Al-Azhar University - Gaza

Pharmaceutical Chemistry and Pharmacognosy Department

CNS Stimulants
Antidepressants and Psychomotor stimulants

Medicinal Chemistry III

First Semester 2020-2021

Prof. Ihab Almasri

CNS Stimulants (ANALEPTICS)

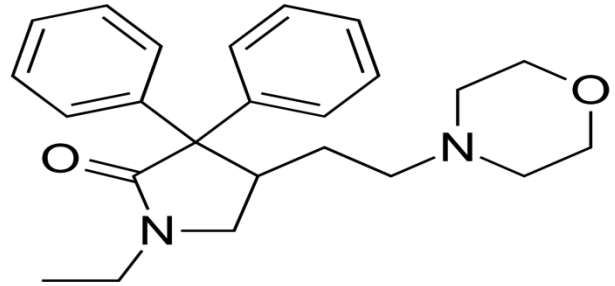
- The traditional analeptics are a group of potent and relatively nonselective CNS stimulants. The convulsive dose lies near their analeptic dose. They can be illustrated by picrotoxinin and pentylenetetrazole. Both are obsolete as drugs but remain valuable research tools in determining how drugs act.

- Newer agents, **modafinil** and **doxapram**, are more selective and have use in narcolepsy and as respiratory stimulants.

- CENTRAL SYMPATHOMIMETIC AGENTS (PSYCHOMOTOR STIMULANTS)

Doxapram HCl (Dopram):

- Good selectivity as a respiratory stimulant
- Doxapram stimulates chemoreceptors in the carotid arteries, which in turn, stimulates the respiratory centre in the brain stem.



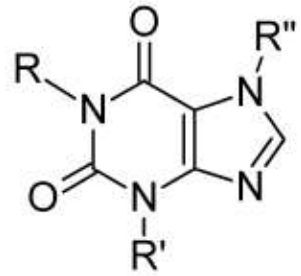
Methylxanthines:

Caffeine CNS stimulant ;Theophylline bronchial asthma therapy.
Theobromine (some derivatives: Trental) intermittent claudication.

MOA:

•Phosphodiesterase inhibition
•Antagonize adenosine at A1 receptors

Problems with these agents: lack of receptor selectivity. unwanted effects on the heart.



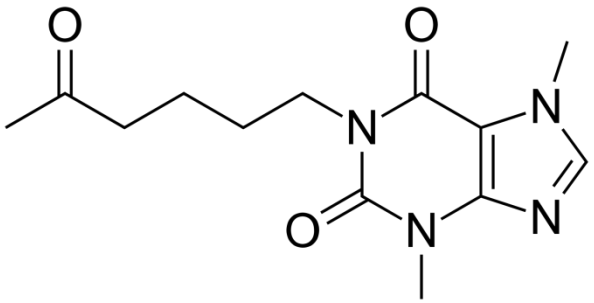
Xanthine

(R, R', & R" = H)

Compound	R	R′	R″	Common Source
Caffeine	CH_3	CH_3	CH_3	Coffee, tea
Theophylline	CH_3	CH_3	H	Tea
Theobromine	H	CH_3	CH_3	Cocoa

TABLE 15.2 Relative Pharmacological Potencies of the Xanthine Alkaloids

Xanthine	CNS Stimulation	Respiratory Stimulation	Diuresis	Coronary Dilation	Cardiac Stimulation	Skeletal Muscle Stimulation
Caffeine	1[a]	1	3	3	3	1
Theophylline	2	2	1	1	1	2
Theobromine	3	3	2	2	2	3

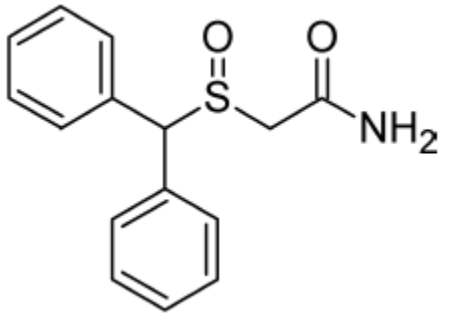


Pentoxifylline

antioxidative and neuroprotective effects

Modafinil (Provigil)

- has overall wakefulness-promoting properties similar to those of central sympathomimetics. Inhibits the reuptake of dopamine. It is considered an atypical α1-norepinephrine (NE) receptor stimulant and is used to treat daytime sleepiness in narcolepsy patients. Oral administration.



less potential for abuse

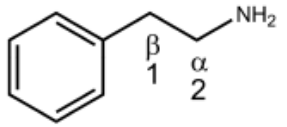
<u>Central sympathomimetic agents:(psychomotor stimulants)</u>

a few simple structural changes in the peripheral agents produce compounds that are more resistant to metabolism, more non-polar, and better able to cross the BBB.

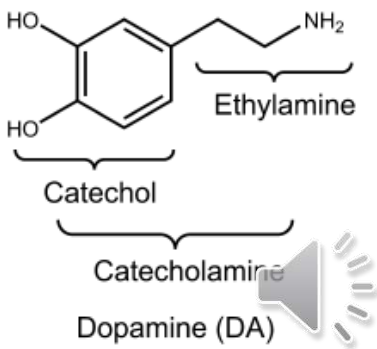
Effects: CNS stimulant (excitation; increased wakefulness and anorexiant effect.

MOA: noradrenergic (mainly), dopaminergic, serotoninergic (some)

Some agents act as <u>anorexiants</u> by their serotoninergic effect.



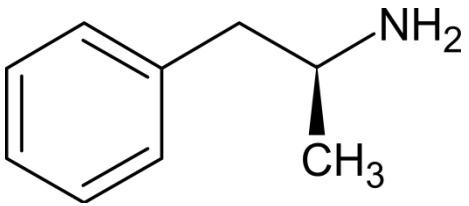
β-Phenylethylamine



Dopamine (DA)

SAR

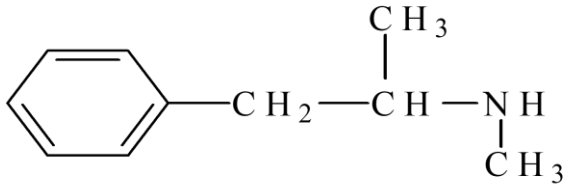
- β-phenethylamine moiety give some selectivity for pre- or postsynaptic noradrenergic.
- β-phenethylamine, given peripherally, is without central activity because of it's fast metabolism by MAOs.
- Branching with lower alkyl groups on the carbon atom adjacent (α) to the amino nitrogen increases CNS, rather than peripheral activity presumably by **retarding metabolism**.
- α-branching generates a chiral center, the dextro-(S) isomer of amphetamine is up to 10 times more potent than levo-(R) isomer for alerting activity (Attention-deficit/hyperactivity disorder (ADHD).
- Hydroxylation of the ring or hydroxylation on β-carbon to the nitrogen decrease activity by decreasing ability to cross the BBB.
- Halogenation F, Cl, Br of the aromatic ring decreases sympathemimetic activity, other activities may increase e.x parachloramphetamine has strong central serotoninergic activity.



Amphetamine/Dextroamphetamine (S)

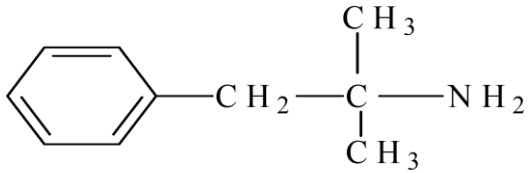
MOA: the alerting actions appear to relate to increase NE available to interact with postsynaptic receptors by release of NE from the nerve terminal.
Small contribution: inhibition of uptake of NE.

- Methoxyl substitution on the ring will give psychotomimetic agents Suggesting trophism for dopaminergic (D2) receptors.
- N-methylation increases activity. e.x methamphetamine > dextroamphetamine.
- Di-N-methylation decreases activity.
- Mono-N-substituents larger than methyl decreases excitatory properties, but many compounds retain anorexiant properties



Methamphtamine HCl: stronger than amphetamine

- N-methyl analogue of dextroamphetamine.

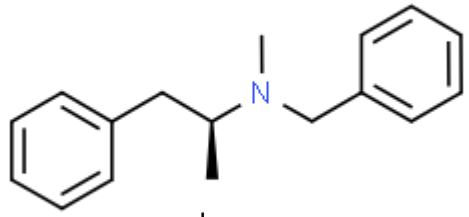


Phentermine

- α,α-dimethylphenethylamine use as appetite suppressant.

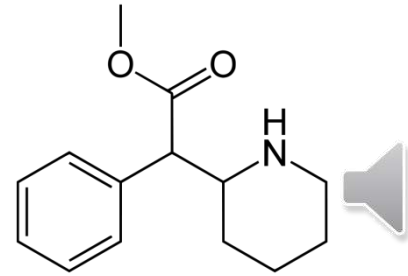
Benzphetamine HCl:

- Large (benzyl) N-Substituent decreases excitatory properties. Suppress appetite with few CNS stimulation



Methylphenidate Hydrochloride

- Methylphenidate, probably largely via its p-hydroxy metabolite, blocks NE reuptake, acts as a postsynaptic agonist, depletes the same NE pools as reserpine, and has effects on dopaminergic systems, such as blocking DA reuptake.



