Anti-depressant drugs

Depression

- **Depression**: ↓ of biological amines in postsynaptic sites (pathological depression).
- **Affection mode disorders**: **Unipolar** [depression without mania] & **Bipolar** (alternating episodes of mania & depression)

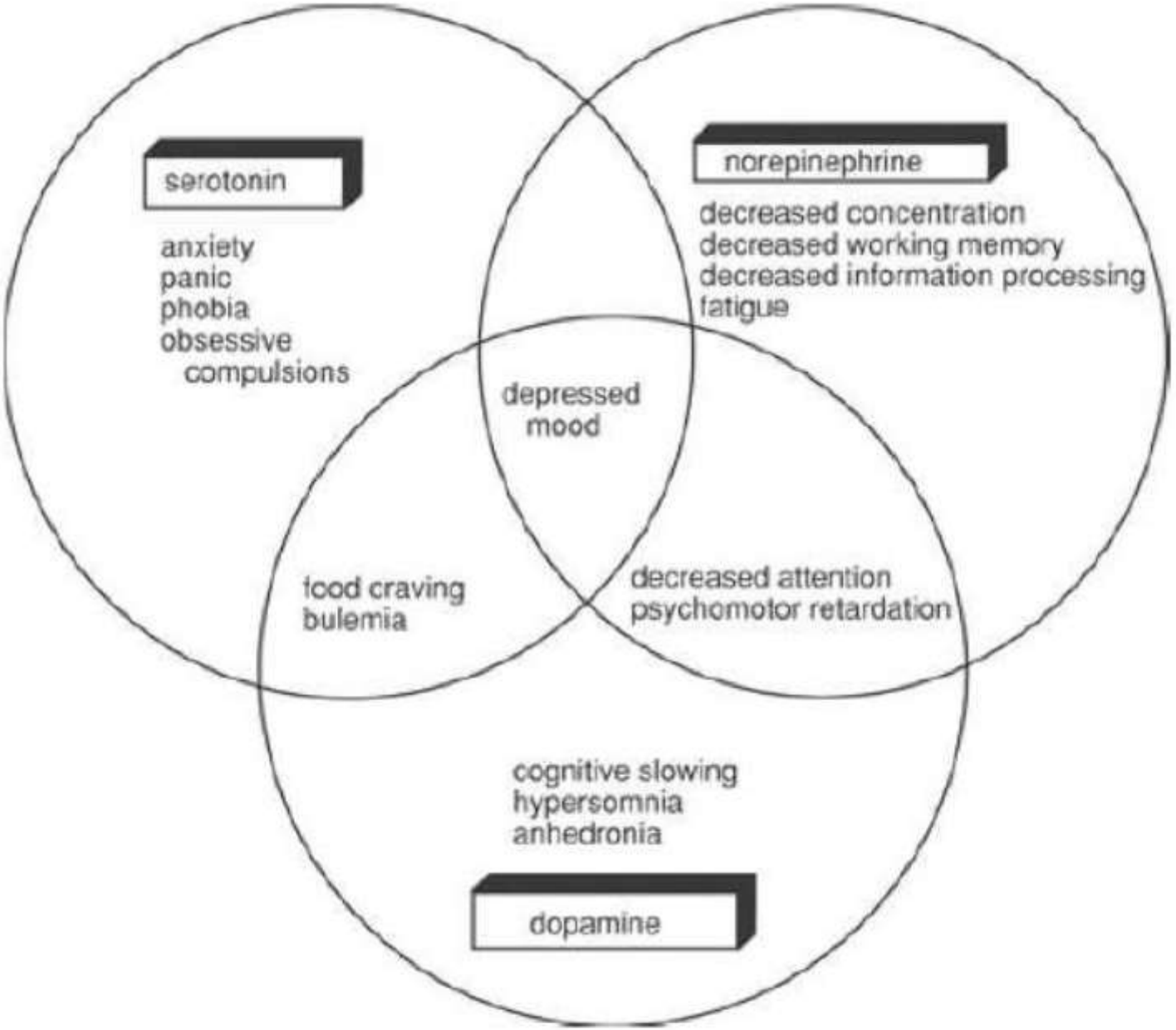


Fig. 21.1. Neurotransmitter deficiency syndromes and their interactions.

