

NEUROPSYCHIATRY DSM (PYDI 0416) — FALL, 1999
MEDICINAL CHEMISTRY OF ANTIPSYCHOTICS — DR. RILEY

A. INTRODUCTION

Antipsychotic (neuroleptic) agents are primarily used in the therapy of schizophrenia, organic psychoses, the manic phase of manic-depressive illness and other acute or chronic idiopathic psychotic illnesses.

B. MECHANISM OF ACTION

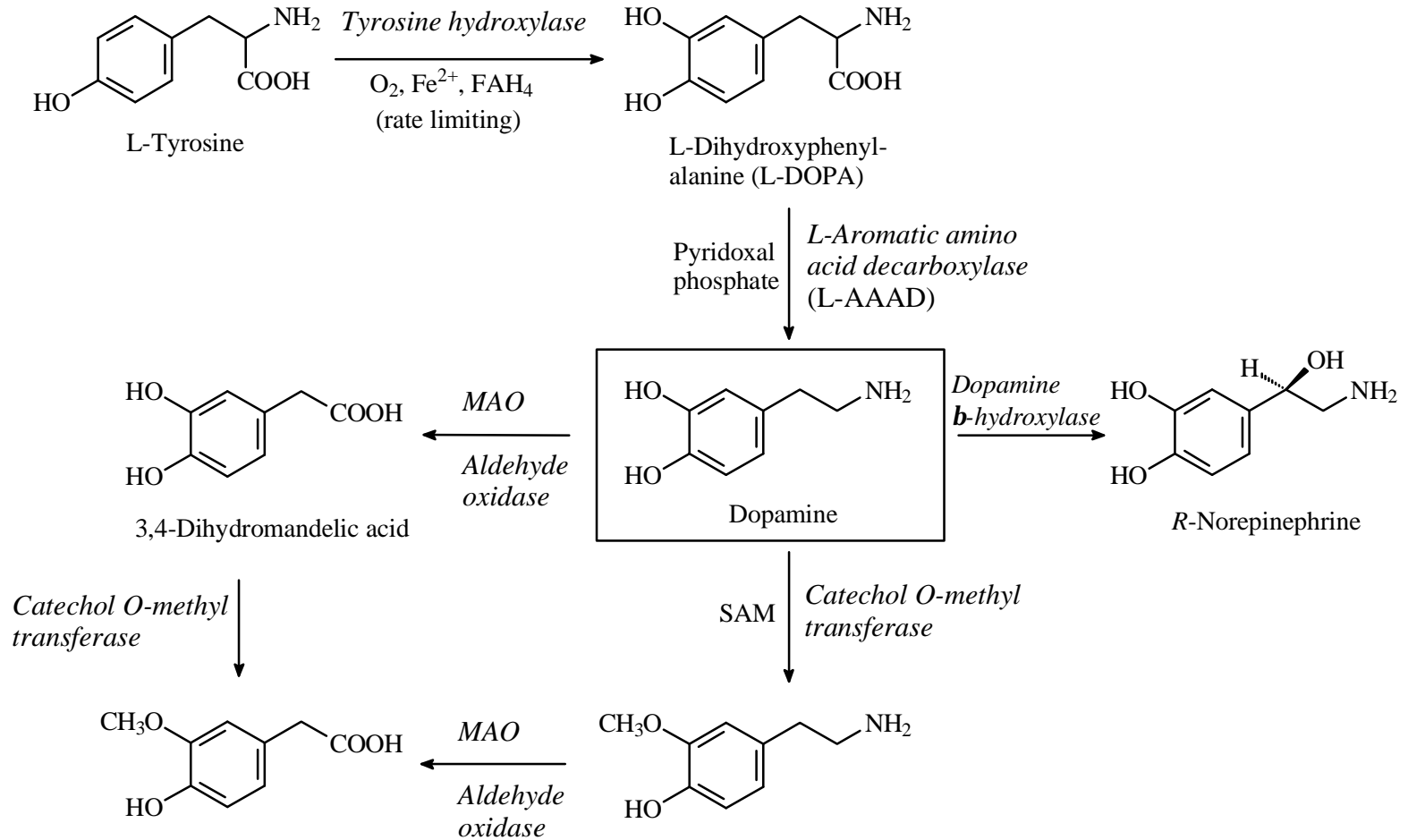
Evidence supports the hypothesis that the etiology of psychotic disorders lies in neurochemical defects of **dopaminergic** and **serotonergic** pathways in the brain. This hypothesis is supported by the fact that the primary pharmacological action of antipsychotic agents is antagonism of dopamine and/or serotonin receptor in the CNS.

