SEMESTER IV

MEDICINAL CHEMISTRY I

BP402TP

Important questions with answers

1. Define sedative and hypnotics. Classify with at least three drug examples and one structure of each category.
2. Define Insomnia. Explain mechanism and structure activity relationship of Barbiturates derivatives.
3. Give SAR of Benzodiazepines.
4. Give chemical classification of Antipsychotics and discuss the SAR of Phenothiazine.
5. What are antiepileptic drugs? Give their mechanism of action. Classify with examples.
6. Give SAR of anticonvulsants.
7. What are Analgesics? Write SAR and mode of action of morphine.
8. What are NSAIDs? Classify them with two examples of each class. Write synthesis of one NSAID having one chiral center.
9. Write a note on narcotic antagonists with its mechanism.
10. Enlist various physicochemical parameters that affect biological activity of drugs. Explain the effect of protein binding and hydrogen bonding on action of drugs.
11. Discuss the role of Partition coefficient and solubility in drug's biological action.
12. Explain how Ionization affects biological activity of a drug.
13. Write a note on Bioisosterism.
14. Explain Optical and Geometrical isomerism affecting drug activity.
15. Explain oxidation reaction of Phase-I metabolism.
16. Write a note on glucuronide conjugation of phase II metabolism.
17. Explain factors affecting drug metabolism including stereo chemical aspects.
18. Write in detail Neurochemistry of Acetylcholine.
19. Explain SAR of Acetylcholine in detail.
20. Write a note on Parasympathomimetics.
21. Write a note on parasympatholytic agents.
22. Write SAR of muscarinic antagonists. OR Explain the SAR of parasympatholytics.
23. Write in detail about neurochemistry of catecholamines.
24. Write a short note on sympathomimetics.
25. Describe SAR of β-phenylethanolamine.
26. Write a note on sympatholytic agent.
27. Write SAR of β-blockers. Give synthesis of Propranolol.
28. Classify General anesthetics and give synthesis of Halothane.
29. Write structure and IUPAC name of following:
    Alprazolam. Aspirin. Hydroxyamphetamine, Carbamazepine, Carvedilol, Chlorpromazine, Chlorprothixene, Clonazepam, Diclofenac, Glutethmide, Halothane, Ibuprofen, Indomethacin, Labetalol Naproxen, Oxazepam, Paraldehyde, Pentazocine, Secobarbital, Scopolamine Hydrobromide, Thiopental sodium,Valproic acid
30. Give synthesis of following drugs:
    Salbutamol, Dicyclomine hydrochloride, Barbital, Chlorpromazine hydrochloride, Phenytoin, Carbamazepine, Halothane, Methohexital sodium, Propranolol

Q. 1 Define Sedatives and Hypnotics. Classify with at least three drug examples and one structure of each category.

❖ Definition:

Sedatives: *"Sedatives are the drugs which decreases activity, moderate excitement, calms the anxiety of the patient by producing mild depression of CNS without producing drowsiness or sleep."*

Hypnotics: *"Hypnotics are the drugs which produce drowsiness, compelling the patient to sleep similar to normal arousal sleep by depressing the CNS, particularly the reticular activity which characterizes wakefulness."*

❖ Classification:

1 **Barbiturates:**
   - I. **Long acting (6 Hrs or more):** Barbital, Phenobarbital, Mephobarbital
   - II. **Intermediate acting (3 to 6 Hrs):** Amobarbital, Butabarbital, Probarbital
   - III. **Short acting (Less than 3 Hrs):** Pentobarbital, Secobarbital, Cyclobarbital, Heptabarbital
   - IV. **Ultra-short acting (Less than half an Hr):** Hexobarbitone, Thiopentone, Methohexitone

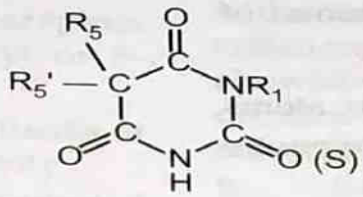
2 **Benzodiazepines:**
   - I. **Hypnotics:** Diazepam, Nitrazepam, Temazepam
   - **II.** **Antianxiety:** Diazepam, Oxazepam, Alprazolam, Chlordiazepoxide, Lorazepam, Chlorazepate
   - **III.** **Anticonvulsants:** Diazepam, Clonazepam, Clobazam

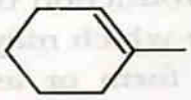
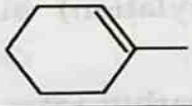
3 **Newer Non-Benzodiazepines:** Zolpidem, Zopiclone

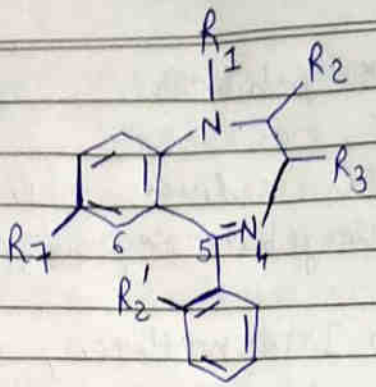
4 **Miscellaneous agents:**
   - I. **Alcohol and Carbamate derivatives:** Meprobamate, Ethchlorvynol
   - II. **Amides and Imides:** Glutethimide
   - III. **Aldehyde and their derivatives:** Triclophos sodium, Paraldehyde

Principle

Table 8.2 : Barbiturate Classification

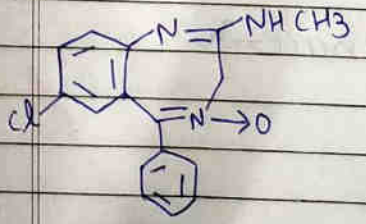


Name	Substituents R_1	R_5	R_5'	Sedati (r
1. Long acting Barbiturates :				
Barbital	H	C_2H_5	$-C_2H_5$	
Phenobarbital	H	C_2H_5	$-C_6H_5$	15
Mephobarbital	CH_3	C_2H_5	$-C_6H_5$	30
2. Intermediate acting Barbiturates :				
Amobarbital	H	C_2H_5	$-CH_2CH_2CH(CH_3)_2$	
Butabarbital	H	C_2H_5	$-CH(CH_3)-CH_2CH_3$	
Probarbital	H	C_2H_5	$-CH-(CH_3)_2$	
3. Short acting Barbiturates :				
Cyclobarbital	H	C_2H_5		
Heptabarbital	H	C_2H_5		
Pentobarbital	H	C_2H_5	$-CH(CH_3)-CH_2CH_2CH_3$	
Secobarbital	H	$-CH_2CH=CH_2$	$-CH(CH_3)-CH_2CH_2CH_3$	
4. Ultra-short acting Barbiturates :				
Hexobarbitone	CH_3	CH_3		
Thiopentone	H	C_2H_5	$-CH(CH_3)-CH_2CH_2CH_3$	

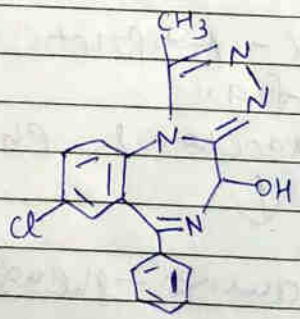


5-aryl-1,4-benzodiazepine

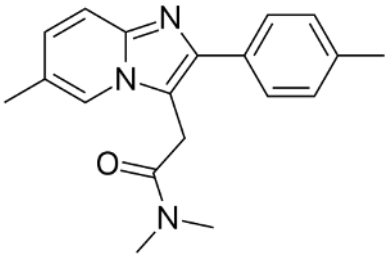
	R_1	R_2	R_3	R_7	R_2'
Diazepam	CH_3	=O	H	Cl	H
Nitrazepam	H	=O	H	$-NO_2$	H
Temazepam	CH_3	=O	OH	Cl	H
Oxazepam	H	=O	OH	Cl	H
Lorazepam	H	=O	OH	Cl	Cl
Clorazepate	H	=O	COOH	Cl	H
Clonazepam	H	=O	H	NO_2	Cl



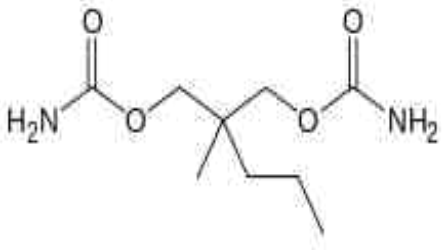
Chlordiazepoxide



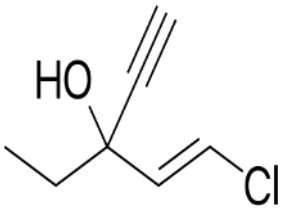
Alprazolam



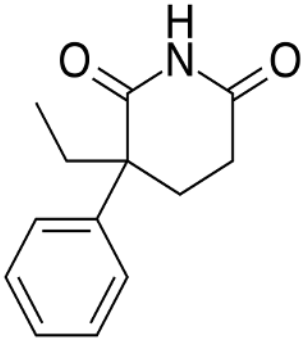
Zolpidem



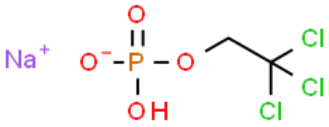
Meprobamate



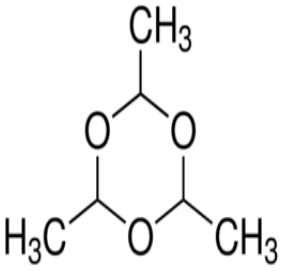
Ethchlorvynol



Glutethimide



Triclophos sodium



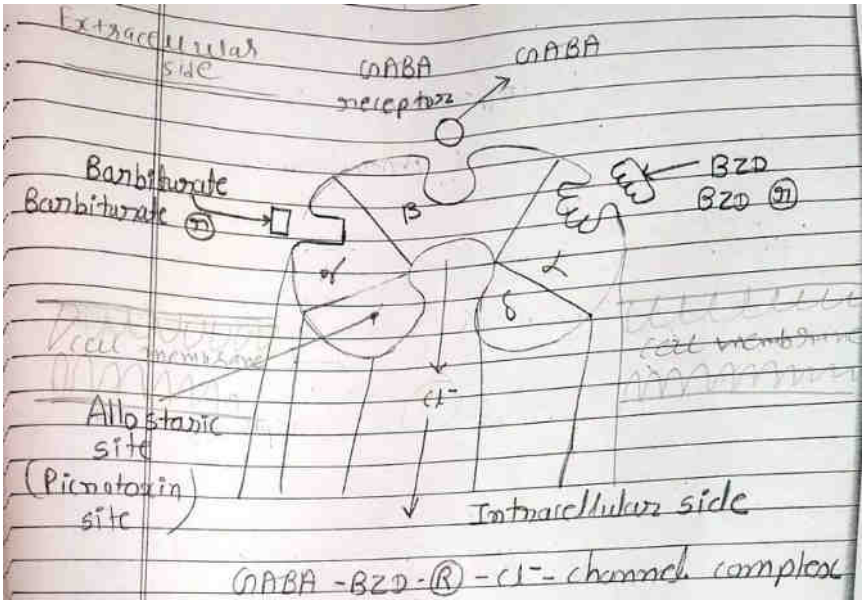
Paraldehyde

Q. 2 Define Insomnia. Explain mechanism and structure activity relationship of Barbiturate derivatives.

Insomnia:

Insomnia is a state of sleeplessness. "*It is defined as condition requiring longer than 30 minutes to fall asleep, awakenings throughout night, early morning awakening or total sleep time decreased to less than 6 hours.*"

Mechanism of action of Barbiturates:

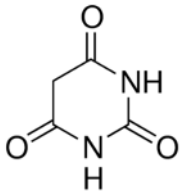


- The principal mechanism of action of barbiturates is believed to be their affinity for the GABA-A receptor (Acts on **GABA: BZD receptor Cl^- channel complex**).
- GABA is the principal inhibitory neurotransmitter in the mammalian CNS.
- Barbiturates bind to the GABA-A receptor at the alpha subunit, which are binding sites distinct from GABA itself and also distinct from the benzodiazepine binding site. Like benzodiazepines, barbiturates potentiate the effect of GABA at this receptor.
- Barbiturates produce their pharmacological effects by **increasing the duration of Cl^- ion channel opening** at the GABA-A receptor (Pharmacodynamics: this increases the efficacy of GABA), whereas benzodiazepines **increase the frequency of the chloride ion channel opening** at the GABA-A receptor (Pharmacodynamics: this increases the potency of GABA),
- Barbiturates donot bind to the BZD receptor but bind to another site on the same macromolecular complex to exert **GABA facilitatory action.**
- They also enhance BZD binding to its receptor.

- At high concentrations, barbiturates directly increase Cl^- conductance which means barbiturates have **GABA-mimetic-action**; contrast to BZDs which have only GABA-facilitatory action.
- In addition to this GABA-ergic effect, barbiturates also block the AMPA receptor-a subtype of glutamate receptor. Glutamate is the principal excitatory neurotransmitter in the mammalian CNS.
- Taken together, the findings that barbiturates potentiate inhibitory GABA-A receptors and inhibit excitatory AMP receptors can explain the CNS-depressant effects of these agents.
- At higher concentration, they inhibit the Ca^{2+}-dependent release of neurotransmitters.
- At very high concentrations, barbiturates depress Na^+ and K^+ channels also.

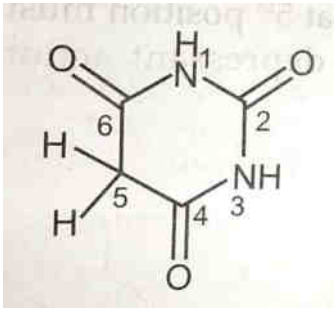
Structure Activity Relationship of Barbiturate derivatives:

Prototype drug in this category is Barbituric acid i.e. Malonyl urea.



It lacks CNS depressant activity, but substitutions at various positions give many compounds having sedative-Hypnotic activity.

Generally, substitution has been done at 1st and 5th position.



In 1951, Sandberg postulated that, a good hypnotic barbituric acid derivative must have –

(a) Acidity within certain limits**:**

(b) Lipid-water solubility (partition coefficient) between certain limits.

(a) Acidity:

- The acidity value within certain limits is essential to give a proper ratio of ionised (dissociated) and unionised (undissociated) forms which is important to cross blood-brain-barrier.
- It takes approximately 40-60 % dissociation to enable a barbiturate to cross BBB and exerts an effect on CNS. A determination of the pKa can thus be predictive of CNS activity.

- On the basis of acidity values, barbiturates are divided into two classes.

Hypnotic Class

(i) 5, 5-disubstituted barbituric acids.

(ii) 5, 5-disubstituted thiobarbituric acids.

(iii)1, 5, 5-trisubstituted barbituric acids.

Inactive Class

(i) 1-substituted barbituric acids

(ii) 5-substituted barbituric acids

(iii) 1, 3- disubstituted barbituric acids.

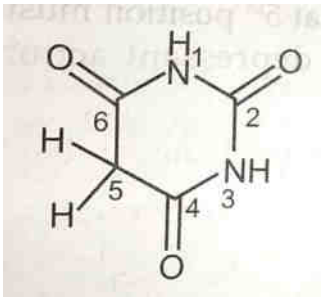
(iv) 1, 5-disubstituted barbituric acids.

(v) 1, 3, 5, 5-tetrasubstituted barbituric acids

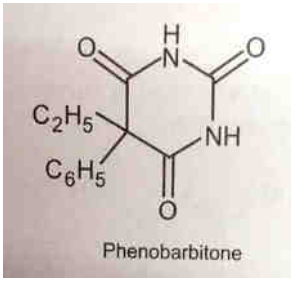
Inactive class is inactive since they are not acidic. They upon metabolism, produce 1, 5, 5-trisubstituted barbituric acids, which are acidic.

(b) Lipid-water solubility (partition coefficient):

- Once the acidity value criteria is satisfied, the lipid-water solubility or partition coefficient is calculated to find out whether the compound is active or not.
- The following structural skeleton is essential for hypnotic activity.



(1) Both 'H' atoms at 5th position replaced by alkyl group or aryl group results in a drug which can easily cross BBB. For example, Phenobarbitone



(2) The sum of the carbon atoms of both substituents at carbon 5 should be between 6 and 10 in order to attain optimal hypnotic activity. This sum is also an index of duration of action.

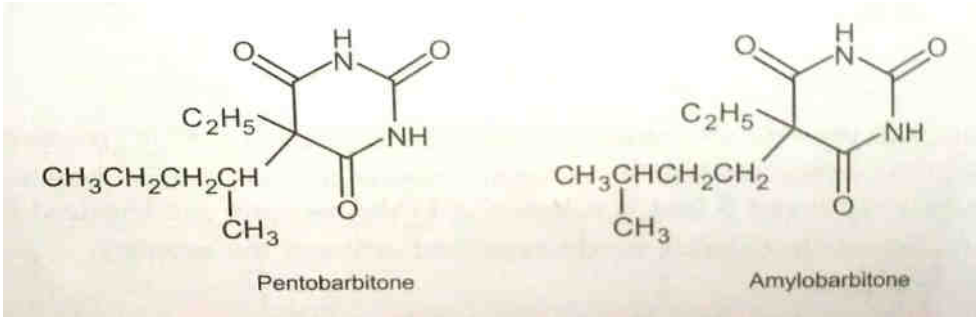
Sum value	Duration of action
7 - 9	Rapid onset and shortest duration

5 - 7	Intermediate duration action
4	Slowest onset and longest duration (Two ethyl groups or an ethyl and a phenyl)

(3) Within the same series, the branched chain isomer has greater lipid solubility and hypnotic activity but has shorter duration action.

Branched, cyclic or unsaturated chains at 5th position generally reduce the duration of action due to increased ease of metabolic conversion to a more polar, inactive metabolite.

The greater the branching, more potent will be the drug e.g. pentobarbital is more potent than amobarbital.



(4) Shortening of alkyl chain resist oxidation of the drug and it act as a long acting drug. e.g. Barbirone

(5) However, the stereoisomers possess approximately same potencies.

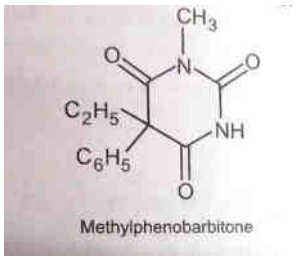
(6) Within the same series the unsaturation (i.e. allyl, alkenyl, cycloalkenyi analogues) may result in greater potency than the saturated analogues with the same number of carbon atoms.

(7) Alicyclic or aromatic substituted analogues are more potent than analogues with aliphatic substituents with the same number of carbon atoms.

(8) Introduction of a halogen atom into the 5-alkyl substituent increases potency.

(9) Introduction of a polar substituent (OH, NH_2, COOH, CO, RNH, SO_3H) into the aromatic group at C-5 results in decreased lipid solubility and potency.

(10) Substitution of $-CH_3$ group at 1st position increases lipid solubility with shorter duration of action. e.g. Methylbarbirone



Methylphenobarbitone

(11) Substitution to both N_1 and N_3 by alkyl groups eliminates sedative action of a drug.

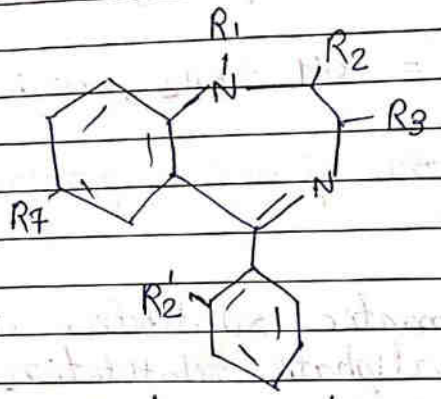
(12) Isosteric replacement of oxygen at 2nd position by sulphur gives thiobarbiturates having increased liphophilicity and shorter duration of action. Drug will have increased CNS depressant activity and known as ultrashort acting barbiturates. For example, Thiopentone

Thiopentone

(13) Isosteric replacement of oxygen at position 2,4,6 by more sulphur atoms abolishes the hypnotic activity of the compound.

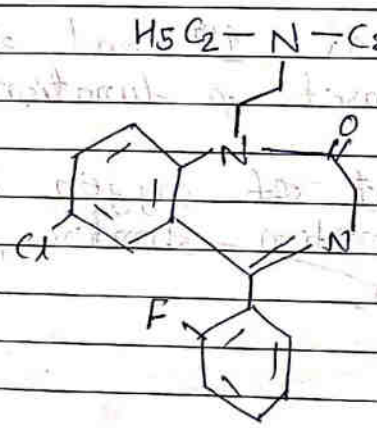
Q. 3 Give SAR of Benzodiazepines.

SAR of BZD;



5-aryl 1,4 benzodiazepine.

i) Position 1;
$-CH_3$ at R_1, metabolically easily removed, clinically useful.
eg. Flurazepam



ii) Position 2;
Replacement of C=O by two hydrogen
↓
Less potent.
eg. Medazepam.

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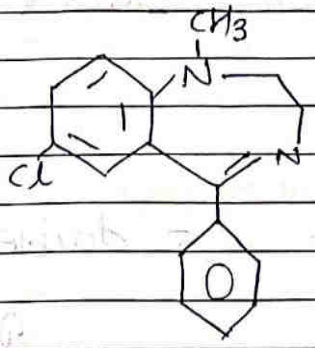
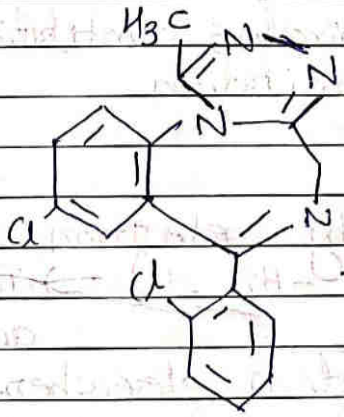


→ Triazole ring at α-face of 1,4 benodiazepine in place of amide ⟶ Increase activity.



→ Triazolam

iii) Position 1 & 2;
Additional ring joining at 1st & 2nd are more active than 1-methyl BZD.

iv) Position 3;
- Replacement of one hydrogen with -OH group → decrease activity.

- Carboxyl functional group at 3rd position Increase duration of action and

favours formation of water soluble salt.

Posi

v) Position 4 & 5;
- Saturation of 4,5 double bond → Decrease Potency.

vi) Position 5;
- All CNS- depressants are usually 5-aryl or 5-cyclohexenyl substituted.

Phenyl substitution
α-pyridyl derivative substitution } Increase Potency.
Cycloalkyl substitution

vii) Position 7;
- Substitution by electron withdrawing groups (-Cl, -Br, ...) → Increase activity.
while substitution elsewhere in this ring → Decrease activity.

viii) R2 position;
→ Same as 7th possition.
Electron withdrawing group → Increased activity
→ Other substitution → Decreased activity.

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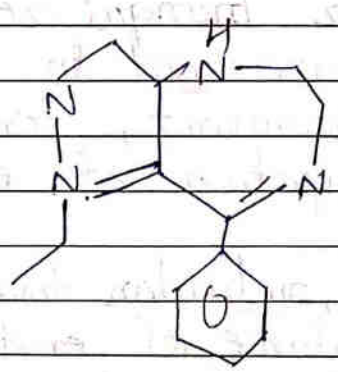
ix) Replacement of benzene ring by hetero aromatic (Pyrazole) →

More anxiolytic activity.

eg. Ripazepam.



Q. 4 Give chemical classification of Antipsychotics and discuss the SAR of Phenothiazine.

Chemical classification of Antipsychotics:

Anti-Psychotics — Major tranquillizers
Anti-Schizophrenics
Neuroleptics

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A. Typical Anti-Psychotics: Dopamine antagonist

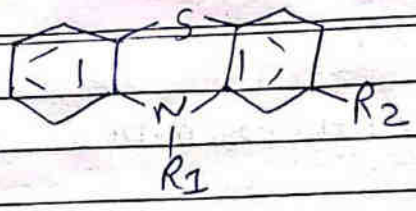
1. Phenothiazines:
   - i) Aliphatic side chain: Promazine, chlorpromazine, Trifluopromazine
   - ii) Piperidine " " : Thioridazine, Mesoridazine
   - iii) Piperazine " " : Prochlorperazine, Trifluoperazine
2. Rauwolfia alkaloids: Reserpine
3. Thioxanthenes: Thiothixene, Chlorprothixene
4. Fluoro Butyrophenone: Haloperidol, Droperidol
5. Dibenzoxazepine: Loxapine

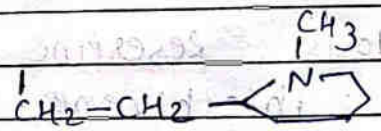
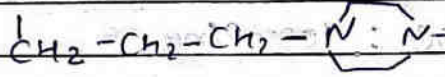
B. Atypical Anti-Psychotics: 5-HT2 antagonist, less extrapyramidal side effects than typical.

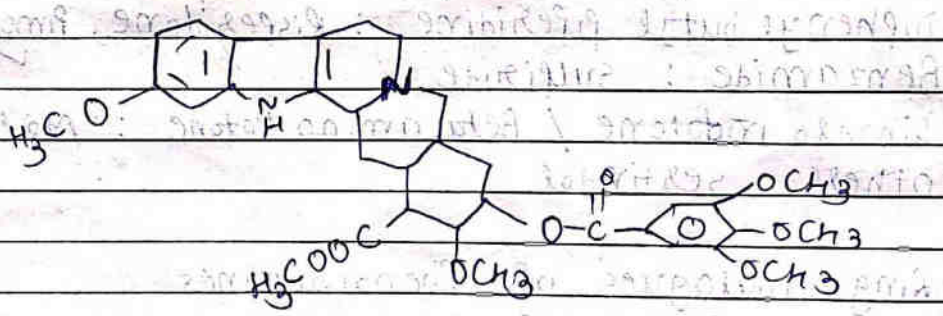
1. Dibenzodiazepine: clozapine, olanzapine
2. Diphenyl butyl piperidine: Risperidone, Pimozide
3. Benzamide: sulpiride
4. Dihydro indolone / Beta amino ketone: Molindone
5. others: sertindol

⇒C. Ring analogues of Phenothiazines:
Thiothixene, Chlorprothixene, Loxapine, clozapine.

Phenothiazine:

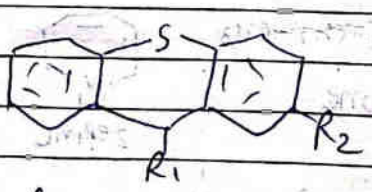


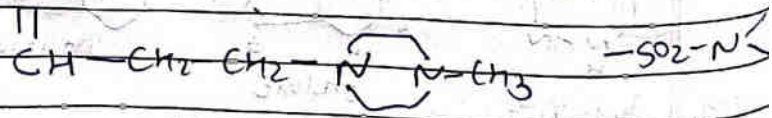
	R_1	R_2
Promazine	$-(CH_2)_3-N<$	H
Chlorpromazine	"	Cl
Trifluoperazine	"	CF_3
Thioridazine		$S-CH_3$
Prochlorperazine		Cl
Trifluoperazine	"	CF_3

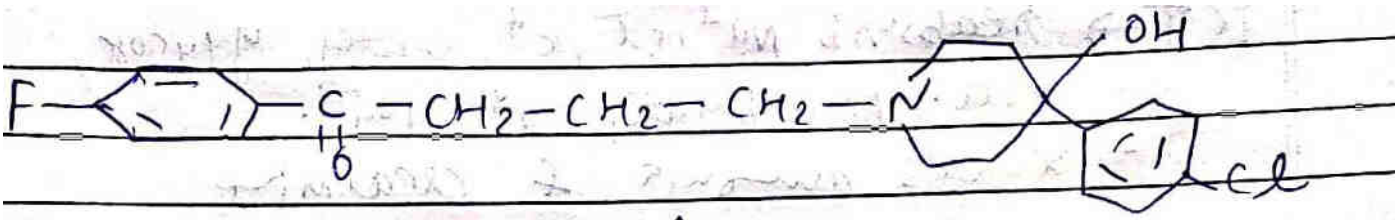


Reserpine

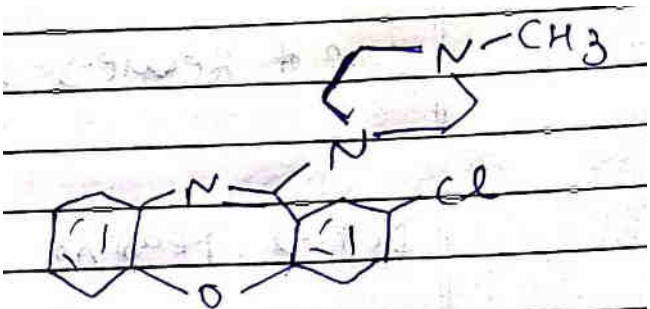
Thioxanthene:



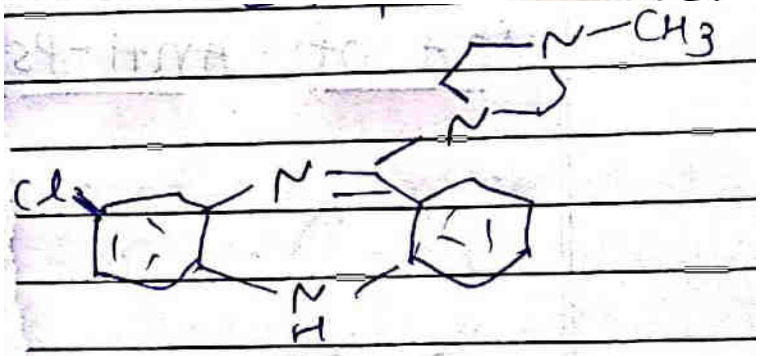
	R_1	R_2
Thiothixene		
Chlorprothixene	"	Cl



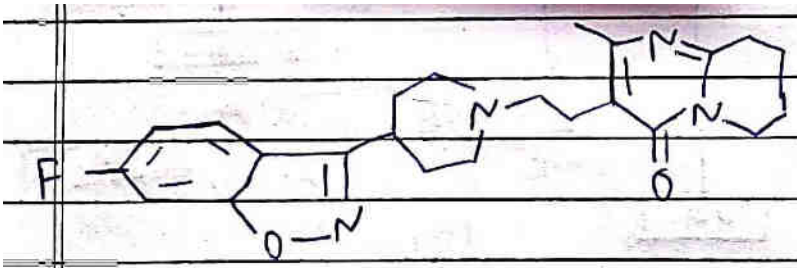
Haloperidol



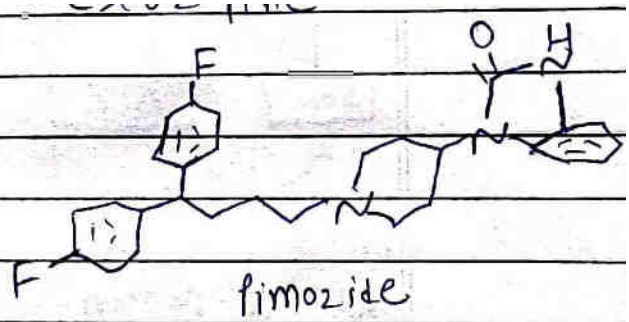
Loxapine.



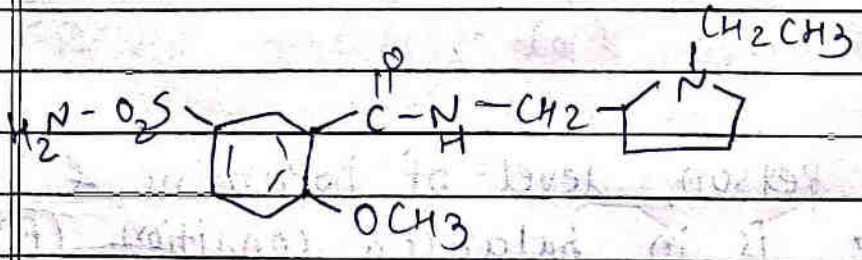
Clozapine



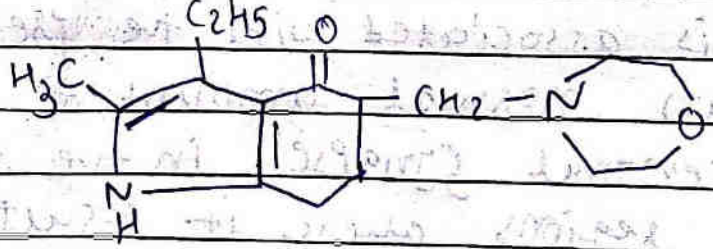
Risperidone



Pimozide



Sulpiride

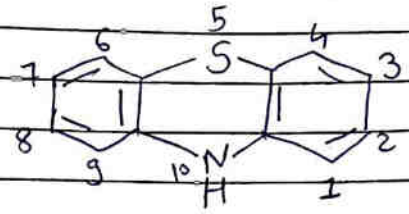


Molindone

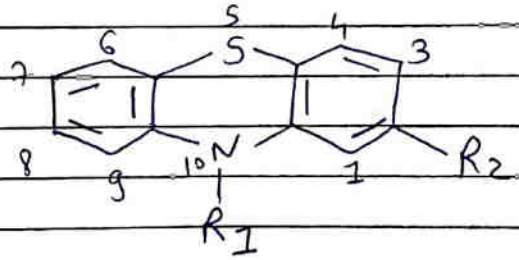
SAR of Phenothiazine:

SAR of Phenothiazine derivatives:

- Basic structure of phenothiazine ring is



- Unsubstituted phenothiazine has no activity, but good lipophilicity for brain penetration.
- Substitution at C-2 & C-10 is required for activity.
- So, general structure of phenothiazine derivative is



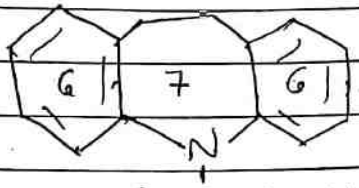
- The sites of modification includes:

1. Tricyclic ring system
2. Phenothiazine ring
3. Alkyl side chain at (N→10) (R_1)
4. Basic Amino group

1) Tricyclic ring;

a) Most of these compounds have either a six-membered central ring eg. Phenothiazine class (6-6-6) → Maximum potency.

b) A seven membered central ring (6-7-6) → decrease activity. eg. Imipramine

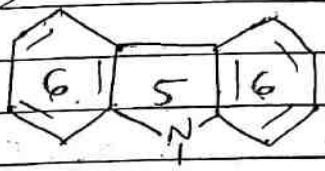


$(CH_2)_3-N-(CH_3)_2$

Imipramine

c) Compound having larger central ring are usually devoid of significant antipsychotic activity.

d) Compound with a five-membered central ring eg. Carbazole (6-5-6), also lacks antipsychotic activity and produce only antidepressant effects.



$(CH_2)_3-N-(CH_3)_2$

Carbazole

e) Analogues of tricyclic compounds that lack a central ring, are generally devoid of antipsychotic activity.

(2) Phenothiazine ring substitution;

→ With some exceptions substitution at position 2 is optimal for neuroleptic potency. In general, potency increases in following order of position of ring substitution:

$$7 < 4 < 3 < 2$$

→ C2 - substitution of the phenothiazine nucleus increases the neuroleptic potency in the following order:

$$OH < H < CN < CH_3 < Cl < CF_3$$

→ Di substitution and trisubstitution have little effect or harmful to potency.

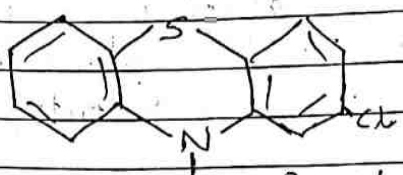
→ Oxidation of sulfur at 5th position decrease activity.

(3) (a) Alkyl side chain ; (N → 10)

a) Amino group separated from nitrogen of nucleus by three carbon → Maximum potency gives confirmation similar to dopamine.

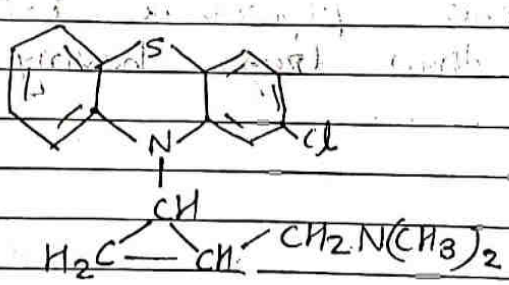
Page No.. Date : / /

b) The homologue of chlorpromazine in which the ring and amino nitrogen is separated by four methylene units doesnot produced desired effects. → No activity.

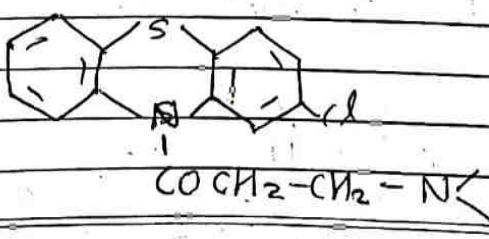


c) Methyl group at position 1, decrease antipsychotic activity and may result in imipramine-like activity.

d) If position 1 of the side chain is incorporated into a cyclopropane ring, potent imipramine like action. → decrease activity.

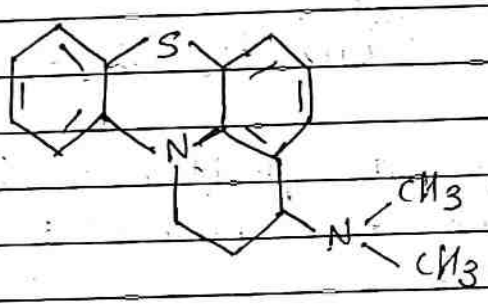


e) If Oxygen is introduced into the position 1 of the 3 amino propyl side chain, it result into potent anti-depressant like action.
eg. Etc. Chloracizine



f) Introduction of a CH_3 substituent at position 2 or position 3 of the side chain apparently has little influence on activity.

g) Bridging of position 3 of the side chain to position 1 of the phenothiazine nucleus, reduces the neuroleptic activity.



h) Alkylation with groups larger than methyl group decreases activity.

i) Piperidine & piperazine derivatives are less potent than drugs having aliphatic side chain.

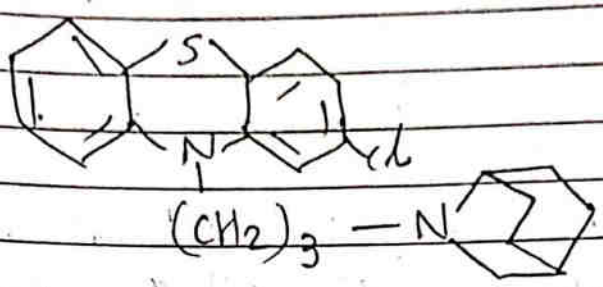
(4) (B) Basic amino group;

a) Primary and secondary amine are less potent than tertiary amine.

b) Alkylation of amino group with group larger than methyl decreases activity.

