DOPAMINE ANTAGONISTS: PHENOTHIAZINE/THIOXANTHENE SAR

PC Objective: The pathophysiology and pharmacology of antipsychotic drug therapy:

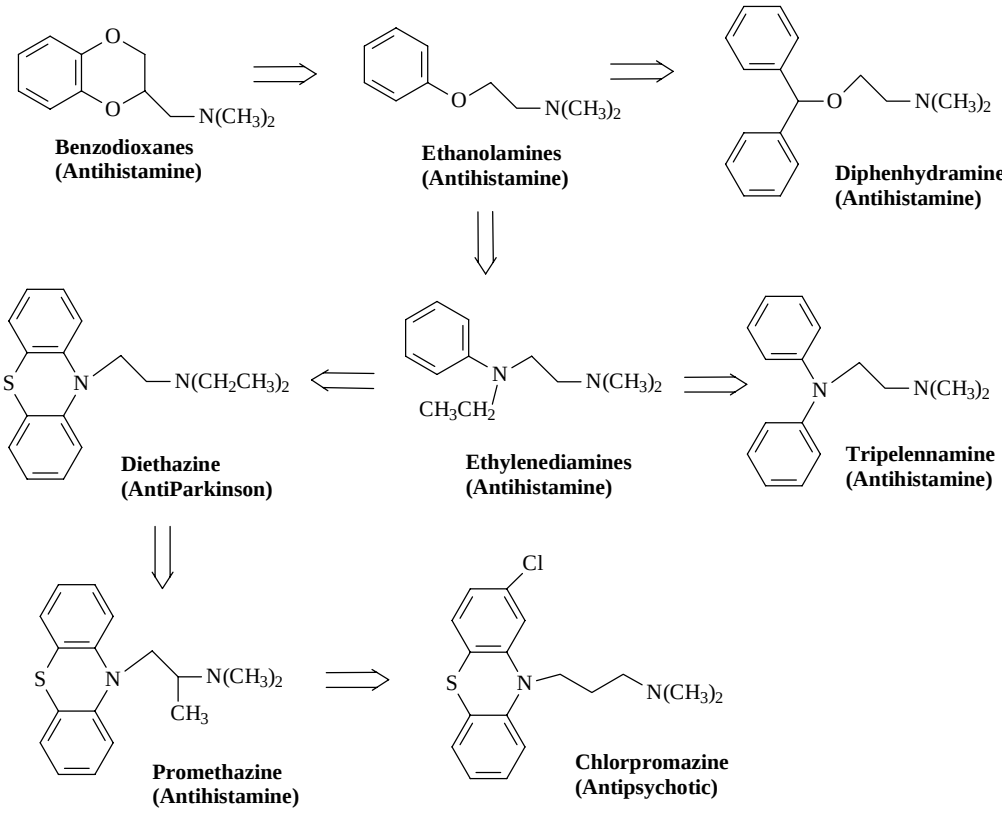
- The pathophysiology of schizophrenia is complex and not completely understood. Early theories focused solely on the involvement of the dopaminergic system in the etiology of this complex syndrome; however, serotonergic pathways have recently been implicated, and newer hypotheses address the interplay not only between these two systems but also the involvement of muscarinic, alpha-adrenergic and histaminic systems. Symptoms are generally categorized into two groups, positive (delusions, disorganized speech, hallucinations and behavior disturbance) and negative (avolition, flattened affect, anhedonia and social withdrawal). Pharmacotherapy is aimed at improving these target symptoms while maintaining the most tolerable side effect profile at the lowest possible dose.

- The phenothiazines and structurally related thioxanthines, along with the butyrophenones (phenylbutylpiperadines), diphenylbutylpiperadines and the indolones comprise the socalled "typical" (conventional) antipsychotics. As a group, the typical antisychotics are dopamine receptor antagonists with a higher affinity for D2 over D1 receptors. They also exhibit varying degrees of selectivity among the cortical dopamine tracts; nigrostriatal (movement disorders), mesolimbic (relief of hallucinations and delusions), mesocortical (relief of psychosis, worsening of negative symptoms) or tuberoinfundibular (prolactin release). They also bind with varying affinities on nondopaminergic sites, such as cholinergic (muscarinic), alpha-1-adrenergic and histamine-1 receptors, which can partially explain the varied side effect profiles for each agent. Typical antipsychotics have similar efficacies when used in equipotent doses and are likely to induce extrapyramidal side effects (EPS). Lower-potency agents (lower DA antagonist activity such as the aliphatic phenothiazines) tend to be more sedating and high-potency agents (piperazine phenothiazines) usually have a higher incidence of acute EPS due to a combination of high DA receptor blockade and lower muscarinic receptor blockade.

- The principle differences between the different types of phenothiazine antipsychotics the type and severity of side effects. Most (but not all!) side effects are predictable based on the relative strength of interaction between different phenothiazine types with an array of neurotransmitter receptors. Depending of their receptor binding profiles, the phenothiazines and other antipsychotics may produce:

  - Histamine-1 Receptor antagonist (antihistaminic): Sedation
  - Serotonergic receptor antagonism: weight gain
  - Dopamine receptor antagonism (D2): EPS, prolactin release and **therapeutic actions**
  - Muscarinic receptor antagonism: urinary retention, dry mouth, blurred vision, constipation, sinus tachycardia, cognition and memory effects
  - Alpha-1-receptor antgaonism: orthostatic hypotension, reflex tachycardia

MC Objective: Development of the Phenothiazine Antipsychotics: Design of compounds with dopamine receptor antagonist activity



MC Objective: The Phenothiazines and Dopamine Receptor Binding (relative to DA):

