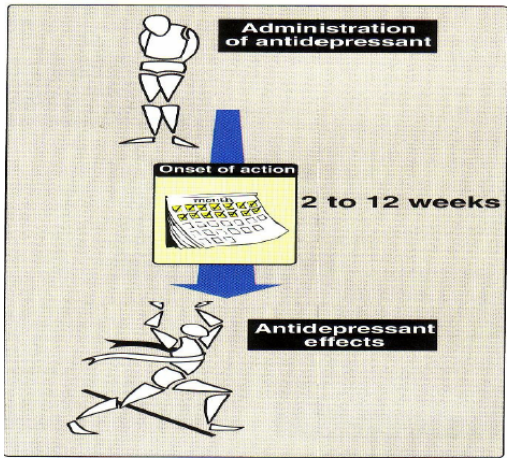
Antidepressants

NEPHAR 305
Pharmaceutical Chemistry I



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Antidepressants

What is depression?

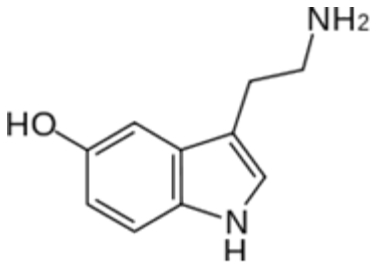
Depression is not a disease per se, but a clinical disorder that is manifested by a variety of symptoms that likely represent several neurochemical/neuropathological disorders in the brain.

Depression is a kind of mood disorder (mania, depression, anxiety) with symptoms such as intense feelings of sadness, hopelessness, despair, lack of motivation and inability to experience pleasure in usual activity.

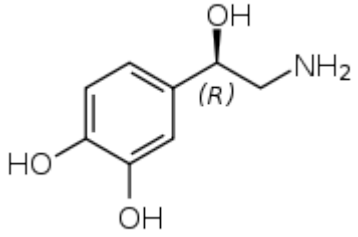
"Amine hypothesis of depression"

states that depression is caused by a deficiency of monoamines, particularly **norepinephrine** (noradrenaline, NE) and **serotonin** (5-Hydroxytryptamine, 5-HT). Depression can be alleviated by drugs that increase the availability of noradrenaline and serotonin.

The therapeutic efficacy of all Antidepressants is not immediate, but requires repetitive administration over a prolonged period of time (at least 2-3 weeks before improvement starts)



Serotonin, 5-HT



Norepinephrine (**NE**), or **noradrenaline**

Classes of Antidepressants

1. Tricyclic anti-depressants (TCAs).
Imipramine, desipramine, nortriptyline,protryptyline, amytriptiline, doxepin.

2. Monoamine oxidase inhibitors (MAOIs).
Isocarboxacid, phenelzine, tranylcypromine. Lithium (bipolar disorder only)

3. Selective serotonin reuptake inhibitors (SSRIs).
Fluoxetine, sertraline, paroxetine, citalopram, escitalopram

4. Atypical anti-depressants.
New TCAs, duloxetine, venlafaxine, mirtazapine, trazodone

Tricyclic Antidepressants

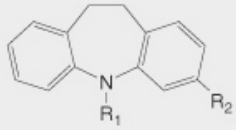
Tricyclic antidepressants (**TCAs**) are chemical compounds used primarily as antidepressants.

✓ Increase levels of norepinephrine and serotonin by preventing their neuronal reuptake => extended duration of post-synaptic effects

Some commonly used tricylics and heterocyclics

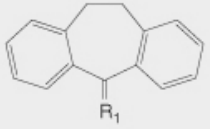
- Amitriptiline (Elavil®) - Metabolite is **nortriptyline**
- Imipramine (Trofanil®) - the prototype TCA
- Desipramine (Norpramine®)- active metabolite of imipramine.
- Clomipramine (Anafranil®)
- Doxepin (Sinequin®)

Dibenzazepines



Drug	R_1	R_2
Imipramine	$-CH_2CH_2CH_2N(CH_3)_2$	H
Desipramine	$-CH_2CH_2CH_2NHCH_3$	H
Clomipramine	$-CH_2CH_2CH_2N(CH_3)_2$	Cl

Dibenzcycloheptenes

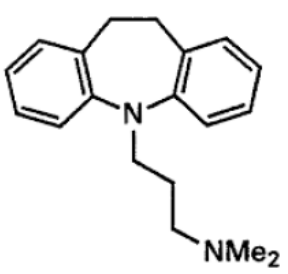


Drug	R_1
Amitriptyline	$=CHCH_2CH_2N(CH_3)_2$
Nortriptyline	$=CHCH_2CH_2NHCH_3$

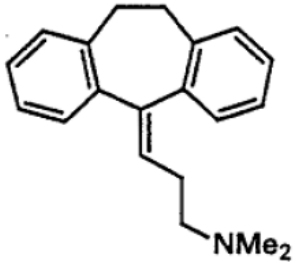
Tricyclic Antidepressants (TCAs)

- These are the “older antidepressants”, also referred to as the 1st generation antidepressants
- Structurally related to the phenothiazine antipsycotics
- Tricyclic antidepressants can be either tertiary or secondary amines

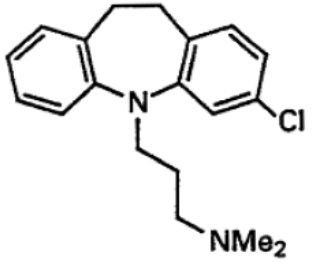
TCA’s are highly related in their chemical structures



