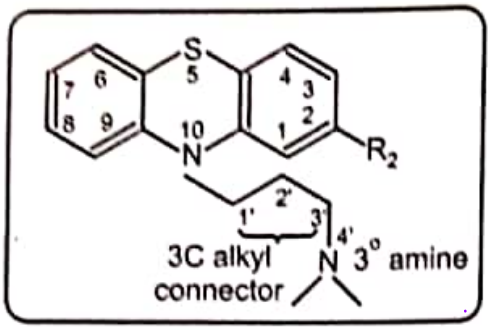
5.5.2 Structure Activity Relationship of Phenothiazine

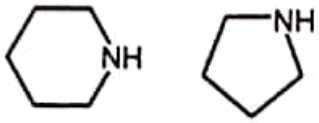
Position 5
Replacement of S with S=O
decrease antipsychotic activity.

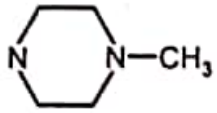
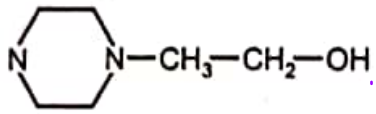


Position 2
$CF_3 > Cl > CH_3 > CN > H > OH$

Position 10

1. Nitrogen atom 3° at the end of side chain
2. Increase or decrease of C-atom side chain between N atoms decrease antipsychotic activity.

3. $N(CH_3)_2 >$ 

4-  

increase activity

Phenothiazines possess a high degree of lipophilicity (Log P 4-5.5) which is balanced by the cationized amine function at physiologic pH. The phenothiazines possess two amino functional groups, one at 10th position of ring other at the end of alkyl-bridge. Usually, Phenothiazines are non-selective competitive D_1 and D_2 antagonists and also block α-adrenoreceptors, serotonine, cholinergic, nicotinic, and muscarinic receptors. It is envisaged that cationized amine of Phenothiazine interact with the anionic site (Aspartic acid-113) on the receptor.

5.5.2.1 At Position 2

1. Substitution at this position with electron withdrawing groups increases Antipsychotic activity as $SO_2NR_2 > CF_3 > COCH_3$, $Cl > CH_3 > CN > H > OH$
2. Di-and tri-substitution at this position has little effect on Antipsychotic activity.

5.5.2.2 At Position 5

Oxidation of sulphur of antipsychotic phenothiazine decreases antipsychotic activity.

5.5.2.3 At Position 10

1. Three carbon atoms chain at position 10 and aliphatic amino nitrogen atom is essential for antipsychotic activity.
2. Maximum antipsychotic activity in amino alkylated phenothiazine follow 3° > 2° > 1°. Hence, nitrogen at the end of side chain must be 3°.
3. Alkylation of basic 3° amine group with groups larger than $-CH_3$ or dealkylation leading to decrease antipsychotic activity.

$-CH_3 > -H$, $-C_2H_5 > -C_3H_7$.

5.5.2 Structure Activity Relationship of Phenothiazine

Position 5
Replacement of S with S=O
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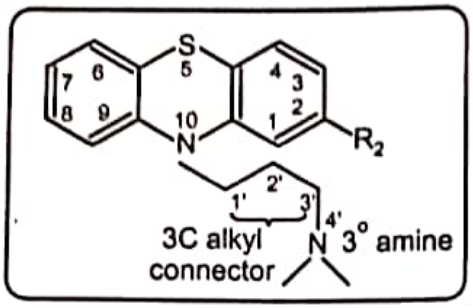

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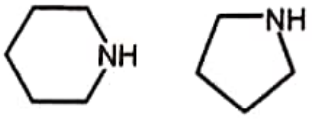
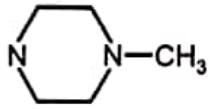
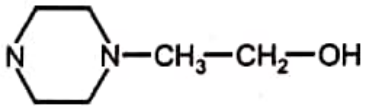
3. $N(CH_3)_2 >$ 

4-  

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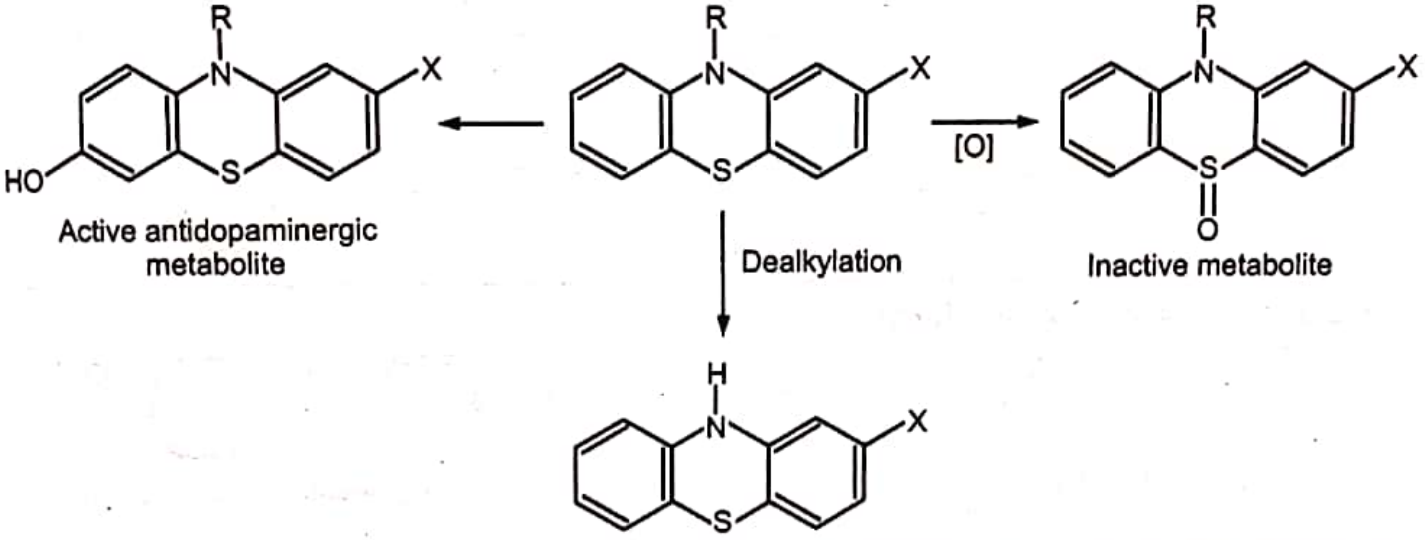
$-CH_3 > -H, -C_2H_5 > -C_3H_7$.

