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Antipsychotics

Presented By;-

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Specialization:- Pharmaceutical Chemistry

Antipsychotics

Antipsychotics (also called **neuroleptics** or **major tranquilizers**) are drugs *used to treat* psychotic disorders, especially **schizophrenia**, **bipolar disorder**, **delusions**, and **hallucinations**.

Classification of Antipsychotics

1. **Phenothiazines:-** Promazine hydrochloride, Chlorpromazine hydrochloride*, Triflupromazine, Thioridazine hydrochloride, Piperacetazine hydrochloride, Prochlorperazine maleate, Trifluoperazine hydrochloride.
2. **Ring Analogues of Phenothiazines:-** Chlorprothixene, Thiothixene, Loxapine succinate, Clozapine.
3. **Fluro buterophenones:-** Haloperidol, Droperidol, Risperidone.
4. **Beta amino ketones:-** Molindone hydrochloride.
5. **Benzamides:-** Sulpieride.

Phenothiazines

Introduction

Phenothiazines are a major class of **typical antipsychotic drugs** (first-generation antipsychotics).

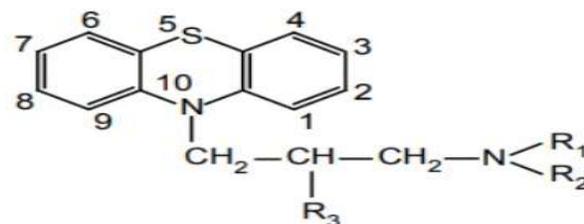
They are primarily used to treat:

- ✓ Schizophrenia
- ✓ Psychosis
- ✓ Severe nausea/vomiting
- ✓ Intractable hiccups
- ✓ Preoperative sedation

Mechanism of Action

- I. Phenothiazines
↓
- II. Block **D₂ receptors** in mesolimbic pathway
↓
- III. reduce Dopamine transmission
↓
- IV. Relief of positive symptoms of schizophrenia
(Hallucinations, delusions, agitation)

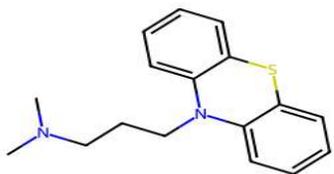
SAR of Phenothiazines



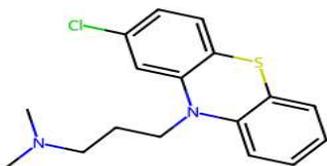
Structural Feature	Relationship to Activity (Antipsychotic)	Details
C-2 Position Substituent	Activity is increased by electron-withdrawing groups	Potency order: $-\text{SO}_2\text{NR}_2 > -\text{CF}_3 > -\text{CO}-\text{CH}_3 > -\text{Cl}$. The most potent position for substitution is the 2-position of the ring.
N-10 Position Side Chain Length	Optimal activity requires a specific chain length	A three-carbon chain (propyl bridge) between the N-10 atom and the terminal amino group is essential for optimal neuroleptic activity. Shortening the chain to two carbons changes the activity profile (e.g., antihistamine activity).
Terminal Amino Group	Must be a tertiary amine	The amino function must be tertiary for maximum activity. Primary and secondary amines are less potent.
Terminal Amino Group Substituents	Small substituents are preferred	Alkylation of the amino group with groups larger than methyl decreases antipsychotic activity.
Phenothiazine Ring System	Tricyclic ring is required	The central C_4SN ring of the phenothiazine nucleus is typically bent or folded. The basic structure is important for receptor binding.
Piperazine/Piperidine Rings	Activity varies with substitution	Compounds containing a piperazine or piperidine ring are generally less potent than dimethylamino derivatives, but substitution at the 4th position (e.g., by a hydroxyethyl group) can substantially increase activity.

