Al-Azhar University - Gaza

Pharmaceutical Chemistry and Pharmacognosy Department

4. Antipsychotic Drugs

Medicinal Chemistry III

First Semester 2020-2021

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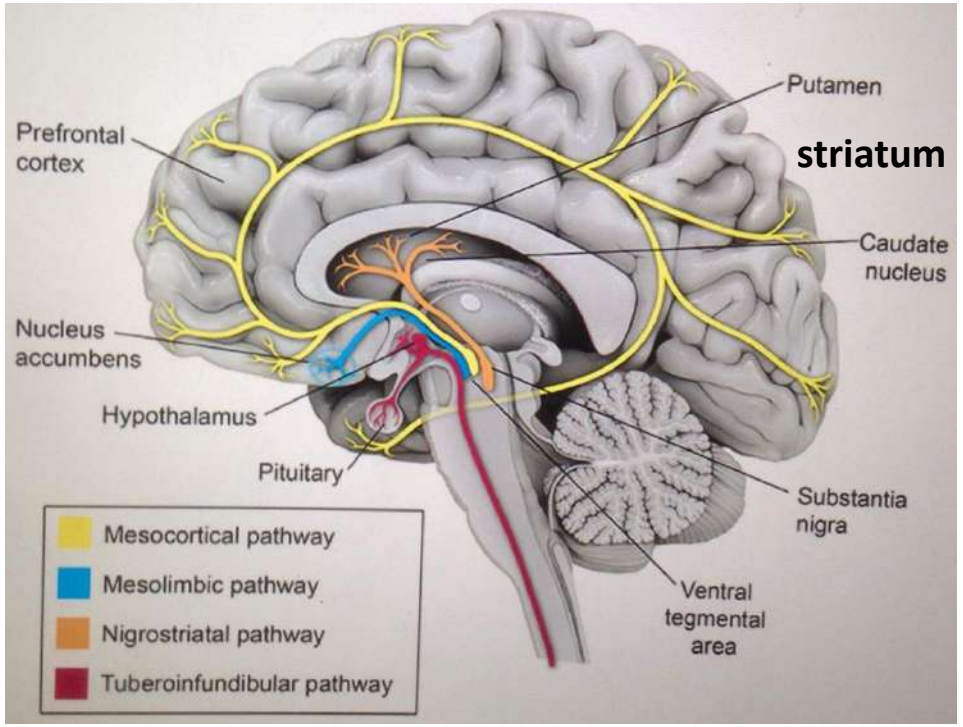
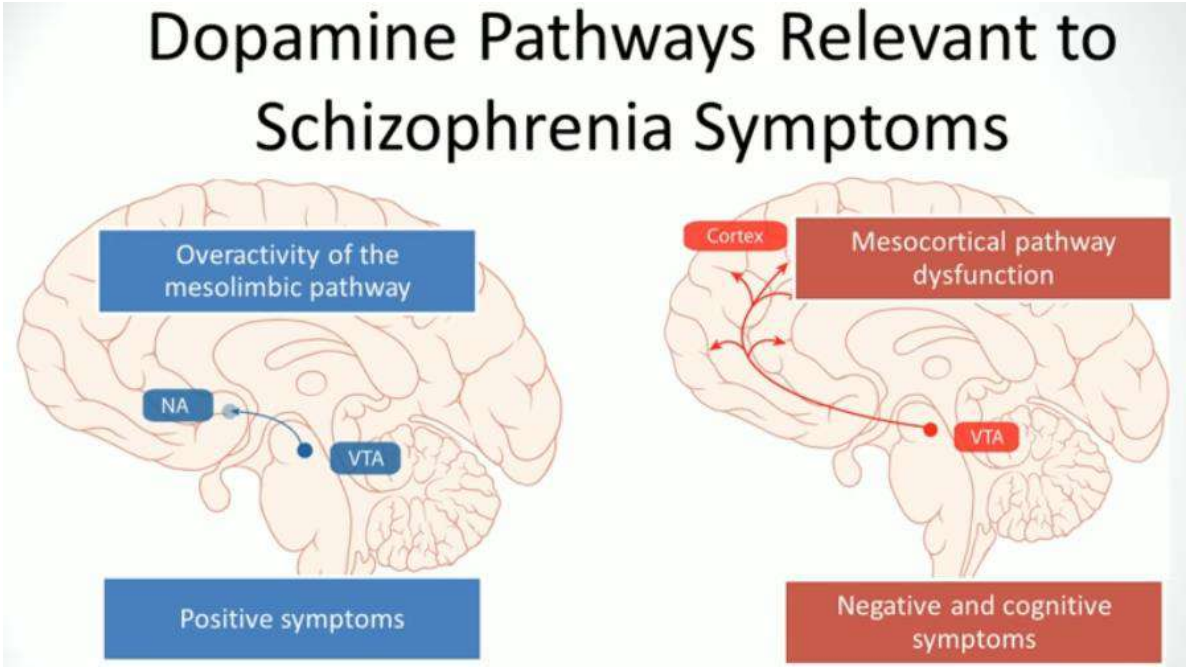
CNS Acting Drugs

- **Sedative and hypnotics** (benzodiazepines, barbiturates and others)
- **General anesthetics** (parenteral, inhaled)
- **Anti-seizure drugs** (anticonvulsants or antiepileptic)
- **Psychotherapeutic agents** (antipsychotic, anti-depressants)
- **Psychomotor stimulants and anti-parkinsonism**

DA hypothesis for schizophrenia

Major dopamine pathways in Brain





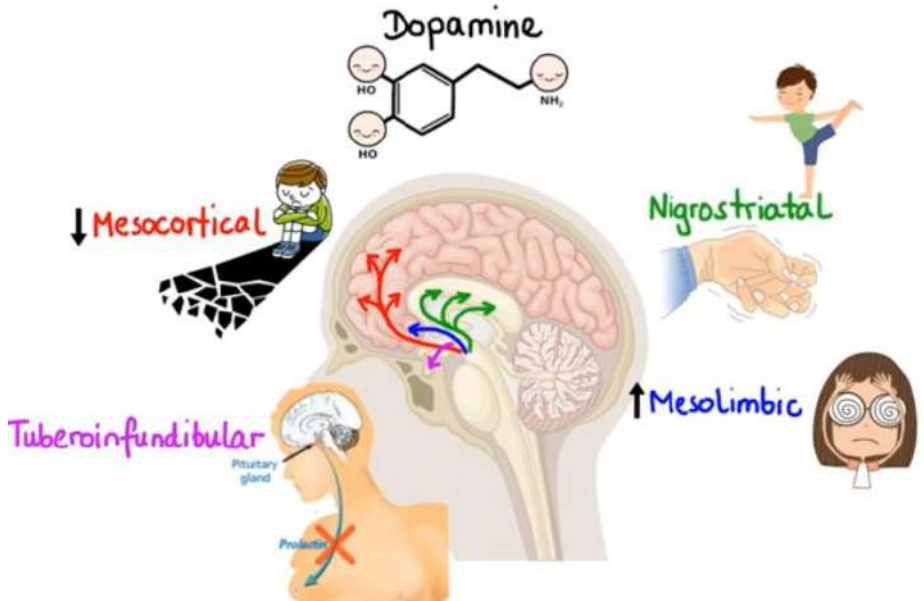
The four pathways relevant to the pharmacology of antipsychotics in the treatment of schizophrenia are:

