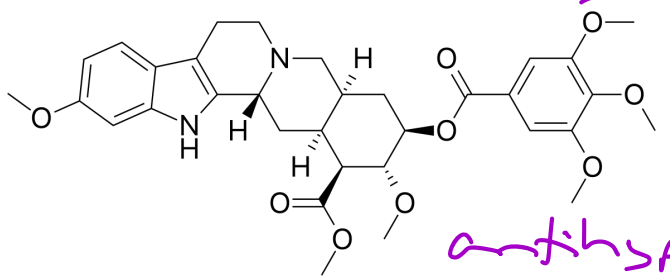
Antidepressants

Major Depression is one of the 4 major mood disorders

- hopelessness
- loss of mood reactivity

reserpine – 1950's studied as



antihypertensive

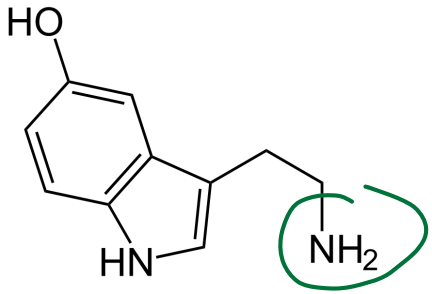
patients became depressed

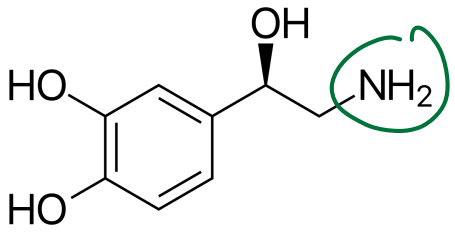
depletes NE

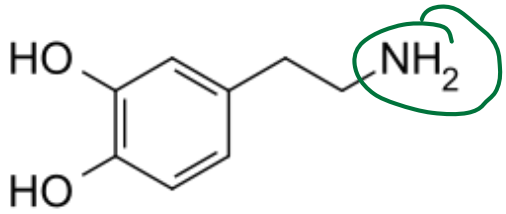
Monoamine Hypothesis (Biogenic Amine Hypothesis)

Deficiencies in NT's

5-HT, NE, DA

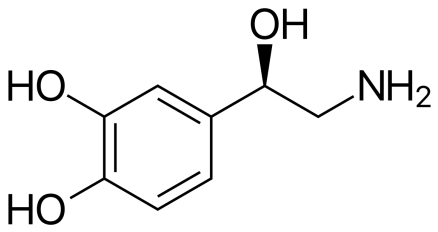


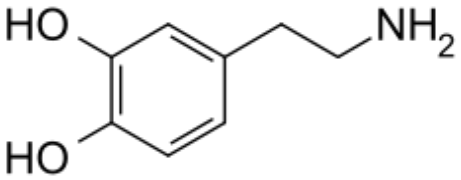




5-hydroxytryptamine (serotonin)

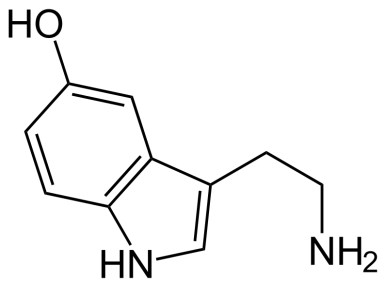
Catecholamine Hypothesis :

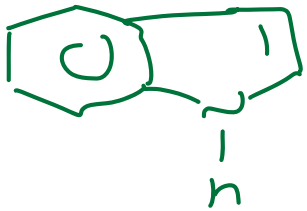




depression caused by low levels of NE + DA

Indole Amine Hypothesis :





not enough serotonin

Antidepressants 2 approaches

MAOI's 1) decrease the rate of metabolism

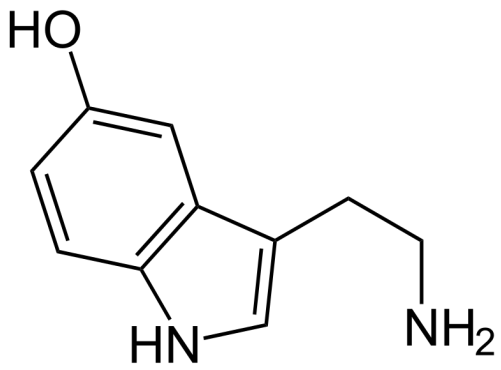
↑

monoamine oxidase inhibitors

Tricyclic antidepressants, reuptake inhibitors

2) decrease rate of reuptake

Serotonin (5-hydroxytryptamine; 5-HT)

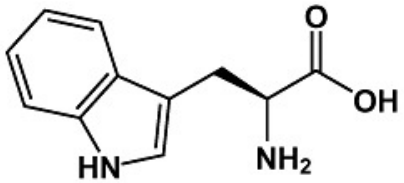


- NT
- found in smooth muscle
  cardiovascular
  GI
- has some involvement in
  slow wave sleep

low levels

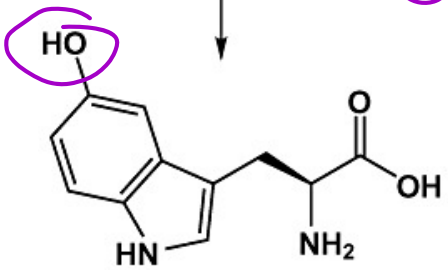
depression
problems controlling anger
OCD
trouble sleeping
carb cravings

Biosynthesis



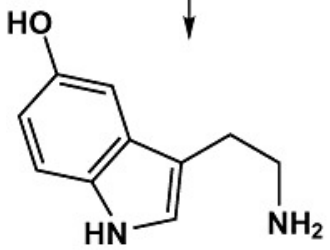
L-Tryptophan

TRH, TPH ○ Trp hydroxylase



5-Hydroxy-L-tryptophan (5-HTP)

AADC — Decarboxylase

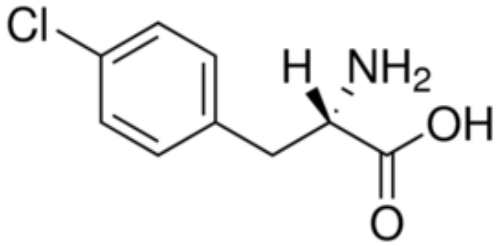


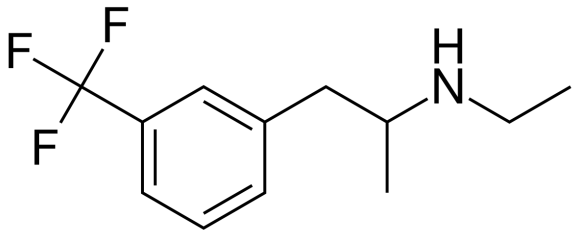
Serotonin (5-HT)