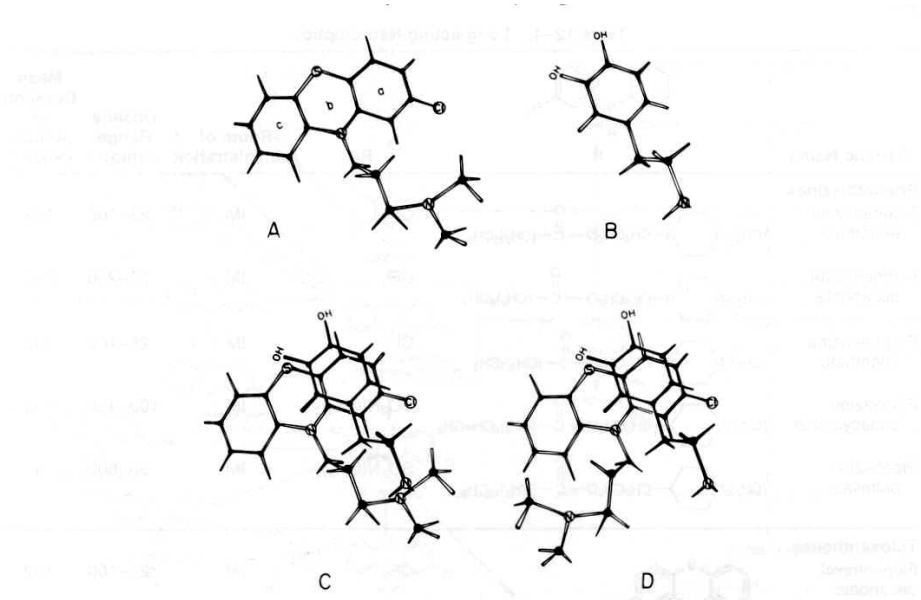
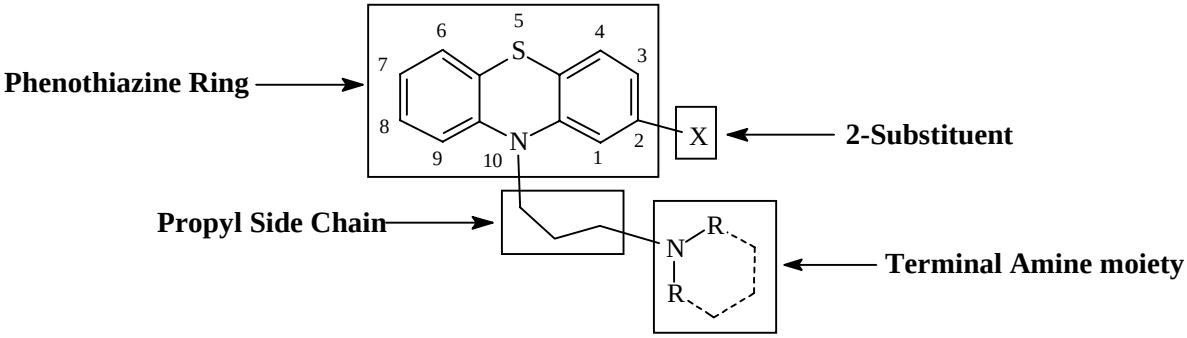


Fig. 12–11. Conformations of chlorpromazine (A), dopamine (B), and their superposition (C), determined by x-ray crystallographic analysis. The a, b, and c in (A) designate rings. D shows another conformation in which the alkyl side chain of chlorpromazine is in the *trans* conformation (ring a and amino side chain), which is not superimposable on dopamine. (Adapted from A. S. Horn and S. H. Snyder, *Proc. Natl. Acad. Sci. U.S.A., 68,* 2325[1971].)

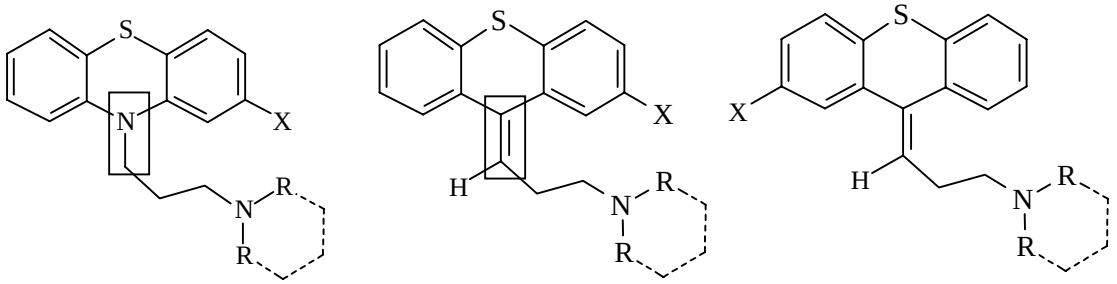
MC Objective: Describe the general structural features and numbering system for the phenothiazine drugs:



MC Objective: The functional groups that contribute toward DA receptor binding and therefore therapeutic activitity (see conformation figure) include:

- The phenothiazine or isosteric thioxanthene ring system (Ring binding site)
- the 2-substituent (Electronic effect on binding?)
- the propyl side chain ("spacer group" between phenothiazine and amine group)
- the terminal amino moiety (Protonated amine moiety bound at receptor)

MC Objective: 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:

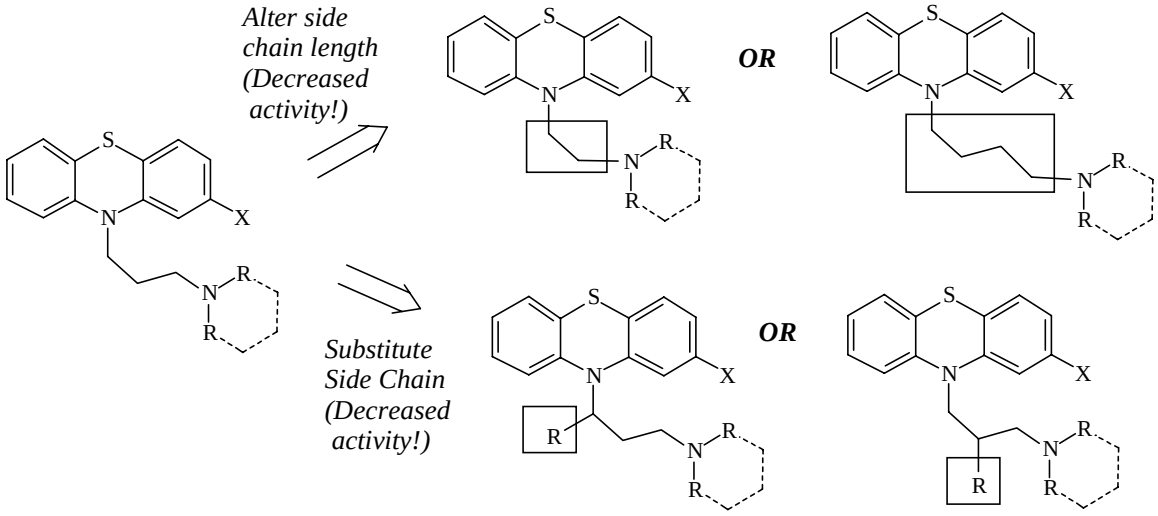


Phenothiazine **Z: Thioxanthene** **E: Thioxanthene**

MC Objective: The 2-substituent should be an **electron withdrawing** moiety for optimal DA receptor affinity. Substituents at positions 1,3 and 4, decrease activity:

- 1-substituents interfere with side chain conformation required for DA binding
- 3-substituents: may be tolerated
- 4-substituents interfere with S binding to DA receptor
- Additional ring substituents generally decrease activity

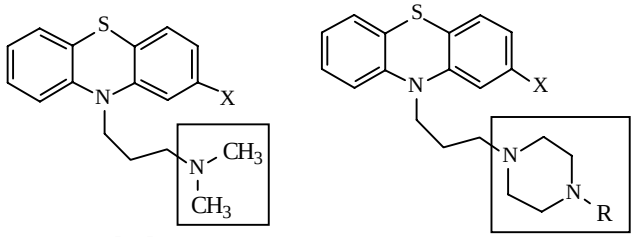
MC Objective: A three carbon chain for optimal DA receptor binding: shorter chain derivatives have increased affinity for ACh and H-1 receptors (side effects). Substitution and branching in side chain generally reduces DA receptor affinity (except on the carbon alpha-to the terminal amine:

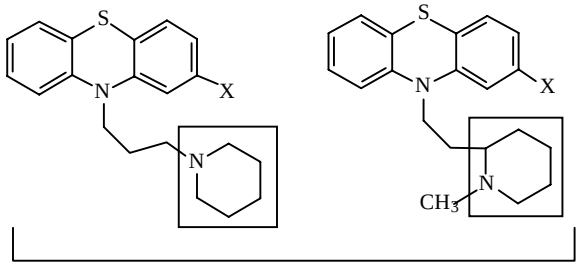


MC Objective: Terminal amine moiety requirements for optimal DA receptor affinity:

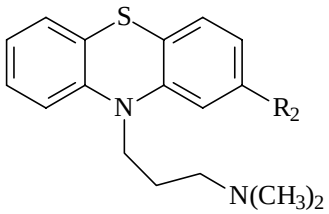
- Basic (protonated), tertiary amine: Secondary and primary amines less active
- Substituents larger than N-ethyl or ring equivalents are less active
- Major DA receptor ligands have N,N-dimethylamine, (aliphatic), piperidine or piperazine terminal N-substituent.

MC Objective: Different terminal amine substituents have different receptor binding profiles and thus different antipsychotic potencies and adverse reactions. These trends are illustrated in the following two Tables. **SEE INIDIVIDUAL PHENOTHIAZINE PRODUCTS ON NEXT PAGE**

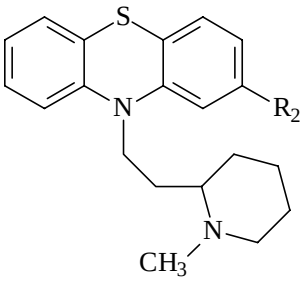




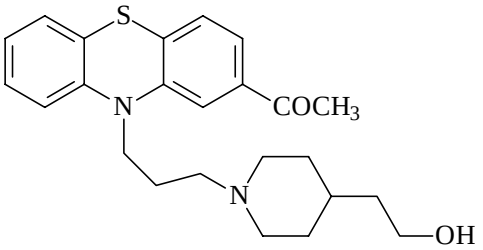
THE PHENOTHIAZINE AND THIOXANTHENE PRODUCTS



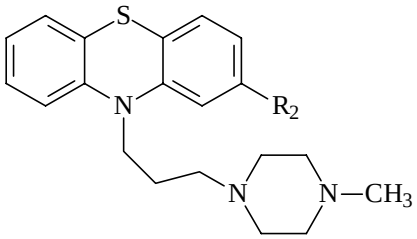
Promazine (Sparine): R_2 = H
Chlorpromazine (Thorazine): R_2 = Cl
Triflupromazine (Vesprin): R_2 = CF_3



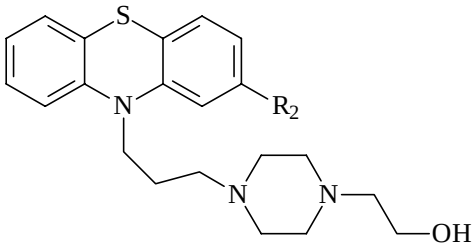
Thioridazine (Mellaril): R_2 = SCH_3
Mesoridazine (Serentil): R_2 = $SOCH_3$



