ANTI PSYCHOTIC DRUGS

Psychosis

- The psychoses affect approximately 1% of the population in all cultures.
- They are psychogenic mental disorders involving a loss of contact with reality.
- The psychotic disorders include **schizophrenia and the manic phase of bipolar** (manic–depressive) illness.
- The psychoses (eg: schizophrenia) are among the most severe mental illnesses.

Schizophrenia (Split-Mind)

- The most common is schizophrenia, in which perception, thinking, communication, social functioning, and attention are altered.
- Schizophrenia is defective dopamine neurotransmission relative excess of central dopaminergic activity.

Mechanism of action

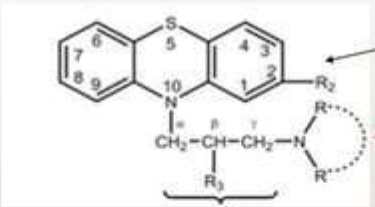
- The antipsychotic mechanism of action of neuroleptics involves modulation of dopamine neurotransmission in the mesolimbic- mesocortical pathway.
- This may achieve via direct D2 receptor interaction and include functional spectrum antagonism, inverse agonism and/or partial agonism.
- These drugs clinical efficacy however not only depends on D2 receptor interaction , other CNS system receptors are also involved (ach, histamine, norepinephrine and serotonin) appears to be involved , specially for the atypical drugs.

Classification of Antipsychotic Drugs

A) Typical Antipsychotics (more EPS, D2 blokage)	B) Atypical Antipsychotics (less EPS, D2 and 5HT2a blokage)	C) Both (Typical and Atypical)
1) Phenothiazine: **a) aliphatic:** Chlorpromazine Triflupromazine Promazine Levomepromazine **b) Piperidine:** Thioridazine Mesoridazine Pericyazine pipotiazine **c) Piperizine:** Fluphenazine Perphenazine Trifluoperazine	**1) Diphenylbutylpiperidine:** Pimozide	**1) Dihydroindolones:** Molindone
2) Thioxanthenes: Chlorprothixene Flupenthixol	**2) Benzioxazole:** Resperidone	**2) Benzamide:** Remoxipride
3) Fluorobutyrophenones: Haloperidol Droperidol	**3) Dibenzodiazepine:** Loxapine Clozapine	

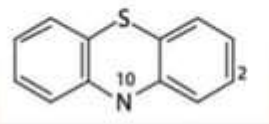
SARs of phenothiazines

- Phenothiazines have a tricyclic structure (6-6-6 system) in which two benzene rings are linked by sulfur and a nitrogen atom



1) Unsubstituted Phenothiazines has no activity but has enough lipophilicity for good brain penetration.

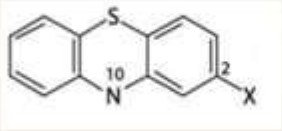
Substitution at C2 and N10 is required for activity.



Position 2

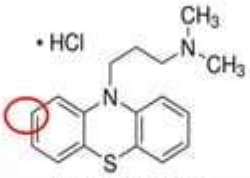
2) The best position for substitution is the 2-position. C2 must have an electrowithdrawing group.

- Activity increases as electron-withdrawing ability of the 2-substituent increases.
- The activity for these various group is as X = - SO2NR2 > -CF3 > -CO-CH3 > -Cl.

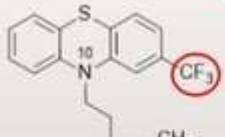


Position 2

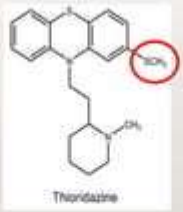
low antipsychotic activity



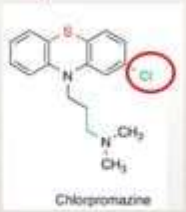
Promazine HCl



Triflupromazine



Thioridazine



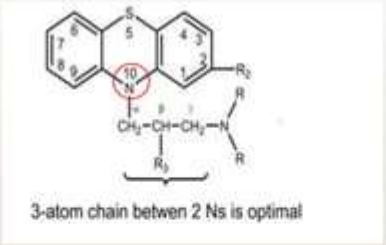
Chlorpromazine

Levomepromazine

Position 10

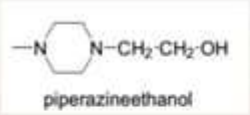
3) The three-carbon chain between position 10 and the aliphatic amino nitrogen is critical for neuroleptic activity.

- Shortening or lengthening the chain at this position drastically decreases the activity.
- The three-atom chain length may be necessary to bring the protonated amino nitrogen in proximity with the 2-substituent.
- Shortening the chain to two carbons has the effect of amplifying the antihistaminic and anticholinergic activities

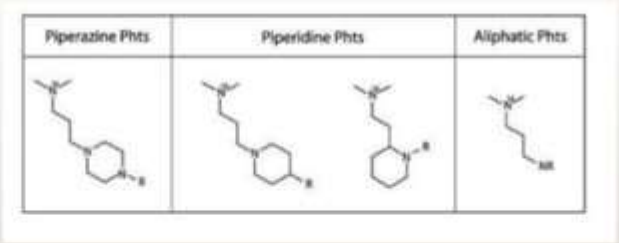


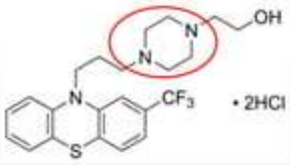
4) A terminal amino substituent must be present at N10. It can be piperazine, piperidine or aliphatic and their intensity could be ranked as follows:

Piperazine ethanol > piperazine group >piperidine group > aliphatic chain

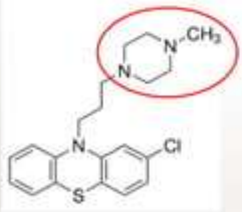


piperazineethanol

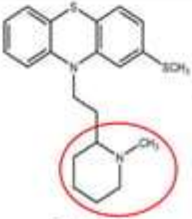




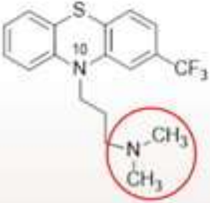
Fluphenazine HCl



Prochlorperazine



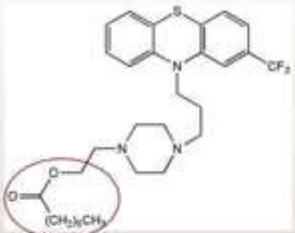
Thioridazine



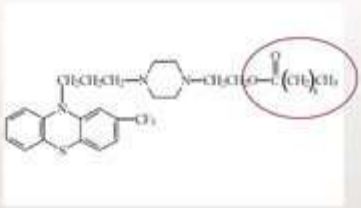
Triflupromazine

5) Esterification of the OH containing piperazine derivatives extensively increases the duration of action.

Long –acting neuroleptics for IM Depot injection

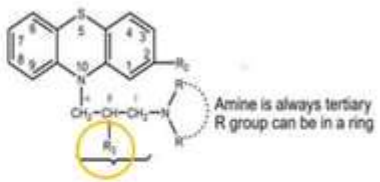


Fluphenazine enanthate

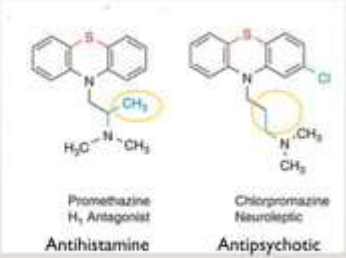


Fluphenazine decanoate

6)Methyl branching on the β-position has a variable effect on activity.



- There must be an linear (unbranched) alkyl linker between the core ring and the terminal amino ring those length is optimum at three methylene units CH2-CH2-CH2
- Reduction of these carbon number changes receptor affinity



7) The sulfur atom at position 5 is in a position analogous to the p-hydroxyl group of DA, and it was also assigned a receptor-binding function.

- In this conformation the aromatic ring and sulfur of phenothiazine correlates with the structure of dopamine (S with pOH of dopamine)

Chlorpromazine Hydrochloride:

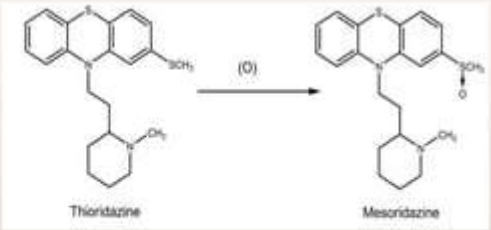
- Chlorpromazine was the first phenothiazine compound used in treatment of schizophrenia.
- It is still useful as an antipsychotic
- Other uses as antiemetic agent and against hiccups
- Has high incidence of Extra Pyramidal side effects .
- Oral doses of chlorpromazine and thioridazine have systemic availability of 25% to 35% because of significant first-pass metabolism.
- Chlorpromazine and other phenothiazines are metabolized extensively by CYP2D6.
- In contrast, bioavailability of chlorpromazine may be increased up to 10-fold with injections, but the clinical dose usually is decreased by only threefold to fourfold.
- It's metabolite has strong antiadrenergic, weak anticholinergic and slight antihistaminergic and antiserotonergic properties (not parent molecule).

MOA:

- It antagonizes Dopamine D2 in the Mesocortical and Mesolimbic pathway

Thioridazine Hydrochloride:

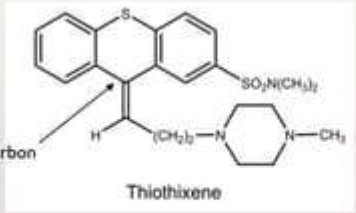
- The drug has high anticholinergic activity, and this activity in the striatum, counterbalancing a striatal DA block, may be responsible for the low EPS.
- The drug has sedative and hypotensive activity in common with chlorpromazine and less antiemetic activity.
- At high doses, pigmentary retinopathy has been observed.
- Its major metabolites include N-demethylated, ring hydroxylated, and S-oxidized products.
- Thioridazine is prominently converted to the active metabolite mesoridazine which probably contributes to the antipsychotic activity of thioridazine.



Thiothixene:

- The thioxanthene system differs from the phenothiazine system by replacement of the N-H moiety with a carbon atom doubly bonded to the propylidene side chain. With the substituent in the 2-position, Z-and E-isomers are produced.
- In accordance with the concept that the presently useful antipsychotics can be superimposed on DA, the Z-isomers are the more active antipsychotic isomers.
- The compounds of the group are very similar in pharmacological properties to the corresponding phenothiazines. Thus, thiothixene displays properties similar to those of the piperazine subgroup of the phenothiazines.

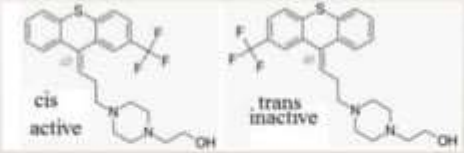
Replacement of the N-H moiety with a carbon atom doubly bonded



Thiothixene

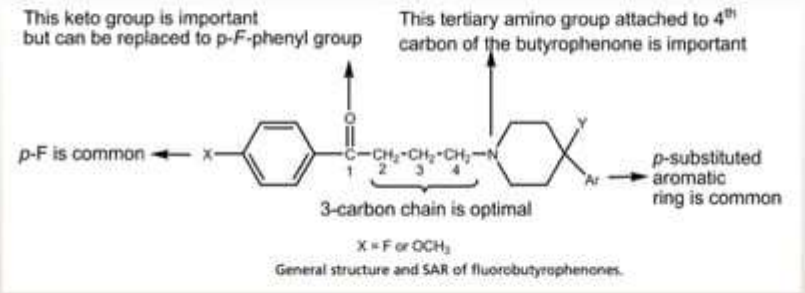
Flupenthixol ;

- It is a Thioxanthine derivative used for treatment of schizophrenia
- It can exist in cis and trans form and only cis is active because it mimics the conformation of Dopamine
- It's duration of action is long (2-3 weeks) and hence useful in patients who have a poor compliance with medication MOA- It is nonselective and antagonizes both Dopamine D1 and D2 in the Mesocortical and Mesolimbic pathway



Fluorobutyrophenones

SAR of Butyrophenones

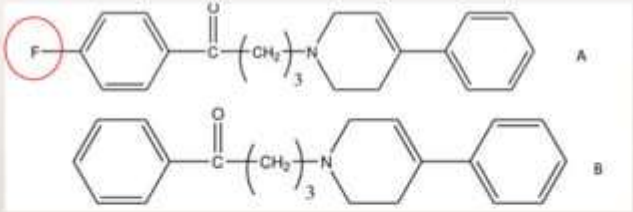


General structure and SAR of fluorobutyrophenones.

