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MEDICINAL CHEMISTRY – I

UNIT 4

TOPIC :

- **B. Antipsychotics**

  Phenothiazeines : SAR of Phenothiazeines- Promazine hydrochloride, Chlorpromazine hydrochloride*, Triflupromazine, Thioridazine hydrochloride, Piperacetazine hydrochloride, Prochlorperazine maleate, Trifluoperazine hydrochloride.

  Ring Analogues of Phenothiazeines : Chlorprothixene, Thiothixene, Loxapine succinate, Clozapine.

  Fluro buterophenones : Haloperidol, Droperidol, Risperidone.

  Beta amino ketones : Molindone hydrochloride.

  Benzamides : Sulpieride

Antipsychotics (Neuroleptics / Major Tranquilizers)

- Antipsychotics are drugs that produce a specific sedative effect and improve attitude, calm behavior, and reduce agitation in psychotic patients.
- They are also called neuroleptics or major tranquilizers.
- They do not cure the disorder but reduce symptoms such as hallucinations, delusions, thought disturbances, and aggression.

Psychosis

- A severe mental disorder characterized by a loss of contact with reality.
- Causes / Types of Psychotic Disorders:
  - Schizophrenia
  - Bipolar disorder (mania with psychosis)
  - Psychotic depression
  - Schizoaffective disorder
  - Drug-induced psychosis (e.g., due to LSD, amphetamines, cocaine)

Classification of Antipsychotics

1. **Phenothiazines** (Tricyclic antipsychotics)
   - Promazine hydrochloride
   - Chlorpromazine hydrochloride
   - Trifluprомazine
   - Piperacetazine hydrochloride
   - Thioridazine hydrochloride
   - Prochlorperazine maleate
   - Trifluoperazine
2. **Ring Analogues of Phenothiazines**
   - Chlorprothixene
   - Thiothixene
   - Loxapine succinate
   - Clozapine

3. **Butyrophenones**
    - Haloperidol
    - Droperidol
    - Risperidone
4. **Butylamino ketones**
    - Molindone hydrochloride
5. **Benzamides**
    - Sulpiride

Phenothiazines

- Oldest class of antipsychotics, also called **tricyclic antipsychotics**.

Mechanism of Action

- They are non-selective, competitive antagonists at dopamine (D1, D2) receptors in the brain.
- Blockade of D2 receptors in mesolimbic pathway reduces positive symptoms (hallucinations, delusions).
- They also have moderate sedative and antiemetic effect (due to chemoreceptor trigger zone blockade).

Examples

- Promazine hydrochloride
- Chlorpromazine hydrochloride
- Piperacetazine hydrochloride
- Trifluprομazine
- Thioridazine hydrochloride
- Prochlorperazine maleate
- Trifluoperazine

SAR of Phenothiazines

1. **Tricyclic Ring System**
    - The phenothiazine nucleus is essential for activity.

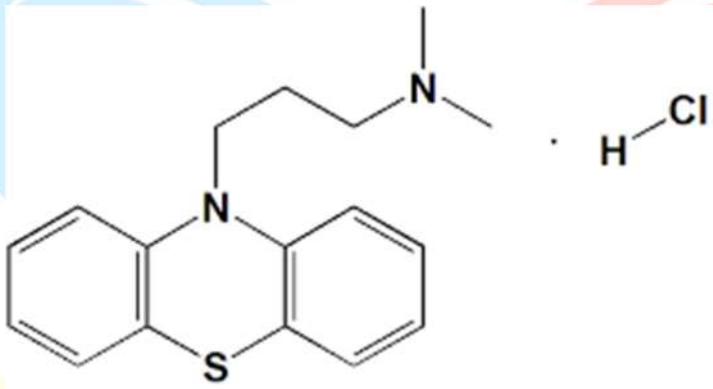
- Consists of two benzene rings linked by a central ring containing sulfur and nitrogen atoms.

2. **Substitution at Position-2**
   - An electron-withdrawing group (e.g., –Cl, $–CF_3$) at position-2 increases potency by enhancing receptor binding.
3. **Side Chain at Nitrogen (N-10 position)**
   - A 3-carbon side chain ending in a terminal amine is essential for activity.
   - The nature of the terminal amine determines subtype of phenothiazine:
     - Aliphatic side chain → more sedative, less potent (e.g., Chlorpromazine).
     - Piperidine side chain → moderate potency, less EPS (e.g., Thioridazine).
     - Piperazine side chain → highly potent, more EPS (e.g., Trifluoperazine, Prochlorperazine).