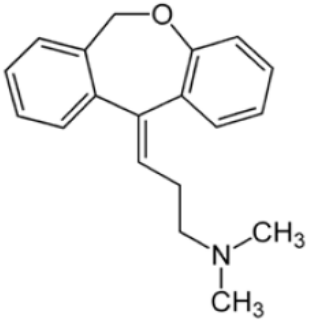
Imipramine



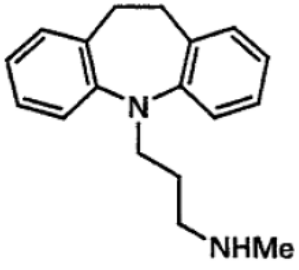
Amitriptyline



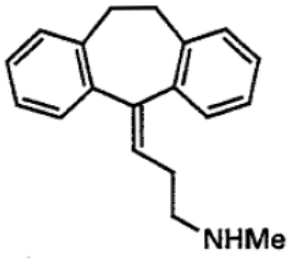
Chlorimipramine



Doxepin



Desipramine

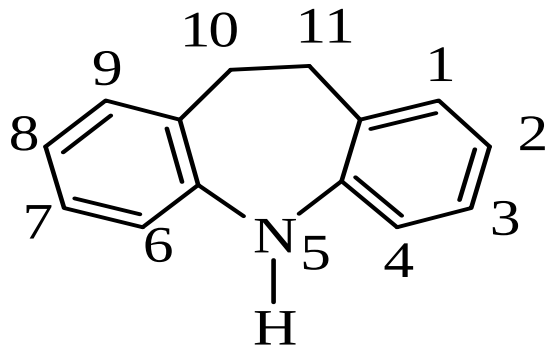


Nortriptyline

Structure Activity Relationship of Tricyclic Antidepressants

Tricyclic antidepressants have similar structures to antipsychotic phenothiazines. However as the angle between the tricyclic rings are different they have different activities.

Side alkyl chain and amino group do not affect the activity as much.

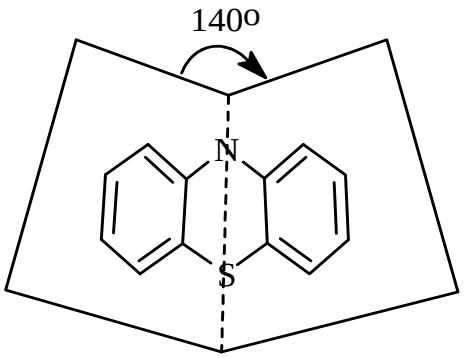


10,11-Dihidro-5H-dibenz[b,f]azepin

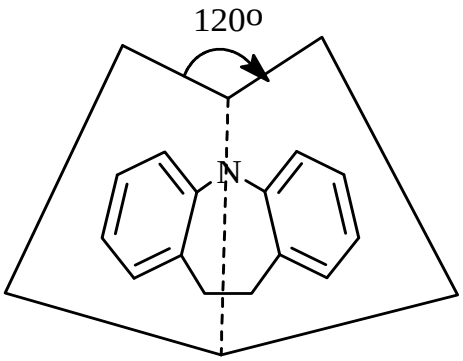
Structure Activity Relationship of Tricyclic Antidepressants

- **General Structure**: Two aromatic rings held in skewed arrangement by a third central ring and a three or sometimes two atom chain bonded to a aliphatic amino group that is monomethyl or dimethyl substituted

- Central ring of the **tricyclic ring of antidepressants** is made of 7 or 8 atoms. This enables tthe molecule to bend more and have a smaller angle relative to phenothiazines.
- For example in chlorpromazine the angle between two phenyl rings is 139°, whereas in antidepressant imipramine it is 130°.

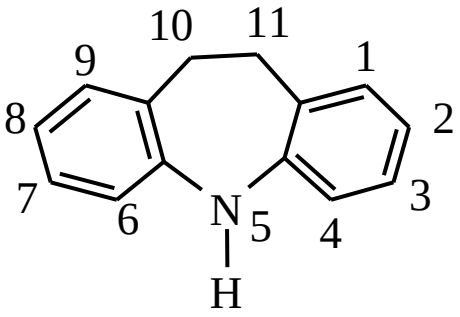


Phenothiazine (Neuroleptic)

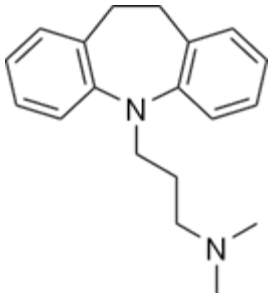


Dibenzazepine (Antidepressant)

Structure Activity Relationship of Tricyclic Antidepressants



10,11-Dihydro-5H-dibenz[b,f]azepin

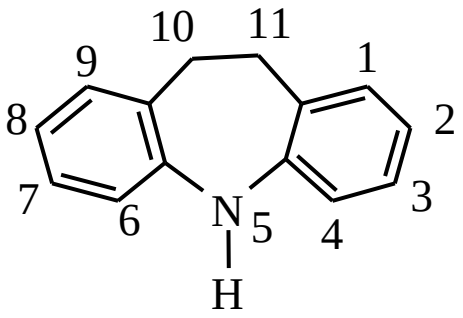


Imipramine

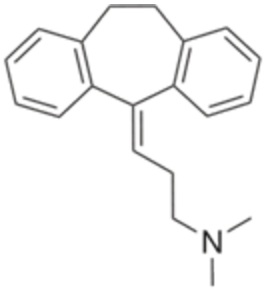
- Side chain of Antidepressants are made up of 3 carbon atoms similar to neuroleptics, in some compounds side chain has 2 carbon atoms. Presence of 4 carbon atoms or branching decreases activity.

- Amino group is tertiary or secondary, methyl substituents on amino group increase activity. Substituents larger than methyl such as ethyl reduce actiity and increases toxicity.

Structure Activity Relationship of Tricyclic Antidepressants



10,11-Dihydro-5H-dibenz[b,f]azepin



Amitriptyline

- There may or may not be unsaturation at **C10-C11** bond inBibenz[b,f]azepin and its derivatives.