↑ stored in vesicles

Serotonin Synthesis Inhibitors

5-HT synthesis inhibitors act here

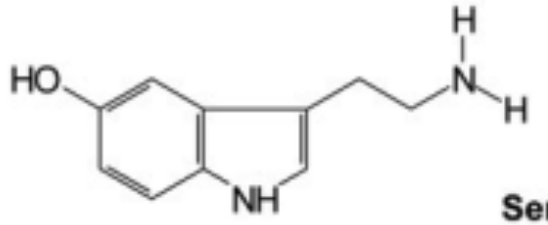




fenfluramine (appetite suppressant)

an anorectic —

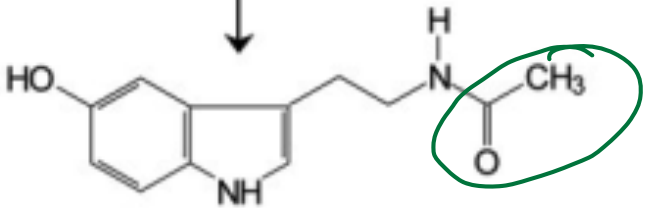
reduces appetite



Serotonin

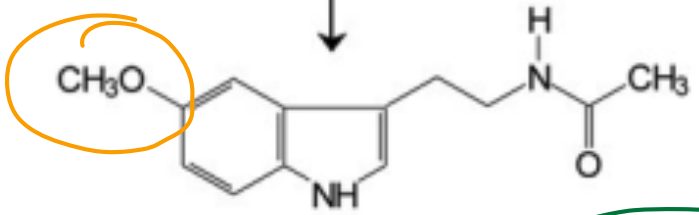
also used to make melatonin

acetylase



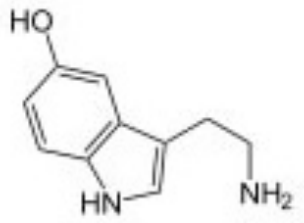
***N*-acetylserotonin**

O-methyl transferase



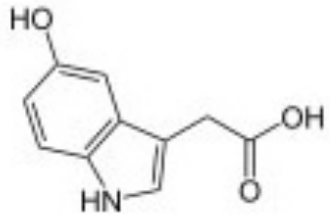
Melatonin promotes sleep onset

5-HT Deactivation — primarily be reuptake
some by MAO



5-HT

MAO



5-hydroxyindole-3-acetic acid

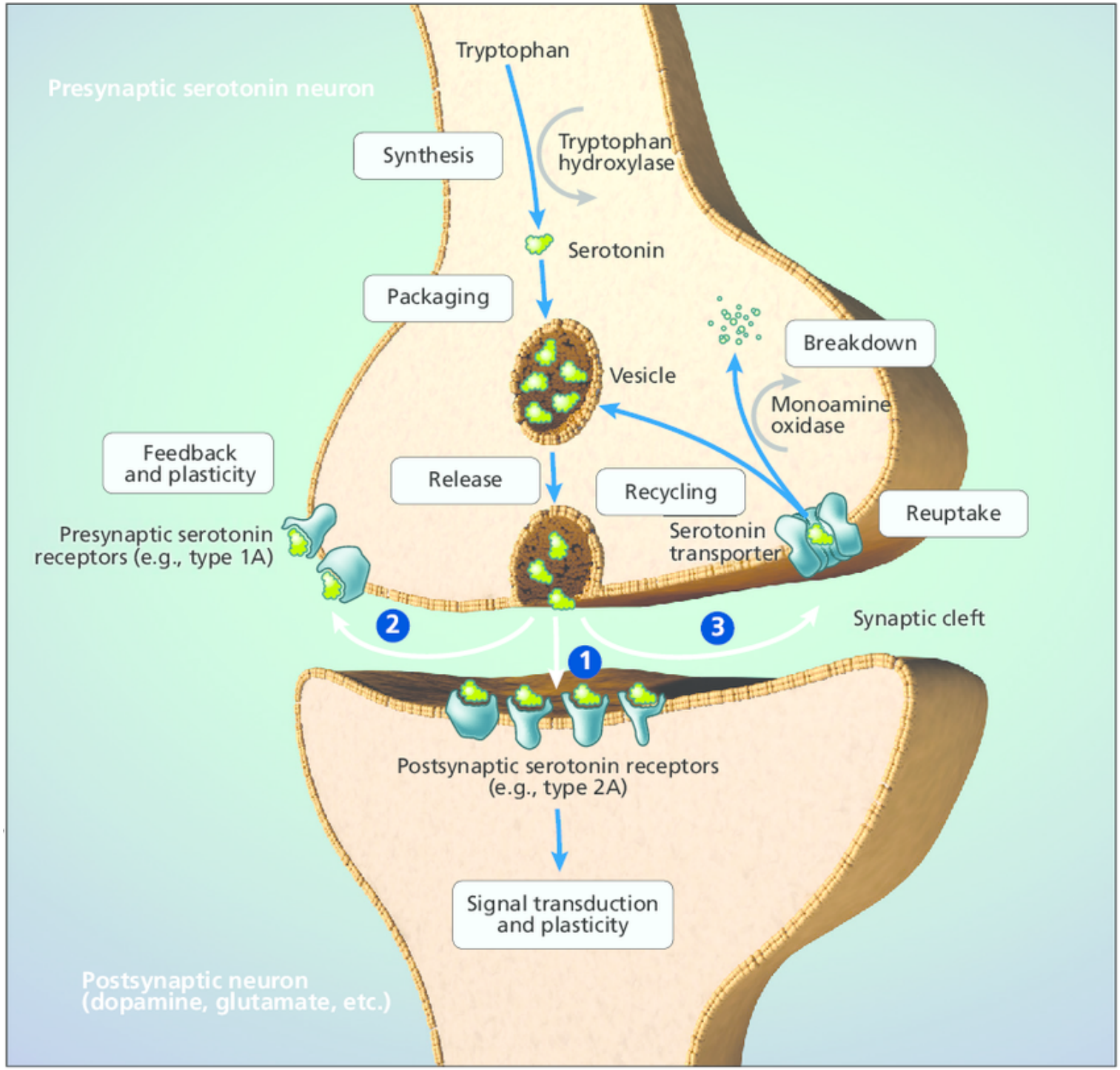

Presynaptic serotonin neuron
Tryptophan
Synthesis
Tryptophan hydroxylase
Serotonin
Packaging
Vesicle
Breakdown
Monoamine oxidase
Feedback and plasticity
Release
Recycling
Reuptake
Presynaptic serotonin receptors (e.g., type 1A)
Serotonin transporter
2
3
Synaptic cleft
1
Postsynaptic serotonin receptors (e.g., type 2A)
Signal transduction and plasticity
Postsynaptic neuron (dopamine, glutamate, etc.)

