Antipsychotic agents
FAR 344/4

Dr. Aisyah Saad

Some definitions

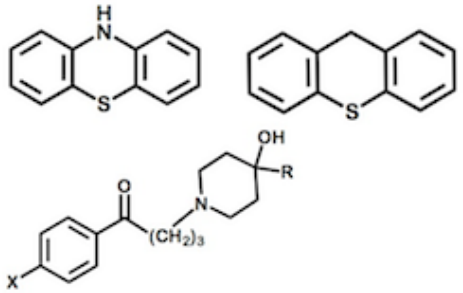
- Antipsychotics
  - "Anti": against; opposite of
  - "Psycho-": (Gk) psukhē means 'breath, soul, mind'
- Neuroleptics - 'mood-stabilisation' effects
  - "Neuro-" - nerves

Definitions of Antipsychotics/

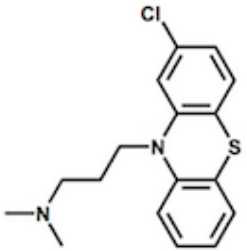
- A class of drugs that is used to treat psychosis.
- Psychosis is the term used to describe severe mental disorder, characterized by :
  - confused, agitated personality &
  - loss of contact with reality &
  - aggressive and impulsive behaviours.
- Conditions include schizophrenia, mania & delusional disorder
- Neuroleptics (or antipsychosis, or major tranquilizer) stabilises moods, calm and exert anti-hallucinogenic effects on patients

Types of Neuroleptics

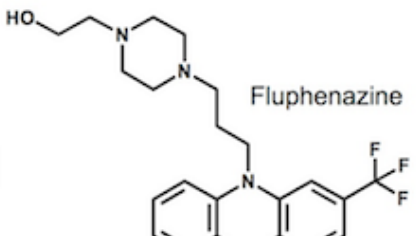
- Typical Neuroleptics
  - Phenothiazines
  - Thioxanthene
  - Butyrophenones
  - Pimozide
- Atypical Neuroleptics
  - Sulpiride & Clozapine



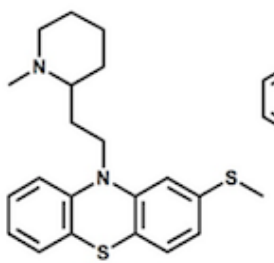
Phenothiazines



Chlorpromazine



Fluphenazine



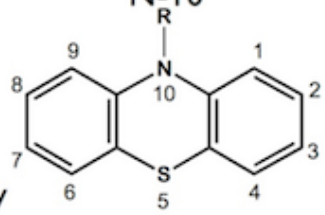
Thioridazine

Phenothiazine ring & SAR

Optimal length of R: propyl
If R = ethyl, reduced neuroleptic activity

No protonation at N-10

Electron withdrawing groups has great influence on its chemical behaviour

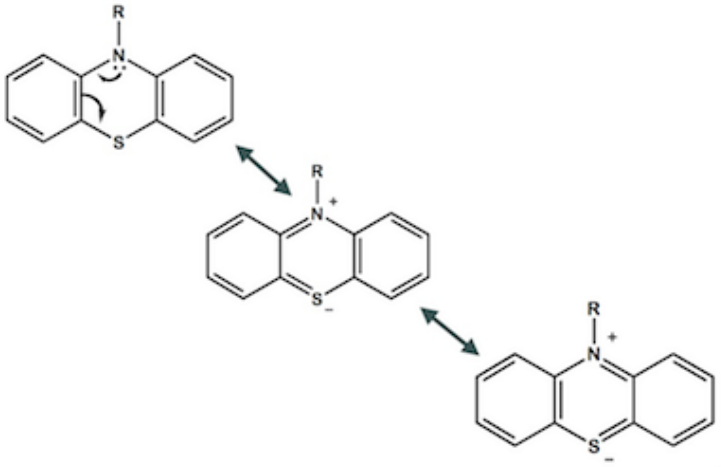


Fused ring system of two benzene rings and a 1,4-thiazine

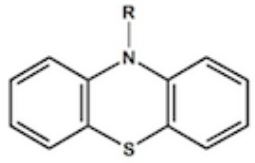
Loss of activity occurs on oxidation of S-5

Therapeutic phenothiazines are always substituted at N-10 & C-2.
At C-2: always Cl. Without C-2 Cl, no activity.

Mesomeric Resonance Structures of Phenothiazines

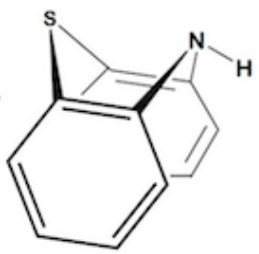


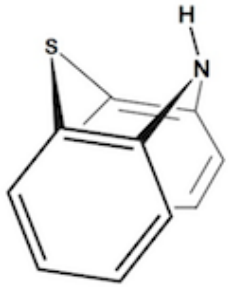
Is phenothiazine as flat as a pancake?!



Tetragonal folded configuration

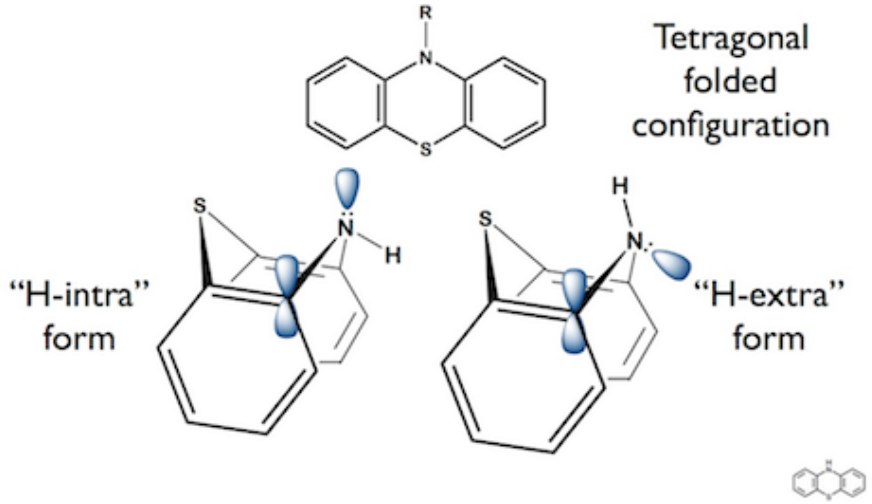
"H-intra" form



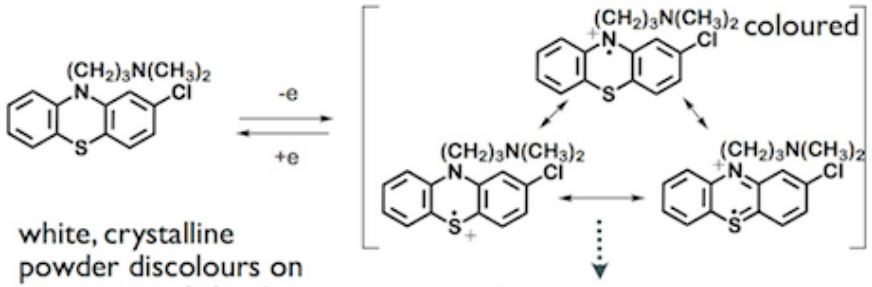


"H-extra" form

Phenothiazines reactivity & Shape

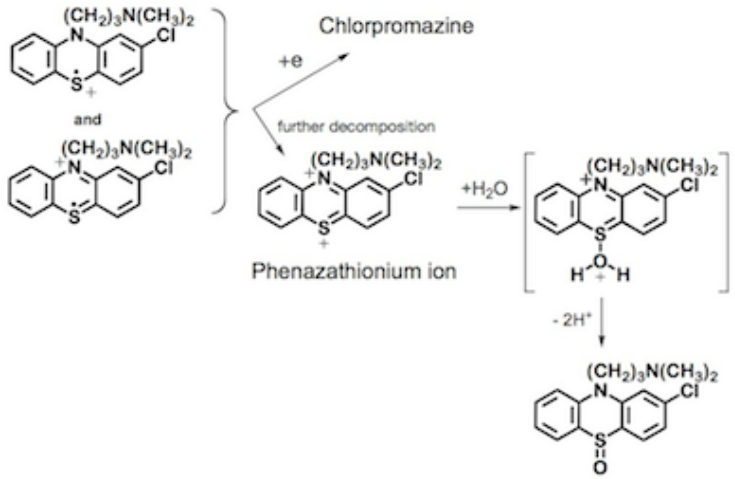


How do Phenothiazines behave on exposure to Light

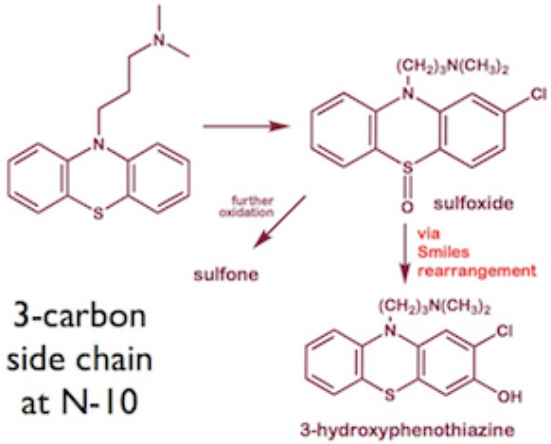


white, crystalline powder discolours on exposure to light & oxygen

Phenothiazines' behaviour towards Light and Oxygen Disproportionation products



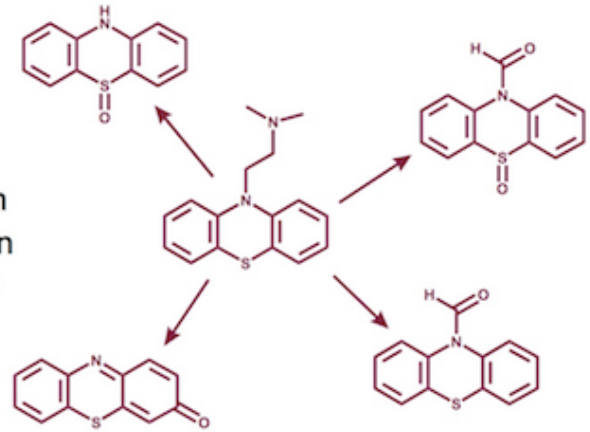
Influence of N-10 substituent on Phenothiazine's reactivity

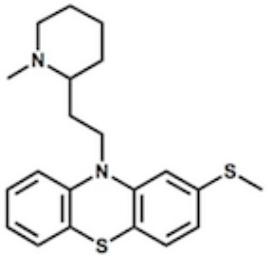


3-carbon side chain at N-10

Influence of N-10 substituent on

2-carbon side chain at N-10





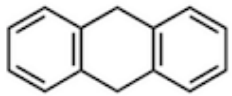
Thioridazine

(R,S)-10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine

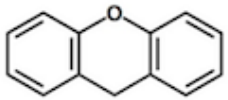
- Piperidine-substituted phenothiazine
- Less side effects esp. tardive dyskinesia
- Sold as a racemic mixture
- Discovered later that -
  - (*R*)-enantiomer : 2.7x affinity for D2 receptor but, (*S*)-enantiomer : 10x affinity for D receptor
  - Development of a more potent enantiomer may lead to 'atypical' drug - more selective and less side effects

Metabolites :
- Thioridazine-2-sulphoxide (Mesoridazine)
  - further to Sulforidazine
  - both > potent than parents.
- Thioridazine-5-sulphoxide

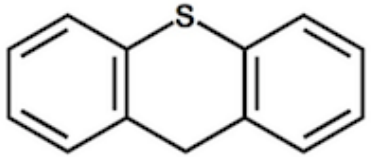
Thioxanthene



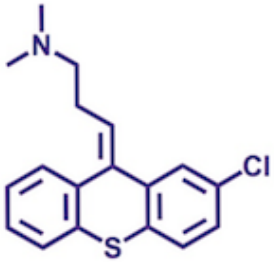
9,10-dihydroanthracene



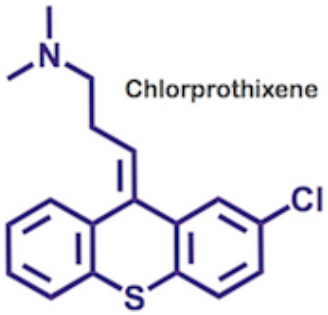
Xanthene



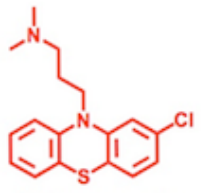
Thioxanthene



Chlorprothixene



Chlorprothixene

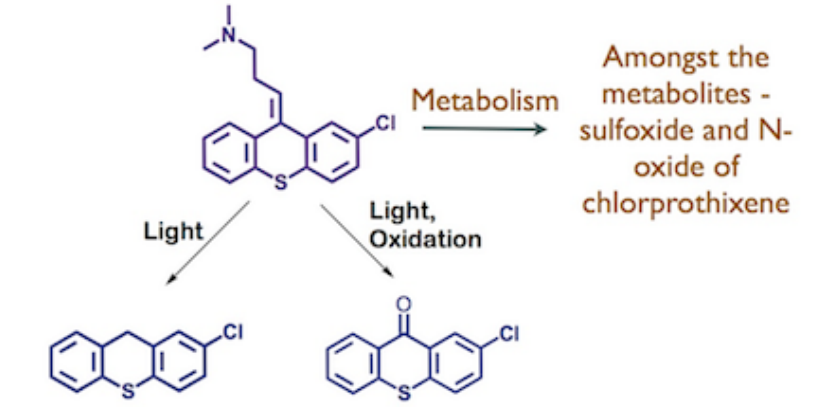


Chlorpromazine

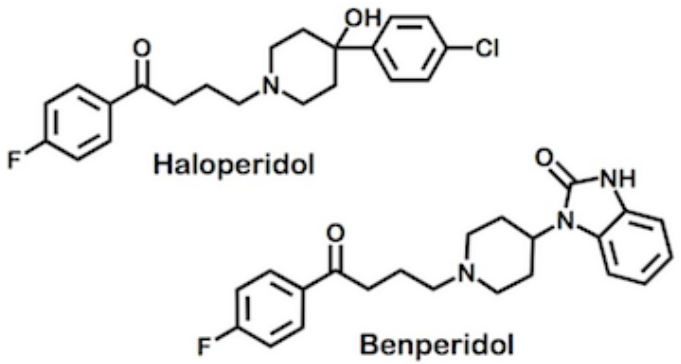
(Z)-3-(2-chlorothioxanthen-9-ylidene)-N,N-dimethylpropylamine

- much lower potency cf chlorpromazine
- Promiscuous activity : D1-3 receptors; H1; muscarinic etc.
- Structurally related to chlorpromazine - shares the side effects
- Chemistry : Stable towards dilute acids/alkalis and thermally stable
- though still light-sensitive...

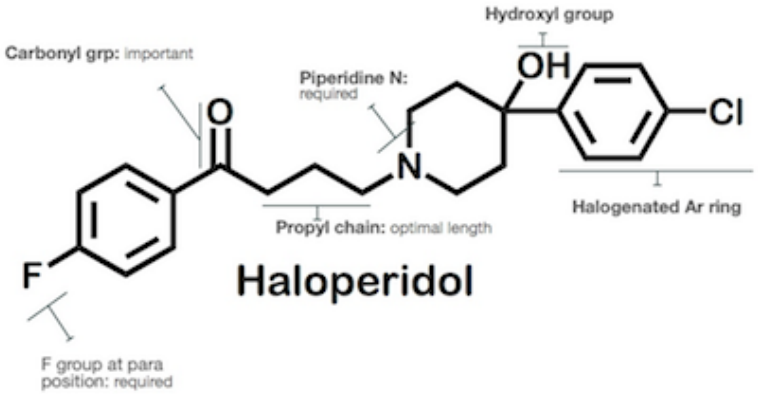
Decomposition of Chlorprothixene

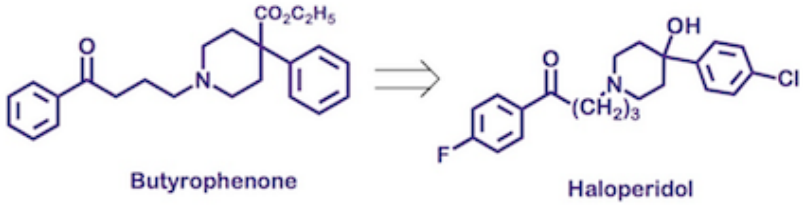


Butyrophenone derivatives



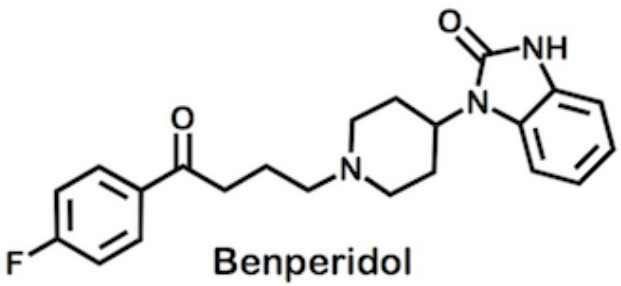
SAR of Butyrophenones





4-[4-(chlorophenyl)-4]-hydroxypiperidino-[4-fluoro]-butyrophenone

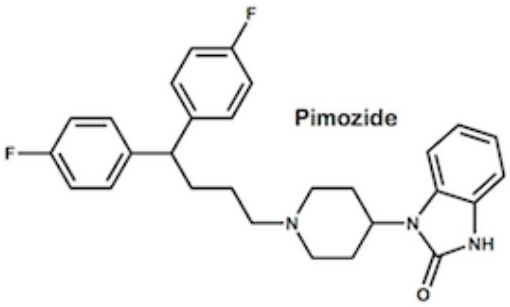
- a butyrophenone neuroleptic
- more potent than chlorpromazine - weight by weight
- administered as a prodrug haloperidol decanoate - therapeutic level lasts up to 4 weeks



Benperidol

1-1-(3-(p-Fluorobenzoyl)propyl)-4-piperidyl-2-benzimidazolinone

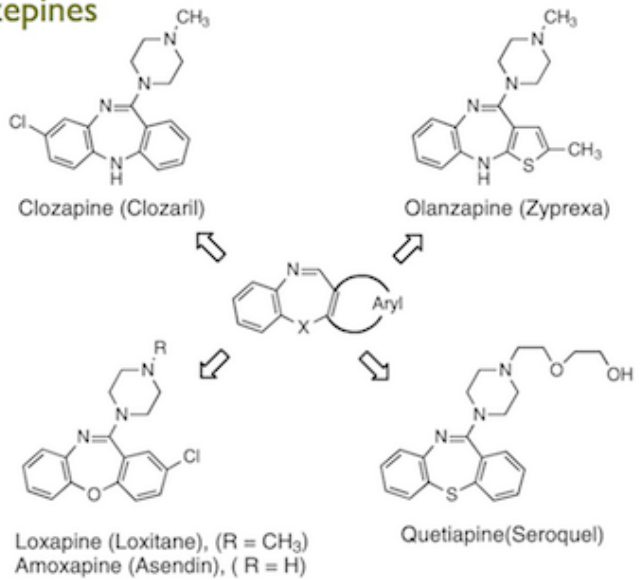
- a butyrophenone with a benzimidazolone side chain
- much more potent than chlorpromazine
- many extrapyramidal side-effects due to D_2 blockade but still valuable in schizophrenia



- structurally related to benperidol
- a diphenylbutyropiperidine with a benzimidazolone side chain
- not sedative in large doses compared to other neuroleptics
- less extrapyramidal side-effects but
  - on withdrawal triggers 'epileptiform convulsion'

Benzazepines

Atypical neuroleptics



Clonazepine - Metabolism