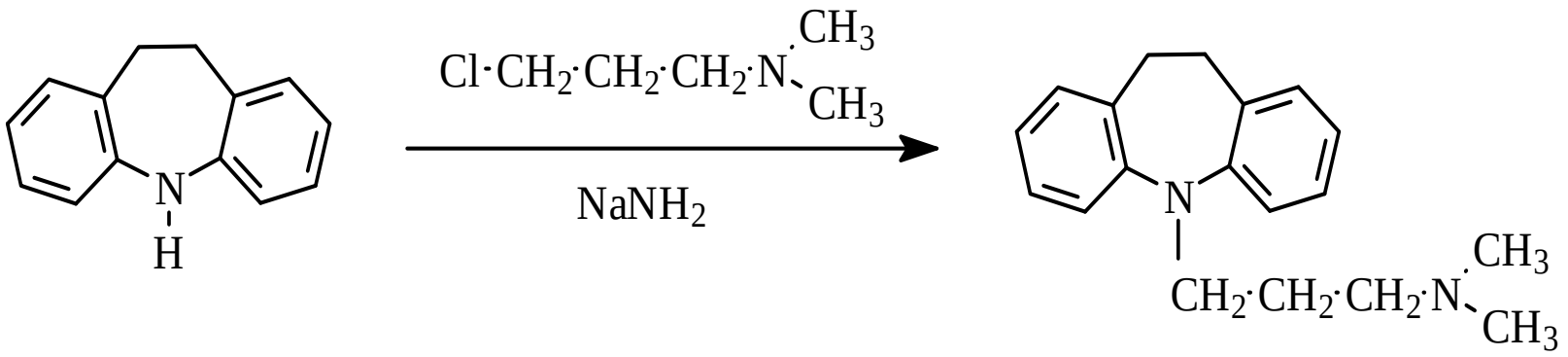
- CH10-C11 bridge can be replaced by its **isosteres** $–CH_2-N-$, $–CH_2-O-$ ve $–CH_2-S-$ groups.

- **Replacing N atom at 5- position with C atom** does not affect activity. 3-chloro, 10-methyl or 10,11-dimethyl substitions improve activity.

- Removal of one of the benzene ring from the tricyclic structure makes it inactive.

Tricyclic Antidepressants - Imipramine

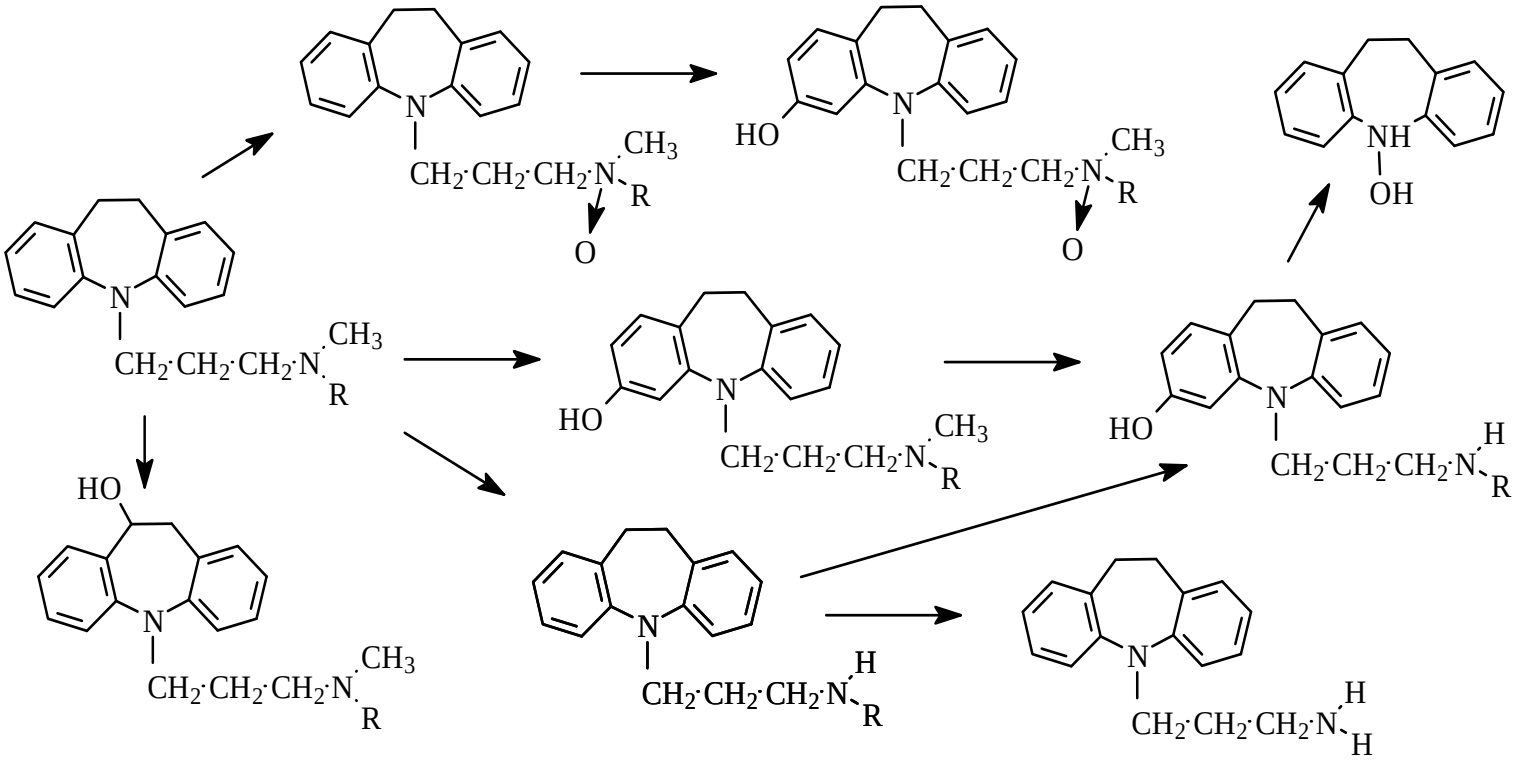
Synthesis: 10,11-dihydro-5H-dibenz[b,f]azepin and 3-dimethylaminopropyl chloride reacts in the presence of sodium amide to give imipramine.



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

Metabolism of Imipramine

- Hydroxylation takes place at 2- and10- position, hydroxylated metabolites also show activity.
- After conjugation with glucuronic acid they are eliminated
- Another metabolic pathway is N-oxide formation.