Table of Serotonin Receptor Subtypes

Receptor Name	Location, Effects, Agonists and Antagonists
5-HT_{1A}	Location: CNS Effects: Regulates sleep, feeding, and anxiety Antagonists: Yohimbine
5-HT_{1B}	Location: CNS Effects: neuronal inhibition, behavioral changes Antagonists: Yohimbine.
5-HT_{m}	Location: CNS, vascular Effects: Locomotor, vasoconstriction Antagonists: Yohimbine. Agonists: Sumatriptan
5-HT_{2A}	Location: CNS, smooth muscle, platelets Effects:cellular excitiation, behavior, muscle contraction, vasoconstriction Antagonists: LSD, Chlorpromazine
5-HT_{2B}	Location: Stomach Antagonists: Yohimbine, Chlorpromazine
5-HT_{2C}	Location: CNS Effects: Anxiety
5-HT_{3}	Location: Sensory nerves Effects: Vomiting
5-HT_{4}	Location: CNS, ENS Effects: Gut Motility
5-HT_{5A}	Location: CNS Effects: Unknown
5-HT_{6}	Location: CNS Effects: Unknown
5-HT_{7}	Location: CNS, ENS, blood vessels Effects: Unknown

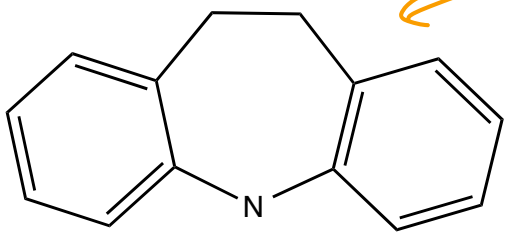
Adapted from Mohammad-Zadeh et al, 2008

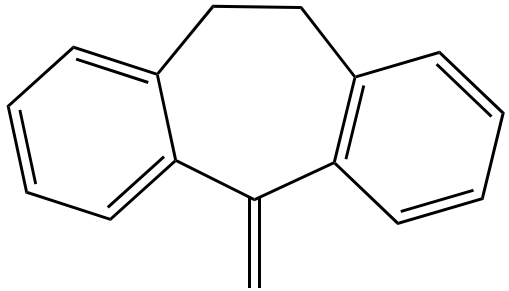
7 major classes
most GPCR's

(thymoleptics)

Tricyclic Antidepressant

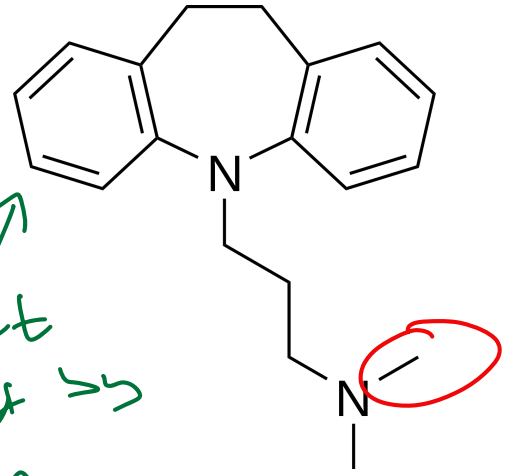
curved, not coplanar (distinguishes them from antipsychotics)





- Block reuptake of NE
- Also block 5-HT

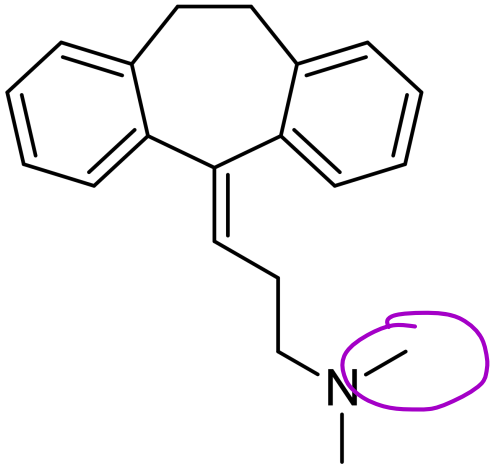
originally developed as antihistamines + Sedatives



Imipramine (parent of this class)

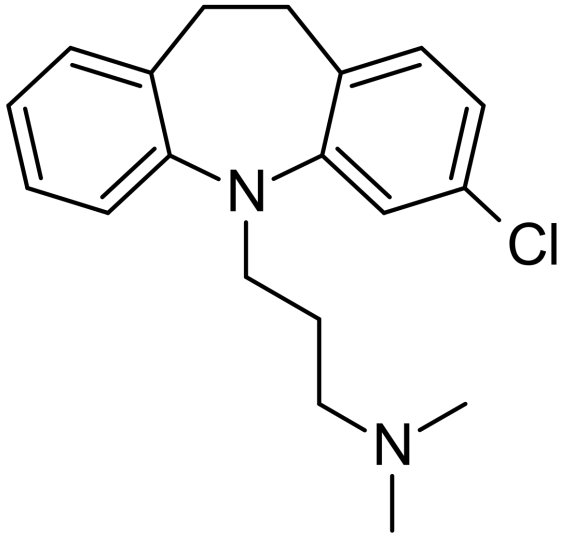
start net by -OH here

remove to make desmethylimipramine



Amitriptyline (Elavil)