A. Phenothiazine Antipsychotics

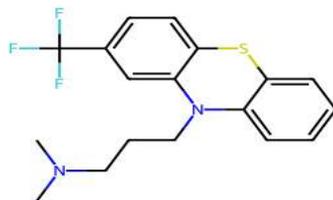
Drug	Introduction	Mechanism of Action (MOA)	Uses
Promazine hydrochloride	Aliphatic phenothiazine; low-potency antipsychotic; highly sedative.	Blocks D ₂ receptors in mesolimbic pathway → reduces dopamine activity.	Mild–moderate psychosis, agitation, pre-operative sedation.
Chlorpromazine hydrochloride*	Prototype phenothiazine; low-potency; strong sedative and anticholinergic actions.	D ₂ receptor blockade; also blocks α ₁ , H ₁ , M ₁ receptors → sedation & hypotension.	Schizophrenia, mania, agitation, intractable hiccups, nausea/vomiting.
Triflupromazine	Trifluoromethyl-substituted phenothiazine; more potent than chlorpromazine.	Potent D ₂ antagonist + α ₁ & H ₁ blockade.	Schizophrenia, severe agitation, antiemetic use.
Thioridazine hydrochloride	Piperidine phenothiazine; low EPS, high anticholinergic effect.	D ₂ receptor blockade; moderate 5-HT antagonism.	Schizophrenia, psychosis with anxiety; fewer EPS.
Piperacetazine hydrochloride	Piperazine-substituted phenothiazine; high potency.	Strong D ₂ antagonism; less sedation.	Schizophrenia, severe psychotic disorders.
Prochlorperazine maleate	Piperazine derivative; strong antiemetic; moderate antipsychotic.	Potent D ₂ blockade, especially in the chemoreceptor trigger zone (CTZ).	Nausea/vomiting, vertigo, schizophrenia (moderate).
Trifluoperazine hydrochloride	High-potency piperazine phenothiazine; strong antipsychotic.	Strong D ₂ blockade in mesolimbic pathway; minimal sedation.	Schizophrenia, severe anxiety, acute psychosis.



Promazine HCl



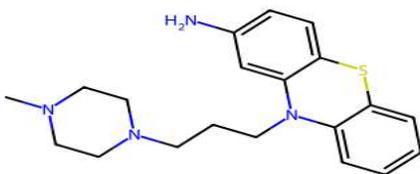
Chlorpromazine HCl



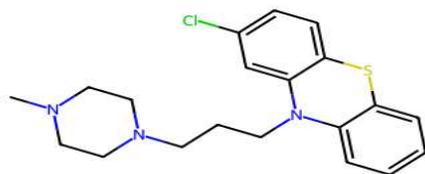
Triflupromazine



Thioridazine HCl



Piperacetazine HCl

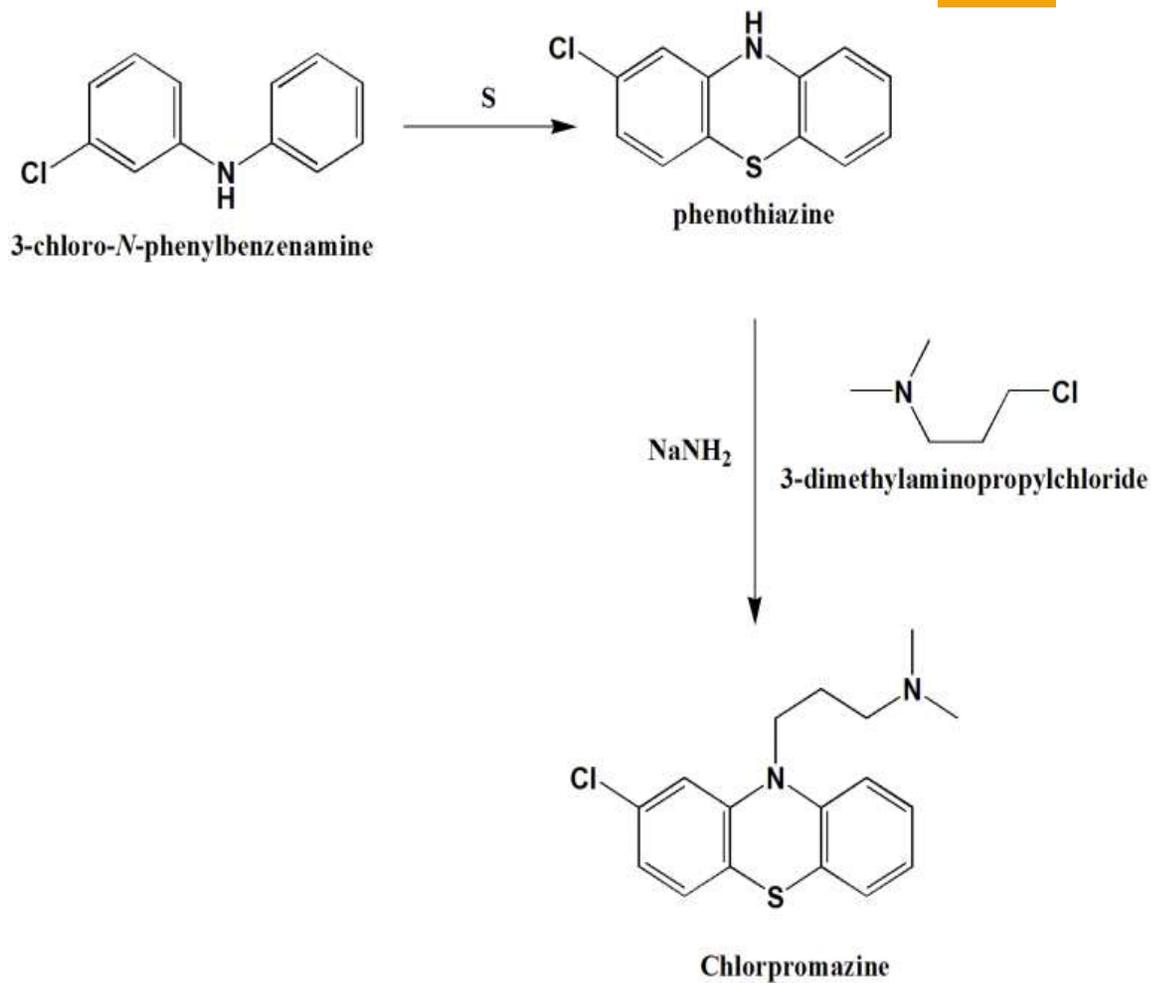


Prochlorperazine maleate



Trifluoperazine HCl

Synthesis of Chlorpromazine



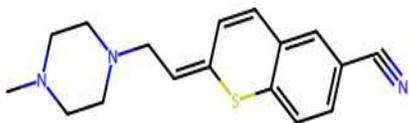


B. Ring Analogues of Phenothiazines

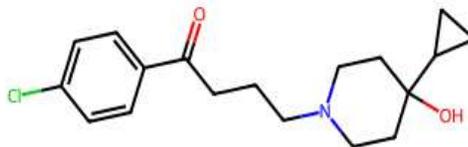
Drug	Introduction	Mechanism of Action (MOA)	Uses
Chlorprothixene	Thioxanthene analogue of phenothiazines; moderate-potency antipsychotic.	Blocks D ₂ receptors; also blocks H ₁ , M ₁ , and α ₁ receptors → sedation, hypotension.	Schizophrenia, agitation, acute mania.
Thiothixene	Potent thioxanthene antipsychotic; stronger than chlorprothixene.	High-potency D ₂ receptor antagonist in mesolimbic pathway.	Schizophrenia, severe psychotic disorders.
Loxapine succinate	Dibenzoxazepine derivative; intermediate atypical antipsychotic.	Blocks D ₂ and 5-HT _{2A} receptors.	Schizophrenia, bipolar agitation.
Clozapine	Prototype atypical antipsychotic from dibenzodiazepine class; low EPS.	Strong 5-HT _{2A} blockade, weak D ₂ blockade; high affinity for D ₄ receptors.	Treatment-resistant schizophrenia, suicidal behavior in schizophrenia.



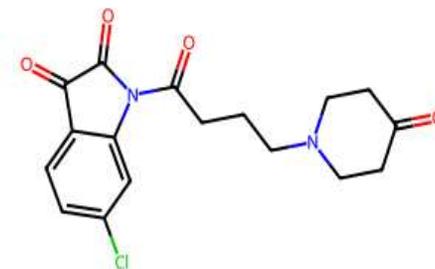
Chlorprothixene



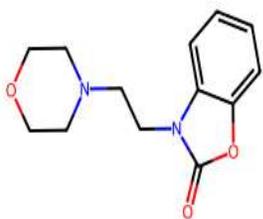
Thiothixene



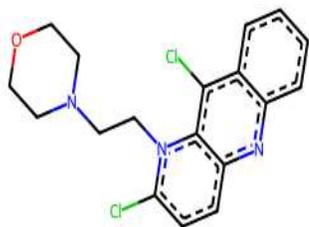
Haloperidol



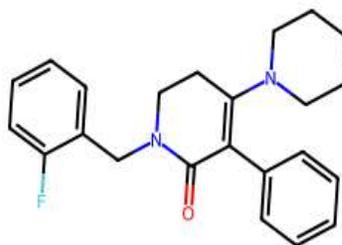
Droperidol



Loxapine



Clozapine



Risperidone



Molindone HCl

B. Fluorobutyrophenones

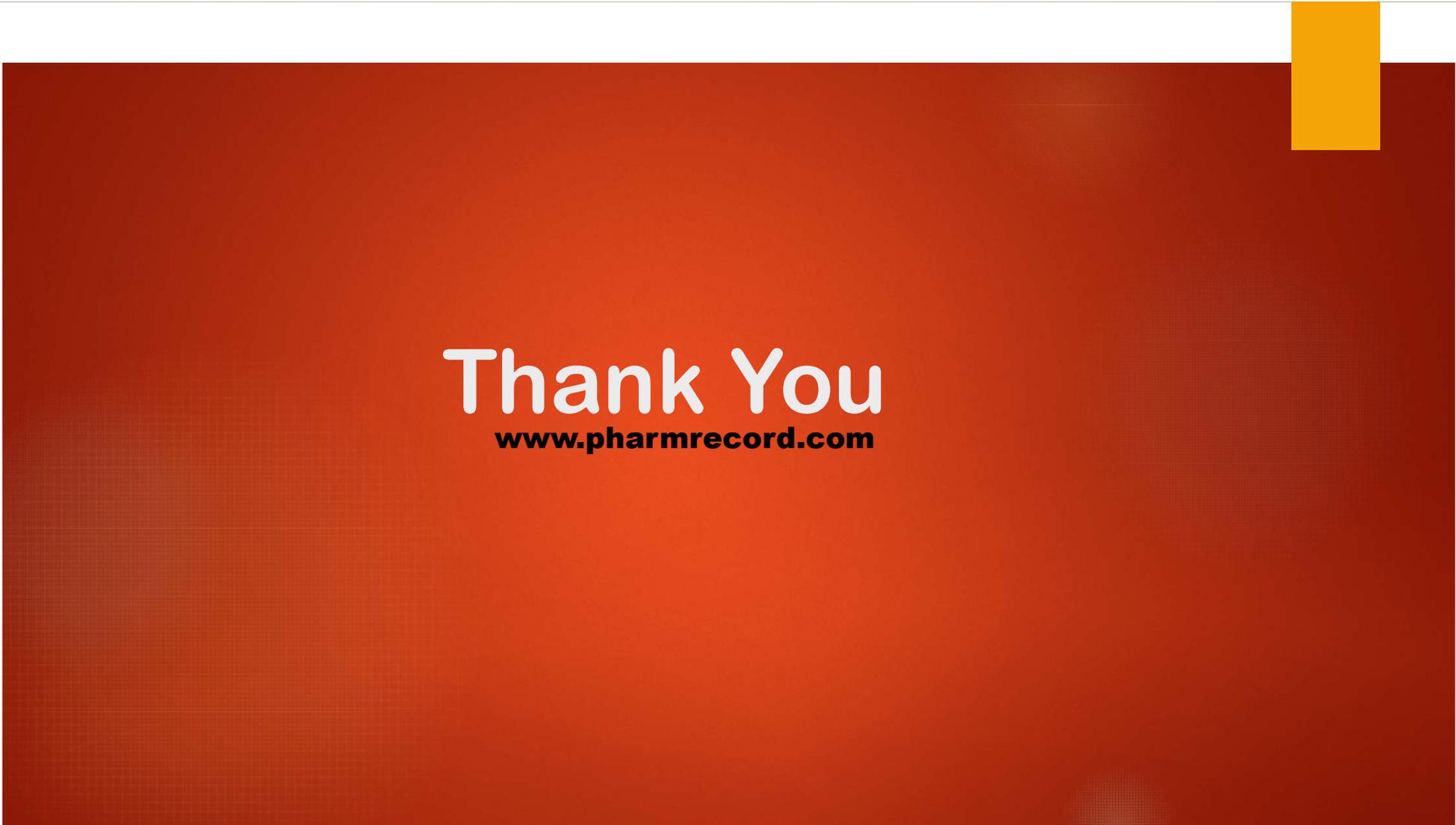
Drug	Introduction	Mechanism of Action	Uses
Haloperidol	High-potency typical antipsychotic; major representative of butyrophenones.	Strong D ₂ receptor antagonist; minimal anticholinergic effect.	Schizophrenia, acute psychosis, mania, Tourette's syndrome.
Droperidol	Potent butyrophenone; used mainly in anesthesia.	D ₂ blockade + sedation via H ₁ & α-blockade.	Neuroleptanalgesia (with fentanyl), antiemetic, agitation.
Risperidone	Atypical antipsychotic with high potency; benzisoxazole derivative.	Blocks D ₂ and 5-HT _{2A} receptors strongly.	Schizophrenia, bipolar disorder, aggression in autism.

C. Beta-Amino Ketones

Drug	Introduction	MOA	Uses
Molindone hydrochloride	Indole-based antipsychotic; moderate potency; weight-neutral.	Primarily D ₂ receptor blockade; mild 5-HT ₂ effects.	Schizophrenia, psychosis (less weight gain than others).

D. Benzamides

Drug	Introduction	MOA	Uses
Sulpiride	Substituted benzamide; atypical antipsychotic with low EPS.	Selective D ₂ and D ₃ receptor antagonist.	Schizophrenia (negative symptoms), depression, somatic symptom disorders.



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