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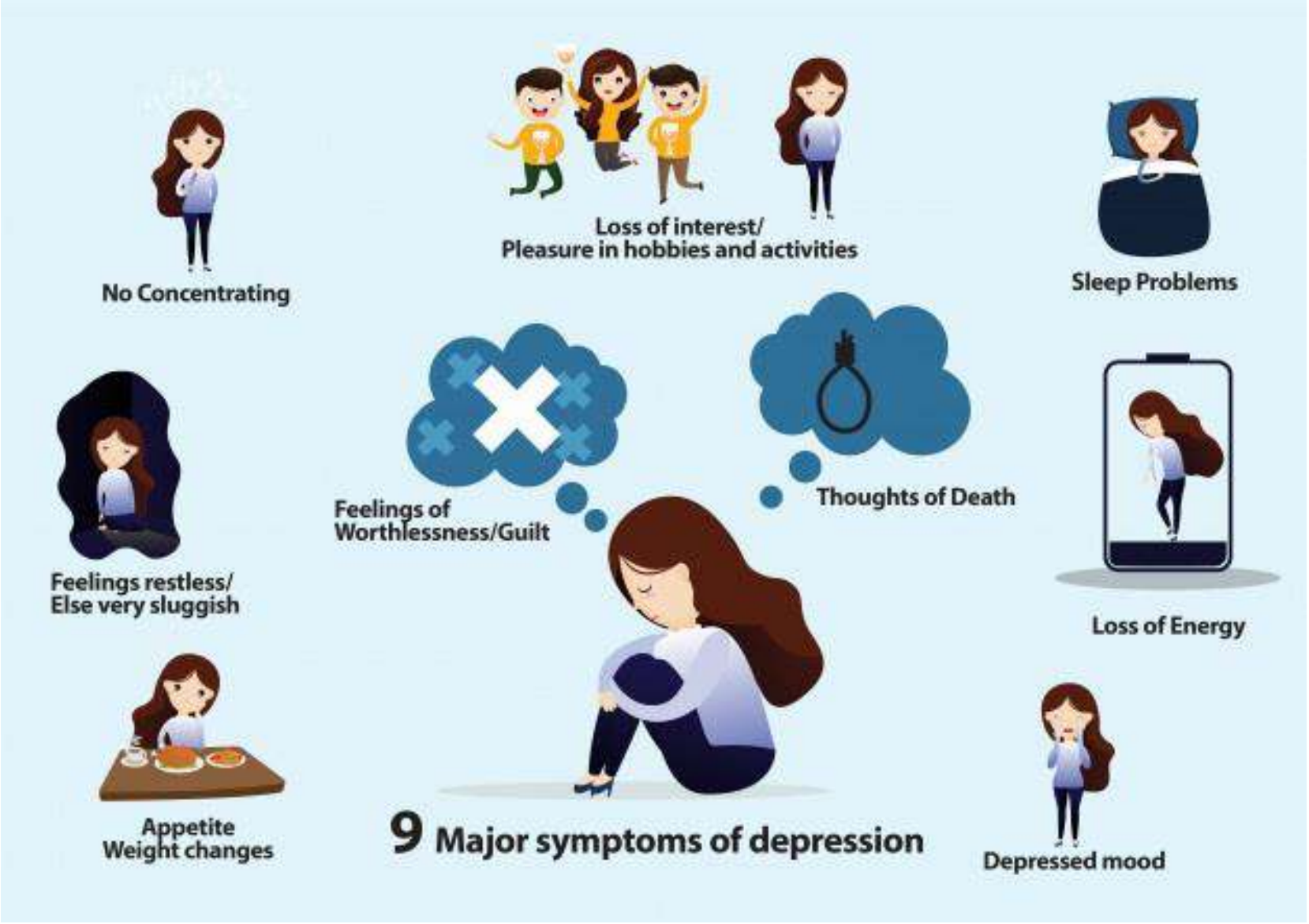
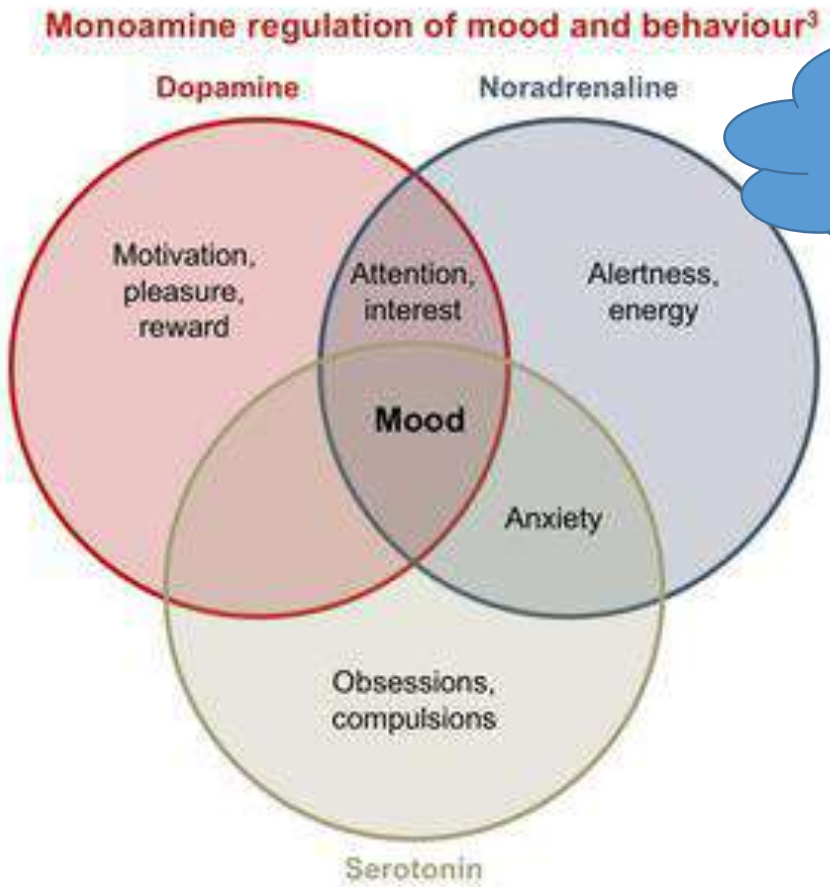
CNS Stimulants (analeptics)
Anti-depressants

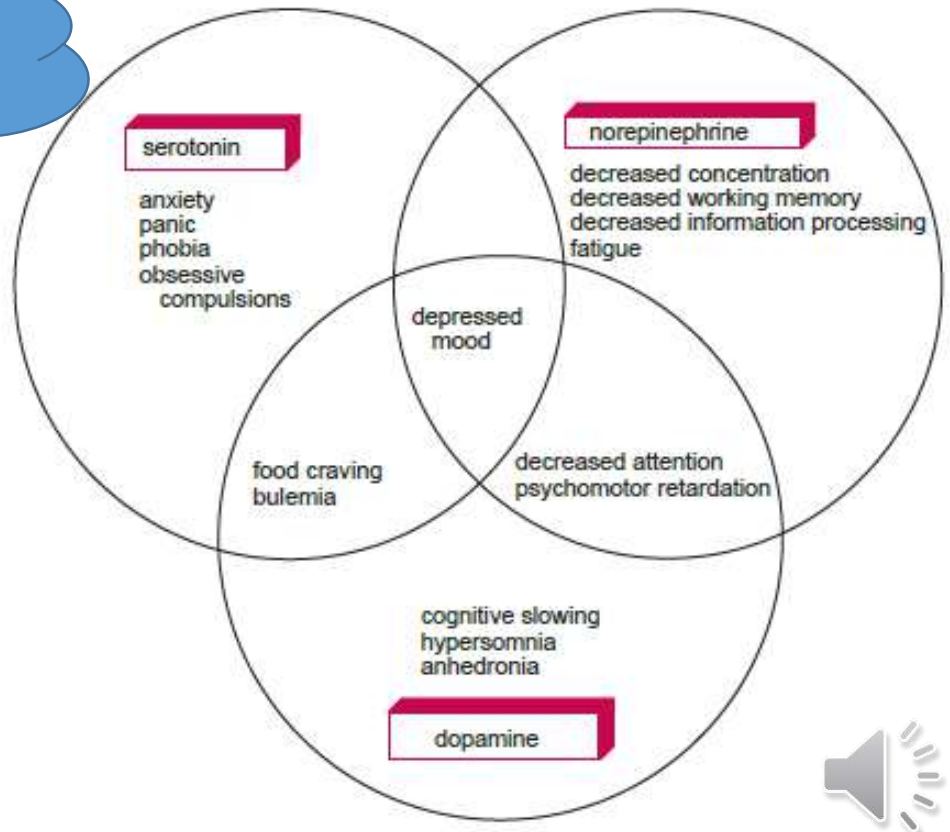


ANTIDEPRESSANTS: *Introduction*

Imbalances in the neurotransmitters ***serotonin*** (5-HT) ***norepinephrine*** (NE) and ***dopamine*** (DA) play a role in depression and can initiate symptoms associated with depression causing changes in cognitive thought, body functions, memory, appetite, and the ability to feel positive or pleasure.



Serotonin and NE affect depressive mood



Neurochemical factors – the monoamine hypothesis

- The broad range of symptoms associated with major depressive disorder implicates several brain circuits and regions, and multiple neurotransmitter systems[1]
- The three main monoamine systems associated with the pathophysiology of depression are serotonin, noradrenaline, and dopamine[2]
- The 'monoamine hypothesis' postulates that a low activity of at least one of these neurotransmitters is responsible for the corresponding features of depression[2]
- However, because of the inter-connectivity of the CNS, an attempt to enhance the levels of a single specific neurotransmitter may produce decreases in other neurotransmitters[1]

Treatment is generally aimed at counteracting this low or abnormal monoamine activity; increasing at least one of serotonin, noradrenaline, or dopamine[1,2]

Antidepressants Classification

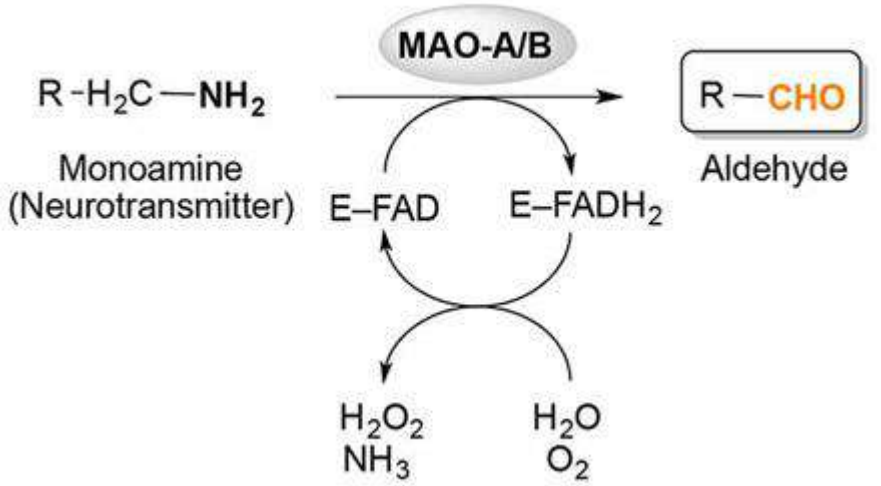
1) **Monoamine Oxidase Inhibitors (MAOI):** Phenelzine, Moclobemide.