A development-based classification of antipsychotic drugs:

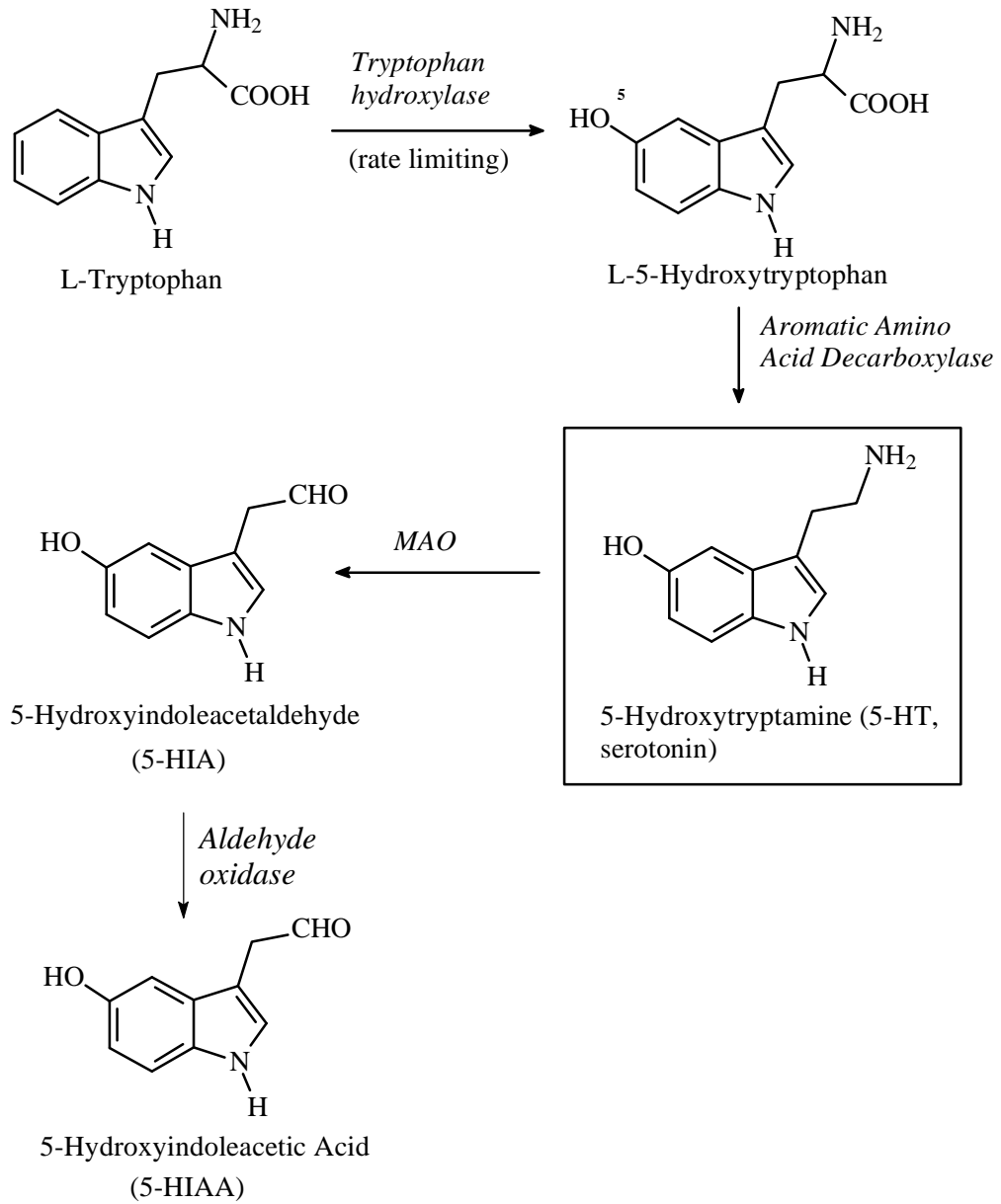
Order of binding affinity for CNS NT receptors