-The **mesolimbic pathway** (positive symptoms)

-The **mesocortical pathway** (negative symptoms)

-The **nigrostriatal pathway** (extrapyramidal symptoms and tardive dyskinesia)

-The **tuberoinfundibular pathway** (hyperprolactinemia)



Introduction

***Psychosis*:** is a mental illness could be broadly categorized into: schizophrenia, anxiety disorder, Mood and panic disorders

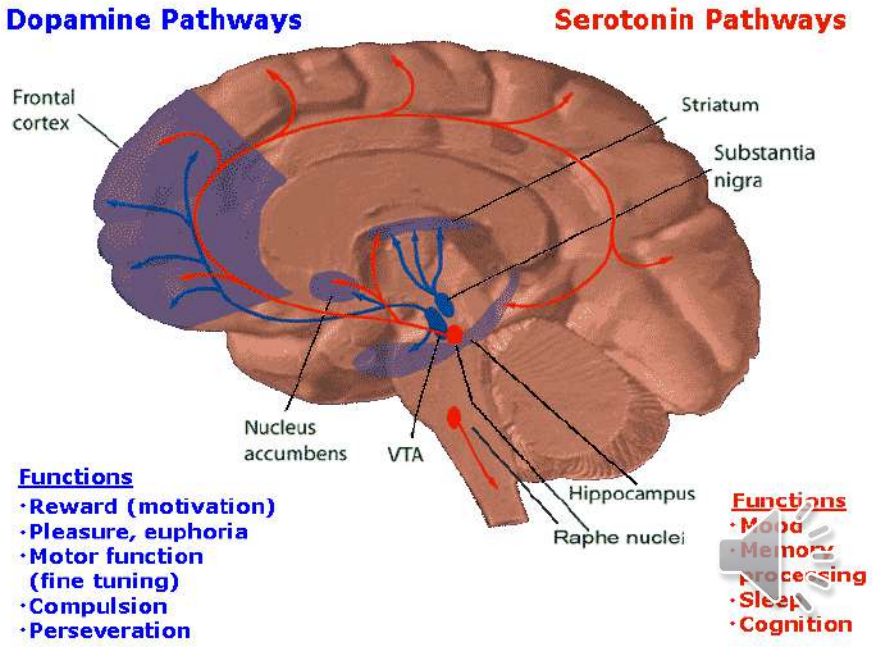
Psychosis is characterized by: Hallucinations (usually auditory) with incoherent speech; Difficulty in understanding reality and their own conditions; Delusions, Thinking tends to become illogical

The most widely used class of drugs in the treatment of psychotic disorders is the so-called ***neuroleptics (antipsychotic)***.

1. First generation (typical neuroleptics):

- Potent ***dopamine D2*** receptor ***antagonist*** activity
- High propensity for extrapyramidal side effects (***ESP***).
- Provide calming, mood-stabilizing, and anti-hallucinatory effects
- Better for treating positive signs than negative signs

- Chemical classes of typical neuroleptics include:
    1. **Phenothiazines**
    2. **Thioxanthenes**
    3. **Butyrophenones**



2. Second generation (atypical antipsychotics):

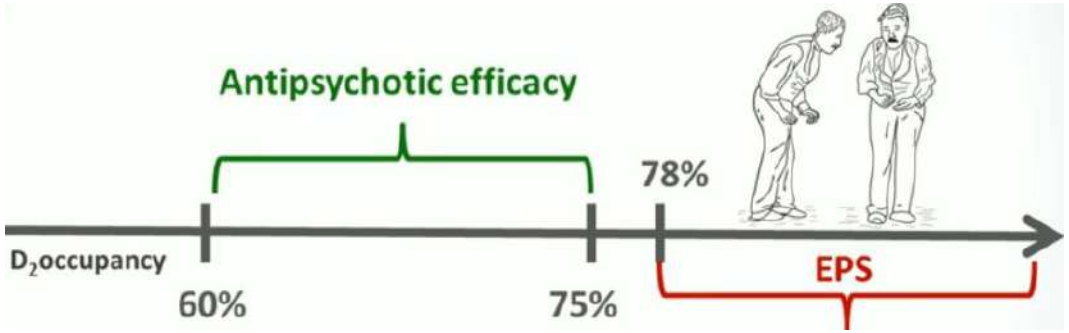
- less affinity for D2 receptors
- less incidence of movement disorder side effects (**EPS**)
- For treating negative signs. The bases of the atypical group's activity against negative symptoms may be serotonin-2A receptor (5- HT2A) block.
- have significant activity at brain ***serotonin 5- HT2A*, adrenergic α1/α2, muscarinic**, and/or ***histamine H1*** receptors, in addition to some activity at dopamine receptors.

- Chemical classes of atypical antipsychotic drug classes include:
    1. Benzazepines
    2. Benzisoxazoles

SGAs Dissociate Rapidly from D_2 Receptors

FGA	Clozapine and other SGAs
Binding to D_2 receptors: "Tight"	Binding to D_2 receptors: "Loose"

First Generation Antipsychotics	Second Generation Antipsychotics
• D_2 antagonism	• 5-HT_{2A} / D_2 antagonism • Rapid D_2 dissociation • 5-HT1_{1A} agonism



1. First-Generation (Typical) Antipsychotic Drugs

Mechanism of action:

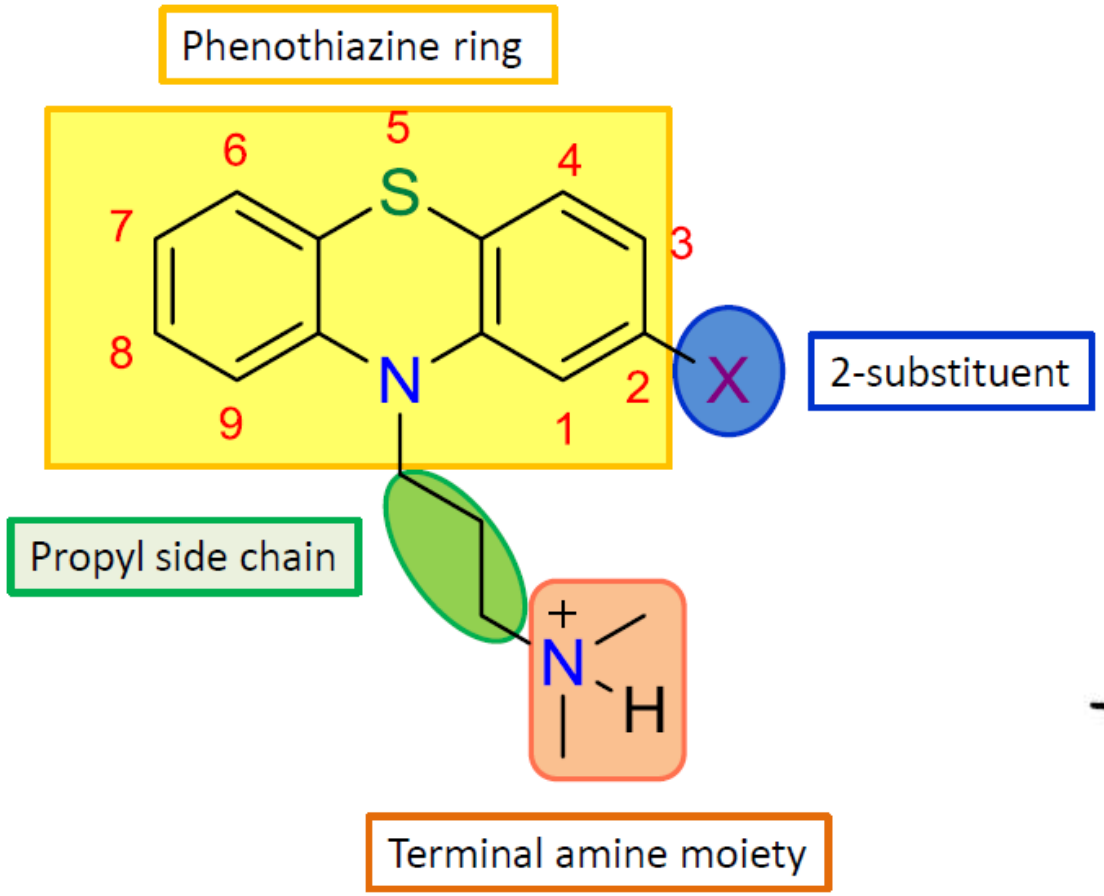
Modulation of dopamine neurotransmission in the mesolimbic pathways. This is achieved via ***direct interaction with D2-type receptors***

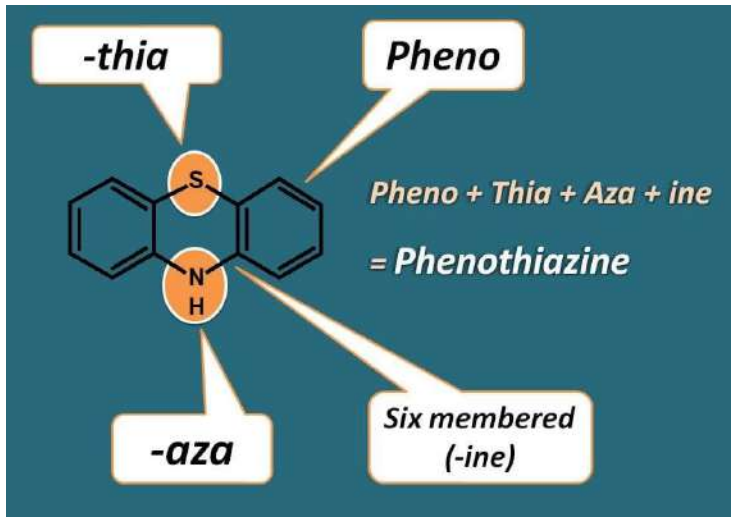
Side effects:

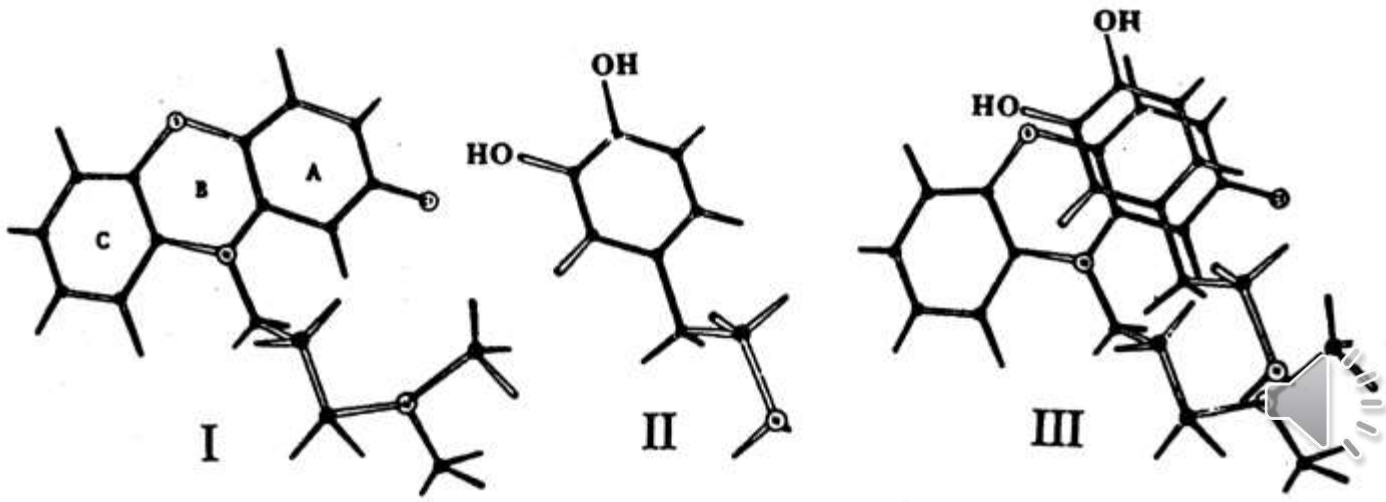
- Sedation, hypotension, sexual dysfunction resulting from blockade of histamine H1 and adrenergic α1/α2 receptors.
- Cardiac, ophthalmic, gastro-intestinal, and genitourinary side effects resulting from anti-muscarinic (M1–5) effects.
- Extrapyramidal side effects. The anticholinergic effects (anti-muscarinic) could be beneficial in softening the Parkinson's like side effects!!
- Metabolic and endocrine side effects, such as weight gain, hyperprolactinemia, and gynecomastia.
- Antagonism of dopamine D2-type receptors in the chemoreceptor trigger zone in the brainstem leading to antiemetic effects.