Promazine Hydrochloride

Structure

- Chemical class: Phenothiazine derivative.
- Tricyclic structure: two benzene rings fused to a central thiazine ring containing sulfur and nitrogen.
- Substituted at position 2 (electron-withdrawing groups can increase potency) and N-10 side chain (3-carbon chain ending with terminal amine).



Promazine hydrochloride

Mechanism of Action (MOA)

- Blocks dopamine D1 and D2 receptors in CNS → reduces dopaminergic transmission.
- Produces antipsychotic effects: sedation, calming of agitated patients, and reduction of hallucinations/delusions.
- Also has antiemetic activity via dopamine receptor blockade in the chemoreceptor trigger zone (CTZ).

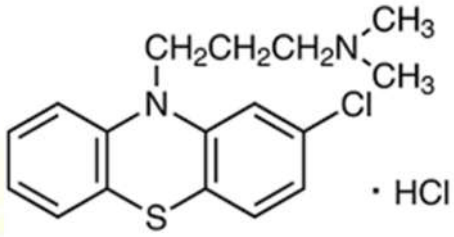
Therapeutic Uses

- Psychotic disorders (schizophrenia, acute psychosis).
- Agitation and anxiety.
- Antiemetic in nausea and vomiting (less commonly used today).

Chlorpromazine Hydrochloride

Structure

- Chemical class: Phenothiazine derivative.
- Tricyclic structure: Two benzene rings fused to a central thiazine ring containing sulfur and nitrogen.
- Substitutions:
  - Chlorine atom at position 2 → increases potency.
  - N-10 side chain: 3-carbon chain ending in a terminal amine.



Mechanism of Action (MOA)

- Non-selective dopamine receptor antagonist (blocks D1 and D2 receptors in CNS).
- Reduces dopaminergic activity, leading to:
  - Sedation
  - Antipsychotic effect (reduces hallucinations, delusions, agitation)
  - Antiemetic action via blockade at the chemoreceptor trigger zone (CTZ)
- Also has mild anticholinergic and antihistaminic effects.

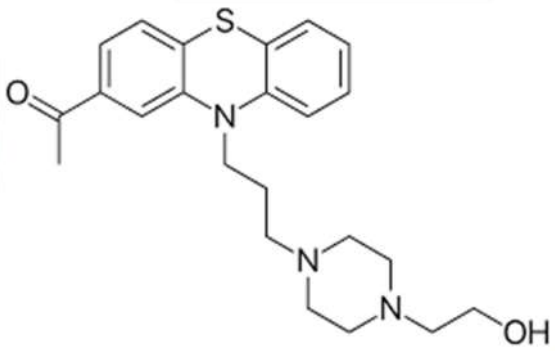
Therapeutic Uses

- Schizophrenia and other psychotic disorders.
- Acute mania and agitation.
- Nausea and vomiting (antiemetic, less commonly used today).
- Hiccups (refractory cases).

Piperacetazine Hydrochloride

Structure

- Chemical class: Phenothiazine derivative.
- Tricyclic structure: Two benzene rings fused to a central thiazine ring containing sulfur and nitrogen.
- Substitutions:
  - N-10 side chain contains a 3-carbon linker ending with a terminal amine.
  - Lacks substitution at position 2, giving slightly different potency and side effect profile compared to other phenothiazines.



Mechanism of Action (MOA)

- Dopamine receptor antagonist (primarily D2 blockade) in the CNS.
- Reduces dopaminergic neurotransmission → antipsychotic effect:
  - Calms agitation
  - Reduces hallucinations and delusions
- Also exhibits anticholinergic, antihistaminic, and sedative effects to varying degrees.

