Tranquilizers / Neuroleptics (Antipsychotics)

NEPHAR 305
Pharmaceutical Chemistry I

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Tranquilizers

Tranquilizer is a drug that is used to reduce anxiety, fear, tension, agitation, and related states of mental disturbance.
Tranquilizers fall into two main classes, major and minor.

Major tranquilizers, which are also known as antipsychotic agents, or neuroleptics, are so called because they are used to treat major states of mental disturbance in schizophrenics and other psychotic patients.

Minor tranquilizers, which are also known as antianxiety agents, or anxiolytics, are used to treat milder states of anxiety and tension in healthy individuals or people with less serious mental disorders.

Minor Tranquilizers

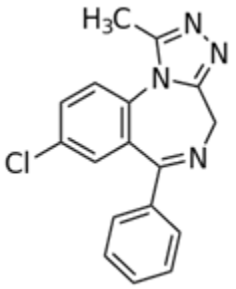
Minor Tranquilizers

The principal minor tranquilizers are the **benzodiazepines**, among which are **diazepam (Valium), chlordiazepoxide (Librium), and alprazolam (Xanax).** These drugs have a calming effect and eliminate both the physical and psychological effects of anxiety or fear.

Benzodiazepines' **mechanism of action** is enhancing the action of the neurotransmitter gamma-aminobutyric acid (GABA), which inhibits anxiety by reducing certain nerve-impulse transmissions within the brain.

Other, less commonly used minor tranquilizers include **meprobamate (Equanil, Miltown) and buspirone (BuSpar).**

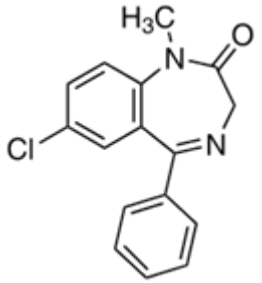
Minor Tranquilizers-Benzodiazepine Derivatives



Alprazolam (Xanax)

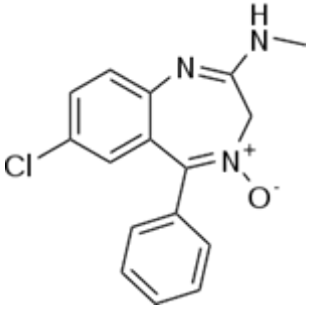
8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Diazepam (Valium)



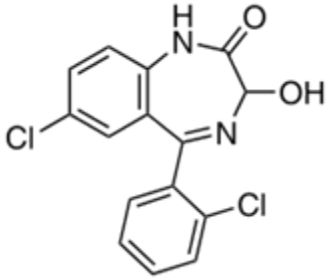
7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2(3*H*)-one

Chlordiazepoxide (Librax)



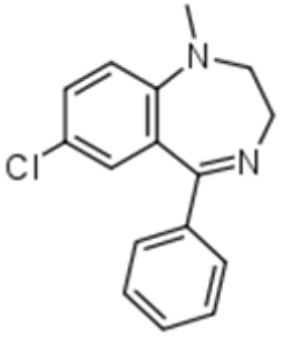
7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide

Lorazepam (Ativan)



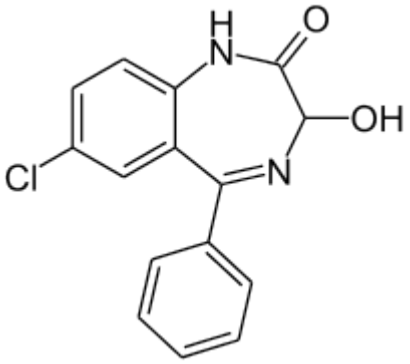
7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one:

Minor Tranquilizers-Benzodiazepine Derivatives



Medazepam

7-chloro-1-methyl-5-phenyl-2,3-dihydro-1,4-benzodiazepine



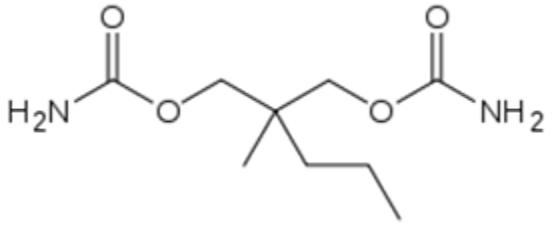
Oxazepam (Serepax)

7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one

Minor Tranquilizers- Propandiol Dicarbamate Derivatives

Meprobamate

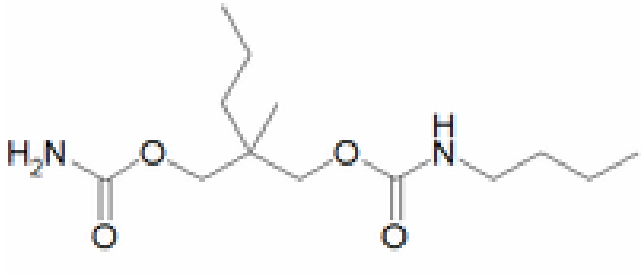
It was the best-selling minor tranquilizer for a time, but has largely been replaced by the benzodiazepines