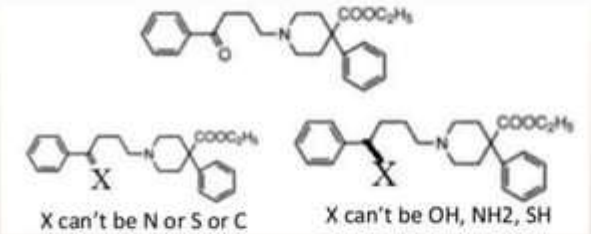
SAR of Butyrophenones

1) Modification of benzoyl group:

- Anything other than fluorine in the para position lowers activity
- A is 4 times more potent than B due to F

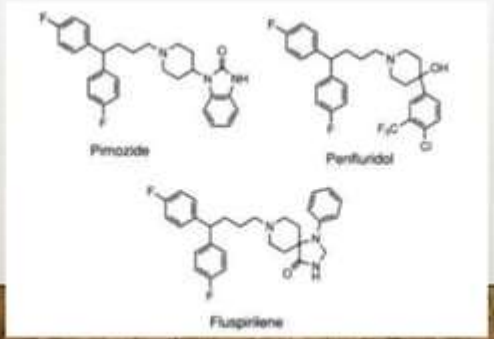


2) Replacing the carbonyl group with isoteric group or any other functional group lowers activity X can't be N or S or C X can't be OH, NH2, SH.



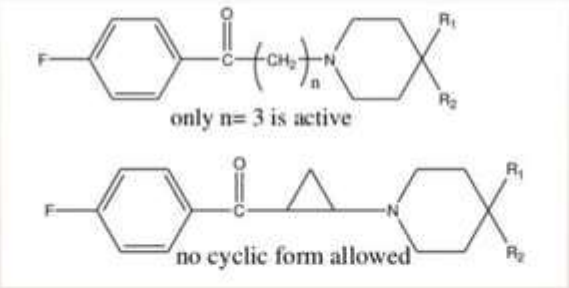
- **An important exception - Diphenylbutylpiperidines**
  - Replacement of the carbonyl of haloperidol with para fluro phenyl group creates a new class of compounds called **diphenylbutylpiperidines** that has following advantage:
- ✓ Long acting
- ✓ NO sedative, autonomic, extrapyrimidal side effects
- ✓ Useful in autism (Autism is a mental disorder in children characterized by impaired social interaction and verbal and non-verbal communication, and by repetitive behavior)

Diphenylbutylpiperidines
The keto group has been replaced with para Fluro group



3) Modification of the -CH2- linker group

- The linker has to be a propylene.
- Any alteration to the -CH2- linker region such as shortening, lengthening, branching, or incorporation into a ring system, results in a marked decrease or even complete loss of neuroleptic activity.

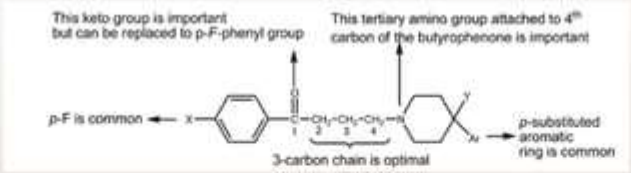


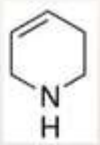
4) Modification of the amino group

a) A tertiary amino group should be present

b) A tertiary amine in some cyclic form (piperidine, tetrahydropyridine or piperazine ring) increases potency

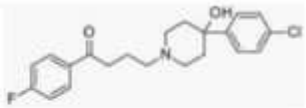
c) Further modification of the ring at para position can de done for better potency and reducing toxicity





tetrahydropyridine

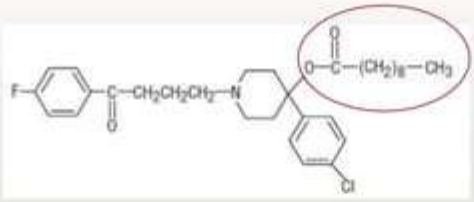
Haloperidol, (Haldol):



- It is a Butyrophenone derivative used in the treatment of schizophrenia , delirium and in psychoses associated with brain damage.
- It can also help prevent suicide in people who are likely to harm themselves. It also reduces aggression and the desire to hurt others. It can decrease negative thoughts and hallucinations.
- It has High incidences of Extra Pyrimidal Side effects (EPS – tremor and motor dysfunction) but Low hypotension and low autonomic side effects and sedative effects lower than Chlorpromazine.

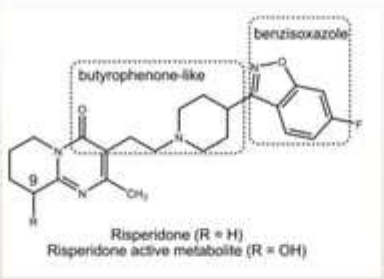
Haloperidol decanoate

- Decanoate Esterifation at the OH group forms a long acting derivative .
- Haloperidol decanoate is used for long-term treatment of a certain mental/mood disorder (schizophrenia).
- It may be used in people who have trouble remembering to take medication every day.
- This medicine helps you to think more clearly, feel less nervous, and take part in everyday life



Risperidone (Risperdal, a benzisoxazole):

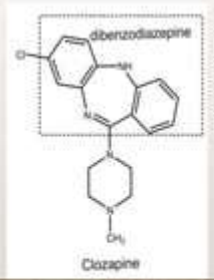
- Risperidone has the structural features of a hybrid molecule between a butyrophenone antipsychotic and a trazodone-like antidepressant. It is an important atypical antipsychotic.



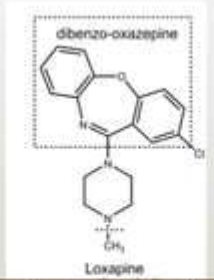
Ring Analogs of Phenothiazines:

Benzazepines, Dibenzoxazepines, and Dibenzodiazepines:

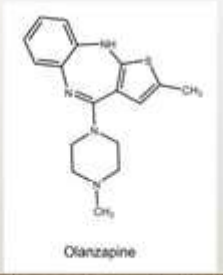
- Additional tricyclic antipsychotic agents are the benzazepines, containing a seven-membered central ring (6-7-6 system).
- These newer atypical antipsychotics include dibenzodiazepines (clozapine with 2-Cl), dibenzoxazepines (loxapine with 2-Cl), thienobenzodiazepines (olanzapine without 2-substituent), and dibenzothiazepines (quetiapine without 2-substituent)



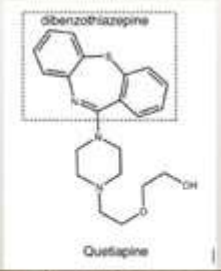
Clozapine



Loxapine



Olanzapine



Quetiapine

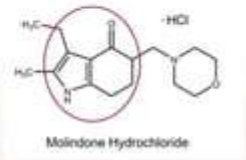
5-THA2A - D2 block

Both (Typical and Atypical):

Dihydroindolones:

- **Molindone Hydrochloride.**

- Molindone hydrochloride (Moban) is about as potent an antipsychotic as trifluoperazine. Overall, side effects resemble those of the phenothiazines.

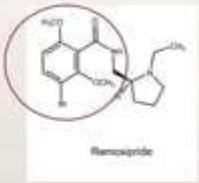


Molindone Hydrochloride

Benzamides:

- **Remoxipride (Roxiam).**

- Remoxipride is a D_2 receptor blocker. It is as effective as haloperidol with fewer EPS
- . Negative symptoms of schizophrenia are diminished.
- The drug is classed as an atypical antipsychotic. Life-threatening aplastic anemia was reported with its use, which prompted its withdrawal from the market.


Remoxipride