Classical Antipsychotics (phenothiazines)	$D_2 \approx D_1 > \alpha_1 \approx 5HT_2$
Atypical (SDA) Antipsychotics	
• First-generation (butyrophenones)	$D_2 > D_1 \approx 5HT_2 > \alpha_1$
• Second-generation (risperidone, clozapine)	$D_2 \approx 5HT_2 \gg D_1 > \alpha_1$

Dopamine Biosynthesis and Catabolism



Serotonin Biosynthesis and Catabolism



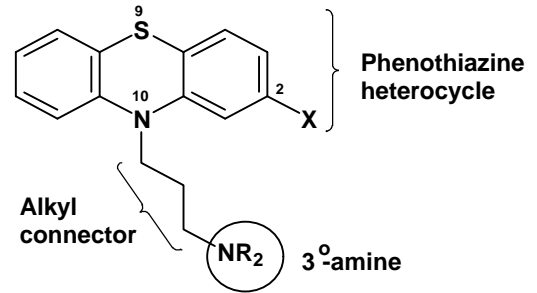
C. ANTIPSYCHOTIC DRUG CLASSES

PHENOTHIAZINE DERIVATIVES

- The first-used class of efficacious antipsychotic agents – Chlorpromazine, the prototypical member of this class, was first used to treat mental disease in 1951.
- Nonselective DA-receptor antagonists; also act at other neurotransmitter receptors giving rise to significant AR profiles

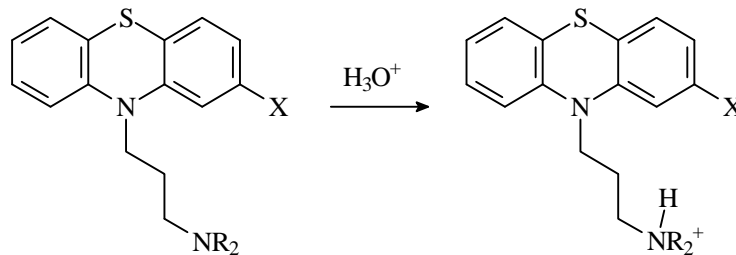
1. Structural Properties

- phenothiazine or bioisosteric heterocycle
- a *connector* alkyl (side) chain terminated by
- an aliphatic 3°-amine function

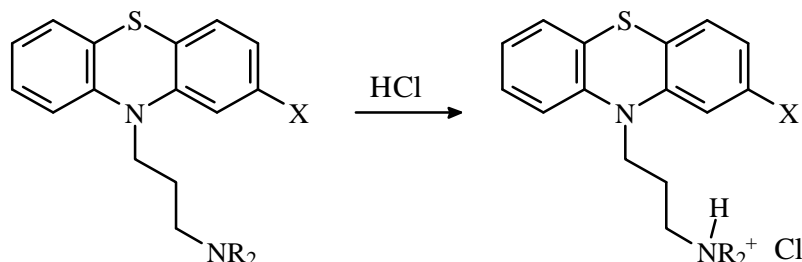


2. Physicochemical Properties

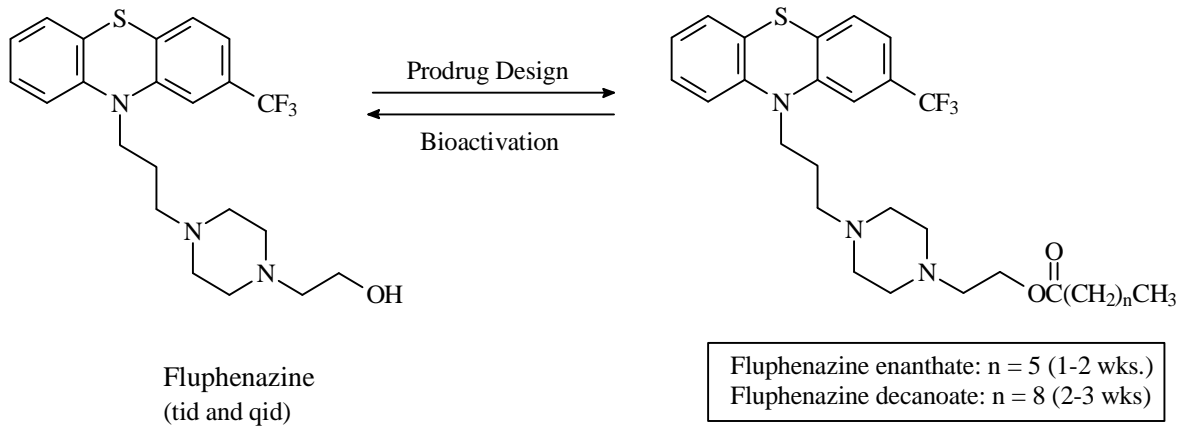
- the phenothiazine heterocycle confers a high degree of lipophilicity on these antipsychotics which is balanced (solubility) by the cationized (at physiologic pH) amine function
- the phenothiazines possess two potentially basic functional groups:
 - ▶ the N¹⁰-amine which is very weakly basic (pK_b >10) because of the electron-withdrawing effects of the 2 benzene rings attached to it and is not appreciably cationized at phys. pH,
 - ▶ the side chain tertiary amine function which confers strong organic basicity on the antipsychotic phenothiazines.