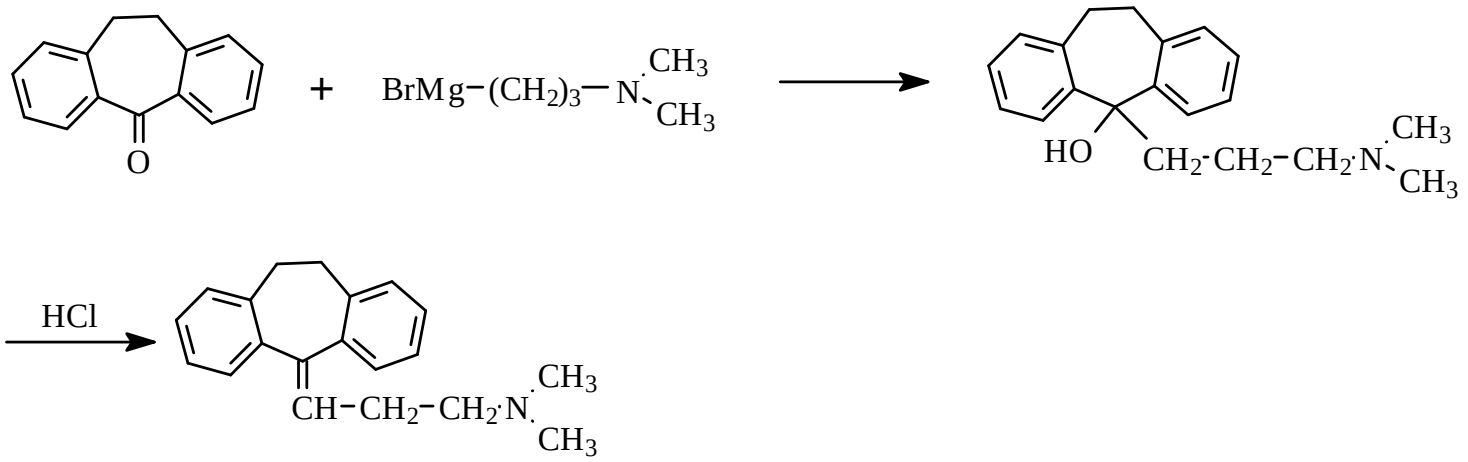
Desipramine

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

Tricyclic Antidepressants - Amitriptyline

Amitriptyline (Elavil), is a tricyclic antidepressant and it is the most widely used.

Synthesis: 5-Oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptadien and 3-dimethylaminopropyl magnesium bromide reacts followed by treatment with HCl to obtain **Amitriptyline** after dehydration.

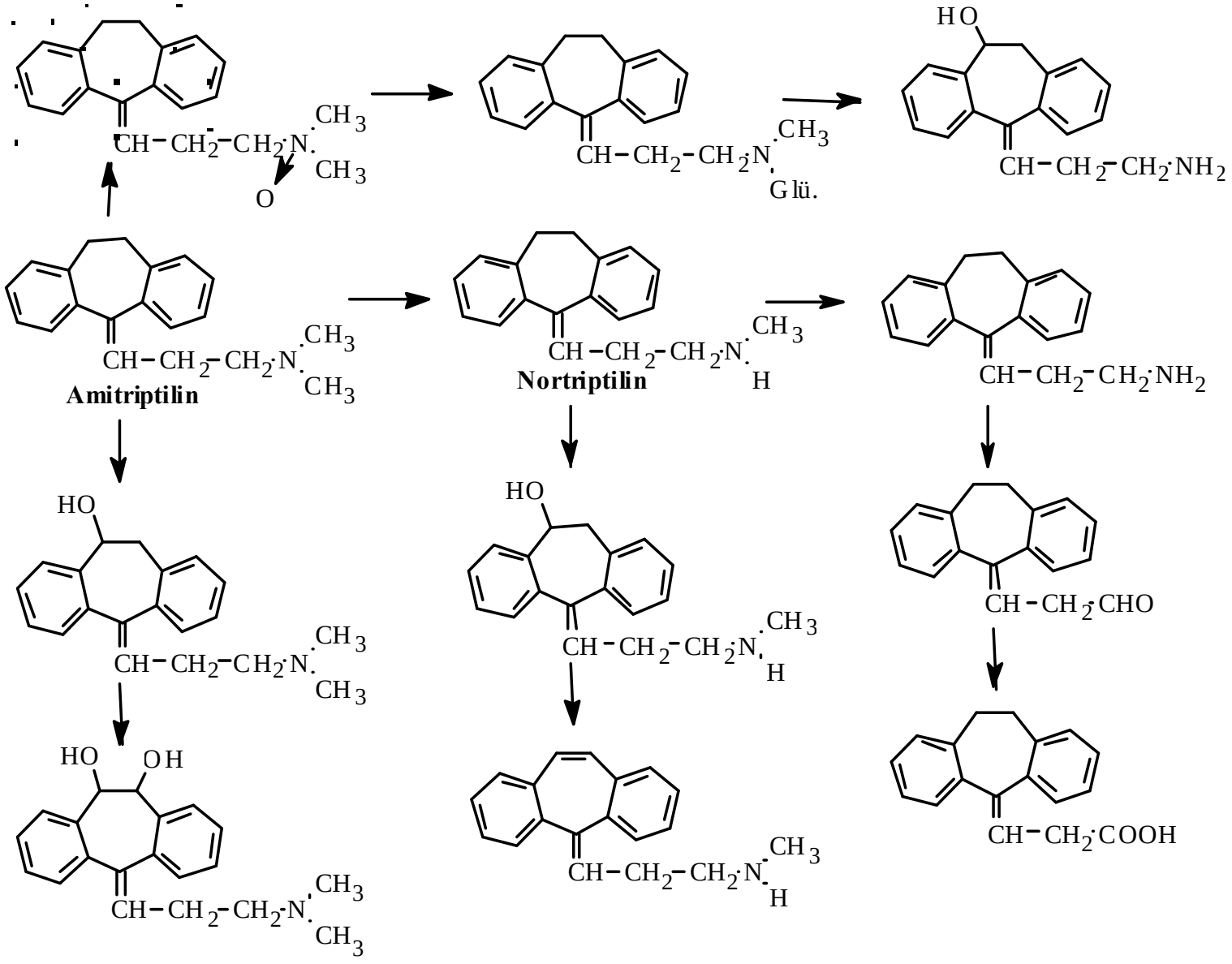


3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ylidene)-*N*,*N*-dimethylpropan-1-amine

Metabolism of Amitriptiline

Demethylation of the side chain, hydroxylation of the ring (10- position) and conjugation are the main metabolic pathways for amitriptiline.
Demethylated metabolite is **nortriptyline** which is also sold as antidepressant.