[i] MAO Inhibitors

- M.O.A:
- Inhibition of ***intraneuronal MAO-A enzyme*** (which metabolize NE, 5-HT, DA) → ↑ level of amines → anti-depressant effect.
- N.B:
- MAO-B enzyme (metabolize Dopamine only) so, by inhibition → ↓ DA → parkinsonism ttt.
- COMT: Another enzyme metabolizes endogenous amines but present ***Extra-neuronal***.

S.E. of MAOIs

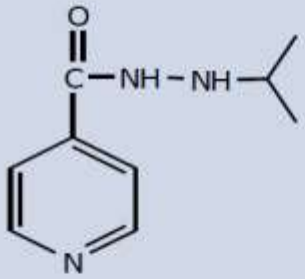
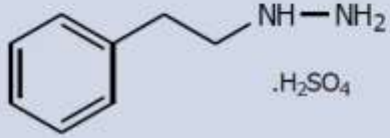
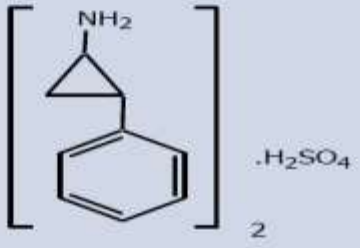
Excess tyramine (amino acid) in circulation causes the release of noradrenaline from sympathetic nerves

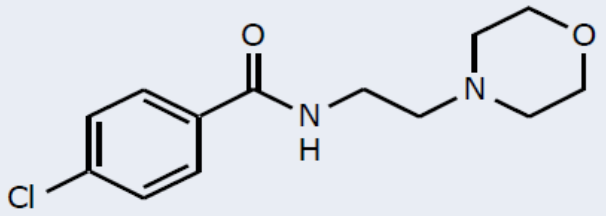
Increased BP, increased HR,

People taking MAOI's for depression should avoid foods rich in tyramine (cheese, hot dogs, beans)

MAOI's are contraindicated in people with CV disease, hepatic disease, epilepsy. People taking sympathomimetics,