- H₂O solubility of the AP phenothiazines is increased for oral dosage formulation by treatment with an acid:

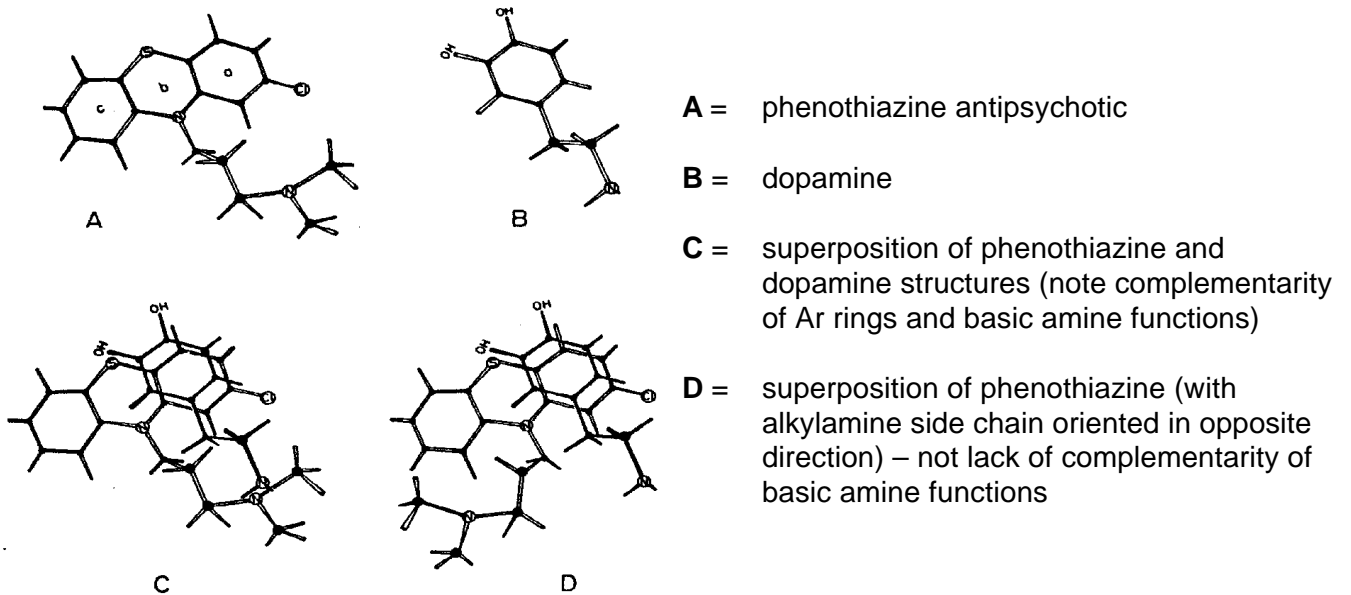


- conversely, the H₂O soly of these drugs can be reduced through the formation of bioreversible hydrocarbon esters (prodrugs) thereby lowering dissolution rates and facilitating formulation of long-acting (1-3 weeks) depot injections:

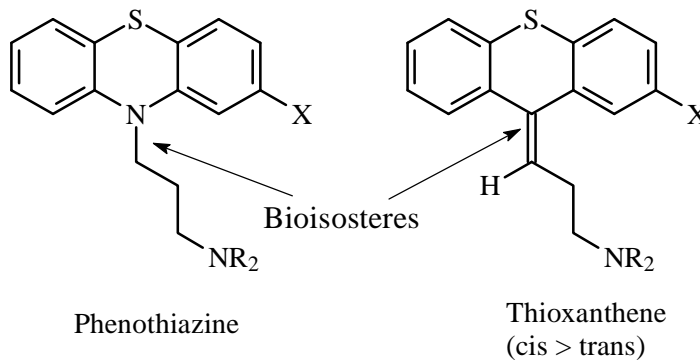


3. Structure-activity Relationships

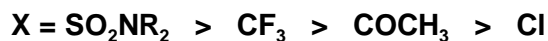
- structural/steric complementarity has been demonstrated between the phenothiazines and the CNS neurotransmitter dopamine providing an explanation for the ability of the antipsychotic molecules to interact in an antagonistic fashion with DA-receptors:



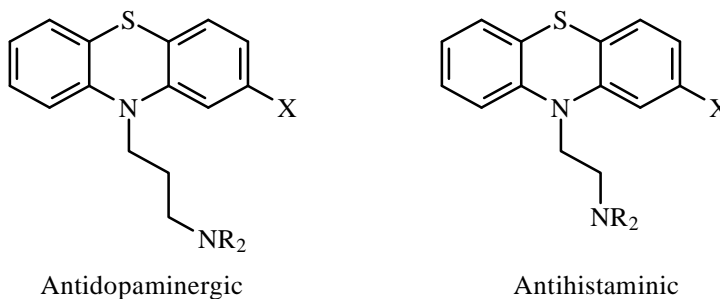
- structural modification of the phenothiazines:
 - thioxanthene* bioisosteres - derived by replacing the N-CH₂ structural feature of the phenothiazines with a bioisosteric double bond:



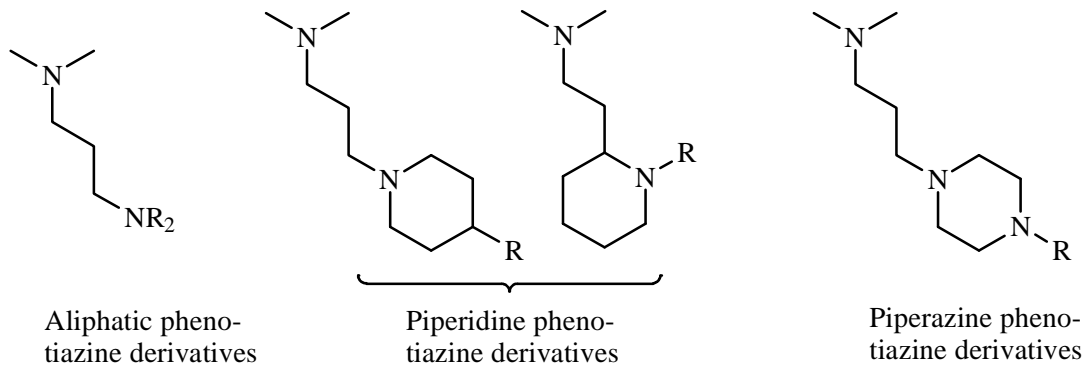
- addition of an electronegative atoms/group at C2 of the phenothiazine ring enhances antipsychotic potency, e.g.:



- a 3-carbon alkyl connector between phenothiazine heterocycle and terminal 3°-amine function is optimal for dopamine-receptor blockade and antipsychotic activity. Shortening of the chain to 2-carbons results in a change in receptor affinity from DA to CNS histamine receptors.



(4) Structural modification of the side chain amine function yields three AP phenothiazine subclasses:

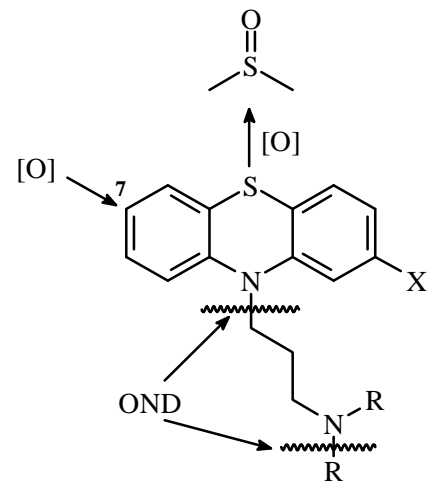


(5) pharmacologic/therapeutic profiles of these 3 classes of antipsychotics differ as follows:

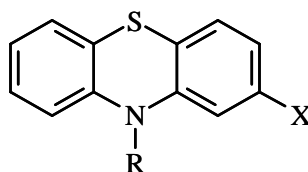
Antipsychotic potency:	piperazines	>	piperidines	>	aliphatics
EPS frequency:	piperazines	>	piperidines	>	aliphatics
Sedation:	aliphatics	≈	piperidines	>	piperazines
Hypotension:	aliphatics	>	piperidines	>	piperazines

4. Biotransformation of the Antipsychotic Phenothiazines

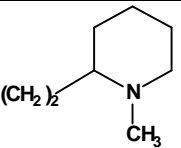
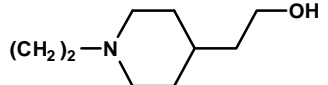
- as depicted, several different biotransformation reactions occur for the same phenothiazine molecule, numerous metabolites are formed and excreted,
- the 7-OH metabolite is an active antidopaminergic while the sulfoxide (S=O) metabolite is inactive
- note that the thioxanthene derivatives do not form aromatic hydroxylated metabolites
- metabolic pathways are significantly altered by a variety of factors (age, sex, interaction with other drugs, route of administration, etc.)

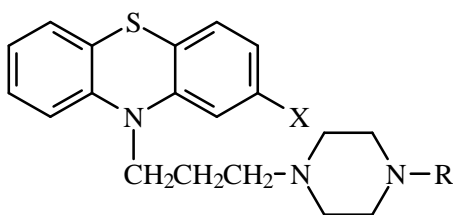


4. Therapeutic Phenothiazines



Aliphatic and Piperidine
Phenothiazines

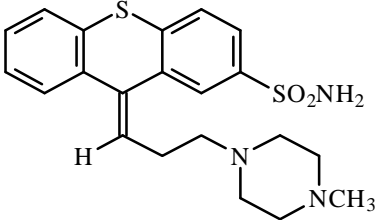
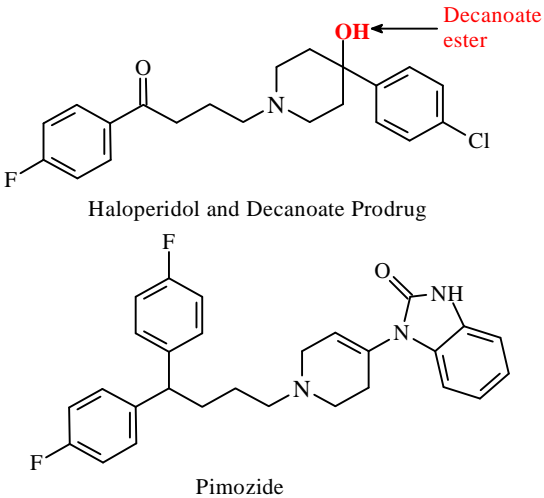
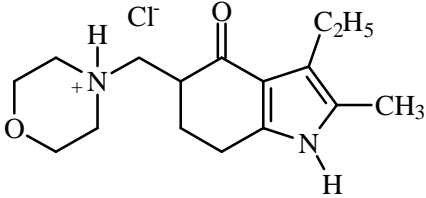
Name	R =	X =
Chlorpromazine	$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	Cl
Triflupromazine	$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	CF_3
Promazine (antiemetic)	$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	H
Thioridazine Mesoridazine		SCH_3 SOCH_3
Piperactazine Perphenazine		COCH_3 Cl

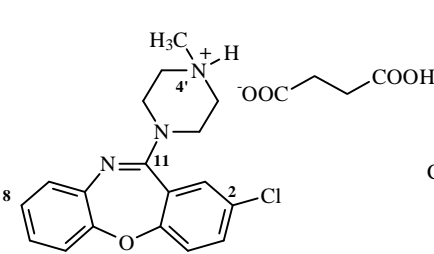
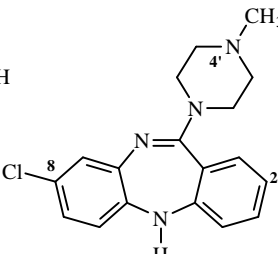
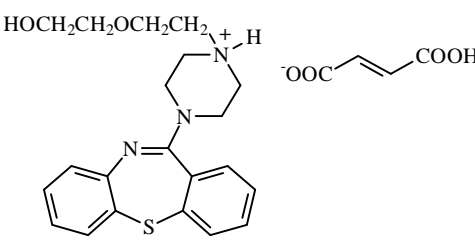
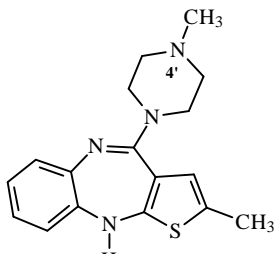
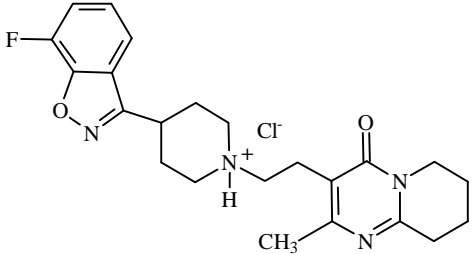