1. 1. Phenothiazine Neuroleptics

SAR of phenothiazine:







The phenothiazine ring:

1-Increase in activity by Substitution at position 2 or 3→

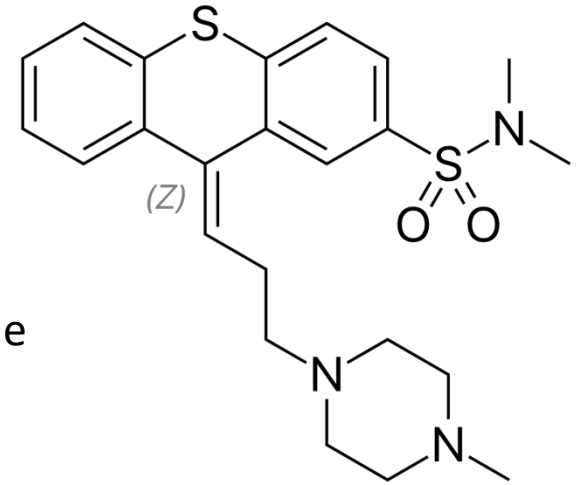
2-position >> 3-position > no substitution

2- ↑↑ electron-withdrawing (***electron negative***) ability of the substituent → ↑ activity

3- Having an unshared electron pair on an atom or atoms of the 2-substituent → more potent compounds. (such as SO_2NR_2 > CF_3 > $COCH_3$ > Cl. interact with the quaternary ammonium at the side chain).

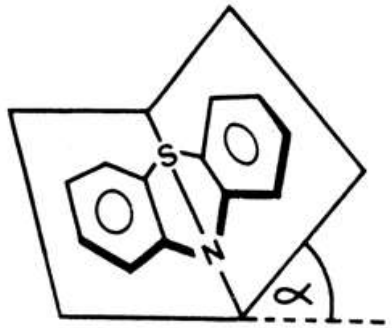
4- Decreasing in activity by Substitution at position 1 or 4→

position 1 > 4-position.



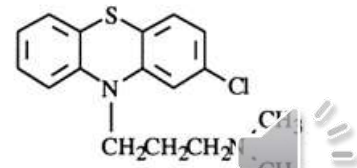
Thiothixene

5- A ***phenothiazine (N-10)*** or isosteric thioxanthene (C=C-10) has the optimal structure and conformation for binding to the DA receptor. A thioxanthene is an unsymmetrical alkene and should have the Z- (cis) configuration for optimal receptor affinity



The side chain:

- The side chain should be ***3 carbons*** length.
- Methyl branching on the β-position→ variable effect on activity.
- Side chain tilts away from midline toward chlorine-substituted ring (Z geometry).
- ***Branching of the 3Cs*** such as (phenyl (big) or polar) will abolish the activity.
- Thioxanthene (thiothixene); exist as cis or trans with the cis is more active to 7 folds than trans or saturated one.



Chlorpromazine

α = 55°

The terminal amine:

- The side chain amine will be ***ionized*** at physiological pH.
- Tertiary amine is the most active ***3°>2°>1°.***
- ***Only methyl*** groups are tolerated, except when it is a part of a ring. Its substitution has three classes:

  1- Aliphatic (Propyl Dialkylamino**)** derivatives (Names are ending by "–promazine)

  2- Piperidine derivatives

  3- Piperazine derivatives.

  - Their classification as antipsychotics: 3> 2> 1
  - Their classification as sedation induction: 1=2 > 3
  - Their classification as hypotensive: 1> 2> 3
  - Their classification as EPS: 3> 2> 1

↑↑ Potency:

- by the presence of (CF_3) group at position 2.
- increasing the overall chain length, as in N2-substituted piperizino compounds
- → this precise fit in the DA receptors is involved in the action of these compounds.

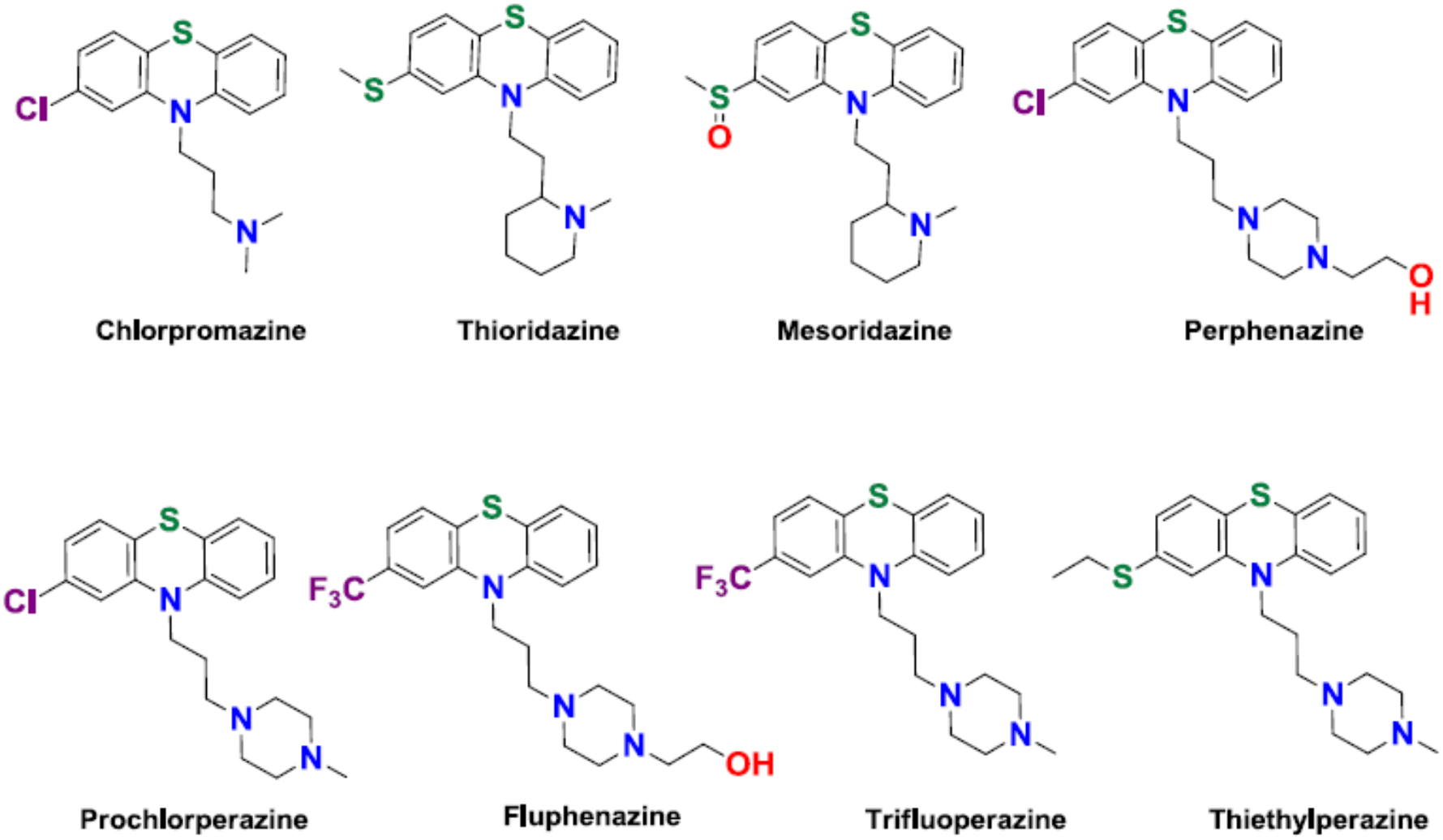
→Propyl piperazine side chain yield more potent antipsychotics relative to other substituents.