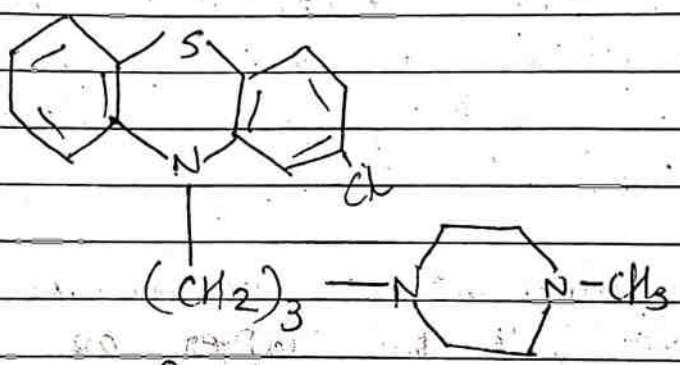
c) When amino group is included in piperidine & piperazine cyclic system no effect on activity.

d) Bridging of piperidine derivative having more activity.



Bridge piperidine derivative

e) Substitution at fourth position with -OH, -CH3 or hydroxyethyl group increase activity.



Prochlorperazine

Q. 5 What are antiepileptic drugs? Give their mechanism of action. Classify with examples.

❖ Definition:

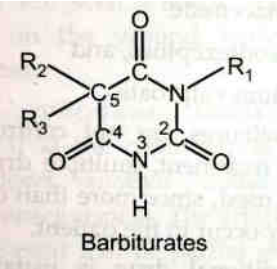
Antiepileptic drugs are the drugs used invariably in adequate and impressive control and management of Epilepsy which is CNS disorder essentially characterized by recurrent transient attacks of disturbed brain function which ultimately give rise to motor (convulsive), sensory (seizure) and psychic sequence of events.

❖ Classification:

A. Based on chemical nature
B. Based on MOA

A. Based on chemical nature:

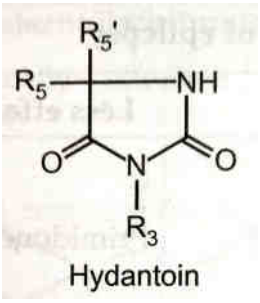
1. Barbiturates:



Barbiturates

Drug example	R_1	R_2	R_3
Phenobarbitone	H	C_2H_5	C_6H_5
Mephobarbitone	CH_3	C_2H_5	C_6H_5
Metharbital	CH_3	C_2H_5	C_2H_5

2. Hydantoins:



Hydantoin

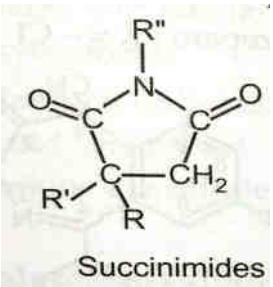
Drug example	R_3	R_5	R_5'
Phenytoin	H	C_6H_5	C_6H_5
Mephenytoin	CH_3	C_2H_5	C_6H_5
Ethotoin	C_2H_5	H	C_6H_5

3. Oxazolidine diones:

Oxazolidinediones

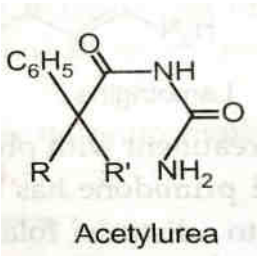
Drug example	R_3	R_5	R_5'
Trimethadione	CH_3	CH_3	CH_3
Paramethadione	CH_3	CH_3	C_2H_5

4. Succinimides:



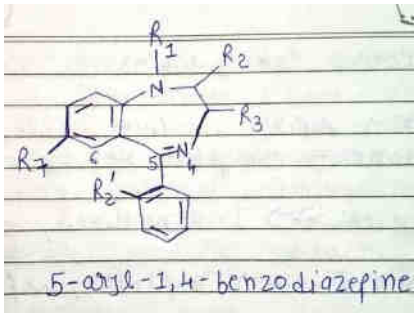
Drug example	R	R'	R"
Phenysuximide	C_6H_5	H	CH_3
Methsuximide	C_6H_5	CH_3	CH_3
Ethosuximide	C_2H_5	CH_3	H

5. Acetyl Urea:



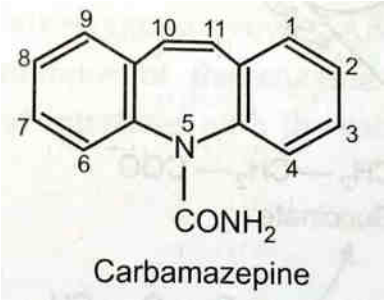
Drug example	R	R'
Phencemide	H	H

6. Benzodiazepines:

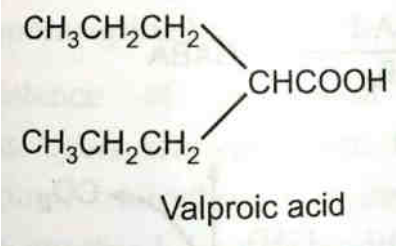


Drug example	R_1	R_2	R_3	R_7	R_2'
Diazepam	CH_3	=O	H	Cl	H
Clonazepam	H	=O	H	NO_2	Cl
Nitrazepam	H	=O	H	NO_2	H

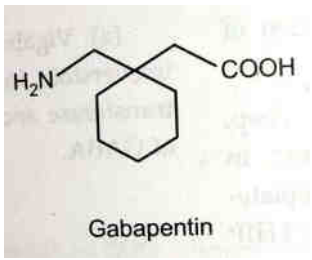
7. Iminostilbens:



8. Aliphatic carboxylic acid:



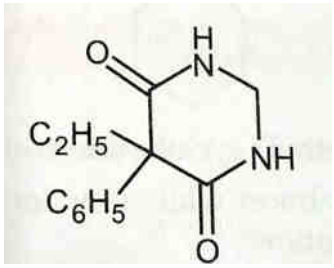
9. **New and potent Anticonvulsants:**



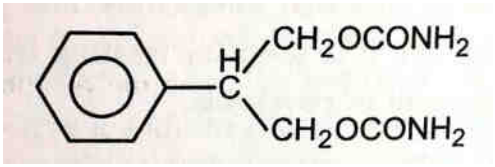
Gabapentin

Vigabatrin

10. **Miscellaneous:**



Primidone



Felbamate

B. Based on MOA:

1. **Drugs inhibiting Sodium channel:**
   - Phenytoin, Mephenytoin
   - Valproate
   - Lamotigine
   - Carbamazepine

2. **Drugs affecting Calcium channel:**
   - Funarizine
   - Trimethadiones
   - Ethosuximide, Phensuximide, Methosuximide
   - Valproate

3. **Drugs affecting GABA:**
   a. **GABA Transaminase inhibitor:** Vigabatrine, Sodium valproate
   b. **GABA reuptake inhibitor:** Tigabine
   c. **GABA receptor stimulator acting on GABA chloride ionophore complex:**
      - Progabide
   d. **Drugs which release GABA:** Gabapentin

4. **Drugs which bind through Barbiturate receptor:** Phenobarbitone, Mephobarbitone
5. **Drugs which bind through Benzodiazepine receptor:** Diazepam, Clonazepam
6. **NMDA receptor antagonist:** Phencyclidine, Barbiturates, Felbamate

❖ Mechanism of Action:

Goals of treatment of Epilepsy:

- ✓ Normalization of seizure foci
- ✓ Prevention of origin of seizure from the foci
- ✓ Prevention of PTP (Post-titenic potential)
- ✓ Blockage of propogation of seizure
- ✓ Elevation of excitatory synaptic threshold
- ✓ Potentiation of pre or post-synaptic inhibition
- ✓ Prolongation of the refractory period
- ✓ Blockage of repetitive neuronal firing
- ✓ Blockage of synchronization of neuronal discharge

These goals can be achieved by following strategies:

- ✓ Modification of ion conductances
  This includes
  - Blockage of voltage gated sodium and calcium channels
  - Activation of voltage gated potassium channels
- ✓ Increasing inhibitory (GABAergic) transmission
- ✓ Decreasing excitatory (Glutamatergic-NMDA) activity

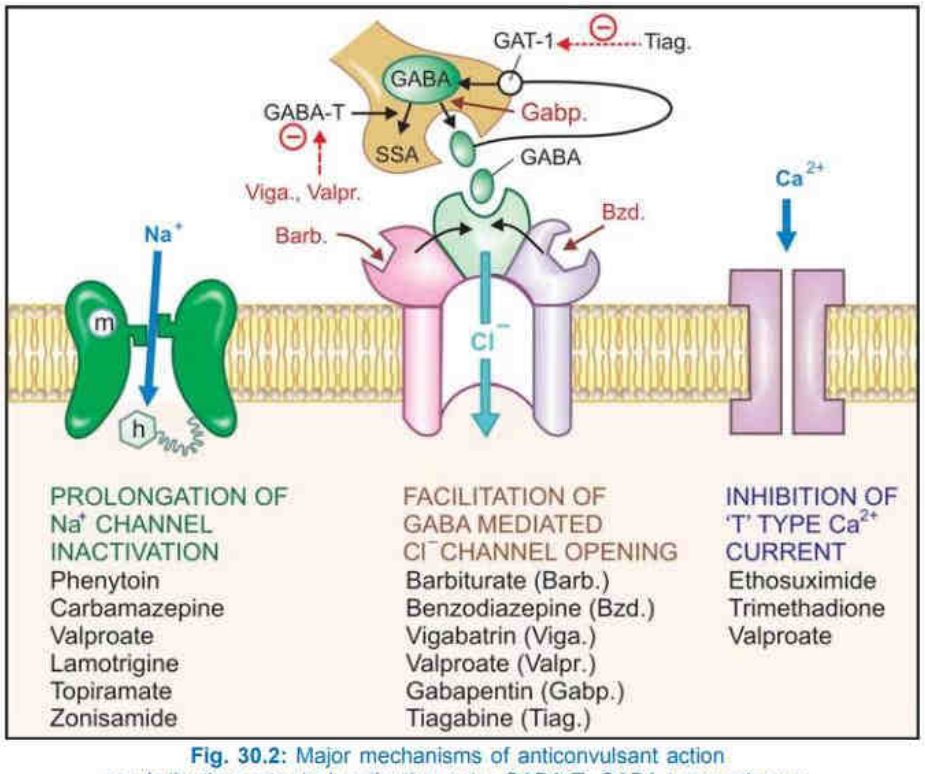


Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde; GAT-1: GABA transporter

This figure is just for explanation. No need to draw in exam.

1. **Drugs inhibiting Sodium channel:**
   Drugs of this class act on sodium channels on the neuronal cell membrane preventing repetitive detonation of normal brain cells during "*depolarization shift*" that occurs in epilepsy.
   This is achieved by
   i. Prolonging the inactivated state of the voltage sensitive neuronal Na^+ channel and governs the refractory period. As a result high frequency discharges are inhibited with little effect on low frequency discharge.
   ii. Promoting sodium efflux from neurons stabilizing the threshold against hyper excitability.
   iii. Reducing PTP at synapses. Loss of PTP prevents corticle seizure foci from detonating adjacent corticle areas.

2. **Drugs affecting Calcium channel:**
   They probably act by reducing threshold T-type Ca^{++} currents in thalamic neurons and hence stabilizes neuronal membrane.

3. **Drugs affecting GABA:**
   Drugs of this class increase concentration of GABA. GABA is major inhibitory neurotransmitter. Hence, increase in concentration of GABA produces antiepileptic effect. Drugs of this class increase concentration of GABA by
   - ✓ Inhibiting GABA Transaminase enzyme
   - ✓ Inhibiting GABA reuptake
   - ✓ Stimulating GABA receptor

4. **Drugs which bind through Barbiturate receptor:**
   They operate through GABAergic mechanism. They potentiate action of GABA.

5. **Drugs which bind through Benzodiazepine receptor:**
   They operate through GABAergic mechanism. They potentiate action of GABA.

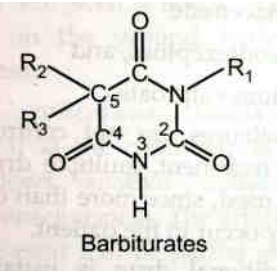
6. **NMDA receptor antagonist:**
   NMDA (N-methyl-D-aspartate) is an excitatory neurotransmitter. NMDA receptor antagonist blocks effect of NMDA giving antiepileptic effect.

Q. 6 Explain SAR of Anticonvulsants:

SAR of Anticonvulsants incldes SAR of following classes because they are main classes of Anticonvulsants.

1. SAR of Barbiturates
2. SAR of Hydantoins
3. SAR of Oxazolidine diones
4. SAR of Succinimides
5. SAR of Acetyl Urea
6. SAR of Benzodiazepines
7. SAR of Aliphatic carboxylic acid

1. SAR of Barbiturates:

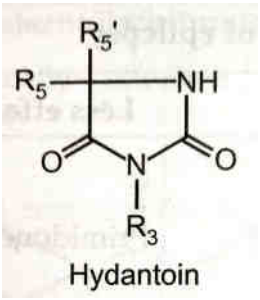


Barbiturates

Drug example	R_1	R_2	R_3
Phenobarbitone	H	C_2H_5	C_6H_5
Mephobarbitone	CH_3	C_2H_5	C_6H_5
Metharbital	CH_3	C_2H_5	C_2H_5

- Optimum activity is observed when one of the substituents at C_5 is phenyl.
- The 5, 5 - diphenyl derivative has less activity than phenobarbitone.
- N_2 and N_3 substitutions, in some cases also resulted in an increased activity.
- 5, 5 - dibenzyl barbituric acid, causes convulsions.

2. SAR of Hydantoins:



Hydantoin

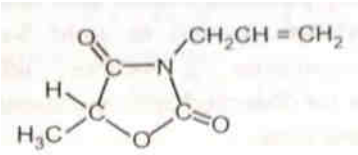
Drug example	R_3	R_5	R_5'
Phenytoin	H	C_6H_5	C_6H_5
Mephenytoin	CH_3	C_2H_5	C_6H_5
Ethotoin	C_2H_5	H	C_6H_5

- A 5-phenyl or other aromatic substituent is essential for the activity.
- Alkyl substituents at position 5 may contribute to sedation, a property absent in phenytoin.
- Among other hydantoins, like spiro-hydantoins, thiohydantoins, dithiohydantoins and 1, 3-disubstituted hydantoins, some exhibit activity against chemically induced convulsions while remaining are ineffective against electroshock induced convulsions.

3. SAR of Oxazolidine diones:

Drug example	R_3	R_5	R_5'
Trimethadione	CH_3	CH_3	CH_3
Paramethadione	CH_3	CH_3	C_2H_5

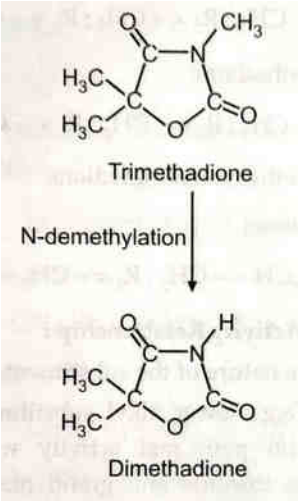
- The nature of the substituents on C_5 is important e.g., lower alkyl substituents tend towards anti petit mal activity while aryl substituents towards anti grand mal activity e.g.,



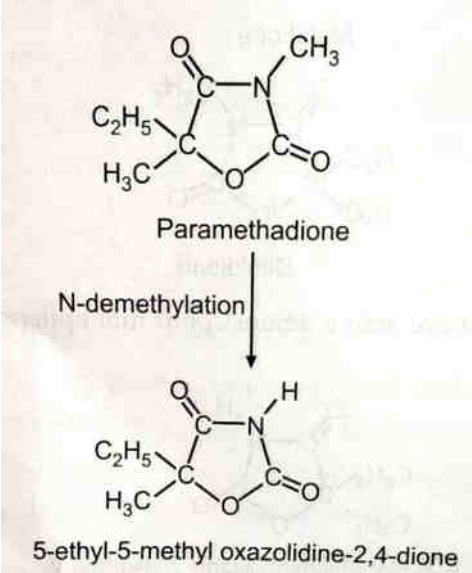
Both are active against petit mal epilepsy. While,

It is active against grand mal epilepsy.

- The N-alkyl substituent does not affect the activity since all clinically used agents from this class, undergo N-dealkylation in metabolism. e.g. The anticonvulsant activity of trimethadione is due to mainly its N-demethylated metabolite, dimethadione.

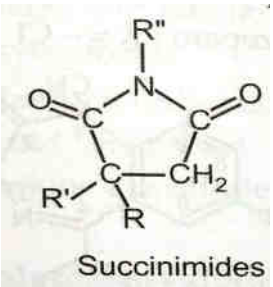


- Similarly paramethadione also undergoes N-demethylation in-vivo to yield 5-ethyl-5-methyl oxazolidine -2, 4-dione, which is responsible for observed anticonvulsant action of paramethadione.



Paramethadione is similar to trimethadione but less effective and less toxic.

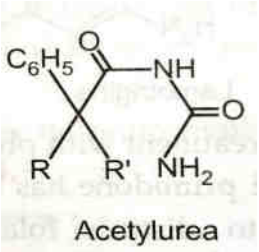
4. SAR of Succinimides:



Drug example	R	R'	R"
Phenysuximide	C_6H_5	H	CH_3
Methsuximide	C_6H_5	CH_3	CH_3
Ethosuximide	C_2H_5	CH_3	H

- Methsuximide and phensuximide have phenyl substituents which make them active against electrically induced convulsion.
- N-methylation decreases activity against electroshock seizures and impart more activity against chemically induced convulsions.
- α-Methylalkoxyphenyl succinimides and alkoxybenzylsuccinimides were active anticonvulsants. The length of the alkoxy group here determines the activity.

5. SAR of Acetyl Urea:

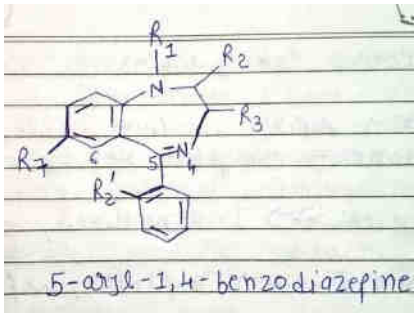


Drug example	R	R'
Phencemide	H	H

- Among aliphatic acetyl ureas, the highest anticonvulsant activity is found in those derived from branched chain acids of about seven carbon atoms.

- With a further increase in molecular weight, the anticonvulsant activity gradually terminates and hypnotic effect predominates.
- Phenacemide is most active agent amongst the aromatic acetylurea.
- Any substitution on the nitrogen of phenacemide does not increase further the anticonvulsant activity.
- Activity decreases with aromatic substitution of phenacemide with a gradual increase in hypnotic activity.
- Diphenylacetylurea is inactive.

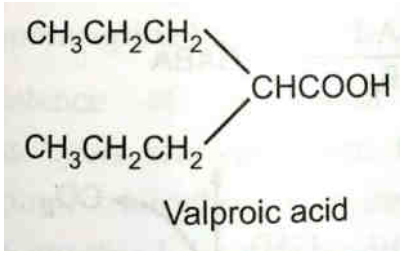
6. SAR of Benzodiazepines:



Drug example	R_1	R_2	R_3	R_7	R_2'
Diazepam	CH_3	=O	H	Cl	H
Clonazepam	H	=O	H	NO_2	Cl
Nitrazepam	H	=O	H	NO_2	H

- The electron withdrawing atom or group at position 7 increases the anti-epileptic activity while electron donating substituents at 7, 8 or 9 positions decrease it.
- A phenyl group at position 5 is necessary for activity. But only halogen substituents are allowed in the ortho position.
- The electron withdrawing groups at ortho or diortho positions at 5-phenyl increase the activity while any substituent on meta or para position at 5-phenyl decreases the activity.
- Methyl substitution at position 1 confirms high activity.

7. SAR of Aliphatic carboxylic acid:



- The anticonvulsant activity increases with increased chain length.
- Introduction of a double bond decreases the activity.
- Introduction of a secondary or tertiary hydroxyl group or replacement of carboxyl by hydroxyl group has no effect.

Q. 7 What are Analgesics? Write SAR and mode of action of morphine.

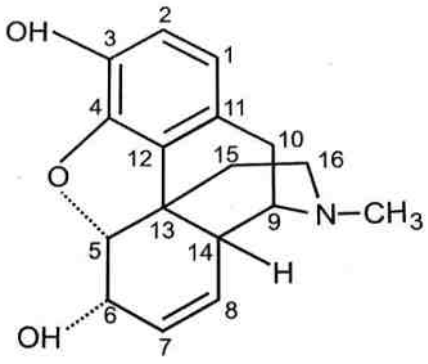
❖ Analgesics:

- Analgesia is a state where there is sensitivity to pain without loss of consciousness.
- Analgesics are the drugs which produced analgesia.
- They can be defined as-*"Analgesics are the agents which produce symptomatic relief from pain without curing cause of pain, by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness."*

❖ Mode of Action of Morphine:

- Morphine acts as agonist of the mu and kappa opioid receptors.
- Agonist activity at opioid receptors opens potassium channels and prevents the opening of voltage-gated calcium channels. This reduces neuronal excitability and inhibits the release of pain neurotransmitters.
- Due to this release of substance P (Neurotransmitter of pain modulation) from the primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neuron is inhibited. This results in analgesia.

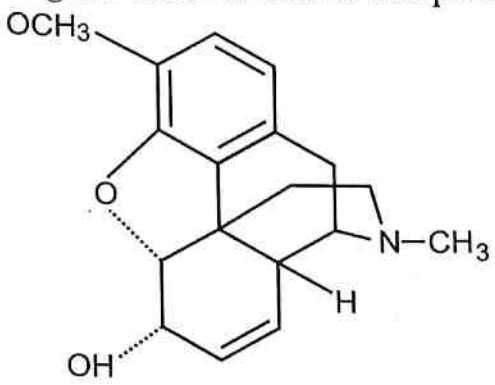
❖ **Structure activity relationship of Morphine:**



Morphine

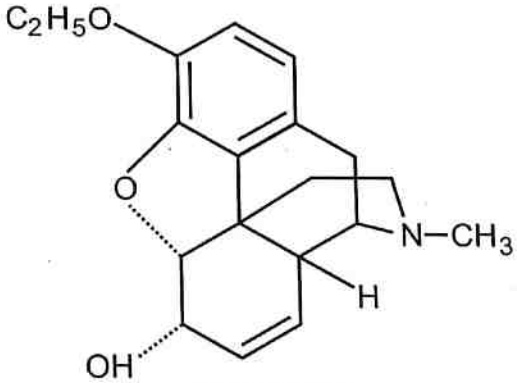
I. Modification of phenol –OH group at position 3 : The phenolic –OH group at position 3 of morphine is important for analgesic activity as it helps in binding to the receptor through H-bonding. Change in this –OH group changes the analgesic activity.

a) Acetylation or methylation changes the activity. For example, codeine produced by methylation has 1/10th the analgesic effect to that of morphine.



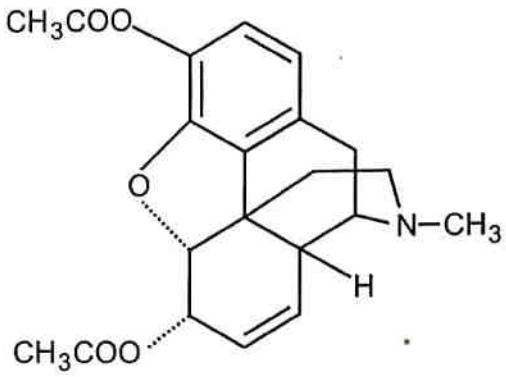
Codeine

b) Ethylation produces ethylmorphine which is less effective than codeine.



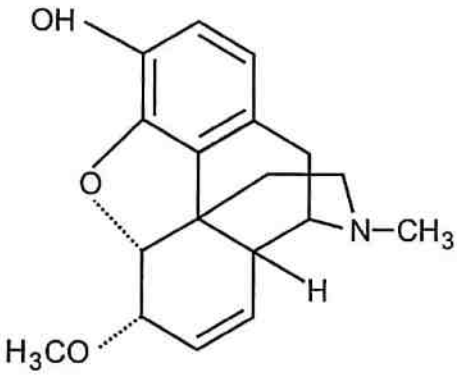
Ethylmorphine

c) Acetylation of morphine produces Diamorphine, which is highly addictive and is twice as active as morphine.

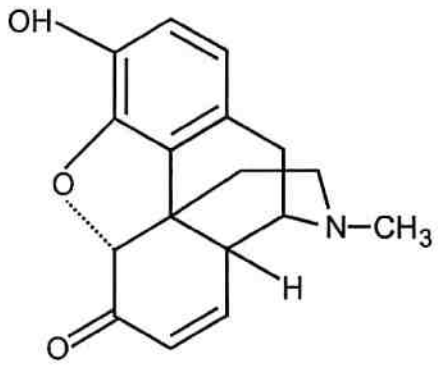


Diamorphine

II. Modification of Alcoholic–OH at position 6 : The alcoholic –OH group at position 6 of morphine can be modified to produce active derivatives. For example, Hetero codeine and Morphinone are more active than Morphine.

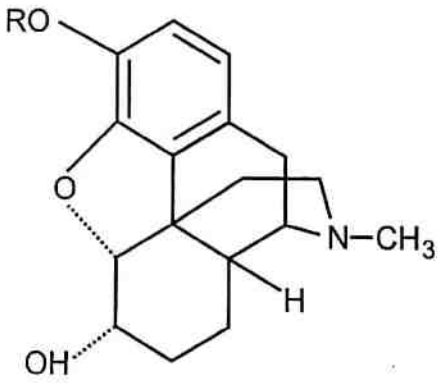


Heterocodiene



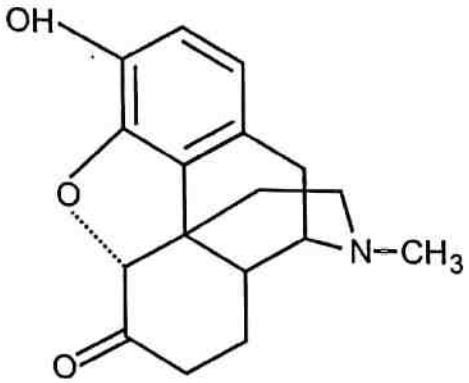
Morphinone

III. Modification of double bond at position 7 & 8 : The double bond present at position 7 and 8 is not essential for analgesic activity. It can be removed to give compounds with reduced duration of action and increased activity. For example Dihydromorphine and Dihydrocodeine.



Dihydromorphine R=H
Dihydrocodeine R=CH_3

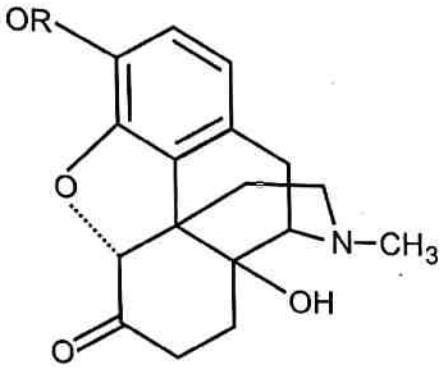
Similarly, Dihydromorphinone is 10 times more potent than morphine as an analgesic.



Dihydromorphinone

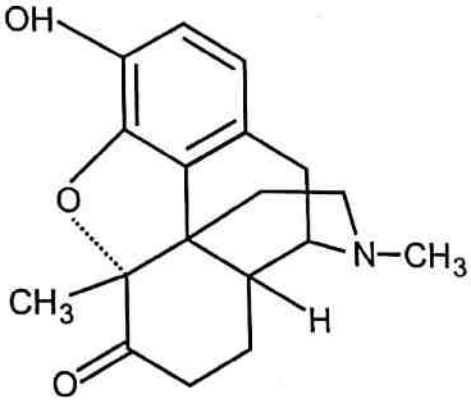
IV. Introduction to Substitutents at C-14 and C-5 :

Introduction of –OH group at C–14 gives potent compounds. For example, oxymorphone and oxycodone has increased potency as –OH group provides an additional H-bonding.



Oxymorphone R=H
Oxycodone R=CH_3

Addition of –CH_3 group at C-5 is dihydromorphinone gives the drug which is orally effective. For example, Metopon



Metopon

V. Replacement of N-methyl group by other groups :

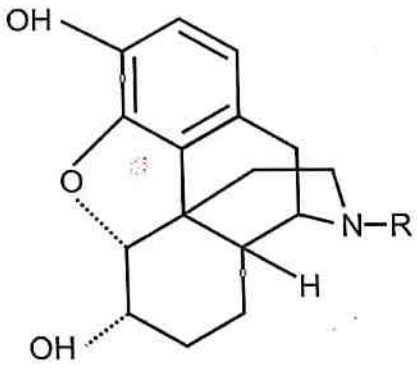
This replacement produces various qualitative changes like drugs produced may be agonist, antagonist or mixed agonist-antagonist in nature.

a) N-CH_3 group provides sufficient partition coefficient to the drug. So, if N–CH_3 is replaced by N-H this decreases the activity. For example, N-normorphine

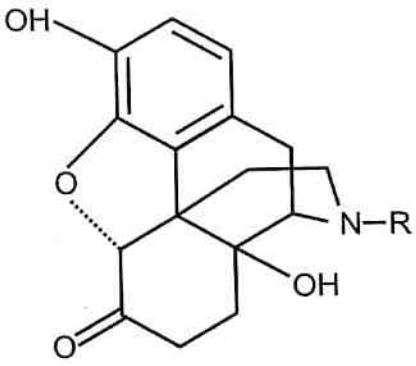
b) Higher alkyl substitutents on 'N' decreases the activity.

c) Aromatic substituent on 'N' increases the activity. For example, N-phenethylnormorphine is more potent than morphine.

d) If N–CH_3 group of morphine is replaced by N-alkene, N-cycloalkylmethyl group, it will produce drugs with antagonistic activity. For example, Nalorphine, Naloxone and Naltrexone are morphine antagonists.



Nalorphine
R=$-CH_2-CH=CH_2$



Naloxone R=$-CH_2-CH=CH_2$
Naltrexone R=$-CH_2-$

Q. 8 What are NSAIDs? Classify them with two examples of each class. Write synthesis of one NSAID having one chiral center.

❖ Definition:

"NSAIDs are the drugs used primarily to treat inflammation (Anti-inflammatory), mild to moderate pain (Analgesic) and fever (Antipyretic). They are called Non-steroidal as they lack steroidal nucleus in their structure".

NSAIDs have three major actions:

- ✓ **Anti-inflammatory**
- ✓ **Analgesic**
- ✓ **Antipyretic**

They are also known as Non-narcotic analgesics with antipyretic and Anti-inflammatory action.

❖ Classification:

1 **Non-selective COX inhibitors:**

I. **Salicylates:** Aspirin (Acetyl salicylic acid), Sodium salicylate

II. **Pyrazolon derivatives:** Phenylbutazone, Oxyphenbutazone

III. **Indole derivatives:** Indomethacin, Sulindac

IV. **Propionic acid derivatives:** Ibuprofen, Naproxen

V. **Fenamates or Anthranic acid derivatives:** Mephenamic acid, Meclophenamate

VI. **Aryl acetic acid derivatives:** Diclofenac, Tolmetin

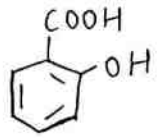
VII. **Oxicam derivatives:** Piroxicam, Tenoxicam

VIII. **Pyrrolo-Pyrrole derivatives:** Ketorolac

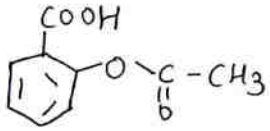
2 **Preferential COX-II inhibitors:** Nimesulide, Meloxicam

3 **Selective COX-II inhibitors:** Celecoxib, Rofecoxib

4 **Analgesic-Antipyretic with poor Anti-inflammatory action:** Paracetamol, Phenacetin

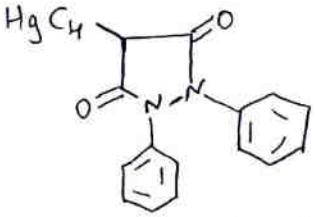


Salicylic acid

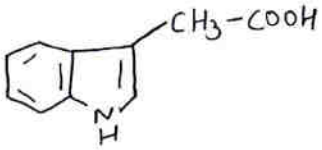


Acetyl salicylic acid
(ASPIRIN)

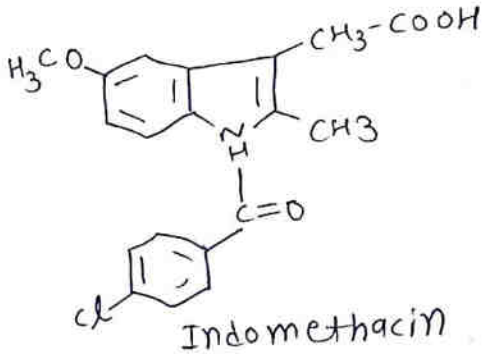
Pyrazolone



Phenyl butazone



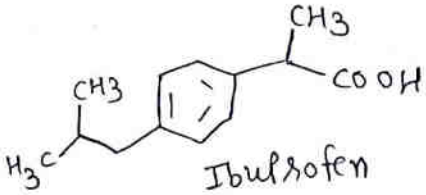
Indole acetic acid



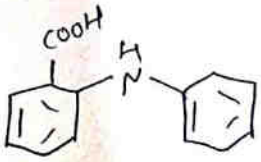
Indomethacin

CH_3-CH_2-COOH

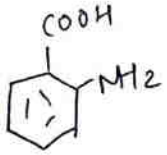
Propionic acid



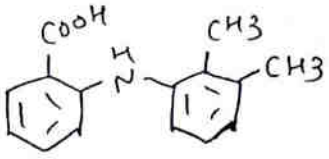
Ibuprofen



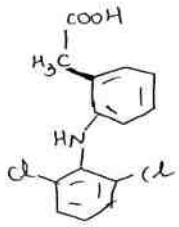
Fenamic acid



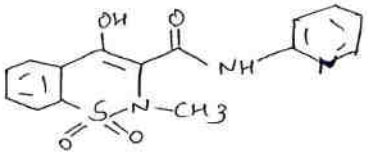
Anthranilic acid



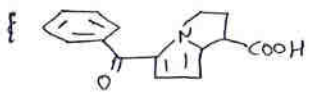
Mefenamic acid



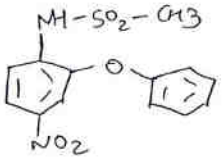
Diclofenac



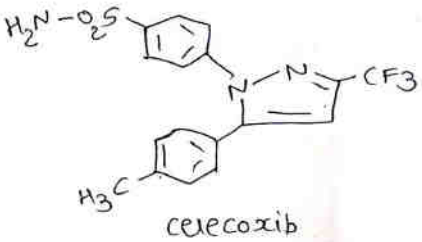
Piroxicam



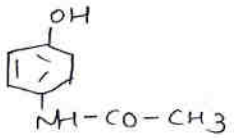
ketorolac



Nimesulide



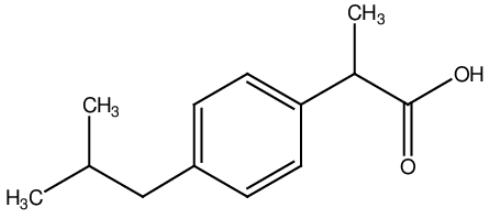
celecoxib



paracetamol

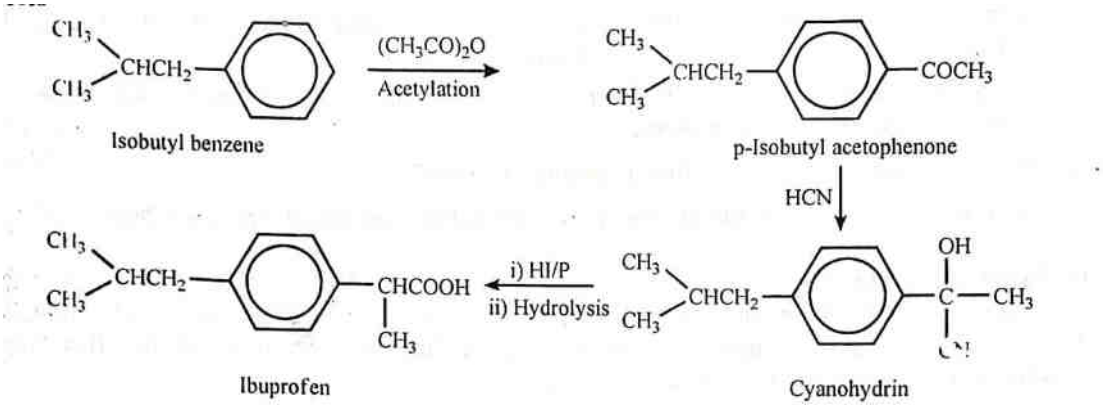
Synthesis of one NSAID having one chiral center:

Ibuprofen has one chiral center.



Ibuprofen

Synthesis of Ibuprofen:



Isobutyl benzene

p-Isobutyl acetophenone

Ibuprofen

Cyanohydrin

Q. 9 Write a note on narcotic antagonists with its mechanism.

These are the drugs which competitively antagonises the effects of opioid analgesics by binding with specific opioid receptor. These drugs bind to the opioid receptors with great affinity than agonists and blocks the receptor and thus body do not responds to endorphins and opioids. Narcotic antagonists reverses the effects of morphine like substances.

Martin and Gilbert (1977) postulated that there are three subspecies of opioid receptors. These are :

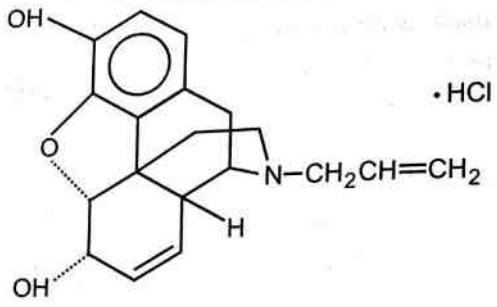
1. μ subspecies : Produces analgesia, addiction, respiratory depression and reduced gastrointestinal motility.
2. κ receptor subspecies : Responsible for sedation and spinal analgesia.
3. σ subspecies : Produces hallucinations and respiratory stimulation.
4. δ subspecies : Causes analgesia, addiction and antidepression.

Drugs have different relative affinities for these subspecies of receptors. Depending upon this relative affinities, narcotic antagonists can be classified as :

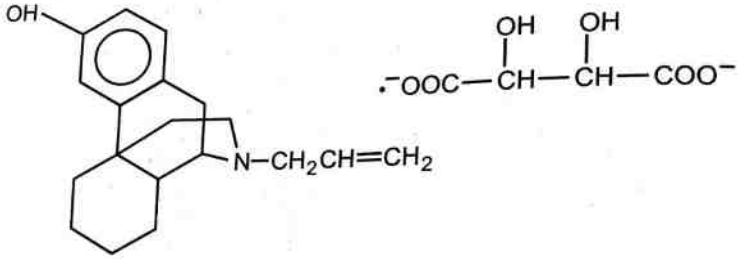
A) Pure antagonists : e.g. Naloxone

B) Partial antagonists : e.g. Nalorphine and Levallorphan

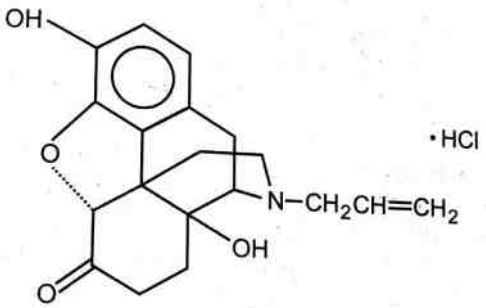
C) Partial agonist : e.g. Propiram and Profadol



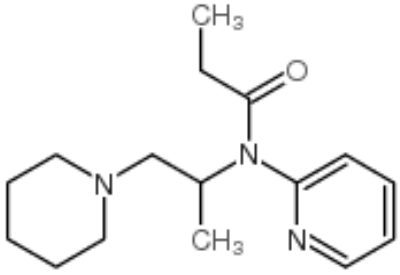
Nalorphine Hydrochloride



Levallorphane Tartarate



Naloxone Hydrochloride



Propiram

Mechanism of action:

Narcoitc antagonists act by antagonizing opioid receptors. Pure antagonists have fully antagonizing action for opioid receptors. Partial antagonists have more antagonist and less agonist action for opioid receptors. Partial agonists have less antagonist and more agonist action for opioid receptors.