remove nortryptaline



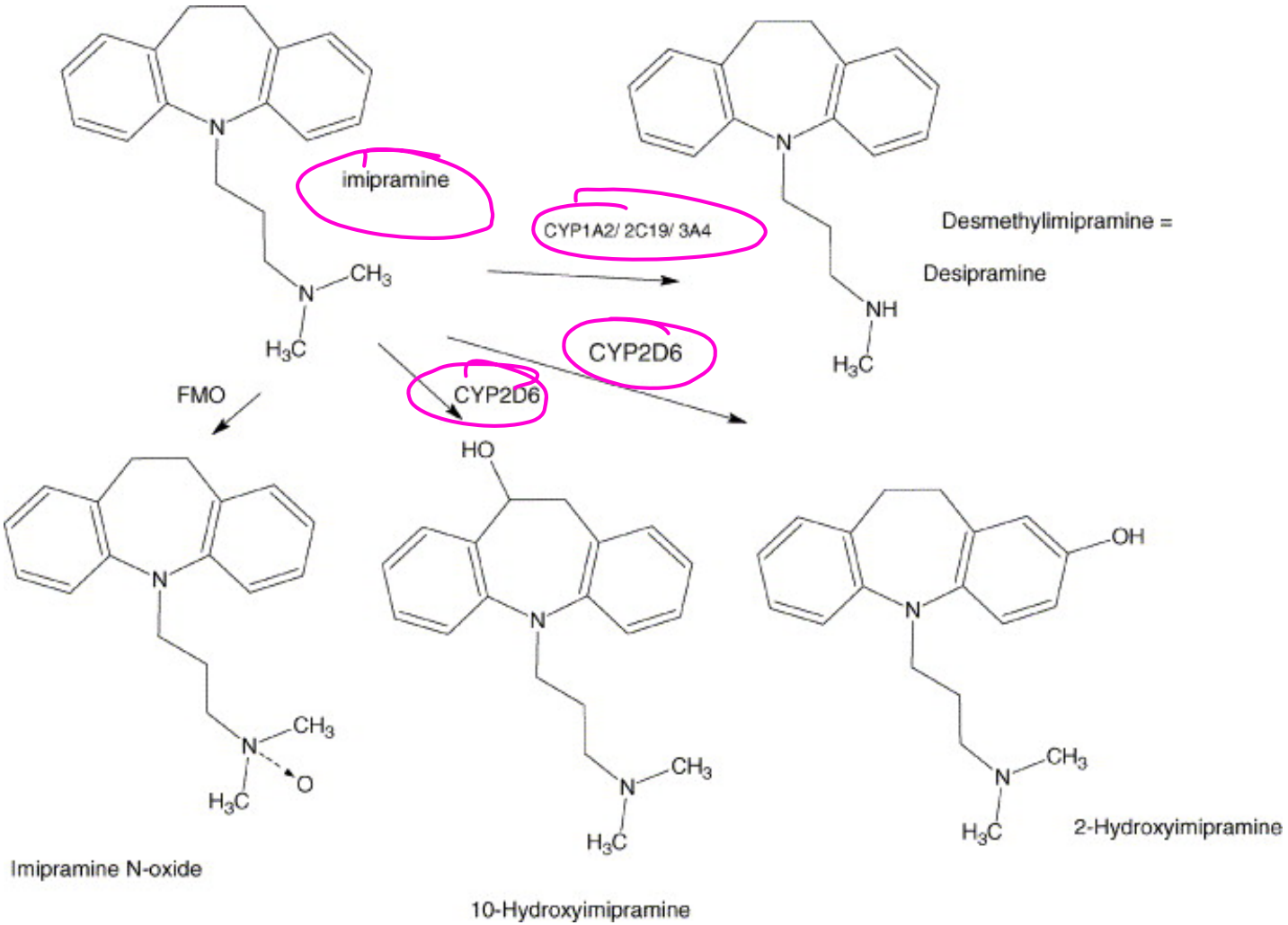
Clomipramine

more selectin for 5-HT

has been used
for OCD + panic attacks

highly metabolized

some products also active



TCA Side Effects

hypotension ← act on α_1 receptors

sedation ← H_1 receptors

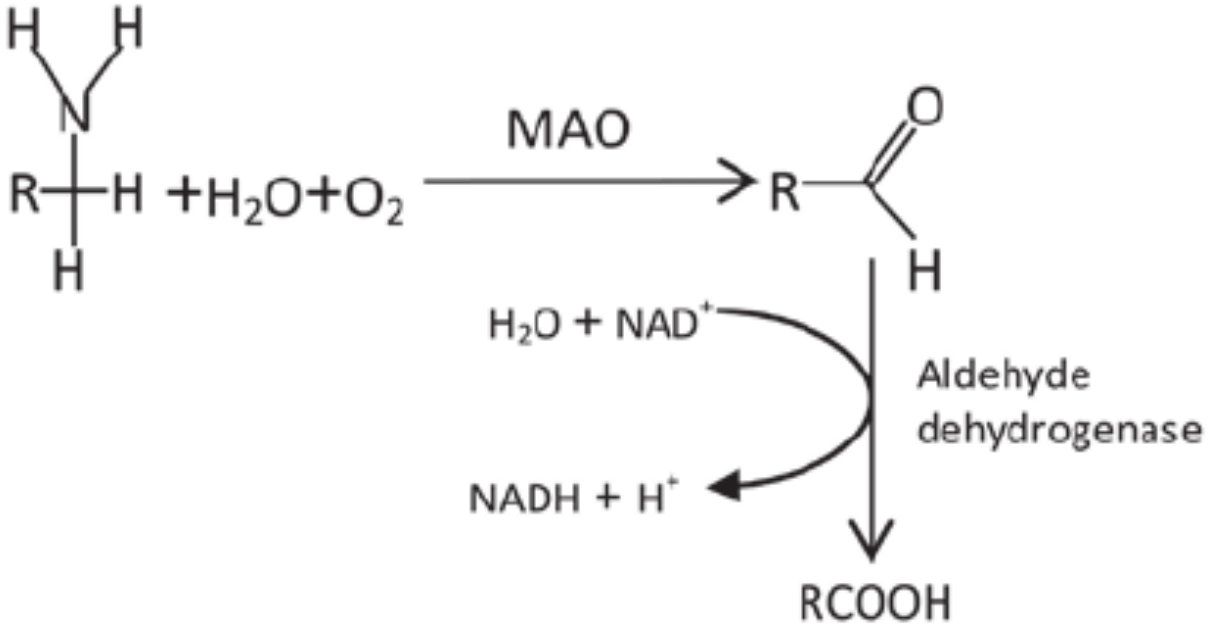
tremors

psychosis

reduced HR

- take 1-4 weeks to see positive effects

Monoamineoxidase Inhibitors



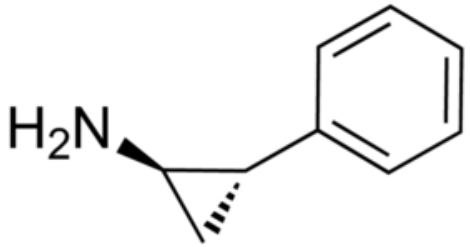
2 Types

A: DA
E
NE
5-HT
found everywhere

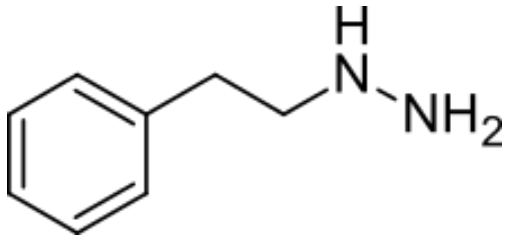
B: DA
primarily in brain

First Generation MAOI's

- irreversible inhibitors
- deactivate enzyme

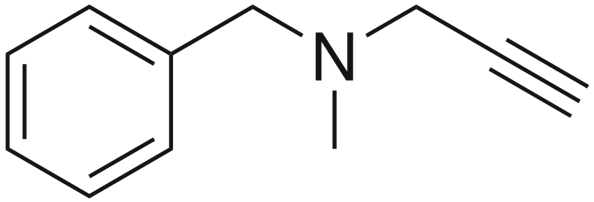