2) **The monoamine reuptake inhibitors**

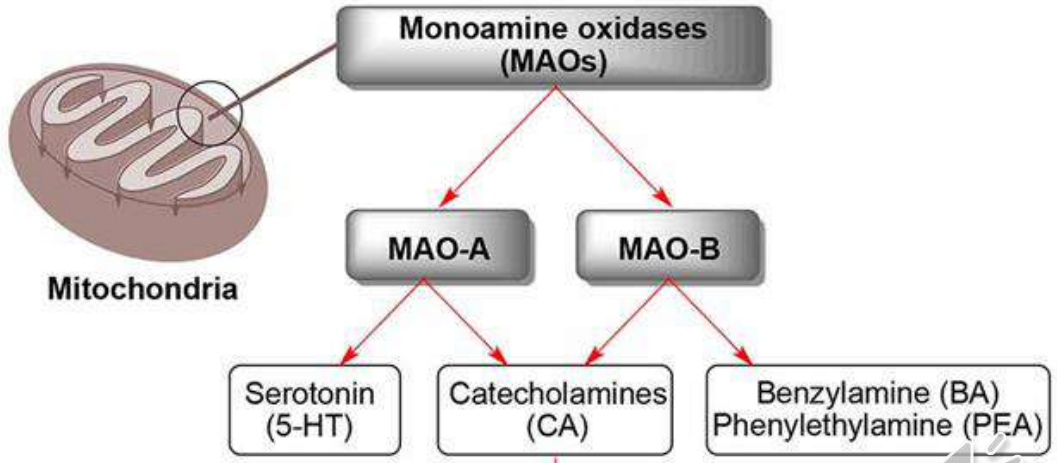
- Tricyclics and Tetracyclics (TCA): Imipramine, Doxepin, Amoxepine, Amitriptyline
- Selective Serotonin Reuptake Inhibitors (SSRIs): Fluoxetine, Sertraline, Citalopram
- Selective Norepinephrine Reuptake Inhibitors: Reboxetine
- Dopamine and Norepinephrine Reuptake Inhibitor (DNRI): Bupropion

3) **Mood stabilizer:** Lithium Carbonate

1- Metabolic protective agents: MAO inhibitors:



- Monoamine oxidase enzymes catalyze the ***deamination*** of endogenous catecholamine messengers.
- There are two types of MAO enzymes: **MAO-A** and **MAO-B**. Both types present in **brain** and it was found that MAO-B is linked to Parkinson disease.
- Outside the central nervous system:
  - MAO-A: presents in peripheral adrenergic terminals, GIT and placenta.
  - MAO-B: presents in platelets.
- The inhibition of MAO-B will conserve the presynaptic dopamine by retarding its catabolism by MAO.
- Non-selective inhibition of MAO enzymes will lead to side effects (cardiovascular).



MAO-A

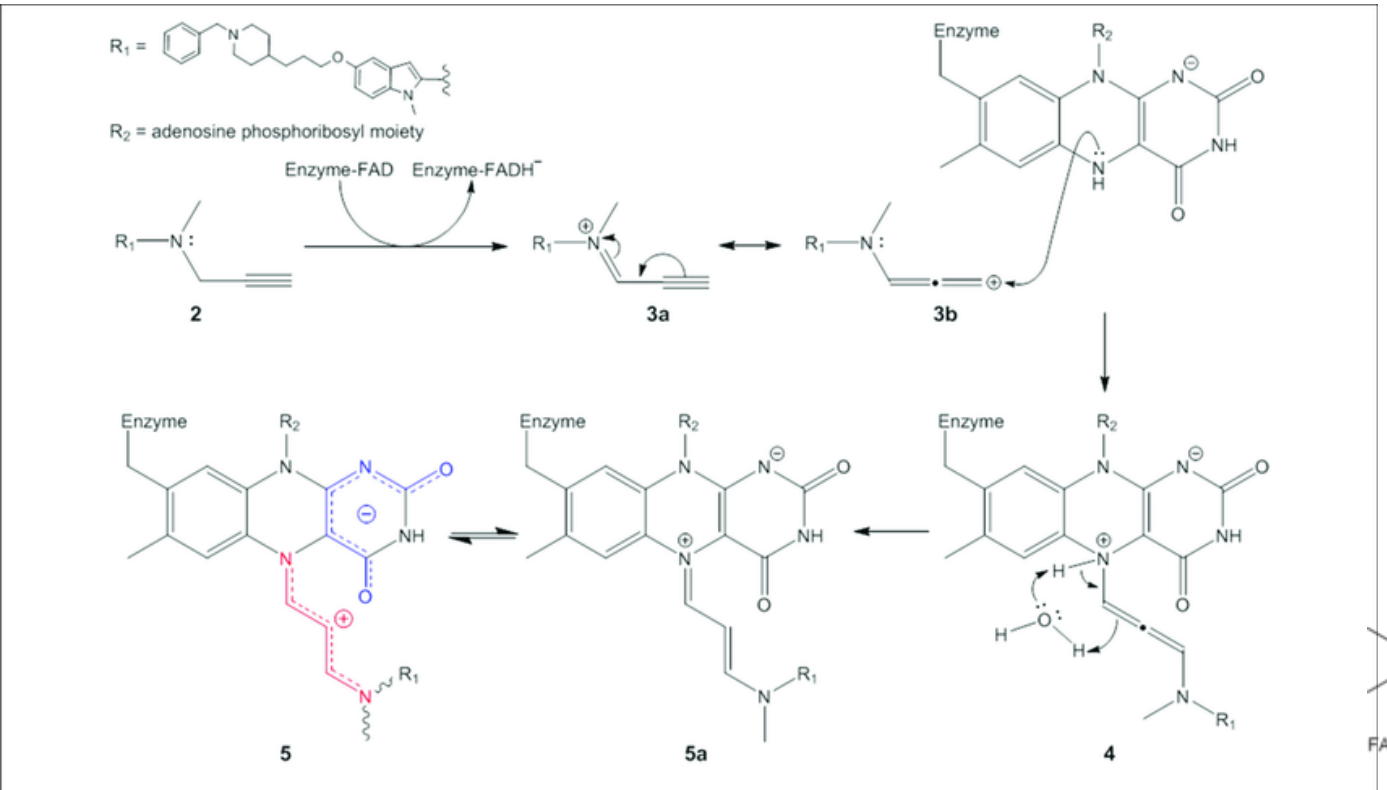
MAO-A preferentially deaminates Serotonin, Epinephrine and Norephinephrine

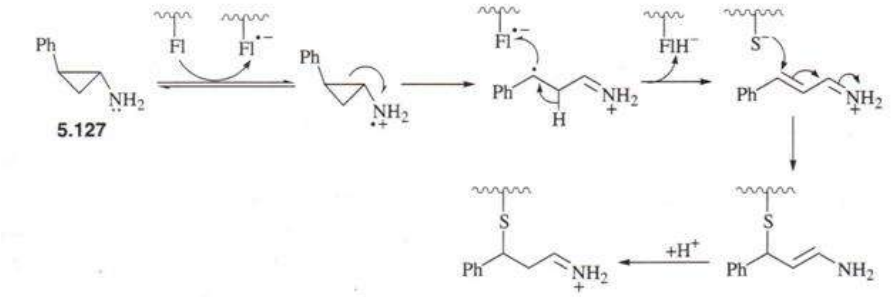
MAO-A Inhibitor: Antidepressant

MAO-B

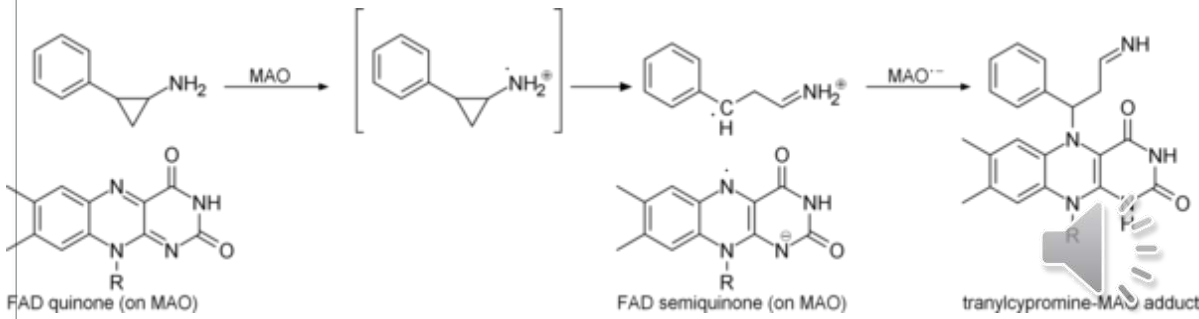
MAO-B preferentially deaminates phenylethylamine and trace amines. Dopamine is equally deaminated by both types.

MAO-B Inhibitor: Antiparkinson activity





Tranylcypromine



1. Monoamine Oxidase Inhibitors

Those compounds showed ***CNS stimulation*** as a result of ***MAO inhibition***, resulting in higher synaptic levels of NE and 5-HT. it was used as an antidepressant agent.

Selegiline:

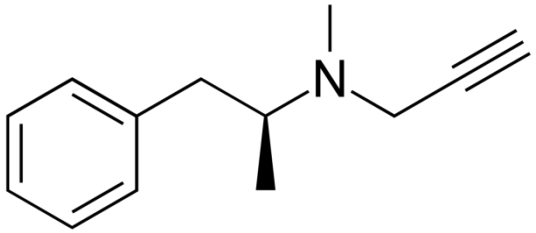
Active as R enantiomer. ***Irreversible*** as suicide inhibitor, converted by MAO to electrophilic species that combine irreversibly with flavin cofactor at the active site. Presently, selective MAO-B inhibition, however, has value in treating ***Parkinson*** disease.

Rasagiline:

It is ***selective*** for MAO type B over type A by a factor of fourteen.

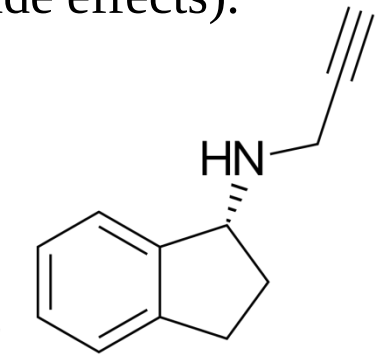
Moclobemide:

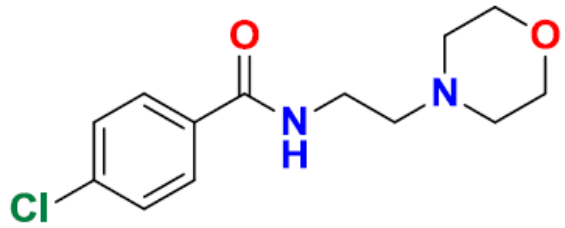
Reversible inhibitor of ***MAO-A***, it is considered an effective ***antidepressant*** and permits metabolism of dietary tyramine (no hypertensive side effects).



Selegiline

Rasagiline





Moclobemide

2. Monoamine Reuptake Inhibitors

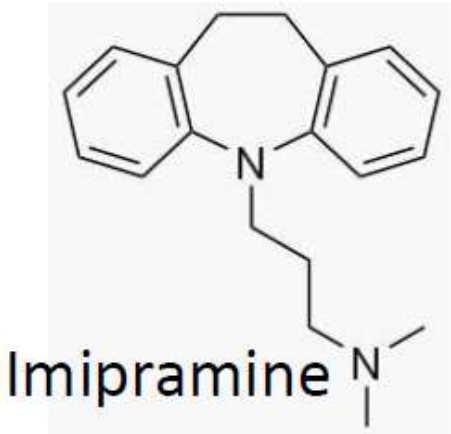
Reuptake inhibition by these agents is at the level of the respective monoamine ***transporter*** via ***competitive*** inhibition of binding of the monoamine to the substrate-binding compartment.

The ***net effect*** of the drug is to ***increase*** the level of the monoamine in the synapse. ***Sustained high*** synaptic levels of 5-HT, NE, or both appear to be the basis for the antidepressant effect of these agents.