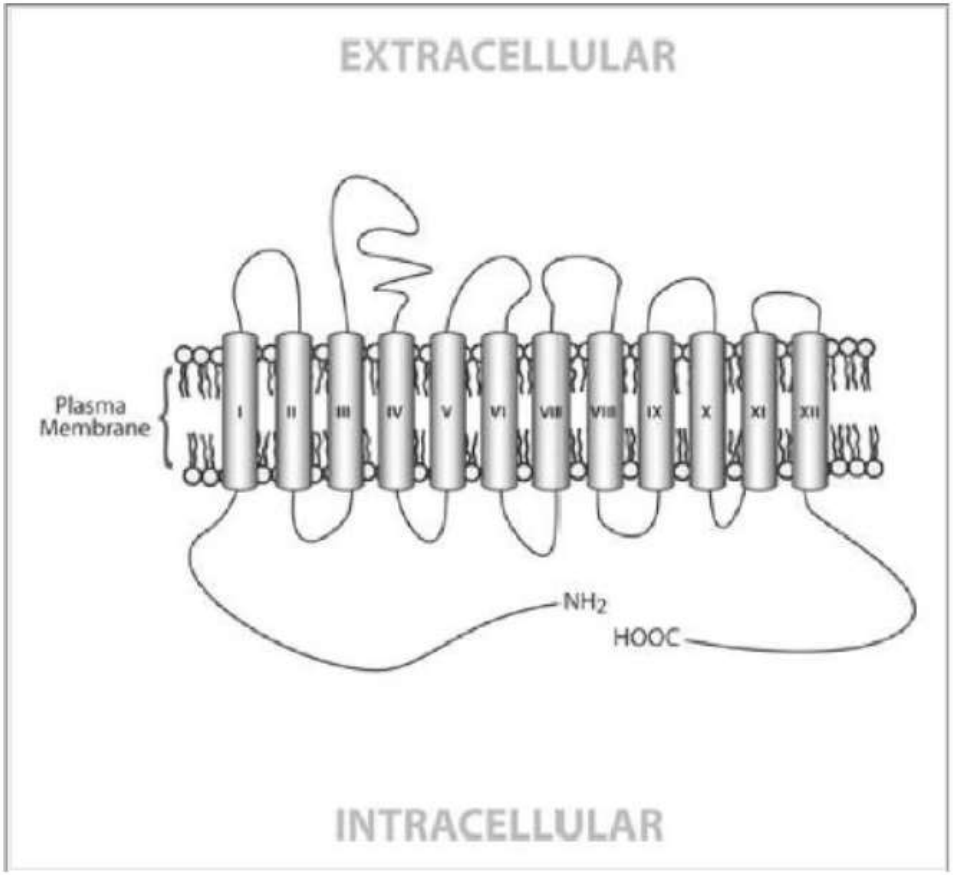
A. Irreversible non-selective MAOIs

Iproniazide	Phenelzine SO_4	Tranylcypromine
		

B) Irreversible	C) Reversible preferential for MAO_A
Deprenyl	**Moclobemide**
MAO_B inhibitor (anti-parkinsonism)	

[II] Tricyclic Antidepressant (Thymoleptics)

- **MOA**: **Block transporters** of NE & 5-HT (due to the structural similarities).
- **Advantage:** ***More safe > MAOIs*** → No diet control (***may be used for children for nocturnal enuresis***).



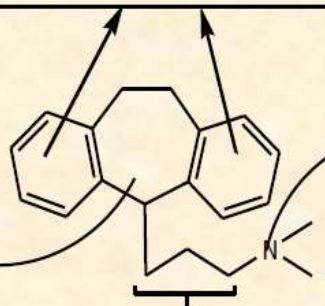
Monoamine reuptake transporter.

SAR

- The phenyl rings are more noncoplanar than those in phenothiazines

- If 6 membered ring --> structural similarity with phenothiazine (with anti-psychotic activity)

- If 7-membered ring --> similar to NE, 5-HT (with Anti-depressant activity)



- Aliphatic amine is essential for activity.
- CH_3 must be present
- May be mono methylated (2ry amine) or di methylated (3ry amine)
- 3ry amine metabolized to active 2ry amine deriv.

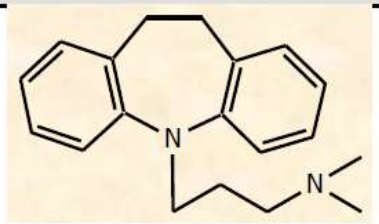
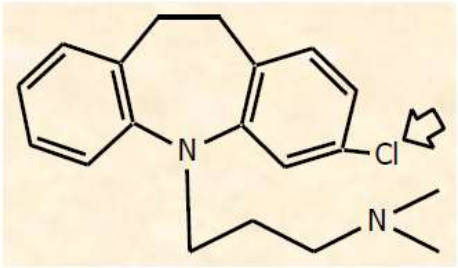
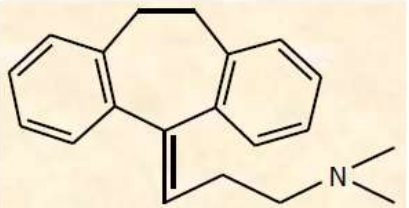
- If Ethyl or Propyl --> Inctive