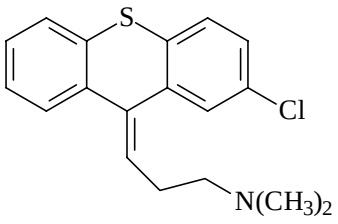
Piperacetazine (Quide)



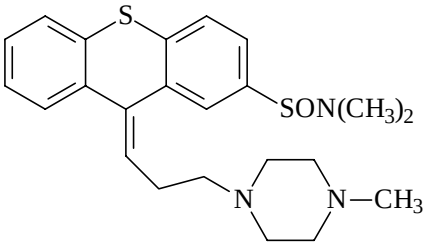
Perchlorperazine (Compazine): R_2 = Cl
Trifluoperazine (Stelazine): R_2 = CF_3



Perphenazine (Trilafon): R_2 = Cl
Fluphenazine (Permitil): R_2 = CF_3
Acetophenazine (Tindal): R_2 = $COCH_3$
Thiethylperazine (Torecan): R_2 = SCH_2CH_3



Chlorprothixene (Taractan)



Thiothixene (Navane)

- Note in Table 1 that **piperazine** phenothiazines and thioxanthines have HIGHER affinities for dopamine receptors and are more potent as antipyschotics (and in producing some AD-related side effects)

- Note that the **piperazine** phenothiazines and thioxanthines have LOWER affinities for muscarinic, histamine-1 and alpha-1 receptors (antagonists!). Thus these compounds are less likely to produce sedation, orthostatic hyoptension, and other effects mediated by muscarinic and alpha-adrenergic receptors (see Page 1).

- Note that the **Piperidines** have the LOWEST incidence of EPS. This is a result of their combined dopamine and muscarine receptor activities. Piperidines have intermediate DA-receptor blocking activity (contributes to EPS) and relatively high anti-muscarinic activity (decreases the likelihood of EPS). This combined receptor binding profile results in relatively low EPS.

- Retinal toxicity is primarily a function note of the piperidine ring, but the sulfur containing 2-substituents present in these compounds.

Table 1 Summary of the Receptor Binding Profiles and Key Side eEffects associated with the Phenothiazine and Thioxanthines

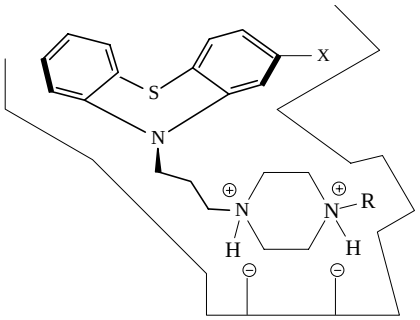
Pharmacologic/Therapeutic Property	Relative Activity
DA receptor affinity	Piperazine > Piperidines > Aliphatics
MACh receptor affinity	Piperidines = Aliphatics > Piperazines
Alpha-1 receptor affinity	Piperidines = Aliphatics > Piperazines
H-1 receptor affinity	Piperidines = Aliphatics > Piperazines
Antipsychotic potency	Piperazines > Piperidines > Aliphatics
EPS Frequency	Piperazines > Aliphatics > Piperidines
Sedation	Piperidines = Aliphatics > Piperazines
Orthostatic Hypotension	Aliphatics > Piperidines > Piperazines
Dermatitis	Aliphatics = Piperidines > Piperazines
Convulsions	Aliphatics > Piperidines = Piperazines
Retinal Toxicity	Piperidines > Piperazines = Aliphatics
Ejaculatory Disturbances	Aliphatics = Piperidines > Piperazines

Table 2. Overall Dosage and Pharmacologic Parameters of Antipsychotics (Facts and Comparisons)

Antipsychotic agent	Approx equiv. dose (mg)	Adult daily dosage range (mg)	Sedation	EPS	Anti-MACh	Orthostatic Hypotension
Phenothiazines: Aliphatic						
Chlorpromazine	100	30 to 800	+++	++	++	+++
Promazine	200	40 to 1200	++	++	+++	++
Trifluprомazine	25	60 to 150	+++	++	+++	++
Phenothiazines: Piperazine						
Fluphenazine	2	0.5 to 40	+	+++	+	+
Perphenazine	10	12 to 64	++	++	+	+
Prochlorperazine	15	15 to 150	++	+++	+	+
Trifluoperazine	5	2 to 40	+	+++	+	+
Phenothiazines: Piperidines						
Mesoridazine	50	30 to 400	+++	+	+++	++
Thioridazine	100	150 to 800	+++	+	+++	+++
Thioxanthenes:						
Thiothixene	4	8 to 30	+	+++	+	++
Butyrophenone (Phenylbutylpiperadines)						
Haloperidol	2	1 to 15	+	+++	+	+
Diphenylbutylpiperadines						
Pimozide	0.3- 0.5	1 to 10	++	+++	++	+
Dihydroindolones:						
Molindone	10	15 to 225	++	++	+	+
Dibenzoxazepines						
Loxapine	15	20 to 250	+	++	+	+
Clozapine	50	300 to 900	+++	+	+++	++
Thienbenzodiazepine						
Olanzapine		5 to 20	+++	+	+++	++
Dibenzothiazepine						
Quetiapine		50 to 800	++	+	0	++
Benzisoxazoles:						
Risperidone		4 to 16	+	+/++	0	+

+++ = High incidence of side effects ++ = Moderate incidence of side effects + = Low incidence of side effects (**over the therapeutic dose range**!). At doses > 10 mg/day, risperidone's EPS profile is similar to typical antipsychotics.