Naloxone has high affinity for μ receptor than δ receptor and lowest for κ receptor.

Nalorphine has competitive antagonist action on μ receptor and agonist at κ receptor.

Levallorphan act as an antagonist of μ receptor and as an agonist of κ receptor.

Uses:

1. Narcotic antagonists are used to counter the effects of opioid overdose.
2. It helps in overcoming opioid addiction.
3. These are used for the treatment of alcohol addiction.
4. Narcotic antagonists reduces the intensity of various undue effects of opioids like vomitting, drowsiness etc.

Q. 10 Enlist various physicochemical parameters that affect biological activity of drugs. Explain the effect of protein binding and hydrogen bonding on action of drugs.

Physicochemical parameters that affect biological activity of drugs are as follows:

- Ionization,
- Solubility,
- Partition Coefficient,
- Hydrogen bonding,
- Protein binding,
- Chelation,
- Bioisosterism,
- Optical and Geometrical isomerism.

Protein binding:

Binding of drugs falls into two classes:

1) Plasma proteins;
2) Blood cells.

2.9 Plasma Protein Binding:

- Many drugs are bound to some extent to plasma proteins.
- It is important to know to what extent a drug is bound to plasma proteins.
- Protein bound drug is large complex that can not easily cross the biological membranes and have a restricted distribution.
- Protein bound drugs are usually pharmacologically inactive.
- The plasma protein binding is expressed as "fraction bound" that is ratio of bound concentration over total (bound plus free) concentration.

$$\text{Fraction bound} = \frac{\text{Bound concentration of drug } (D_P)}{\text{Total concentration of drug } (D_F + D_P)}$$

(bound + free)

$$(DF + DP = Dt)$$

$$\% \text{ bound} = \frac{\text{Bound concentration}}{\text{Total concentration}} \times 100$$

- Free fraction equals to one minus the bound fraction.

$$\text{Free fraction drug} = (1 - \text{bound fraction})$$

- Plasma proteins bound with drugs by formation of mainly Vander-waals forces, hydrophobic bonding, hydrogen bonding and ionic interaction.
- For most drugs the binding of drugs to plasma protein is a reversible process with rapid rates of association and dissociation.
- The degree of binding is determined by affinity, (association constant), capacity (number of binding site per molecule of protein), protein concentration and drug concentration.

The most significant protein involved in the binding of drug is albumin, which is more than half of all blood proteins. Other proteins are α_1-acid glycoprotein, lipoproteins.

Major drug binding proteins in plasma is summarized in Table 2.7.

Protein	MW g/mole	Normal concentration g/litre	Type of drugs bound	Example
Albumin	67,000	3.5 – 5	acidic, basic	warfarin
α_i - acid glycoprotein	42,000	0.04 – 0.1	basic, neutral	propronolol
Lipoprotein	200000 – 2,400,000	varies	Lipophilic basic & neutral	Cyclosproine

Table 2.7 : Major drug binding proteins

2.1.2.7.2. Binding of Drugs to Blood Cells

More than 40% of the blood comprises of blood cells of which the major cell component is the RBC. The RBCs constitute 95% of the total blood cells. Thus, significant RBC drug binding is possible. The red cell is 500 times in diameter as the major plasma protein binding component albumin. The RBC comprises of three components each of which can bind to drugs:

1) **Haemoglobin:** It has a molecular weight of 64,500 (almost equal to that of HSA) but is 7 to 8 times the concentration of albumin in blood. Drugs like phenytoin, pentobarbital and phenothiazines bind to haemoglobin.

2) **Carbonic Anhydrase:** Drugs known to bind to it are acetazolamide and chlorthalidone (i.e., carbonic anhydrase inhibitors).

3) **Cell Membrane:** Imipramine and chlorpromazine are reported to bind with the RBC membrane. It has been shown that the rate and extent of entry into RBC is more for lipophilic drugs, e.g., phenytoin. Hydrophilic drug like ampicillin do not enter RBC.

2.9.1 Factors affecting protein binding:

1. **Drug related:** Physicochemical properties of drug like lipophilicity, anionic, acidic binding sites, basic binding sites, concentration of drug are major factors affect protein binding.

2. **Number of binding sites:** Number of binding sites are also important factor for protein binding. At low concentration of drug, fraction of binding sites are occupied, but at high concentration of drug most binding sites are occupied and free fraction becomes concentration - gradient.

   Concentration - dependent changes in drug binding are most likely to occur with drugs that have a high affinity to protein and given in larger doses. e.g. aspirin, phenyl butazone, some penicillins and cephalosporins.

   Albumin has more binding sites. Tamoxifen and Dicumarol binds to 10 and 20 sites of albumin. Indomethacin binds to 3 sites.

   Competition between drugs for binding site may occur when given in combination. Administration of phenylbutazone to warfarin result in hemorrhagic reaction.

3. **Competition between drug and normal constituents:** Free fatty acids (FFA) competes with albumin. Free fatty acids concentration are increased in fasting, due to exercise or infection, albumin bound drugs may displaced from their binding sites.

   Allosteric changes in protein molecule by drug or its metabolite may change the protein binding. e.g. aspirins acetylating the lysine of albumin. So modifying the capacity of NSAIDs binding.

   In renal failure, waste products that accumulate in blood and compete for protein binding.

4. **Pathological condition:** Plasma protein concentration often changes in pathological condition and binding with drug will changes.

   In various disease states (such as renal failure, liver disease, inflammation), in pregnancy and in neonatal period, hyperalbuminemia is observed.

   α_1- acid glycoprotein concentration rise in inflammatory diseases, stress and malignancy and fall in liver disease.

5. **Patient related:** Age, genetic and environmental factors, disease state of patient also play important role in plasma protein binding.

- Binding to other macromolecular components like immunoglobulins and erythrocytes generally occur in smaller extent.

Hydrogen bonding:

- Hydrogen bonds are specific, short range, and directional non-bonded interactions. They occur between hydrogen atom bound covalently to an electronegative atoms (usually N, O or S) and an additional electronegative atom (Table 2.3).
- Distance of 2.5 – 3.2 A° between H-bond donor X and Y. Bond angles of 130 – 180° are mainly found. Bond strength varies depending on group from 1 – 7 kcal/mol. Binding affinities increase by about one order of magnitude per hydrogen b... The compounds that are capable of forming H-bond are soluble in water.

Strength of H-bond	Donor	Acceptor
Very strong	$\overset{+}{N}H_3$, F – H	CO_2^-, O^-, N^-, F^-
Strong	O – H, N – H, Hal – H (Cr, Br)	O = C, O – H, S = C, F – H, Hal^-
Weak	C – H, S – H, P – H	C = C, Hal – C, π, S – H, Hal - H

Table 2.3 : H-bond donor and acceptor with their strength of interaction

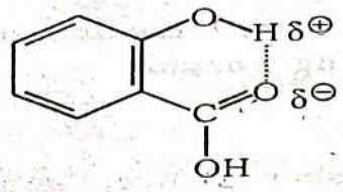
Hydrogen bonding is classified in to two types:

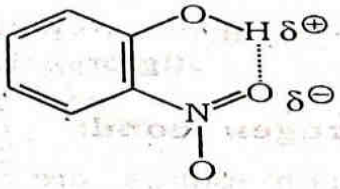
(a) Intramolecular Hydrogen bond

(b) Intermolecular Hydrogen bond

(a) Intramolecular hydrogen bond:

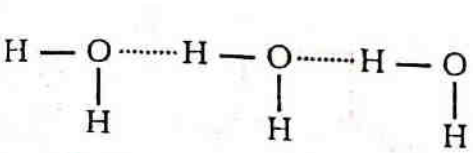
When H-bond is formed between two atoms within a molecule, is called an intramolecular H-bond. This result in formation of ring known as chelation. e.g. salicylic acid, o-nitrophenol.



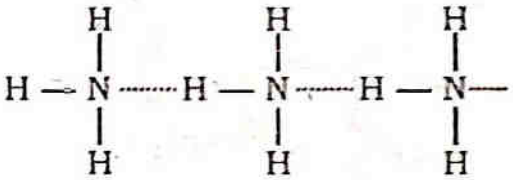


(b) Intermolecular hydrogen bond:

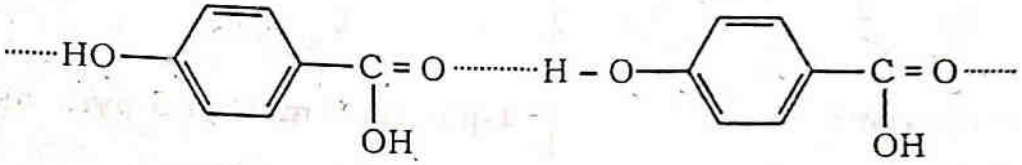
When H-bond is formed between two or more molecules, it i... known as intermolecular H-bond. This gives association o... molecules and forms dimers, trimers or polymeric aggregate. e.g... p-hydroxy benzoic acid, p-nitrophenol, water, ammonia etc.



Water



Ammonia

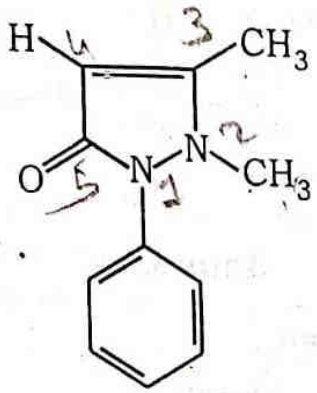


p-hydroxy benzoic acid

Importance of H-bond:

- Many physical properties are affected by hydrogen bonding. Boiling point, melting point and solubility of compounds are greatly affected by H-bond. Intramolecular H-bonds generally decrease melting point, boiling point and solubility. Intermolecular H-bonds generally increase boiling, melting point and solubility.
- Strength of acids and bases are also affected by H-bond. Surface tension and viscosity have been changed by H-bonds in molecules.
- Hydrogen bond helps in stabilizing the conformers of many macromolecules. α - helix and β - sheet conformation of peptides and proteins, double helical structure of DNA is due to hydrogen bond. H-bond is very important in chemistry of genetic code.
- Hydrogen bonding is very important in drug receptor interaction and as well as their biological activity. This can be explained by some examples.

1. o-hydroxybenzoic acid (Salicylic acid) is good antibacterial agent but p-hydrobenzoic acid having less antibacterial activity.
2. Antipyrine (1-phenyl-2,3-dimethyl-5-pyrazolone) is analgesic but 1-phenyl-3-methyl-5-pyrazolone is devoid of analgesic activity.



Antipyrine

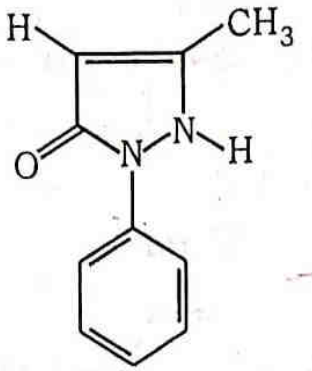
Good analgesic agent

M.P. = 112°C

Soluble in water

Does not form intermolecular H-bond

Cross biological membrane



1-phenyl-3-methyl-5-pyrazolone

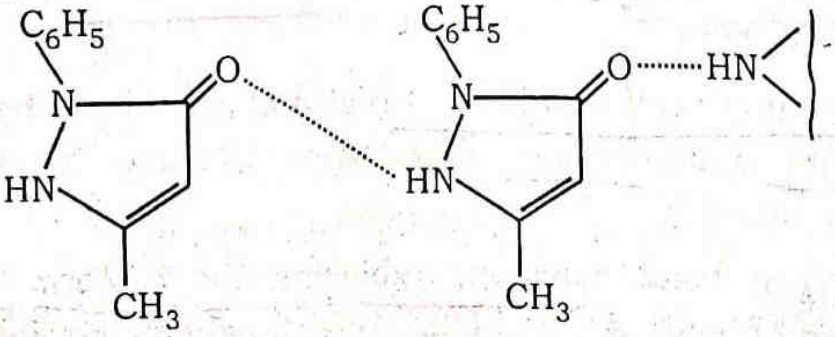
No analgesic property

M.P. = 127°C

Insoluble in water

Forms intermolecular H-bond

Do not cross biological membrane



Intermolecular H-bond

3. Vancomycin is especially form H-bond with peptide having a terminal D-Ala-D-Ala moiety in bacterial cell through five H-bonds and show antibacterial activity.

Q. 11 Discuss the role of Partition coefficient and solubility in drug's biological action.

Partition coefficient:

- As we know solubility is first requirement for drug to transported in membrane surface. but diffusion across the membrane is depends upon lipophilicity (lipid solubility). biological membranes are lipidic in nature.
- The rate of diffusion of drugs across the cell membrane is not only concentration dependent but also depends upon oil/water partitioncoefficient of drug.
- The ability of drug to dissolve in lipid phase when an aqueous phase is also present, often called as lipophilicity. The lipophilicity is characterized by partition coefficient.
- Partition coefficient is defined as the equilibrium constant of drug concentration for "unionizable" molecule in lipid phase and aqueous phase.

$$P = \frac{[drug]_{lipid}}{[drug]_{aqueous}}$$

- For ionizable molecules, when α is the degree of ionization in aqueous solution.

$$P = \frac{[drug]_{lipid}}{(1 - \alpha)[drug]_{aqueous}}$$

- Partition coefficient is very important parameter which affect drug absorption and distribution.
- Partition coefficient is depends upon the various functional groups present in compound. Lipophilic and hydrophilic character of molecule decides the partition coefficient.
- Partition coefficient greatly influence drug transport across membrane. Effect of partition coefficient on percentage absorption of some barbituric acid derivatives are shown below.

Barbiturate	Partition coefficient	% absorbed
Barbitol	0.7	12
Phenobarbitol	4.8	20
Cyclobarbitol	13.9	24
Secobarbitol	50.7	40
Hexabarbitol	> 100	44

- Partition coefficient also affect drug distribution and amount of drug that reach at site of action.
- Polar and hydrophilic compounds such as ceftrixime, gentamicin and streptokinase are poorly absorbed after oral absorption and must be given parenterally. Lipid soluble drugs with favourable partition coefficient are well absorbed after oral administration.
- Addition of non-polar groups like alkyl, halogen, nitro, phenyl mainly improve the partition coefficient.

2.3.1 Measurement of Partition Coefficient:

- Partition coefficient is determined *in vitro* by shaking a weighed amount of drug in measured volumes of water-saturated n-octanol and n-octanol-saturated water.
- The aqueous phase is usually buffer with pH 7.4.
- Concentration in both n-octanol and water (buffer) is measured after shaking the mixture for specified time in separating funnel.
- Other system are also been used.

  hexane-water

  chloroform - water
- Lipidic character of n-octanol is similar to biological membrane, it is non-volatile, high boiling solvent, forms true biphase and non-toxic.
- Concentration of drug in both phases now be determined by HPLC (High Performance Liquid Chromatography), TLC (Thin Layer Chromatography) or any other analytical method.
- Partition coefficient is theoretically calculated because each atom type is assumed to contribute a fixed amount of the chemicals partition coefficient.

Solubility:

2.2 Solubility:

The dissolution of solute in a solvent means the formation of a homogenous mixture of the two. The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute. Three interactions are mainly important.

a. Solute-solute interaction
b. Solute-solvent interaction
c. Solvent-solvent interaction

The necessary condition for dissolution of a solute in solvent is: Solvent-solute interaction should equal or exceed the solute-solute an solvent-solvent interaction.

- In organic compounds, solute-solute interaction are:
  - London forces
  - Dipole-dipole interaction
  - Hydrogen bond
- Polar compounds are soluble in polar solvents like water, ethanol by H-bond formation.
- Non-polar compounds are soluble in non-polar solvents like chloroform, benzene, CCl_4 by either dipole-dipole interaction or London forces. Here "like dissolves like" is a rule of dissolution because it is thermodynamically favourable.
- Solubility of solute is depends upon temperature, pH, particle size, crystal form, pressure etc.

2.2.1 Importance of Solubility:

1. Solubility is very important in formulation of dosage form. Drug must be in solution before it can absorbed by biological membrane and show its activity.
2. Drugs must be in solution to interact with receptors. Polar compounds form H-bonds and binds with receptor. Non-polar compounds interact with lipids and get dispersed.

2.2.2 Improvement of Solubility of Drugs:

The solubility of organic medicinal agent may be expressed in terms of affinity / philicity or repulsion / phobicity for the either aqueous or lipid solvent.

$$K_{solubility} = \frac{K_{sol}}{K_{ppt}}$$

The solubility can be improved by following methods:

(A) Structural modification:

Addition of polar groups in chemical structure increasing H-bonding and interaction with water. Polar groups are carboxylic acids, ketones, amines etc.

Salt formation of compound is most common method to improve water solubility. Salt formation is also applicable to reduce solubility for masking the taste and smell etc.

Common pharmaceutical salts are summarized in Table 2.1.

Salt class	Examples
Anions	
Inorganic acids	HCl, sulphate, nitrate
Sulphonic acids	Mesylate, tosylate, besylate
Carboxylic acids	Acetate, maleate, salicylates, fumarate
Hydroxy acids	Citrate, lactate, tartarate
Fatty acids	Octanoate, stearate
Insoluble salts	Pamoate, sulphonate
Cations	
Organic amines	Diethylamine, ethylene diamine
Metallic salts	Sodium, potassium, calcium, zinc
Insoluble salts	Procaine, benzothine

Methyl predinisolone is water insoluble, its sodium salt is water soluble.

Chloramphenical having bitter taste, its palmitate salt is insoluble and having no bitter taste.

Using surfactant: Surfactants can be used to enhance solubility.

Use of co-solvents: Co-solvents is mixture of solvents in specified amount. Co-solvents are mainly used to improve solubility of compounds in formulation. Examples of solvents are ethanol, sorbitol, propylene glycol.

The addition of co-solvents can increase the solubility of hydrophobic molecule by reducing dielectric constant of solvent. Main problems with co-solvents are precipitation of drug with dilution of solvent mixture, tissue damage and pain upon injection.

Complexation: It is less commonly use method for solubilization. Some complex forming agent improve the solubility,

Q. 12 Explain how Ionization affects biological activity of a drug.

Drug absorption and distribution is influenced by mainly physiological factors. Additionally, it depends upon many physicochemical properties of the drug itself.

Ionization, dissociation constant and pH of fluid at the site of absorption determines the extent of absorption from a solution.

The function of the drug existing in its un-ionized form in a solution is a function of both the dissociation constant of the drug and the pH of the solution.

The dissociation constant for both weak acids and bases are expressed as pKa (negative logarithm of dissociation constant, Ka).

According to Lowry-bronsted theory an acid is proton donor and a base is proton accepter.

An acid on dissociation in water gives a conjugate base. A base on dissociation in water gives a conjugate acid.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^- \quad \text{.....(1)}$$

Acid — Conjugate base

$$B + H_2O \rightleftharpoons BH^+ + OH^- \quad \text{.....(2)}$$

Base — Conjugate acid

The Henderson - Hasselbach equation for the ionization of weak acid HA can be derived from the equation (1).

$$K_a = \frac{[H_3O^+]\,[A^-]}{[HA]\,[H_2O]} \quad \text{.....(3)}$$

K_a = Equilibrium or dissociation constant.

Since water is in excess, molar concentration remains constant, equation (3) is simplified to

$$K_a = \frac{[H_3O^+]\,[A^-]}{[HA]} \quad \text{.....(4)}$$

The negative logarithm of Ka is pKa.

Thus $pKa = -\log Ka$

Taking logarithm in equation (4),

$$\log K_a = \log [H_3O^+] + \log \frac{[A^-]}{[HA]}$$

Taking negative sign,

$$-\log K_a = -\log [H_3O^+] - \log \frac{[A^-]}{[HA]}$$

$$-\log [H_3O^+] = pH$$

$$\therefore \quad pKa = pH - \log \frac{[A^-]}{[HA]}$$

.....(5)

$$\therefore \quad pH = pKa + \log \frac{[A^-]}{[HA]}$$

This is Henderson - Hasselbach equation for acids. $[A^-]$ is ionized form and [HA] is un-ionized form of weak acid.

$$\therefore \quad pH = pKa + \log \frac{[\text{ionized}]}{[\text{unionized}]}$$

.....(6)

This equation is used to calculate pH of solution of weak acids as well as to calculate pH of buffers.

If α is the fraction of ionized species and $1 - \alpha$ is fraction of remaining as unionized form, equation (6) can be written as

$$pH - pKa = \log \frac{\alpha}{1 - \alpha}$$

$$\text{or} \quad \frac{\alpha}{1 - \alpha} = \text{Antilog } (pH - pKa)$$

.....(7)

Using equation (7) amount of drug absorbable and unabsorbable can be calculated, if pH at site of administration is known.

Similarly, dissociation of weak bases and dissociation constant for weak bases can be derived.

$$B + H_2O \rightleftharpoons BH^+ + OH^{\ominus}$$

$$\therefore \quad pK_a + pK_b = pK_w$$

K_w = dissociation constant of water

K_b = dissociation constant of base

$\therefore$ Even K_b is dissociation constant of base. For conventionally K_a is used for relationship.

$$\therefore \quad pKa - pH = \log \frac{[\text{ionized}]}{[\text{unionized}]}$$

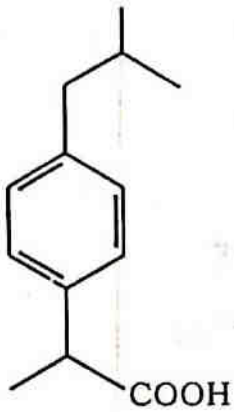
.....(8)

Most weakly acidic drugs are in unionized form at lower pH of gastric fluid and therefore be absorbed from stomach.

Some weakly acidic drugs like phenobarbitol, phenytion have pKa value near to 7.0. So there are unionized in all pH values. There absorption are independent to pH.

Most weakly basic drugs are unionized form at high pH value of large intestine and absorbed from the intestine. In stomach there drugs gets ionized and not absorbed.

Example: Ibuprofen is acidic drug with pKa 4.5.



It's ratio of ionized and unionized can be calculated at different pH value.

In stomach pH = 2.5

$$2.5 = 4.5 + \log \frac{B}{A}$$

$$\therefore \quad -2 = \log \frac{B}{A}$$

B = ionized
A = unionized

$$\therefore \quad \boxed{\frac{B}{A} = \frac{1}{100}}$$

In intestine pH = 7.5

$$7.5 = 4.5 + \log \frac{B}{A}$$

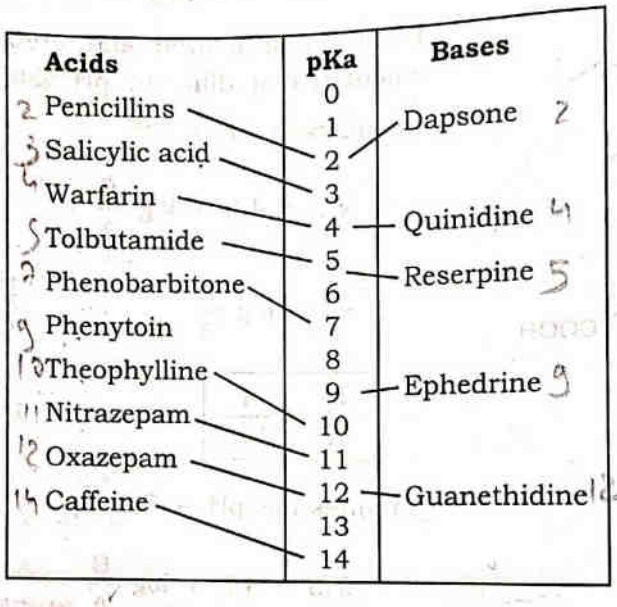
$$\therefore \quad 3 = \log \frac{B}{A}$$

$$\therefore \quad \boxed{\frac{B}{A} = \frac{1000}{1}}$$

In stomach ibuprofen is mainly in unionized form and well absorbed.
In intestinal pH it is in ionized form and less absorbed.

pKa		Strength
≤ 2	=	strong acid
4 – 6	=	weak acid
8 – 10	=	very weak acid (weak base)
≥ 12	=	no acidic properties (strong base)

pKa values of some drugs are given in Figure 2.2.



Summary of Ionization:

- The lower the pH relative to the pKa greater is fraction of protonated drug (may be charged or unchanged).
- Weak acids at acidic pH : more lipid soluble because it is uncharged, readily passes through biological membrane (absorption).

  pKa < 2 = more absorbed in stomach
  pKa = 4 – 5 = less absorbed in stomach
  pKa > 8 = not absorbed in stomach

- Weak bases at basic pH = more lipid soluble because it is uncharged readily. passes through biological membrane.

  pKa > 12 = more absorbed in intestine
  pKa = 10–12 = less absorbed in intestine
  pKa < 6 = not absorbed in intestine

- Absorption of neutral drugs with pKa 6 – 8 are independent to pH.
- Lipophilicity (partition coefficient) is also important with the ionization of drug for absorption and distribution.

Q. 13 Write a note on Bioisosterism.

"Bioisosterism is a strategy of medicinal chemistry for the rational design of new drugs, applied with a lead compound as a special process of molecular modification."

- Bioisosterism is used
  - To design new drugs
  - To improve biological activity
  - to achieve selectivity for specific receptor or enzyme
  - To reduce adverse effects
  - To optimize pharmacokinetics of the lead compound.

★ Background / History of Bioisosterism :

- In 1919, Langmuir gaves the concept of isosterism. According to this concept,
  "Isosterism is the concept of atoms / organic / inorganic molecules s possess same no. of electrons & / or arrangement of electrons."

  eg. i) $O^{-2} \equiv F^{-} \equiv Ne \equiv Na^{+} \equiv Mg^{+2}$

  ii) $N=N \equiv C=O$

  iii) $N=N=N \equiv C=N=O$

- In 1925, Grimm formulated hydride displacement law to describe "similarities between groups that have same no. of valance electrons but may have diff. no. of atoms."
- Hydride means $H^{\ominus}$

eg. C N O F Ne

→ CH NH OH HF

→ CH_2 NH_2 OH_2

→ CH_3 NH_3

→ CH_4

Here, N & CH are isosters,
O, NH & CH_2 are isosters.

- In 1932, Erlenmeyer redefined isosters as atoms, ions of molecules in which peripheral layer of electrons can be considered to be identical.

- In 1951, Fridemann & Thomber gave the term Bioisosterism.
Acco. to them "Bioisosterism are substituents of groups having chemical of physical similarities & which produce broadly similar biological properties."

★ Classification of Bioisosterism :

Bioisosterism

Classical

i) Monovalent atoms of groups
ii) Divalent " "
iii) Trivalent " "
iv) Tetravalent " "
v) Ring equivalent

Non-classical

eg. i) Functional groups
ii) Cyclic Vs Acyclic
iii) Retroisosterism

- In 1970, Alfred Burger classified bioisosterism in two broad categories: Classical & Non-classical bioisosterism

i) Classical bioisosterism:

"They are atoms / molecular ~~subunit~~ subunits / f^n groups of same valance & ring equivalents."

- They possess similar valence electron configuration.

eg. oxygen & sulfur are both in column VI of the periodic table.
Thus, Thio-ether (-C-S-C) is bioisostere classical for an ether (-C-O-C).

ii) Non-classical bioisosterism:

- Functional groups with dissimilar valence electron configuration are Non-classical Bioisosteres.
- They are atoms / groups / molecules which did not fit in the definition of first class.
- They don't have same no. of atom & don't fit the stearic & electronic rule of classical bioisosteres.
But they produce similar biological properties.

eg. Tetrazole moiety may be used to replace a carboxylate moiety because many biological systems are unable to differentiate between these two very structurally distinctive functional groups.

★Examples of Classical Bioisosters :

i) Monovalent atoms of groups: $-OH, -NH_2, -CH_3$
$-F, -Cl, -Br$.

ii) Divalent " " : $-CH_2-$, $-NH-$, $-O-$
$-COCH_2R-$, $-CONHR-$, $-CO_2R-$

iii) Trivalent " " ; $-CH=$, $-N=$, $-P=$, $-As=$

iv) Tetravalent " " : $=C=$, $=N^+=$, $=P^+=$, $=As^+=$
$=S=$.

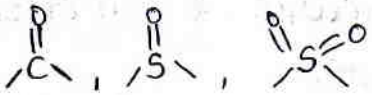
v) Ring equivalents: 

★Examples of Non-classical Bioisosters :

i) Functional group replacement:

a) Halogens: $-X$, $-CF_3$, $-CN$, $-N(CN)_2$, $-C(CN)_3$

b) Hydroxyl group: $-OH$, $-CH_2OH$, $-NHCONH_2$, $-NHCSNH_2$.

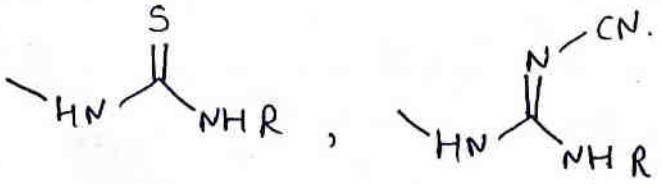
c) Carboxyl group: 

d) Carboxylic acidic group: $-COOH$, Tetrazole, $-SO_3H$, $-SO_2NH_2$

e) Amide: $-CONH-$, $-NHCO-$, $-NHCS-$, $-NHCO_2-$.

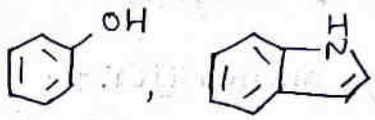
f) Thioethers: 

g) Thiourea:

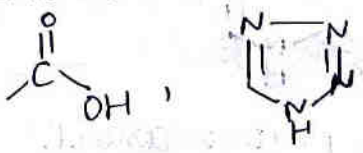


ii) Cyclic Vs Acyclic.

a) Phenol substitution by Indole.

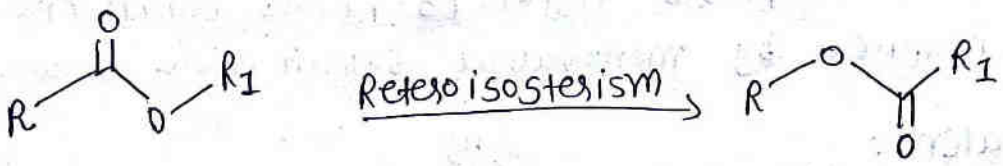


b) Carboxylic acid substitution by Tetrazole.



iii) Retroisosterism:

It is based on inversion of specified group preser in the lead compound structure producing an isos



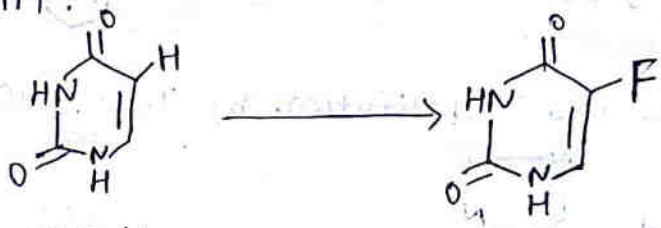
★ Applications of Bioisosterism:

- The purpose of molecular modification by bioisosterism is
- to improve biological activity,
- to improve potency,
- " " duration of action
- to achieve selectivity for specific receptors of ⓡ.
- to reduce adverse effects.
- to optimize Pharmacokinetics of the lead compound.

These applications can be understood by following examples.

=> Examples of classical Bioisosterism:

i) Monovalent:

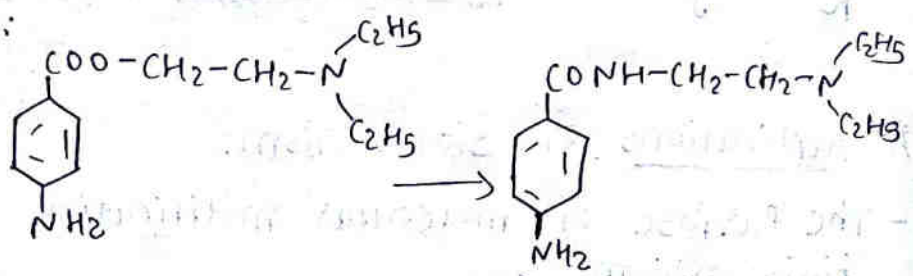


Uracil

5-Fluoro uracil.
(Anti-neoplastic agent).

- Uracil is one of the four nucleobases of RNA.
- An Anti-neoplastic agent (5-Fluoro uracil) can be Produced by monovalent substitution of uracil.

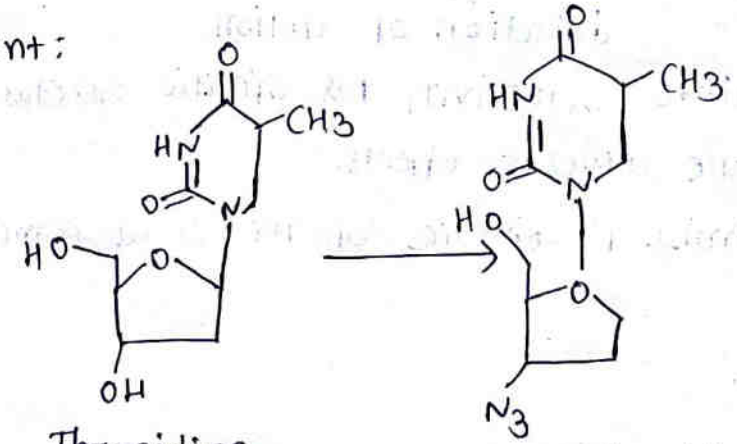
ii) Divalent:



Procaine
(Local anaesthetic)

Procainamide
(Anti-arrhythmic)

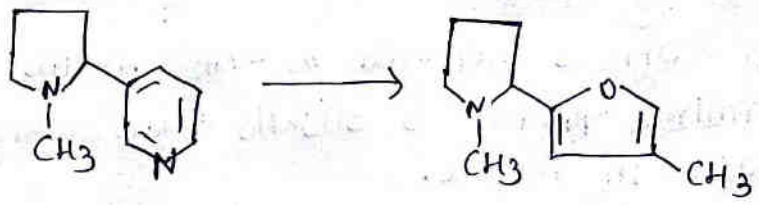
iii) Trivalent:



Thymidine
↓
(Pyrimidine deoxynucleoside)

Azidothymidine (AZT)
(Zidovudine)
↓
Anti-HIV agent

iv) Ring equivalent:

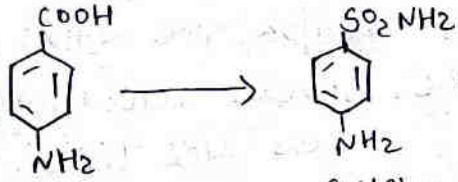


Nicotine
(Analgesic)

ABT-418
(Anti-alzheimes)

=> Examples of Non-classical Bioisosterism:

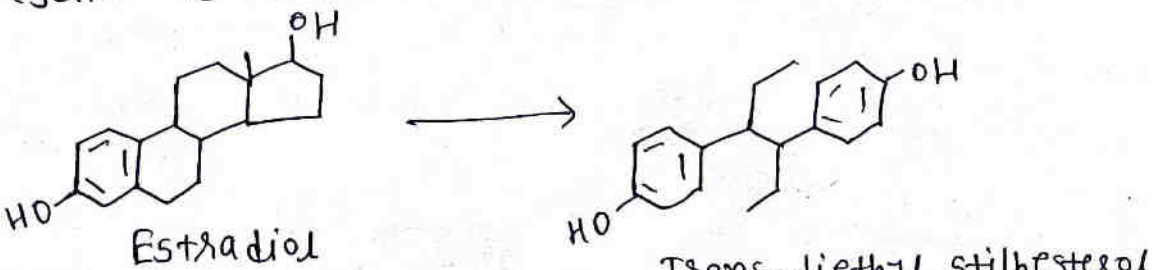
i) Functional group replacement:



PABA
(P-amino benzoic acid)

Sulphanilamide
(Anti-bacterial)

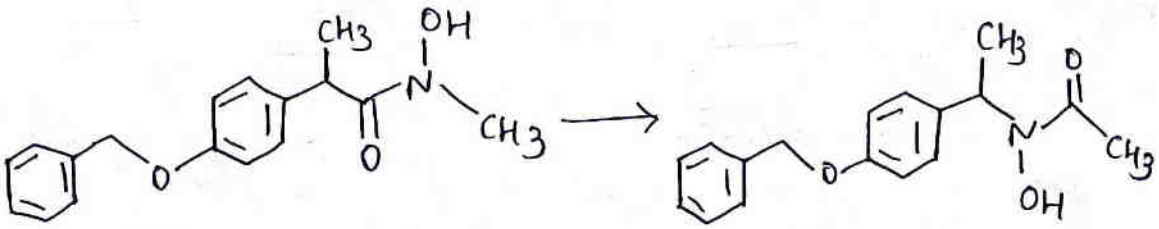
ii) Cyclic Vs Acyclic



Estradiol
(Estrogen Hormone)

Trans-diethyl stilbesterol
(Estrogen medication).

iii) Reteroisosterism



Lead compound

A-63162
(Anti-asthmatic)

- Some bioisosterism can also alter physicochemical properties of compound.

  eg. when -OH is replaced by $-NH_2$ means phenol to aniline, phenol is slightly acidic while aniline is basic in nature.

  - pKa values are also been changed, which is responsible for the distinct pKinetic profiles.
  - Furthermore, in terms of molecular recognition of a given receptor site, ~~the~~ we have changed on negatively charged group to positively charged, which may probably abolish the activity.
  - Thus, in this example, severe alterations of molecular properties occurs like lipidic-aqueous solubility, enzymatic activity, chemical reactivity

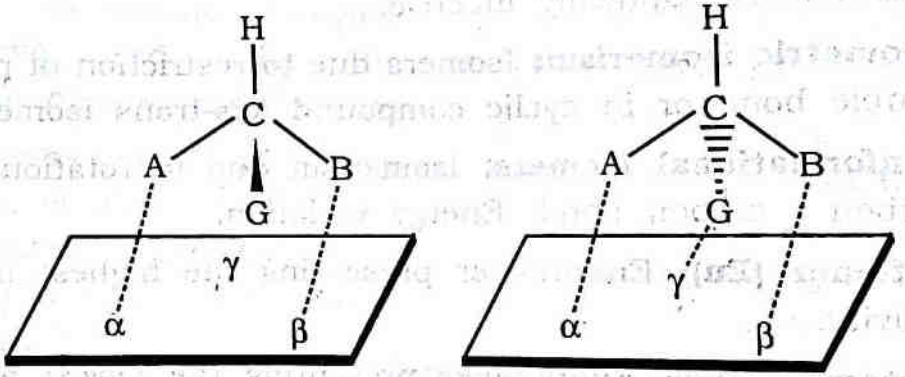
Q. 14 Explain Optical and Geometrical isomerism affecting drug activity.