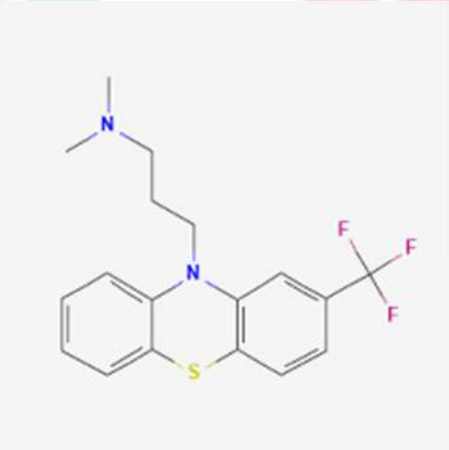
Therapeutic Uses

- Schizophrenia and other psychotic disorders.
- Severe agitation and behavioral disturbances.
- Less commonly used today due to side effect profile compared to newer antipsychotics.

Triflupromazine

Structure

- Chemical class: Phenothiazine derivative.
- Tricyclic structure: Two benzene rings fused to a central thiazine ring containing sulfur and nitrogen.
- Substitutions:
  - Trifluoromethyl (-CF_3) group at position 2 → increases potency.
  - N-10 side chain: 3-carbon chain ending with terminal amine.



Mechanism of Action (MOA)

- Non-selective dopamine D1 and D2 receptor antagonist in CNS.
- Reduces dopaminergic activity, producing:
  - Antipsychotic effects (reduces hallucinations, delusions, agitation)
  - Sedation
  - Antiemetic action via CTZ dopamine blockade
- Mild anticholinergic and antihistaminic effects also present.

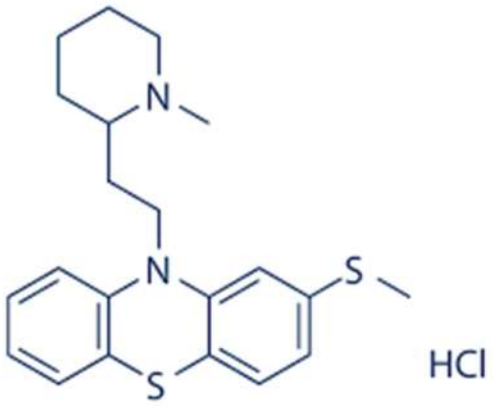
Therapeutic Uses

- Schizophrenia and psychotic disorders.
- Severe agitation or behavioral disturbances.
- Nausea and vomiting (less commonly used today).

Thioridazine Hydrochloride

Structure

- Chemical class: Phenothiazine derivative.
- Tricyclic structure: Two benzene rings fused to a central thiazine ring containing sulfur and nitrogen.
- Substitutions:
  - Piperidine side chain at N-10 → contributes to sedative and antipsychotic activity.
  - Lacks electron-withdrawing substituents at position 2 → lower potency but more sedative properties.



Mechanism of Action (MOA)

- Dopamine D1 and D2 receptor antagonist in the CNS.
- Reduces dopaminergic activity, producing:
  - Antipsychotic effect (reduces hallucinations, delusions, agitation)
  - Sedation (more pronounced than many other phenothiazines)
- Also exhibits anticholinergic, antihistaminic, and alpha-adrenergic blocking effects → contributes to side effects like dry mouth, hypotension.

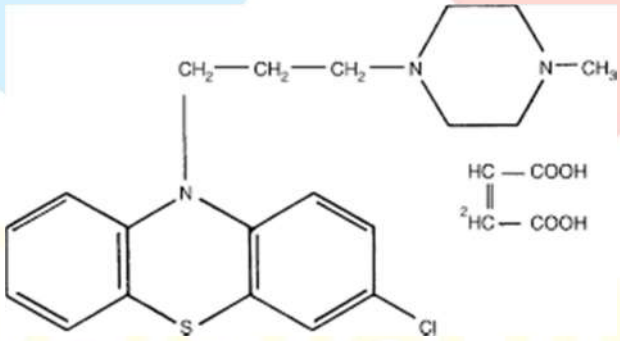
Therapeutic Uses

- Schizophrenia, particularly with prominent agitation or aggression.
- Psychotic disorders where sedative effect is desirable.
- Historically used for severe behavioral disturbances, but limited today due to cardiotoxicity (QT prolongation) risk.