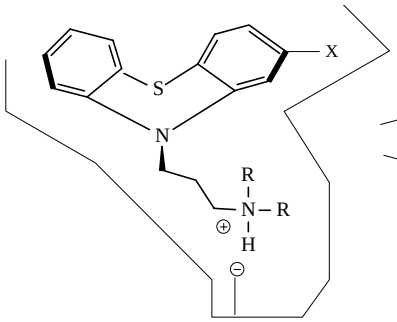
MC Objective: Describe the relationship between phenothiazine and thioxanthene structure and antagonist actions at alpha-1, muscarinic and histamine-1 receptors. Understand how these relate to the differences in the realtive side effect profiles of these drugs!



Antipsychotic Effects

Dopaminergic Side Effects (EPS)

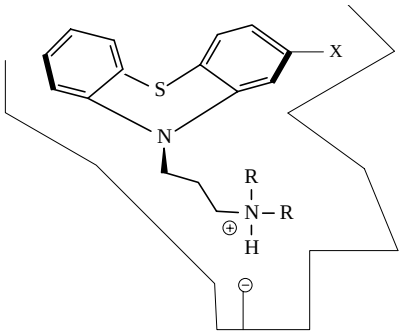
DA RECEPTOR



Antimuscarinic Side Effects

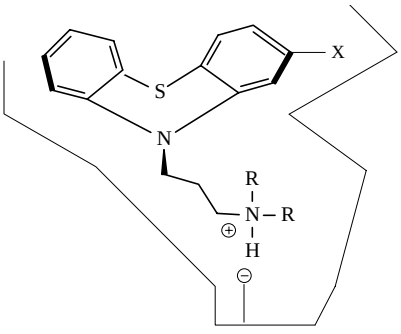
Anti-EPS Action
(Counter-balances DA Blockade)

MACh RECEPTOR



Anti-Adrenergic Side Effects
(Hypotension)

Alpha-1 RECEPTOR



Anti-Histaminic Side Effects
(Sedation)

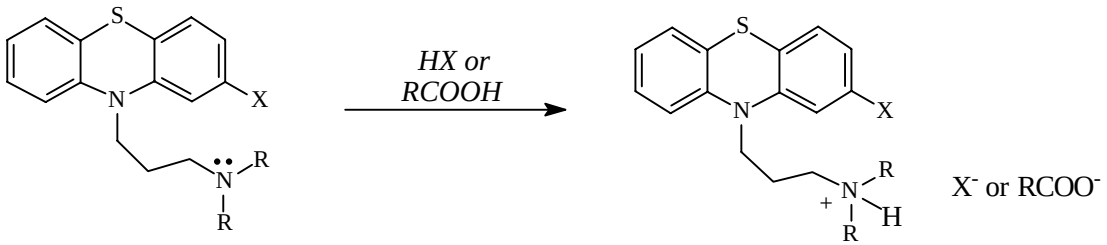
Histamine-1 RECEPTOR

MC Objective: Describe the chemical properties of the phenothiazine and thioxanthene dopamine antagonists:

- Relatively lipophilic due to the tricyclic ring ring structure
- Basic (pKa>10) due the presence of one or more basic nitrogen atoms
- Relatively stable chemically.
- Metabolically unstable: Subject to many transformations as noted below

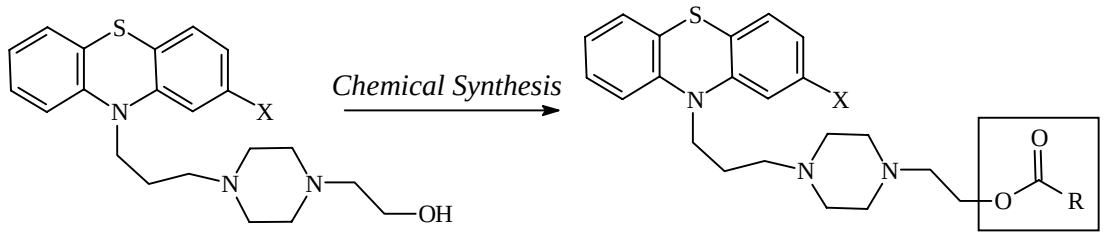
MC Objective: Describe the different phenothiazine and thioxanthene products and dosage forms.

- Free base form
- Mineral acid or organic acid salts
- Ester prodrugs (IM)



Free Base

Mineral acid salts (X-) and Organic acid (RCOO-) Salts



Piperazines (Hydroxyethyl derivatives)

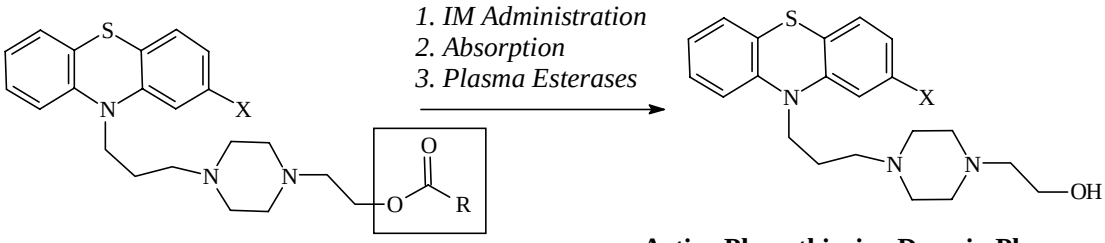
Piperazine Lipophilic Prodrug
R = C_6H_{13} to $C_{15}H_{31}$ (aliphatic)

MC Objective: Describe the oral bioavailability profiles of the phenothiazine and thioxanthene dopamine antagonists:

- **Absorption:** Lipophilic drugs and the non-ionized form is generally well absorbed from the small intestine
- **Oral Bioavailability** variable, erratic and LOW (<50%) due to extensive first pass metabolism (see metabolism below). Oral liquid forms are most predictably absorbed. Conventional tablets are preferred over sustained release forms, which are usually more expensive and not necessary because of long duration of action of these agents.
- Peak plasma levels are seen 2 to 4 hours after oral use for most (range 1-8hrs).