A. Tricyclic Antidepressants:

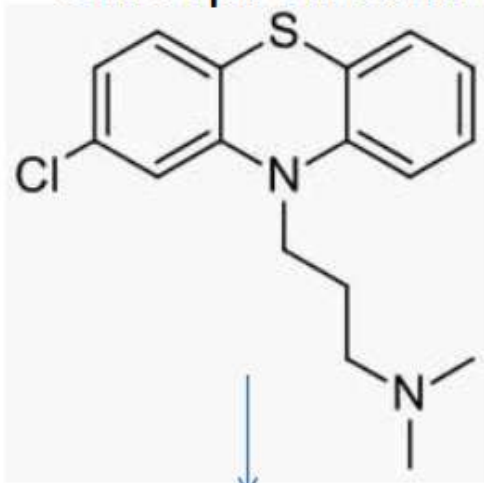
- Are generally ***nonselective*** and block both Norepinephrine and Serotonin transporters (NET, SERT).
- ***High Vd***, which suggest protein binding & CNS distribution.
- Secondary amine concentration is more than Tertiary.
- ***No*** Affinity for dopamine transporters (DAT).
- ***Used*** mainly for major depression with failed SSRI or SNRI.
- They have anticholinergic, Antihistaminic, and α1-antiadrenergic ***side effects***.
- ***Cardiotoxicity*** due to effects on Na channel.

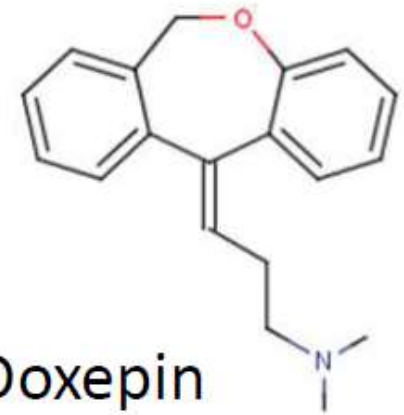
Discovery of TCA's



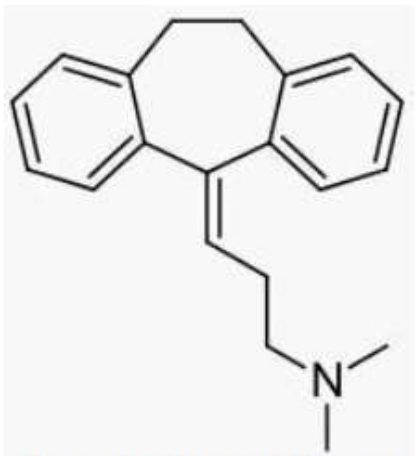
Imipramine

Chlorpromazine

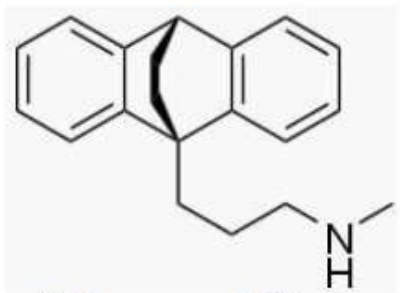




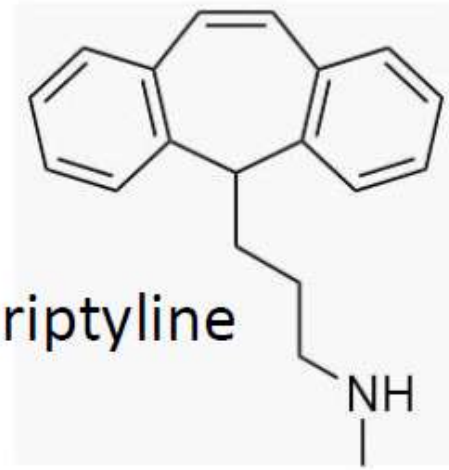
Doxepin



Amitriptyline



Maprotiline



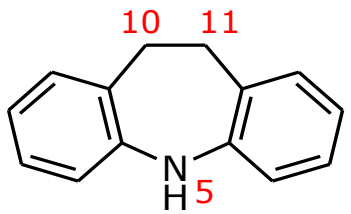
Protriptyline

- Chlorpromazine (CPZ) was the first anti-phycotic drug.
- **TCA's were the first anti-depressents**. They were accidentally discovered while searching for better derivative of CPZ. Hence they appear similar in structure

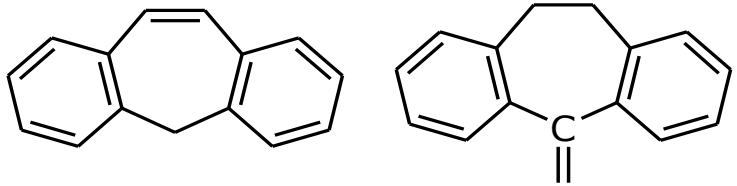
Structures of Antidepressants

Structure of Antidepressant

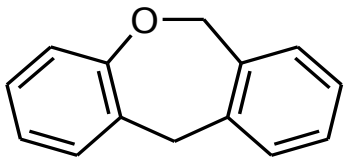
- Dihydordibenzazepines (imipramine, clomipramine)
- Dihydrodibenzocycloheptenes (amitriptyline, nortriptyline)
- Dibenzoxepins & Dibenzothiepins (doxepin, dothiepin)
- Arylpiperazines
- Non Tricyclics (bupropion, fluoxetine, trazodone)



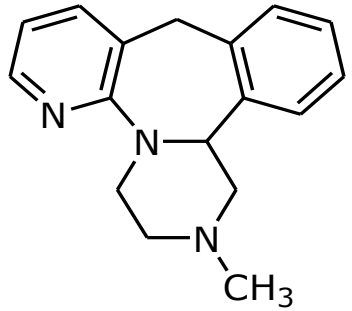
dibenzazepine



dibenzocyclohepene

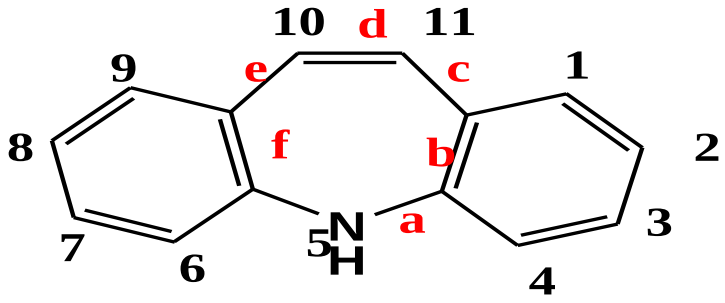


dibenzoxepine

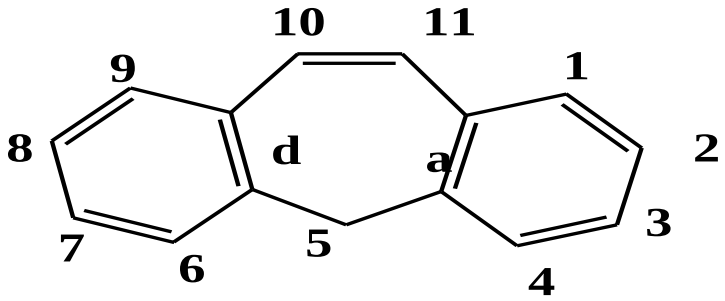


pyrazinopyridobenzazepine

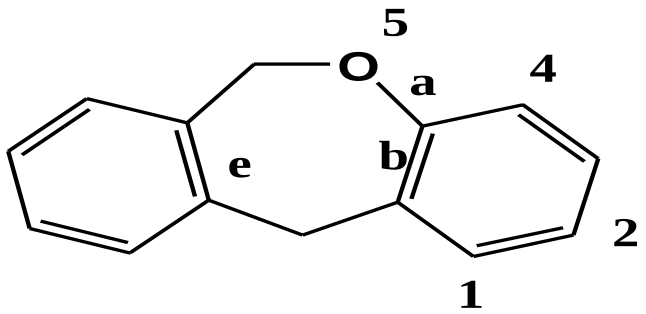
Tricycles(6,7,6)



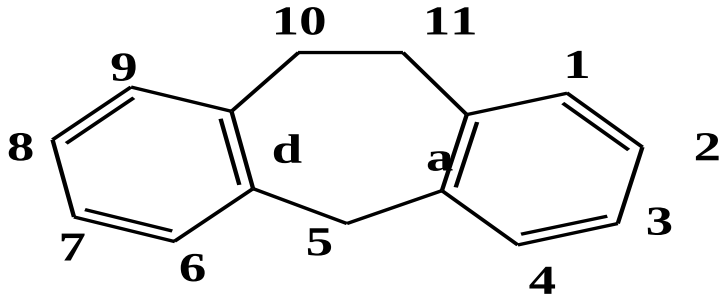
Dibenzazepine



Dibenzocyclohetadine



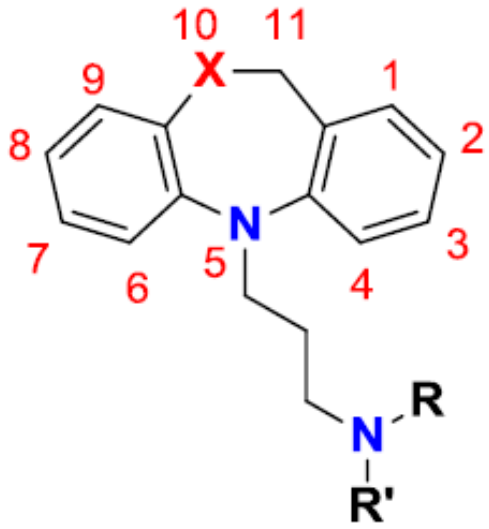
Dibenzoxepine

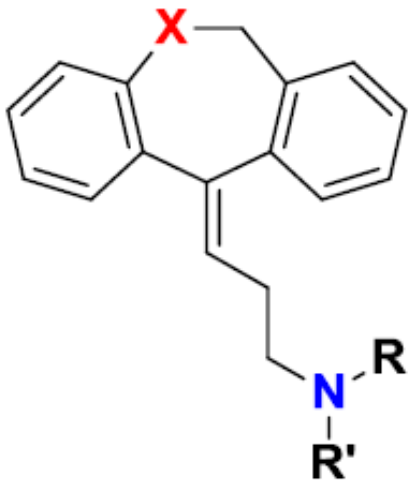


dibenzo-10,11-dihydrocycloheptadine

In summary the SARs for the TCAs is:

- A ***large***, ***bulky*** group encompassing two aromatic rings, preferably held in a ***skewed*** arrangement by a third central ring.
- A three (more active) or, sometimes, two-atom ***chain*** to an ***aliphatic amino*** group that is monomethyl or dimethyl substituted.