tranylcypromine

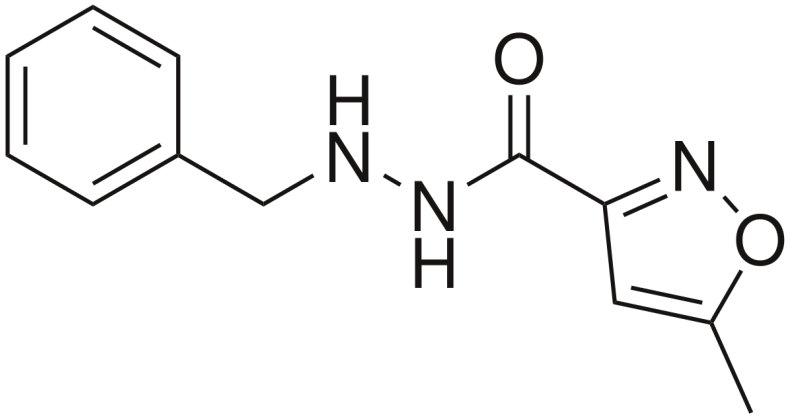


phenylzine

Irreversible Nonselective MAOIs

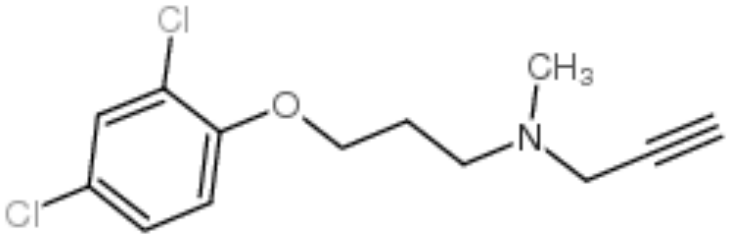


Pargyline



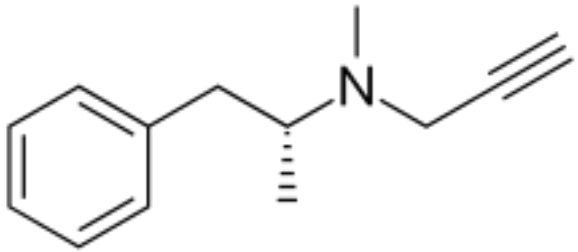
Marplan

Irreversible Preferential MAOIs



Chlorgyline

MAO-A



Selegiline

MAO-B

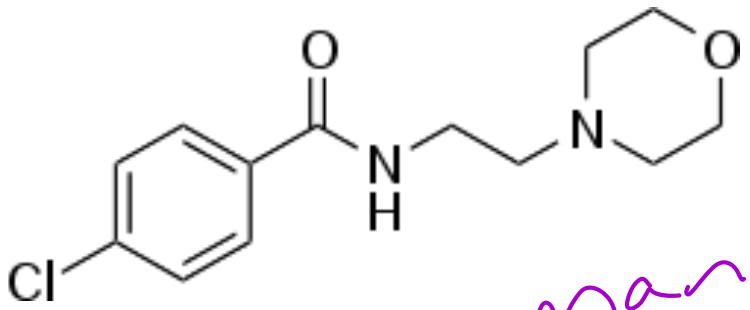
↑

just DA

doesn't effect

5-HT levels

Second Generation MAOI's



RIMA's
(reversible inhibitor)

manerix

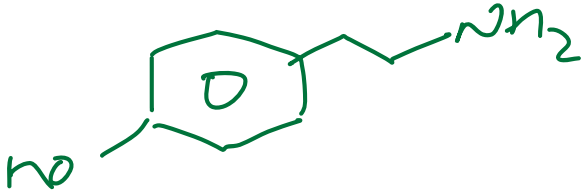
MAO : Drug-Drug Interactions

↑ used for drug metabolism

- other drugs may need lower concentrations

- interferes with metabolism of tyramine — can cause hypertension
  - aged cheese
  - fermented foods