Piperazine
Phenothiazines

Name	R =	X =
Prochlorperazine	CH_3	Cl
Fluphenazine	$(\text{CH}_2)_2\text{OH}$	CF_3
Trifluoperazine	CH_3	CF_3
Acetophenazine	$(\text{CH}_2)_2\text{OH}$	COCH_3
Thiethylperazine	$(\text{CH}_2)_2\text{OH}$	SCH_2CH_3

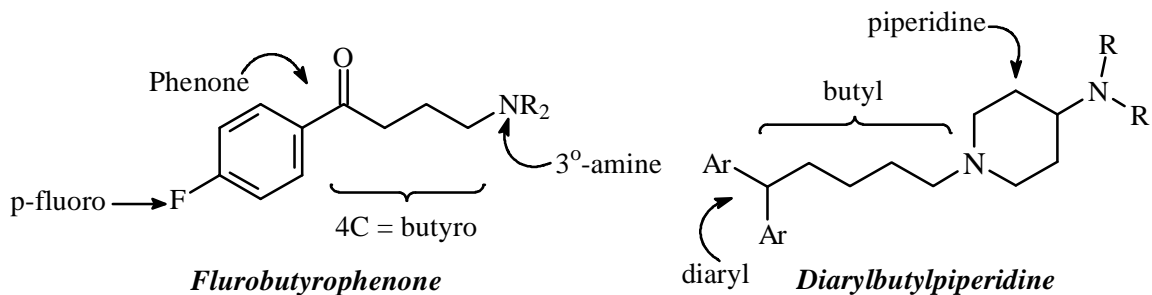
HETEROCYCLIC ANALOGUES OF THE PHENOTHIAZINES

Structural Class	Structure
<p>Thioxanthenes</p> <ul style="list-style-type: none"> ▶ olefin bioisosteres of the phenothiazines ▶ e.g. Thiothixene 	
<p>Arylbutylpiperidines</p> <ul style="list-style-type: none"> ▶ potent D2 receptor antagonists ▶ two structural variants: <ol style="list-style-type: none"> 1) Fluorobutyrophenone (Haloperidol) 2) Diarylbutylpiperidine (Pimozide) 	 <p style="text-align: center;">Haloperidol and Decanoate Prodrug</p> <p style="text-align: center;">Pimozide</p>
<p>Dihydroindolones</p> <ul style="list-style-type: none"> ▶ Molindone Hydrochloride 	

Structural Class	Structure
<p>Dibenzazepines</p> <ul style="list-style-type: none"> ▶ four structural variants 1) Dibenzoxazepine (X=O) (Loxapine) 2) Dibenzodiazepine (X=NH) (Clozapine) 3) Dibenzothiazepine (X=S) (Quetiapine) 4) Thienobenzodiazepine (X=NH) (Olanzapine) 	<div style="display: flex; flex-wrap: wrap; justify-content: space-around;"> <div style="text-align: center; width: 45%;">  <p><i>Loxapine succinate</i></p> </div> <div style="text-align: center; width: 45%;">  <p><i>Clozapine</i></p> </div> <div style="text-align: center; width: 45%;">  <p><i>Quetiapine fumarate</i></p> </div> <div style="text-align: center; width: 45%;">  <p><i>Olanzapine</i></p> </div> </div>
<p>Benzisoxazoles</p> <ul style="list-style-type: none"> ▶ Risperidone 	