Prochlorperazine Maleate

Structure

- Chemical class: Phenothiazine derivative.
- Tricyclic structure: Two benzene rings fused to a central thiazine ring containing sulfur and nitrogen.
- Substitutions:
  - Piperazine side chain at N-10 → contributes to potent antipsychotic and antiemetic activity.
  - No electron-withdrawing group at position 2 → slightly lower sedation compared to other phenothiazines.



Mechanism of Action (MOA)

- Dopamine D2 receptor antagonist in the CNS.
- Blocks dopaminergic transmission in the chemoreceptor trigger zone (CTZ) → antiemetic effect.
- Reduces dopaminergic activity in the mesolimbic pathway → antipsychotic effect.
- Mild anticholinergic and antihistaminic activity may occur.

Therapeutic Uses

- Nausea and vomiting, especially post-operative or chemotherapy-induced.
- Schizophrenia and other psychotic disorders, particularly with agitation.
- Occasionally used for severe anxiety or behavioral disturbances.

Ring Analogues of Phenothiazines

- Ring analogues are compounds that have a similar tricyclic ring system to phenothiazines but with slight structural modifications in the central ring.
- These changes lead to differences in receptor selectivity, potency, and side effect profile.
- They are used as antipsychotics in the treatment of schizophrenia, bipolar disorder, and other psychotic illnesses.

Mechanism of Action

- Primarily act by blocking dopamine D_2 receptors in the mesolimbic pathway → reduces positive symptoms of psychosis (hallucinations, delusions).
- Some analogues also act on serotonin (5-HT_2), histamine (H_1), and adrenergic receptors, which:
  - Improves mood and sleep.
  - Reduces aggression and anxiety.
  - Causes side effects like sedation, weight gain, or orthostatic hypotension.

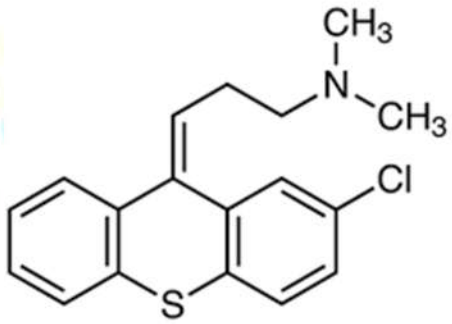
Examples

1. Chlorprothixene
2. Thiothixene
3. Loxapine succinate
4. Clozapine

Chlorprothixene

Structure

- Chemical class: Thioxanthene derivative (ring analogue of phenothiazines).
- Tricyclic structure: Two benzene rings fused to a central thioxanthene ring containing sulfur.
- Substitutions:
  - Double bond between carbon and central ring → distinguishes it from phenothiazines.
  - Piperazine side chain at N-10 → contributes to antipsychotic and sedative effects.



Mechanism of Action (MOA)

- Dopamine D1 and D2 receptor antagonist in the CNS → reduces dopaminergic transmission.
- Produces antipsychotic effects: decreases hallucinations, delusions, and agitation.
- Mild anticholinergic and antihistaminic effects may occur.
- Some activity at alpha-adrenergic receptors → can cause hypotension.

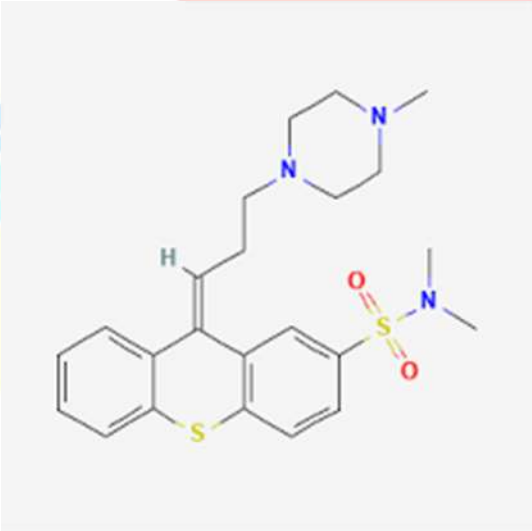
Therapeutic Uses

- Schizophrenia, especially with agitation or aggressive behavior.
- Acute psychotic episodes.
- Historically used for anxiety associated with psychosis.