products

- **Propyl Piperazine Side Chain**

The piperazine subgroup of the phenothiazine is characterized by:

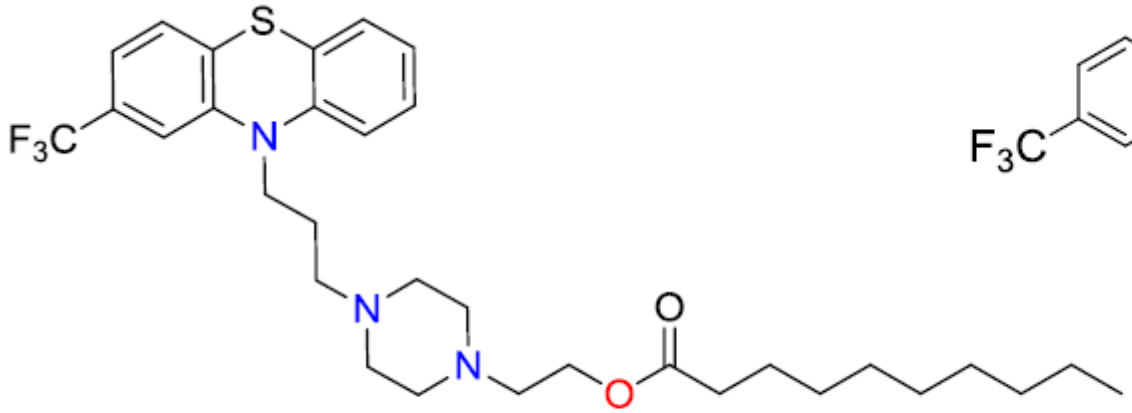
- High antipsychotic potency.
- A high prevalence of EPS.
-And low sedative and autonomic effects.



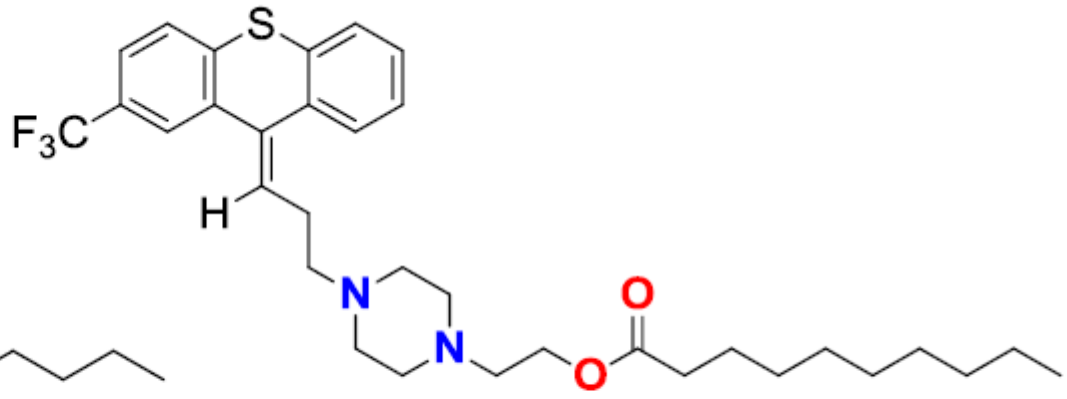
Sedative and hypotensive effects are low

Long-Acting Phenothiazines

- Applied to drugs containing ***terminal hydroxyl group*** (OH), such as; Fluphenazine enanthate, Fluphenazine decanoate and Perphenazine enanthate.
- Flupenthixol decanoate also long acting from Thioxanthene group.
- Has the advantage to be given as ***depot injection*** every 2-3 weeks; so increase the patient compliance.



Fluphenazine decanoate

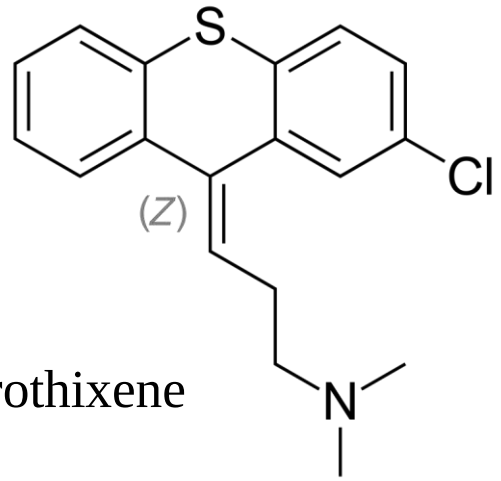


Flupenthixol decanoate

B. Ring Analogues of Phenothiazines:

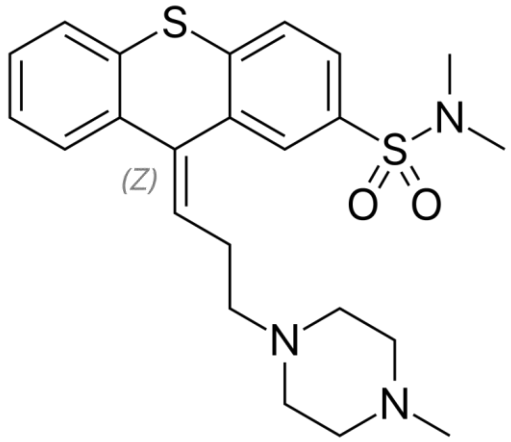
-Close structural relatives of phenothiazines.