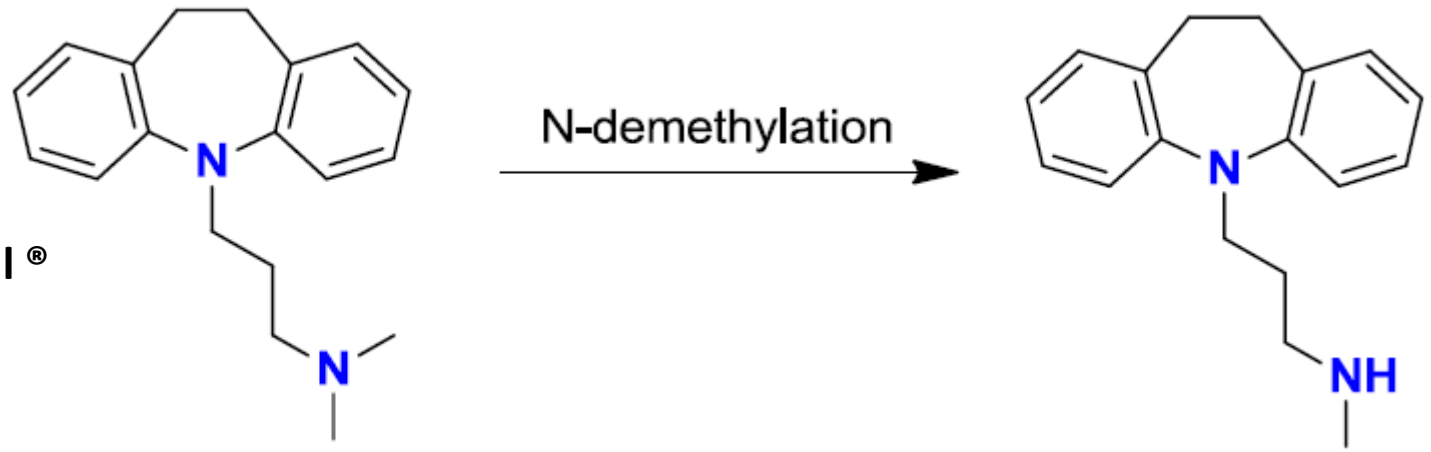
X can be a CH_2, O, S, or NH

R, R' can be H, H; H, CH_3; or CH_3, CH_3

- The ***dimethylamino*** compounds tend to be sedative, whereas the ***monomethyl*** relatives tend to be stimulatory.
- The ***dimethyl*** compounds have higher ***5-HT*** to NE reuptake block ratios: in the ***monomethyl*** compounds, the proportion of ***NE*** uptake block tends to be higher and, in some cases, is considered selective NE reuptake.
- The compounds have ***anticholinergic*** properties, usually higher in the dimethylamino compounds.
- When treatment is begun with a dimethyl compound, a significant accumulation of the monomethyl compound develops as ***N-demethylation*** proceeds.
- ***Ring substitution*** is not important. If present usually it ***decreases*** activity.
- ***Branching*** in the side chain is not tolerated.
- The TCAs are extremely ***lipophilic*** and, accordingly, very highly tissue bound outside the CNS.

Imipramine and Desipramine

- It has anticholinergic and sedative (central ***H1 block***) effects.
- It has high 5-HT-to-NE uptake block ratio and can be called a (***SERTI***).
- ***N-demethylation*** occurs, with a build up of norimipramine (or ***desimipramine***) with less anticholinergic, less sedative, and more stimulatory and is a ***SNERI***. ***Overall, the effect is nonselective 5-HT versus NE reuptake***.

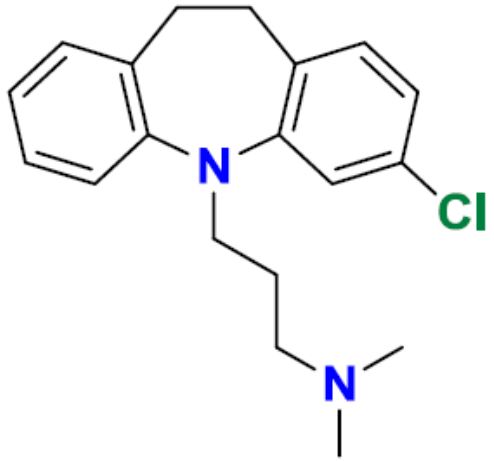


Tofranil ®

5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H-dibenz[b,f]azepine*

Clomipramine

- Is up to **50** times as potent as imipramine in some bioassays.
- **Nonselective** TCA.
- The chloro replacing the H-substituent could **increase** potency by increasing **distribution** to the CNS.
- Dihydrodibenzazepine derivative.
- It is used in obsessive–compulsive disorder (**OCD**).

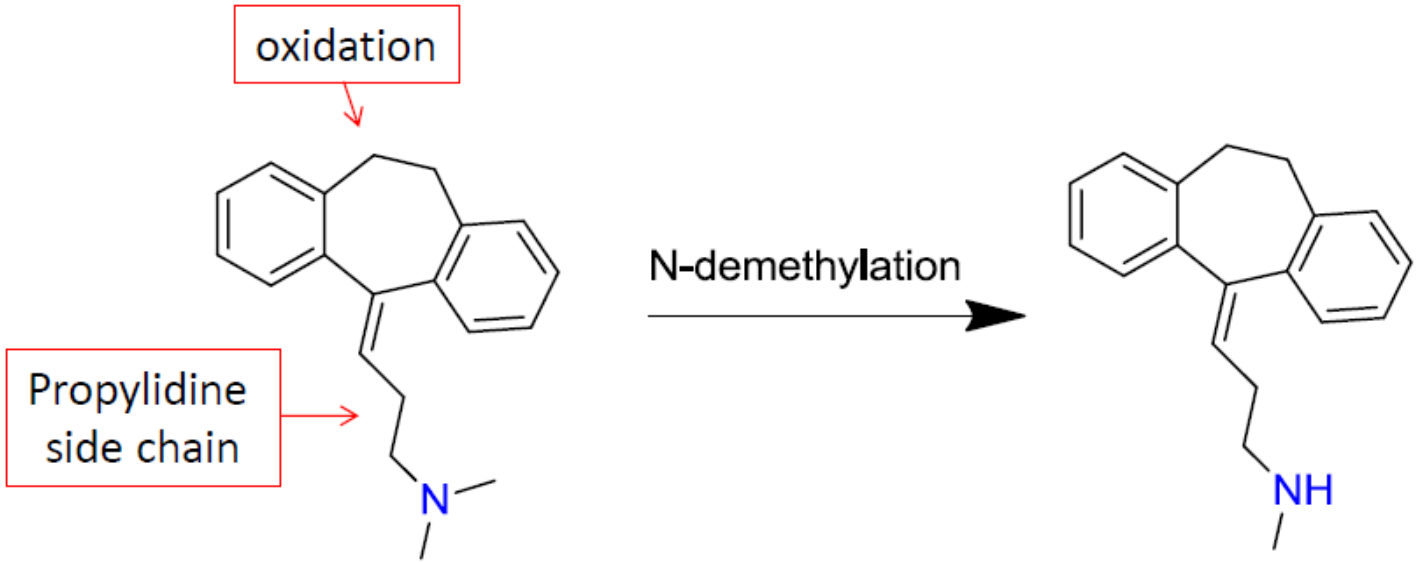


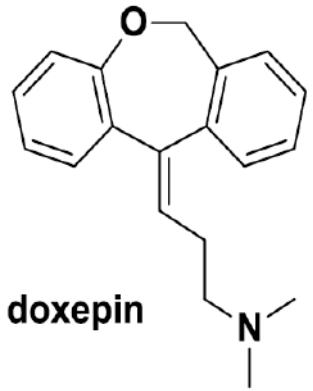
3- Chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H-dibenz[b,f]azepine*

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

Amitriptyline and nortriptyline

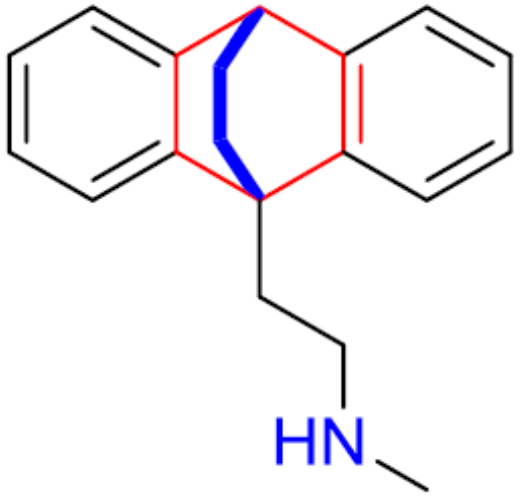
- Is one of **the most anticholinergic and sedative** of the TCAs.
- Because it lacks the ring-electron-enriching nitrogen atom of imipramine, **metabolic** inactivation mainly proceeds at the **benzylic** 10- position.
- **N-demethylation** occurs, and **nortriptyline** is produced, which has a less anticholinergic, less sedative, and more stimulant action than amitriptyline. Nortriptyline is a **SNERI**.
- The composite action of drug and metabolite is **nonselective**.



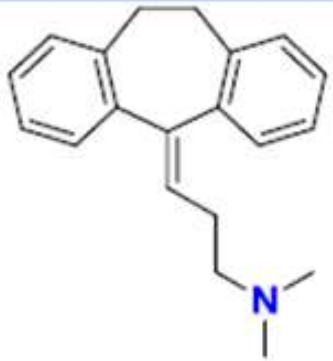


Maprotiline

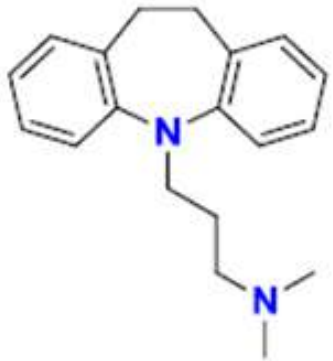
- Is sometimes described as a ***tetracyclic*** rather than a tricyclic antidepressant.
- It is a dibenzobicyclooctadiene.
- Can be viewed as a TCA with an ethylene-bridged central ring.
- N-demethylated metabolite is ***active***.
- Exhibit highest affinity & selectivity for NET (***SNERI)***.
- Cause sedation to the patients.
- Share the same side effects of TCAs regarding cardiovascular effects.



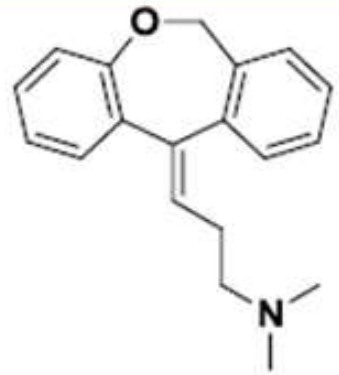
None selective reuptake inhibitors (NSRIs – TCAs)



Amitriptyline
Dibenzocycloheptadiene.