[2-(carbamoyloxymethyl)-2-methyl-pentyl] carbamate

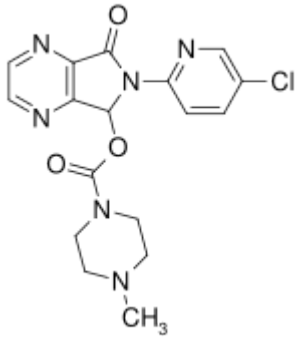
Tybamate

It is a prodrug for meprobamate



[2-(carbamoyloxymethyl)-2-methylpentyl] N-butylcarbamate

Minor Tranquilizers- Cyclopyrrolones Derivatives

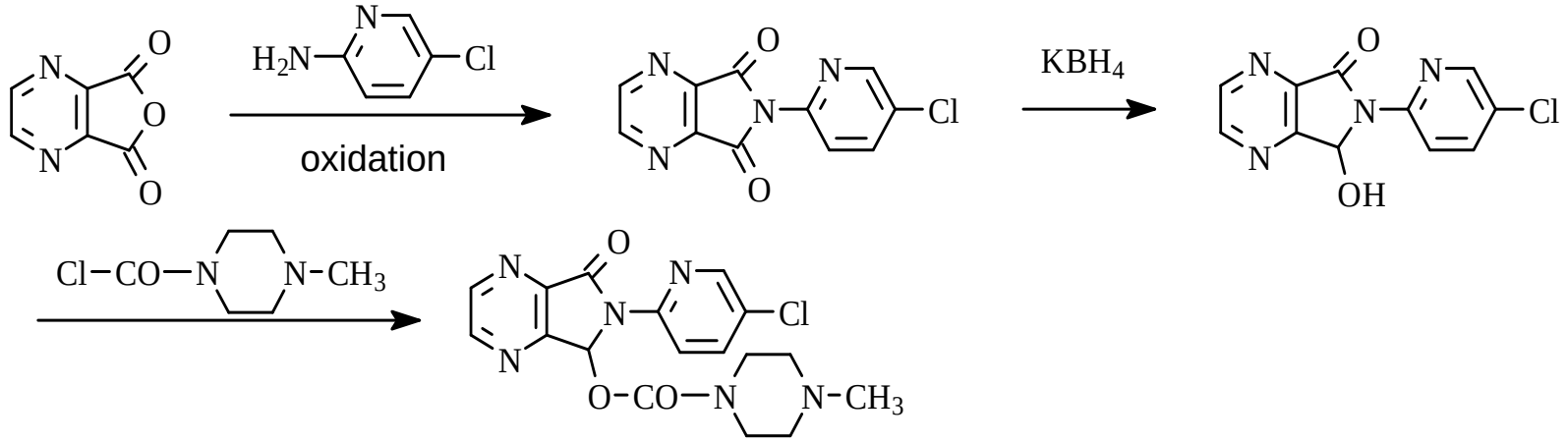


Zopiclone (Imovane)

- ✓ its active stereoisomer is **eszopiclone** (Lunesta)
- ✓ may be illegal to possess Zopiclone without a prescription

(*RS*)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate

Synthesis: Reaction of pyrazine-2,3-dicarboxylic acid anhydride and 2-amino-5-chloropyridine followed by reduction with potassium borohydride and then reaction with 4-methylpiperazine-1-carbonyl chloride gives **Zopiclone.**



ANTIPSYCHOTICS
(Neuroleptics, Ataractics, Major tranquilizers)

Major Tranquilizers (Antipsychotics, or Neuroleptics)

What are antipsychotic medications?
They are a range of medications that are used for some types of mental distress or disorder - mainly **schizophrenia** and **manic depression (bipolar disorder**).
They can also be used to help severe **anxiety** or **depression**.

✓They all affect the action of a number of chemicals in the brain called **neurotransmitters** – chemicals which brain cells need to communicate with each other.

✓**Dopamine** is the main neurotransmitter affected by these medications. It is involved in how we feel: It is also involved in the control of muscle movements.

✓If parts of the dopamine system become overactive, they seem to play a part in producing **hallucinations, delusions and thought disorder.**

✓The basic aim is to help feel better, without making one feel slowed down or drowsy.

Antipsychotics

- Antipsychotics, known also as neuroleptics, and major tranquilizers, not only calm severly disturbed pyschiatric patients but also relieve them of the symptoms of their disease.

- Like other psychoactive drugs, neuroleptics do not cure mental diseases, but rather treat only their target symptoms such as hallucinations or manias.

- Neuroleptics usually do not shorten the duration of psychotic phasis in schizophrenia, but they do decrease the severity of mania and depressions.

- Contrary to the effect caused by hypnotic and sedatives, they do not cloud consciousness or depress vital centers.

Antipsychotics

Typical Antipsychotics

• A class of antipsychotic drugs first developed in the 1950s
• Commonly used but not the best and not very selective

Examples:

Phenothiazine compounds
Thioxanthene compounds
Butyrophenone compounds

Atypical Antipsychotics

•Also known as second generation antipsychotics
•Less side effects (Parkinson like), more selective

Examples:

Clozapine
Risperidone
Olanzapine
Ziprazidone
Quetiapine
Amisulpride

Antipsychotics

✓ The basic types of **Antipsychotics** are the **phenothiazines, thioxanthines, butyrophenones, clozapine,** and **rauwolfia alkaloids**.

✓ The phenothiazines are the most widely used of these and include the drug **chlorpromazine**.
✓ They are thought to work by blocking the neurotransmitter dopamine in the brain. This leads to a reduction of psychotic symptoms but can also result in unwanted side effects

✓ The butyrophenones, chief among which is **haloperidol** (Haldol), are similar to the phenothiazines.

✓ Another drug, **clozapine**, whose exact mode of action remains unclear relieves schizophrenic symptoms in some patients who are not helped by phenothiazines.
✓ Clozapine lacks the side effects of the phenothiazines but tends to induce an infectious disease known as agranulocytosis.

✓ The rauwolfia alkaloids, such as **reserpine**, are no longer in common use.

Antipsychotics

Mechanism of Action:

The mechanism of action of antipsychotic drugs are only partially known.

Although the antipsychotic drugs represent a wide variety of chemical structures, their pharmacological and clinical activities are remarkably similar.

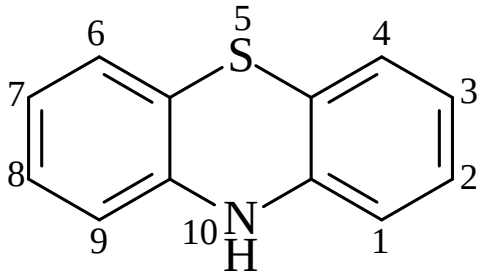
The theory that most antipsychotic agents act as antagonists at pre- and postsynaptic dopamine receptors, that is, by blocking dopamine from binding to its receptor sites.

Antipsychotics

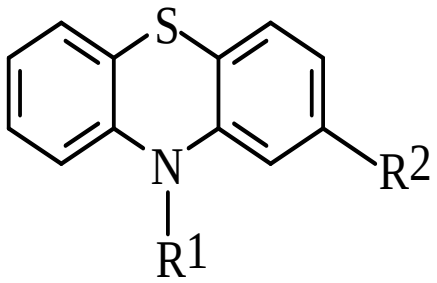
PHENOTHIAZINE DERIVATIVES

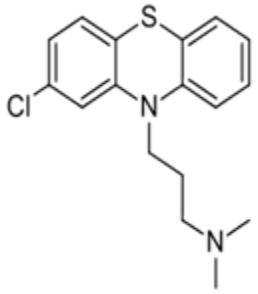
✓ First synthesized in 1950, chlorpromazine was the first drug developed with specific antipsychotic action, and would serve as the prototype for the phenothiazine class of drugs.

✓ Phenothiazine derivatives are chemically characterized by a lipophilic fused tricyclic system (the phenothiazine nucleus) linked through the nitrogen atom of the central ring to a hydrophilic aminoalkyl substitutent (the tertiary basic side chain).



