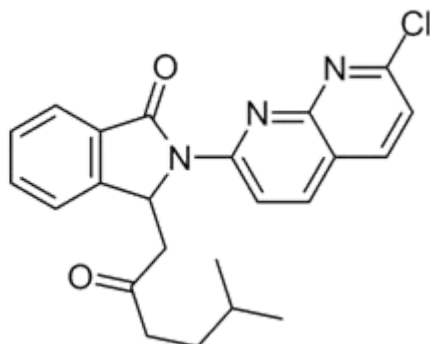
## Inverse agonists

# Benzodiazepine receptor ligands



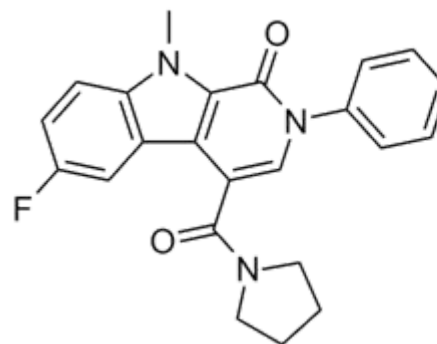
**8.1: Zolpidem**

$\alpha_1$	+++
$\alpha_2$	0
$\alpha_3$	0
$\alpha_5$	0



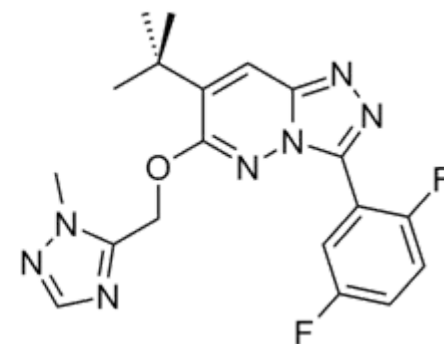
**8.2: Pagoclone**

$\alpha_1$	+
$\alpha_2$	+++
$\alpha_3$	+?
$\alpha_5$	+?



**8.3: SL 651498**

$\alpha_1$	+
$\alpha_2$	+++
$\alpha_3$	++
$\alpha_5$	+?



**8.4: L-838417**

$\alpha_1$	Antag.
$\alpha_2$	++
$\alpha_3$	++
$\alpha_5$	++

Selective agonists