MC Objective: Describe the bioavailability profiles of the phenothiazine and thioxanthene ester prodrugs:

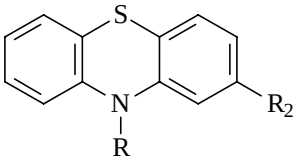
- Ester prodrugs are even more lipophilic than the corresponding parent drugs
- Administered IM and are slowly absorbed to the plasma from IM site
- In the plasma the esters are efficiently hydrolyzed to the pharmacologically active parent drug:

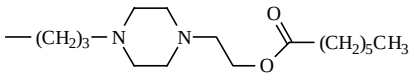
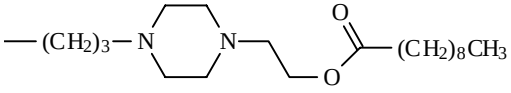
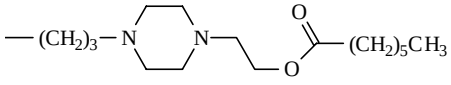
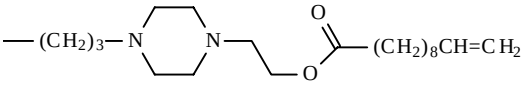
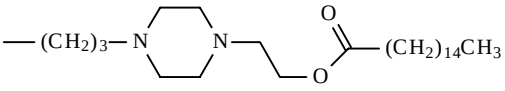


Piperazine Lipophilic Prodrug
R = C_6H_{13} to $C_{15}H_{31}$ (aliphatic)

Active Phenothiazine Drug in Plasma

- IM use provides 4 to 10 times more active drug than oral doses (limited first pass)
- IM use provides prolonged plasma levels of active drugs (WEEKS!) enhancing compliance (a major problem in the psychotic patient population
- Ester prodrug products are presented in the table below:



Phenothiazine	R group	R_2 Group	Durtn (wks)
Fluphenazine Enanthate		$-CF_3$	1-2
Fluphenazine Decanoate		$-CF_3$	2-3
Perphenazine Enanthate		-Cl	1-2
Pipotiazine Undecylenate		$-SO_2N(CH_3)_2$	1-2
Pipotiazine Palmitate		$-SO_2N(CH_3)_2$	4

MC Objective : Describe the distribution profile of the phenothiazine and thioxanthene dopamine antagonists:

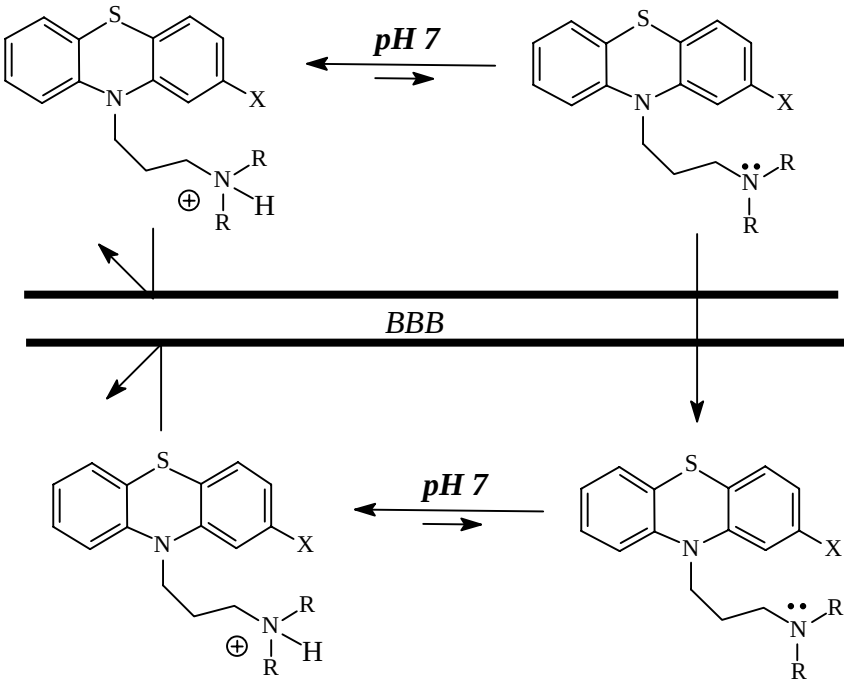
- Because plasma concentrations of phenothiazines/thioxanthenes are **highly variable** from patient to patient (variable oral bioavailbility and first pass metabolism), plasma monitoring of these agents may not be useful for determining therapeutic response. Plus, therapeutic levels are only available for a small number of these agents. However, monitoring may help decrease the incidence of toxicity because plasma levels are relatively stable in each individual.

- Exist primarily in their ionized form at physiologic pH (see below)

- The phenothiazines and thioxanthenes are highly bound to plasma proteins (91% to 99%) as a result of their ionized cationic center and lipophilic ring system: Both groups contribute to plasma protein binding.