Chemical Abstract system

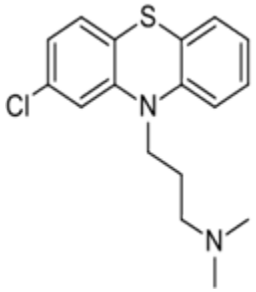




Chlorpromazine

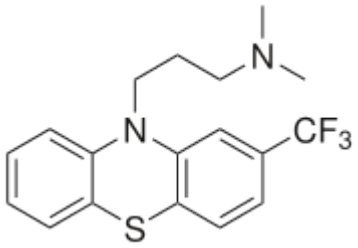
PHENOTHIAZINE DERIVATIVES

✓ Aliphatic compounds



Chlorpromazine (Thorazine Sonazine, Chlorprom, Largactil)

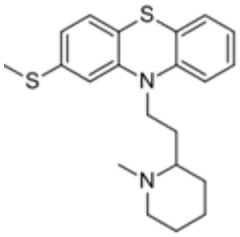
3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethyl-propan-1-amine



Triflupromazine (Clinazine, Vesprin)

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

✓ Piperidines

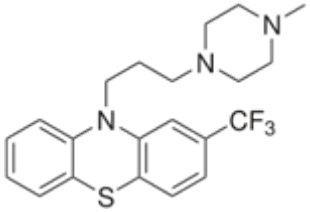


Thioridazine (Mellaril)

10-{2-[(*RS*)-1-Methylpiperidin-2-yl]ethyl}-2-methylsulfanylphenothiazine

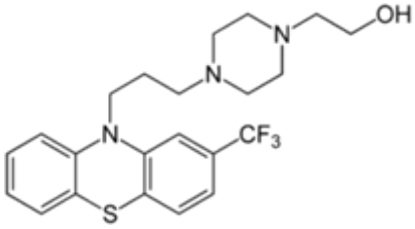
PHENOTHIAZINE DERIVATIVES

✓ **Piperazines**



Trifluoperazine
(Eskazinyl, Stelazine, Triftazin)

10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)-10*H*-phenothiazine



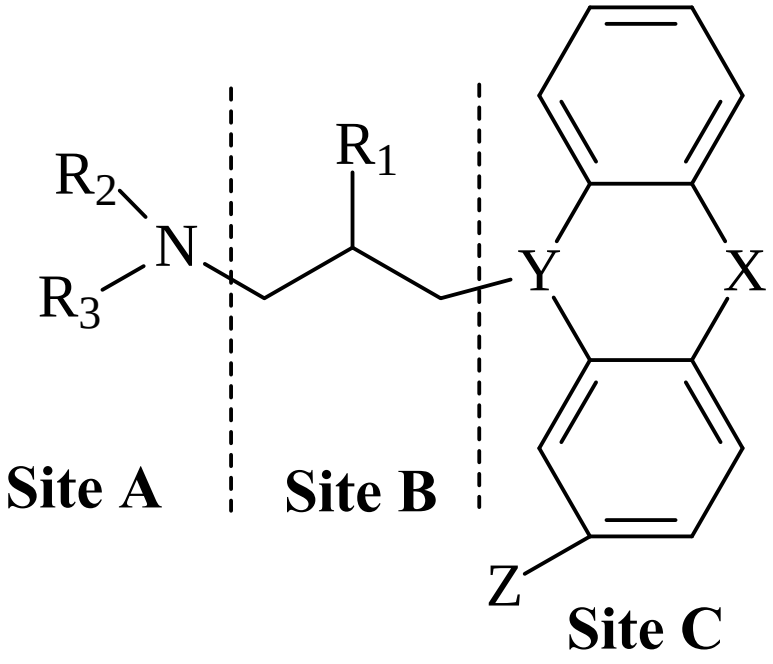
Fluphenazine
(Prolixin, Permitil, Modecate, Moditen)

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

PHENOTHIAZINE DERIVATIVES

Structure-Activity Relationships

It is postulated that phenothiazines interact with dopamine receptors at three distinct sites, A, B, C. The order of importance in terms of structure activity is B > C > A.



The pendent amine functionality (**Site A**)

Intervening alkyl chain between the central ring and the terminal amino group (**Site B**)

A tricyclic ring system with six- or seven-membered central ring (**Site C**)

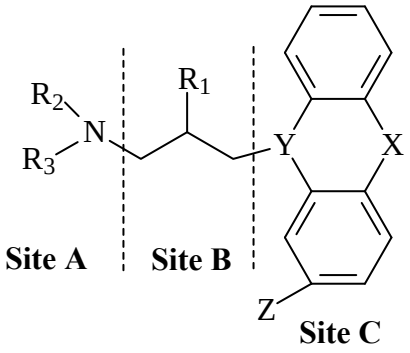
Y=N, X=S

PHENOTHIAZINE DERIVATIVES

Structure-Activity Relationships

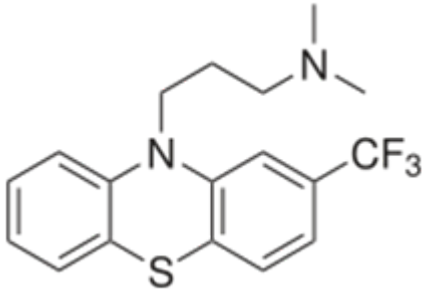
SITE B

- A three carbon atom chain is needed for optimum neuroleptic activity
- This alkyl group should be bonded to a nitrogen atom
- A substituent at 2-position of this 3 carbon atom chain affects activity. Whe R_1 is a H atom the activity is optimal.
- Whereas small alkyl substituents such as methyl are tolerated at the C2 carbon, larger substituents (for example R_1: phenyl, dimethylamino) that restrict the free rotation decrease neuroleptic potency.



Y=N, X=S

Triflupromazine



Structure-Activity Relationships of Phenothiazines

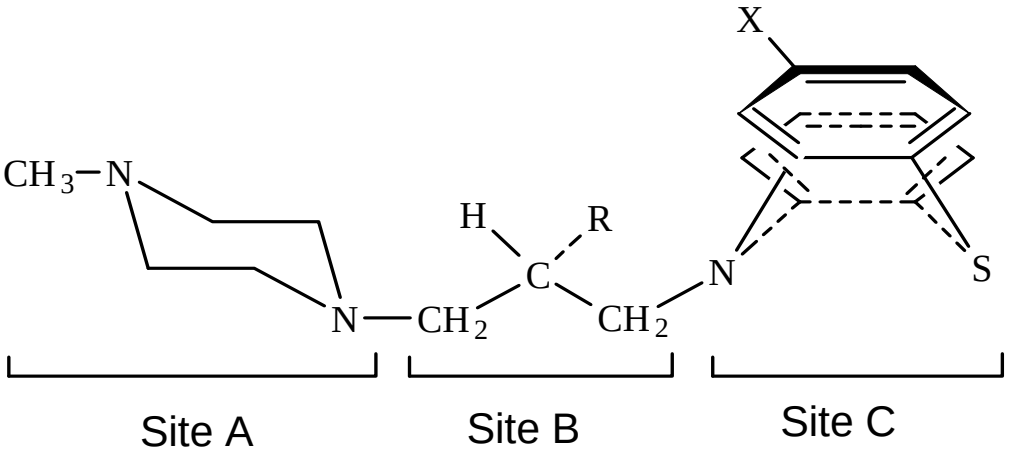
SITE C

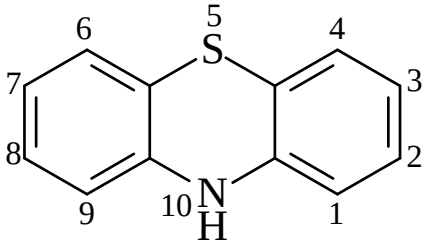
• The phenothiazine ring is not planar. For example, the angle between the two phenyl planes is 159^{o} in chlorpromazine and 141^{o} in perphenazine.

•Phenothiazine ring is not necessary for neuroleptic activity. Other planar tricyclic systems like thioxanthenes are active.

• Substituents at 2-position (X) of the phenyl ring improve activity. Electron withdrawing substituents such as halogens, methoxy, acetyl, trifluoromethyl increase activity.

• Substituents at 1, 3, 4-positions decrease activity.





Chemical Abstract system

Structure-Activity Relationships of Phenothiazines

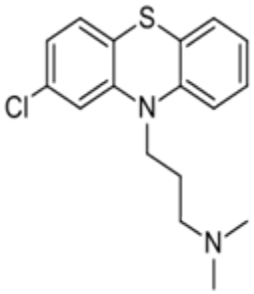
SITE A

Nature of the amino group

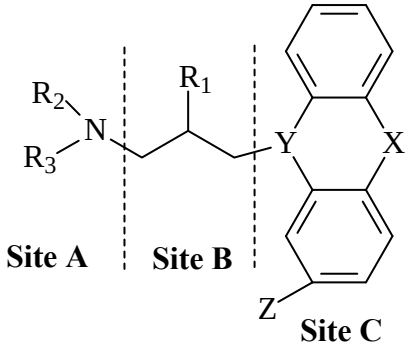
- The size and nature of the basic amino group has considerable influence on the behavior of the phenothiazine neuroleptics, because the molecule has to fit into a narrow space.

- A tertiary amine has optimal activity; presence of alkyl groups larger than methyl or replacing methyl groups with hydrogen atoms decrease activity.

- On the other hand, if the nitrogen is part of a heterocyclic ring (such as in *N*-methylpiperazine and piperidine compounds), neuroleptic potency may not be reduced. The effective size of the piperazine ring for instance, is smaller than that of the diethylamino group.

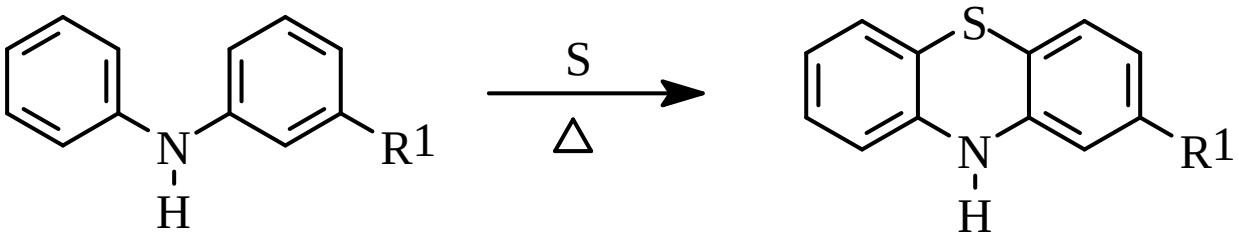


Chlorpromazine

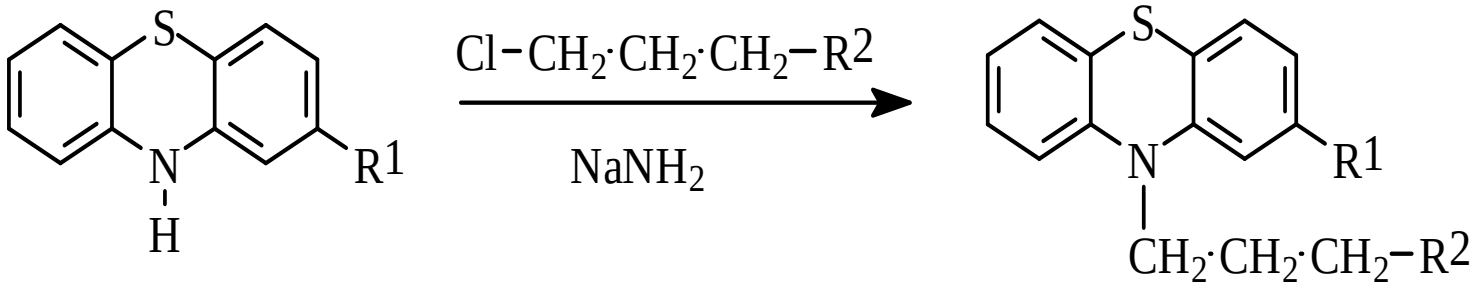


PHENOTHIAZINE DERIVATIVES

Synthesis:



• Heating of appropriate diphenylamine (or 3-substituted diphenyl amine) with sulfur yields the desired phenothiazine ring (*Bernthsen* method).



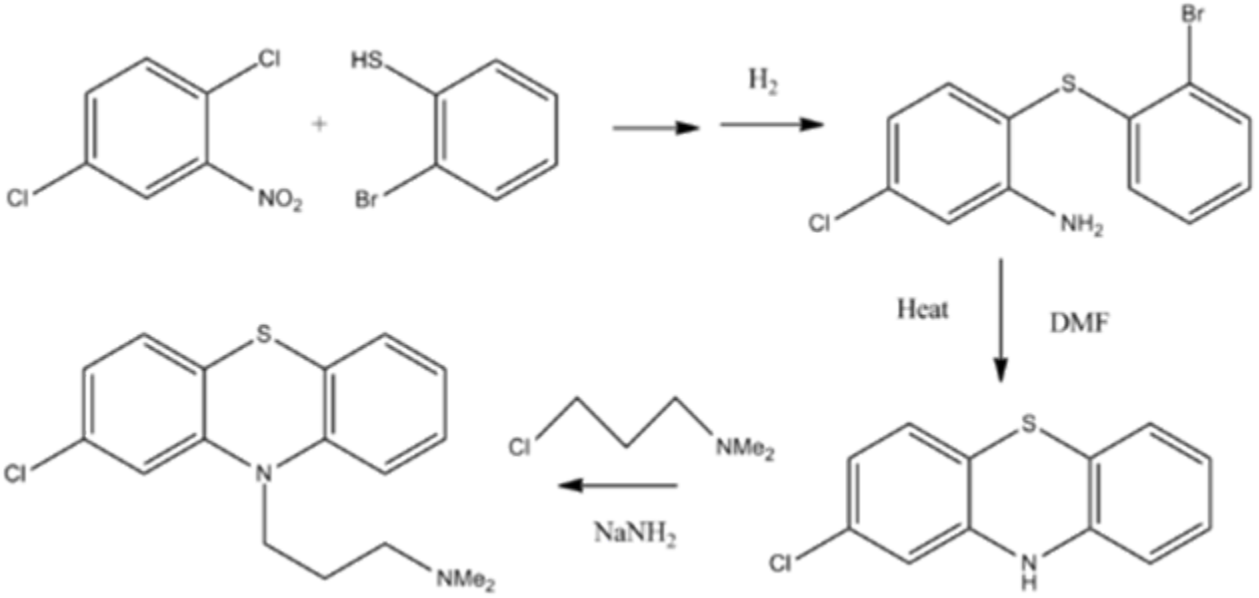
Alkylation of phenothiazine ring with various amino alkyl halogens by means of sodium amide results in desired phenothiazine derivatives.

Synthesis of Chlorpromazine

✓ The synthesis begins with the reaction of 1,4-dichloro-2-nitrobenzene with 2-bromobenzenethiol. Hydrogen chloride is evolved as a by-product of this step and a thioether is formed as the product.

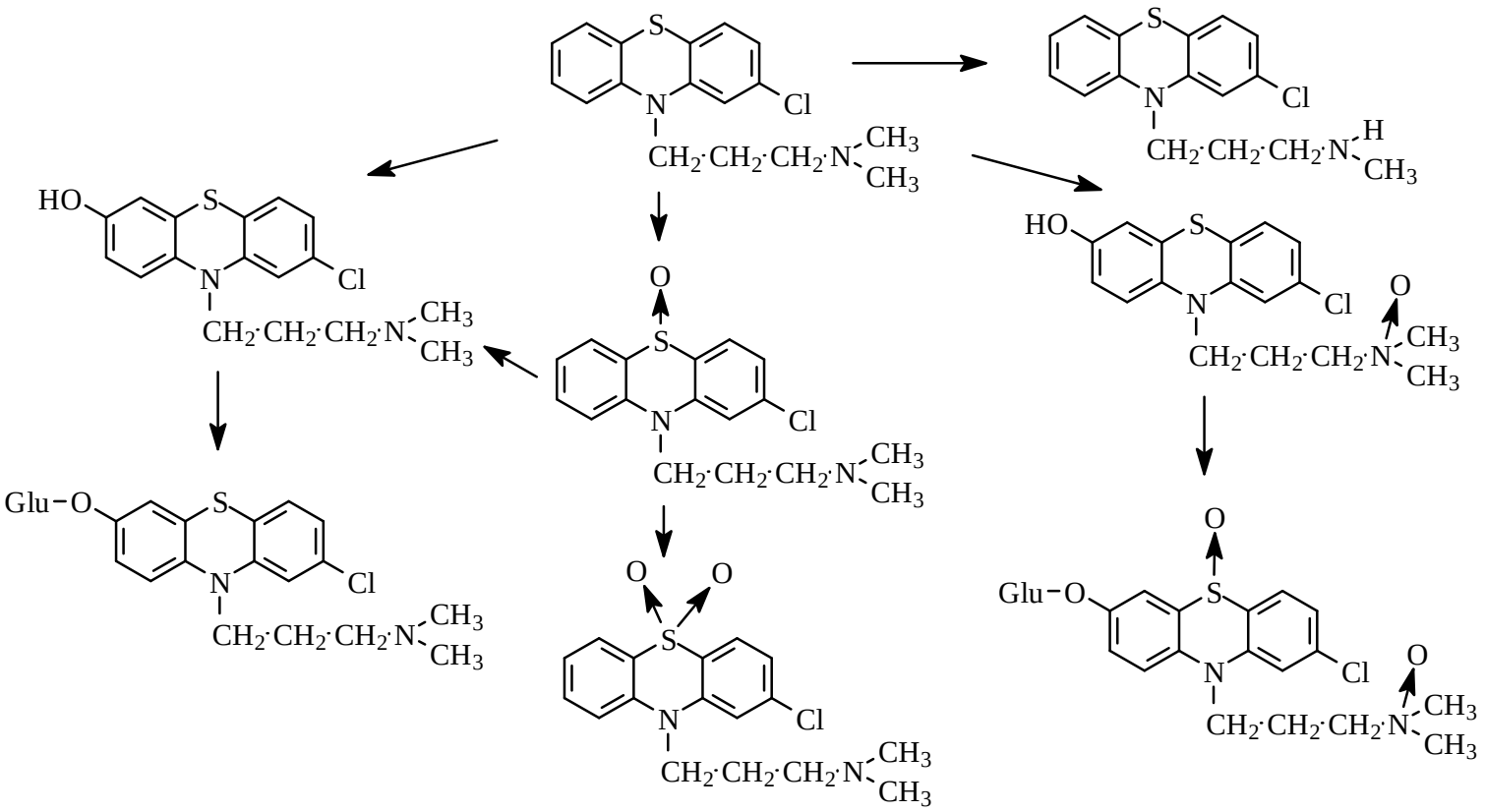
✓ In the second step the nitro group is reduced with hydrogen gas. Upon heating in dimethylformamide (DMF) solvent, ring cyclization occurs.

✓ The 2-chloro-10H-phenothiazine thus produced is combined with 3-chloro-N,N-dimethylpropan-1-amine in the presence of sodium amide base to form chlorpromazine.



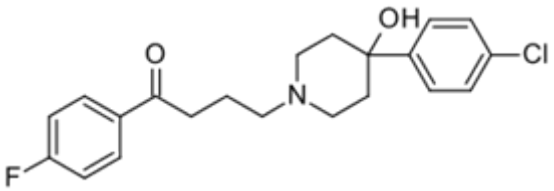
Biotransformation of Phenothiazines Derivatives

Phenothiazines undergo extensive biotransformation which include aromatic hydroxylation, N- , S- oxidation and N-delakylation. The metabolites are excreted to a large extent as glucronides.



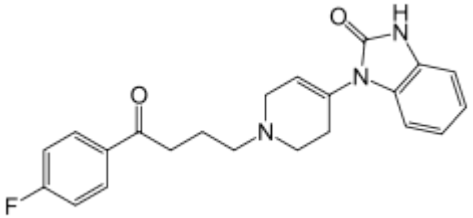
Antipsychotics - Butyrophenones

Haloperidol, the most widely used classical antipsychotic drug in this class
Droperidol, often used for neuroleptanalgesic anesthesia and sedation in intensive-care treatment
Benperidol, the most potent commonly used antipsychotic (200 times more potent than chlorpromazine)



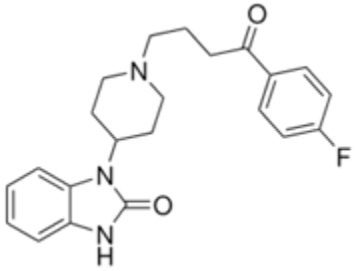
Haloperidol (Haldol)

4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidyl]
-1-(4-fluorophenyl)-butan-1-one



Droperidol (Innovar)

1-{1-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,5,6-
tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one

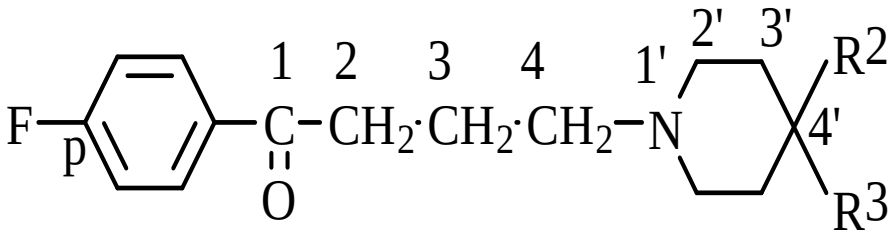


Benperidol

1-{1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl}-
1,3-dihydro-2*H*-benzimidazol-2-one

Structure Activity Relationships of Butyrophenones

All butyrophenone derivatives displaying high antipsychotic activity have the following general structure:

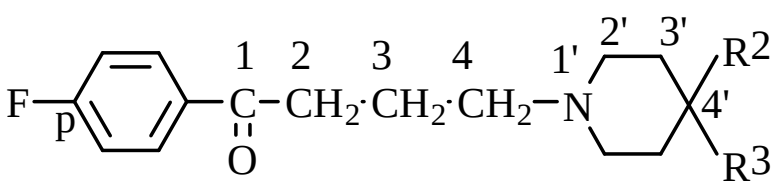


•*p*-fluorobutyrophenone skeleton is essential for neuroleptic activity.

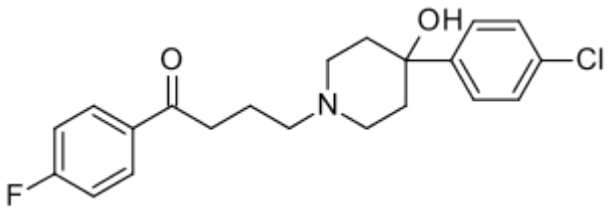
• All potent compounds have a fluorine substituent in the *para* position of the benzene ring. Replacing F with other groups like Cl-, Br-, -OCH_3 decreases activity

Structure Activity Relationships of Butyrophenones

- Replacement of the keto group by a thioketone group decreases neuroleptic activity.
- Reduction of the keto group to alcohol decreases potency.
- Lengthening, shortening, or branching of the three carbon (propyl) chain decreases neuroleptic potency.
- Variations are possible in the tertiary amino group without loss of neuroleptic potency. Nitrogen atom is usually incorporated into a six membered ring (piperidine, tetrahydropyridine, or piperazine), which usually has another substituent in position 4.
- R2 group should be aromatic. R3 group helps with activity, could be a –OH group as in the case of haloperidol.

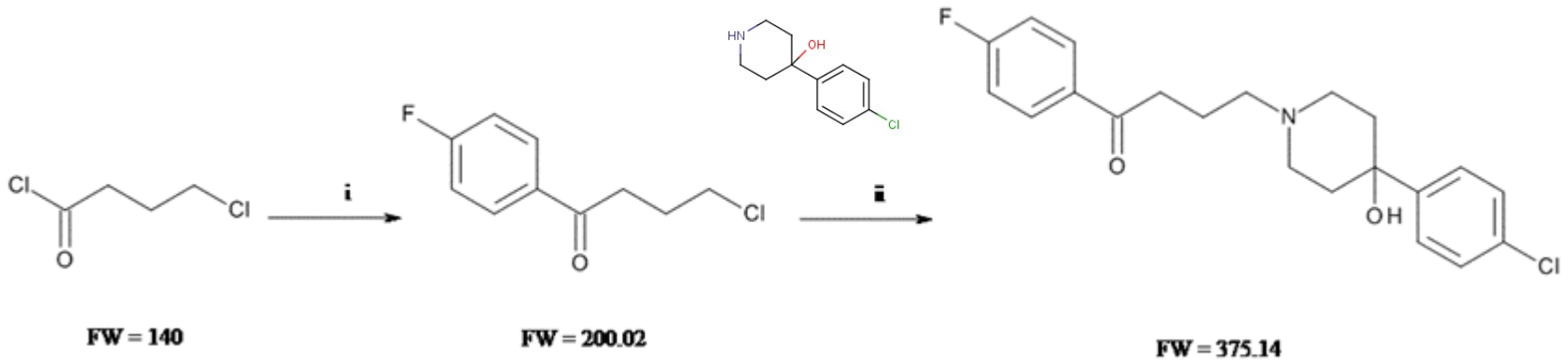


haloperidol



Synthesis of Haloperidol

4-chlorobutanoyl chloride 1 was reacted with fluorobenzene in presence of aluminum chloride using carbon disulfide as solvent at ambient temperatures to give 4-chloro-1-(4-fluorophenyl)butan-1-one.
Heating this compound with 4-(p-chlorophenyl)piperadine-4-ol in presence of potassium iodide as catalyst and toluene as solvent affords **Haloperidol.**

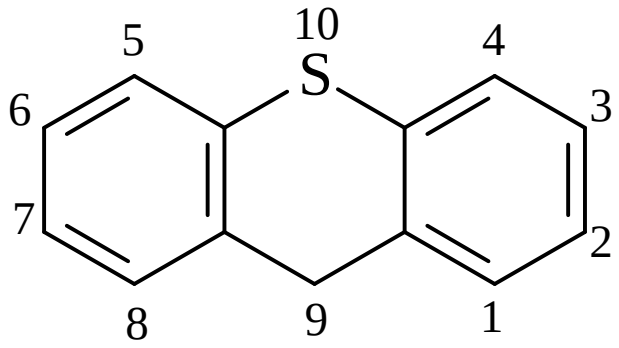


FW = 140 FW = 200.02 FW = 375.14

Conditions:

i. Fluorobenzene, aluminum chloride, carbon disulfide, room temperature, 2 h,
ii. 4-(p-chlorophenyl)piperadine-4-ol, potassium iodide, toluene, 100 - 110 ºC

Antipsychotics – Thioxanthene Derivatives



• Structurally related to phenothiazine derivatives, they resulted from isosteric replacement in chlorpromazine and analogs.

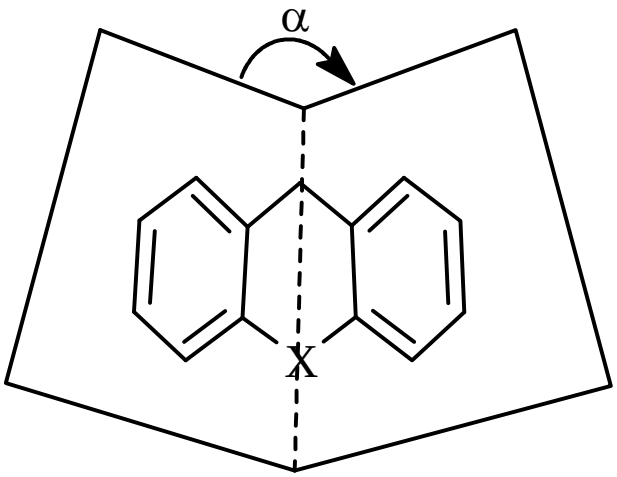
• Their pharmacological actions and adverse effects are very similar to those of phenothiazine derivatives.

• Examples include **chlorprothixene, flupentixol, and thiothixene**.

Structure Activity Relationships of Thioxanthene Derivatives

The structure-activity relationship of the thioxanthene mimic that of the phenothiazines:

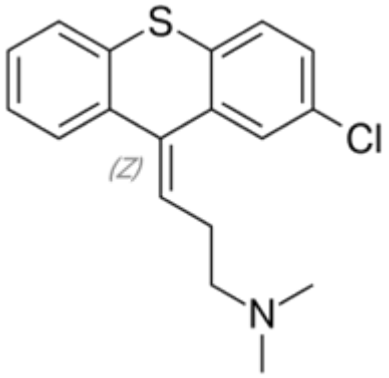
• The thioxanthene ring is also nonplanar: the angle between the two phenyl planes is 142^{o} in chlorprothixene, 150^{o} in flupentixol, and 142^{o} in thiothixene.

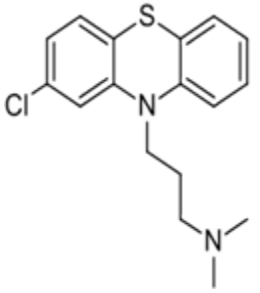


Thioxanthene Derivatives

✓ **Chlorprothixene** (**Cloxan**, **Taractan**, **Truxal**) is a typical antipsychotic drug of the thioxanthene class and was the first of the series to be synthesized

✓ Cis thioxanthene analog of chlorpromazine

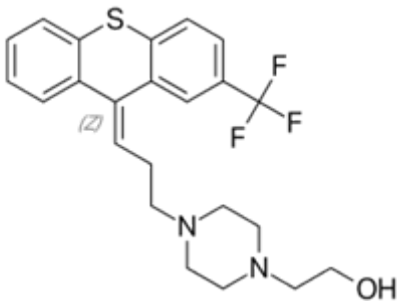


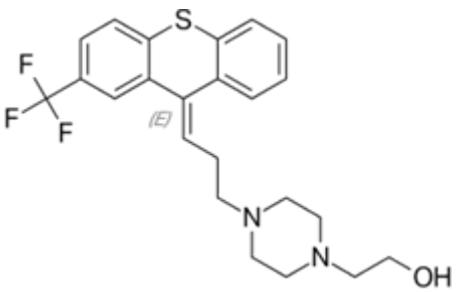


Chlorpromazine

(Z)-3-(2-chlorothioxanthen-9-ylidene)-*N*,*N*-dimethyl-propan-1-amine

✓ **Flupentixol**



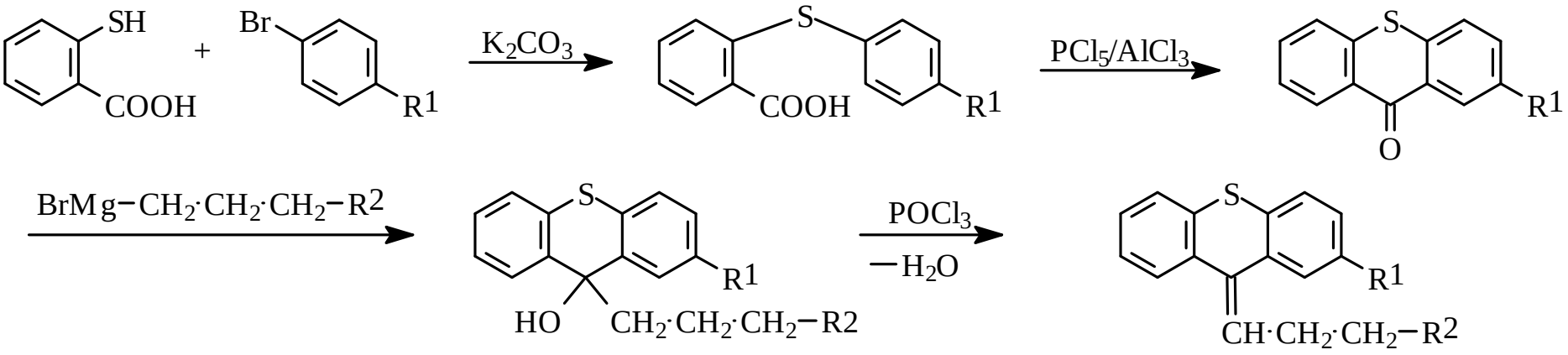


(EZ)-2-[4-[3-[2-(trifluoromethyl)thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethanol

Synthesis of Thioxanthene Derivatives

✓ 2-substituted-9*H*-thioxanthen-9-one is prepared by the reaction of 2-mercaptobenzoic acid and 4-substituted bromobenzene and following Friedel Crafts reaction in the presence of a strong Lewis acid catalyst (such as aluminium chloride).

✓ Then 2-substituted-9*H*-thioxanthen-9-one is combined with an appropriate alkyl magnesium bromide to give 9-alkyl-2-substituted-9*H*-thioxanthen-9-ol. Treatment with a dehydration agent gives the corresponding 9-propylidene derivative.



Atypical Antipsychotics

✓ Neuroleptics having dopamine receptor-blocking properties are frequently responsible for the development of movement disorders.

✓ **Atypical antipsychotics** are newer antipsychotic agents that have a pharmacological profile different from older or typical antipsychotic drugs.

✓ They cause **less extrapyramidal side effects** compared to the older typical antipsychotic drugs.

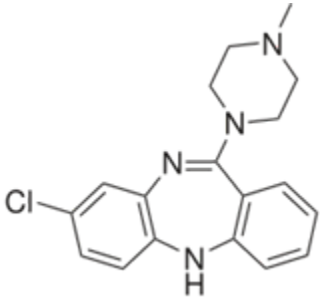
✓ They are more effective in treatment-resistant patients and have a greater efficacy to treat negative symptoms, compared to the typical antipsychotics.

✓ The three most accepted atypical drugs are; **clozapine, risperidone and olanzapine**

Atypical Antipsychotics

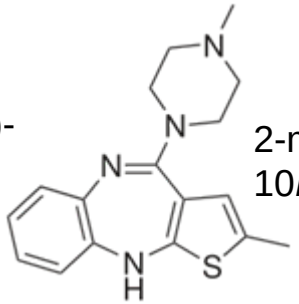
Clozapine is an medication used in the treatment of schizophrenia, and is also sometimes used off-label for the treatment of bipolar disorder. It is the first of the atypical antipsychotics to be developed.

Clozapine (Clozaril, FazaClo)



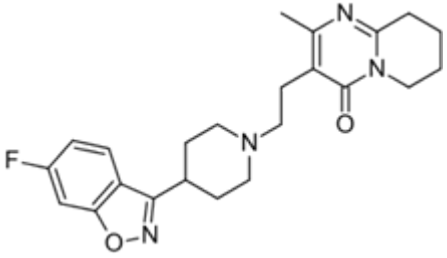
8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine

Olanzapine (Zyprexa)



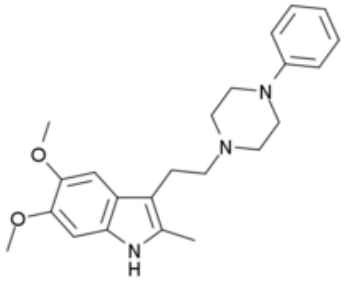
2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine

Risperidone (Risperdal)



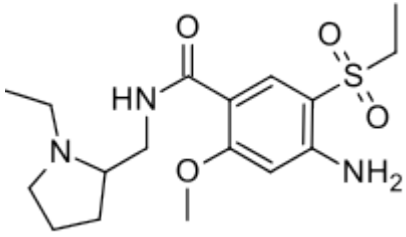
4-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one

Oxypertine (Equipertine, Forit)



5,6-dimethoxy-2-methyl-3-[2-(4-phenylpiperazin-1-yl)ethyl]-1*H*-indole

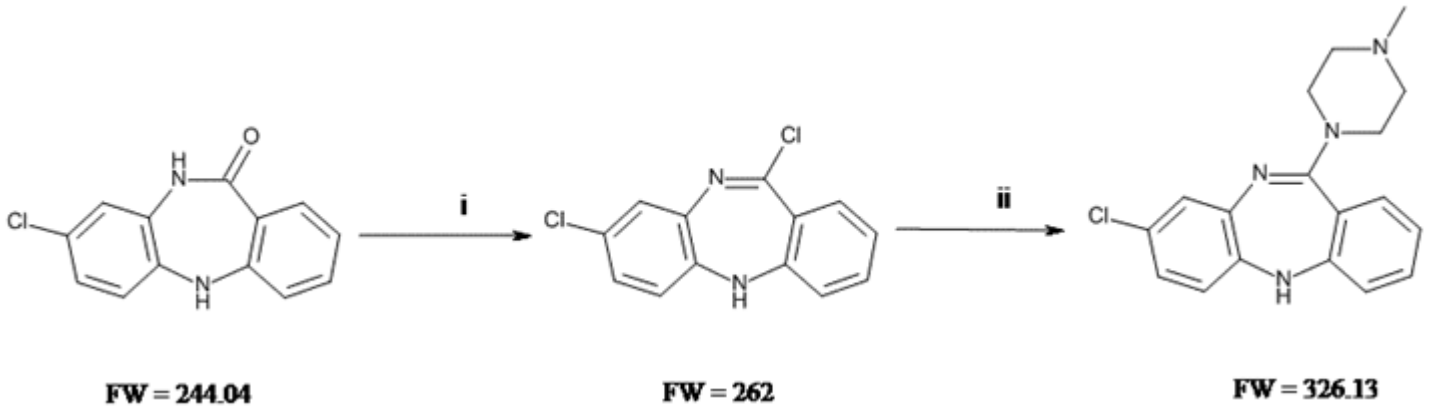
Amisulpride (Amipride , Amival, Sulpitac)



(*RS*)-4-amino-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-ethylsulfonyl-2-methoxy-benzamide

Synthesis of Clozapine

3-chloro-5,11-dihydrobenzo[b][1,4]benzodiazepin-6-one was treated with phosphoroxichloride in presence of dimethylformamide as catalyst using chloroform as solvent to give 3,6-dichloro-11H-benzo[b][1,4]benzodiazepine.
Treatment of this with N-methylpiperazine in refluxing dioxane affords **Clozapine**.



FW = 244.04 **FW = 262** **FW = 326.13**

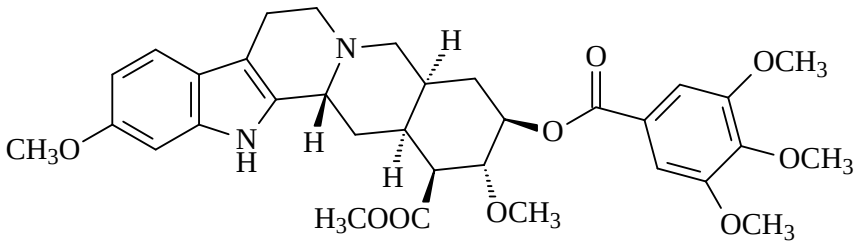
Conditions:

i. Phosphoroxichloride, Dimethylformamide, chloroform, reflux, 2 h,
ii. N-methylpiperazine, dioxane, reflux, 4 h

RESERPINE AND RELATED ALKALOIDS

Reserpine was isolated in 1952 from the dried root of *Rauwolfia serpentina* (Indian snakeroot) and is an indole alkaloid antipsychotic.
It is now mainly of historic interest in psychiatry.
It is less effective as a neuroleptic than the other drugs already discussed, and it is now used only on occasions when patients can not tolerate other classes of antipsychotic drugs.

Rezerpine



Rauvolfia serpentina