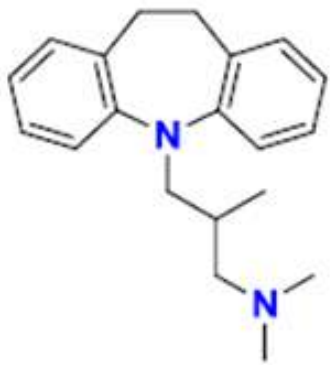


Imipramine
Dihydrodibenzazepine

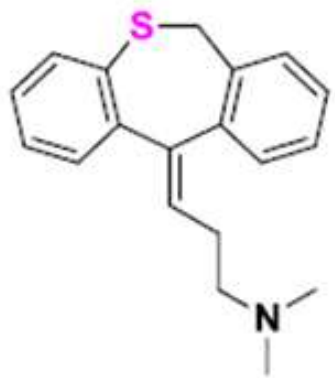


Doxepin
Dibenzoxepine

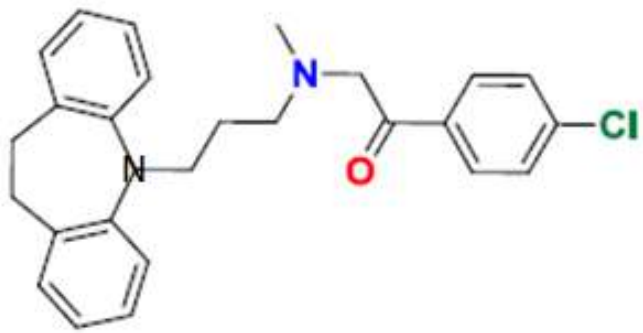
Clomipramine
Dihydrodibenzazepine



Trimipramine
Dihydrodibenzazepine



Dosulepin
Dibenzothiepin

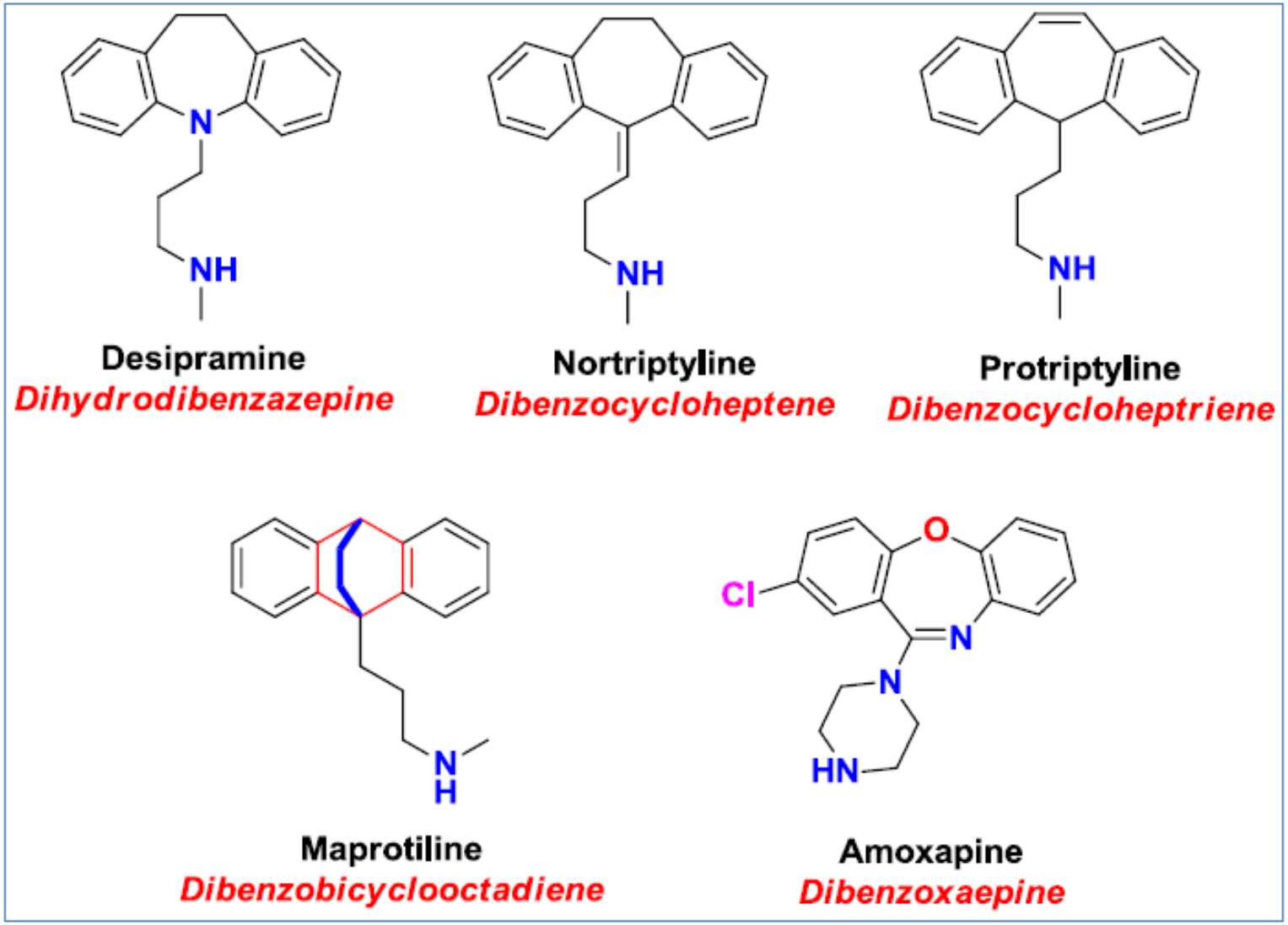


Lofepramine
Dihydrodibenzazepine

dothiepin

Desipramine has the weakest antihistamine and anticholinergic effects

Selective Norepinephrine Reuptake Inhibitors (SNRIs – TCAs)

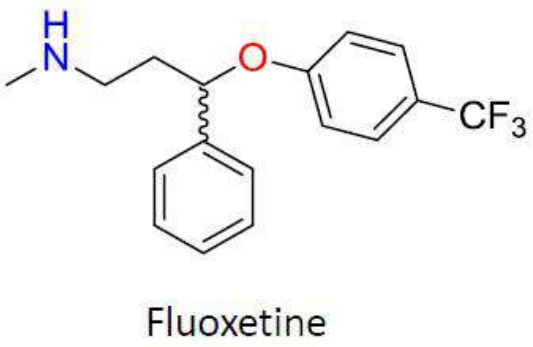


B. Selective Serotonin Reuptake Inhibitors (SSRIs):

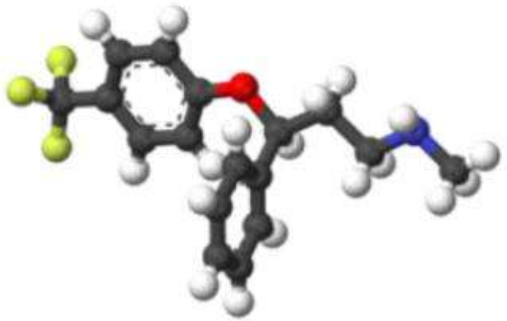
Fluoxetine

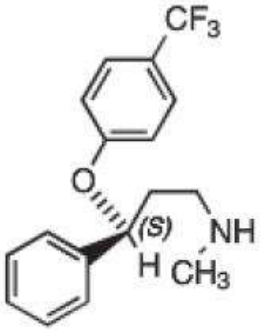
- The protonated amino group can H-bond to the ether oxygen electrons, which can generate the ***β-arylamino–like group***, with the other aryl serving as the characteristic "extra" aryl. The *S*-isomer is much more ***selective for SERT*** than for NET. The major metabolite is the *N*-demethyl compound, which is as potent as the parent and more selective (SERT versus NET).

- *To illustrate a difference between selectivity for a SERT and a NET, if the **para** substituent is moved to the **ortho** position (and is less hydrophobic), a NET selectivity is obtained.*