Thiothixene

Structure

- Chemical class: Thioxanthene derivative (ring analogue of phenothiazines).
- Tricyclic structure: Two benzene rings fused to a central thioxanthene ring containing sulfur.
- Substitutions:
  - Double bond between central ring and side chain → differentiates it from phenothiazines.
  - Piperazine side chain at N-10 → contributes to potent antipsychotic activity.



Mechanism of Action (MOA)

- Dopamine D1 and D2 receptor antagonist in the CNS.
- Reduces dopaminergic transmission in the mesolimbic and mesocortical pathways → decreases hallucinations, delusions, and agitation.
- Mild anticholinergic and antihistaminic effects.
- Some alpha-adrenergic blockade → may cause hypotension.

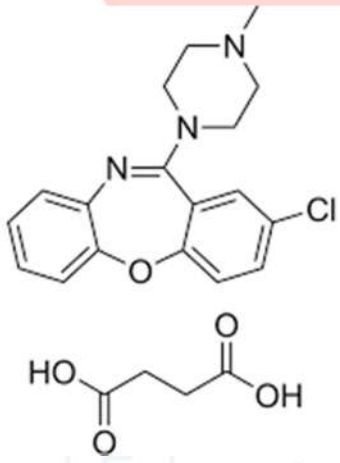
Therapeutic Uses

- Schizophrenia, particularly positive symptoms.
- Acute psychotic episodes.
- Severe agitation associated with psychotic disorders.

Loxapine Succinate

Structure

- Chemical class: Dibenzoxazepine derivative (ring analogue of phenothiazines).
- Tricyclic structure: Two benzene rings fused to a central seven-membered oxazepine ring containing nitrogen and oxygen.
- Substitutions:
  - Piperazine side chain → increases antipsychotic activity.
  - Functional groups on the aromatic rings enhance dopamine receptor binding.



Mechanism of Action (MOA)

- Dopamine D2 receptor antagonist in the CNS → reduces dopaminergic overactivity.
- Also has moderate serotonin (5-HT2) receptor antagonism → helps with negative symptoms of schizophrenia.
- Reduces psychotic symptoms like hallucinations, delusions, and agitation.
- Mild anticholinergic and antihistaminic effects may occur.

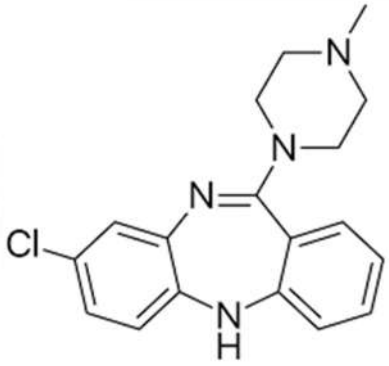
Therapeutic Uses

- Schizophrenia, including acute and chronic forms.
- Psychotic episodes with agitation.
- Sometimes used in patients unresponsive to typical antipsychotics due to balanced dopamine-serotonin activity.

Clozapine

Structure

- Chemical class: Atypical antipsychotic, dibenzodiazepine derivative.
- Tricyclic structure: Two benzene rings fused to a central seven-membered diazepine ring containing nitrogen.
- Substitutions:
  - Chlorine at position 8 → increases dopamine receptor affinity.
  - Nitrogen side chain → contributes to receptor selectivity.
  - Aromatic substitutions enhance serotonin (5-HT2) receptor binding.



Mechanism of Action (MOA)

- Dopamine D1 and D2 receptor antagonist → reduces positive symptoms of schizophrenia.
- Serotonin 5-HT2A/2C receptor antagonist → improves negative symptoms and cognitive function.
- Low affinity for D2 in striatal pathways → minimal extrapyramidal side effects (EPS).
- Mild anticholinergic, antihistaminic, and alpha-adrenergic blockade may occur.

Therapeutic Uses

- Treatment-resistant schizophrenia.
- Schizoaffective disorder.
- Reduces risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

Fluoro Butyrophenones

- Fluoro butyrophenones are a group of antipsychotic drugs derived from the butyrophenone nucleus with a fluorine substitution that enhances potency.
- They are classified as typical (first-generation) antipsychotics.
- Mainly used in the management of schizophrenia, acute psychosis, mania, and severe agitation.