Metabolism of Amitriptyline

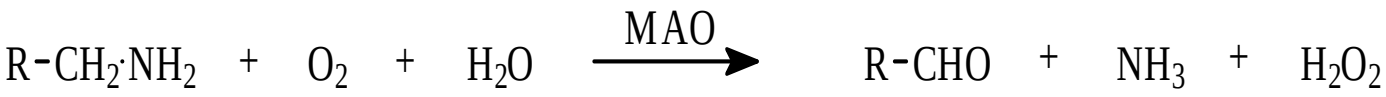


Monoamine oxidase inhibitors (MAOIs)

✓ **Monoamine oxidase inhibitors** (**MAOIs**) are chemicals which inhibit the activity of the monoamine oxidase enzyme family. They have a long history of use as medications prescribed for the treatment of depression.

✓ **MAOI**s increase levels of norepinephrine, serotonin and dopamine by preventing their metabolism

✓ **Monoamine oxidase** (MAO) is the principal enzyme responsible for the metabolism of 5-HT, NE, tyramine and dopamine through deamination reaction



✓ Because of potentially lethal dietary and drug interactions, monoamine oxidase inhibitors historically been reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example selective serotonin reuptake inhibitors and tricyclic antidepressants) have failed.

Monoamine Oxidase Inhibitors (MAOIs)

MAO:

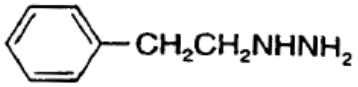
---Regulates free intraneuronal concentration of NE or 5-HT

---Regulates inactivation of endogenous and ingested amines

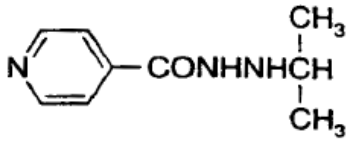
Side effects: few anticholinergic, adrenergic side effects but toxicity associated with dietary interactions (tyramine)

Hydrazines

Pheneizene

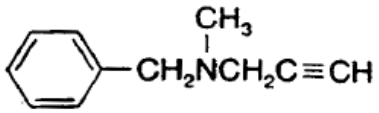


Iproniazid

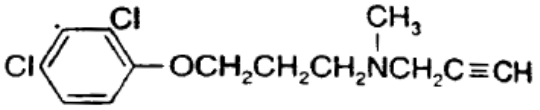


Propargylamines

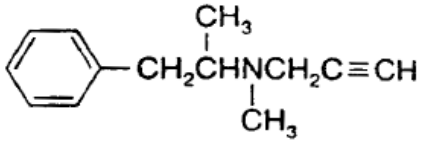
Pargyline



Clorgyline

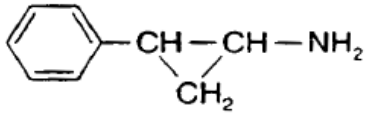


Selegiline



Cyclopropylamines

Tranylcypromine

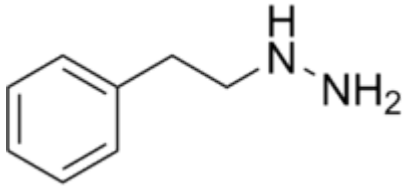


Reversible inhibitor

Moclobemide

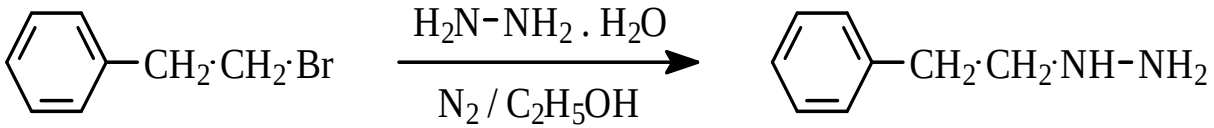
(MAOI) - Phenelzine

Phenelzine (**Nardil, Nardelzine**) is a non-selective and irreversible monoamine oxidase inhibitor (MAOI) of the hydrazine class



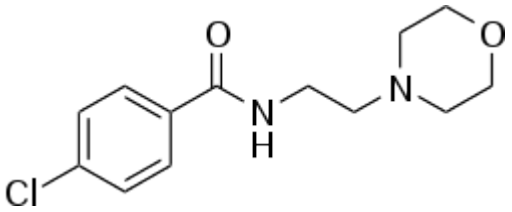
2-phenylethylhydrazine

Synthesis : Phenylethyl bromide and hydrazine hydrate are heated in ethanol under N_2 atmosphere giving **Phenelzine**.



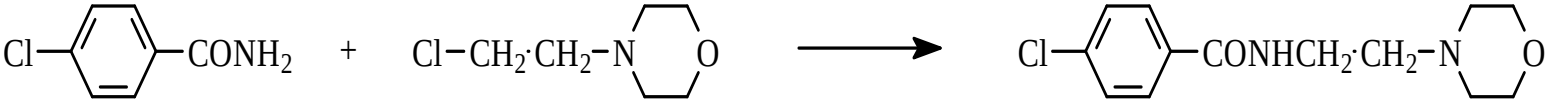
(MAOI) - Moclobemide

Moclobemide is a reversible monoamine oxidase inhibitor (MAOI)



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

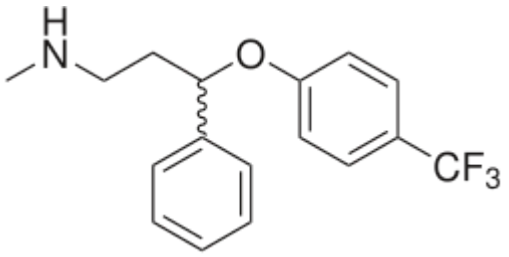
Synthesis: 4-Chlorobenzamide and N-(2-chloroethyl)morpholine reaction gives moclobemide.