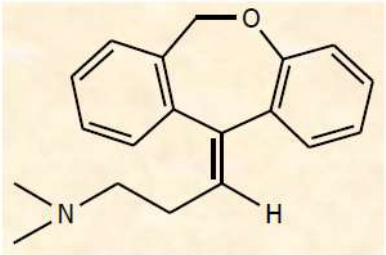
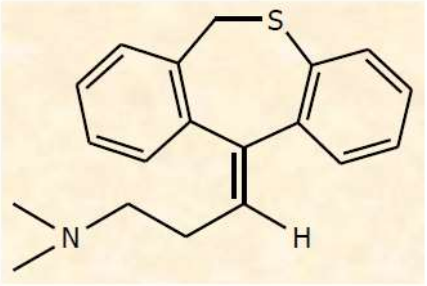
- Chain of 3-C is optimum for activity (may be 2C)

with spatial similarity to NE ---> Trans conformer of B-aryl amine superimpose on TCA structure

Epinephrine

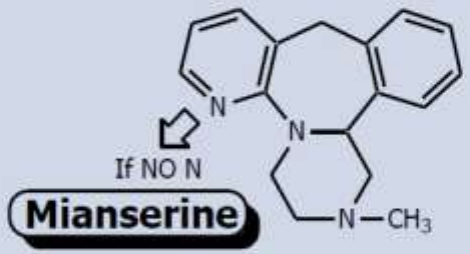
3ry Amines	2ry Amine
↓ 5-HT reuptake [> NE]→ ↑ 5-HT	↓ NE reuptake → ↑ NE
↑ anti-cholinergic S.E	↓ anti-cholinergic S.E.
With ↑ sedation	Stimulatory

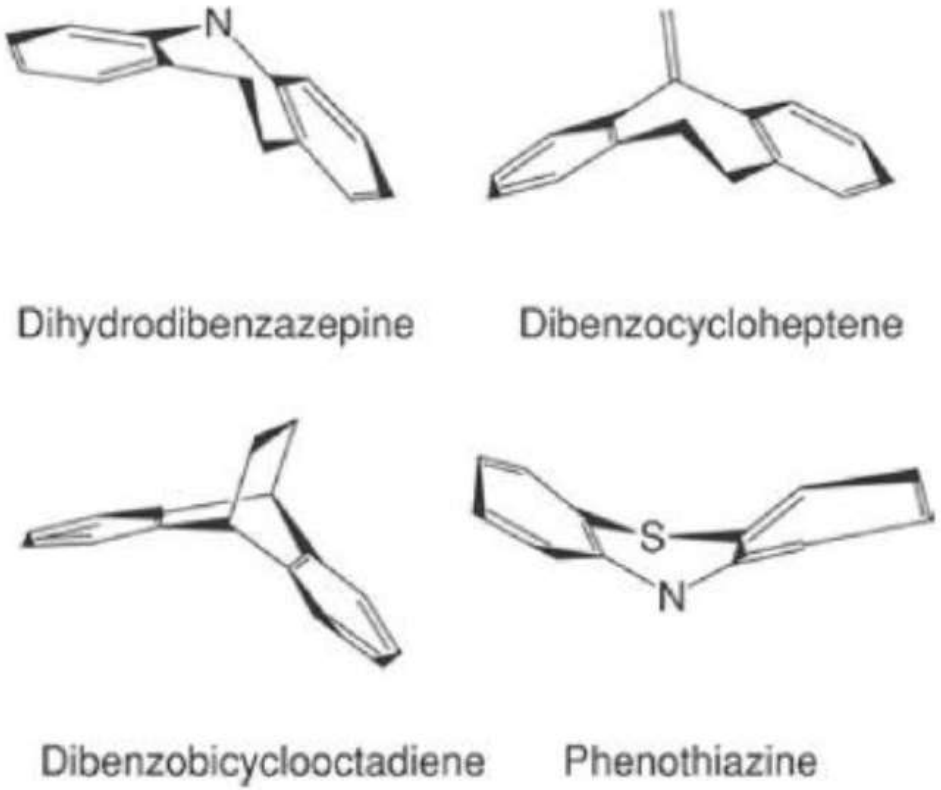
Azepine derivatives		Cylcoheptane derive.
Imipramine (tofranil)	**Chlorimipramine** (Anafranil)	**Amitryptiline** (Tryptizole)
 **Parent Cpd**		 **(NO geometrical isomers)**
Metabolism → **Desipramine** [2ry amine]→ **more active**	• With ***higher lipophilicity*** → ***more potent***. • ***Cl form H bond with protonated N → stabilize β-aryl amine structure.***	**Metabolism** → **Nortriptyline** (2ry amine) → active.