-They share many clinical properties with phenothiazine antipsychotics.

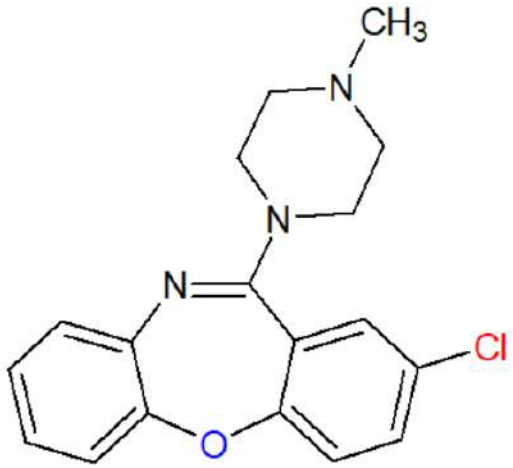


Chlorprothixene

Thioxanthene

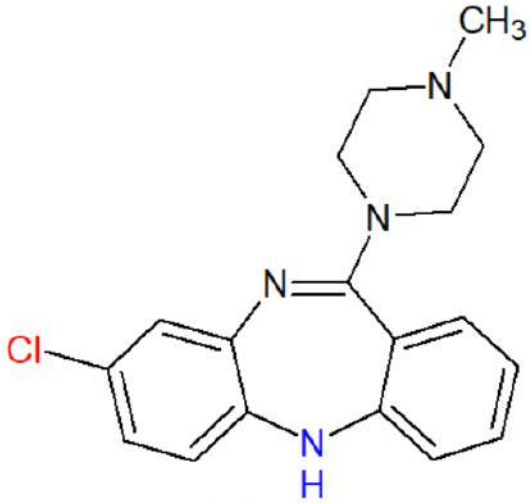


Thiothixene



Loxapine

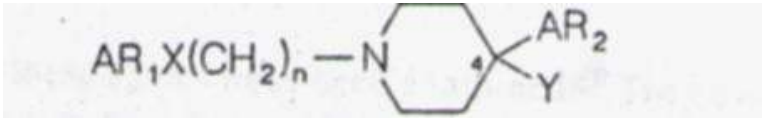
Dibenzoxazepines



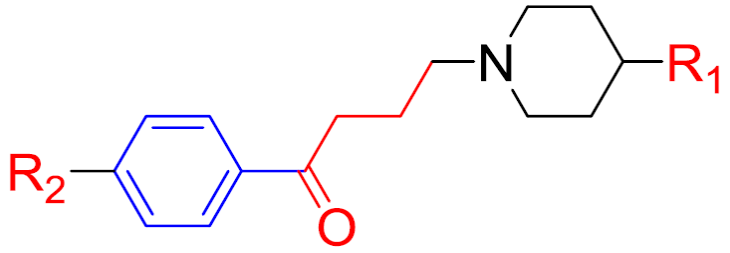
Clozapine

Dibenzodiazepines

1. 2. Butyrophenone Neuroleptics



SAR of butyrophenone:

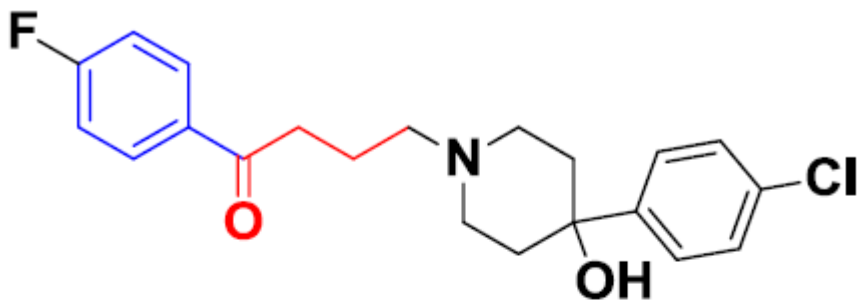


- The attachment of **a tertiary amino** group to the fourth carbon of the butyrophenone skeleton is essential for neuroleptic activity.
- ***Lengthening, shortening, or branching*** of the three-carbon propyl chain decreases neuroleptic potency.
- ***Replacement of the keto*** moiety with the thioketone group, with olefinic or phenoxy groups, or reduction of the carbonyl group decreases neuroleptic potency.
- Most potent butyrophenone compounds have a ***fluorine*** substituent in the para position of the benzene ring.

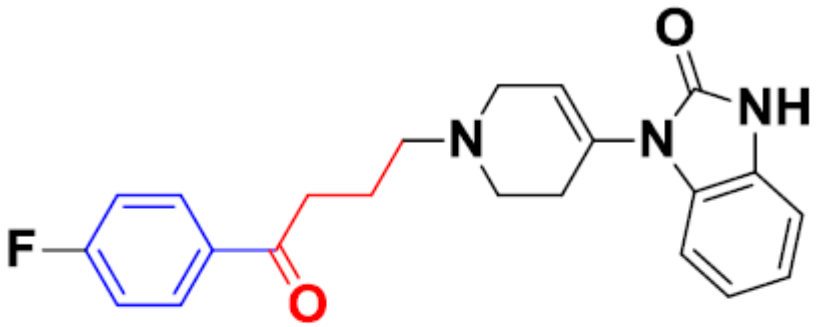
- Variations are possible in the tertiary amino group without loss of neuroleptic potency; for example, the basic nitrogen usually is incorporated into a **six-membered ring** (piperidine, tetrahydropyridine, or piperazine) that is substituted in the para position.

  - Available butyrophenones include:

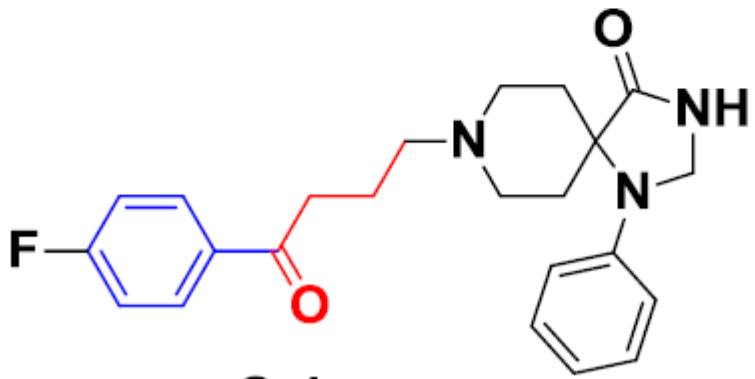
    1. **Haloperidol**: Haloperidol decanoate has been introduced as depot maintenance therapy. When injected every 4 to 6 weeks, the drug appears to be as effective as daily orally administered haloperidol (higher patient compliance).
    2. **Spiperone**: very potent.
    3. **Droperidol**: a short-acting, sedating butyrophenone, used in anesthesia for its sedating and antiemetic effects and, sometimes, in psychiatric emergencies as a sedative-neuroleptic. Droperidol often is administered in combination with the potent narcotic analgesic fentanyl for pre-anesthetic sedation and anesthesia.
    4. **Trifluperidol**.