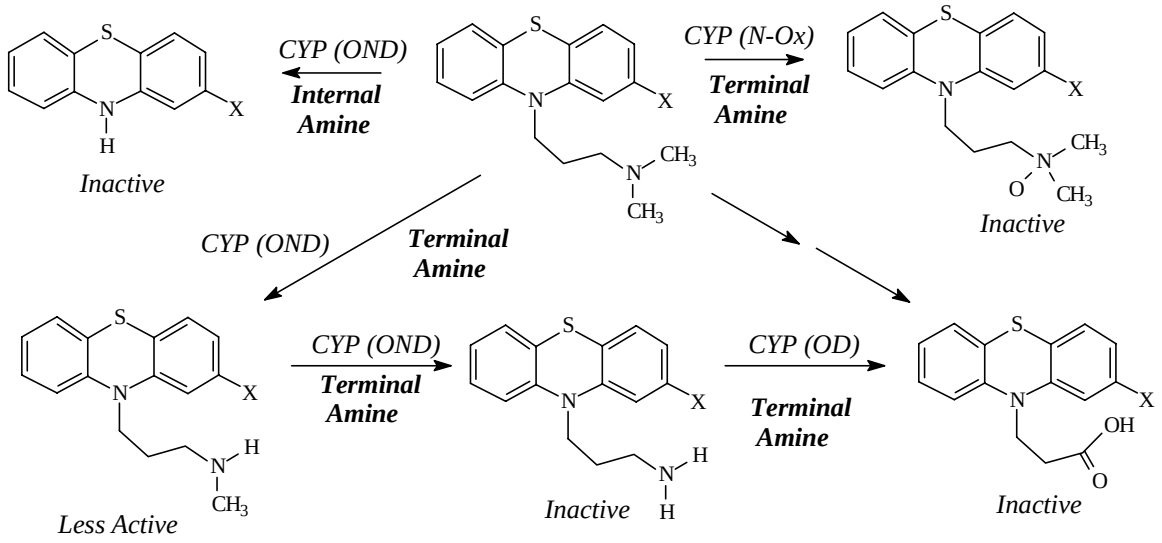
- Because they are highly lipophilic, the phenothiazines and non-polar metabolites are widely distributed and accumulate in the brain, lungs and other tissues with high blood supply. Typically CNS concentrations exceed those in plasma (as much as 5x).

- The phenothiazines are stored in these tissues and may be found in urine for up to 6 months after the last dose.

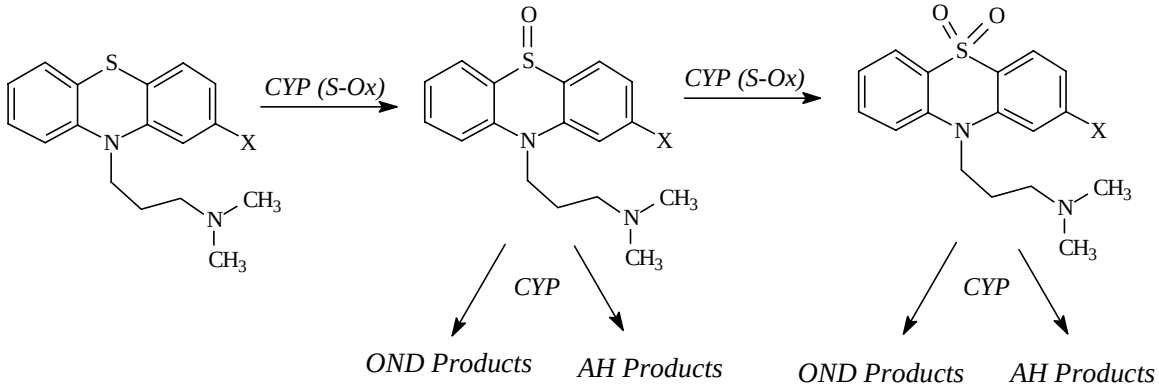


MC Objective: Describe the METABOLIC profile of the phenothiazine and thioxanthene dopamine antagonists:

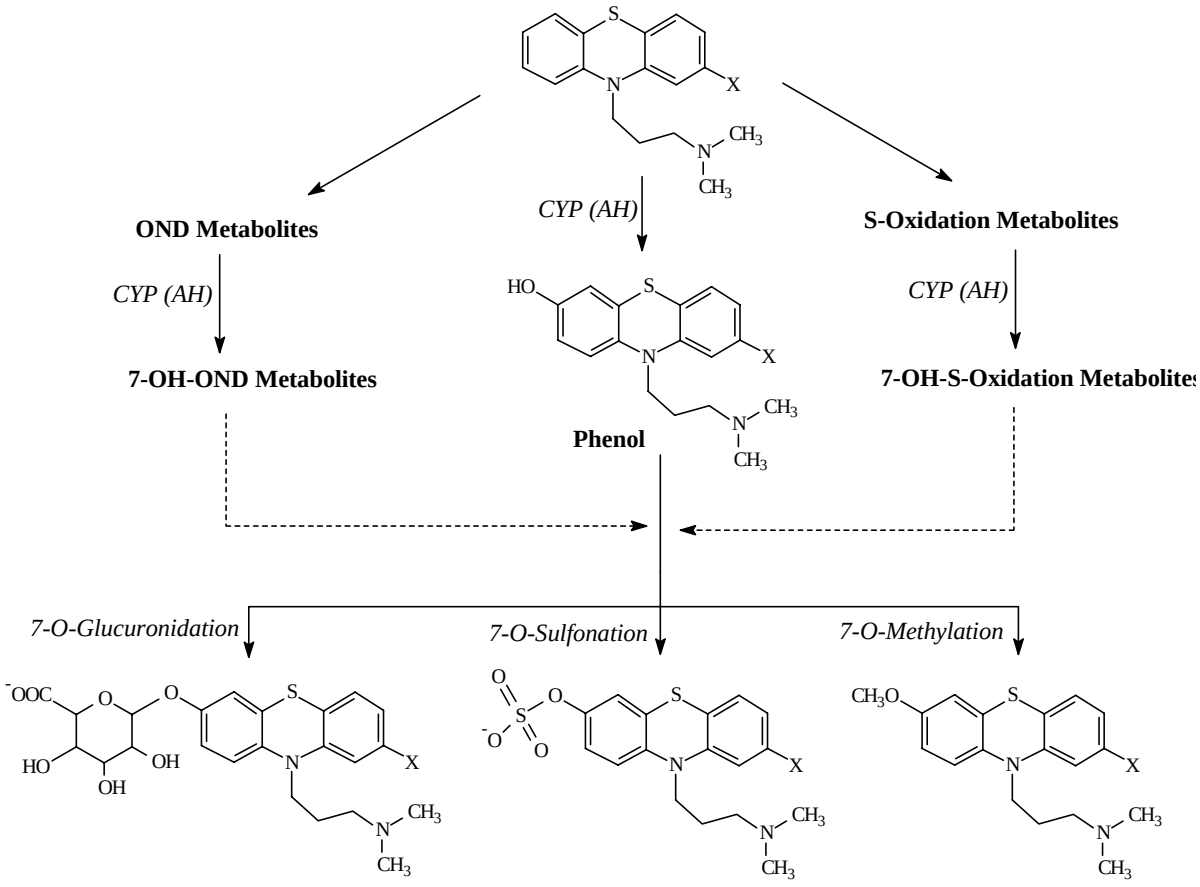
- Extensive biotransformation occurs in the liver (first pass and secondary metabolism)
- Numerous active and inactive metabolites are formed and these may persist for prolonged periods, have important side effects and contribute to the biological activity of the parent drug.
- The major metabolic pathways are oxidative N-dealkylation (OND), N-oxidationm (N-OX) aromatic hydroxylation (AH), sulfur oxidation (S-Ox) and conjugation by glucuronidation, sulfonation or methylation:
- Oxidative N-dealkylation (OND) is cytochrome mediated and may occur at the "terminal" or "internal" amine as shown below. Either reaction results in deactivation or inactivation of the drug. Of course, the ring C-N system is resistant to OND!