Oxepine derivative	Thiepine derivative
Doxipene	**Dothiepine** (Prothiaden)
	
E Isomer is used	
Bioisosters to Amitryptiline [O or S instead of CH_2]	

[III] Second generation Anti-depressants

- A. Tetracyclic Anti-depressants

Maprotiline (Ludiomel®)	**Mirtazepine** (Tolvon®)
	
Selective NE reuptake inhibitors	Related to **Mianserine** **Pyrazino-azepine derivative**
- not stimulant (block other receptors)	• Central α_2-blocker → ↑ NE release.

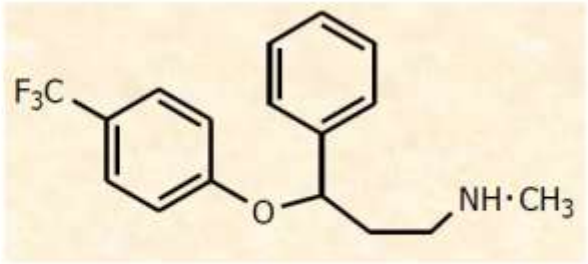


Three-dimensional models of the tricyclic and tetracyclic ring

D. Selective Serotonin reuptake Inhibitors (SSRI)

- **1st line of treatment - with phenyl ring, basic N (resemble 5-HT) & halogen.**
- **Bind to SERT [Serotonin Transporter]**
- **Adverse effects; Sexual dysfunction** is a common side effect with SSRIs. Specifically, side effects often include difficulty becoming aroused, lack of interest in sex, and anorgasmia (trouble achieving orgasm). Genital anesthesia, loss of or decreased response to sexual stimuli, and ejaculatory anhedonia are also possible. Although usually reversible, these sexual side effects can last for months or years after the drug has been completely withdrawn. This is known as **post SSRI sexual dysfunction**.

Fluoxetine (Prozac®)



SAR of Fluoxetine:

CF_3 → must be Para. [if m → ↓ selectivity 10 fold] [if O → ↓ selectivity 90 fold].

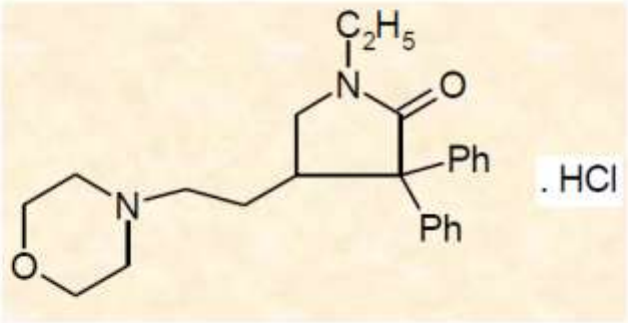
CF_3 if replaced by ortho-Methoxy (**Nesoxitine**) → NE reuptake inhibitor.

Degree of methylation on N not affect selectivity or potency [**Norfluoxetine is active**].

Fluoxetine → R & S are equal in activity [but S is slowly eliminated].

4- Analeptics (respiratory stimulants)

- **M.O.A.** : ↑ *respiratory center in brain.*
- Doxapram

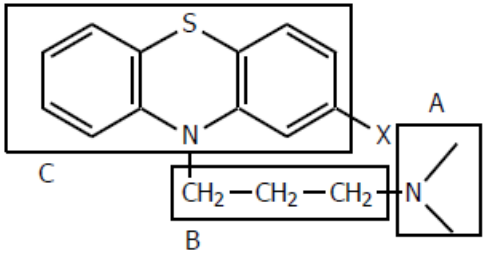


•Taken by **I.V**.infusion in divided doses with 5 min interval.
* ↑ selectivity & ↓ duration → ↓ S.E.s.
* Uses: ttt of *acute or post operative or opioid-induced* resp.depression.

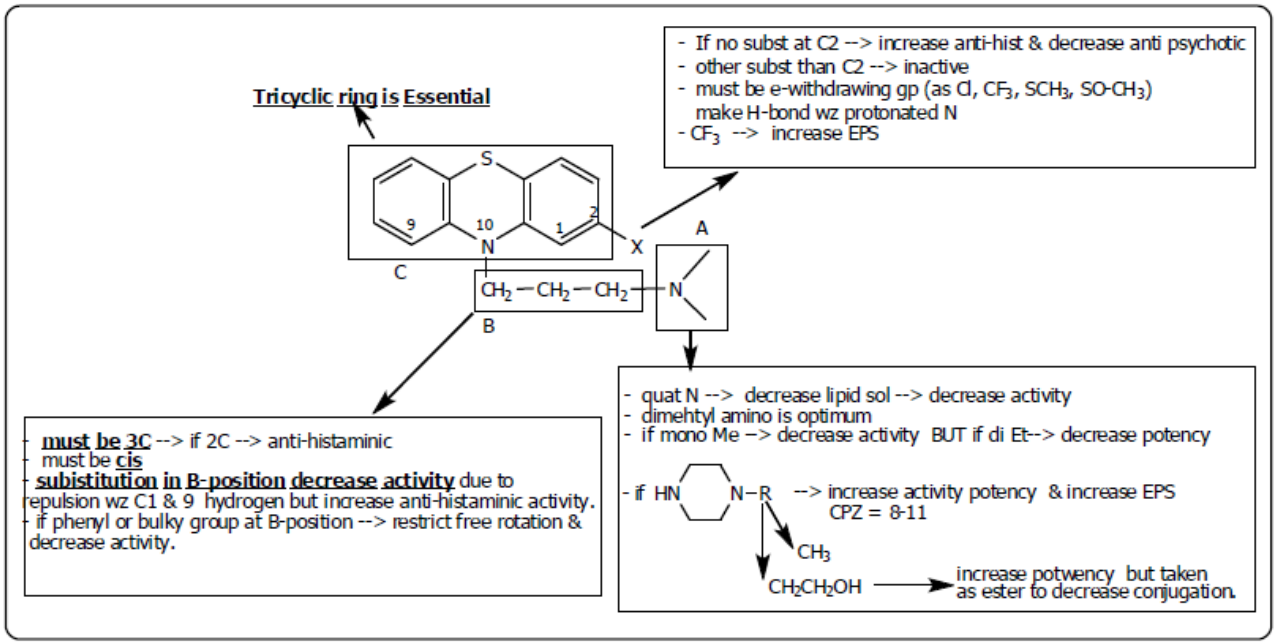
Anti-psychotic drugs
[Neuroleptics] [Major tranquilizer]

- Uses: Psychosis, Hallucination, Excitation, anti-emetic [D_2-blocker at CTZ].
- **S.E:**
- ① **Extra-pyramidal symptoms (EPS)** → Parkinsonism like symptoms.
- **If typical [↑ potency, ↑ EPS] BUT if Atypical [↓ potency, ↓ EPS]**
- ② **Anti-cholinergic** (↓ EPS)
- ③ Anti-histaminic (H_1-blocker) → sedation.
- ④ Anti-adrenergic (α_1-blocker) → hypotension.
- ⑤ Photosensitivity. ⑥ Retinal toxicity.

[i] Phenothiazines

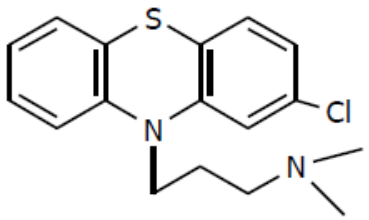
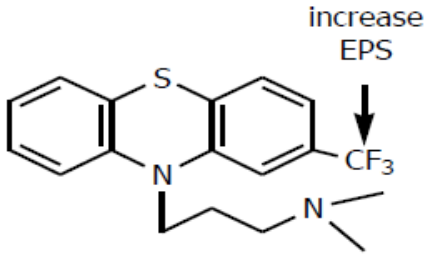


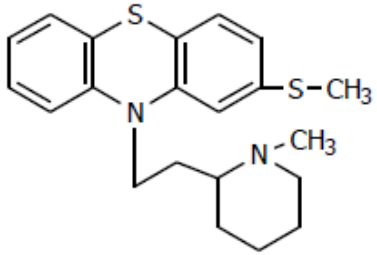
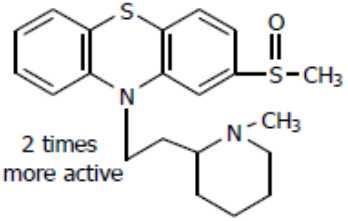
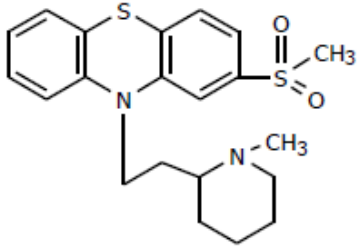
- The <u>prototype</u> is <u>Chlorpromazine (CPZ)</u> → obtained from <u>promethazine</u> (antihistaminic).
- <u>CPZ index:</u> relate the anti-psychotic drug activity to that of CPZ (for CPZ = 1)
- <u>Requirements:</u>
- ① Linear tricycle.
- ② B = 3 Cs.
- ③ X gp at C_2 → ***<u>e-withdrawing gp</u>*** → is ***<u>essential</u>*** to attract +ve on protonated N of side chain → ***<u>superimposition on dopamine receptor</u>***.



Assay of phenothiazines:

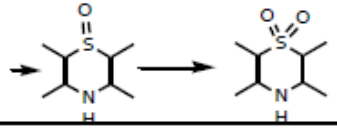
3ry amine (weak base) → ***non-aqueous titration*** [dissolve in glacial acetic acid → titrate against $HClO_4$ with crystal violet indicator].

Propyl dialkylamino side chain	
CPZ	**Triflupromazine**
	
Metabolized by ***N- dealkylation*** & ***C_7 Hydroxylation***	
S.E: sedation & hypotension Due to α_1-blockage	**Adv**: less sedation & less hypotensive than CPZ

Alkyl piperidyl side chain [Atypical → ↓ EPS & ↑ anti-cholinergic]		
Thioridazine	**Mesoridazine**	**Sulphoridazine**
		

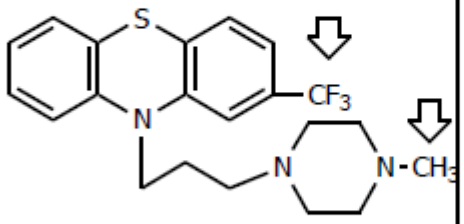
Metabolism:

① **1** → **2** → **3** (side chain sulphoxidation)

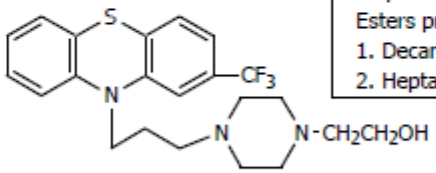
② **Ring Sulphoxidation:**  both are inactive

Propyl piperazine side chain [with piperazine → the most potent → ↑ EPS]

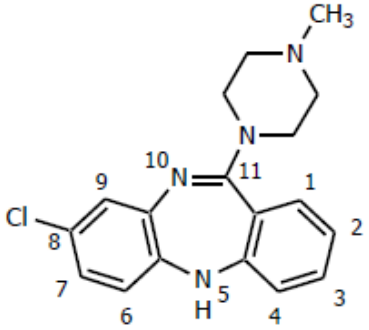
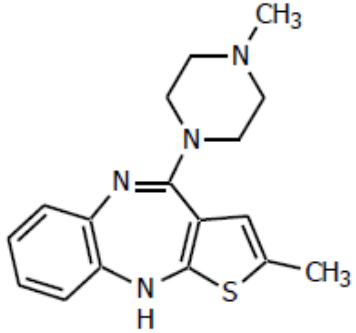
Trifluperazine



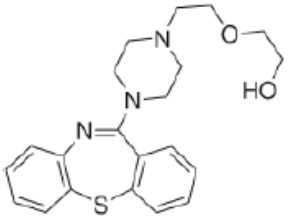
Fluphenazine



- Fluphenazine is short acting, So-->
  Esters prodrug used --> latenation of ation (depot IM)
  1. Decanoate [-O-CO-$(CH_2)_8$-CH_3] --> 2-3 weeks
  2. Heptanoate [-O-CO-$(CH_2)_5$-CH_3] --> 1-2 weeks

[ii] Dibenzodiazepine	[iii] thienobenzodiazepine
Clozapine (leponex)	Olanzapine (Zyprexa)
	
• ***Atypical → ↓ potency due to wrong orientation of N-methyl piperazino gp relative to Cl atom.*** • ***↓ EPS.***	• ***Atypical with ↓ EPS.*** • ***More potent*** antagonist at D_2 & serotonin $5\text{-}HT_{2A}$ receptors > Clozapine.

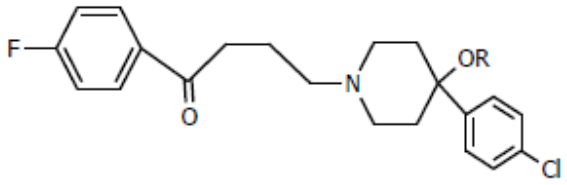
Quetiapine (Seroquel)



- Atypical antipsychotic, for schizophrenia, bipolar disorders and major depressive disorders.
- Quetiapine is one of the most well tolerated neuroleptics of other atypical antipsychotics by reducing the incidence of extrapyramidal symptoms.
- Quetiapine has the following pharmacological actions:
- D1, D2, D3 and D4 receptor antagonist.
- 5-HT1A, 5-HT2A, 5-HT2C and 5-HT7 receptor antagonist.
- α1 and α2-adrenergic receptor antagonist.
- H1 receptor Antagonist.
- mACh receptor antagonist.

[iv] Butyrophenone
Haloperidol (Haldol)

Active orally with lower sedation thn CPZ



R = H Or = decanoete ester --> depot IM/4 weeks

Typical with ↑potency & ↑ EPS , NO anti-cholinergic

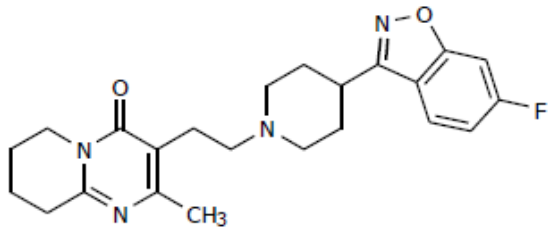
Uses: 1. Drug of choice in terminate **mania**.

2. **Gille de la tourette syndrome** (GDTS) → abnormal voice, movement.

[v] Benzisoxazole

Risperidone (Risperdal)

-



5-HT$_{2A}$ (main excitatory receptor subtype among the G-protein coupled receptors for 5-HT) ***& D$_2$ antagomist***

- ***Atypical.***
- ***Not inhibit DA neurotransimission in striatum*** & cortex → ***low EPS.***

BUT maintain blockage of D_2-limbic receptor.