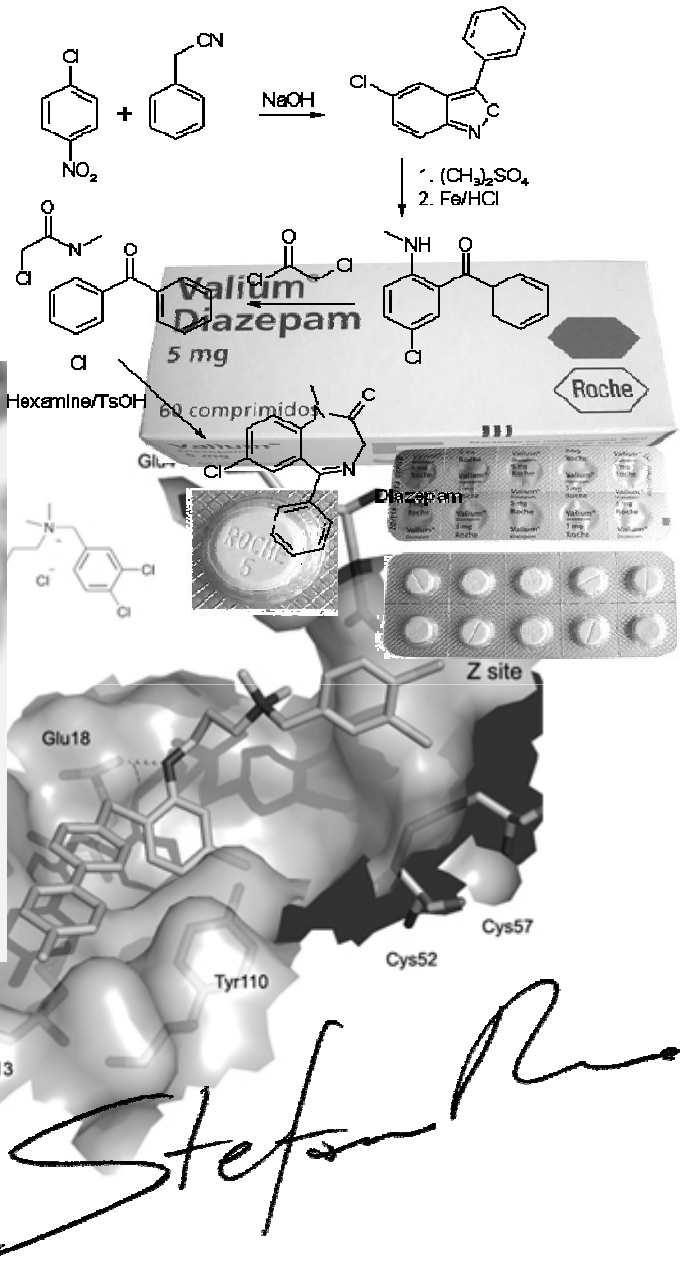
Chimica Farmaceutica e Tossicologica – Parte II



Mi ripeto ancora… la più importante per noi!

NON CONFONDEREMO MAI LA *CALCOLATRICE* CON LE *CIFRE* CHE ESSA PRODUCE!!!

Neurobiology of Depression and Antidepressants

Parte II

1. Psychotic disorders introduction

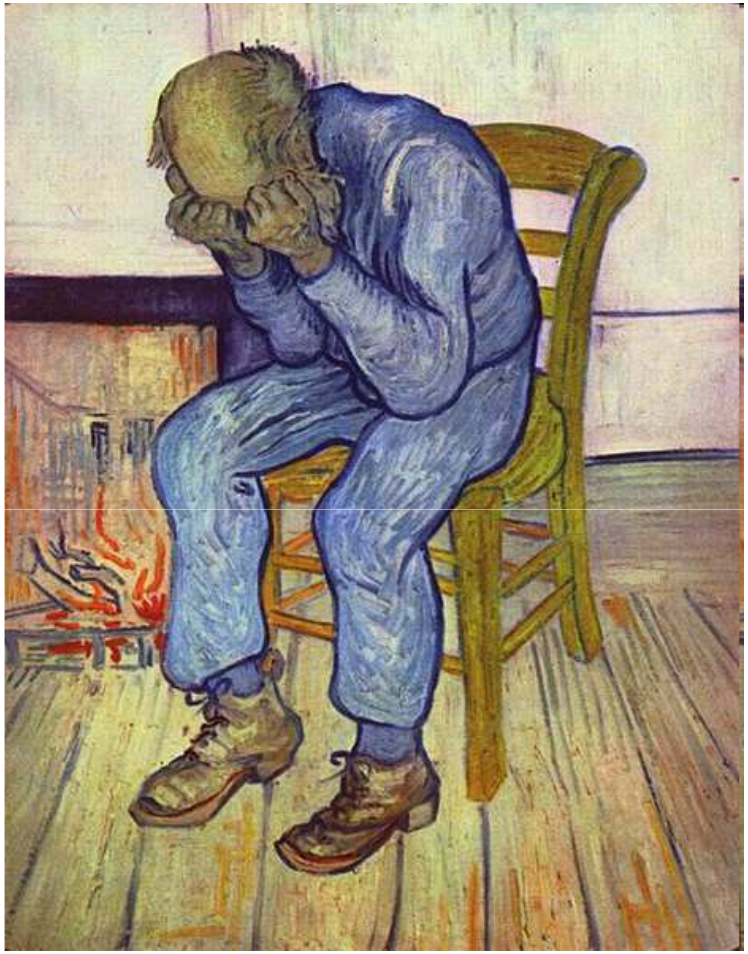
The psychotic disorders are classified into 3 major groups:

1. **Anxiety disorders** (*phobia and sleeping disorders*)
2. **Effective/mood disorders** (*depression*)
3. **Personality disorders** (*schizophrenia*)

1. Psychotic disorders introduction

- Anxiolytic Drugs:
  - Benzodiazepines (BDZ)
  - Barbiturate
  - Azaspirones
- **Antidepressant Drugs:**
  - **Tricyclic/Plycyclic**
  - **Monoamine oxidase inhibitors**
  - **Selective serotonin-reuptake inhibitors (SSRI)**
- Neurolytic Drugs:
  - Phenothiazin
  - Buteopheanol

2. Depression and antidepressant drugs

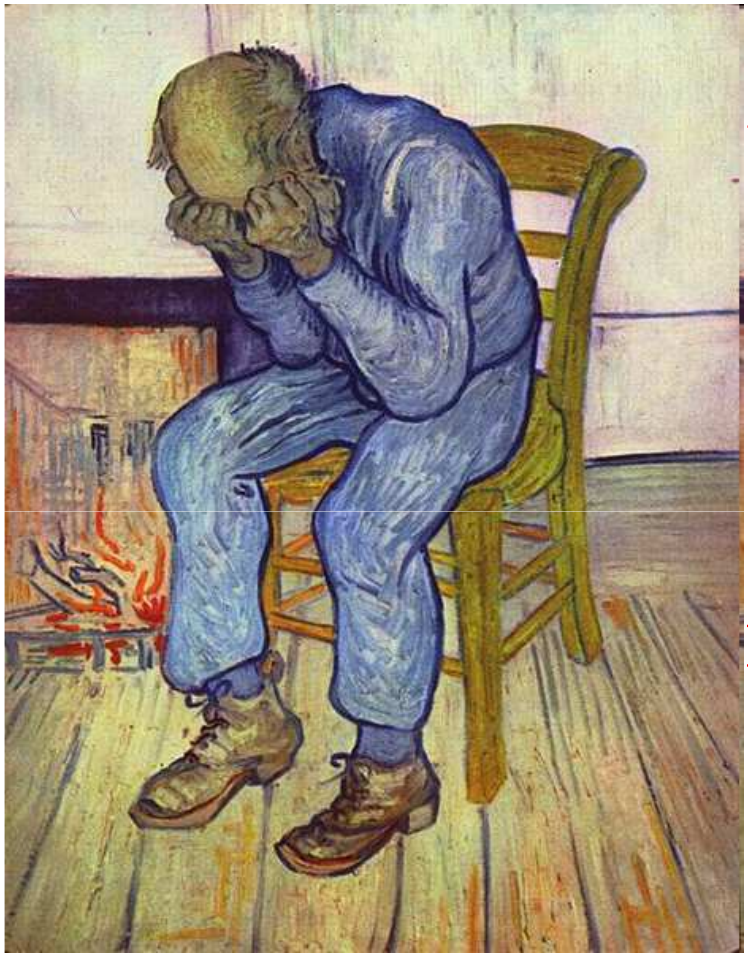


Vincent van Gogh's 1890 painting *At Eternity's Gate*

Definition:

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to ***suicide***, a tragic fatality associated with the loss of about 850000 lives every year.

2. Depression and antidepressant drugs



Vincent van Gogh's 1890 painting *At Eternity's Gate*

Definition:

Unipolar depression (major depression): **is a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem, and by loss of interest or pleasure in normally enjoyable activities.**

Bipolar disorder (manic–depressive disorder): **is a psychiatric diagnosis that describes a category of mood disorders defined by the presence of one or more episodes of abnormally elevated energy levels, cognition, and mood and one or more depressive episodes.**

2. Depression and antidepressant drugs

Monoamine Hypothesis of Depression

1960's - 1990's

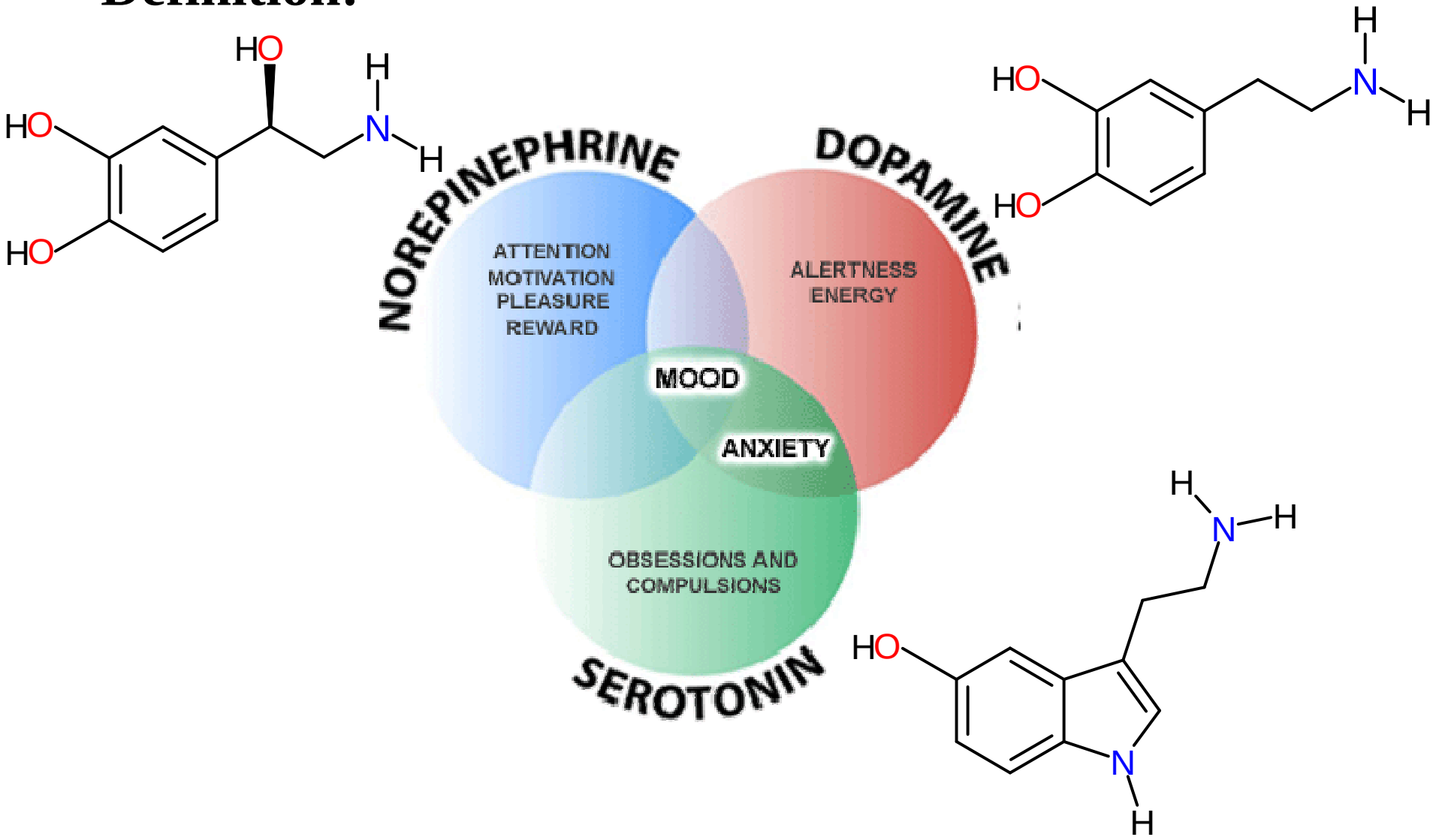
The hypothesis:

Major depression

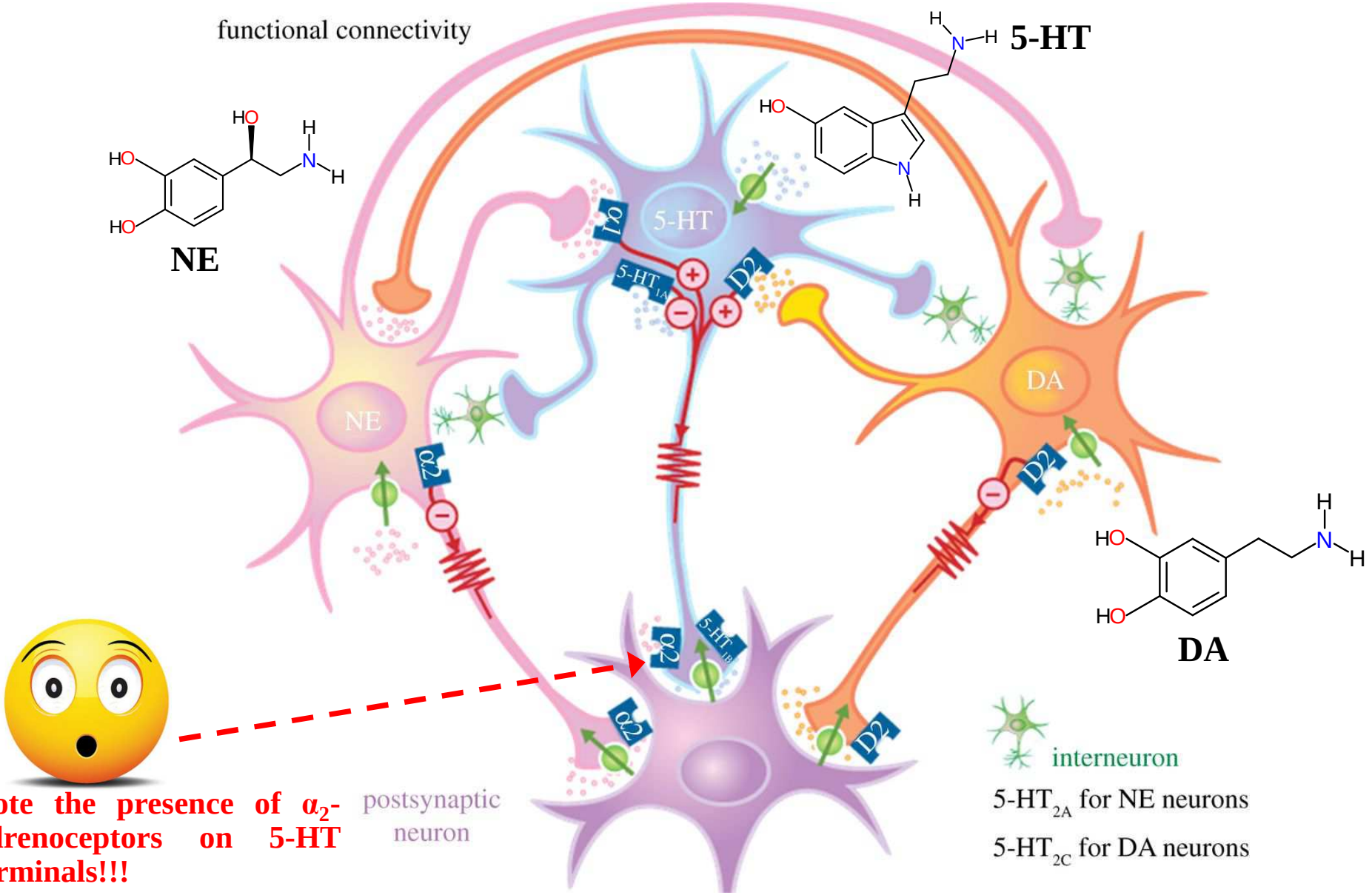
- caused by a lack of norepinephrine, serotonin, or both (or maybe DA, too) .
- Treated by correcting this monoamine deficiency.

2. Depression and antidepressant drugs

Definition:



2. Depression and antidepressant drugs



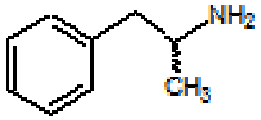
Note the presence of α_2-adrenoceptors on 5-HT terminals!!!

2. Depression and antidepressant drugs

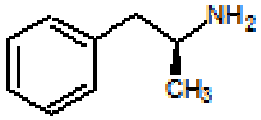
Why do Antidepressants Take So Long to Work?

- Not just a simple deficit of 5-HT or NE
  - No consistent NE or 5-HT deficits found
  - **Amphetamines, cocaine increase 5-HT & NE, but are not antidepressants!!**

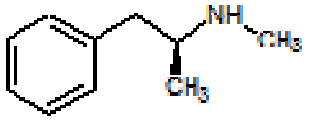
Do you remember amphetamines?



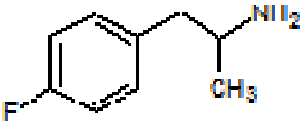
Amphetamine/Benzedrine
[1-phenylpropan-2-amine]



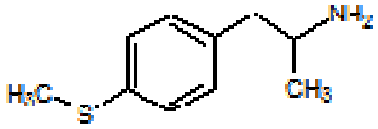
Dextroamphetamine
[(2*S*)-1-phenylpropan-2-amine]



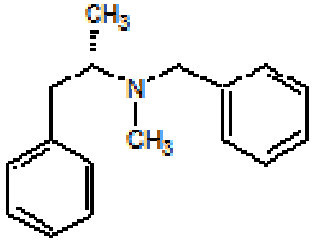
Methamphetamine (crystal meth)
[(2*S*)-*N*-methyl-1-phenylpropan-2-amine]



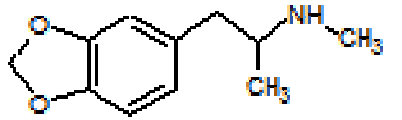
4-FMP
[1-(4-fluorophenyl)propan-2-amine]



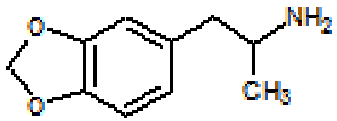
4-MTA
[1-[4-(methylthio)phenyl]propan-2-amine]



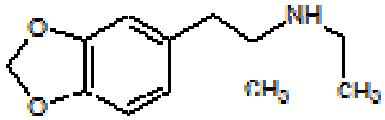
Benzphetamine
[(2*S*)-*N*-benzyl-*N*-methyl-1-phenylpropan-2-amine]



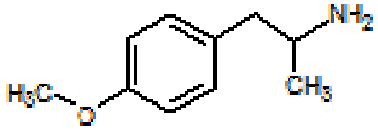
MDMA (Ecstasy)
[1-(1,3-benzodioxol-5-yl)-*N*-methylpropan-2-amine]



MDA
[1-(1,3-benzodioxol-5-yl)propan-2-amine]



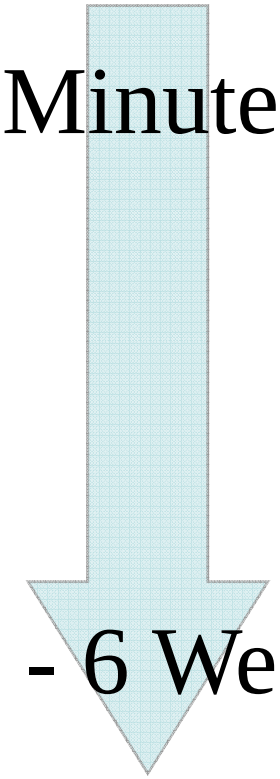
MDEA
[1-(1,3-benzodioxol-5-yl)-*N*-ethylpropan-2-amine]



PMA
[1-(4-methoxyphenyl)propan-2-amine]

2. Depression and antidepressant drugs

Why do Antidepressants Take So Long to Work?



Minutes

2 - 6 Weeks

↑5-HT, Norepinephrine, (dopamine)

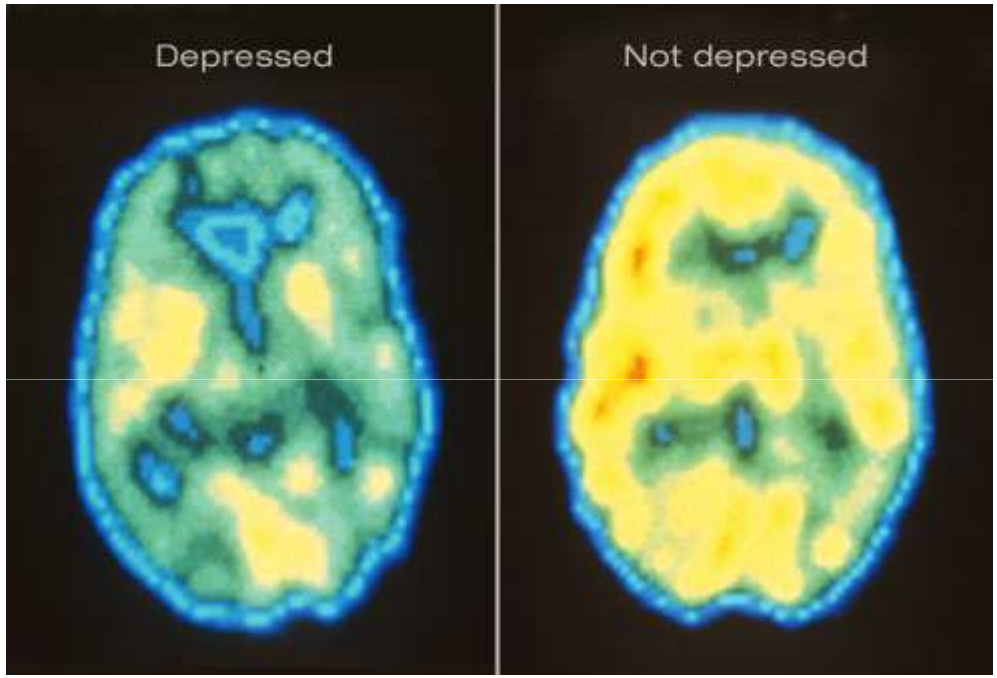
Changes in 5-HT, NE, DA receptor stimulation, neuronal activity

Changed neuronal sensitivity, growth factors (BNDF), gene expression, cell number & morphology

Antidepressant effects take time: 2-6 weeks

2. Anxiety and anxiolytic drugs

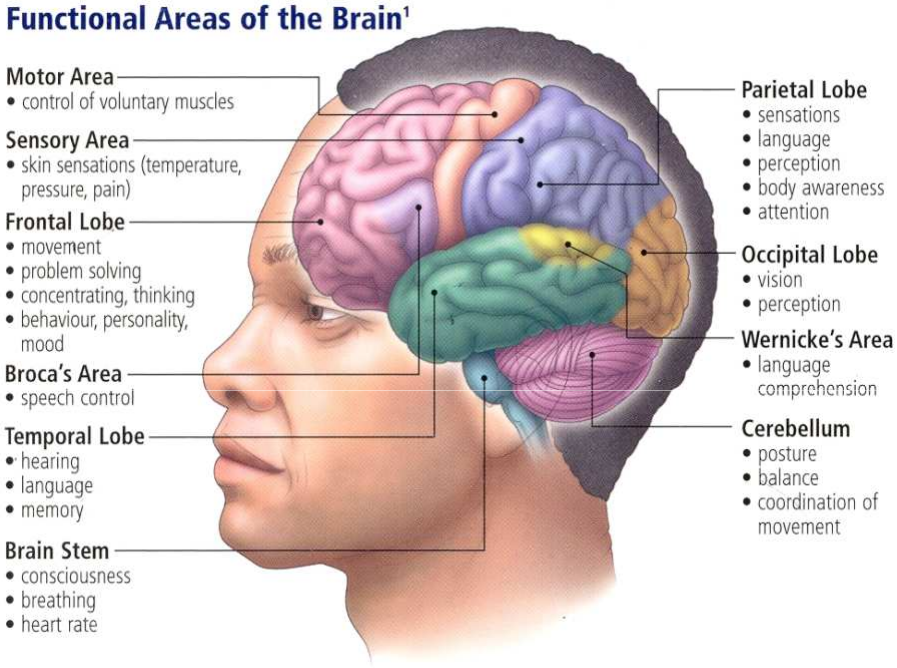
Serotonin in the brain and depression

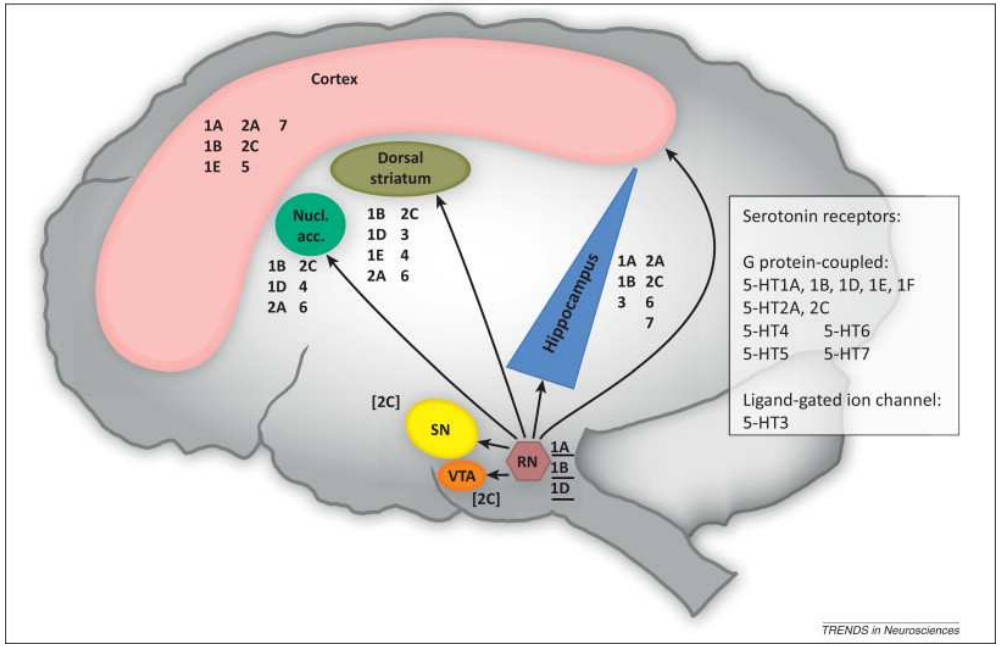


The PET scan of two brains shows the different levels of serotonin between a depressed and a non-depressed brain.

2. Anxiety and anxiolytic drugs

Serotonin – 5HT pathways in the brain





Abbreviations: SN, sustantia nigra RN, Raphe nuclei; VTA, ventral tegmental area

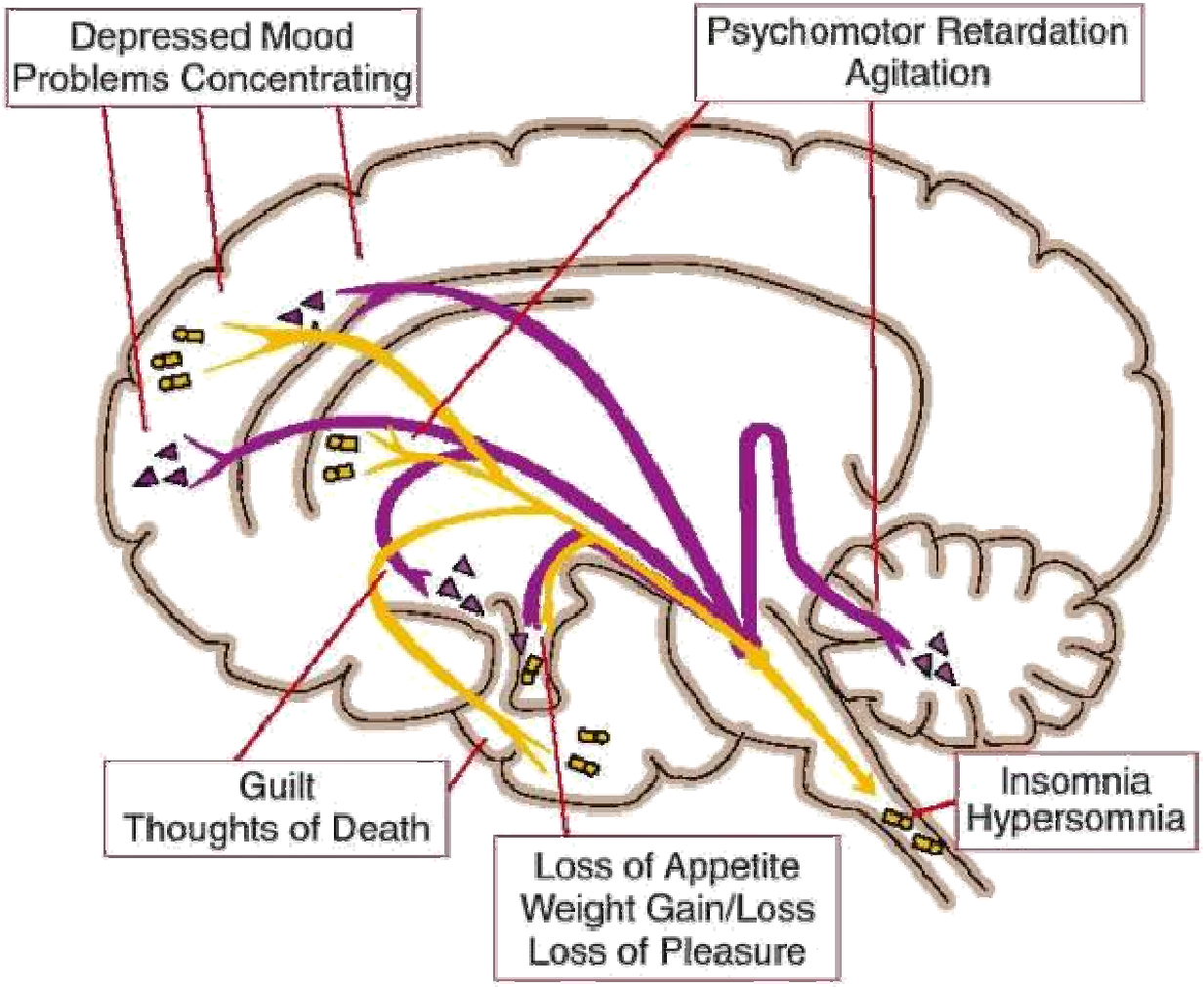
2. Anxiety and anxiolytic drugs

Serotonin – 5HT pathways in the brain

Raphe nuclei (RN) and distribution of serotonin receptors in the brain. **Dorsal RN innervate several regions of the basal ganglia, including the striatum, ventral tegmental area (VTA), substantia nigra (SN) pars reticulata, and to a lesser extent SN pars compacta. Moreover, serotonergic (5-HT) neurons in the brainstem project to limbic brain areas, including the cortex and hippocampus. 5-HT neurons innervate both dopaminergic (DA) neuronal cell bodies of the SN and the region of their terminal projections in the striatum. The anatomical interaction of the 5-HT system with DA components of the basal ganglia facilitates functional modulation of DA neurotransmission by serotonin in the normal, non-parkinsonian brain.**

2. Anxiety and anxiolytic drugs

Serotonin and Noradrenaline in the brain

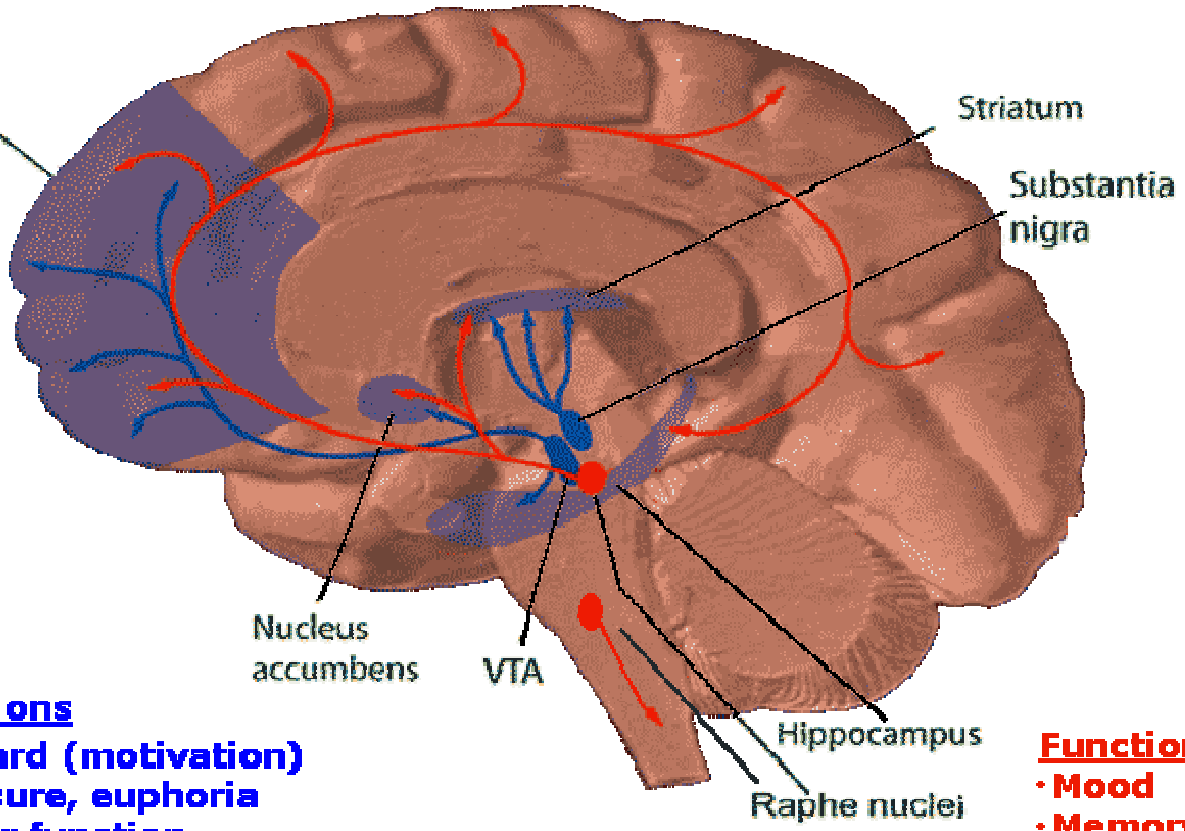


2. Anxiety and anxiolytic drugs

Serotonin and Dopamine in the brain

Dopamine Pathways

Serotonin Pathways



Functions

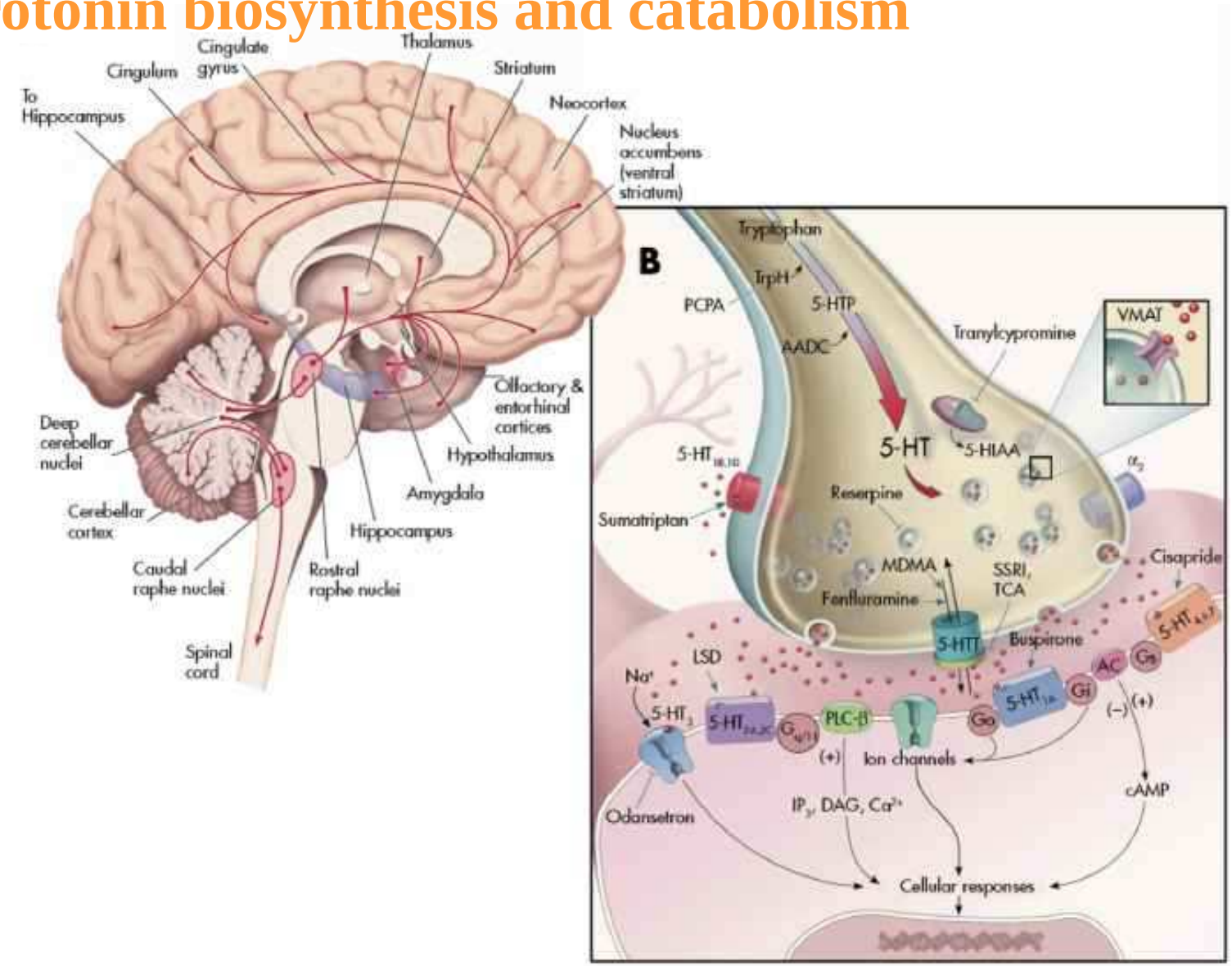
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions

- Mood
- Memory processing
- Sleep
- Cognition

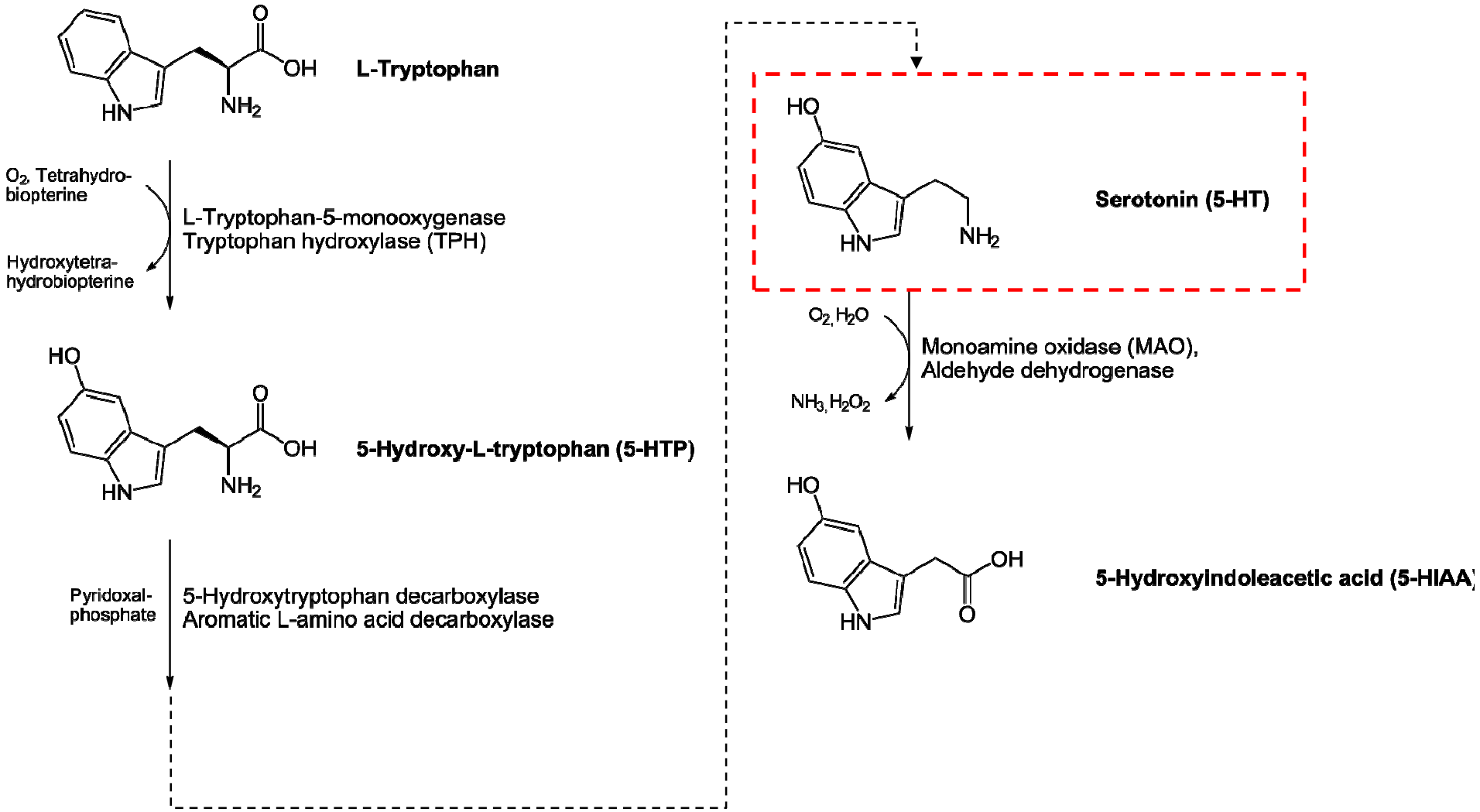
2. Anxiety and anxiolytic drugs

Serotonin biosynthesis and catabolism



2. Anxiety and anxiolytic drugs

Serotonin biosynthesis and catabolism



2. Anxiety and anxiolytic drugs

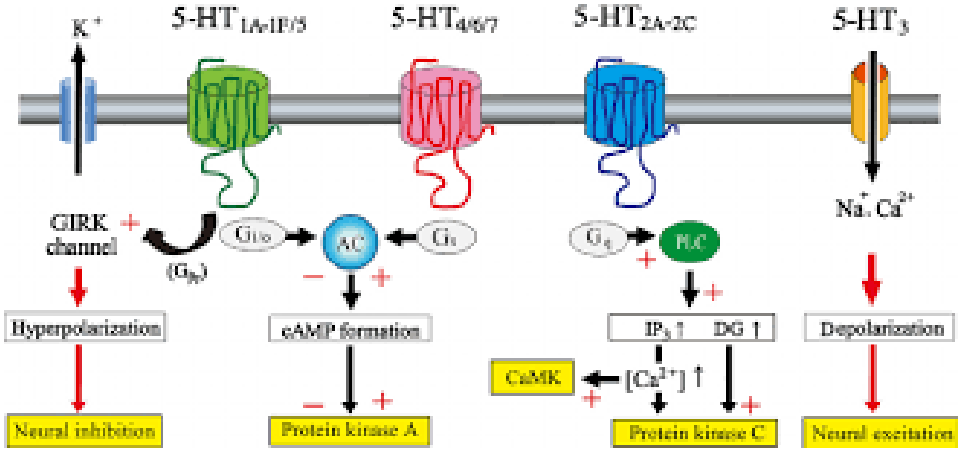
Serotonin – 5HT receptor families

Family	Type	Mechanism	Potential
5-HT_1	G_i/G_o-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT_2	G_q/G_{11}-protein coupled.	Increasing cellular levels of IP_3 and DAG.	Excitatory
5-HT_3	Ligand-gated Na^+ and K^+ cation channel.	Depolarizing plasma membrane.	Excitatory
5-HT_4	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT_5	G_i/G_o-protein coupled.[4]	Decreasing cellular levels of cAMP.	Inhibitory
5-HT_6	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT_7	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory

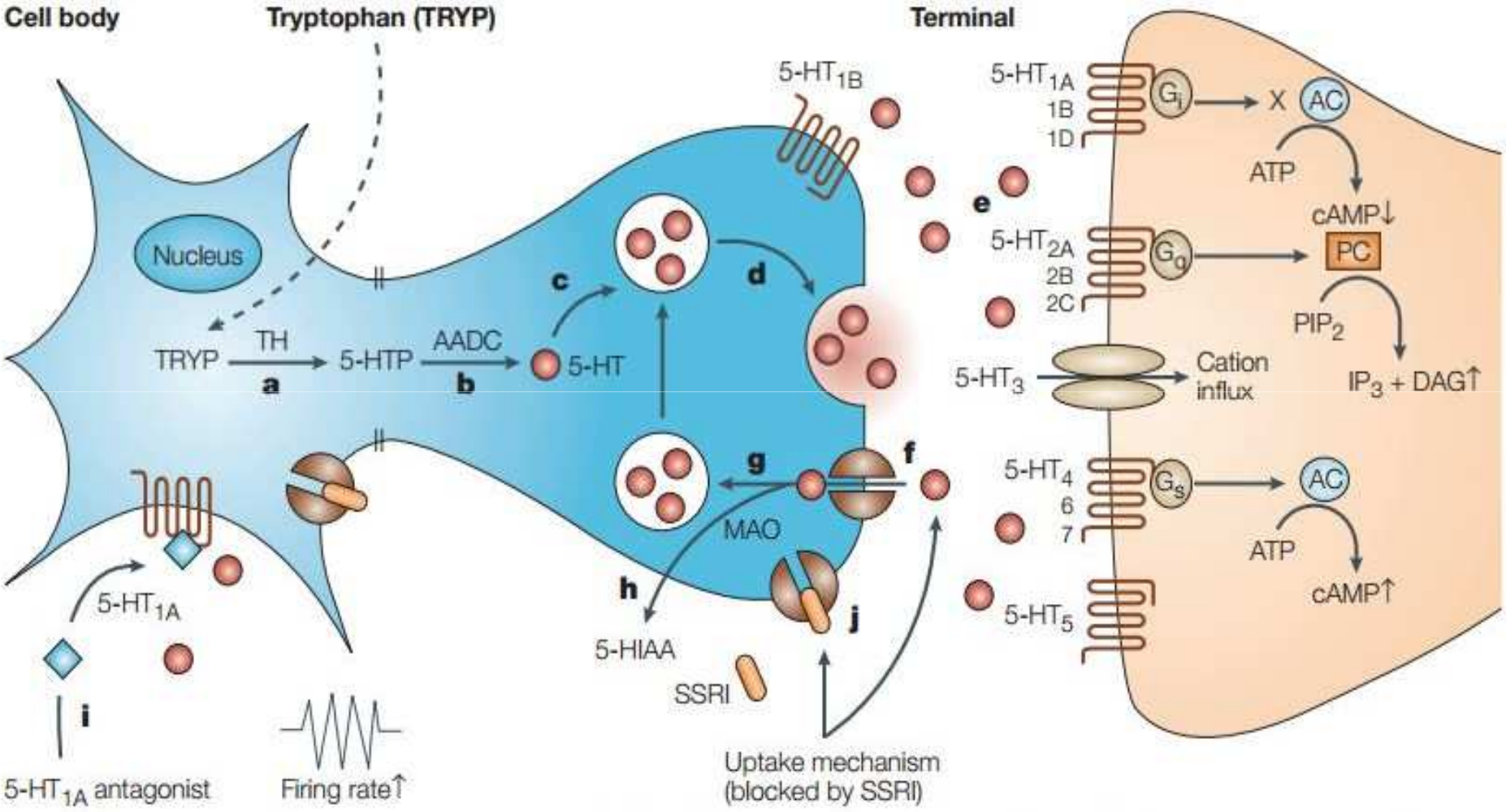
With the exception of the 5-HT3 receptor, a ligand-gated ion channel, all other serotonin receptors are G protein-coupled receptors that activate an intracellular second messenger cascade to produce an excitatory or inhibitory response. Within these general classes of serotonin receptors, a number of specific types have been characterized.