Mechanism of Action

- Act as potent antagonists of dopamine D_2 receptors in the mesolimbic and mesocortical pathways.
- Reduce positive symptoms of psychosis (hallucinations, delusions, aggression).
- High D_2 blockade in nigrostriatal pathway may lead to extrapyramidal side effects (EPS).
- Some also have effects on α-adrenergic and serotonin (5-HT_2) receptors, contributing to sedation and mood effects.

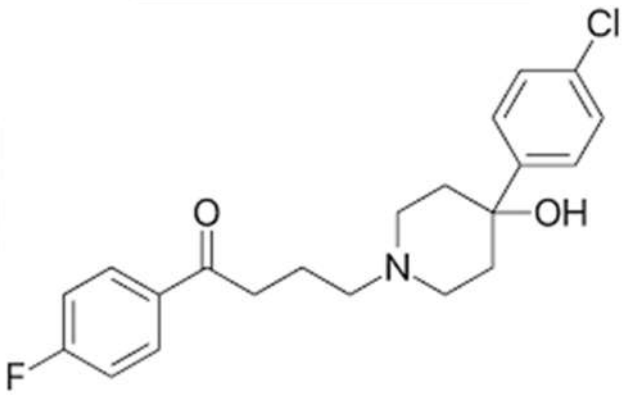
Examples

1. Haloperidol
2. Droperidol
3. Risperidone

Haloperidol

Structure

- Chemical class: Butyrophenone derivative (first-generation typical antipsychotic).
- Core structure:
  - Butyrophenone moiety (aromatic ketone) linked to a piperidine ring.
  - Substitutions on the aromatic ring (fluorine or other groups) enhance potency and receptor binding.



Mechanism of Action (MOA)

- Potent dopamine D2 receptor antagonist in the CNS.
- Reduces dopaminergic activity in the mesolimbic pathway → decreases positive psychotic symptoms (hallucinations, delusions).
- Weak antagonism at serotonin, histamine, and alpha-adrenergic receptors.
- High D2 blockade in the nigrostriatal pathway → may cause extrapyramidal side effects (EPS).

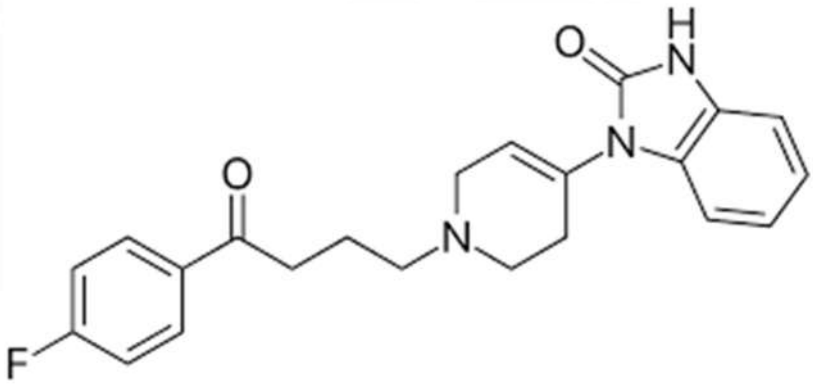
Therapeutic Uses

- Schizophrenia (acute and chronic psychosis).
- Acute psychotic episodes with agitation.
- Tourette's syndrome (to control tics).
- Severe behavioral disorders in children (off-label).

Droperidol

Structure

- Chemical class: Butyrophenone derivative (typical antipsychotic).
- Core structure:
  - Butyrophenone moiety (aromatic ketone) attached to a piperidine ring.
  - Substitutions on the aromatic ring enhance dopamine receptor affinity.



Mechanism of Action (MOA)

- Dopamine D2 receptor antagonist → blocks dopamine activity in the CNS.
- Reduces positive symptoms of psychosis such as hallucinations and agitation.
- Also acts as a central antiemetic by blocking dopamine receptors in the chemoreceptor trigger zone (CTZ).
- Minimal serotonin and alpha-adrenergic receptor antagonism.