Selective Serotonin Reuptake Inhibitors (SSRIs)

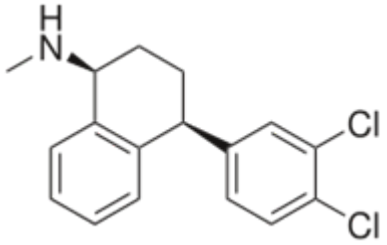
- Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants.
- Increase levels of serotonin specifically by preventing their neuronal reuptake.
- Same efficacy as TCAs, but fewer side effects and not as sedating as many of the tricylic compounds.
- The SSRIs are structurally distinct form the tricyclics and are not chemically related or chemical "look-alikes" to each other. Thus, if a patient does not respond to one SSRI, they may respond to a different SSRI.

Fluoxetine (Prozac®) The first FDA approved and prototype SSRI (1987), the least 5-HT selective, most widely prescribed antidepressant, sales exceed 1 bill. $ / year.
Demethylated active metabolite, ***norfluoxetine*** resulting in considerable drug accumulation.

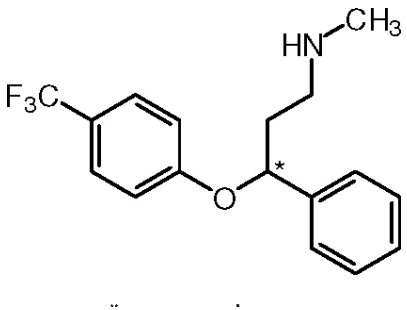


Selective Serotonin Reuptake Inhibitors (SSRIs)

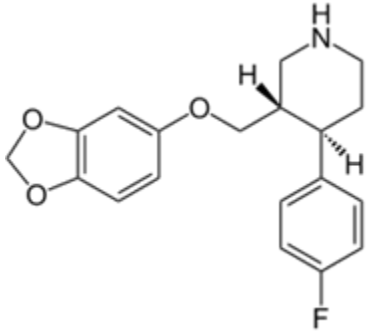
- **paroxetine (Paxil®)** - the highest affinity for the 5-HT transporter, no active metabolites
- **sertraline (Zoloft®)** - has desmethyl active metabolite
- **citalopram (Celexa®)** – the most selective for the 5-HT transporter, active desmethyl metabolite
- **escitalopram (Lexapro®)** - the S(+) isomer of (±) citalopram, that retains the highest 5-HTselectivity
- **fluvoxamine (Luvox®)** - no active metabolites, shorter half live (4-10hrs) than other SSRIs



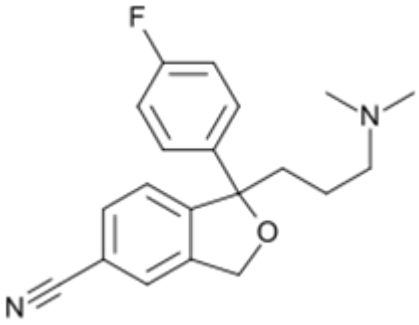
Sertraline



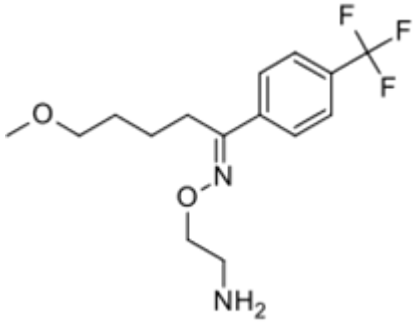
Fluoxetine



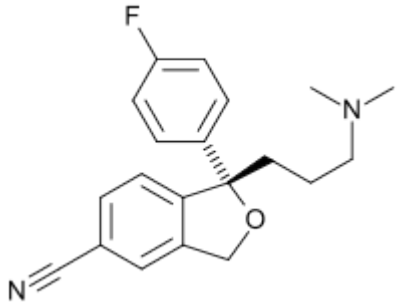
Paroxetine



Citalopram



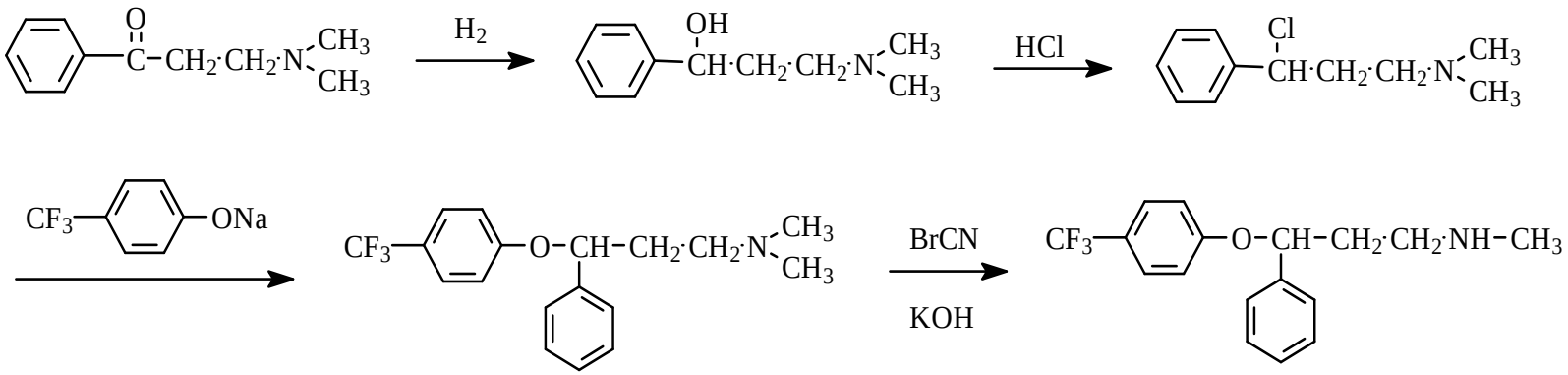
Fluvoxamine



Escitalopram

SSRIs – Fluoxetine (Prozac®)

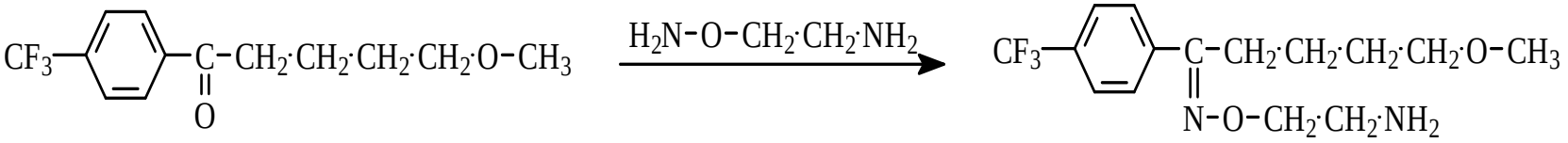
Synthesis: Reduction of 1-phenyl-3-(N,N-dimethylamino)propanone followed by acidification gives 1-phenyl-3-(N,N-dimethylamino)propyl chloride. This reacts with sodium 4-trifluoromethyl phenolate and cyanogen bromide to give fluoxetine.