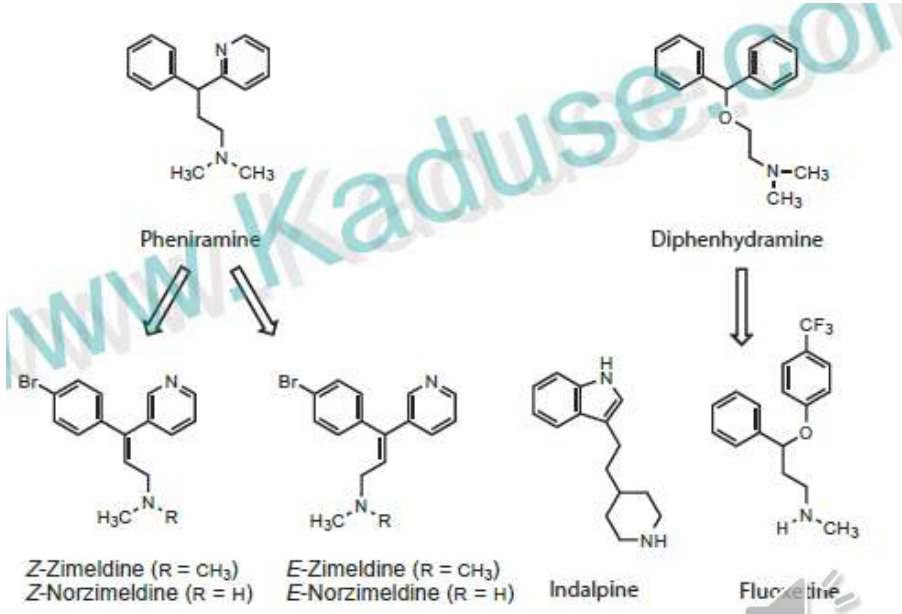


Fluoxetine



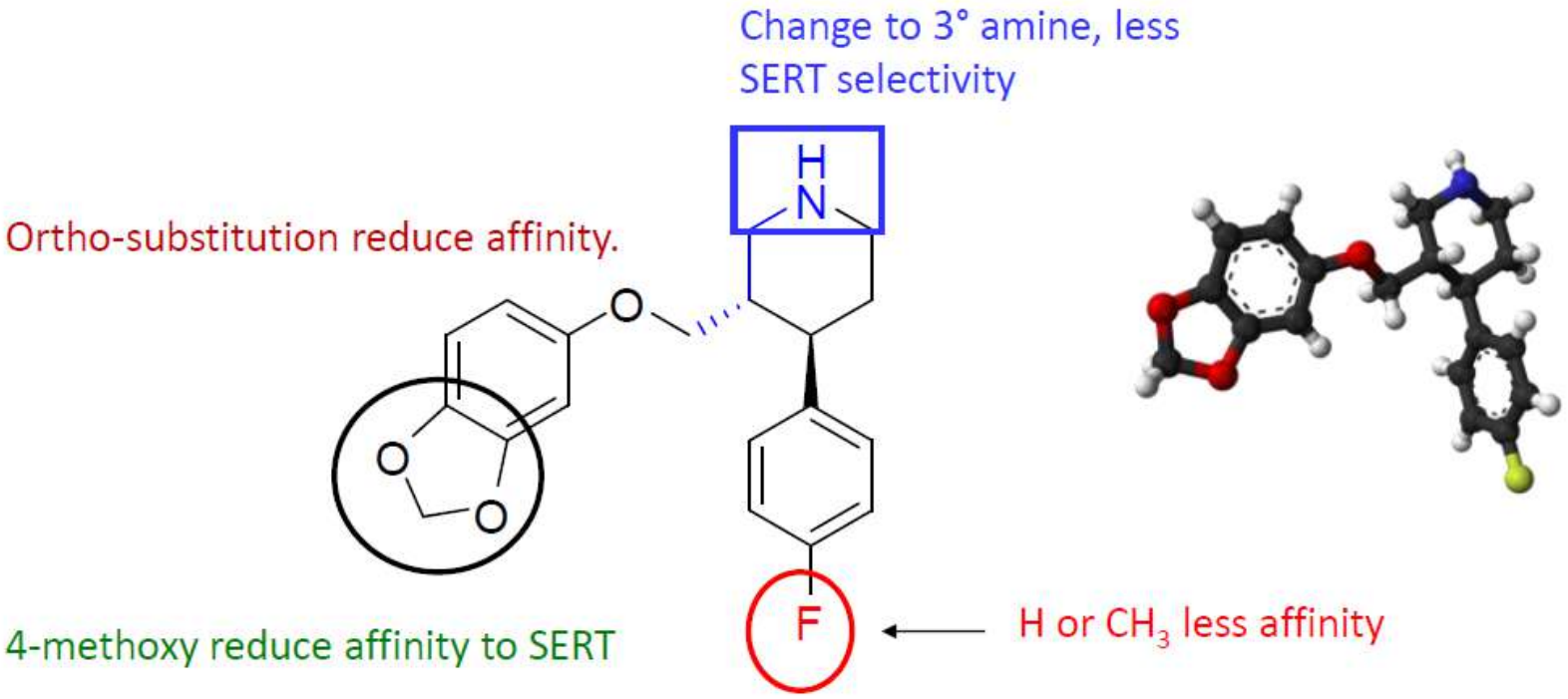


S-Fluoxetine



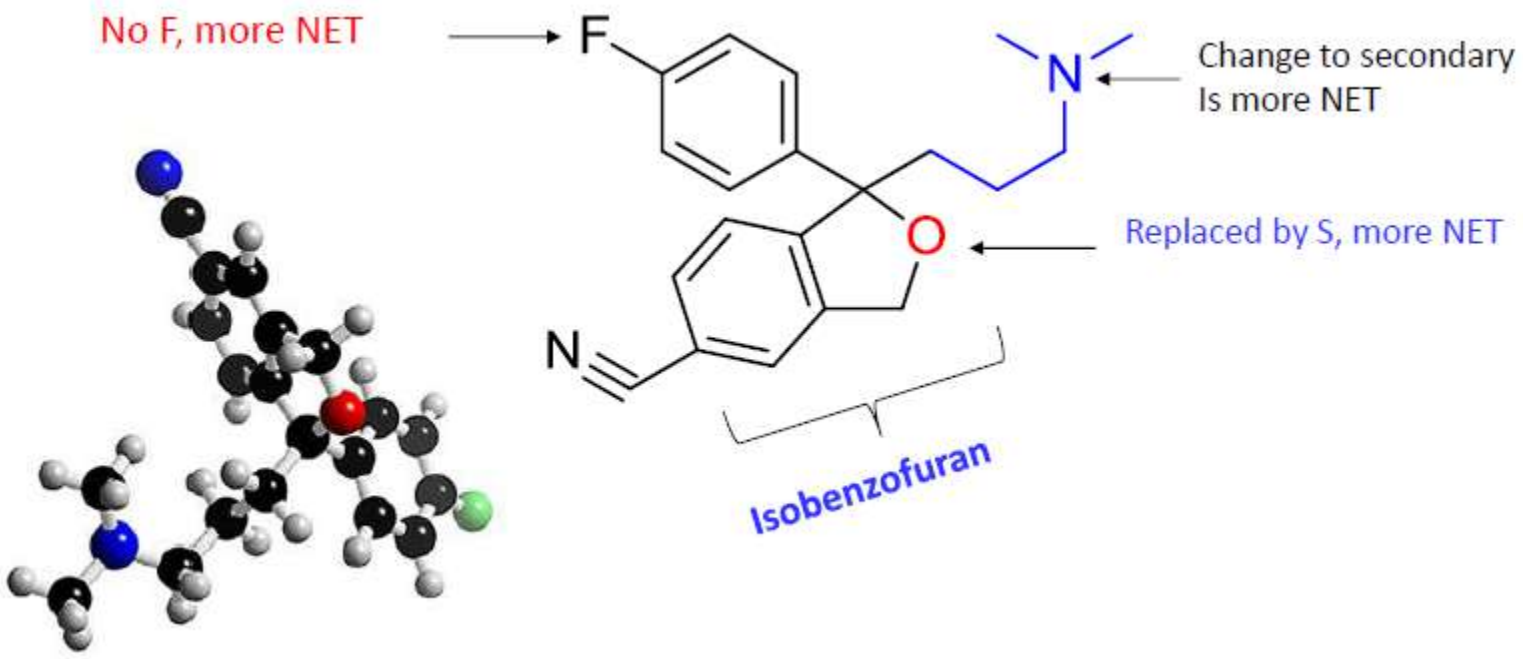
Paroxetine

- An amino group, protonated in vivo could H-bond with the –CH_2–O– unshared electrons. A ***β-arylamine–like*** structure with an extra aryl group results.
- The compound is a very ***highly selective for SERT***. As expected, it is an effective antidepressant and anxiolytic.
- Para substituted with an ***EWG***.

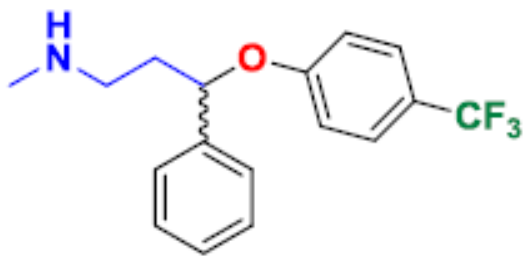


Citalopram and Escitalopram

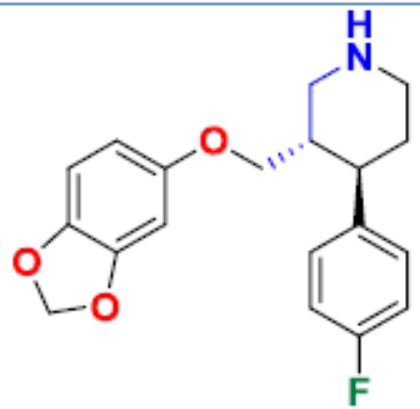
- Is a racemic mixture and is ***very SERT selective*** (Most selective SSRI).
- The *N*-monodemethylated compound is slightly less potent but is as selective.
- The aryl substituents are important for activity.
- The ether function is important and probably interacts with the protonated amino group to give a suitable shape for SERT binding.



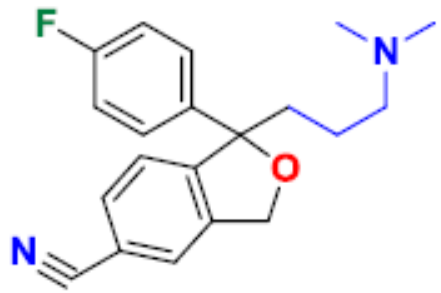
SSRIs Structures



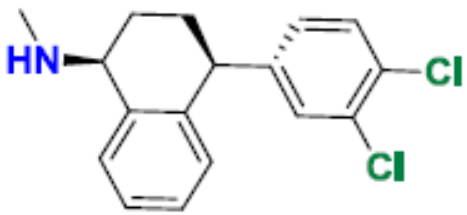
Fluoxetine
Phenoxyphenyl alkylamines



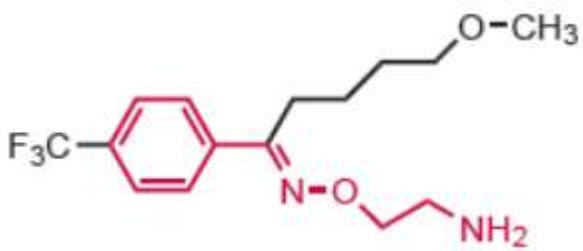
Paroxetine
Phenoxyphenyl alkylamines



Citalopram
Phenoxyphenyl alkylamines



Sertraline
Phenylaminotetraline

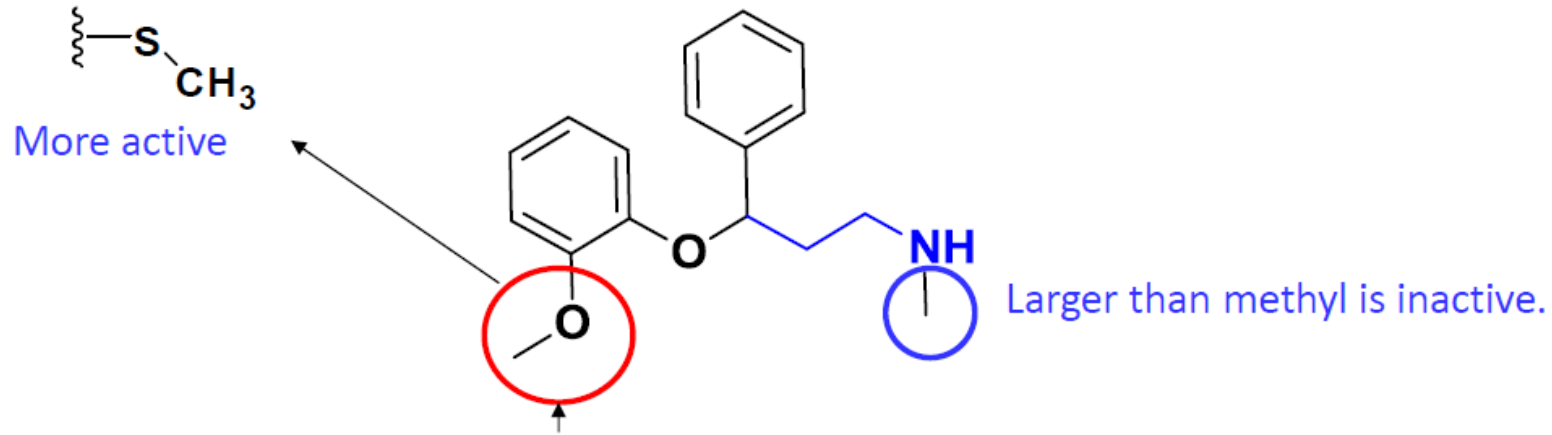


Fluvoxamine
Oxime ether derivative

C. Selective Norepinephrine Reuptake Inhibitors

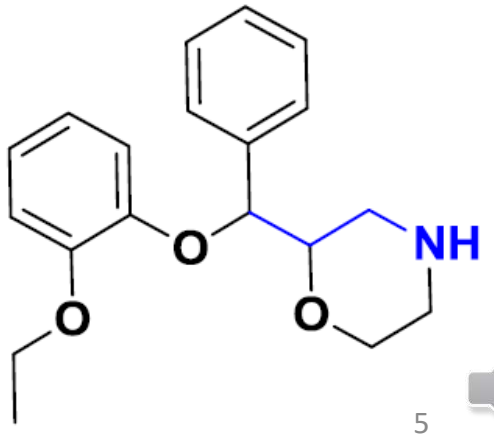
Nisoxetine

is a SNERI and is an antidepressant. Most activity resides in the ***β-isomer***.