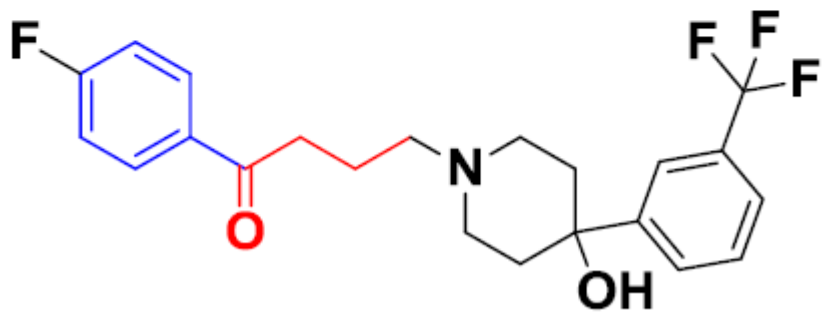
Haloperidol



Droperidol



Spiperone



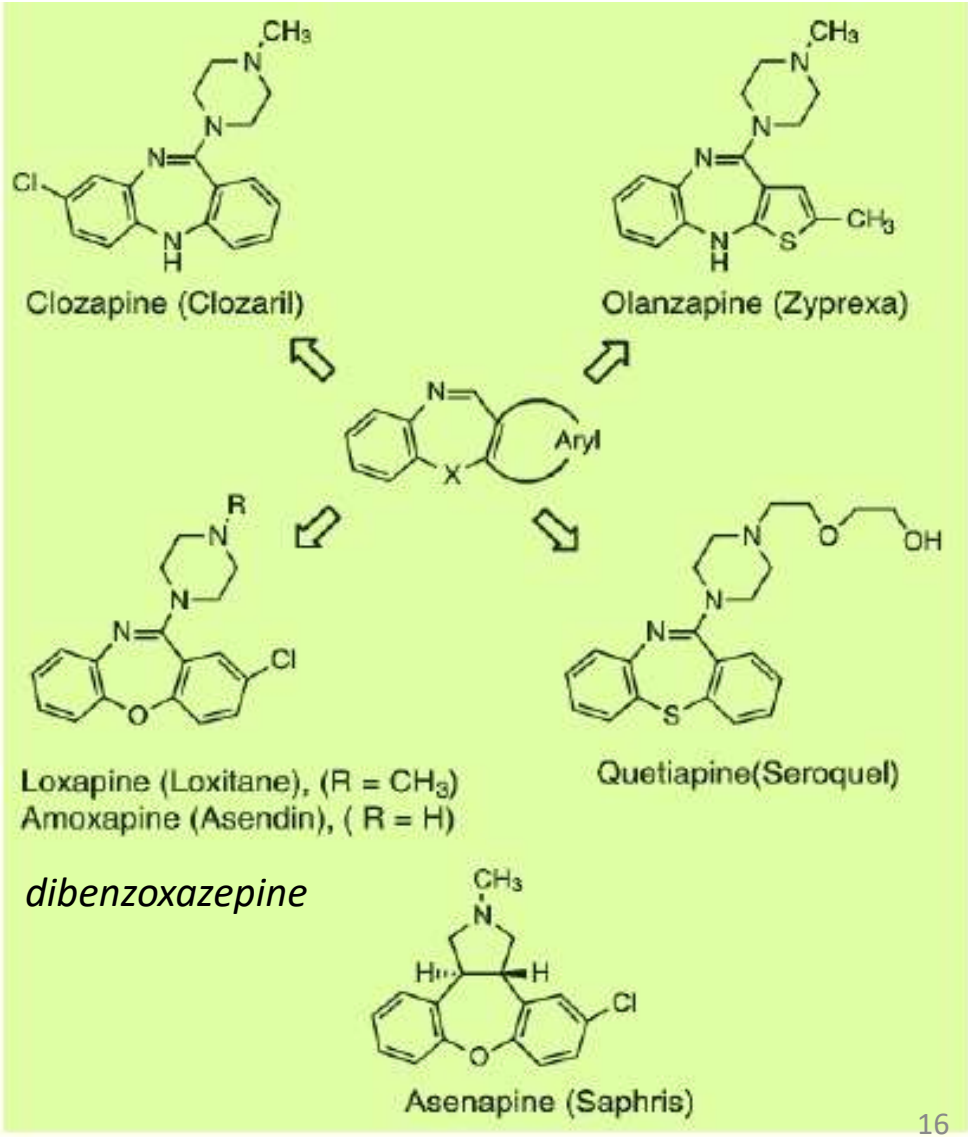
Trifluperidol

2. Second-Generation (Atypical) Antipsychotic Drugs

- The high ***5-HT$_{2A}$*** receptor affinity and reduced affinity for ***D$_2$ receptors*** of second-generation antipsychotics may account for their low propensity to cause extrapyramidal side effects.

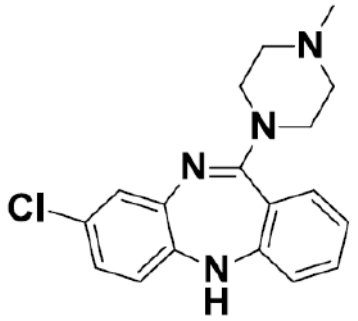
Benzazepine and Related Analogs

The structures of the **benzazepine** derivatives, clozapine, olanzapine, loxapine, amoxapine, and quetiapine, and the related dibenzo-oxepine asenapine



Clozapine:

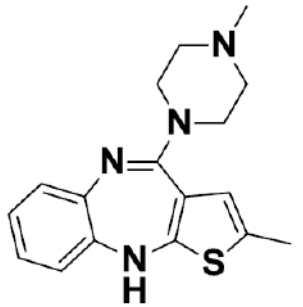
- Cause less EP side effects and minimal tardive dyskinesia.
- Could cause lethal agranulocytosis (lowered white blood cell count).
- Caffeine increase the EPS and smoking reduce its levels in blood.