4. Decreasing the size dimethyl amino decreases antipsychotic activity.
5. Introduction of O atom at first position leading to antidepressant like activity.
6. Replacement of dimethylamine at first position with piperidinyl and pyrrolidinyl result in decrease antipsychotic activity with increase in antihistaminic and anticholinergic activity.
7. Piperazine phenothiazine may be esterified with long chain fatty acids to produce slowly absorbed, long acting, lipophilic drugs.
8. Introduction of –OH, $-CH_3$ and $-CH_2-CH_2-OH$ group at 4^{th} position of piperidinyl and pyrrolidinyl moieties leading to increase antipsychotic activity.

5.5.3 Metabolism of Phenothiazine



Several different metabolic reactions takes place for the same phenothiazine to give active and inactive metabolite.

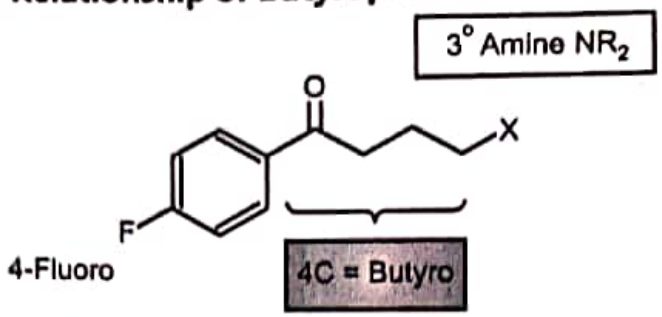
5.5.4 Clinical Uses of Phenothiazine

1. Phenothiazines offer improved therapeutics and are well-tolerated to treat serious mental disorders, including schizophrenia and other psychotic disorders.
2. Prochlorperazine and chlorpromazine, are used to treat nausea, vomiting, and hiccups.
3. Phenothiazine like Prochlorperazine and levomepromazine are used in chemotherapy-induced emesis.

5.5.5 Adverse Effects of Phenothiazine

Drowsiness, dizziness, decreased alertness and concentration, headache, low blood pressure, and blurred vision are most common adverse effect of Phenothiazines.

5.6.2 Structure Activity Relationship of Butyrophenones



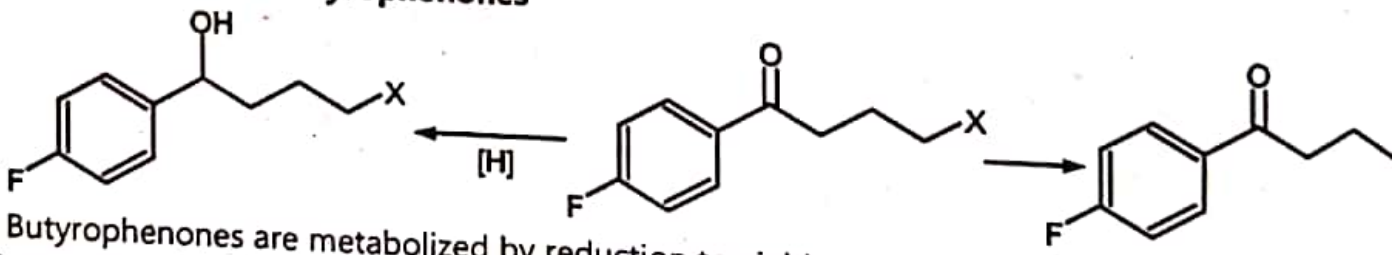
Butyrophenones are lipophilic hence 3° amine, in form of piperidine is required for bioactivity.

1. Incorporation of strong electronegative substituent like 4-Fluoro or similar (e.g. CF_3, Cl) is required for maximal potency.

$$SO_2NR_2 > CF_3 > COCH_3, Cl > CH_3 > CN > H > OH$$

2. Shortening, lengthening or branching of the butyro chain decreases antipsychotic potency.
3. Terminal Basic amine (3° amine) function especially in form of 6-membered heterocyclic ring piperidine is required for antipsychotic activity.
4. Replacement of a carbonyl (C=O) group with a aromatic (CH-Ar) structural feature yields more useful Bis(4-fluorophenyl)butylpiperidines derivatives (e.g. Fluspirilene, Pimozide).

5.6.3 Metabolism of Butyrophenones



Butyrophenones are metabolized by reduction to yield corresponding hydroxyl derivative and deaminated to form 1-(4-Fluorophenyl)butan-1-one metabolite.

5.6.4 Clinical Uses of Butyrophenones

Butyrophenones are used for the following conditions:

1. In the treatment of Schizophrenia
2. In the treatment of acute psychosis
3. In post-operative nausea

5.6.5 Common Adverse Effects of Butyrophenones

1. Hypotension,
2. Extrapyramidal syndrome,
3. Dyskinesia,
4. Hyperprolactinemia