Reboxetine

- Potent and selective agent.
- Racemic with S,S more active enantiomer.
- Orally active and could be de-ethylated via metabolism.



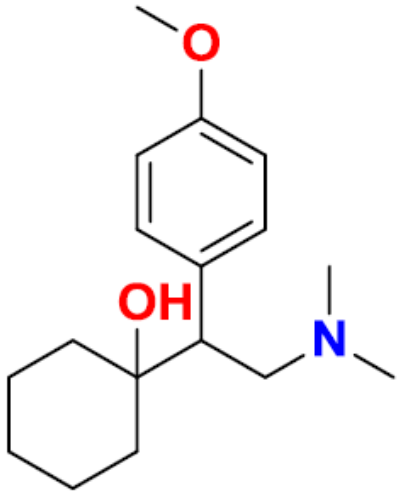
SAR of SNERIs:

- The type and position of ring substitution is very critical to determine the selectivity of these agent for NET or SERT inhibition.
- ***Unsubstituted*** phenoxy ring is ***weak*** NET & SERT inhibitor.
- ***2-substitution*** into the phenoxy ring ***except*** (triflouromethyl) is creating compounds that are ***NET*** selective.
- ***4-substitution*** will give compounds that are ***SERT*** selective; where the triflouromethyl is the ***most*** active.

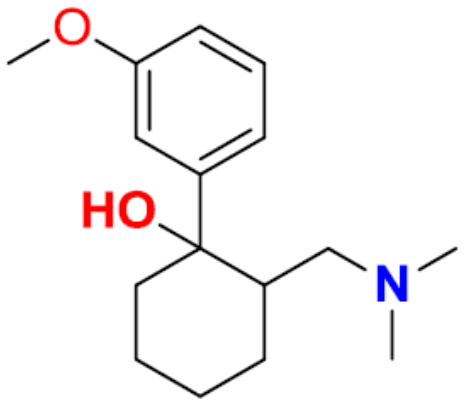
D. Newer (Nontricyclic) Nonselective 5-HT And NE Reuptake Inhibitors

Venlafaxine

- is a serotonin- norepinephrine reuptake inhibitor (***SNRI***).
- Generate ***faster and greater*** antidepressant effect than SSRIs alone.
- Structurally resemble tramadol, an atypical opioid analgesic.
- Has **active metabolite** O-desmethyl (Desvenlafaxine).
- Has narrow therapeutic index.



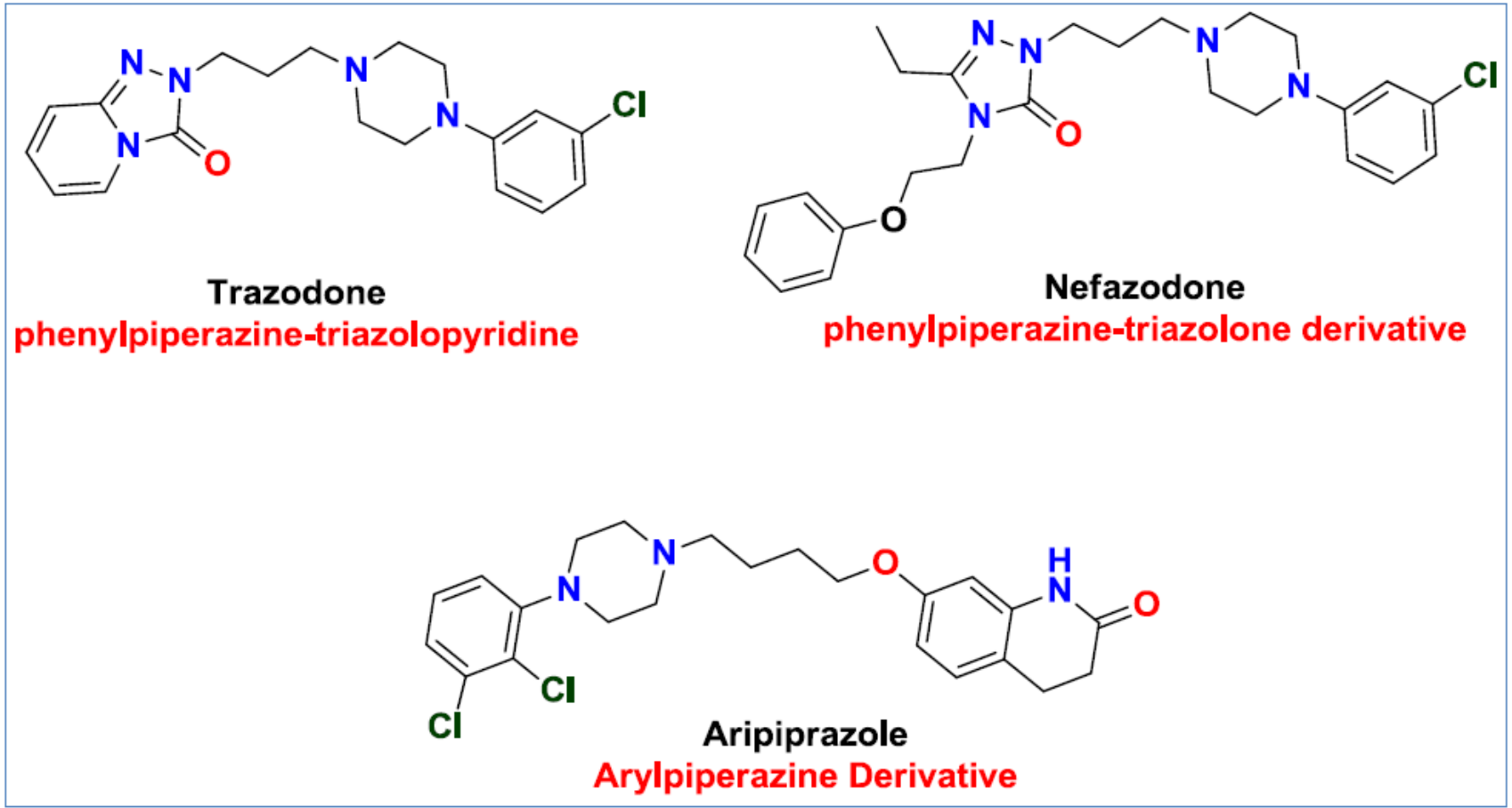
Venlafaxine



Tramadol

E. Selective Serotoninergic Reuptake Inhibitors and 5-HT$_{2A}$ Antagonists

The SSRIs and 5-HT2A antagonists are represented by trazodone, nefazodone , and Vilazodone.



- The structures of these compounds ***derive*** from those of the ***fluorobutyrophenone*** antipsychotics. They have ***β-arylamine-like*** structures that permit binding to the SERT and inhibit 5-HT reuptake. Additionally, they are ***5-HT$_{2A}$ antagonists***. 5-HT$_{2A}$ antagonists appear to have antidepressant and anxiolytic activities.

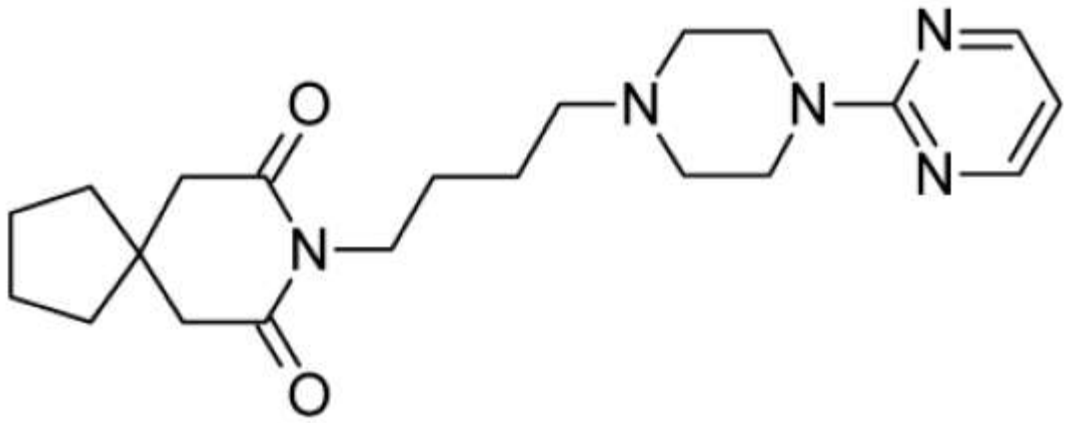
- The first two compounds yield the same compound on *N*-dealkylation. It is a serotonin reuptake inhibitor.

- The most common use of trazodone is not as an antidepressant. A 100-mg dose can be used as a sedative–hypnotic.

F. 5-HT$_{1A}$ Agonists and Partial Agonists

Buspirone

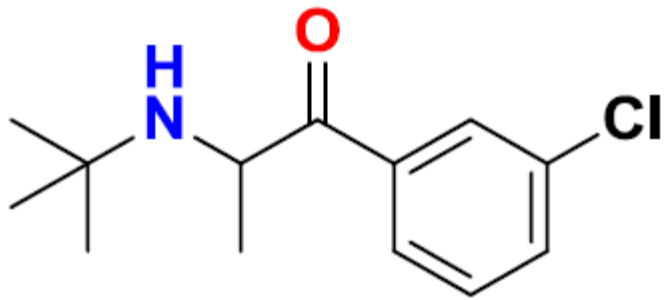
It has anxiolytic and antidepressant activities. Because it is a ***partial agonist***, it can stimulate postsynaptic receptors when 5-HT levels are low in the synapse, as is the case in depression.



D. NE & DA Reuptake Inhibitors

Bupropion

- The mechanism of action of bupropion is considered complex and reportedly involves a ***block*** of ***DA reuptake*** via the dopamine transporter (DAT). Also it ***induces*** the release of DA and NE.
- Is structurally related to ***methamphetamine*** and cathinone, a CNS stimulants.
- Used as off-Label as drug for smoking cessation.



Bupropion