Clozapine

Olanzapine:

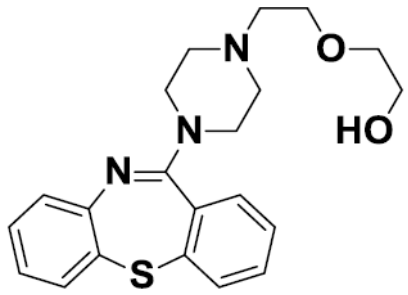
- Thienobenzodiazepine derivative.
- Less causing side effects with no agranulocytosis.
- Given as pamoate for long term injection



Olanzapine

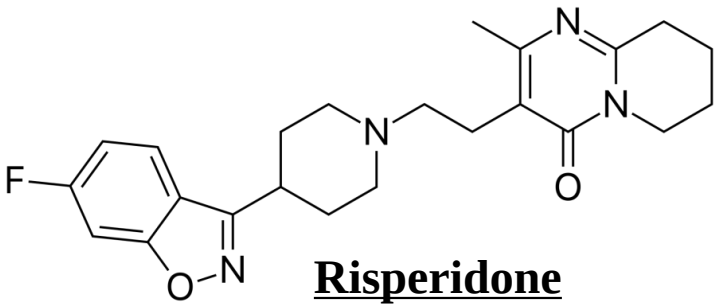
Quetiapine:

- Dibenzothiazepine derivative.
- Not affected by smoking or caffeine.

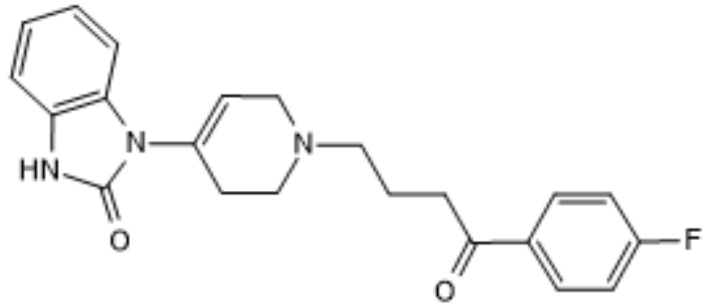


Quetiapine

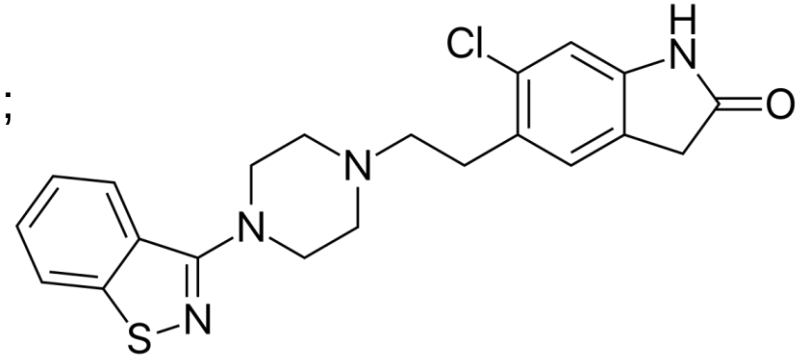
- **Risperidone** (Risperdal) is hybrid of a butyrophenone antipsychotic and a trazodone-like antidepressant. Coexisting anxiety and depressive syndromes were also benefited. This is reported to be a consequence of the compound's combination $5HT_2$-D_2 receptor antagonistic (antidepressant and antipsychotic) properties.



Risperidone

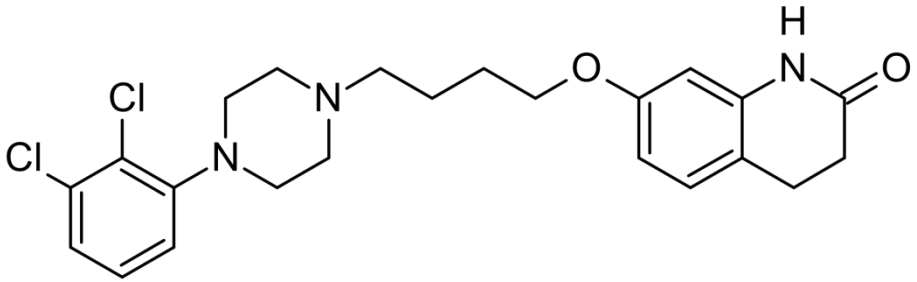


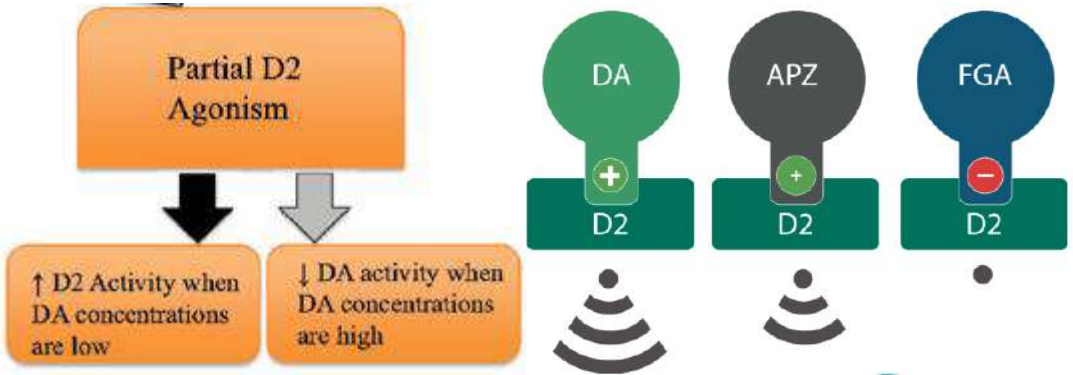
• **Ziprasidone** - treat bipolar disorder. Prolonged QT interval a concern;



• **Aripiprazole** - Among the newest (2006) atypical antipsychotics;

Dopamine partial agonists:





Classic and commonly used terms	Proposed new terms (WPA)
Neuroleptics (conventional antipsychotics, typical antipsychotics)	First generation antipsychotics
Atypical antipsychotics (serotonin-dopamine antagonists)	Second generation antipsychotics
Dopamine partial agonists (Aripiprazole)	Third generation antipsychotics

FGA	SGA
• **Chlorpromazine** • Loxapine • Fluphenazine • Perphernazine • Haloperidol	• **Clozapine** • Risperidone • Paliperidone • Iloperidone • Quetiapine • Olanzapine • Ziprasidone • Asenapine • Lurasidone

SGA advantages

- Lower EPS risk
- Efficacy against cognitive and negative symptoms
- Lack of prolactin elevation
- Efficacy for treatment-resistant patients