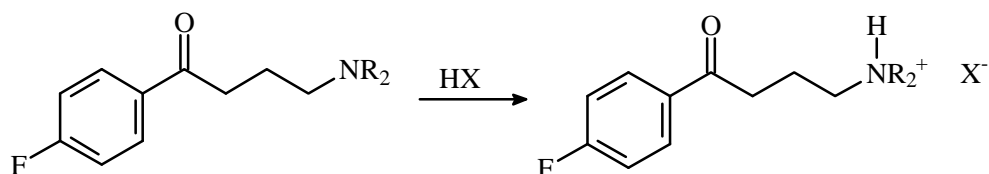
ARYLBUTYLPIPERIDINES

- **Structural Variants:**



- **Physicochemical Properties**

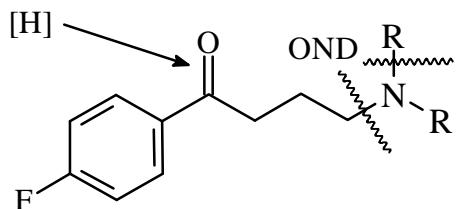
- ▶ lipophilic
- ▶ basic (3°-amine) - forms H₂O-soluble salts



- **Structure-activity Relationships**

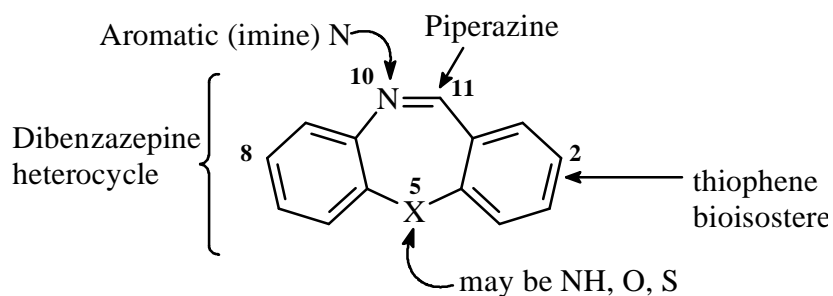
- ▶ para-F or similar electronegative substituent (e.g. CF₃) provides maximal potency,
- ▶ lengthening, shortening or branching of the butyro (4 carbon) chain decreases neuroleptic potency,
- ▶ terminal basic amine function may vary in structure but is usually incorporated in a 6-membered heterocyclic ring
- ▶ replacement of the C=O function with a CH-Ar structural feature yields therapeutically-useful antipsychotics (e.g. pimozide)

- **Metabolism**



DIBENZAZEPINES

- A class of neuroleptics that utilizes the tricyclic dibenzazepine heterocycle as a basic structural feature,
- The dibenzazepine heterocycle is a lipophilic structure with very weakly basic properties,
- Structural variants of dibenzazepines:
 - ▶ *Dibenzoxazepine* (X = O)
 - ▶ *Dibenzodiazepine* (X = NH)
 - ▶ *Dibenzothiazepine* (X=S)
 - ▶ Piperazine substitution at C-11 providing a center (N⁴) of basicity for H₂O-solubilizing salt formation to facilitate oral dosage formulation

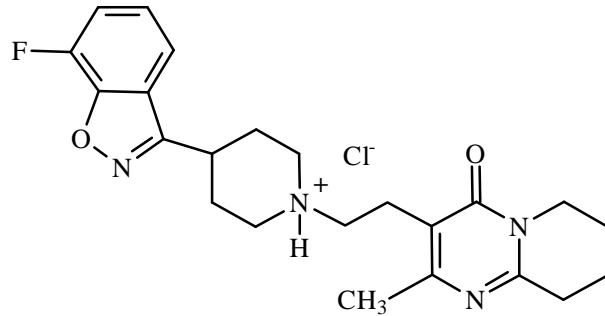


X = NH: dibenzdiazepine
X = O: dibenzoxazepine
X = S: dibenzothiazepine

- atypical antipsychotics:
 - clozapine
 - quetiapine
 - olanzapine

RISPERIDONE

- a benzisoxazole derivative with high affinity for central serotonergic 5-HT₂, dopaminergic D₂ (SDA ratio ≈ 5) and adrenergic α₁-receptors *in vivo*
- has improved efficacy vs. both positive (delusions and hallucinations) and negative (diminished emotions, low motivation) symptoms of schizophrenia and reduced EPS
- HCl salt used for oral formulation



- Metabolism

- (1) Alicyclic hydroxylation ([O]) – the 9-OH metabolite is a potent atypical antipsychotic
- (2) Oxidative N-dealkylation (OD)
- (3) Benzisoxazole ring cleavage