Optical Isomerism:

- Optical isomerism is the most common in medicinal chemistry. There are many example where difference in biological activities of two isomers (enantiomers) is observed in drug molecule with one chiral centre.
- In 1933, Easson and Stedman reasoned that difference in the biological activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor. They postulated that minimum three point fit is require with receptor which is known as "Easson - Stedman principle" of three point attachment.
- Easson - Stedman principle: If binding is specific for enantiomeric pairs, then a three point attachment must occur between the enantiomer and dissymmetric surface.

Model of three point attachment:

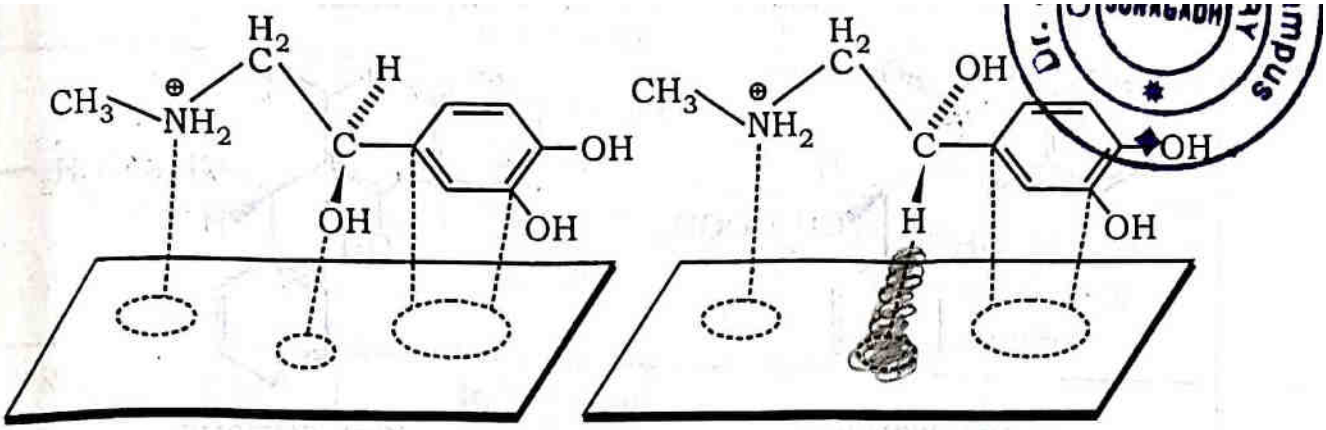
- Compound A and B are enantiomers. Where B binds better than A due to points A, B and G are algin with α, β and γ on the receptor. This shows 3 point binding. If A and B bind equally, than A binds with α and β and not the γ site. This is 2 point binding.
- Evidence of specificity of biological systems, relative binding of enantiomers may be used to judge the specificity of an interaction.



Compound A Compound B

Figure 2.4 Model of three point attachment

- **Example:** Binding of Epinephrine to an α-adrenergic receptor.
- R (–) Epinephrine shows three point of interaction with receptor site:
  - Substituted aromatic ring
  - β-hydroxyl group
  - Protonated secondary ammonium group
- Stimulate receptor (strongest acting)
- S (+) Epinephrine shows two point of interaction with receptor site:
  - Substituted aromatic ring
  - Protonated secondary ammonium group
- Cannot interact properly (weak acting)



R(–) epinephrine (active) **S(+) epinephrine (less active)**

Figure 2.5 Example of three point attachment model

- **Optical Isomerism and Pharmacodynamic Aspects:**

The biological response induced by a pair of enantiomers can differ in potency (quantitative) or in nature (qualitative) difference. It is assumed that one enantiomer act at one receptor site, whereas its other isomer having different activity and toxicity profile.

(A) Difference in potency between two enantiomers:

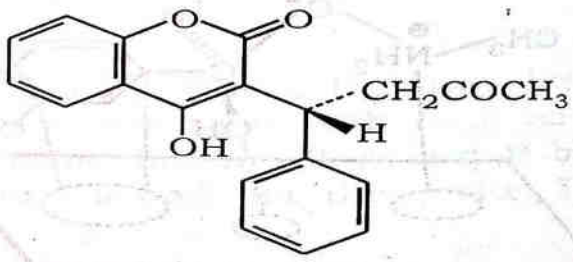
➢ There are many drugs where two isomers have qualitative similar pharmacological activity but have different quantitative potencies. This is summarized in Table 2.8.

Compound	Relative activity	Biological Response
Warfarin	S (–) > R (+) (5 : 1)	Anticoagulant
Terbutaline	– > + (3000 : 1)	Trachea Relaxation
Propranolol	S > R (100 : 1)	Block tachycardia
Methadone	– > + (3 : 1)	Respiratory depression
Hyoscyamine	– > + (20 : 1)	Mydriatic action
Amphetamine	+ (S) > – (R) (4 : 1)	CNS stimulant
Ketamine	S > R (4 : 1)	Anesthesia
Verapamil	– > + (10 : 1)	Block AV conduction

Table 2.8 : Difference in potency between enantiomers

Structure of some optically active compounds:

S(–) warfarin



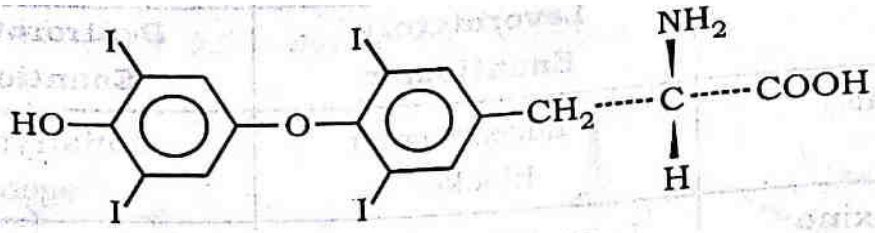
R(+) warfarin

(B) Difference in the pharmacological profile of two enantiomers:

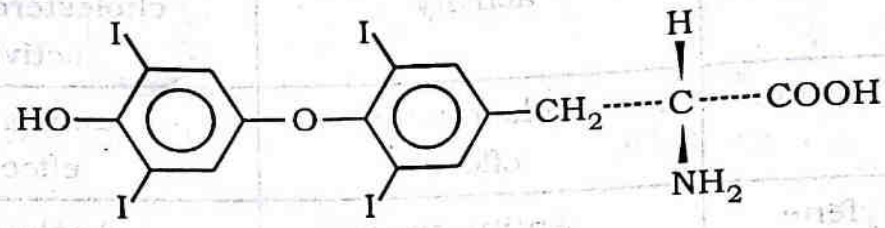
➢ Besides the difference in potency, it often happens that two enantiomers show difference in their pharmacological profile.

Compound	Levorotatory Enantiomer	Dextrorotatory Enantiomer
Sotalol	β-adrenocepter blocker	antiarrythmic agent
Thyroxine	L or (S) = thyroid activity	D or (R) = antihyper-cholesterolemic activity
Racemorphane	Indacrinone effect	analgesic effect
Propoxyfene	Antitussive (1R, 2S)	Analgesic (1S, 2R)
Tetramisole	Immunostimulant	antidepressant
Quinine / quinidine	Quinine antimalarial	Quinidine antiarrythmic

Table 2.9 : Difference in pharmacological profile of Enantiomers



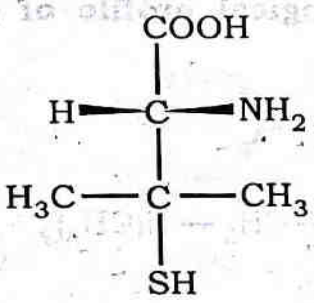
L-Thyroxine



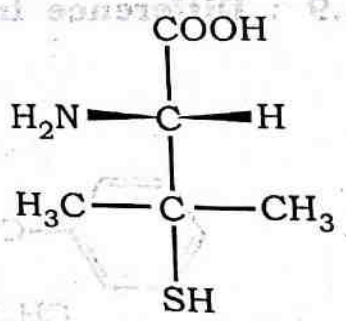
D-Thyroxine

(C) One enantiomer is active. Other isomer is responsible for side effect or toxicity.

- D-penicillamine is antiarthritic drug while L-penicillamine is toxic.



D-penicillamine

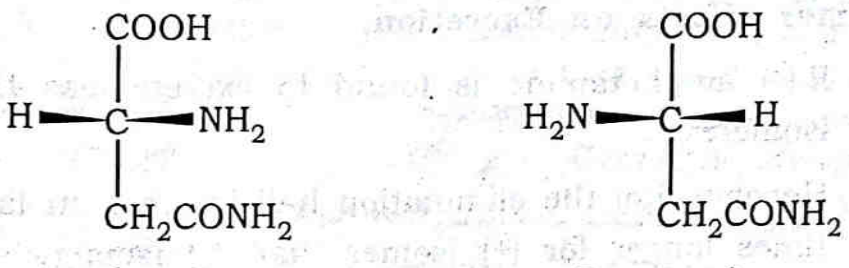


L-penicillamine

- (S, S) Ethambutol is an antitubercular while (R, R) Ethambutol having ocular toxicity.
- (R) - fluoxetine used in treatment of depression. Its isomer having anxiety and sexual dysfunction problem.
- (E) Levocetrizine is used in allergic rhinitis and less sedative than cetrizine.
- L-dopa is used in parkinson's disease. Its D-form causes granulocytopenia.
- Thalidomide: R (+) enantiomer is sedative while S (–) isomer has teratogenic effect (Thalidomide tragedy).

(D) Difference in organoleptic characters:

- L-asparagine is tasteless while D-aspargine has sweet taste.



D-aspargine **L-aspargine**

- (R) carvone has caraway odour while (S) carvone has spermint odour.

Optical isomerism and pharmacokinetic effects:

- After administration and before arrives at site of action drug is subjected to a variety of processes absorption, distribution, metabolism, excretion. Many of these processes are steroselective. One isomer shows good pharmacokinetic properties than other isomer.

(A) Isomer effects on absorption:

- Examples: S (+) isomer of hexobarbital was shown more CNS level than R (+) isomer due to better CNS crossing.
- D-methotrexate / L-methotrexate = 0.025 (Ratio of absorption).

(B) Isomer effects on distribution:

Drug	Free	fraction	Ratio (+/–) of distribution
Ibuprofen	0.006	0.0039	1.5
Verapamil	0.064	0.11	0.6
Methadone	0.092	0.124	0.7
Propranolol	0.203	0.176	1.2
Diisopyramide	0.27	0.39	0.7

5

(C) Isomer effects on metabolism:

- Since all enzymes are chiral in nature, therefore posses some degree of asymmetry at reactive centre.
- The levo isomers of 3-hydroxy-N-methyl-morphinan and methadone are demethylated 2-3 times rapidly than dextro isomers in rat.
- S (+) enantiomer of hexobarbitol is metabolised twice as rapidly as R (–) enantiomers by allylic hydroxylation.

(D) Isomer effects on Excretion:

- R (–) amphetamine is found to excrete less than its S (–) isomer.
- Hexobarbitol the elimination half life in man is about three times longer for (+) isomer than (–) isomer.

Geometrical Isomerism:

2.11.4 Geometric Isomerism:

- Geometric isomerism is cis / trans isomerism and due to restricted rotation due to carbon - carbon double bond or in rigid ring system.
- Cis - trans isomers have different physical and chemical properties. The biological activity and pharmacokinetics are also different.
- Difference in reactivity of geometric isomers at the receptor site can be explained by the proposed receptor drug interaction shown in figure 2.5.
- In compound A : group b and c are cis

  In compound B : group b and c are trans

  So compound A is more active than B.

  Similarly,

  compound C : a, b and c all are cis

  compound D : a, b cis and c trans

  So compound C is more active than D.

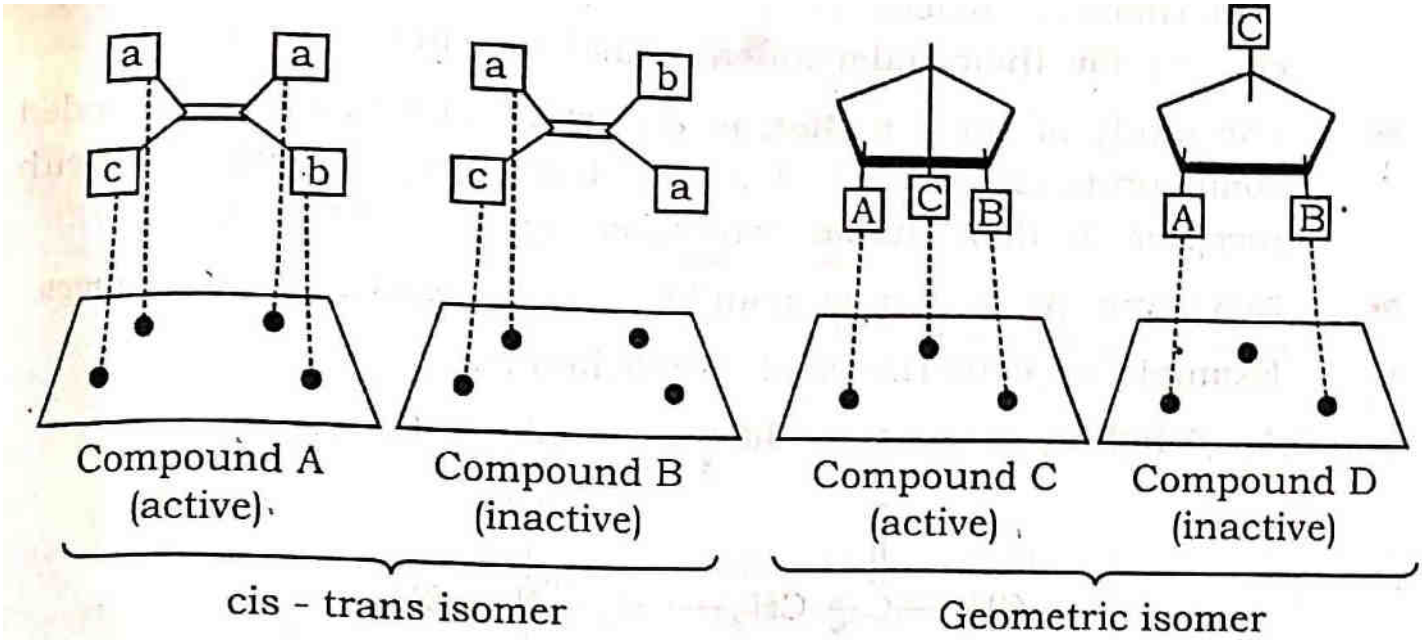
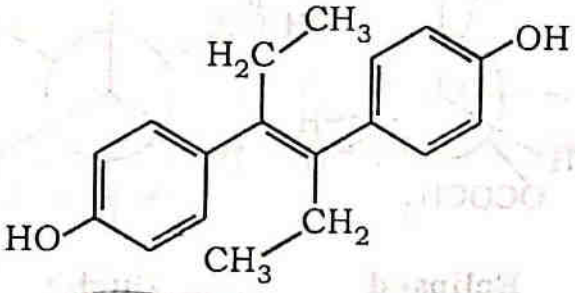


Figure 2.5

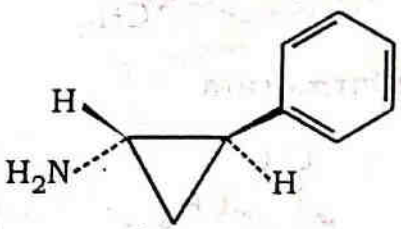
Examples:

1. E -isomer of stilbesterol is oestrogenic while Z isomer is only 7 % active.

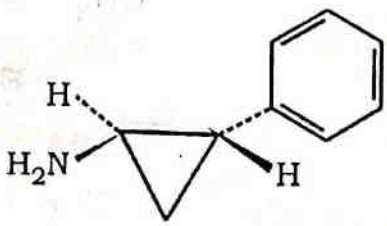


E-isomer of stilbesterol

2. (+) trans-2-phenyl cyclopropylamine is active inhibitor of monoamine oxidase. (–) isomer is effective as blocker of amine uptake mechanisms.



(+) Tranylcypromine

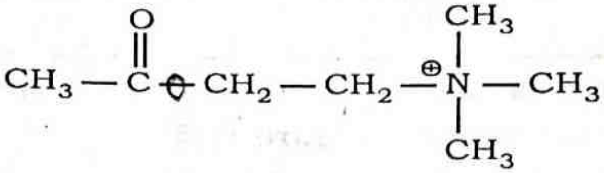


(–) Tranylcypromine

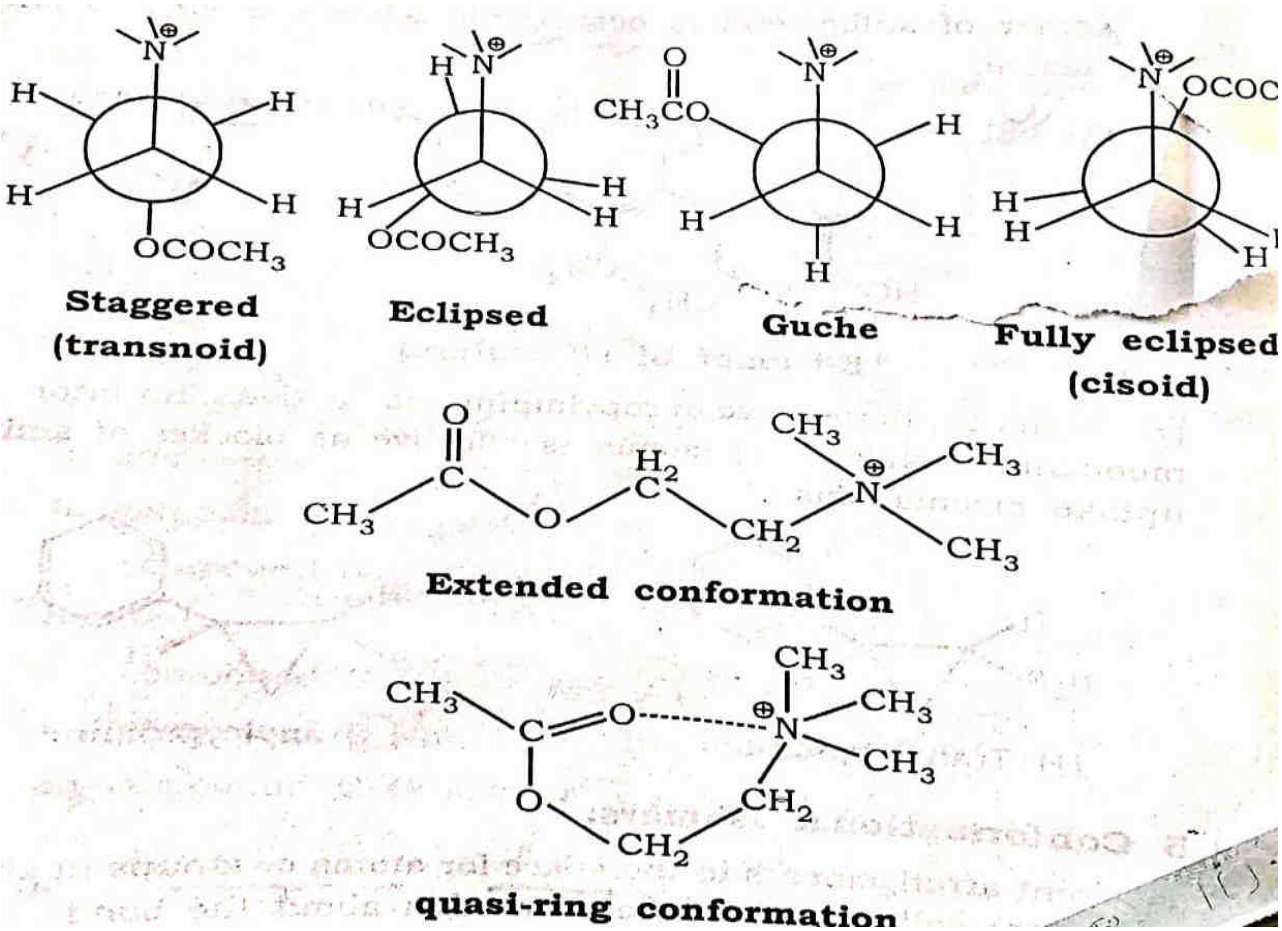
2.11.5 Conformational Isomers:

- Different arrangements in the space for atoms or groups in single bonds are called conformation. Rotation about the bonds show conformation isomers. The energy barrier between isomers is hig enough for their independent existence and reaction.
- The study of conformation is important in many singly bonde compounds and their biological action. Drugs mainly bind wi receptor in their stable conformer (least energy conformer).
- Newmann projection is mainly used to represent conformers
- Example of conformers of acetylcholine. –

Actylcholine is exist in different conformations.



acetylcholine



- Acetylcholine: Muscarinic receptor binding
  - Staggered (transnoid)
  - Extended conformation
- Nicotinic receptor:
  - Guche conformation
  - Quasi-ring conformation
- Many compounds specially steroids and polyene compounds exhibited in different conformation and show different biological action.
- Cyclohexane is also having different conformation like chair, boat, twist-boat conformations. These are important in steroids.

(Conformation of cyclohexane)

- Polypeptides, proteins, DNA and other biomolecules are stabilized by stable conformation.

Q. 15 Explain oxidation reaction of Phase-I metabolism.

2.1.5.1. Phase I Reactions

Oxidation, reduction or hydrolysis reactions catalysed by a phase I enzymes leads to the introduction of a functional group, which results in a modification of a foreign compounds and a moderate increase in its water solubility. In the case of a drug, the introduction of a functional group can lead to an alteration in biological properties of the drug.

The product of phase I metabolism subsequently serves as the substrate for the phase II conjugation reaction. Major reactions catalysed by phase I enzymes in metabolic pathways include N-dealkylation, O-dealkylation, aliphatic and aromatic hydroxylation, N-oxidation, S-oxidation, epoxidation, and hydrolysis.

2.1.5.1.1. Oxidative Reactions

Oxidative reactions are the most important and most common metabolic reactions. Almost all drugs that undergo phase I biotransformation undergo oxidation at some stage or the other. A simple reason for oxidation being a predominant reaction is that energy in animals is primarily derived by oxidative combustion of organic molecules containing carbon and hydrogen atoms. Oxidative reactions increase hydrophilicity of xenobiotics by introducing polar functional groups such as –OH. Such a polar metabolite can thus rapidly undergo phase II reaction or is excretable by the kidneys.

Oxidation of xenobiotics is non-specifically catalyzed by a number of enzymes located in the microsomes. Such enzymes require both molecular oxygen (O2) and the reducing agent NADPH to effect reaction. They are therefore referred to as the mixed function oxidases. The overall stoichiometry of this reaction involving the substrate RH which yields the product ROH, is given by the following equation:

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$$

Where, NADPH = reduced nicotinamide adenine dinucleotide phosphate.

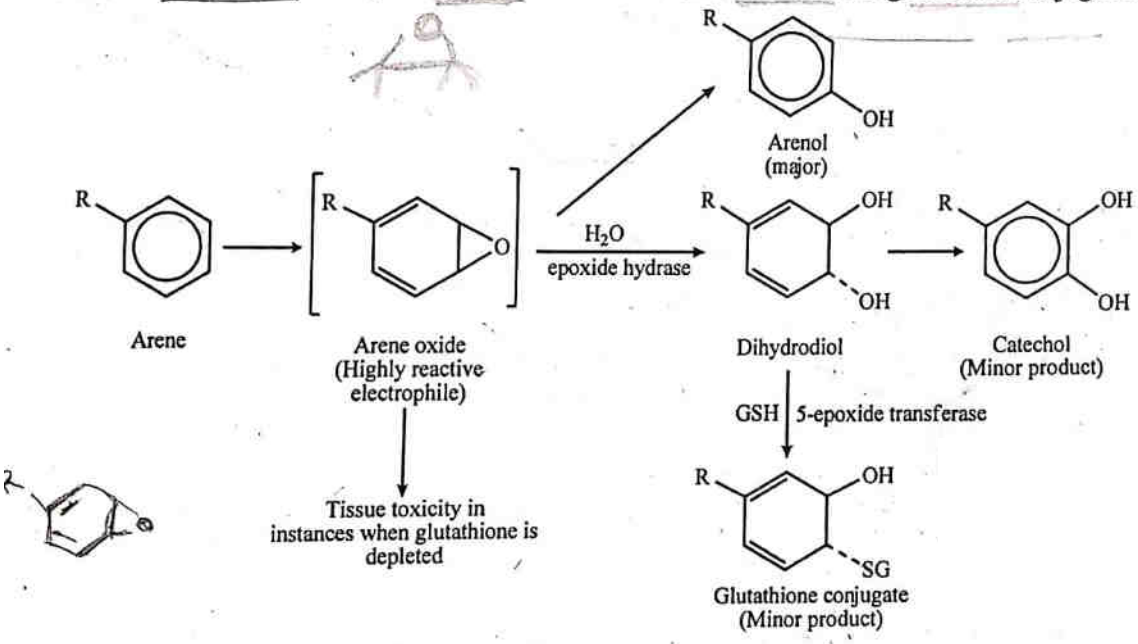
Since only one oxygen atom from the molecular oxygen (dioxygen or O_2) is incorporated in the product formed, the mixed function oxidases are also called as monooxygenases. Quite often, the product of such a reaction contains a hydroxyl function; hence, the enzymes are sometimes also called as hydroxylases.

Various oxidative reactions are:

1) Oxidation of Aromatic Carbon Atoms (Aromatic Hydroxylation),
2) Oxidation of Olefins,
3) Oxidation of Benzylic Carbon Atoms,
4) Oxidation of Allylic Carbon Atoms,
5) Oxidation of Carbon Atoms Alpha to Carbonyls and Imines,
6) Oxidation of Aliphatic Carbon Atoms (Aliphatic Hydroxylation),
7) Oxidation of Alicyclic Carbon Atoms (Alicyclic Hydroxylation),
8) Oxidation of Carbon-Heteroatom Systems,
9) Oxidation of Carbon-Nitrogen Systems,
10) Oxidation of Carbon-Sulfur Systems,
11) Oxidation of Carbon-Oxygen Systems,
12) Oxidation of Alcohol, Carbonyl and Carboxylic Acid,
13) Miscellaneous Oxidative Reactions.

2.1.5.1.1.1. Oxidation of Aromatic Carbon Atoms (Aromatic Hydroxylation)

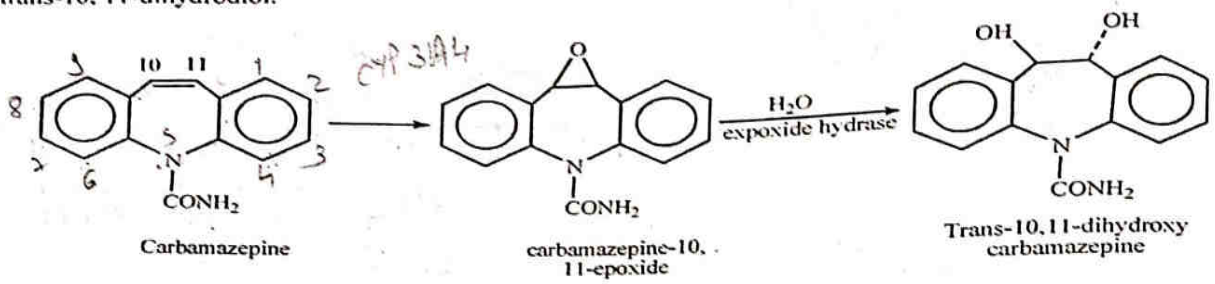
This reaction proceeds via formation of a reactive intermediate arene oxide (epoxide) which in most cases undergoes re-arrangement to yield arenols and in some cases catechols and glutathione conjugates.



The arene oxide intermediate is highly reactive and known to be carcinogenic or cytotoxic in some instances, e.g., epoxides of bromobenzene and benzo(a)pyrene.

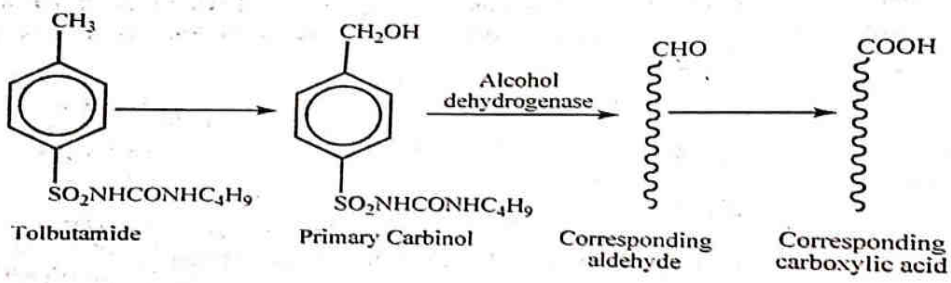
2.1.5.1.1.2. Oxidation of Olefins

Oxidation of non-aromatic carbon-carbon double bonds is analogous to aromatic hydroxylation, i.e., it proceeds via formation of epoxides to yield 1, 2-dihydrodiols. A better known example of olefinic oxidation is conversion of carbamazepine to carbamazepine-10, 11-epoxide; the latter is converted to corresponding trans-10, 11-dihydrodiol.



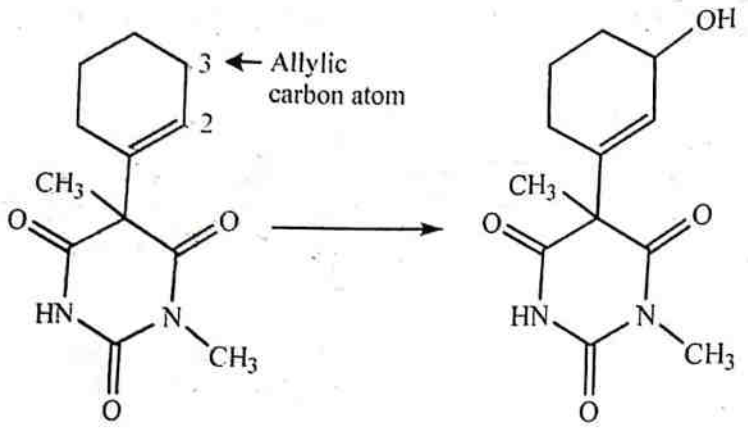
2.1.5.1.1.3. Oxidation of Benzylic Carbon Atoms

Carbon atoms attached directly to the aromatic rings (benzylic carbon atoms) are hydroxylated to corresponding carbinols. If the product is a primary carbinol, it is further oxidized to aldehydes and then to carboxylic acids, e.g., tolbutamide. A secondary carbinol is converted to ketone.



2.1.5.1.1.4. Oxidation of Allylic Carbon Atoms

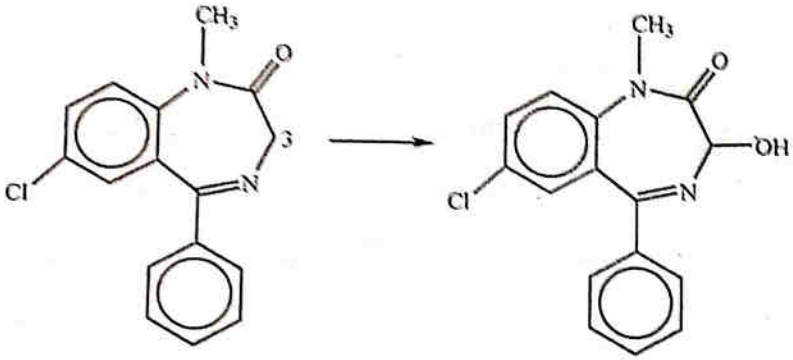
Carbon atoms adjacent to olefinic double bonds (are allylic carbon atoms) also undergo hydroxylation in a manner similar to benzylic carbons, **e.g.,** hydroxylation of hexobarbital to 3´-hydroxy hexobarbital.



Hexobarbital — 3'-Hydroxy hexobarbital

2.1.5.1.1.5. Oxidation of Carbon Atoms Alpha to Carbonyls and Imines

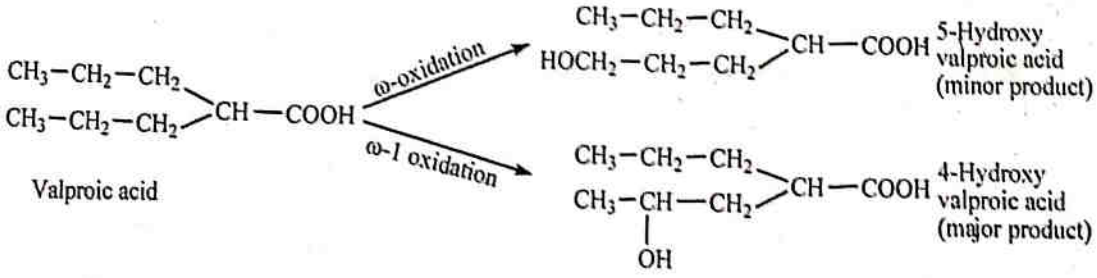
Several benzodiazepines contain a carbon atom (C-3) alpha to both carbonyl (C=O) and imino (C=N) functions which readily undergoes hydroxylation, **e.g.,** diazepam.



Diazepam — 3-Hydroxy diazepam (N-methyl oxazepam)

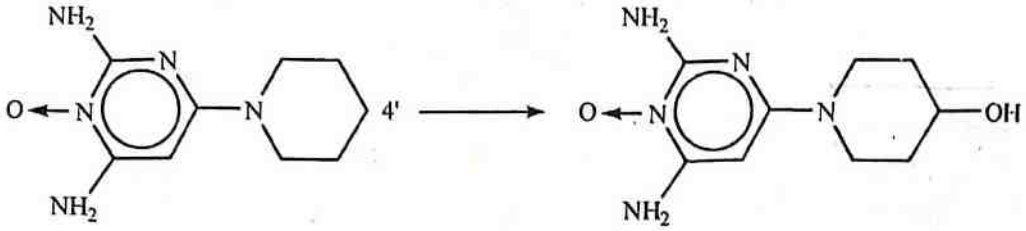
2.1.5.1.1.6. Oxidation of Aliphatic Carbon Atoms (Aliphatic Hydroxylation)

Alkyl or aliphatic carbon atoms can be hydroxylated at two positions – at the terminal methyl group (called as ω-oxidation) and the penultimate carbon atom (called as ω-1 oxidation) of which the latter accounts for the major product, **e.g.,** valproic acid. Hydroxylation at other carbon atoms in long chain compounds is less common.



2.1.5.1.1.7. Oxidation of Alicyclic Carbon Atoms (Alicyclic Hydroxylation)

Cyclohexane (alicyclic) and piperidine (non-aromatic heterocycle) rings are commonly found in a number of molecules, **e.g.,** acetohexamide and minoxidil respectively. Such rings are generally hydroxylated at C-3 or C-4 positions.



Minoxidil 4'-Hydroxy minoxidil

2.1.5.1.1.8. Oxidation of Carbon-Heteroatom Systems

Biotransformation of C-N, C-O and C-S systems proceed in one of the two ways:

1) Hydroxylation of carbon atom attached to the heteroatom and subsequent cleavage at carbon-heteroatom bond, **e.g.,** N-, O- and S- dealkylation, oxidative deamination and desulfuration.
2) Oxidation of the heteroatom itself, **e.g.,** N- and S-oxidation.

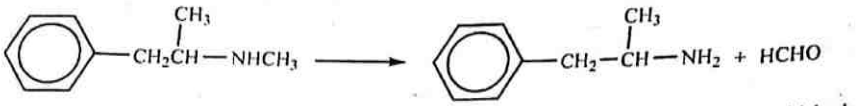
2.1.5.1.1.9. Oxidation of Carbon-Nitrogen Systems

1) **N-Dealkylation:** Alkyl groups attached directly to nitrogen atom in nitrogen bearing compounds are capable of undergoing N-dealkylation reactions, **e.g.,** secondary and tertiary aliphatic and aromatic amines, tertiary alicyclic amines and N-substituted amides and hydrazines. Since N-dealkylation of amines yield amines and amides yield amides, the reaction is said to undergo without any change in the state of oxidation.

It is however the removed alkyl group that is oxidized. Mechanism of N-dealkylation involve oxidation of α-carbon to generate an intermediate carbinolamine which re-arranges by cleavage of C-N bond to yield the N dealkylated product and the corresponding carbonyl of the alkyl group (a primary alkyl is transformed to aldehyde and a secondary alkyl to ketone).

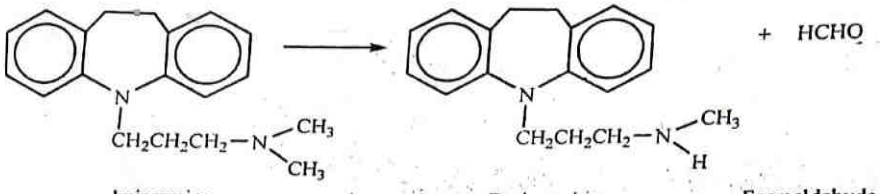
Tertiary nitrogen attached to different alkyl groups undergoes dealkylation by removal of smaller alkyl group first.

Secondary aliphatic amine, **e.g.,** methamphetamine.



Methamphetamine Amphetamine Formaldehyde

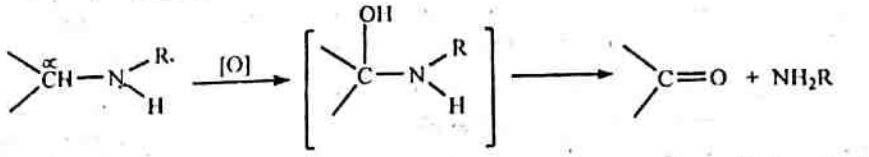
Tertiary aliphatic amine, **e.g.,** imipramine.



Imipramine Desipramine Formaldehyde

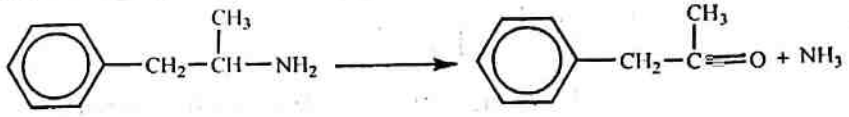
Secondary and tertiary amines are rare among therapeutic agents.

2) **Oxidative Deamination:** Like N-dealkylation, this reaction also proceeds via the carbinolamine pathway but here the C-N bond cleavage occurs at the bond that links amino group to the larger portion of the drug molecule.



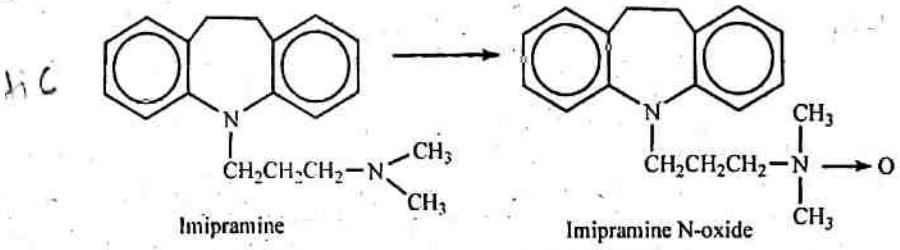
Carbinolamine — where, R=H or alkyl

Primary aliphatic amines readily undergo deamination, **e.g.,** amphetamine, while secondary and tertiary amines are deaminated only when bulky groups are attached to nitrogen, **e.g.,** propranolol.

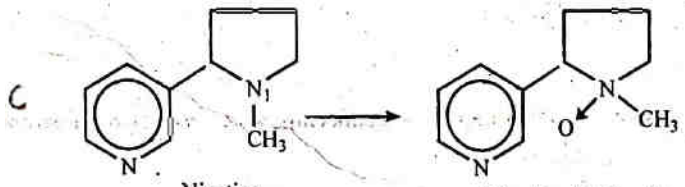


Amphetamine — Phenylacetone — Ammonia

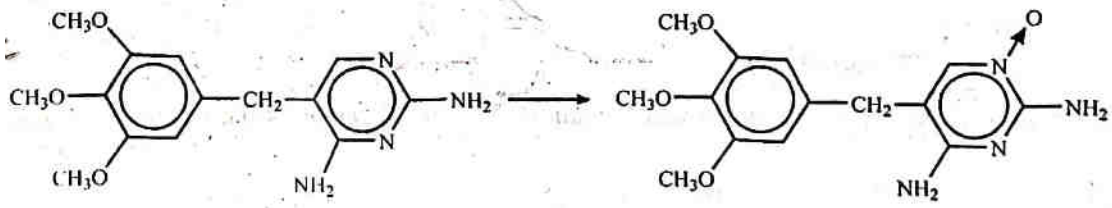
3) **N-Oxide Formation:** N-oxides are formed only by nitrogen atoms having basic properties. Thus, amines can form N-oxides but amides cannot. Generally, the tertiary amines yield N-oxides. Four categories of tertiary amines that form N-oxides are – aliphatic amines (**e.g.,** imipramine), alicyclic amines (**e.g.,** nicotine), nitrogen atoms of aromatic heterocycles (**e.g.,** trimethoprim) and amines attached to aromatic rings (**e.g.,** N,N-dimethyl aniline).



Imipramine — Imipramine N-oxide



Nicotine — Nicotine-1'-N-oxide

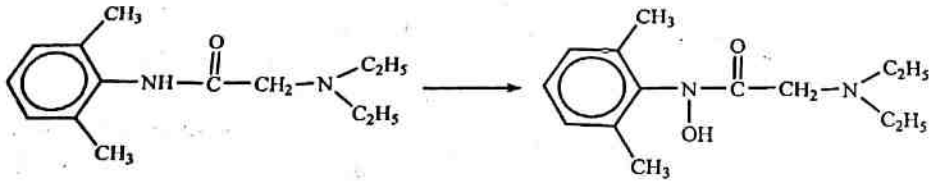


Trimethoprim — Trimethoprim-1-N-oxide

N,N-Dimethyl aniline — N-Oxide metabolite

The N-oxide products are highly water-soluble and excreted in urine. They are however susceptible to reduction to the corresponding amine.

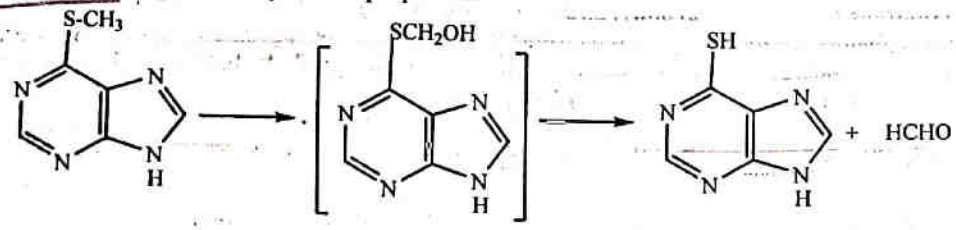
4) **N-Hydroxylation:** Converse to basic compounds that form N-oxides, N-hydroxy formation is usually displayed by non-basic nitrogen atoms such as amide nitrogen, **e.g.,** lidocaine.



Lidocaine N-Hydroxy lidocaine

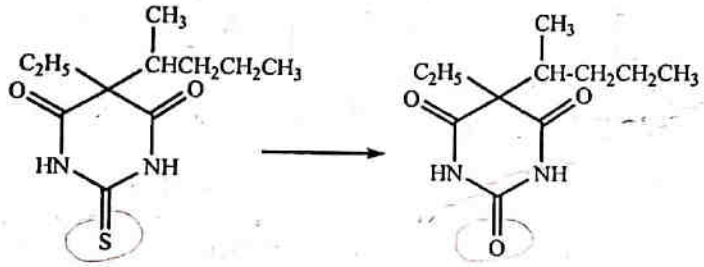
2.1.5.1.1.10. Oxidation of Carbon-Sulfur Systems

1) **S-Dealkylation:** The mechanism of S-dealkylation of thioethers (RSR') is analogous to N-dealkylaiton, i.e., it proceeds via α-carbon hydroxylation. The C-S bond cleavage results in formation of a thiol (RSH and a carbonyl product, **e.g.,** 6-methyl mercaptopurine.



6-Methyl mercaptopurine Hydroxylated intermediate 6-Mercaptopurine

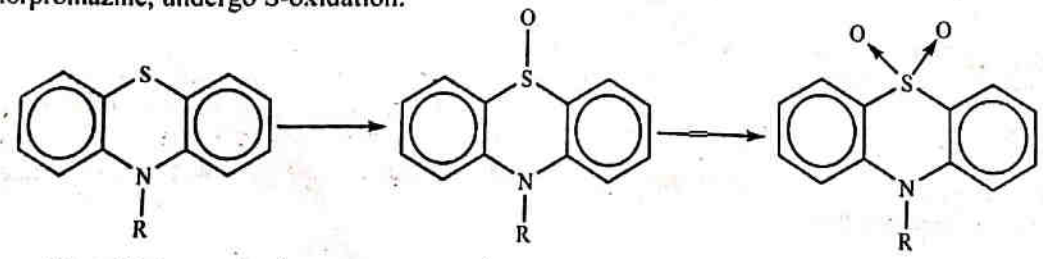
2) **Desulfuration:** This reaction also involves cleavage of carbon-sulfur bond (C=S or thiono). The product is the one with C=O bond. Such a dusulfuration reaction is commonly observed in thioamides (RCSNHR') such as thiopental.



Thiopental Pentobarbital

Desulfuration also occurs with compounds containing P=S bonds such as the organophosphate pesticides, e.g., parathion.

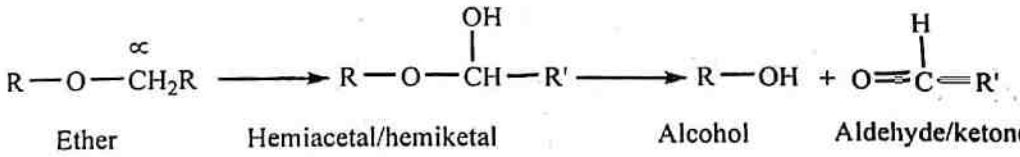
3) **S-Oxidation:** Apart from S-dealkylation, thioethers can also undergo S-oxidation reactions to yield sulfoxides which may be further oxidized to sulfones (RSO_2R). Several phenothiazines, e.g., chlorpromazine, undergo S-oxidation.



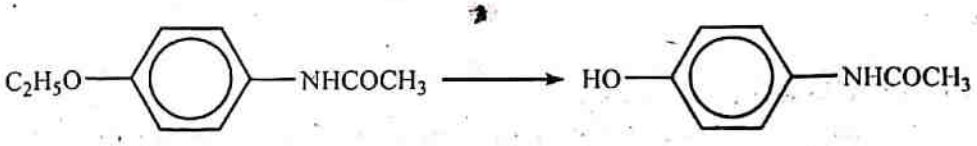
Phenothiazine Phenothiazine sulfoxide Phenothiazine sulfone

2.1.5.1.1.11. Oxidation of Carbon-Oxygen Systems

This reaction is also similar to N-dealkylation and proceeds by α-carbon hydroxylation to form an unstable hemiacetal or hemiketal intermediate which spontaneously undergoes C-O bond cleavage to form alcohol (arenol or alkanol) and a carbonyl moiety.

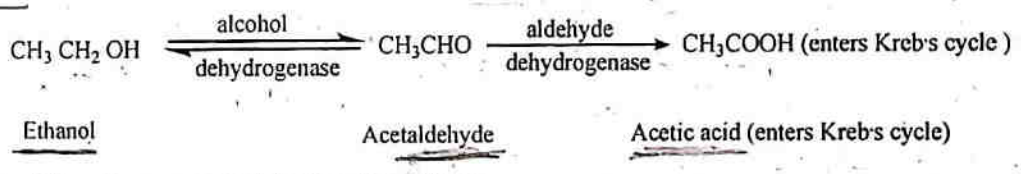


The reaction generally leads to formation of active metabolites, **e.g.,** phenacetin to paracetamol, and codeine to morphine.



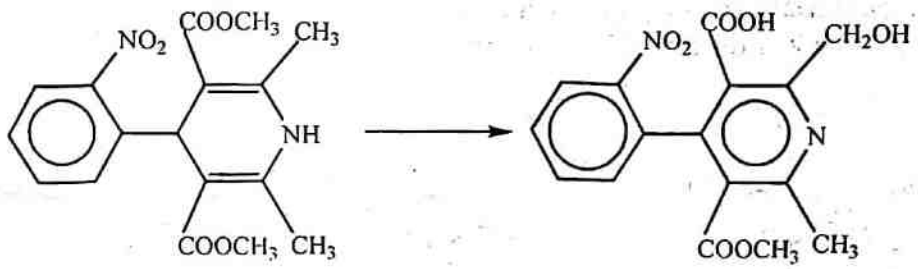
2.1.5.1.1.12. Oxidation of Alcohol, Carbonyl and Carboxylic Acid

These reactions are mainly catalyzed by non-microsomal enzymes, dehydrogenases. Primary and secondary alcohols and aldehydes undergo oxidation relatively easily but tertiary alcohols, ketones and carboxylic acids are resistant as such a reaction involves cleavage of C-C bonds.

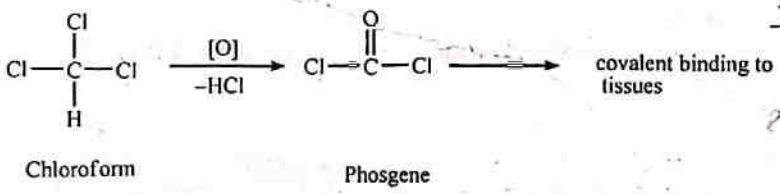


2.1.5.1.1.13. Miscellaneous Oxidative Reactions

1) **Oxidative Aromatization/Dehydrogenation:** An example of metabolic aromatization of drugs is nifedipine.



2) **Oxidative Dehalogenation:** This reaction is common with halogen containing drugs such as **chloroform.** Dehalogenation of this drug yields phosgene which may result in electrophiles capable of **covalent binding** to tissues.



Oxidative ring cleavage, oxidation of arenols to quinones, etc., are other oxidative reactions.

Q. 16 Write a note on glucuronide conjugation of Phase II metabolism.

2.1.5.2. Phase II Conjugation

Phase II reactions add to a functional group already present in the molecule or to one which was placed there in a phase I reaction, a moiety derived from lipid, carbohydrate or protein. The added group serves the dual purpose of blocking the functional group and further decreasing the lipophilicity of the molecule, thus facilitating its excretion. The conjugate is almost always pharmacologically inactive (unlike the products of phase I reactions) and less lipid soluble. The groups most often involved in conjugate formation are glucuronyl, sulphate, methyl, acetyl, glycyl, and glutamyl.

Various Phase II conjugation reactions are:

1) Glucuronide Conjugation,
2) Sulphate Conjugation,
3) Acetylation and Acylation,
4) Methylation,
5) Glycine Conjugation,
6) Glutathione and Mercapturic Acid Synthesis,
7) Conjugation with Alpha Amino Acids,
8) Miscellaneous Conjugation Reactions.

2.1.5.2.1. Glucuronide Conjugation

The most commonly encountered conjugation reaction is glucuronide formation and this usually accounts for the major portion of the metabolite formed in the excreta. Glucuronic acid is an organic acid derived from glucose in which the presence of four extra hydroxyl groups confers great water solubility. Glucuronide formation involves the formation of a high-energy phosphate compound Uridine Diphosphate Glucuronic Acid (UDPGA) from which the glucuronic acid part is transferred to an electron rich atom (N, O, or S) on the substrate forming an amide, ester, or thiol bond. This is catalyzed by an enzyme, UDP glucuronyl transferase, has very broad substrate specificity, so the reaction occurs with a wide variety of drugs and other foreign molecules. UDPGA is synthesized in a two stage process starting from glucose-1-phosphate which is first coupled to uridine triphosphate to give UDP-glucose. UDP-glucose is then oxidized by the enzyme UDPG dehydrogenase which uses NAD as co-factor to give UDPGA **(Figure 2.1)**.

UDPGA
Uridine-diphosphate-Glucuronic Acid

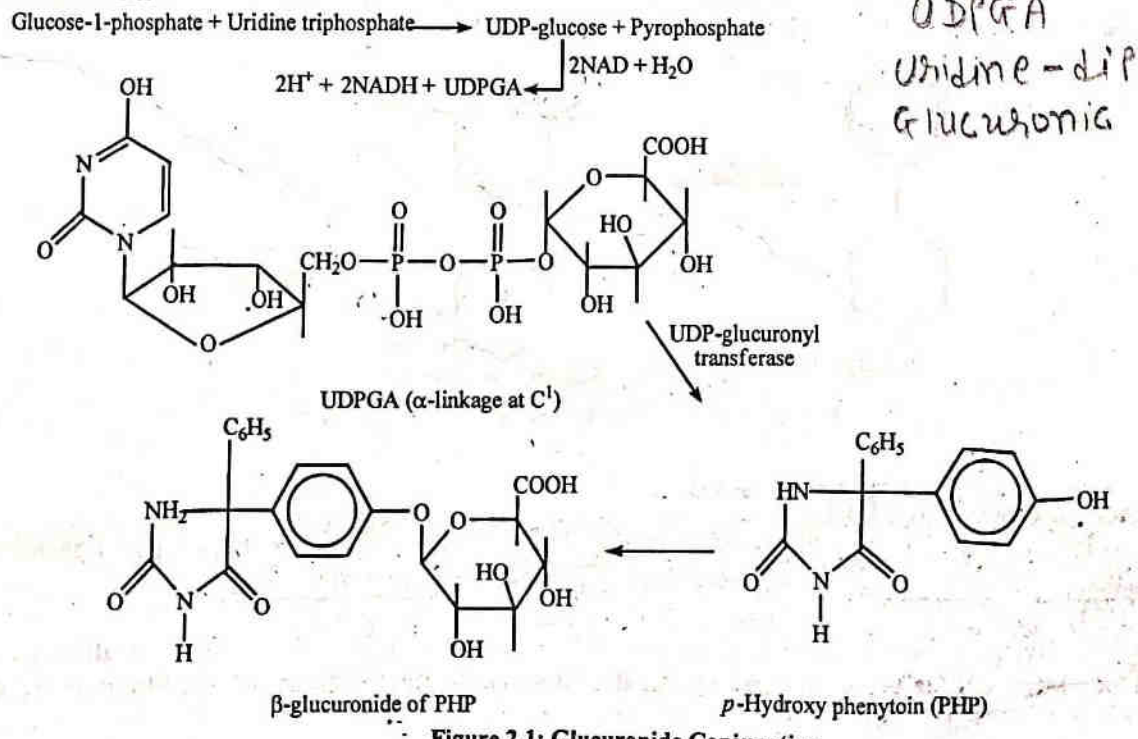


Figure 2.1: Glucuronide Conjugation

Q. 17 Explain factors affecting drug metabolism including stereo chemical aspects.

A large number of physical, chemical and biological factors affect the metabolism of a drug. Various factors which affect the rate of drug metabolism are :

1) **Physiochemical properties of the drug molecule :** Physiochemical properties like molecular size and shape, acidity and basicity, lipophillic character, solubility, pKa value of the drug molecule affects its metabolism. Steric and electronic characters of a drug also affects its metabolism.

2) **Chemical factors :** Various chemical affects the metabolism of the drug. Presence of enzyme inducers and enzyme inhibitors alters the actions of drug metabolising enzymes. Different chemical factors are :

a) **Enzyme inducers :** are the chemicals which increases the activity/ability of the enzymes which causes metabolism. For example, 3-methyl cholanthrene and cigarette smoke increases the metabolism of some drugs. Alcohol increases metabolism of coumarins and phenytoin. Barbiturates increases metabolism of oral contraceptives, cortisol and coumarins.

Various drugs like rifampicin, meprobamate, cyclophosphamide etc. stimulate their own metabolism (self-induction).

b) **Enzyme inhibitors :** are the chemicals and drugs which decreases the activity/ability of the enzymes which causes metabolism. Inhibition may be direct, competitive, or non-competitive and indirect. For example, Erythromycin, Ketoconazole.

MAO inhibitors decreases metabolism of barbiturates and coumarins decreases the biotransformation of phenytoin.

Various halogenated pesticidies like DDT, organophosphate insecticides, heavy metals like mercury, tin, nickel, cobalt and arsenic decreases the metabolism of various drugs.

3) **Environmental factors :** Environmental factors like pressure, temperature, atmosphere, humidity etc. affects drug metabolism.

4) **Biological factors :** Various biological factors which affect metabolism of drug are-

a) Age of the patient

b) Sex of the patient

c) Diet

d) Altered physiological state like- pregnancy, disease state and hormonal imbalance etc.

e) Species and strain differences.

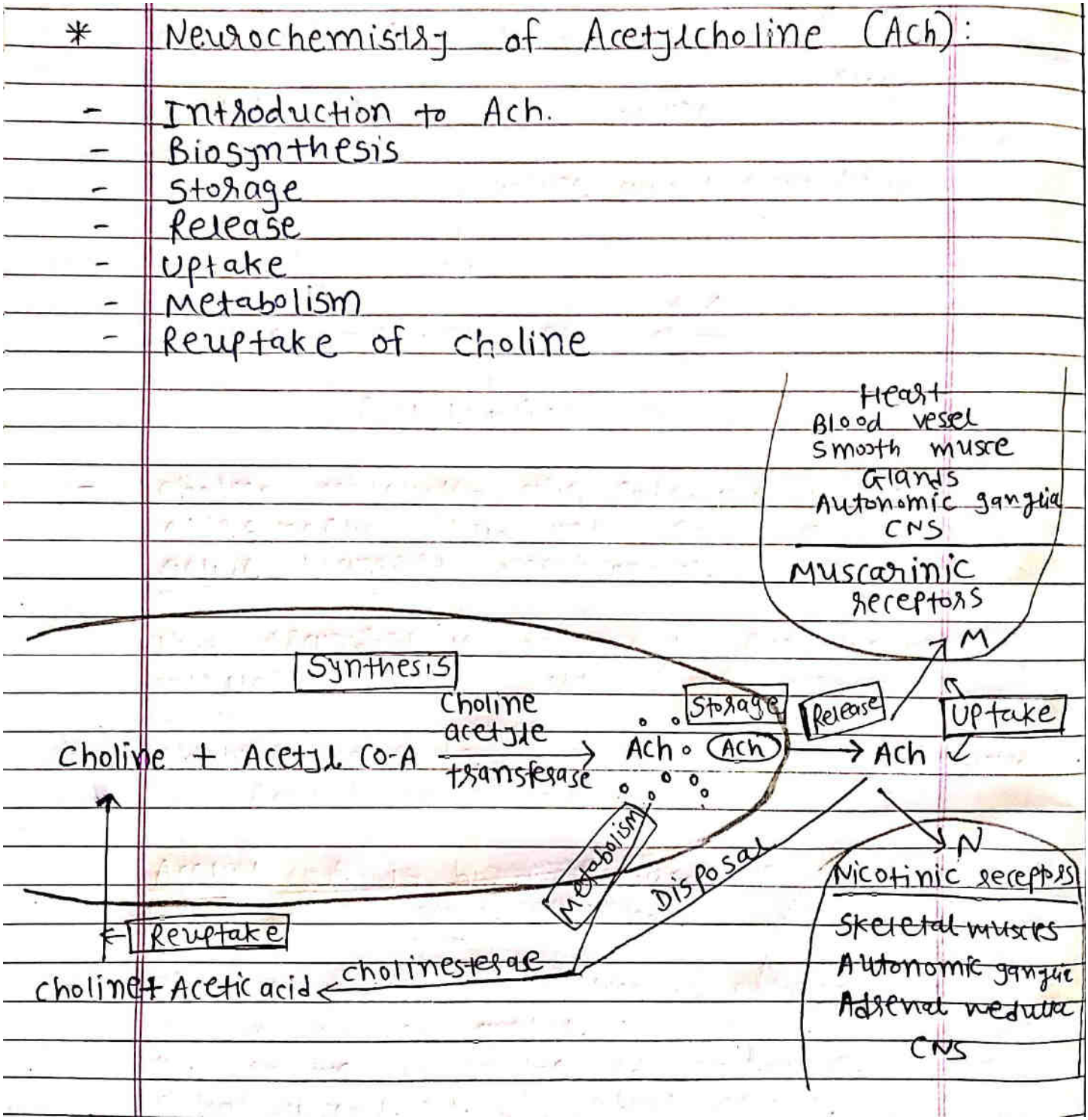
5) **Stereochemical aspects of the drug molecule :** Stereochemistry of the drug also affects its metabolism by different enzymes. Stereoselective metabolism of drugs is a common example in this case. Metabolizing enzymes have different preference for one enantiomers than the other and hence results in enantioselectivity. For example,

i) (–) quinine treats the malaria fever but (+) quinine does not.

ii) D (+) glucose gets easily metabolised in the body to give CO_2 and H_2O but L(–) glucose is not metabolised and is excreted as such.

iii) Some bacteria ferment the dextro form of a compound without affecting the laveo form.

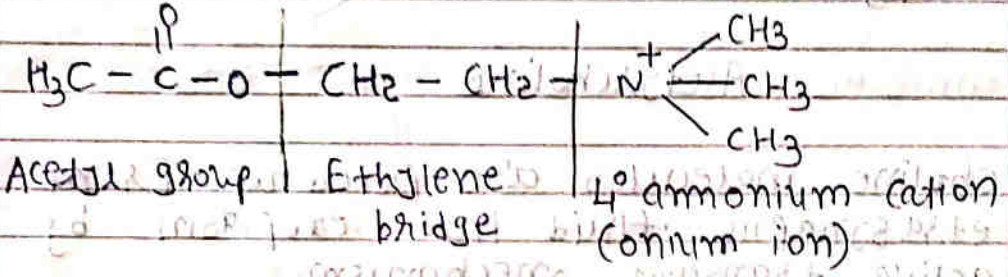
Q. 18 Write in detail Neurochemistry of Acetylcholine.



=> Introduction to Acetylcholine:

Acetylcholine (Ach) is the neurotransmitter in all ganglia, Neuromuscular junction of postganglionic synapses of parasympathetic syste.

- It is major neurotransmitter which lead to parasympathetic functions.



- Chemicaly it is an estel of acetic acid & Choline - an amino alcohol.

- on structural basis, it offeres 3 sites for molcewas modification:
  a) acetyl group
  b) Ethylene bridge
  c) Quartesnary amonium group.

- Quartesnary amonium group (onium group) is linked by an ethylene bridge to an ester group.

- Ach is stable in acidic solutions but it is very unstable in alkaline media.

=> Ach Biosynthesis:

Ach is syntesized in nerve ending of pre-synaptic nerve from choline & Acetyl Coenzyme A.

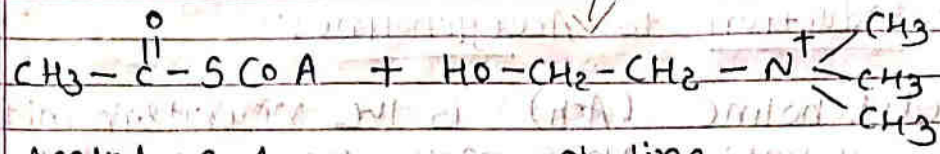
Pyruvate

Serine

Serine + Carboxylase

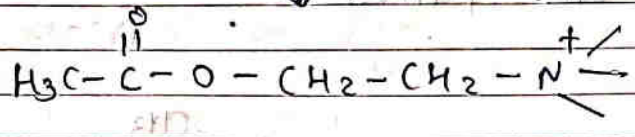
एकलव्य
Pg.No :
Date: / /201

PDH complex
FAD
TPP



Acetyl CoA + choline

Choline acetyl transferase



Acetylcholine

- Choline molecules are picked up from extrasynaptic fluid into cytoplasm by active transport mechanism.

This transport is dependent upon the intra-cellular conc. of Na^+ & K^+ ions.

- Choline molecule is acetylated in cytoplasma by Acetyl coenzyme A.

- Acetyl CoA is biosynthesized in mitochondria present in nerve terminal.

- The acetylation of Choline is catalyzed by enzyme choline acetyl transferase.
This enzyme is synthesized within perikaryon & has a mol. wt. of about 68,000.
In peripheral Cholinergic nerves, it is present in higher conc.

- As soon as Ach is synthesized, it is sequestered within the synaptic vesicles.

⇒ **Ach Storage:**

The biosynthesized Ach is stored within Synaptic vesicles immediately inside the membrane of nerve terminal.

- Most newly biosynthesized Ach is actively transported into cytosolic storage vesicles (Synaptic vesicles) located in presynaptic nerve endings, along with Ca^{++} & Mg^{++} ions until it is released.
- Each vesicle contains about 5,000 to 10,000 molecules of Ach.
- The no. of such vesicles present in nerve terminal varies in diff. organs.
  For eg., a motor nerve terminal may contain 300,000 or more Synaptic Vesicles.
- Some Ach molecules remain in the cytosol & eventually hydrolysed.
- Only stored form of Ach acts as neurotransmitter.

⇒ **Ach release:**

- The arrival of a nerve signal leads to the release of Ach.
- When an impulse reaches to nerve terminal, depolarisation causes an activation of calcium ionophore.
- It allows an influx of extracellular Ca^{++} ions.
- Ca^{++} ions influx is an essential step for the rupturing of storage vesicles of almost all neurotransmitters.

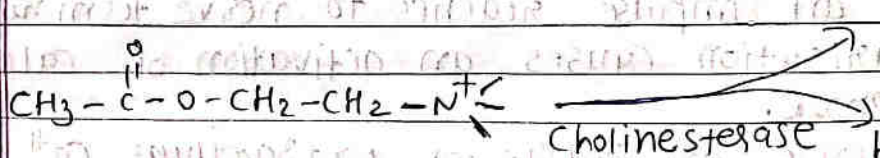
- Thus, influx of extracellular Ca^{++} ions lead to rupture of Ach synaptic vesicles and by that Ach is released.
- 4 Ca^{++} ions are taken up for each molecule of Ach released.
- The ruptured synaptic vesicles again re-shape to store fresh Ach.
- The vesicular release of Ach is reported to be inhibited by excess of Mg^{++} ions.

=> **Ach Uptake:**

Released Ach crosses the synaptic gap and binds to cholinergic receptors leading to stimulation of the second nerve.
Cholinergic receptor means Muscarinic and Nicotinic receptors.

=> **Ach Metabolism and reuptake of choline:**

- The free Ach present in blood & other tissues, gets quickly hydrolysed by cholinesterase enzyme into Acetic acid & Choline molecule.



Choline binds to the choline receptors on the presynaptic nerve & is taken up into the cell by an

efficient transport system to continue the cycle.

- Composition of cholinesterase enzyme is as follows:

- Cholinesterase enzyme is of two types:

i) e-cholinesterase → present in erythrocytes
ii) S- " → " " serum.

- In autonomic ganglia, cholinesterase is usually present in the preganglionic fibre
- while serum esterase is present in glial cells, plasma, livers & at other sites.

- This enzyme is present in high conc. in the synapses of both cholinergic & somatic nerves and striated muscle.

- This enzyme is present in two diff. forms:
i) Simple oligomers of a 70,000 dalton catalytic subunit
ii) Elongated forms of complex structure.

- Cholinesterases are not very selective type of enzyme. Both of these forms can hydrolyse a large no. of esters, choline & carboxylic acids.
- It is one of the most efficient enzyme present in body.

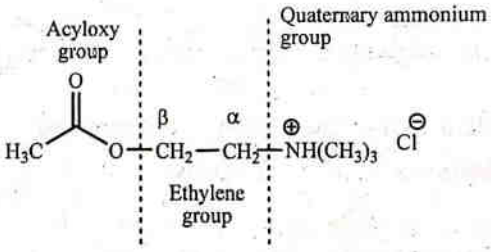
- It can hydrolyse about 3×10^5 Ach molecules per mole per minute.

Q. 19 Explain SAR of Acetylcholine in detail. OR Describe SAR of parasympathomimetic agents. OR Give SAR of cholineesters (Parasympathomimetics). OR Explain SAR of Cholinergic agonists in detail with suitable example.

Acetylcholine is the prototype of the category Parasympathomimetic drugs. A large number of modifications have been made to synthesize new derivatives which are more selective and having longer duration of action.

3.11.4.3.1. Structure Activity Relationship

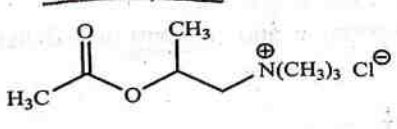
Structural modifications of acetylcholine influence the ability of analogues to function as cholinergic agonists.



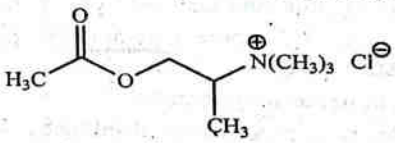
These modifications fall into four categories:

1) **Modification of the Quaternary Ammonium Group**
   i) Analogues of acetylcholine in which the nitrogen atom was replaced by arsenic, phosphorus, or sulphur have been synthesised. Although they exhibited some of the activity of acetylcholine, these compounds are less active and are not used clinically.
   ii) Only compounds possessing a positive charge on the atom in the position of nitrogen had appreciable muscarinic activity.
   iii) Compounds in which all three methyl groups on the nitrogen are replaced by larger alkyl groups are inactive as agonists. When the methyl groups are replaced by three ethyl groups, the resulting compound is a cholinergic antagonist. Replacement of only one methyl group by an ethyl or propyl group affords a compound that is active, but so much less than acetylcholine. Furthermore, successive replacement of one, two, or three of the methyl groups with hydrogen atoms to afford a tertiary, secondary, or primary amine, respectively, leads to successively diminishing muscarinic activity.

2) **Modification of the Ethylene Bridge**
   i) Synthesis of acetic acid esters of quaternary ammonium alcohols of greater length than choline led to a series of compounds with activity that was rapidly reduced as the chain length increased.
   ii) There should be no more than five atoms between the nitrogen and the terminal hydrogen atom for maximal muscarinic potency.
   iii) The muscarinic receptor cannot successfully accommodate molecules larger than acetylcholine and still produce its physiologic effect. Although larger molecules may bind to the receptor, they lack efficacy and demonstrate antagonist properties.
   iv) Replacement of the hydrogen atoms of the ethylene bridge by alkyl groups larger than methyl affords compounds that are much less active than acetylcholine.
   v) Introduction of a methyl group on the carbon β to the quaternary nitrogen affords acetyl-β-methylcholine (methacholine), which has muscarinic potency almost equivalent to that of acetylcholine and much greater muscarinic than nicotinic selectivity.
   vi) A methyl group on the carbon α to the quaternary nitrogen affords acetyl-α-methylcholine. Although activity relative to acetylcholine is reduced at both muscarinic and nicotinic receptors, it exhibits greater nicotinic than muscarinic potency. This compound is not currently used as a therapeutic agent.



Acetyl-β-methylcholine chloride (Methacholine)



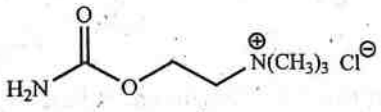
Acetyl-α-methylcholine chloride

3) **Modification of the Acyloxy Group**

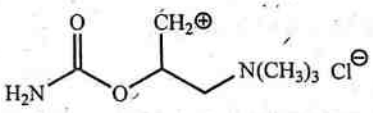
i) When the acetyl group is replaced by higher homologues (i.e., the propionyl or butyryl groups), the resulting esters are less potent than acetylcholine.

ii) Because the fleeting pharmacological action and chemical instability of acetylcholine result from its rapid hydrolysis, a logical approach to the development of better muscarinic therapeutic agents was to replace the acetyloxy functional group with a functional group more resistant to hydrolysis.

iii) Esters derived from carbamic acid are referred to as carbamates, and because their carbonyl carbon is less electrophilic, they are more stable than carboxylate esters to hydrolysis. Carbachol is less readily hydrolysed by gastric acid, AChE, or butyryl-cholinesterase than acetylcholine is, and it can be administered orally.



Carbachol

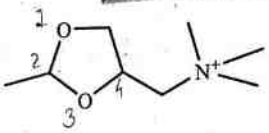


Bethanechol

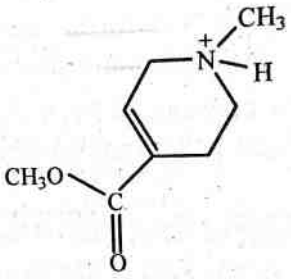
iv) Methacholine and led to synthesis of its carbamate ester, bethanechol, an orally effective potent muscarinic agonist with almost no nicotinic activity at therapeutic doses.

v) Muscarinic receptors exhibit stereoselectivity for the two optical isomers of bethanechol, and similar to methacholine, the S-(+)-enantiomer exhibits greater binding affinity at muscarinic receptors than the R-(−)-enantiomer in isolated receptor preparations.

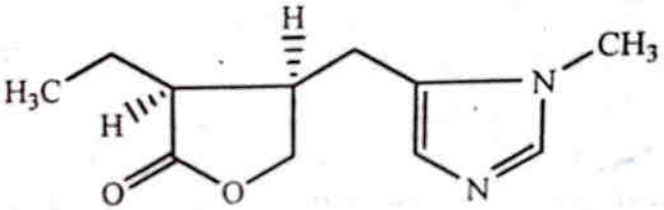
4) **Cyclic Analogues of Ach:** Cyclic ACh analogues include the naturally occurring agonist muscarine, pilocarpine, and arecoline, all of which are muscarinic compounds. Dioxolanes such as 2-methyl-4-trimethyl-ammonium methyl-1,3-dioxolane are muscarinic analogues of very high potency. Cyclization is a good drug design strategy in that in constrains conformational flexibility, thereby increasing receptor specificity.



2-methyl-4 trimethyl-
ammonium-methyl-1, 3-dioxolane



Arecoline



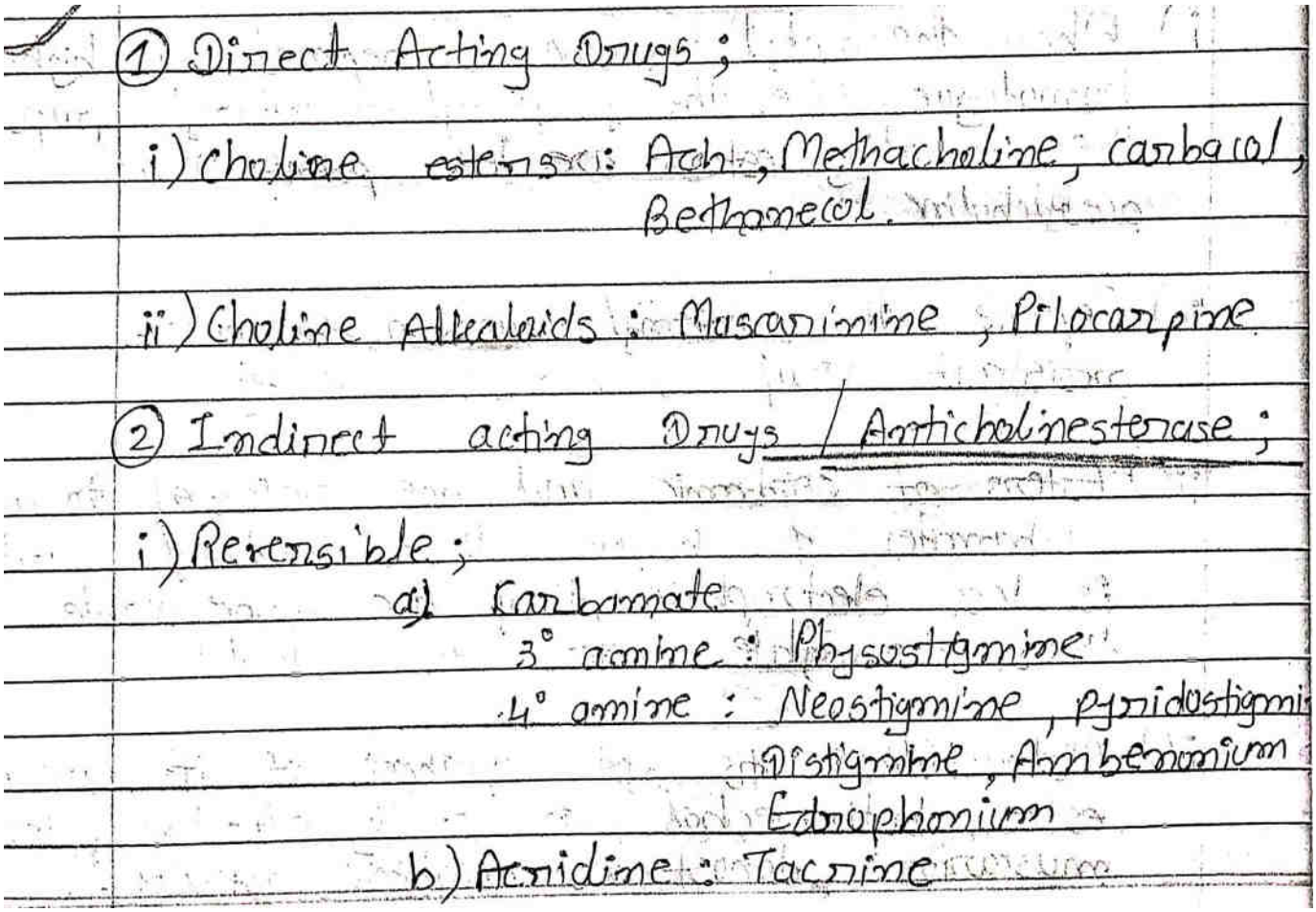
Pilocarpine

Q. 20 Write a note on Parasympathomimetics.

Parasympathomimetic agents are the compounds which mimic the actions of acetyl choline, which is the major neurotransmitter i.e. causes nerve stimulation. Parasympathomimetic agents are classified on the basis of their direct or indirect action on the acetylcholine receptor. These agents are of two types :

1. **Direct acting parasympathomimetics** : These drugs bind to the nicotinic or muscarinic receptors and causes excitation of cholinergic system.
2. **Indirect acting parasympathomimetics** : These drugs inhibits the hydrolysis of acetylcholine by acetyl cholinesterases and hence increases the life of acetylcholine and causes increased conentration of ACh at the receptor site to produce excitation of cholinergic system. These agents are also known as anticholinesterases.

Classification:



ii) Irreversible : ~~Dibydeo flouro~~ Diisopropyl fluro p
Tetra ethyl pyrophosphate.,
Tabum, Serin, Soman,
Pesticides, Merathion.

- Direct acting ;

i) Choline esters ;

→ $H_3C-\underset{\underset{O}{\|}}{C}-O-CH_2-CH_2-\overset{+}{N}(CH_3)_3$

Acetylcholine

→ $H_3C-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{CH_3}{|}}{CH}-CH_2-\overset{+}{N}(CH_3)_3$

Methacholine

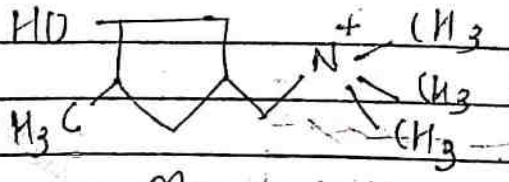
→ $H_2N-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{CH_3}{|}}{CH}-CH_2-\overset{+}{N}(CH_3)_3$

Bethanechol

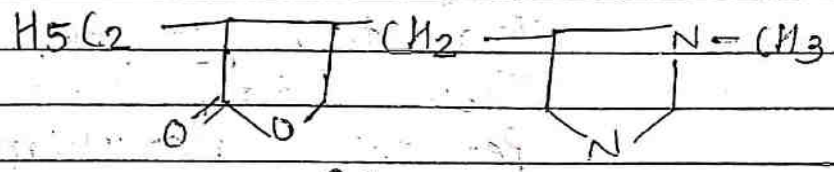
→ $H_2N-\underset{\underset{O}{\|}}{C}-O-CH_2-CH_2-\overset{+}{N}(CH_3)_3$

Carbachol

ii) Choline alkaloides ;



Muscarinic



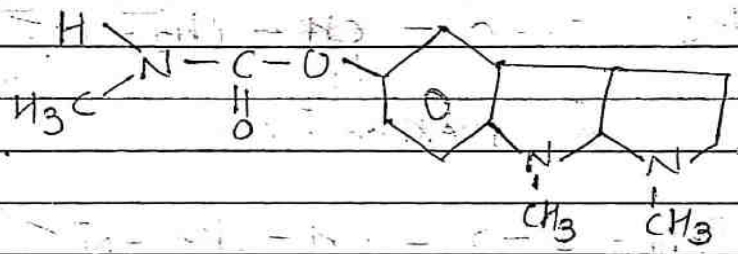
Pilocarpine

- Indirect acting

i) Reversible

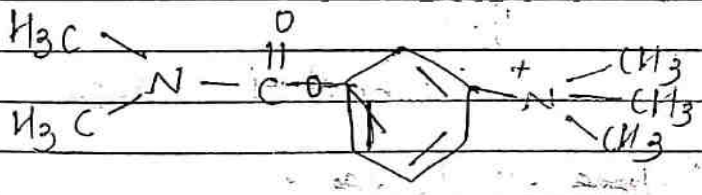
a) Carbamate ;

3° amine ;

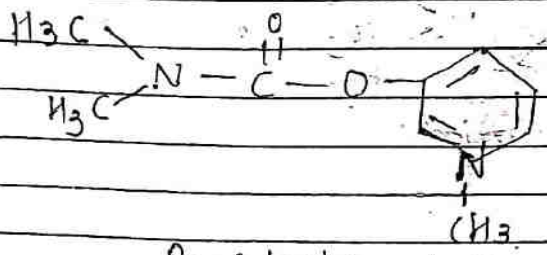


Physostigmine

4° amine ;

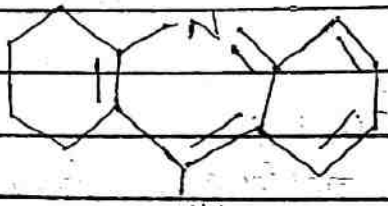


Neostigmine



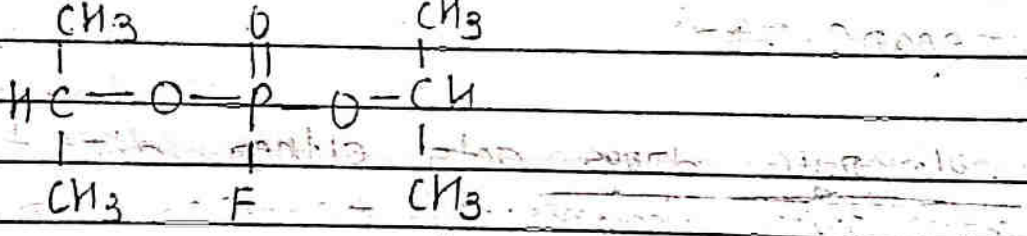
Pyridostigmine

b) Acridine ;

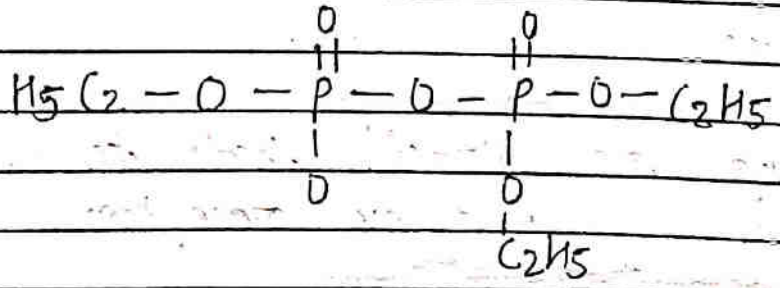


Tacrine

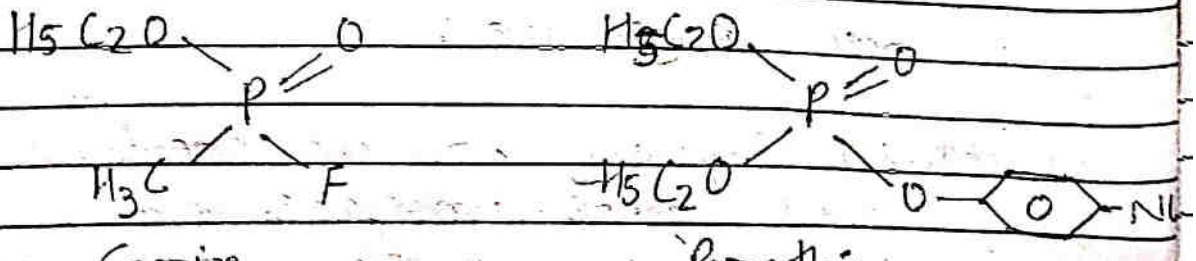
ii) Irreversible ;



Diisopropyl fluro phosphate



Tetra ethyl pyrophosphate



Sarin

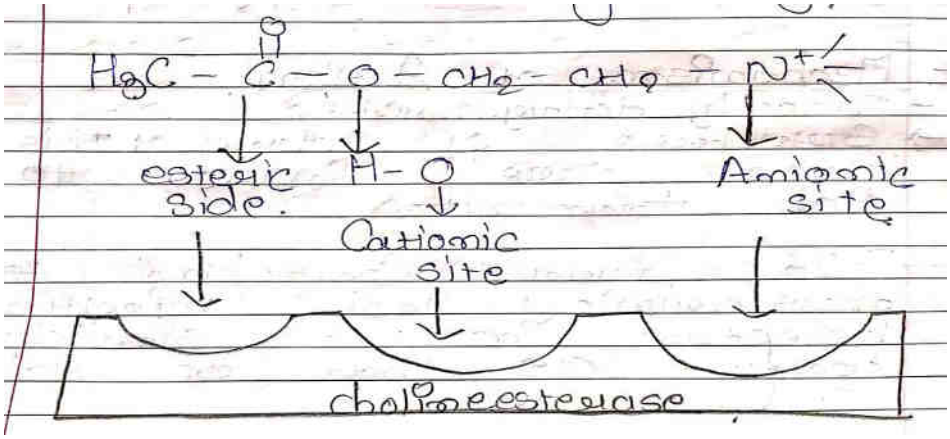
Parathion

Mechanism of action:

Directly acting Drugs:

Structure of drugs of this class are similar to Ach. So, They can bind to muscarinic and nicotinic receptor in a same way as that of Ach. Due to binding with receptors, they lead to activation of receptor on effector cell or directly bound organ function. Due to this activation, they give biological action similar to Ach and thus, enhance activity of Ach.

Indirectly acting Drugs:



Cholinesterase enzyme hydrolyses Ach in its free form.

This enzyme has 3 acting sites through which it can bind to Ach leading its hydrolysis.

1. Anionic site
2. Cationic site
3. Esteric site

Reversible acting drugs combine to anionic and esteric sites of cholinesterase enzyme and form complex which is reversible. After breakdown of this complex, the enzyme is still available in its original form capable to cause hydrolysis of Ach.

Thus, Reversible acting drugs have shorter duration of action.

Irreversible acting drugs combine to esteric sites of cholinesterase enzyme and initiate esterification of the enzyme. After esterification, the enzyme will not be available in its original form capable to cause hydrolysis of Ach. The complex formed by combination of Irreversible acting drugs with cholinesterase is irreversible.

Thus, hydrolysis of Ach is inhibited through inhibiting the activity of cholinesterase enzyme indirectly.

Uses:

- Open and narrow angle glaucoma
- Mydriasis
- Arterial tachycardia
- Urinary retention
- Atonic bladder
- Atonic constipation
- Post-operative and post-partum intestinal ileus

- Paralytic ileum
- Myasthenia gravis
- Atropine poisoning
- Curare poisoning
- As nerve gas, As insecticide and pesticide (Organophosphorous compounds)

Adverse effects:

3.11.4.3.4. Adverse Effects

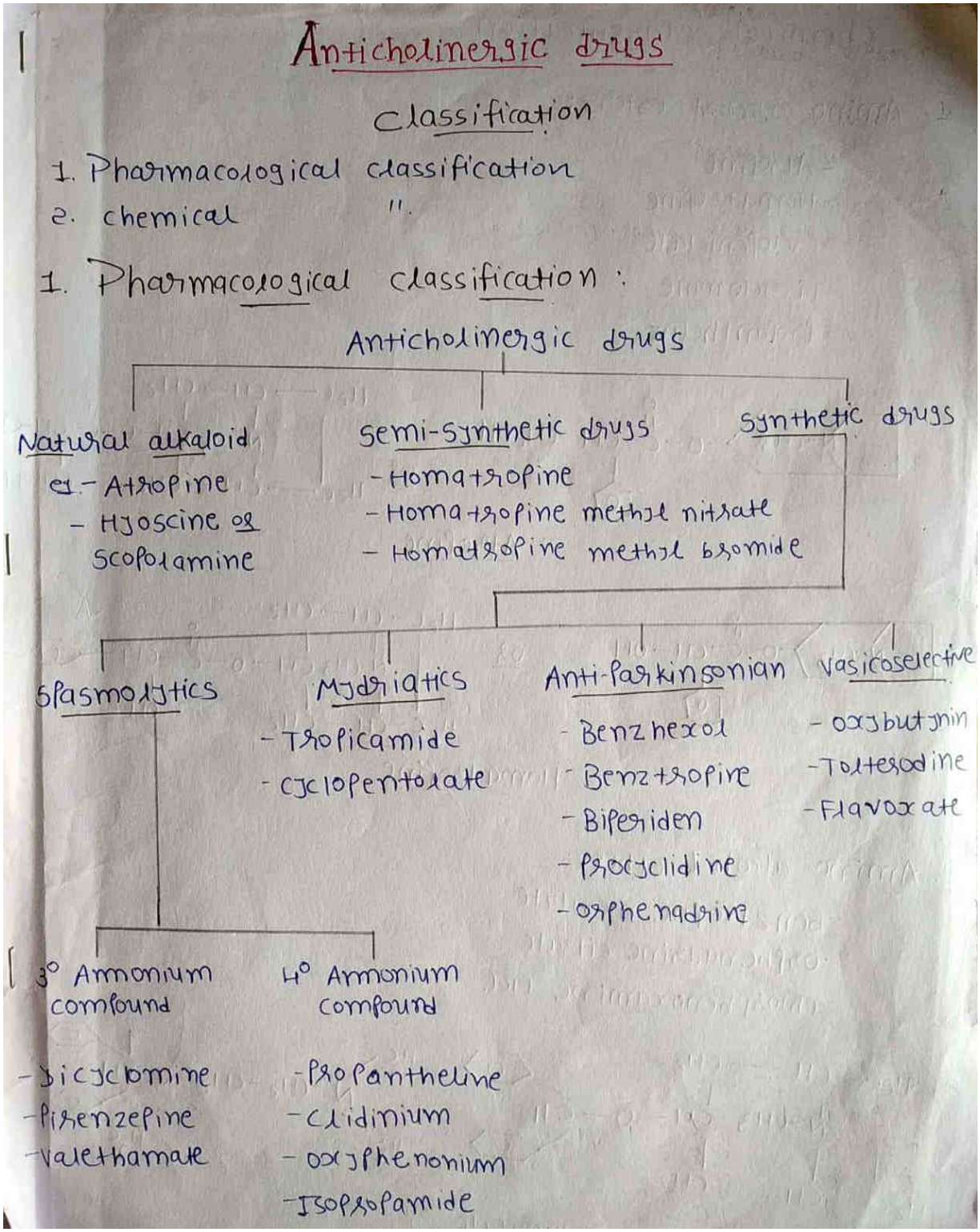
When used properly, cholinergic drugs will increase muscle strength in patients with **myasthenia gravis**. In ey drop form, they can reduce the intraocular pressure in glaucoma.

The possible adverse effects of cholinergic drugs are:

1) Slow heart beat, possibly leading to cardiac arrest.
2) Muscle weakness, muscle cramps, and muscle pain.
3) Convulsions.
4) Weak breathing, inability to breath.
5) Increased stomach acid and saliva.
6) Nausea and vomiting.
7) Dizziness, drowsiness, and headache.

Q. 21 Write a note on Parasympatholytic agents.

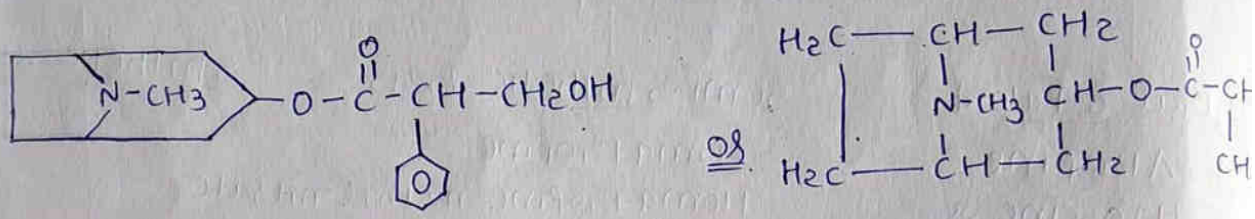
Parasymapathomimetics or Anticholinergics are chemical substances that block or antagonize the effect of Acetylchline neurotransmitter in CNS.



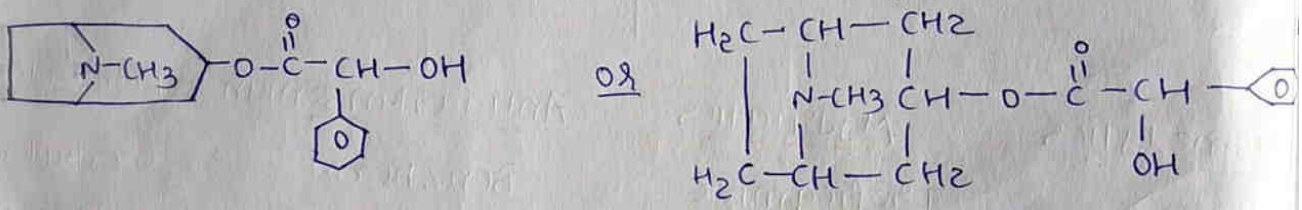
2. Chemical classification:

1. Amino alcohol esters:

- Atropine
- Homatropine
- Cyclopentolate
- Dicyclomine
- Propantheline



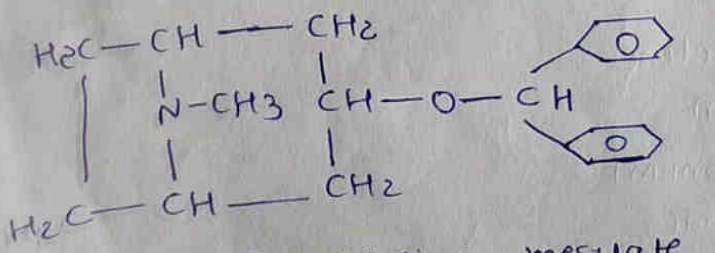
Atropine



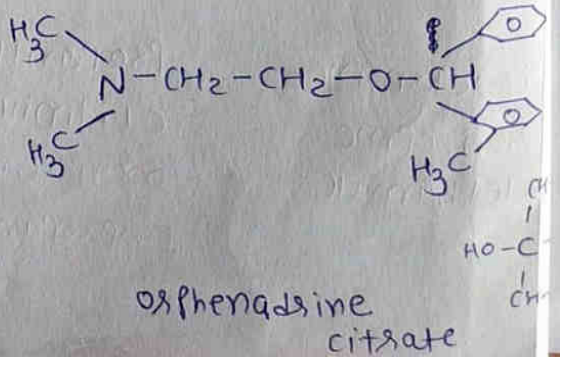
Homatropine

2. Amino alcohol ethess:

- Benztropine mesylate
- Orphenadrine citrate
- Chlorphenoxamine Hcl



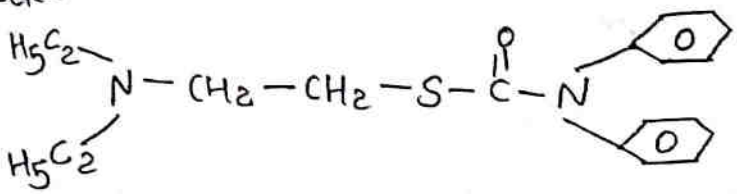
Benztropine mesylate



Orphenadrine citrate

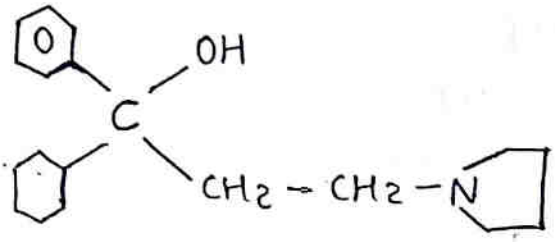
3. Amino alcohol carbamate:

- Fencarbamide



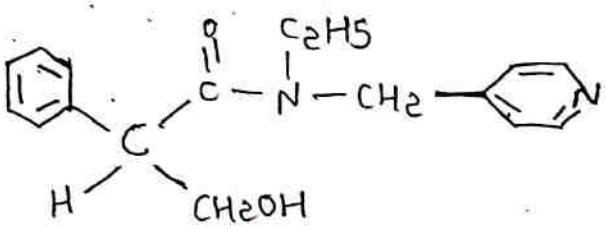
4. Amino alcohols:

- Benzhexol HCl. →
- Procyclidine HCl.



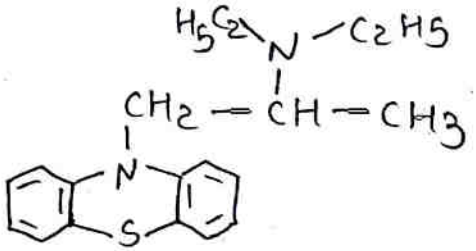
5. Amino amide:

- Isopropamide
- Tropicamide →



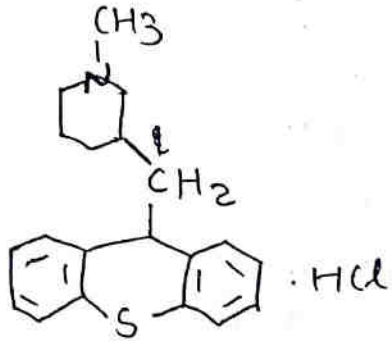
6. Di amine :

- Diethazine
- Etho Propazine · HCl. →



7. Miscellaneous:

- Diphemanil Methisulphate
- Ethoprazine · HCl
- Methixene · HCl →
- Pirenzepine



Mechanism of Action:

- An attractive concept views a mutual fit occuring between agonist & its receptor. ~~of Enzyme perturbation by Belgaev~~
- The receptor alter its confirmation to fit the agonist. Because receptor is bound to the membrane, it sufficiently changes membrane structure to alter the transport of ions through the membrane to generate muscle contraction.
- When an agonist binds to the receptor, the confirmational change generated in the receptor is favourable for contraction. &
- When an antagonist binds, an alternate confirmation results in which the flow of ions through the membrane is not suitable for contraction.
- However, the receptor is occupied & is not available to Ach.
- Cholinergics & Anticholinergics show structural similarities indicating that both may react with a single receptor & may attach themselves with a similar manner.
  But, the difference is in the size of the acyl group & the substituents on nitrogen atom.
- Anticholinergics have great affinity for the receptor & compete favourably with Ach.
- The large groups of Anticholinergics not only increase affinity of it but through an "umbrella effect" also block the approach of Ach to the receptor (or) to closely related receptors.

- The applicability of Bellaeu's concept of Enzyme perturbation is further enhanced by the fact that as the size increases in the series of compounds with cholinergic activity, there is not an abrupt change from cholinergic to anticholinergic activity.

e.g. $CH_3-(CH_2)_n-N^{+}(CH_3)(CH_3)(CH_3)$

When, n = 1 to 4, potency ↑es
n = 5 to 7, Partial agonisty
n = > 7, compound is antagonist.

Uses:

→ Amino alcohol esters:

i) Used as an anti-secretory agent
- " " " pre-anaesthetic medication :- it reduces excess salivation & respiratory secretions.
- Used in Peptic ulcer :- it reduces gastric secretions.

ii) Used As an anti-spasmodic.
- used in gastritis, Gastric hypermotility, Urinary frequency & urinary urgency.
- In bronchial asthma
- As mydriatic & Cycloplegic → Paralysis of ciliary muscle of the eye, resulting in a loss of accomodation
- As cardiac vagolytic → Inhibit action of vagus nerve of heart, GIT & other organs
- used in Parkinsonism (as an adjuvant to levodopa), in motion sickness, CNS disorders.
in organophosphorous & insecticide poisoning.

→ Amino alcohol ethers:
- Used in parkinsonism, in acute spastic disorders of skin caused by trauma, tension, vertebral disk dissociation.
- They have been more widely used as anti-parkisonism agents rather than anti-muscarinic agents.
- Also used in EPS induced by reserpine & phenothiazine.

→ Amino alcohols:
- Used in symptomatic treatment of postencephalitic parkinsonism &
- in EPS induced by reserpine & phenothiazine.

→ Amino amide:
- Used as mydriatic & cycloplegic.

→ Diamine:
- Used in parkinsonism
- it reduce ~~rigid~~ rigidity & tremor.

→ Miscellaneous:
Used in management of pylorospasm, biliary dyskinesia, gastritis, duodenal ulcer, to relieve gastro intestinal spasm.

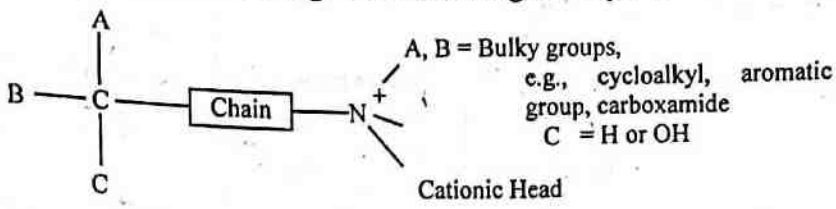
Adverse effects:
- Mild to moderate pain at the site of injection
- Dryness of mouth
- Nausea
- Flushing
- Vomiting
- Impotency
- Constipation
- confusion
- Urinary hesitance
- Blurred vision
- Photophobia
- Palpitation
- Abdomenal distension
- Headache
- Tachycardia
- Dizziness

Q. 22 Write SAR of muscarinic antagonists. OR Explain the SAR of parasympatholytics.

3.11.5.2.1. Structure-Activity Relationship of Muscarinic Antagonist

A wide variety of compounds possess anticholinergic/ antimuscarinic activity. The development of such compounds has been largely empiric and based principally on atropine as the prototype.

Anticholinergic compounds may be considered chemicals that have some similarity to ACh but contain additional substituents that enhance their binding to the cholinergic receptor.



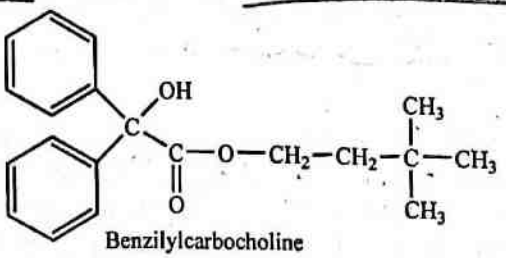
As depicted in above structure, an anticholinergic agent may contain a quaternary ammonium function or a tertiary amine that is protonated in the biophase to form a cationic species. The nitrogen is separated from a pivotal carbon atom by a chain that may include an ester, ether, or hydrocarbon moiety.

The substituent groups A and B contain at least one aromatic moiety capable of Vander Waal's interactions to the receptor surface and one cycloaliphatic or other hydrocarbon moiety for hydrophobic bonding interactions. C may be hydroxyl or carboxamide to undergo hydrogen bonding with the receptor.

Substitution on Cationic Head

1) It is generally considered that the anticholinergic molecules have a primary point of attachment to cholinergic sites through the cationic head (i.e., the positively charged nitrogen).
2) For quaternary ammonium compounds, there is no question of what is implied, but for tertiary amines, one assumes, with good reason, that the cationic head is achieved by protonation of the amine at physiological pH.
3) The nature of the substituents on this cationic head is critical in so far as a parasympathomimetic response is concerned.
4) Steric factors that cause diffusion of the onium charge or produce a less-than-optimal drug-receptor interaction result in a decrease of parasympathomimetic properties and allow the drug to act as an antagonist because of other bonding interactions.
5) Ariens has shown that carbocholines (e.g., benzilylcarbocholine) engage in a typical competitive action with ACh, though they are less effective than the corresponding compounds possessing a cationic head, suggesting that hydrophobic bonding may play an important role in these drug-receptor interactions.

Arenes -> Aromatic Hydrocarbon



Benzilylcarbocholine

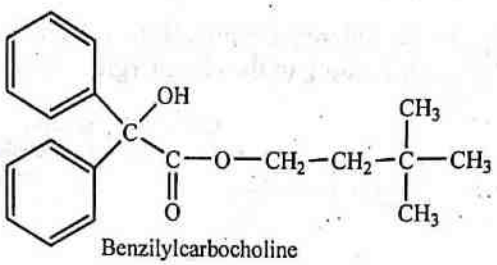
Hydroxyl Group Replacement

1) A suitably placed alcoholic hydroxyl group enhances antimuscarinic activity over that of a similar compound without the hydroxyl group.
2) The position of the hydroxyl group relative to the nitrogen appears to be fairly critical, with the diameter of the receptive area estimated to be about 2 to 3 Å.
3) It is assumed that the hydroxyl group contributes to the strength of binding, probably by hydrogen bonding to an electron-rich portion of the receptor surface.

Esteratic Group Alteration

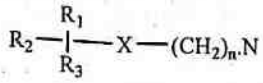
1) Many of the highly potent antimuscarinic compounds possess an ester grouping, and this may be a contributing feature for effective binding. This is reasonable because the agonist (i.e., ACh) possesses a similar function for binding to the same site.
2) An esteratic function is not necessary for activity, since several types of compounds do not possess such a group (e.g., ethers, aminoalcohols).

Cyclic Substitution



Benzilylcarbocholine

1) Examination of the active compounds reveals that at least one cyclic substituent (phenyl, thienyl, or other) is a common feature in almost all anticholinergic molecules.
2) Aromatic substitution is often used in connection with the acidic moiety of the ester function. Virtually all acids used, however, are of the aryl-substituted acetic acid variety.
3) Use of aromatic acids leads to low activity of these compounds as anticholinergics but potential activity as local anaesthetics.



4) Substituents R_1 and R_2 should be carbocyclic or heterocyclic rings for maximal antagonist potency. The rings may be identical, but the more potent compounds have different rings. Generally, one ring is aromatic and the other saturated or possessing only one olefinic bond. Substituents R_1 and R_2, however may be combined into a fused aromatic tricyclic ring system, such as that found in propantheline. The size of these substituents is limited.
5) The R_3 substituent may be a hydrogen atom, a hydroxyl group, a hydroxymethyl group, or a carboxamide, or it may be a component of one of the R_1 and R_2 ring systems. When this substituent is either a hydroxyl group or a hydroxymethyl group, the antagonist usually is more potent than the same compound without this group. The hydroxyl group presumably increases binding strength by participating in a hydrogen bond interaction at the receptor.

Q. 23 Write in detail about neurochemistry of catecholamines.

Catecholamines are derivatives of catechol (o-dihydroxy benzene) with aminoethyl side chain. They are neurotransmitters of adrenergic system.

Neurochemistry of catecholamines involves their

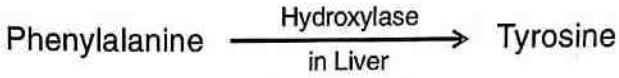
- Biosynthesis
- Storage
- Release
- Catabolism
- Reuptake

Biosynthesis of catecholamines:

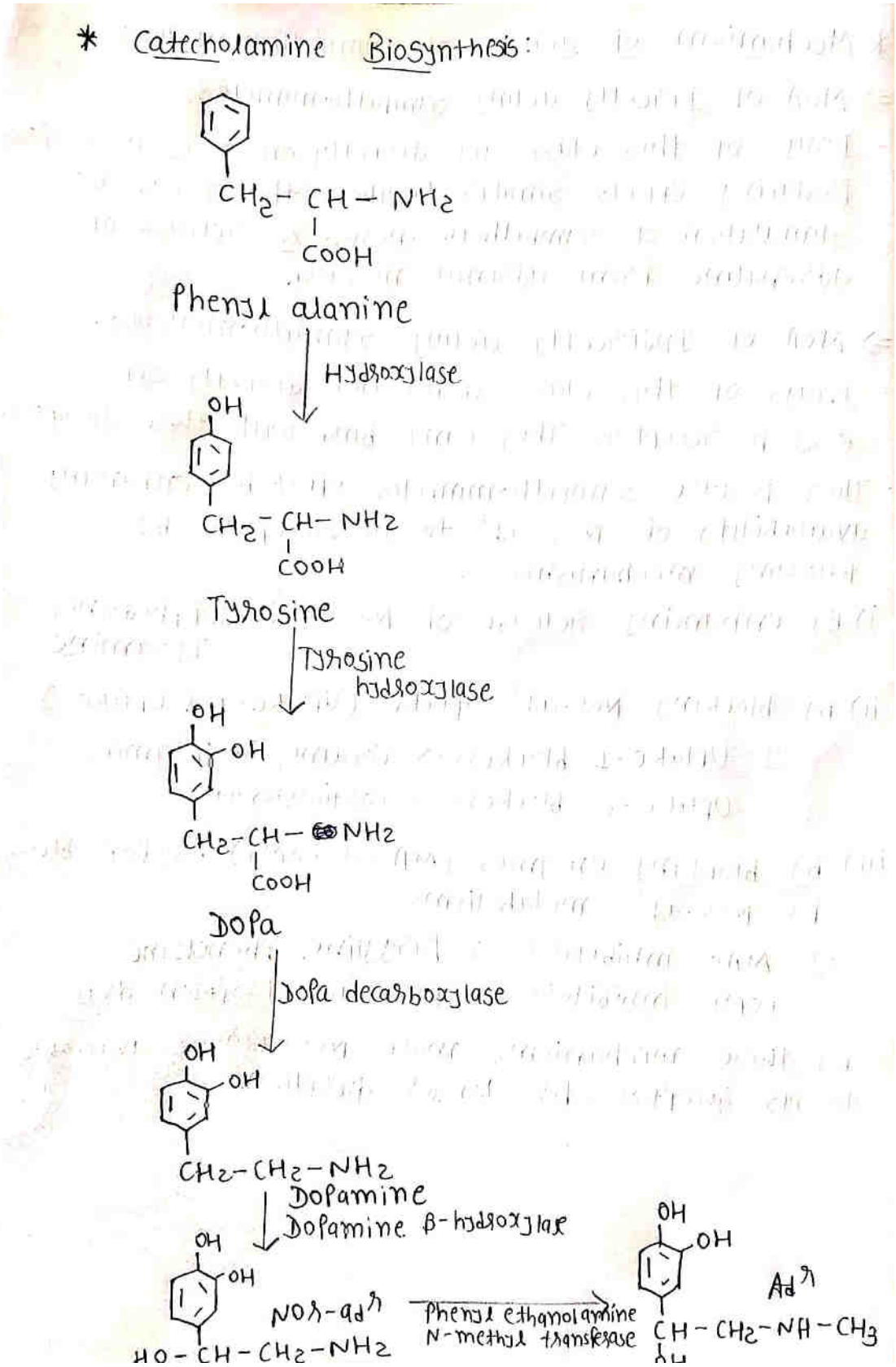
The biosynthesis takes place in adrenergic and dopaminergic neurons in the CNS, in sympathetic neurons in the ANS and in the adrenal medulla. Various enzymes which are responsible for biosynthesis are :

1. Tyrosine hydroxylase (tyrosine-3-monooxygenase)
2. DOPA decarboxylase
3. Dopamine-β-hhydroxylase
4. Phenylethanolamine-N-methyl transferase

Various steps involved in the biosynthesis of adrenergic neurotransmitters are as follows :



1. L-tyrosine gets hydrolyzed into L-3,4 dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. This is the rate limiting step in the biosynthesis. This step takes place in the cytoplasm of neurons.
2. Dopa decarboxylase causes decarboxylation of L-DOPA to form Dopamine (3,4-dihydroxyphenylethylamine). This dopamine formation takes place in the cytoplasm of the neuron.
3. Dopamine formed in the cytoplasmm is then transported into storage vesicles by VMAT-2 where it gets hydroxylated by the enzyme dopamine-β-hydroxylase to form Noradrenaline.
4. In the adrenal medulla, Noradrenaline gets converted into Adrenaline with the help of the enzyme phenylethanolamine-N methyltransferase (PNMT) and S-adenosylmethionine (SAM).


* Catecholamine Biosynthesis:
CH2-CH-NH2
COOH
Phenyl alanine
Hydroxylase
OH
CH2-CH-NH2
COOH
Tyrosine
Tyrosine hydroxylase
OH
OH
CH2-CH-NH2
COOH
Dopa
Dopa decarboxylase
OH
OH
CH2-CH2-NH2
Dopamine
Dopamine β-hydroxylase
OH
OH
NOR-gd
HO-CH-CH2-NH2
Phenyl ethanolamine N-methyl transferase
OH
OH
Ad
CH-CH2-NH-CH3

STORAGE AND RELEASE OF NEUROTRANSMITTERS

The Noraadrenaline formed in the nerve endings remains stored in vesicles in the form of ATP complex. Noradrenaline stored in vesicles (2-5nm diameter) diffuses out in the cytoplasm and gets methylated into Adrenaline. Adrenaline then enters into chromaffin granules and gets stored. These neutrotransmitters will release only when there is increase in the permeability of the nerve terminal membrane to Ca^{+2} because of an action potential. This process causes release of Ca^{+2} which in turn helps in fusion of the vesicles resultting in exocytosis of the vesicles and releases neurotransmitters.

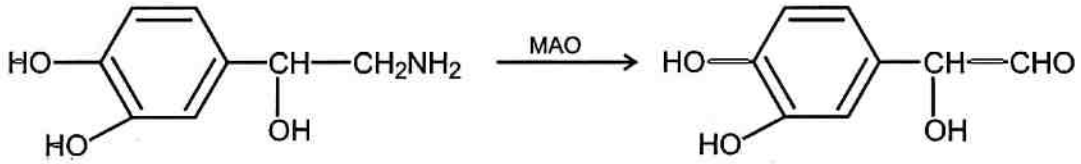
CATABOLISM OF CATECHOLAMINES

The actions of catecholamines can be terminated throuugh catabolism or metabolic transformation. In this process, the particular enzymes changes the structure of the catecholamines so that they do not interact with adrenergic receptors to produce effect. Two major enzymes involved in catabolism are

- Monoamine oxidase (MAO)
- Catechol O-methyl transferase (COMT)

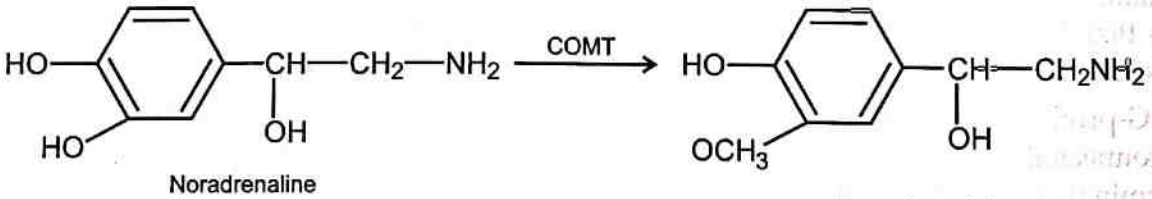
MAO (monoamine oxidase) is present in both intraneurons and extraneurons. Two types of isozymes of MAO are present in CNS and in peripheral tissues i.e. MAO-A and MAO-B.

Monoamine Oxidase (MAO) produces deamination of a variety of catecholamines and phenylethylamines. For example,



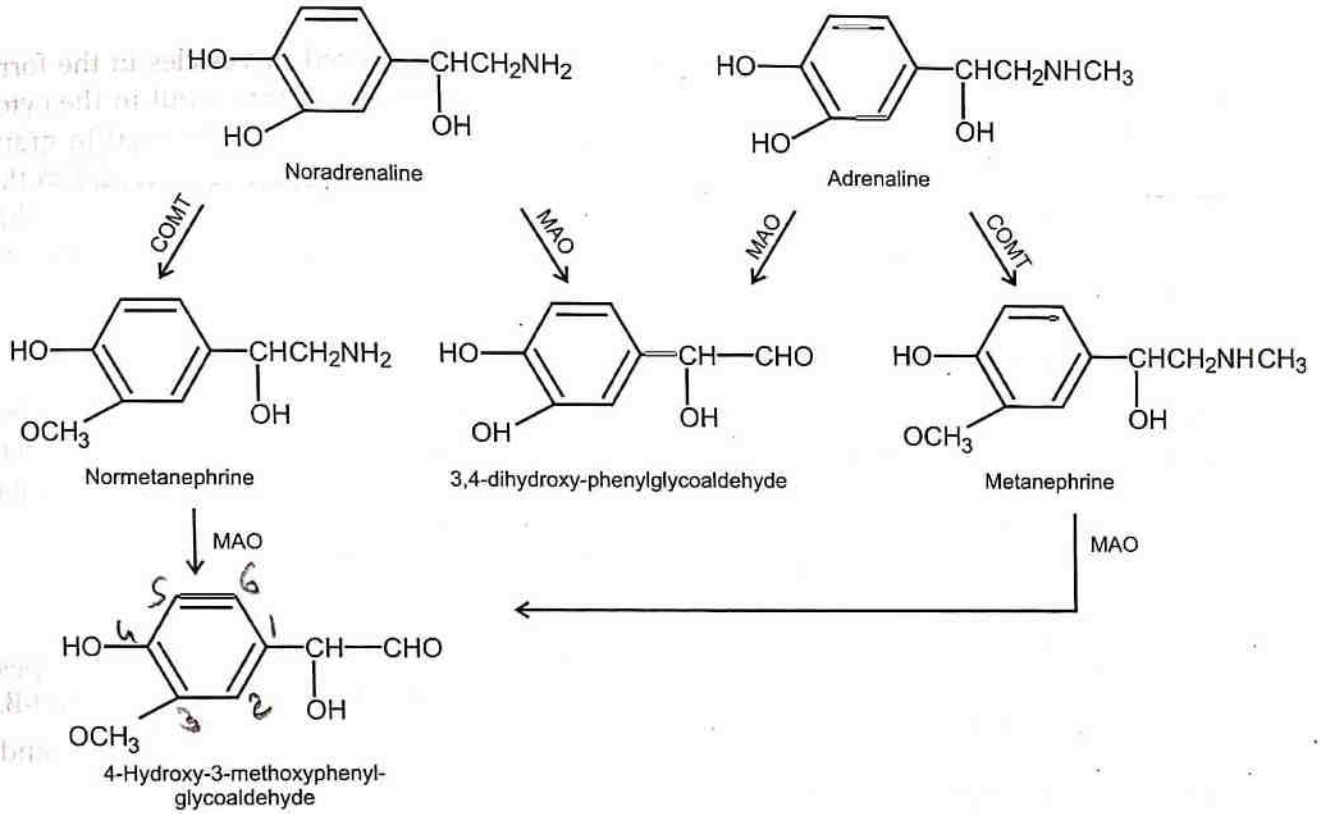
Noradrenaline — 3,4-dihydroxyphenyl glycoaldehyde

COMT (Catechol-O-Methyltransferase) is a cytoplasmic enzyme and causes methylation of 3-hydroxyl group of catechol ring of the neurotransmitter with the help to the isoenzyme S-adenosylmetthionine and makes the neurotransmitters inactive.



Noradrenaline — Normetanephrine

Catabolism can be summarised as :

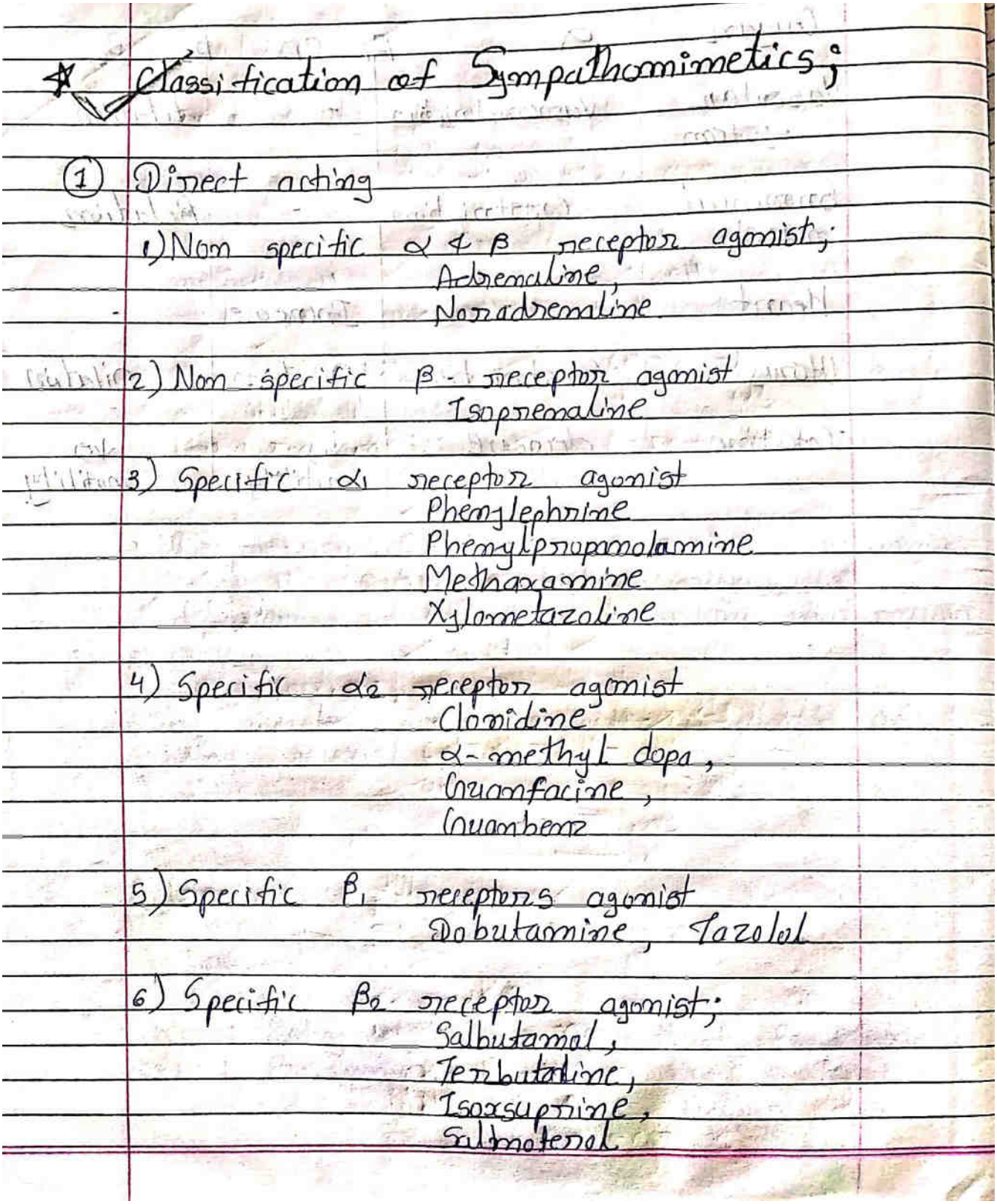


Reuptake of catecholamines:

Noradrenaline thus released acts on α - adrenoceptors to produce its effects. Majority of its action is terminated by the *uptake mechanism*. The act of noradrenaline being taken back from the synaptic cleft to the neurone is uptake$_1$ or *neuronal uptake*. From the neurone, noradrenaline is also taken back into synaptic vesicles and is stored as usual. This is *granular uptake*. Besides neuronal and granular uptake, the transmitter may be circulated and is taken up by other organs like spleen, heart etc. This is reffered to as uptake$_2$ or *Extraneuronal uptake*.

Q. 24 Write a short note on sympathomimetics.

Sympathomimetics are the drugs which mimic action of sympathetic nervous system.



* Classification of Sympathomimetics;

(1) Direct acting

1) Non specific α & β receptor agonist;
   Adrenaline,
   Noradrenaline

2) Non specific β - receptor agonist
   Isoprenaline

3) Specific α1 receptor agonist
   Phenylephrine
   Phenylpropanolamine
   Methoxamine
   Xylometazoline

4) Specific α2 receptor agonist
   Clonidine
   α-methyl dopa,
   Guanfacine,
   Guanbenz

5) Specific β1 receptors agonist
   Dobutamine, Tazolol

6) Specific β2 receptor agonist;
   Salbutamol,
   Terbutaline,
   Isoxsuprine,
   Salmeterol

PAGE :
DATE : / /

(2) Indirect acting ;

1) Increase release of nor, adrenaline ;
Ephedrine ;
Amphetamine
Tyramine

2) Inhibit uptake 1 ;
Cocaine ,
Desipramine

3) Inhibit uptake 2 ;
Corticosteroids

4) MAO inhibitors ;
Pargyline ,
Phenelzine
Isocarboxazide

5) COMT inhibitors ;
Pyrogallol
Tropolone derivatives ,

(3) Mixed acting ;

Increase release of noradrenaline ;
Ephedrine ,
Amphetamine ,
Tyramine ,

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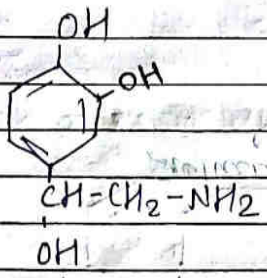
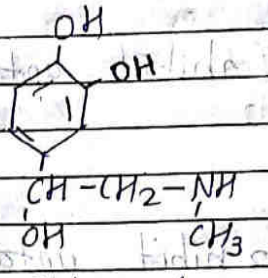
Structures;

- Direct acting

i) Non specific α & β receptor agonist

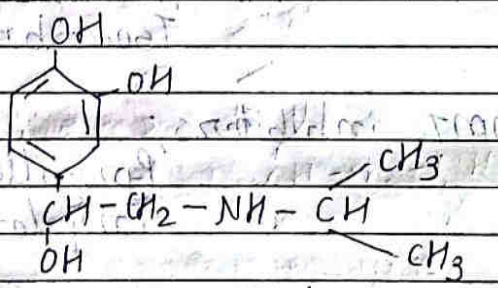


Noradrenaline



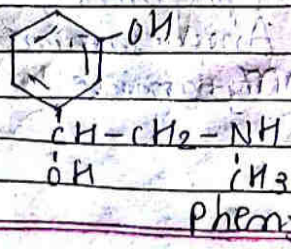
Adrenaline

ii) Non specific β - receptor agonist



Isoprenaline

iii) Specific α receptors agonist



Phenylephrine

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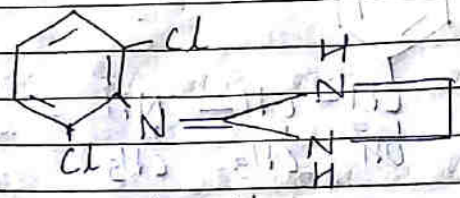
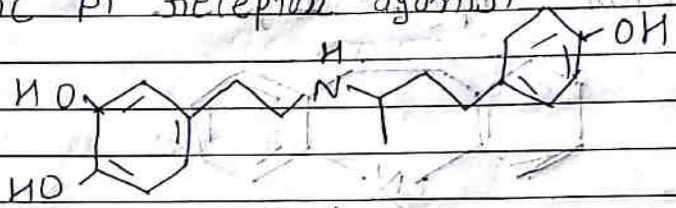
iv) Specific α_2 receptor agonist



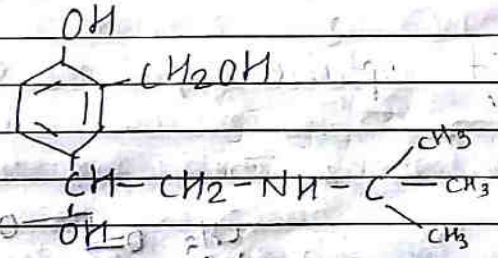
Clonidine

v) Specific β_1 receptor agonist



Dobutamine

vi) Specific β_2 receptor agonist;



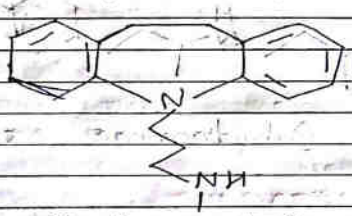
Salbutamol

- Indirect acting

i) Increase release of endogenous adrenaline;

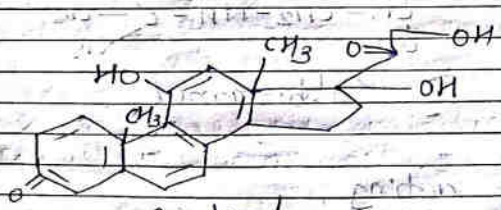
Ephedrine

ii) Inhibit uptake 1 ;



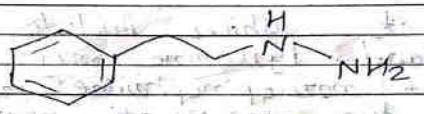
Desipramine

iii) Inhibit uptake 2 ;



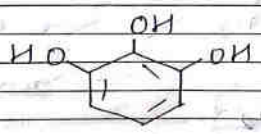
Cortisol
(Hydrocortisone)

iv) MAO inhibitors ;



Phenelzine

v) COMT inhibitors ;



Pyrogallol

* Mechanism of action of Sympathomimetics:

=> MOA of Directly acting sympathomimetics:

- Drugs of this class act directly on α or β receptors producing effects similar to those that occur by stimulation of sympathetic nerves or release of adrenaline from adrenal medulla.

=> MOA of Indirectly acting sympathomimetics:

- Drugs of this class don't act directly on α or β receptors. They can't bind with these receptors.
- They produce sympathomimetic effect by enhancing availability of NOR-adr to its receptors by following mechanisms.

i) By enhancing release of NOR-adr. eg. Ephedrine, Tyramine

ii) By blocking NOR-adr uptake (Uptake-1 & Uptake-2).

eg. Uptake-1 blockers → Cocaine, Desipramine
Uptake-2 blockers → Corticosteroids

iii) By blocking enzymes (MAO & COMT) responsible for NOR-adr metabolism.

eg. MAO-inhibitors ⇒ Pargyline, Phenelzine
COMT-inhibitors → Pyrogallol, Tropolon dvts.

- By these mechanisms, more NOR-adr is available to its receptors for longer duration.

- Uses ;

→ They are used as,

i) As a pressor agent
ii) Cardiasyncope
iii) Local heamostasis
iv) For chromogration of local anaesthetic action
v) As a nasal decongestant
vi) As a antiasthmetic
vii) As utcrine relaxant
viii) Miadriatic
ix) As an anorectics
x) As ~~anathyla~~ anthylaptic shock
xi) CNS stimulants.

→ The drugs which are used for the deaseses are as;

- Adverse effects ;

i) Hypertension
ii) Headache
iii) Cardiac heart failulare
iv) Pupil¢ dilation
v) Peripheral vasodilation
vi) Hypersensitivity including bronchio spasm
vii) Impaired glucose tolerance in diabetice
viii) Dizziness
ix) Vomiting
x) Constipation
xi) Dryness in mouth.

Q. 25 Describe SAR of β-phenylethanolamine.OR Discuss SAR of adrenergic agonist. OR Discuss SAR of sympathomimetics.

SAR OF SYMPATHOMIMETIC AGENTS

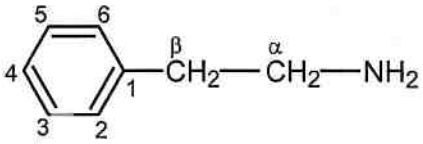
Sympathomimetic drugs are considered as derivatives of β-Phenylethylamine (Parent compound). Structurally, substitution is possible on-

–The aromatic ring

–Substitution on β-carbon

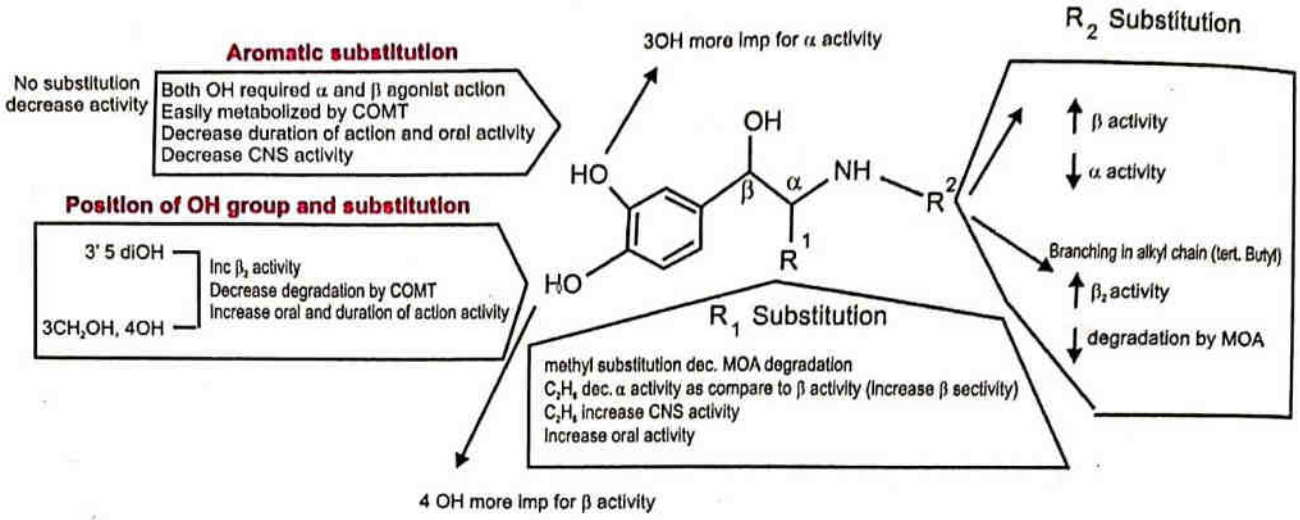
–Substitution on α-carbon

–Substitution on the amino group



β-phenylethylamine (Parent compound)

Graphic representation of Structure Activity Relationship Adrenergic Drugs

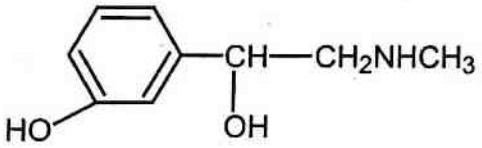


SAR of sympathomimetic drugs can be explained as-

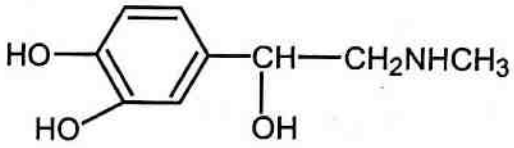
A) Substitution on the Aromatic Ring of β-phenylethylamine

1. The presence of –OH group in the benzene ring at 3 and 4 positions gives maximum α, β activity. If any of these –OH group is absent, the overall potency gets decreased. For example

   Phenylephrine is less potent than adrenaline

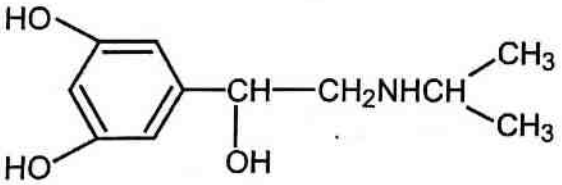


Phenylephrine
(Less potent)

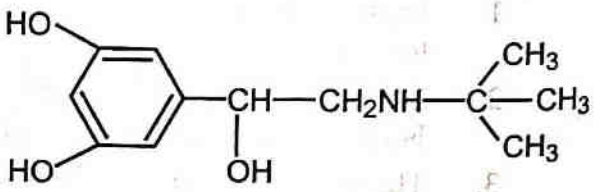


Adrenaline
(More potent)

2. The presence of –OH groups at 3 and 5 position with bulky substituents on the amino nitrogen gives β_2 selective drug. For example, Orciprenaline and Terbutaline relaxes bronchial muscles without effecting cardiac muscles.

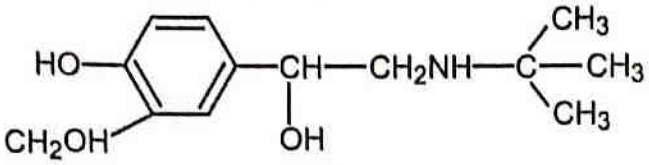


Orciprenaline



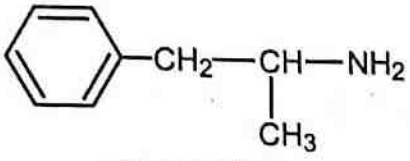
Terbutaline

3. Drugs having substituents other than –OH group have greater selectivity for adrenergic receptors. For example Salbutamol is β_2-selective.

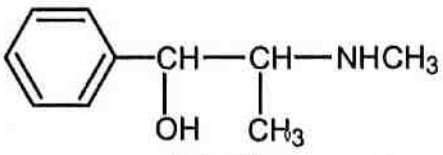


Salbutamol ($\beta_2$selective)

4. The unsubstituted or alkyl substituted adrenergic amines easily crosses the blood brain barrier and have more CNS activity. For example, Amphetamine & Ephedrine.



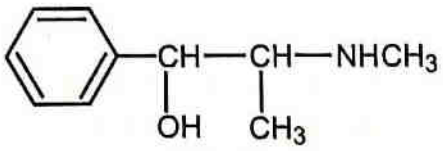
Amphetamine



Ephedrine

B) Substitution on the β-carbon :

A –OH group on the β-carbon decreases the central stimulant action due to lower lipid solubility of the drug (OH gives polar effect). This increases agonist activity of the drug at α and β receptor. For example, Ephedrine has less central stimulant effect than amphetamines but more bronchial dilating effect.



Ephedrine

C) Substitution on the α-carbon :

Drugs having substituents on the α-car.bon blocks the metabolism (deamination) caused by MAO and hence these have longer duration of action. For example Amphetanime resists degradation by MAO.

D) Substitution on the amino group :

1. Lesser the substitution on the amino group, higher will be selectivity for α-receptors. For example, adrenaline is highly α-selective than noradrenaline.
2. More the size of alkyl substituent, higher will be β-selective action. For example, Isoprenaline, terbutaline and Salbutamol have selective β_2-activity.
3. The phenylring must be separated from the side chain amino group by two carbon atoms.

Q. 26 Write a note on sympatholytic agent.

Sympatholytics are the drugs which block or antagonize the action of sympathetic nervous system.

☆ Sympatholytics ;

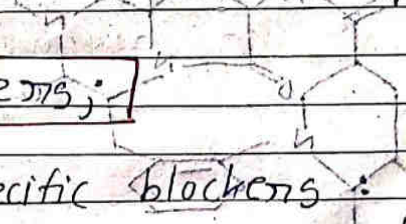
- Classification ;

(1) α - blockers ;

i) Non specific blockers ;
   a) Ergot alkaloid : Ergotamine, Ergotoxine, Ergocrystine
   b) Haloalkyl amine derivatives : Phenoxybenzamine, Diamine
   c) Imidazole derivatives Phentolamine Tolazoline

ii) Specific α1 - blockers : Prazosin, Terazosin, Doxazocin

iii) Specific α2 - blocker : Yohimbine, Rauwolscine



(2) β - blockers ;

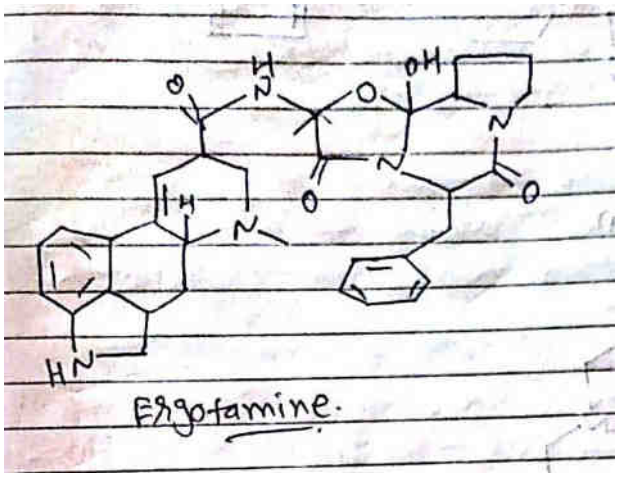
i) Non specific blockers : Propranolol, Bisoprolol, Timolol, Sotalol

ii) β_1 blockers : Atenolol, Metoprolol
Ritodrine

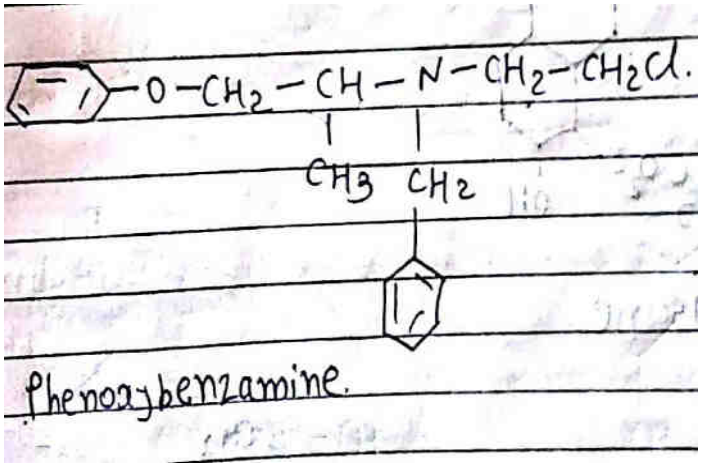
iii) β_2 - blockers : Butoxamine,
α-methyl propranolol

(3) Mixed or α/β blockers;
Labetalol,
Carvedilol

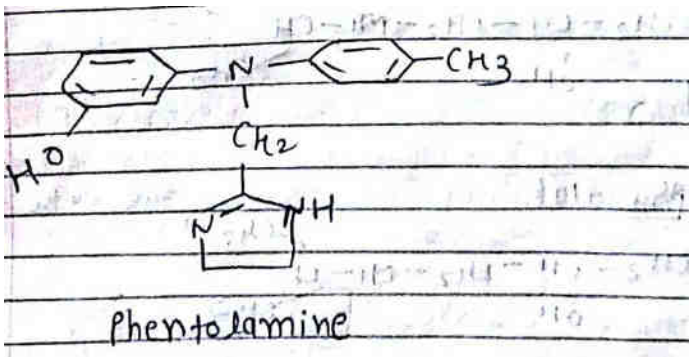
(4) Adrenergic neuron blockers : Bretylium
Guanethidine



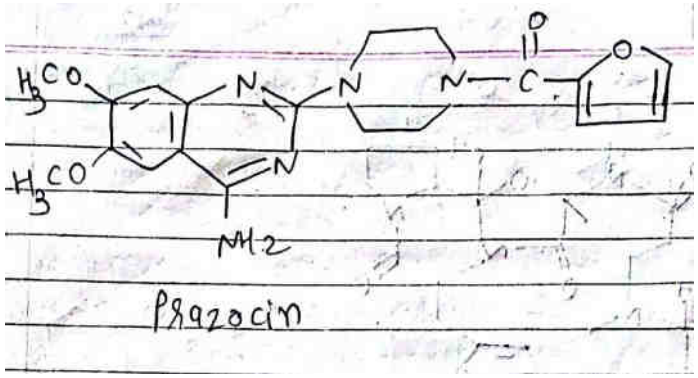
Ergotamine.



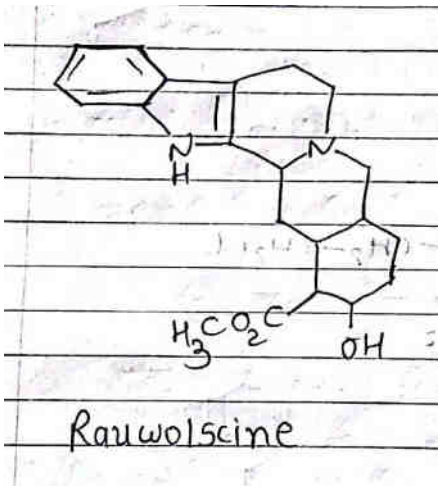
Phenoxybenzamine.



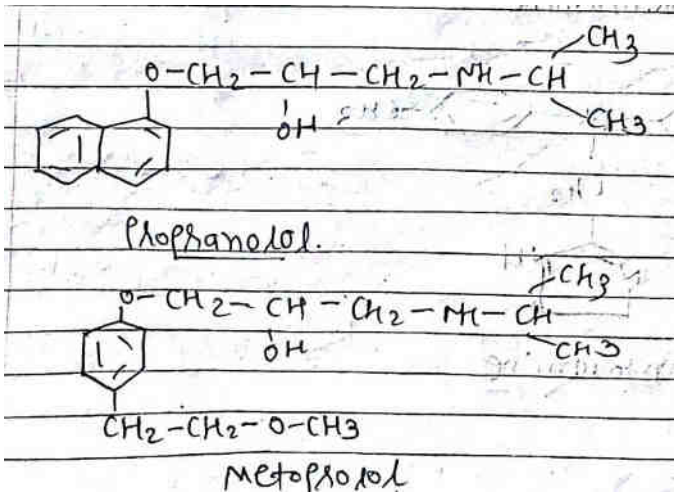
Phentolamine



Prazocin

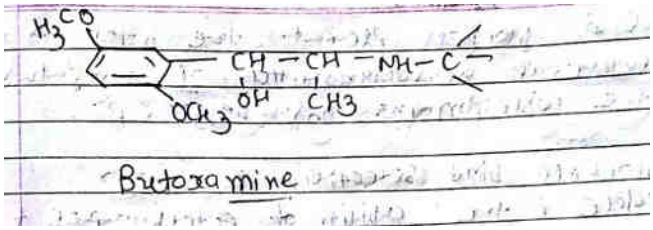


Rauwolscine

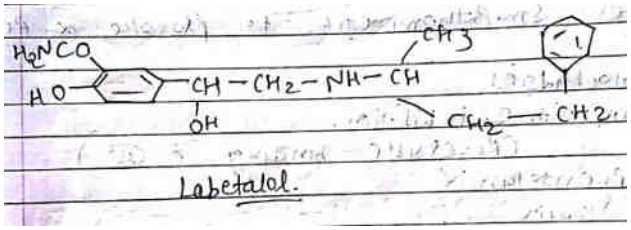


Propranolol.

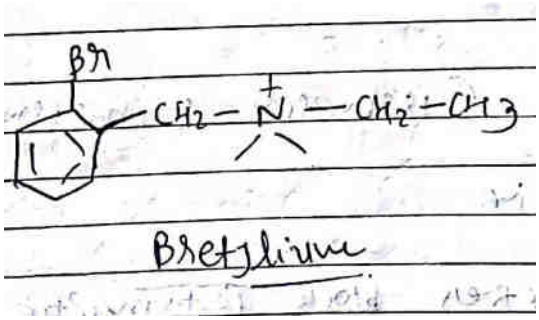
Metoprolol



Butoxamine



Labetalol.



Bretylium

MOA :

① Conformational changes which
↓
flow of ions.
↓
blocking effect

② Most of sympathalytic drug postsynaptically action.
↓
Ad. & Noradr.
↓
Signaling pathway block

Exception ; α_2 → Presynaptically
α_1, β_1, β_2, β_3 → Postsynaptically

(3) Neuron blocker likes bretylium & guanethidine → block release of catecholamines.

(4) Reserpine block
↓
storage of catecholamine
↓
by VMAT (Vasicular monoamine transporter).

Uses & Adverse effect

α - blockers :

Use : → Hypertension
→ ~~Phenom Tyrobromocytoma~~ Pheochromocytoma
→ Peripheral vascular diseases
→ Migraine
→ Post partural haemorrage
→ Aiding ~~in~~ from uterus
→ Uterine constraction after surgery
→ Abortion after third trimester

Adverse effect :
Ergot : Nausea, vomiting, diarrhea, confusion, dizziness, headache
Common : Miosis, Postural hypotension, peptic ulcer, depression, ~~reflex~~ reflux tachycardia.

β-blockers :

Use : → Hypertension
→ Angina ~~pectoris~~ Pectoris
→ ~~Phiobromicithoma~~
→ Glaucoma
→ Anxiety
→ Alcoholism
→ Heroine addiction
→ Arrhythmia

Adverse effect : → Bronchoconstriction,
→ Cardiac failure
→ sudden hypotension,
→ Bradycardia,
→ Constipation, nausea,
→ Vomitting
→ Hypoglycemia
→ Fatigue
→ cold extrimities

Q. 27 Write SAR of β-blockers. Give synthesis of Propranolol.

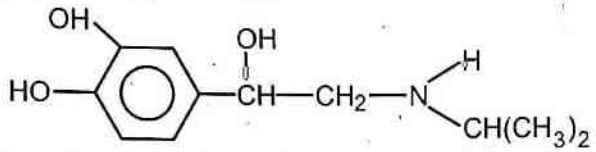
SAR of β-blockers

β-blockers are classified according to structure into two classes-

i) Arylethanolamines
ii) Aryloxypropanolamines

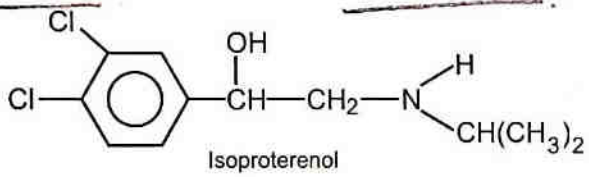
SAR of arylethanolamines :

Basic drug in this category is Isoproterenol



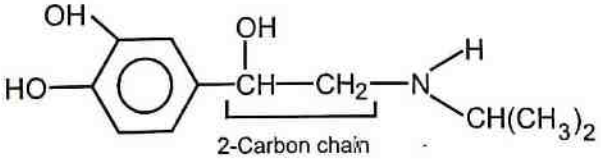
Various modifications have been made to the structure of Isoproterenol these are :

1) Phenolic –OH groups are important for agonist activity. Replacement of 4–OH group by other groups leads to removal of agonist activity and will make the compound antagonist. For example, replacement of catechol–OH groups by chlorine gives dichloroisproterenol, which is the first useful β-blocker.



Isoproterenol

2) The two carbon side chain is required for the activity. It cannot be decreased or increased i.e. two carbon chain must be there is should not be less than and more than two.

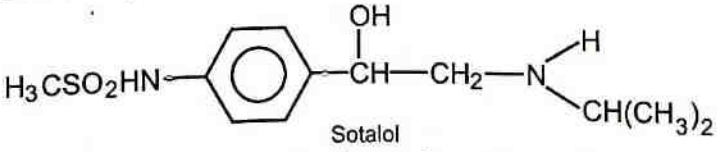


2-Carbon chain

3) Small substituents on N produces α-activity, for β-activity larger groups must be substituted on 'N'. Various substitutions on 'N' are as follows :

a) N,N-disubstituted compounds are inactive.
b) Phenylethyl, hydroxy-phenylethyl groups when added to 'N' maintains the β-blocker activity.
c) Cyclic alkyl substitution provides better pharmacological activity than open chain substituents at 'N' atom of amine.
d) Alpha methyl substitution decreases the activity.

4) p-OH group on the phenyl ring can be replaced by methylsulphonamide to increase the activity. For example, Sotalol

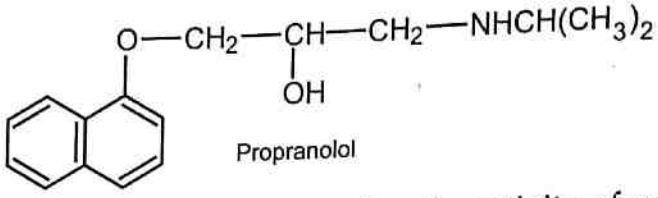


Sotalol

p-OH group on phenyl ring can also be replaced by nitro group to produce good activity.

SAR OF ARYLOXY PROPANOLAMINES :

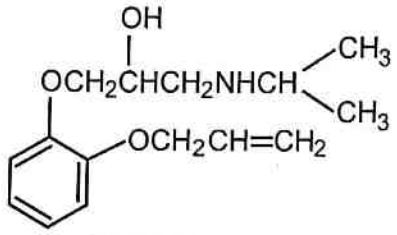
Prototype drug in this category is -Propranolol which is a potent β-antagonist.



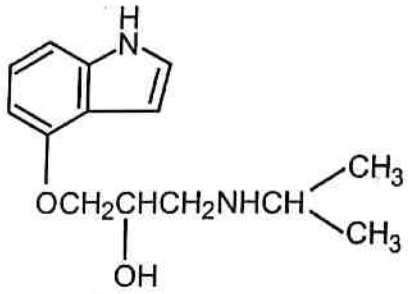
Propranolol

Various modifications have been made to alter the activity of aryloxypropanolamines. These are as follows :

1. The –OCH_3 group is placed between the aromatic ring and the ethanolamino side chain, which is essential for the activity.
2. Most of the derivatives have substitued phenyl rings in place of naphthyl ring. These aryl rings are of different types like phenylether ring in oxprenolol, naphthalene (propranolol), indoles in (Pindolol)

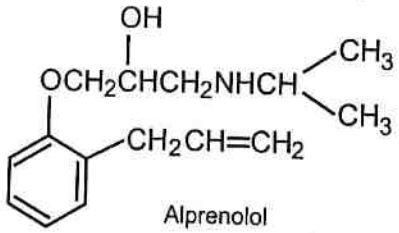


Oxprenolol



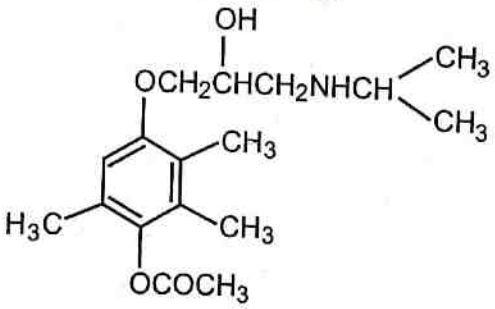
Pindolol

3. Alkenyl and alkenyloxy groups when present in the ortho positions on phenyl ring, gives good β-antagonist activity. For example, Oxprenolol and Alprenolol



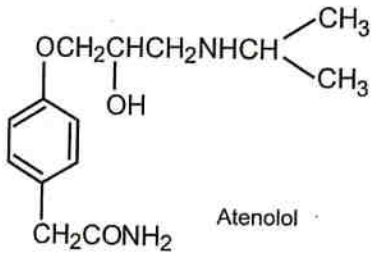
Alprenolol

4. Substitution of –CH_3, –OCH_3, –NO_2 groups on the phenyl ring generally done at 2 and 3 positions and if occur at 4-position it is least favoured. For example, Metipranolol

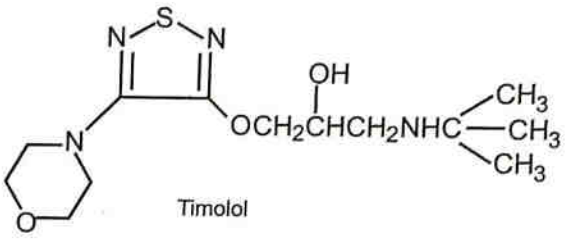


Metipranolol

5. Isopropyl and t-butyl groups present on the amino group provides nucleophilicity to the amino group, hence most favoured. For example, Atenolol and Timolol



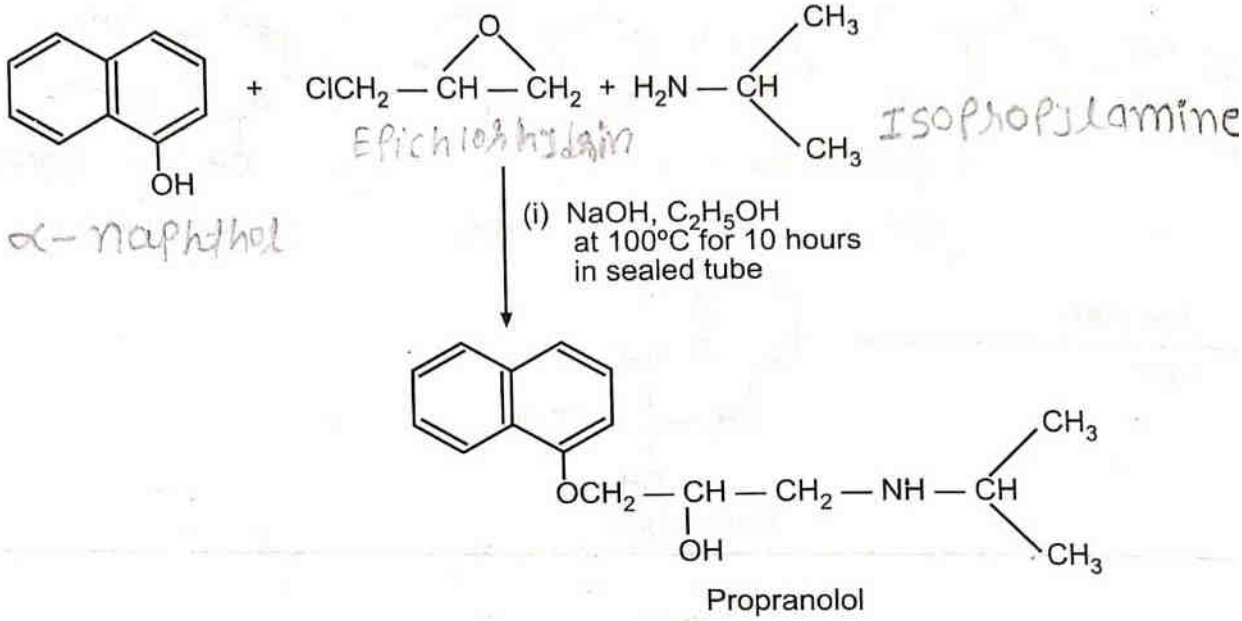
Atenolol



Timolol

Synthesis of Propranolol:

(e) Propranolol :



Propranolol

Q. 28 Classify General anesthetics and give synthesis of Halothane.

Classification of General anaesthetics:

i) Based on chemical basis
ii) Based on physical state basis
iii) Based on route of administration

1) Based on chemical basis;

a.) Hydrocarbon : Cyclopropane
Ethylene

b.) Halogenated hydrocarbon; Halothane
Chloroform
Trichloroethylene
Enflurane
Sevoflurane
Methoxyflurane
Desflurane,
Isoflurane

c.) Ethers :
Diethyl ether
Divinyl ether

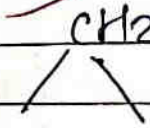
d.) Alcohol :
Trichloro ethanol

e) Ultra short acting barbiturates;
Thiopenta sodium
Methohexital sodium

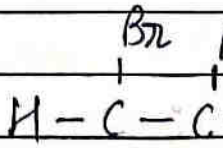
f) Miscellaneous:

- Nitrous oxide
- Ketamine - HCl
- Propanidid
- Propofol
- Diazepam

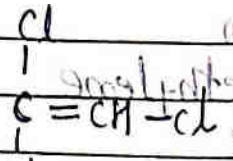
} Practically used.



Cyclopropane



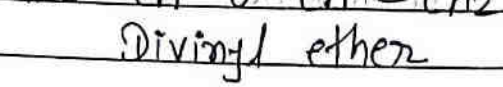
Halothane



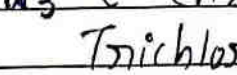
Trichloro-ethylene

$CHCl_3$

Chloroform



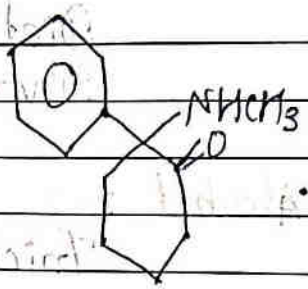
Divinyl ether



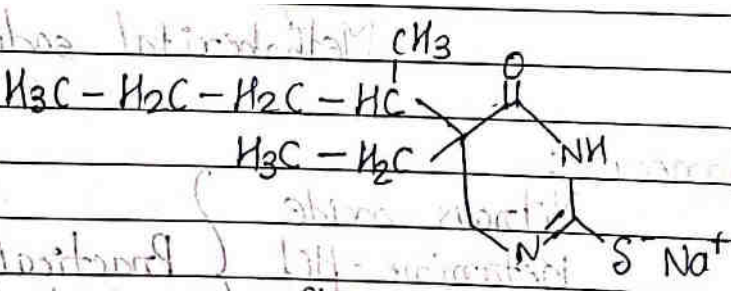
Trichloro ethanol

N_2O

Nitrous oxide



Ketamine · HCl



Thiopentyl sodium

2) Based on Physical state;

a.) Gaseous :
- Nitrous oxide
- Cyclopropane

b) Volatile :
- Ether,
- Chloroform
- Trichloro ethylene
- Halothane
- Divinyl ether

c) Non volatile :
- Ultra short acting barbiturates
- Ketamine
- Propemidid

3) Based on route of administration;

i) Inhalational anaesthetics;

a) Gaseous : Nitrous oxide

b) Liquid - : ether
Halothane
Enflurane
Desflurane
Sevoflurane
Methoxyflurane
Isoflurane.

ii) Intravenous anaesthetics;

a) Inducing agents : Thiopenta sodium
Propofol
Methoxital sodium.

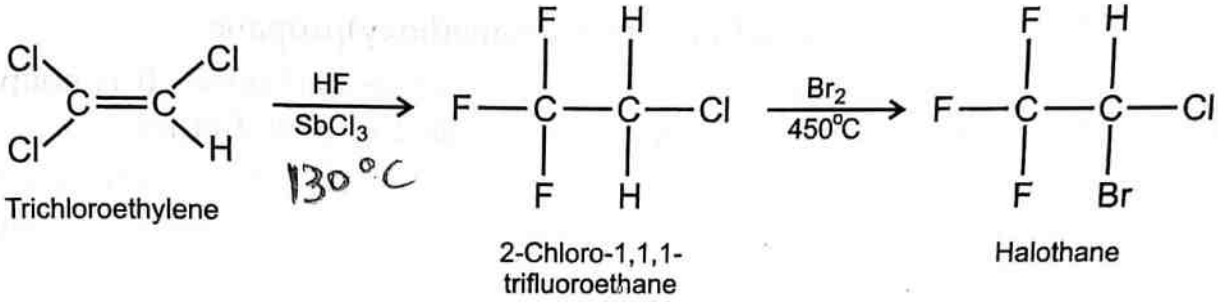
b) Slow acting drug;

i) Benzodiazepine : Diazepam
Chlorzepam

ii) Dissociative anesthetics : Ketamine

iii) Neuroleptic analgesia : Fentanyl + Domperidone.

Synthesis of Halothane:



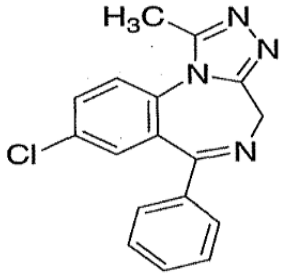
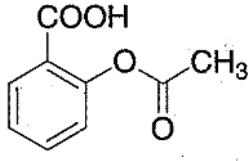
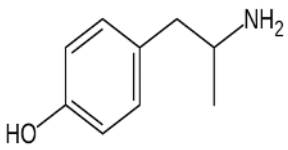
Trichloroethylene

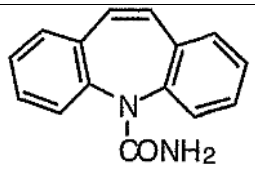
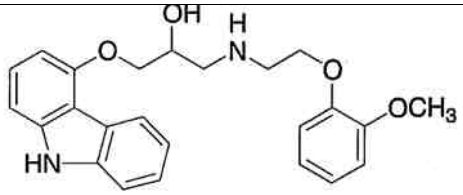
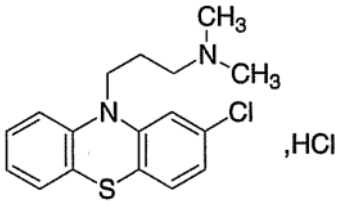
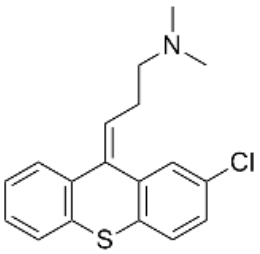
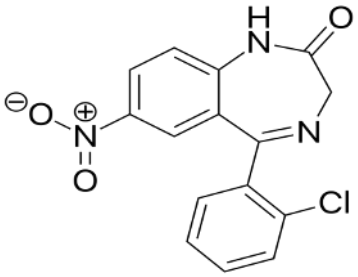
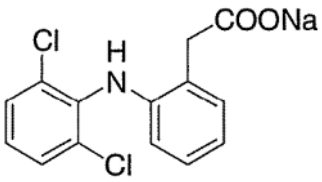
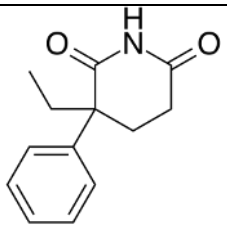
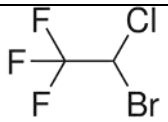
2-Chloro-1,1,1-trifluoroethane

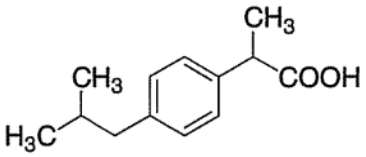
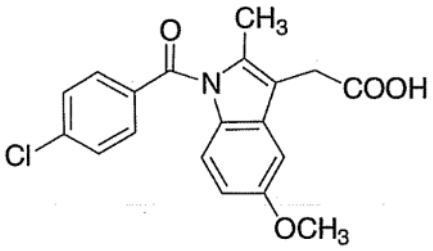
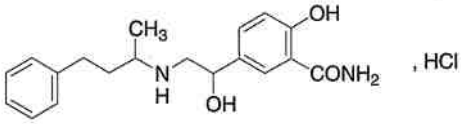
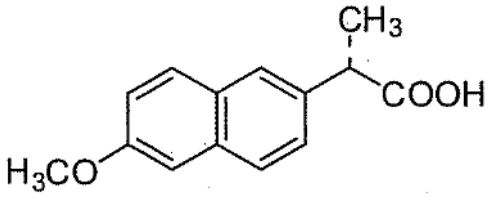
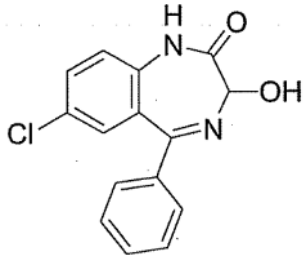
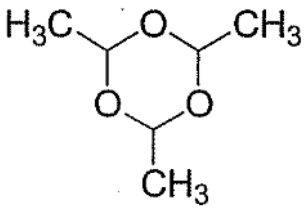
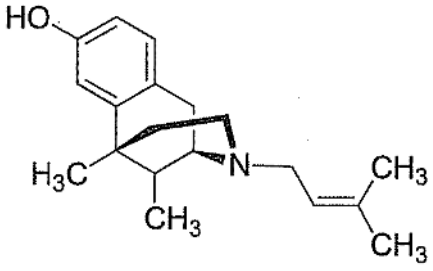
Halothane

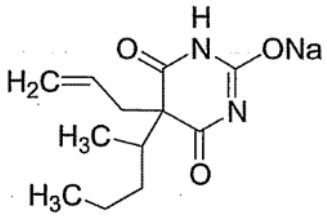
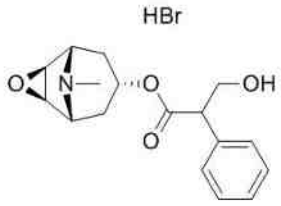
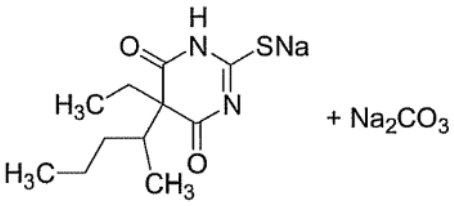
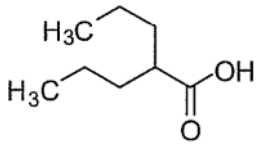
Q. 29 Write structure and IUPAC name of following: (Each carries 1 or 2 marks).

1. **Alprazolam**
2. **Aspirin**
3. **Hydroxyamphetamine**
4. **Carbamazepine**
5. **Carvedilol**
6. **Chlorpromazine**
7. **Chlorprothixene**
8. **Clonazepam**
9. **Diclofenac**
10. **Glutethmide**
11. **Halothane**
12. **Ibuprofen**
13. **Indomethacin**
14. **Labetalol**
15. **Naproxen**
16. **Oxazepam**
17. **Paraldehyde**
18. **Pentazocine**
19. **Secobarbital**
20. **Scopolamine Hydrobromide**
21. **Thiopental sodium**
22. **Valproic acid**

Sr. No.	Drug	Structure	IUPAC name
1.	Alprazolam		8-chloro-1-methyl-6-phenyl-4H-1,2,4triazolo[4,3-a] [l,4]benzodiazepine
2.	Aspirin		2-acetoxybenzoic acid.
3.	Hydroxyampheta-mine		4-(2-aminopropyl)phenol

4.	Carbamazepine		5H-dibenz[b,f]azepine-5~carboxarnide
5.	Carvedilol		(RS)-I-(9H-carbazol-4-yloxy)-3[[2-(2-methoxyphenoxy)ethyl]amino] propan-2-ol
6.	Chlorpromazine		2-chloro-10-(3dimethylaminopropyl) phenothiazine hydrochloride
7.	Chlorprothixene		(3E)-3-(2-chlorothioxanthen-9-ylidene)-N,N-dimethylpropan-1-amine
8.	Clonazepam		5-(2-chlorophenyl)-7-nitro-1,3~dihydro ~2H-1,4-benzodiazepin-2-one
9.	Diclofenac sodium		Sodium 2-[(2,6-dicWorophenyl)amino] phenylacetate
10.	Glutethmide		3-ethyl-3-phenylpiperidine-2,6-dione
11.	Halothane		(RS)-2-bromo-2-chloro-1,1,1-trifluoroethane

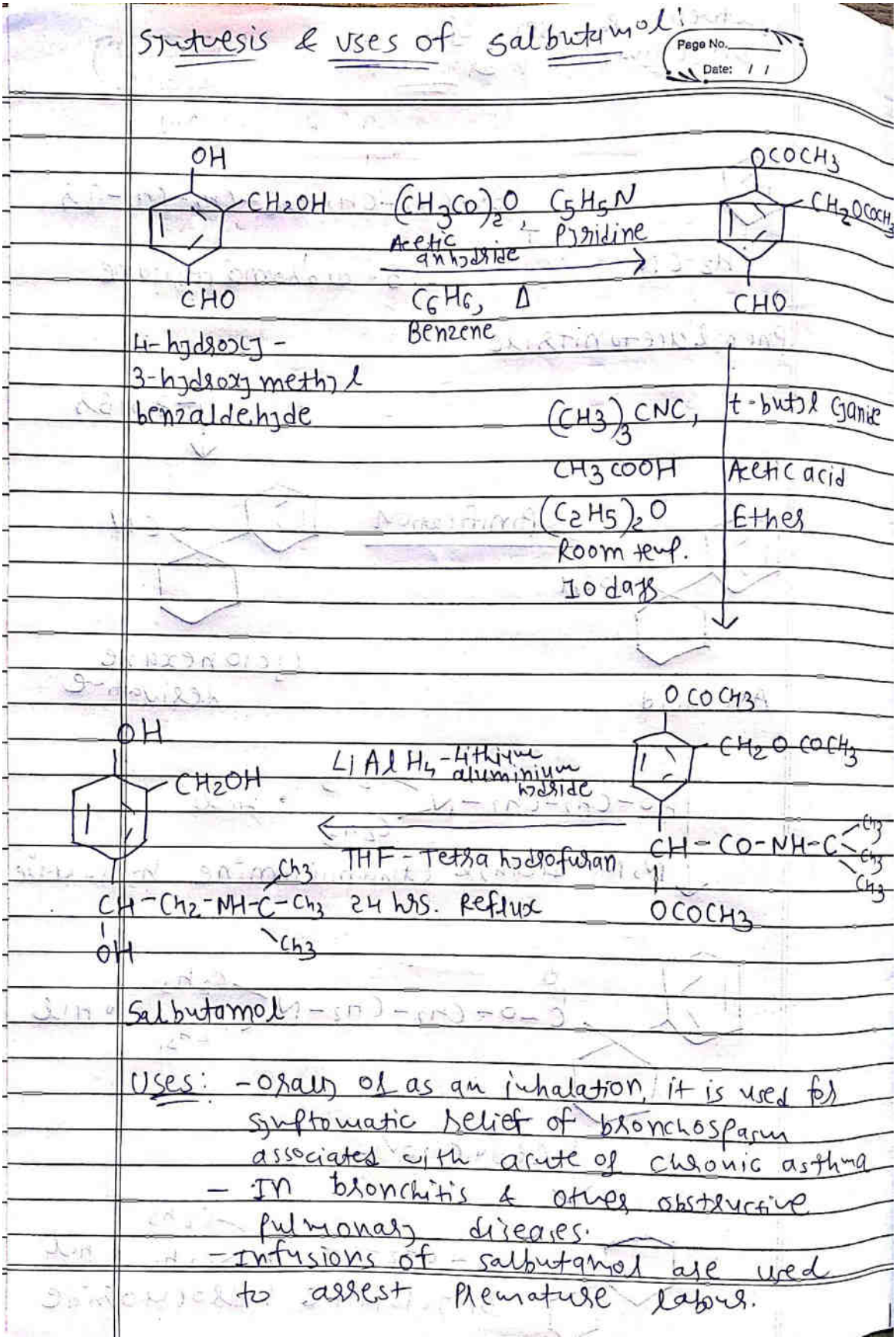
12.	Ibuprofen		(RS)-2-(4-isobutylphenyl)propionic acid.
13.	Indomethacin		1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-ylacetic acid.
14.	Labetalol Hydrochloride		all-rac-2-hydroxy-5- [l-hydroxy2-(1-methyl -3 phenylpropylamino) ethyl]benzamide hydrochloride.
15.	Naproxen		(2S)-2-(6-methoxynaphthalen-2-yl) propionic acid.
16.	Oxazepam		7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H1,4-benzodiazepin-2-one.
17.	Paraldehyde		2,4,6-trimethyl-1 ,3,5-trioxane
18.	Pentazocine		(2RS, 6RS, llRS)-6, II-dimethyl-3-(3-methylbut2-enyl)- 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol

19.	Secobarbital Sodium		sodium (RS)-5-allyl-5-(Imethylbutyl) barbiturate.
20.	Scopolamine Hydrobromide		[(1S,5R)-9-methyl-3-oxa-9-azatricyclo [3.3.1.02,4]nonan-7-yl] (2S)-3-hydroxy-2-phenylpropanoate; trihydrate; hydrobromide
21.	Thiopental sodium		Thiopentone Sodium is a mixture of Sodium(RS)-5-ethyl5-(1-methylbutyl) -2 thiobarbiturate and anhydrous sodium carbonate
22.	Valproic acid		2-propylpentanoic acid

Q. 30 Give the synthesis of following drugs: (Each carries 1 or 2 or 2.5 marks)

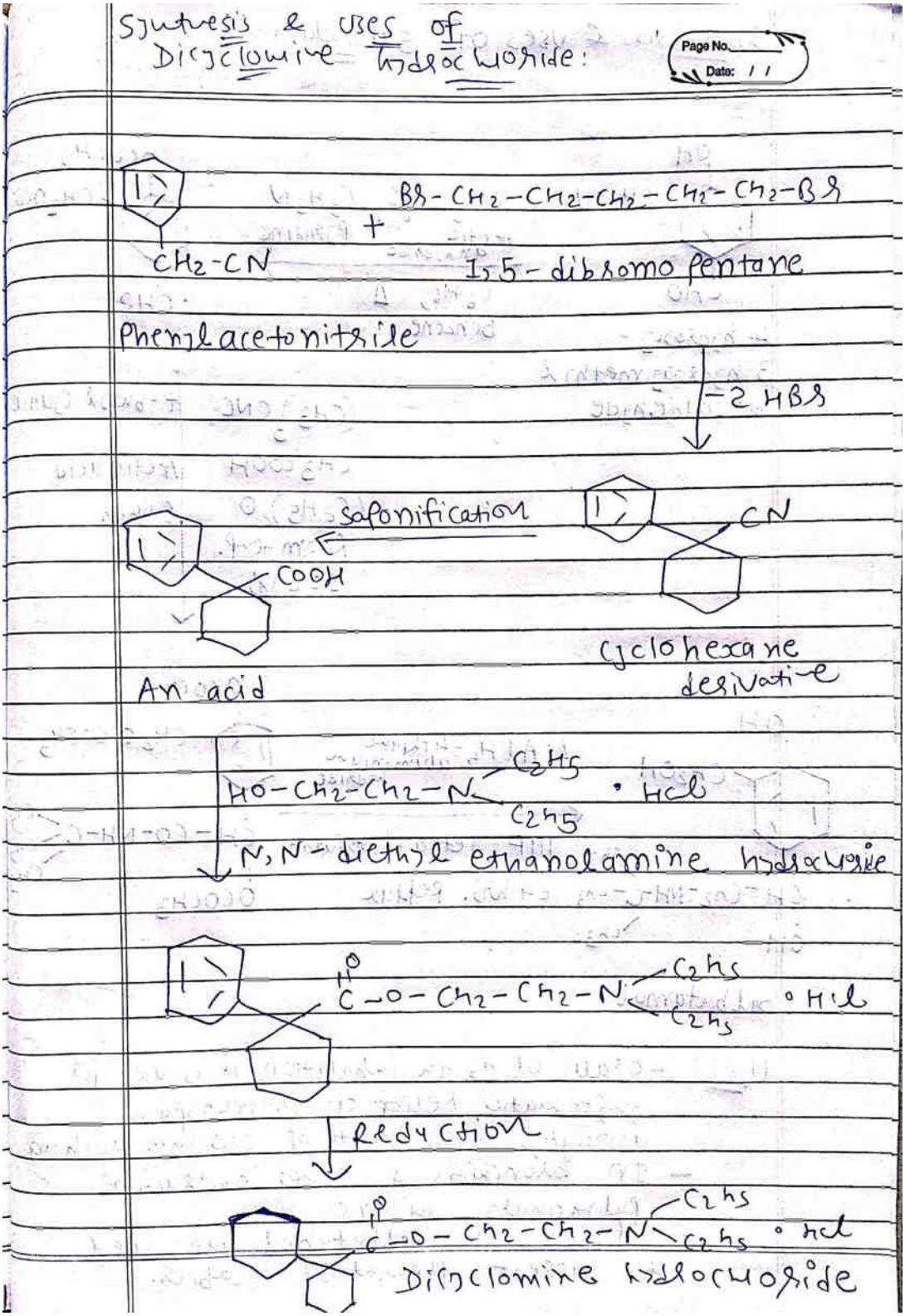
1. **Salbutamol**
2. **Dicyclomine hydrochloride**
3. **Barbital**
4. **Chlorpromazine hydrochloride**
5. **Phenytoin**
6. **Carbamazepine**
7. **Halothane**
8. **Methohexital sodium**
9. **Propranolol**

1. Salbutamol

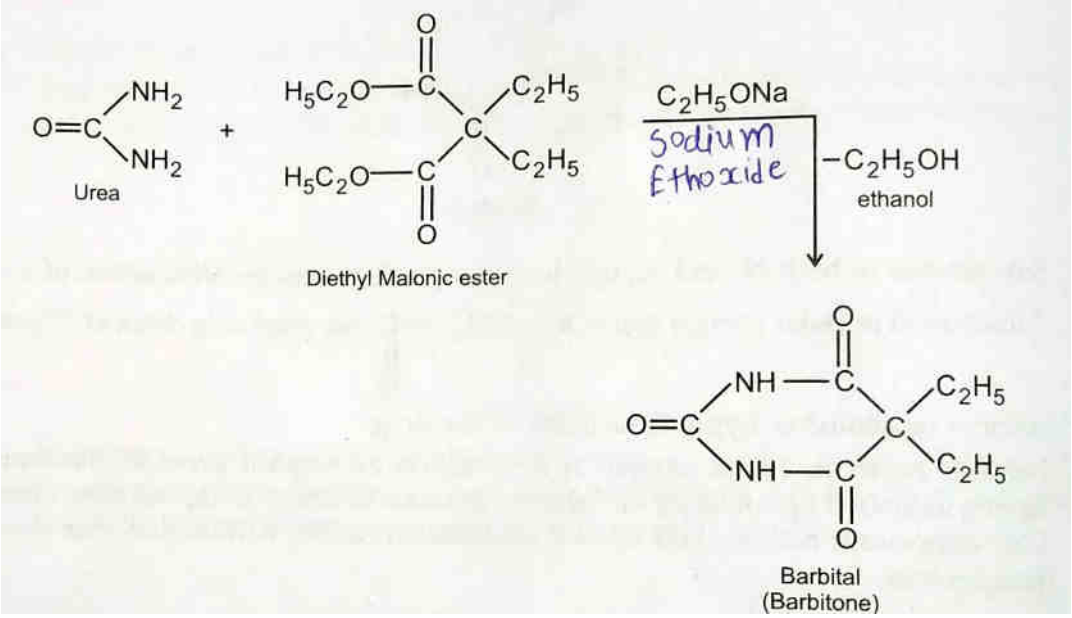


Uses:
- Orally or as an inhalation, it is used for symptomatic relief of bronchospasm associated with acute or chronic asthma
- In bronchitis & other obstructive pulmonary diseases.
- Infusions of salbutamol are used to arrest premature labour.

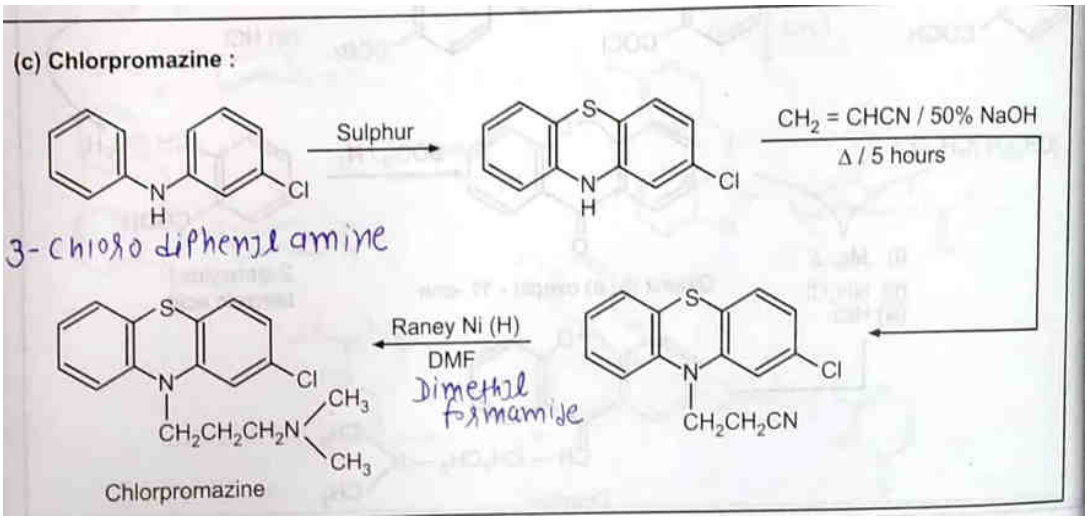
2. Dicyclomine hydrochloride



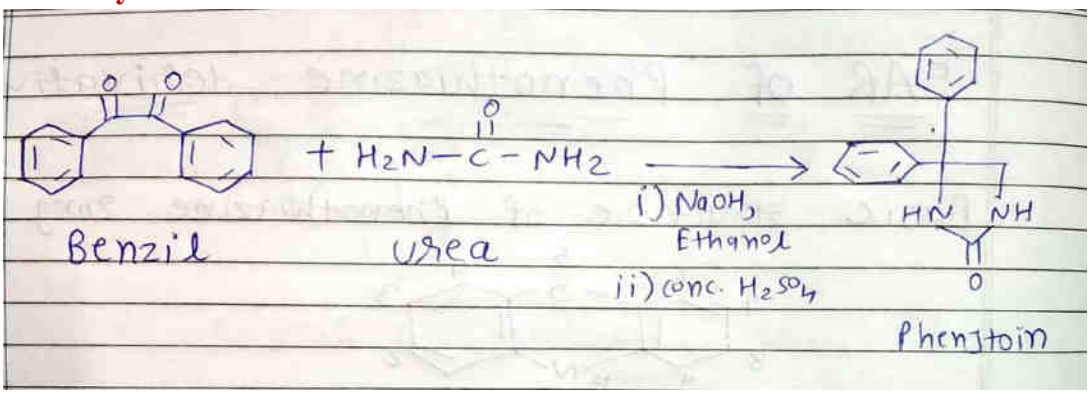
3. Barbital



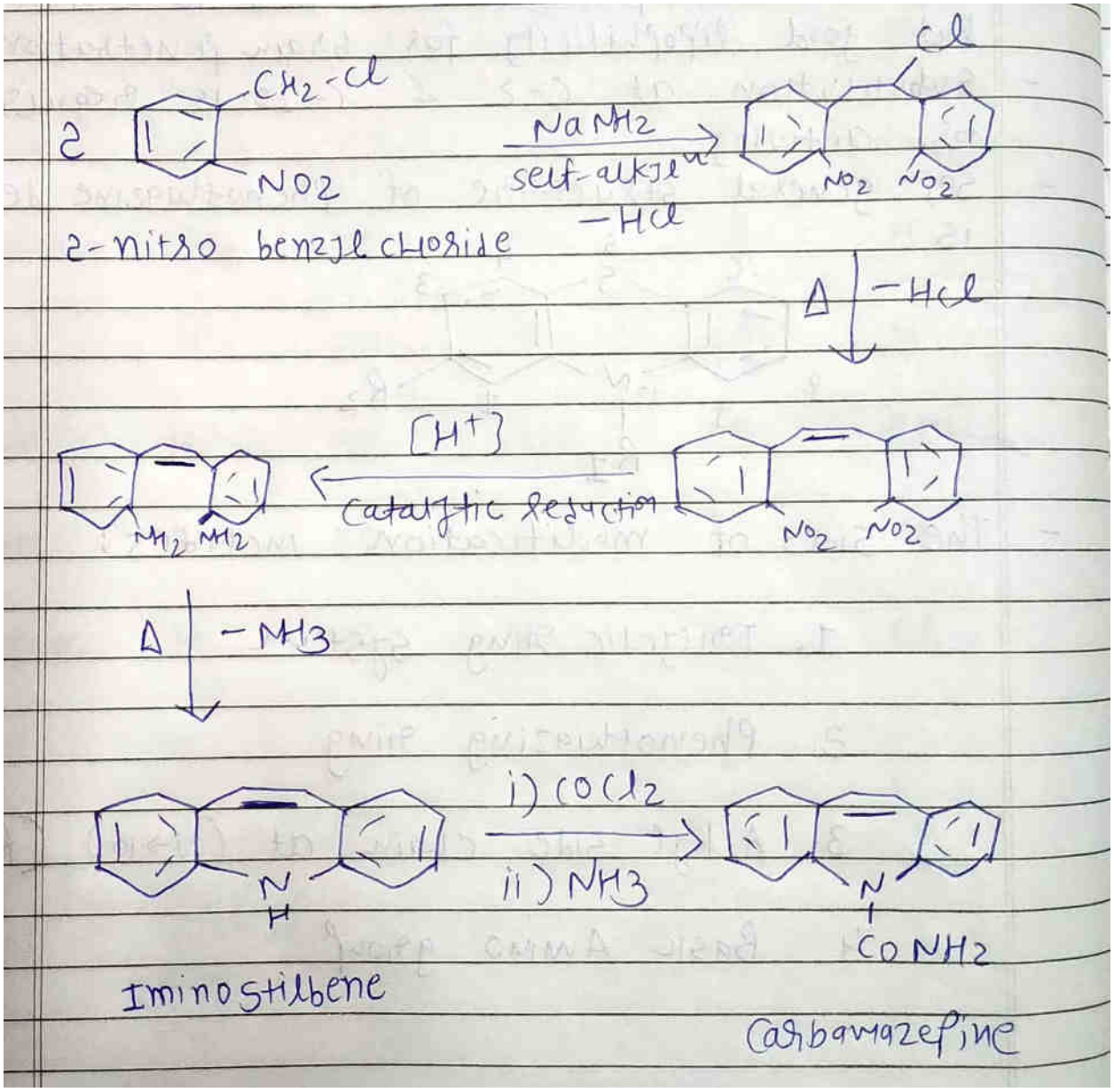
4. Chlorpromazine hydrochloride



5. Phenytoin

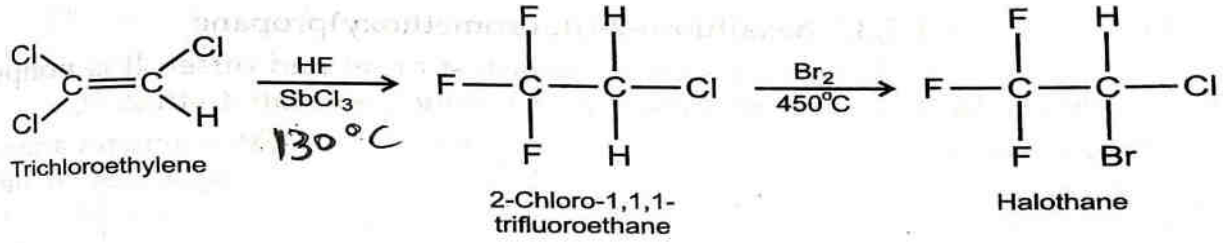


6. Carbamazepine



2 moles of 2-nitro benzyl chloride undergoes self alkylation in the presence of sodium amide. The resulting intermediate undergoes heating, catalytic reduction and then further heating to give iminostilbene. Iminostilbene is first reacted with Phosgene and then with ammonia to get carbamazepine.

7. Halothane

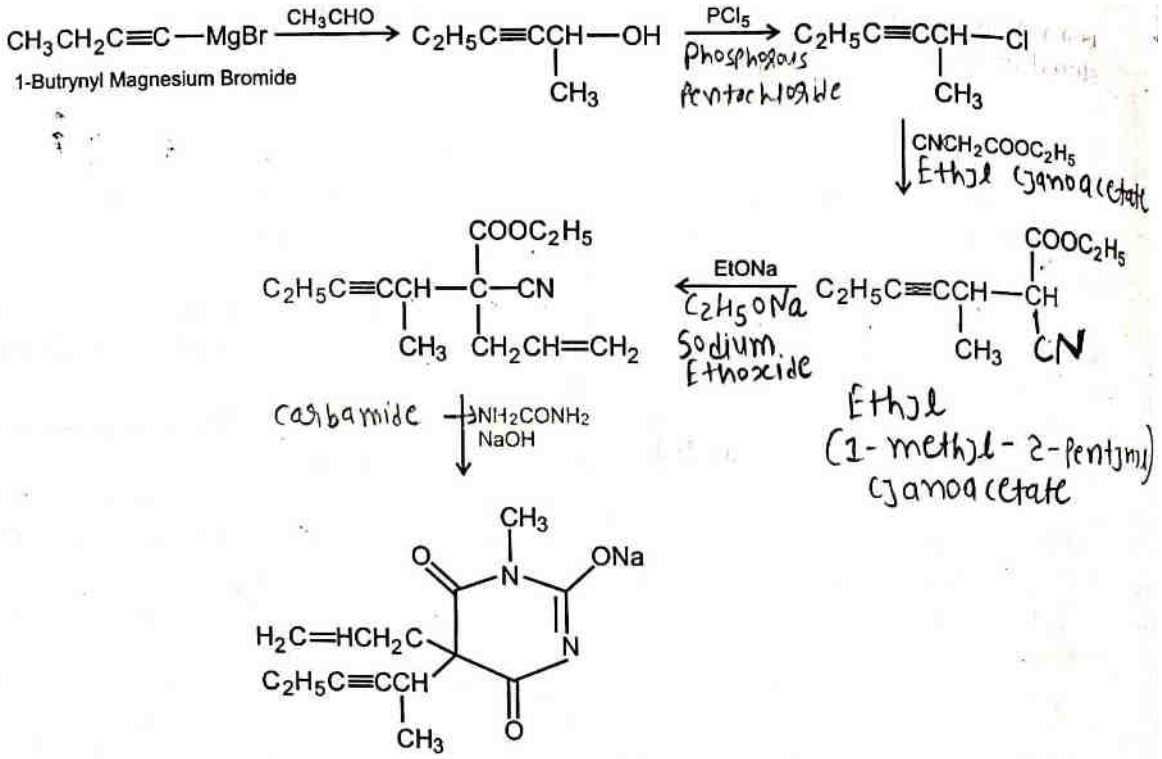


Trichloroethylene

2-Chloro-1,1,1-trifluoroethane

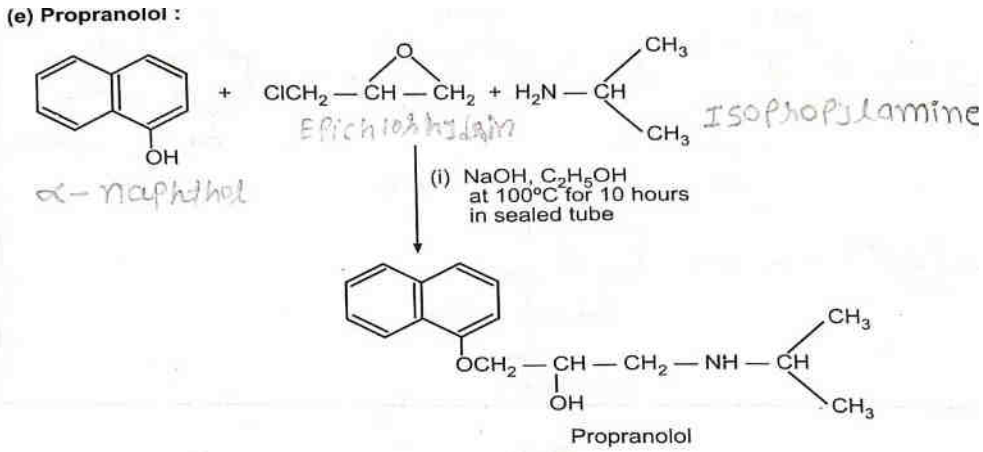
Halothane

8. Methohexital sodium



Methohexital sodium

9. Propranolol



Propranolol