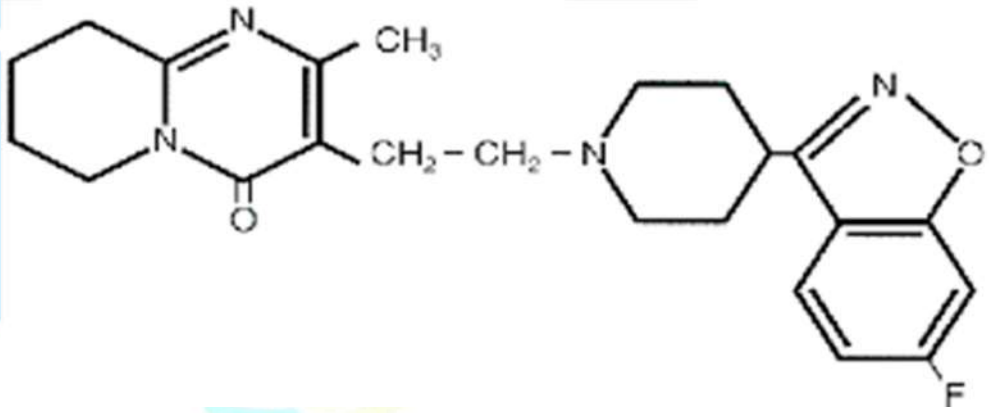
Therapeutic Uses

- Preoperative sedation and tranquilization.
- Control of nausea and vomiting (antiemetic).
- Acute psychotic episodes (off-label use in agitation).
- Sometimes used in combination with opioids for neuroleptanalgesia.

Risperidone

Structure

- Chemical class: Atypical antipsychotic, benzisoxazole derivative.
- Core structure:
  - Benzisoxazole ring fused to a piperidine ring.
  - Substitutions enhance affinity for dopamine and serotonin receptors.



Mechanism of Action (MOA)

- Dopamine D2 receptor antagonist → reduces positive symptoms of schizophrenia (hallucinations, delusions).
- Serotonin 5-HT2A receptor antagonist → improves negative symptoms (apathy, social withdrawal) and reduces risk of extrapyramidal side effects.
- Partial antagonism at alpha-1 adrenergic, histamine H1, and muscarinic receptors → mild sedation, hypotension, and anticholinergic effects.

Therapeutic Uses

- Schizophrenia (acute and chronic).
- Bipolar disorder (manic or mixed episodes).
- Irritability in autism spectrum disorders.
- Adjunct in major depressive disorder (as combination therapy).

Beta Amino Ketones

- Beta amino ketones are compounds containing:
  - A ketone group (C=O)
  - An amino group (-NH_2 or substituted amino group)
  - Both separated by two carbon atoms (β-position).
- They form a small group of antipsychotic agents with structural similarity to both amphetamines and ketones.
- They show unique CNS actions, with effects on dopamine and norepinephrine systems.

Example

- Molindone Hydrochloride

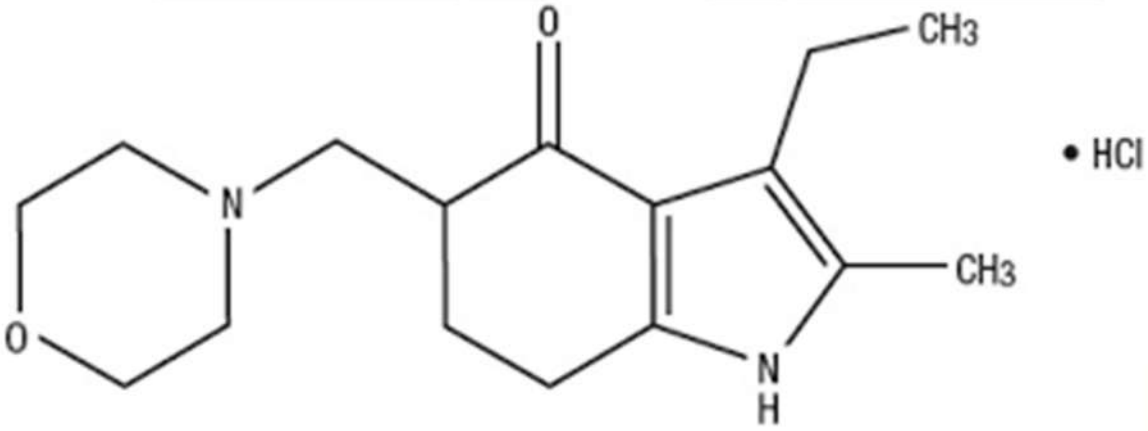
Mechanism of Action

- Acts primarily by modulating brain neurotransmitters, especially:
  - Dopamine (D_2 receptors): antagonistic effect → reduces positive psychotic symptoms.
  - Norepinephrine: mild modulatory effect → may improve alertness and mood.
- Overall effect:
  - Reduces psychotic symptoms like hallucinations and delusions.
  - Improves behavioral control and decreases aggression.
- Unlike typical antipsychotics, Molindone produces less weight gain, but still causes EPS due to D_2 antagonism.