(±)-N-Methyl-3-phenyl-3-[(4-trifluromethyl)phenoxy]propanamine

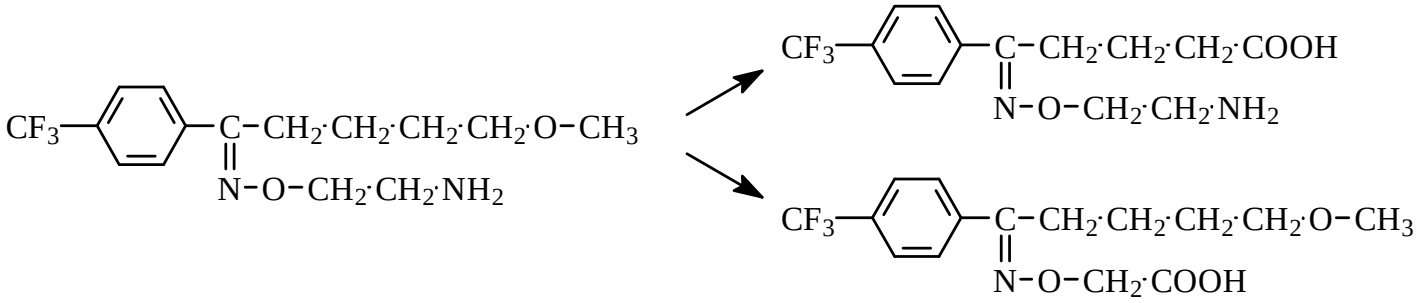
SSRIs – Fluvoxamine (Luvox®)

Synthesis: 1-(4'-Trifloromethyl)phenyl-5-methoxypentanone and O-(2-aminoethyl)hydroxylamine reaction gives Fluvoxamin.



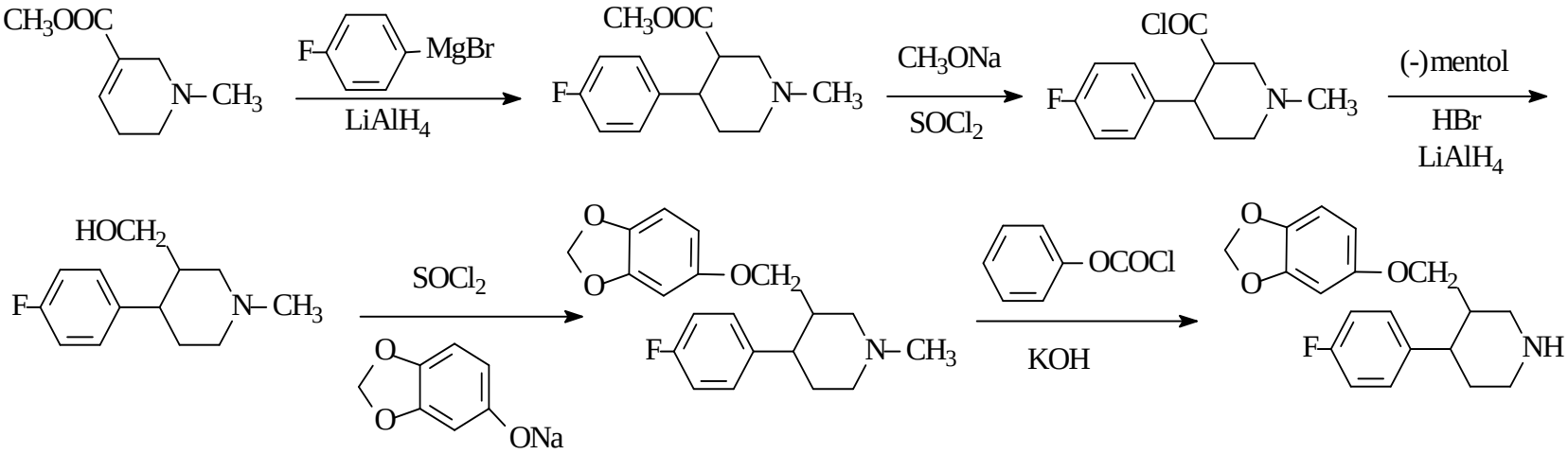
E)5-Methoxy-1-[4-trifluoromethyl)phenyl]-1-pentanon O-(2-aminoethyl)oxime

Metabolism of Fluvoxamine involves oxidation of methoxy group to carboxylic acid and oxidative deamination.



SSRIs - Paroxetine (Paxil®)

Synthesis

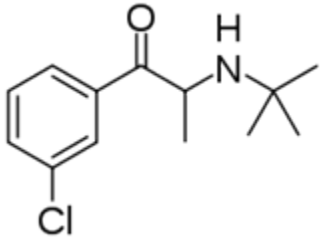


(3S-trans)-(-)-4-(4-Fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine

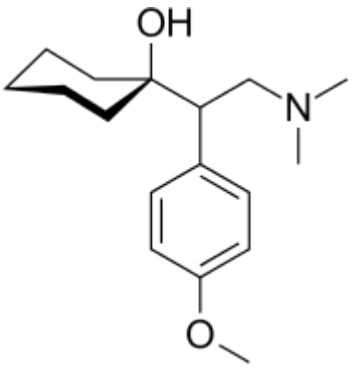
Atypical Antidepressants

Atypical antidepressants are not typical — they don't fit into other classes of antidepressants. They are each unique medications that work in different ways from one another. These antidepressants are newer (second-generation) antidepressants and tend to have fewer side effects than older (first-generation)