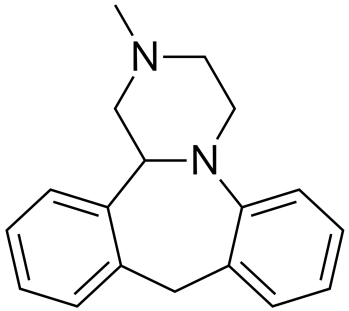
⇓

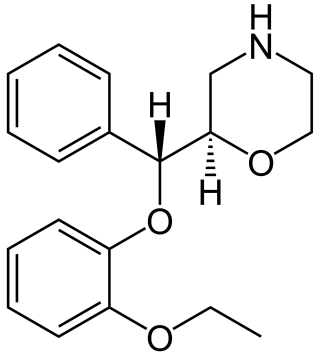


gets taken up by cells + displace NE in the vesicles causing NE release

+ increased BP

NARI's : Noradrenaline Reuptake Inhibitor





mianserin

reboxitine

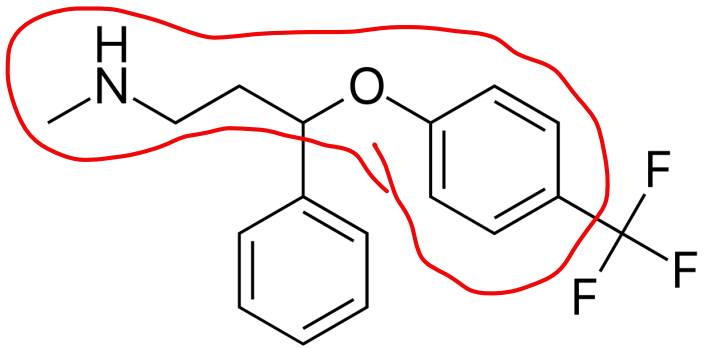
Serotonin Reuptake Inhibitors

SRI's

SSRI's

Selective

fewer anticholinergic side effects

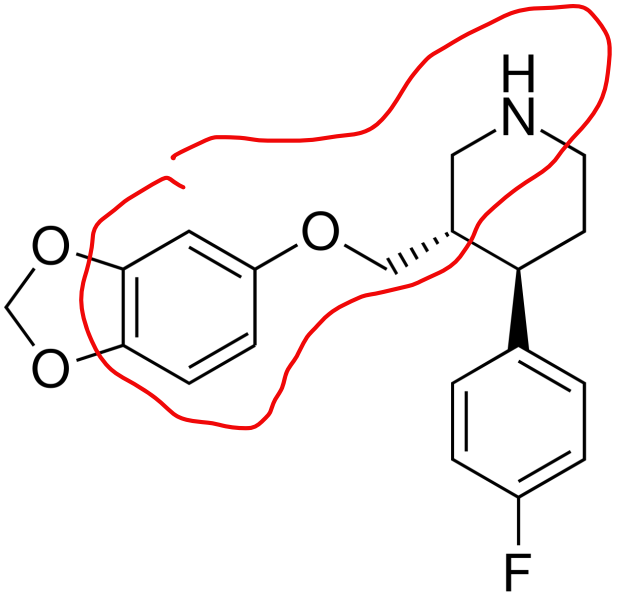


Ar$_2$ + aryloxy alkyl amines

← Prozac

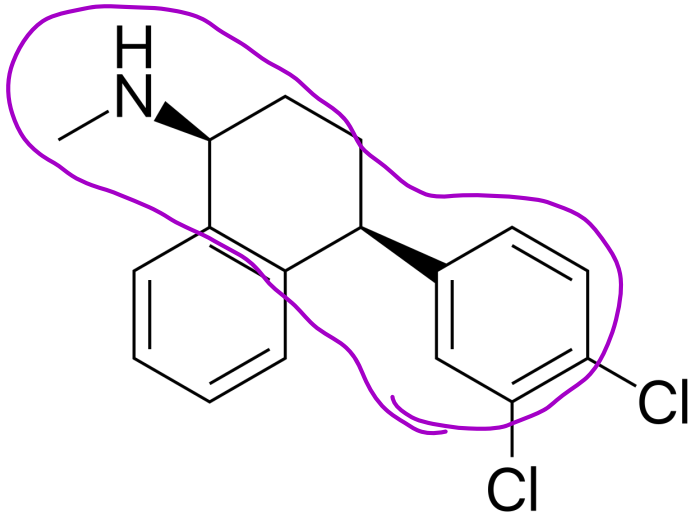
fluoxetine

decrease rate 5-HT is taken back up



Paxil

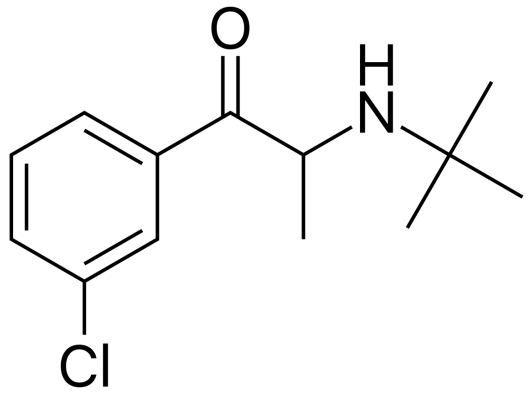
paroxetine



Sertraline

Zoloft

Monocyclic Antidepressants



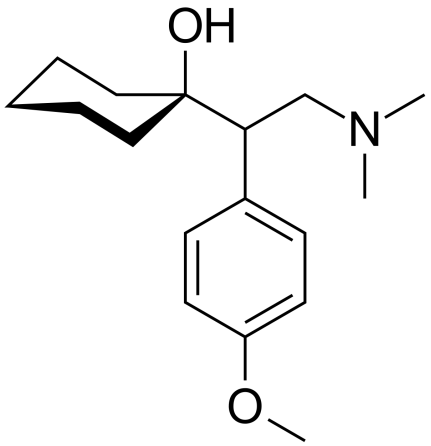
Bupropion

(wellbutrin)

NE reuptake inhibitor

DA reuptake inhibitor

SNRI : Serotonin and Norepinephrine Reuptake Inhibitor

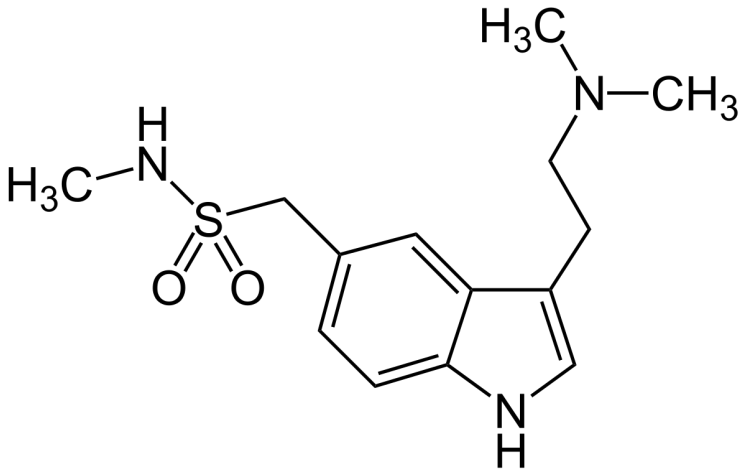


Effexor

(venlafexine)

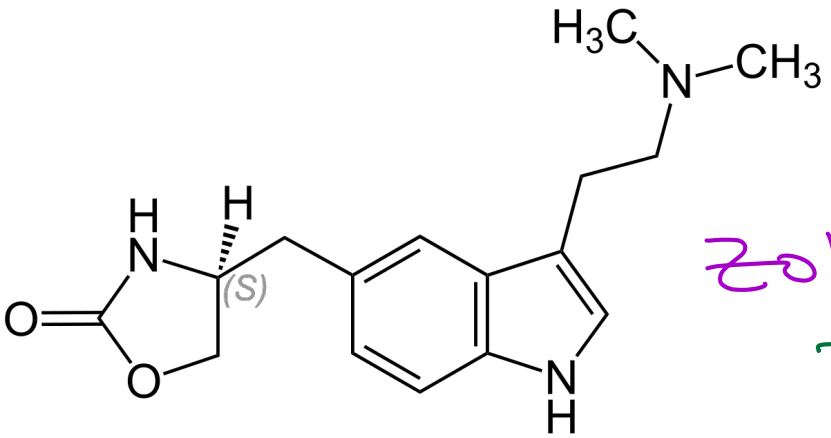
Serotonin Agonists

Tryptans

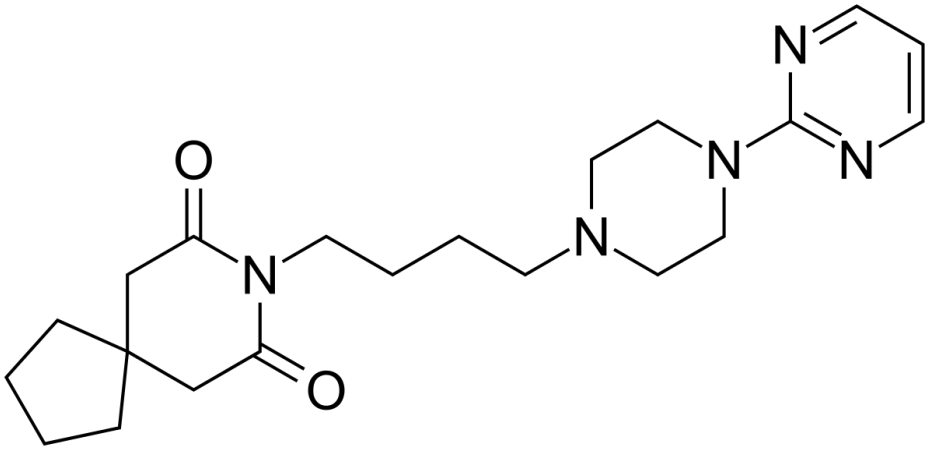


Sumatriptan
Imitrex

- used for migraines
- act on 5-HT$_{1B}$ receptors
- cause vasoconstriction



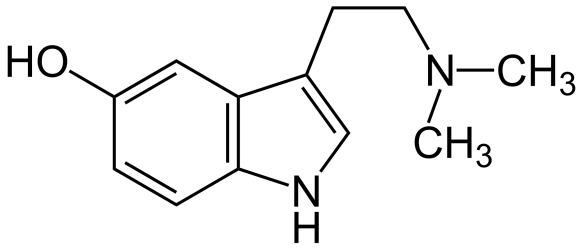
Zolmitriptan
Zomig



Buspirone

anxiety + depression

5-HT_{1A} agonist



Bufotenin

toad

- hallucinogenic?
- cardiovascular

↑ Stimulant

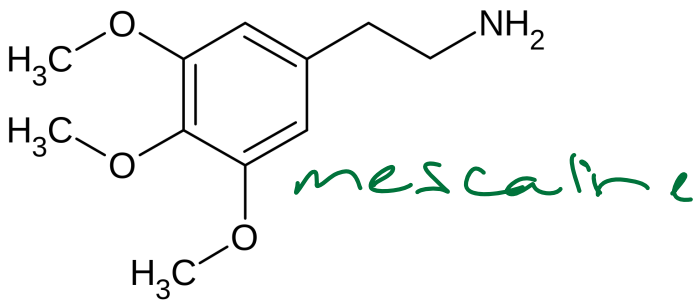
digitalis like

↑

tryptan

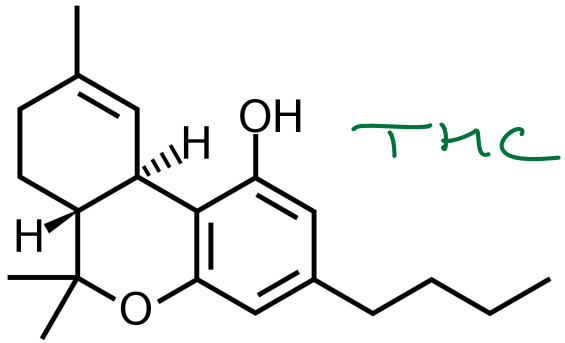
Psychotomimetics –

1. Phenylethylamines



mescaline

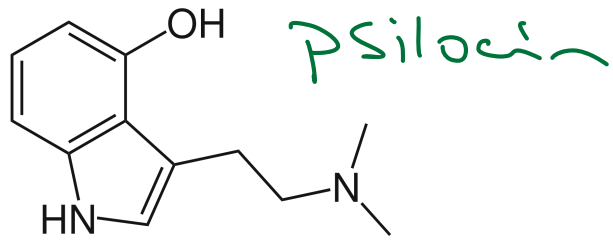
2. Cannabis derivatives



THC

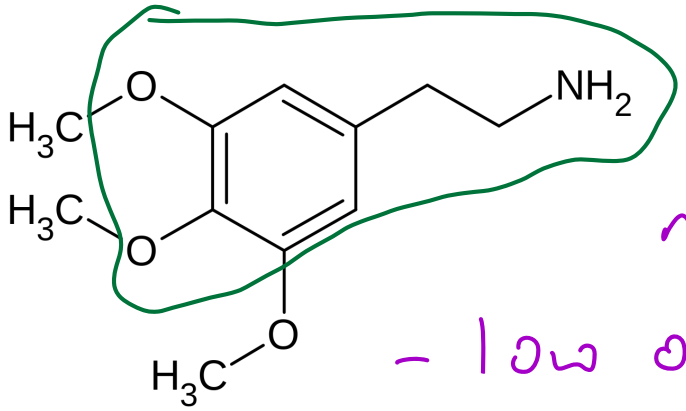
3. LSD/derivatives and Indoles

↑ ergot alkaloids



psilocin

mono or di substituted is inactive

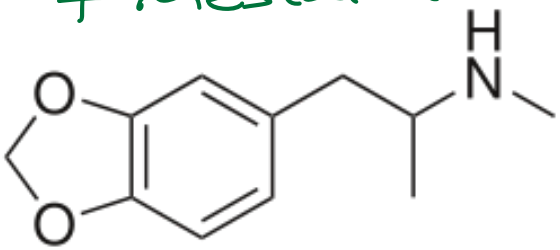


mescaline

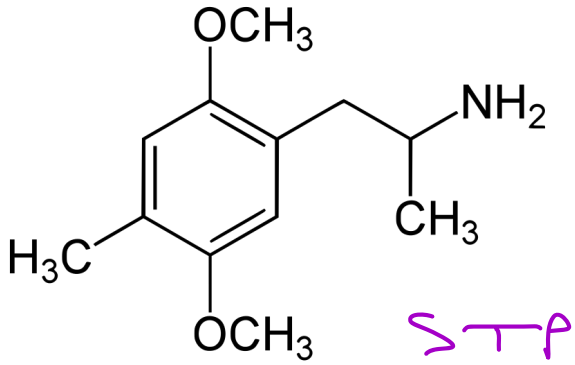
mexican cactus

- low oral potency
- quickly metabolized

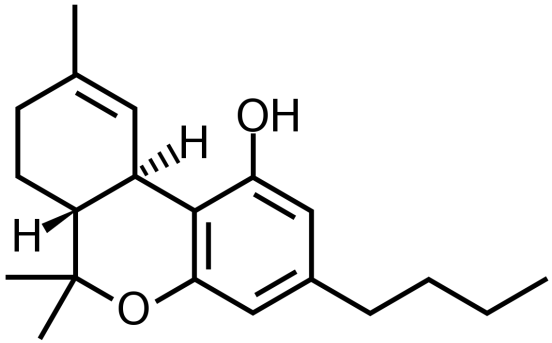
pentasubstituted is 7 mescaline units



MDMA (ecstasy)



STP



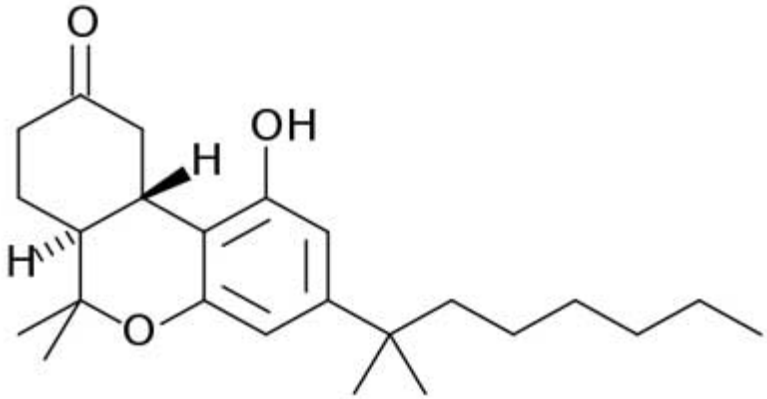
Δ^9-tetrahydrocannabinol

THC

not considered hallucinogenic

psychotomimetic

(at high doses)



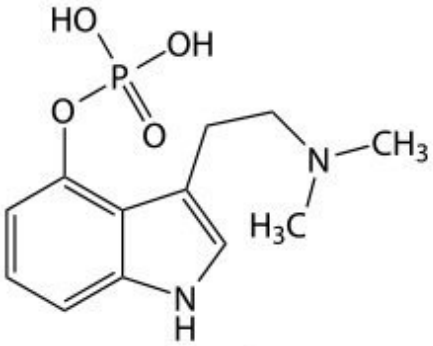
nabilone

THC derivative

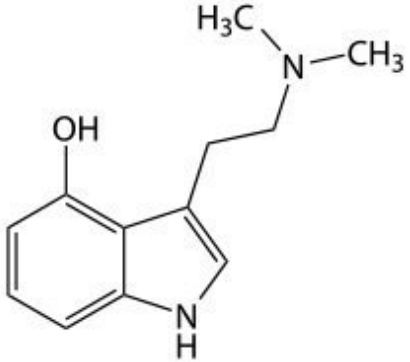
antiemetic

anticonvulsant

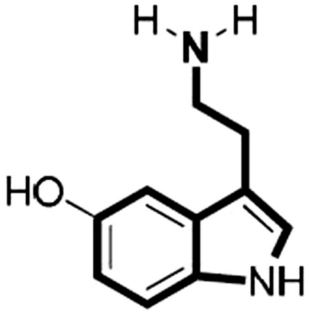
analgesic



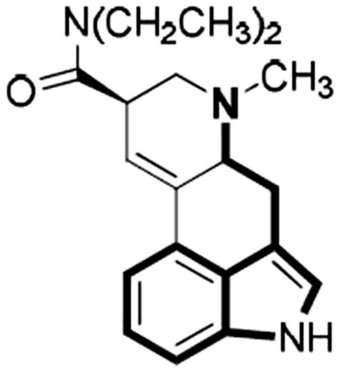
Psilocybin



Psilocin



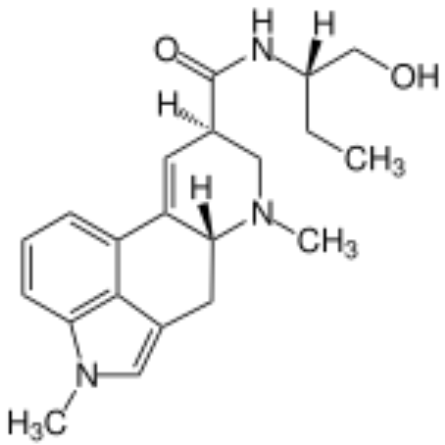
Serotonin; 5-HT



LSD

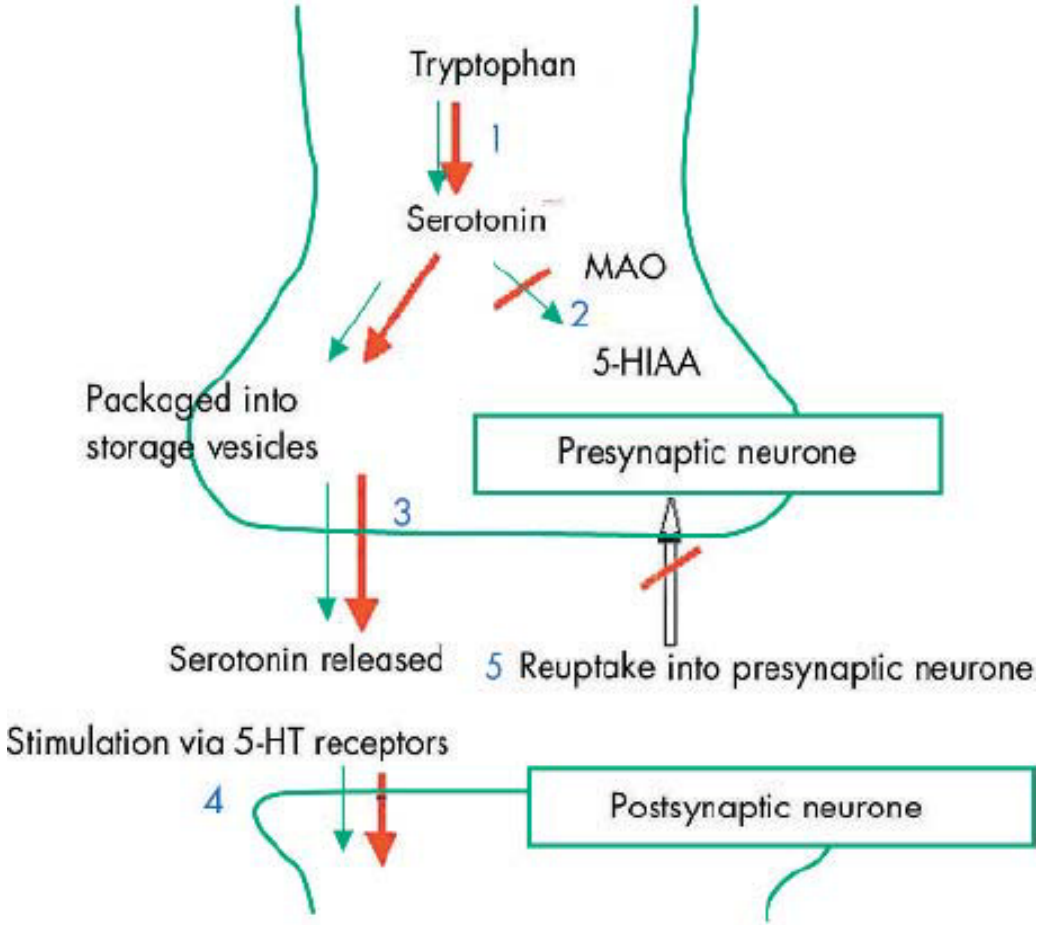
all of these bind to 5-HT (receptors (agonists)

Serotonin Antagonists



methsergide

- used for migraines
- Semisynthetic analogue of LSD



1 Increased substrate
2 Inhibited serotonin metabolism
3 Increased release of serotonin into synaptic cleft
4 Postsynaptic receptor stimulation
5 Inhibited serotonin reuptake