Molindone Hydrochloride

Structure

- Chemical class: Typical antipsychotic, indole derivative.
- Core structure:
  - Indole ring system with side chains that confer dopamine receptor antagonism.
  - Hydrochloride salt form increases water solubility for oral administration.



Mechanism of Action (MOA)

- Dopamine D2 receptor antagonist → blocks dopaminergic activity in the CNS.
- Reduces positive symptoms of schizophrenia (hallucinations, delusions, agitation).
- Minimal serotonergic, adrenergic, or histaminergic receptor activity → lower risk of sedation compared to some other typical antipsychotics.

Therapeutic Uses

- Schizophrenia (acute and chronic psychotic disorders).
- Psychotic symptoms associated with bipolar disorder (off-label).
- Occasionally used for behavioral disturbances in elderly patients (with caution).

Benzamides

- Benzamides are chemical compounds derived from benzoic acid (benzene ring + carboxylic acid) combined with an amine group.
- They form a distinct class of drugs with actions on the CNS and gastrointestinal tract.
- Some benzamides are used as antipsychotics, while others are used as prokinetic (GI motility) agents.

Examples

- Sulpieride.

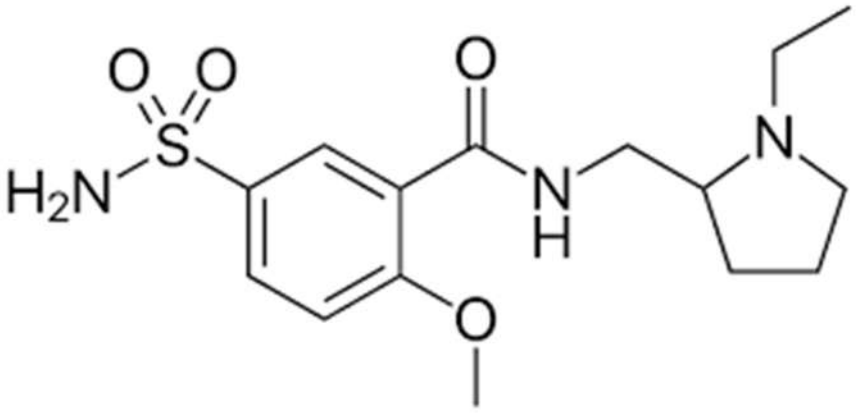
Mechanism of Action

- Benzamides mainly act by blocking dopamine (D_2) receptors:
  - In the brain (CNS): reduces positive psychotic symptoms such as hallucinations, delusions, and agitation.
  - In the gut (GIT): enhances gastrointestinal motility, prevents nausea and vomiting (via chemoreceptor trigger zone blockade).
- Some (e.g., Amisulpride) also block 5-HT_7 receptors, contributing to antidepressant and mood-stabilizing effects.

Sulpiride

Structure

- Chemical class: Benzamide derivative, atypical antipsychotic.
- Core structure:
  - Substituted benzamide moiety.
  - Contains a sulfonyl group and a piperidine side chain which enhances dopamine receptor selectivity.



Mechanism of Action (MOA)

- Selective dopamine D2 and D3 receptor antagonist → blocks dopaminergic neurotransmission in the CNS.
- Higher selectivity for limbic system D2 receptors than striatal D2 receptors → lower risk of extrapyramidal side effects.
- Minimal effect on serotonin, histamine, and adrenergic receptors → mild sedation and low anticholinergic activity.

Therapeutic Uses

- Schizophrenia (positive and negative symptoms).
- Psychotic depression (adjunct therapy).
- Hyperprolactinemia (due to D2 antagonism in pituitary).
- Occasionally used for anxiety disorders and behavioral disturbances.