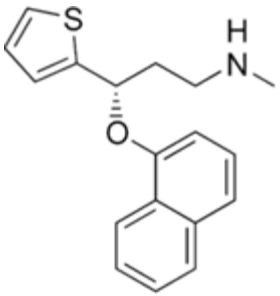
Examples:
Bupropion (Wellbutrin), Duloxetine (Cymbalta), Venlafaxine (Effexor)
Mirtazapine (Remeron), Trazodone (Desyrel)



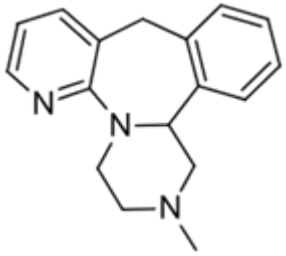
Bupropion



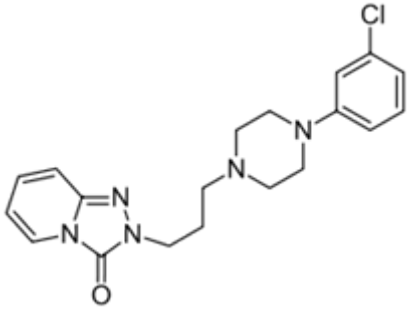
Venlafaxine



Duloxetine



Mirtazapine



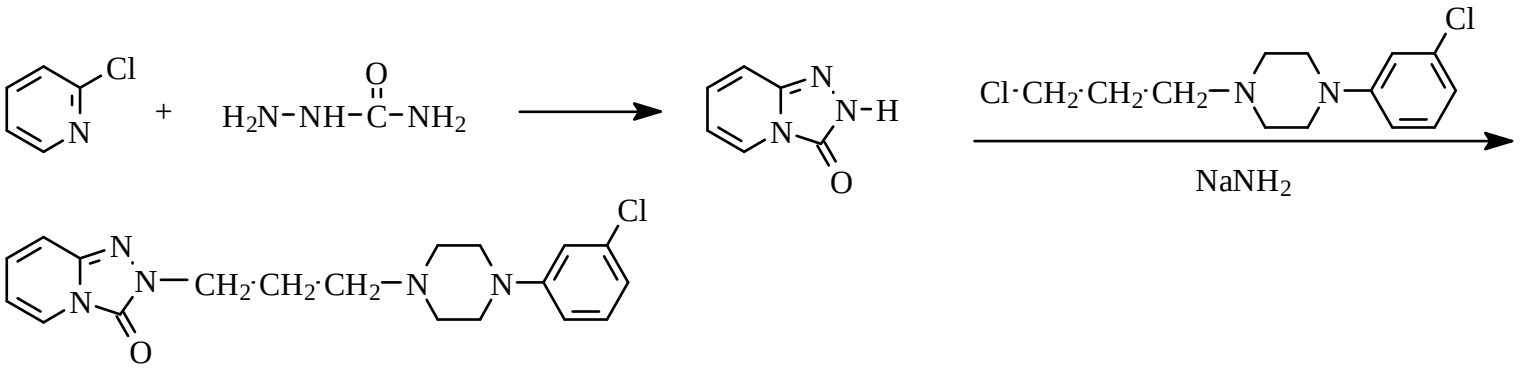
Trazodone

Atypical Antidepressants - Trazodone (Desyrel)

✓ is an antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) class. It is a phenylpiperazine compound.

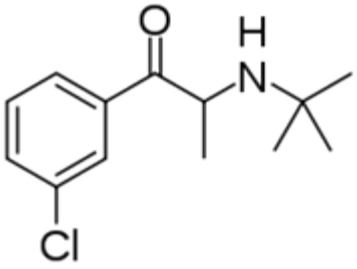
Synthesis of Trazodone: 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one

2-Chloropyridine raects with semicarbazide in presence of catalytic amount of acid resulting in cyclization of triazolopyridine ring. This ring then reacts with sodium amide and 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine giving **trazodone**



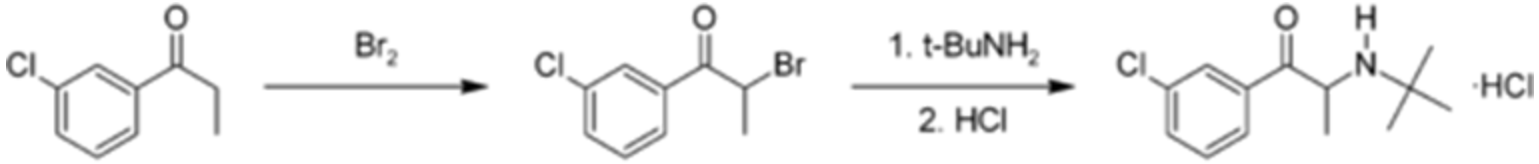
Atypical Antidepressants - Bupropion (Wellbutrin®; Zyban®)

- **Bupropion** is a drug primarily used as an atypical antidepressant and also effective in treating tobacco addiction
- Bupropion is one of the most widely prescribed antidepressants,
- Structurally related to the tricyclics, but seems to have a different therapeutic mechanism, related to altered release of NE



(±)-2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one

Synthesis: in two chemical steps starting from 3'-chloro-propiophenone.
The alpha position adjacent to the ketone is first brominated followed by nucleophilic displacement of the resulting alpha-bromoketone with *t*-butylamine and treated with hydrochloric acid to give bupropion as the hydrochloride salt.



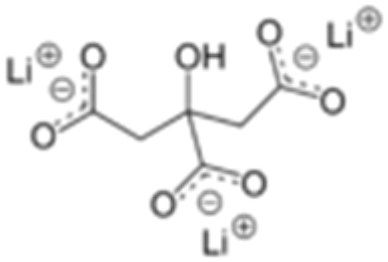
Lithium Compounds

✓ A number of salts of lithium are used as mood-stabilizing drugs (anti-mania drug), primarily in the treatment of **bipolar disorder**

✓ Upon ingestion, lithium becomes widely distributed in the central nervous system and interacts with a number of neurotransmitters and receptors, decreasing norepinephrine (noradrenaline) release and increasing serotonin synthesis.

Lithium carbonate (Li_2CO_3)

Lithium citrate ($Li_3C_6H_5O_7$)



Lithium orotate