2. Anxiety and anxiolytic drugs

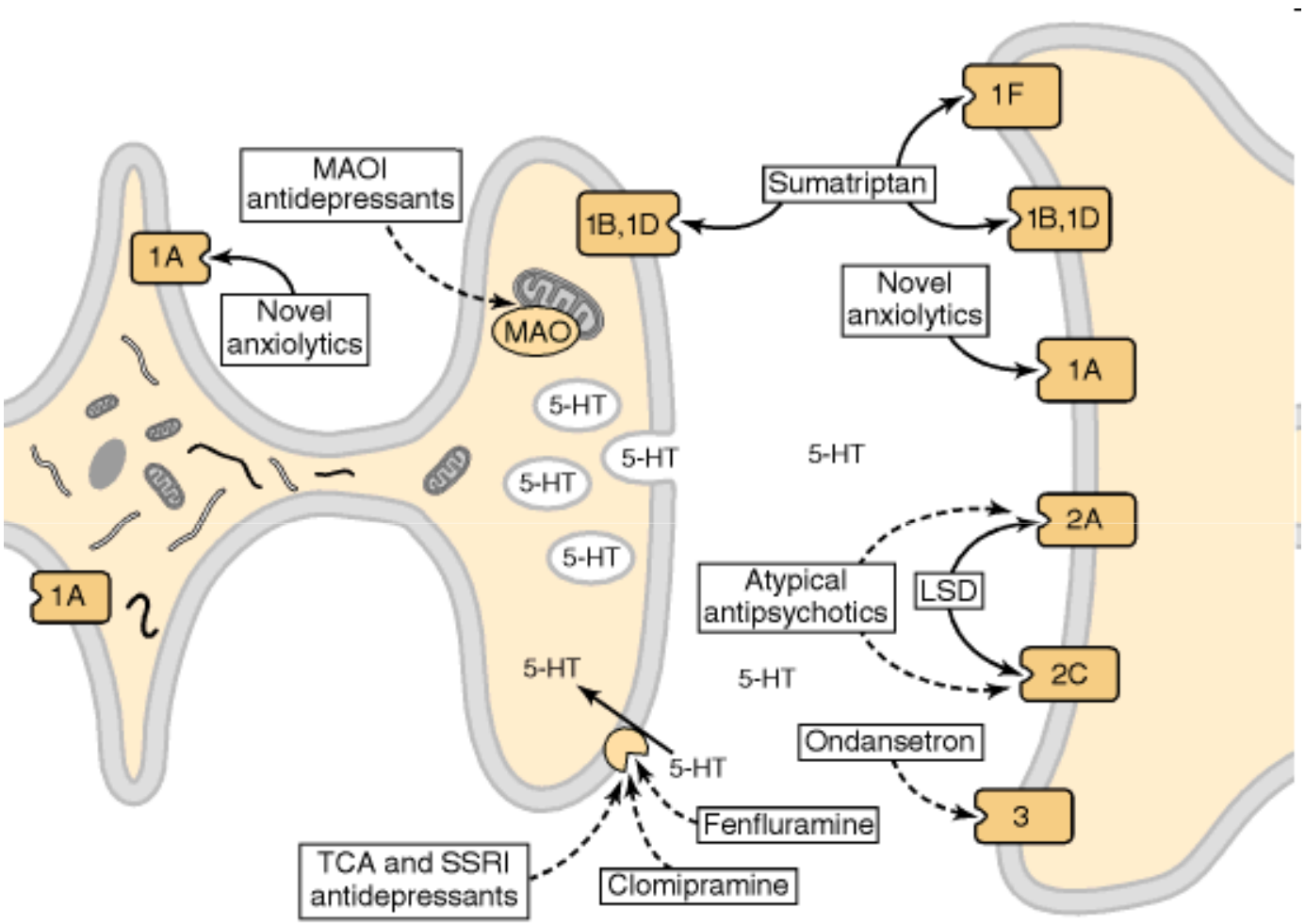
Serotonin – 5HT receptor families



2. Anxiety and anxiolytic drugs

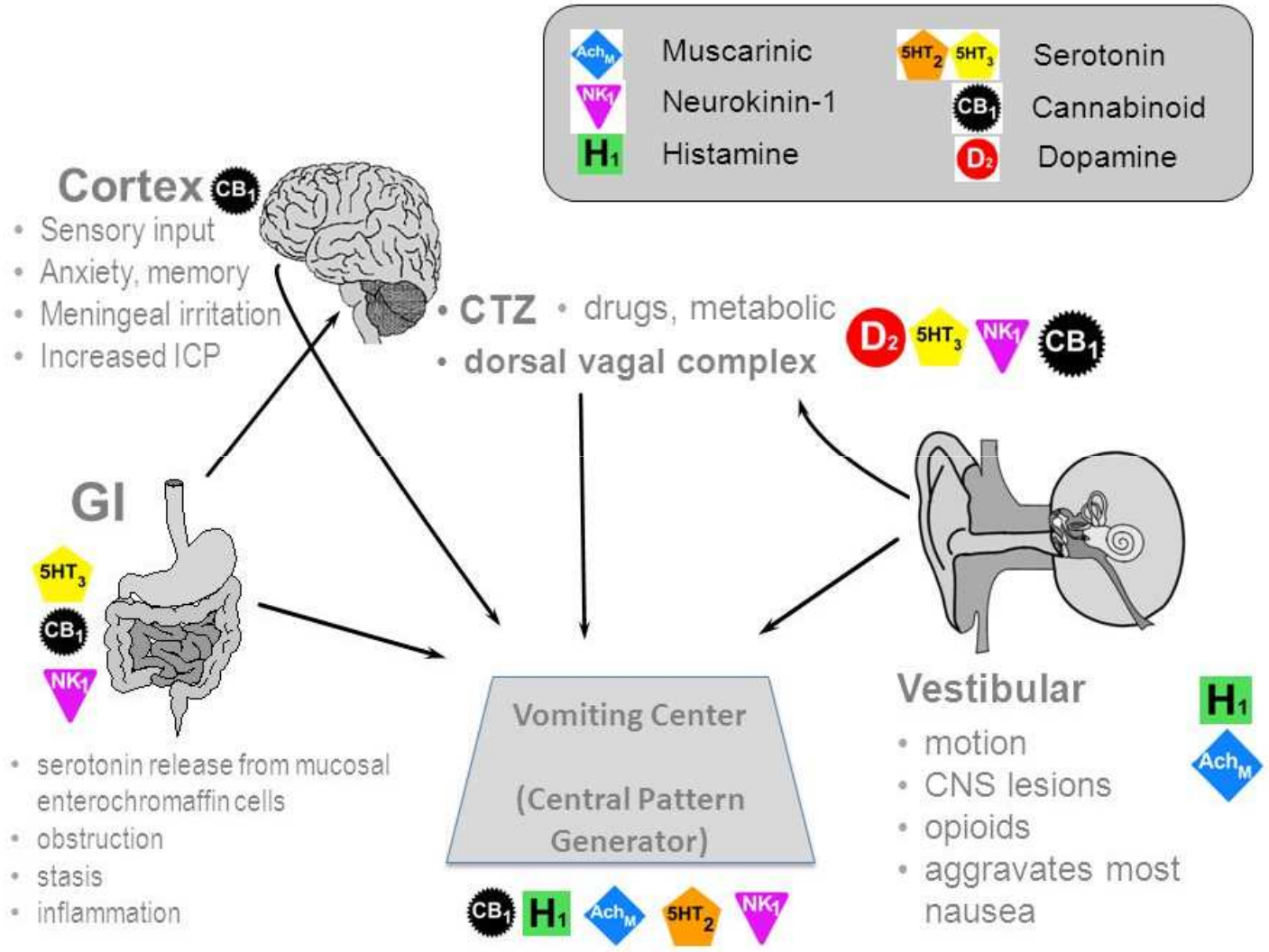


2. Anxiety and anxiolytic drugs

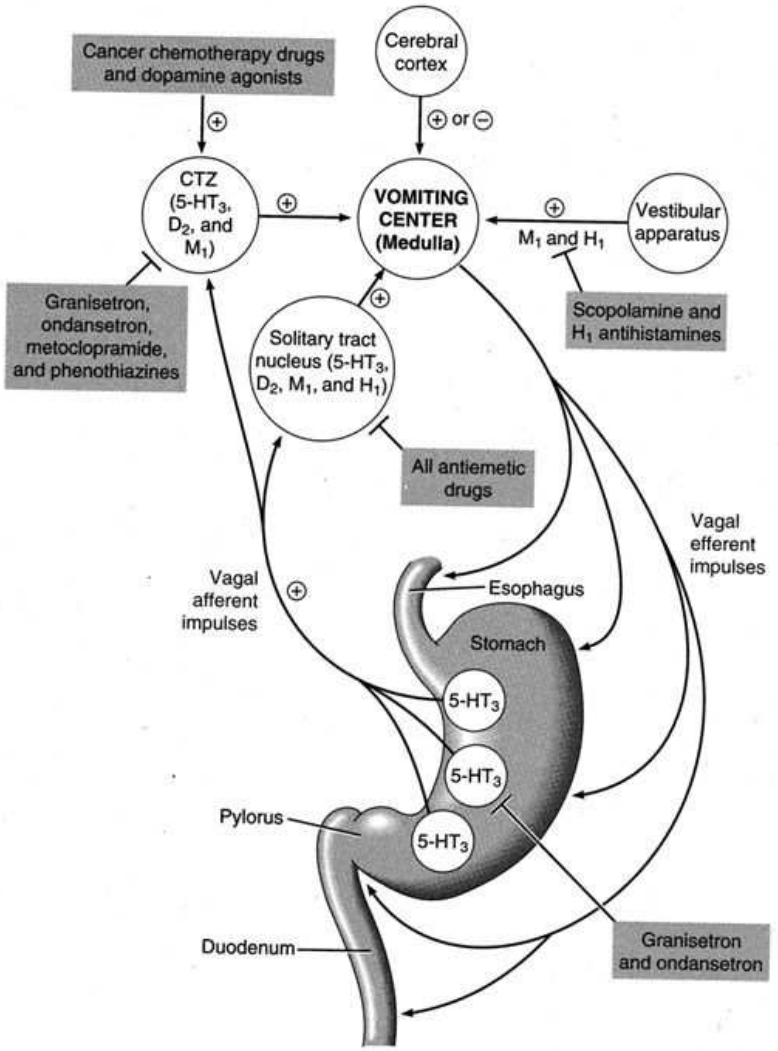


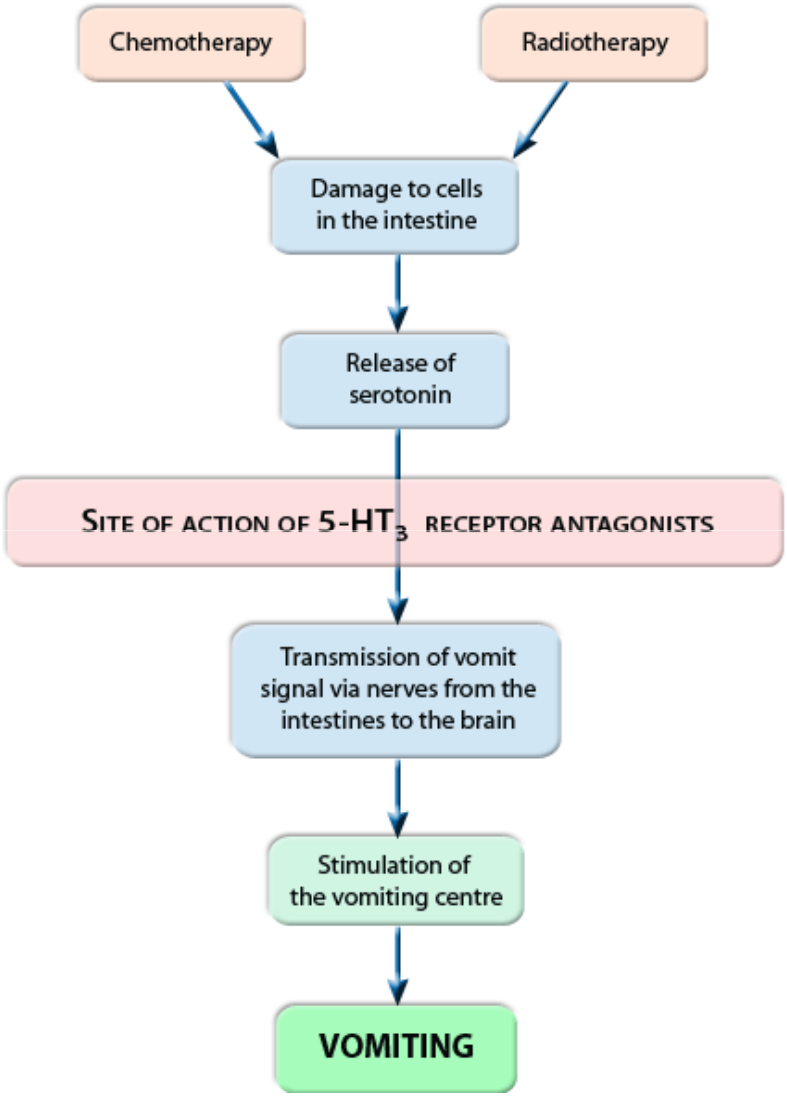
Drugs that act as agonists are indicated by solid-line arrows, whereas antagonists or inhibitors are shown with broken-line arrows.

… a small deviation relative to the 5-HT3 receptor:



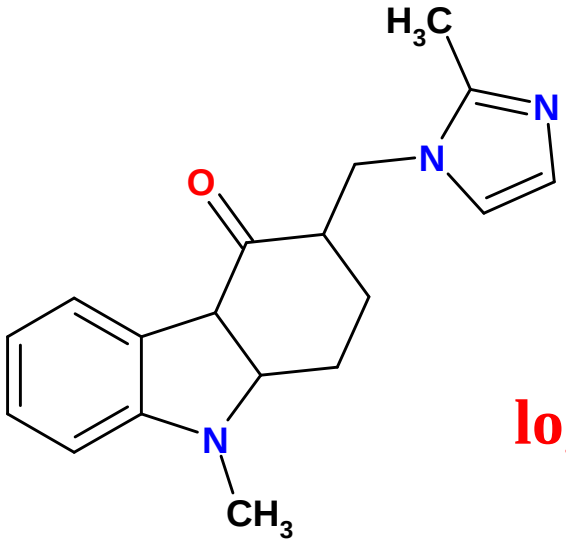
Serotonin: 5HT-3 receptor and antiemetic drugs

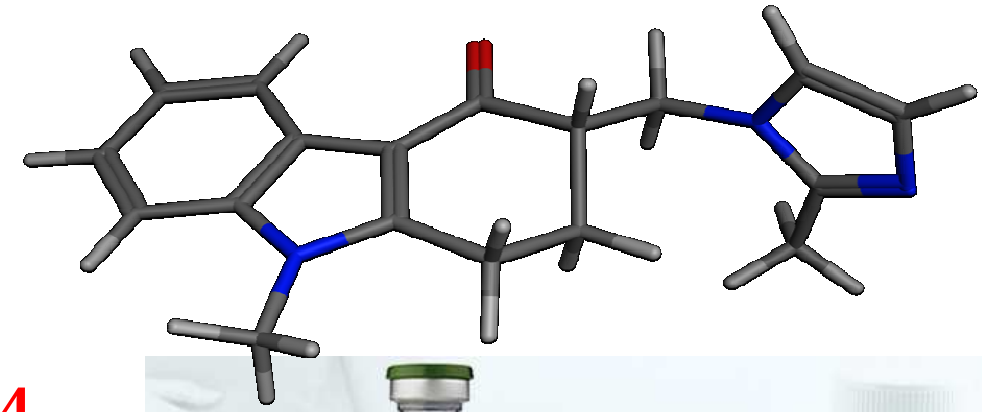




2. Anxiety and anxiolytic drugs

Serotonin: 5HT-3 receptor and antiemetic drugs





logP = 2.4

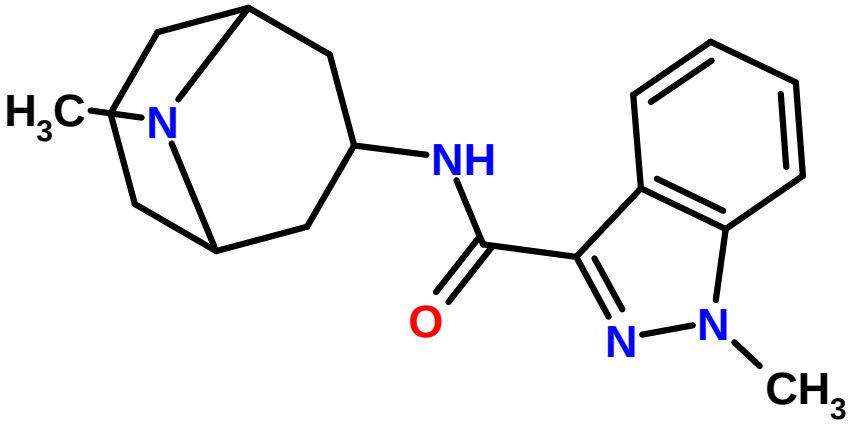
Ondansetron (Zofran®)

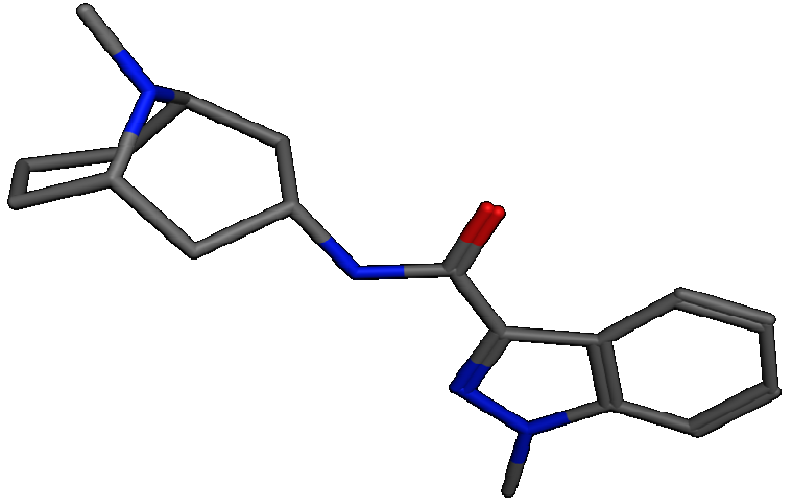
9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3,4,9-tetrahydro-1H-carbazol-4-one

Ondansetron is a selective serotonin 5-HT$_3$ receptor antagonist. The antiemetic activity of the drug is brought about through the inhibition of 5-HT$_3$ receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT$_3$ receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone.

2. Anxiety and anxiolytic drugs

Serotonin: 5HT-3 receptor and antiemetic drugs





logP = 2.6

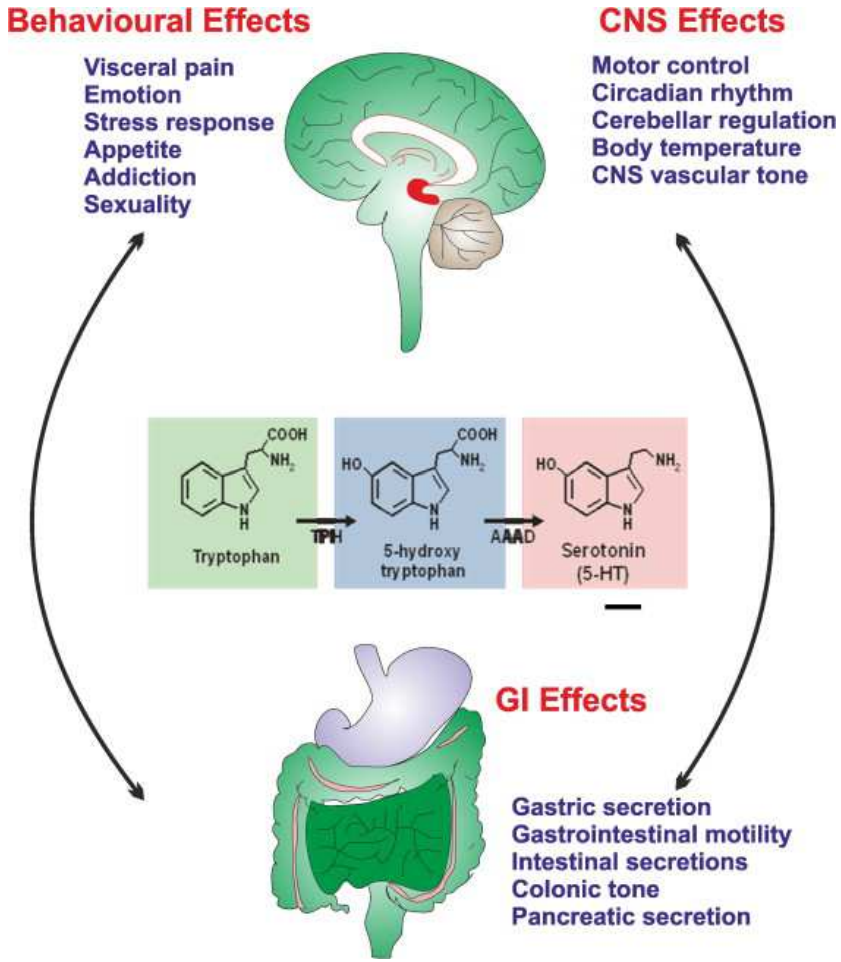
Granisetron (Kytril ®)

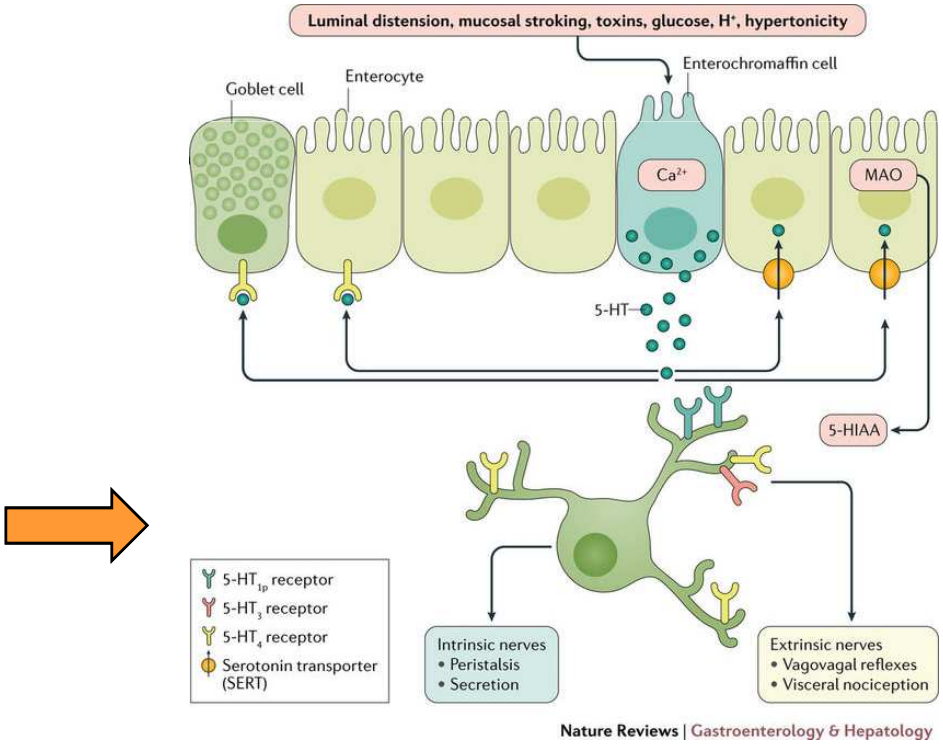
1-metil-N-((1R,3r,5S)-9-metil-9-azabiciclo[3.3.1]nonan-3-il)-1H-indazole-3-carbossamide

Granisetron is a potent, selective antagonist of 5-HT_3 receptors. It is a longer acting and more potent of Ondansetron. Administered by intravenous infusion or orally. The most common side effect of Granisetron is headache.

2. Anxiety and anxiolytic drugs

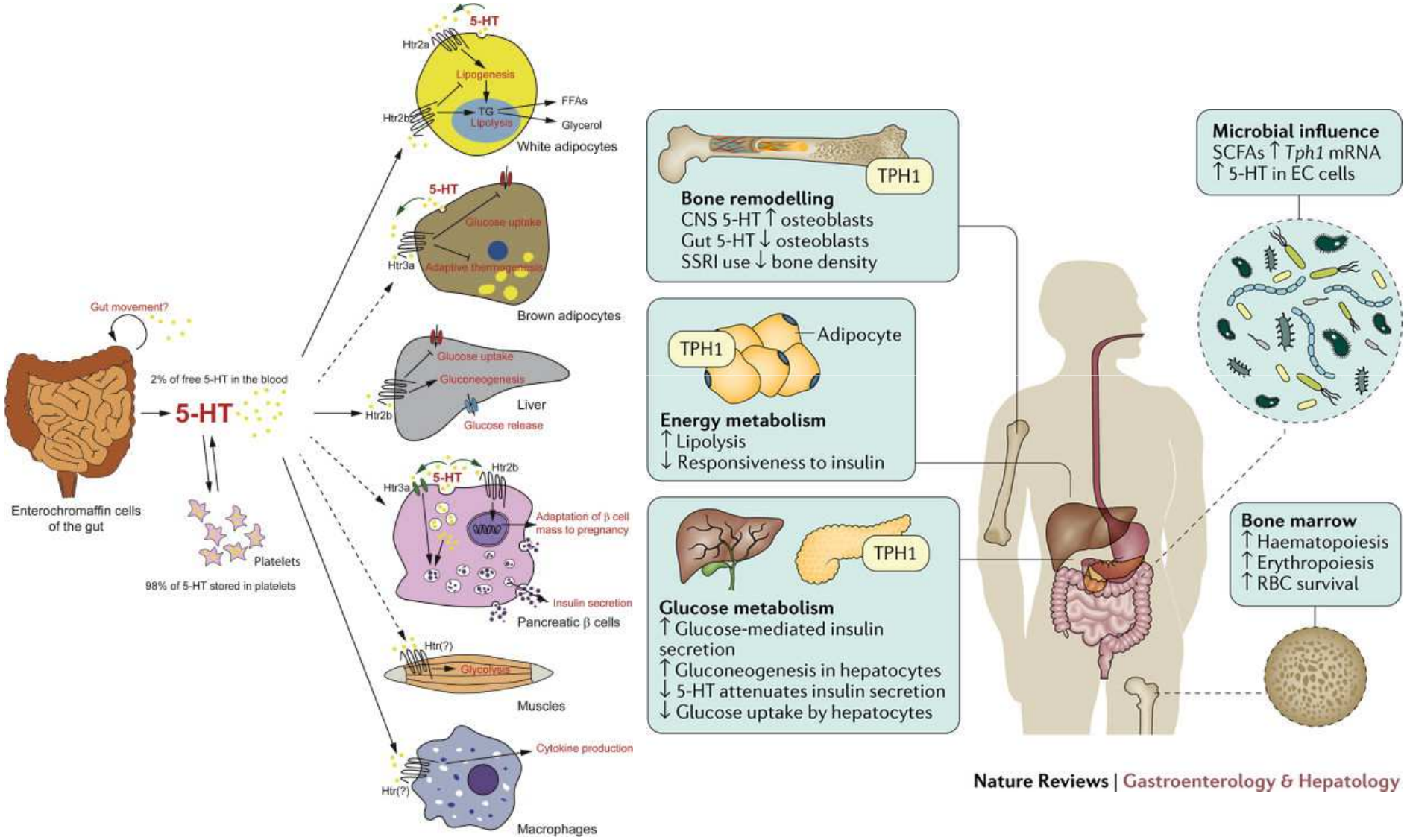
Serotonin – 5HT pathways in periphery





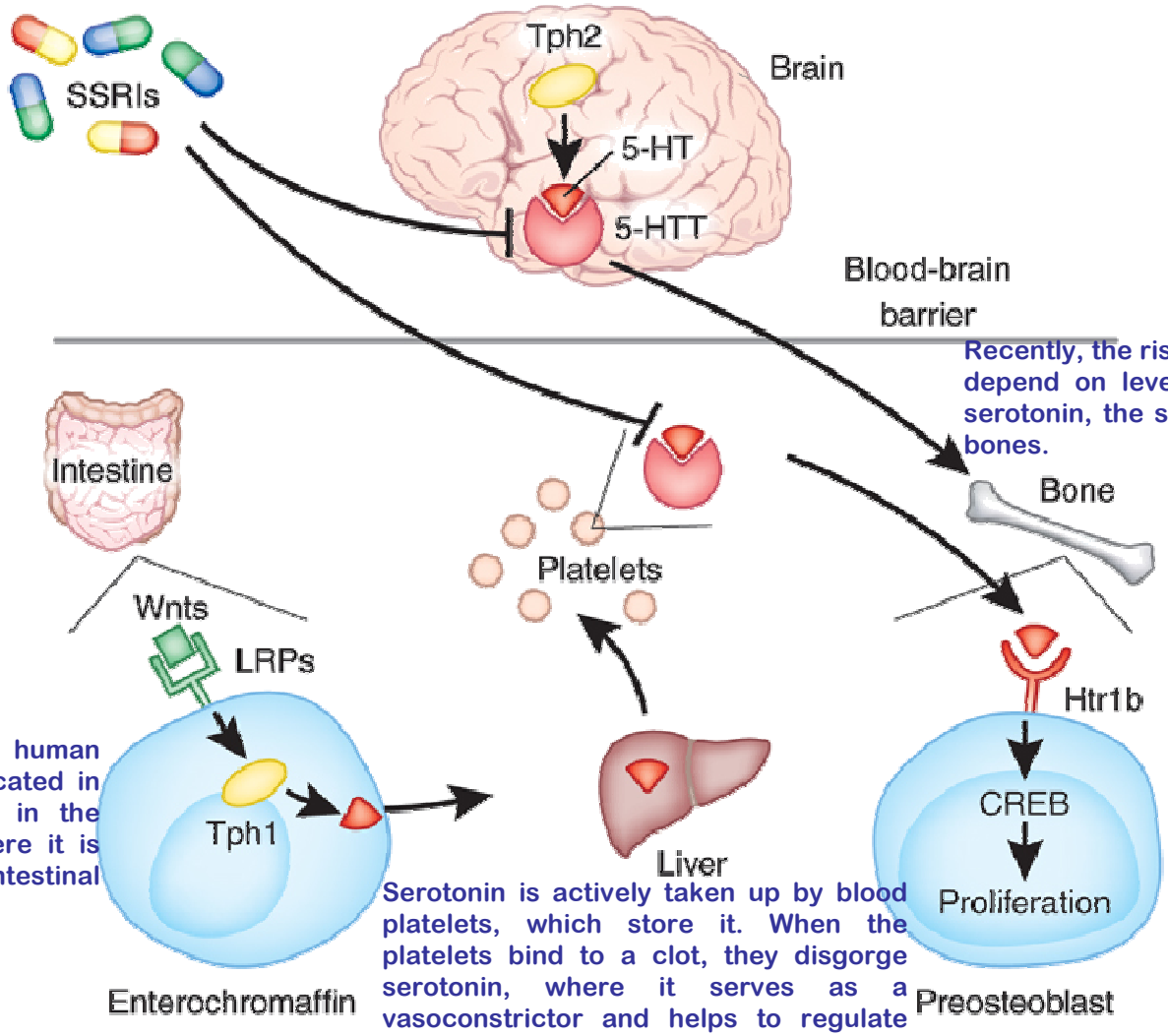
2. Anxiety and anxiolytic drugs

Serotonin – 5HT pathways in periphery



2. Anxiety and anxiolytic drugs

Serotonin – 5HT pathways in periphery



Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the alimentary canal (gut), where it is used to regulate intestinal movements.

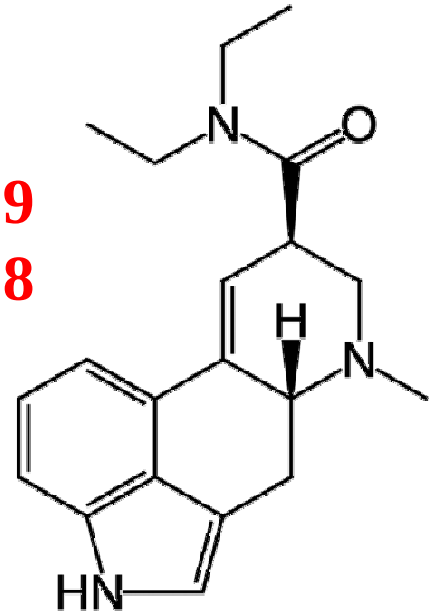
Serotonin is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they disgorge serotonin, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting.

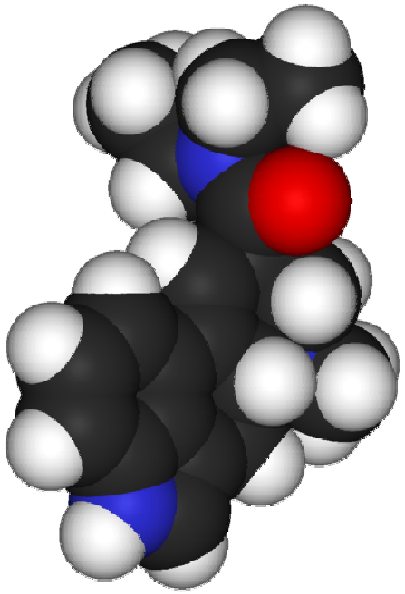
Recently, the risk of osteoporosis, seems to depend on levels of serotonin, The more serotonin, the study found, the weaker the bones.

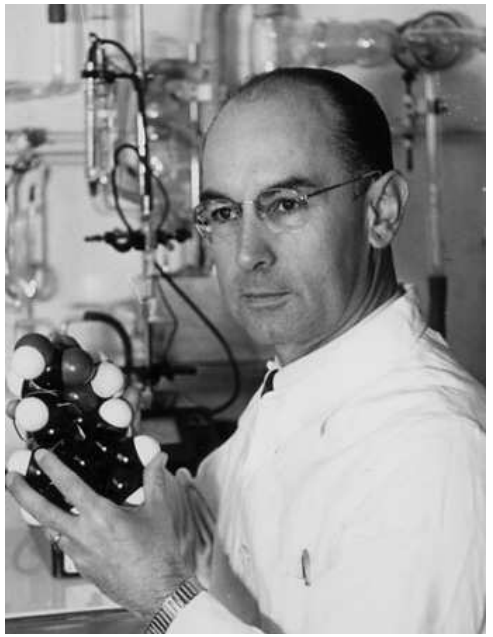
2. Anxiety and anxiolytic drugs

Lysergic acid diethylamide (LSD)

logP = 2.9
pKa = 7.8



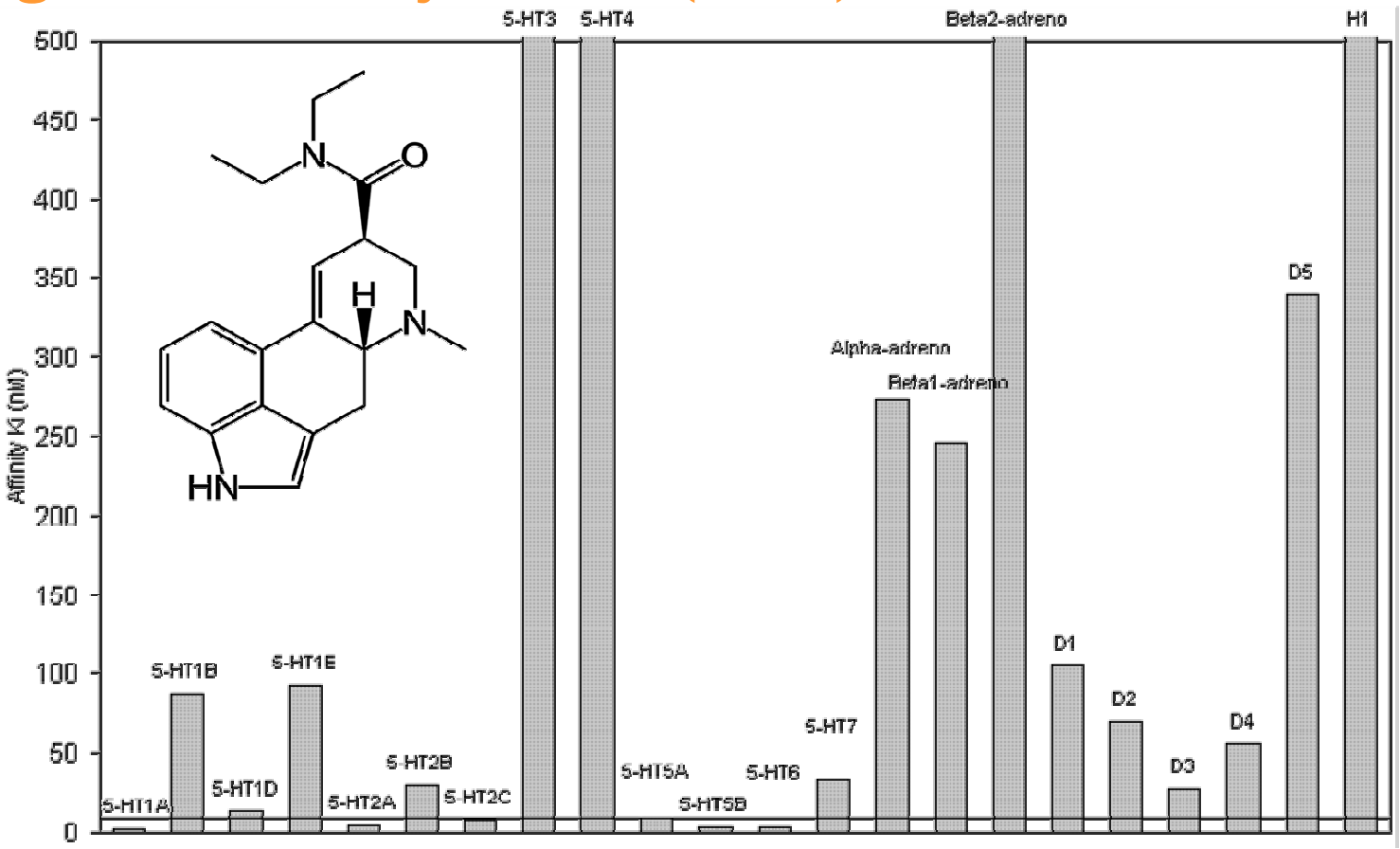




LSD is an ergoline derivative. It is commonly synthesised by reacting diethylamine with an activated form of lysergic acid. LSD was first synthesized on November 16, 1938 by Swiss chemist *Albert Hofmann* at the Sandoz Laboratories in Basel, Switzerland as part of a large research program searching for medically useful ergot alkaloid derivatives. LSD's psychedelic properties were discovered 5 years later when Hofmann himself accidentally ingested an unknown quantity of the chemical. LSD is well known for its psychological effects which can include altered thinking processes, closed- and open-eye visuals, synesthesia, an altered sense of time and spiritual experiences, as well as for its key role in 1960s counterculture**.**

2. Anxiety and anxiolytic drugs

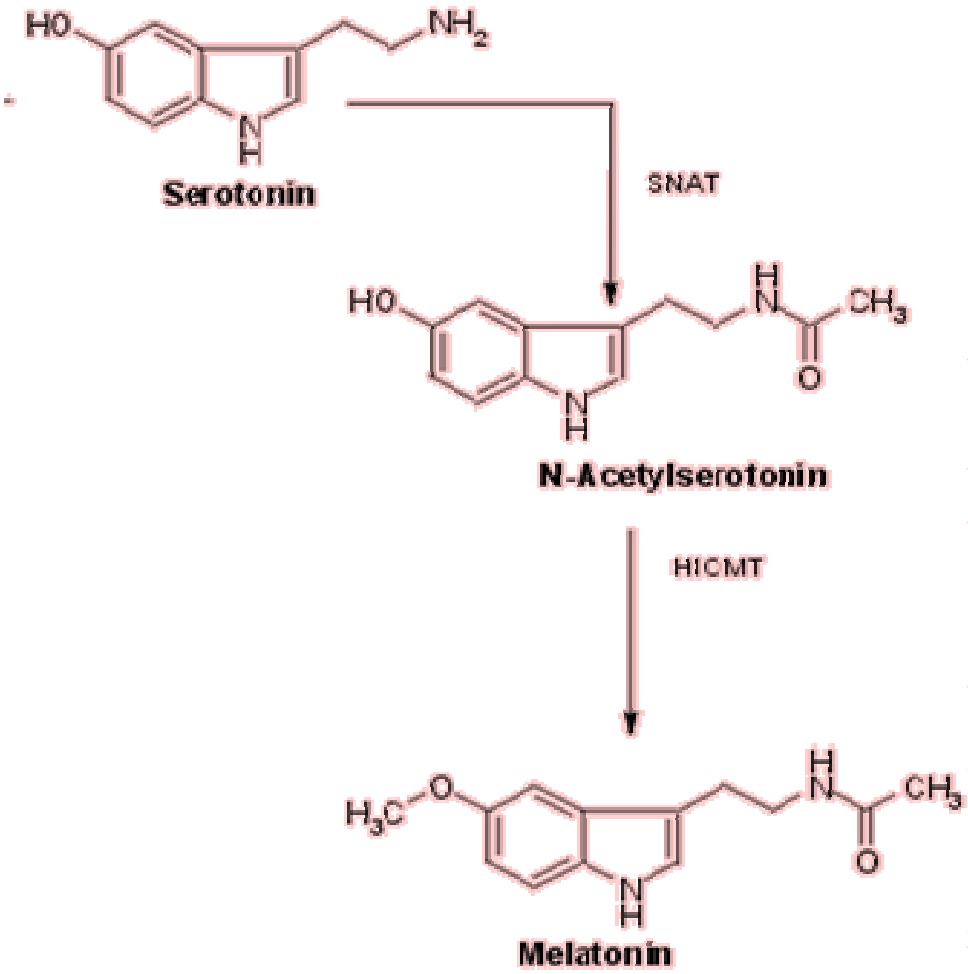
Lysergic acid diethylamide (LSD)



LSD affects a large number of the G protein-coupled receptors, including all dopamine receptor subtypes, and all adrenoreceptor subtypes, as well as many others. Most serotonergic psychedelics are not significantly dopaminergic, and LSD is therefore rather unique in this regard. LSD's agonism of D2 receptors contributes to its psychoactive effects.LSD binds to most serotonin receptor subtypes except for 5-HT3 and 5-HT4.

2. Anxiety and anxiolytic drugs

Serotonin and Melatonin

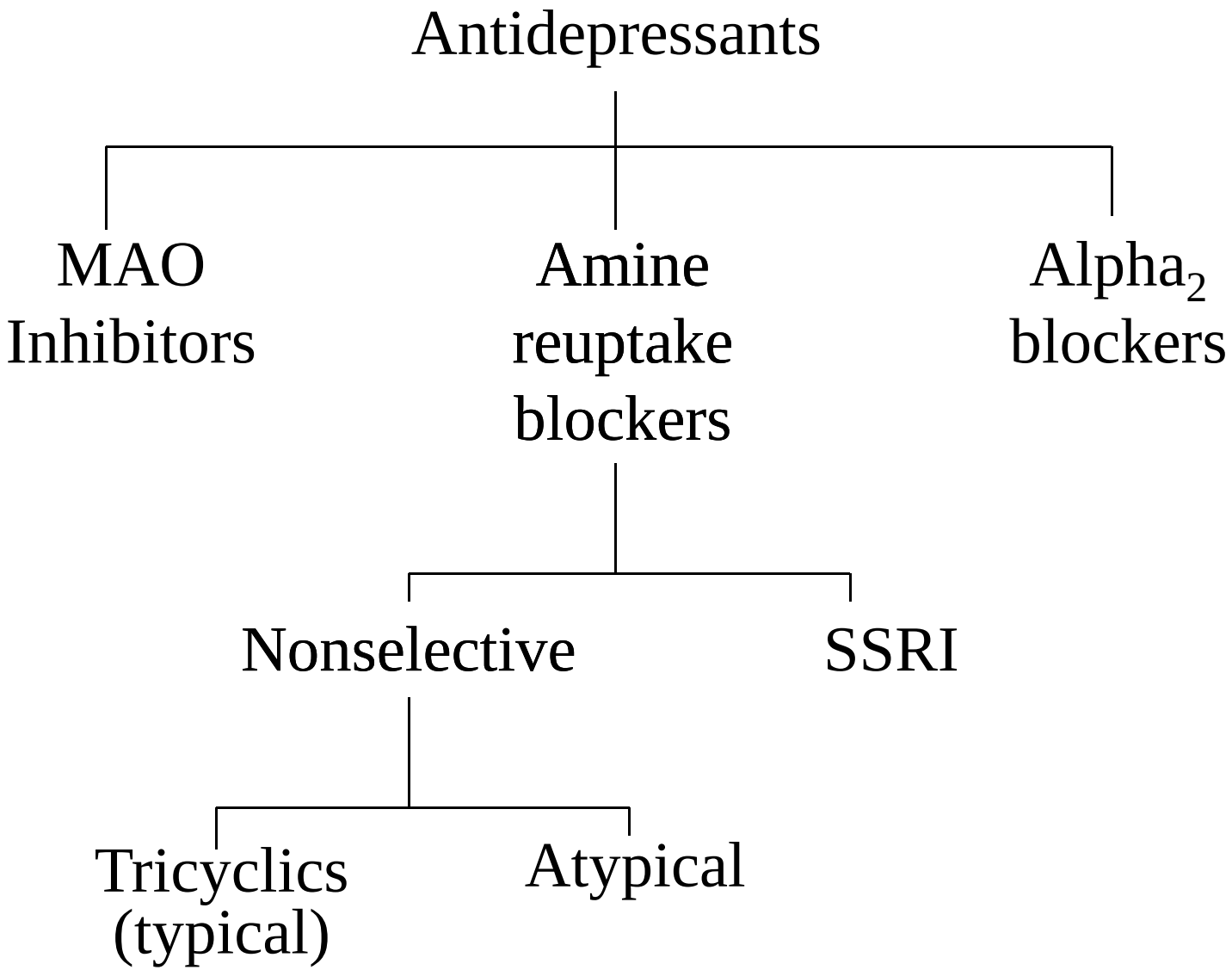


***N*-acetyl-5-methoxytryptamine**

In humans, melatonin is produced by the pineal gland, a small endocrine gland located in the center of the brain but outside the blood–brain barrier. The melatonin signal forms part of the system that regulates the *sleep–wake cycle* by chemically causing drowsiness and lowering the body temperature, but it is the central nervous system (specifically the suprachiasmatic nuclei, or SCN) that controls the daily cycle in most components of the paracrine and endocrine systems rather than the melatonin signal (as was once postulated).

Many biological effects of melatonin are produced through activation of melatonin receptors, G protein-coupled receptors (GPCR) . In human two melatonin receptors have been cloned. The MT1 subtype's expression in the pars tuberalis of the pituitary gland and suprachiamatic nuclei of the hypothalamus is indicative of melatonin's circadian and reproductive functional involvement.

2. Depression and antidepressant drugs



2. Depression and antidepressant drugs

2.0 General problems of antipsychotic treatments

TRANSPORTERS **RECEPTORS**

ADR SER DOP ADR SER DOP ACH H

D1-like family **(D_1 and D_5): GPCRs coupled to Gαs. D_1 are exclusively expressed on the postsynaptic neurons has a moderate stimulatory effect on locomotor activity.**

D2-like family **(D_2, D_3 and D_4): GPCRs coupled to Gαi. The roles of the D_2 and D_3 are much more complex than D_1 dopamine receptors because they result from both presynaptic and postsynaptic expression.**

2. Depression and antidepressant drugs

2.0 General problems of antipsychotic treatments

TRANSPORTERS **RECEPTORS**

ADR SER DOP ADR SER DOP ACH H

Extrapyramidal syndrome (EPS) is due to the blockade of dopamine receptors (both D1 and D2) in the basal ganglia, leading to Parkinson-like symptoms such as slow movement (bradykinesia), stiffness, and tremor.

***Typical* Antipsychotics**

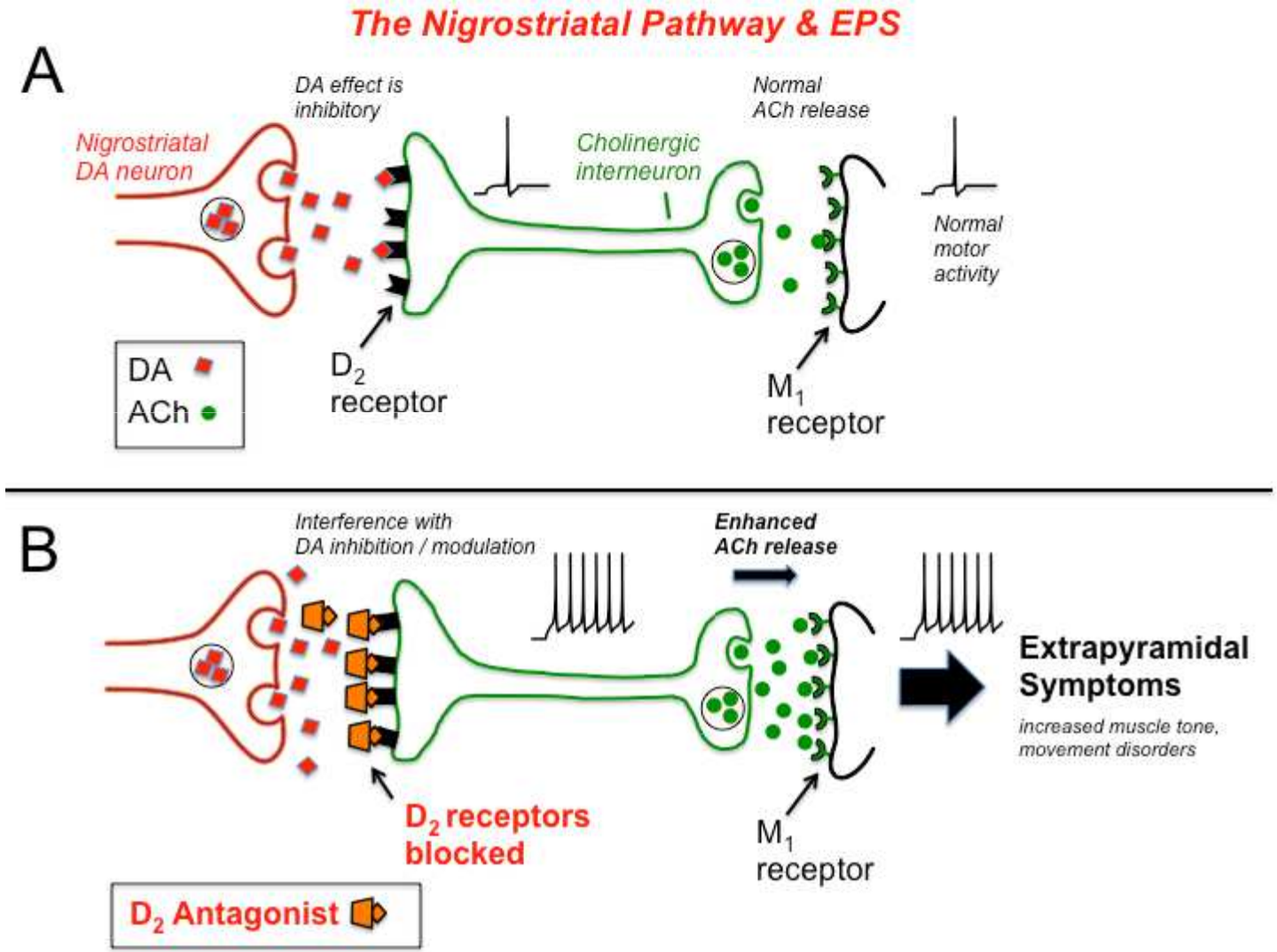
- Phenothiazines — D2 ≅ D1 > α1 ≅ 5HT2

***Atypical* Antipsychotics**

- First-generation (butyrophenones) — D2 > D1 ≅ 5HT2 > α1
- Second-generation (risperidone, clozapine) — D2 ≅ 5HT2 >> D1 > α1

2. Depression and antidepressant drugs

2.0 General problems of antipsychotic treatments



2. Depression and antidepressant drugs

2.0 General problems of antipsychotic treatments

TRANSPORTERS **RECEPTORS**

ADR SER DOP **ADR SER DOP ACH H**

More recent research has demonstrated the side effect profile of "atypical" drugs is similar to older drugs, causing the leading medical journal The Lancet to write in its editorial "*the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction.*"

The spurious advance of antipsychotic drug therapy

to others. Antipsychotic drugs differ in their potencies and have a wide range of adverse-effect profiles, with nothing that clearly distinguishes the two major groups. Importantly, the second-generation drugs have no special atypical characteristics that separate them from the typical, or first-generation, antipsychotics. As a group they are no more efficacious, do not improve specific symptoms, have no clearly different side-effect profiles than the first-generation antipsychotics, and are less cost effective.[6-8] The spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed. But how is it that for nearly two decades we have, as some have put it,[9] "been beguiled" into thinking they were superior?

Tyler, P and Kendall, T The Lancet, Volume 373, Issue 9657, Pages 4 - 5, 2009

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants

The majority of the TCAs act primarily as ***serotonin-norepinephrine reuptake inhibitors (SNRIs)*** by blocking the *serotonin transporter (SERT)* and the *norepinephrine transporter (NET)*, respectively, which results in an elevation of the extracellular concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. *Notably, the TCAs have negligible affinity for the dopamine transporter (DAT), and therefore have no efficacy as dopamine reuptake inhibitors (DRIs), and hence, do not elevate dopamine levels.* Both serotonin and norepinephrine have been highly implicated in depression and anxiety, and it has been shown that facilitation of their activity has beneficial effects on these mental disorders.

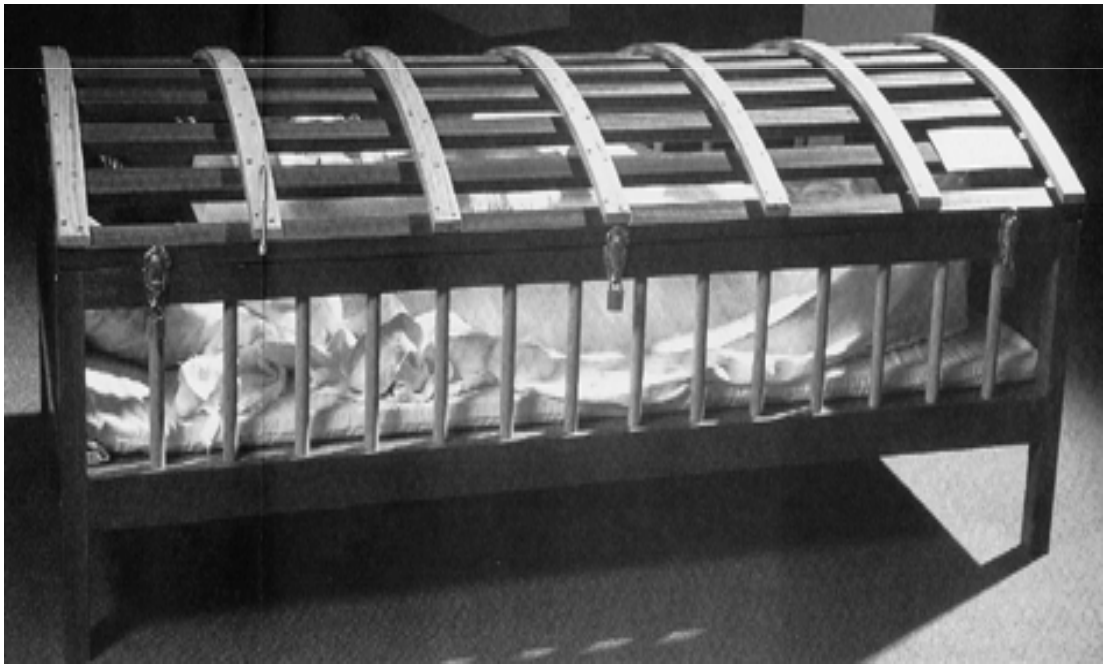
In addition to their reuptake inhibition, many TCAs also have high affinity as ***antagonists*** at the 5-HT2 (5-HT2A and 5-HT2C), 5-HT6, 5-HT7, α1-adrenergic, and NMDA receptors, and as ***agonists*** at the sigma receptors (σ1 and σ2), some of which may contribute to their therapeutic efficacy, as well as their side effects. The TCAs also have varying but typically high affinity for ***antagonizing*** the H1 and H2 histamine receptors, as well as the muscarinic acetylcholine receptors. As a result, they also act as potent antihistamines and anticholinergics. These properties are generally undesirable in antidepressants, however, and likely contribute to their large side effect profiles.

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants: history

Phillipe Pinel, (First Psychiatric Revolution)

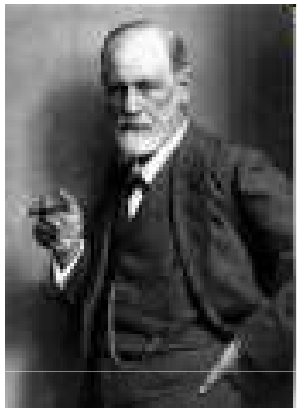
(20 April 1745 - 25 October 1826) was a French physician who was instrumental in the development of a more humane psychological approach to the custody and care of psychiatric patients, referred to today as moral treatment. He also made notable contributions to the classification of mental disorders and has been described by some as "the father of modern psychiatry".

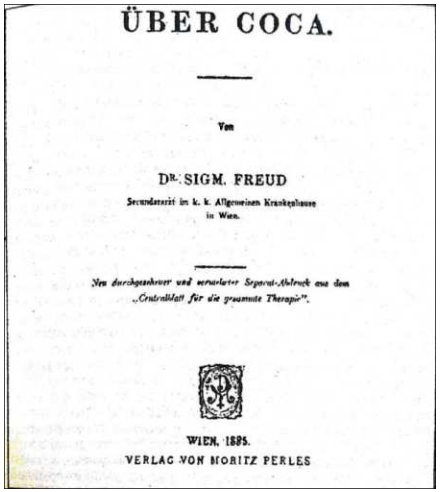


2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants: history

Sigmund Freud, Psychoanalyse (2nd Psyhciatric Revolution)
(6 May 1856 – 23 September 1939), was an Austrian neurologist who founded the psychoanalytic method of psychiatry.




ÜBER COCA.

Von

DR. SIGM. FREUD

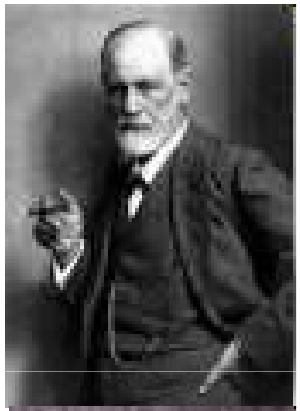
Secundararzt im k. k. Allgemeinen Krankenhause in Wien.

Neu durchgesehener und vermehrter Separat-Abdruck aus dem „Centralblatt für die gesammte Therapie".

WIEN, 1885.
VERLAG VON MORITZ PERLES

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants: history



Sigmund Freud, Psychoanalyse (2nd Psyhciatric Revolution)

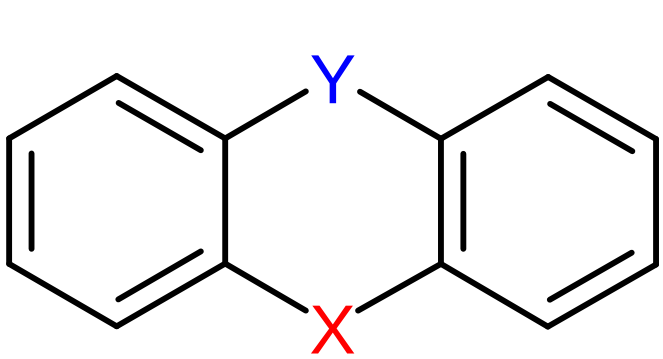
(6 May 1856 – 23 September 1939), was an Austrian neurologist who founded the psychoanalytic method of psychiatry.

Pierre Deniker (3rd Psychiatric Revolution)

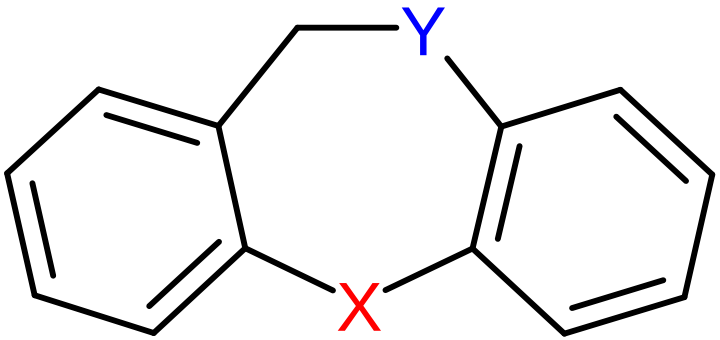
The first published clinical trial was that of Jean Delay and **Pierre Deniker** at the Hôpital Sainte-Anne in Paris in 1952, in which they treated 38 psychotic patients with daily injections of ***chlorpromazine*** without the use of other sedating agents. The response was dramatic; treatment with chlorpromazine went beyond simple sedation with patients showing improvements in thinking and emotional behavior.

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants and antipsychotic



6-6-6



6-7-6

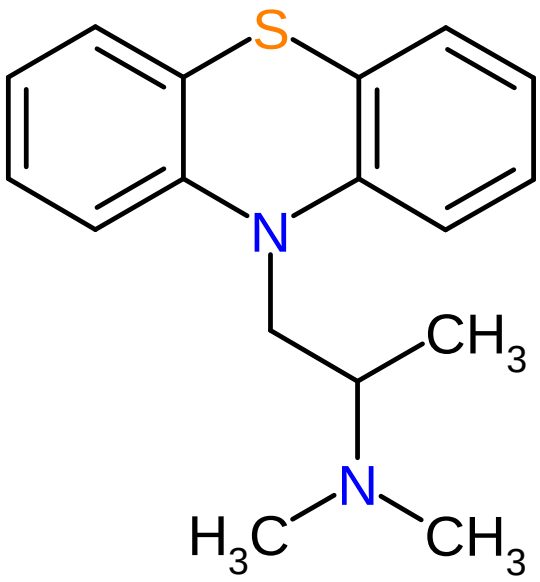
Tricyclic antidepressants (TCAs) are heterocyclic chemical compounds used primarily as antidepressants. They are named after their chemical structure, which contains three rings of atoms. The ***tetracyclic antidepressants*** (TeCAs), which contain four rings of atoms, are a closely related group of antidepressant compounds.

In recent times, the TCAs have been largely replaced in clinical use in most parts of the world by newer antidepressants such as the ***selective serotonin reuptake inhibitors (SSRIs)*** and ***serotonin-norepinephrine reuptake inhibitors (SNRIs)***, among others, though they are still sometimes prescribed for certain indications.

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants: history

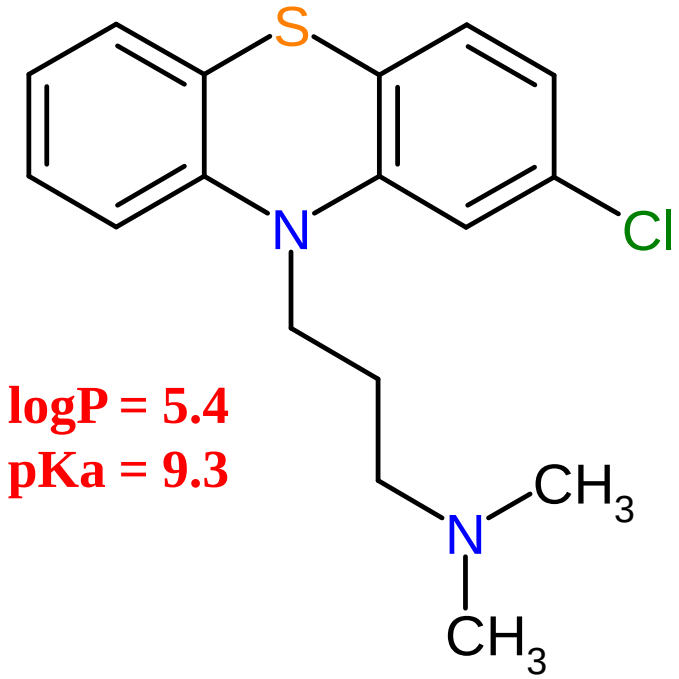
In 1933, the French pharmaceutical company Laboratoires Rhône-Poulenc began to search for new anti-histamines (H_1 receptor). In 1947, it synthesized ***promethazine***, a *phenothiazine* derivative, which was found to have more pronounced sedative and antihistaminic effects than earlier drugs. The chemist Paul Charpentier produced a series of compounds and selected the one with the least peripheral activity, known as RP4560 or ***chlorpromazine***, on 11 December 1950.



logP = 4.8
pKa = 9.1

Promethazine

(*RS*)-*N*,*N*-dimethyl-1-(10*H*-phenothiazin-10-yl) propan-2-amine

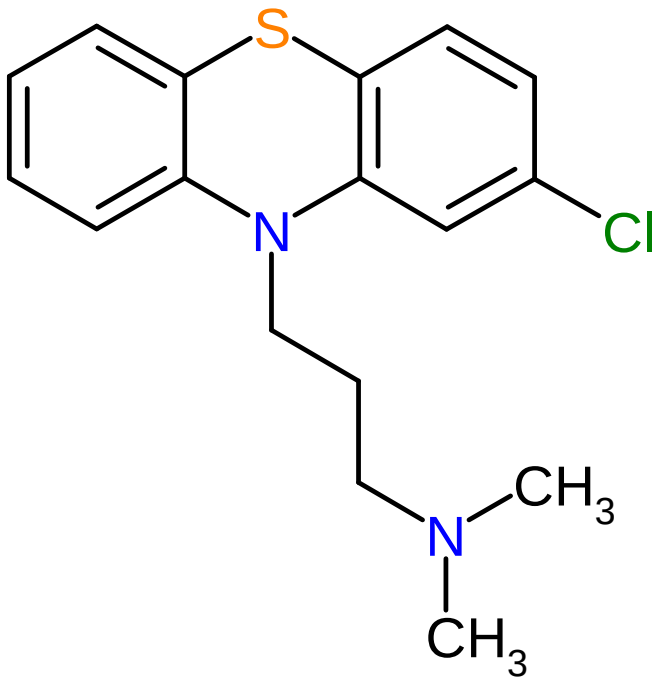


logP = 5.4
pKa = 9.3

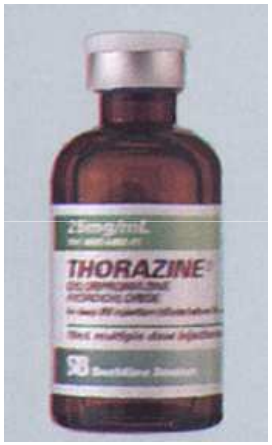
Chlorpromazine

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants: history

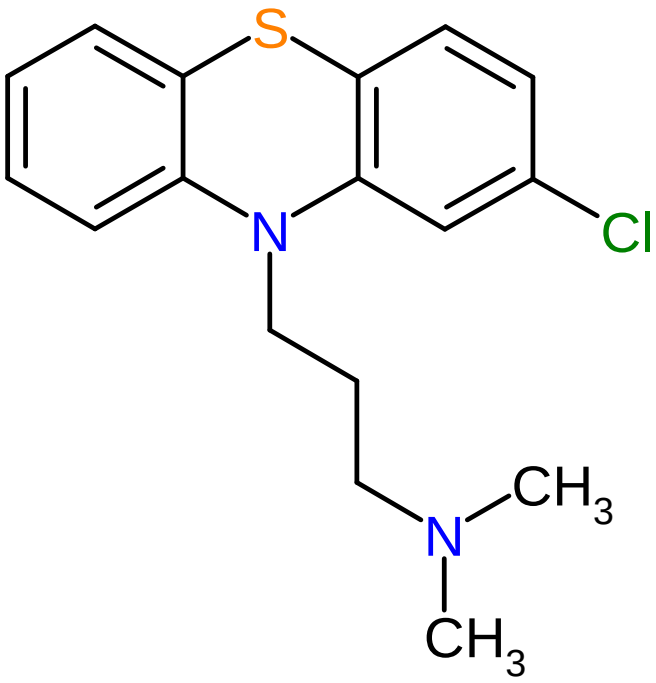


Chlorpromazine (Thorazine®)



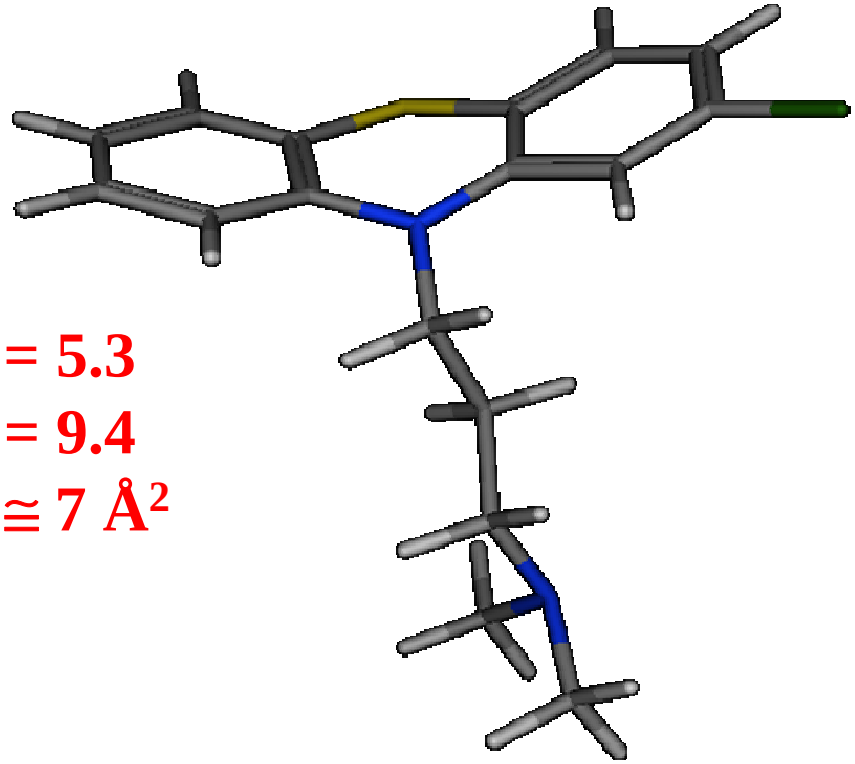
Paul Charpentier

2. Depression and antidepressant drugs



Chlorpromazine

3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-
-dimethyl-propan-1-amine



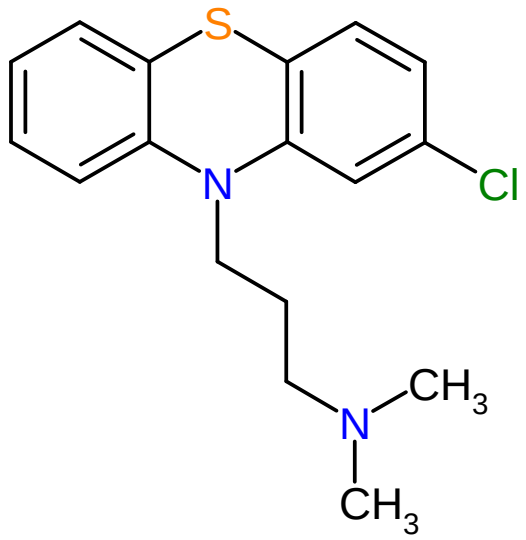
logP = 5.3

pKa = 9.4

PSA ≅ 7 Å²

Chlorpromazine was the first drug developed with specific antipsychotic action. Its use has been described as the single biggest advance in psychiatric treatment, dramatically improving the prognosis of patients in psychiatric hospitals worldwide. It was the prototype for the phenothiazine class, which later grew to comprise several other agents.

2. Depression and antidepressant drugs



Chlorpromazine is a very effective antagonist of D_2 dopamine receptors and similar receptors, such as D3 and D5.

Unlike most other drugs of this family, it also has a high affinity for D_1 receptors.

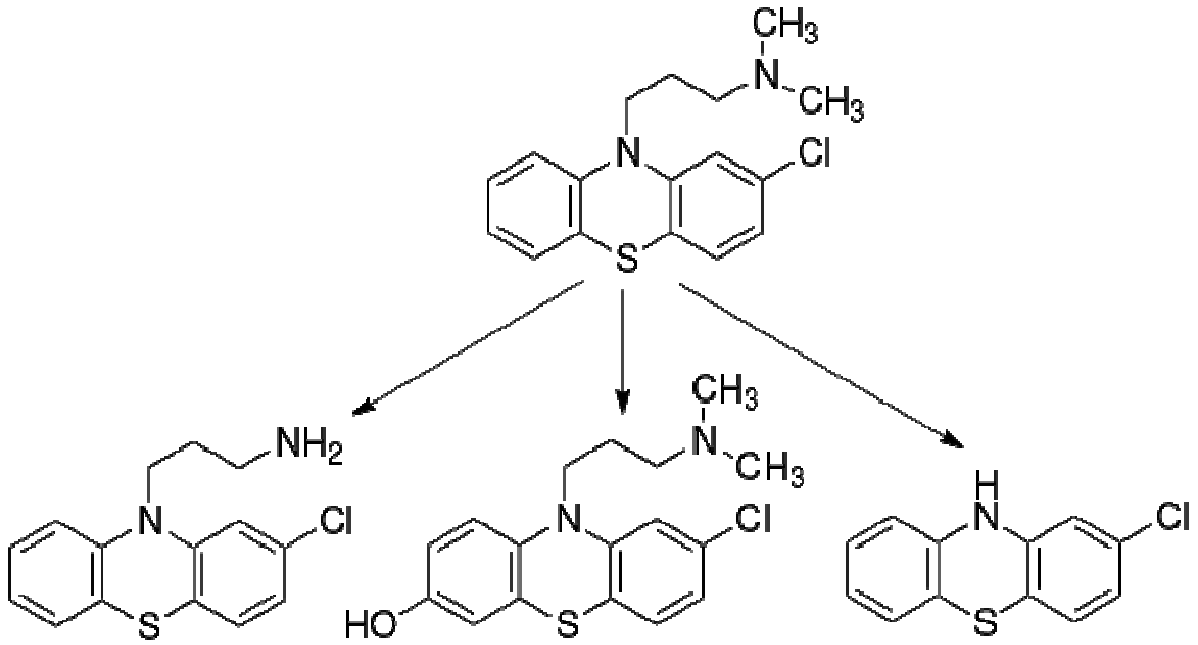
Chlorpromazine acts as an antagonist on different other postsynaptic receptors: serotonin receptors (5-HT_1 and 5-HT_2), histamine receptors (H_1 receptors), α_1- and α_2-adrenergic receptors, M_1 and M_2 muscarinic acetylcholine receptors.

It is classified as a ***dirty drug***.

The main side effects of chlorpromazine are due to its anticholinergic properties; these effects overshadow and counteract, to some extent, the *extrapyramidal side effects* typical of many early generation antipsychotics.

2. Depression and antidepressant drugs

Chlorpromazine: metabolic destiny…

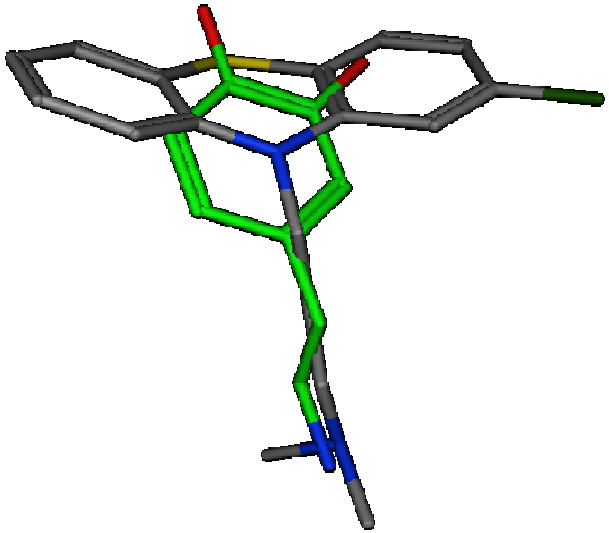


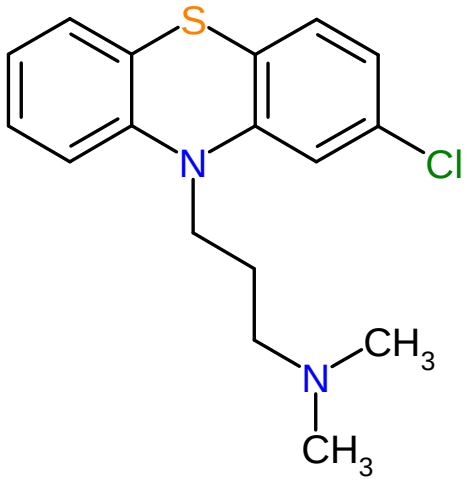
CYP2D6 and CYP1A2 mediated into over 10 major metabolites. The major routes of metabolism include hydroxylation, N-oxidation, sulphoxidation, demethylation, deamination and conjugation.

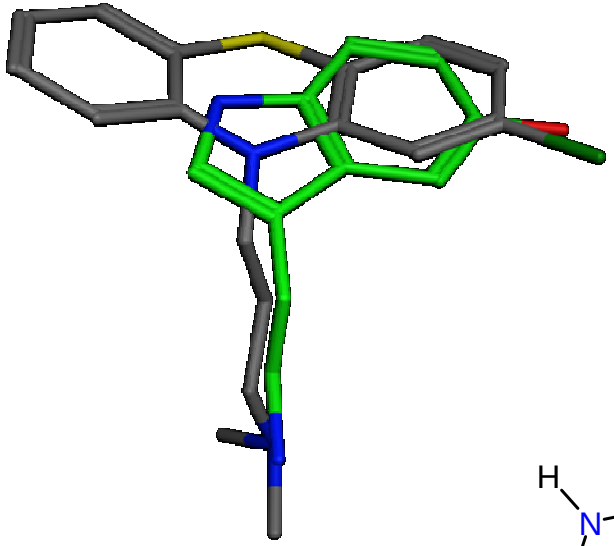
Its high lipophilicity allows it to be detected in the urine for up to *18 months*.

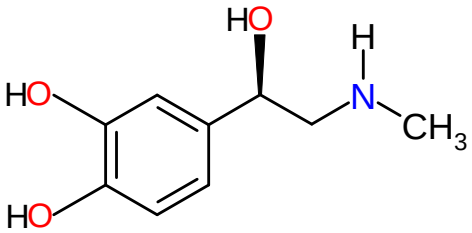
2. Depression and antidepressant drugs

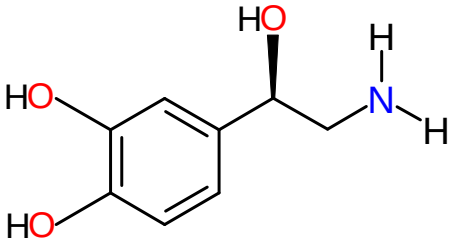
Can you understand why “dirty”?

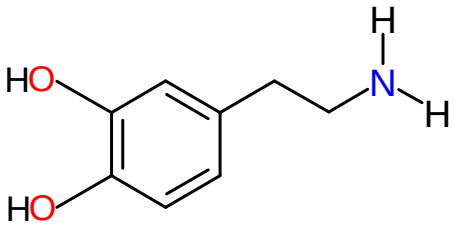


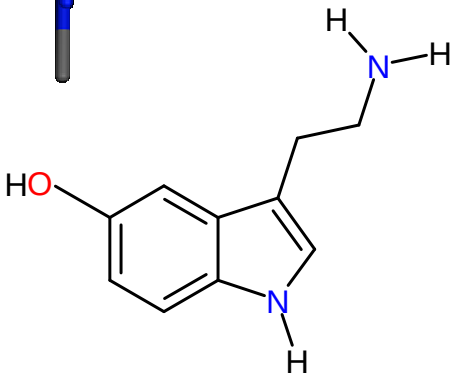




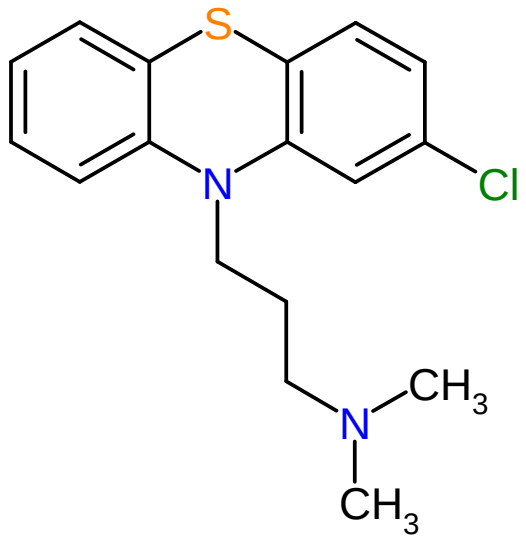




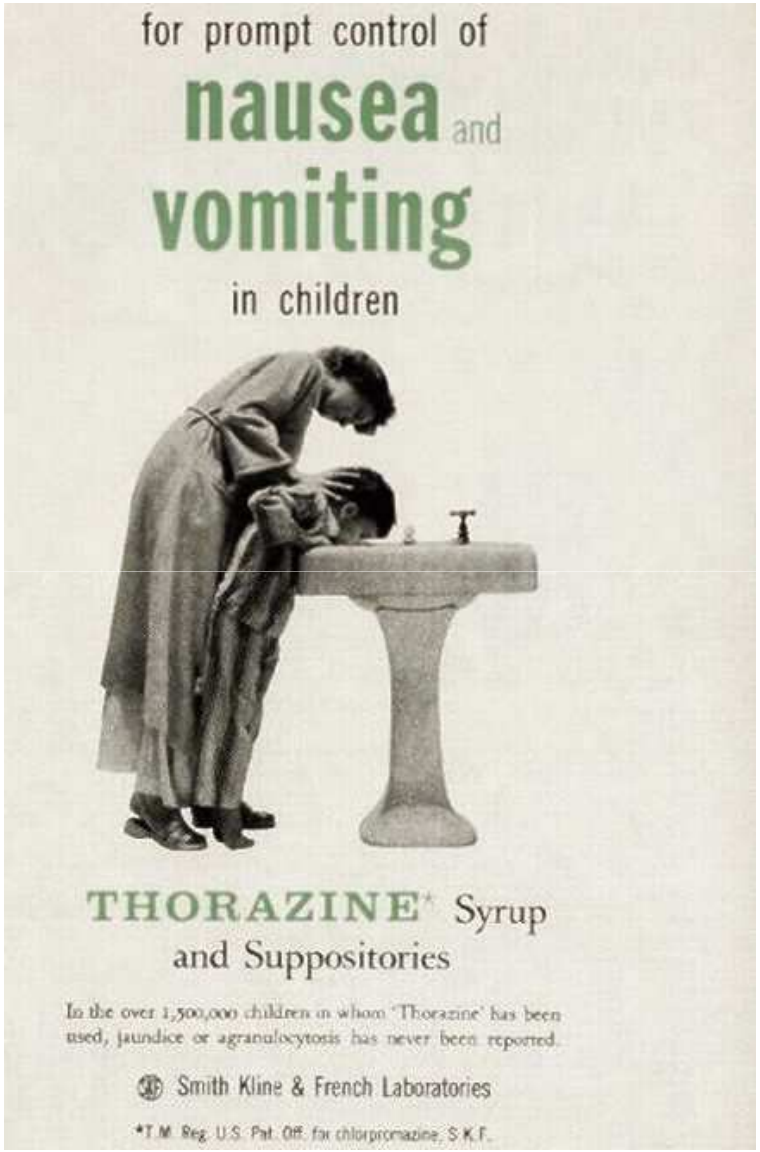




2. Depression and antidepressant drugs



Chlorpromazine



2. Depression and antidepressant drugs

Pipamazine

Pipamazine (trade names Mornidine) is a drug of the phenothiazine class formerly used as an antiemetic. It is chemically related to chlorpromazine, but has negligible antipsychotic activity and produces few extrapyramidal side effects. It was eventually withdrawn from the U.S. market after reports of hepatotoxicity (liver injury).

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants typical

Imipramine (Tofranil)
Desipramine (Norpramin, Pertofrane)

Amitriptyline (Elavil)
Nortriptyline (Pamelor, Aventyl)

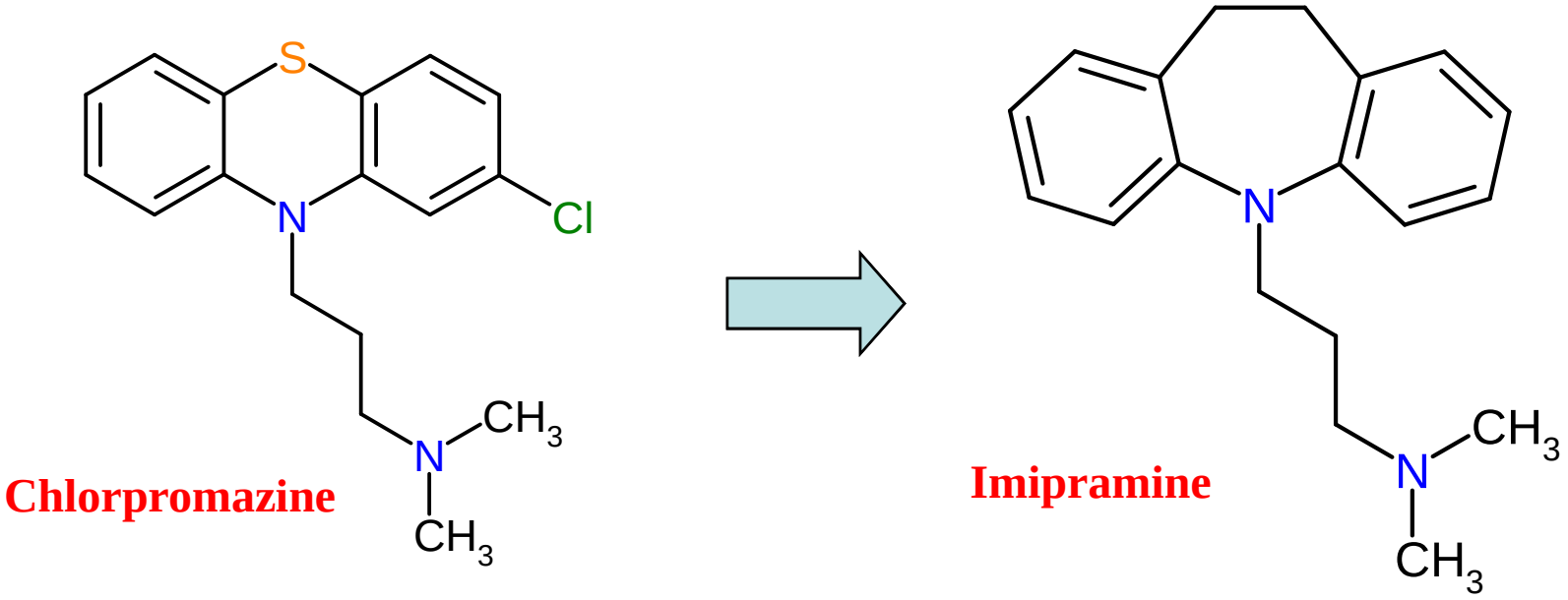
Doxepin (Aponal)

2. Depression and antidepressant drugs

2.1 Commonly Prescribed TCAs

- Anafranil (clomipramine)
- Asendin (amoxapine)
- Elavil (amitriptyline)
- Norpramin (desipramine)
- Pamelor (nortriptyline)
- Sinequan (doxepin)
- Surmontil (trimipramine)
- Tofranil (imipramine)
- Vivactil (protiptyline)

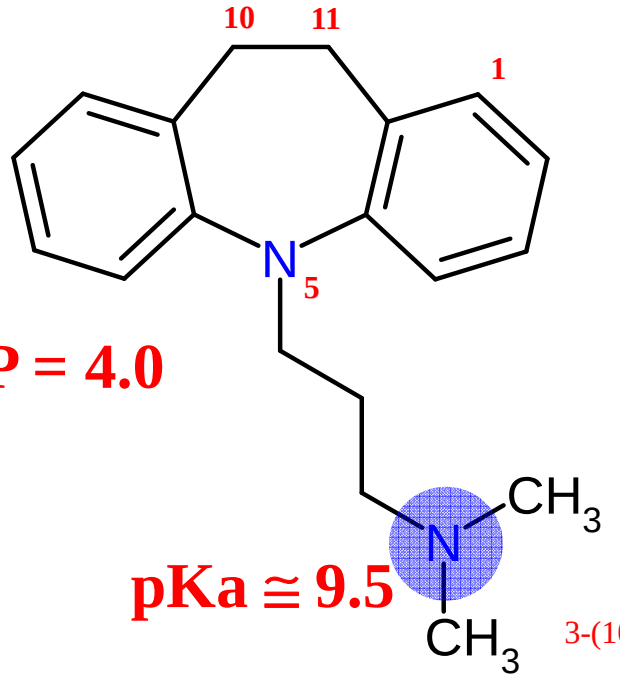
2. Depression and antidepressant drugs



Meanwhile, the 1952 introduction of chlorpromazine, the first modern psychotherapeutic medication, which was effective in treating schizophrenia, inspired the search for antidepressant agents among similar compounds, a familiar class of drugs found in many cough syrups known as the antihistamines. After testing several antihistamines, *Robert Kuhn* (by Ciba-Geigy) discovered one such compound, ***imipramine***, effective at treating depression without producing the stimulation experienced by those taking iproniazid. This he took as evidence that this antihistamine worked on the root of depression rather than by simply masking it with an energy burst. The drug in fact produced sedation, not elevation of mood, in undepressed subjects. Imipramine proved to be effective in over 60% of classical depression cases.

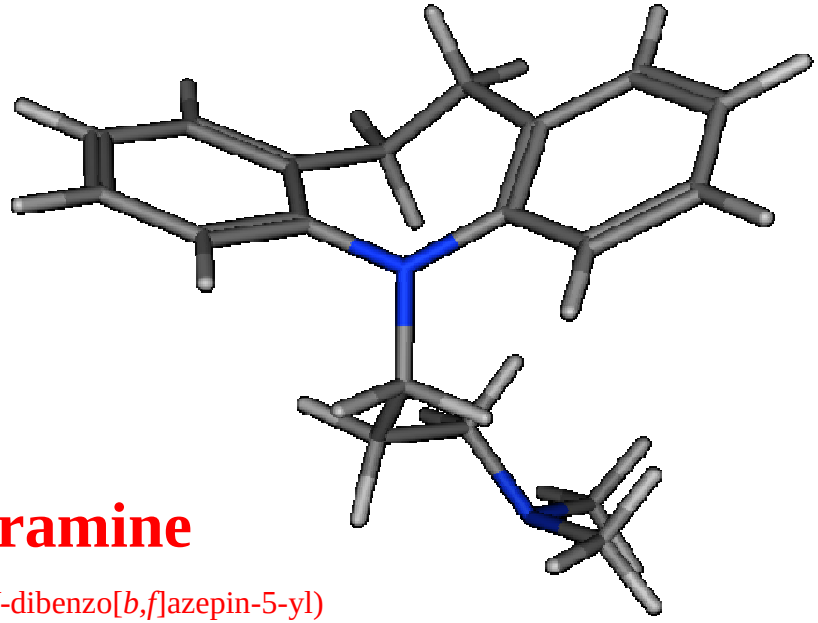
2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants typical



logP = 4.0

pKa ≅ 9.5



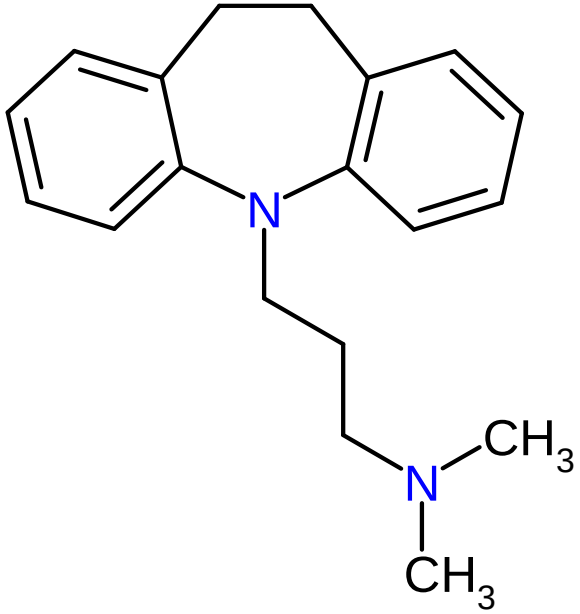
Imipramine

3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)
-*N*,*N*-dimethylpropan-1-amine

Imipramine, also known as melipramine, is an antidepressant medication, a tricyclic antidepressant of the dibenzazepine group. Imipramine is mainly used in the treatment of major depression and enuresis (inability to control urination). It has also been evaluated for use in panic disorder.

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants typical

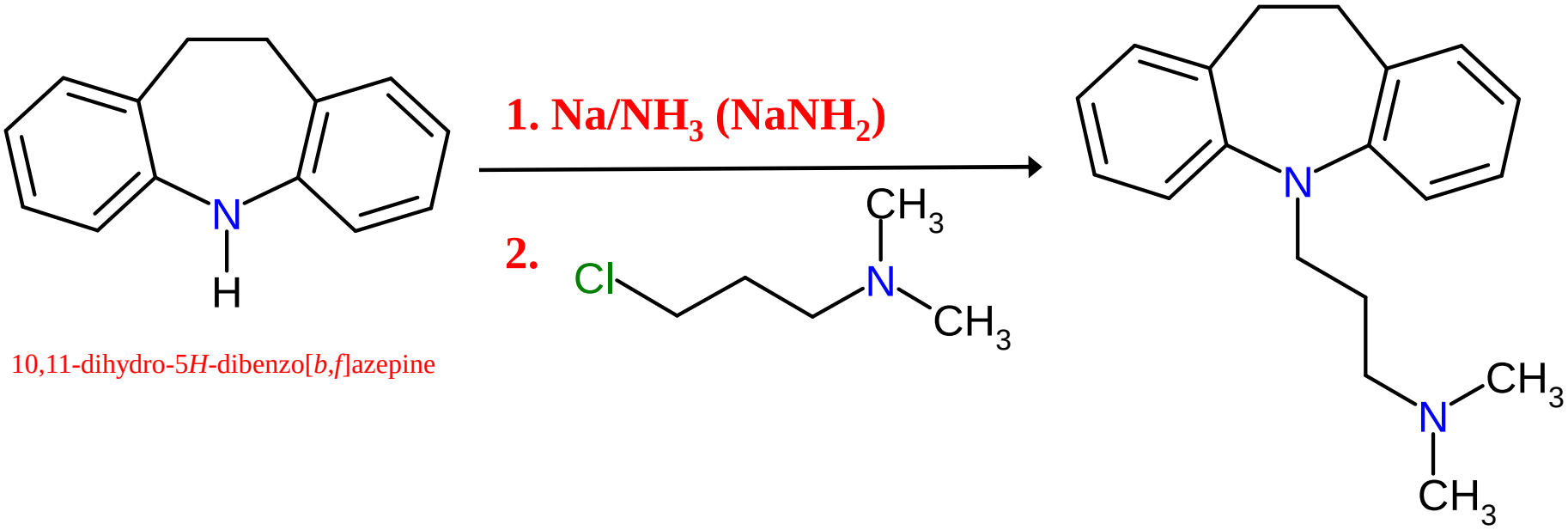


Imipramine

Imipramine was, in the late 1950s, the first tricyclic antidepressant to be developed (by Ciba-Geigy). It was first tried against psychotic disorders, such as schizophrenia, but proved insufficient. During the clinical studies, its antidepressant qualities were unsurpassed by other antidepressants. The mechanisms of Imipramine's medicinal action include, but are not limited to, effects on: norepinephrine, serotonin, dopamine, epinephrine, sigma receptor, enkephalinase, histamine, muscarine, and acetylcholine. Imipramine has been shown to interact with opioid systems in the central nervous system, possibly explaining some of its pain-relieving properties.

2. Depression and antidepressant drugs

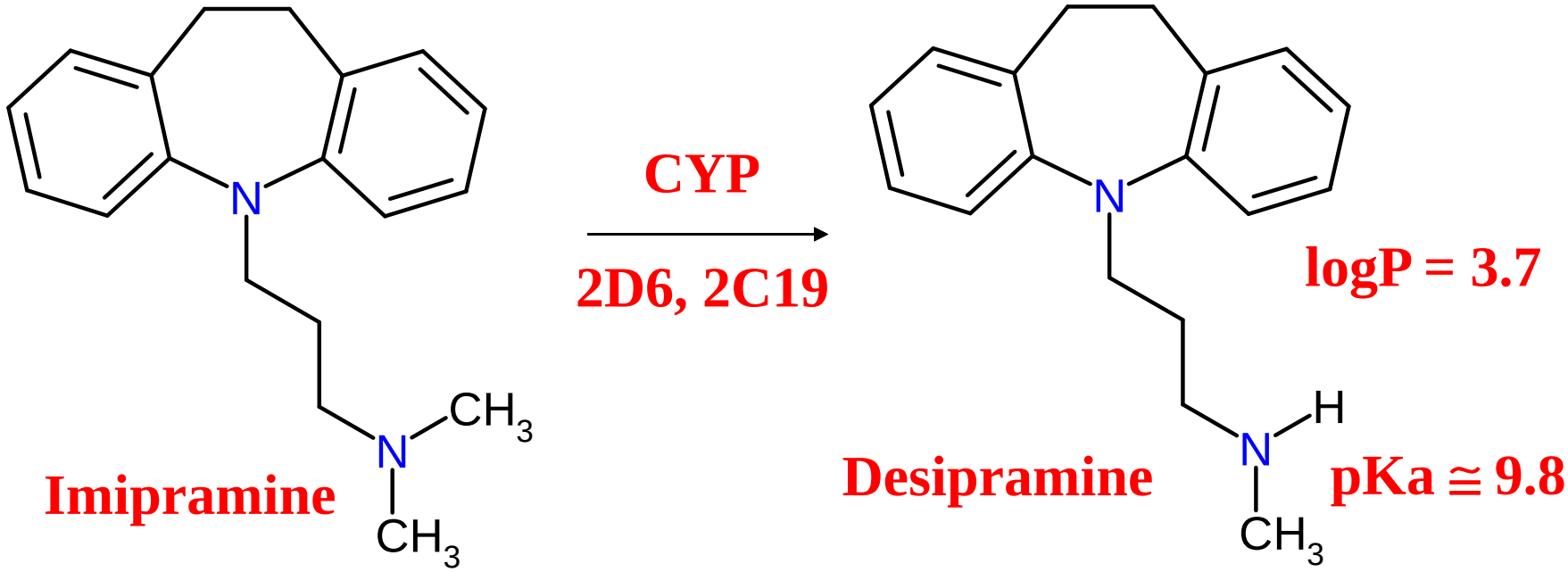
Synthesis Path



10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine

2. Depression and antidepressant drugs

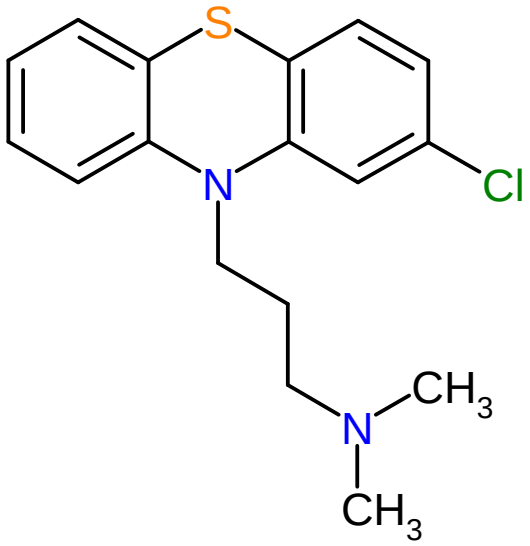
2.1 Tricyclic antidepressants typical



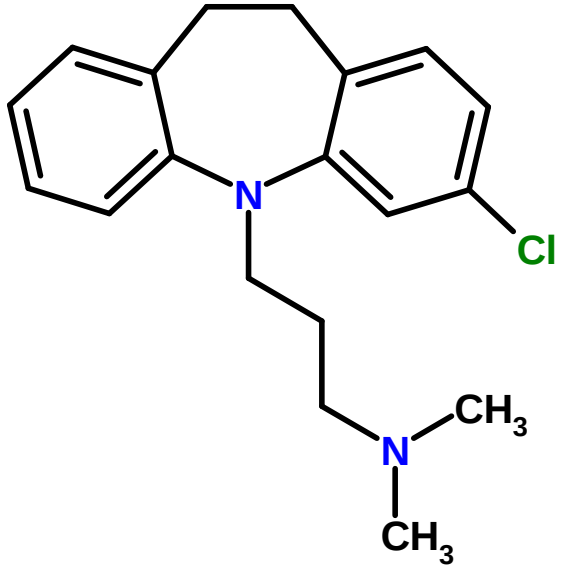
Desipramine, is a tricyclic antidepressant (TCA). It inhibits the reuptake of norepinephrine and to a lesser extent serotonin. It is used to treat depression, but not considered a first line treatment since the introduction of SSRI antidepressants. *Desipramine is an active metabolite of imipramine*. Along with other tricyclics, desipramine has found use in treating neuropathic pain.

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants typical



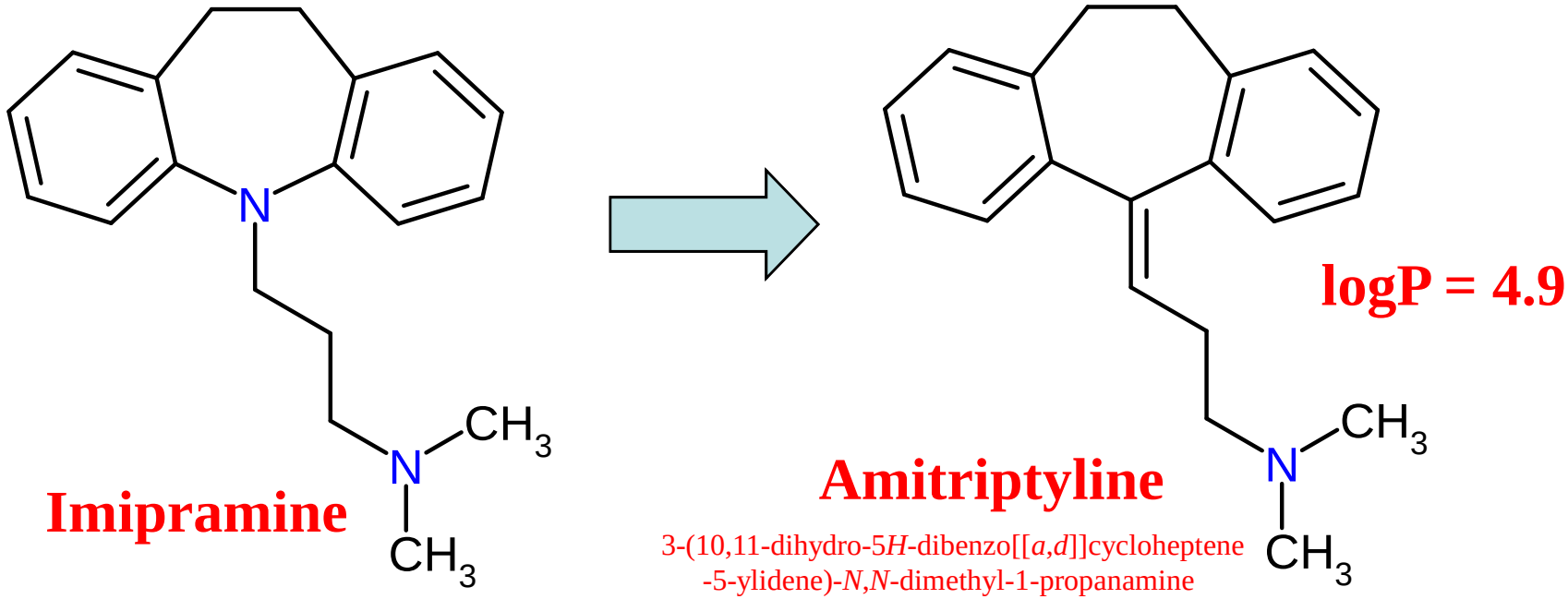
Chlorpromazine **logP = 5.3**
pKa = 9.4



Clomipramine **logP = 5.2**
pKa = 9.2

2. Depression and antidepressant drugs

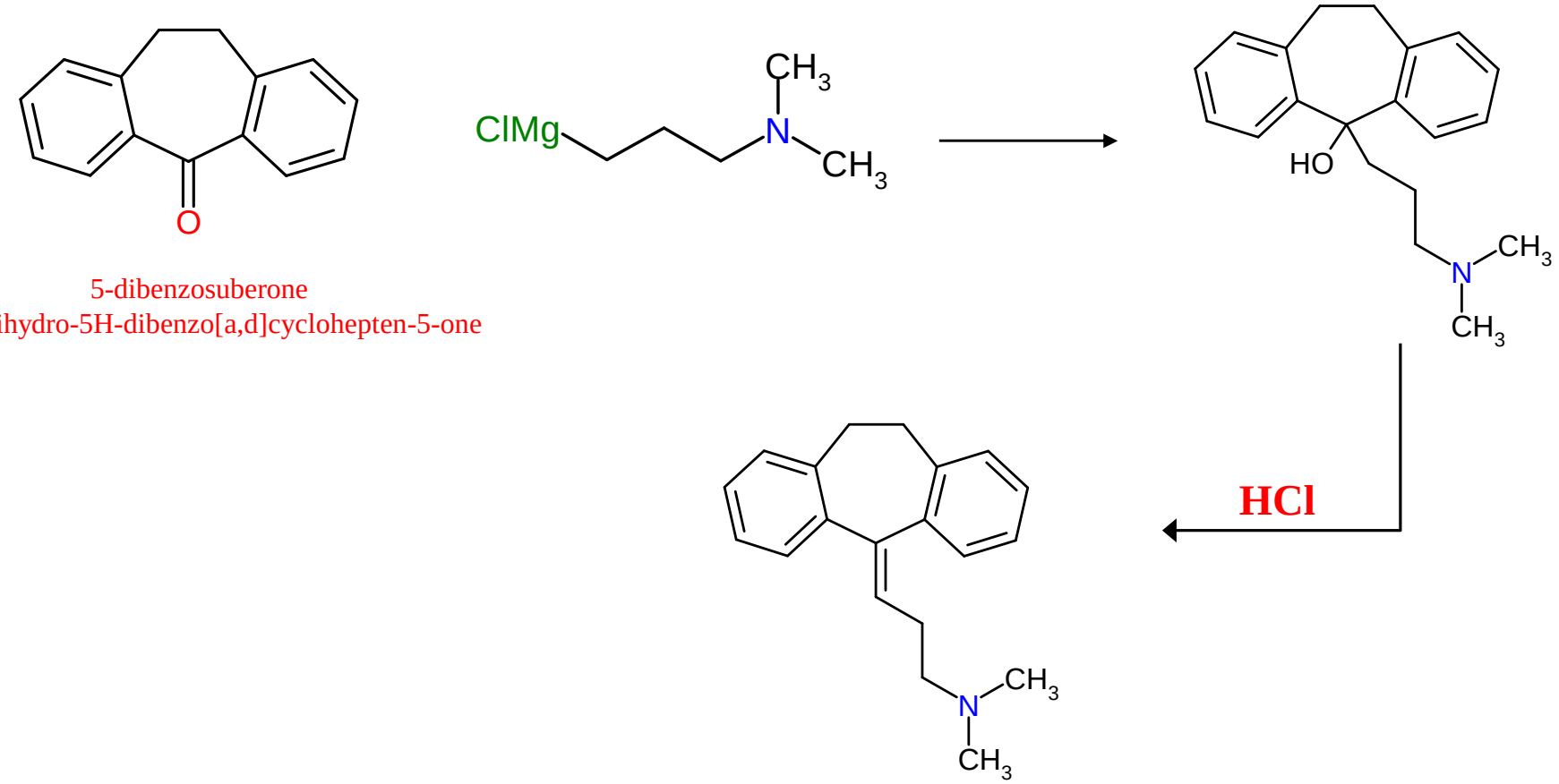
2.1 Tricyclic antidepressants typical



Amitriptyline is a tricyclic antidepressant. It is the most widely used TCA and has equal efficacy against depression to the newer class of SSRIs. Amitriptyline, under the brand name **Elavil**, was developed by Merck and approved by the FDA on April 7, 1961 for the treatment of major depression in the United States. It has seen widespread usage throughout the world ever since.

2. Depression and antidepressant drugs

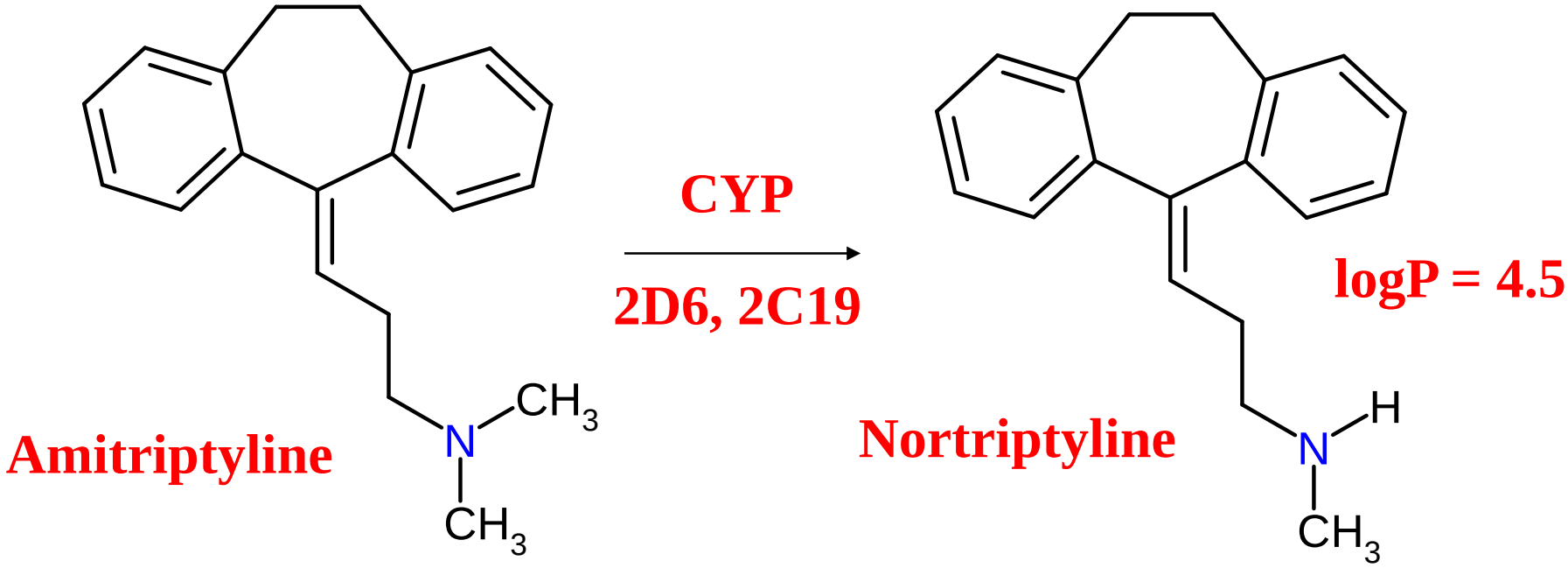
Synthesis Path



5-dibenzosuberone
10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one

2. Depression and antidepressant drugs

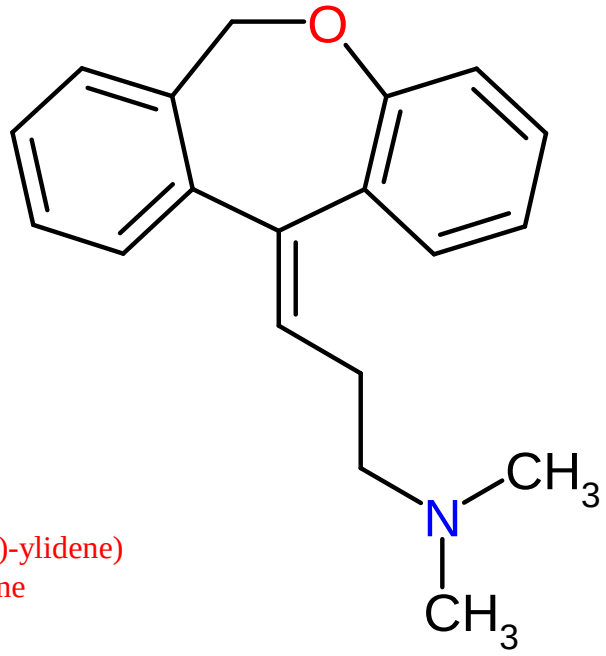
2.1 Tricyclic antidepressants

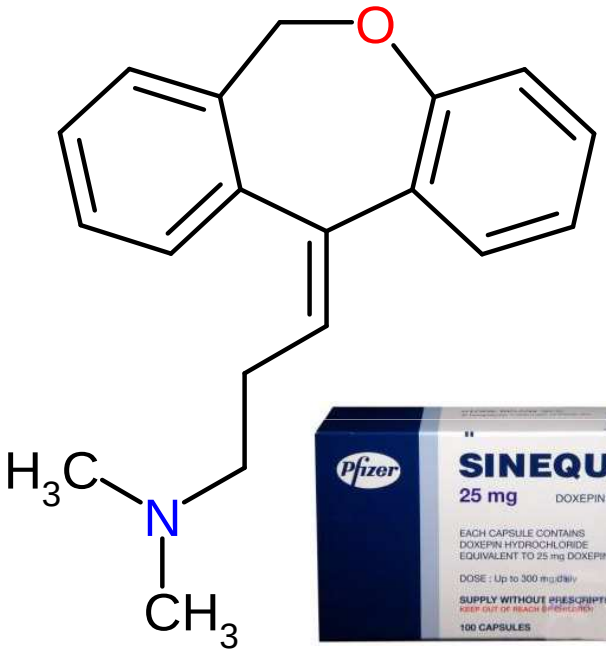


Nortriptyline is a second-generation tricyclic antidepressant (TCA) marketed as the hydrochloride salt. It is used in the treatment of major depression and childhood nocturnal enuresis (bedwetting). In addition, it is sometimes used for chronic illnesses such as chronic fatigue syndrome, chronic pain and migraines, and labile affect in some neurological conditions.

2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants typical





Doxepin

logP = 4.3

(*E*,*Z*)-3-(dibenzo[b,e]oxepin-11(6H)-ylidene)
-N,N-dimethylpropan-1-amine

Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant (TCA). In non-depressed individuals, doxepin does not affect mood or arousal, but may cause sedation. In depressed individuals, doxepin exerts a positive effect on mood. TCAs are potent inhibitors of serotonin and norepinephrine reuptake. Tertiary amine TCAs, such as doxepin and amitriptyline, are more potent inhibitors of serotonin reuptake than secondary amine TCAs, such as nortriptyline and desipramine. TCAs also down-regulate cerebral cortical β-adrenergic receptors and sensitize post-synaptic serotonergic receptors with chronic use. The antidepressant effects of TCAs are thought to be due to an overall increase in serotonergic neurotransmission. TCAs also block histamine H_1 receptors, α_1-adrenergic receptors and muscarinic receptors, which accounts for their sedative, hypotensive and anticholinergic effects (e.g. blurred vision, dry mouth, constipation, urinary retention), respectively.

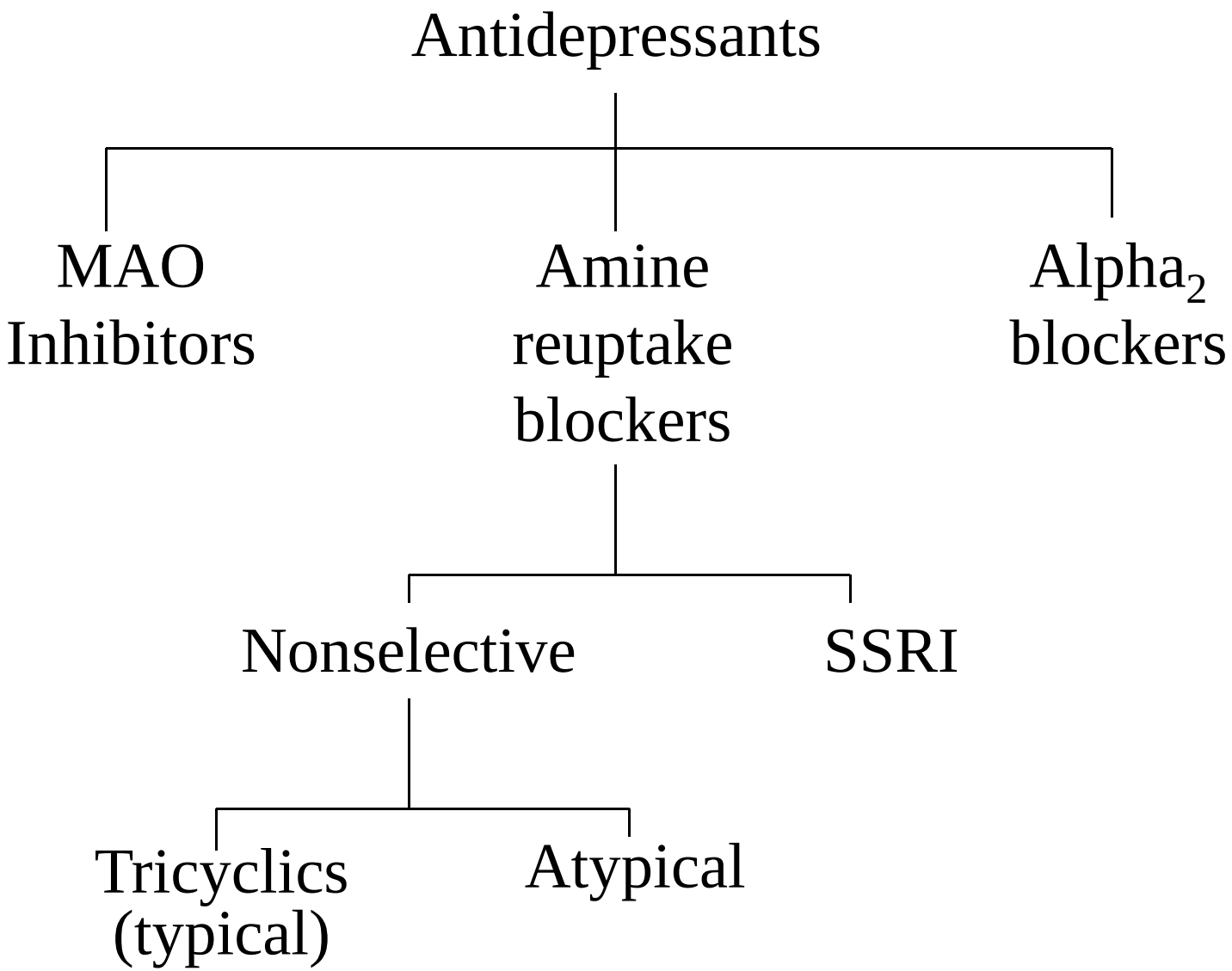
2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants typical

Drug	NE Transporter	SE Transporter	DE transporter	alpha1 blockade	D2 blockade	H1 blockade	muscarinic blockade	5HT2 blockade
imipramine	**2.7**	**70**	**0.012**	**1.5**	**0.05**	**9.1**	**1.1**	**1.2**
desipramine (also an imipramine metabolite)	128	5.7	0.024	0.77	0.03	0.91	0.5	0.38
amitriptyline	2.9	23	0.023	3.7	0.1	91	5.6	3.4
clomipramine	2.7	360	0.045	2.6	0.53	3.2	2.7	3.7
paroxetine	2.5	800	0.2	0.025	0.003	0.03	0.93	0.005
citalopram	0.035	98	0.0038	0.053	0	0.21	0.045	0.34

Potency (affinity) data are expressed as the inverse of equilibrium dissociation constant multiplied by a factor of 10^{-7}. **So, the higher the number, the higher the blocking power.**

2. Depression and antidepressant drugs

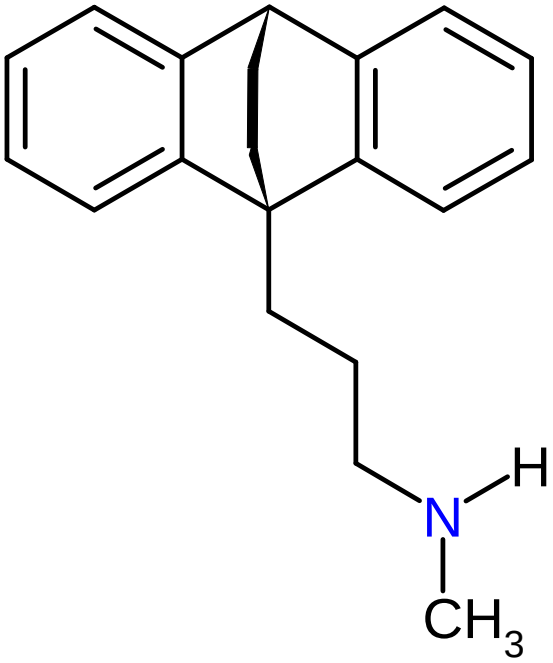


2. Depression and antidepressant drugs

2.2 Tricyclic antidepressants “atypical”

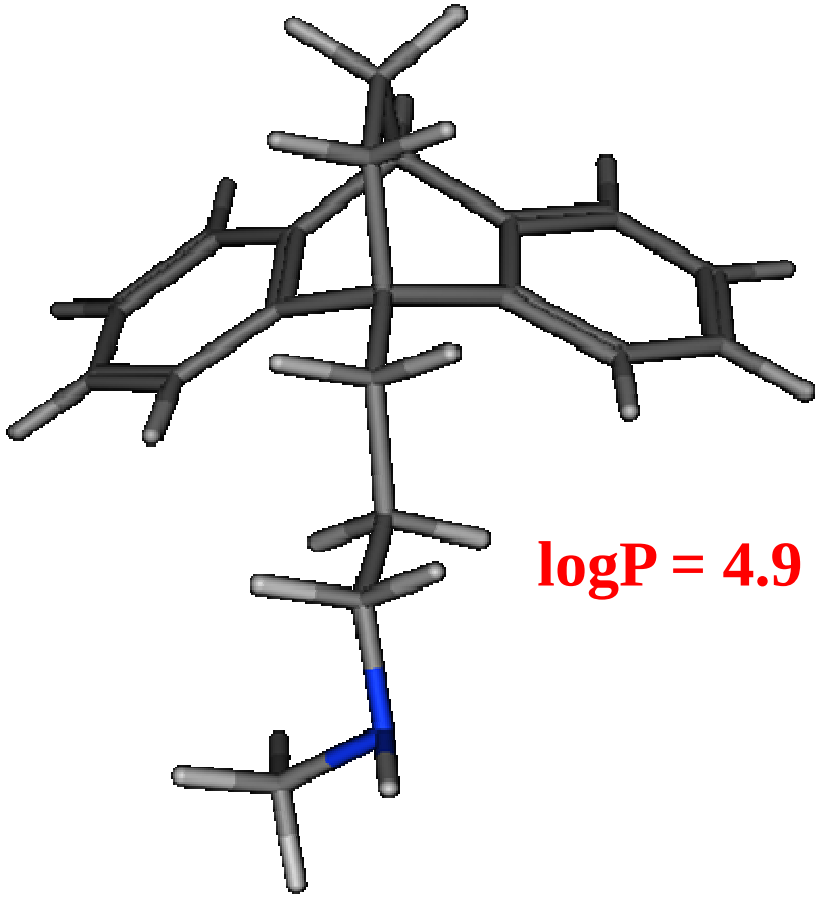
- **Developed in the late 1970’s and 1980’s**
- ***Maprotiline* – one of the first clinically available antidepressants, has a long half life and blocks NE reuptake**
- ***Amoxapine* – primarily a NE reuptake inhibitor**
- ***Trazodone* – not a potent blocker of NE or 5-HT, its active metabolite blocks a subclass of 5-HT receptors**
- ***Bupropion* – selectively inhibits DA reuptake, used for ADHD, side effects include: anxiety, restlessness, tremors, and insomnia**

2. Depression and antidepressant drugs



Maprotiline

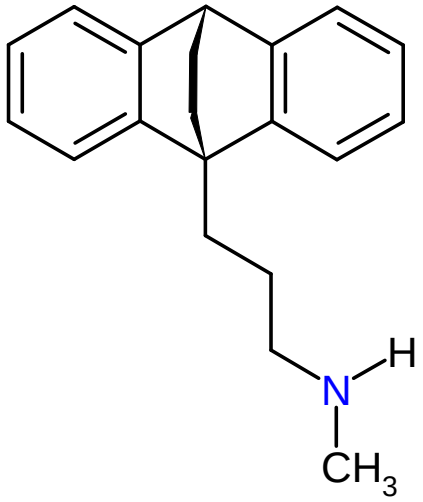
N-Methyl- 9,10-ethanoanthracene-
9(10H)- propanamine



logP = 4.9

Maprotiline is a *tetracyclic* antidepressant (TeCA). It is a strong norepinephrine reuptake inhibitor with only weak effects on serotonin and dopamine reuptake. Maprotiline was developed and has been marketed by the Swiss manufacturer Geigy (now Novartis) since the early 1980s under the brand name Ludiomil. Generics are widely available.

2. Depression and antidepressant drugs



Maprotiline

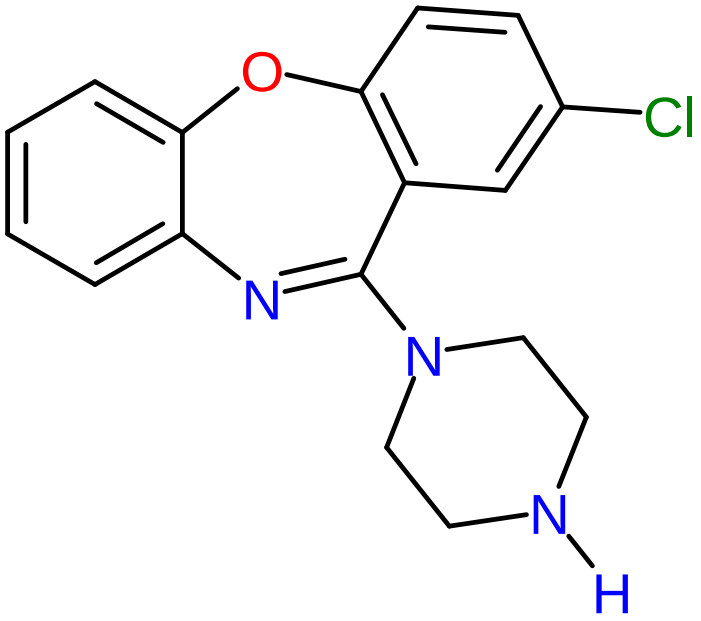
TRANSPORTERS

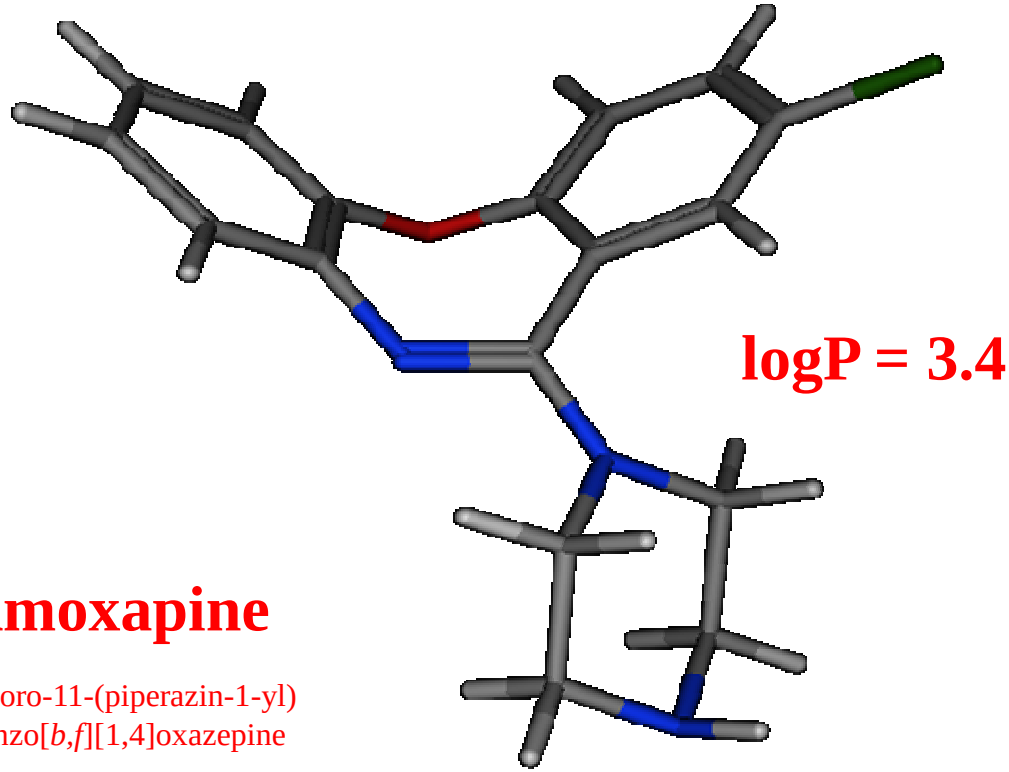
ADR	SER	DOP
+++	+	+

RECEPTORS

ADR	SER	DOP	ACH	H
α_1	HT_2	D_2	M_1	H_1
++	++	+	+	+++

2. Depression and antidepressant drugs





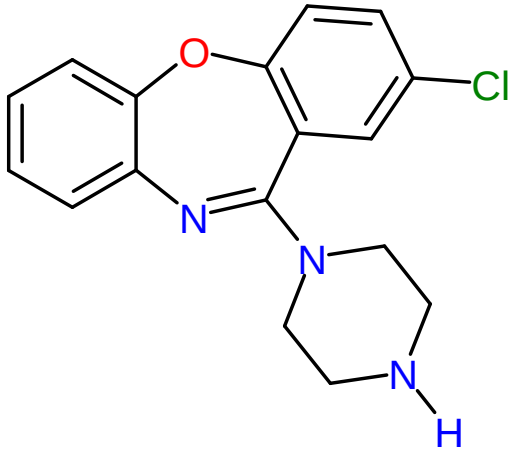
logP = 3.4

Amoxapine

2-chloro-11-(piperazin-1-yl)
dibenzo[*b*,*f*][1,4]oxazepine

Amoxapine is a tetracyclic antidepressant (TeCA) of the dibenzoxazepine class. Amoxapine is a strong norepinephrine reuptake inhibitor and weak serotonin reuptake inhibitor. It also possesses antiadrenergic, anticholinergic, antidopaminergic, antihistamine, and antiserotonergic actions. Amoxapine is used in the treatment of depression, anxiety disorders, panic disorder, and bipolar disorder.

2. Depression and antidepressant drugs



Amoxapine

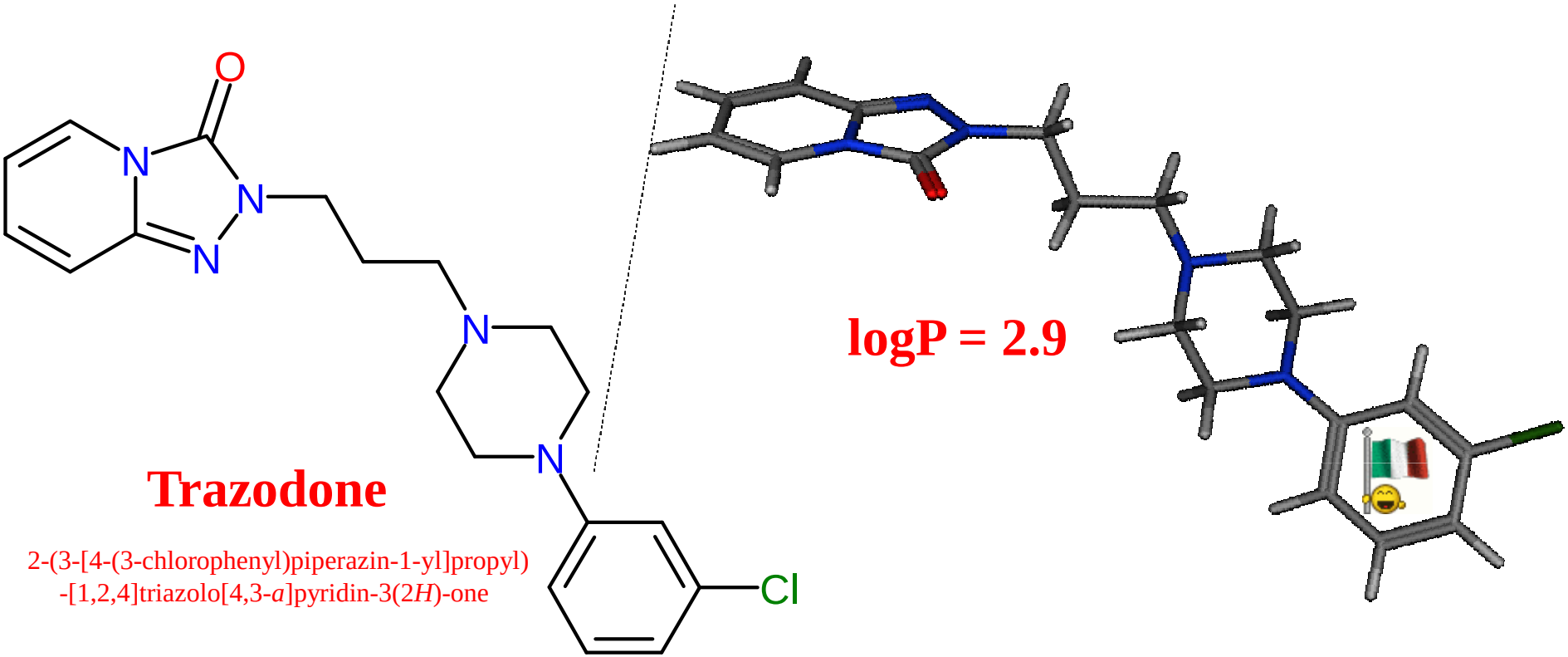
TRANSPORTERS

ADR	SER	DOP
+++	++	-

RECEPTORS

ADR	SER	DOP	ACH	H
α_1 ++	$HT_{2,3,6,7}$ +/++	$D_{2,3,4}$ +/++	M_1 -	H_1 ++

2. Depression and antidepressant drugs

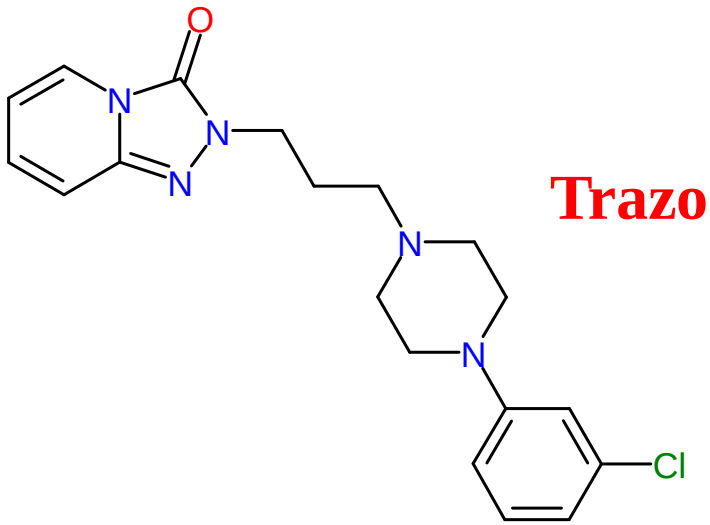


Trazodone

2-(3-[4-(3-chlorophenyl)piperazin-1-yl]propyl)
-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one

Trazodone was originally discovered and developed in Italy in the 1960s by Angelini research laboratories as a second-generation antidepressant. It was developed according to the mental pain hypothesis, which was postulated from studying patients and which proposes that major depression is associated with a decreased pain threshold. Trazodone was patented and marketed in many countries all over the world. It was approved by the Food and Drug Administration (FDA) at the end of 1981.

2. Depression and antidepressant drugs



Trazodone

TRANSPORTERS

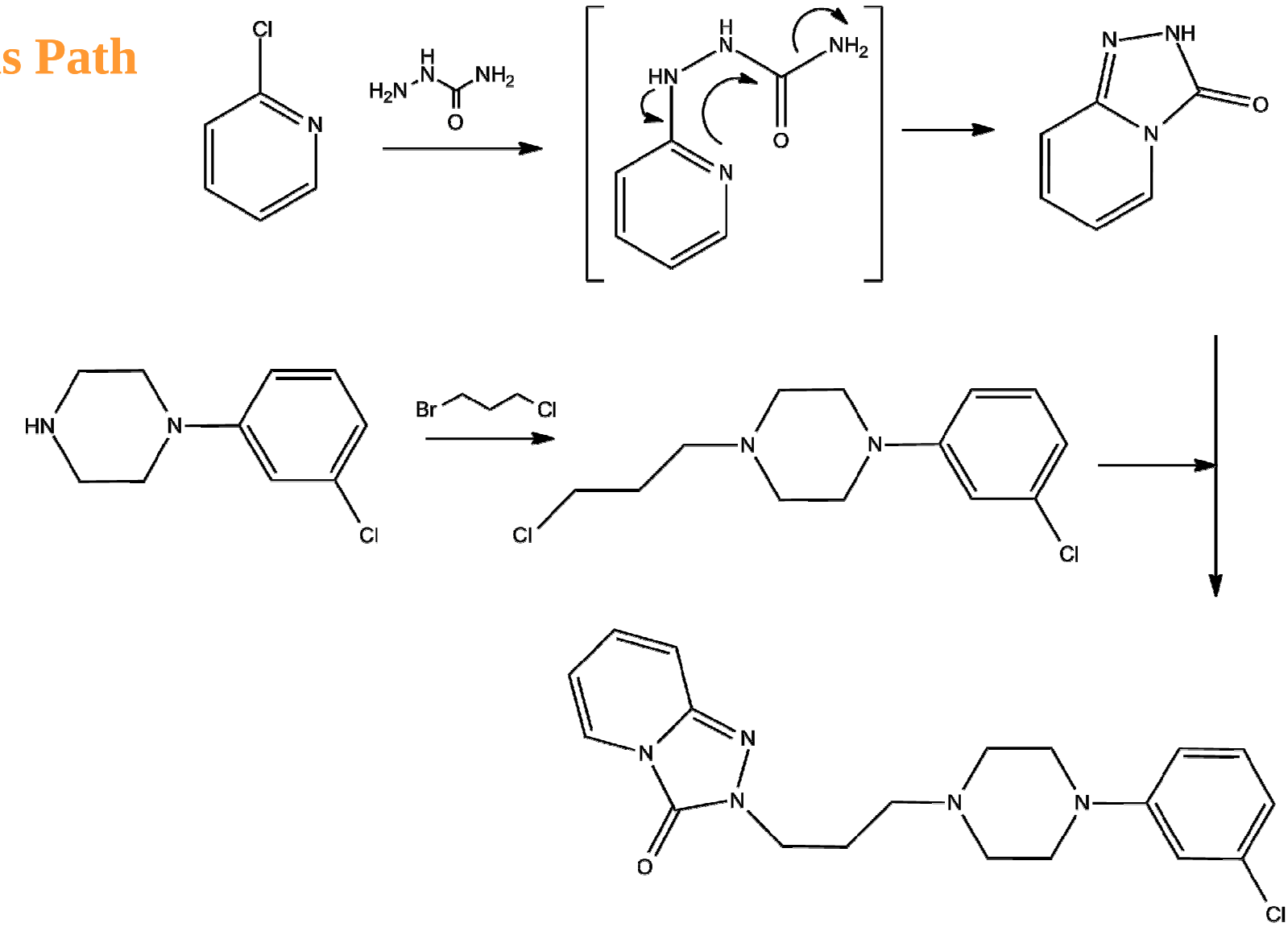
ADR	SER	DOP
-	++	-

RECEPTORS

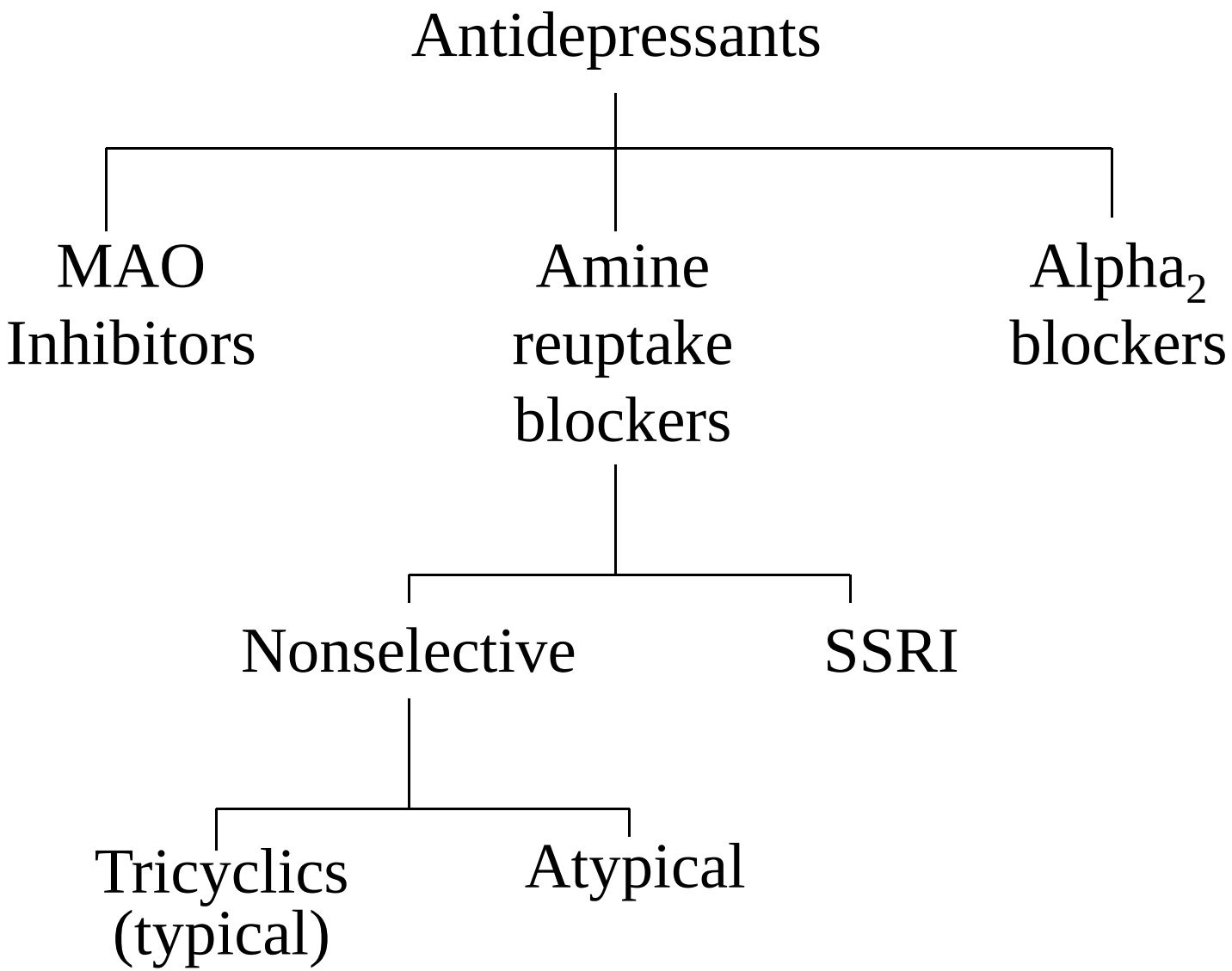
ADR	SER	DOP	ACH	H
α_1	$HT_{1,2}$	$D_{2,3,4}$	M_1	H_1
++	+/++	+	-	-/+

2. Depression and antidepressant drugs

Synthesis Path

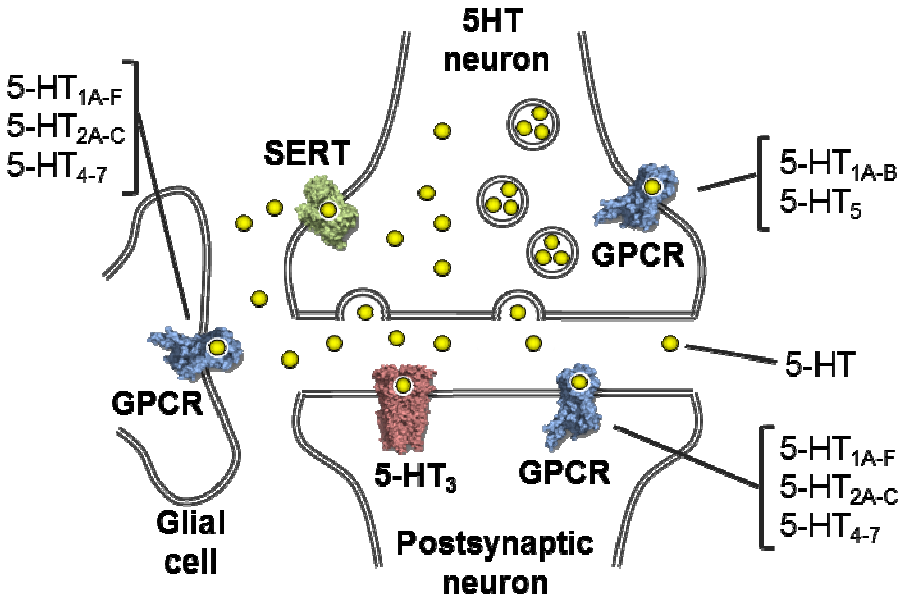


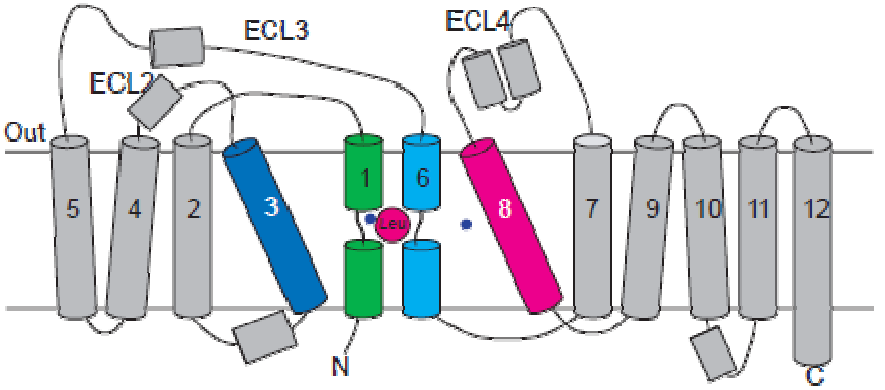
2. Depression and antidepressant drugs



2. Depression and antidepressant drugs

2.3 Serotonin transporter (SERT)

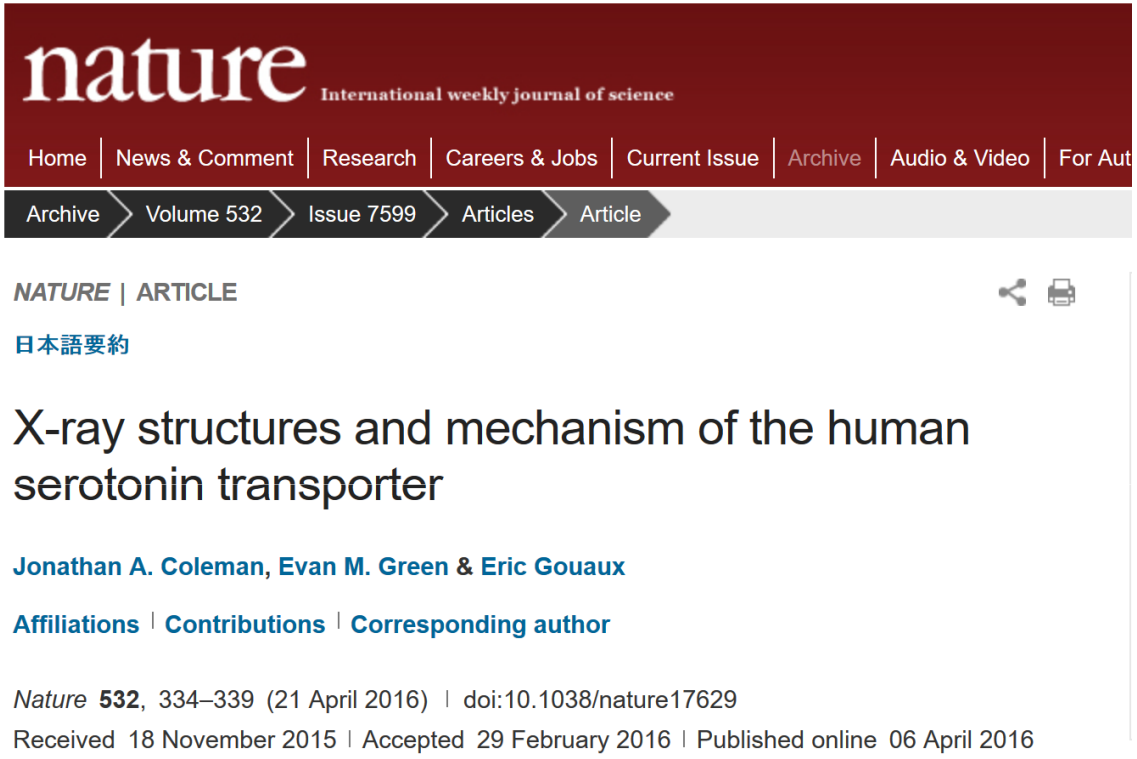




The **serotonin transporter (SERT)** transports serotonin across plasma membranes. As a member of the *neurotransmitter/sodium symporter* (NSS) family of proteins, SERTs assist in the termination of the neurochemical signaling through re-uptake of serotonin into serotonergic neurons and surrounding glia. SERTs are a target of multiple anti-depressant drugs as well as substances of abuse such as cocaine and ecstasy.

2. Depression and antidepressant drugs

2.3 Serotonin transporter (SERT): a real breakthrough…



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NATURE | ARTICLE

日本語要約

X-ray structures and mechanism of the human serotonin transporter

Jonathan A. Coleman, Evan M. Green & Eric Gouaux

Affiliations | Contributions | Corresponding author

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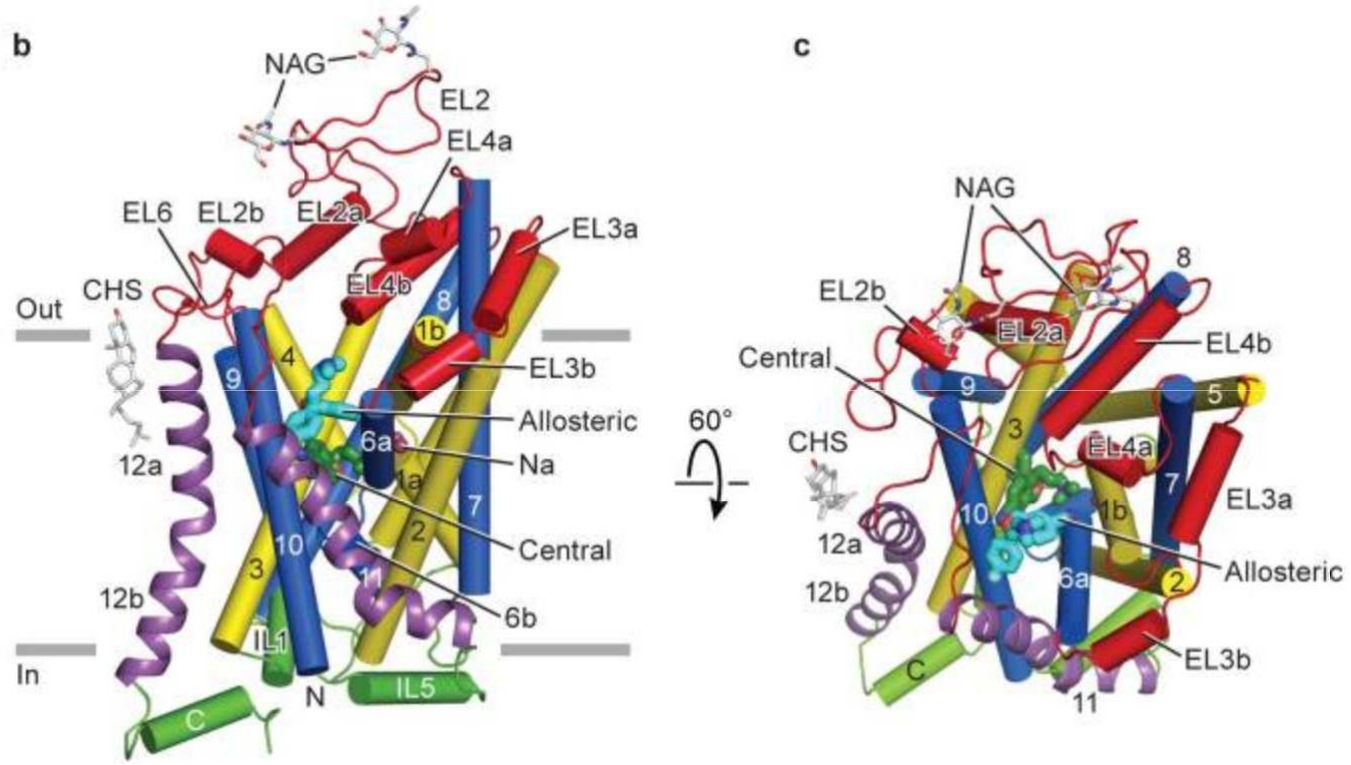
The serotonin transporter (SERT) terminates serotonergic signalling through the sodium- and chloride-dependent reuptake of neurotransmitter into presynaptic neurons. SERT is a target for antidepressant and psychostimulant drugs, which block reuptake and prolong neurotransmitter signalling. Here we report X-ray crystallographic structures of human SERT at 3.15 Å resolution bound to the antidepressants (*S*)-citalopram or paroxetine. Antidepressants lock SERT in an outward-open conformation by lodging in the central binding site, located between transmembrane helices 1, 3, 6, 8 and 10, directly blocking serotonin binding. We further identify the location of an allosteric site in the complex as residing at the periphery of the extracellular vestibule, interposed between extracellular loops 4 and 6 and transmembrane helices 1, 6, 10 and 11. Occupancy of the allosteric site sterically hinders ligand unbinding from the central site, providing an explanation for the action of (*S*)-citalopram as an allosteric ligand. These structures define the mechanism of antidepressant action in SERT, and provide blueprints for future drug design.

2. Depression and antidepressant drugs

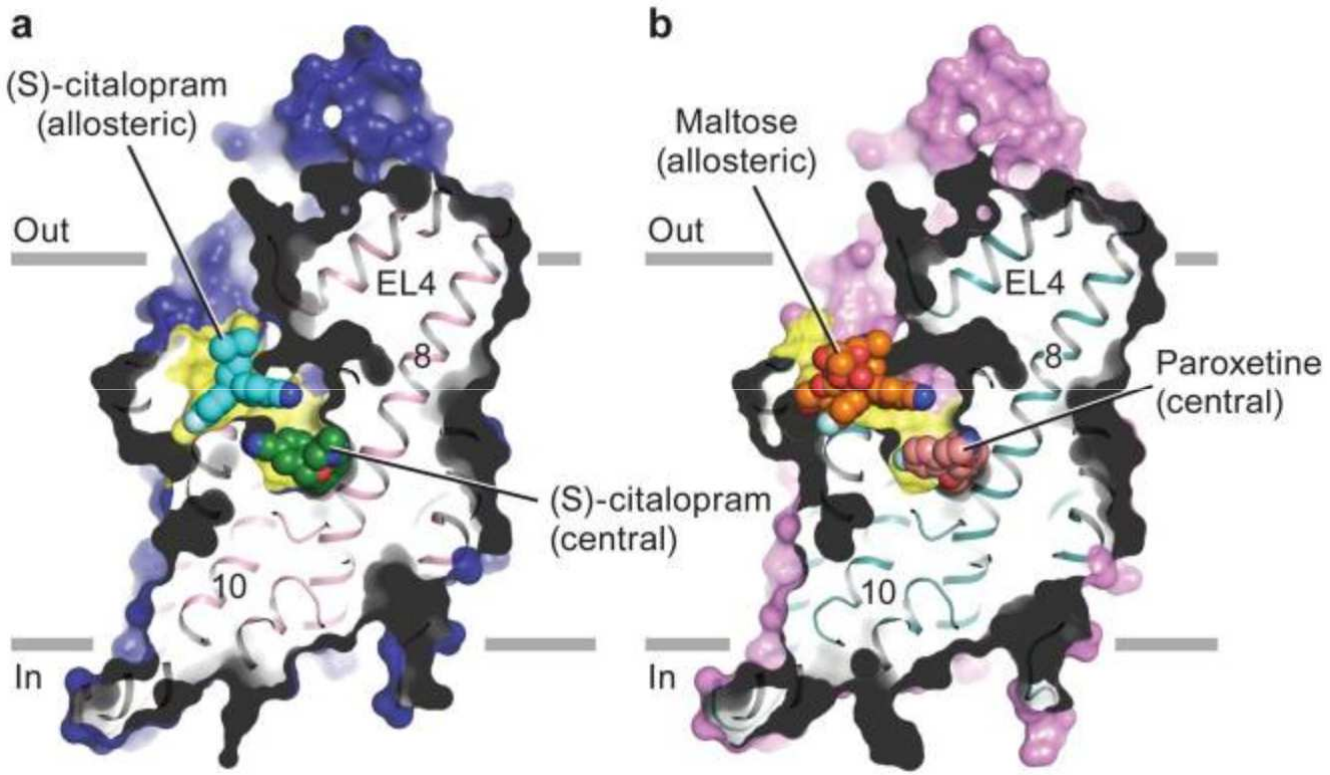
2.3 Serotonin transporter (SERT): a real breakthrough…



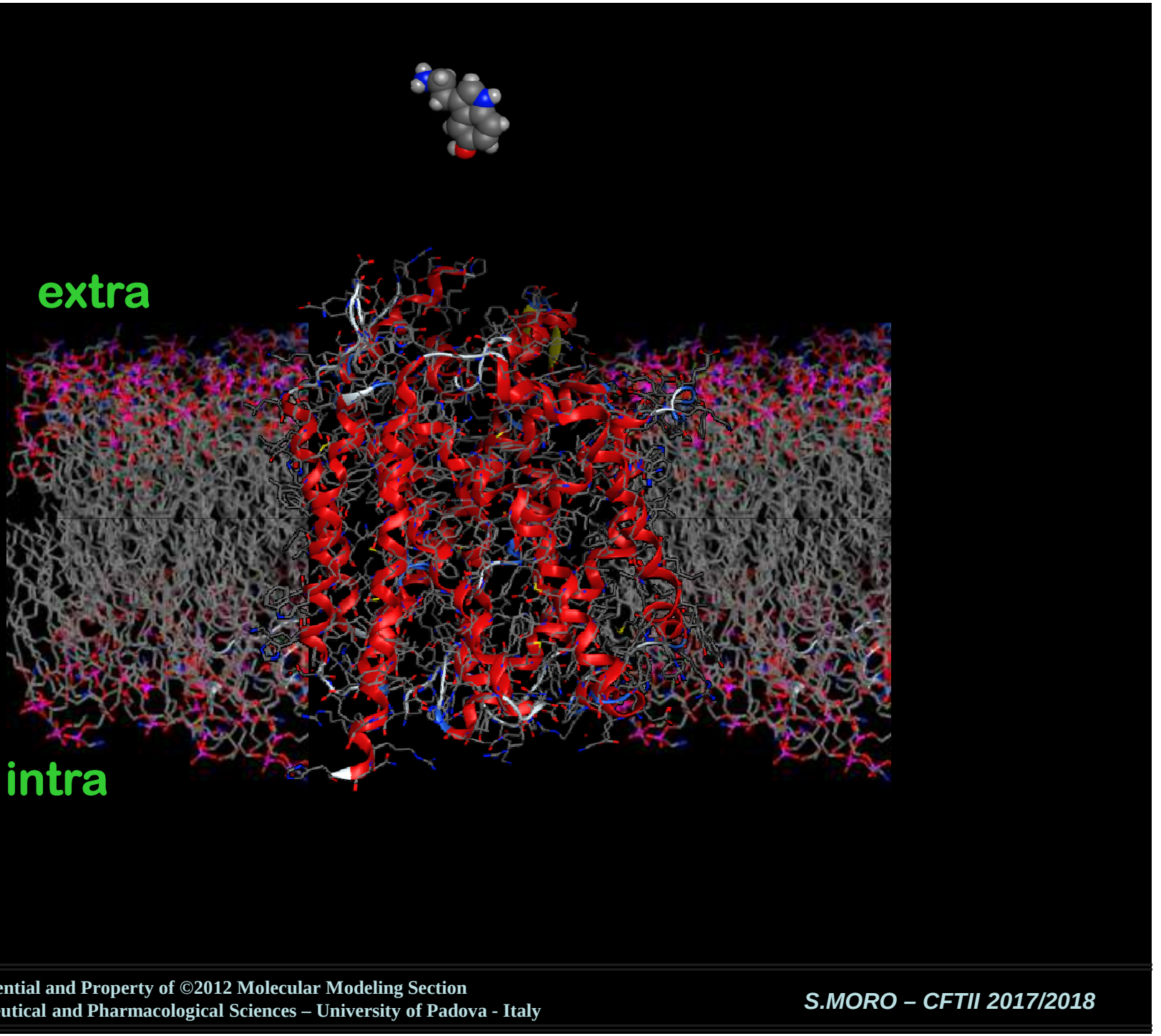
Nature. 2016 Apr 21; 532(7599): 334–339.

2. Depression and antidepressant drugs

2.3 Serotonin transporter (SERT): a real breakthrough…



Nature. 2016 Apr 21; 532(7599): 334–339.



2. Depression and antidepressant drugs

2.4 Selective Serotonin Reuptake Inhibitors (SSRI)

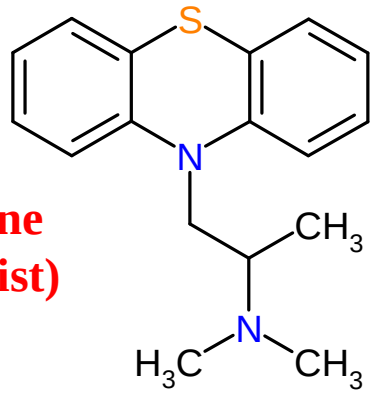
Selective Serotonin Reuptake Inhibitors (SSRIs) are currently the most commonly administered drug for treating major depression or dysthymia. **Due to their high potency and reduced side-effects, SSRIs serve as first-line therapeutics against depression.** A contributing factor to the development of depression is thought to be the imbalance of neurotransmitters in the brain – these molecules allow communication between neurons in the brain. One of the neurotransmitters implicated is serotonin; specifically, it is the reduction in serotonin levels that is believed to be a factor in causing depression.

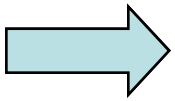
SSRIs function by the preventing the reuptake of serotonin from the chemical synapse between two neurons in the brain. Approximately 90% of the serotonin released from the receptors is recycled back into the pre-synaptic cell – this is accomplished by neuronal monoamine transporters. This results in an increased concentration of the serotonin neurotransmitter in the synaptic cleft and hence, greater activation of the post synaptic receptor is allowed. Enhanced stimulation of the recipient neuron results in reduced symptoms of depression. The majority of the serotonin receptors are G protein coupled receptors linked to ion channels; however, one of the receptors is linked directly to an ion channel.

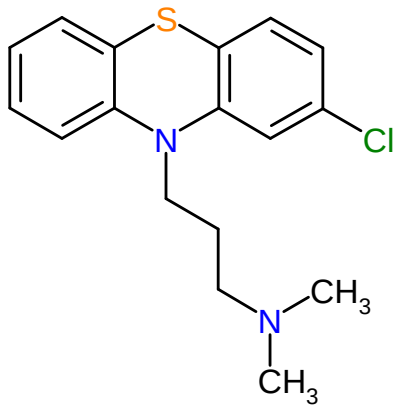
2. Depression and antidepressant drugs

2.4 Selective Serotonin Reuptake Inhibitors (SSRI)

Promethazine (H1 antagonist)



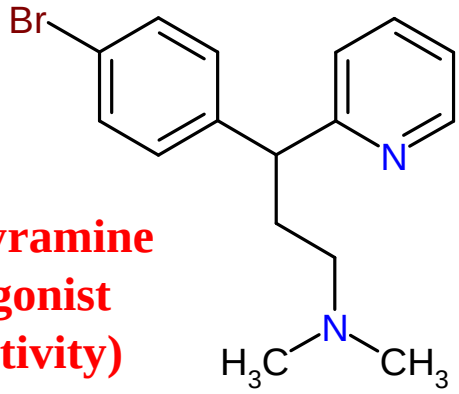


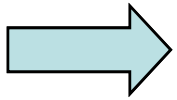


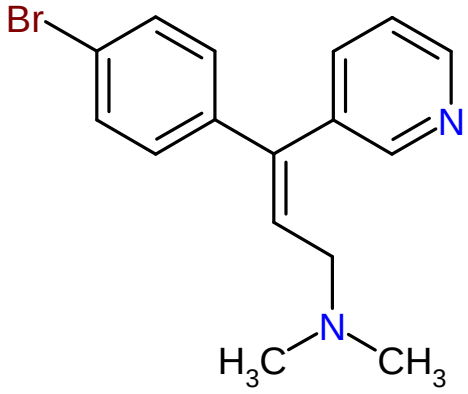
Chlorpromazine (TCA)

Bromphenyramine (H1 antagonist + SSRI activity)

logP = 3.4

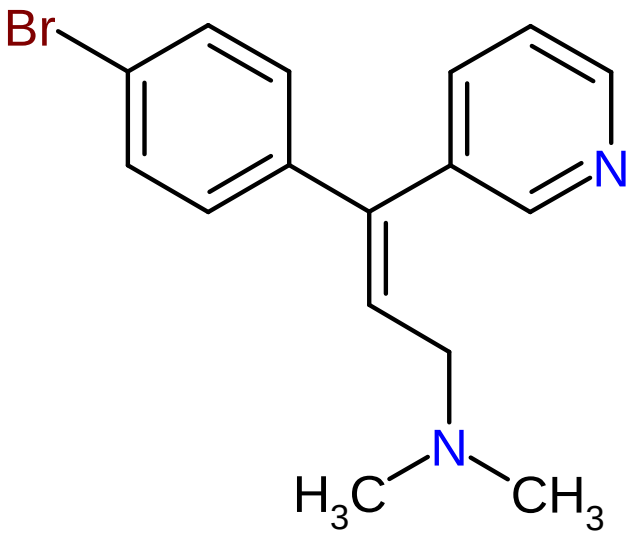




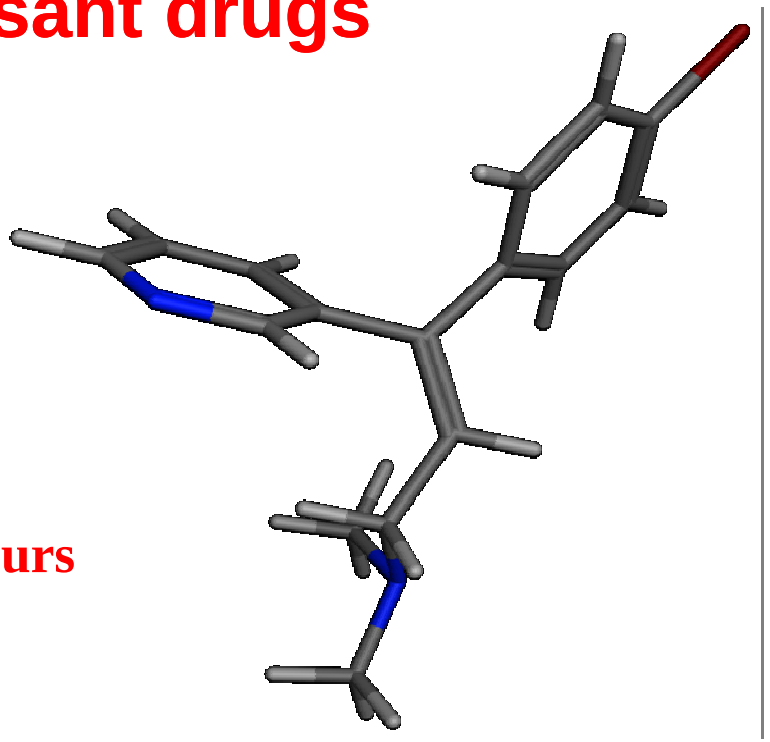


Zimelidine, 1982 (SSRI)

2. Depression and antidepressant drugs



logP = 3.6
pKa = 8.6
PSA ≅ 16 Å²



half life = 6÷10 hours

Zimelidine

(*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(pyridin-3-yl)prop-2-en-1-amine

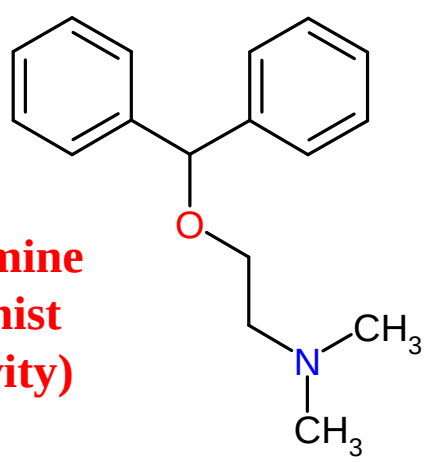
Zimelidine was the first selective serotonin reuptake inhibitor (SSRI) antidepressant to be marketed. Zimelidine was developed in the late 1970s and early 1980s by *Arvid Carlsson*, who was then working for the Swedish company Astra AB. I

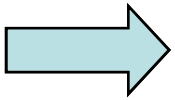
Zimelidine has been banned worldwide due to serious, sometimes fatal, cases of central and/or peripheral neuropathy known as Guillain-Barré syndrome and due to a peculiar hypersensitivity reaction involving many organs including skin exanthema, flu-like symptoms, arthralgias, and sometimes eosinophilia. Additionally, zimelidine was charged to cause an increase in suicidal ideation and/or attempts among depressive patients.

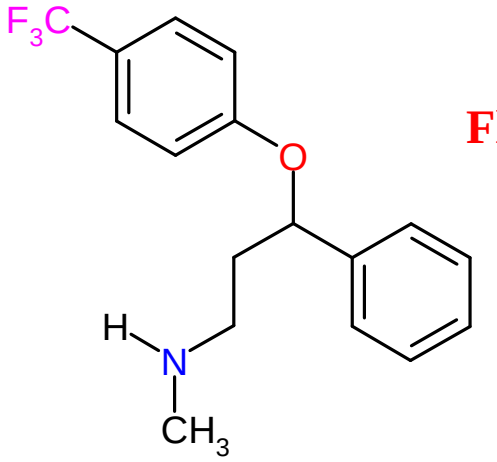
2. Depression and antidepressant drugs

2.4 Selective Serotonin Reuptake Inhibitors (SSRI)

Diphenydramine (H1 antagonist + SSRI activity)



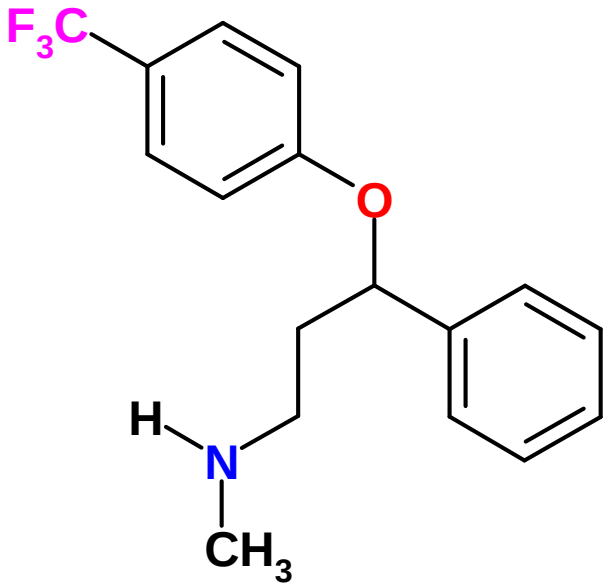




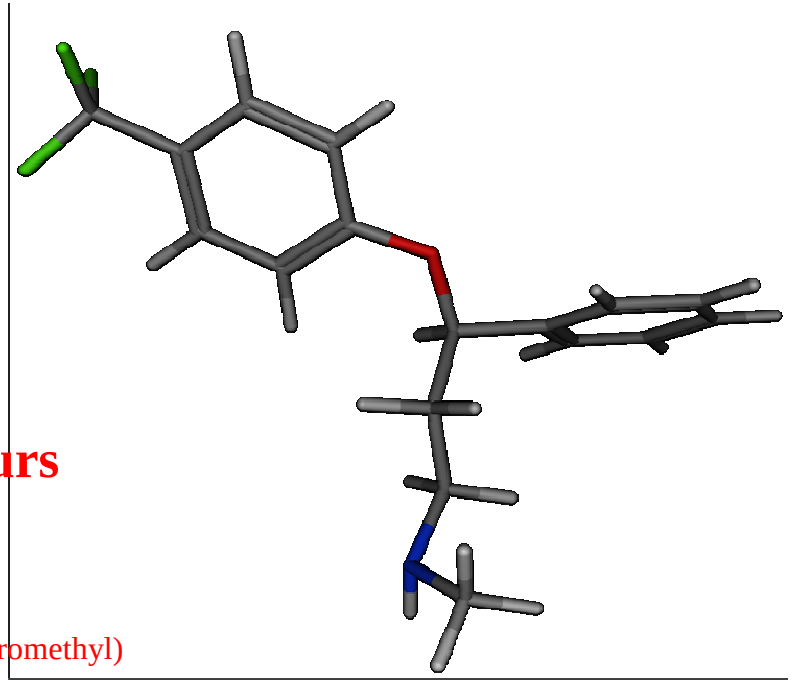
Fluoxetine, 1987 (SSRI)

As acknowledged by the Lilly scientists, the development of fluoxetine was based on concepts developed by Carlosson research group and started from our discovery that diphenhydramine has 5-HT- and noradrenaline-reuptake inhibitory properties. Fluoxetine has a chemical structure closely related to diphenhydramine.

2. Depression and antidepressant drugs



logP = 4.6
pKa = 10.0
PSA ≅ 20 Å²



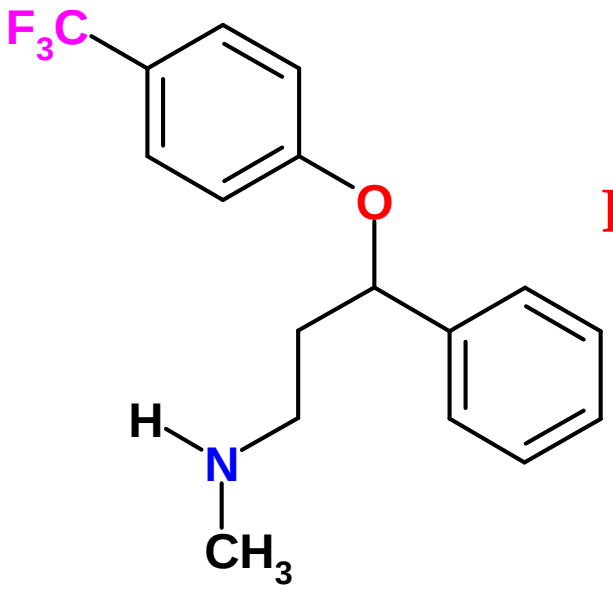
half life = 24÷72 hours

Fluoxetine

(*R*,*S*)-N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy]propan-1-amine

Fluoxetine (trade names: Prozac, Sarafem) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Fluoxetine is approved for the treatment of major depression (including pediatric depression), obsessive-compulsive disorder (in both adult and pediatric populations), bulimia nervosa, panic disorder and premenstrual dysphoric disorder.

2. Depression and antidepressant drugs



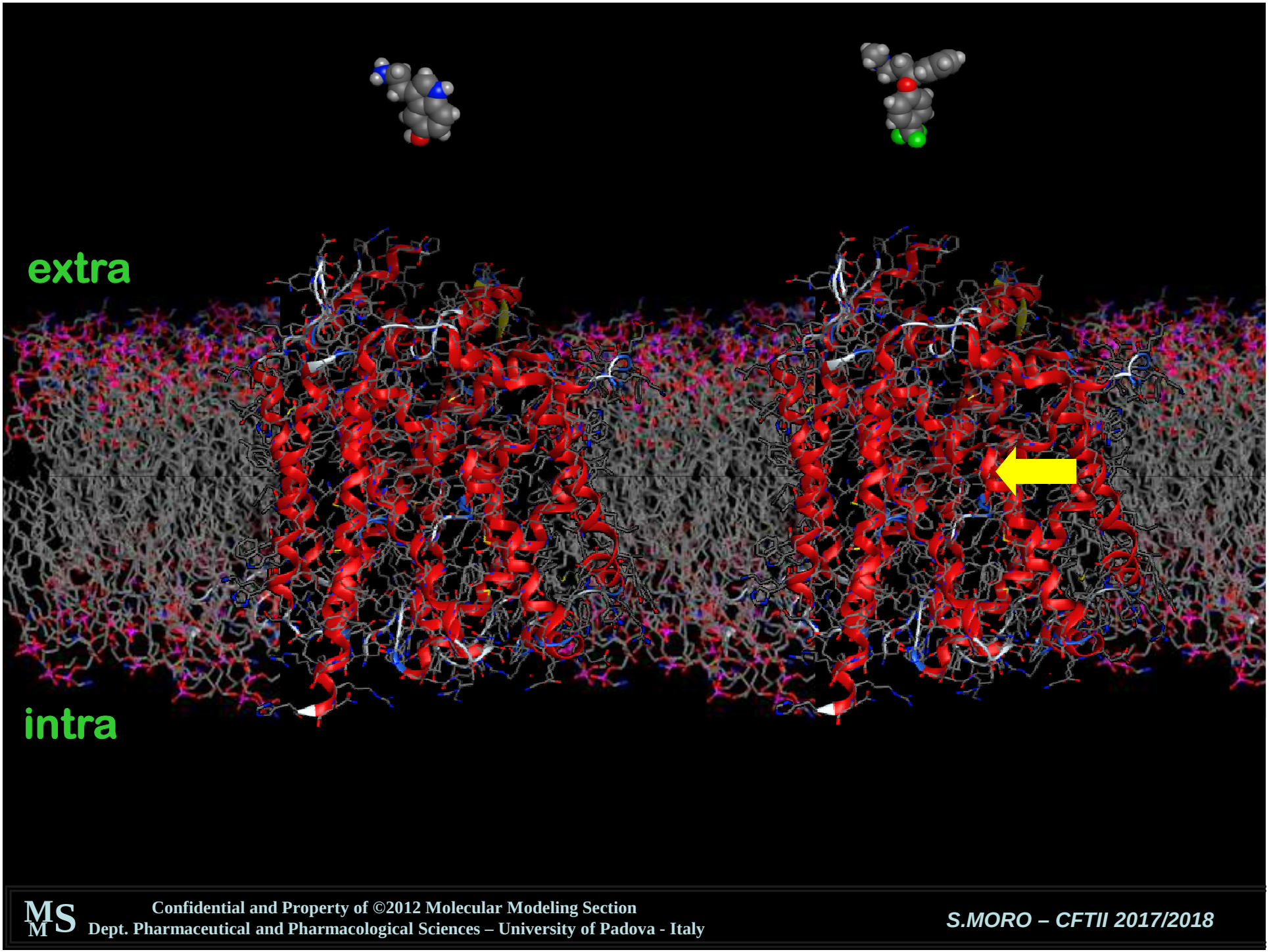
Fluoxetin

TRANSPORTERS

ADR	SER	DOP
-	+++	-

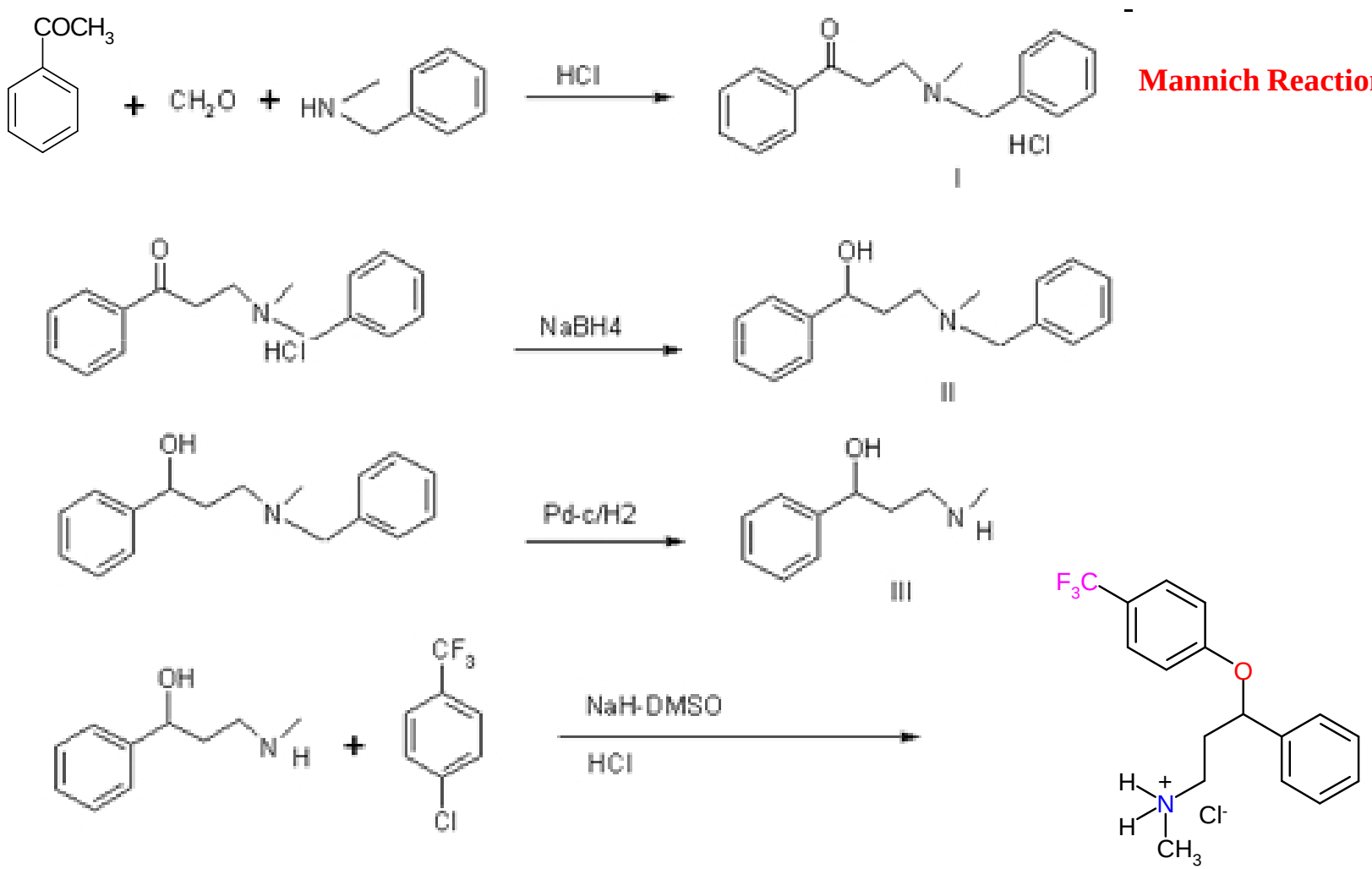
RECEPTORS

ADR	SER	DOP	ACH	H
α_1	HT_2	$D_{2,3,4}$	M_1	H_1
-/+	+/++	-	-	-/+



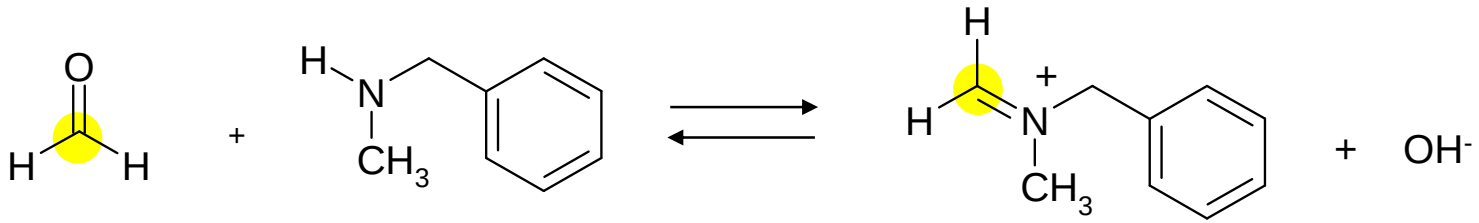
2. Depression and antidepressant drugs

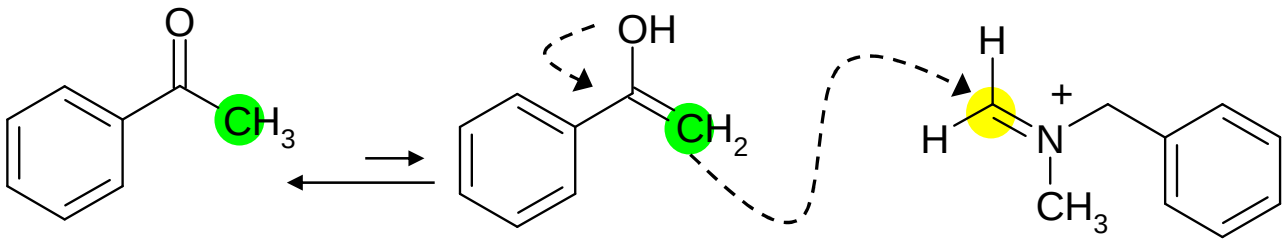
Synthesis Path

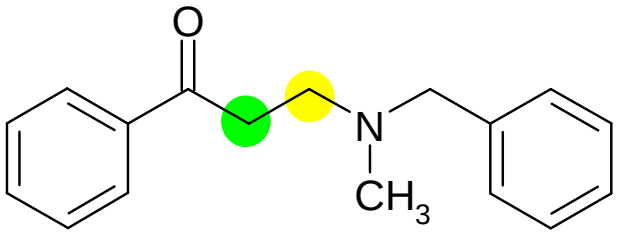


Mannich Reaction!!!

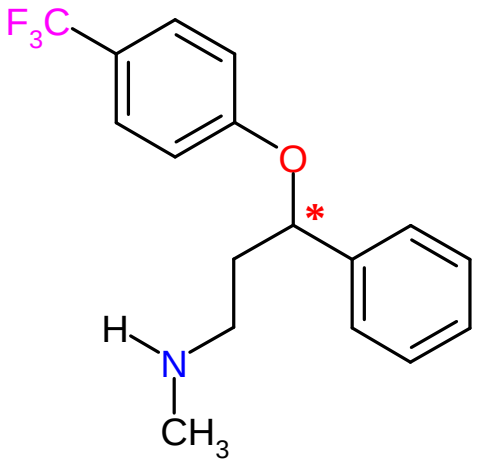
Do you remember Mannich reaction?



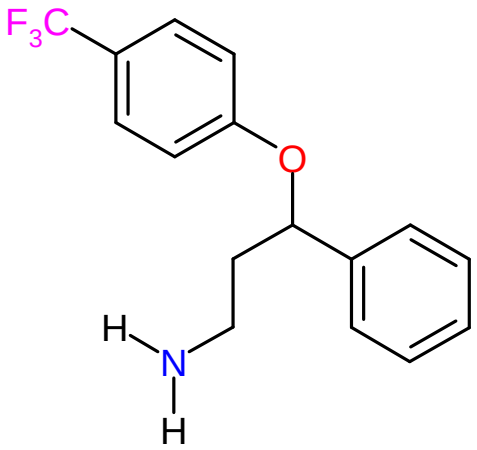




2. Depression and antidepressant drugs



Fluoxetine is a racemate; the (*S*) enantiomer of fluoxetine has shown to be 6.5 times more selective than the (*R*) enantiomer for the rat serotonin transporter. There is a 92% sequence identity between rat and human SERTs.

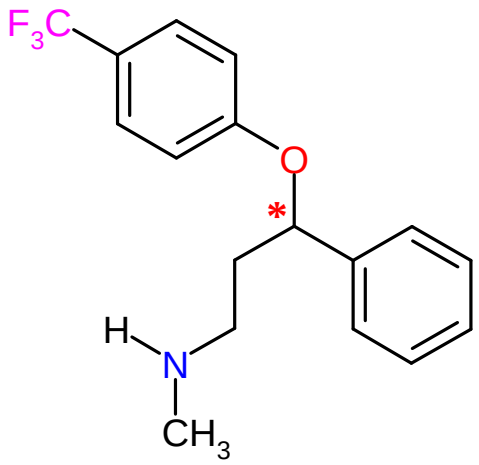


Norfluoxetine

Upon ingestion, Fluoxetine is metabolized into its bioactive state by an enzyme called cytochrome P450 2D6 (CYP2D6), an isoenzyme of the cytochrome P450 family. The bioactive metabolite is called ***norfluoxetine***. Fluoxetine has a bioavailability which is less than 90% because of hepatic first-pass metabolism. Within 6 to 8 hours it reaches its maximum plasma concentrations.

The bioactive metabolite norfluoxetine is as potent as fluoxetine but has a higher selectivity for the SERT.

2. Depression and antidepressant drugs



Common side-effects of Prozac include:

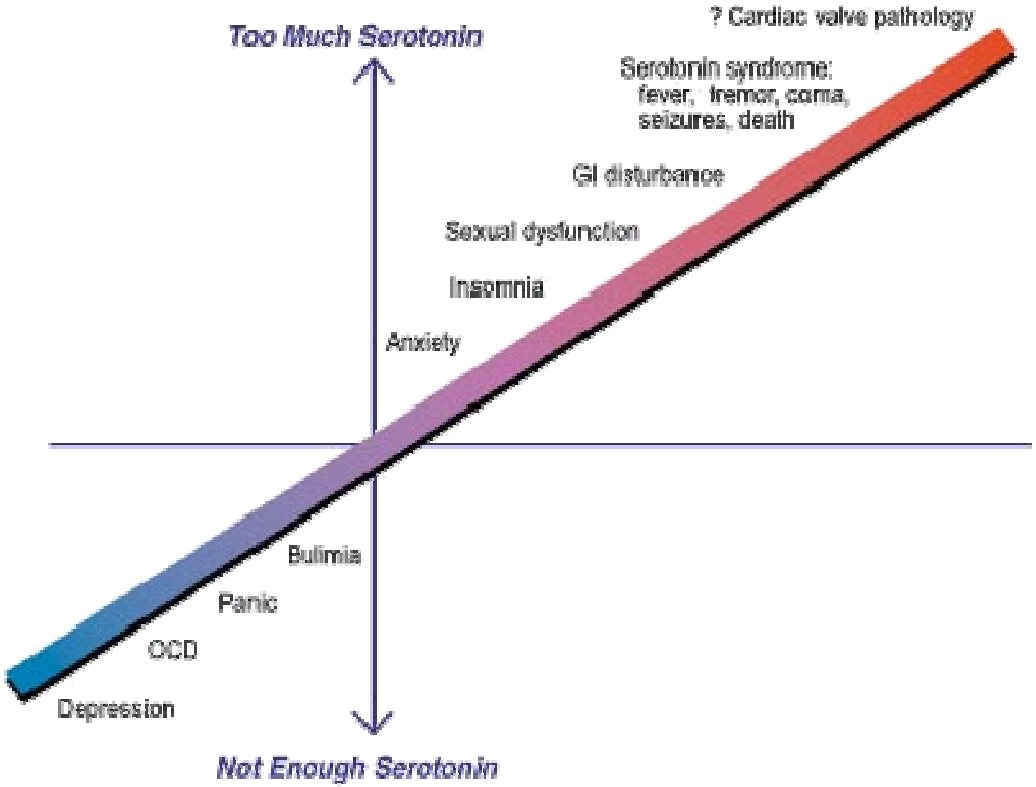
Nausea	Headaches
Anxiety	Diarrhea
Sexual dysfunction	Heartburn
Insomnia	Drowsiness

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Prozac or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD).

2. Depression and antidepressant drugs

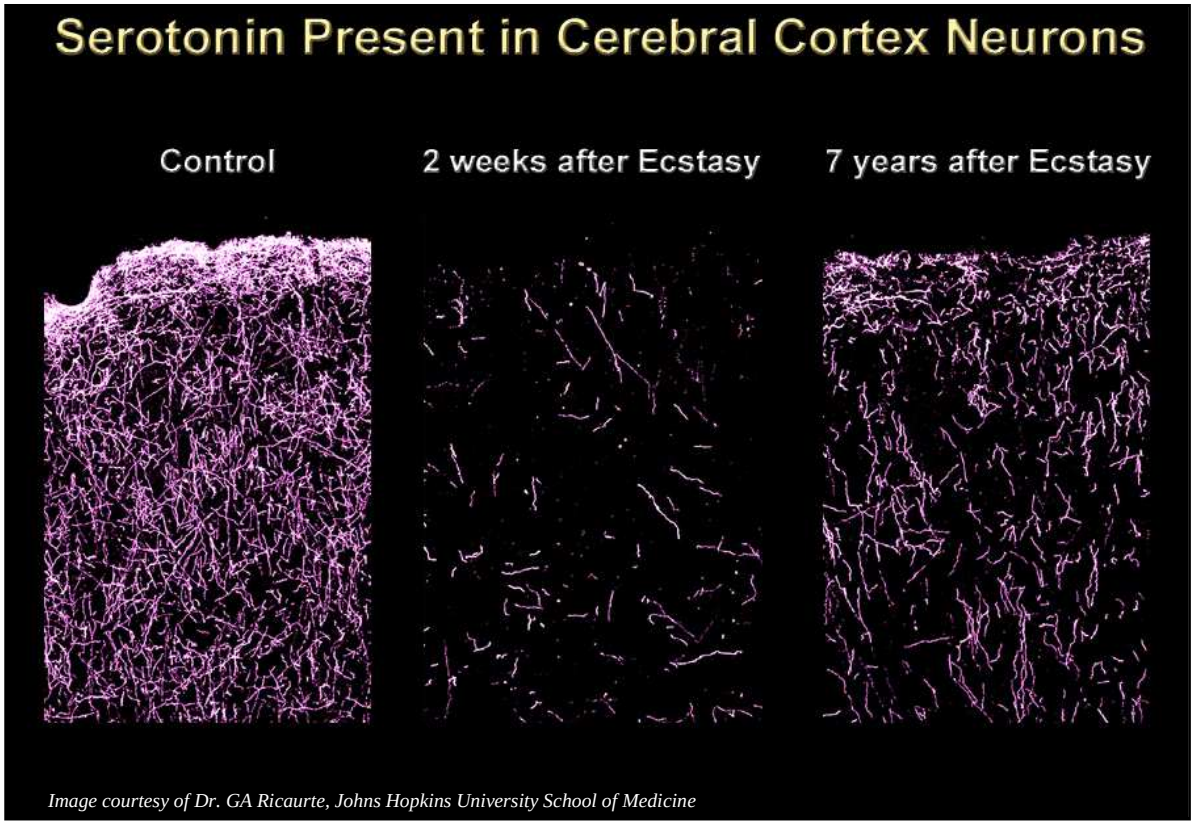
SSRIs side effects



When the SSRIs are administered, they increase serotonin in every serotonin pathway and at every one of the dozen or more serotonin receptor subtypes. Although this is something akin to dunking the brain into a bucket of serotonin, the net consequence is not only antidepressant action, but also therapeutic effects in a number of other conditions, including obsessive-compulsive disorder, panic attacks, bulimia, and others.

2. Depression and antidepressant drugs

2.5 Drug of Abuse



This first slide shows sections taken from the neocortex of monkeys that were given ecstasy twice a day for 4 days (control monkeys were given saline). The section on the left, taken from the brain of a control monkey, shows the presence of a lot of serotonin. The middle section shows a section from a monkey two weeks after receiving ecstasy. Point out that most of the serotonin is gone. The section on the right shows a section from a monkey 7 years after receiving ecstasy. Point out that although there has been some recovery of serotonin, the brain still has not returned to normal.

2. Depression and antidepressant drugs

2.4 Selective Serotonin Reuptake Inhibitors (SSRI)

Nevertheless, a 2010 meta-analysis published in JAMA indicated that :

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Review

Antidepressant Drug Effects and Depression Severity

A Patient-Level Meta-analysis

Jay C. Fournier, MA; Robert J. DeRubeis, PhD; Steven D. Hollon, PhD; Sona Dimidjian, PhD; Jay D. Amsterdam, MD; Richard C. Shelton, MD; Jan Fawcett, MD

JAMA. 2010;303(1):47-53.

Context Antidepressant medications represent the best established treatment for major depressive disorder, but there is little evidence that they have a specific pharmacological effect relative to pill placebo for patients with less severe depression.

Objective To estimate the relative benefit of medication vs placebo across a wide range of initial symptom severity in patients diagnosed with depression.

Data Sources PubMed, PsycINFO, and the Cochrane Library databases were searched from January 1980 through March 2009, along with references from meta-analyses and reviews.

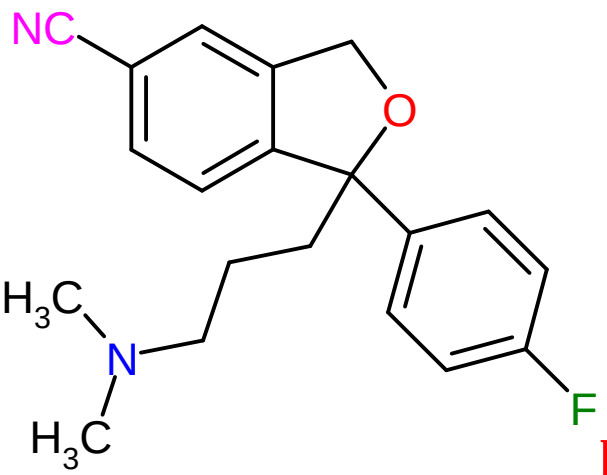
Study Selection Randomized placebo-controlled trials of antidepressants approved by the Food and Drug Administration in the treatment of major or minor depressive disorder were selected. Studies were included if their authors provided the requisite original data, they comprised adult outpatients, they included a medication vs placebo comparison for at least 6 weeks, they did not exclude patients on the basis of a placebo washout period, and they used the Hamilton Depression Rating Scale (HDRS). Data from 6 studies (718 patients) were included.

Data Extraction Individual patient-level data were obtained from study authors.

Results Medication vs placebo differences varied substantially as a function of baseline severity. Among patients with HDRS scores below 23, Cohen *d* effect sizes for the difference between medication and placebo were estimated to be less than 0.20 (a standard definition of a small effect). Estimates of the magnitude of the superiority of medication over placebo increased with increases in baseline depression severity and crossed the threshold defined by the National Institute for Clinical Excellence for a clinically significant difference at a baseline HDRS score of 25.

Conclusions The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. For patients with very severe depression, the benefit of medications over placebo is substantial.

2. Depression and antidepressant drugs

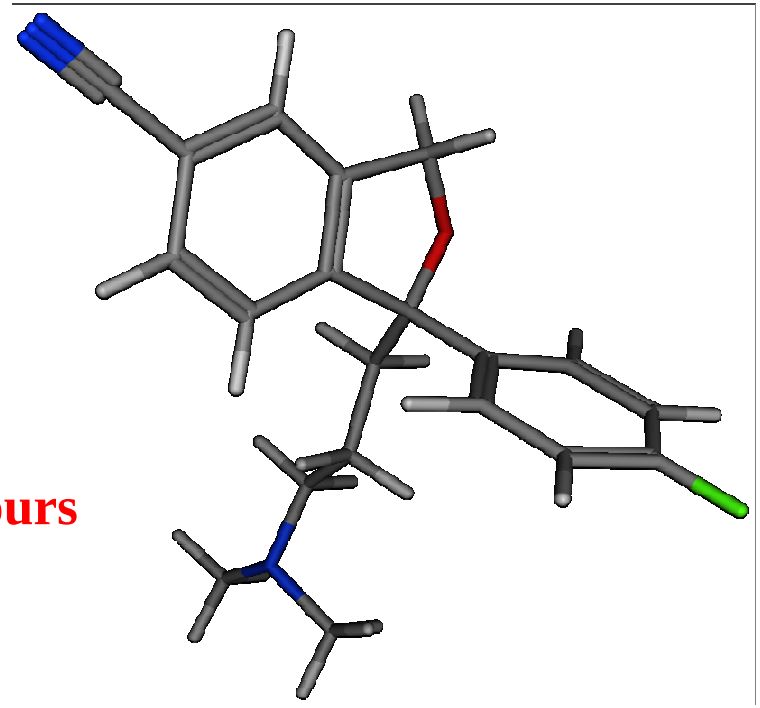


Citalopram

(*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile

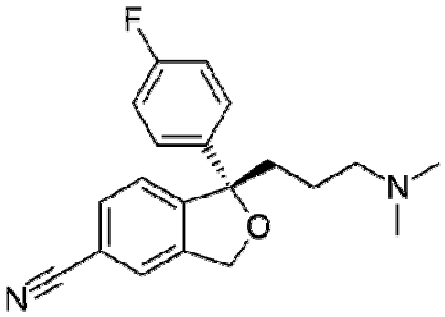
logP = 3.5
pKa = 9.6
PSA ≅ 36 Å²

half life = 30÷40 hours

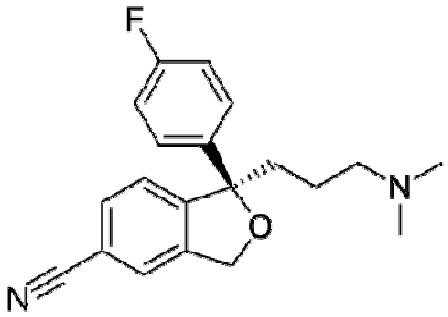


Citalopram (trade names: Celexa, Cipramil) is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class. Most often used to treat major depression, it is also used on occasion in the treatment of body dysmorphic disorder, anxiety, and panic disorder. It was originally created in 1989 by the pharmaceutical company Lundbeck.

2. Depression and antidepressant drugs



(*S*)-(+)-citalopram



(*R*)-(–)-citalopram

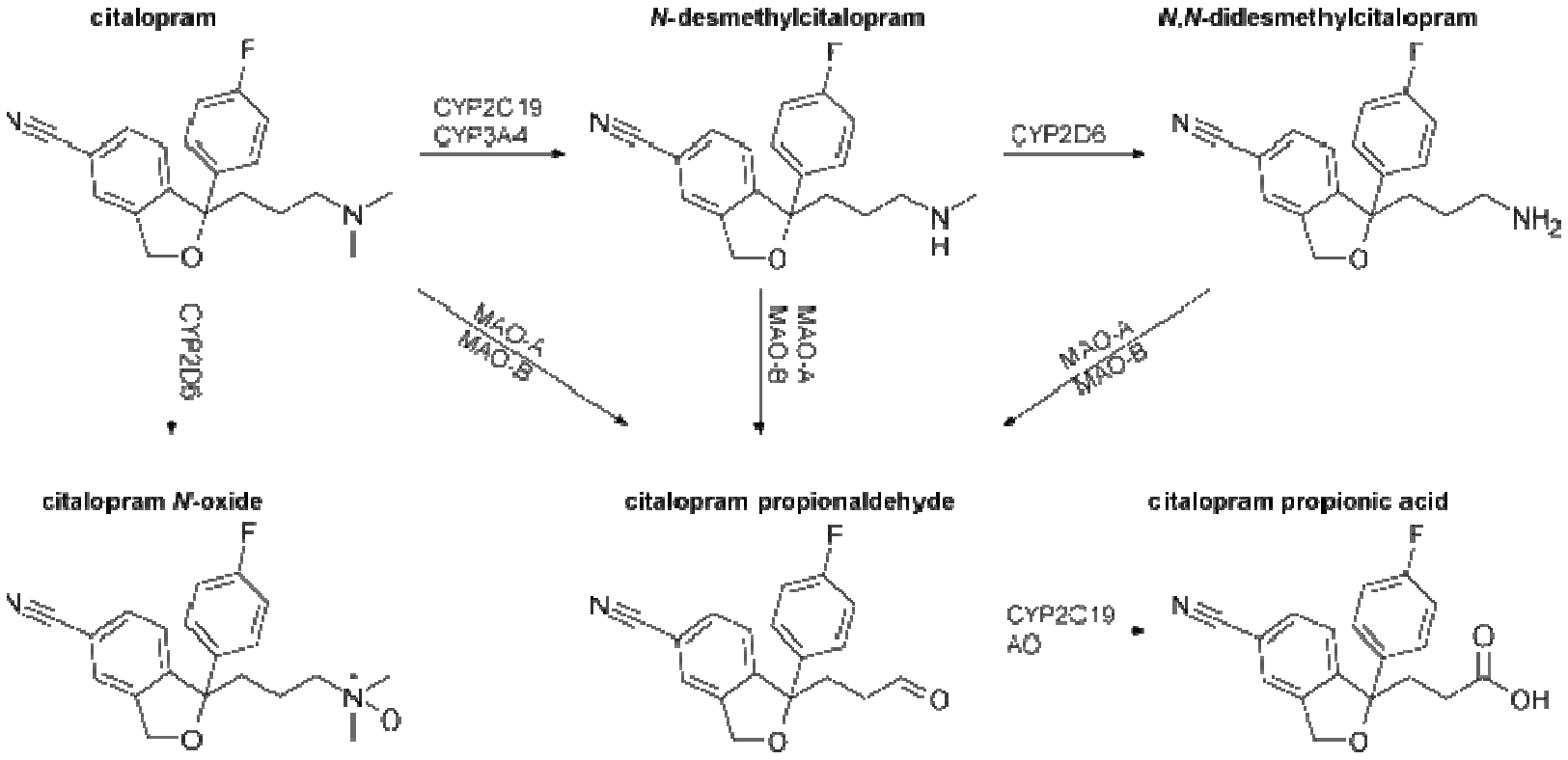
Citalopram is sold as a racemic mixture, consisting of 50% (*R*)-(−)-citalopram and 50% (*S*)-(+)-citalopram.

Only the (*S*)-(+) enantiomer has the desired antidepressant effect (*Int Clin Psychopharmacol. 2014, 19 (3), 149–155*)

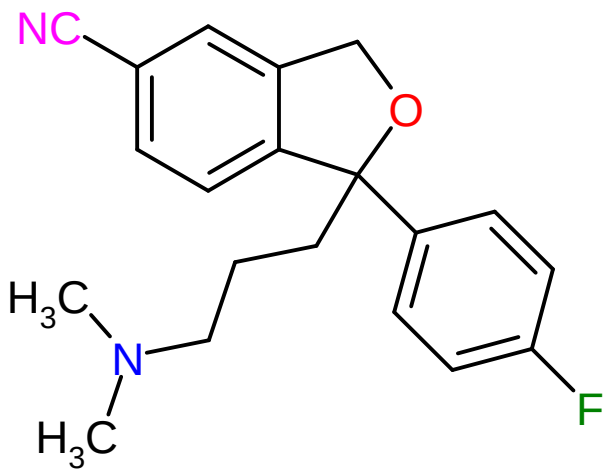
Binding Profile:

Receptor	K_i (nM)
SERT	1.6
NET	6190
5-HT_{2C}	617
α_1	1211
M_1	1430
H_1	283

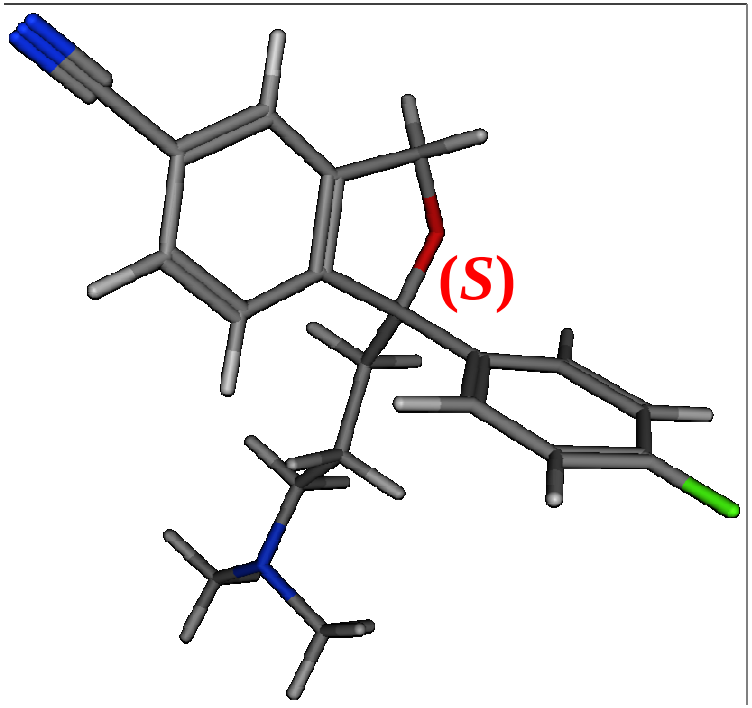
2. Depression and antidepressant drugs



2. Depression and antidepressant drugs

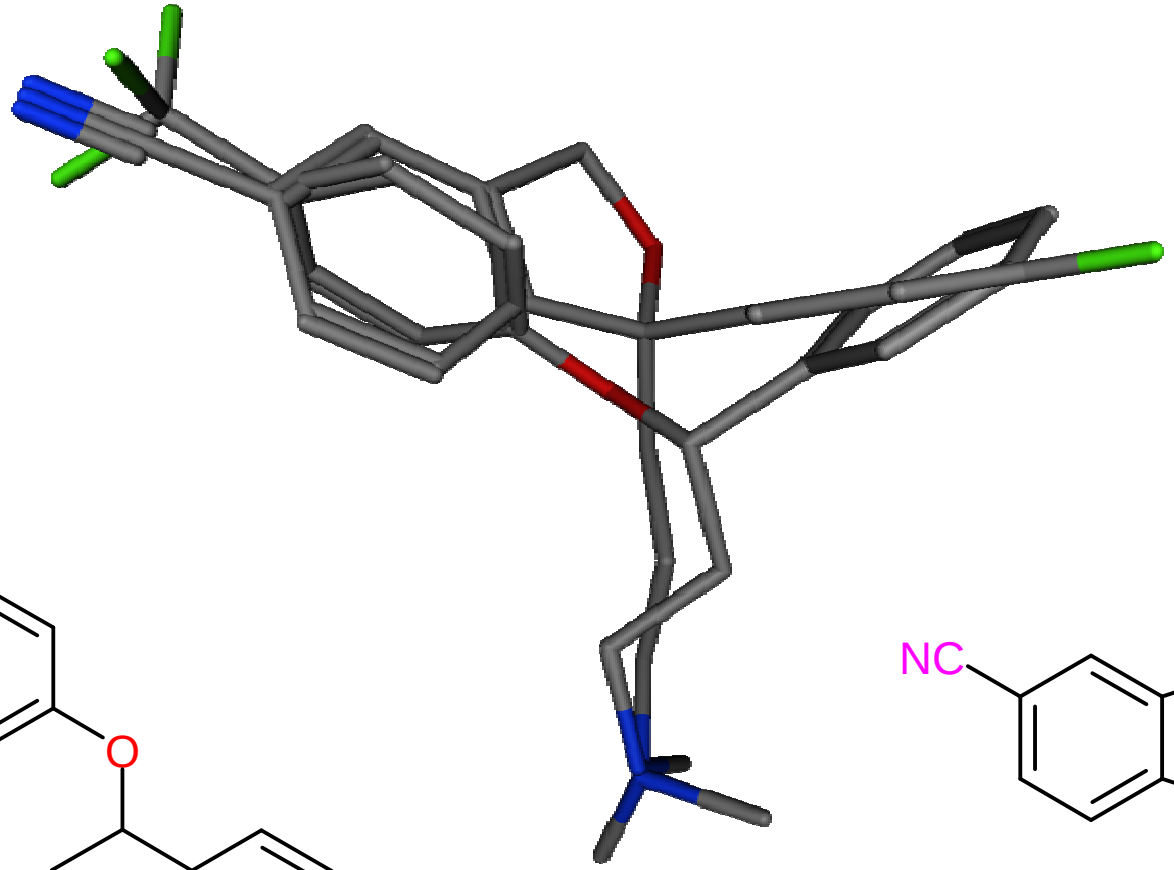


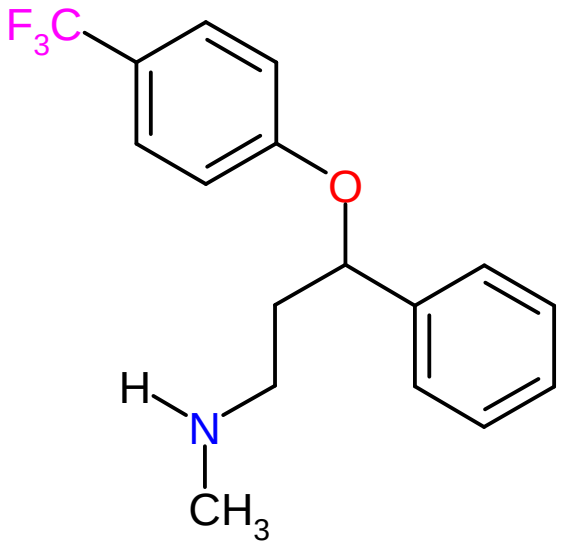
Citalopram



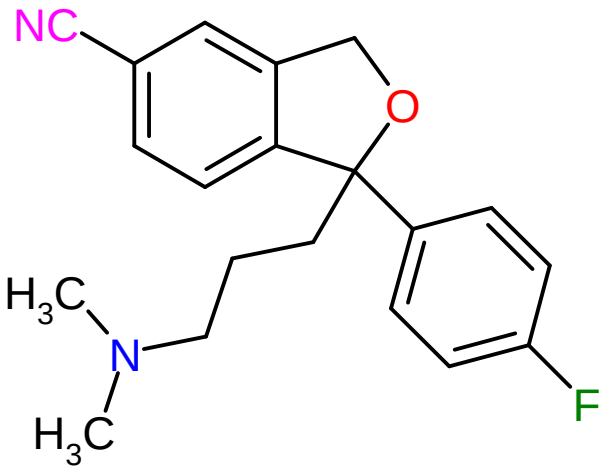
Citalopram is sold as a racemic mixture, consisting of 50% (*R*)-(−)-citalopram and 50% (*S*)-(+)-citalopram. Only the (*S*)-(+) enantiomer has the desired antidepressant effect. Lundbeck now markets the (*S*)-(+) enantiomer, the generic name of which is ***Escitalopram***.

2. Depression and antidepressant drugs



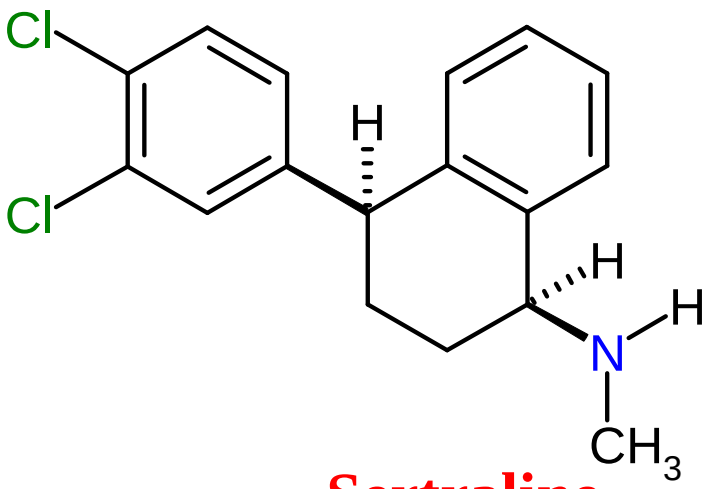


(*S*)-Fluoxetine



(*S*)-Citalopram

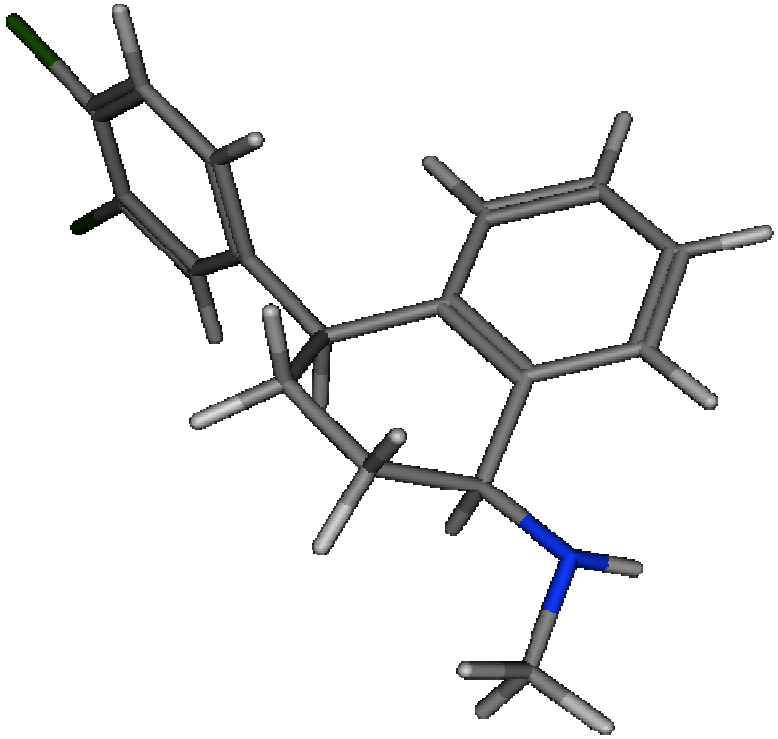
2. Depression and antidepressant drugs



Sertraline

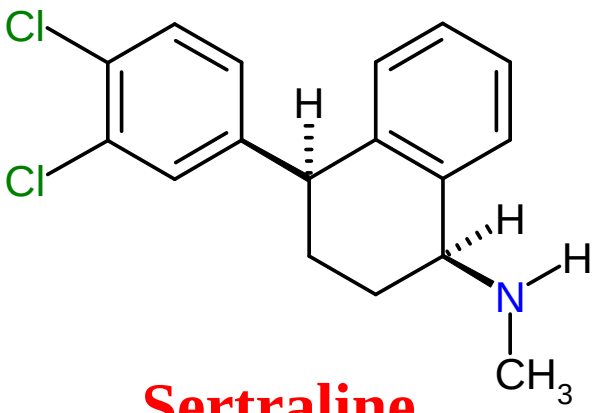
(1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl
-1,2,3,4-tetrahydronaphthalen-1-amine

logP = 5.1
pKa = 9.5
PSA ≅ 12 Å²



Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. It was introduced to the market by Pfizer in 1991. Sertraline is primarily used to treat major depression in adult outpatients as well as obsessive-compulsive, panic, and social anxiety disorders in both adults and children. Sertraline is statistically similar in efficacy to other SSRIs such as paroxetine, citalopram, escitalopram and venlafaxine (SNRI). Evidence suggests that sertraline may be more effective than fluoxetine (Prozac) for some subtypes of depression.

2. Depression and antidepressant drugs

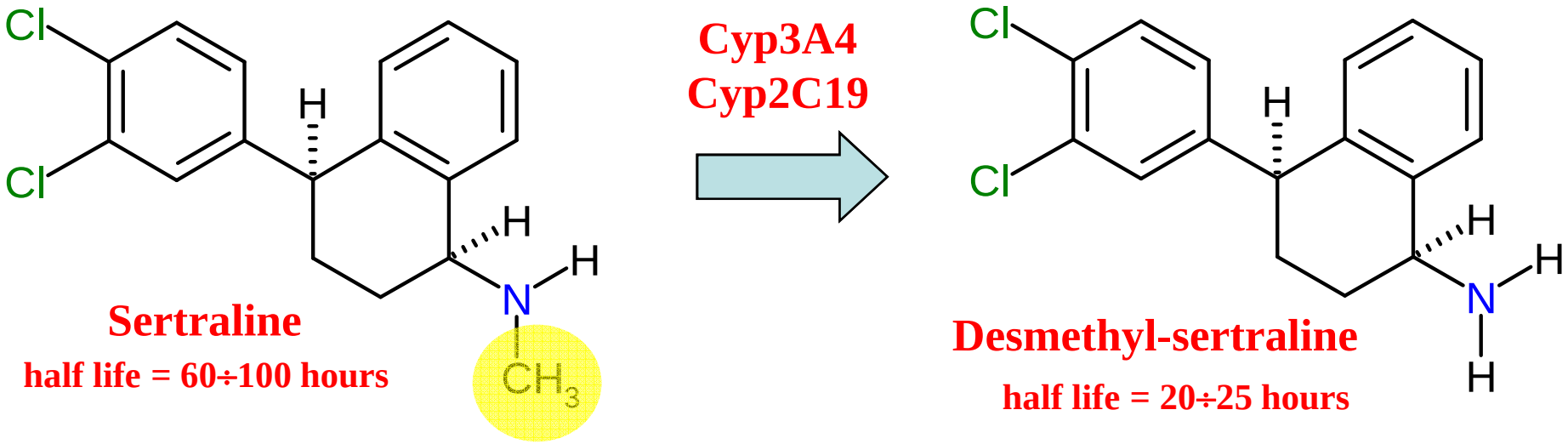


Sertraline

Binding Profile:

Receptor	K_i (nM)
SERT	2.8
NET	925
DAT	315
5-HT_{2C}	2,298
α_1	188
M_1	427
H_1	6,578

2. Depression and antidepressant drugs

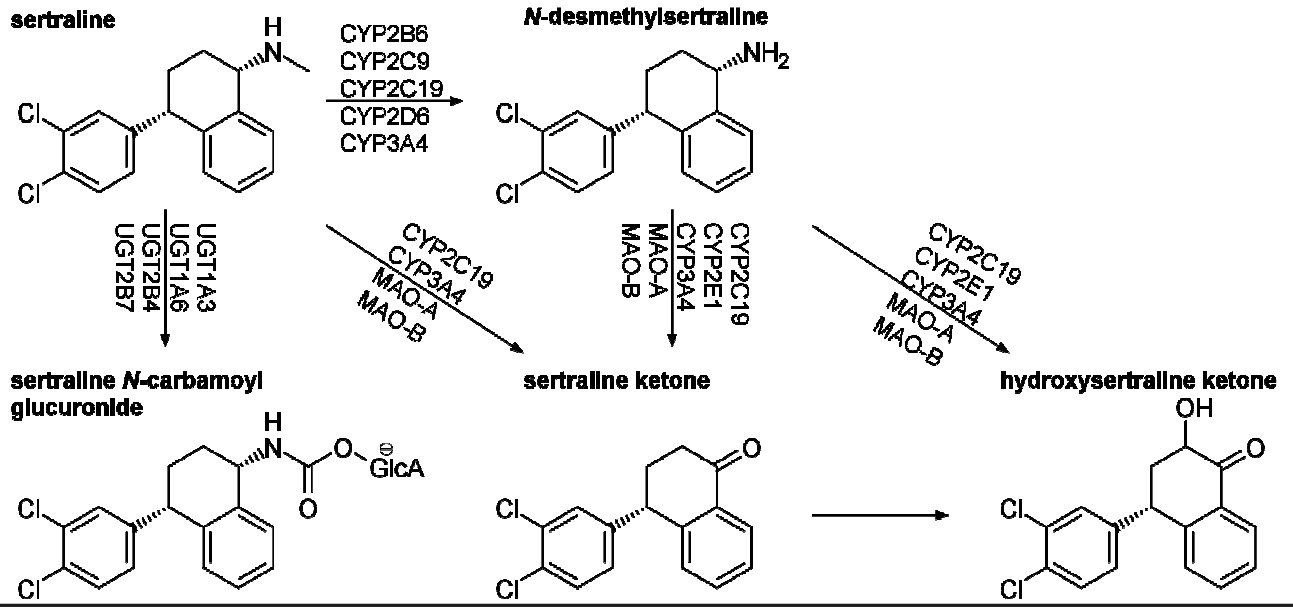


Sertraline

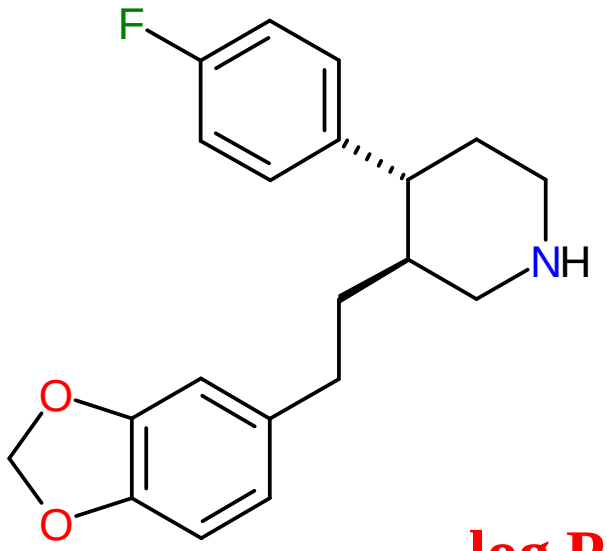
half life = 60÷100 hours

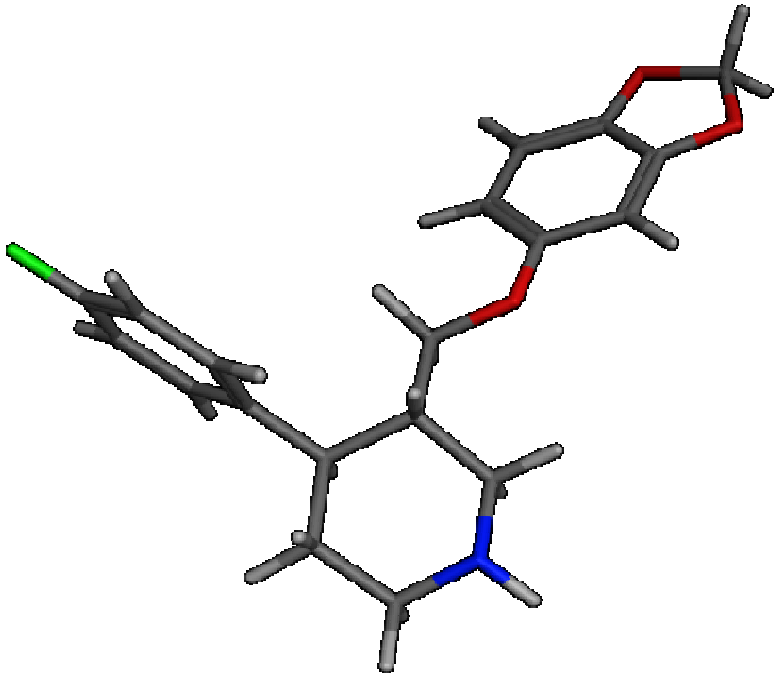
Desmethyl-sertraline

half life = 20÷25 hours



2. Depression and antidepressant drugs





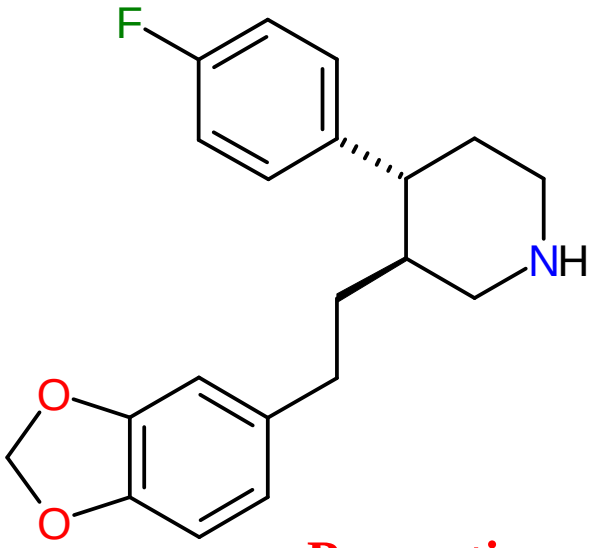
log P = 3.6

Paroxetine

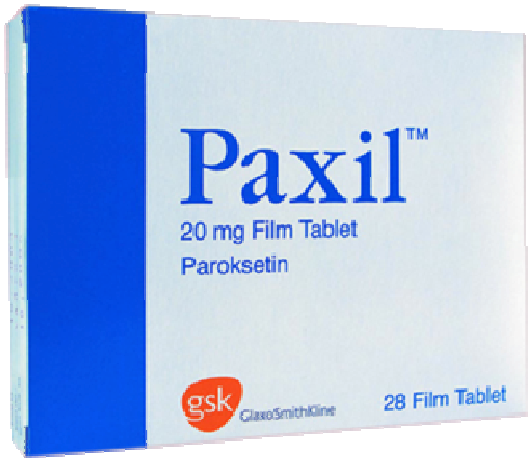
(3*S*,4*R*)-3-[(2H-1,3-benzodioxol-5-yloxy)methyl]
-4-(4-fluorophenyl)piperidine

Paroxetine, an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) type, has no active metabolites and has the highest specificity for serotonin receptors of all the SSRIs. It is used to treat depression resistant to other antidepressants, depression complicated by anxiety, panic disorder, social and general anxiety disorder, obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder, premature ejaculation, and hot flashes of menopause in women with breast cancer. In human platelets, paroxetine blocks the uptake of serotonin.

2. Depression and antidepressant drugs



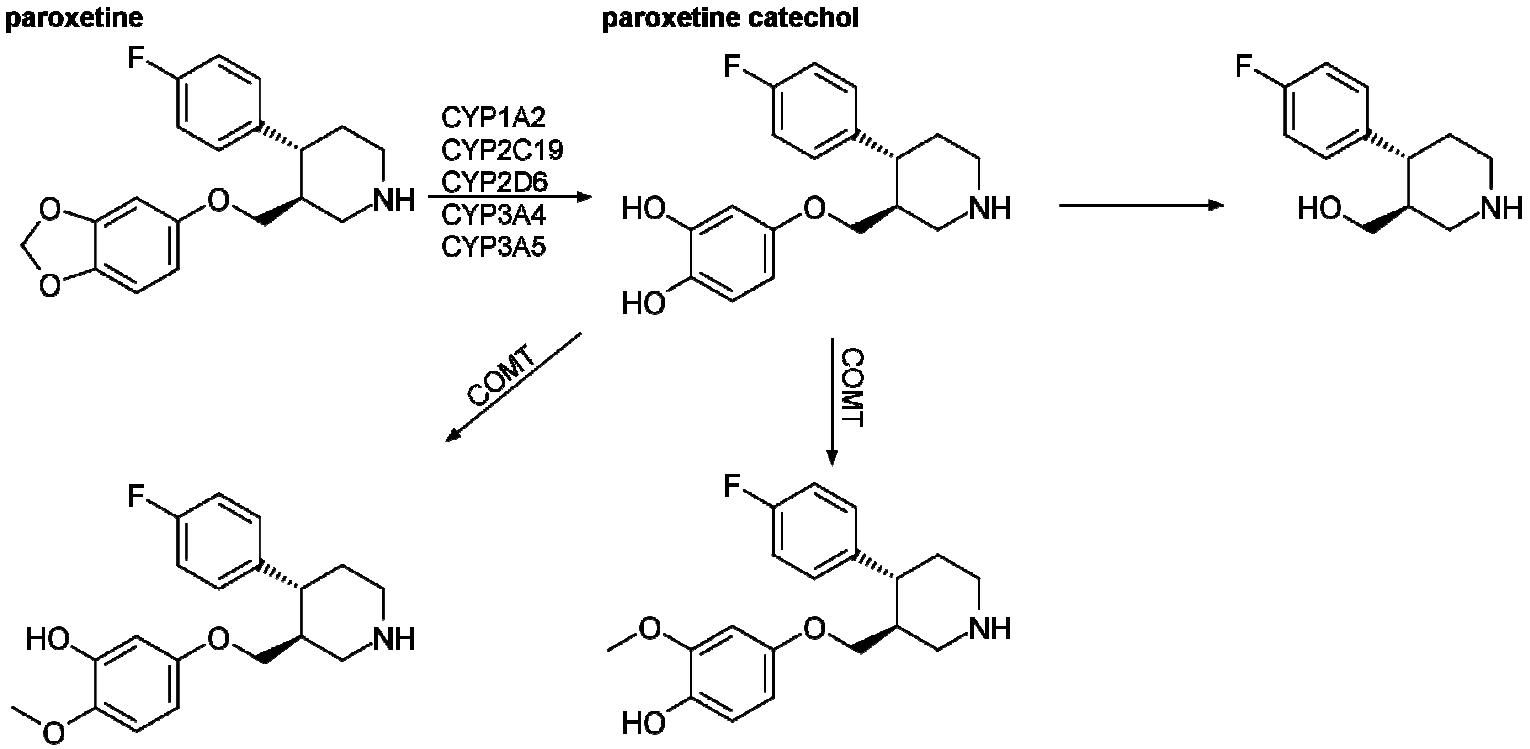
Paroxetine

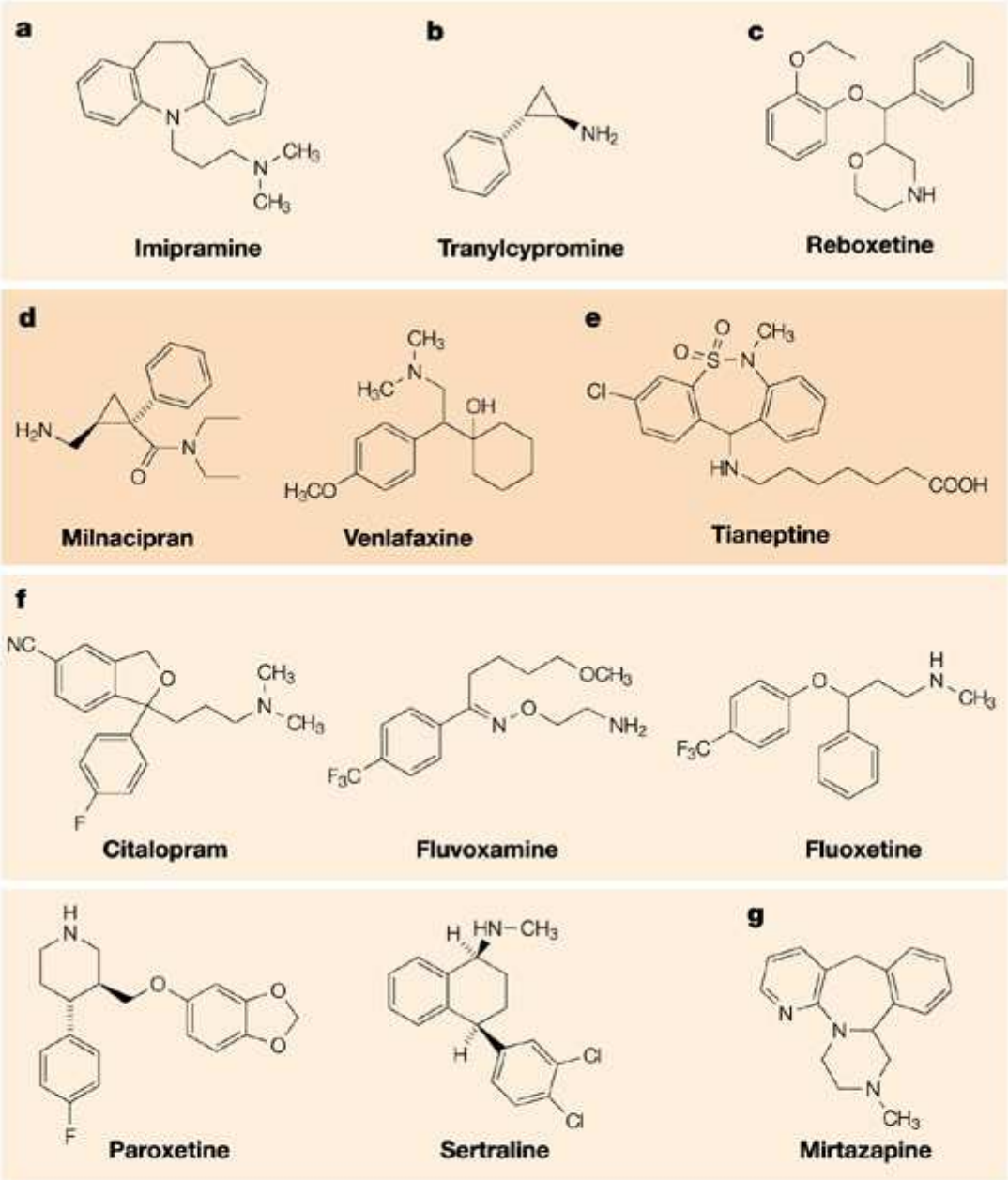


Binding Profile:

Receptor	K_i (nM)
SERT	0.34
NET	156
DAT	7,700
D_2	963
5-HT_{1A}	21,200
5-HT_{2A}	6,300
5-HT_{2C}	9,034
α_1	2,741
α_2	3,900
M_1	72
M_2	340
M_3	80
M_4	320
M_5	650
H_1	>10,000

2. Depression and antidepressant drugs





a. Prototypical tricyclic antidepressant: imipramine.

B Prototypical monoamine oxidase inhibitor: tranylcypromine.

C Selective noradrenaline reuptake inhibitor: reboxetine.

D Selective serotonin and noradrenaline reuptake inhibitors: milnacipran and venlafaxine.

E Selective serotonin reuptake activator: tianeptine.

F Selective serotonin reuptake inhibitors: citalopram, fluvoxamine, fluoxetine, paroxetine and sertraline.

G Noradrenergic and specific serotonergic antidepressant with minimal effects on monoamine reuptake: mirtazapine.

Personality Disorders

Parte III

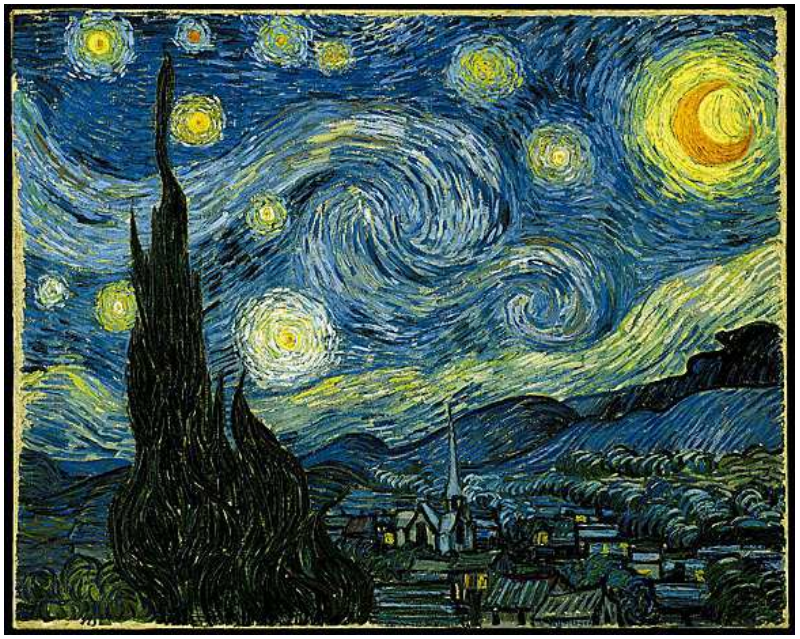
1. Psychotic disorders introduction

The psychotic disorders are classified into 3 major groups:

1. **Anxiety disorders** (*phobia and sleeping disorders*)
2. **Effective/mood disorders** (*depression*)
3. **Personality disorders** (*schizophrenia*)

1. Psychotic disorders introduction

National Institute of Mental Health



Vincent van Gogh "*The Starry Night* " 1889

Schizophrenia is a chronic, severe, and disabling brain disorder that has affected people throughout history. The English term schizophrenia comes from two Greek words that mean "*split mind*."

People with the disorder may hear voices other people don't hear. They may believe other people are reading their minds, controlling their thoughts, or plotting to harm them. This can terrify people with the illness and make them withdrawn or extremely agitated.

People with schizophrenia may not make sense when they talk. They may sit for hours without moving or talking. Sometimes people with schizophrenia seem perfectly fine until they talk about what they are really thinking

1. Psychotic disorders introduction

The symptoms of schizophrenia fall into three broad categories: positive symptoms, negative symptoms, and cognitive symptoms.

Positive symptoms

Positive symptoms are psychotic behaviors not seen in healthy people. People with positive symptoms often "lose touch" with reality. These symptoms can come and go. Sometimes they are severe and at other times hardly noticeable, depending on whether the individual is receiving treatment. They include the following: **Hallucinations, Delusions, Thought disorders, Movement disorders.**

Negative symptoms

Negative symptoms are associated with disruptions to normal emotions and behaviors. These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions. These symptoms include the following: **Flat affect (a person's face does not move or he or she talks in a dull or monotonous voice), Lack of pleasure in everyday life, Lack of ability to begin and sustain planned activities, Speaking little, even when forced to interact.**

Cognitive symptoms

Cognitive symptoms are subtle. Like negative symptoms, cognitive symptoms may be difficult to recognize as part of the disorder. Often, they are detected only when other tests are performed. Cognitive symptoms include the following: **Poor "executive functioning" (the ability to understand information and use it to make decisions), Trouble focusing or paying attention, Problems with "working memory" (the ability to use information immediately after learning it).**

1. Psychotic disorders introduction

We have already reported that The 5-HT2A receptor seems to be important for this, since psychedelic drugs that activate them produce hallucinations.

Psychosis has been traditionally linked to the neurotransmitter dopamine. In particular, the dopamine hypothesis of psychosis has been influential and states that psychosis results from an overactivity of dopamine function in the brain, particularly in the mesolimbic pathway. The two major sources of evidence given to support this theory are that dopamine receptor D2 blocking drugs (i.e., antipsychotics) tend to reduce the intensity of psychotic symptoms, and that drugs that boost dopamine activity (such as amphetamines and cocaine) can trigger psychosis in some people (see amphetamine psychosis). However, increasing evidence in recent times has pointed to a possible dysfunction of the excitory neurotransmitter glutamate, in particular, with the activity of the NMDA receptor.

1. Psychotic disorders introduction

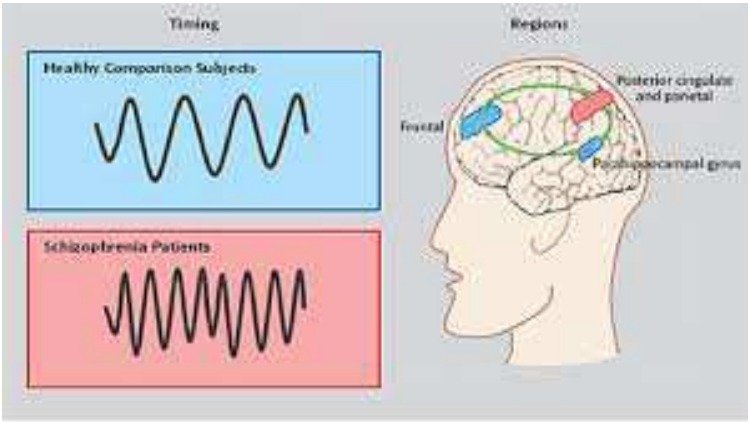
National Institute of Mental Health

The Default Mode Network (DMN) and the Positive Task Network (TPN) are two of the main circuits involved in the mediation of some cognitive functions.

In particular, the Positive Network Task starts when the brain is member of the action and, therefore, is orientated towards the outside world.

Instead, the Default Mode Network is activated when the brain is in a phase of introspection or self-referential thought, e.g. in daydream or during the development of plans, projects and actions.

The activity of DMN is regulated by the action of this neurotransmitter D2 receptors present in a particular core of the base of the brain, the Striatum.



Mood stabilizers:

Treatment	Efficacy in Acute Mania	Efficacy in Acute Depression
Aripiprazole	++	-
Lamotrigine	-	++/+
Lithium	++	++/+
Olanzapine	+++	++/+
Quetiapine	++	+++
Risperidone	+++	-
Valproate	++/+	-
Ziprasidone	++/+	-

Legend: - negligible/very low/clinically insignificant effect; + weak effect; ++ moderate-level effect; +++ strong effect.

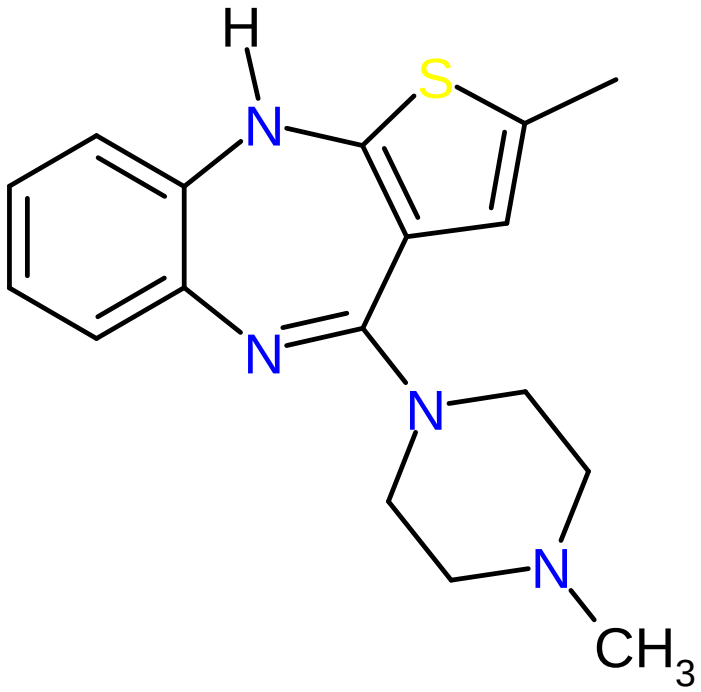
Lithium salts:

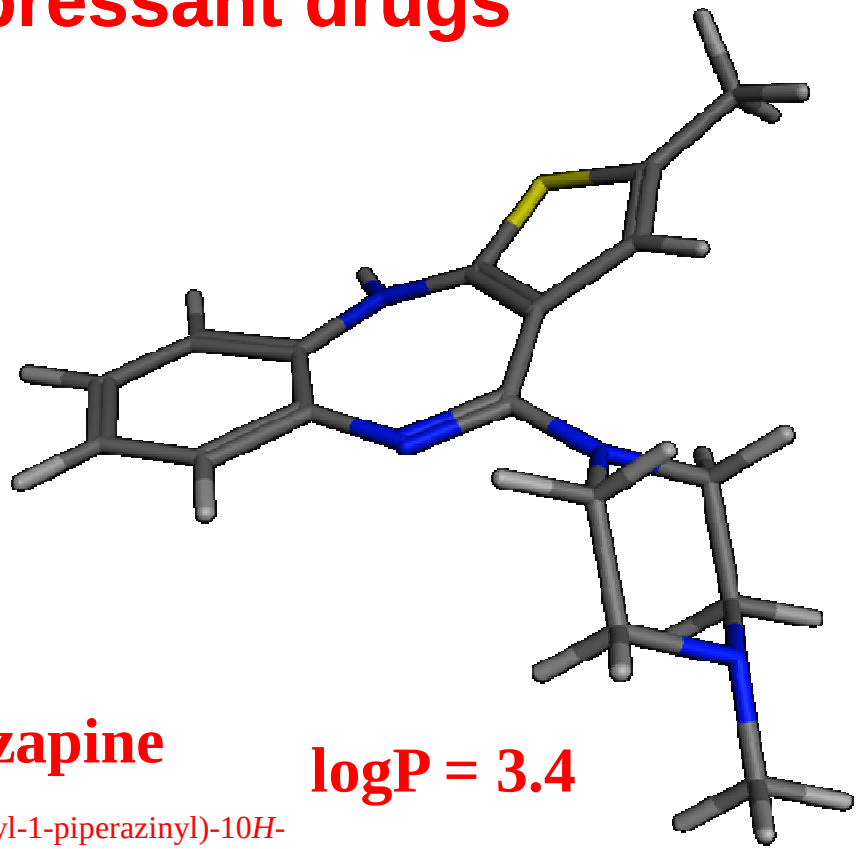
The use of **lithium salts** as a treatment of bipolar disorder was first discovered by Dr. John Cade, an Australian psychiatrist who published a paper on the use of lithium in 1949.

Lithium salts had been used for a while, as a first-line treatment for bipolar disorder. In ancient times, doctors would send their mentally ill patients to drink from "alkali springs" as a treatment. They did not know it, but they were really prescribing lithium, which was present in high concentration in the waters. The therapeutic effect of lithium salts appears to be entirely due to the lithium ion, Li^+.

Its exact mechanism of action is uncertain, although there are several possibilities such as inhibition of inositol monophosphatase, modulation of G proteins or regulation of gene expression for growth factors and neuronal plasticity. There is strong evidence for its effectiveness in acute treatment and prevention of recurrence of mania. It can also be effective in bipolar depression, although the evidence is not as strong. It is also effective in reducing the risk of suicide in patients with mood disorder.

2. Depression and antidepressant drugs





Olanzapine

logP = 3.4

2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine

Olanzapine, an atypical antipsychotic agent, is used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia. Future uses may include the treatment of obsessive-compulsive disorder and severe behavioral disorders in autism. Structurally and pharmacologically similar to clozapine, olanzapine binds to alpha(1), dopamine, histamine H1, muscarinic, and serotonin type 2 (5-HT2) receptors.

2. Antipsychotics (or neuroleptics)

2. Depression and antidepressant drugs

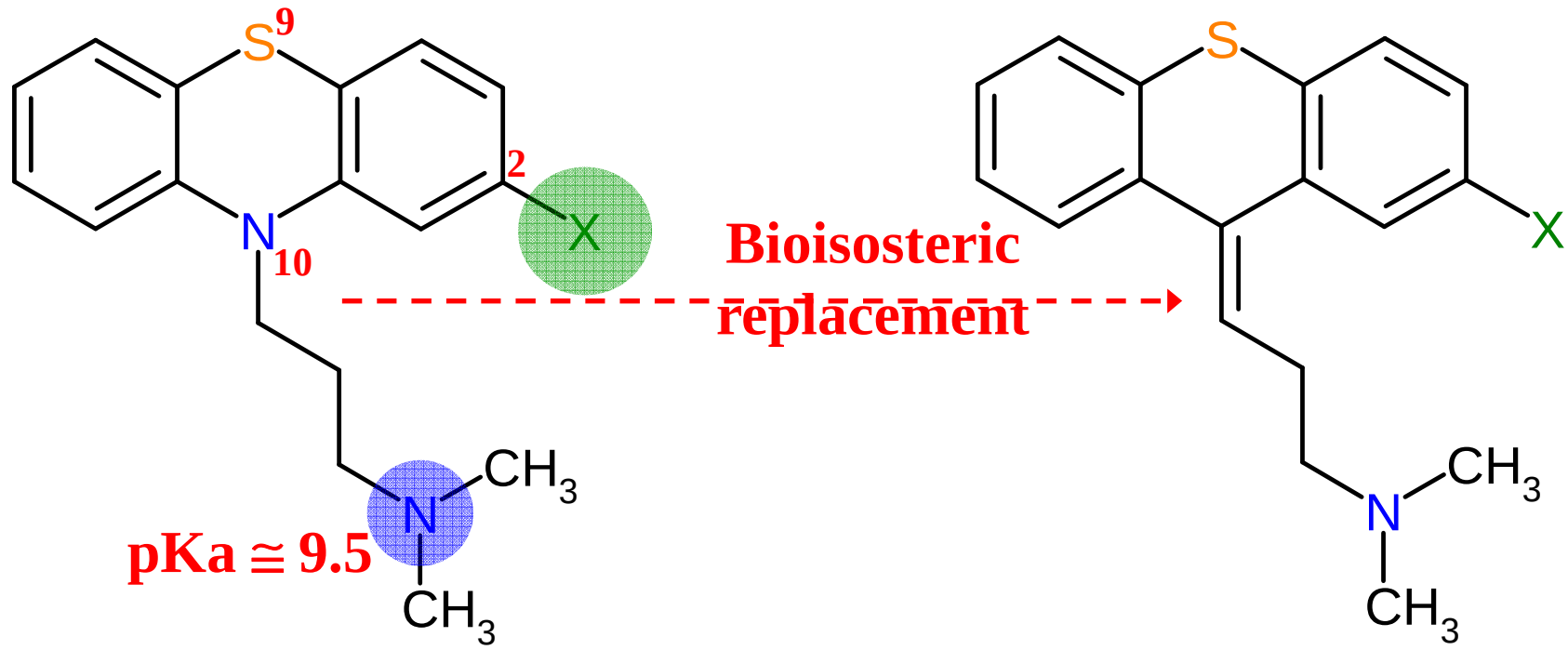
2.1 Tricyclic antipsychotics

Compound	SERT	NET	DAT	5-HT_{1A}	5-HT_{2A}	α_1	α_2	D_2	H_1	mACh
Amitriptyline	4.30	35	3,250	320	24	26	815	1,230	1.03	13.8
Butriptyline	1,360	5,100	3,940	7,000	380	570	4,800	?	1.1	35
Clomipramine	0.28	38	2,190	7,000	27	38	3,200	190	31	37
Desipramine	17.6	0.83	3,190	6,700	315	115	6,350	3,400	85	132
Dosulepin	8.6	46	5,310	2,300	258	470	2,400	?	3.6	25
Doxepin	68	29.5	12,100	283	26	24	1,185	1,380	0.21	52
Imipramine	1.40	37	8,500	7,650	115	61	3,150	1,310	24	68
Iprindole	1,620	1,262	6,530	2,800	280	2,300	8,600	?	130	2,100
Lofepramine	70	5.4	18,000	4,600	200	100	2,700	2,000	360	67
Nortriptyline	18	4.37	1,140	302	43	58	2,265	1,885	8.2	94
Protriptyline	19.6	1.41	2,100	3,800	70	130	6,600	2,300	25	25
Trimipramine	149	2,450	3,780	8,000	32	24	680	180	0.27	58

Most, if not all, of the TCAs also potently inhibit sodium channels and L-type calcium channels, and therefore act as sodium channel blockers and calcium channel blockers, respectively. The former property is responsible for the high mortality rate upon overdose seen with the TCAs via cardiotoxicity.

2. Depression and antidepressant drugs

Structure-activity relationships

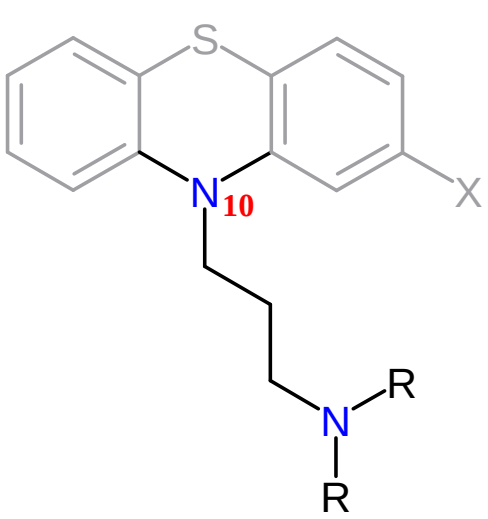


X = SO_2NR_2 > CF_3 > $COCH_3$ > Cl

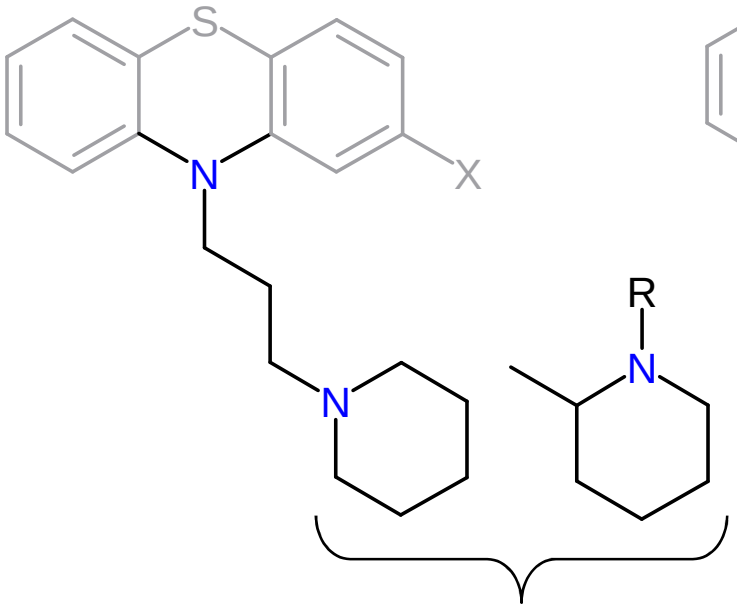
Thioxanthene
(cis > trans)

2. Depression and antidepressant drugs

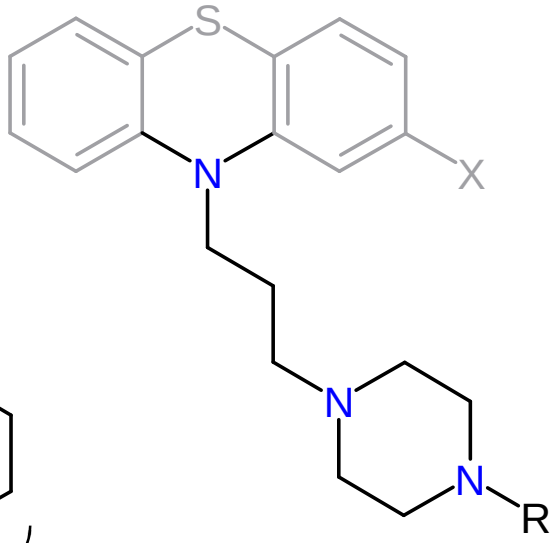
Structure-activity relationships



Aliphatic phenotiazines



Piperidine phenotiazines



Piperazine phenotiazines

Antipsychotic potency: piperazines > piperidines > aliphatics

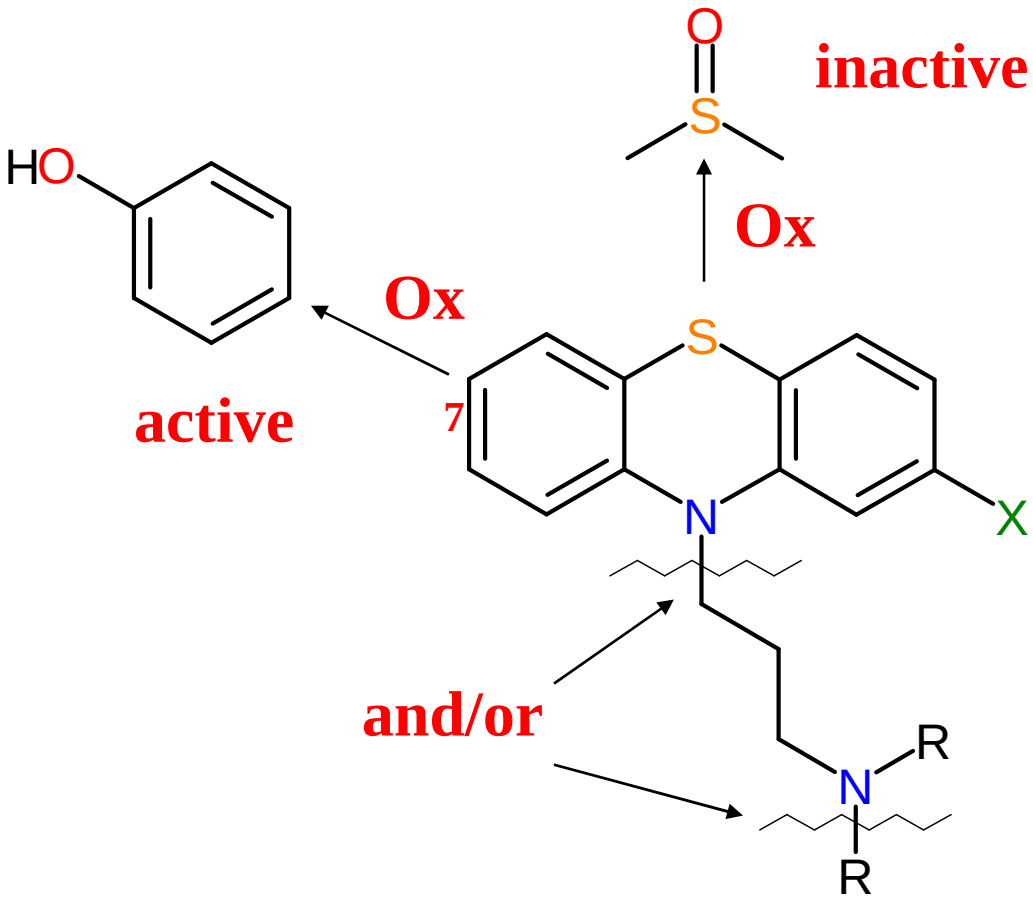
EPS frequency: piperazines > piperidines > aliphatics

Sedation: aliphatics ≅ piperidines > piperazines

Hypotension: aliphatics > piperidines > piperazines

2. Depression and antidepressant drugs

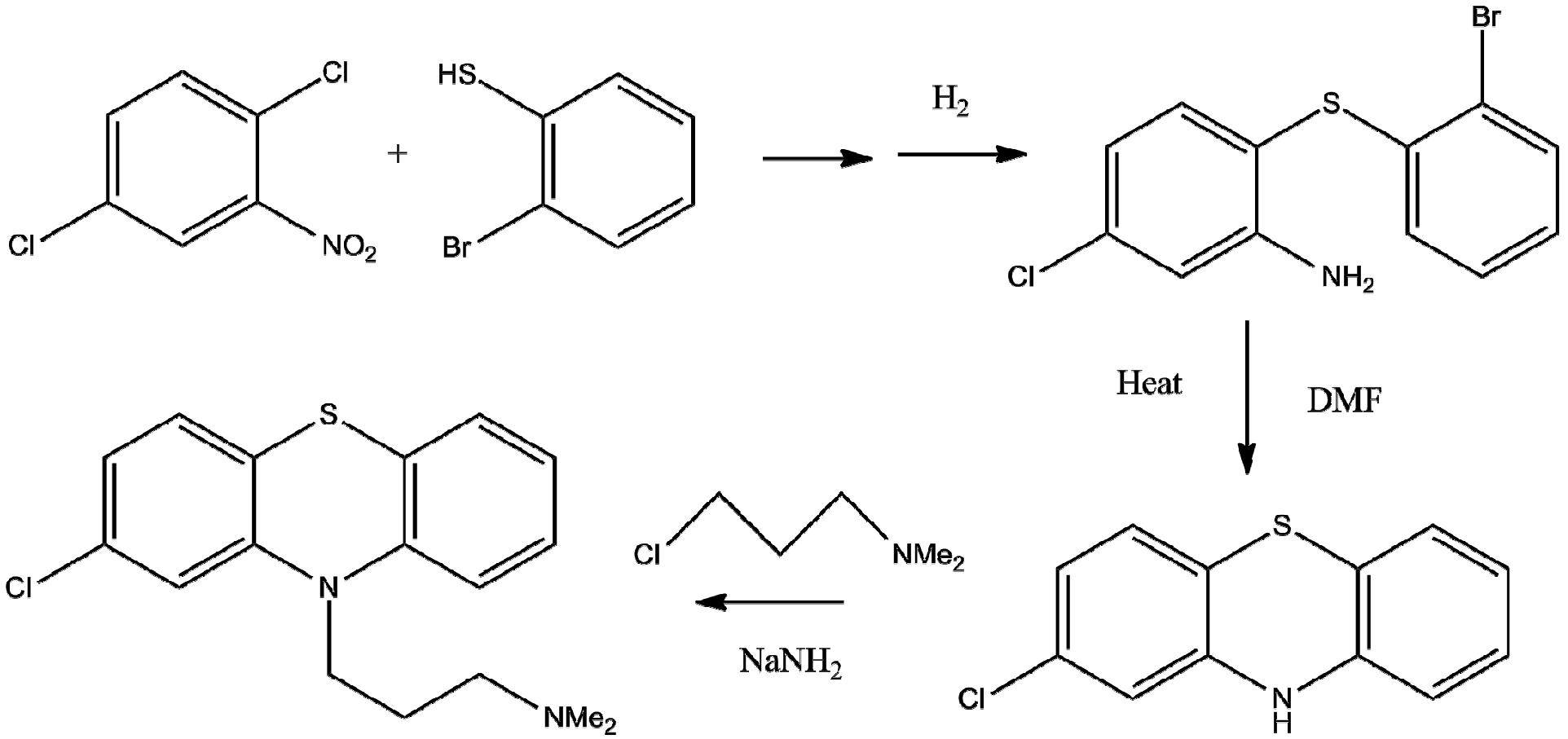
Biotransformation of the Antipsychotic Phenothiazines



Metabolic pathways are significantly altered by a variety of factors (age, sex, interaction with other drugs, route of administration, etc.)

2. Depression and antidepressant drugs

Synthesis Path



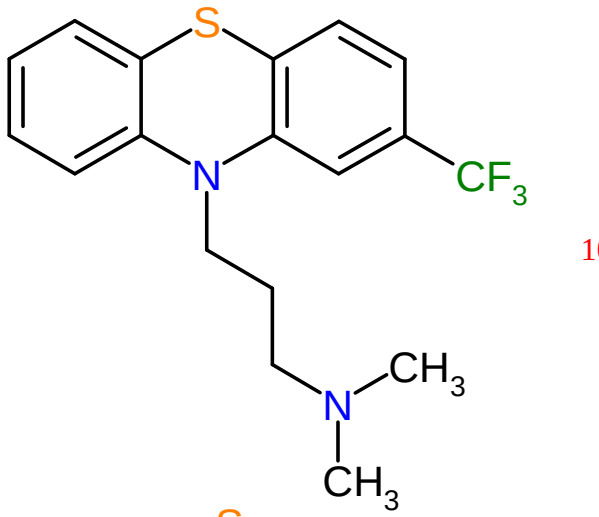
2. Depression and antidepressant drugs

2.1 Tricyclic antidepressants

A measure of "**chlorpromazine equivalence**" is used to compare the relative effectiveness of antipsychotic.
The measure specifies the amount (mass) in milligrams of a given drug that must be administered in order to achieve desired effects equivalent to those of 100 milligrams of chlorpromazine.
Drugs with a potency comparable to chlorpromazine at the same dose range (*ca.* 100 milligrams) would be considered "***low potency***". Agents with a chlorpromazine equivalence ranging from 5 to 10 milligrams would be considered "***medium potency***", and agents with 2 milligrams would be considered "***high potency***".

2. Depression and antidepressant drugs

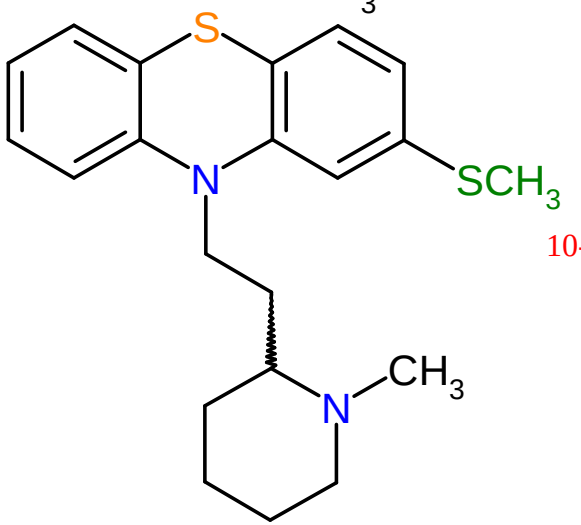
2.2 Typical tricyclic antidepressants



Triflupromazine

N,*N*-dimethyl-3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]-propan-1-amine

logP = 4.9



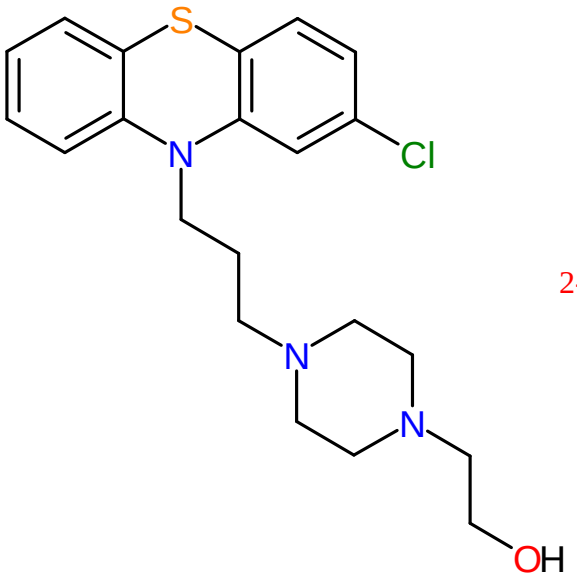
Thioridazine

10-{2-[(RS)-1-Methylpiperidin-2-yl]ethyl}-2-methylsulfanyl-phenothiazine

logP = 5.9

2. Depression and antidepressant drugs

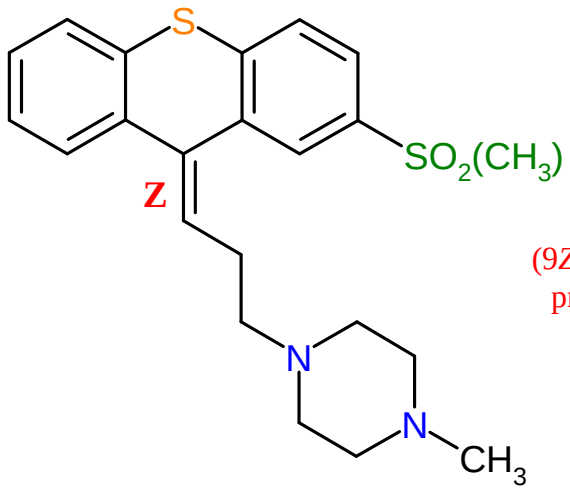
2.2 Typical tricyclic antidepressants



Perphenazine

2-[4-[3-(2-chloro-10H-phenothiazin-10-yl) propyl]piperazin-1-yl]ethanol

logP = 3.9



Thiothixene

(9*Z*)-*N*,*N*-dimethyl-9-[3-(4-methylpiperazin-1-yl) propylidene]-9*H*-thioxanthene-2-sulfonamide

logP = 3.8

2. Depression and antidepressant drugs

2.3 Atypical tricyclic antidepressants

The **atypical antipsychotics (AAP) (also known as second generation antipsychotics)** are a group of antipsychotic drugs used to treat psychiatric conditions. Some atypical antipsychotics are FDA approved for use in the treatment of schizophrenia. Some carry FDA approved indications for acute mania, bipolar depression, psychotic agitation, bipolar maintenance, and other indications. ***Atypicals differ from typical antipsychotics in that they have less of a propensity for causing extrapyramidal symptoms (EPS). EPS include parkinsonian-type movements, rigidity and tremor.***

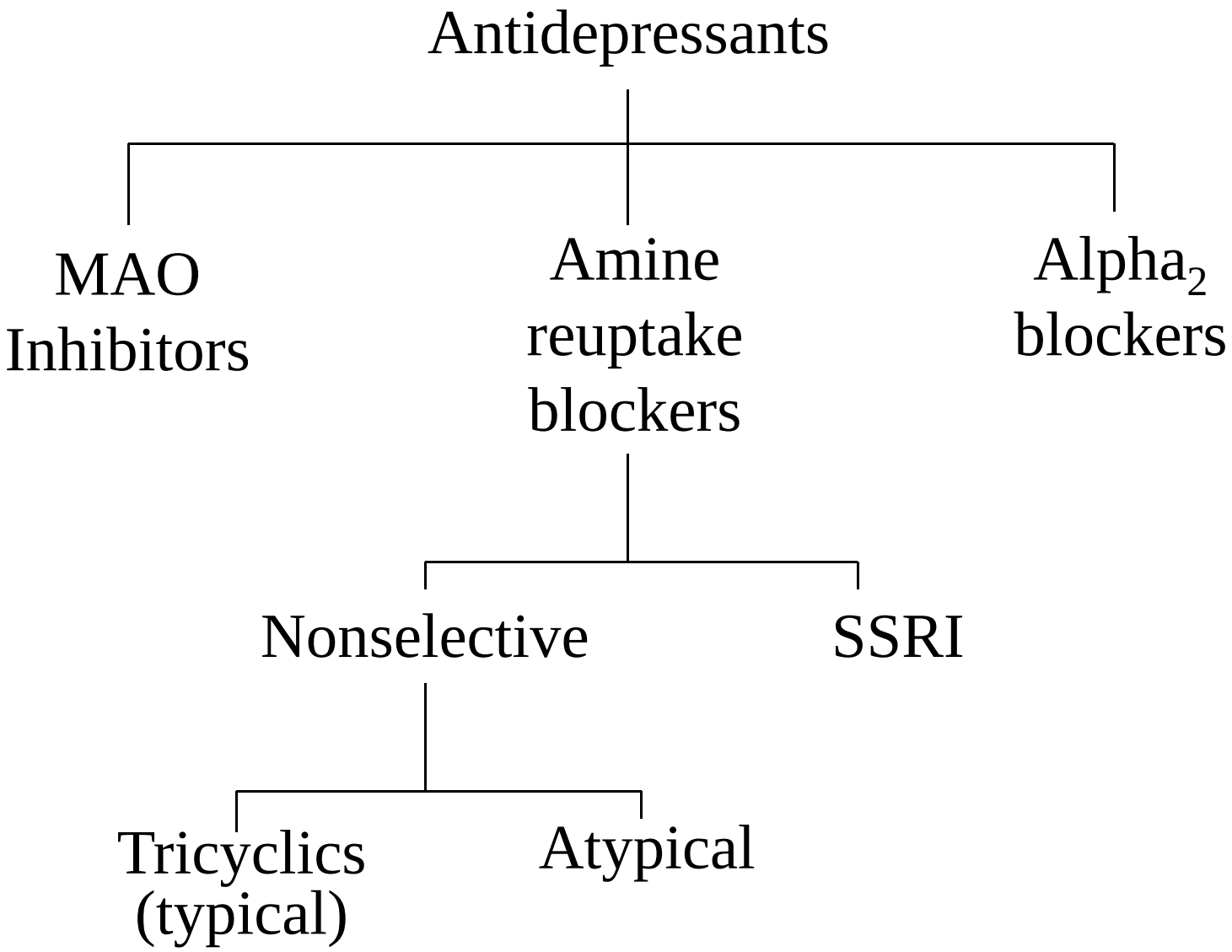
2. Depression and antidepressant drugs

2.3 Atypical tricyclic antidepressants

The **atypical antipsychotics (AAP) (also known as second generation antipsychotics)** are a group of antipsychotic drugs used to treat psychiatric conditions. Some atypical antipsychotics are FDA approved for use in the treatment of schizophrenia. Some carry FDA approved indications for acute mania, bipolar depression, psychotic agitation, bipolar maintenance, and other indications. ***Atypicals differ from typical antipsychotics in that they have less of a propensity for causing extrapyramidal symptoms (EPS). EPS include parkinsonian-type movements, rigidity and tremor.***

During the course of treatment atypical antipsychotics are associated with the following benefits; higher rate of responders, efficiency in patients with refractory disease, lower risk of suicides, better functional capacity and an improved quality of life.

2. Depression and antidepressant drugs



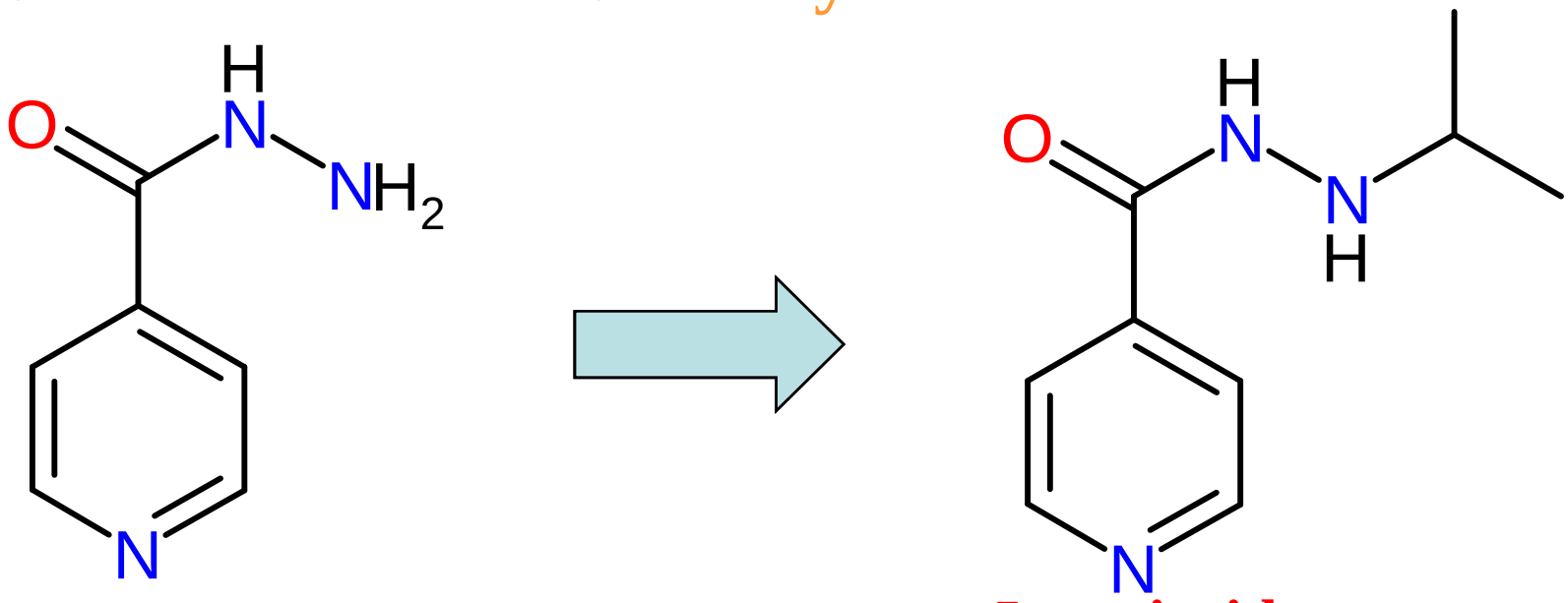
2. Depression and antidepressant drugs

2.6 MAO inhibitors:

- **MAOIs still useful**
- **May be most potent in severe depression**
- **"Atypical" depression: ↑Weight, ↑ Sleep**
  - ***May be treatment of choice***
- **Refractory depression**
  - ***May work where tricyclics, SSRIs fail***

2. Depression and antidepressant drugs

2.6 MAO inhibitors: history



Isonoazid

Pyridine-4-carbohydrazide

Iproniazid

N-isopropyl-pyridine-4-carbohydrazide

Iproniazid was the first antidepressant ever marketed. It was originally intended for the treatment of tuberculosis. In 1952, its antidepressant properties were discovered when researchers noted that the patients given iproniazid became "inappropriately happy". It was subsequently developed as an antidepressant and was approved for use in 1958. It was later withdrawn in 1961 due to the unacceptable incidence of hepatitis and was replaced by less hepatotoxic drugs like *isocarboxazid* (Marplan), *phenelzine* (Nardil), and *tranylcypromine* (Parnate).

Iproniazid was developed using the same hydrazine that was used to power German V-2 rockets.

2. Depression and antidepressant drugs

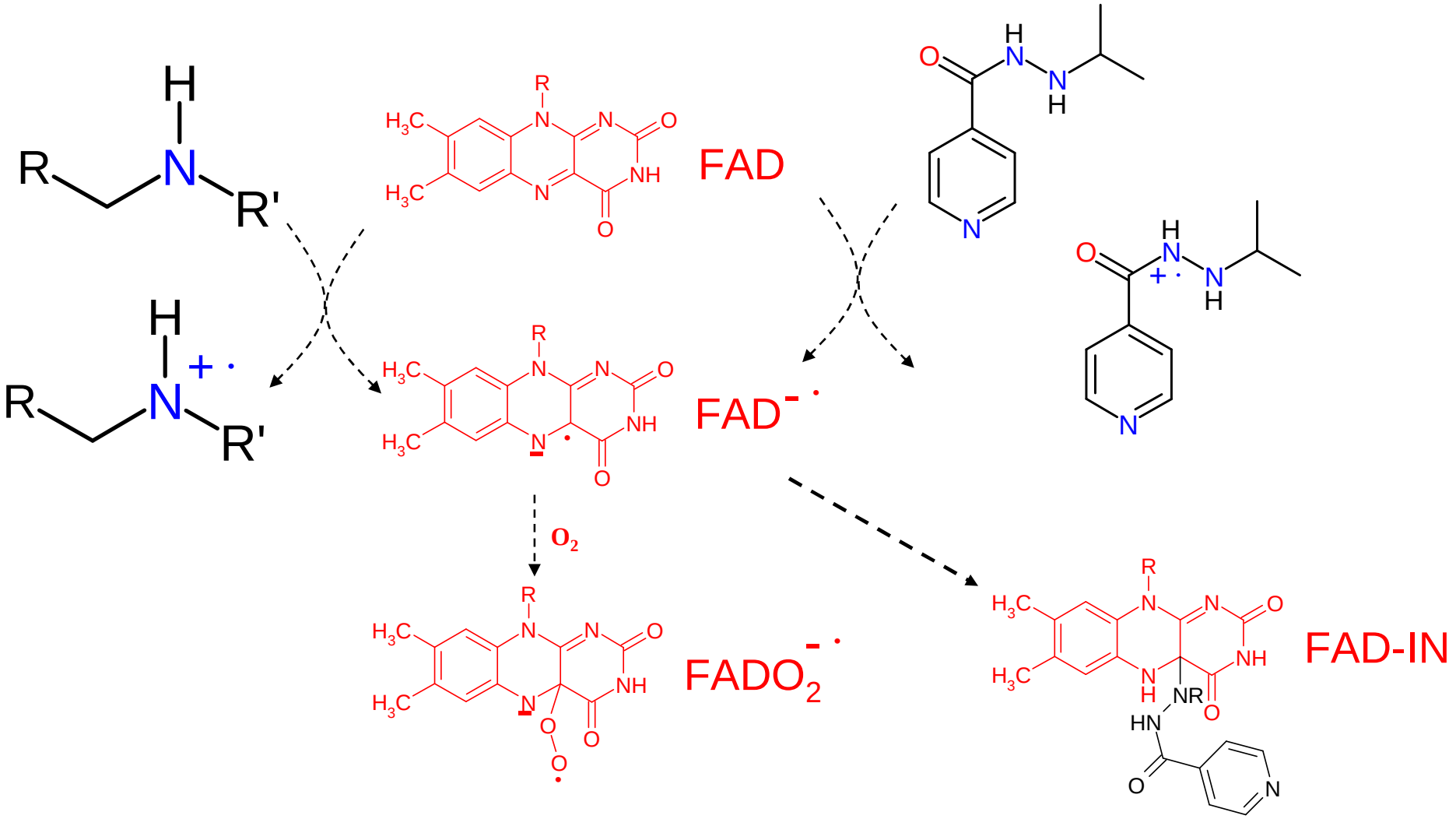
2.6 MAO inhibitors: selectivity

MAO-A inhibition reduces the breakdown of primarily ***serotonin, epinephrine, and norepinephrine*** and thus has a higher risk of serotonin syndrome and/or a hypertensive crisis. Tyramine is broken down by MAO-A, therefore inhibiting its action may result in excessive build-up of it, so diet must be monitored for tyramine intake.

MAO-B inhibition reduces the breakdown mainly of ***dopamine and phenethylamine*** so there are no dietary restrictions associated with this. Two such drugs, selegiline and rasagiline have been approved by the FDA without dietary restrictions, except in high dosage treatment where they lose their selectivity.

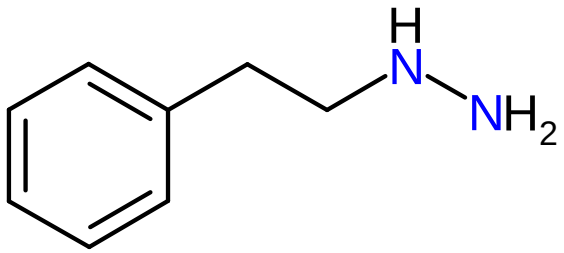
2. Depression and antidepressant drugs

2.6 MAO inhibitors: irreversible mechanism of action



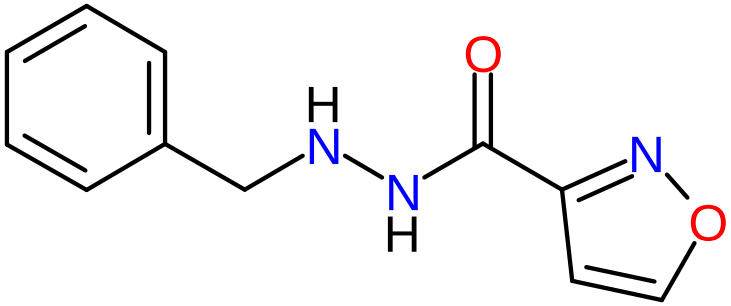
2. Depression and antidepressant drugs

2.6 MAO inhibitors: irreversible inhibitors



Phenelzine

2-phenylethylhydrazine



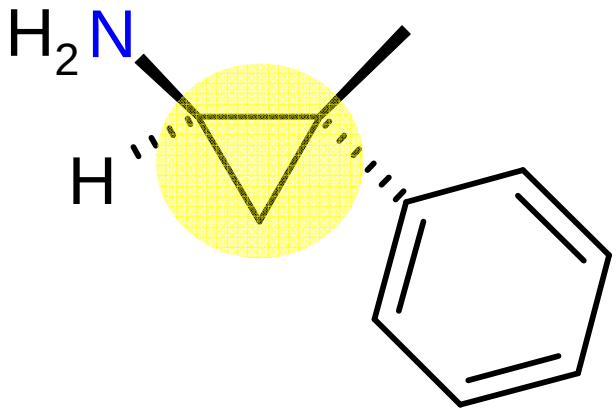
Isocarboxazid

N′-benzyl-5-methylisoxazole-3-carbohydrazide

Both drugs are an ***irreversible*** and ***nonselective*** monoamine oxidase inhibitors (MAOI) of the hydrazine chemical class used as an antidepressant and anxiolytic.

2. Depression and antidepressant drugs

2.6 MAO inhibitors: irreversible inhibitors



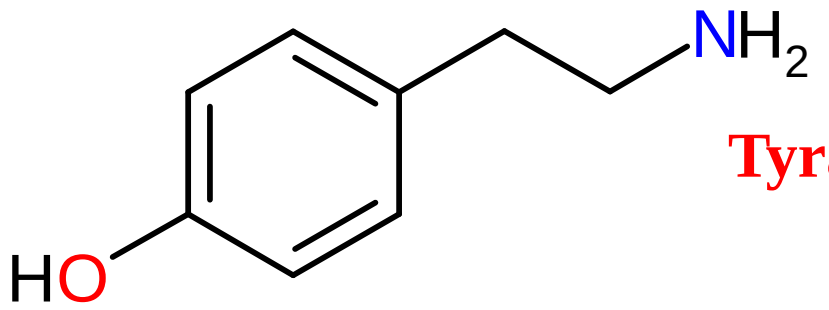
Tranylcipromine

(±)-*trans*-2-phenylcyclopropan-1-amine

Tranylcypromine is a drug of the substituted phenethylamine and amphetamine classes which acts as a monoamine oxidase inhibitor (MAOI)—it is a ***non-selective*** and irreversible inhibitor of the enzyme monoamine oxidase (MAO). It is used as an antidepressant and anxiolytic agent in the clinical treatment of mood and anxiety disorders, respectively.

2. Depression and antidepressant drugs

2.6 MAO inhibitors: “cheese effect”



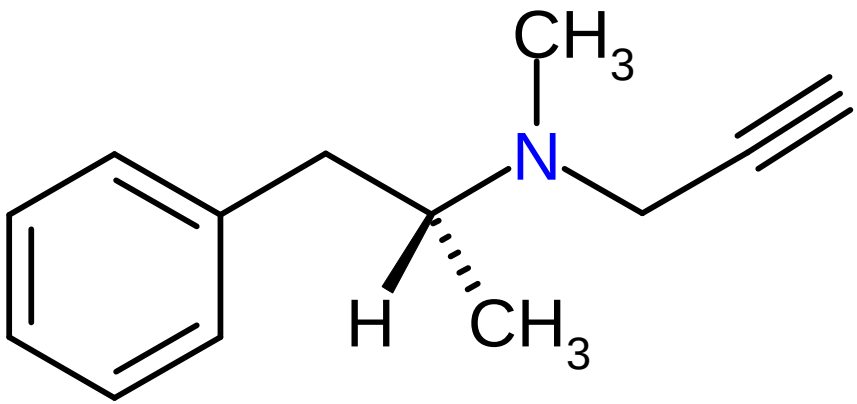
Tyramine (logP = 0.7)

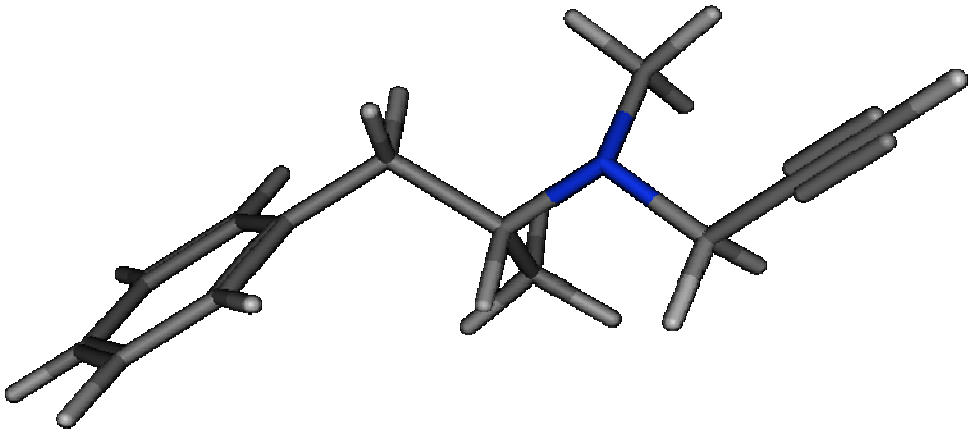
4-(2-aminoethyl)phenol

Foods high in endogenous monoamine precursors or exogenous monoamine compounds may cause adverse reactions. The most common example of this, is the ***hypertensive crisis*** caused by the ingestion of **tyramine**, which is found in foods like *aged cheeses, cured meats, tofu and certain red wines*. Some, such as yeast extracts like Bovril and Marmite, contain enough tyramine to be potentially fatal in a single serving. Spoiled food is also likely to contain dangerous levels of tyramine. Notably, however, it is unable to cross the blood-brain-barrier (BBB), resulting in only non-psychoactive peripheral sympathomimetic effects. When ingested unintentionally from certain foods in conjunction with a monoamine oxidase inhibitor (MAOI), tyramine is responsible for the so-called "***cheese effect***" often seen with their use.

2. Depression and antidepressant drugs

2.6 MAO inhibitors: irreversible inhibitors (MAO-B)





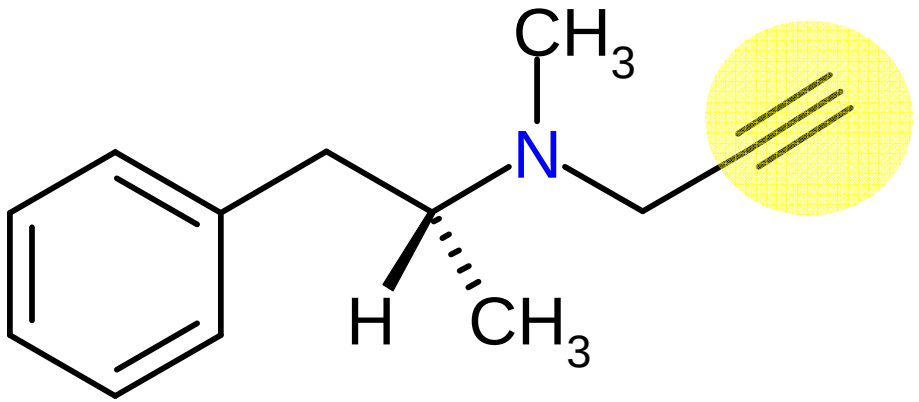
Selegiline

(*R*)-*N*-methyl-*N*-(1-phenylpropan-2-yl)prop-2-yn-1-amine

Selegiline is a drug used for the treatment of early-stage Parkinson's disease, depression and senile dementia. In normal clinical doses it is a selective irreversible MAO-B inhibitor, however in larger doses it loses its specificity and also inhibits MAO-A.

2. Depression and antidepressant drugs

2.6 MAO inhibitors: irreversible inhibitors (MAO-B)

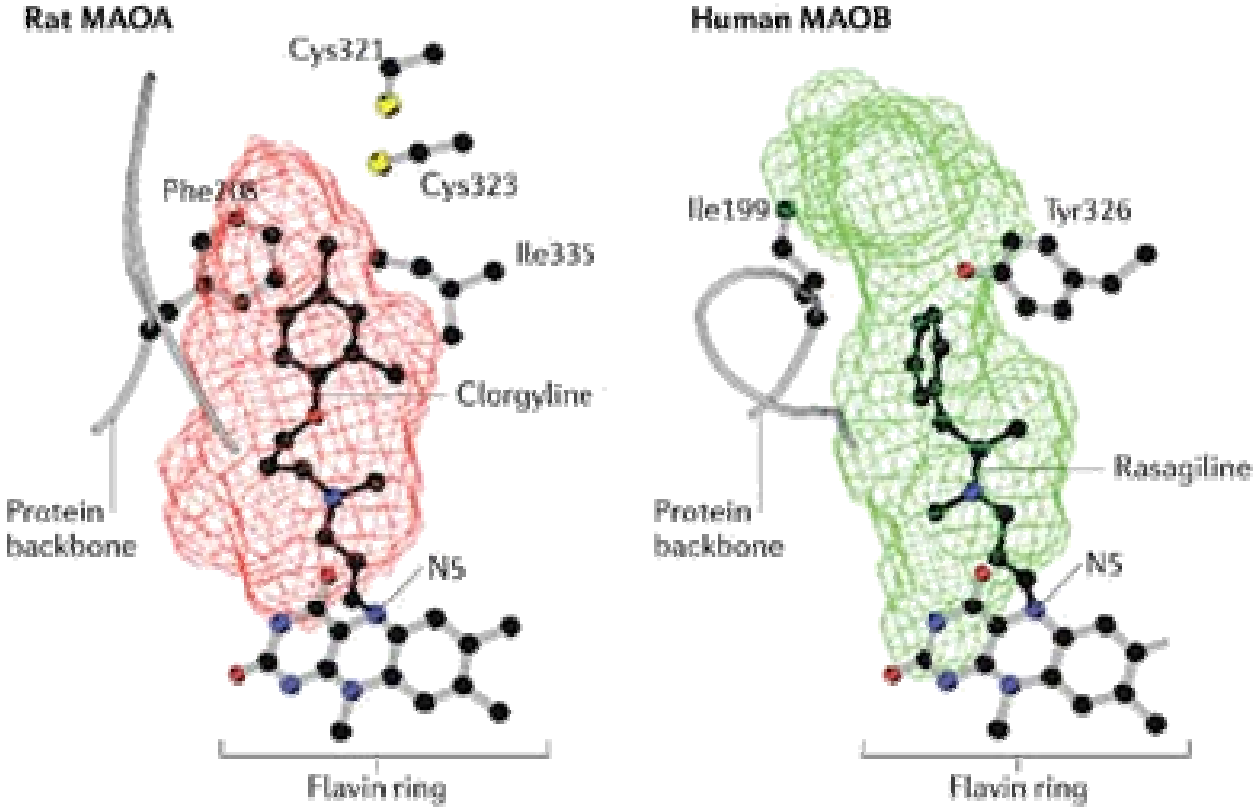


Selegiline

Dopamine is an essential chemical that occurs in many parts of the body. It is the premature degradation of dopamine that results in the symptoms of Parkinson's disease. Monoamine oxidase (MAO) is an enzyme which accelerates the breakdown of dopamine. Selegiline can prolong the effects of dopamine in the brain by preventing its breakdown through seletively blocking MAO. It also may prevent the removal of dopamine between nerve endings and enhance release of dopamine from nerve cells.

2. Depression and antidepressant drugs

2.6 MAO inhibitors: MAO-A vs. MAO-B selectivity



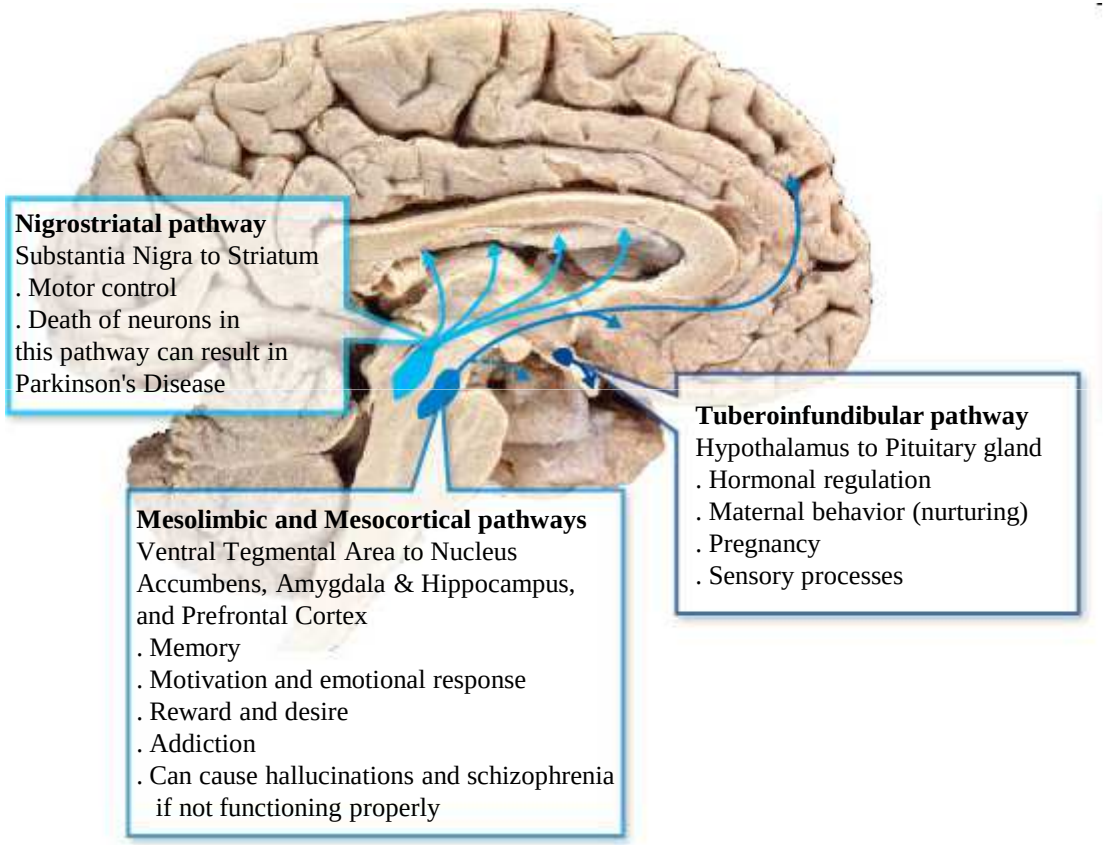
The combined volume of the fused cavities in human monoamine oxidase B (MAOB) is ≅700 Å^3 and that of the rat MAOA cavity is ≅450 Å^3.

Youdim *et al. Nature Reviews Neuroscience* **7**, 295–309 (April 2006)

2. Anxiety and anxiolytic drugs

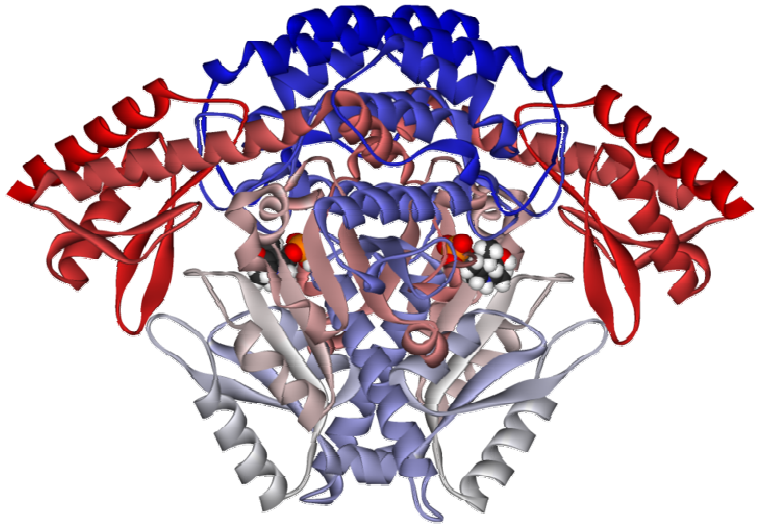
Dopamine – pathways in the brain

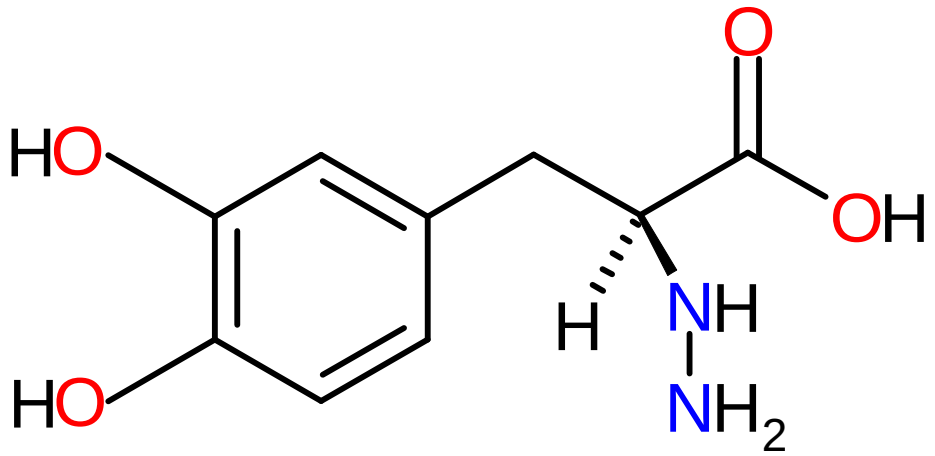
Dopamine is the neurotransmitter used by the reward pathway (also called the mesolimbic pathway, which is closely associated with the mesocortical pathway). But there are two other important pathways in the brain that utilize dopamine: the nigrostriatal pathway and the tuberoinfundibular pathway. Generally, drugs that affect dopamine levels in the brain affect all three of these dopamine pathways.



DOPA decarboxylase:

Besides the CNS, L-DOPA is also converted into dopamine from within the peripheral nervous system (PNS). The resulting hyperdopaminergia is the cause of many of the adverse side-effects seen with sole L-DOPA administration. In order to bypass these effects, it is standard clinical practice to co-administer a peripheral DOPA decarboxylase inhibitor (DDCI) such as ***carbidopa***.

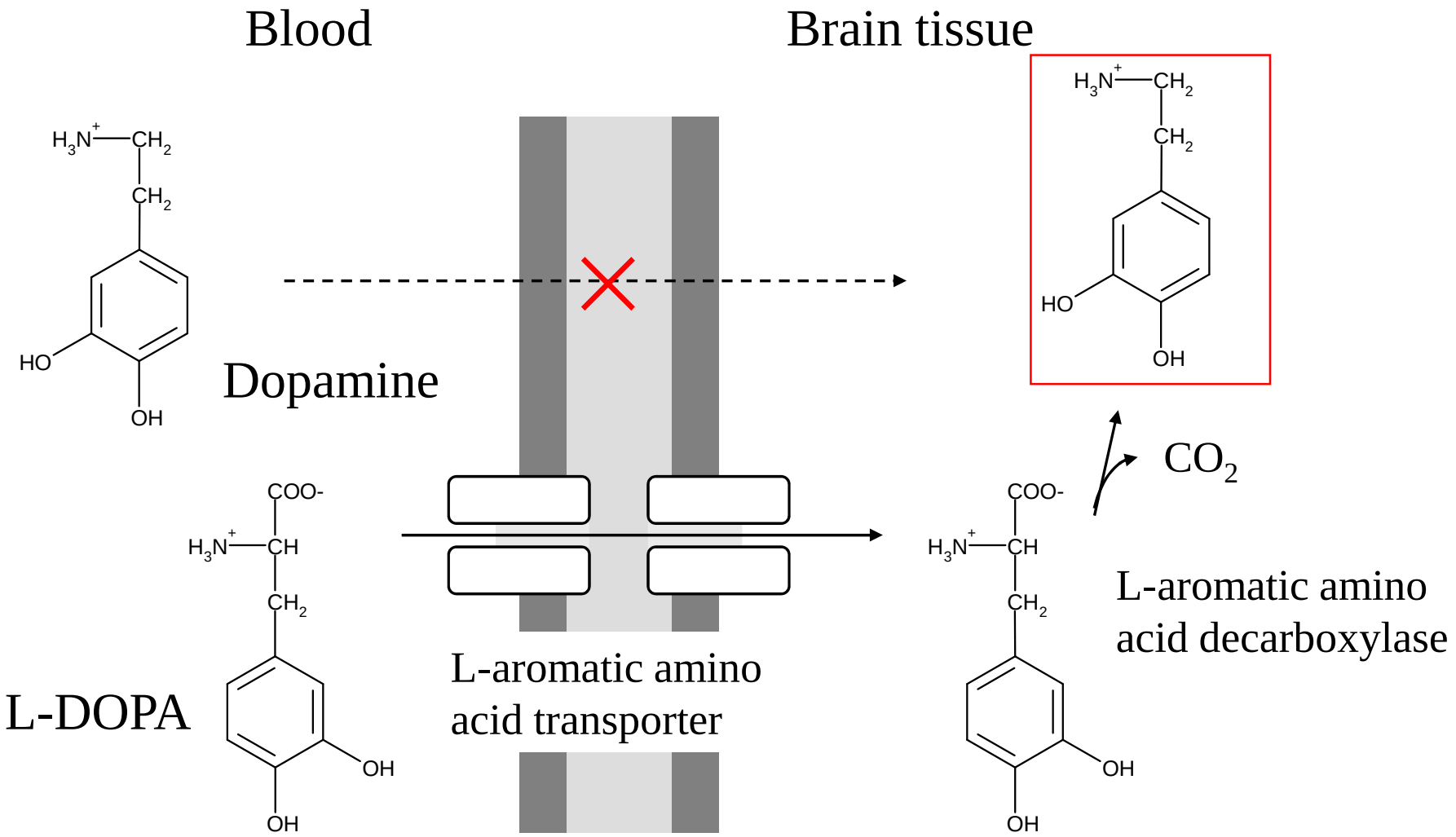




(2*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid

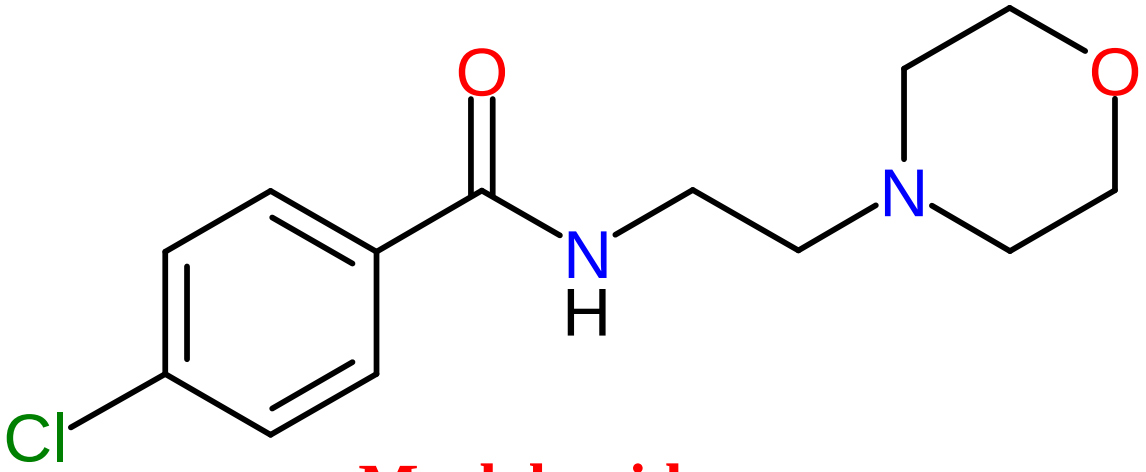
Parkinson disease:

Parkinson's disease (PD) is a long-term, progressive neurodegenerative disease involving the nervous system. When cells that normally produce dopamine in the brain are damaged or die, control of movement is hindered/ signs of Parkinson's become apparent.



2. Depression and antidepressant drugs

2.6 MAO inhibitors: reversible inhibitors (MAO-A)



Moclobenide

4-chloro-*N*-(2-morpholin-4-ylethyl)benzamide

The early MAOIs inhibited monoamine oxidase irreversibly. When they react with monoamine oxidase, they permanently deactivate it, and the enzyme cannot function until it has been replaced by the body, which can take about two weeks. A few newer MAOIs, notably ***moclobemide***, are reversible, meaning that they are able to detach from the enzyme to facilitate usual catabolism of the substrate. The level of inhibition in this way is governed by the concentrations of the substrate and the MAOI.

2. Depression and antidepressant drugs

2.6 MAO inhibitors: reversible inhibitors

Moclobemide is a reversible inhibitor of monoamine oxidase A (RIMA), a type of monoamine oxidase inhibitor (MAOI), and acts on serotonin, norepinephrine (noradrenaline), and dopamine. Unlike standard MAOIs, possible side effects do not include cardiovascular complications (hypertension) with encephalopathy, liver toxicity or hyperthermia.

A single 300 mg dose of **moclobemide inhibits 80% of monoamine oxidase A (MAO-A) and 30% of monoamine oxidase B (MAO-B)**, blocking the decomposition of norepinephrine, serotonin and, to a lesser extent, dopamine. No reuptake inhibition of any of the neurotransmitters occurs. The pharmacodynamic action encompasses activation, elevation of mood, and improvement of symptoms like dysphoria, fatigue, and difficulties in concentration. The duration and quality of sleep may be improved. In the treatment of depression the antidepressant effect often becomes evident in the first week of therapy (earlier than typically noted with TCAs/SSRIs).

Moclobemide should not generally be taken concurrently with other antidepressants, because of the likelihood of significant drug interactions. Some very specific regimens may combine moclobemide with a tricyclic or SSRI antidepressant. A washout period of two days is necessary when switching to a tricyclic antidepressant, and for SSRIs, a washout period of at least four to five half-lives is required.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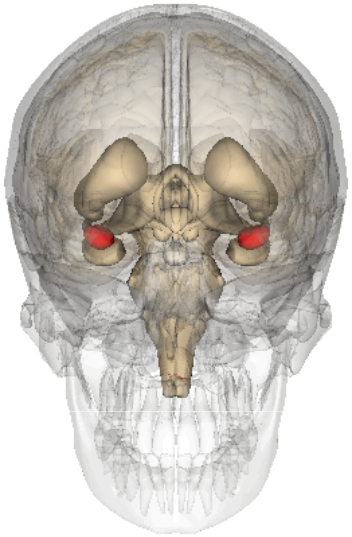
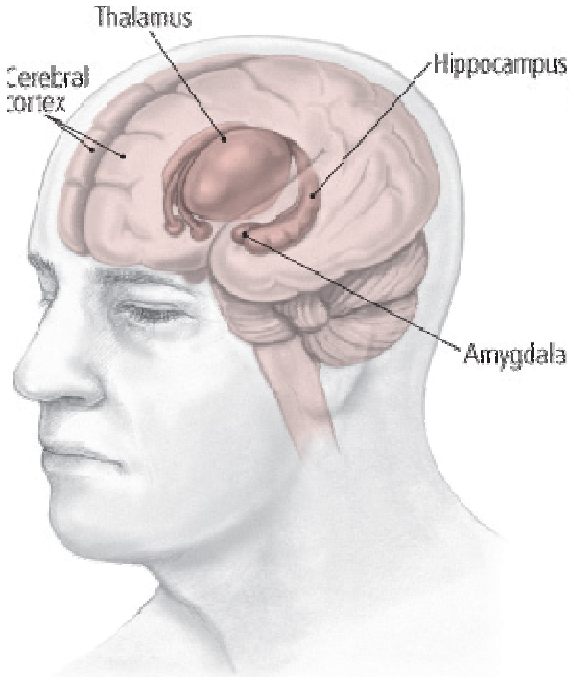
DATE
SCENE
TAKE

2. Anxiety and anxiolytic drugs

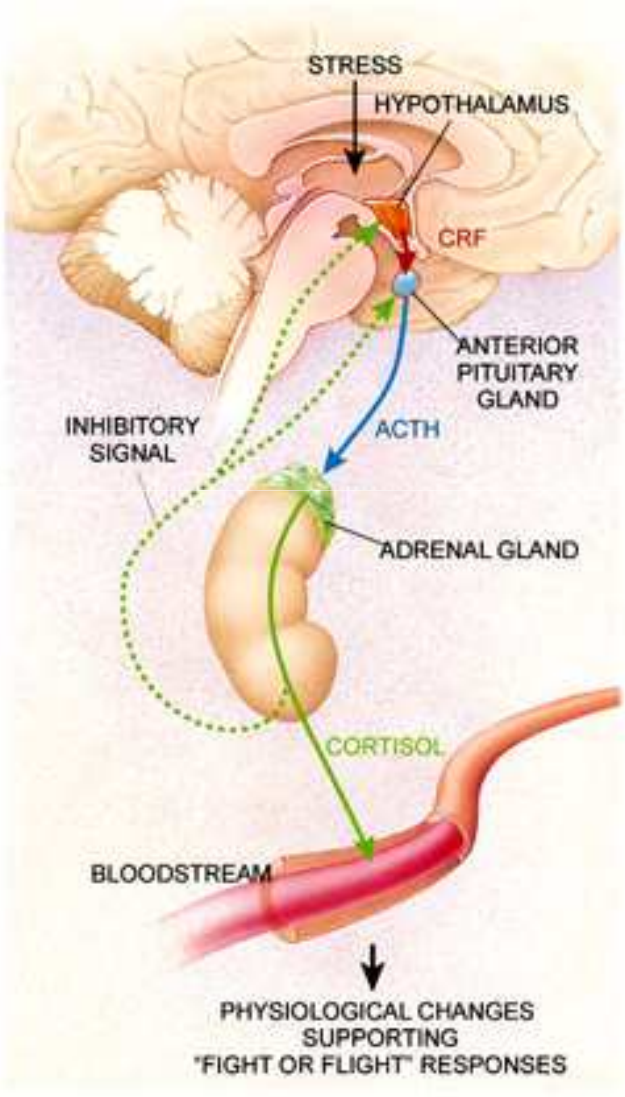




Hippocampus: The hippocampus is part of the limbic system and has a central role in processing long-term memory and recollection. Interplay between the hippocampus and the amygdala might account for the adage “once bitten, twice shy.” It is this part of the brain that registers fear when you are confronted by a barking, aggressive dog, and the memory of such an experience may make you wary of dogs you come across later in life. **The hippocampus is smaller in some depressed people, and research suggests that ongoing exposure to stress hormone impairs the growth of nerve cells in this part of the brain.**

2. Anxiety and anxiolytic drugs

HYPOTHALAMUS-PITUITARY-ADRENAL AXIS



Stress can be defined as an automatic physical response to any stimulus that requires you to adjust to change. Every real or perceived threat to your body triggers a cascade of stress hormones that produces physiological changes. We all know the sensations: your heart pounds, muscles tense, breathing quickens, and beads of sweat appear. This is known as the stress response.

The stress response starts with a signal from the part of your brain known as the ***hypothalamus***. The hypothalamus joins the pituitary gland and the adrenal glands to form a trio known as the hypothalamic-pituitary-adrenal (HPA) axis, which governs a multitude of hormonal activities in the body and may play a role in depression as well.

When a physical or emotional threat looms, the hypothalamus secretes ***corticotropin-releasing hormone (CRH)***, which has the job of rousing your body. Hormones are complex chemicals that carry messages to organs or groups of cells throughout the body and trigger certain responses. CRH follows a pathway to your pituitary gland, where it stimulates the secretion of ***adrenocorticotropic hormone (ACTH)***, which pulses into your bloodstream. When ACTH reaches your adrenal glands, it prompts the release of ***cortisol***.

The boost in cortisol readies your body to fight or flee. Your heart beats faster — up to five times as quickly as normal — and your blood pressure rises. Your breath quickens as your body takes in extra oxygen. Sharpened senses, such as sight and hearing, make you more alert.

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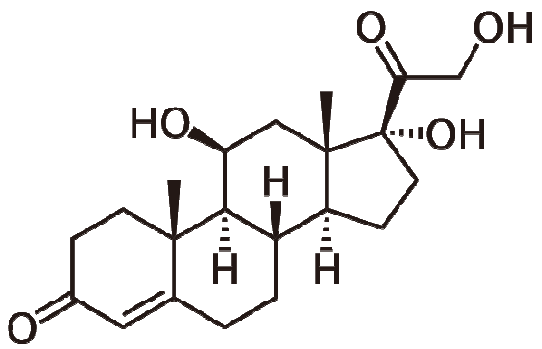


Cortisol

(11β)-11,17,21-trihydroxypregn-4-ene-3,20-dione

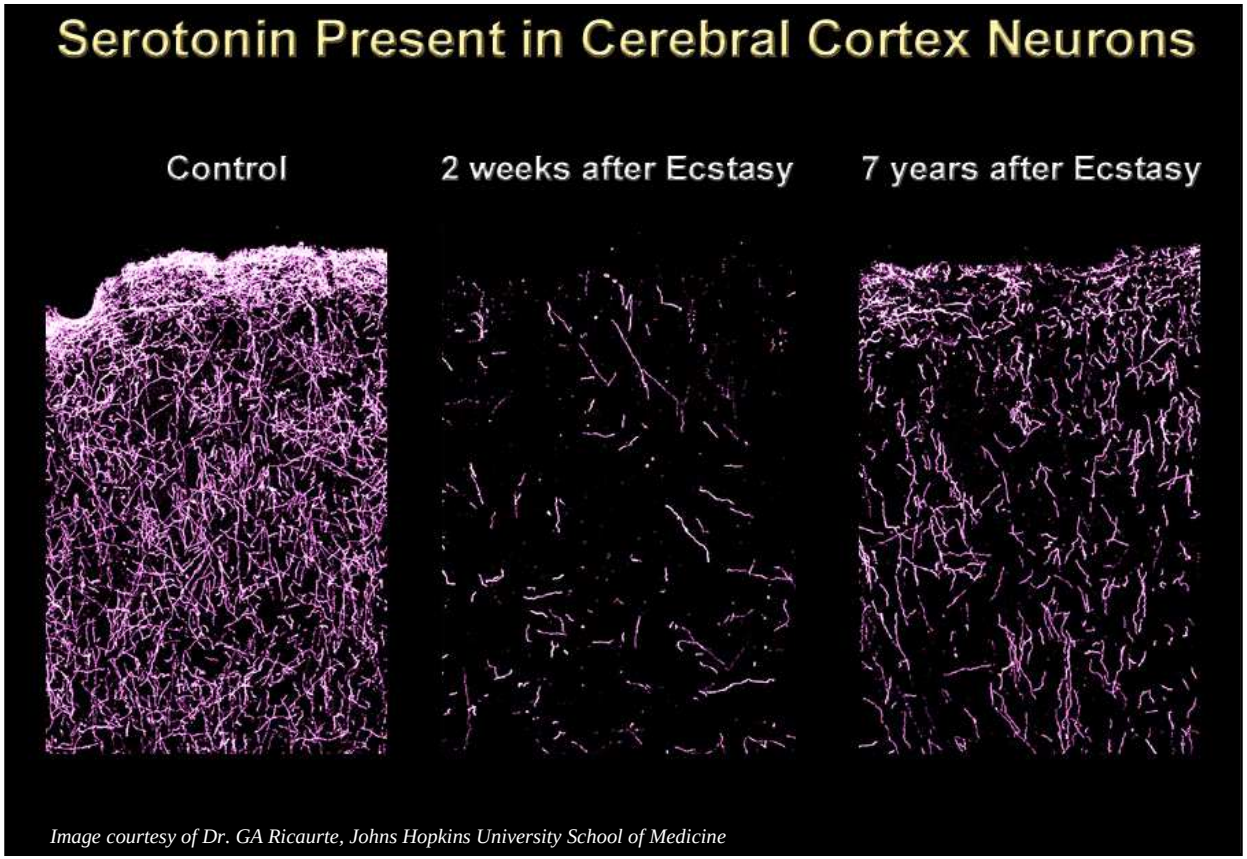
CRH also affects the cerebral cortex, part of the amygdala, and the brainstem. It is thought to play a major role in coordinating your thoughts and behaviors, emotional reactions, and involuntary responses. Working along a variety of neural pathways, it influences the concentration of neurotransmitters throughout the brain. Disturbances in hormonal systems, therefore, may well affect neurotransmitters, and vice versa.

Normally, a feedback loop allows the body to turn off "fight-or-flight" defenses when the threat passes. In some cases, though, the floodgates never close properly, and cortisol levels rise too often or simply stay high. This can contribute to problems such as high blood pressure, immune suppression, asthma, and possibly depression.

Studies have shown that people who are depressed or have dysthymia typically have increased levels of CRH. Antidepressants and electroconvulsive therapy are both known to reduce these high CRH levels. As CRH levels return to normal, depressive symptoms recede. Research also suggests that trauma during childhood can negatively affect the functioning of CRH and the HPA axis throughout life.

2. Depression and antidepressant drugs

2.5 Drug of Abuse

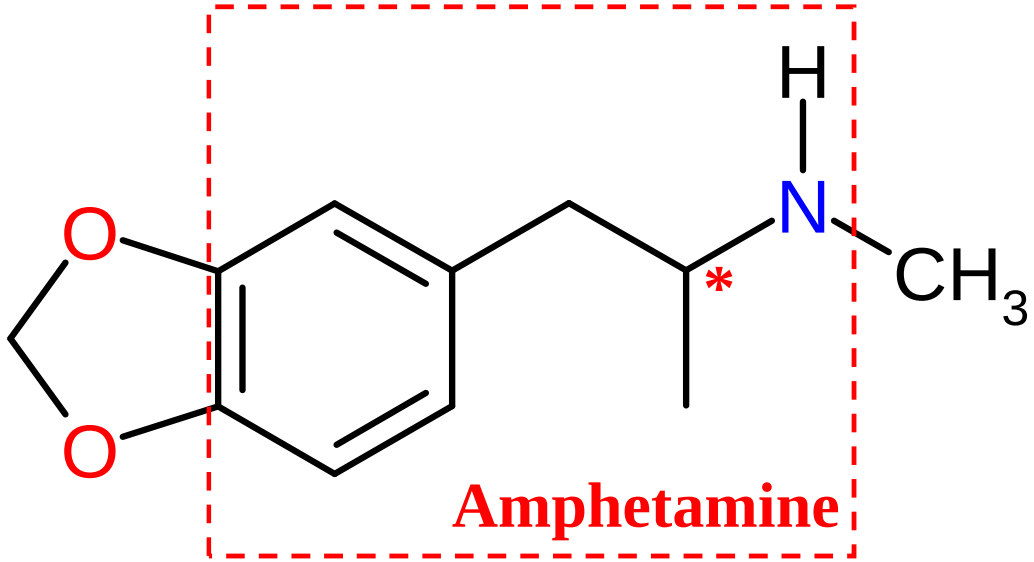


This first slide shows sections taken from the neocortex of monkeys that were given ecstasy twice a day for 4 days (control monkeys were given saline). The section on the left, taken from the brain of a control monkey, shows the presence of a lot of serotonin. The middle section shows a section from a monkey two weeks after receiving ecstasy. Point out that most of the serotonin is gone. The section on the right shows a section from a monkey 7 years after receiving ecstasy. Point out that although there has been some recovery of serotonin, the brain still has not returned to normal.

2. Depression and antidepressant drugs

2.5 Drug of Abuse

MDMA (3,4-MethyleneDioxyMethAmphetamine, commonly known as *ecstasy*):



MDMA was first synthesized in 1912 by Merck chemist Anton Köllisch. MDMA is a chiral compound and has been almost exclusively administered as a racemate. However, an early uncontrolled report suggests that the (*S*)-enantiomer is significantly more potent in humans than the (*R*)-enantiomer indicate that the disposition of MDMA is stereoselective, with the *S*-enantiomer having a shorter elimination half-life and greater excretion than the *R*-enantiomer.

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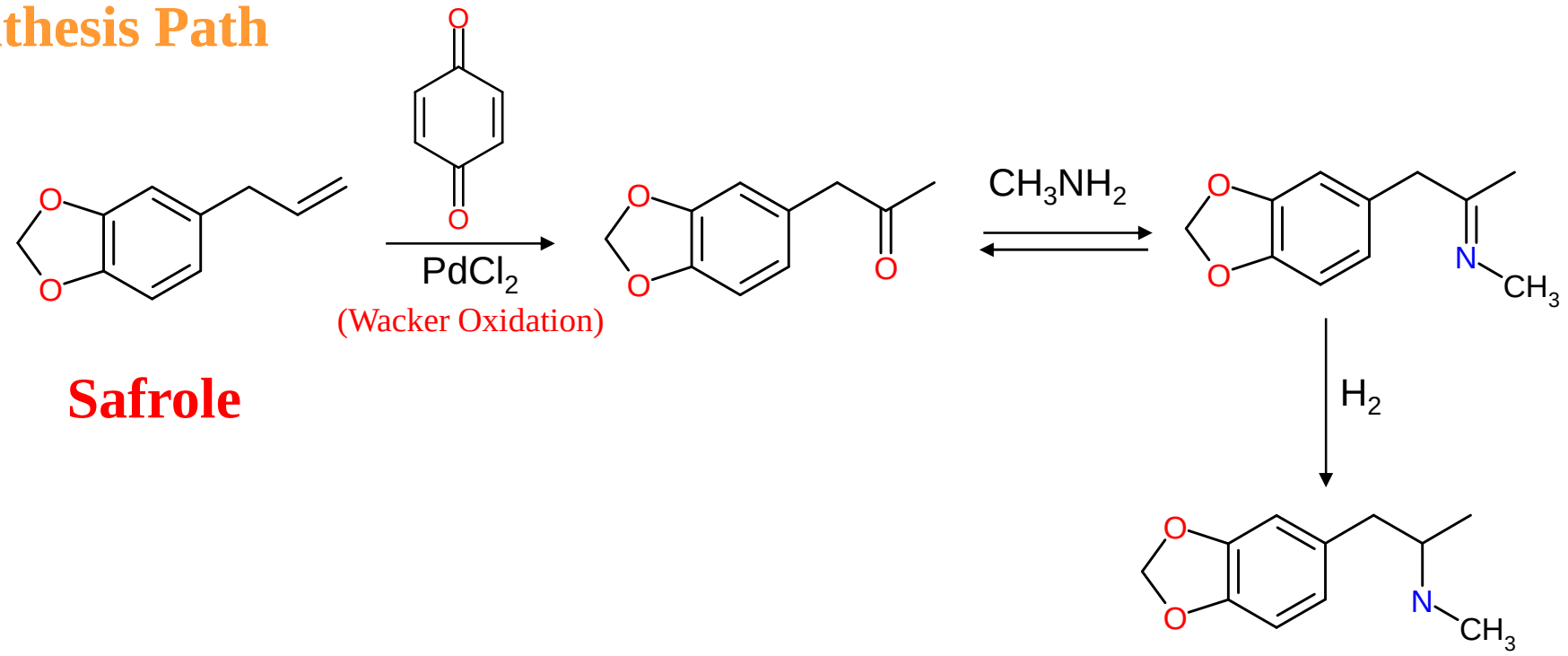
2.5 Drug of Abuse

Synthesis Path



Safrole

Disclaimer: *This is for theoretical argument only. IF someone chooses to follow this synthesis, note that the product has been prohibited by the Italian law, and offenders can be prosecuted. In no way do I condone this activity.*

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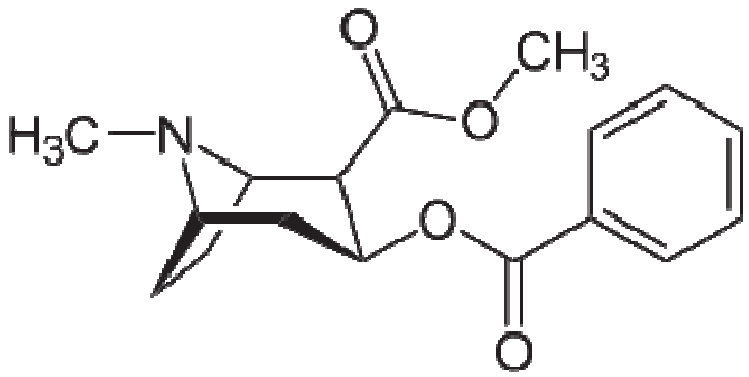
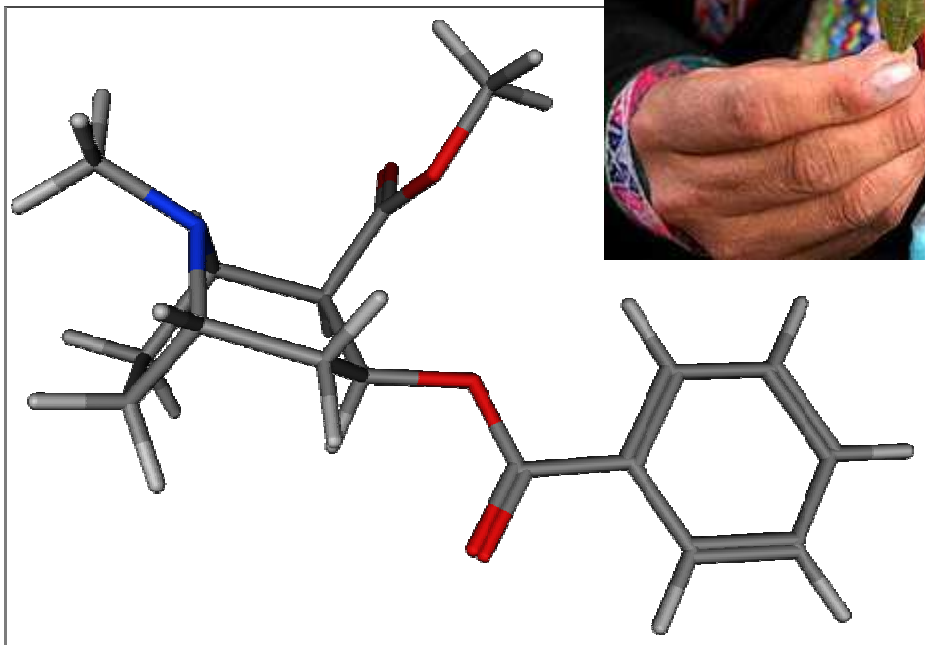
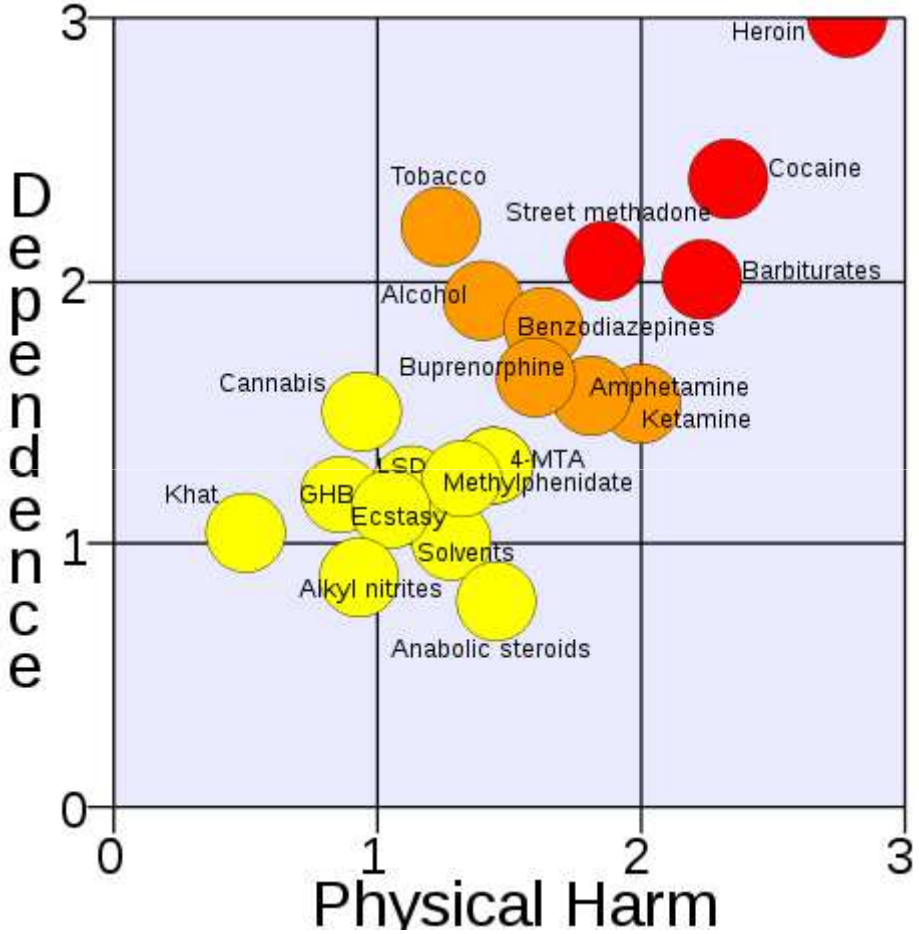




Cocaine (benzoylmethylecgonine) is a crystalline tropane alkaloid that is obtained from the leaves of the coca plant. The name comes from "coca" in addition to the alkaloid suffix *-ine*, forming *cocaine*. It is a stimulant of the central nervous system and an appetite suppressant. Specifically, it is a serotonin-norepinephrine-dopamine reuptake inhibitor, which mediates functionality of such as an exogenous catecholamine transporter ligand. Because of the way it affects the mesolimbic reward pathway, cocaine is addictive. Cocaine is also a local anesthetic.

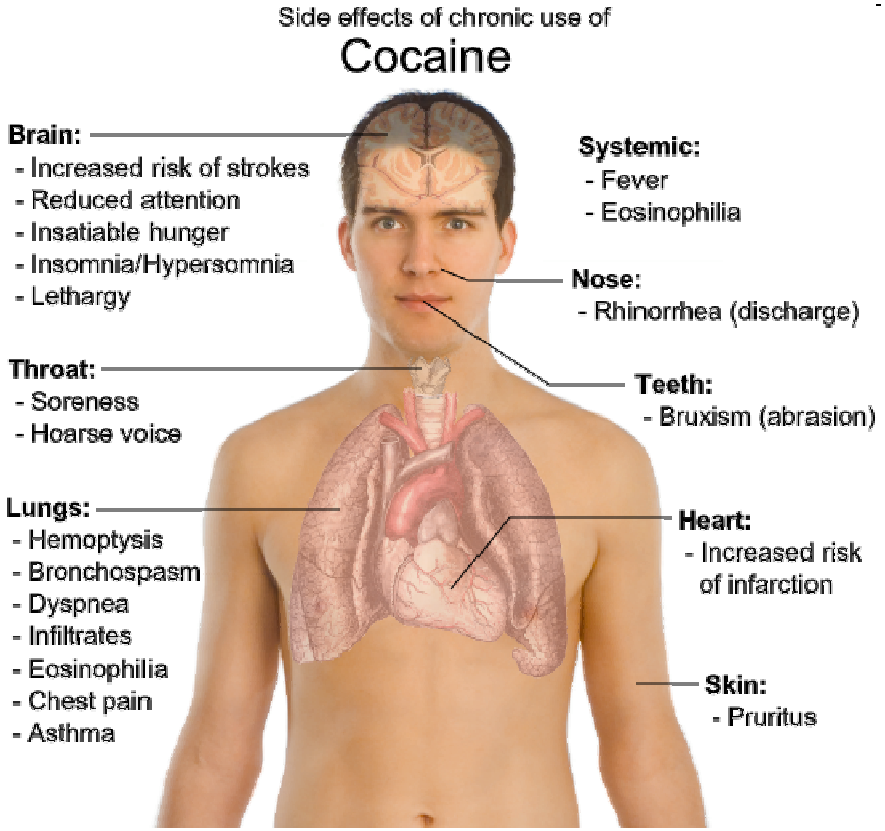
2. Depression and antidepressant drugs

2.5 Drug of Abuse



Nutt D, King LA, Saulsbury W, Blakemore C (2007). "Development of a rational scale to assess the harm of drugs of potential misuse". *Lancet* 369, 1047–53.

Data from *The Lancet* suggests Cocaine as the 2nd most dependent and 2nd most harmful of 20 drugs. Some pharmacologists however rate nicotine dependency higher than cocaine.



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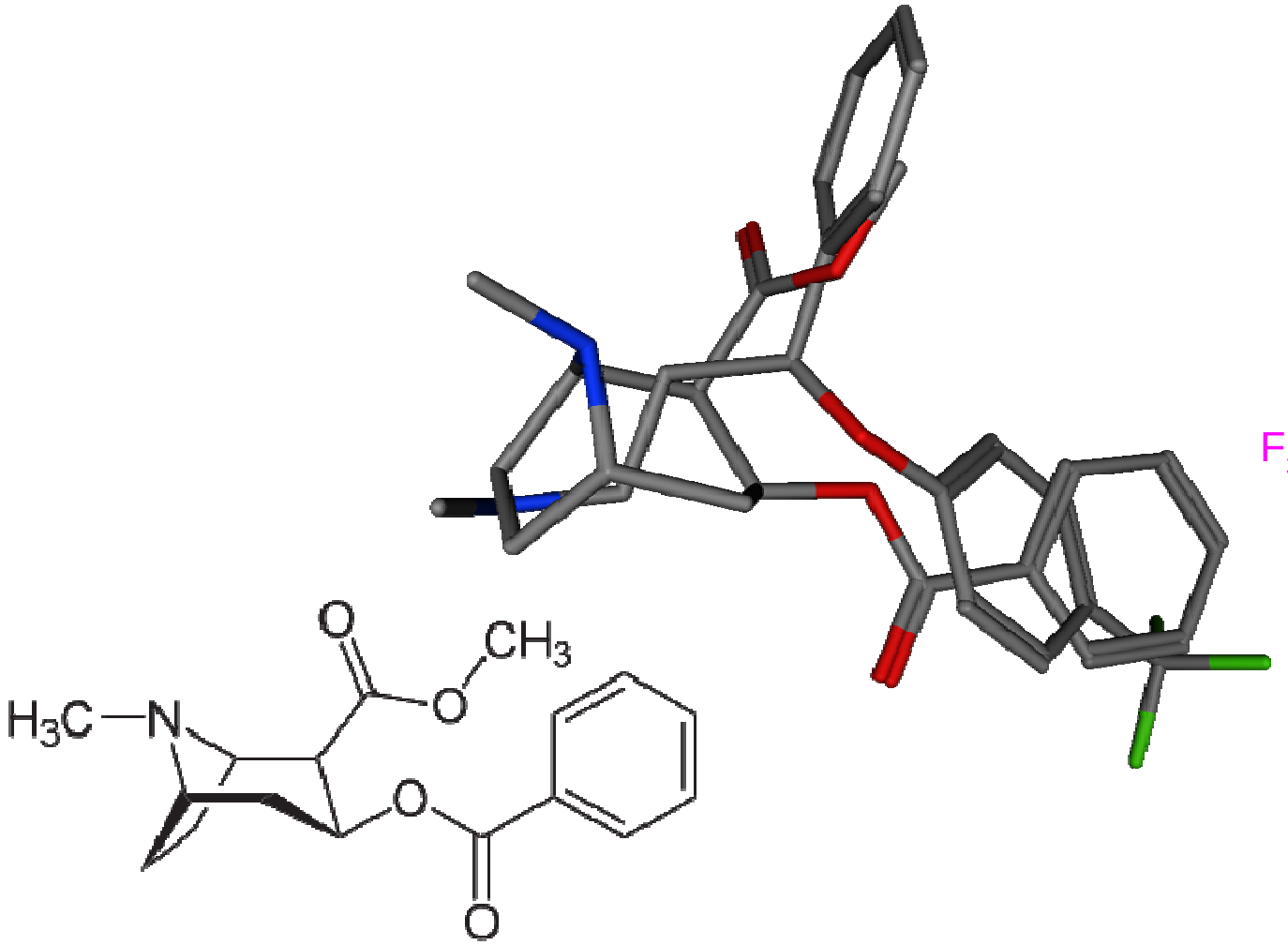
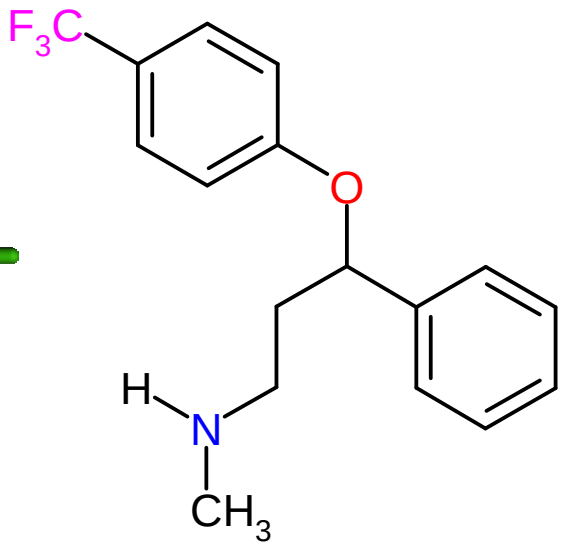


Cocaine



(*S*)-Fluoxetine

"The good physician treats the disease, but the great physician treats the person."

William Osler