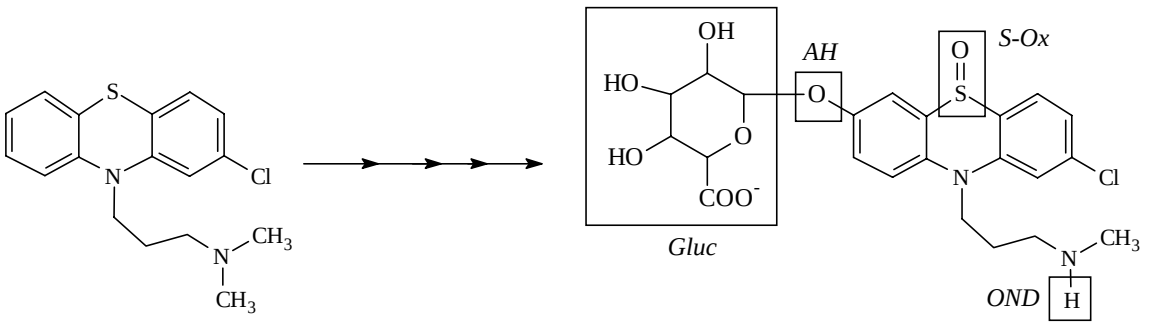
- S-Oxidation is cytochrome-mediated and may occur sequentially to form a sulfone:



- Aromatic Hydroxylation (AH) is cytochrome mediated and occurs primarily at the most electron rich aromatic center, the 7-position. AH may occur on the parent phenothiazine, or on the OND or S-Ox metabolites as shown below. The phenol metabolites formed may be conjugated by glucuronidation, sulfonation or methylation:



- **It is important to note that multilpe metabolic transformations may occur on the parent phenothiazines drugs AS WELL AS the metabolites formed by OND, AH, S-Ox, etc. Thus for some phenothiazines MORE THAN 100 metabolites have been identified. The potential for multilpe metabolic transformations is illustrated by the example below:**



Chlorpromazine

7-O-Glucuronide-nor-chlorpromazine-sulfoxid

MC Objective: Describe the ELIMINATION profile of the phenothiazine and thioxanthene dopamine antagonists:

- Approximately 50% of the excretion of these agents occurs via the kidneys and the other half occurs through enterohepatic circulation.
- Elimination half-lives range from 10 to 20 hours or most, but may be as long as 100 hrs.
- Less than 1% is excreted as unchanged drug.
- The fetus, the infant and the elderly have diminished capacity to metabolize and eliminate antipsychotic agents; children tend to metabolize these drugs more rapidly than do adults.

MC Objective: Describe the DRUG INTERACTION profile of the phenothiazine and thioxanthene dopamine antagonists:

- Anticholinergics: The anticholinergic effects may be potentiated by some of these agents.
- Antihypertensives: The hypotensive effects may be potentiated by some of these agents.
- CNS drugs: Given the primary CNS effects of some of these agents, caution is advised in using them concomitantly with other CNS-active drugs.
- P450 system: Agents that induce or inhibit CYP isozymes or glucoronyl transferase enzymes could affect drug metabolism.

MC Objective: Describe the ADVERSE REACTION profile of the phenothiazine and thioxanthine dopamine antagonists:

- Neuroleptic malignant syndrome (NMS):
- Tardive dyskinesia:
- Extrapyramidal events: Pseudoparkinsonism (4% to 40%); akathisia (7% to 20%); dystonias (2% to 50%).
- Behavioral effects:
- Autonomic:
- Cardiovascular: Hypotension, direct myocardial depression
- CNS: Headache to Seizures
- Endocrine - Lactation gynecomastia, Hyperpyrexia
- Hematologic - Agranulocytosis
- Hepatic - Jaundice
- Hypersensitivity - Contact dermatitis
- Ophthalmic:
- Respiratory: