Faculty of Pharmacy

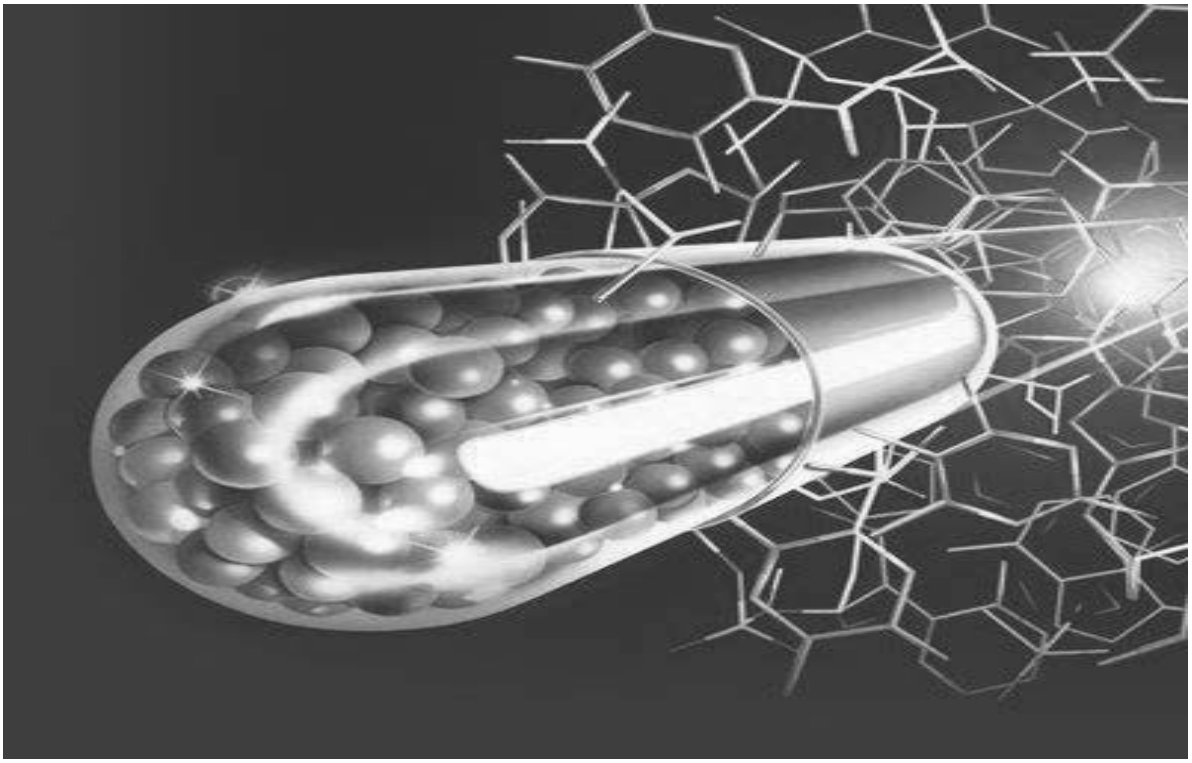
Menoufia University

Pharmaceutical Chemistry

For

Third Year Pharmacy Students

Second Semester



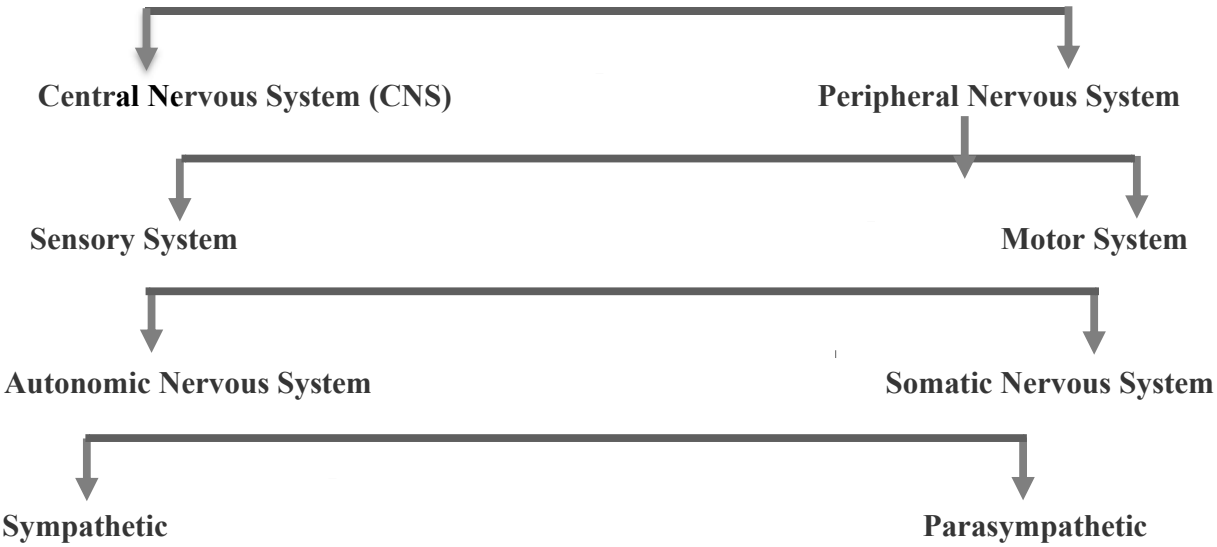
By Staff Members Of

Pharmaceutical Chemistry Department

AUTONOMIC NERVOUS SYSTEM

The drugs which act on the **'autonomic nervous system' (ANS)** and control the vital internal processes which ordinarily, are not under volition, are known as **autonomic drugs**.

Organization of The Nervous System



i) It consists of two classes:

Sympathetic nervous system	parasympathetic nervous system
Chemical mediator: ***Norepinephrine*** **(NEP),** ***Epinephrine*** **(EP) (**adrenal medulla). **"Adrenergic"** term refers to**:** a) **Nerves** that liberate norepinephrine. b) **Organs** that influenced by EP & NEP. c) **Drugs** whose action is similar to EP & NEP. d) **Receptors** stimulated by EP & NEP.	Chemical mediator: ***Acetylcholine*** **(ACH).** **"cholinergic" term refers to:** a) **Nerves** that liberate ACH. b) **Organs** that influenced by ACH. c) **Drugs** whose action is similar to ACH. d) **Receptors** stimulated by ACH.

[I] SYMPATHETIC NERVOUS SYSTEM

Adrenergic receptors:

Receptor type	Site	Action on stimulation
α_1	Vascular endothelium (capillaries)	Vasoconstriction (↑ in blood pressure)
α_2	presynaptically	Self-inhibition of NEP release
β_1	Heart	↑ heart rate & contractility force
β_2	-Bronchial smooth muscles -Blood vessels of SK. Muscles -Uterine wall muscles	-Bronchodilation -Vasodilatation -Muscle relaxation of uterine wall

SYMPATHOMIMETIC AGENTS

Definition: Drugs that mimic the action of sympathetic N.S.

Classification: According to the ***mechanism*** of action:

1] Direct acting agents	Interacts directly with adrenergic receptors.
2] Indirect acting agents	Acts through liberation of NEP from adrenergic nerves terminals.
3] Drugs with **mixed** mechanism	Has direct and indirect action.

CLASSIFICATION

The **autonomic drugs** may be classified into the following categories, namely:

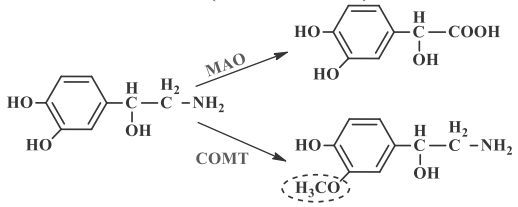
I-Adrenergic Drugs
II-Adrenergic Blocking Agents
III- Parasympathetic Nervous System
IV-Antimuscarinic Drugs.
V-Ganglionic Blocking Agents.
VI- Adrenergic Neurone Blocking Agents.

The above categories of autonomic drugs have been treated separately, including typical examples from each group.

I) ADRENERGIC DRUGS

1] DIRECT ACTING SYMPATHOMIMETICS

Examples: Catecholamines (EP & NEP)



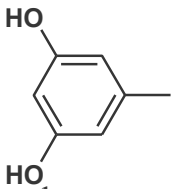
Metabolism:

MAO = monoamine oxidase

COMT = catechol ortho methyl transferase

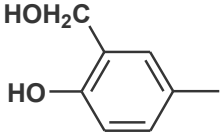
So, EP & NEP metabolized rapidly ***(not used orally)*** How to overcome?

1) Replacement of catechol with resorcinol:



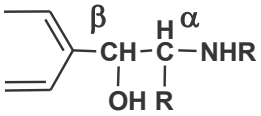
- It is not a substrate to COMT.
- Orally used with longer duration.
- e.g.: Metaprotrenol

2) replacement of **3OH** by hydroxymethyl:



- It is not metabolized by COMT.
- Orally used with longer duration.
- e.g.: Albuterol

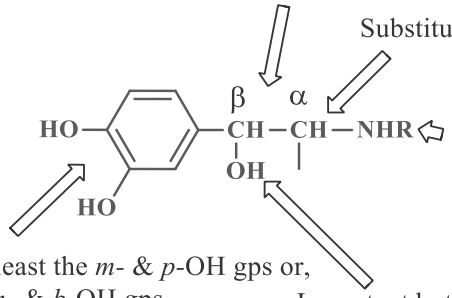
3) Introduction of methyl or ethyl on ***α***-carbon:



- It is not metabolized by MAO.
- Orally used with longer duration.
- e.g.: Isoetharine

SAR:

Distance between catechol gp & NH should be 2C

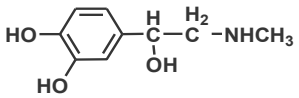
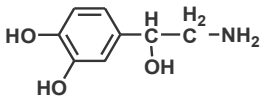
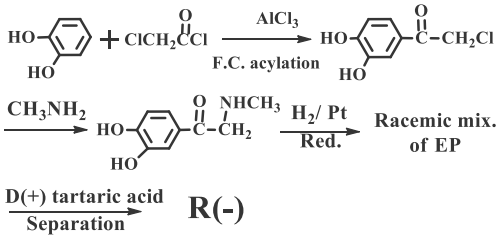
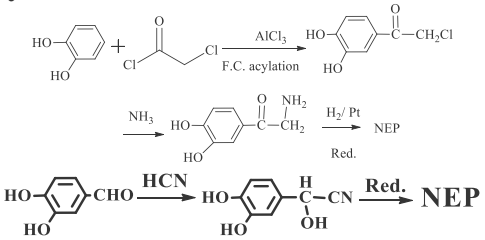


Substitution ⟶ prevent metabolism by MAO(↑ duration)

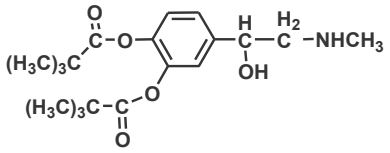
a) Free increase α-activity, decrease β-activity
b) substituted increase β-activity, decrease α-activity
c) R=bulky group ⟶ selective β-activity

Should contain at least the *m-* & *p*-OH gps or, alternatively, the *m-* & *b*-OH gps. exception albuterol

-Important but **not** essential for activity.
-Is chiral the active isomer is **R(-)**.

1] Epinephrine	2] Norepinephrine
	
R(-)-1-(3,4-dihydroxyphenyl)-2-methylamino ethanol	*R(-)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol*
NE [α > β], E [↑ β effect]	
Synthesis: 	**Synthesis:** 
Assay: 1) Non aq. Tit. As weak base using perchloric acid as titrant and crystal violet as indicator. 2) Spectrophotometry.	**Assay:** As EP
Uses: 1) ↑B.P. through stimulation of *α* (vasoconstriction) & β_1 (↑H.R). 2) Locally in treatment of hemorrhage and nasal congestion. 3) Bronchial asthma.	**Uses:** ↑B.P. in acute hypotensive state by stimulation of *α*- receptor only.

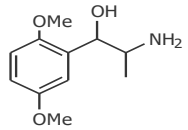
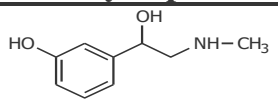
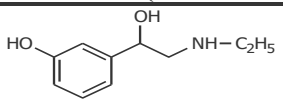
Derivatives of EP:

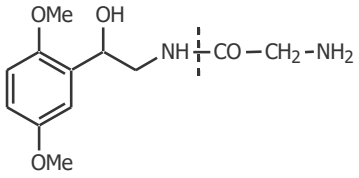
Dipivefrine

Both of them are used topically in treatment of ***open angle glaucoma.***

Note:

1) EP in large dose ↑B.P. by stimulation of *α*- & *β*- receptors, while in small dose it ↓B.P.by stimulation of ***β- receptor only***.
2) NEP acts **mainly** on ***α-*** receptor so it ↑B.P. (***can't be used in bronchial asthma***).

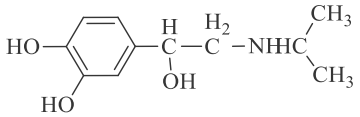
α-Agonists

Methoxamine	Phenyl Ephrin	Etilefrine (Effortil®)
		
Direct **selective α1-agonist** Weak than NE Used in surgery to maintain arterial blood pressure (with spinal anesthesia)	**Pure α1-agonist** (o 4-OH) [synthetic → weaker than NE]	
	Nasal decongestant	Tablets or drops for **Hypotension**

Midodrine	
	**PRODRUG** → by **hydrolysis of amide** give active form. Used in **orthostatic hypotension** & in **urinary incontinence**.

Drugs act mainly on β-receptors

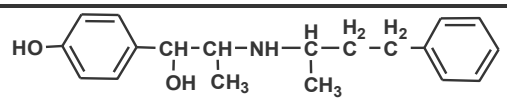
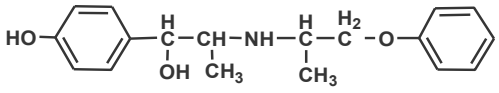
1] Isoprenaline sulfate (isoprotrenol): It is a prototypic, non-selective **β-agonist** invariably employed to stimulate heart rate in heart block and bradycardia.



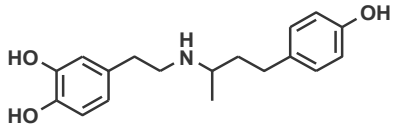
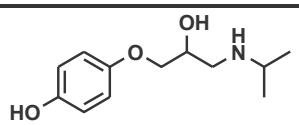
1-(3,4-Dihydroxyphenyl)-2-isopropylaminoethanol

Synthesis: As EP but we use isopropyl amine instead of methyl amine.

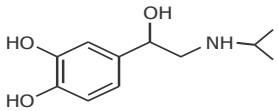
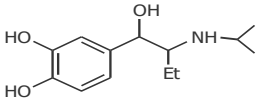
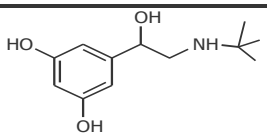
Uses: In treatment of **bronchospasm, asthma (non-selective β agonist).**

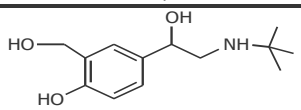
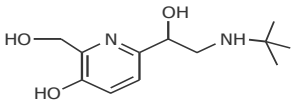
2] Nylidrin	3] Isoxsuprine
	
Both drugs are direct acting *β* agonist	
Uses: 1) Vasodilatation and improvement of peripheral circulation. 2) Relax uterus in dysmenorrheal. 3) Peripheral vascular disease for coldness & numbness of fingers and leg cramps.	

Selective β_1-Agonists

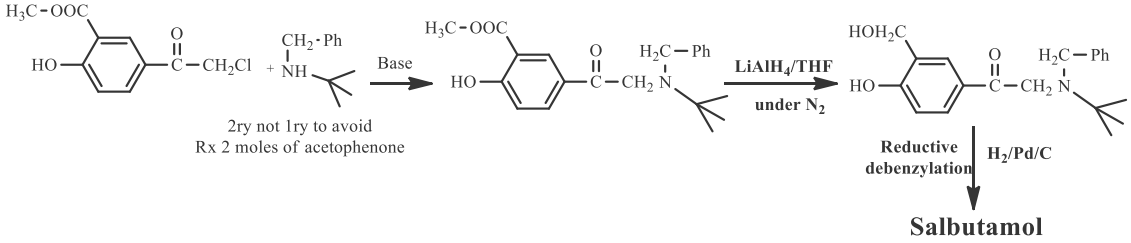
[1] Dobutamine	[2] Prenalterol
	
They are selective β1-agonist which **increase H.R & cardiac output**. A **major limitation** with these drugs is that **tolerance** to their effects may develop with prolonged use.	

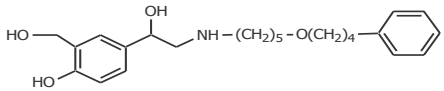
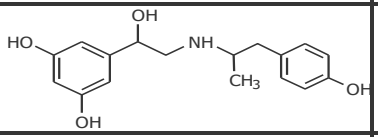
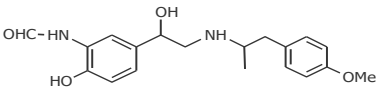
Selective B_2-agonists: → Bronchodilators

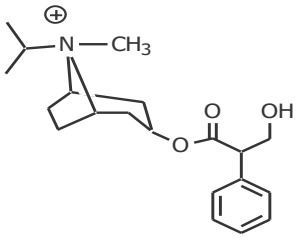
Isopreterenol	Isoethrine	Terbutaline
 **Pure β-agonist**		 *2-tert-butyl amino-1-(3,5-dihydroxy phenyl) ethanol*
-Non-selective (3 & 4-OH) $\beta_2/\beta_1 = 1$ (not used → cardiac stimulant) **-Metabolized by COMT** [contain catechol moiety] → 3-OMe (inactive)	↑ β_2 (not pure B_2)	↑ β_2 **activity** (t-butyl > isopropyl 9 times). Orally active. Rapid onset → for acute asthma as inhaler. Short duration (4-6 hr).

Salbutamol (Ventolin®)	Pirbuterol
 *2-Tert-butyl amino-1-(4-hydroy-3-hydroxy methyl phenyl) ethanol*	
-β_2/β_1 = 59 -Rapid onset → **Inhaler**. -Duration 4-6 hr. **-Salicyl Alcohol derivatives**.	**-Salbutamol Isostere**, **-Pyridine ↓ S.E.** [Vasodilatation & tremors in skeletal muscles]

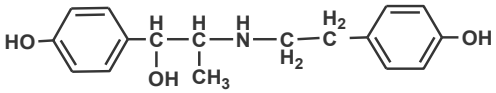
Synthesis of Salbutamol:



Salmeterol (Servant®)	Fenoterol	Formeterol (Foradil®)
		
Salicyl alcohol derivative. **Lipophilic side chain → longer duration** [twice daily] → higher selectivity. Used in **chronic asthma** (take long time to affect → **Not in acute cases**)	More potent > Salbutamol. Orally active.	↑ B_2 & **longer duration** > Salbutamol Due to **formamide group** which make H- bond with amino acid residue on B_2 receptor. Rapid onset.

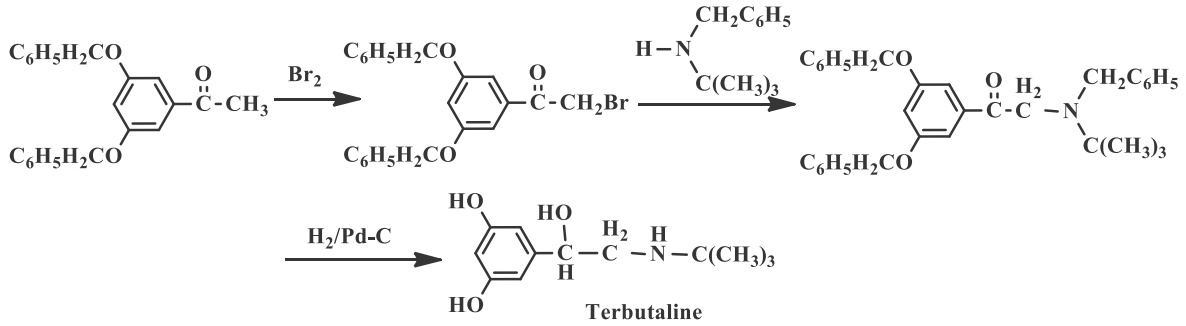
Berodual® → combination of Fenoterol + Ipratropium → asthma & COPD
 **Ipratropium → anti-cholinergic [bronchodilator] derived from atropine** **With quaternary N → polar → NO CNS side effects as aropine**

5] Ritodrine HCl



- Selective β_2 agonist.
- Relaxes ***uterine and bronchial*** smooth muscles.
- Used to control ***premature labor***.

Synthesis:



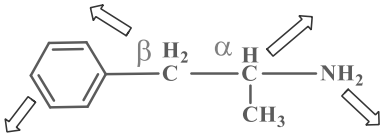
2] Indirect acting sympathomimetics

They are d**rugs** acts as a direct and indirect agonist *i.e.,* it helps in the release of **norepinephrine**. Besides, it also exerts CNS-stimulatory actions. It has been observed that the ephedrine stereoisomer having essentially the (1R, 2S) absolute configuration exhibits direct activity on the receptors, both α and β, as well as an indirect component. It is worthwhile to state here that the (1S, 2R) enantiomer has primarily an indirect activity.

SAR:

Presence of OH decreases indirect activity

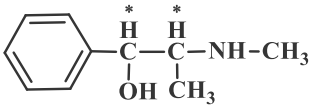
Presence of CH_3 increases indirect activity



Catechol OHs increase potency

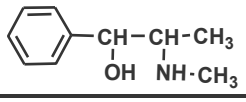
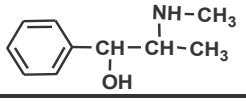
- Substitution decreases indirect activity.
- Tertiary N inactive.

1] Ephedrine HCl:



Erythro (-)-2-methylamino-1-phenylpropan-1-ol

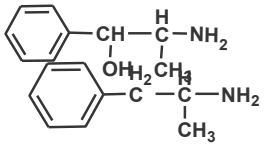
- **It has two forms:**

Erythro form (**Ephedrine**)	**Threo** form (**pseudoephedrine**)
	
- With ***mixed*** mechanism. - ***D(-) is active isomer.*** - Used for ***asthma***, urticaria & low B.P.	- ***Indirect*** acting. - ***L(+) is active isomer.*** - Used as ***nasal decongestant.***

- Ephedrine is active orally, ***NOT*** metabolized by MAO or COMT, but metabolized by *p*-hydroxylation and N-demethylation.

2] Norephedrine HCl:

- Removal of methyl group from ephedrine (norephedrine) →↑ **vasoconstrictor activity and lower toxicity.**
- Not metabolized by MAO or COMT.
- Used as **nasal decongestant.**

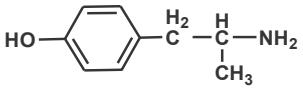


3] Amphetamines:

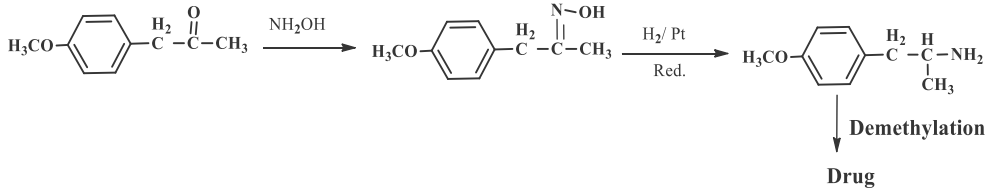
- CNS stimulant.

4] **Hydroxy amphetamine HBr:**

(±) 2-(4-Hydroxyphenyl)isopropylamine



Synthesis:

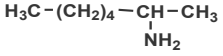
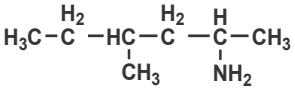
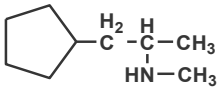
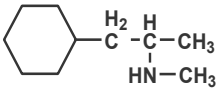


Uses: As ophthalmic drug ***(open angle glaucoma)***.

Assay: **a)** Non aq. Tit. As weak base **b)** bromometric assay.

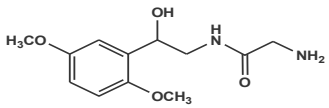
Aliphatic amines sympathomimetics

- **Indirect** acting sympathomimetics.
- All of them are used as **nasal decongestant.**
- **Synthesis: (reduction)**

Tuaminoheptane sulfate	**Methylhexanamine**
 *2-Aminoheptane* - Branching of chain →↑ activity	 *2-Amino-4-methylhexane* - ***Volatile*** sympathomimetic.
Cyclopentamine HCl	**Propylhexedrine (Benzedrex)**
 *1-Cyclopentyl-2-methylaminopropane*	 *1-Cyclohexyl-2-methylaminopropane* - ***Volatile*** sympathomimetic.

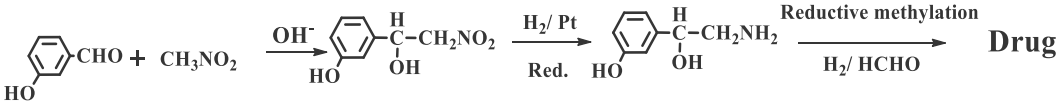
α-Adrenergic receptor agonists

1] Phenylephrine HCl:



1-(3-hydroxyphenyl)-2-methylaminoethanol

Synthesis:



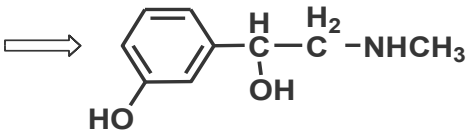
- Not metabolized by COMT but metabolized by MAO.
- Selective α_1 agonist due to lack of *p*-OH group.

Uses:

1) **Nasal decongestant.**
2) Prolong the action of local anesthetics.
3) Treatment of **open angle** glaucoma.

Assay:

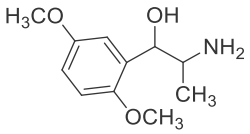
1) Non aq. Tit. As weak base.
2) Bromometrically:



2] **Methoxamine:**

Assay and uses as phenylephrine

3] Midodrine:



2-Amino-1-(2,5-dimethoxyphenyl)propan-1-ol

2- Amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]acetamide

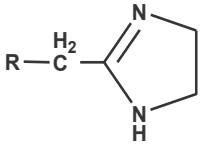
- **PRODRUG** → by **hydrolysis of amide** give active form.
- Used in **orthostatic hypotension**

2-Imidazoline derivatives

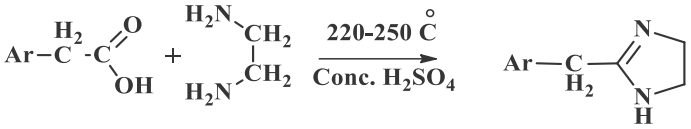
- They are used **as nasal and ophthalmic decongestant.**
- They act directly on α-receptors producing vasoconstriction.

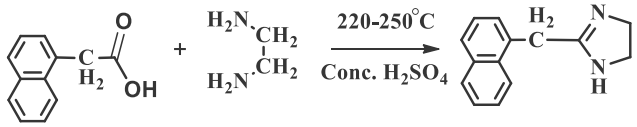
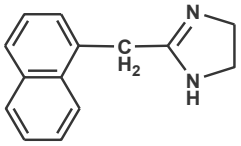
α- Adrenergic receptors agonists

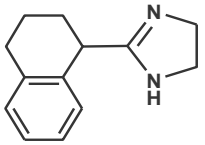
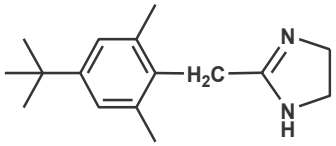
General structure:



General method of synthesis:



1] Naphazoline	
Synthesis:  **Assay:** Dissolve the free base in Xss standard acid then back titrate the Xss acid by standard NaOH using **methylred** as indicator.	 *2-(1-Naphthylmethyl)-2-imidazoline*

2] Tetrahydrozoline	3] Xylometazoline
 *2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-imidazoline*	 *2-(4-t-Butyl-2,6-dimethylbenzyl)-2-imidazoline*

II) Adrenergic blocking agents

- **It blocks adrenergic receptors preventing EP and NEP from its action.**
- **It's called sympatholytic agents or adrenergic antagonists.**

A] *α*-Blockers

1) **Noncompetitive** (*β*-haloalkylamines) e.g. Dibenamine & phenoxybenzamine.
2) **Competitive (imidazolines) e.g. Tolazoline & phentolamine.**

Uses:

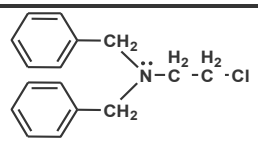
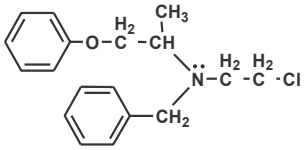
- **Management of pheochromocytoma.**
- **Peripheral vascular diseases.**
- **Benign prostatic hyperplasia.**

They are:

1) **Ergot alkaloids.**
2) **Yohimbine alkaloid.**
3) ***β*- halo alkylamines.**
4) **Imidazolines.**
5) **Quinazolines.**

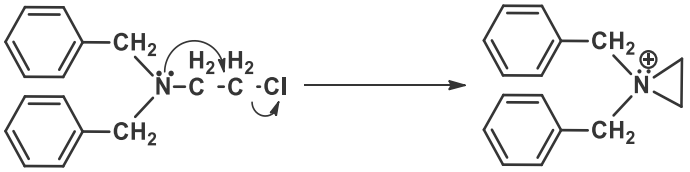
3] *β*-Halo alkylamines (Noncompetitive)

- Its adrenergic blocking action is **NOT** antagonized even by massive dose of NEP.

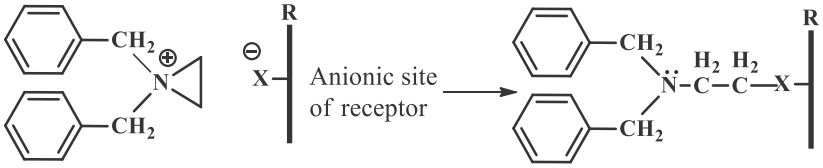
Dibenamine	Phenoxybenamine
	

Mechanism of action: (3 steps)

1) Internal cyclization to form ***azeridinium ion*****:**



2) Electrostatic attraction of +Ve charge to anionic site of α-receptor (**reversible process**):
3) Formation of covalent bond between drug & receptor (**irreversible process**):

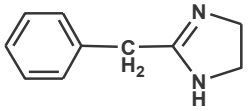
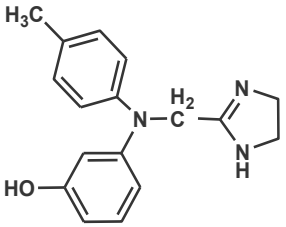
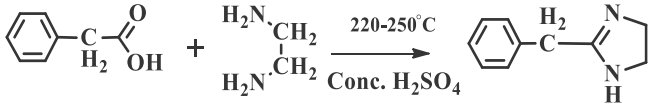
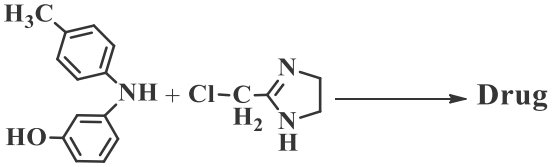


- **It's used to:**
    1) Improvement of peripheral circulation.
    2) ↓↓ B.P.
    3) Management of ***pheochromocytoma***.

Note:

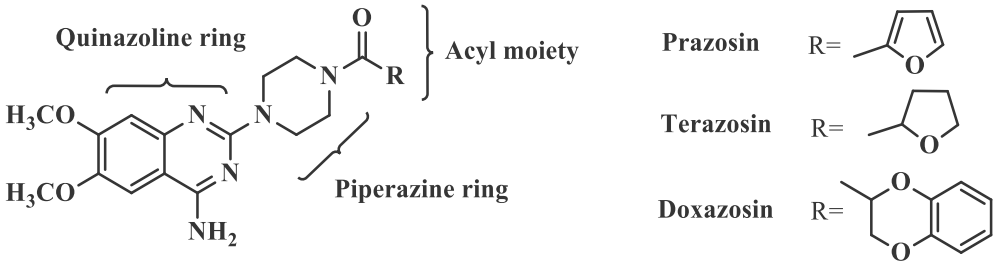
Pheochromocytoma: tumor in adrenal medulla leading to ↑ production & secretion of **NEP** →↑↑ B.P.

4] Imidazolines (competitive)

Tolazoline	Phentolamine
	
Synthesis: 	**Synthesis:** 
Uses: 1) ***Vasodilator*** (histamine like action). 2) Persistent pulmonary hypertension in newborn. 3) Diagnosis of **pheochromocytoma.**	**Uses:** 1) Peripheral vascular disease. 2) Diagnosis & management of pheochromocytoma.
Assay: Extract free base then dissolve in known Xss acid and back titrate with standard NaOH using methyl red indicator.	**Assay:** Spectrophotometrically.

5] Quinazolines

1- **Prazosin**
2- Terazosin
3- Doxazosin



Mainly used in treatment of ***hypertension (selective α_1-blockers)***

Assay:

1) ***1)*** Nonaqueous titration as ***weak base.***
2) Spectrophotometry.

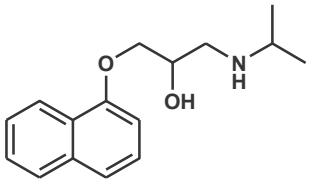
B] β-Blockers

SAR:

1) ***Bulky aliphatic group*** are normally found on the amino of aryloxypropanolamine.
2) For maximum activity, it should be ***2ry amine***.
3) R-(or levo) isomer is less potent than its ***S-(or Dextro)*** isomer, so the β-blocker activity is stereoselective.

Aryloxy propanolamines

1) **Nonselective:** e.g. propranolol, timolol
2) **Selective:** e.g. atenolol, metoprolol

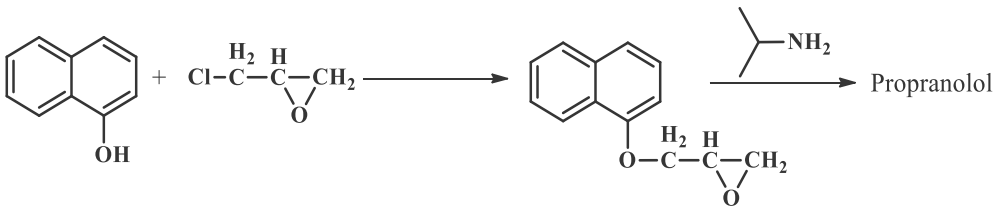


1) Nonselective β-blockers

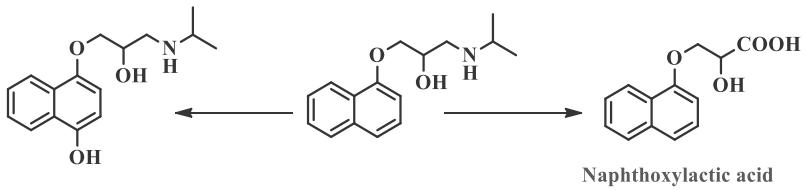
i) Propranolol:

1-Isopropylamino-3-(1-naphthyloxy)-2-propanol

Synthesis:

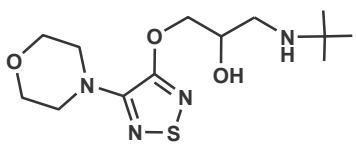
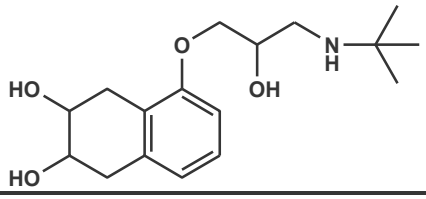


Metabolism:



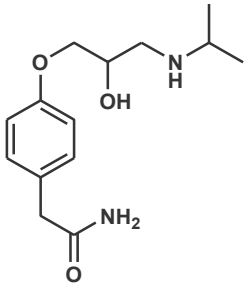
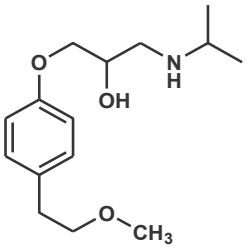
Uses:

1) Treatment of **hypertension, cardiac arrhythmia and angina**.
2) Treatment of myocardial infarction.
3) Headache and **migraine**.

ii)Timolol	iii) Nadolol
	
Used in treatment of **open angle glaucoma**.	Antianginal, antihypertensive and antiarrhythmic agent.

2) Selective β_1-blockers

- Not affect β_2 receptors so it doesn't produce bronchoconstriction (used in patients With **bronchial asthma or bronchitis)**.

Atenolol	Metoprolol
	
2-(4-(2-Hydroxy-3-(isopropylamino)propoxy)phenyl)acetamide	*1-(4-(2-methoxyethyl)phenoxy)-3-(isopropylamino)propan-2-ol*

Uses:

1) Treatment of hypertension.
2) Angina pectoris.
3) Cardiac arrhythmia.

[III] PARASYMPATHETIC NERVOUS SYSTEM

- The main neurotransmitter is ***acetylcholinE*** **(ACh).**

Cholinergic receptors:

1) Muscarinic receptors:

Receptor	Site	Action on stimulation
M_1	Heart	**Bradycardia & ↓** cardiac contractility.
M_2	Smooth muscles	Contraction of all smooth muscles except blood vessels.
M_3	Exocrine glands	↑ Secretion.

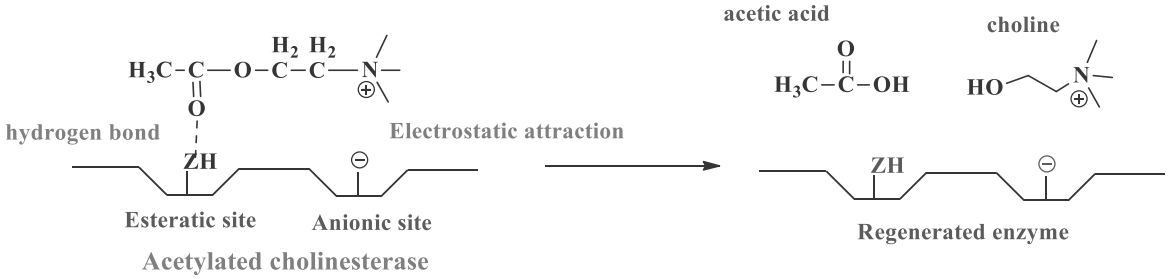
2) Nicotinic receptors:

Nm	Skeletal muscles	Contraction
Nn	Autonomic ganglia	↑ EP & NEP release.

Action of ACh:

① Bradycardia.
② Vasodilatation of blood vessels.
③ ↑ Motility of GIT
④ relaxation of sphincters.
⑤ Salivation, sweating and lacrimation.
⑥ Miosis.

Biotransformation of Ach: by **cholinesterase enzyme**

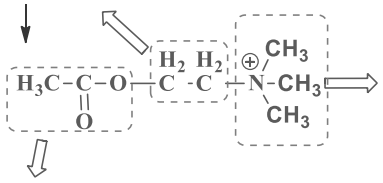


SAR:

- **2** Carbons is **optimum** for activity.

- substitution on β -C by CH_3 → ↑ **M &** ↓ **N** activity (20 times **mor active and less hydrolizable** than **ACh**) due to **resistance to ACHE action.**

- substitution on α -C → ↓↓↓ **M & N activity.**



- Replacement of CH_3 gps by H **decreases M & N activity.**
- Replacement by **ethyl** leading to **loss of activity.**
- Replacement of **N** by **P**, **S** or **As** gives comps. **wz some activity but wz less affinity.**

- Replacement of CH_3 by NH_2 → **less** hydrolizable by ACHE, **longer** duration and **orally active.**

- Replacement of C=O by CH_2 gives **choline ether** → **still active as M but** ↓ **N activity.**

Parasympathomimetic agents

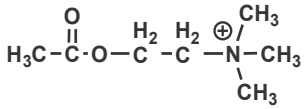
I) Direct acting: cholinesters

II) Indirect acting: ACHE inhibitors

(a) Reversible. **(b) Irreversible.**

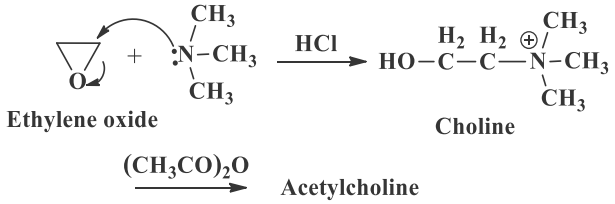
[I] direct acting parasympathomimetic (true cholinergic)

1) Acetylcholine



2-Acetoxyethyltrimethylammonium chloride

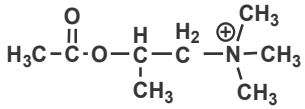
Synthesis:



Metabolism:

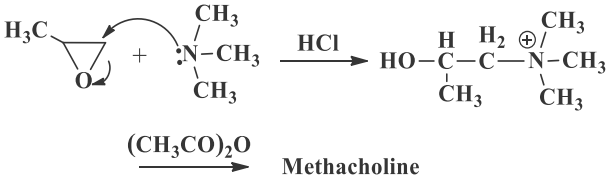
- Rapidly metabolized by ACHE so it's **not taken orally.**
- If taken parentrally it produces various pharmacological actions, so **it's not used clinically.**

2) Methacholine



2-Acetoxy-2-methylethyltrimethylammonium Br

Synthesis:



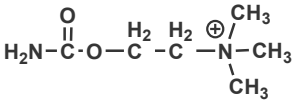
Metabolism:

- *β*- methyl group →↑ resistance to ACHE (longer duration & orally used).

Uses:

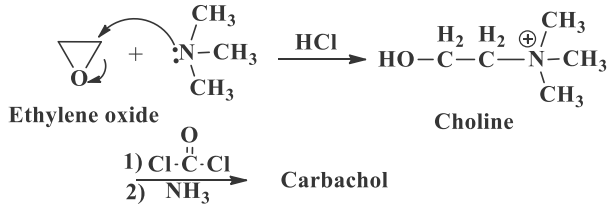
- Diagnosis of **bronchial asthma** (because it produces bronchoconstriction).

3) Carbachol



2-Carbamoyloxyethyltrimethylammonium chloride

Synthesis:



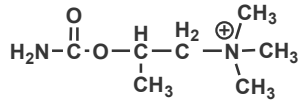
Metabolism:

- Carbamoyl group is **slowly hydrolyzed** than acetyl so it's longer in duration than Ach & methacholine.

Uses:

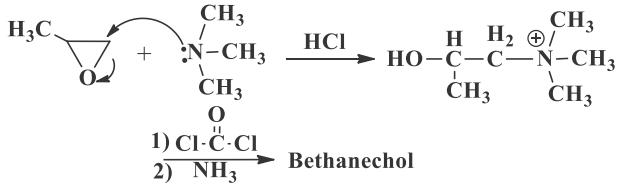
1) Narrow angle glaucoma.
2) ***Urine retention*** after operations.

4) Bethanechol



2-Carbamoyloxy-2-methylethyltrimethylammonium chloride

Synthesis:



Metabolism:

- It has both ***β*-methyl & carbamoyl group** so it's the **most stable** to hydrolysis by ACHE (longest in duration & orally active).

Uses:

1) ***Urine retention*** and abdominal distention after surgery.

Bthanechol > Carbachol > Methacholine > Acetylcholine (in duration)

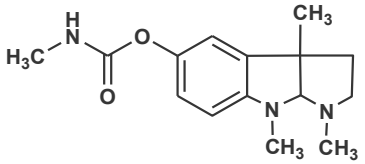
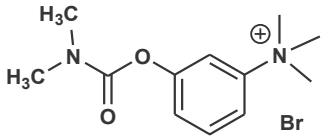
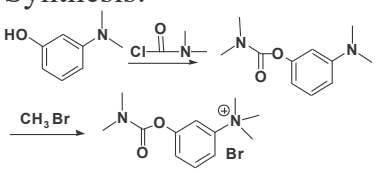
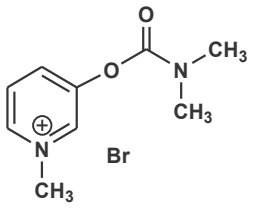
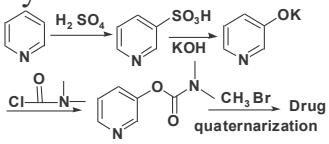
General method of assay:

1) Volhard's method	2) Non aqueous titration
- For halogens which readily ionizable. - Drug + Xss $AgNO_3$ then back titration With NH_4SCN using ferric alum as indicator.	- For quaternary amm. group. As weak base. - Titrant: perchloric acid, solvent: acetic acid. - We add $HgAc_2$ for masking the halide ion which interfere with end point.

[II] Indirect Acting Parasympathomimetics

1) **Reversible:** cause **carbamoylation** of ACHE and **slowly hydrolyzed.**
2) **Irreversible:** cause **phosphorylation** of ACHE and **can't be hydrolyzed.**

Reversible ACHE inhibitors

Physostigmin	Neostigmin	Pyridostigmin
 Naturally occurring alkaloid. **Uses:** 1) Treatment of **glaucoma**. 2) TREATMENT of **anticholinergic toxicity** (atropine). **Note:** it's **NOT** quaternary amm. comp. so it **crosses BBB** and treats **CNS** symptoms of anticholinergic toxicity. It's **miotic** effect is less than neostigmin. **Assay:** Non aq. tit. as **weak base.**	 *3-Dimethylcarbamoyloxy-phenyltrimethylammonium bromide* Synthesis:  **Uses:** 1) TREATMENT of ***myasthenia gravis***. 2) TREATMENT of atony of intestine, bladder & sk. Ms. **Assay:** 1) Non aq. tit. as **weak base** ($HgAc_2$)**.** 2) Volhard's method.	 *3-Dimethylcarbamoyloxy-1-methylpyridinium bromide.* Synthesis:  Uses: 1) TREATMENT of ***myasthenia gravis***. **Assay:** 1) Non aq. tit. as **weak base** ($HgAc_2$)**.** 2) Volhard's method.

Mechanism of action:
They cause **carbamoylation** of ACHE (inhibition) → accumulation of **Ach**.
NOTE: the carbamoylation of ACHE is **more stable** than acetylated form → slowly hydrolyzed to give free enzyme.

Irreversible ACHE inhibitors
Organophosphorus Compounds

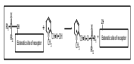
Mechanism of action:

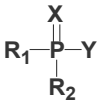
They cause ***phosphorylation*** of ACHE → ***irreversible*** inhibition of ACHE which is **NOT** hydrolyzed to free enzyme.

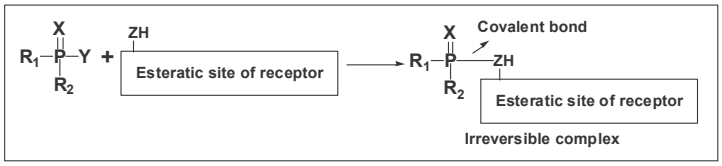
General structure:

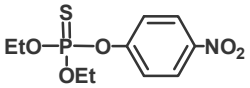
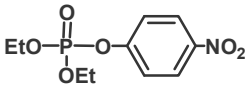
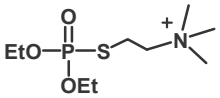
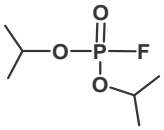
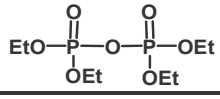
R1, R2 = Alkoxy X=O or S

Y (good leaving group) = P-nitro phenoxy







Parathion	Paroxon
	
Echothiophate	**Isoflurophate (DFB)**
	
Tetraethylpyrophosphate (TEPP)	
- It has advantage that it is hydrolyzed rapidly to nontoxic compound H_3PO_4 & C_2H_5OH	

Uses:

1) Treatment of **glaucoma** (causes long duration of miosis) → Ex: **Echothiophate & Isoflurophate.**
2) **Insecticides** → Ex: **Parathion & Paroxon**

Symptoms of toxicity:

- Nausea**,** vomiting, sweating, salivation and bradycardia.

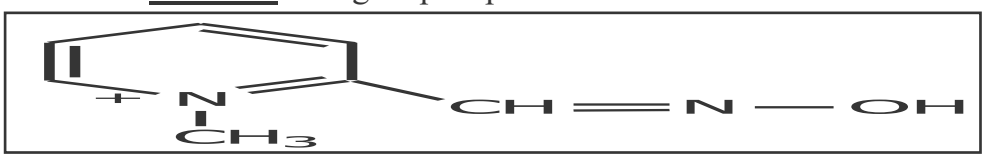
Treatment of toxicity:

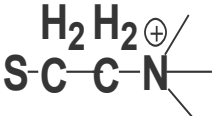
1) Atropine:

To treat **symptoms** of toxicity **BUT** doesn't remove organophosphates from ACHE enzyme.

2) Pralidoxime chloride (PAM):

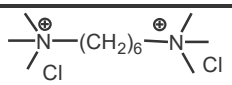
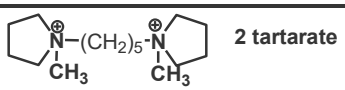
- 2-Aldoxime-1-methylpyridinium chloride.
- **Antidote** of organophosphates.





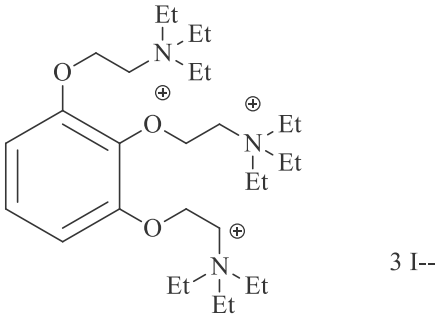
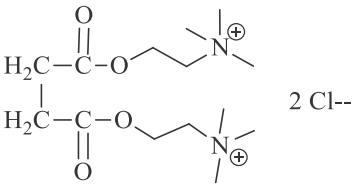
Parasympatholytic Agents
[I] Antinicotinics
A-Ganglionic blocking agents (Nn)

They block Ach action at the ganglionic synapses of both sympathetic & parasympathetic N.S.

Hexamethonium chloride	Pentolinium tartarate
	
Assay: 1) Non aq. Tit. As weak base. 2) Volhard's method. **Uses:** Treatment of ***severe hypertension***.	*Pentamethylene-1,1-bis(1-methylpyrolidinium) bitartarate* **Assay:** Non aq. Tit. As weak base. **Uses:** treatment of ***hypertension***.

B-Neuromuscular blockers (Nm) (Skeletal muscle relaxants)

- Used as **Skeletal muscle relaxant** – **adjuvant to general anesthetics to ↓ dose.**
- ***d*-tubocurarine (parent)** → distance between 2 N^+ → 1-2 nm (one of them bind to anionic site & the other bind to nearby cysteine residue)

Gallamine triethiodide (Flaxedil)	Suxamethonium Cl (succinyl choline)
 3 I--	 2 Cl--
Used as: skeletal muscle relaxant ***for surgery.*** **Antidote**: in case of overdose is **Neostigmin.**	Skeletal muscle relaxant but with potent action and **short duration** (it's rapidly hydrolyzed by ACHE). **NOTE:** used for **diagnosis** not for treatment. **Antidote:** it has **NO** antidote.
Both of them are assayed by: 1) Non aq. Tit. As weak base. 2) Volhard's method for halides.	

[II] Cholinergic blockers (Muscarinic blockers)

Action:

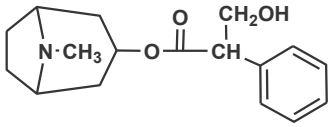
1. Anti-spasmodic (relax smooth muscle of GIT & Urinary tract).
2. Mydriatic (dilatation of eye pupil).
3. **Preanesthetic medication:** decrease gland secretion (decrease sweating & salivation).
4. **Cardiac diseases:** treatment of Bradycardia.
5. **Bronchodilators.**

It includes:

I) **Natural.**
II) **Synthetic.**

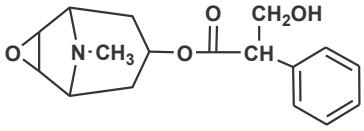
[I] Natural

Atropine

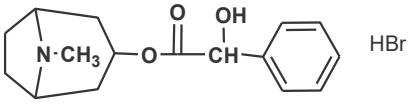


- It's the tropine ester of **racemic** tropic acid.
- Levo form is hyosyamine.

Scopolamine (hyoscine):

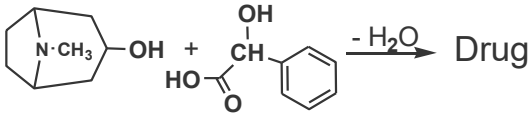


Homatropine HBr

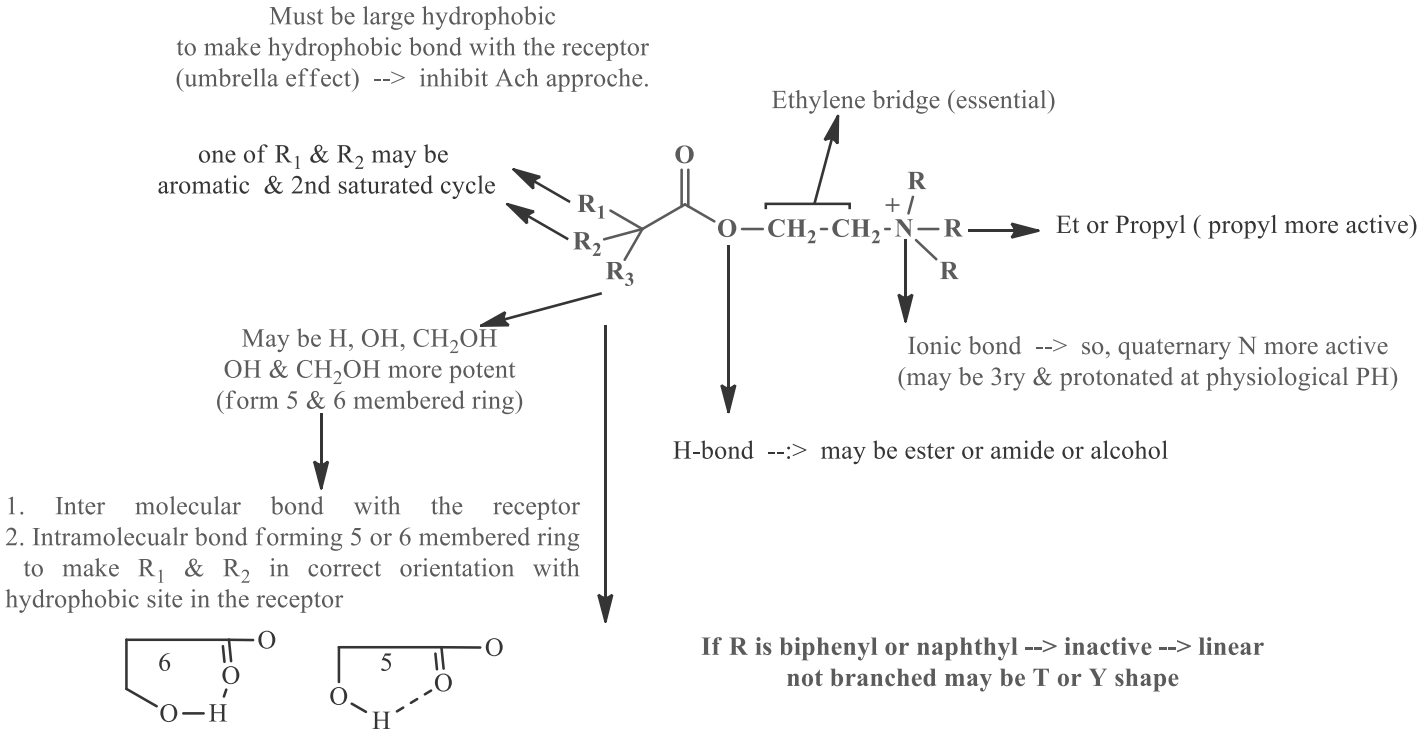


- Water soluble so it's used topically in the form of eye drops for **examination of retina.**

Synthesis:



SAR:

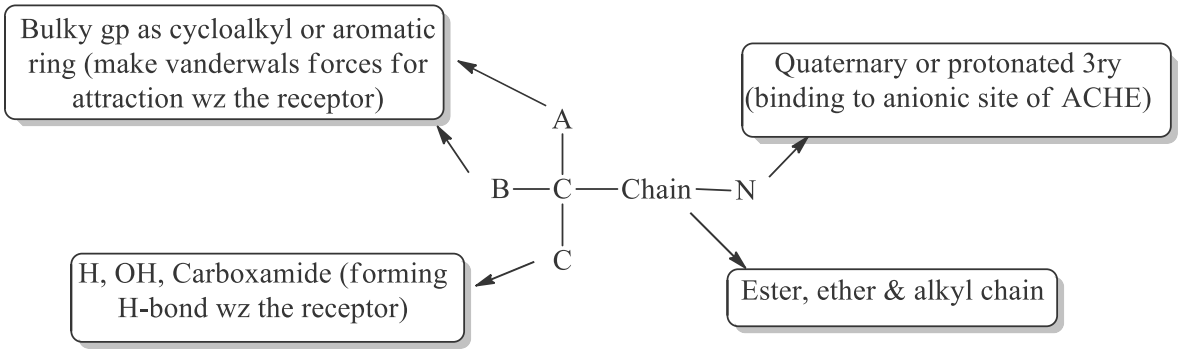


1) **Quaternarization of nitrogen atom produce agents** that block Ach at additional sites **(becomes antinicotinic & antimuscarinic)** SO it's preferred to be **3ry** for selective antimuscarinic activity.
2) **For GIT drugs, it's preferred to be quaternary because it will be LESS absorbable from intestine→ ↑ duration as spasmolytic.**
3) For ophthalmic use, it's preferred to be **3ry** to be absorbed from cornea.
4) N-oxidation (N→O) of this group of drugs → ↑ duration which is **metabolized slowly**.

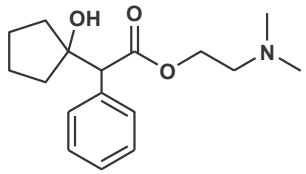
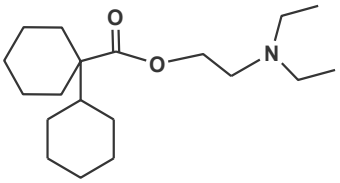
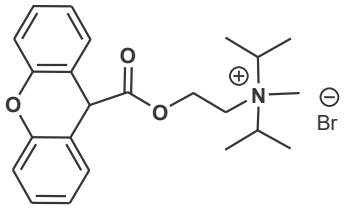
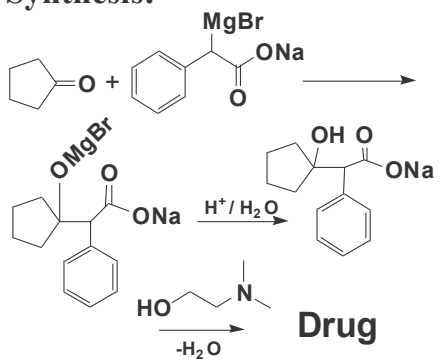
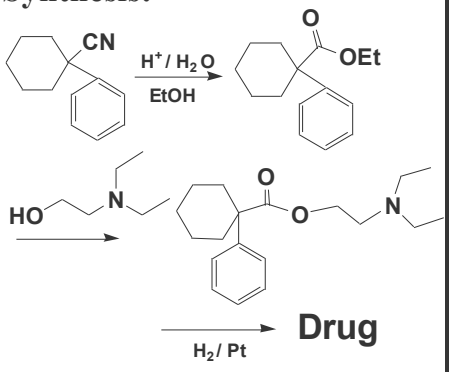
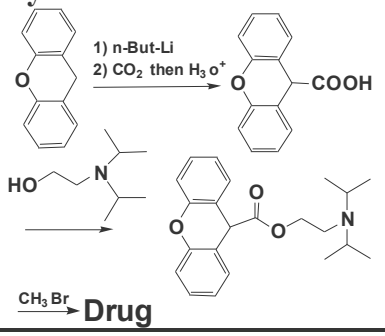
[I] Synthetic

A. Aminoalcohol ester.
B. Aminoalcohol ether.
C. Aminoalcohol.
D. Diamines.
E. Aminoamides.

General formula:

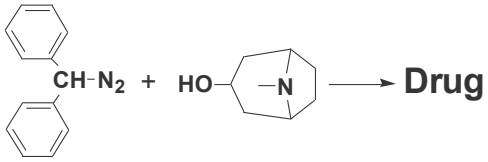
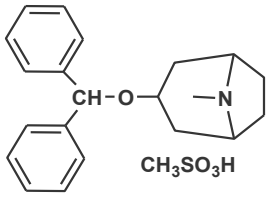


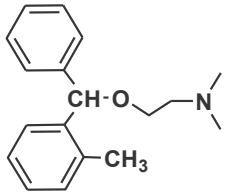
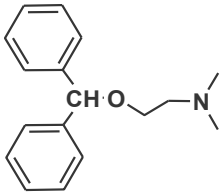
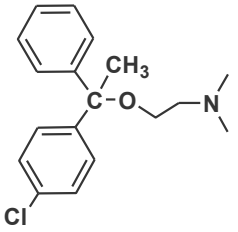
A. Aminoalcohol ester

Cyclopentolate	Dicyclomine	Propantheline
		
2-Dimethylaminoethyl α-(1-hydroxycyclopentyl) α-phenylacetate **Uses:** In ophthalmology as **mydriatic**. **Assay:** Non aq. Tit. As weak base. **Synthesis:** 	**NOTE:** it's **safe for <u>patient with glaucoma.</u>** **Uses:** **Antispasmodic** (it's action like papaverine). **Assay:** Non aq. Tit. As weak base. **Synthesis:** 	**Uses:** 1) Antispasmodic & treatment of ***<u>peptic ulcer.</u>*** 2) Antimuscarinic & antinicotinic due to quaternary N. **Assay:** Non aq. Tit. As weak base. **Synthesis:** 

B. Aminoalcohol ether

- It has **antihistaminic** as well as **antimuscarinic** and local anesthetic action.
- It's used in treatment of **parkinsonism.**

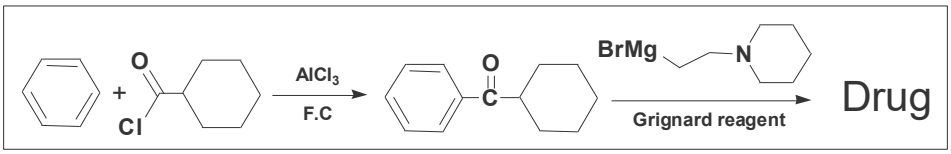
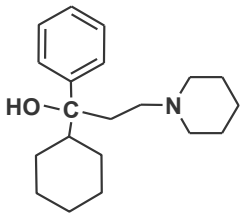
1) Benzotropine mesylate	
3-Diphenylmethoxytropane methane sulphonate **Synthesis:**  	

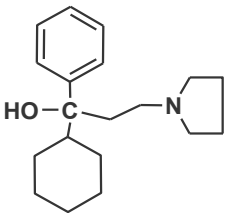
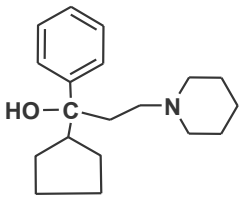
2) Orphenadrine	3) Diphenhydramine	4) Chlorphenoxamine
 	 	

- All of them are **antihistaminic** used in treatment of **Parkinsonism** while **benzotropine is antimuscarinic** used in treatment of **Parkinsonism as bedtime** medication**.**
- **Assy for all:** Non aqueous titration as **weak base** using standard perchloric acid.

C. Aminoalcohol

- They are used mainly in treatment of **parkinsonism.**

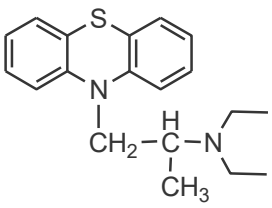
1) Trihexyphenidyl	
1-Cyclohexyl-1-phenyl-3-piperidino-1-propanol **Synthesis:**  	

2) Procyclidine	3) Cycrimine
 	

- **Assay for all:** Non aqueous titration as ***weak base*** using standard perchloric acid.

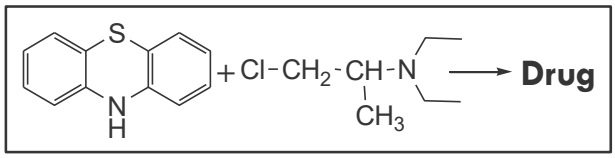
D. Diamines

Ethopropazine HCl:



10-(2-Diethylaminopropyl) phenothiazine

Synthesis:



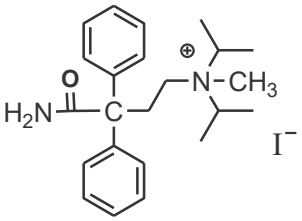
Assay: **Kjeldahl** nitrogen determination

Uses: Has antihistaminic, anticholinergic activity and used in **parkinsonism**.

E. Aminoamides

Isopropamide iodide:

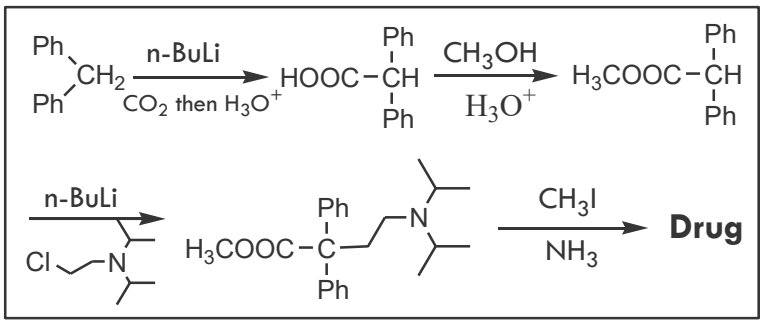
2,2-Diphenyl-4-diisopropylaminobutanamide methiodide



Uses:

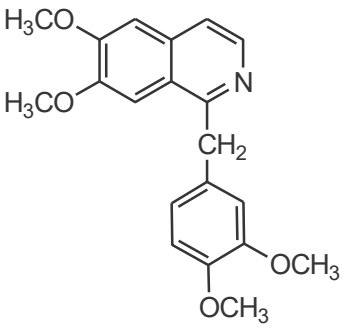
1) Treatment of hyperacidity and peptic ulcer.
2) Antisecretory for symptoms of ***common cold.***

Synthesis:



Papaverine HCl (natural)

- Nonspecific antagonist.
- It has a broad **antispasmodic action** on the Muscarinic receptors.

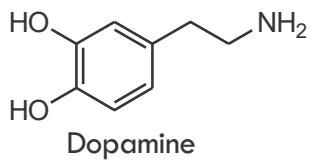


Antiparkinsonian Agents

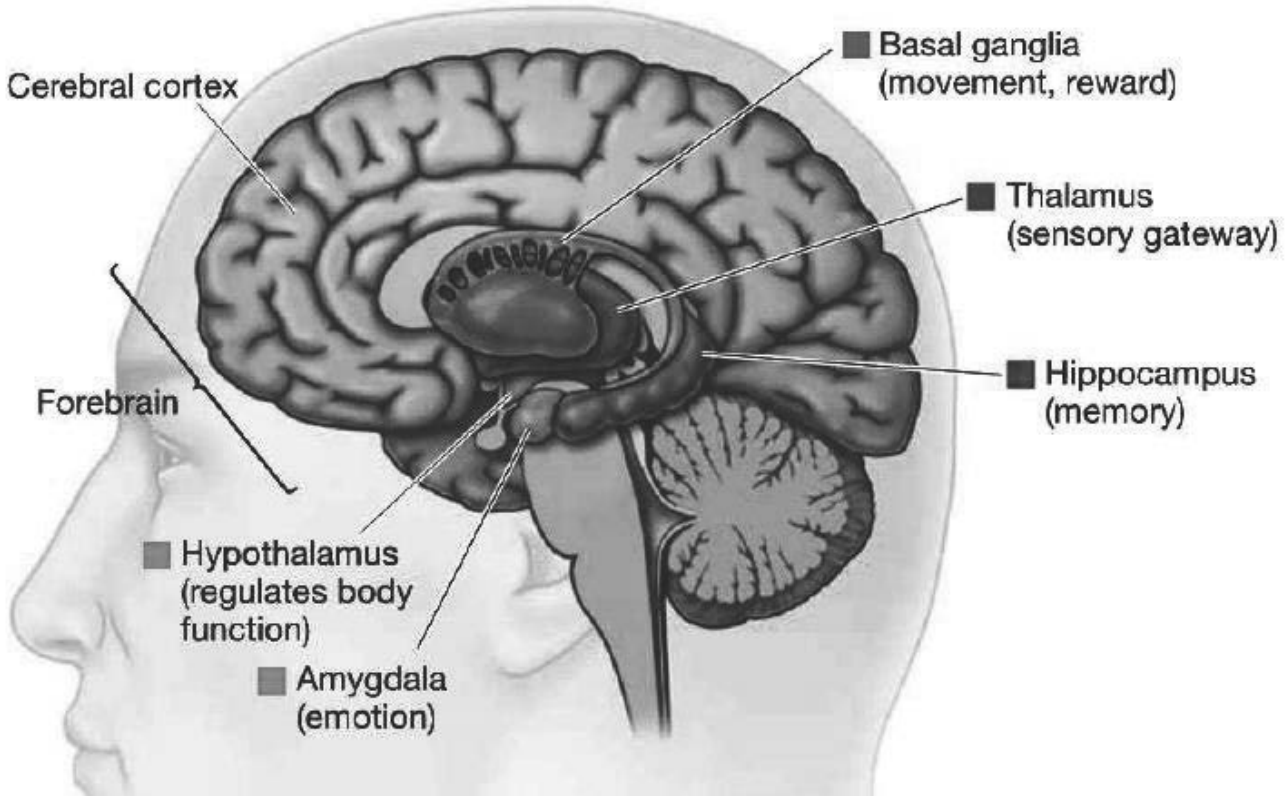
- Parkinson's disease is degenerative disorder of the CNS dopaminergic neurons which shows mainly motor and sometimes cognition (thinking) related symptoms.
- Movement-related (motor) shaking, rigidity, slowness of movement and difficulty with walking Cognitive problems Dementia.
- **Causes:**
- Parkinson is caused due to imbalance of dopamine (DA) and acetylcholine (Ach)
- Ach and DA need to be balanced for smooth movement. DA causes muscle relaxation while Ach causes contraction.
- Reduction of DA, in the basal ganglia results in imbalance of those two and causes motor disorders.
- In some cases, at later stages of the disease reduction of Ach which is also involved in learning and attention leads to dementia

N.B.:

- Parkinson has no cure. Drugs only used to control symptoms
- So, if we need to treat these symptoms we should:
  1) **Use anticholinergics** ex: Benzotropine, Trihexyphenidyl.
  2) **Antihistaminics** (↓ the action of Ach).
  3) Drugs which ↑ the level of dopamine.



Dopamine



Classification

1-Anti-Cholinergic drugs: atropine, **Benzhexol**

- Reduces acetylcholine effects (treatment for tremors in early stages)

2-Cholinesterase inhibitors: Rivastigmine

- Promotes acetylcholine effects (treatment for dementia in later stages)

3-Dopamine precursors: levodopa

- Prodrug of dopamine

4-**Dopamine decarboxylase inhibitors: Carbidopa**, benserazide

- Inhibits *peripheral* metabolic degradation of dopamine

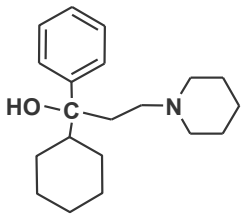
5-**Catechol-O-methyl Tranferase (COMT) inhibitors: Entacapone**

- Inhibits COMT based metabolism of **Levodopa**

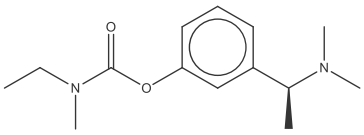
6-**Dopamine agonist:** bromocryptin, **Amantadine**

- Promotes dopamine effect in the brain.

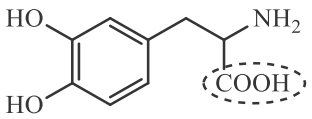
Anticholinergics

Trihexyphenidyl	
➢ It is an antimuscarinic drug that blocks Ach effect on M_1 receptor. ➢ In Parkinson DA and Ach levels are imbalanced that causes motor defects. DA levels are reduced while Ach levels remain constant. Benzhexol lowers Ach levels and maintains the balance. ➢ Trihexyphenidyl is used for the symptomatic treatment of Parkinson's disease in mono and combination therapy with L-Dopa. ➢ Also used to control drooling of children with cebebrum paralysis that effects movement. ➢ In older patients with Parkinsonism it can increases chances of dementia since Ach is involved in cognition too.	 *1-Cyclohexyl-1-phenyl-3-piperidino-1-propanol*

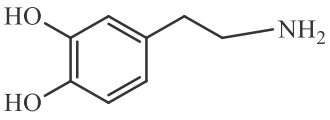
Cholinesterase inhibitors

Rivastigmine (Exelon®)	
➢ It is acetylcholinesterase inhibitor used for the treatment of mild to moderate Alzheimer's disease and Parkinson's. ➢ The drug can be administered orally or via a transdermal patch. ➢ It increases level of Ach by blocking its degradation from the enzyme acetyl cholinesterase. ➢ This improves cognitive functions like memo and awareness. ➢ Side effects are mostly nausea and vomiting and at low doses it is generally safe. ➢ It can sometimes dangerously slow heartbeat in which case atropine (Ach blocker) is used.	 *(S)-3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate*

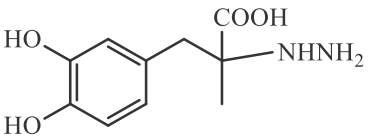
Which is more hydrophillic or less lipophilic?



Levodopa



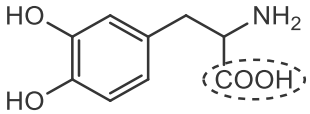
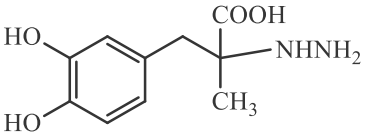
Dopamin



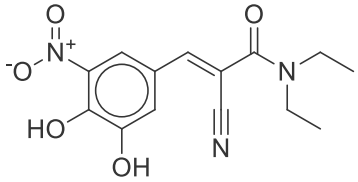
Carbidopa

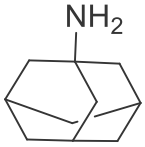
- External DA can't cross BBB but the prodrug Ldopa can. L-Dopa is dopamine with acid group to create an amino acid functional group. The blood brain barrier has Amino Acid Transporter which allows penetration of L-dopa, even though LDopa is less lipophillic than DA
- In the brain it gets metabolized into dopamine by the enzyme DOPA decarboxylase.
- Thus, L-DOPA is used to increase dopamine concentrations in the brain which is lowered in Parkinson.
- It is most preferred and safest drug in Parkinson
- Metabolism outside the brain can lower the efficacy of L-Dopa
- Thus L-Dopa is given with carbidopa which blocks Dopamine decarboxylase mediated peripheral metabolism and allows high dose of L-Dopa to penetrate brain. Carbidopa itself doesn't penetrate the brain.

Drugs that ↑ the level of dopamine

1] levodopa	2] Carbidopa
	
Mechanism: It is decarboxylated to dopamine by **DOPA decarboxylase** enzyme **BUT** this process takes place **peripherally and in CNS,** so we use carbidopa with it to prevent decarboxylation peripherally (carbidopa **doesn't** penetrate BBB).	➢ It is not a true drug but used with levodopa to prevent its peripheral decarboxylation. ➢ It is a Dopamine decarboxylase inhibitor. ➢ Its purpose is to increase efficacy of L-Dopa by preventing its peripheral metabolic degradation and thus allowing more L-Dopa to penetrate the brain. ➢ While Dopamine decarboxylase exists both inside and outside the brain, Carbidopa only blocks metabolism outside the brain because it can't penetrate the brain.

Catechol-O-methyl Tranferase (COMT) inhibitors: Entacapone

Entacapone

➢ It is a Catechol-O-methyl Tranferase (COMT) inhibitors ➢ Entacapone prevents COMT from metabolizing L-DOPA into inactive metabolite 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the periphery. ➢ Thus, more L-Dopa can penetrate the brain ➢ It itself doesn't cross BBB

Amatidine

➢ It promotes Dopamine release and prevents reuptake of dopamine in the CNS ➢ Exact MOA is not known. It promotes dopamine, noradrenaline and serotonine and blocks monoamine oxidase A and NMDA receptors, ➢ It has amine group with pKa of 10.8. Although mostly protonated in the blood, the unique cage structure provides a very high lipophilicity for good penetration into brain and prevents metabolism such that it is excreted from kidney in unchanged form.

CNS ACTING DRUGS

- Central Nervous System formed of Brain and Spinal cord.
- Any material to give CNS effect should be with high lipophilicity to pass BBB.
- Damage to CNS endothelial cells by toxins [if CNS infections]; alter CNS permeability selectivity → allow passage of foreign substances and drugs.

CNS ACTINGS DRUGS

CNS Depressants	CNS Stimulants
i. Sedative – Hypnotics and Anxiolytics. ii. Centrally acting skeletcal muscle relaxants. iii. Anti-psychotics. iv. Anti-convulsants. v. General anaesthetics [Local anaesthetics]. vi. Anti-Parkinsonism agents.	➢ Analeptics [Respiratory simulants]. ➢ Xanthins. ➢ Psychomotor stimulants. ➢ Anti-Depressants.

CNS DEPRESSANT DRUGS

Central nervous system (CNS) depressants are drugs that can be used to slow down or "depress" the functions of the CNS.

CNS depressants include only anxiolytics, sedative-hypnotics and antipsychotics.

Antipsychotic drugs previously known as neuroleptic, anti- schizophrenic or major tranquilizers are used in the symptomatic treatment of thought disorders (psychoses), most notably the schizophrenias.

Sedatives are chemical agents tend to produce a calming effect, relax muscles, and relieve feelings of tension, anxiety, and irritability. At higher doses, most of these sedative drugs will also produce drowsiness and eventually produce sleep. Drugs that have such a sleep-inducing effect are called hypnotic drugs.

Both hypnotic and sedative properties usually reside in the same drug; a small dose of the same drug would act as a sedative, whereas a large dose of a drug may act as a hypnotic.

There are a few exceptional cases a compound exerts only one specific effect, *e.g.,* **potassium bromide** is a good sedative and exhibits no hypnotic action; likewise, certain powerful hypnotics, *e.g.,* **thiopental sodium** cannot be used as a sedative.

In reality, almost any drug that calms, soothes, and reduces anxiety is also capable of relieving insomnia.

General Mechanism of Actions of CNS Depressants:

1. Positive modulation of actions of GABA [common in all classes].
2. Others may inhibit voltage-gated sodium channels with decreased neuronal excitation.
3. Anti-psychotics: antagonize the action of dopamine [on D_2 & D_3 receptors in limbic system].

I-SEDATIVES, HYPNOTIC AND ANXIOLYTIC AGENTS

In addition to benzodiazepines, barbiturates, and a miscellaneous group, many drugs belonging to other pharmacological classes may possess one or more of the anxiolytics, sedative, and hypnotic activities. An arbitrary classification of these agents is as follows:

1-$GABA_A$ receptor modulators

a) **Benzodiazepines** are highly effective anxiolytic and hypnotic agents (e.g., diazepam, chlordiazepoxide, prazepam, clorazepate, oxazepam, alprazolam, flurazepam, lorazepam, triazolam, temazepam, estazolam, and quazepam). They bind to benzodiazepine-binding sites on $GABA_A$ receptor.

b) **Nonbenzodiazepine hypnotics (Z-drugs):** Imidazopyridine (zolpidem), pyrazolo pyrimidine (zaleplon), and cyclopyrrolone (zopiclone and its [S]-[+]-enantiomer eszopiclone).

c) **Barbiturates** including amobarbital, aprobarbital, butabarbital, pentobarbital, phenobarbital, and secobarbital are largely obsolete and replaced by benzodiazepines. Their use is now confined to anesthesia and treatment of epilepsy.

d) General anesthetics and ethanol.

2. **Melatonin-1 receptor (MT1) agonists:** e.g. Ramelteon (Rozerem) that has been approved for insomnia.

3. **Miscellaneous drugs** such as glutethimide, meprobamate, and chloral hydrate are no longer recommended, but occasionally used.

4. **Atypical azaspirodecanediones:** Buspirone is a partial 5-HT_1A receptor agonist and an anxiolytic. It is less sedative and has less abuse potential.

5. **Antipsychotics and anticonvulsants.** It has been proposed that DA has a facilitative and active role in the sleep wakefulness cycle. Waking appears to be a

state maintained by D_2 receptor activation, whereas blocking D_2 receptor appears to cause sedation.

6. **Antidepressants:** Many antidepressants cause sedation, of which trazodone, doxepin, and mirtazapine have been shown to be effective in the treatment of insomnia in patients with depression. Several selective serotonin reuptake inhibitors (SSRIs), including escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, became the firstline therapy for some anxiety disorders in 1990s because they are not as addictive as benzodiazepines.

7. **Sedative H1-antihistamines:** diphenhydramine and doxylamine: Diphenhydramine is sometimes used as sleeping pills, particularly for wakeful children. It is proposed that histamine may have an involvement in wakefulness and rapid eye movement (REM) sleep. Histamine-related functions in the CNS are regulated at postsynaptic sites by both H_1 and H_2 receptors, whereas the H_3 receptors appear to be a presynaptic autoreceptor regulating the synthesis and release of histamine. The H_1 receptor agonists and the H_3 receptor antagonists increase wakefulness, whereas the H_1 receptor antagonists and H_3 receptor agonists have the opposite effect. Another example of H_1-antihistamines is doxylamine.

8**. β-Adrenoceptor antagonists** (e.g., propranolol) are sometimes used by actors and musicians to reduce the symptoms of stage fright, but their use by snooker players to minimize tremor is banned as unsportsmanlike.

1-$GABA_A$ RECEPTORS, BENZODIAZEPINES, AND RELATED COMPOUNDS

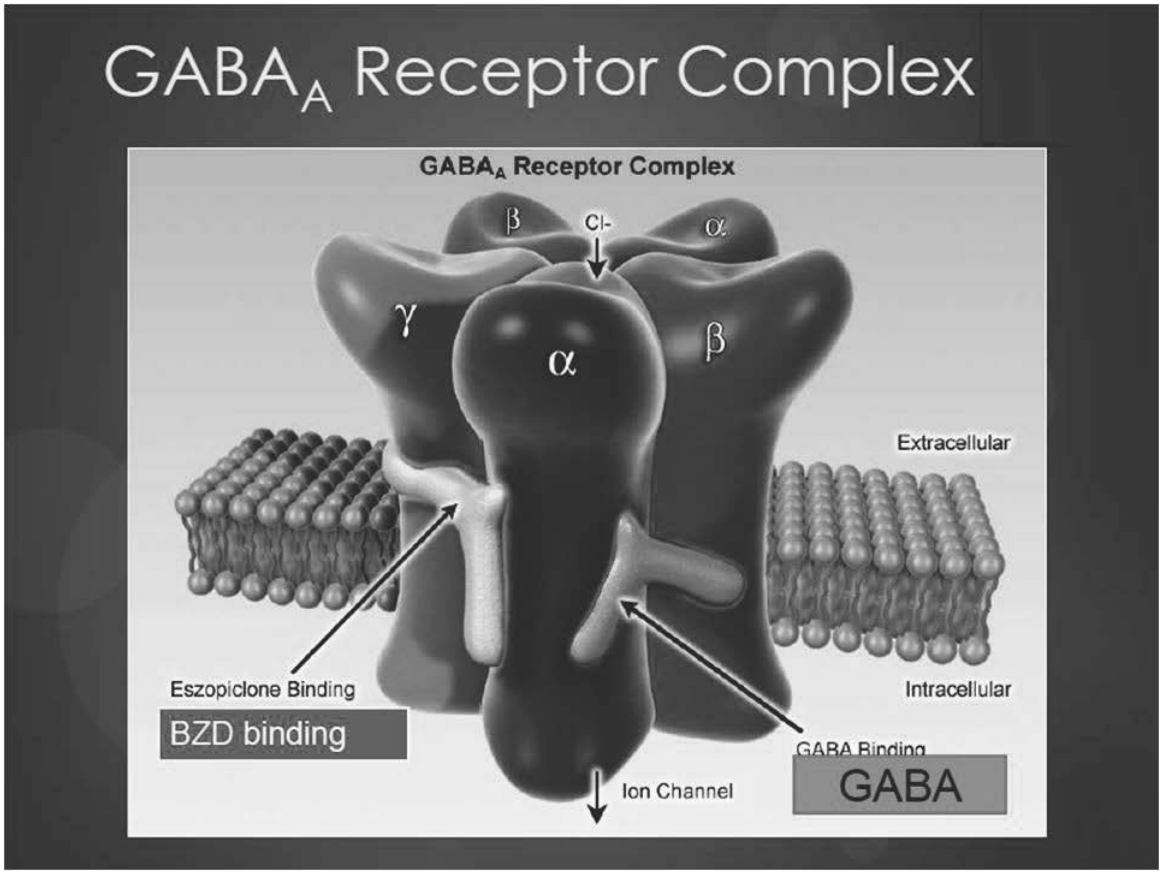
Gamma-aminobutyric acid (GABA) system (deficiency of GABA activity in CNS) is important in the pathophysiology of anxiety and insomnia.

[A]BARBITURATES

The barbiturates were used extensively as sedative-hypnotic drugs. Except for a few specialized uses, they have been replaced largely by the much safer benzodiazepine. Barbiturates act throughout the CNS. However, they exert most of their characteristic CNS effects mainly by binding to an allosteric recognition site on $GABA_A$ receptors that positively modulates the effect of the $GABA_A$ receptor-GABA binding.

Unlike benzodiazepines, they bind at different binding sites and appear to increase the duration of the GABA-gated chloride channel openings. In addition, by binding

to the barbiturate modulatory site, barbiturates can also increase chloride ion flux without GABA attaching to its receptor site on $GABA_A$. This has been termed a GABA mimetic effect. It is thought to be related to the profound CNS depression that barbiturates can produce.

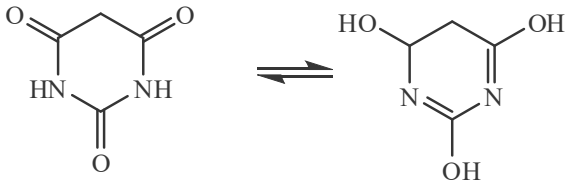


The barbiturates are 5,5-disubstituted barbituric acids. Consideration of the structure of 5,5-disubstituted barbituric acids reveals their acidic character. Those without methyl substituents on the nitrogen have pKa's of about 7.6; those with a methyl substituent have pKa's of about 8.4. The free acids have poor water solubility and good lipid solubility (the latter largely a function of the two hydrocarbon substituents on the 5-position, although in the 2-thiobarbiturates, the sulfur atom increases lipid solubility). Sodium salts of the barbiturates are readily prepared and are water soluble. Their aqueous solutions generate an alkaline pH. A classic incompatibility is the addition of an agent with an acidic pH in solution, which results information and precipitation of the free water-insoluble disubstituted barbituric acid. Sodium salts of barbiturates in aqueous solution decompose at varying rates by base-catalyzed hydrolysis, generating ring-opened salts of carboxylic acids.

Barbiturates produce a wide spectrum of CNS depression, from mild sedation to coma, and have been used as sedatives, hypnotics, anesthetics and anticonvulsants. But they can be addictive and abused.

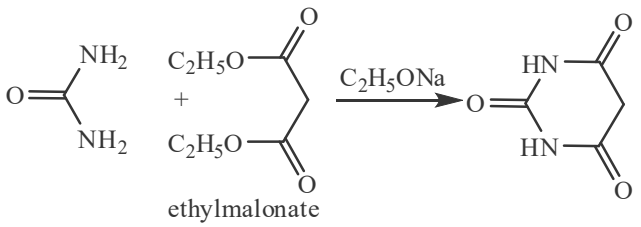
Chemistry of Barbiturates:

1. Barbiturates are derivatives of barbituric acid (2,4,6-trioxyhexahydropyrimidine) which is devoid of hypnotic and sedative activities.



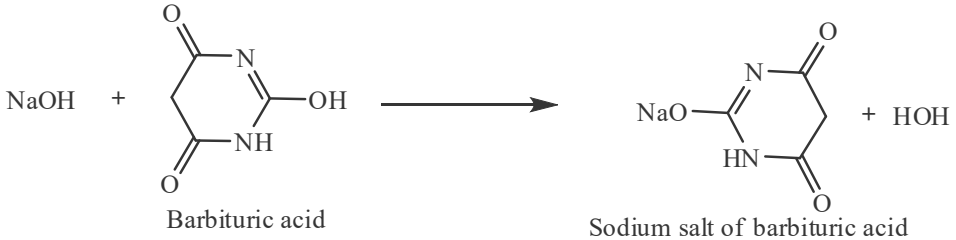
Keto-enol tautomerism of barbituric acid

2. Barbituric acid may be described as a "cyclic ureide of malonic acid". Barbituric acid can be made by condensing urea with ethyl malonate in presence of sodium ethoxide.



ethylmalonate

3. Clinically important hypnotic-sedative barbiturates have substitutions at sites 1, 2 and, especially, 5 of barbituric acid.
4. Keto-enol tautomerism of barbituric acid and barbiturates allows formation of water-soluble salts with a strong base.
5. The barbiturates do not dissolve readily in water, their sodium salts dissolve readily in water.



Barbituric acid

Sodium salt of barbituric acid

6. Buffering action of Na_2CO_3 plus atmospheric CO_2 maintains pH at 10 to 11. In less alkaline solutions, these barbiturates may precipitate as the free acids; so, do not reconstitute barbiturates with normal saline and do not mix with acidic solutions of other drugs.
7. Barbituric acid with Pka = 4.12 and Monosubistituted derivative with Pka = 4.75 → strong acid (at physiological PH are polarized and not penetrate BBB).
8. 5,5-Disubistitution with Pka = 7.6 and Disubstituted with Me substitution on nitrogen → weak acid (can cross BBB at physiological PH).

So, for good hypnotic activity of barbiturate we need: 1. Weak acid 2. ↑ Partition coefficient (to certain limit)

Mechanism of Action of Barbiturates:

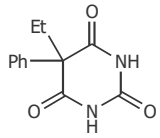
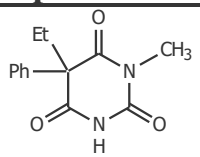
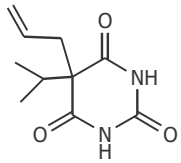
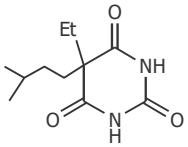
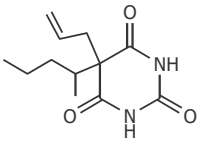
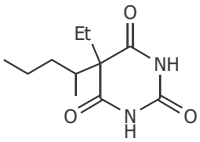
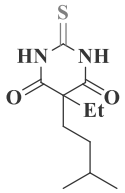
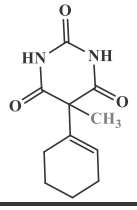
(*a*) Potentiation of the **$GABA_A$-mediated chloride ion conductance**.

(*b*) Enhancement of binding between **GABA** and **benzodiazepine**,

Barbiturate Abuse:

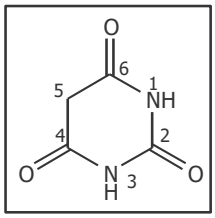
- Prolonged use of barbiturates causes habituation and tolerance to increase dose and physical dependence.
- Phenobarbital → Hepatic Microsomal Enzyme Inducing Drug [HME Inducer] → tolerance + many drug-drug Interaction.

Classification of Barbiturate

<table>
<tr><th colspan="4">1. Long acting (> 6 hrs)</th></tr>
<tr><th colspan="2">Phenobarbital</th><th colspan="2">Mephobarbital</th></tr>
<tr><td colspan="2"> 
5-Ethyl-5-phenyl barbituric acid</td><td colspan="2"> 
5-Ethyl-1-methyl-5-phenyl barbituric acid</td></tr>
<tr><th colspan="2">2. Intermediate acting (3-6 hr)</th><th colspan="2">3. Short acting (< 3 hr)</th></tr>
<tr><th>Aprobarbital</th><th>Amobarbital</th><th>Secobarbital</th><th>Pentobarbital Na</th></tr>
<tr><td> 
5-allyl-5-isopropyl barbituric acid</td><td> 
5-ethyl-5-isopentyl barbituric acid</td><td> 
5-allyl-5-(1-methyl butyl) barbituric acid</td><td> 
5-ethyl-5-(1-methyl butyl) barbituric acid</td></tr>
<tr><th colspan="4">4. Ultra short acting [G.A] [10-30 min.]</th></tr>
<tr><th colspan="2">Thiopental</th><th colspan="2">Hexobarbital</th></tr>
<tr><td colspan="2">  </td><td colspan="2">  </td></tr>
<tr><td colspan="4">Administered by injection [as sodium salts], for induction of anesthesia with immediate onset [10 sec] & very short duration → with ↑ lipophilicity & ↑ plasma protein binding [>70%].</td></tr>
</table>

SAR:

a) C_5:



1. C_5-H atoms must be substituted (summation of both subistituants should be 6-10 Cs).
2. Branching, unsaturation, replacement of alkyl group with alicyclic or aromatic groups → all ↑ lipid sol → ↑ potency.
3. Introduction of halogen atom into 5-alkyl subs → ↑ potency.

4. Introduction of polar group (OH, NH_2, RNH, CO, COOH & SO_3H) to 5-alkyl group → ↓ lipid sol → destroys the potency.

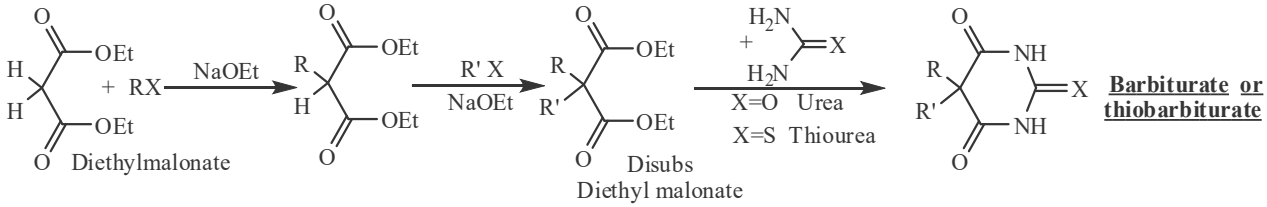
b) N atoms:

1. Methylation of N_1 or N_3 → ↑ lipid solubility → quick onset & short duration.
2. Subistitution of both N atoms → non-acidic → inactive.

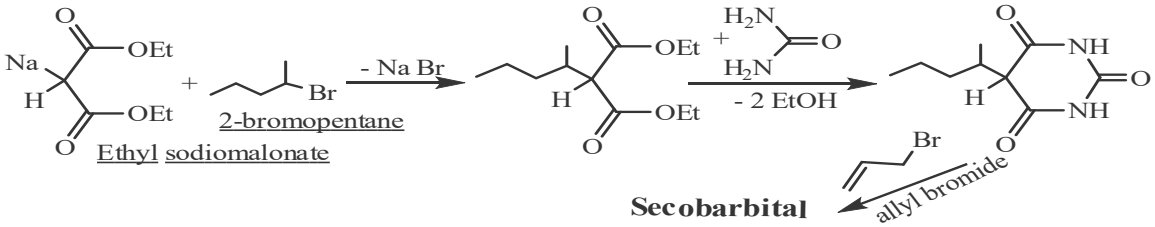
c) O atoms:

1. Replacement of C=O by C=S → ↑ lipid solubility → rapid onset & short duration (So, thiobarbiturate used as IV anesthetics).
2. Introduction of more S atoms (2, 4-dithio) → destroy activity (↓ hydrophilic characters below required limits, no dissolution).

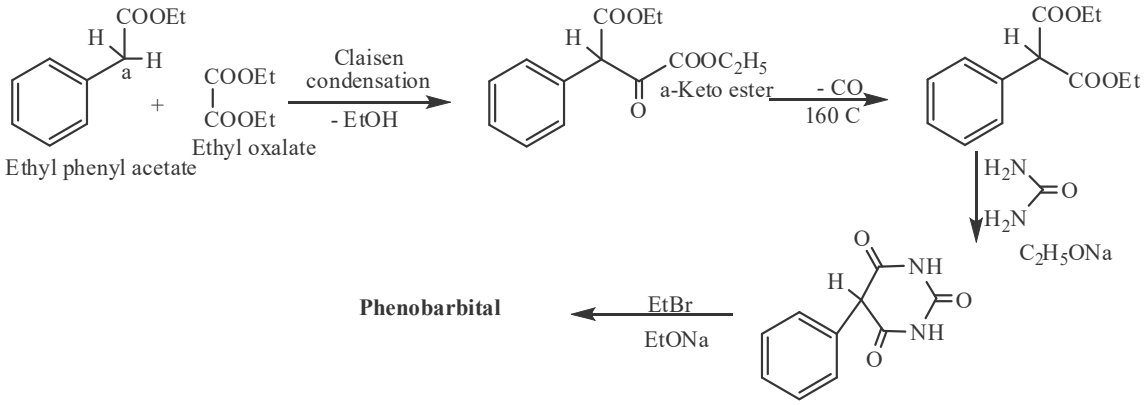
Synthesis of 5, 5-disubstituted:



Synthesis of Secobarbital:



- Synthesis of Phenobarbital: [can be applied for Mephobarbital]
- General synthetic method cannot be applied as Aryl halide not reactive to react with sodiomalonic acid ester. so, the following methods used:



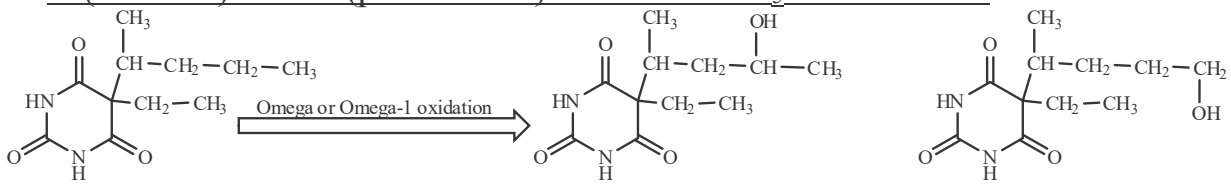
Assay of Barbiturate (Phenobarbital):

1. **Argentometric titrations:** Dissolve in pyridine → add excess $AgNO_3$ → HNO_3 which is titrated against standard NaOH (using thymol blue as indicator) (1 mol. Phenobarbital = 2 mol. NaOH).
2. **Non–aqueous titration** as weak acid dissolved in DMF and titration against NaOMe.

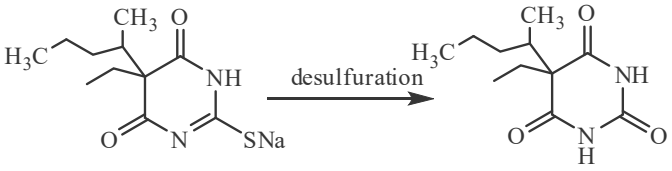
Metabolism of Barbiturate:

Barbiturate loss activity by metabolism in liver as follow:

1. ω (ultimate) or ω-1 (penultimate) oxidation of C_5 subistituants.



2. Desulfuration of 2-thiobarbiturate yielding more hydrophilic barbiturate.



Thiopental phenobarbital

3. N-demethylation: during mephobarbital therapy a definite blood level of Phenobarbital established

4. Hydrophilic cleavage of the ring yielding acetamide + acetylurea.

[B] BENZODIAZEPINES (BZPS)

Benzodiazepine is a psychoactive drug whose core chemical structure is the fusion of a benzene ring and a diazepine ring.

Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties.

Benzodiazepines are categorized as short-, intermediate-, or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety.

Uses benzodiazepines (BzPs (Drug of Choice):

1. Anxiolytics.
2. Pre-anesthetic (induction of anesthesia)
3. Hypnotic.
4. Anticonvulsant.
5. Central acting skeletal muscle relaxant.
6. Alcohol withdrawal

Advantage over barbiturates:

1. More safe (overdose → no respiratory depression)
2. Low tendency of drug interaction.
3. Preferred over barbiturate for patient with suicidal intention.

Disadvantage:

Slow eliminated from body → due to formation of active metabolite in brain and liver → hangover effect and accumulation on repeated dose.

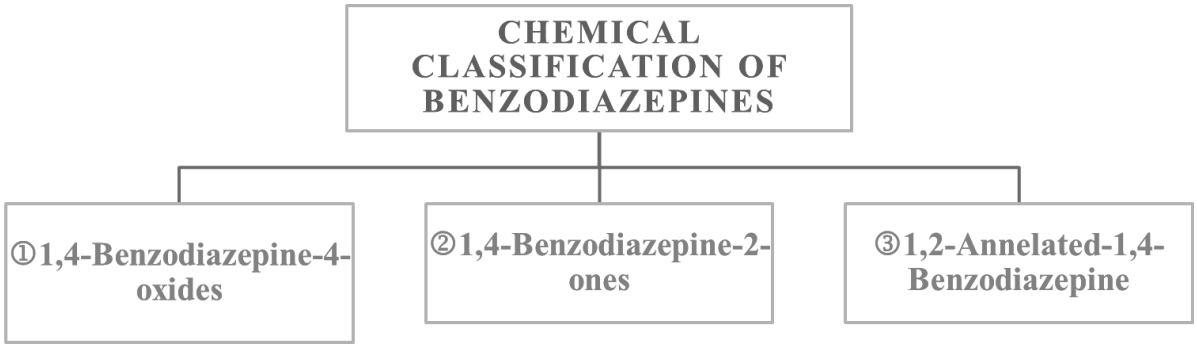
N.B.

- BZPs potency depend on lipid solubility → ↑ lipophilicity will ↑ potency → (more distributed to the brain).
- BZPs duration → depend on metabolism.

M.O.A:

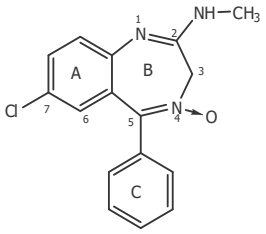
They bind to BZPs binding sites on $GABA_A$ receptor (also known as benzodiazepine receptor [BzR]) → enhancing effect of $GABA_A$ receptors → As a result, the frequency of Cl^- channel openings are increased, and the cell is further hyperpolarized, yielding a more pronounced decrease in cellular excitability.

CLASSIFICATION OF BENZODIAZEPINES



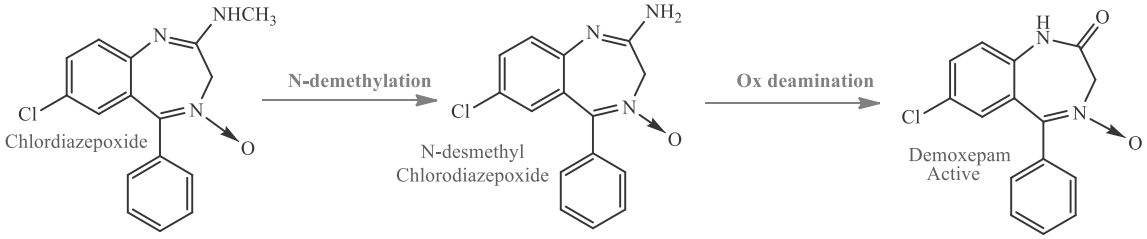
①1,4-BENZODIAZEPINE-4-OXIDES

Chlordiazepoxide *(Librium)*®



7-Chloro-2-(methyl amino)-5-phenyl-3H-1,4-benzodiazepine-4-oxide

- Chlordiazepoxide is the prototype and the most potent member. It is rapidly metabolized to a series of active benzodiazepine-2-ones.
- Chlordiazepoxide + Clidinium Br^- (anti-cholinergic drug) *(Librax®)*
- The half-life of chlordiazepoxide is 6 to 30 hours.
- N-demethylation and hydrolysis of the condensed amidino group are rapid and extensive, producing demoxepam as a major metabolite.

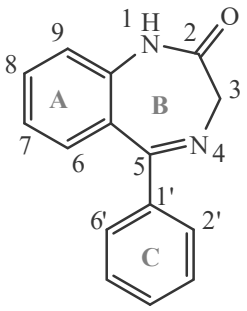


SAR:

- ↑ Size of subistituents at C_2 → ↓ potency.
- Replacement of the phenyl group at C_5 by other subs → ↓ activity.
- The N_1-imidino function is NOT essential for activity → as the drug metabolized to 1,2-lactam structure (Demoxepam) and still active.
- The N-imino structure is essential for activity.
- It's long acting drug due to formation of several active metabolites

②1,4-BENZODIAZEPINE-2-ONES

Ring System



5-Phenyl-1,4-benzodiazepin-2-one

SAR:

Ring A:

- Electron withdrawing group at C_7 is essential (Cl, Br, F, NO_2, CN) [the more electron attracting effect → the more activity].
- C_7 → NO_2 (intermediate duration) → due to metabolism of NO_2 into NH_2 → Acetylation (inactive metabolites).
- Position 6,8,9 should not substituted.

Ring B:

- The presence of 7-membered imino-lactam ring is essential.
- The 2-carbonyl function is essential for activity.
- The N1-substitution should be small → except if active matabolits produced as (flurazepam and prazepam)
- Alkyl subs at C_3 → ↓ activity.
- The presence or absence of 3-OH sis important pharmakokinetically.

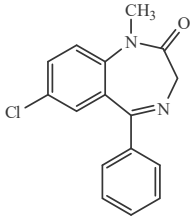
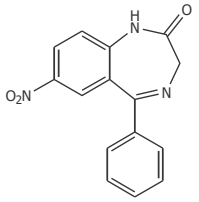
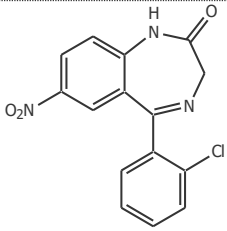
* Without 3-OH → non-polar (long duration).

* With 3-OH → more polar → more easily excreted as glucuronides → short duration.

- COOH at C_3 → prodrug with long half-life.
- C_5 phenyl group promotes activity.
- Saturation of double bond between C_4, C_5 OR its shift to C_3, C_4 → ↓ activity.

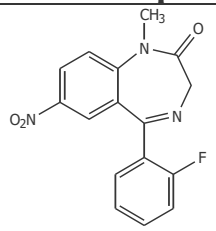
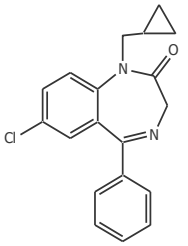
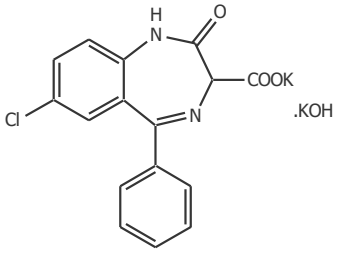
Ring C:

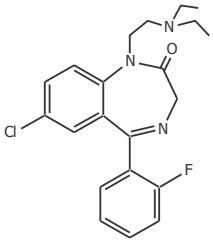
- The presence of ortho or diortho substitution with electron-attracting effect → ↑ activity.
- Para substitution → ↓ activity.

Diazepam (Valium®)	Nitrazepam	Clonazepam
		 **Anti-convulsant drug**

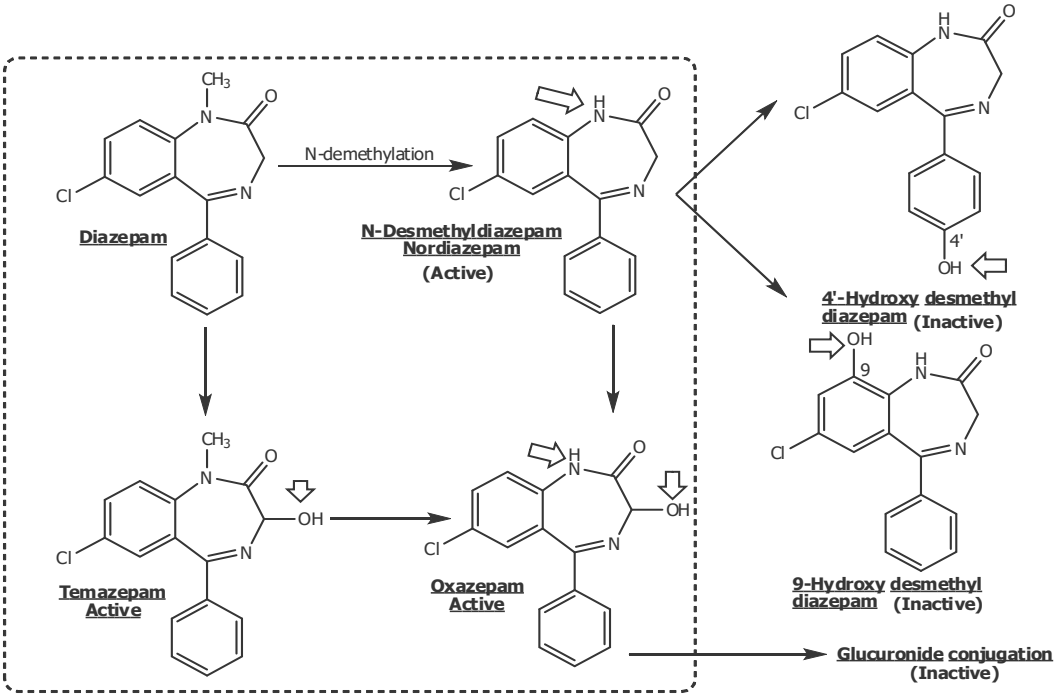
Diazepam (Valium)®:

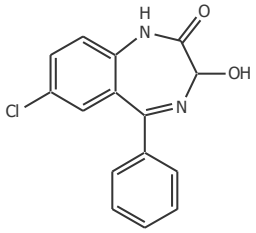
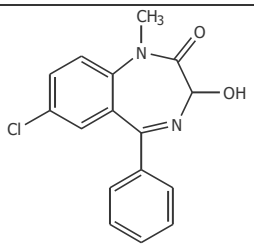
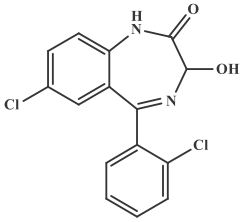
- Prototype of this class.
- It is very lipophilic and is thus rapidly and completely absorbed after oral administration → very potent.
- With long duration (maximum peak blood concentration occurs in 2 hours and elimination is slow, with a half-life of about 46 hours) → active metabolites.

Flunitrazepam	Prazepam	Chlorazepate dipotassium
 *F and methyl → ↑ lipophilicity and potency*	 *Prodrug → N-dealkylation to Nordiazepam*	 **Prodrug** → activated by decarboxylation in stomach to Nordiazepam (active)→ with long t1/2 (water sol → IV)

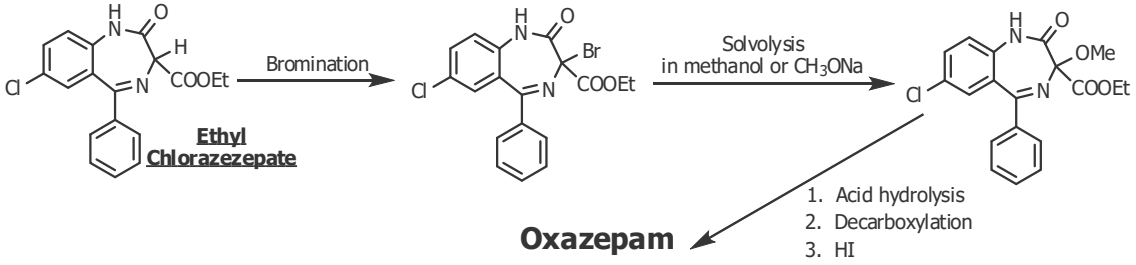
Flurazepam
 Prodrug → N-dealkylation to active form (with long t1/2)

Metabolism of Diazepam:



Oxazepam	Temazepam	Lorazepam
 The prototype for 3-OH compounds. Much more polar than diazepam → Undergo rapid conjugation with glucuronic acid → short duration and low accumulation in the body.		 *7-Chloro-5-(2-chloro phenyl)-1,3-dihydro-3-hydroxy-1,4-benzodiazepine-2-one*

Synthesis:



③1,2-ANNELATED-1,4-BENZODIAZEPINE

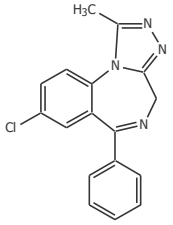
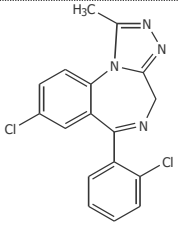
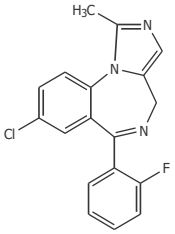
Modification of BZPs by the addition of the ring of a cyclic compound to form a polycyclic compound. Characterized by high affinity for BZR and reduced side effects.

The fused heterocycle is triazole as triazolam & alprazolam and imidazole in medazolam.

Alprazolam: Is rapidly absorbed from the GI tract. Protein binding is lower (~70%) than with most benzodiazepines because of its lower lipophilicity→ due to rapid oxidation of $-CH_3 \rightarrow -CH_2OH \rightarrow$ conjugation and excretion.

Triazolam: It is an ultra-short-acting hypnotic because it is rapidly α-hydroxylated to the 1-methyl alcohol, which is then rapidly conjugated and excreted. Consequently, it has gained popularity as sleep inducers, especially in elderly patients, because it causes less daytime sedation.

Midazolam: This drug is used intravenously as a short-acting sedative-hypnotic and as an induction anesthetic because of its short half-life for the same reason.

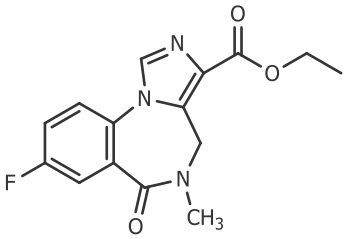
Alprazolam (Xanax)®	Triazolam	Midazolam
		
8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4] benzodiazepine	*8-Chloro-6-(o-chloro-phenyl)-1-methyl-4H-s-triazolo[4,3-a][1,4] benzodiazepine*	**Used as general anesthetic**

Assay of Diazepam:

By non-aqueous titration: dissolve in acetic anhydride, titrate with perchloric acid using Nile blue indicator. [Benzodiazepines are weak bases while barbiturates were weak acids].

Benzodiazepine Antagonist

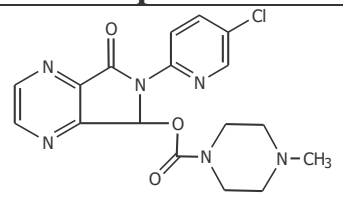
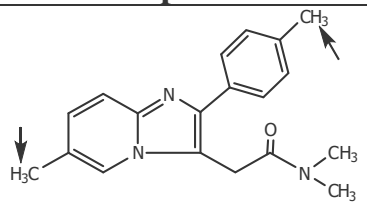
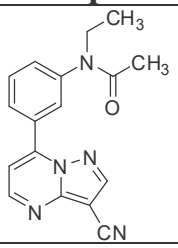
Flumazenil is an imidazobenzodiazepinone with selective benzodiazepine receptor antagonist.



[C]-NONBENZODIAZEPINE BZRAS (Z-DRUGS):

Nonbenzodiazepine hypnotics (Z-drugs): Imidazopyridine (zolpidem), pyrazolopyrimidine (zaleplon), and cyclopyrrolone (zopiclone and its [S]-[+]-enantiomer eszopiclone). They are nonbenzodiazepines and have been introduced as short- and moderate-acting hypnotics, respectively. Zolpidem exhibits a high selectivity for the α_1-subunit of benzodiazepine-binding site on $GABA_A$ receptor complex, whereas eszopiclone is a "superagonist" at BzRs with the subunit composition $\alpha_1\beta_2\gamma_2$ and $\alpha_1\beta_2\gamma_3$.

Zolpidem has a rapid onset of action of 1.6 hours and good bioavailability (72%), mainly because it is lipophilic and has no ionizable groups at physiological pH. Food can prolong the time to peak concentration without affecting the half-life probably for the same reason.

[1] Cyclopyrolone deriv.	**[2] Imidazopyridine**	**[2] Pyrazolopyrimidine**
Zopiclone	**Zolpidem**	**Zaleplon**
		
Advantage: 1. No withdrawal symptoms. 2. No accumulation after repeated doses. 3. Rapidly induce sleep.	**Advantage:** 1. Rapid onset and short duration. 2. No rebound effects upon withdrawal of the drug	It is similar to zolpidem; both are hypnotic agents with short half-lives. It also has selective high affinity for α_1-subunit containing BzRs but produces effects at other $BzR/GABA_A$ subtypes as well.
Metabolism: 1. **Major:** N-Oxide zopiclone (less active) 2. **Minor:** N-des methyl zopiclone (inactive)	**Metabolism:** Hydroxylation of the methyl groups →followed by further oxidation →→ the carboxylic acid which then conjugated for excretion.	**Metabolism:** It is primarily metabolized by aldehyde oxidase to **5-oxo-zaleplon** and is also metabolized to a lesser extent by CYP_3A_4.

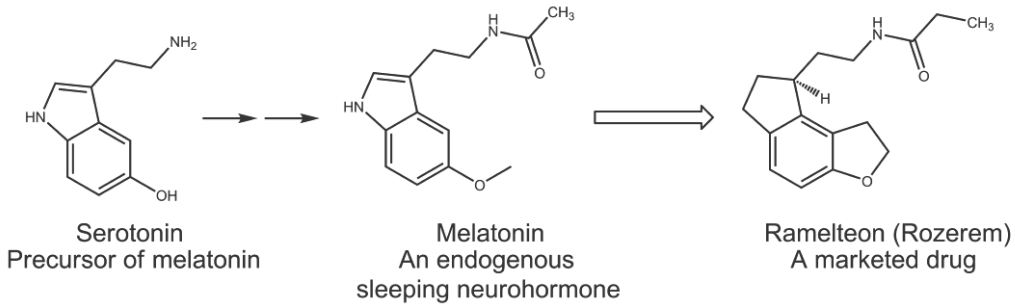
2-MELATONIN RECEPTOR AGONIST: RAMELTEON

In the brain, three melatonin receptors (MT_1, MT_2, and MT_3). Activation of the MT_1 receptor results in sleepiness, whereas the MT_2 receptor may be related to the circadian rhythm. MT_3 receptors may be related to intraocular pressure.
Melatonin (N-acetyl-5-methoxytryptamine), referred to as "the hormone of darkness," is biosynthesized and released at night and may play a role in the circadian rhythm of humans.

Ramelteon (Rozerem)®:
The melatonin molecule was modified mainly by replacing the nitrogen of the indole ring with a carbon to give an indane ring and by incorporating 5-methoxyl group in the indole ring into a more rigid furan ring. The selectivity of the resulting ramelteon for MT_1 receptor is eight times more than that of MT_2 receptor. Unlike melatonin,

Ramelteon is more effective in initiating sleep (MT_1 activity) rather than to readjust the circadian rhythm (MT_2 activity).

It is more efficacious than melatonin but less efficacious than benzodiazepines as a hypnotic but it has no addiction liability, so it has been recently been approved for the treatment of insomnia.



Serotonin
Precursor of melatonin

Melatonin
An endogenous
sleeping neurohormone

Ramelteon (Rozerem)
A marketed drug

3-MISCELLANEOUS SEDATIVE–HYPNOTICS

A wide range of chemical structures (e.g., imides, amides, alcohols) can produce sedation and hypnosis resembling those produced by the barbiturates. Despite this apparent structural diversity, the compounds have generally similar structural characteristics and chemical properties: a nonpolar portion and a semipolar portion that can participate in H-bonding. In some cases, modes of action are undetermined. As a working hypothesis, most of the agents can be envisioned to act by mechanisms similar to those proposed for barbiturates and alcohols.

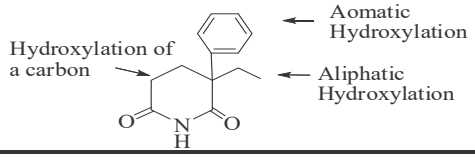
[i]-Amides and Imides (Piperidinediones)

Structurally and biologically like barbiturate and also enzyme inducer.

Glutethimide

It is one of the most active nonbarbiturate hypnotics that is structurally similar to the barbiturates, especially phenobarbital.

Glutethimide is a pyridine derivative. Chemically it is 2-ethyl-2-phenyl- glutarimide and is a substitute for barbiturates, to treat insomnia. It is fast acting sedative (30 minutes) with a long duration (6 hrs.). Effectiveness lasts for longer a period (5–7 days).

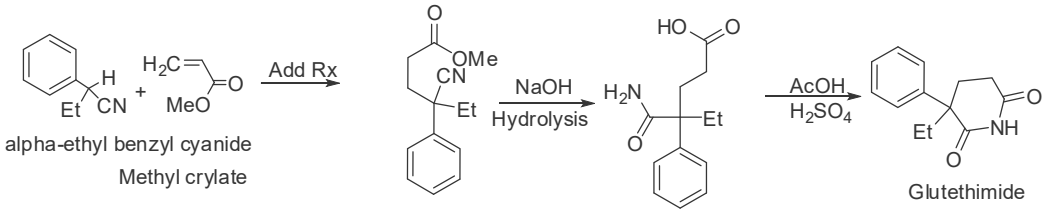
Glutethimide

or 2-ethyl-2-phenyl glutarimide

Metabolism of Glutethimide:

1. Hydroxylation of the α–carbon to carbonyl group → ***4-hydroxyglutethimide***.
2. ***Aliphatic hydroxylation*** (ω-1 OH)
3. ***Aromatic hydroxylation*** (minor metabolite)

Synthesis of Glutethimide:

Glutethimide is prepared by treating benzyl cyanide with ethyl chloride in presence of sodamide to yield α-ethyl benzyl cyanide

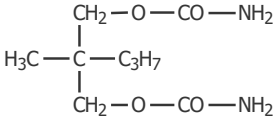
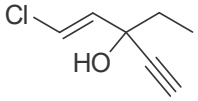


[ii]-Alcohols and Their Carbamate Derivatives

The very simple alcohol ethanol has a long history of use as a sedative and hypnotic. It is widely used in self-medication as a sedative-hypnotic. Because this use has so many hazards, it is seldom a preferred agent medically.

SAR:

1. CNS depressant potency increases up to eight carbon atoms, with activity decreasing thereafter.
2. Branching of the alkyl chain increases depressant activity and, in an isometric series, the order of potency is tertiary > secondary > primary, this may be because tertiary and secondary alcohols are not metabolized by oxidation to the corresponding carboxylic acids.
3. Replacement of a hydrogen atom in the alkyl group by a halogen increases the alkyl portion and, accordingly, for the lower molecular weight compounds, increases potency.
4. Carbamylation of alcohols generally increases depressant potency. Carbamate groups are generally much more resistant to metabolic inactivation than hydroxyl functions.
5. Less active than BZPs as Anxiolytics.
6. Mepromate and Carisoprodol are used as muscle relaxant agent.

Meporamate	Ethchlorvynol
 *2-Methyl-2-propyl trimethylene dicarbamate*	 *1-Chloro-3-ethyl-1- penten-4-yn-3-ol*

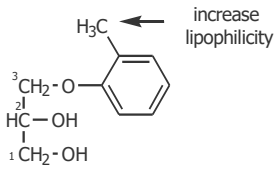
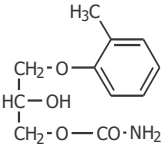
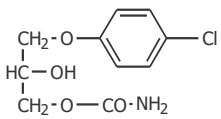
Meprobamate: (Equanil)

Meprobamate, is officially indicated as an antianxiety agent. It is also a sedative-hypnotic agent.

Ethchlorvynol:

It is a mild sedative-hypnotic with a quick onset and short duration of action (t1/2-5.6 hours). Because of its highly lipophilic character, it is extensively metabolized to its secondary alcohol (90%) prior to its excretion. It reportedly induces microsomal hepatic enzymes. Acute overdose shares several features with barbiturate overdose.

Propanediol Carbamate derivatives (Aryl Glycerol Monoethers)

Mephenesin	Mephenesin carbamate	Chlorphenesin carbamate
		 *3-(p-Chlorophenoxy)-1,2-prpanediol-1-carbamate*
The prototype. Weak activity & short duration → due to rapid metabolism of OH	More active > Mephenesin (OH is protected → Carbamoylation ↑ activity)	P-Chlorination → ↑ lipophilicity and block P-posotion hydroxylation

[iii]-Aldehydes and their derivatives

Few aldehydes are valuable hypnotic drugs. The aldehyde in use, chloral (as the hydrate), is thought to act principally through a metabolite, **trichloroethanol**. Acetaldehyde is used as the cyclic trimer derivative, paraldehyde, which could also be grouped as a cyclic polyether.

Chloral hydrate: (Noctec)

$$CCl_3CH(OH)_2$$

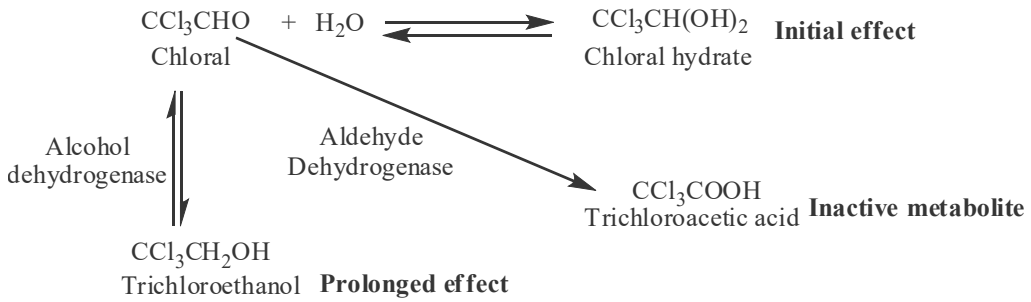
Trichloroacetaldehyde monohydrate

It is a sleep-inducing drug used in the early 1900's but seldom used today. Chloral hydrate is used as hypnotic to treat insomnia and to allay anxiety as sedative.

Chloral hydrate is unstable in alkaline solutions, under-going the last step of the haloform reaction to yield chloroform and formate ion.

Metabolism:

Chloral hydrate is very quickly converted to trichloroethanol, which is generally assumed to account for almost all of the hypnotic effect. The trichloroethanol is metabolized by oxidation to chloral and then to the inactive metabolite, trichloracetic acid which is also extensively metabolized to acyl glucuronides via conjugation with glucuronic acid.



- Both Chloral hydrate and Trichloroethanol are equipotent → reduced (detoxified) to the inactive Trichloroacetic acid.
- Trichloroehtanol → accounts for hypnotic activity. It is still use as a sedative in small operations for the pediatric patient.

Mechanism of Action:

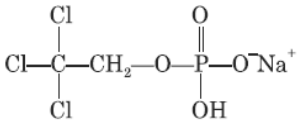
- Act on GABA receptors → [bind to other site than Barbiturates and BZP]
- All enhance GABA inhibitory effect centrally.

Advantage: not cause respiratory center depression.

Disadvantage:

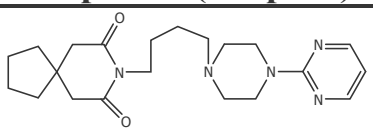
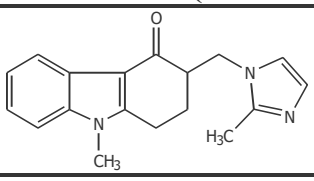
1. Unpleasant odour and taste.
2. GIT irritant → nausea and vomiting due to it is weak acid because its CCl_3 group is very strong electron withdrawing.
3. They thought that the combination of ethanol and chloral hydrate is the basis for the lethal effect.

Triclofos Sodium



- Triclofos is 2,2,2-trichloroethylhydrogen orthophosphate, which occurs as its sodium salt.
- Triclofos sodium is hygroscopic, white colored, water soluble powder.
- Triclofos is used as hypnotic and sedative.

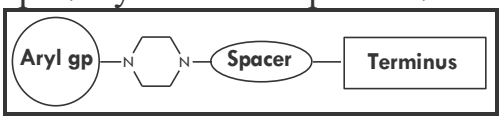
iv-Atypical Azaspirodecanediones

Buspirone (Buspar®)	**Ondansetron (Zofran®)**
 *Aza spirodecanedione derivative*	
Uses: Anxiolytic and Antidepressant **M.O.A: 5-HT$_{1A}$ partial agonist.** **S.E.:** Block Dopamine receptors → (EPS)	- **Uses:** Anxiolytic, Anti-depressant and Anti-emetic and anti-psychotic. - **M.O.A:** 5-HT$_3$ antagonist.

Buspirone:

● Member of Long Chain Aryl Piperazines (LCAPs) ●They show effects of these parts on SAR.

● In Buspirone: Aryl group → Pyrimidine / Spacer → 4C / Terminus → amide



II-Centrally Acting Skeletal Muscle Relaxants

Uses:

Muscle spasm (due to spinal cord trauma), Arthritis, joint inflammation, low back bain, disk syndrome.

M.O.A:

Block inter-neuronal properties at the spinal cord by *inhibiting polysynaptic & monosynaptic transmission.*

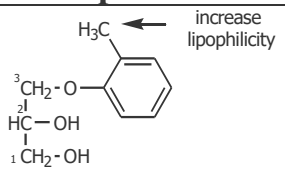
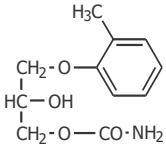
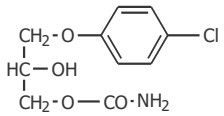
Classification:

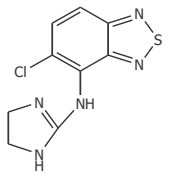
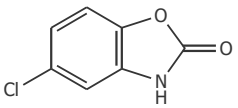
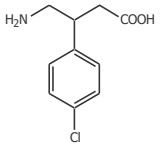
i. **Propanediol carbamate derivatives.**
ii. **Aryl glycerol monoethers.**
iii. **Miscellaneous.**

i) Propanediol Carbamate Derivatives.

Meprobamate and Carisoprodol (N-isopropyl-2-methyl-2-propyl-1,3-propane diol dicarbamate)

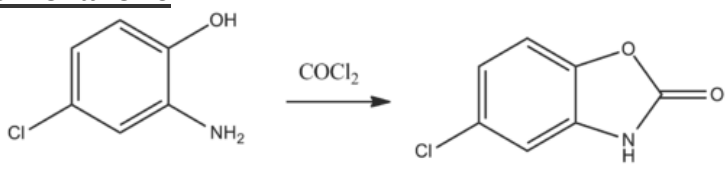
[ii] Aryl Glycerol Monoethers.

Mephenesin	Mephenesin carbamate	Chlorphenesin carbamate
		 *3-(p-Chlorophenoxy)-1,2-prpanediol-1-carbamate*
The PROTOTYPE. Weak activity &short duration → due to rapid metabolism of OH	More active > Mephenesin (OH, is protected → Carbamoylation ↑ activity)	P-Chlorination → ↑ lipophilicity & block P-posotion hydroxylation

Tizanidine (Sirdalaud®)	Chlorzoxazone [Myolgin®]	Baclofen
		 *(RS)-4-Amino-3-(4-chlorophenyl) butanoic acid* (GABA Analogue) Used in disease of spinal cord

Tizanidine: is a centrally acting α_2 adrenergic agonist. It is used to treat spasms, cramping, and tightness of muscles.

Synthesis of chlorzoxazone

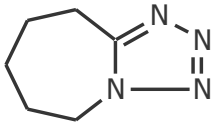


Chlorzoxazone, is synthesized by a hetercyclization reaction of 2-amino-4-chlorophenol with phosgene.

[III]-ANTICONVULSANT [ANTIEPILEPTICS]

- The epilepsies are a group of disorders characterized by chronic, recurrent, paroxysmal changes in neuralgic function caused by abnormalities in electrical activity of the brain. They are one of the common neuralgic disorders, estimated to affect 0.52% of the population and can occur at any age. The terms convulsion and seizure are often used interchangeably and basically have the same meaning.
- **It's imbalance between excitatory neurotransmitter (Glutamate) and inhibitory neurotransmitter (GABA).**
- It can be induced or diagnosed by:

1. Injection of phenylene tetrazole. **2**. Electric shock.



Antiepileptics: are drugs that are used to prevent and control epileptic seizures.

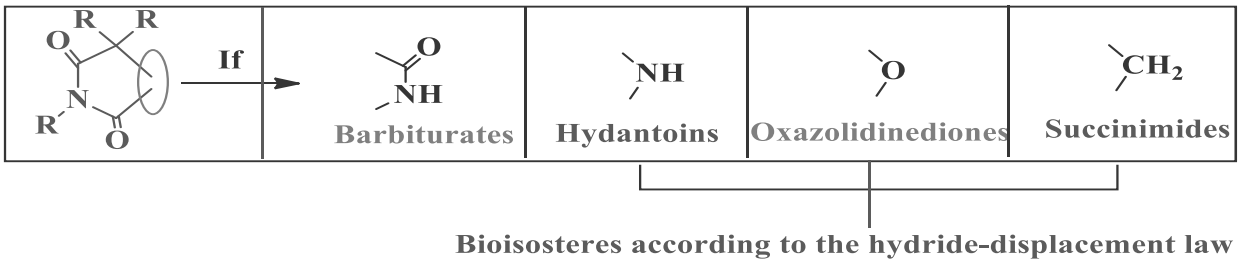
Types of seizures:

1. **Generalized seizure**: it involves the entire brain and it is either:
   a. **Tonic-clonic seizures (Grand mal)** is normally characterized by complete loss of consciousness, followed by transient muscular rigidity (tonic phase) and ultimately plunges into violent clonic convulsions embracing all voluntary muscles.
   b. **Non-convulsant, absence (Petit mal**) → brief loss of consciousness with no motor activity.
2. **Partial seizure**: (Simple focal).
3. **Unilateral seizure:** Involve one entire side of the body.
4. **Myoclonic seizure**: in newborn.
5. **Unclassified seizure**: sever seizures associated with high mortality.
   - The only effective way to control epilepsy is to use of drug.
   - The first drug used (KBr, 1857) followed by barbiturates (1912) and phenytoin (1938).

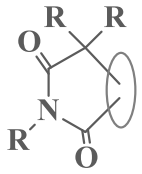
Classification:

I) Cyclic ureides and imides. II) Ureas e.g: Phenacemide. III) Miscellaneous

[I] Cyclic Ureides and Imides



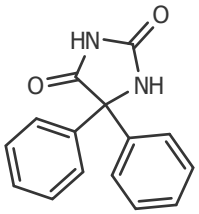
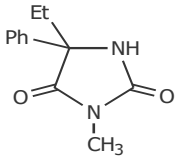
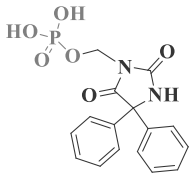
The general SAR:



1. The substitution pattern at C_5 of the hydantoins and oxazolidinediones or C_2 of the succinimides determines the type of anti-convulsant activity.
2. Hydantoins with at least one C_5 phenyl group are the drug of choice in → generalized tonic-clonic seizure (grand mal). The diphenyl substitution pattern ↑potency of anti-grand mal > single substituent.
3. Oxazolidinediones subistitution at C_5 with small alkyl chain (Me or Et.) more effective against absence seizure (Petit mal) but less effective against grand mal seizures.
4. Oxazolidinediones are toxic; succinimides are safer as alternative for Petit mal.
5. The most potent anti-petit mal succinimides have small alkyl groups at C_2.
   Note: R_1, R_2 → Lower alkyl → petit mal, but Phenyl → grand mal.

1) Hydantion

- They are Na channel blockers →↓ glutamic acid release.
- Used against Grand-mal epilepsy [as soluble Na salts].
- All are metabolized by aromatic hydroxylation followed by conjugation.

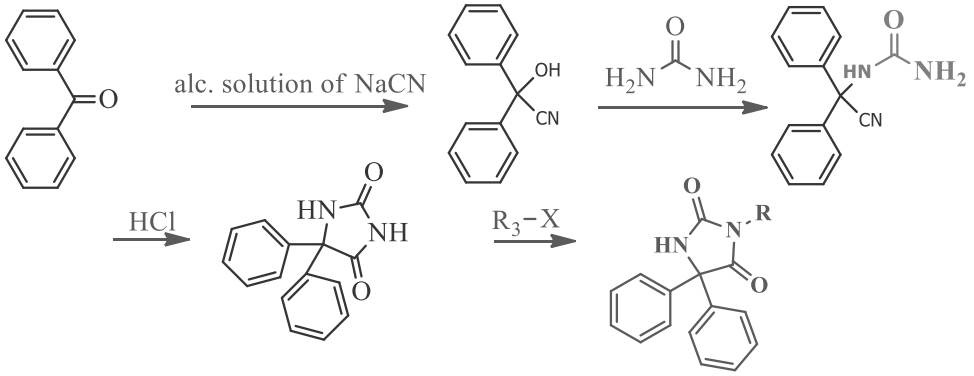
Phenytoin	Mephenytoin	Fosphenytoin
		
5,5-Diphenyl imidazilidine-2,4-dione	*5-Ethyl-3-mehtyl-5-phenyl hydantoin*	
Structurally close to barbiturates (differ in lacking the 6-oxo moiety) with anti-generalized tonic clonic >> Anti-absence.		
Anti-convulsant activity separated from sedative-hypnotic activity. Metabolized by P-hydroxylation only.	Metabolized by N-dealkylation then by aromatic hydroxylation → conjugation.	

Fosphenytoin (Cerebyx)

- Phenytoin, the drug may be incompletely or erratically absorbed from sites of administration because of its very low water solubility.
- Fosphenytoin, a prodrug of phenytoin, was developed and marketed to avoid complications such as vein irritation, tissue damage, and muscle necrosis associated with parenteral phenytoin administration.

- Fosphenytoin is rapidly absorbed either by intravenous or intramuscular administration.
- It is converted into phenytoin through phosphatase catalyzed hydrolysis of the phosphate ester.

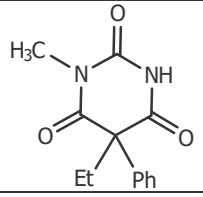
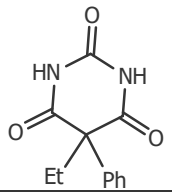
Synthesis of 5,5-disubs hydantoins:



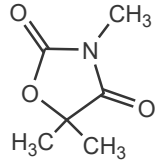
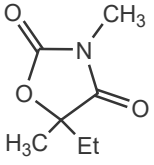
Assay: As barbiturates

1) Non aqueous titration as weak acid, solution in DMF is titrated with NaOMe
2) $AgNO_3$ is added to solution of hydantion in pyridine then titration of the liberated HNO_3 by standard NaOH.

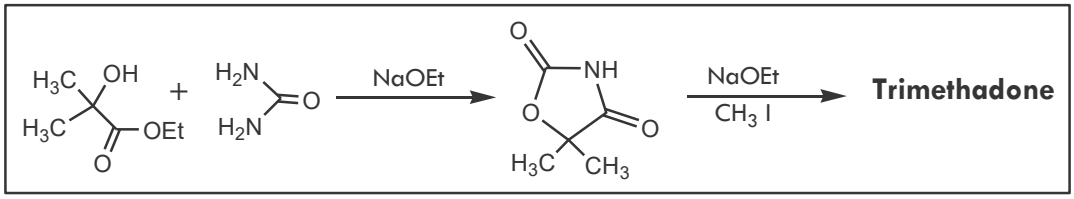
2) Barbiturates

Mephobarbital	Phenobarbital
	
Mephobarbital (prodrug) by metabolism (N-dealkylation) → Phenobarbital (active form)	
Used in generalized and partial seizures (**Grand-mal epilepsy**)	

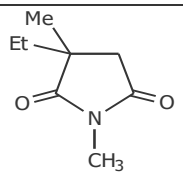
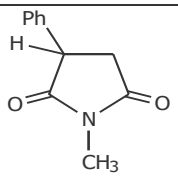
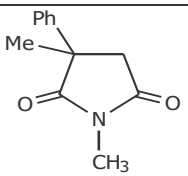
3) Oxazolidindione

Trimethadone		Paramethadone	
	*3,5,5-Trimethyl-1,3-oxazolidine-2-4-dione.* **Side effects:** bone marrow depression.		*5- Ethyl-3,5-dimethyl-2,4-oxazolidindione*
Both of them are used in treatment of petit mal seizures			

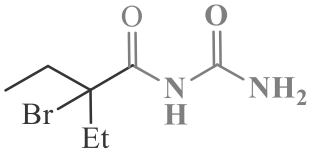
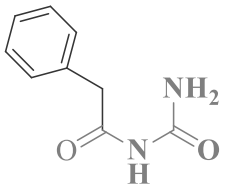
Synthesis of Trimethadone:



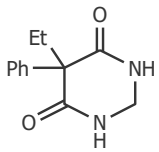
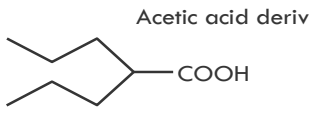
4) Succinimide

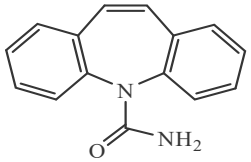
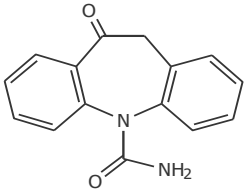
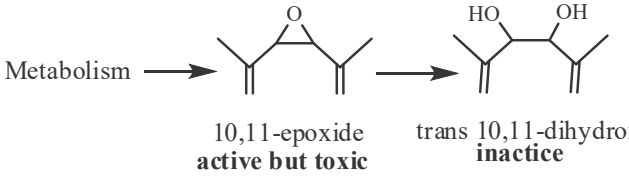
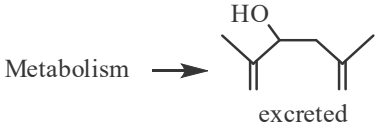
Ethosuximide	Phensuximide	Methuximide
		
2-Ethyl-2-methyl succinimide	*N-methyl-2-phenyl succinimide*	*N,2-Dimethyl-2-phenyl succinimide*
More effective and less toxic than trimethadione → for pitit mal seizures.	due to the Phenyl group → some activity against generalized seizure	Used in absence and partial seizures

[II] UREAS

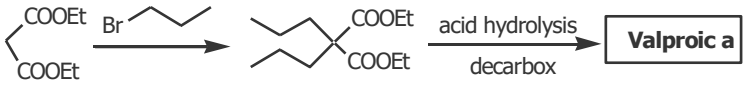
Carbamol	Phenacemide
 *2-bromo-N-carbamoyl-2-ethylbutanamide*	 *N-carbamoyl-2-phenyl acetamide*
Prolonged use not recommended → **Toxicity** (as Br^- released in vivo by enzymatic debromination)	

[III] Miscellaneous Anticonvulsant Drugs

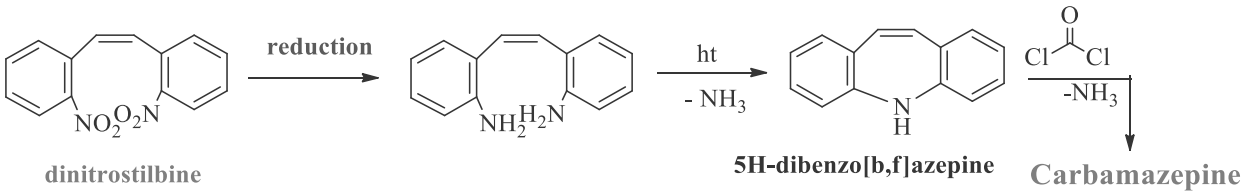
Primidone	Valproic acid (Depakin®)
 5-Ethyl-5-phenyl perhydrpyrimidine-4,6-doine	 2-propyl pentanoic acid
Grand mal seizures **Metabolism:** **Phenobarbital** (may be responsible for activity) + **PEMA** (phenyl ethyl malonyl diamide).	M**.O.A:** Act as Na channel blocker & ↑ GABA in CNS. **Uses:** Drug of choice for absence seizures **Metabolism**: ① **direct conjugation** (COOH) ② ω or ω-1 oxidation → **5-hydroxy** & **4-hydroxy derivative** [5-Hydroxy → **2-n-propyl glutamic acid**.

Carbamazepine (Tegretol®)	Oxacarbazepine
 5-H-Dibenz[b,f]azepine-5-carboxamide	
 10,11-epoxide **active but toxic** trans 10,11-dihydroxy **inactice**	 excreted
Drug of choice for grand mal and used for partial not against petit	Less side effects No epoxide formation

Synthesis of Valproic acid:



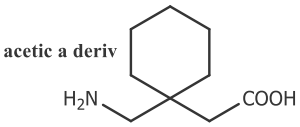
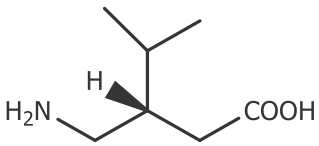
Synthesis of Carbamazepine:



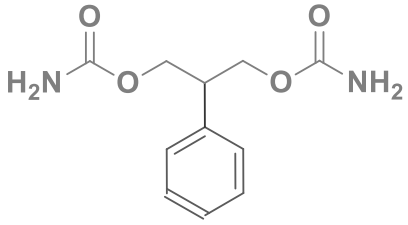
dinitrostilbine

5H-dibenzo[b,f]azepine

Carbamazepine

Gabapentin [Neurontin]®	Pregbalin [Lyrica]®
 Gabapentin *1-(Amino methyl)-cyclohexane acetic acid*	 *(S)-3-isopropyl-GABA*
Broad spectrum AEP - GABA analogue but not acting on GABA receptors	
MOA: 1. Modulate Ca influx. 2. Stimulate GABA biosynthesis 3. Compete with glutamic acid synthesis may due to structure similarity to (L-Leucine). **Metabolism:** more than 95 % excreted unchanged Gabapentin 60 % bioavailability but pregbalin 95 % bioavailability	

FELBAMATE [FBM](Felbatole)



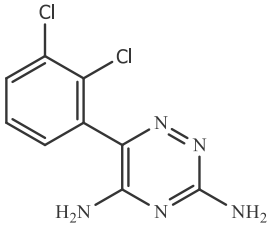
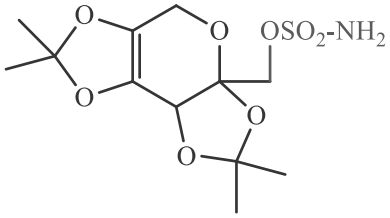
It is a potent and effective AED with a broad spectrum of action. It is a carbamate ester of 2-phenyl-1,3-propanediol, structurally like the anxiolytic drug meprobamate.

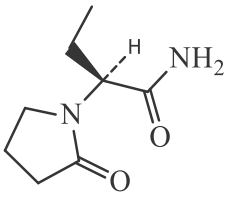
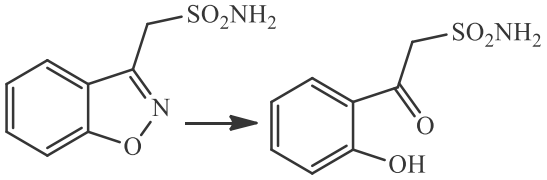
The carbamate ester is stable to esterase's and therefore provides good oral bioavailability.

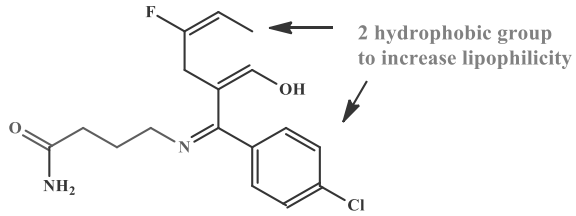
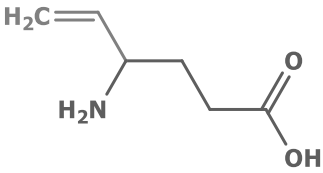
M.O.A: Block NMDA, Ca channels and potentiating GABA action.

Uses: Used for partial seizures in adults and partial and generalized seizures associated with **Lennox Gas taut Syndrome in children**. However, the FBM therapy was found to be associated with rare but severe side effects such as aplastic anemia and hepatic failures within 6 months of its market introduction.

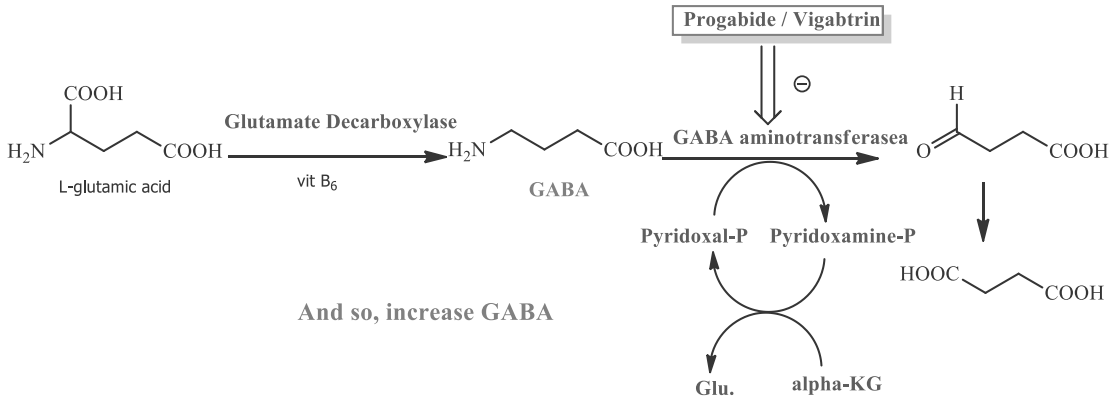
Novel Broad-Spectrum Anticonvulsants

Lamotrigine [Lamectal]®	**Topiramate [Topomax]®**
 6-(2,3-Dichloro phenyl)-1,2,4-triazine-3,5-diamine	 Sulfamate-substituted monosaccharide → Derived from D-Fructose
for partial, myoclonic typical absence seizurea	**Broad spectrum** Antiepileptic.
MOA: **block both Na, Ca channels repetitive firing.** ➢ Block glutamate release	**MOA**: Derived from D-Fructose that exhibits **broad spectrum Antiepileptic** at both glutamate and GABA receptors.

Levetiracetam [LEV]	Zonisamide
 Modulation of voltage-gated Na^+ ion channels	
Only the *S-isomer has anticonvulsant* activity. LEV has few drug interactions with other AEDs thereby can be used in <u>combination to treat refractory epilepsy</u>	It metabolized by reductive ring cleavage of the 1,2-benzisoxazole ring to 2-sulfamoyl-acetyl-phenol
Levetiracetam has no affinity for GAB_A receptors, BZD receptors, the various excitatory amino acid related receptors, its mechanism remains unclear, but it may modulate voltage-gated ion channels (K^+).	Approved for adjunctive therapy in the treatment of partial seizures in adults with epilepsy It may modulate voltage-gated ion channels (Ca^{2+}, Na^+).

Progabide	Vigabatrin
	
Structurally similar to GABA → inhibition of GABA aminotransferase (for partial seizures)	

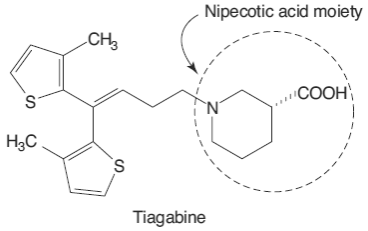
M.O.A:



Anticonvulsants Acts on a Selective Molecular Target

Tiagabine (Gabitril)

- It blocks GABA reuptake as a major mode of its anticonvulsant activity.
- Only used as R (-)-enantiomer. **Its use is against partial seizures**



IV-ANTIPSYCHOTICS DRUGS

[Neuroleptics][Major Tranquilizer]

Psychoactive drugs are also known as tranquilizers. These drugs are used in the treatment of abnormalities of mental function. The psychoactive drugs render the patient calm and peaceful by reducing agitation and anxiety.

Psychoactive drugs do not cure mental disorders, but the available drugs do control most symptomatic manifestations and behavioral deviances, facilitate the patient's tendency toward remission and improve the capacity of patient for social, occupational, and familial adjustment.

The psychotic disorders include schizophrenia, the manic phase of bipolar (manic-depressive) illness, acute idiopathic psychotic illness, and other conditions marked by severe agitation.

Uses of Anti-psychotic drugs:

- **Anti-psychotic drugs** are used to treat **psychoses** like schizophrenia, mania, senile dementia, behaviour disorders in children and anti-emetic [D_2-blocker at CTZ].
- These drugs act by depressing the CNS (by decreasing dopamine levels) and by producing sedation without producing sleep. Thus, the antipsychotics are employed to reduce excitation, agitation, agressiveness and impulsiveness. Hence, they are also known as antischizophrenic drugs or neuroleptic drugs or major tranquilizers.

Mechanism of action:

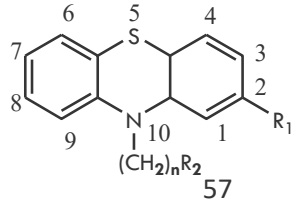
- Dopamine receptor antagonist **(D_2 blockers)**.

The drugs used in the treatment of psychoses are classified as follows:

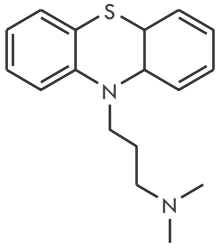
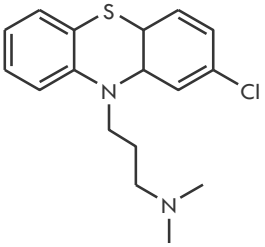
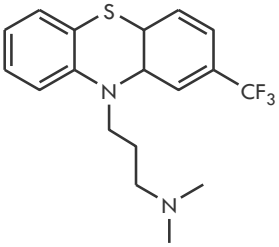
1) **Phenothiazines.**
2) **Thioxanthines.**
3) **Dibenzazipines.**
4) **Butyrophenones.**
5) **Miscellaneous.**

[1] Phenothiazines

- The prototype is Chlorpromazine (CPZ) → typical antipsychotic drugs, obtained from promethazine (antihistaminic).
- Phenothiazines act exclusively on specific postsynaptic receptors and block the postsynaptic dopamine receptors. They work on the positive symptoms of psychosis such as hallucinations, delusions, disorganized speech and looseness of association.
- Phenothiazines are chemically constituted by a lipophilic, linearly fused tricyclic system having a hydrophilic basic amino alkyl chain.
- Typical antipsychotic drugs.
  They are classified according to the type of substitution on the nitrogen atom into three main classes:
  A) Propyldimethylamino **(Promazines).**
  B) Propylpiperazinyl **(Perazines).**
  C) Alkylpiperidinyl **(Ridazines).**



[A]Promazines

1) Promazine	2) Chlorpromazine (CPZ)	3) Triflupromazine
		 the most active because (CF_3) is powerfull electron withdrowing gp.
All of them are used as **antiemetics.**		

Uses:

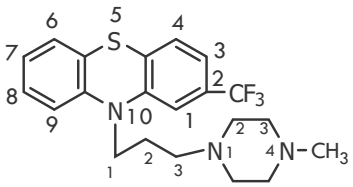
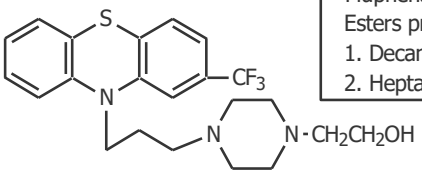
1. CPZ is used in the management of psychotic conditions. It also controls excitement, aggression and agitation.
2. It has antiemetic, antipruritic, anti-histaminic and sedative properties.

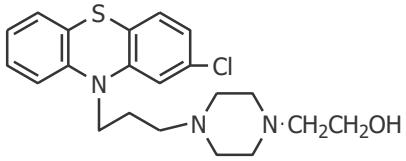
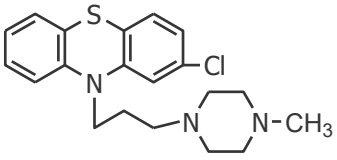
Common side effects:

Extra pyramidal symptoms, hypertension, orthostatic hypotension, blurred vision, dry mouth, anorexia, nausea, vomiting, constipation, diarrohea, weight gain, impotence, amenorrhea, photosensitivity.

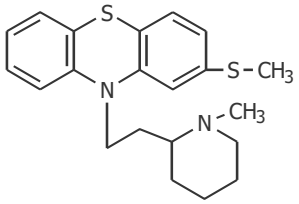
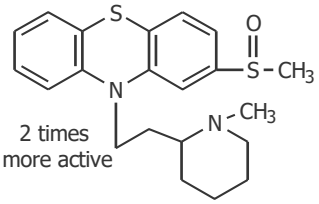
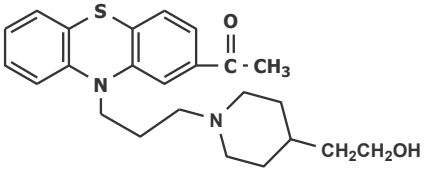
[B] Perazines

- They are the ***most active.***

Trifluperazine	Fluphenazine
	 - Fluphenazine is short acting, So--> Esters prodrug used --> latenation of ation (depot IM) 1. Decanoate [-O-CO-$(CH_2)_8$-CH_3] --> 2-3 weeks 2. Heptanoate [-O-CO-$(CH_2)_5$-CH_3] --> 1-2 weeks *10-[3-[4-(2-Hydroxy ethyl)-piperazinyl]-propyl-2-trifluoro methyl phenothiazine*

Perphenazine	Prochlorperazine
	

[C] Redazine

Thioridazine	Mesoridazine	Piperacetazine
	 2 times more active	

Chemical nomenclature:

- **Trifluperazine:**

2-Triflurомethyl-10-[3-(4-methyl-1-piperazinyl)propylphenothiazine

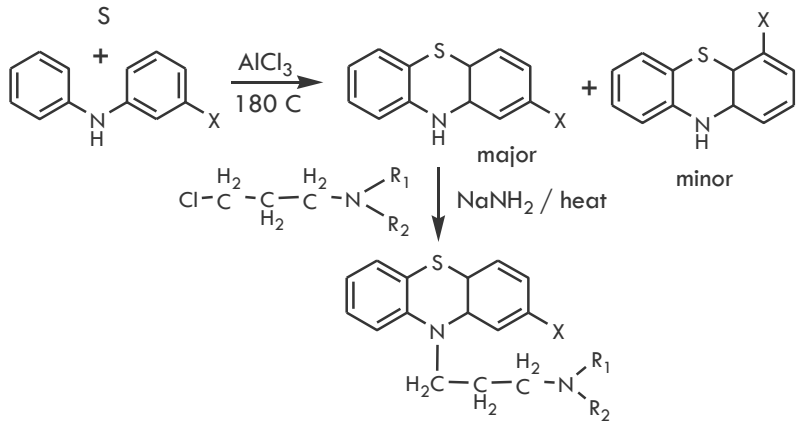
Long acting phenothiazines:

- By esterification of OH group containing derivatives with long chain fatty acid.

Advantages:

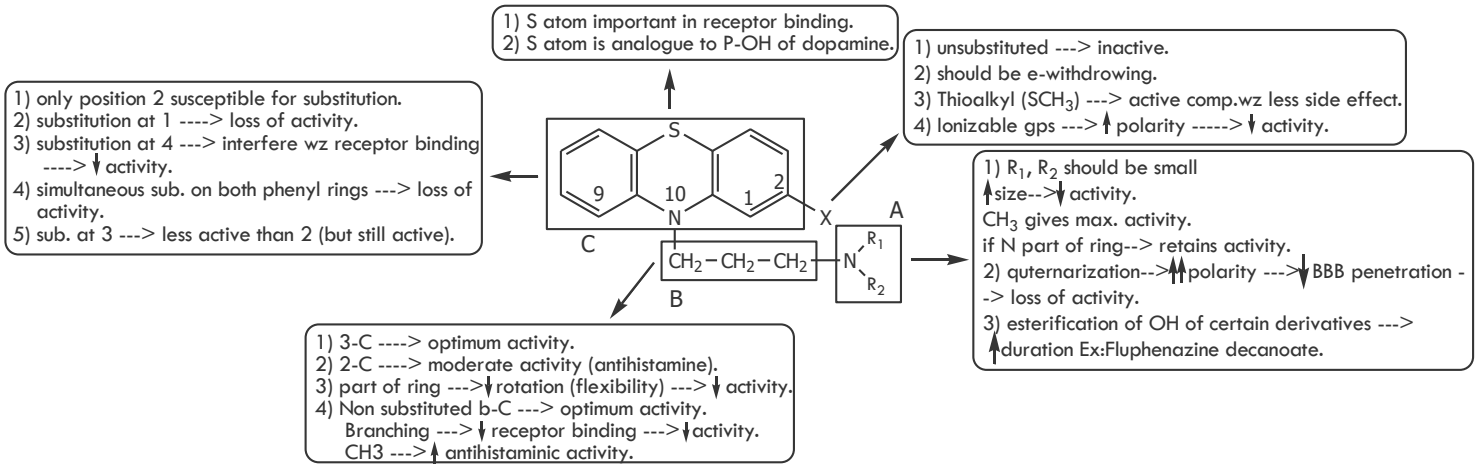
1) Treatment of psychotic patients who don't take their medication.
2) Patients who are subject to frequent relapse.

General method of synthesis:



SAR: in physiological pH R_3N converted to R_3N^+H

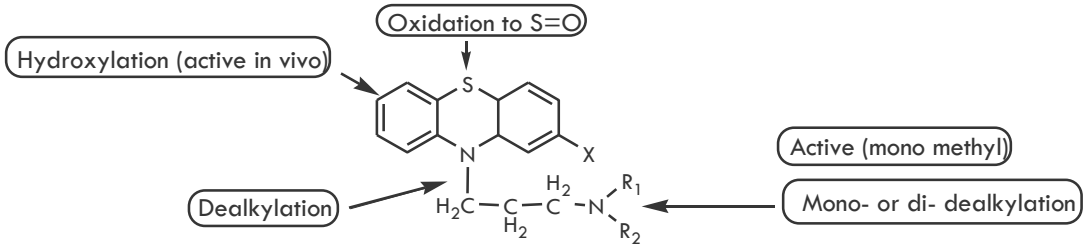
- The highest degree of specificity is required for **site B followed by C then A.**



Assay:

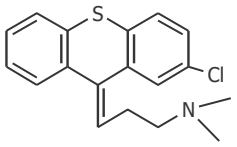
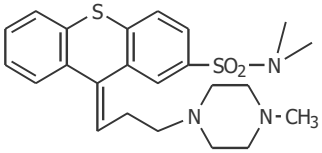
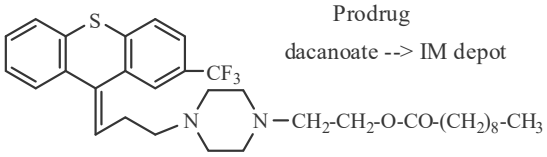
1) **Chlorpromazine tab.:**
   Titrate with **cerric ammonium sulfate** using ferroin as indicator.
2) Non aqueous titration as **weak base**:
   Solvent: glacial acetic acid.
   Titrant: perchloric acid.
   Indicator: crystal violet.

Metabolism:



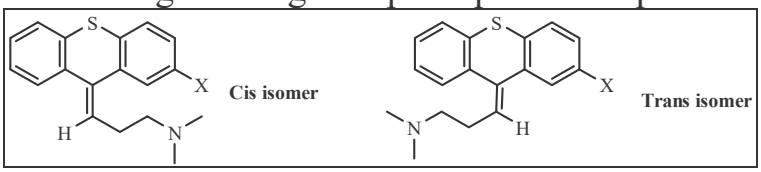
[2] THIOXANTHINES

- Isosters to phenothiazines by replacement of N by C.

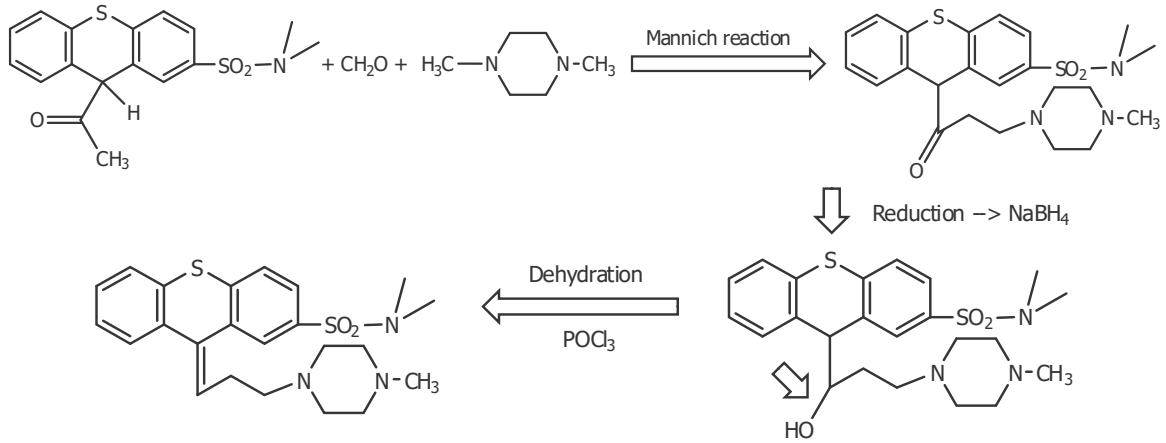
Chlorprothixine	Thiothixine	Flupenthixol
		
Very similar to phenothiazine derivatives		

SAR of thioxanthines:

They are present in two isomers; Z and E. (**Z is the active isomer** due to X which make bonding with N causing the drug to superimpose on dopamine receptors)



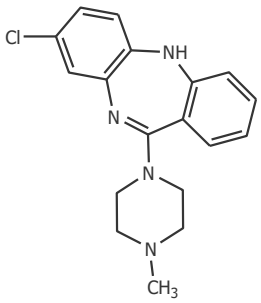
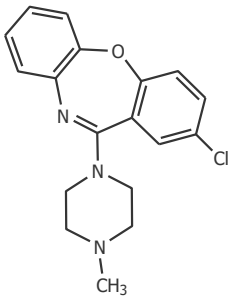
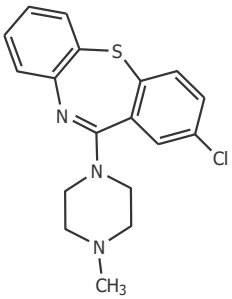
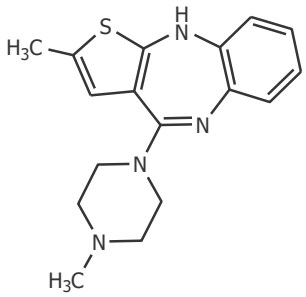
Synthesis of Thiothixene:



[3] DIBENZAZEPINES

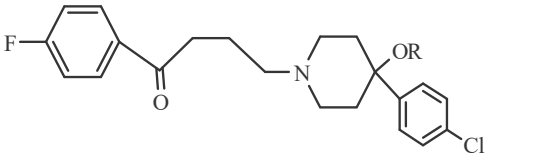
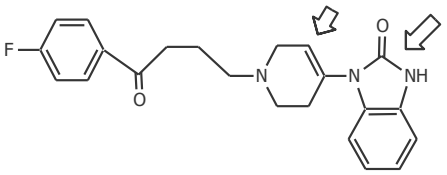
Clozapine:

- *8-Chloro-11-(4-methyl piperazin-1-yl)-5H-dibenzo[b,e][1,4-diazepine*
- ↓potency due to wrong orientation of N-methyl piperazinogroup relative to Cl atom

Clozapine	Loxapine	Clothiapine	Olanzapine
			 Thienobenzodiazipine derivative
Atypical → ↓ potency due to wrong orientation of N-methyl piperazino group relative to Cl atom. ↓ EPS → block striatal cholinergic receptors [block limbic receptors > striatal D_2 receptors] **Side Effect:** agranulosytosis. *So, it's **not used now.***			Used for ***schizophrenia*** Atypical with ↓ EPS. More potent antagonist at D_2 and serotonin $5\text{-}HT_{2A}$ receptors > Clozapine with no agranulosytosis.

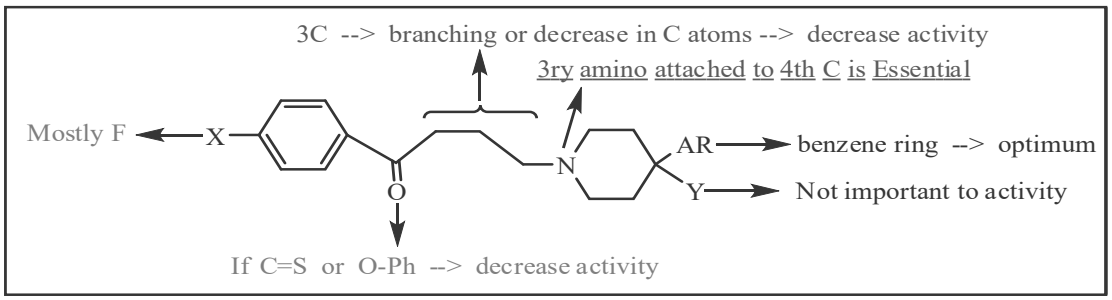
[4] BUTYROPHENONES

The fluorobutyrophenones belong group of compounds which possess high antipsychotic activity

Haloperidol [Orap Fort] ®	Droperidol
 Active orally with lower sedation than CPZ R = H Or = decanoete ester --> depot IM/4 weeks *4-[4-(4-Chloro phenyl)-4-hydroxy -1-piperidino]-4-fluoro butyrophenone*	
Typical with ↑potency and ↑ EPS, NO anti-cholinergic	
Uses: 1. Drug of choice in terminates mania. 2. Gille de la tourette syndrome (GDTS) → abnormal voice, movement.	

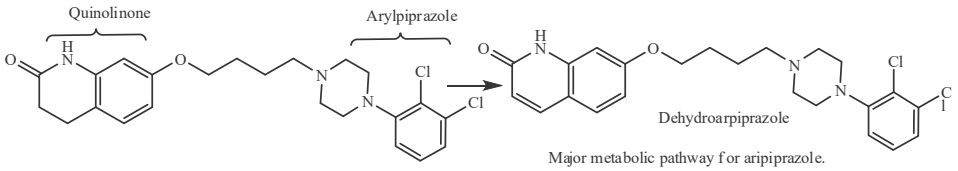
Structural features (SAR):

1) Attachment of a tertiary amino group to the fourth carbon of the butyrophenone skeleton is essential for neuroleptic activity.
2) Lengthening, shortening, or branching of the three- carbon propyl chain decreases neuroleptic potency.
3) The aliphatic amino nitrogen is required, and highest activity is seen when it is incorporated into a cyclic form.
4) P-fluoro substituent increases the activity.
5) The Y group can vary and assist activity, and an example is the hydroxyl group of haloperidol. The empirical SARs could be construed to suggest that the 4-aryl piperidino moiety is superimposable on the 2-phenylethylamino moiety of DA and, accordingly, could promote affinity for D_2 and D_3 receptors.
6) The long N-alkyl substituent could help promote receptor affinity and produce receptor antagonism activity.



Highly potent → strong D_2-antagonist

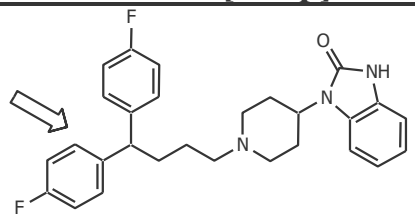
Aripiprazole: (Abilify®)



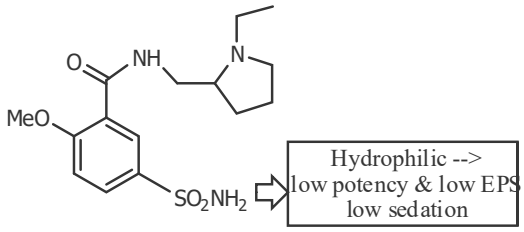
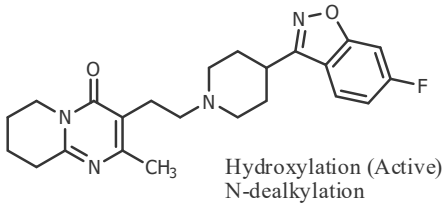
Major metabolic pathway for aripiprazole.

- Aripiprazole is the newest, long acting aripiprazole (an arylpiperazine quinolinone derivative), appears to be partial agonist of D_2 receptors (i.e., it stimulates certain D_2 receptors while blocking others depending on their locations in the brain and the concentration of drug).
- It is metabolized by dehydrogenation oxidative hydroxylation, and N-dealkylation, largely mediated by hepatic CYPs 3A4.
- The diphenylbutylpiperidine class can be considered a modification of the fluorobutyrophenone class. Because of their high lipophilicity, the compounds are inherently long acting.

[5] Diphenyl butyl piperidine derivatives

Pimozide [Orap]®
   ↑ hydrophobic → long acting and ↑ in protein binding   Used in treatment of schizophrenia

[6] Miscellaneous agents

1) Benzamides e.g. (Sulpiride)	2) Benzisoxazole	3) Lithium salts.
 **Sulpiride**	**Risperidone** 	**lithium CO_3/ Li_2 citrate** Its action depends on **similarity to Na^+.** It has many side effects.
• Pyrolidinyl containing benzamide. • ↓ incidence of extrapyramidal symptoms	- Risperidone used in treatment of schizophrenia. - It is atypical &5HT/D_2 antagonist. - Not inhibit DA neurotransmission in striatum and cortex → low EPS. BUT maintain blockage of D_2-limbic receptor.	

[V]-GENERAL ANESTHETICS

General anesthetics are the drugs, which produce controlled, reversible depression of the functional activities of the CNS producing loss of sensation and consciousness.

Stages of General Anesthesia.

When an inhalation anesthetic is administered to a patient some of the following well defined stages are produced by increasing the blood concentration of the agent. They are;

- **Stage I (Stage of analgesia):** This stage lasts from onset of drowsiness to loss of eyelash reflex. Variable levels of amnesia and analgesia are seen in this stage. The patient is considered unconscious at the end of stage I.
- **Stage II (Stage of delirium or excitement):** This period characterized by agitation and delirium. During this stage, salivation may be copious. Heart rate and respiration may be affected. Induction agents are designed to move the patient through this undesirable stage quickly. The patient may laugh, vomit or struggle and for this reason it is called the stage of excitement.
- **Stage III (Stage of surgical anesthesia):** In this stage excitement is lost and skeletal muscle relaxation is produced. Most types of surgeries are done in this stage.
- **Stage IV (Stage of medullary depression):** Overdose of the anesthetic may bring the patient to this stage. Respiratory and circulatory failure occurs in this stage.

The ideal anesthetic combination will allow the patient to proceed quickly from stage I to stage III and avoid stage IV. Inhaled anesthetics are used in combination with other drugs to induce anesthesia.

CLASSIFICATION OF GENERAL ANESTHETICS

The general anesthetics are classified according to their nature (**volatile** or **non-volatile**) at room temperature into:

1. Volatile Inhalation general anesthetics: They are administered by inhalation and are further subdivided as;

- **Gases:** Ex: Nitrous oxide, Cyclopropane, Ethyl chloride.
- **Liquids:** Diethyl ether, Halothane, Chloroform, Trichloroethylene.

2. Non-Volatile or Intravenous anesthetics. They are non-volatile at room temperature and are administered by intravenous route. They are;

- **Barbiturates:** Thiopental sodium, Methohexital sodium.
- **Non-barbiturates:** Propanidid, Propofol and ketamine.

Induction of General Anesthesia

Barbiturates induce general anesthesia rapidly and painlessly. They have maximum effect in about 1 minute and duration about 5-8 minutes. Induction doses produce the

highest blood concentration, the greatest effects on body systems and the most side effects. Usual, recommended induction doses of thiopental:

Adults 2.5-4.5 mg/kg,
Children 5-6 mg/kg,
Infants 7-8 mg/kg

Since, some individuals seem "particularly sensitive" to thiopental, a conservative technique might be to inject 1/4 of the calculated (above) dose and observe patient response. If this smaller dose has great effect, reduce calculated subsequent dose.

Characteristic Features of Ideal Anesthetics

An ideal general anesthetic should possess the following characteristic features:

1. It should be potent, non-inflammable, inexpensive and inert.
2. Minimally soluble in the blood and tissues.
3. It should produce analgesia and muscle relaxation in addition to anesthesia.
4. It should be non-irritating to mucous membrane and pleasant to inhale.
5. It should produce rapid and smooth anesthesia.
6. It should not produce severe hypotension, nausea and vomiting.
7. It should be compatible with adjuvant drugs used in anesthesia.
8. It should be stable to heat, light and alkalies.

Solubility:

The ideal general anesthetic will have low solubility in blood conveyed by the blood:gas partition coefficient listed in the following table:

Properties of the Inhaled Anesthetics			
Anesthetic	**MAC (%)**	**Blood:Gas**	**Oil:Gas**
Nitrous oxide	**104**	**0.46**	**1.1**
Halothane	**0.75**	**2.4**	**137**
Enflurane	**1.68**	**1.8**	**98**
Isoflurane	**1.15**	**1.43**	**90.8**

(MAC)=Minimum Alveolar Concentration

The blood:gas partition coefficient is defined as the ratio of the concentration of the drug in the blood to the concentration of the drug in the gas phase (in the lung), at equilibrium. The volatile anesthetic is inhaled into the lungs, diffuses into the blood, and when equilibrium is reached, it diffuses into tissues.

For the drug to have a quick onset, the solubility in the blood should be low, thus saturation will occur quickly, and the drug can then move into the tissue compartment.

Recovery is also expected to be faster for those drugs with a low blood:gas partition coefficient as the drug will be eliminated quicker if it has a low solubility in the blood and quickly passes into the lungs for exhalation.

When a patient is exposed to the volatile gas for prolonged procedures, the solubility of the drug in the tissues will also affect the recovery period.

MINIMUM ALVEOLAR CONCENTRATION (MAC):

It is the alveolar concentration of an anesthetic at 1 atmosphere that prevents movement in 50% of patients in response to a noxious stimulus (e.g., surgical incision).

- The MAC is a measure of the potency of an anesthetic. A low MAC means high potency.
- An anesthetic's potency is correlated with its lipophilicity (i.e., low MAC = very lipophilic).
- MAC is age-dependent: Highest in infants; drops to about half by age 80.
- Analgesia begins at about 0.3 MAC; Amnesia at about 0.5 MAC.

Mechanism of Action of General Anesthetics:

The general anesthetics inhibit CNS neuronal activity. But their precise mechanism of neuronal inhibition is not clear. Several mechanisms were proposed to explain general anesthesia. They are:

[1] Antagonist of N-methyl-D-aspartate (NMDA) [block glutamate action]

- If this receptor activated → ↑ flow of K to extracellular fluid and Ca, Na intracellular → ↑ **NO** [important mediator for consciousness].
- Example: Ketamine, Halothane.

[2] Activation of inhibitory GABA receptor-controlled channel:

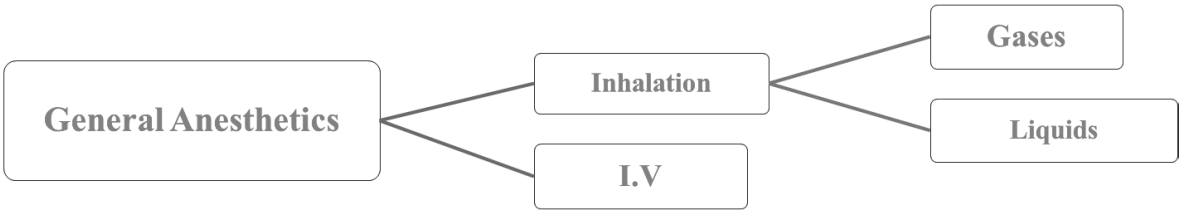
- Binding of GABA → open Cl^- ion channel → influx of Cl^- → hyperpolarization of neurons.
- Examples: Benzodiazepine (BZP), Barbiturates, Halothane, Isoflurane.

Adjuvant to General Anesthetics:

[1] **Narcotic analgesics** [Morphine and Meperidine] → ↓ anxiety.
[2] **Sedatives** [as BZP] → cause sedation and ↓ anxiety.
[3] **Anti-cholinergics** [Scopolamine] → inhibit excess respiratory secretion.
[4] **Skeletal muscle relaxants** [Succinyl choline and Vancuronium] → relax muscles for optimum surgical working.

SPECIFIC GENERAL ANESTHETICS

Classification



[I] GASES [Inhalation Anesthetics]

- Inhaled and exhaled gas equilibrates with lung tissues and then with blood.
- **Recovery** → by stopping delivery of anesthetic.
- Most general anesthetic agents are **non-specific agents** → activity depend on lipophilicity not on structure.
- If **has ↑ solubility in blood** → **slow onset + long duration** [and vice versa].

[1]-NITROUS OXIDE[N_2O]

Chemistry:

Nitrous oxide was the first anesthetic. Joseph Priestly first reported nitrous oxide preparation in 1772. It is prepared by heating ammonium nitrate to 200°C.

$$NH_4NO_3 \rightarrow N_2O + H_2O$$

Properties:

- Nitrous oxide is available as a colourless, tasteless and odourless gas
- It is supplied in blue coloured metal cylinders.
- It is soluble in water, alcohol and ether.
- Laughing gas → **↓ activity** [not used alone].
- **↓ Toxicity** with **poor muscle relaxation**.

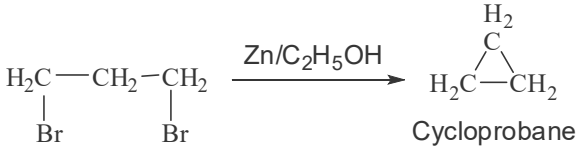
Uses:

- **Nitrous oxide is used to induce anesthesia and is followed by ether, halothane or methoxy flurane.**
- It is also used for short dental operations.
- Induction → 70 % nitrous oxide + 30% oxygen for 2-3 min.
- Maintenance → 30-70 % nitrous oxide with oxygen.

[2] CYCLOPROPANE (NON-HALOGENATED H.C.) [CYCLOPROPANE] Δ

Chemistry:

Cyclopropane is a cyclic aliphatic hydrocarbon. It is prepared from 1,3-dibromopropane with zinc and alcohol in absence of water.



Cycloprobane

Properties:

- Cyclopropane is a colourless **flammable gas** with characteristic odour and pungent taste. It is supplied in compressed form in metal cylinders.
- Cyclopropane forms explosive mixture with air.
- The cylinders of cyclopropane are painted red.

Uses:

- Cyclopropane is used as general anesthetic. It produces rapid and smooth induction at conc. 20%, good muscle relaxation and has wide margin of safety. It is administered by inhalation. But it has **CVS toxicity.**

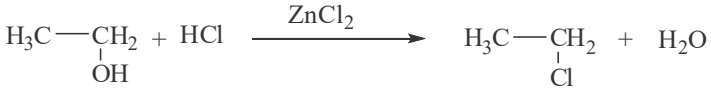
[3]-ETHYL CHLORIDE

Chemistry:

Ethyl chloride is a chloro derivative of ethane. It is gas at normal conditions and is available in compressed form.

Synthesis:

Ethyl chloride is prepared from ethyl alcohol by passing dry hydrogen chloride into it.



Ethyl alcohol EthylChloride

Properties:

- Ethyl chloride is a volatile liquid having a pleasant ethereal odour and burning taste.
- It is slightly soluble in water and also miscible with alcohol and ether.

Uses:

Ethyl chloride is used as a general anesthetic administered by inhalation.

2] LIQUIDS:

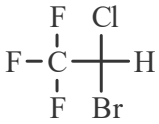
1. **Halogenated hydrocarbons.**
2. **Ethers.**
3. **Halogenated ethers.**

[1] HALOGENATED HYDROCARBONS

- Halogen → ↓ flammability and ↑ potency.
- But halogen may → cause arrhythmia or renal and hepatic toxicity.
- If Br only → not useful / If Cl → toxic causing arrhythmia / so, use fluorinated hydrocarbons.

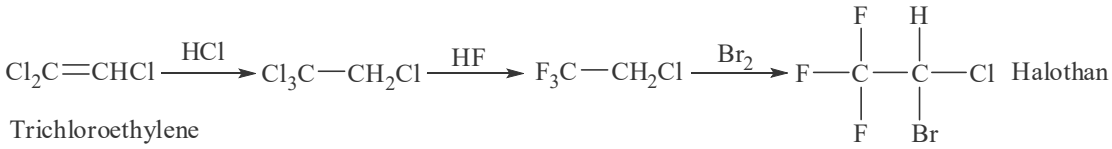
- F → ↓ flammability, boiling point and incidence of catechol-induced arrhythmia which ↑ as size of halogen ↑ → F is the smallest.

HALOTHANE



2-Bromo-2-chloro-1,1,1-trifluroethane

Synthesis: Chemically halothane is 2-bromo,2-chloro,1,1,1-trifluoroethane. It is prepared from trichloroethylene by the following chemical reactions.



Properties:

- Halothane is a colourless, non-inflammable liquid having chloroform like odour.
- It is non-irritant to the skin and mucous membrane.

Uses:

- Halothane is one of the most widely used potent anesthetic agents (2-2.5%). It is usually administered through N_2O-air mixture. It has more rapid induction and recovery compared to ether (generally discouraged as an explosive hazard) and methoxyflurane.
- It is more potent than chloroform and ether.

Disadvantages of halothane are;

- It reduces cardiac output [↑ possibility of arrhythmia] + -ve effect on liver.
- It causes peripheral vasodilation leading to **hypotension** or **low blood pressure.**
- It is a dose-dependent respiratory depressant.
- If repeated dose → toxicity due to **fluro acetyl chloride metabolite]**

[2] ETHERS

DIETHYL ETHER

[↑ Chain → ↑ potency and ↑ toxicity]

Chemistry:

Diethyl ether was the first compound to be used as an anesthetic by American doctor. In 1846, James Simpson popularized the use of ether as an anesthetic in surgical operations.

It is prepared in the laboratory and on the large scale by heating mixture of ethyl alcohol in presence of H_2SO_4 and purified with sodium hydroxide followed by drying on anhydrous calcium chloride.

$$2CH_3CH_2OH + HOSO_3H \rightarrow CH_3CH_2\text{-}O\text{-}CH_2CH_3 + H_2SO_4 + H_2O$$

Properties:

- Diethyl ether is a colourless, volatile, highly inflammable liquid, having sweet burning taste and characteristic odour.
- The anesthetic ether should be stored in well-closed, light resistant containers in a cool place.
- Stabilizers like sodium pyrogallate, hydroquinol, or propylgallate are added to anesthetic ether.

Uses:

- It is a safe general anesthetic.
- It is inexpensive.

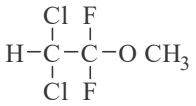
DIVINYL ETHER $(CH_2{=}CH_2)\text{-}O\text{-}(CH_2{=}CH_2)$

- Explosive but cause rapid induction & recovery with minimum excitation.

[3] HALOGENATED ETHERS

METHOXYFLURANE

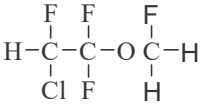
Methoxyflurane is the most potent of all inhalation anesthetics. Chemically methoxyflurane is 2,2-dichloro-1,1-difluoro-1-methoxyethane. It is available as a colorless liquid with sweet odor.



Methoxyflurane is nonflammable, nonexplosive, and a potent analgesic. Low vapor pressure makes it the only agent suitable for the open drop method. A disadvantage of methoxyflurane, compared to other inhalents, is a relatively slow induction phase that can result in a modest respiratory and cardiovascular depression. Perhaps the biggest disadvantage is that metabolization leads to flouride ion release which is **nephrotoxic.** An appropriate scavanging system must be in place to protect personnel.

ENFLURANE

- Chemically enflurane is *2-chloro-1,1,2-trifluoroethyldifluoromethylether*. Enflurane is available as a clear, colourless non-inflammable liquid with sweet odour.

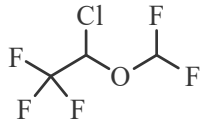


- Non-flammable → mixed with oxygen and nitrous oxide.
- The induction and emergence from anesthesia of is smooth and moderately rapid.
- Enflurane **has advantages over halothane** → **lower blood/gas P.C** → more rapid induction and recovery and ↓ arrhythmia.

- **It is used as an alternative to halothane.**
- **<u>↓ F release</u>** → ↓ nephrotoxicity [but if patient take **<u>I.N.H</u>** → facilitate deflurination → renal damage].

<u>ISOFLURANE</u>

<u>1-Chloro-1-(difluro methoxy)-2,2,2-trifluroehane</u>



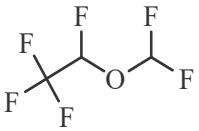
- ✓ Isoflurane is an isomer of enflurane. Chemically isoflurane is 2-chloro-2-(trifluoromethoxy)-1,1,1-trifluoroethane. It is available as clear, colourless liquid at room temperature, with sweet taste. It is miscible with organic liquids including fats and oils. Isoflurane is nonflammable and nonexplosive.
- ✓ Isoflurane has a more rapid induction and emergence than halothane. It has higher margin of safety than enflurane or halothane.

<u>Compared to halothane, isoflurane causes:</u>

- Less depression of cardiopulmonary function
- Less sensitization of the heart to catecholamine (β-adrenoceptor agonist) release
- Less profound respiratory depressant effect
- Isoflurane reduces renal blood flow, glomerular filtration rate and urinary flow.
- Isoflurane's metabolism to organic and inorganic flourides is less than any other halogenated agent available, so if a minimally metabolized anesthetic is needed, **isoflurane is the choice.**

<u>Desflurane</u>

1-(Difluro methoxy)-1,2,2,2-tetrafluoro ethane



- Non-flammable → pungent.
- **<u>Replace Cl in isoflurane with F.</u>** → **<u>↓ blood/gas P.C.</u>** → twice rapid in induction & recovery → used in out-patient surgical procedures.
- **<u>C-F → stable bond,</u>** so, only 0.02% of drug metabolized to F ions and trifluroacetic acid → NOT associated with hepato or nephrotoxicity.

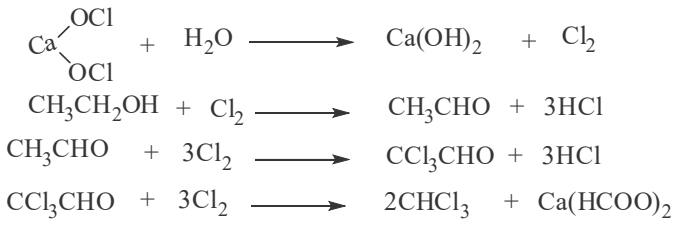
<u>Chloroform ($CHCl_3$)</u>

<u>Properties:</u>

- ✓ Chloroform is an important halogenated hydrocarbon.
- ✓ It is a colorless, volatile liquid having characteristic odour and burning taste
- ✓ It is non-inflammable and is freely miscible with ether and ethyl alcohol
- ✓ Chloroform must be protected from light and air, otherwise poisonous **<u>phosogene</u>** is formed.

<u>Chemistry:</u>

It is prepared from bleaching powder and ethyl alcohol by the following chemical reactions.



Uses:

- ✓ Chloroform is a widely used general anesthetic agent.
- ✓ It is used as solvent for fats and oils.

[II] I.V. ANESTHESIA

- ✓ **Non-explosive solids** that cause rapid loss of conscious but insufficient anesthesia [not used alone].
- ✓ **Oxygen** administration is recommended → especially if Barbiturates or thiobarbiturates.
- ✓ **They classified into**:

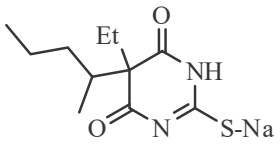
1-Barbiturates: Thiopental sodium, Methohexital sodium.

2-Non-barbiturates: Ketamine, Propofol, Propanidid.

1-Ultra-Short Acting Barbiturates

- **Rapid action** → used to initiate anesthesia [maintenance with volatile anesthetics]
- **Long side chain at C_5** → ↑ lipid solubility → ↑ penetration through BBB.

Thiopental Na



Chemistry: Thiopentone is an intravenous anesthetic. It is a barbituric acid derivative and is synthesized by condensing thiourea with ethyl (ethyl 1-methyl butyl) malonate.

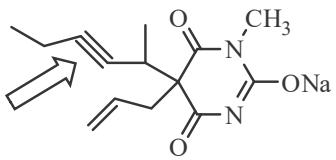
Properties:

- Thiopental is available as thiopental sodium.
- It is a yellowish hygroscopic powder, having characteristic odour and bitter taste.

Uses:

- Thiopental sodium solutions (2.5%) as the **most widely used** and administered by intravenous route to produce anesthesia. It has short duration of actions → **S ↑ lipophilicity.**
- **Short acting** → due to partitioning form the brian into body fat.
- It is also used to control convulsions.

Methohexital



- **N-methylated** with pka 8.4 [if not methylated, pka=7.6].
- **pka** → ↑ concentration of lipid-soluble acid form at physiological pH.
- **Metabolized at CH_2 α to triple bond.**

Chemistry:

Methohexital is also a derivative of barbituric acid. It is prepared by condensation of ethylcyanoacetate with 2-chloro-3-pentyne in presence of sodium ethylate yields ethyl-

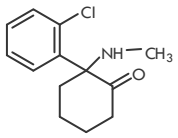
1-methyl-2-pentnyl cyanoacetate which on further condensation with allylbromide yields ethyl(1-methyl-2-pentynyl)allylcyanoacetate. Reaction with N-methyl urea yields the iminobarbituric acid which on acid catalyzed hydrolysis forms methohexital.

Properties:

- ✓ Methohexital is available as methohexital sodium.
- ✓ It is a colourless or slightly yellowish crystalline powder.
- ✓ Methohexital sodium is freely soluble in water.

Uses

- ✓ It is used as a general anesthetic and hypnotic. It is administered either by intravenous route or intramuscular route.
- ✓ It is more potent than thiopentone sodium.



2- Ultra-Short Acting Non-Barbiturates

Ketamine

2-(2-Chloro phenyl)-2-(methyl amino) cyclohexanone

- Ketamine is available as colorless crystalline compound having characteristic odor. It melts at 258°C.
- Very potent → **rapid acting → short duration** [10-25 min.]
- Act by **blocking NMDA controlled channels** located at excitatory synapses on the pyramidal cells.
- Suitable for **diagnosis and surgical procedures that do not require muscle relaxation.**
- **For patients > 16 years** → wild dreams and hallucination during emergence → may last for 24 hrs → **so, only indicated for children < 16 years.**

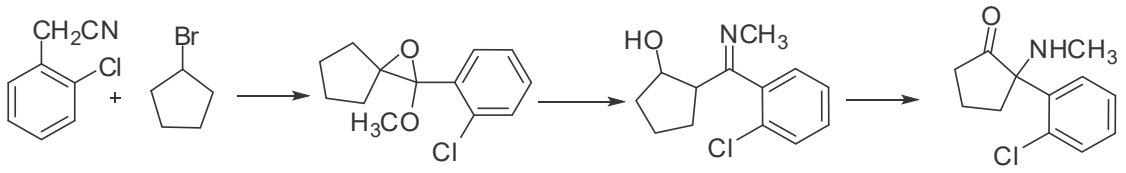
Metabolism:

Ketamine metabolized in liver to **Norketamine** [active] → **long duration.**

Ketamine is a **cyclohexanol derivative.**

Synthesis:

Chemically ketamine is (+) 2(o-chlorophenyl)-2-methylaminocyclohexanone. Ketamine is prepared by Griganard reaction of *o*-chlorobenzonitrile with bromocyclopentane in presence of strong alkali to form an expoxy compound, which converts to an imine by the action of methylamine. The imine rearranges to ketamine on heating with HCl.

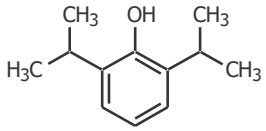


Uses:

- ✓ Ketamine is used as a general anesthetic
- ✓ It also has analgesic effect
- ✓ Ketamine relaxes skeletal muscles.

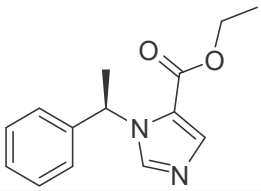
Propofol

Propofol is a liquid short-acting general anesthetic. Chemically it is *2,6-diisopropylphenol.*



- **Short acting** [5 min] → act by ↑ **GABA neurotransmission in CNS.** → bind allosterically to GABA receptor at a site differ from that of BZP.
- **Maintenance** achieved by **volatile anesthetics** or addition of propfol.
- **Poor water solubility** → 1-2 % emulsion in soybean oil or glycerol.
- **More effective than thiopental** → frequently associated with vomiting.
- Given repeatedly in **out-patient surgical procedures**.
- Metabolism → Glucuronide & sulfate conjugation.

Etomidate



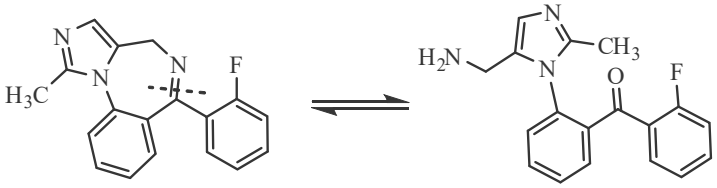
Ethyl 3-[(1R)-1-phenylethyl]imidazole-5-carboxylate

- ✓ Etomidate is a carboxylated imidazole intended for the induction of general anesthesia.
- ✓ It is marketed as the more potent R (+) isomer. It is believed to exert its anesthetic effect via positive modulation of the $GABA_A$ receptor.
- ✓ **Etomidate** has little effect on cardiac output, peripheral, or pulmonary circulation.
- ✓ **Etomidate** should only be used for induction of anesthesia.
- ✓ The lipid solubility of the drug allows it to rapidly penetrate into the brain with peak concentrations occurring within 1 minute of administration.
- ✓ Etomidate is rapidly metabolized in the plasma and liver via esterases. About 75% of the drug is eliminated in the urine as the inactive ester hydrolyzed carboxylic acid.

Benzodiazepine (Bzp)

Cause→ **Induction of anesthesia** by their sedative, muscle relaxant and anesthetic properties.

Midazolam Maleate

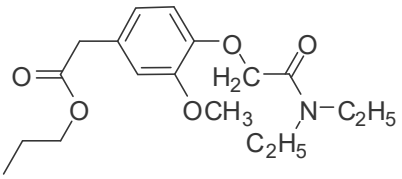


- Act allosterically to ↑ GABA opening of chloride channel.
- Short duration → due to metabolic hydroxylation then conjugation.

- Maleate salt → reversible ring opening → less than pH 4, opening between 4,5-double bond allowing midazolam to dissolve in aqueous solution for injection → closed at physiological pH.
- Twice as active as Diazepam.

Propanidid

Chemistry: Propanidid is a non-barbiturate general anesthetic. It has the following structure:



Properties

- ✓ Propanidid is available as a colourless or pale greenish-yellow hygroscopic liquid and having a faint odor.
- ✓ It is slightly soluble in water but miscible with alcohol, chloroform and ether.

Uses

- ✓ Propanidid has been used as a short acting general anesthetic.
- ✓ It also possesses local anesthetic activity.

LOCAL ANESTHETICS

- **Local Anesthesia:** Loss of sensation or loss of motor function in an area of the body.
- **Local Anesthetics**: Drugs given topically or by injection → reversible blockage of nerve conductance that transmit pain from this area to the brain.
- They achieve this by preventing the transient increase in sodium permeability of the excitable membrane.
- **Local anaesthetics** are used to abolish the sensation of pain in a restricted area of the body and for minor surgical operations when loss of consciousness is not desirable.

The main classes of Local anesthetics according to uses are:

a) **Surface or Topical Anesthesia:** The **local anesthetic** is applied to the mucous membrane, *e.g.,* conjunctiva, larynx, throat, damaged skin surface, etc.

b) **Infiltration Anaesthesia:** The **drug** is injected subcutaneously to paralyse the sensory nerve endings around the area to be rendered insensitive, *e.g.,* an area to be incised or for tooth extraction.

c) **Nerve Block Anesthesia:** The **local anesthetic** is injected as close as possible to the nerve trunk supplying the specific area to be anaesthetized. This blocks conduction in both sensory and motor fibers and minor operations on the limb are possible.

d) **Spinal Anesthesia:** The **drug** is injected into the subarachnoid space, *i.e.,* into the cerebrospinal fluid, to paralyse the roots of the spinal nerves. This method is used to induce anesthesia for abdominal or pelvic surgical operations.

e) **Epidural Anesthesia:** This is a special type of nerve block anesthesia in which the drug is injected into the epidural space. It is technically a more difficult procedure. The roots of the spinal nerves are anaesthetized.

f) **Caudal Anesthesia:** This is smaller to **epidural anesthesia** where the injection is made through *sacral hiatus* into the vertebral canal which contains the *cauda equina.* It is used for operations on the pelvic viscera.

Local anesthetics are used to remove pain caused by a wide variety of situation; they are used in:

1. Dentistry
2. In ophthalmology
3. In minor surgical operation including endoscopy.
4. In relieving pain in intractable medical condition like tumor growing in spine.
5. Local anesthetics are used also topically for temporary relief of pain from insect bites, burns and any other form of surface wounds.

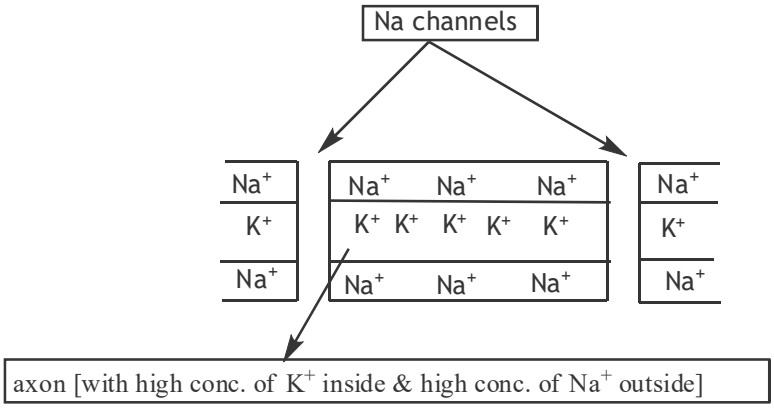
Characters of ideal Local Anesthetics:

1. Non-irritant to tissues [not cause permanent damage].
2. Rapid onset and sufficient duration of action.
3. ↓ Systemic toxicity.

4. Effective either injected or applied topically on skin or mucous membrane.

Nervous tissue:

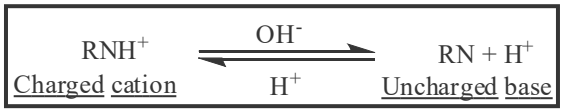
- Function of nervous tissue based on two fundamental properties:
    1. Irritability [ability to react to various stimulating agents].
    2. Conductibility [ability to transmit excitation].
- Local Anesthetics block both properties of nervous tissues.
- Each nerve fiber called axon and its cell membrane is made up of lipid with some proteins.



- Depolarization occur in nerve by movement of Na^+ in and K^+ to out → by using Local Anesthetics → block these movements.
- Local Anesthetics to prevent these movements → must enter cell membrane → this is done by aromatic ring which is soluble in lipid layer.

Local Anesthetics structure:

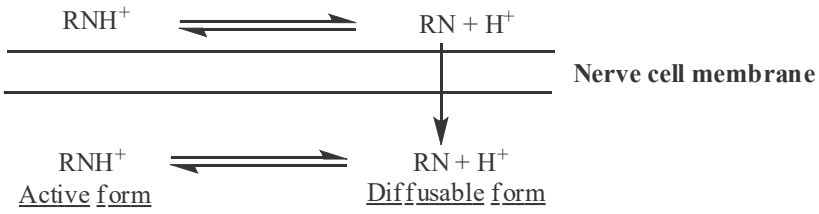
- All of them contain: ① Aromatic ring. ② Intermediate chain [ester or amide] ③ Amine.
- They are weak bases → combined with acids forming salts → can combine with water or saline → stable injectable solution.
- In any anesthetic solution → molecular structure shifts between:



- The two forms are in equilibrium depending on pH of the solution:
- In acidic pH → ↑↑ RNH^+
- In basic pH → ↑↑ RN.
- Pka = pH at which [RN]=[RNH^+].

How Local Anesthetics enter cell membrane:

- Neutral molecule [RN] →diffuse through cell membrane → inside the axon it's protonated to active form [RNH^+] that binds to the receptor.



Anesthesia to infected areas is difficult:

- In infection → pH of tissues is about 5-6 times more acidic → ↓ concentration of diffusible form [RN].

How can pH of tissues and pka of local anethetics affect the % of diffusible local anethetics:

- As pka becomes closer to pH [Mepivacine -----> pka = 7.6 and pH = 7.4] → ↑↑ [RN] relative to [RNH^+]→ ↓ onset time.
- ↑↑ pka relative to pH [Lidocaine -----> pka = 9.1 and pH = 7.4] → ↓↓ [RN] → ↑ onset time.

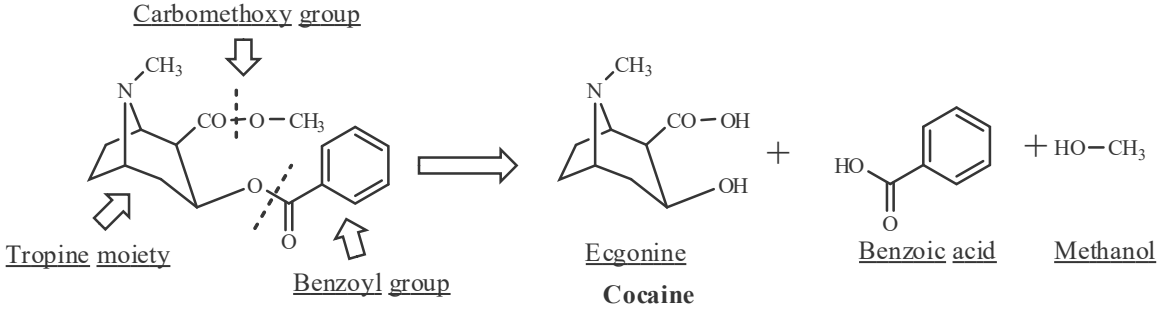
The higher the % of [RN] → The quicker the onset of L.A.

Classification of The Local Anesthetics According to Their Chemical Structures:

I- The Ester Local Anesthetics

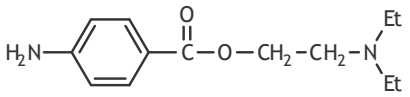
[1] Cocaine

- It was the First one → but with ↑undesirable side effects [① Addiction ② Allergy ③ Tissue irritation ④ Poor stability in aqueous medium]
- By hydrolysis of cocaine → Ecgonine + Benzoic acid + Methanol.



- Preparation of benzoyl esters of amino alcohols → L.A. action without addiction.
- Some benzoic acid esters exhibited significant local anesthetic properties, as benzocaine hydrochloride; procaine hydrochloride, tetracaine hydrochloride; butacaine sulfate, etc

2] Procaine [Novocaine]: [Prototype]



[N,N-Diethyl aminoethyl ester of P-amino benzoic acid]

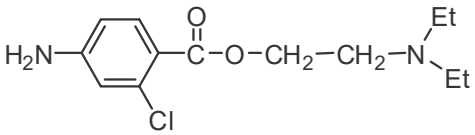
- Procaine is the first synthetic local anesthetics [removal of 2-carbomethoxy group → ↓ addiction].
- It is lacks local irritation, minimal systemic toxicity and low cost.

Uses:

- It can be effectively used by infiltration, epidural block or spinal anaesthesia.

Disadvantages: ① Ester → allergic reactions ② ↓ potency ③ Short duration.

[3] Chloropropane

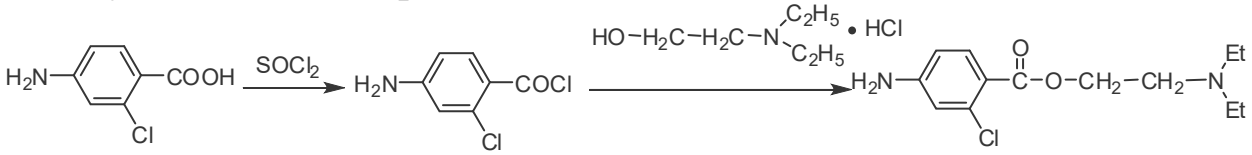


2-Diethylaminoethyl ester of 2-chloro-4-aminobenzoic acid

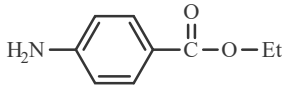
Uses:

- In situations requiring fast-acting pain relief.
- It is also used in infiltration anesthesia.
- In spinal and epidural anesthesia.

Synthesis of Chloroprocaine



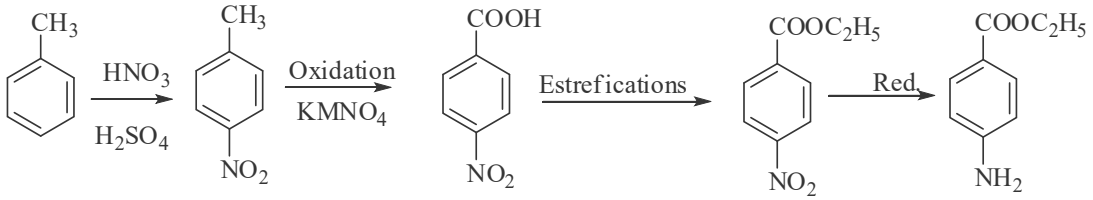
[4] Benzocaine:



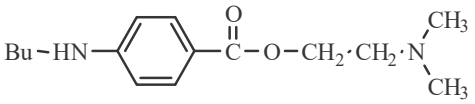
Ethyl P-amino benzoate

- ↓ Aqueous solubility [due to absence of terminal N in side chain] → **used only topically not by injection.**
- Of ↓ basicity that lone pair of N involved in resonance → if make salt → too acidic → can't be taken parentrally.

Synthesis of Benzocaine:



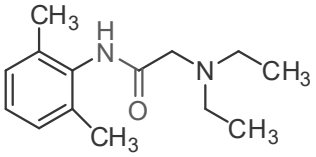
[5] Tetracaine



- Tetracaine is the most strong, long-lasting local anesthetic.
- It is primarily used in spinal cord anesthesia.

[II] The Amino Amide Local Anesthetics

1]-Lidocaine [Xylocaine]



- Lidocaine is the most widely used local anesthetic.
- The first amide local anesthetic with advantage of being hypoallergic.

Advantages

- fast-acting
- It suitable for practically any clinical use
- being hypoallergic

Disadvantages

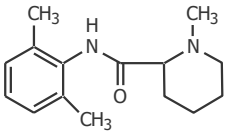
- Short duration of action) it's Vasodilator)

To overcome this problem, add small concentration of vasoconstrictor agent such as adrenaline to slow down absorption by restricting amount of blood and plasma entering and leaving site of injection.

Uses:

- For terminal infiltration
- Dentistry, otolaryngology, obstetrics and gynecology

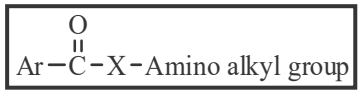
2]-Mepivacaine [Carbocaine]

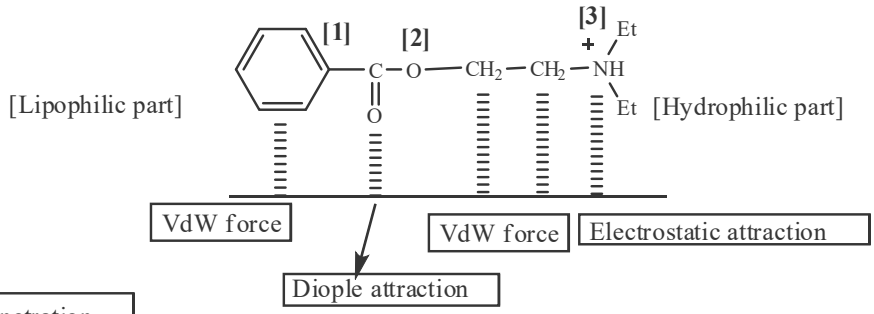


- **Mepivacaine** with less vasodilatation effect than lidocaine → can be used without epinephrine vasoconstrictor.
- Can be used when vasoconstrictor agent can't be used [can't use Lidocaine] as in:

1. Patients with ↑ B.P. taking non-selective β-blockers.
2. Patients taking tricyclic anti-depressant [Imipramine].
3. In fingers, toes, tip on nose → as vasoconstrictor may cause necrosis and death of tissues.

SAR:
Benzoic acid derivatives:





[1] essential for penetration

- conjugatio of C=O with aromatic ring ----> increase e-density on C=O ----> increase binding to receptor.
- any aryl substitution that increase e-density on C=O ---> increase potency [E.g. NH_2 in Procaine / RNH in Tetracaine]
- substitution with e-withdrawing group [NO_2] ---> decrease binding to receptor ----> decrease potency.
- Insertion of CH_2 between phenyl ring & C=O ---> prevent mesomeric effect from reaching C=O ----> decrease potency.

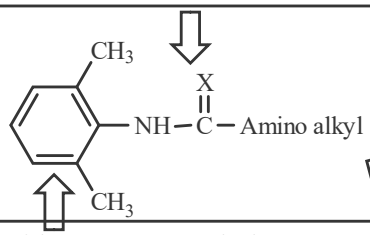
[2]
- O, N or S [isosteric modification] ---> decreas potency from S-->O-->C-->N
- these modification also affect duration & toxicity [Amide more resistant to hydrolysis than esters]

[3] important for solubility by forming salts

- 3ry amine > 2ry > 1ry in use [1ry ---> irritation]

Lidocaine derivatives:

X = O [Lidocaine] and = N [Phenacaine]



As before

Substitution with 2 or 2,6- methyl ---> decrease metabolism of amide bond [by increasing steric hinderance] & so, increase potency.

Importance of addition of vasoconstrictors:

- We add small concentration of Adrenaline [Epinephrine] to L.A. as vasoconstrictor.
- All L.A. are vasodilators [except Coccaine] → so, vasoconstrictor is needed to ↓ blood supply into and out the site of injection. So,
  a) ↓ Rate of removal of L.A. → ↑ duration.
  b) ↓ Systemic toxicity of L.A.
  c) ↓ Esterase enzyme → ↓ metabolism of ester L.A. → ↑ duration.
  d) Aids in hemostasis in wound care.
  e) They need acid as preservative → this acid help in ↓ amount of neutral basic radical [R-N] which is the diffusible form → converting it into [RNH^+] that not diffused → ↑ onset time of action of L.A.

Conditions in which vasoconstrictor can't be used: [Use Mepivacaine]

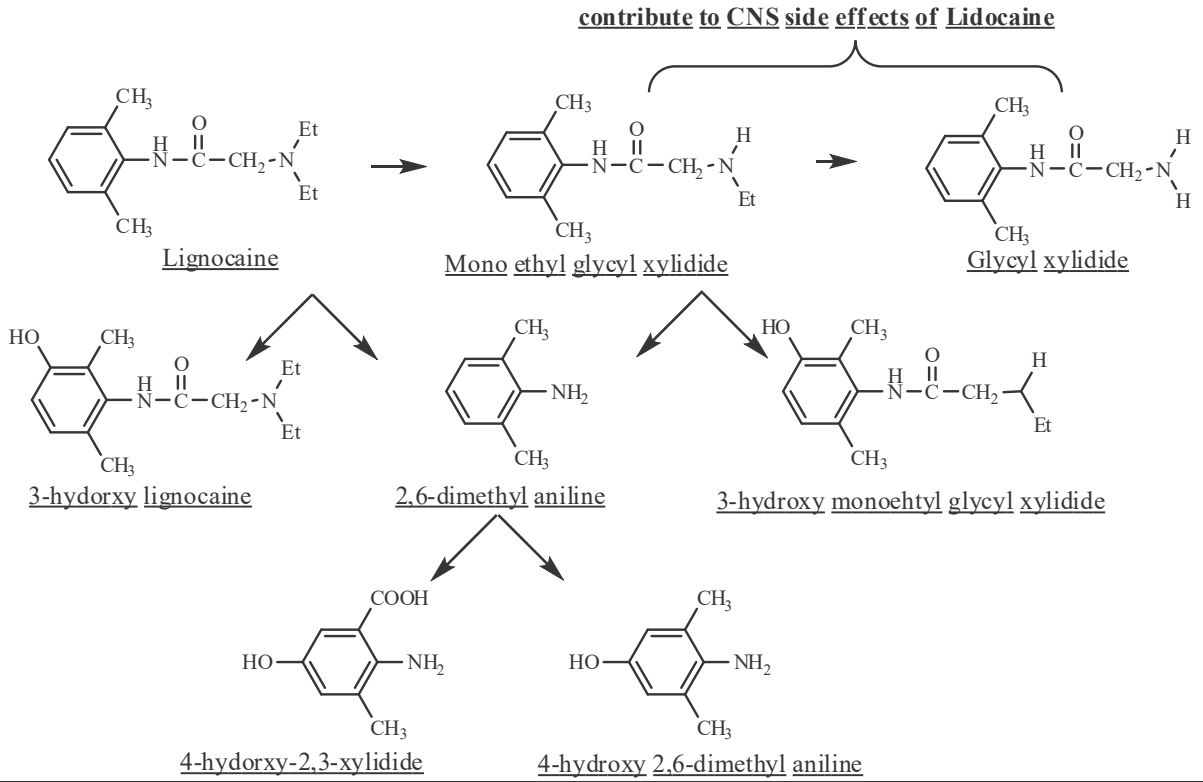
a) Uncontrolled hypertension.
b) Uncontrolled hyperthyroidism.
c) Angina patients.
d) Patients taking non-selective β-blockers.
e) Patients taking tricyclic anti-depressants.

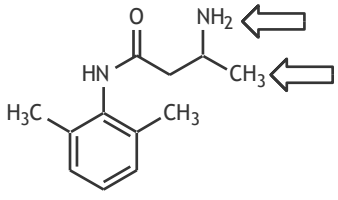
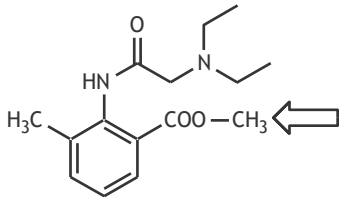
Toxicity and side effects:

- Amide L.A. [Lidocaine] → produce more CNS side effects [convulsions] > Ester type [Procaine].
- Ester L.A. → allergic reactions.
- Esters of PABA → not taken with sulfa drugs [PABA antagonists].

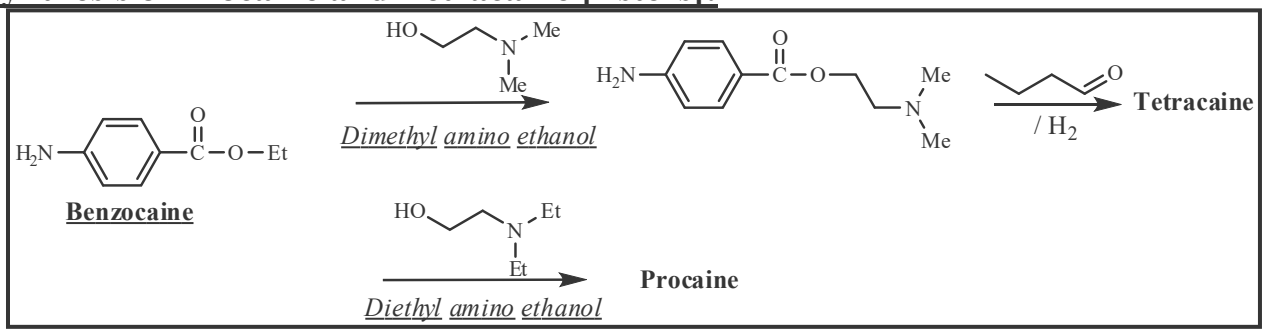
Metabolism:

- **Ester type** → by Esterase [widely distributed in tissues]. E.g. Procaine and Benzocaine → PABA + corresponding alcohol.
- **Non-ester type:**

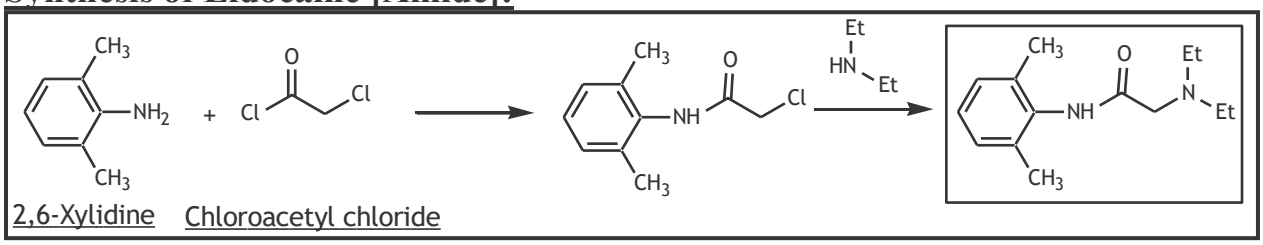


3]-Tolcainide	4]-Tolycaine
	
α-Methyl → protection from amidase + 1ry amine	Carbomethoxy group by hydrolysis → COOH → polar not cross BBB.
With lower CNS side effects	

Synthesis of Procaine and Tetracaine [Esters]:



Synthesis of Lidocaine [Amide]:

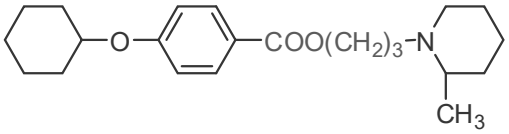


III. TOPICAL ANESTHETICS

1]-Benzocaine

- Benzocaine is used in topical anesthesia on the skin and mucous membranes in the form of aerosols, or as creams for reduction of pain caused by itching, cuts, bites, etc.
- It begins to work 15–30 sec after application and lasts for 12–15 mins.

2] Cyclomethycaine



- Cyclomethycaine is also used in topical anesthesia on the skin or mucous membranes for cuts, bites, and also for urological examinations.

CNS STIMULANTS

They are substances that increase excitability within various regions of the brain or spinal cord which results in:

a) Increased mental alertness.
b) Decreased fatigue.
c) Improved concentration.
d) Increased energy motivation.
e) Elevation of mood.

Mechanism of Action:

1- Selective blocking of neural inhibition (both postsynaptic and presynaptic).
2- Direct neural excitation.

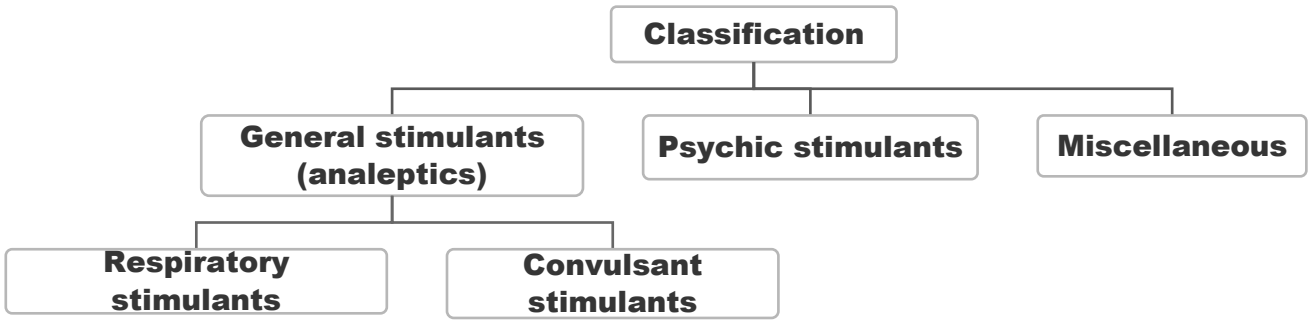
Uses:

1-Attention Deficit Hyperactivity Disorder (ADHD); lack the ability to be involved in any one activity for longer than a few minutes.

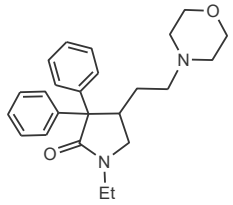
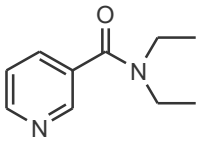
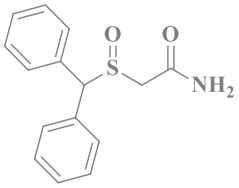
2-Narcolepsy: It is a relatively rare **sleep disorder**, that is characterized by **uncontrollable bouts of sleepiness during the day.** It is sometimes accompanied by **catalepsy**, a loss in muscle control, or even paralysis brought on by strong emotion, such as laughter.

3-Obesity (anorectic agents).

Side effects: Extreme nervousness, agitation, anxiety and seizures.

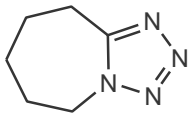


Respiratory stimulants

1) Doxapram	2) Nikethamide	) Modafinil (Provigil)
 *1-Ethyl-4-(2-morpholino-ethyl)-3,3-diphenyl-2-pyrrolidinone HCl.*	 *N,N-Diethylnicotinamide.*	 *N,N-Diethylvanillamide.*
Treats acute respiratory insufficiency in chronic obstructive pulmonary disease (COPD).	Limited use in treat acute respiratory insufficiency in (COPD) May be used in correcting respiratory depression caused by oxygen therapy in COPD	Considered an atypical 1-norepinephrine (NE) receptor stimulant. Used orally to treat daytime sleepiness in narcolepsy patients.

Convulsant Stimulants

- Not used clinically but used as experimental tool in epilepsy studies.
- Examples:
  Natural: Picrotoxin and Strychnine.
  Synthetic: Pentylenetetrazole (Metrazole).



II) Psychic (Psychomotor) Stimulants

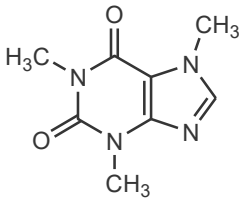
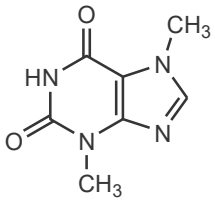
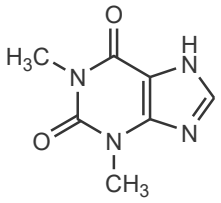
Called cerebral stimulants, stimulate cerebral cortex and medullary centers.

Classification:

1) **Methylxanthenes.**
2) **Central sympathomimetics.**
3) **Antidepressant:**
   i. **MAO inhibitors.**
   ii. **Tricyclic compounds.**
   iii. **Miscellaneous.**

} **Antidepressant**

1| Methylxanthenes

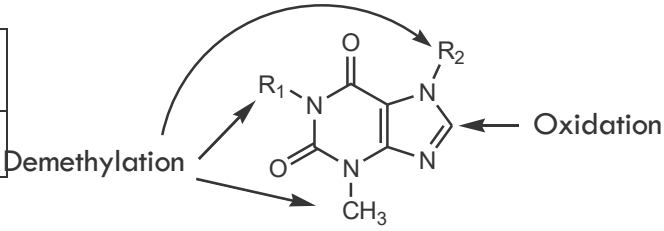
1) Caffeine	2) Theophylline	3) Theobromine
		
Most potent	Less potent	Least potent

Actions:

1) Enhances mental alertness and wakefulness.
2) Diuretics.
3) Enhances concentration.
4) Lessens fatigue.

Metabolism:

Caffeine	1,3-Dimethyluric acid **or** 1-Methyl, 7-methyl
Theophylline	1-Methyl, 1,3-dimethyluric acid



Some excreted unchanged.

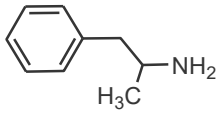
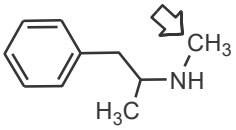
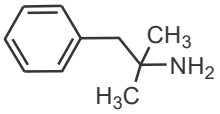
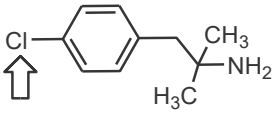
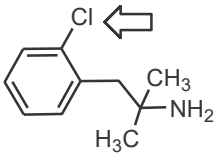
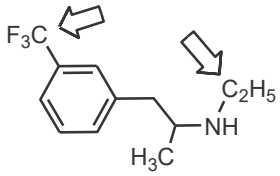
Mechanism of action:

- Inhibition of cAMP phosphodiesterase
  - Promote NE release
  - Promote intracellular Ca^{+2} release
- Phosphodiestrase-inhibiting ability through antagonism to adenosine at $A_{1,2}$ receptors.

2] Central sympathomimetics
A) CNS Adrenergics

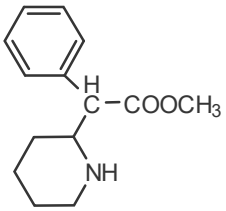
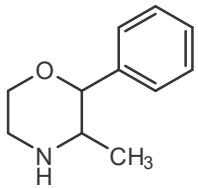
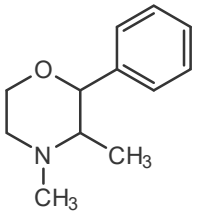
Mechanism of action:

1) Direct α_1-adrenergic receptor stimulation.
2) Inhibit reuptake.
3) Enhances neuronal release of catecholamines.
4) MAO inhibition in high concenteration.

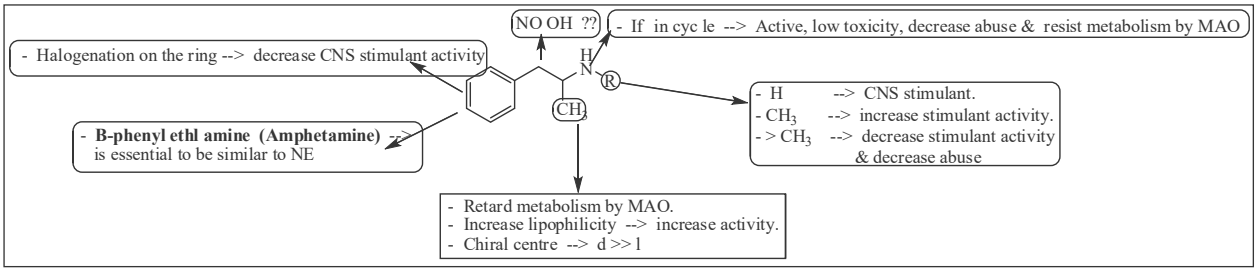
Amphetamine	Methamphetamine	Phenteramine
		
Chlorphenteramine	**Chlortermine**	**Fenfluramine**
		

B) CNS Adrenergic substitutes

- Developed to substitute the amphetamines because of their toxicity and abuse potentials.

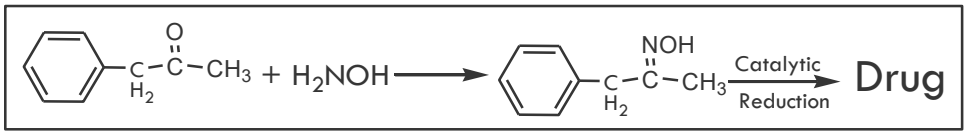
Methylphenidate	Phenmetrazine	Phendimetrazine
		
Methyl 2-phenyl-2-(piperidin-2-yl)acetate	dl-3-Methyl-2-phenylmorpholine	d-3,4-Dimethyl-2-phenylmorpholine

SAR:

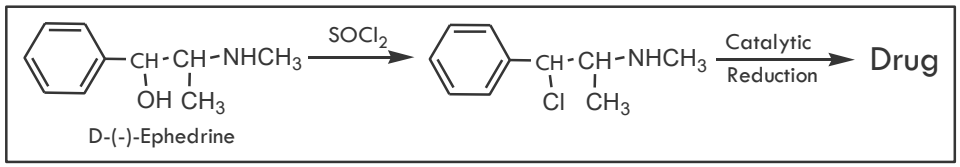


Synthesis:

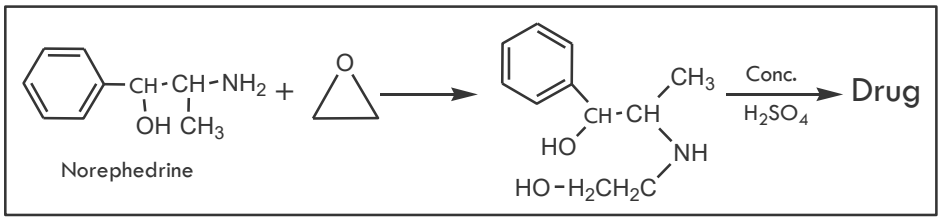
- **Amphetamine:**



- **Methamphetamine:**



- **Phenmetrazine:**



3)-ANTI DEPRESSANTS

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

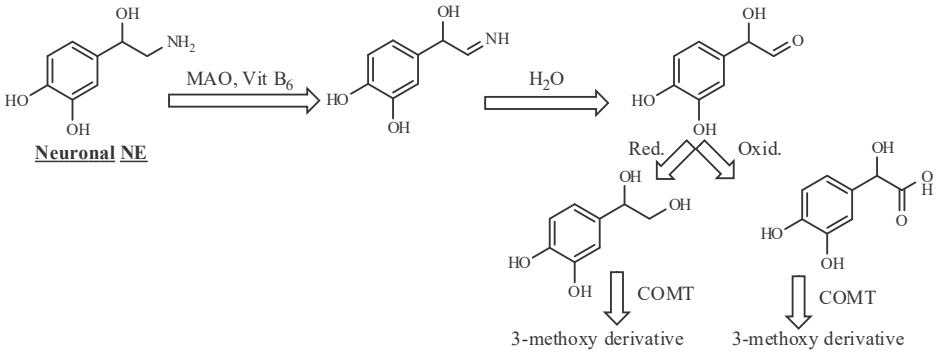
[I] MAO Inhibitors

Mechanism of Action:

Inhibition of intraneuronal MAO-A enzyme (which metabolize NE, 5-HT, DA) → ↑ level of amines → anti-depressant effect.

N.B:

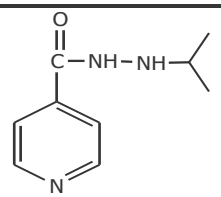
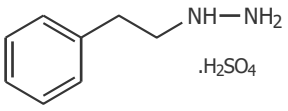
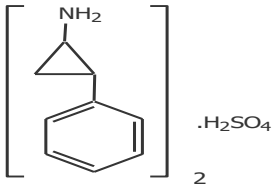
- MAO-B enzyme (metabolize Dopamine only) so, by inhibition → ↓ DA → Parkinsonism treatment.
- COMT: Another enzyme metabolizes endogenous amines but present extra-neuronal.



Side effects of MAOIs:

If taken with sympathomimetics (amphetamine) or food contain tyramine (cheese) → Hypertensive crisis [cheese effect] so, taken only in severe cases under medical supervision

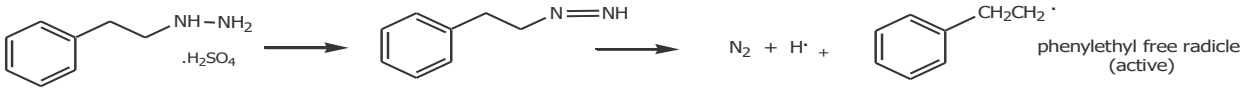
A. Irreversible non-selective MAOIs

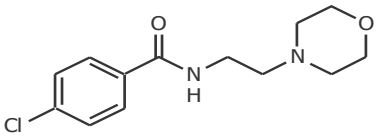
Iproniazide	Phenelzine SO_4	Tranylcypromine
 (isopropyl derive. of I.N.H), **Hepatotoxic not used**	 (Hydrazine derivative)	 (±)-2-phenyl cyclopropyl amine [Cyclic form of amphetamines] • Non-hydrazine.

Assay of Phenelzine:

- $Ph\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}NH_2 + 2\ I_2 + H_2O$ (known excess) $\rightarrow Ph\text{-}CH_2\text{-}CH_2\text{-}OH + HI + N_2$
- $+ NaHCO_3 \rightarrow$ to attract HI and Push the reaction forward $\rightarrow$ Acidify with HCl (to neutralize excess $NaCO_3$)
- Titrate excess I_2 with Standard $Na_2S_2O_3$ and starch indicator.

M.O.A of Phenelzine:



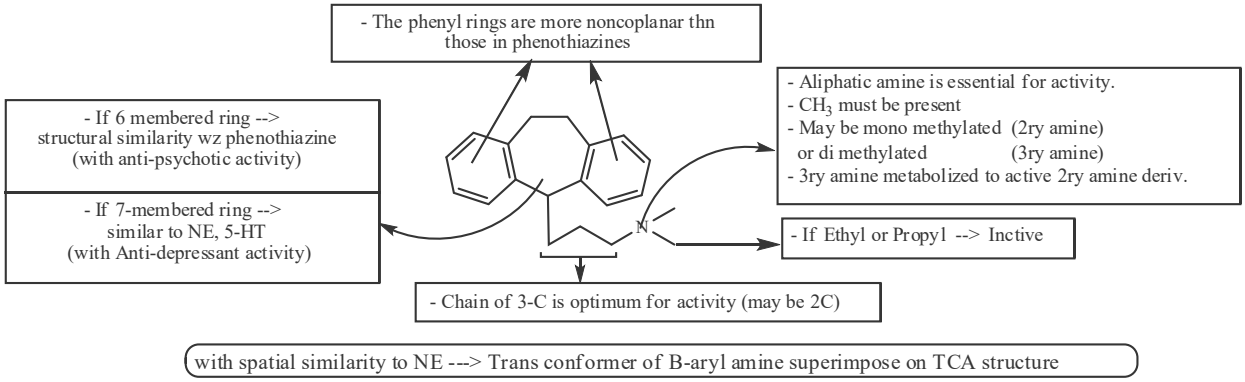
B) Irreversible	C) Reversible preferential for MAO_A
Deprenyl	**Moclobamide**
MAO_B inhibitor (anti-parkinsonism)	 *P-Chloro-N-(2-morpholinoethyl)benzamide* [Non-hydrazine] **Advantage**: Safer with ↓ hypertensive crisis

[II] TRICYCLIC ANTIDEPRESSANT (THYMOLEPTICS)

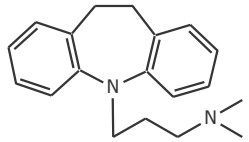
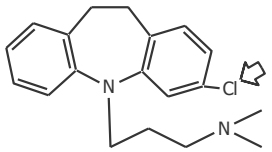
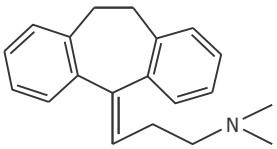
MOA: Block transporters of NE and 5-HT (due to the structural similarities).

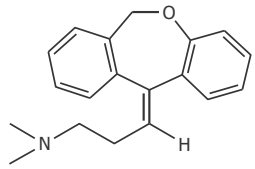
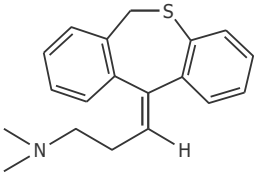
Advantage: Safer than MAOIs → No diet control (may be used for children for nocturnal enuresis).

SAR:

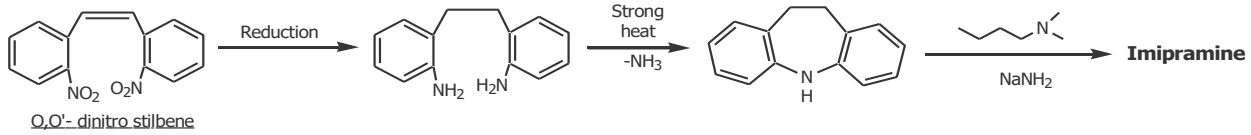


3ry Amines	2ry Amine
↓ 5-HT reuptake [> NE]→ ↑ 5-HT	↓ NE reuptake → ↑ NE
↑ anti-cholinergic S.E	↓ anti-cholinergic S.E.
With ↑ sedation	Stimulatory

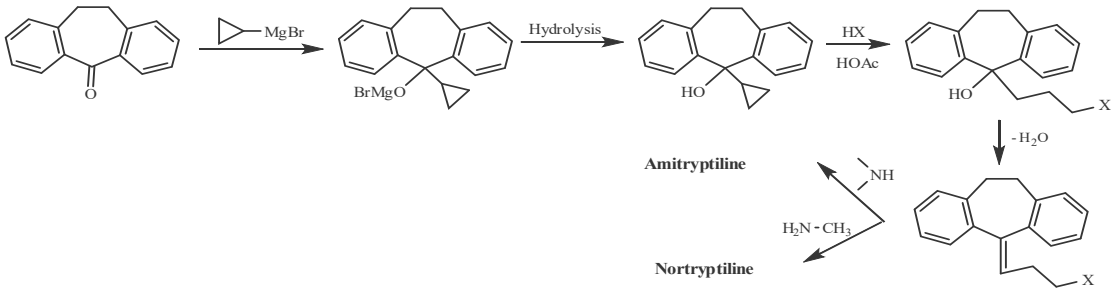
Azepine derivatives		Cylcoheptane derive.
Imipramine	**Chlorimipramine**	**Amitryptiline**
 *3(10,11-Dihydro-5H-dibenz [b,f]azepin-5yl)propyldimethyl amine* Parent		 (No geometrical isomers)
Metabolism → Desipramine [2ry amine]→ more active	-With higher lipophilicity→ more potent. -Cl form H bond with protonated N → stabilize β-aryl amine structure.	Metabolism → Nortriptyline (2ry amine) → active.

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

Synthesis of Imipramine:

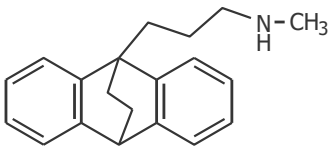
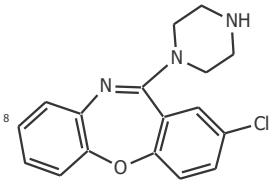
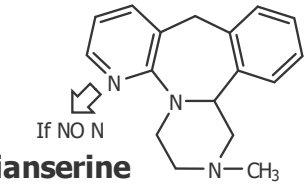


Synthesis of Amitryptiline and Nortryptiline:

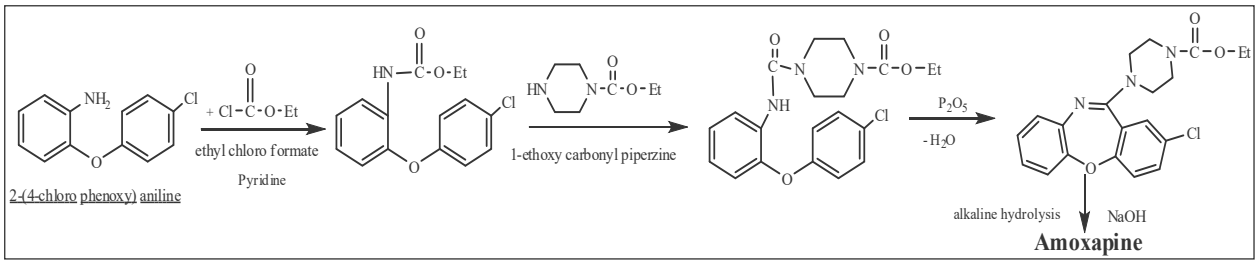


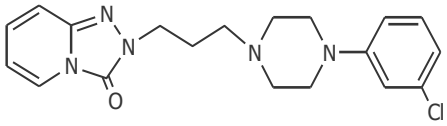
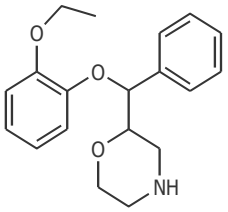
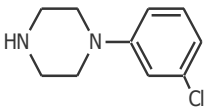
[III] [MISCELLANEOUS]

It is considered as Second-Generation Anti-Depressants

A] Tetracyclic Anti-depressants		
Maprotaline	**Amoxapine**	**Mirtazepine**
	 Oxazepine derivative (Tricyclic derivative)	 Pyrazino-azepine derivative
Selctive NE reuptake inhibitors	Anti-depressant related to Loxapine	Related to Mianserine
- Sedative not stimulant (block other receptors)	Metabolized to 8-OH → D_2-blocker → Antipsychotic.	• Central α_2-blocker →↑ NE release. • ↑ Selective 5-HT transmission (block 5-HT_2 and 5-HT_3) → effects of released serotonin mediated only via 5-HT_1 action.

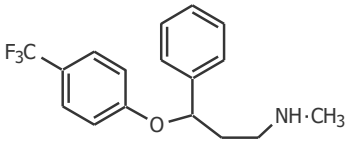
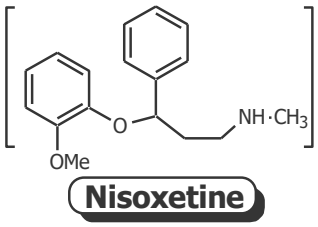
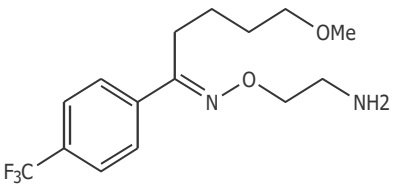
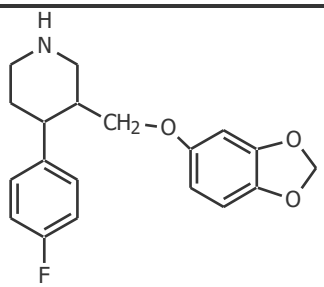
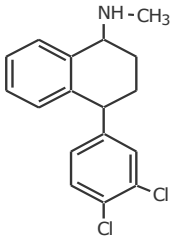
Synthesis of Amoxapine:



B. Trazodone	C. Tianebtine	D. Reboxetine
	Serotonin reuptake accelerator Initial effect → ↓ 5-HT in synapse → then by feedback ↑ release.	 2-[α-(2-ethoxy phenoxy) benzyl] morpholine
Triazolidine derivatives (prevent 5-HT reuptake)		**MOA:** Inhibit NE reuptake (NE factor)
Metabolism → m-chlorophenyl piperazine  → 5-HT agonist		**Uses:** Chronic depression

F-Selective Serotonin reuptake Inhibitors (SSRI)

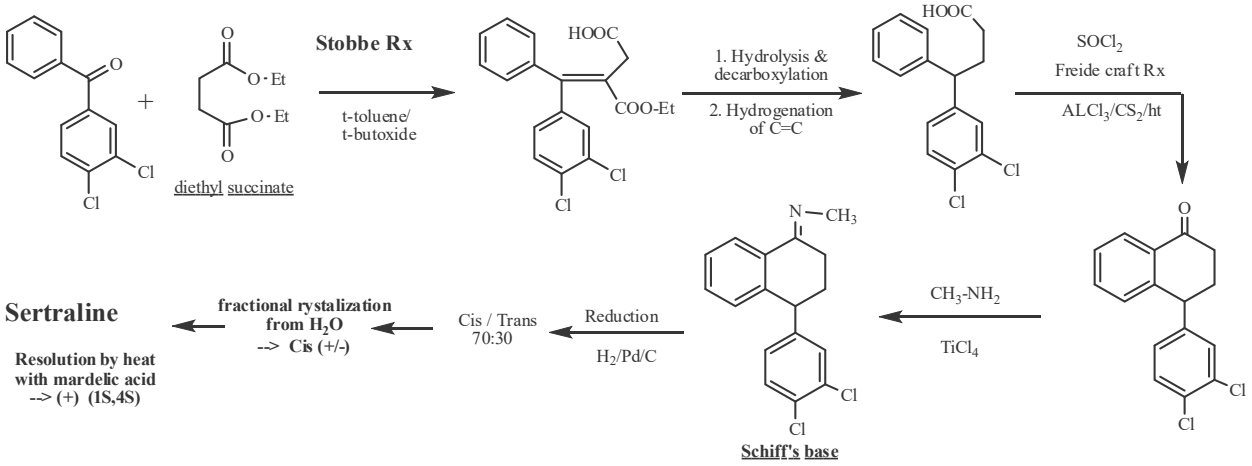
First line of treatment -with phenyl ring, basic N (resemble 5-HT) and halogen. Bind to SERT [Serotonin Transporter]

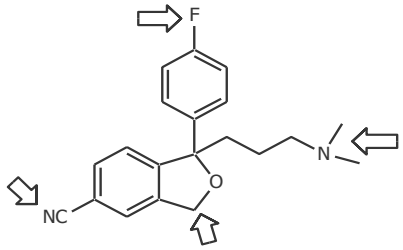
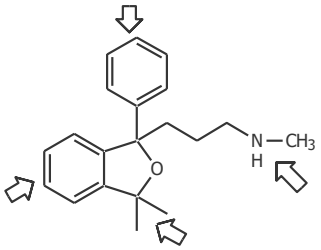
Fluxetine	Fluvoxamine	Sertraline
  Nisoxetine	 **Paroxetine** 	 (1S,4S-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl(methyl)amine[tetrahydro naphthyl amine derivative] Stereoselective • Cis → SSRI and Anorectic • Trans → NE reuptake inhibitor.

SAR of Fluoxetine:

- **CF_3** → must be Para. [if m → ↓ selectivity 10-fold] [if O → ↓ selectivity 90-fold]
- **CF_3** → O-Methoxy (Nesoxitine) → NE reuptake inhibitor.
- **Degree of methylation on N** does not affect selectivity or potency [Norfluxetine is active]
- **Fluxetine** → R and S are equal in activity [but S is slowly eliminated], **Norfluxetine** → S with more selective > R.

Synthesis of Sertraline:

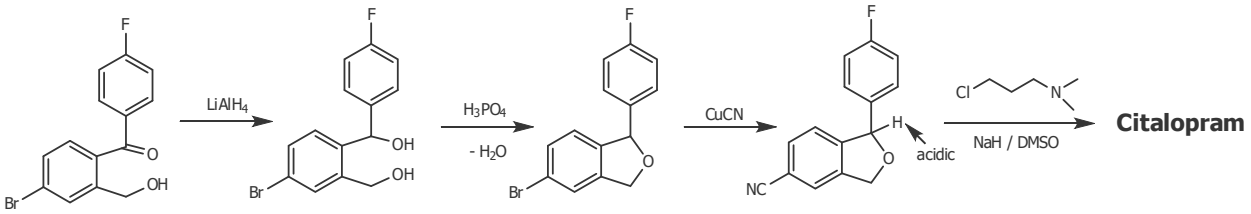


Citalopram	Talopram
	
Steroselective: S-isomer [escitalopram] → 100 times more affinity to sert > R-isomer→ half dose of citalopram 5-HT blocker [SSRI]	NE-blocker

The following ↑ selectivity to 5-HT:

1. Removal of two methyl groups in isobenzofuran ring.
2. Introduction of second methyl to N [3ry]
3. Disubstitution on 5,4-positions → halogenation by Cl, Br, F [dichloro is more selective > mono-chloro derivative].
4. 5-substitution by e-withdrawing group [as CN → chemically & metabolically stable]

Synthesis of Citalopram:



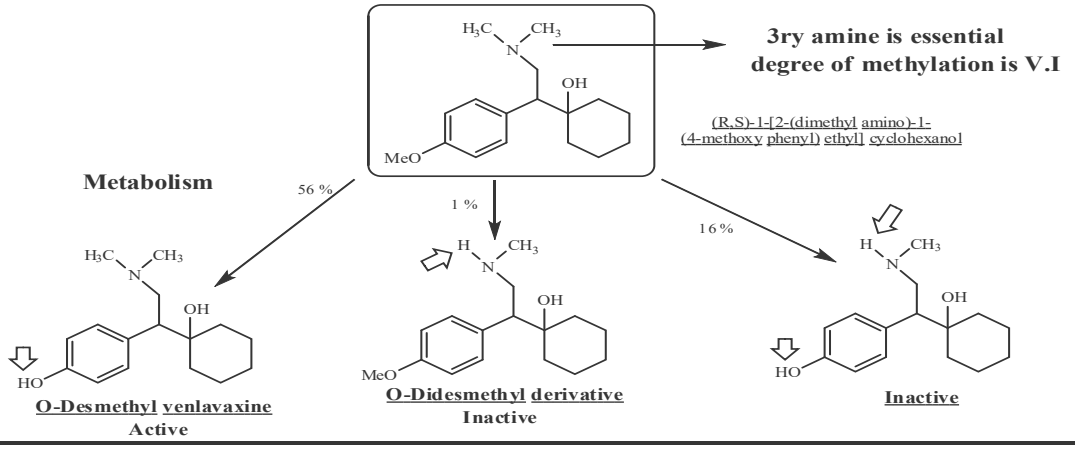
SAR of SSRI:

- Central ring [as in TCA] is abolished here → ↓ anti-cholinergic S.E. [↓ structure similarity] → β-aryl amine-like structure is kept through H-bonding.
- Aromatic ring + basic N → with distance similar to 5-HT.
- Halogen in aryl ring → ↑ selectivity.
- Extra aryl group → ↑ affinity to SERT.

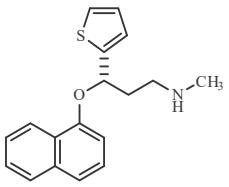
Li Carbonate and Li Citrate	
Uses	1. Prophylaxis and treatment of bipolar depression (manic depression) 2. Prophylaxis of recurrent unipolar depression (+ other anti-depressant)
Disadvantage	With ↓ safety margin (dose should be reduced gradually)

Selective NE Reuptake Inhibitor [SNERI]

Venlafaxine



Duloxetine



- Balanced and potent inhibitor of 5-HT and NE reuptake
- With 3 unrelated indications:

1. Major depression.
2. Stress urinary incontinence.
3. Diabetic peripheral neuropathic pain.

CARDIOVASCULAR SYSTEM
[CVS DRUGS]

	CVS Diseases	Drug types
1	Congestive Heart Failure	Cardiotonic
2	Angina	Antianginals and vasodilators
3	Arrhythmia	Antiarrhythmics
4	Hypertension	Antihypertension
5	Hyperlipidemia	Antihyperlipidemic
5	Blood Coagulation Disorder	Anticoagulants

[I] Cardiotonics

They are drugs that ↑ **contractile force of the heart [INOTROPIC]→ used in CHF [Congestive Heart Failure].**

Congestive Heart Failure [CHF]: inability of the heart to pump blood effectively due to the weakness of cardiac muscles.

Classified into:

Steroidal drugs	Non-steroidal drugs
➢ Cardiac glycosides [e.g. **Digoxin**] **(Sod. Pot. - ATPase inhibitors)**	➢ β_1-agonists [as Dopamine & Doputamine] ➢ Phosphodiesterase Inhibitors [PDEIs]. ➢ Ca channel **opener.**

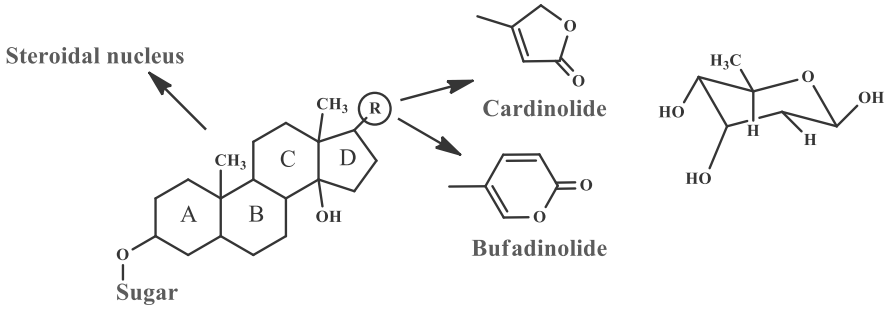
1] Cardiac glycosides

✓ They act by inhibition of **sod. Pot. ATPase** enzyme.

Chemistry:

✓ The molecule consists of **two** main parts:

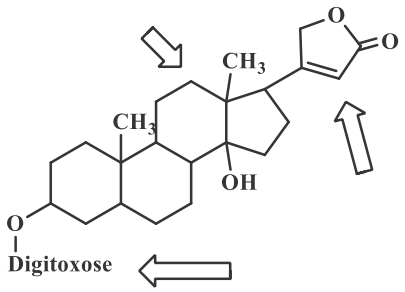
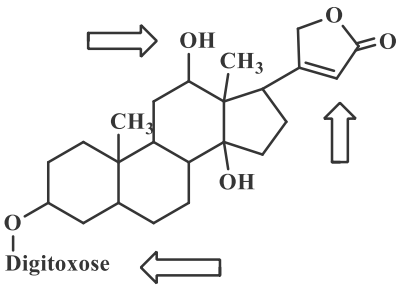
1) A sugar part **(Glycone).**
2) A nonsugar part **(Aglycone).**

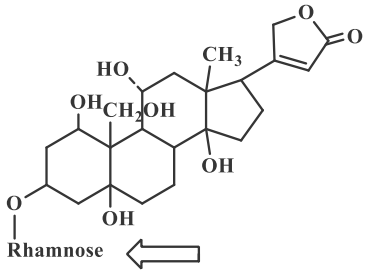


D-glucose; D-digitoxose

Structural features:

1) 1 to 4 sugar residues on C_3-O through β-1,4 linkage.
2) Ring A-B: cis; B-C: trans; C-D: cis (U-shape).
3) Two angular methyl gps at C_{10} and C_{13}.
4) Two β-hydroxyl gps at C_3 (sugar attachment) and C_{14} (free).
5) 17β lactone.

Digitoxin	Digoxin
	
3β,14β-**Dihydroxy**-5β-card-20(22)enolide	3β,12β,14β-**Trihydroxy**-5β-card-20(22) enolide
➢ Two OHs **(more lipophilic)** ➢ 90% PP binding ($T_{1/2}$ 5-7 days) ➢ Metabolized by liver	➢ Three OHs **(less lipophilic)** ➢ 30% PP binding ($T_{1/2}$ 1-2 days) ➢ Excreted by kidney
Assay: Alkaline **picric acid** → orange color (colorimetry)	**Assay: $FeCl_3$** in presence of acetic acid → green color (colorimetry)

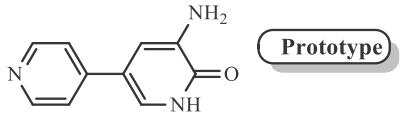
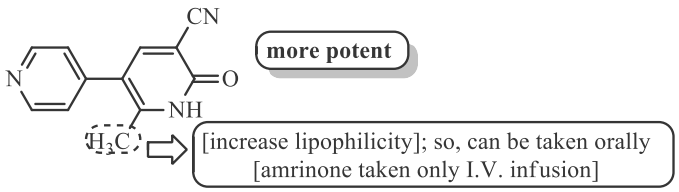
Ouabain	
Used parenterally in **emergencies**, while the others are used in chronic cases. They act through inhibition of **Sod.Pot.-ATPase** →↑ intracellular **Na^+** and accordingly ↑ intracellular **Ca^{++}**	

Stability:

- ✓ They are unstable in **acid** medium due to the **glycoside hydrolysis**.
- ✓ **Ouabain and digoxin are more stable than digitoxin.**
- ✓ **Alkaline** medium cleaves the lactone ring → **inactive.**

2] PDEIs (rinones)

M.O.A: by inhibition of **PDE III** enzyme that hydrolyze cAMP into 5'-AMP → **↑↑ cAMP** → ↑ intracellular Ca^{++} → ↑ force of contraction of the heart **[Inotropic effect].**

Bipyridines	
Amrinone [Inamrinone]	**Milrinone (Primacor®)**
 *5-Amino-[3,4'-bipyridine]-6(1H)-one*	 *5-Cyano-2-methyl-(3,4'-bipyridin)-6-(1H)-one*
Disadvantages: more side effects ① Causes GIT disturbance. ② Taken **only I.V.** → **hydrophilic** drug.	**Taken orally [CN & Me ↑ its lipophilicity]** **More safe, No side effects.**

[III] ANTI-ANGINAL DRUG
[I] Organic Nitrates and Nitrites [NO-Releasers]

They are simple **nitrous or nitric acid esters** of polyhydroxy **alcohols**.

M.O.A:

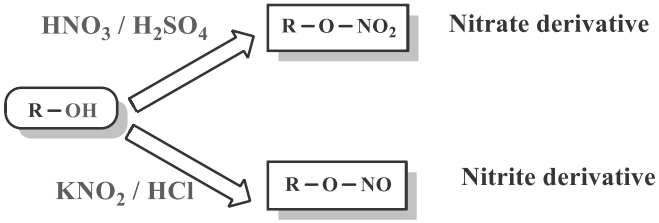
$RONO_2$ + R'-SH [nitrate receptor in coronaries] → RSNO [thionitroso group] → **NO** → activation of guanyl cyclase → ↑ cGMP → **dephosphorylation of Myosin-P** converting it to **Myosin light chain** which can't interact with actin → **relaxation of smooth muscles** → **vasodilatation**.

Side effects of Nitrates:

1. **Rapid tolerance**: due to consumption of tissue thiols.
2. **Headache**, **reflex tachycardia** & **explosive** properties.
3. Some degree of **volatility and sensitive to moisture.**

N.B: there's **no relation** between no. of nitro groups and activity of the drug.

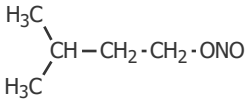
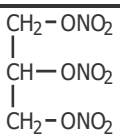
General synthesis:



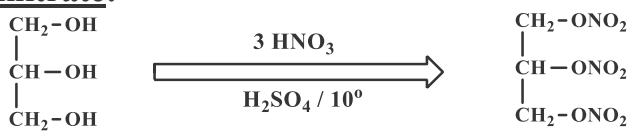
Classified according to their **onset and duration of action** into:

[a] Rapid Acting Drugs:

[Rapid onset, short duration and rapid 1st pass metabolism] → used in ***acute*** cases.

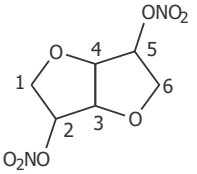
Amyl nitrite [Isopentyl nitrite]	Glyceryl trinitrate (TNG)
	
Taken by **inhalation** in emergency [onset in seconds]	Taken as **sublingual** tablets or **transdermal** patches to prevent **1st pass** effect and fat onset. Redistriubute coronary blood flow to ischemic regions and ↓ myocardial O_2 demand.

Synthesis of glyceryl trinitrate:

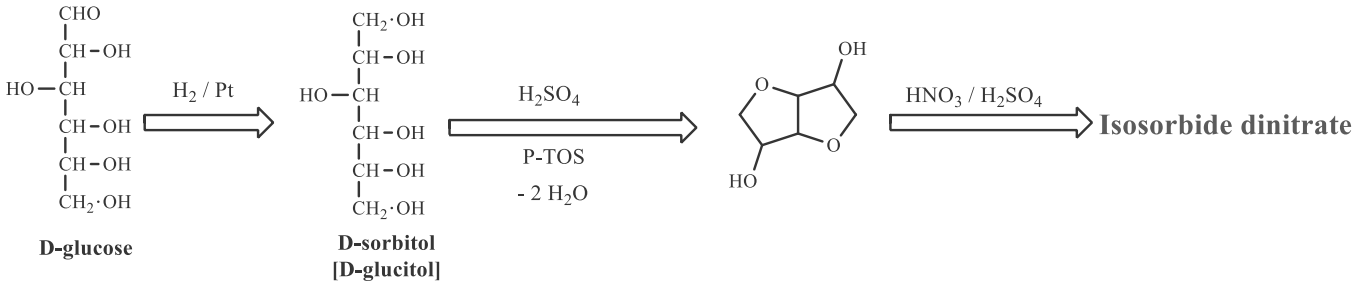


[b] Slow Acting Drugs:

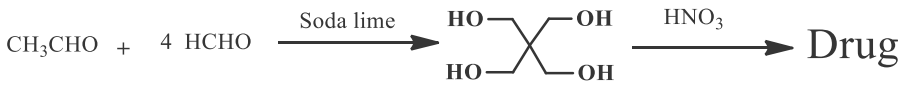
[Used in **chronic** cases for prophylaxis and treatment]

Pentaerythritol tetranitrate	Isosorbide dinitrate [Dinitra®]
 *2,2-bis(hydroxymethyl)-1,3-propandiol tetranitrate*	 *1,4 : 3,6 – dianhydro-D-glucitol-2,5-dinitrate*
With 15 min. onset and 3 hours duration	By metabolism it gives Isosrobide-2-mononitrate and Isosorbide-5-mononitrate [which is active] [5-nitro is used as a drug (Monomack®)]

Synthesis of Isosorbide dinitrate:

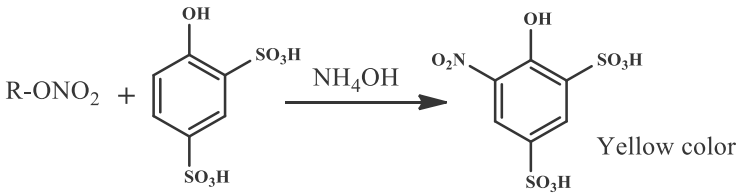


Synthesis of pentaerythritol tetranitrate:



N.B: Isosorbide mononitrtae unlike isosorbide dinitrate, it does not undergo first pass hepatic metabolism, and therefore the bioavailability of isosorbide mononitrate is very high.

Assay:



phenol-2,4-disulfonic acid

2] Calcium Channel Blockers [CCBS]

- Ca Channel blocker [cardio-selective] and β-blockers →used also as anti-anginal drugs

They may act on:

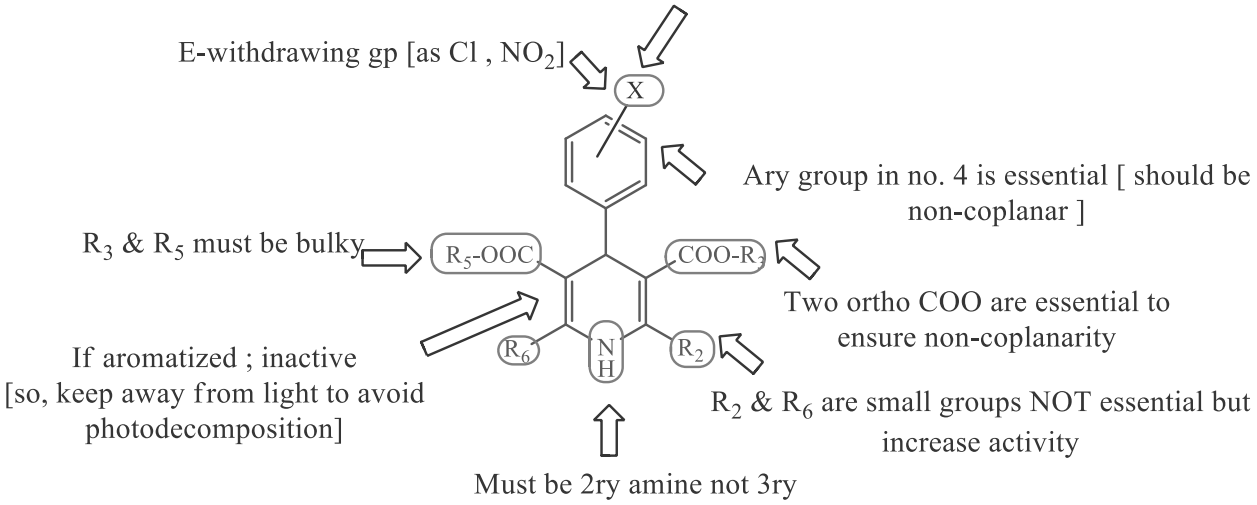
1. **B.V → anti-hypertensive.**
2. **Heart → anti-anginal or anti-arrhythmia.**

Chemical classes:

a) **1,4-Dihydropyridines (dipines e.g nifedipine).**
b) **Phenylalkylamines: verapamil.**
c) **Benzothiazepines: diltiazem.**
d) **Diaminopropanol ethers: bepridil.**

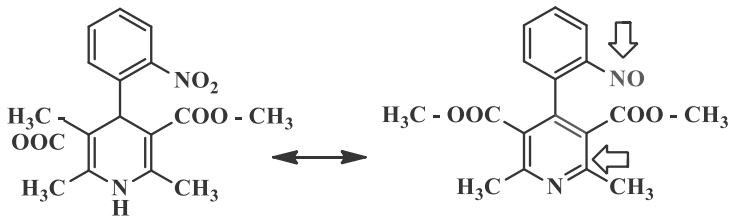
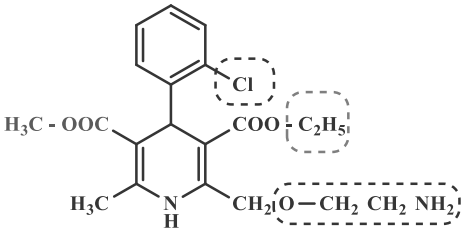
[A] 1,4-Dihydropyridine Derivatives

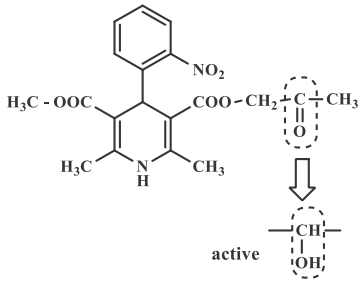
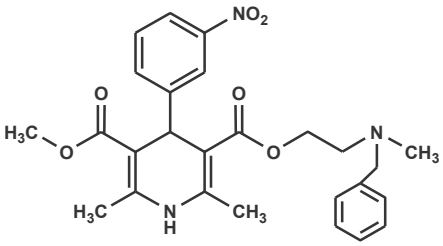
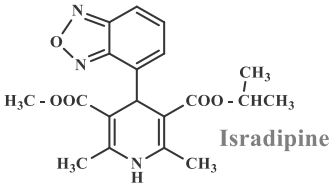
SAR: *O* > *m* > *P* [As steric hinderance make two rings non-coplanar]



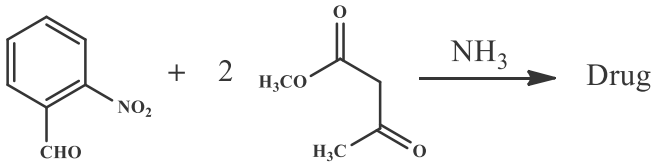
N.B : If R_3 isn't like R_5 ; the compound will be chiral [S>R]

Uses: Used for hypertension [act on B.V. not on heart due to their lipophilicity].

Nifedipine [Epilat®]	**Amlodipine [Norvasc®]**
 *Dimethyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-pyridine-3,5-dicarboxylate*	
• The **PROTOTYPE**. • The main disadvantage is photodecomposition (aromatization and reduction)	• Cl instead of NO_2 → NO photodecomposition. • Ethyl ester instead of methyl → ↑ lipophilicity and ↑ steric hinderance. • Amino methoxy methyl group ↑ lipophilicity [taken once daily] and ↑ absorption.
Chirality leads to marked enhancement of potency.	

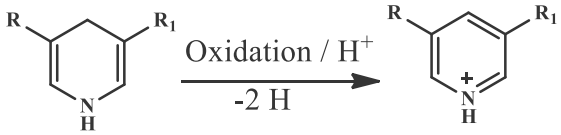
Arandipine	Nicardipine
	
More potent and longer duration than Nifedipine due to its metabolite [by ketone reduction] is as active.	 Isradipine

Synthesis of Nifedipine: (Hansch pyridine synthesis)

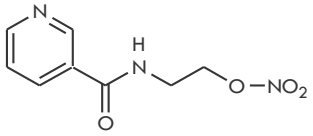
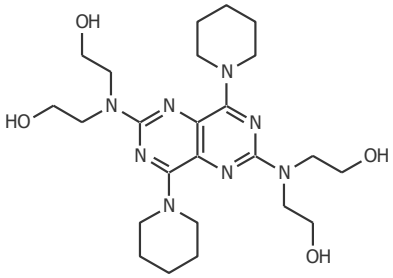


Assay:

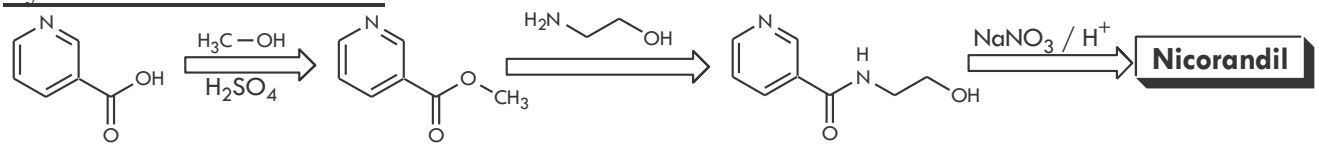
Solution in isobutanol, acidified with perchloric acid, is titrated with **cerric amm. sulfate** using **ferroin** as indicator until the **pink color is discharged.**



[2] MISCELLANEOUS VASODILATORS

Nicorandil (Adancor®)	Dipyridamole [Persantin®]
 N-[2-(nitro oxy)ethyl]-3-pyridine carboxamide **(Nicotinamide derivative)**	
Dual M.O.A: **① Nitrate compound → vasodilator.** **② Act as K-channel activator → hyperpolarization → muscle relaxation**	Used for **prophylaxis from anginal attack** [cause V.D] and **from cerebral ischemic attacks** [anti-platelets]

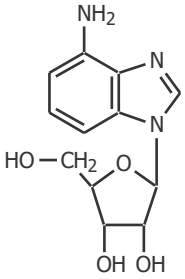
Synthesis of Nicorandil:



Nicotinic acid

M.O.A of Dipyridamole:

1) Depending on **structural similarity between dipyridamol and adenosine** (a natural vasodilator) so it competes to the enzyme **adenosine deaminase** and **prevent reuptake** of adenosine by vascular system → ↑ level of adenosine → **coronary vasodilatation**



Adenosine

2) **Inhibits phosphodiesterase → ↑ cAMP → anti-platelet effect**

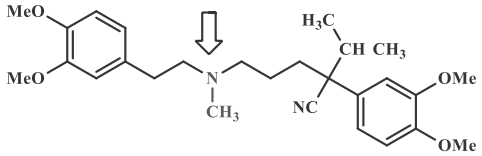
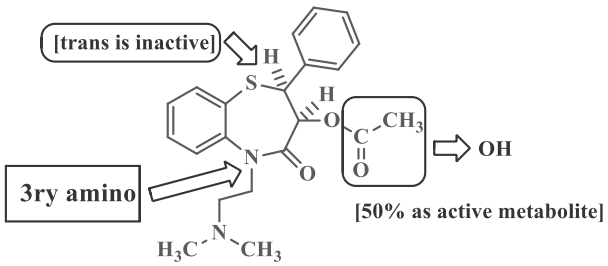
Dipyridamole is the drug of choice for prophylaxis from unstable angina → vasodilator + anti-platelet effect

[3] Cardio-Selective CCBs

Pharmacological effects of CCBs:

1) **Negative** inotropic effect.
2) **Vasodilation** (vascular smooth muscle).

Result: ↓ heart workload and after load.

[b] Phenyl alkyl amines	[c] Benzothiazepines
Verapamil [Isoptin®]	**Deltiazem [Altiazem®]**
 **3ry amino is fully ionized at physiological pH [polar to act on heart]** • With central 3ry amine separated by 2-3 C from aryl moiety. • **With chiral C** → 2 isomers **[levo more potent > dextro].** • **With two active metabolites:** O-desmethyl and N-desmethyl.	**D is the active form**  **Benzothiazepine derivative**
Selective to cardiac muscles → used mainly as **anti-arrhythmic agent.**	**Long acting drug** with **high affinity to cardiac myocardial cells.**

[III] Anti-Arrhythmic drugs

- **Cardiac arrhythmia** is an abnormality of the **cardiacrhythm**. Arrhythmias may cause sudden death, syncope, heart failure, dizziness, palpitations or no symptoms at all. There are two main types of arrhythmia:
  1. **Bradycardia:** the heart rate is slow (< 60 b.p.m.)
  2. **Tachycardia:** the heart rate is fast (> 100 b.p.m.).

Classification:

- According to **pharmacologic effect**:

Class I	Na^+ channel blockers → E.g. Quinidine
Class II	β-Blockers [indirect ↓ in Ca^{++} influx] → E.g. Propranolol
Class III	K^+ channel blockers (prolongs the action potential)
Class IV	Ca^{++} channel blockers → E.g. Verapamil

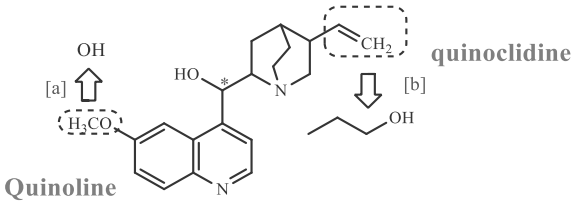
[I] Class I [Na^+ channel blockers] [Membrane stabilizing drugs]

M.O.A:

- By **blocking sodium channels** → ↓ maximal rate of depolarization → ↑ **duration of action potential** → anti-arrhythmic action.
- With **membrane stabilizing effect** → **may be used as L.A** which inhibits the first phase of action potential**.**

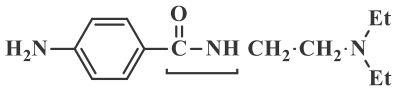
Class Ia [Moderate dissociation → moderate activity]

1) Quinidine

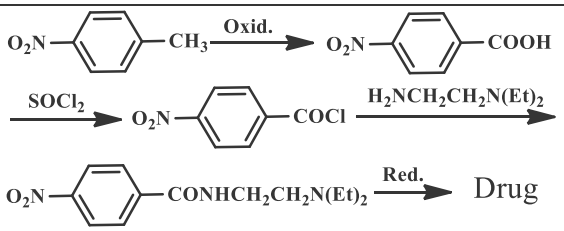


- The prototype drug.
- Present as **D(+) isomer**, if L(-) it's called **quinine** [anti-malarial].
- **Gives 2 active metabolites [a & b].**
- **Cinchonane** derivative.

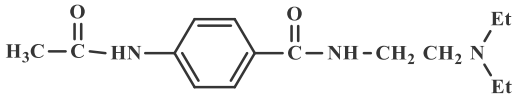
2) Procainamide



4-Amino-N-(2-diethyl amino ethyl) benzamide



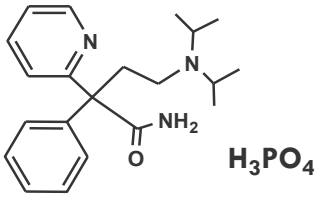
- It's the amide of procaine [local anesthetic].
- Short acting drug [hydrolyzed by amidase].
- By metabolism: N-acetylation giving N-acetyl procainamide [Acecainide] which is class III anti-arrhythmic agent [K^+ channel blocker]



Assayed by Non aq. titration, or by **diazotization (primary aromatic amine).**

3) Disopyramide phosphate

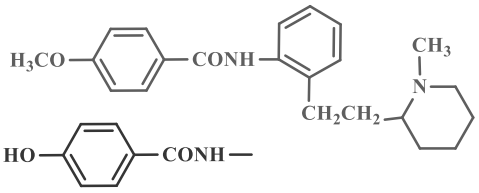
4) Encainide



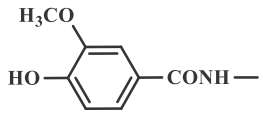
α-[2-(Diisopropylamino)ethyl]-α-phenyl-2-pyridineacetamide

- Not considered first line, must be used with caution Used orally or I.V.
- It's **structurally similar to anti-muscarinic drug** [with **anti-muscarinic side effects** as dry mouth, blurred vision….].

With **–ve inotropic effect** [used with caution if there's congestive heart failure].



Modefication (more potent)

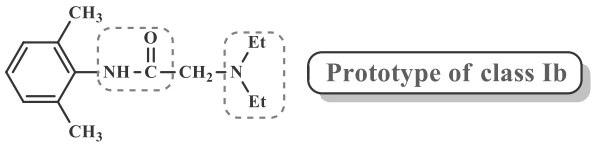


Modefication (equipotent)

4-Methoxy-N-[2-[2-(1-methyl)-2-piperidinyl)ethyl] phenyl]benzamide

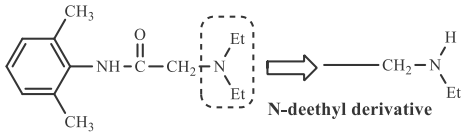
Class Ib [with rapid dissociation → least potent]

Lidocaine [Xylocaine]



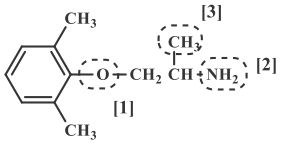
2-(diethyl amino)-N-(2,6-dimethyl phenyl) acetamide

- Used I.V. [**NOT orally**] due to first pass effect; see below]
- **Used as L.A** [as procainamide].
- **2-ortho methyl groups**: essential that they make steric hinderance to ↓ hydrolysis of amide.
- **By metabolism:**



Mono Ethyl Glycine Xylidide [MEGX]
[weakly active; causes Constipation & convulsion]

Mexiletine

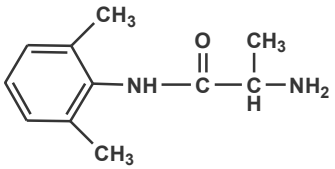


1-(2,6-dimethyl phenoxy)-2-propanamine

It can be taken orally due to:

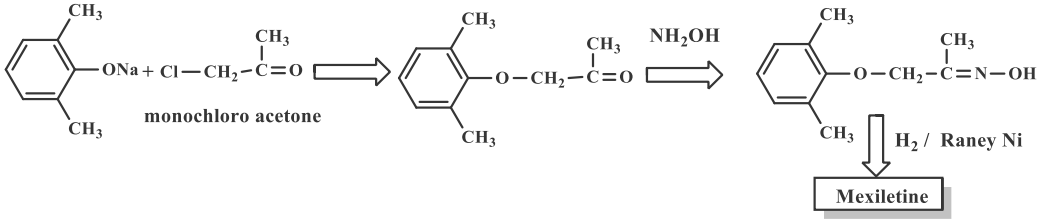
1. **Ether linkage** is more stable than amide linkage to hydrolysis.
2. **Presence of 1ry amine** → no N-dealkylation → no toxic metabolites.
3. **Presence of α-methyl group** which make **steric hindrance** that ↓ hydrolysis of 1ry amine by MAO and also ↑ lipophilicity.

5) Tocainide



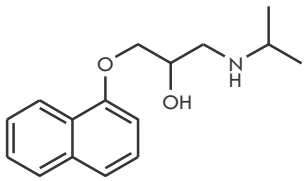
It is the analogue to lidocaine, **orally active** with low hepatic metabolism.

Synthesis of Mexiletine:

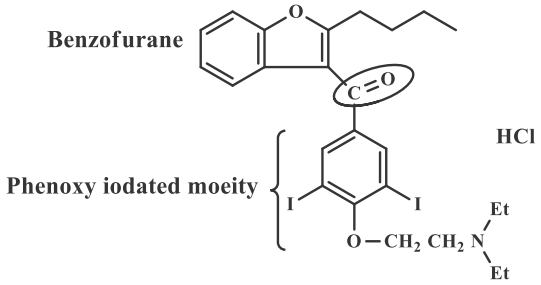
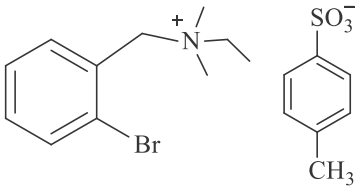


[II] Class II [β-blockers]

1) **Propranolol.**
2) **Sotalol.**



[III] Class III [K^+ channel blockers]
[Prolongs the action potential]

[1] Amiodarone [Cordarone®]	[2] Bretylium tosylate
 *2-Butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone*	 *(o-Bromobenzyl)ethyl-dimethylammonium p-toluene sulphonate*
Side effects: Very slow onset & very long duration [**Hard drug**].	• Used in emergencies. • **Side effects: Sever hypotension.**

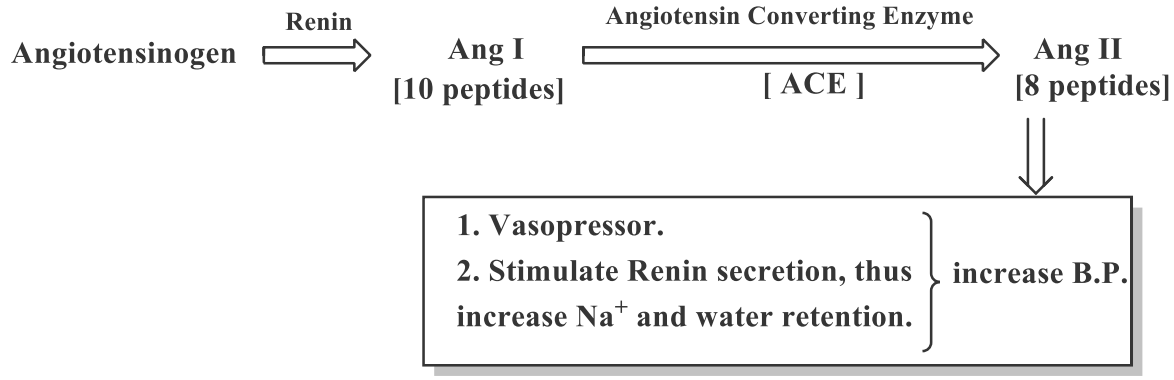
[IV] Class IV [Calcium channel blockers]

1) **Diltiazem HCl.**
2) **Verapamil HCl.**

[IV] Anti-Hypertensive drugs

- **Initial Agents:**
  1) Diuretics.
  2) Calcium channel blockers.
  3) Angiotensin Converting Enzyme Inhibitors. (ACEI)

[3] Angiotensin Antagonists

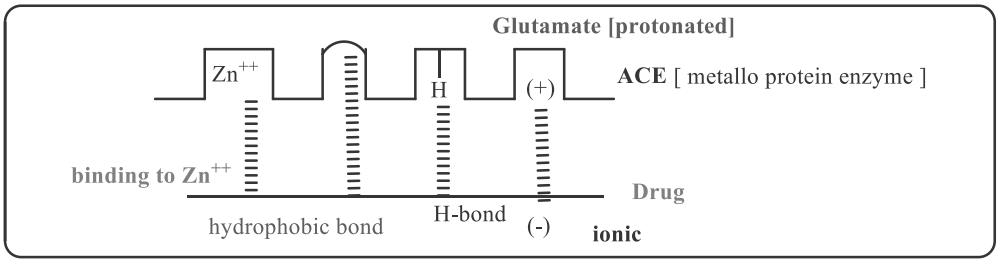


[A] ACE Inhibitors [PRILS]

Major side effects: **dry cough** [due to ↑ bradykinins] → so, contraindicated in asthmatic patients.

This class is effective for **diabetic patients** [with nephropathy] (**NO β-blocker → ↓ insulin release)**

SAR:



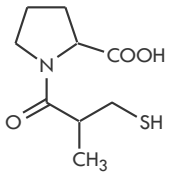
So, the requirements for the ACE inhibitor drug is:

1. Contain anionic site [COO^-]
2. Contain H-bond forming group [C=O]
3. Contain SH, COO^- or phosphinate group to react with Zn^{++}.
4. Contain hydrophobic moiety [if methyl as in captopril → S isomer is more active > R]

1st Generation

Captopril [Capoten®]

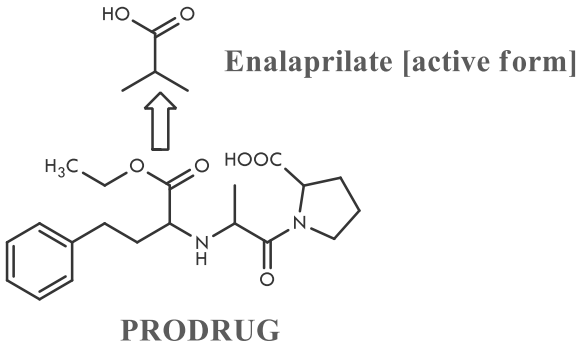
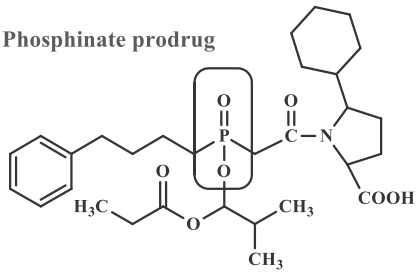
The **prototype of ACE I → used for severe essential and reno-vascular hypertension.**



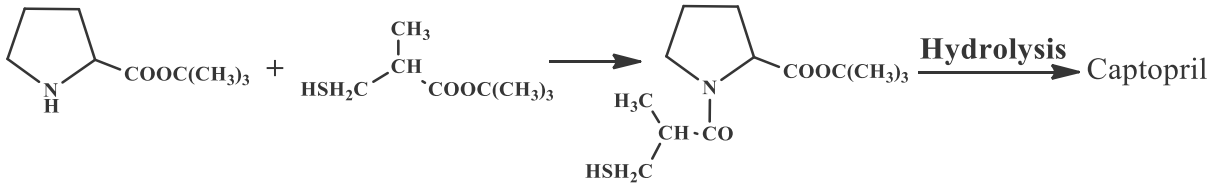
1'-[(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline

Disadvantages:

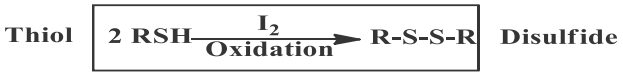
1. **Due to SH group → Rash and loss of taste**.
2. **It's rapidly inactivated by formation of disulfide bridge → short acting.**
3. **dry cough**

2nd Generation [with COOH group → Dicarboxylate]	**3rd Generation [with phsophinate]**
Enalapril [Ezapril®]	**Fosinopril [Monopril®]**
	
Advantages over captopril: 1. **No SH group.** 2. **Phenethyl group** is highly lipophilic, ↑ binding to receptor and ↑ activity. [it's **taken ONCE daily**]. 3. **Containing Alanine as second amino acid → Dipeptide → [better fitting to the enzyme**].	• It **binds to Zn^{++} by phosphinate group**. • It's a **prodrug → Fosinoprilate [active]** • **Less active than dicarboxylate drugs** due to: 1. **Different distance** between L-proline and phenyl separation form phosphinate. 2. Contain **only one amino acid [as captopril]**

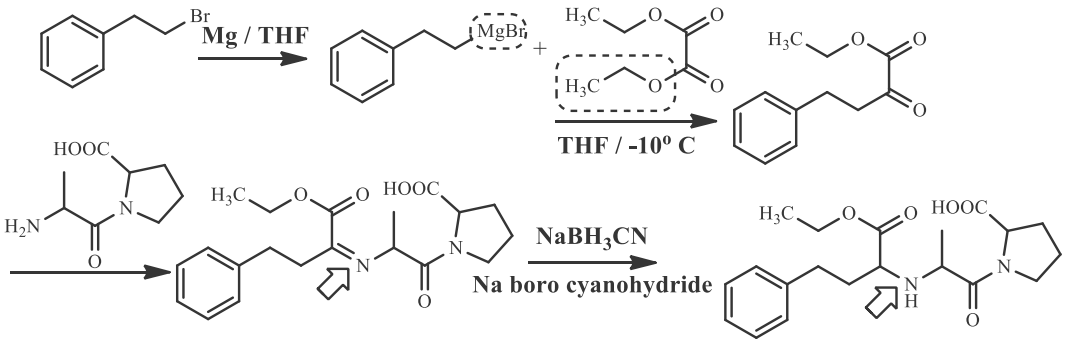
Synthesis of captopril:



Assay: Captopril + KI then titrated by KIO_3 using starch as indicator



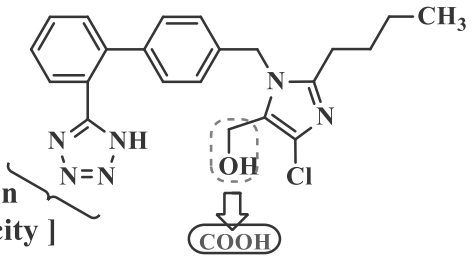
Synthesis of Enalapril:



[B] Angiotensin II Receptor Antagonists [AT_1 Blockers, Sartans]

Advantage over ACE I: NO dry cough.

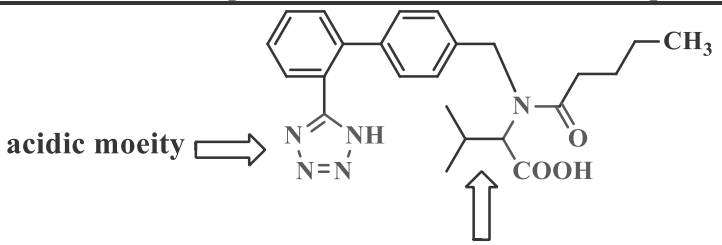
Losartan [Cozaar®]



Tetrazole moeity containing acidic hydrogen
[we not put COOH so as to increase lipophilicity]

[50% as active metabolite] so, losartan is long acting drug.

Valsartan [Non-Imidazole Derivative]



SAR:

1. **Tetrazole → acidic moiety.**
2. **Isosteric replacement.**

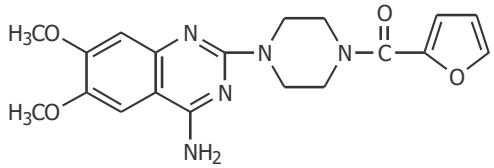
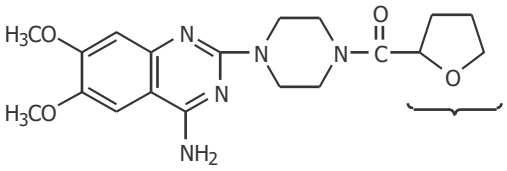
- **Alternatives:**
  1) **Antiadrenergic:**
     a) **β-blockers**
        i) **cardio selective (Atenolol, acebutolol).**
        ii) **Nonselective (propranolol, timolol).**
     b) **α-blockers.**
     c) **Centrally acting.**
     d) **Peripheral antagonists.**
  2) **Direct vasodilators.**
  3) **Ganglionic blocking agents.**

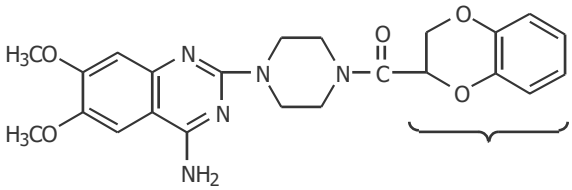
[1] Antiadrenergic agents
[b] Alpha adrenergic antagonists

[a] Non-selective α-blockers:

They are used in pheochromocytoma NOT in hypertension due to their ↑↑ side effects.

[b] Selective α_1-blockers: Cause vasodilatation without ↑ in H.R. or cardiac output [by α_2-blockage].

Quinazolines Derivatives	
Prazosin [Minipress®]	**Terazosin [Itrin®]**
 *1-(4-amino-6,7-dimethoxy quinazolin-2-yl)-4-(2-furanyl carbonyl) piperazine*	
Disadvantage: ↓ lipid solubility and ↓ bioavailability.	Contain **tetrahydrofuran moiety → ↑ lipid solubility→ improve bioavailability and duration [taken once daily].**

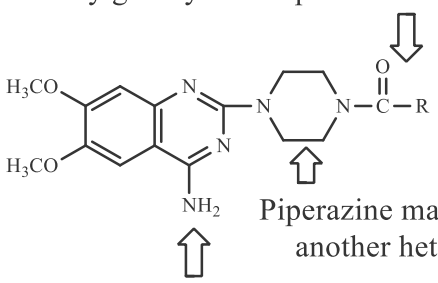
Doxazosin [Cardura®]

Contain 1,4-benzodioxan moiety → ↑ lipid solubility → improve bioavailability a duration [taken once daily].
Used for BPH [Benign Prostatic Hypertrophy]

Side effects:

SYNCOPE: [postural hypotension] especially after 1st dose [***used at bedtime***], palpitation, dizziness.

SAR:

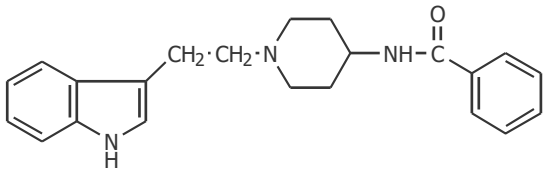
Acyl moeity has great activity greatly affect pharmacokinetic of the drug



Piperazine may be replaced by another heterocyclic ring

4-Amino is Essential for alpha-1 affinity

Indoramine [aryl alkyl amine derivative]

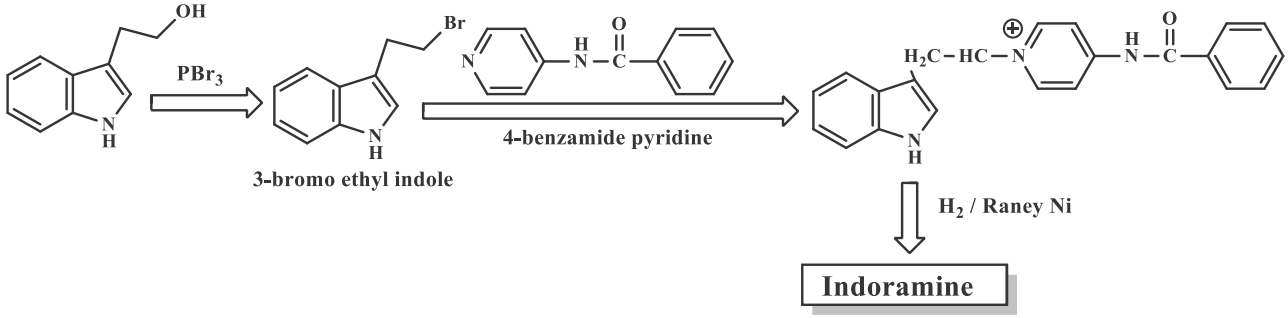


- ✓ It is a piperidine antiadrenergic agent.
- ✓ It is an alpha-1 selective adrenoceptor antagonist with direct myocardial depression action; (**no reflex tachycardia).**
- ✓ It is also used in benign prostatic hyperplasia (BPH).

Advantages over quinoxalines:

- More selective > quinoxalines with no syncope effect.
- Of ↑ lipophilicity [taken once daily]
- More selective for prostate tissue [used for BPH in elderly].
- Used in bronchial asthma as it's H_1-antagonist.

Synthesis of Indoramine:



[i]Centrally Acting Sympatholytics [Centrally Acting α_2-Agonists]

M.O.A:

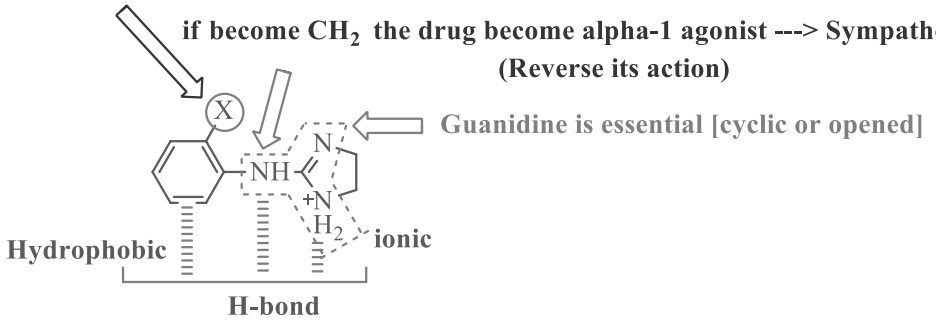
Stimulation of α_2-receptors → ↓ sympathetic flow of NE, Ep from the brain → ↓ B.P.

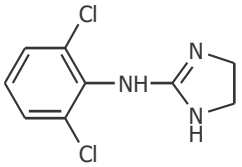
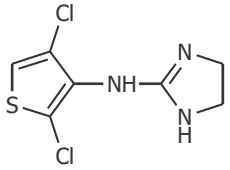
SAR:

At least one ortho lipophilic substituent:

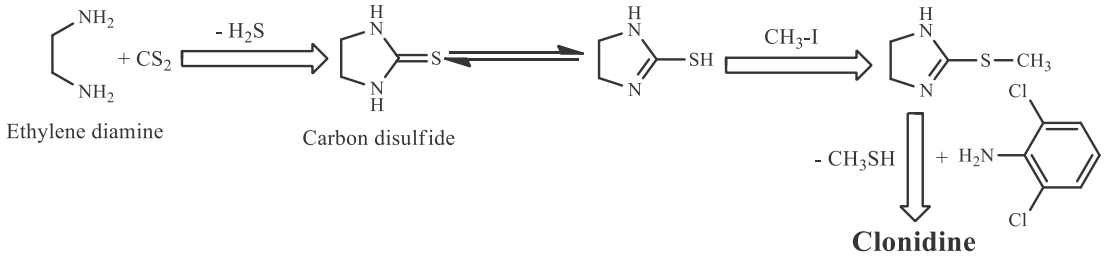
1. Increase lipophilicity and activity---> increase CNS penetration.

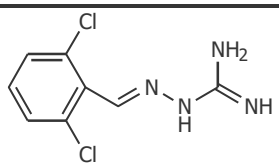
2. Make the two rings non-coplanner.



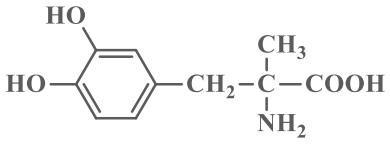
[a] Cyclic Guanidine [2-aryl amino Imidazoline]	
Clonidine [Catapress®]	**Tiamenidine**
 *N-(2,6-|Dichloro phenyl)-4,5-dihydro-(1H)-imidazole-2-amine*	 *N-(2,4-Dichloro-1-thienyl)-4,5-dihydro-(1H)-imidazole-2-amine*
Prototype of this class [used for **hypertension, glaucoma, migraine**]	**Isostere to clonidine** [used in **glaucoma** as eye drops]
• They **act on both α_2-receptors and Imidazoline receptor [I_1].** • As **ratio of action on α_2/ I_1 increase** → side effects as **SEDATION**, palpitation and mental retardation.	
With ↑ α_2/ **I_1 ratio → more sedative**	**With less sedation**

Synthesis of Clonidine:

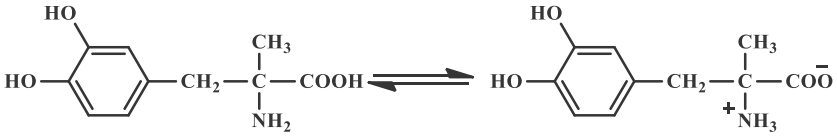


[b] Opened Guanidine
Guanabenz
 *(2,6-dichlorobenzylidene) amino guanidine.*

[c] α-methyl dopa [Aldomet®]

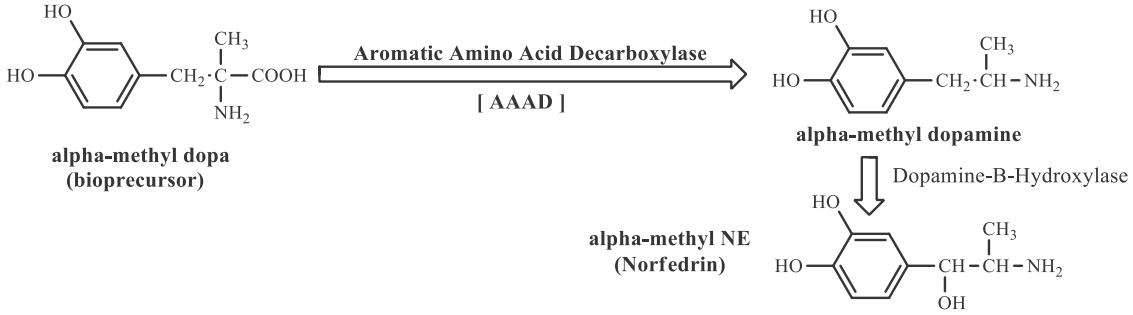


L-3-(3,4-dihydroxy phenyl)-2-methyl alanine



3-Hydroxy-α-methyl-L-tyrosine **Zwitter ion (very insoluble)**

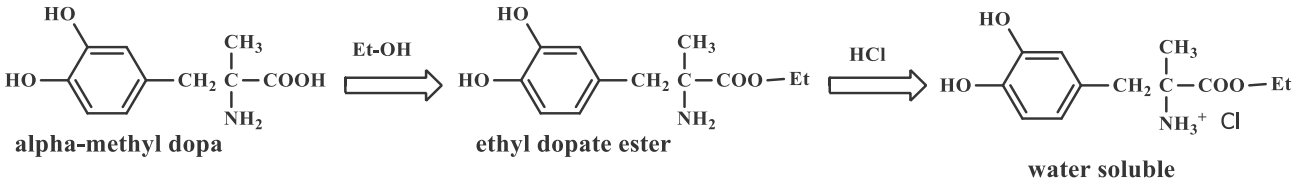
M.OA:



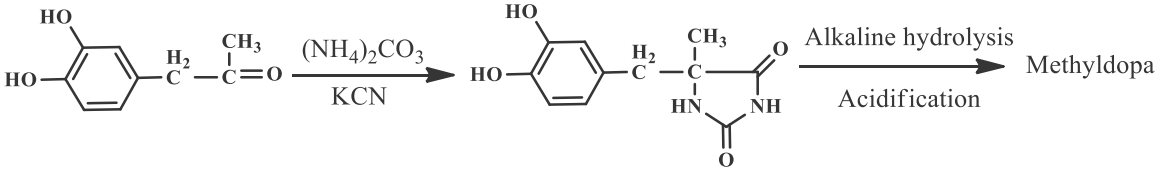
1. Acts as **false neurotransmitter** with weak adrenergic activity.
2. Acts as **α_2-agonist** → ↓ NE and E release [**currently accepted hypothesis].**

Uses:

- Used orally for moderate hypertension but it's sparingly soluble in water [as it presents in zwitter ion form] → safe for pregnancy.
- So, to be used by injection [if hypertensive crisis], we make α-methyl ethyl dopate prodrug which is with free amino to from water soluble HCl salt → which is hydrolyzed in body to give α-methyl dopa.



Synthesis:



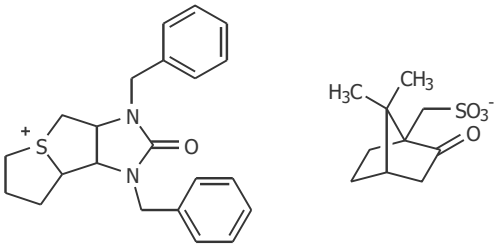
Assay: Non aq. Titration

[d] Peripheral Antagonists

[ii] Peripherally Acting Sympatholytics

[1] Ganglionic Blockers

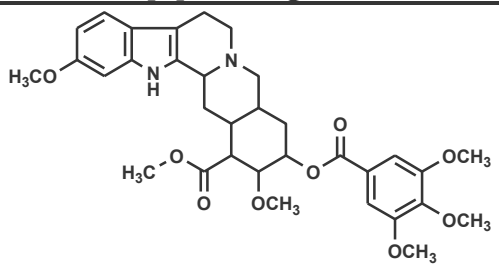
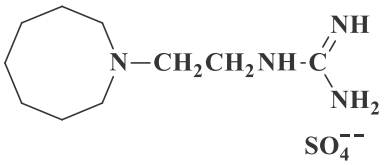
- They block nicotinic receptors at postsynaptic membrane of ganglia and prevent Ach induced depolarization → act on sympathetic and para-sympathetic systems.
- Was used in neurosurgical operation to maintain low B.P. and in hypertensive crisis.
- They are obselet now as they are non-selective with ↑↑ side effects.

Trimetaphan Camsylate	
	• **The only one used for certain neurosurgical procedures.** • Of **short duration [advantage].**

[2] Amine Depletors and Adrenergic Neuron Blockers

M.O.A:

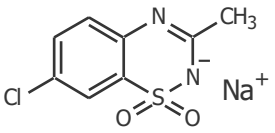
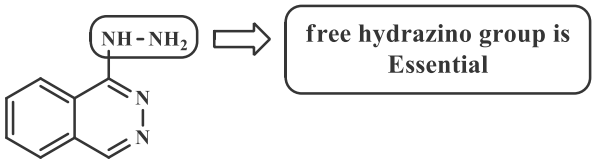
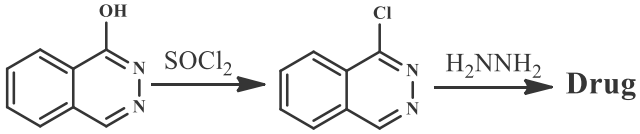
- **peripheral α_2-agonist and block reuptake and deplete NE stores**.
- With **restricted use → orthostatic hypotension**.
- **Examples**: **Reserpine** → natural amine depletor **but acting centrally [cause depression by ↓ amines centrally] → not used for depressed patients.**

[1] Reserpine	**[2] Guanithidine**
	 *1-(2-Guanidoethyl)azacyclooctane*
Depletes postganglionic sympathetic nerves from catecholamines	Deplete the neural granules
Both are of slow onset and very long duration	

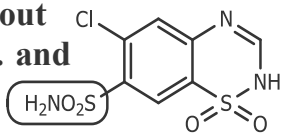
[2] Direct vasodilators

- They are drugs act directly on arterial smooth muscles [without interference with autonomic innervation]
- They are potent drugs used in emergency but with side effects as:
  1. **Reflex tachycardia:** so, used with β-blocker [as anti-arrhythmic agent].
  2. **Na^+ and water retention** [stimulate rennin release from kidney]: so, used with diuretics.

1. **Arterial Vasodilators:** [acts by opening of K^+ channels].

Diazoxide	Hydralazine [Apresoline®]
 *Used as Na salt [soluble] → injection*	 *1-hydrazino phthalazine*
Used in hypertension [emergency]. It ↓ **insulin secretion**, so: May be used for **Endogenous hyperinsulinemia**. If **used for hypertension → combined with hypoglycemic agent.**	Orally active drug **Synthesis:** 

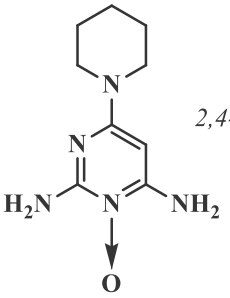
- It's related to **thiazide structure** [diuretic]: **Chlorothiazide. But without diuretic effect due to absence of sulphamoyl group [it causes V.D. and Edema]**



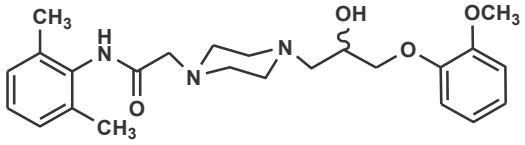
Assay of Hydralazine:

Depending on its reducing properties → titration with oxidizing agent as KIO_3 [Andrew's method]

$$R\text{-}NH\text{-}NH_2 + KIO_3 + 2\ HCl \rightarrow R\text{-}OH + ICl + KCl + 2\ H_2O + N_2$$

Minoxidil [Hairback®]
 *2,4-diamino-6-(1-piperidyl) pyrimidine-3-oxide*
• Used in hypertension in patients unresponsive to other drugs. • **Cause hirsutism → used in Alopecia**. • Orally active drug, long acting.

NEW DRUG

Ranolazine (Ranexa®)	
	N-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide

- Used as **<u>antianginal</u>** and anti-ischemic.
- Partial inhibitor of fatty acid oxidation.
- Ranolazine inhibits persistent or late inward sodium current (*I*Na) in heart muscle in a variety of voltage-gated sodium channels. Inhibiting that current leads to reductions in intracellular calcium levels.

[V] Anti-Hyperlipidemic Drugs

- Lipids transported in blood stream as **lipoproteins**; VLDL, LDL, IDL, HDL.
- Plasma cholesterol & its transporter LDL → **Atherogenic potential.**
- IpCa [specific lipoprotein] → ↓ fibrinolytic activity → **thrombosis**.

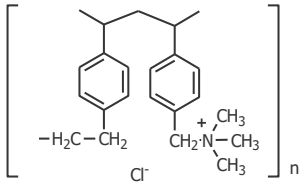
[I] Drugs Affect Lipoprotein Catabolism

[i] Bile acid sequestrants [Anion Exchange Resin]

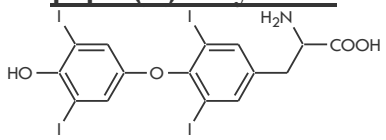
M.O.A:

- They **exchange their anion with bile acid** → binding with bile acid **forming insoluble resin** that is rapidly eliminated → ↓↓ bile acid in body.
- **To compensate → body stimulate cholesterol catabolism in liver** [↑ uptake of cholesterol in blood by ↑ LDL receptors].
- **NOT absorbed → safe drugs.**

Disadvantages: can't be taken in patients with **Homozygous Familial Lipoproteinemia [HFL]** → -ve LDL receptor patients.

Cholestyramine [Questran®]	
	➢ **Polymer of divinyl benzene + styrene + quaternary ammonium compound.** ➢ The **safest drug** for hyperlipidemia.

[ii] D(+) Thyroxin



O-(4-hydroxy-2,4-diiodo phenoxy)-3,5-diiodo-D-tyrosine

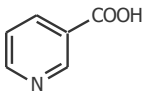
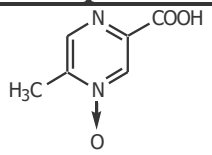
M.O.A: by **stimulation of 17α-cholesterol hydroxylase** which hydrolyzed cholesterol to bile acids.

Side effects: cardiovascular disorders.

[II] Drugs affect lipoprotein synthesis

[i] Nicotinic acid & its derivatives

M.O.A: Inhibit lipolysis → ↓ release of free fatty acids & triglycerides from fatty tissues → ↓ synthesis of VLDL & LDL.

Nicotinic acid [Niacin]	Acipimox
	 5-methyl pyrazine-2-carboxylic acid-4-oxide
➢ Taken in **↑↑ dose** [4 gm / day] → with **short duration.** ➢ If taken in **small doses** → act as **vit.B_3**.	➢ **Nicotinic acid analogue** [isosteric replacement of pyridine ring with piperazine]. ➢ With **higher duration, less side effects.**
➢ Cause flushing, pruritis, arrhythmia.	➢ **Lower potency**.

[ii] Fibrates

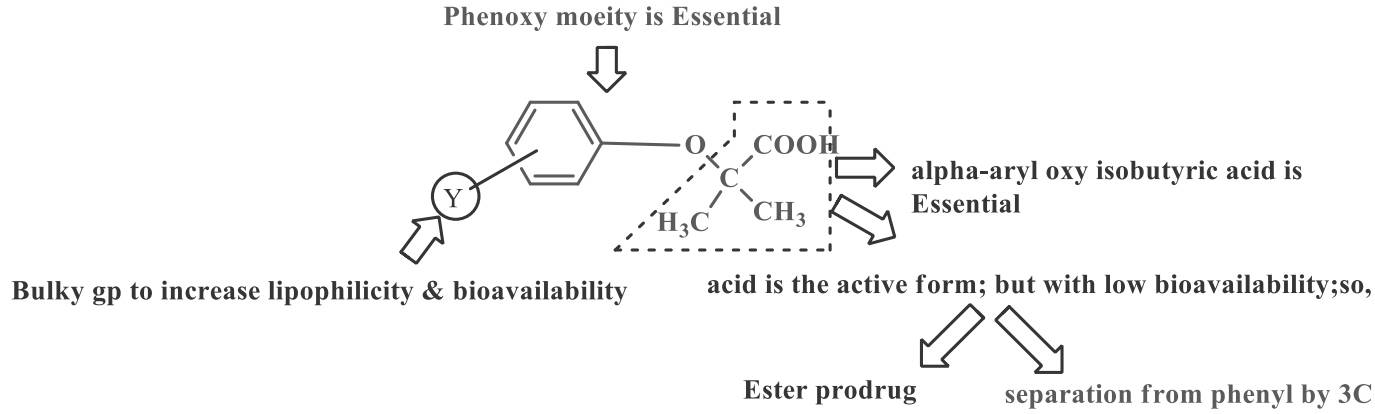
[α-aryl oxy isobutyric acid derivatives] [Clofibric acid derivatives]

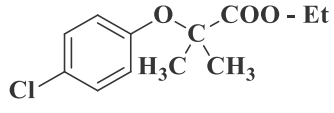
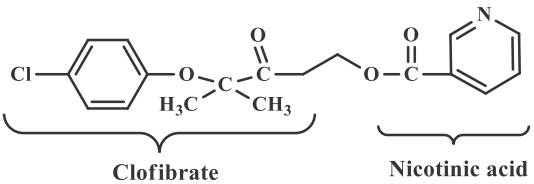
M.O.A:

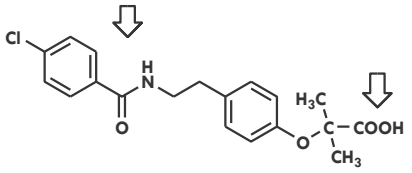
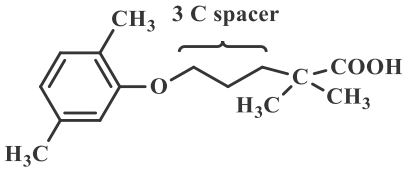
[1] ↑ VLDL catabolism [↑ heptic lipase activity] → ↓ **plasma triglycerides**. [main effect].

[2] **Inhibit incorporation of acetyl CoA into early step of cholesterol synthesis → ↓ cholesterol**.

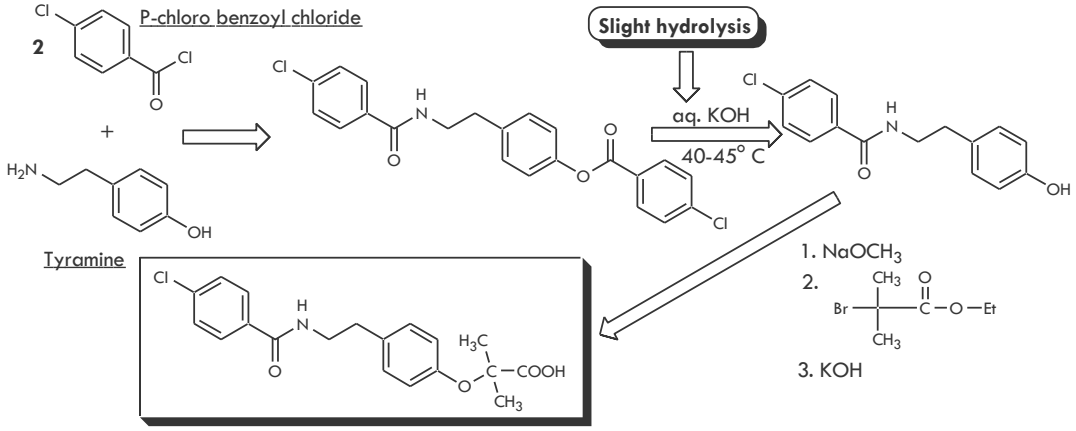
SAR:



Clofibrate	Etofibrate [Lipo-Merz®]
 *2-(4-Chlorophenoxy)-2-methyl propionic acid ethyl ester*	
➢ **The Prototype of fibrates.** ➢ **Prodrug of clofibric acid to ↑ bioavailability**.	➢ **Di-ester prodrug**; by hydrolysis it gives **Clofibric acid** [↓ VLDL & LDL] + **Nicotinic acid** [↓ VLDL] ➢ **Used ≠ all types of hyperlipidemia.**

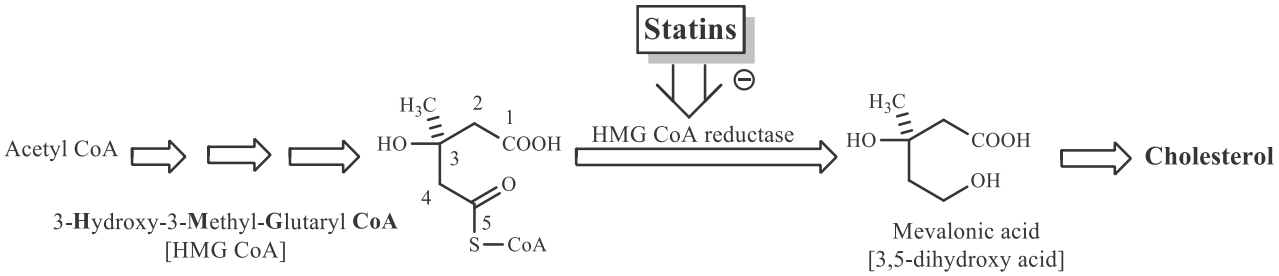
Bezafibrate [Bezalip®]	Gemfibrozil [Lopid®]
 *2-{4-[2-[4-chloro benzoyl)amino] ethyl] phenoxy}-2-methyl propionic acid*	 *5-(2,5-dimethylphenoxy)-2,2-dimethyl pentanoic acid* **(3rd Generation)**
➢ **NOT a Prodrug**. ➢ With **bulky lipophilic group** to ↑ **potency and ↑ duration > clofibric acid.**	➢ **Atypical fibrate [3 C spacer].** ➢ **Not** a prodrug. ➢ **Congener** for clofibrate ➢ ↑ **HDL** also [advantage].

Synthesis of Bezafibrate:

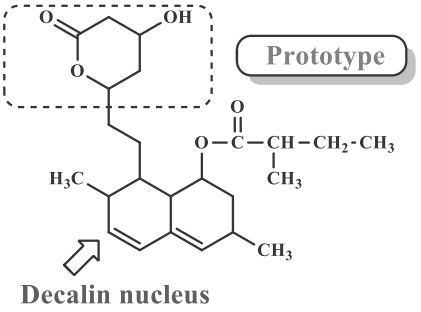
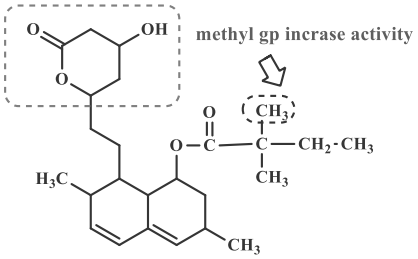
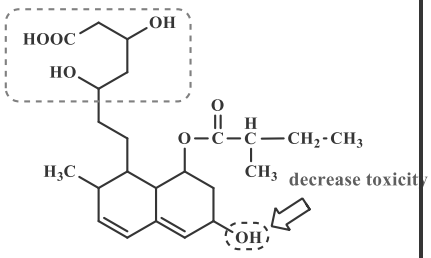


[III] Statins [HMG CoA Reductase Inhibitors]

M.O.A:



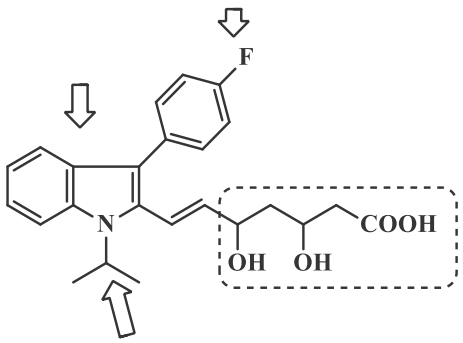
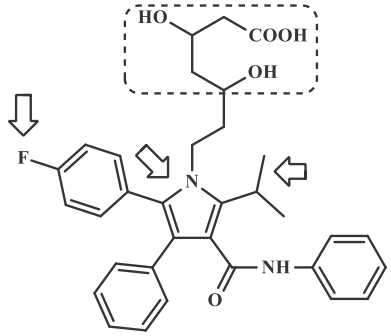
- By inhibition of **HMG-CoA reductase** enzyme → inhibit synthesis of cholesterol.
- Statins should contain **3,5-dihydroxy acid** moiety to be active which is **present either as; lactone ring [prodrug] or free.**

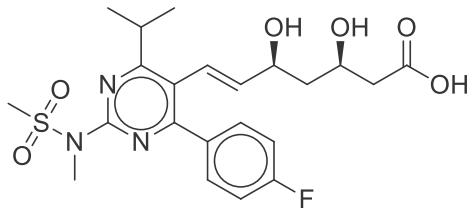
1st Generation		
Lovastatin	**Simvastatin [Zocor®]**	**Pravastatin [Lipostat®]**
		
➢ **Natural** drug isolated from Asperigillus fungi. ➢ **Prodrug**.	➢ **Semi-synthetic** drug. ➢ **Prodrug**. ➢ 3 times more **potent** Homolog of Lovastatin.	➢ **Semi-synthetic** drug. ➢ **NOT** a prodrug. ➢ **OH**: ↑ hydrophilicity & ↓ toxicity.

N.B. on SAR:

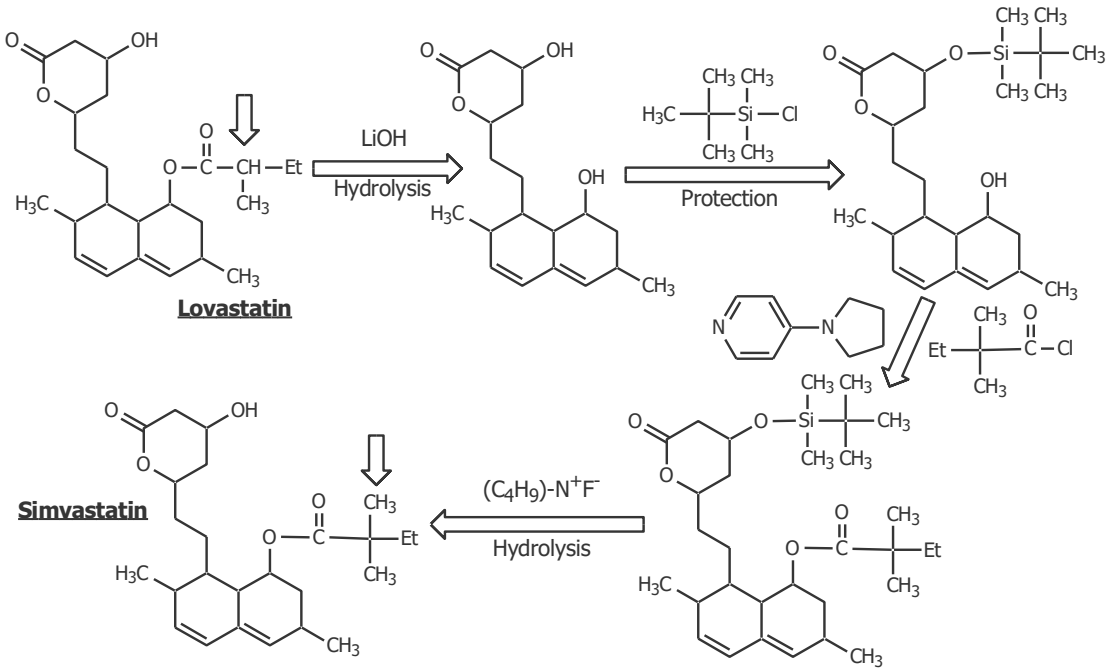
- **3,5-dihydroxy acid** moiety is **ESSENTIAL**.
- **Hexahydronaphthalene** → ↑ lipophilicity & ↑ binding to enzyme.
- It should be separated from active moiety **by 2 C** [if more → inactive].

Side effects: Liver dysfunction and Myopathy [muscle weakness]

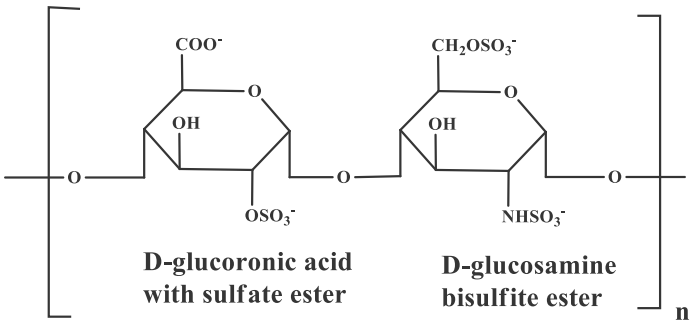
2nd Generation	
Fluvastatin [Lescol XL®]	**Atorvastatin [Lipitor®]**
	
Synthetic, with **heterocycle** + **F** + **Isopropyl group**; they are **not prodrugs.**	

3rd Generation
Rosuvastatin [Crestor®]

Synthetic, with **heterocycle** + **F** + **Isopropyl group**; they are **not prodrugs.**

Semi-synthesis of Simvastatin:



[VI] Anti-Coagulants
[i] Heparin [injectable anti-coagulants]



- **Natural** anti-coagulant; composed of **mucopolysaccharide polysulfonic acid esters** its sugar units are linked together by **α-1,4-glycosidic** linkage**.**
- **Not** used orally [highly ionic **(-ve charge acidic**) + it's sugar] & not taken I.M. [irritant make edema & hematoma].
- Only used **I.V. or S.C.** [rapid onset drug].

M.O.A:

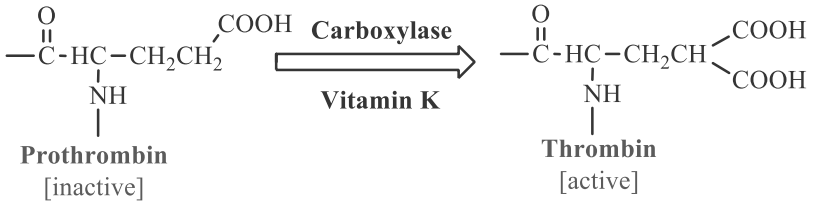
Prothrombin [inactive] + AT III [natural anti-coagulant] —(very slow rate)→ **Degraded Prothrombin**

Prothrombin + AT III + Heparin —(Rapid)→ **Degraded Prothrombin**

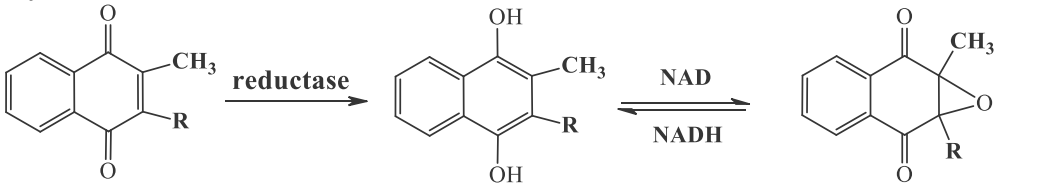
- **So, it inhibits thrombin formation.**
- **Antidote for Heparin [acidic]** is **Protamine Sulphate** [which is basic in nature due to its basic arginine amino acid].
- **Heparinoids →** obtained from heparing through chemical reaction**.**

[ii] Oral anti-coagulants [Indirect acting Vit. K antagonists]

M.O.A: Role of vitamin K:

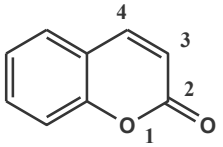
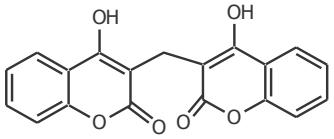
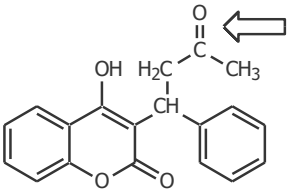


- By inhibition of activation of vitamin K → anti-coagulant effect.
- They inhibit epoxide reductase and naphthaquinone reductase → making vitamin K always in inactive form:

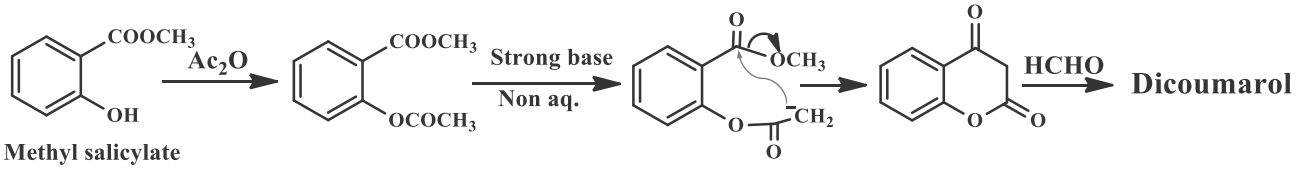


N.B:

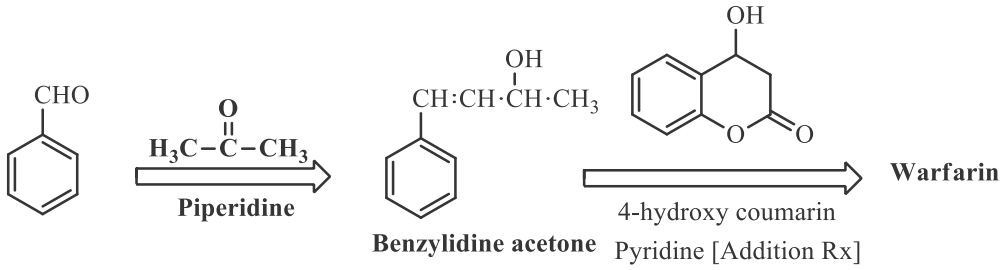
- They are with **slow onset** due to presence of preformed coagulation factors → **not used in emergency.**
- Their effect **last for > one week** after stopping till liver can resynthesize active prothrombin.
- **In emergency** start treatment with heparin + oral anti-coagulant; when effect of oral drug starts to appear → stop heparin.

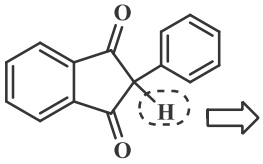
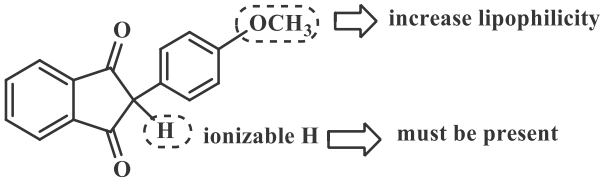
[a] 4-Hydroxy coumarins	
SAR (structural requirements): 4-Hydorxy coumarin is **essential** + **Substitution on C_3** [not essential but ↑ lipid solubility → ↑ bioavailability]	 Coumarine ring
Dicoumarol	**Warfarin [Marevan®]**
 *3,3'-methylene-bis-(4-hydroxycoumarine)*	 *3-(α-Acetonylbenzyl)-4-hydroxycoumarine sod.*
Slow onset – long duration – toxic [obsolete now]	Rapid onset **(36-72 hrs.)** – intermediate duration **(2-5 days)** + nontoxic

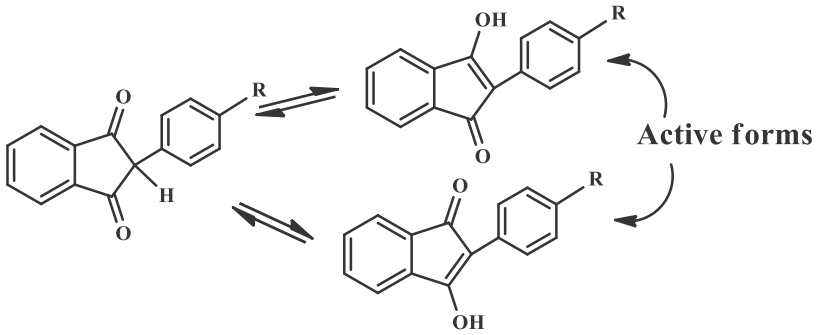
Synthesis of dicoumarol:



Synthesis of Warfarin:



[b] 1,3-Indanediones	
Phenindione [Dindivan®]	**Anisinedione [Miradone®]**
 **ionizable H [must be present] WHY?** *2-phenyl indan-1,3-dione*	 *2-(4-methoxy phenyl) indan-1,3-dione*
	More active + less toxic.
With **slower action** than coumarins and **more toxic (hypersensitivity)**	

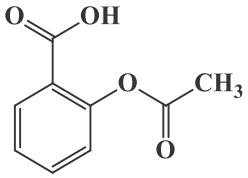


[iii] Platelet Aggregation Inhibitors [PAIS]

[a] COX-Inhibitors: Aspirin [↓ TX synthesis]

- Drugs that inhibit platelets aggregation are useful in reducing the risk of **myocardial infarction.**

- **Aspirin** acts as antiplatelet drug by irreversibly inhibiting platelets aggregation by **acetylation of cyclooxygenase** which in turn inhibits the synthesis of **thromboxane A_2**, a powerful vasoconstrictor and inducer of platelet aggregation.
- **160 mg** aspirin every other day or **80 mg each day** is effective for preventing myocardial infarction.

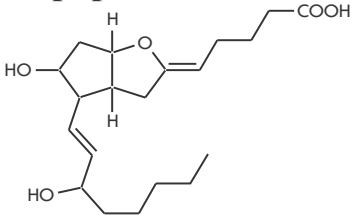


Aspirin

[b] Substances affect cAMP:

Dipyridamole [see before]

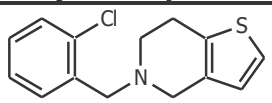
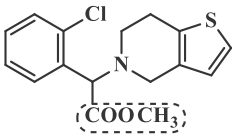
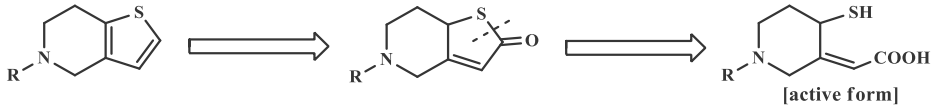
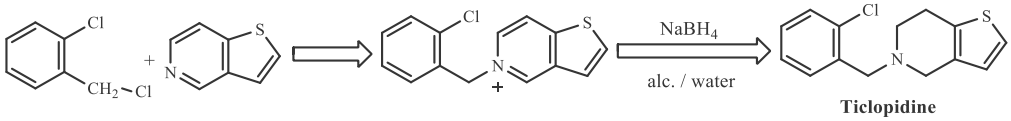
Epoprostenol PGI_2



[c] Platelet Specific Receptor Antagonists

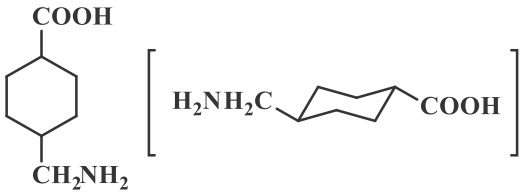
[Adenosine Diphosphate Receptor → ADP-Antagonists]

M.O.A: By **inhibition of this receptor** → which **form fibrinogen bridges between platelets** → **anti-platelet effect.**

Tetrahydro Thieno-Pyridine derivatives	
Ticlopidine [Ticlid®]	**Clopidogrel [Plavix®]**
 *5-(2-chloro benzyl)-4,5,6,7-tetrahydro thieno[3,2-c] pyridine*	
Both are prodrugs [should give active SH group]: 	
Synthesis of Ticlopidine: 	

Hemostatic (Anti-Fibrinolytics)

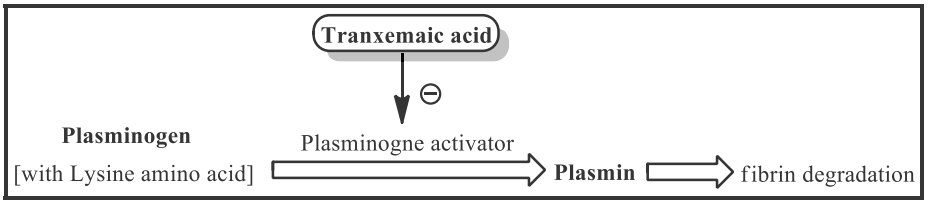
Tranexamic acid [Kapron®]



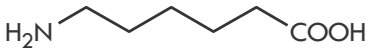
Trans-4-(amino methyl) cyclohexane carboxylic aid

✓ **Used orally & I.V.**

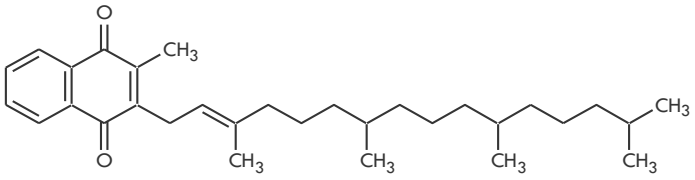
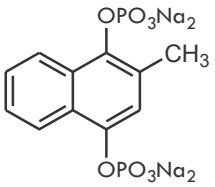
M.O.A:



6-Amino Caproid acid (6-Amino Hexanoic acid)



Similar in action but less potent

Vitamin K	Menadiol disod. phosphate
	

DIURETICS

Definition: Substances that ↑ urine excretion through ↑ excretion of electrolytes [as Na^+, K^+, Cl^- and HCO_3^-] by interfering with their reabsorption from nephron [functional unit of the kidney].

Efficiency depends on:

1. Chemical structure. 2. Site of action. 3. Patient sodium intake. 4. Amount of exracellular fluid.

Uses:

1. Treatment of edema resulting from:
   - Congestive heart failure.
   - Nephritic syndrome.
   - Chronic liver diseases.
2. Hypertension and glaucoma.

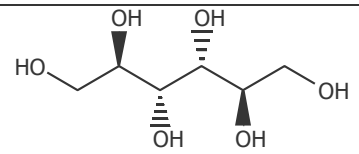
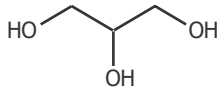
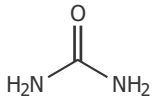
Site of action of diuretics on the nephron:

[I] OSMOTIC DIURETICS

M.O.A: they ↑ tubular fluid osmolarity → ↓ reabsorption of fluids → ↑ excretion of water.

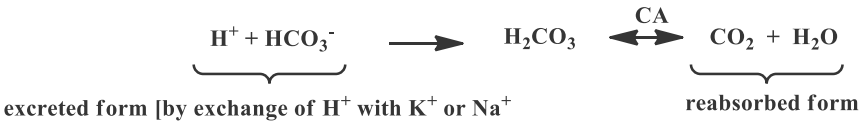
Properties:

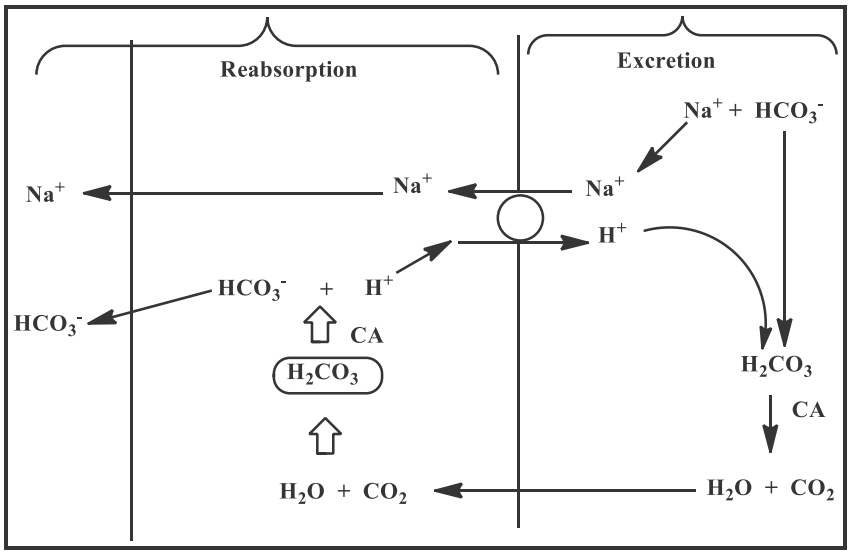
- Of mild potency; used in ↑↑ doses only I.V. [of ↑ water solubility].
- Compounds of ↓ molecular weight.
- Pharmacologically inert.
- With limited or no renal reabsorption or metabolism.
- Act within 10 minutes and used mainly for prophylaxis ≠ renal dysfunction.

Mannitol	Glycerol	Urea
		

[II] CARBONIC ANHYDRASE INHIBITORS

- **Carbonic anhydrase [CA]:** catalyze hydration of CO_2 and dehydration of carbonic acid in tubular cells.

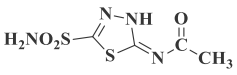
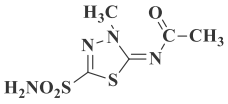
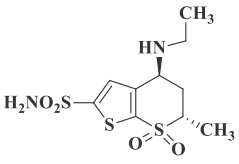
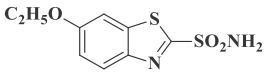
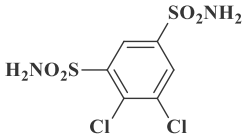




- By inhibition of CA enzyme → ↓ exchange of Na^+ in kidney tubules → Na^+ and HCO_3^- will be more excreted.
- <u>This class of limited use due to</u>:
  1. They are weak diuretics and tolerance rapidly developed.
  2. By <u>prolonged use</u> → urine become more alkaline [↑ Na^+ excretion] → blood become more acidic → acidosis → CA inhibitors lose their activity.

<u>SAR:</u>

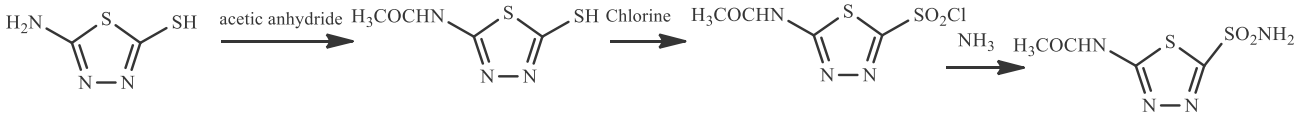
For heterocyclic sulfonamides	For m-disulfamoyl benzene
➢ Free unsubstituted sulfamoyl is essential. ➢ Introduction of methyl group to the ring [Methazolamide] ↓ polarity and ↑ penetration to ocular tissues [100-300 mg/day dose instead of 250-1000 mg/day dose]. ➢ Derivatives with highest lipid/water partition coefficient and with the lowest pKa → greater activity.	➢ Two sulfamoyl groups should be meta to each other. [but 1,3-disulfamoyl benzene with no diuretic activity]. ➢ One of sulfamoyl group should be unsubstituted. ➢ Replacing one sulfamoyl group with similar electrophilic group as; carboxyl or carbamoyl…. Will ↑ diuretic activity but ↓ CA inhibition activity [see mefruside and indapamide]. ➢ Cl, Br, CF_3 or NO_2 substituents in ortho position to one of sulfamoyl groups → maximum diuretic activity [if add another Cl next to ortho Cl; this ↑ activity]. ➢ Amino substituent; ↑ saluretic activity [but ↓ CA inhibition activity].

Acetazolamide	Methazolamide	Dorozolamide [Trusopt®]	Ethoxyzolamide	Dichlorphenamide
 *N-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl] acetamide*			 *6-ethoxy-1,3-benzohtiazole-2-sulfonamide*	 *4,5-dichloro benzene-1,3-disulfonamide*

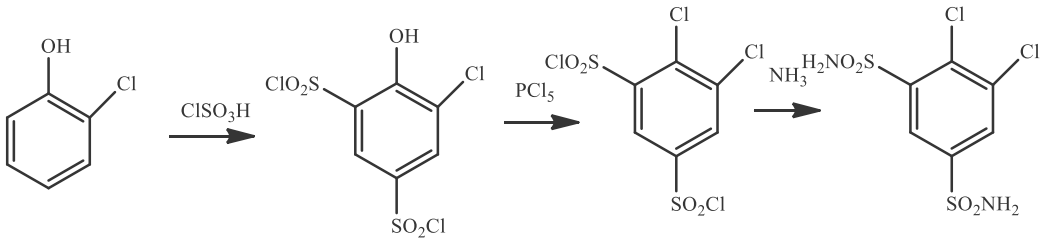
Uses:

1. Glaucoma [by inhibition of CA in eyes → inhibit formation of aqueous humor]
2. Convulsion [by inhibition of CA in CNS].
3. Acetazolamide also used in altitude sickness [for mountains climbers].

Synthesis of Acetazolamide:



Synthesis of Dichlorphenamide:



Assay:

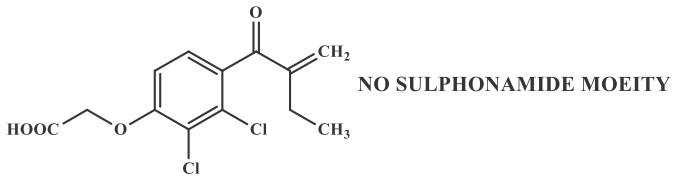
Acetazolamide	Dichlorphenamide
By dissolution in DMF → titrate≠ ethanolic NaOH. Determine end point potentiometrically.	By HPLC; compare area under the peak of the sample relative to a standard at the same retention time and with similar analytical conditions.

[Iii] High Ceiling or Loop Diuretics

- They work on loop of Henle [Loop diuretics], and with ↑↑ activity [High ceiling].
- **Side effects:** ↑ K^+ depletion and ↓ uric acid excretion → Hypokalemia and Hyperuricemia.

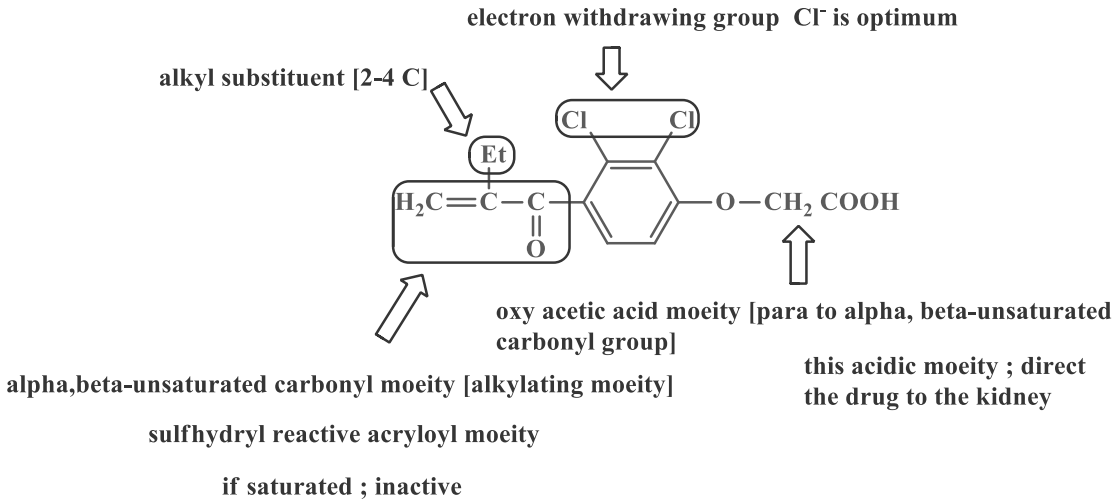
[A] Phenoxy Acetic Acid Derivatives

Ethacrynic Acid

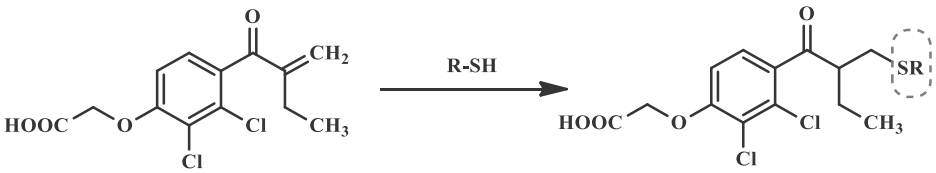


2,3-dichloro-4-(2-methylene-1-oxobutyl) phenoxy acetic acid

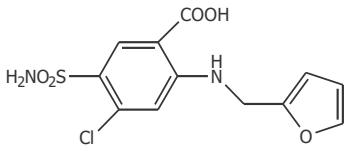
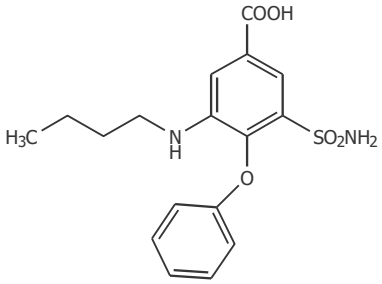
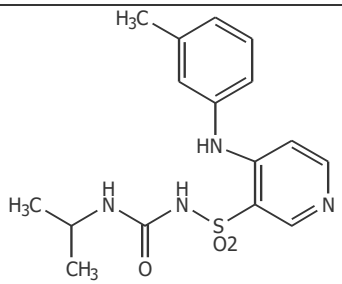
SAR:



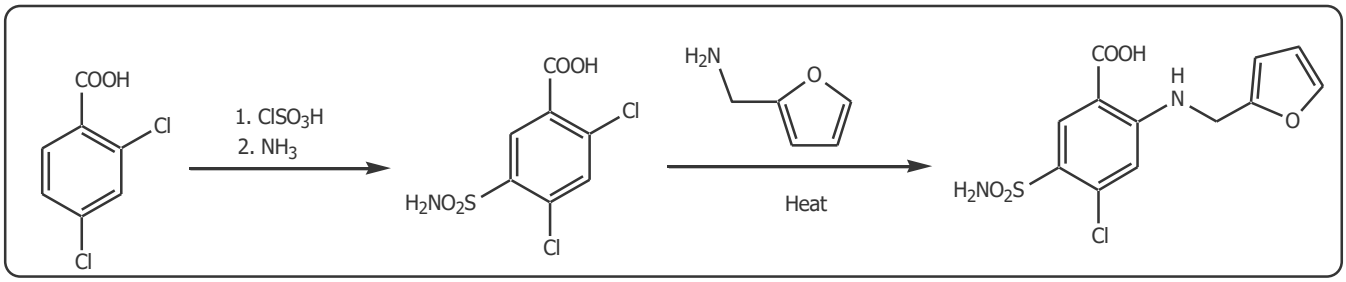
M.O.A:



[B] OTHERS

Benzoic acid Derivatives		Sulfonyl urea derivatives
Furosemide [Lasix®]	**Bumetanide [Burinex®]**	**Torsemide**
 *4-chloro-N-furfuryl-5-sulfamoyl anthranilic acid*	 *3-(butylamino)-4-phenoxy-5-sulfamoyl-benzoic acid*	 *1-isopropyl-3-{[4-(3-(3-methyl phenyl amino-pyridine]-3-sulfonyl} urea*

Synthesis of Furosemide:



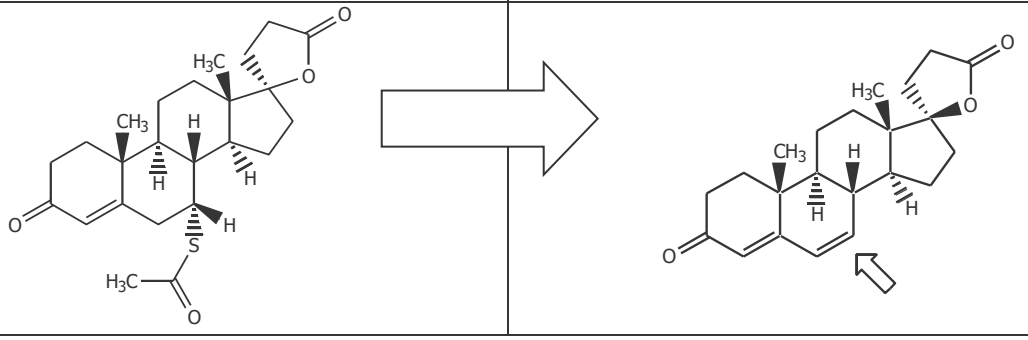
Assay

Ethacrynic acid	Furosemide	Bumetanide
Dissolution in methanol, titration with NaOH [end point dteremined potentiometrically].	Dissolution in DMF, titrate ≠ NaOH using bromothymol blue as indicator [carry out blank].	Dissolution in alcohol, titrate ≠ NaOH using phenol red as indicator.

[IV] Potassium Sparing Diuretics

- They ↑ sodium and chloride excretion and ↓ potassium excretion [sparing].
- Of weak diuretic activity; so, used as adjunct to thiazides and loop diuretics.

A] Aldosterone Antagonist

[i] Spironolactone: [Aldactone®]	Canrenone
	

M.O.A:

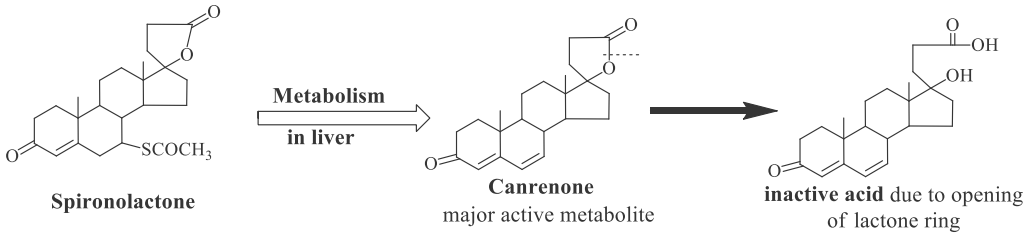
- They are competitive antagonist for Aldosterone.
- Aldosterone receptor present in two forms one is active and the other is not; Spironolactone binds to inactive form of receptor; preventing its conversion to active form, so, aldosterone can't bind to it → no sodium and chloride reabsorption.

- Spironolactone is metabolized to Canrenone [active metabolite] → so, with delayed onset and long duration.
- Spironolactone may cause Gynecomastia in males and menstrual disturbance in females [due to hormonal disturbance]; so, it may be used topically for Acne.
- Canrenone produce less anti-androgenic action than spironolactone [spironolactone and other metabolites responsible for this side effect].

Assay of Spironolactone:

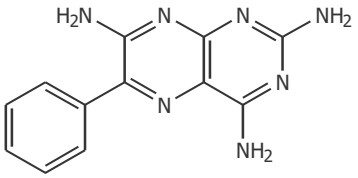
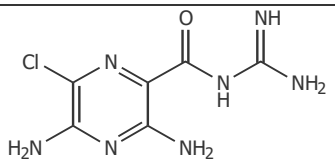
- By dissolution in methanol → measure absorbance at 238 nm [taking specific absorbance at 470 m.

Metabolism:

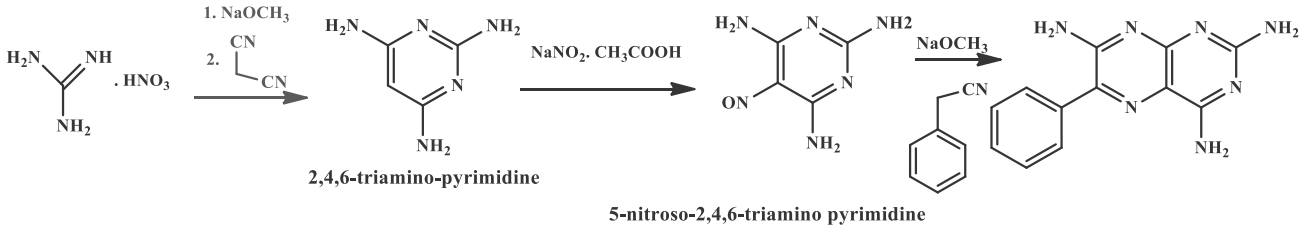


Spironolactone | **Canrenone** major active metabolite | **inactive acid** due to opening of lactone ring

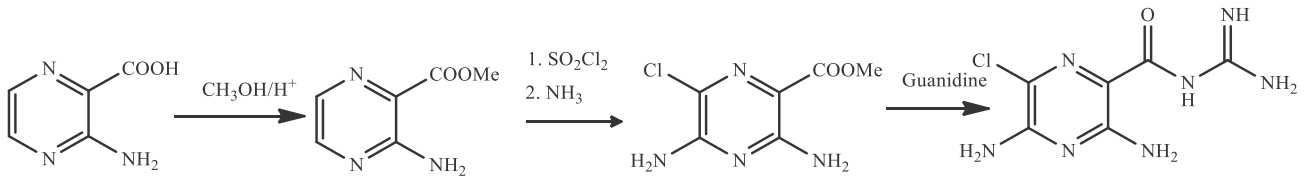
B] Inhibitors of Renal Na ion Channel (Direct Acting Diuretics)

Triamterene	Amiloride [Moduretic®]
 2,4,7-triamino-6-phenyl pteridine	 3,5-diamino-N-amino imino methyl -6-chloro pyrazine carboxamide
➢ They produce their effect in absence of aldosterone [act by other mechanism]	

Synthesis of Triamterene:

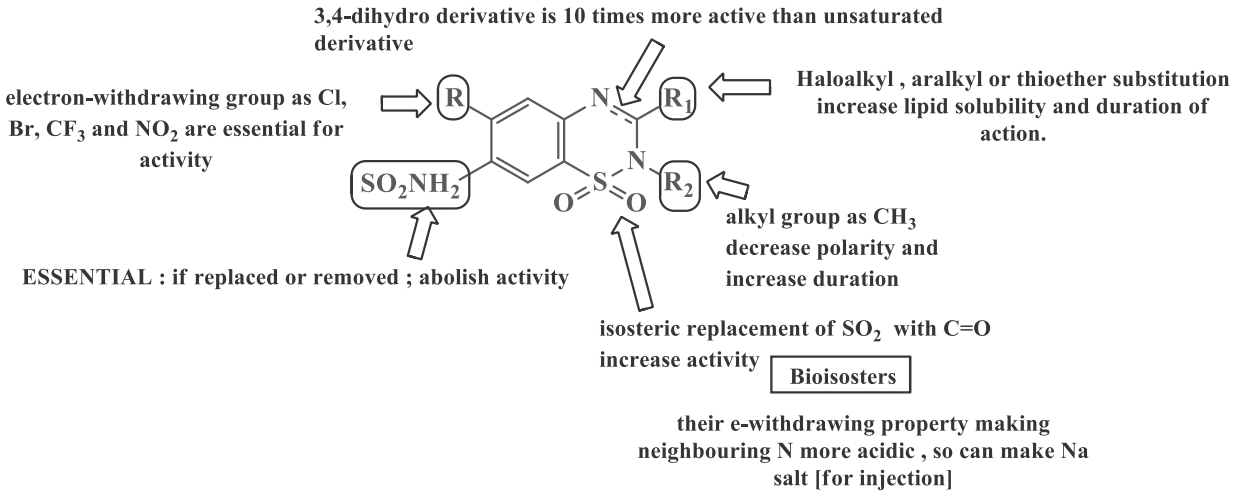


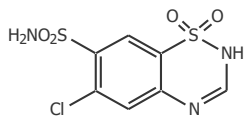
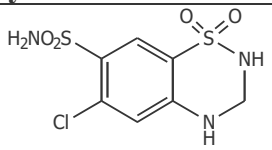
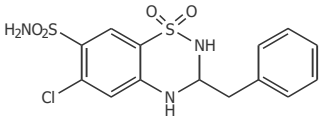
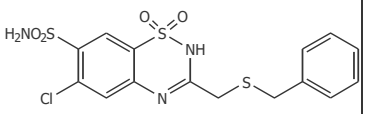
Synthesis of Amiloride:

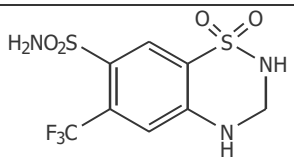
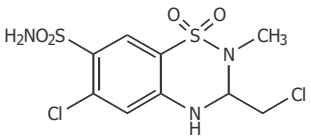
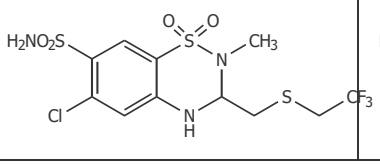
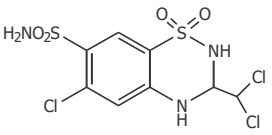
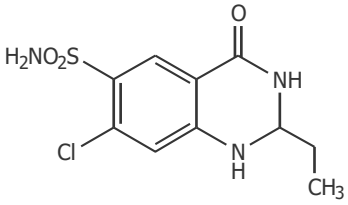
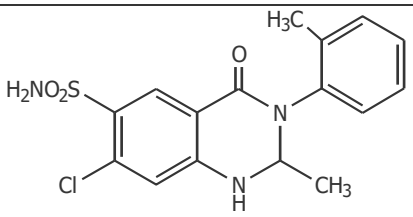


[V] THIAZIDES AND RELATED DIURETICS

SAR:



Chlorothiazide	Hydrochlorothiazide	Bendroflumethazide	Benzthiazide
			

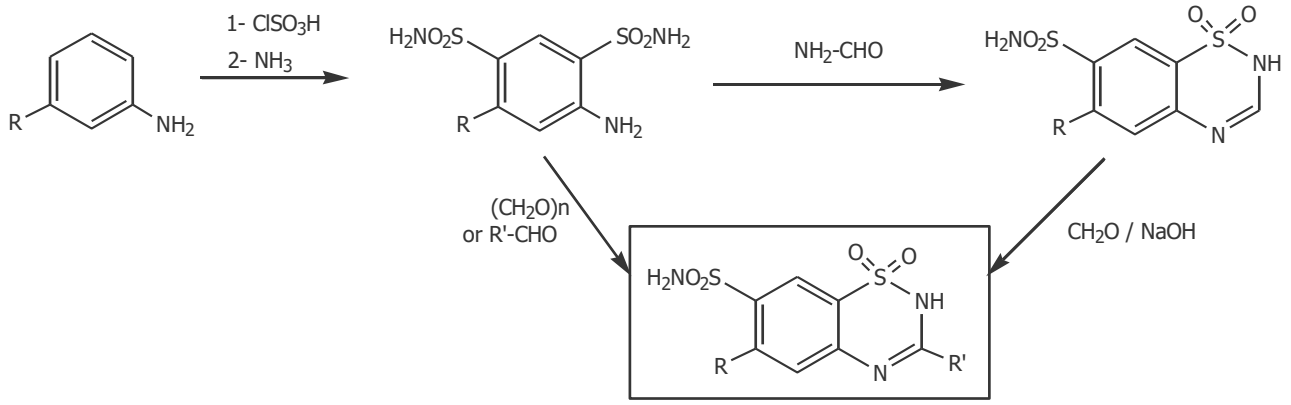
Hydroflumethazide	Methylclothiazide	Polythiazide	Triclomethazide
			
Quinazolines			
Quinethazone		**Metolazone**	
			

Side effects:

1-Hypersensitivity reactions. 2-Gastric irritation.

3-Electrolyte imbalance → **Hypokalemia (↓ K)** due to increased elimination of K ions as well as Na, Cl and Mg, so K and Mg supplement is given.

Synthesis of Chlorothiazide, Hydrochlorothiazide, Hydroflumethazide, Bendroflumethazide:

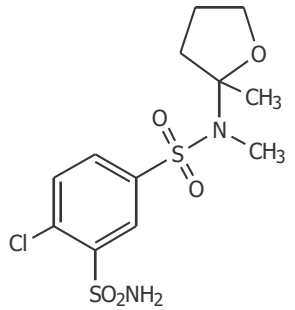
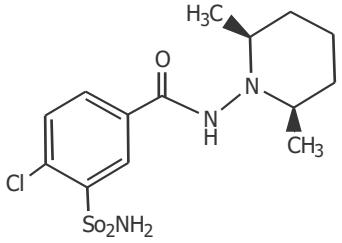
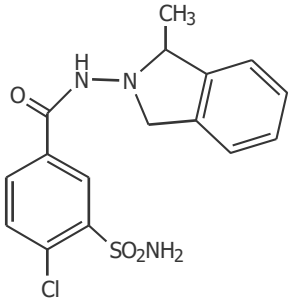


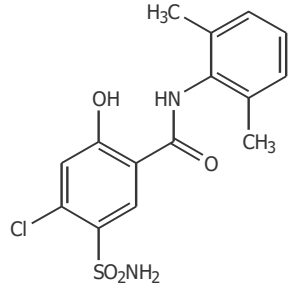
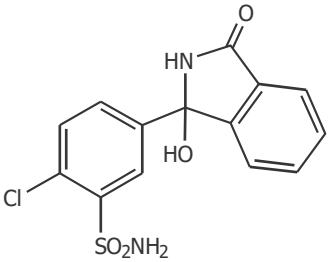
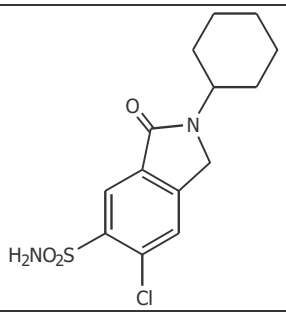
THIAZIDES LIKE DIURETICS

- They are not benzothiadiazine but their site of action, efficacy, electrolyte excretion pattern and adverse effects resemble thiazides

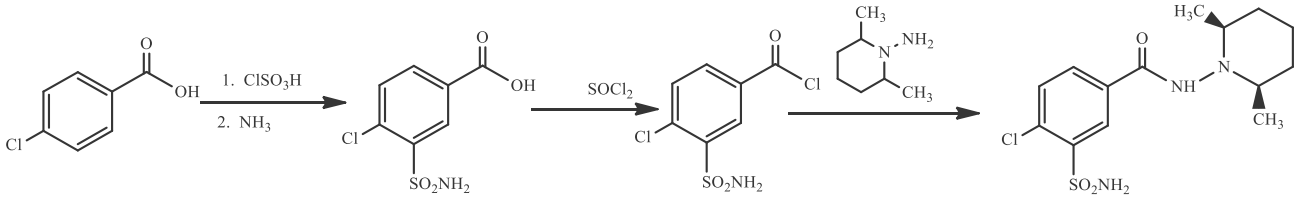
SAR:

- With two sulfamoyl moieties meta to each other.
- One of them is essential while the other is not [may be replaced with similar electrophilic group as amides].
- Cl in ortho position to unsubstituted sulfamoyl → maximum diuretic effect.

Mefruside	Clopamide	Indapamide
		
		2.5 mg/day

Xipamide	Chlorthalidone	Clorexolone
		
	2-3 times / week	

Synthesis of clopmaide:



[VI] ADH ANTAGONISTS

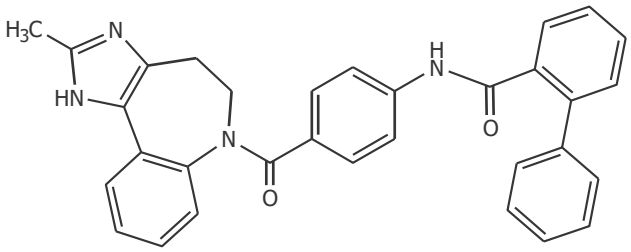
ADH [Anti-Diuretic Hormone]:

- ↓ water free excretion and cause vasoconstriction in peripheral vessels
- By inhibition of ADH → ↑ water free excretion and cause vasodilatation in peripheral vessels.

Uses:

- **CHF, Hyponatremia.**

Conivaptan



VITAMINS

Properties:

- Naturally occurring organic molecule that is a normal constituent of a diet.
- They are unlike each other in chemical composition and function but alike only in that they can't be synthesized at all or at least not at adequate rate in tissues.
- Required by the body in small amounts for various metabolic processes.
- Name Vitamine [by Frank, 1912]: Vita = life and amine that it was believed that all those substances are amines [but this not true that some vitamins have no nitrogen] → so, change name Vitamine to Vitamin.
- They are effective in small amounts, not furnish energy, not used as building units for organism structure.

Functions:

- Regulate metabolism, help convert lipids and saccharides into energy.
- Hormones (vitamin D)
- Antioxidants (vitamin E and C)
- Regulators of cell and tissue growth and differentiation (vitamin A).
- Precursors for enzyme coenzymes (B-complex)

Causes of nutrient deficiencies:

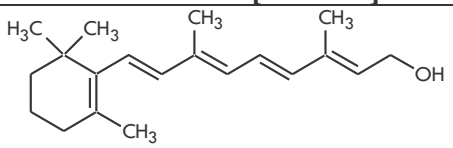
1. **Inadequate ingestion** (poor diet) due to economic deprivation, disease or self-imposed reducing diets.
2. **Inadequate absorption** due to:
    a. Intestinal tract disease [e.g. chronic inflammatory condition and parasites].
    b. Using mineral oil laxatives → may dissolve oil soluble vitamins.
    c. Using ion-exchange resin [e.g. Colestipol, Colestyramine] → form complex with bile acids → interfere with absorption of fat-soluble vitamins.
    d. Using Al antacids → complex with some vitamins.
    e. Cystic fibrosis → fat mal absorption.
3. **Inadequate utilization** → by genetic disease [due to abnormality in enzyme structure for which the vitamin provides a cofactor, so ↓ affinity between enzyme and its cofactor]
4. **↑ requirements >** Recommended Daily Allowances "**RDA**" due to:
    a. Physical activity.
    b. Medical needs [especially if debilitating illness as severe burns, major surgeries and malignancies]
5. **Alcoholism** "Chronic intake of alcohol" → ethanol interferes with uptake, processing or storage of vitamins especially folic acid and thiamine.

Classification:

[i] Fat soluble vitamins	[ii] Water soluble vitamins
• Can be extracted with fat solvents. • Found in fat fractions of animal tissues. • ↑↑ intake → accumulation [dangerous] • E.g. D E K A	• Water soluble. Act as cofactors for specific enzymes. • ↑↑ intake → little effect due to rapid excretion in urine. • Liable to degradation in solution especially if exposed to light. • E.g. Vitamin. C, Bs, Folic acid, Niacin….

[I]FAT SOLUBLEVITAMINS
1-VITAMIN As

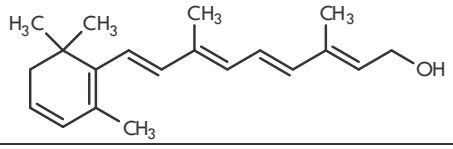
Vitamin A1 [Retinol]



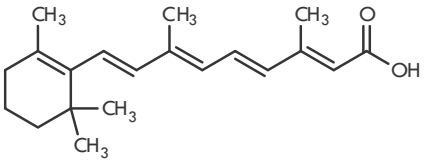
3,7-Dimethyl-9-(2,6,6-trimethyl cyclohex-1-enyl) nono-2,4,6,8-all trans tetaen-1-ol

- ✓ Found in animal fats, fish [cod, tuna, shark], oil, liver, milk.
- ✓ Stored in liver of fish & mammals as esters of fatty acids as palmitic acid.
- ✓ Used for night blindness and some skin disorders as acne and psoriasis.

Vitamin A2 [Dehydro retinol]

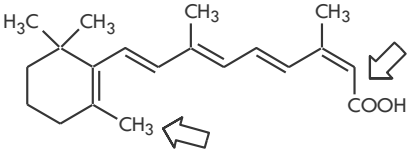


Tretinoin [All-Trans Retinoic acid] [Retin A cream®]

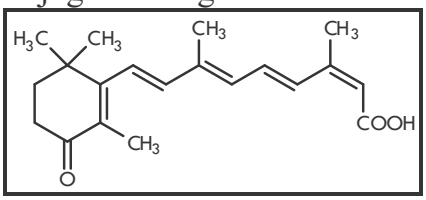


- The most important derivative → used for **Acne** topically.
- It ↑ growth, differentiation and maintenance of epithelial tissue in retinol deficient animals
- Not restore visual, auditory or reproductive functions.
- Not stored in liver → rapidly excreted.

Iso tretinoin [2-cis vitamin A acid]

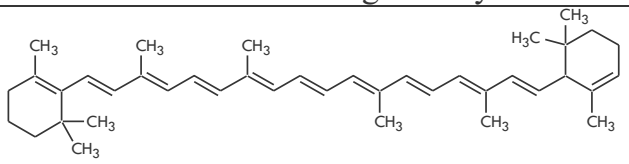


- Metabolized to **4-oxo isotretinoin** → conjugation to glucuronide.

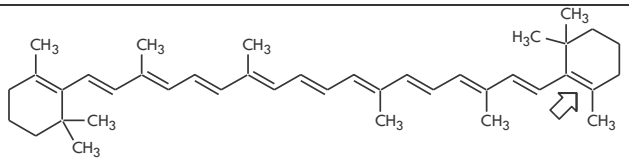


Carotenoids

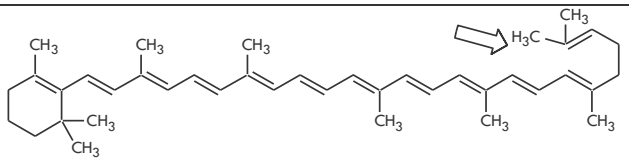
- Vitamin A is closely related to β-carotene [polyene hydrocarbon pigment present in plants as carrots, spinach, orange…..]
- β-Carotene is absorbed intact by intestinal mucosa → then cleaved by β-carotene-15,15'-dioxygenase to 2 molecules of Retinol.
- Other 3 carotenoids → give only one molecule of Retinol.



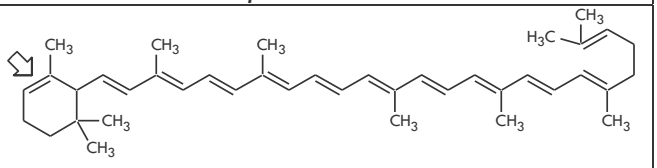
α-carotene



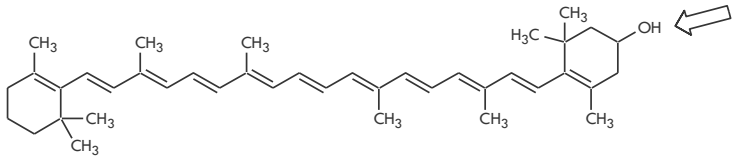
β-carotene



γ-carotene



δ-carotene



Cryptoxanthin

Stability:

- Retinol is rapidly broken by UV light, daylight and oxygen → so, should be covered or shading on the side nearest to light.
- Presence of amino acids, fat emulsion or antioxidant → ↓ degradation.

Absorption:

- Most of dietary retinol in the form of esters (retinyl palmitate) → hydrolyzed in intestine by pancreatic enzymes before absorption.
- May be absorbed directly into circulation → bound to Retinol-Binding Protein (RBP) in plasma.

Metabolism:

- **Vitamin A esters** → hydrolysis by pancreatic enzyme to retinol → absorbed and re-esterified.
- Some retinol stored in liver; other parts make glucuronide conjugation & then oxidation to Retinal & Retinoic acid.
- All metabolites excreted in urine & faces.

Interactions:

- ↓ Absorption by neomycin or liquid paraffin.
- It ↓ effect of corticosteroids.

SAR:

- Conjugated double bonds in vitamin A and β-carotene → Essential [if partially or completely reduced → loss activity]
- β-ionone ring [in Retinol] or dehydro-β-ionone ring [in vitamin A_2] → Essential [if saturation → loss activity]
- Esters and methyl ethers derivatives → equal activity (converted in body to Vitamin A)

Biochemical functions:

- Chemistry of vision.
- Biosynthesis of glycogen and some steroids.
- Promotes mucous production by basal cells of epithelium [in its absence → keratin is formed]
- Retinoic acid [carboxylic acid derivative] → ↑ development of bone, soft tissues and sperms [NOT in vision]

Assay:

[i] **Carr-Price method** [colorimetry]:

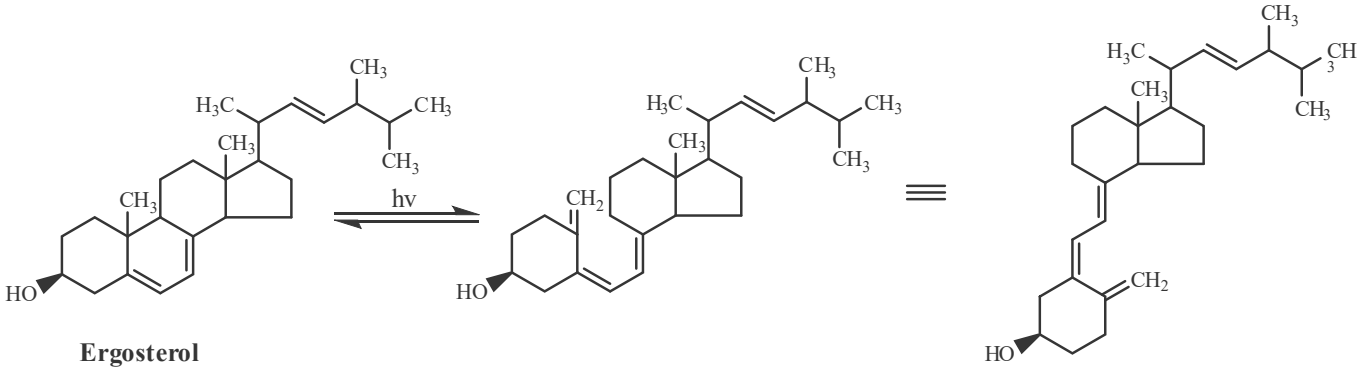
- Due to polyene structure.
- Vitamin A + Antimony trichloride "$SbCl_3$" in chloroform → blue color.

[ii] **Morton and Stubb's method** [Spectrophotometric]

[iii] **HPLC.**

2-VITAMIN D (Antirachitic Action)

VITAMIN D_2 [ERGOCALCIFEROL]



Ergosterol
[Provitamin D_2]

Vitamin D_2
[Ergocalciferol]

Absorption:

- Absorbed from GIT → stored mainly in liver especially in adipose tissue and muscles.

Excretion:

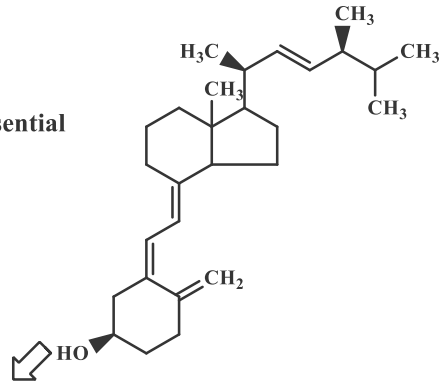
- Excreted in bile and faces [small amount appears in urine].

Interactions:

- Co-administration with Thiazide diuretics and Ca → ↑ risk of Hypercalcemia.

SAR:

Unsaturated Parts ----> Essential



Proper stereo chemistry of 3-OH -----> Essential

Epimerization or Conversion to Ketone -----> decrease activity

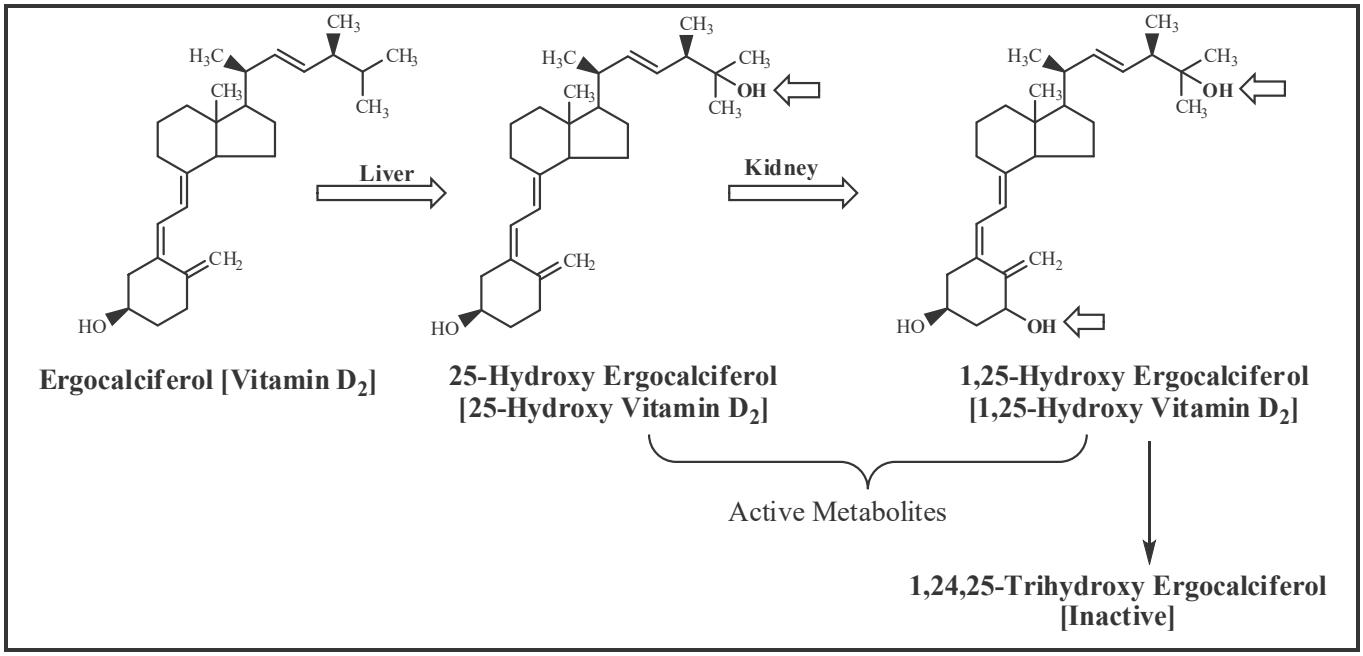
Esters and Ethers that can't be cleaved in body ----> with NO activity

Inversion of 9-H in Ergosterol and other 7-dehydro sterols ---> prevent normal course of irradiation

Assay:

- Minimal amounts → HPLC or UV spectrometry.
- For more concentrated solutions in alcohol [not in oil] → Carr-Price method [give with Antimony trichloride yellow color determined colorimetry].

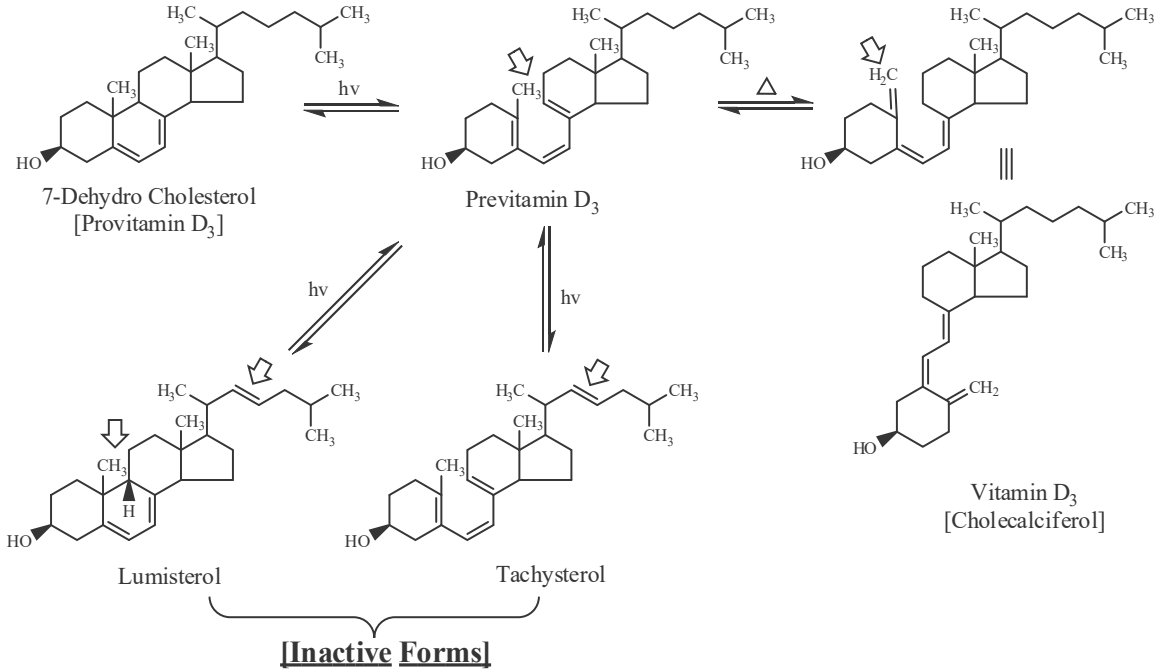
Metabolism:



- The active metabolites bound to specific plasma proteins.

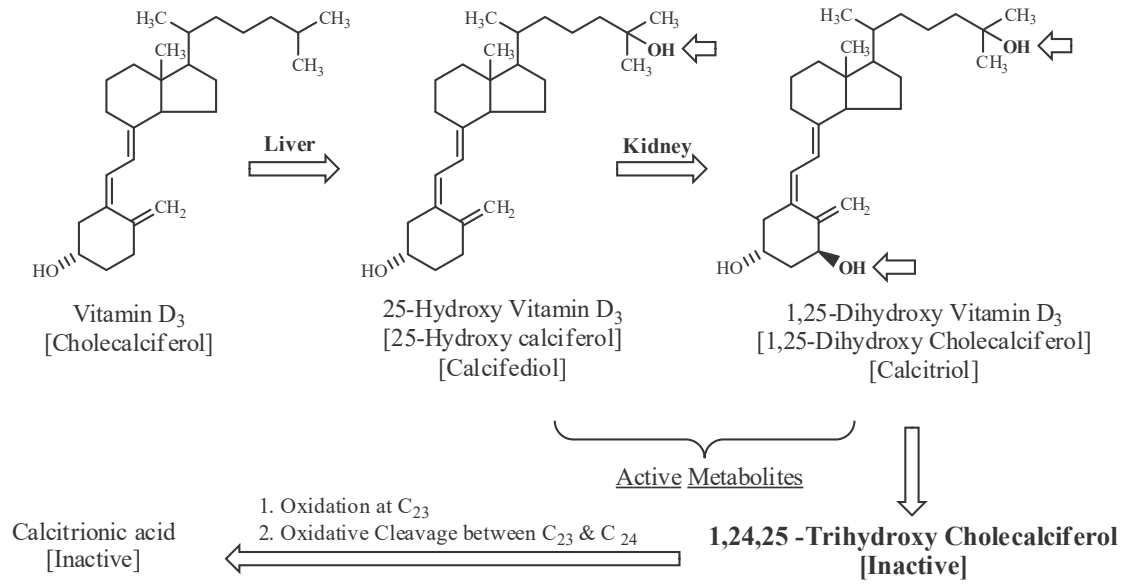
Vitamin D_3 [Cholecalciferol]

- Produced from 7-dehydro cholesterol by UV radiation.



Metabolism:

- Vitamin D_3 is termed now **Provitamin** → because it requires hydroxylation in liver and kidney to be fully active.
- Cholecalciferol does not perform its role directly→must be transformed in liver and kidney.



[1] Mitochondrial CYP-450 Vit. D_3-25-Hydroxylase Enzyme
-----> require molecular oxygen & NADPH [reduced form]
[2] CYP-450-25-Hydroxy Vit.D_3-1-alpha-Hydroxylase Enzyme

Amount of above two enzymes is controlled by:

1]-Parathyroid hormone. 2]-↑ Concentration of Ca & phosphate.
3]-Amount of 1,25-dihydroxy Vitamin D_3.

N.B:

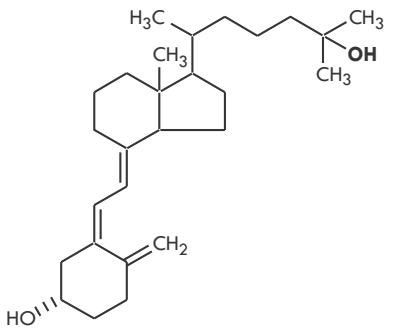
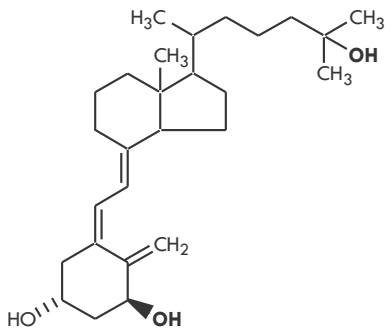
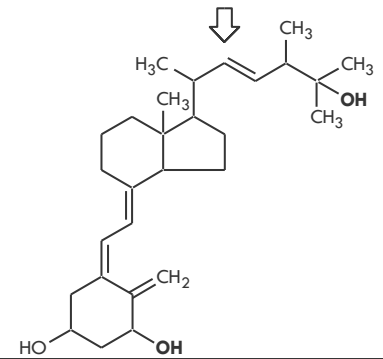
Vitamin D_2 & D_3 → with slow onset & long duration of action [require activation].

- Calcifediol & Calcitriol [active forms of Vitamin D_3] → with rapid onset & short duration [already active]

Biochemical functions:

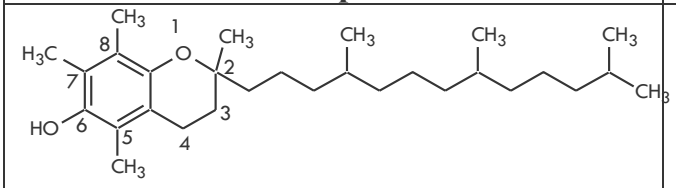
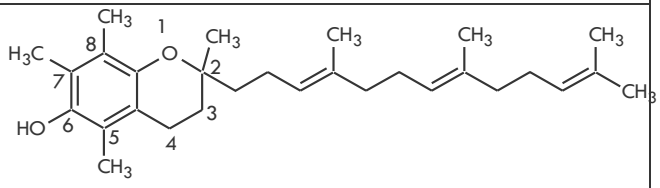
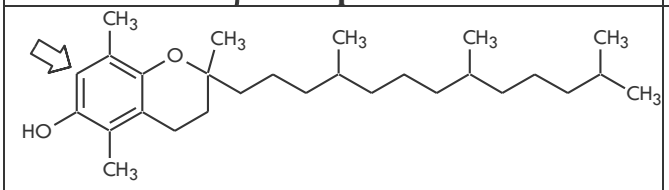
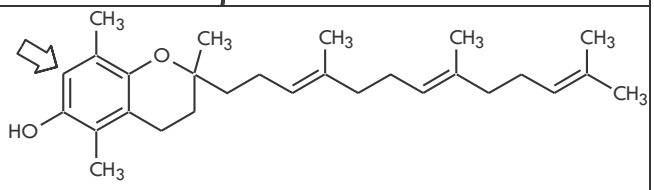
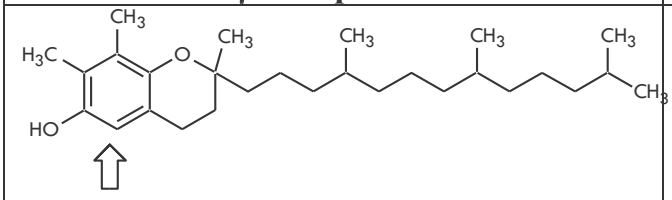
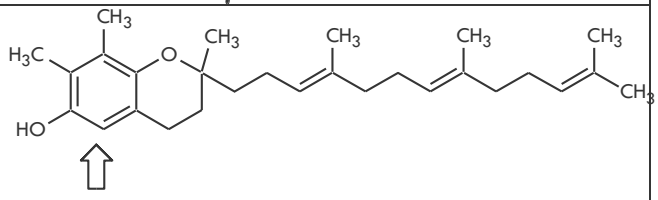
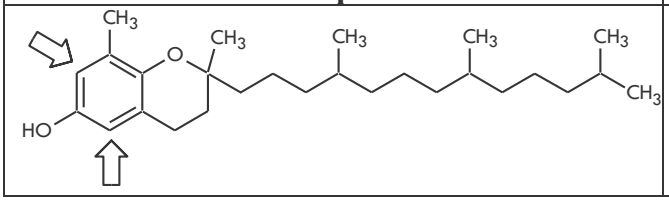
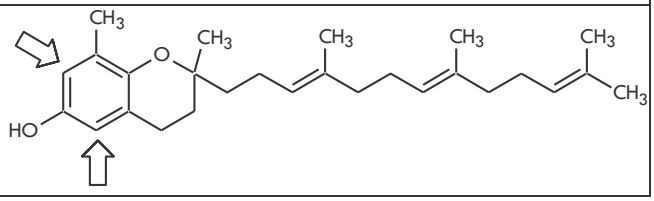
1. Promote Ca & phosphate intestinal absorption.
2. ↑ Renal reabsorption of Ca & phosphate.

Vitamin D Derivatives:

Calcifediol	Calcitriol	Paricalcitol
		
Used for patients receiving long-term renal dialysis.	• Most active form of Vitamin D_3. • Not need activation → it ↑ Ca absorption within 2 hrs of administration.	Used for prevention and treatment of 2ry hyperparathyroidism in patients undergoing chronic renal dialysis.

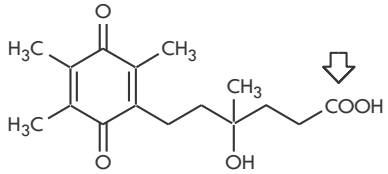
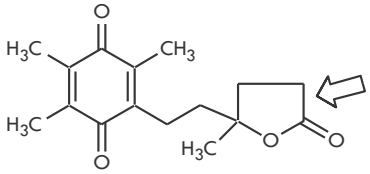
VITAMIN E (TOCHOPHEROLS)

- Often called Anti-Sterility Factor [Tokos = Child and Phero = to bear].
- Used industrially as Antioxidants.
- They are 2,3-dihydro benzopyran derivatives [Chromanol Derivatives]
- Dietary sources: Legumes, cereals as rice and corn, eggs and butter.
- Absorbed from GIT through the mucosa.
- ↑ Dose → ↑ bleeding tendency in vitamin K deficient patients.
- It appears in breast milk but poorly transferred across the placenta.

α-Tocopherol	**α-Tocotrienol**
 *2,5,7,8-Tetramethyl-2-(4,8,12-trimethyl tridecayl)-6-chromanol*	
β-Tocopherol	**β-Tocotrienol**
 *5,8-Dimethyl-2-(4,8,12-trimethyl tridecayl)-6-chromanol*	
γ-Tocopherol	**γ-Tocotrienol**
 *7,8-Dimethyl-2-(4,8,12-trimethyl tridecayl)-6-chromanol*	
δ-Tocopherol	**δ-Tocotrienol**
	

Metabolism:

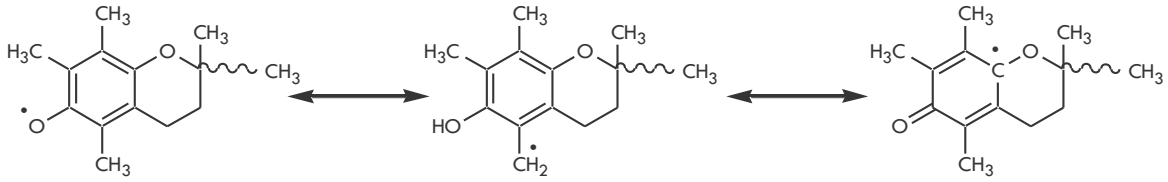
- Mainly to Tocopheronic acid and γ-lactone derivative [Tocopheronolactone] → then glucuronide conjugation.

Tocopheronic acid	**Tocopheronolactone**
	

Biochemical functions:

1. 1ry role is prevention of oxidation of polyunsaturated fatty acids → it reacts with free radicals without formation of other free radicals in the process. [free radicals are the cause of oxidative damage of cell membranes]
2. Role in regulation of protein synthesis [Postulation].
3. Ensure stability & integrity of cellular membranes especially on RBCs.

Resonance-stabilized tocopherol radicals:

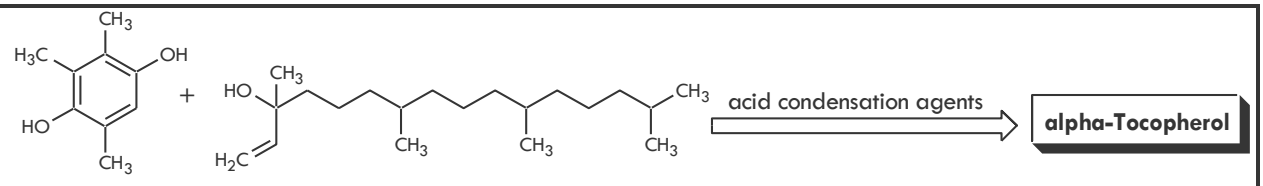


Chromanoxyl Rdaical **Chromanol Methide Radical** **Chromanone-8a Radical**

SAR:

1. Optical isomerism → d-form more active > l-form.
2. β-tocopherol with 1/2 activity of α-tocopherol / γ and δ with 1/100 activity of α.
3. Esters of tocopherol [acetate, propionate and butyrate] → more active > parent compound. While Ethers are inactive.
4. Oxidation to Quinones → inactive.
5. Replacing Methyl with Ethyl → ↓ activity.
6. Double bond inside chain OR ↓ its size → ↓ activity.
7. Double bond in 3,4-position of α-tocopherol → ↓ activity to 2/3.

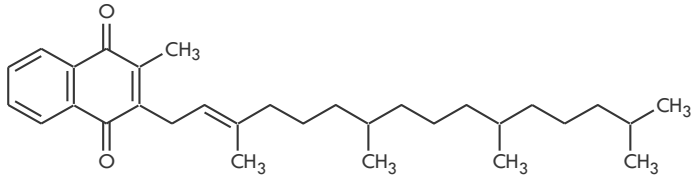
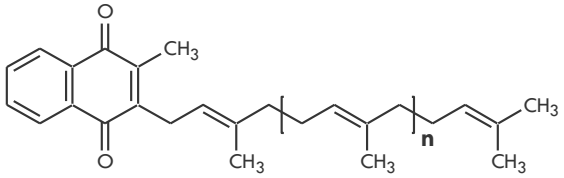
Synthesis:

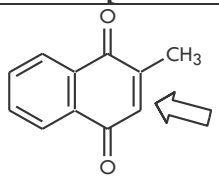


2,3,5-Trimethyl Hydroquinone **Isophytol**

[3] VITAMIN K (ANTIHEMORRHAGIC FACTOR)

Essential for biosynthesis of several coagulation factors. [K from German word Koagulation].

Vitamin K_1 [Phytonadione] [Phyllquinone]

2-Methyl-3-phytyl-1,4-naphthoquinone
Vitamin K_2 [Menaquinones]

(Unhydrogenated isoprenyl units instead of phytyl side chain of vitamin K_1)

Vitamin K_3 [Menadione]

Water Soluble Derivative

- **In animals** →Menaqauinone can be synthesized from vitamin precursor [Vitamin K_3].
- Synthesis of Menaquinones may occur in G+ve bacteria and bacteria of intestinal tract synthesize the large amount of vitamin K contained in human & animal feces.
- All Vitamins K_1, K_2 and K_3 → Redox substances stable in quinone form.

Absorption and storage:

- Vitamin K_1 and K_2 → require bile acid for absorption [NOT vitamin K_3].
- Vitamin K accumulates in liver mainly but stored in body for short period of time.

Interactions and Adverse effects:

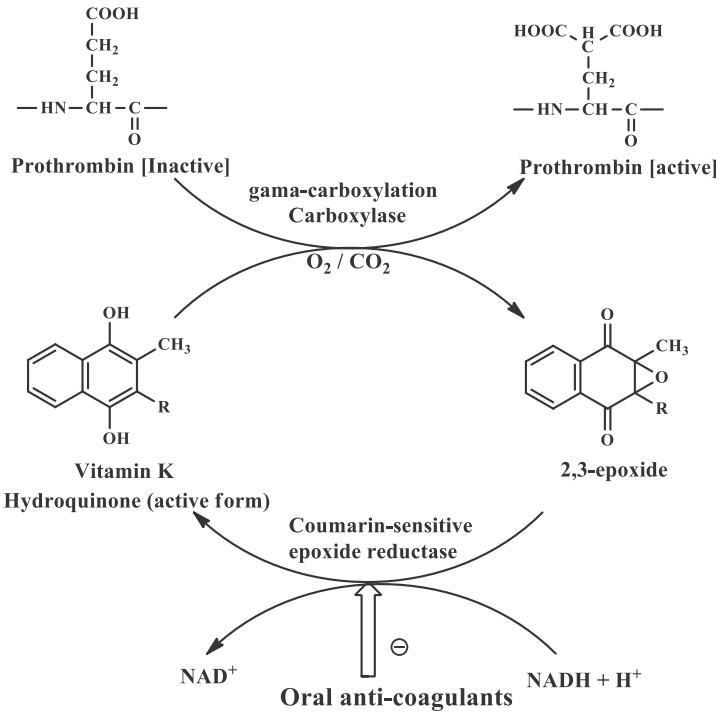
- Vitamin K ↓ effect of oral anti-coagulants.
- I.V. Phytomendaione → severe hypersensitivity reactions [flushing, sweating, chest constriction, pain and cyanosis]. This effect may be due to castor oil used as surfactant in some parenteral formulations.
- ↑ Doses of salicylate → antagonized vitamin K.
- Vitamin K may be benefit for prevention of osteoporosis [so, patients on anti-coagulant therapy with ↑ risk of bone fracture] → some Ca supplements have both vitamin D and K added to their formulations.

Metabolism:

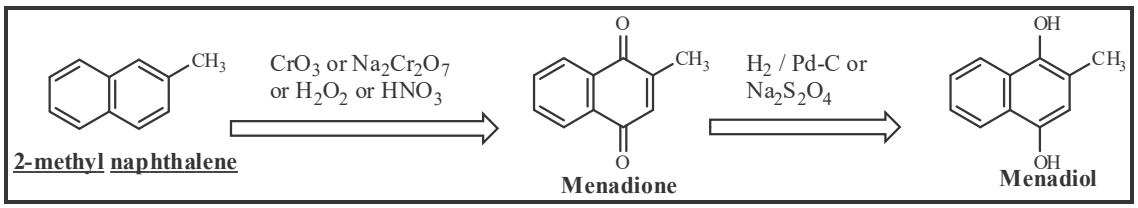
- Phytomenadione → reduction of quinone to hydroquinone [active form].
- Glucuronide conjugation [major urinary metabolite] → occur at COOH derived from shortening of side chain to 5-7 Cs.

Biochemical functions:

1. Promote hepatic biosynthesis of Prothrombin (factor II), factor VII, factor IX and X [with very important role in blood clotting].
2. Hydroquinone (active form) in presence of O_2, CO_2 and microsomal carboxylase enzyme → converted to its 2,3-epoxide and at the same time γ-carboxylation occurs. Hydroquinone form regenerated from 2,3-epoxide by coumarin-sensitive epoxide reductase.



Synthesis of Menadiol derivatives:



SAR:

- Natural vitamin K_1 → Trans / Synthetic → mixture of Cis and Trans [not > 20% Cis].

OH, CO, OR"Me or Et", OAc —> significant activity

Me —> significant activity [> Me decrease activity]

Aromatic or Hydroaromatic —> significant acitivty

Aromatic or Hydroaromatic —> significant acitivty

Unsubstituted
[if substituted —> decrease anti-hemorrhagic activity]

OH, sulfonic acid, dimethyl amino,
alkyl group with 10 or more Cs —> significant activity

Double bond in beta or gama positions
of this alkyl group —> enhance potency

H, OH, NH_2, CO, OR"Me or Et" , Ac ——> significant activity

if OH —> decrease anti-hemorrhagic action /
if OH is side chain --> decreas activity

if Benzenoid ring A, S instead of -CH=CH- in 2-methyl naphthoquinone —> retain some anti-hemorrhagic activity [That benzenoid end may fit into a pocket carefully tailored to it, other end is not so closely surrounded]

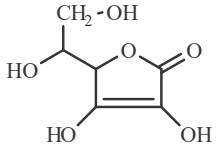
Naphthoquinone containing compounds —> marked anti-hemorrhagic activity
[converted in body to vitamin K_1-type compounds]

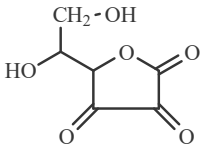
Assay:

- 1st → vitamin K excreted and separated from interfering substances.
- It reacts with Na ethylate → blue color which changes to brown.

[II] WATER SOLUBLE VITAMINS

VITAMIN C (L-Ascorbic Acid)





Ascorbic acid **Dehydro Ascorbic acid**

3,4-Dihydroxy-5-(1,2-dihydroxyethyl)furan-2(5H)-one
Or 2,3,4,5,6-Pentahydroxy-hexa-2-enoic acid-4-lactone

Sources: fresh vegetables, fruits especially citrus, peppers, tomatoes……

- Necessary for prevention and cure of Scurvy [Deficiency disease].
- Anti-scorbutic activity is due to reversible oxidation-reduction reactions.

Stability:

- It's easily oxidized to dehydro form without loss of activity, but lactone ring hydrolyses easily producing inactive open-chain product.
- Aqueous solution easily oxidized especially if alkaline medium, metals as iron, copper, manganese presents.
- Oxidation accelerated by heat, light, alkalis, oxidative enzymes.
- Addition of sucrose → ↑ viscosity and slow down rate of atmospheric oxidation.

Metabolism:

- Reversible oxidation to dehydro ascorbic acid.
- Excess ascorbic acid on our needs → rapidly eliminated unchanged in urine.
- Vitamin C metabolized as oxalate which is the major urinary metabolite (44%), unchanged ascorbate (20%) and the intermediate metabolite 2,3-diketo-L-gulonic acid (20%).

Interactions:

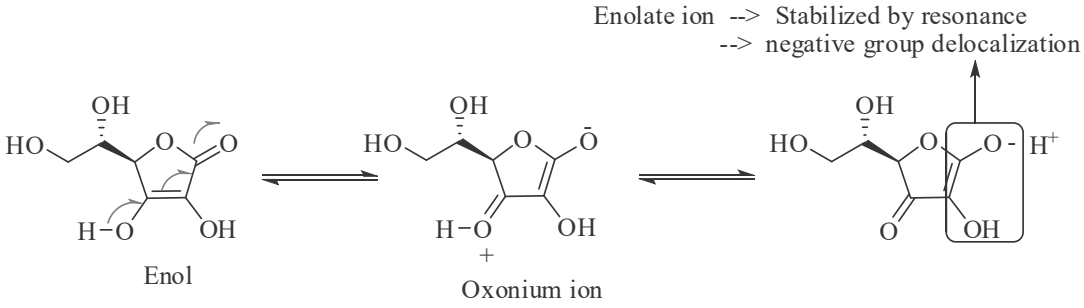
- It cause crystalluria with high doses of acidic drugs (as sulfa drugs and amino salicylic acid) due to acidity of vit C.
- It's incompatible with oxidizing agents (as ferric salts), due to its reducing properties.
- Ascorbic acid injection → incompatible with aminophylline, nafcillin Na, nitrofurantoin Na, $NaHCO_3$ ……..
- ↑ Dose → destroy large amounts of dietary cyanocobalamines.

Biological activity of Vit. C:

- ❑ Reducing agents (It helps in keeping iron in the reduced form which helps its absorption (iron absorbed only in ferrous state).
- ❑ It's a co-factor in hydroxylation and amidation reactions (essential in converting procollagen to collagen, a principle material in the connective tissue).
- ❑ It has Antioxidant effect (a free radical scavenger).

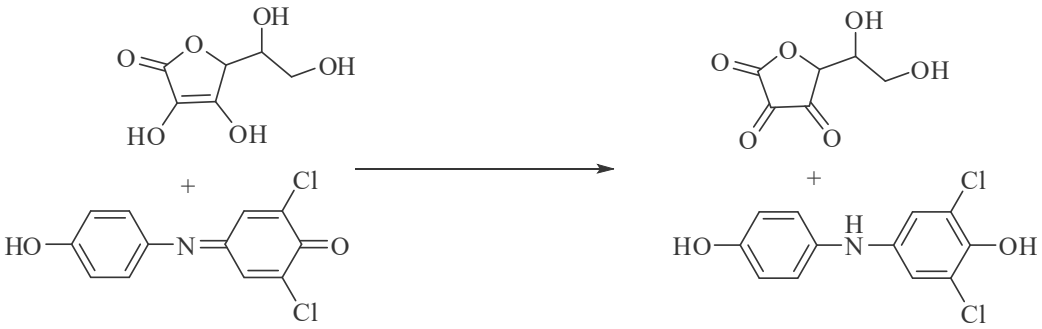
Vitamin C acidity

- It's acidic without having a COOH as a result of the Enol-enolate transformation



Assay:

- Based on its powerful reducing properties → Redox titration.
- Reagents used for titration are:
    1. **Chloramine-T.**
    2. **2,6-Dichloro phenol indo phenol.**
    3. **Iodine.**
- **In ampoules:** Vit. C assayed by I_2 using starch as an indicator.
- **In tablets:** We cannot use I_2 (as they contain starch) so, it assayed by Ce(IV) ammonium sulfate using ferroin indicator.
- **In juices:** It assayed by 2,6-dichlorophenol indophenol (DCIP) an oxidizing agent and a redox indicator.
- Andrew's method → may be used for determination of reducing agents by iodate titration.



Uses of Vitamin C:

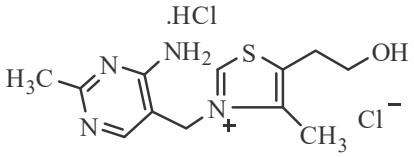
- Antioxidant (prooxidant)
- Cofactor of enzymes used in the synthesis of collagen.
- Adrenalin synthesis.
- Enhances iron absorption by keeping it in Fe^{+2} state.
- Treatment of Common cold and viral influenza.
- Metabolism of bone minerals.
- Tyrosine degradation.
- Bile acids production.
- Carnitine synthesis.
- Treatment of Scurvy.

VITAMIN Bs

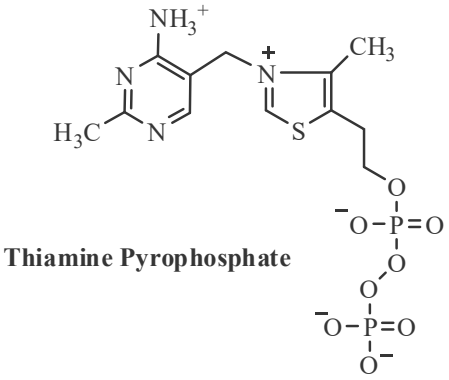
- **Sources:** yeast, cereals, seed embryos, eggs, meat and milk.
- **B vitamins include:**

①Vitamin B_1 [Thiamine, Aneurine]. **② Vitamin B_2 [Riboflavin].**
③ Vitamin B_5 [Pantothenic acid]. **④ Vitamin B_6 [Pyridoxine].**
⑤ Nicotinic acid [Niacin]. **⑥ Cobalamines [Vitamin B_{12}].**
⑦ Folic acid [Vitamin B_9]. **⑧ Biotin [Vitamin B_7].**

VITAMIN B_1 (Thiamine)(Aneurine)



Thiamine



Thiamine Pyrophosphate

3-[(4-Amino-2-methyl-5-pyrimidinyl) methyl]-5-(2-hydroxy ethyl)-4-methyl thiazolium monohydrochloride

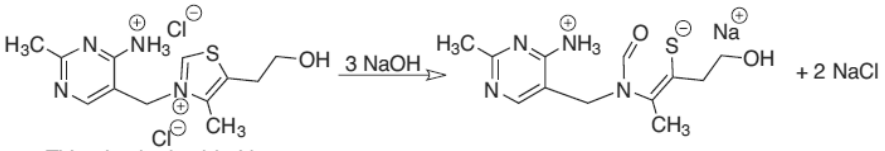
- **Vitamin $B_1$is** the first water soluble vitamin discovered.
- **Sources:** egg yolks, peas, bran, rice, beans, nuts, yeast extracts, vegetables.

Commercial salts:

1. **Thiamine HCl:**
   - Very water soluble, very hygroscobic.
   - Not used in dry formulations → used in liquid and injectable formulations.
2. **Thiamine Nitrate:**
   - Sufficiently water soluble → used in liquid formulations.
   - NON-hygroscobic → can be used in dry formulations.

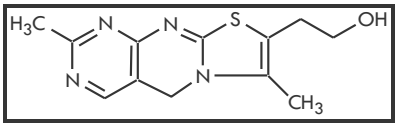
Stability:

- Stable in acid solutions, may be heated without decomposition.
- Unstable in neutral or alkaline solutions → splitting at methylene bridge [in presence of moisture, bisulfite ions].



Thiamine hydrochloride

- Oxidized in alkaline solution to Thiochrome → biologically inactive + highly fluorescent.

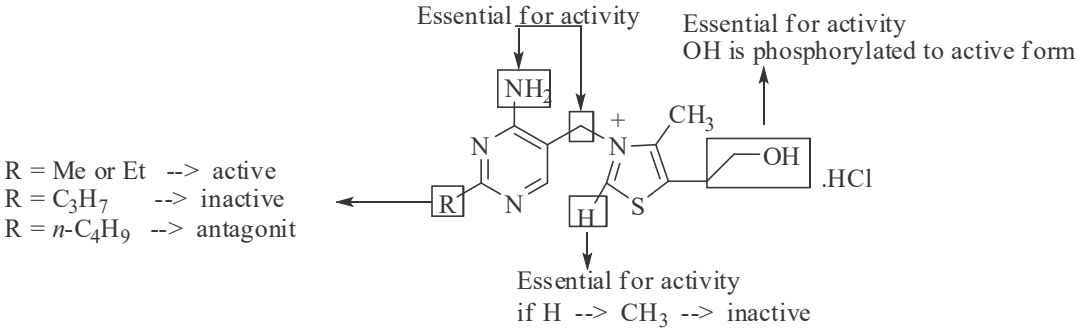


Thiochrome

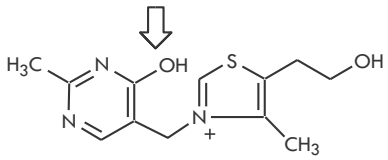
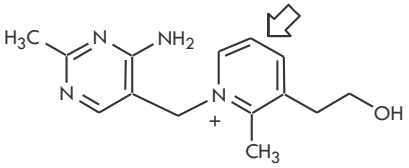
Absorption:

- ↓ Amounts are well absorbed [while large doses with limited absorption].
- Thiamine absorption is Na-dependent.
- It's widely distributed into tissues.

SAR:



Anti-vitamins used in the study of the deficiency state

Oxythiamine	Neopyrithyamine
 *(amine group replaced by hydroxy group)*	 *(thiazole ring replaced by pyridine)*
Competitive inhibitor of thiamine pyrophosphate	Inhibit pyrophosphorylation of thiamine

Interactions:

- Thiamine incompatible with reducing agents [as sulfites]. It's cleaved into pyrimidine and thizole. Rate of hydrolysis ↑ by ↑ pH [rapid at pH=6].
- Atmosphere or oxidizing agents [as H_2O_2, permanganate, alkaline K-ferricyanide] → oxidation to Thiochrome.
- Chemically incompatible with acetates, carbonates, iodides, ferric sulfate and mercuric chloride [copper ions accelerate destruction of thiamine HCl in solution].
- Incompatible with phenobarbital, riboflavin in aqueous solution, penicillin G and dextrose injection containing metabisulfite.

Metabolism:

- Degradation → pyrimidine.
- ↑ Intake → excess excreted unchanged.

Biological functions:

Thiamine pyrophosphate [the physiological active form of thiamine]

- Functions in CHO metabolism as coenzyme in decarboxylation of α-keto acids.
  Examples: [Pyruvate → acetyl Co-A] [α-keto glutarate → succinyl Co-A]
- Functions in metabolism of branched chain amino acids; valine, isoleucine, leucine and methionine.
- Important for synthesis of keto acids.

Assay:

- **Flourimetric method:** Oxidation in alkaline medium → Thiochrome [highly fluorescent → vivid blue fluorescence] → this reaction is the basis of chemical method of estimating thiamine.

- Thiamine content determined gravimetrically as its silicotungstate.
- **Being an HCl salt of a weak base** → Titrated by NaOH → using phenolphthaline, or bromothymol blue as indicator.

Deficiency Syndrome (Beriberi)

- **BERI-BERI**-affecting the peripheral nervous system (polyneuritis) and/or the cardiovascular system, with fatal outcome.

Uses: used for treating **beriberi.**

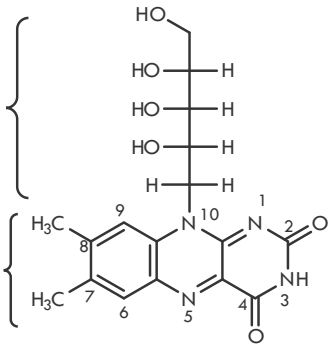
- In treating alcohol induced neuritis or neuritis induced by other causes.

VITAMIN B_2 (Riboflavin)

✓ **Riboflavin** is an N-glycoside of flavin, also known as lumichrome and the sugar ribitol.
✓ It is precursor for the coenzymes FAD and FMN.

D-ribityl group [Derived from D-ribose]

Isoalloxazine ring system

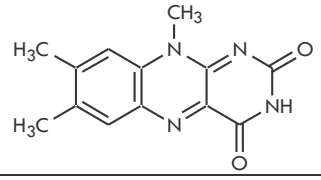
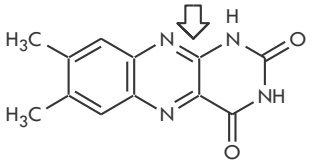


7,8-Diemthyl-10-(D-ribo-2,3,4,5-tetrahydroxy pentyl) isoalloxazine

Sources: milk, cheese, liver, kidney, meat, eggs, green leefy vegetables, fish, whole grain and enriched cereals and bread.

Stability:

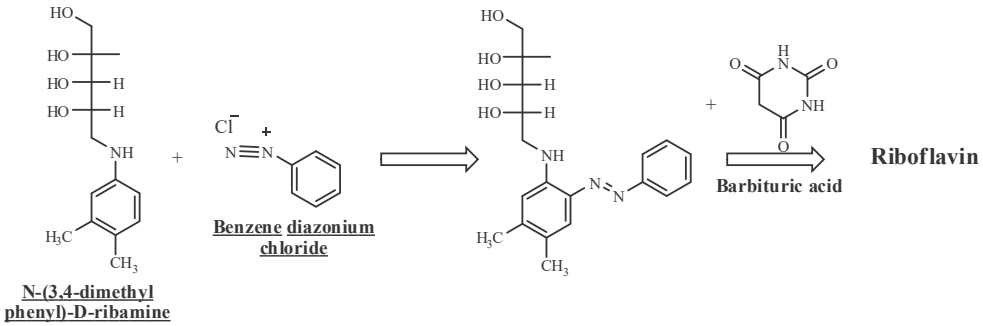
- When dry → not affected by diffused light [in solution → affected by light].
- Deterioration is rapid in presence of **alkali** → producing Lumiflavin.
- Upon irradiation [light] → Lumichrome.

Lumiflavin	Lumichrome
	
both are biologically inactive	

Absorption:

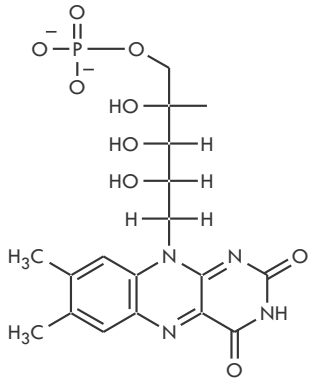
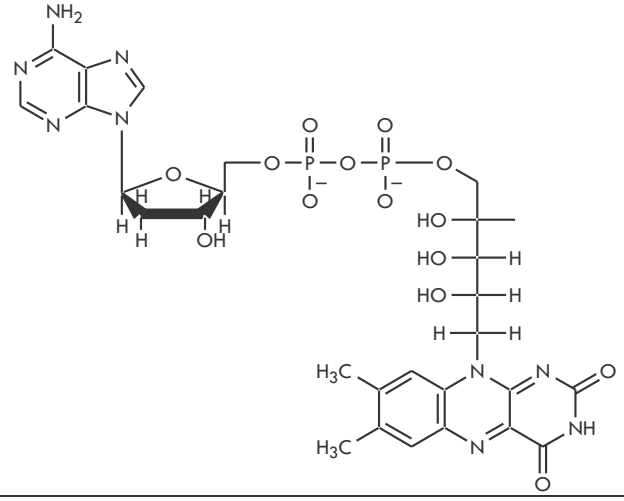
- Readily absorbed → binding to plasma proteins → widely distributed.
- Absorption occurs through active transport → riboflavin is phosphorylated by intestinal mucosa during absorption.

Synthesis of vitamin B_2:



Metabolism:

- Conversion into coenzyme Flavin MonoNucleotide [FMN] (or Riboflavin-5'-phosphate) and then to another coenzyme Flavin Adenine Dinucleotide [FAD] → Two active metabolites.

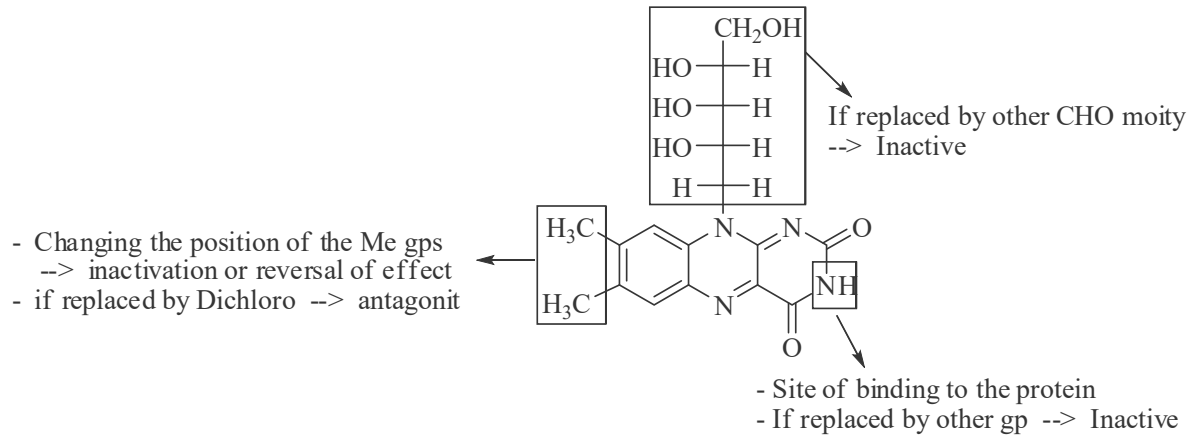
FMN	FAD
	

- 60 % of FMN and FAD → bound to plasma proteins.
- Riboflavin excreted in urine as metabolites (9%) → as the dose↑, high amount excreted unchanged.
- It crosses the placenta and distributed in breast milk.
- Riboflavin distributed to all tissues [little is stored].

Assay:

- **Fluorimetry:** Solution of riboflavin is with yellow-green fluorescence [with λ_{max} 565 nm in acidic pH] with addition of $KMnO_4$ and H_2O_2 to destroy interfering pigments (more sensitive).
- **Colourimetry** → using Denige's reagent (solution of $HgSO_4$) → gives an orange color.

SAR:



Interactions:

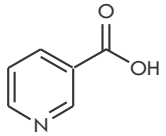
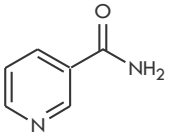
- Riboflavin ↓ anti-bacterial action of Erythromycin & Tetracycline.
- Boric acid [Common household chemical] → complex with riboflavin and promotes its urinary excretion. So, boric acid poisoning → vitamin B_2-deficiency.
- **Therapeutic uses:**
  - ✓ Treatment of Aribovlavonosis.

- ✓ Key role in energy metabolism-required for the metabolism of lipids, saccharides, and proteins.
- ✓ It is the central component of the cofactors FAD (flavin adenin dinucleotide) and FMN (flavin mononucleotide)

Aribovlavonosis: Is severe riboflavin deficiency**.** Symptoms in adults include seborrheic dermatitis, photophobia, peripheral neuropathy, anemia, angular stomatitis, glossitis, and cheilosis. In children, cessation of growth can also occur.

- Aribovlavonosis occurs in chronic alcoholism combined with other vit. deficiencies.
- Aribovlavonosis also resulted from phenothiazine, tricyclic antidepressent and probenecid therapy.

VITAMIN B_3 (Nicotinic (Niacin) &Nicotinamide)

Nicotinic acid (Niacin)	Nicotinamide (Niacinamide)
	
(Pyridine-3-carboxylic acid)	*(Nicotinic acid amide)*
-Lower the triglycerides, cholesterol	-Don't lower the triglycerides, cholesterol.
-Possess vasodilator effect	-Don't possess vasodilatory effect.

Sources: poultry, meat, fish, pork, yeasts, wheat germ, peanut meal and green peas.

- Deficiency of Niacin or Tryptophan [potential precursor of niacin] → Pellagra "Rough Skin".

Stability:

- Niacin is the most stable vitamin:
  - Not destroyed by heating in acid or alkaline solution.
  - With stand mild oxidation.
  - Retain activity during food processing.
- Niacinamide → hydrolyzed to acid by heating in acid or alkaline solution.

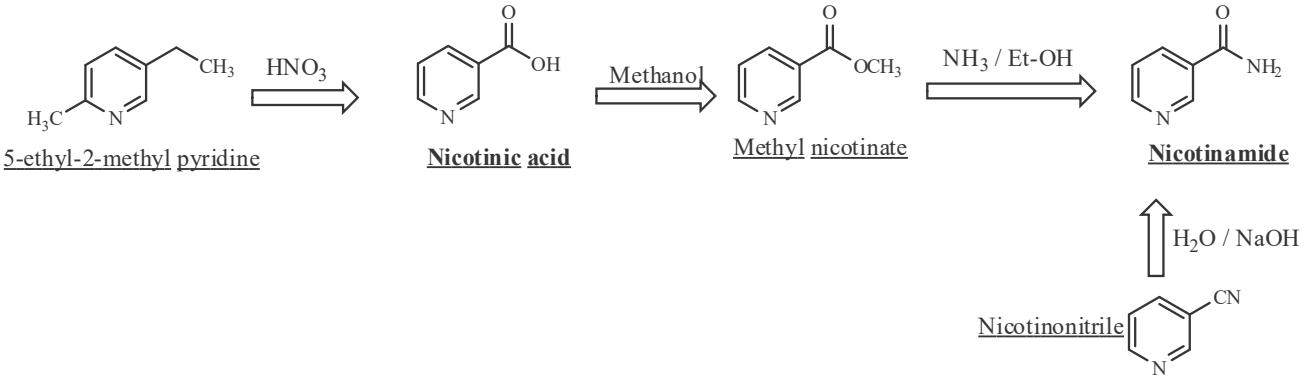
Metabolism:

- Nicotinic acid → N-methyl nicotinamide [florescent compound formed in liver] [Major].
- May form 2-pyridone and 4-pyridone or form Nicotinuric acid [glycine conjugate].
- If ↑ dose → may be found unchanged in urine.

Interactions and incompatibilities:

- Taken with caution with peptic ulcer, diabetes mellitus, gout or impaired liver function.
- Nicotinic acid has vasodilating effect → flushing side effect [so, Nicotinamide is preferred in this case].

Synthesis:



5-ethyl-2-methyl pyridine — **Nicotinic acid** — Methyl nicotinate — **Nicotinamide**

Assay:

- **Colorimetry:** Pyridine ring + cyanogens bromide → then coupling of products with aromatic amine → yellow dye → measured at 436 nm.
- Nicotinic acid → titration ≠ NaOH [ph ph indicator].
- Nicotinamide → Non-aqueous titration as base with perchloric acid [crystal violet indicator].
  - **Deficiency of niacin or tryptophan:** [potential precursor of niacin] leads to **pellagra** "Dry Skin".

Uses:

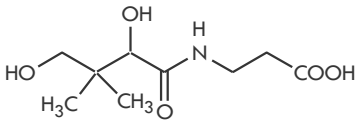
Nicotinic acid posses hypolipidemic activity so it decreases LDL & cholesterol (in large dose).

Treatment of **pellagra**.

Physiological functions:

- Nicotinic acid → converted to NAD [Nicotinamide Adenine Dinucleotide] or NADP [Nicotinamide Adenine Dinucleotide Phosphate] → coneznymes I & II respectively.
- NAD & NADP → oxidizing coenzymes for many dehydrogenases.

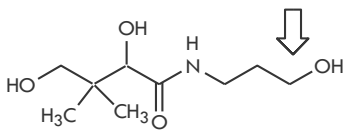
VITAMIN B_5 (Pantothenic acid)



(+)-(R)-3(2,4-Dihydroxy-3,3-dimethyl butyramido) propionic acid

- May be used as D-pantothenyl alcohol [Panthenol] in liquid preparations.

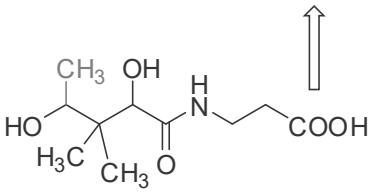
Panthenol:



- Good emollient properties → widely used in cosmetics [skin creams and shampoos].
- Reasonably stable.
- Freely soluble used in injectable and oral dosage forms.

SAR:

If replaced by sulfonic acid (SO_3H) - - → Pantoyl taurine



BOTH are ANTAGONISTS

ω -methylation - - → ω -methyl pantothenic acid

Metabolism:

- Pantothenic acid → not degraded in body [intake = excretion]

Assay:

- Acid or alkaline hydrolysis → cleavage of molecule into alanine + pantoic acid → determined by suitable color reactions.
- HPLC or GC.

Physiological functions:

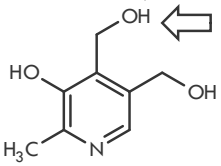
- Pantothenic acid is of the highest biological importance → incorporated in CoA → involved in many vital enzymatic reactions [transfer 2Cs compounds as acetyl group] as:

1. Energy release from CHO.
2. Degradation & metabolism of fatty acids.
3. Synthesis of sterols, steroid hormones, porphyrins & acetylcholine.

Therapeutic uses

1.Treatment of paralytic ileus, Dexapanthenol in combination with choline used in gas retention.
2. An additive in multi-vitamin preparations.
3. Panthenol used in cosmetics as moisturizing agent.

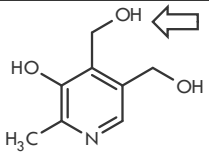
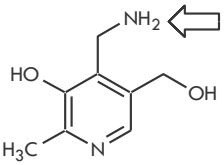
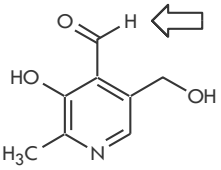
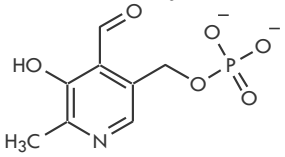
VITAMIN B_6 (PYRIDOXINE)



" 4,5-Bis(hydroxymethyl)-2-methylpyridin-3-ol

Sources: liver, cereal brans, yeast, crude cane molasses & wheat germs.

- It's mixture of 3 compounds inter-converted in body:

Pyridoxine	Pyridoxamine	Pyridoxal
 " 4,5-Bis(hydroxymethyl)-2-methylpyridin-3-ol		
These 3 forms converted in liver into Pyridoxal-5'-phosphate [active form] 		

Interactions:

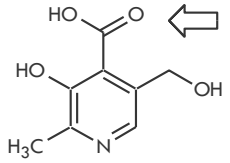
- It ↓ effect of L-dopa [this effect does not occur if dopa-decarboxylase inhibitor is co-given with L-dopa].
- Many drugs ↑ requirements of Vitamin B_6 [as Isoniazid, Hydralazine, Penicillamine, Oral contraceptives], due to hydrazone formation with aldehyde functional group.
- Pyridoxine is antidote for seizures in patients ingest overdose of I.N.H.

Absorption:

- By passive diffusion → transported into liver [main organ for storage, metabolism & interconversion between 3 forms].
- This interconversion requires NAD, FMN & FAD.
- Phosphorylated forms → hydrolyzed in intestine by phosphatases before absorption.
- Pyridoxal → the 1ry form that cross cell membranes [60 % of circulating vitamin B_6 is in the form of pyridoxal phosphate]

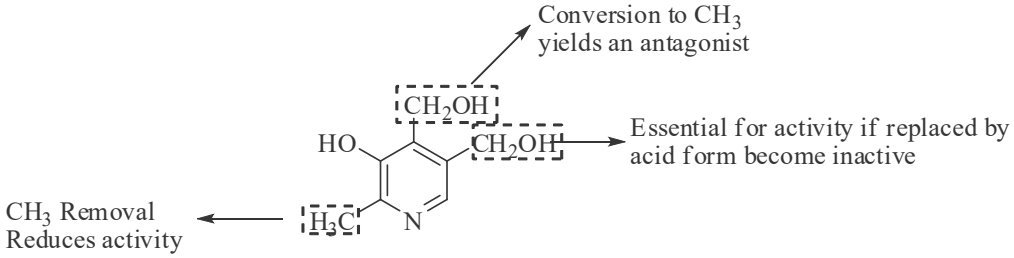
Metabolism:

- All 3 forms oxidized by hepatic aldehyde oxidase → 4-pyridoxic acid [MAJOR]



SAR:

Any small change in structure → inactivation.



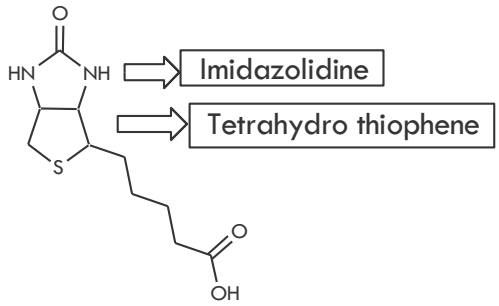
Assay:

- Non-aqueous titration with perchloric acid.
- Scudi's method: titration ≠ 2,6-dichloroquine chlorimide till light blue color.
- Spectrophotometric → measuring the absorption at λmax 290 nm

Uses

- Combined treatment of any Vit. B deficiency.
- Treat vomiting of pregnant.
- Prophylactic with Isoniazid, Hydralazine and Procainamide toxicity

VITAMIN B_7 (BIOTIN) (VITAMIN H)



Cis-hexahydro-2-oxothieno[3,4-d]imidazole-H-valeric acid

Sources: organ meats, egg yolk, liver, milk, fish, nuts, kidney & yeast.

- It's stable to cooking [less stable in alkali].
- Micro organisms synthesize biotin from oleic fatty acid.

Deficiency:

- Cause dermatitis, loss of appetite, sleeplessness.
- Eating raw egg white → induce biotin deficiency [why?] Raw egg contains avidin which make complex with biotin and decrease absorption from GIT causing dermatitis, loss of appetite, sleeplessness.

Uses

- Skin disorders as psoriasis, acne & alopecia.
- Diabetic neuropathy.
- For brittle nails & hair loss.

Metabolism:

- May appear unchanged in urine.
- Small amount metabolized to biotin sulfoxide & bis-norbiotin [appear in urine].

SAR:

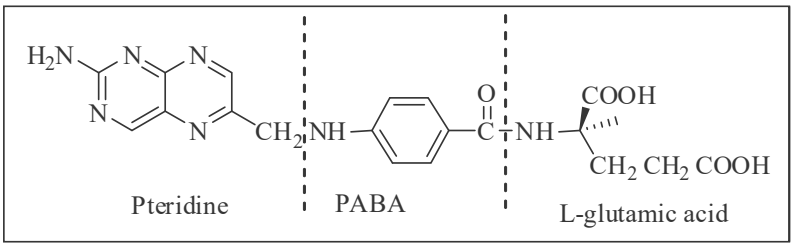
- The d-isomer is the active form [l-form is inactive].
- Sulfur may be replaced with oxygen without reduction in activity.

VITAMIN B_9 (FOLIC ACID)

One of vitamin B group.

Source: combined with several L(+) glutamic acid in liver, kidney, yeast, nuts, leafy green vegetables.

- Consist of 3 parts [Pteridine + PABA + Glutamic acid] → but separately, each one has no vitamin activity.



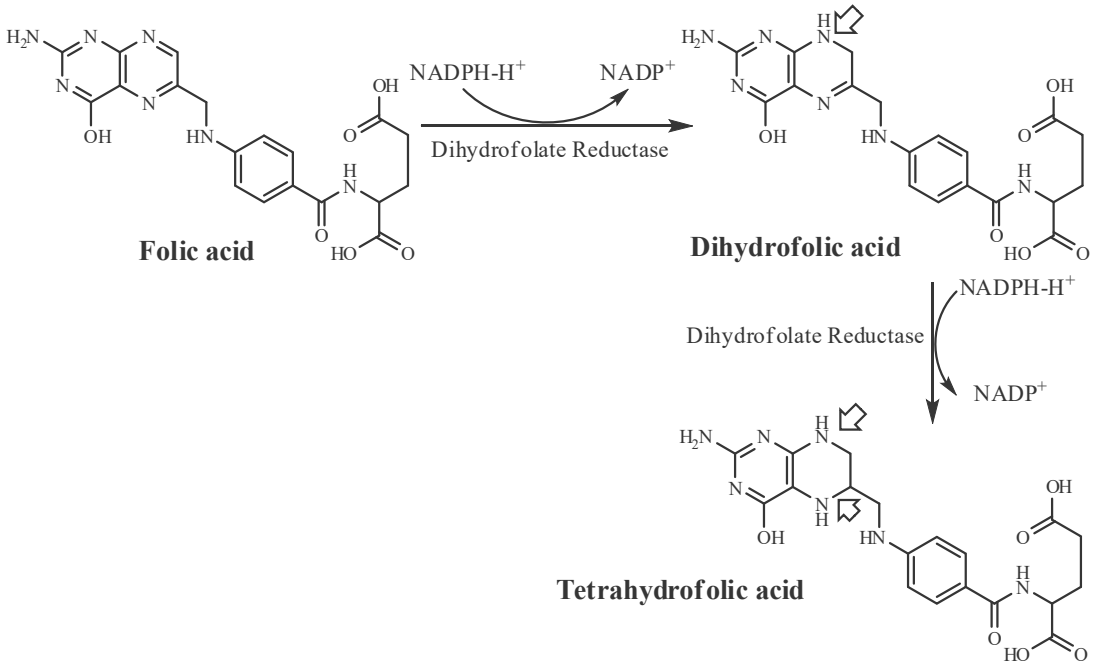
Uses:

- Treatment of megaloblastic anemia.
- Given during/before pregnancy to prevent fetal neural development abnormalities

Stability: readily oxidized + easily destroyed by cooking.

Two biosynthetic pathways must occur 1st:

1. Reduction to Tetrahydro folate by dihydrofolate reductase enzyme "DHFR" [require Niacin].
2. Polyglutamate chain must be attached to γ-carboxyl of parent glutamic acid.



Causes of folic acid deficiency:

1. ↓ Nutrition during period of increase requirements → so, this is the main cause of megaloblastic anemia in pregnancy.
2. Alcoholism.
3. Chronic inflammation of intestinal mucosa.

Interactions:

- Anti-convulsant [Phenytoin] → interfere with folic acid uptake or utilization.
- Other water-soluble vitamins, they are in descending order of effectiveness [Riboflavin, thiamine, ascorbic acid, niacinamide, pantothenic acid & pyridoxine] → this effect may be overcome by inclusion of 70% sugar in mixture.
- Methotrexate: closely related in structure [folic acid antagonist → used as anti-cancer].

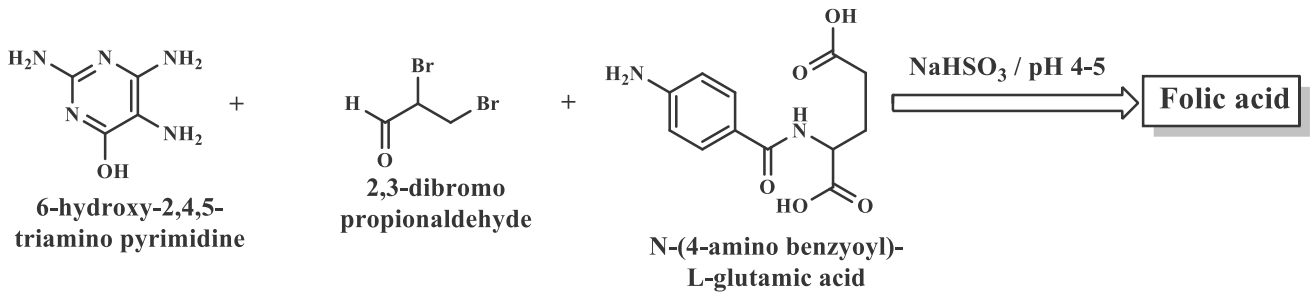
Absorption:

- It presents in diet as Pteroyl-polyglutamates → must be hydrolyzed first to monoglutamate before absorption.
- This hydrolysis catalyzed by pteroyl-γ-glutamyl carboxy-peptidase [called: Conjugate] which is commonly found in intestinal mucosa membrane.

Assay:

- Oxidative cleavage by making solution in NaOH and use Zn pd/HCl [give nascent H for cleavage] → 4-amino benzoyl glutamic acid.
- Diazotization & coupling with N-naphthyl ethylene diamine dil HCl → colored compound → spectrometric.
- Compare absorbance with non-reduced sample.

Synthesis:



Metabolism, Storage & Excretion:

- Naturally occurring form [folate polyglutamate] → deconjugated & reduced by DHFR in intestine → 5-methyl tetrahydrofolate → portal circulation & bind to plasma proteins.
- Externally administered folic acid → enter portal circulation unchanged [it's poor substrate for DHFR] → conversion into metabolically active form 5-methyl tetrahydrofolate in plasma & liver.
- N5-methyl derivative → the main transport & storage form in the body, concentrated in CSF.
- Mainly eliminated via biliary excretion as N5-methyl derivative.
- Folates distributed in breast milk.

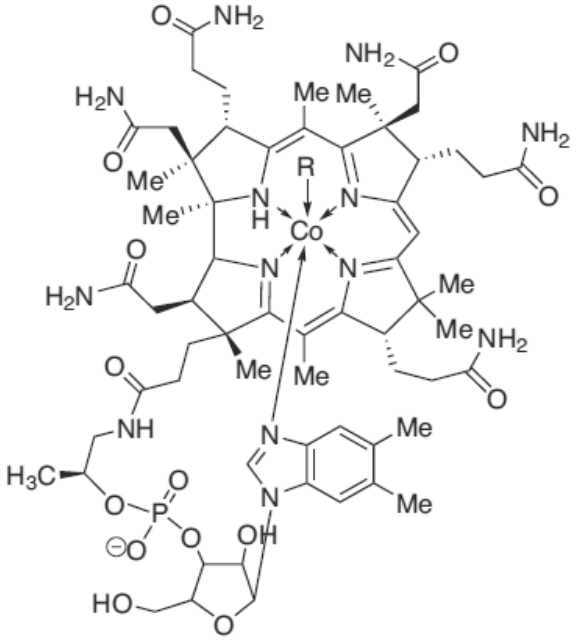
VITAMIN B_{12} (COBALAMINES)

- Most recently discovered of vitamin B group.

Sources: liver, meat, eggs, seafood, dairy products.

Uses: treatment of Addisonian Pernicious Anemia.

- Cobalt-containing compounds → Cyanocobalamine and Hydroxy cobalamine.
- **Storage:** in air-tight containers, protected from light.



- Cyanocobalamine → Vitamin B_{12} [because it's the first form discovered and it's the one occurring in nature]
- 5'-adenosyl form → Coenzyme B_{12}.
- When ligand is methyl → Methyl B_{12}.

Stability:

- Storage at R.T. in presence of ascorbic acid → loss 1.5 % of activity per day.
- Niacinamide → stabilized aqueous solution of cyanocobalamin & folic acid at pH=6-6.5 [but unstable in –complex solution].
- Cyanocobalamin → stable in solution of sorbitol & glycerin but unstable in dextrose or sucrose.

Interactions:

- Absorption of vitamin B_{12} ↓ by neomycin, amino salicylic acid, H_2-antagonists and chloramphenicol.
- ↑ Intake of alcohol for long time → ↓ absorption of vitamin B_{12}.

Physiological functions:

- It occurs in body mainly as Mecobalamin [Methylcobalamin], Cobamide [Adenosylcobalamin] & Hydroxycobalamin.
- Mecobalamin & Cobamide → act as coenzymes in nucleic acid synthesis.
- Generally, → vitamin B_{12} is essential for normal functioning, growth and proliferation of all cells especially cells of bone marrow, nervous system and GIT.

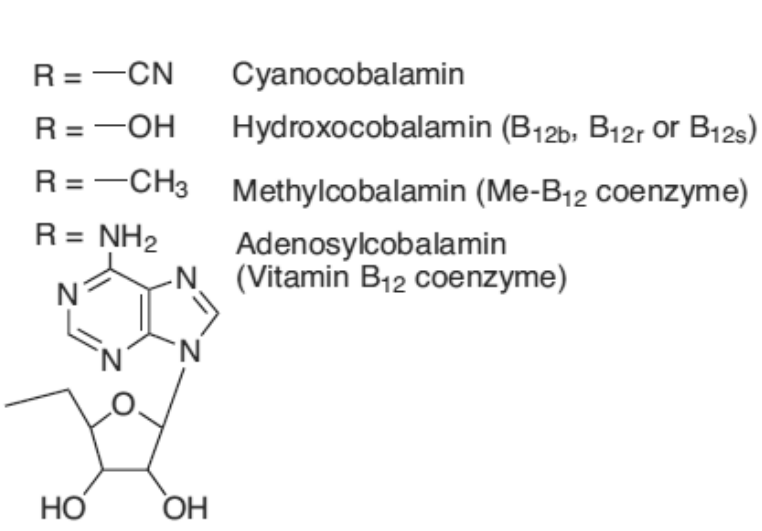
It appears to:

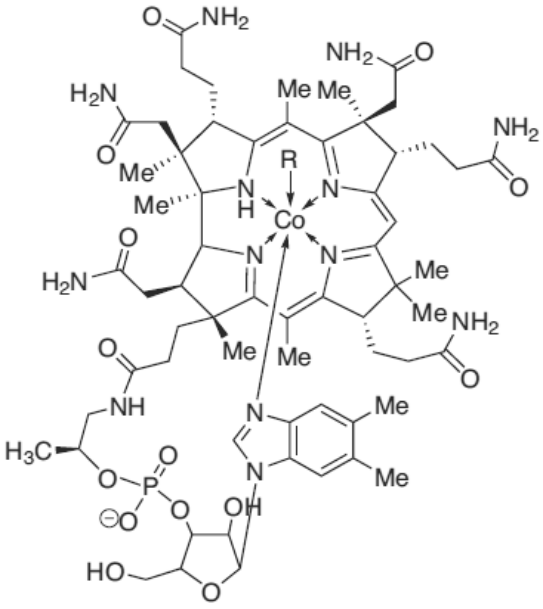
1. Facilitate reduction reactions.
2. Participate in transfer of methyl groups [e.g. methylation of homocysteine to methionine].

Assay: Spectrophotometry

Theraputic Uses:

1. Prenicious anemia.
2. Hydroxycobalamine is used in the treatment of acute cyanide toxicity. It captures the C-N to harmless cyanocobalamine (by coordinate bond) & thiosulfate is also co-administered.





PROSTAGLANDINS

Occurrence:

1) Human seminal plasma 2) Reproductive tissue in both sex with except to genital tissues

Biosynthyesis:

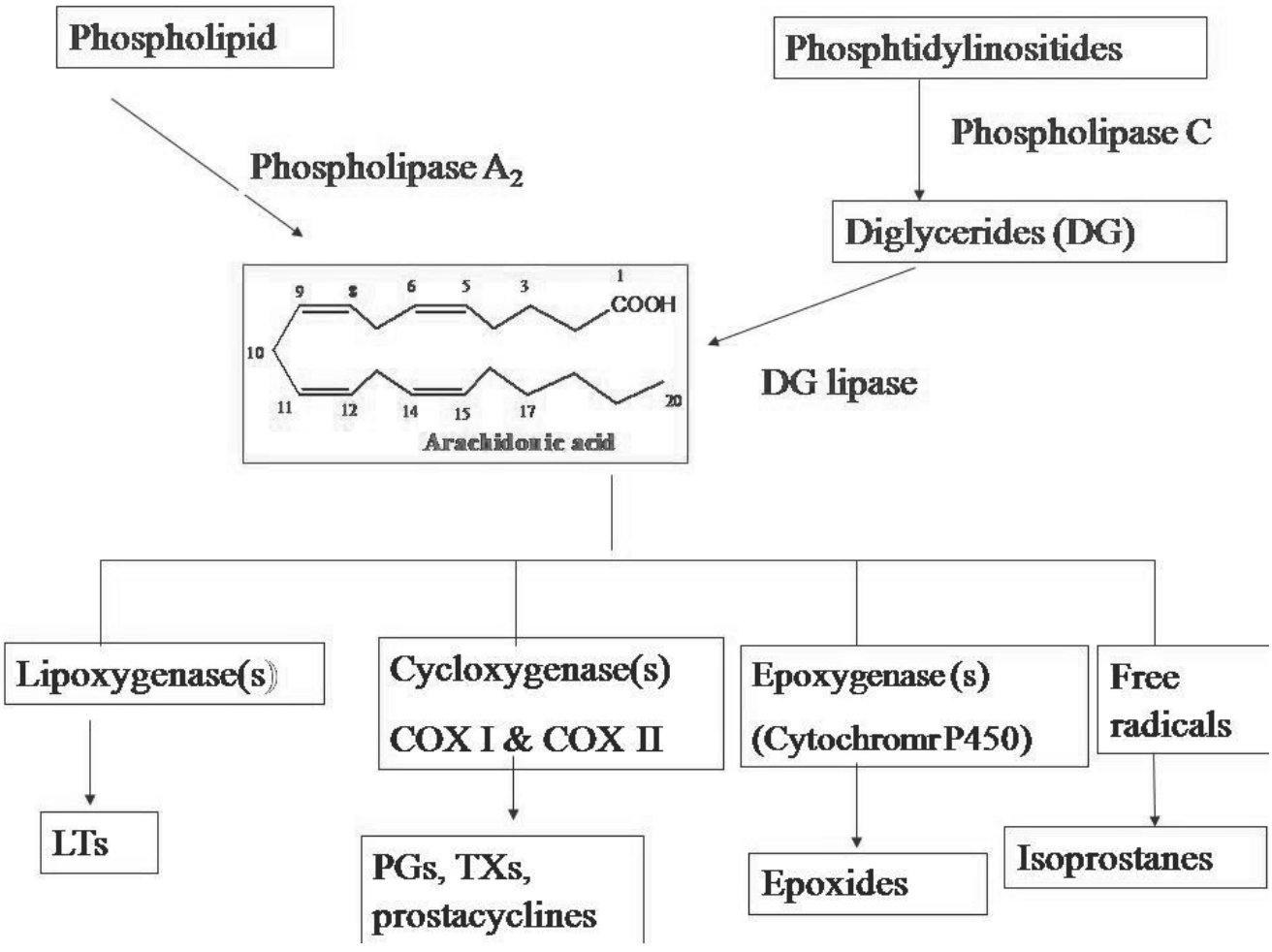
-The unsaturated fatty acids are the source for PGs

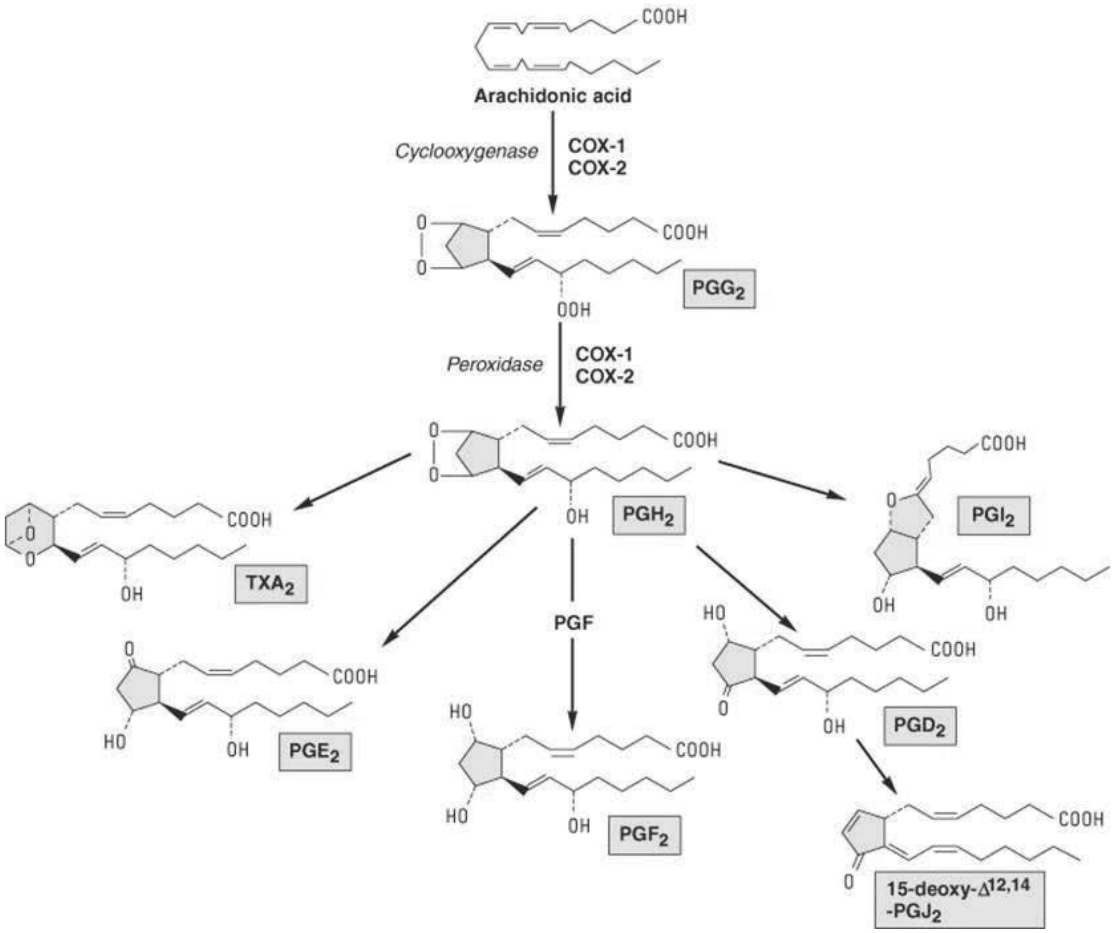
-The number of **double bonds** in the naturally PGs indicating to the precursors fatty acids

a)-PG_1 Type (contain 1 double bond) are derived from **8,11,14 eicosatrienoic acid (Dihomo γ-linoleic acid)**

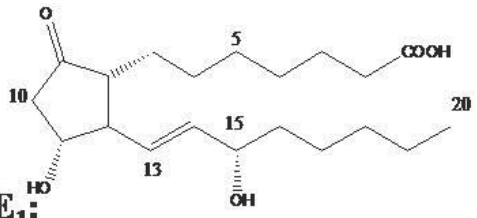
b)- PG_2 Type (cnotain 2 double bond) are derived from **5,8,11,14 eicosatetaenoic acid (Arachidonic acid)**

c)- PG_3 Type are derived from 5,8,11,14,17 eicosapentenoic acid




COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
PGG2
OOH
Peroxidase
COX-1
COX-2
PGH2
OH
TXA2
PGI2
PGF
PGE2
PGF2
PGD2
15-deoxy-Δ12,14
-PGJ2

Chemical features



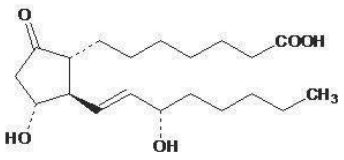
PGE$_1$

All PGs possess a general chemical features as in PGE$_1$:

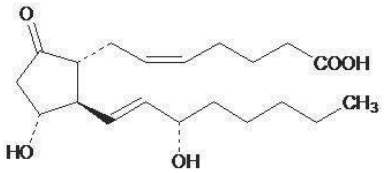
1) 15 α-hydroxy
2) trans double bond at C13
3) Carboxylic group
4) Carboxyl-bearing chain termed α Chain
5) Hydroxyl-bearing chain termed β Chan
6) Two side chains are trans stereochemistry

Classification:

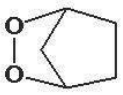
- Prostaglandin (PG)s: are classified by capital letters as A,B,C,D,E,F e.g. PGE, PGF according to the nature and stereochemistry of oxygen substituent at C9 and C11. (see the clinically used PGs)
- Also the number of double bonds in the side chain determined by 1,2,3. when these numbers are subscripted reveal to additional cis double bond configuration.
  - ✸The subscript 2 indicate an additional cis double bond at the C5=C6 position (see PGE$_1$ & PGE$_2$)
  - ✸The subscript 3 indicate a thirds cis double bond at the C17=C18 position



PGE$_1$



PGE$_2$

PGs	C9	C11	Other
PGD	α-OH	C=O	-
PGE	C=O	α-OH	-
PGF	α-OH	α-OH	-
PGG			
PGH			

Metabolism:

1-Rapid oxidation of 15 α-OH to corresponding CO by 15 **PG dehydrogenase**

2-Reduction of C13=C14 by PG reductase to corresponding dihydroketones which represent the major metabolites of PGE_2

3-Enzymes which are involved in *β*- and *ω*-oxidation of fatty acids more slowly cleave the α-chain and oxidize the C20 terminal CH_3 to COOH respectively, hence the dicarboxylic acid derivatives are the major metabolites of PGE_1 and PGE_2 which is excreted. The enzyme exhibit 2 type of activities and the substrate involved is stereospecific. The OH group at position C15 of the substrate must be *S* configuration. One type depend on NAD+ and the other are NADP+ as a cofactors.

Physiological roles:

1-As hormones: $PGP_2\alpha$ act as luteolytic hormone in horses and PGA and E play a role in lowering blood pressure

2-As intercellular messengers: The newly synthesized PGs could function inside the cells as regulators of calcium level. PGs stimulate the release of calcium from its binding sites. Calcium is essential component for of many biological functions of cyclic AMP.

3-As autocoids: PGs are **antihypertensive agents, inhibitors of gastric secretion**, bronchodilators, and are of use in labor induction

SARs

a) Variation in the α-chain

1-Replacement of COOH by isosters tetrazole moiety retain the activity, but with sulfonic moiety abolish the activity

2-Esters and amides act as prodrugs which improve stability and increase the duration of action

3- **Substitution at C2:** small as alkyl or halogen are less active except 2-fluoro of PGE_1 was found more active, and cyano which has ½ the activity

4-Substitution at C3 with 3-methyl, methoxy, or oxo PGE_1 were found inactive while 3-phenyl of methyl ester analogue was show selective active for platelets aggregation and weak small muscle relaxant

5-The 7-keto analogues in PGE is **inactive** while 7-oxa in PGE_1, and $PGF_2\alpha$ show moderate activity

6-The distance separating COOH and the cyclopentane nucleus has been considered critical. Also changing the geometry, or the unsaturation resulting of loss of the activity.

7-Replacement of carbon by hetero atom not effect the geometry much more but diminish lipophilicity and affect the chain interaction.

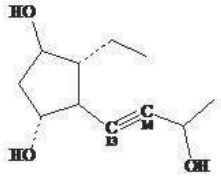
b) Variation of the cyclopentane ring

1-There are great No. of variation in the cyclopentane ring can be carried out and almost lead to decrease the activity as removal or introduction of oxygen at C9 or C11, or replacement C9, C11 by hydroxymethyl

2-Also introduction of fluoro, methyl, ring expansion, and introduction of heteroatom in the cyclopentane ring as oxa, aza, or thia all inactive

c) Variation in the β chain

1- Variation between C15-C20 offer analogues with narrow spectrum activity



2- Aetylenic analogues show enhanced hormonal activity

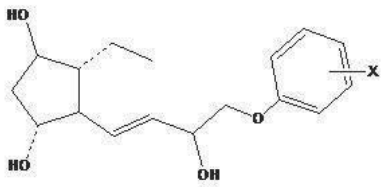
3- C14 chloro or phenyl of $PGF_{2\alpha}$ are inactive while C14 methyl has about 1/20 of the E_2 gastric activity

4- Shortening the β-chain by CH_2- group offer ω-norprostaglandin with equal activity to natural prostaglandin. While lengthening the β-chain by CH_2- group results ½ of the activity. lengthening the β-chain by two CH_2- group results 1/20 of the activity. Further increase by three CH_2- groups results 1/200 from the activity. But incase of $PGF_{2\alpha}$ the addition of two CH_2- groups (ω-dihomo of $PGF_{2\alpha}$) results an 20 times increase of antifertility activity and reduce in smooth muscle stimulating activity by 1/3.

d) Alkoxy substituents

1-Introduction of 2-methoxy or replacement of C18 and C19 by oxygen to afford the their oxa analogues of $PGF_{2\alpha}$ are 4-5 times more hormonal activity than the natural prostaglandin.

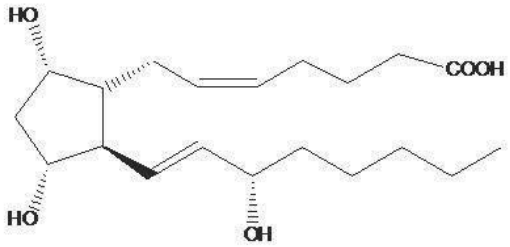
2-The 16 phenoxy derivatives, especially with *p*-substituted phenyl with electron withdrawing groups showed **grater hormonal activity.** These analogues are metabolized by β-oxidation rather than 15-dehydrogenase enzyme



3-The 17 phenyl ω-trinorprostaglandin is 90 times more active as hormonal PG than $PGF_{2\alpha}$.

It was reported that the cyclopentano derivatives have vasodilatation action rather than smooth muscle relaxant effects.

Clinically used prostaglandin:

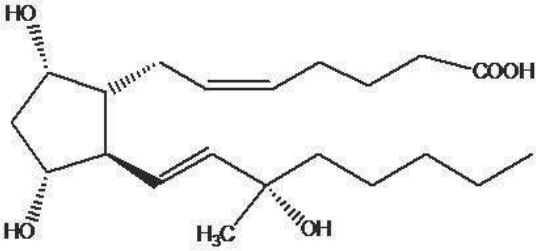


1-Dinoprost ($PGF_{2\alpha}$)

(5Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((S,E)-3-hydroxyoct-1-enyl) cyclopentyl)hept-5-enoic acid

Used for induction of labor or abortion

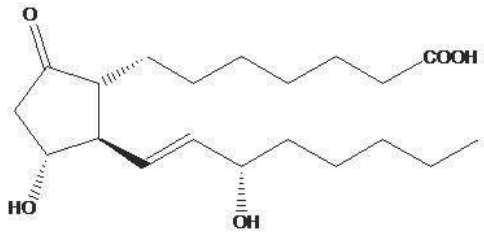
2-Carboprost



15(S)- Methyl $PGF_{2\alpha}$

Used for induction of labor or abortion

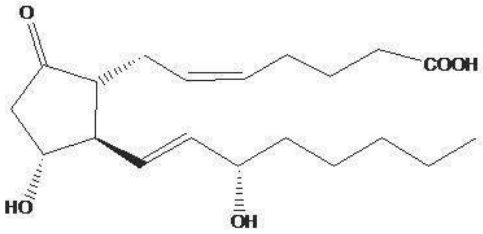
3-Alprostadil (PGE_1)



7-((1R,3R)-3-hydroxy-2-((S,E)-3-hydroxyoct-1-enyl)-5-oxocyclopentyl)heptanoic acid

Used in infants with congenital defects of pulmonary or systemic blood flow

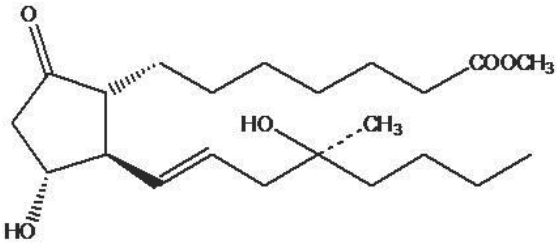
4-Dinoprostone (PGE_2)



(5Z)-7-((1R,2R,3R)-3-hydroxy-2-((S,E)-3-hydroxyoct-1-enyl)-5-oxocyclopentyl)hept-5-enoic acid

Used for induction of labor or abortion

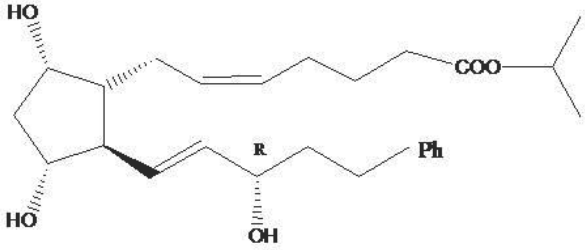
5-Misoprostol



16-(R,S)-methyl-16-hydroxy-PGE_1

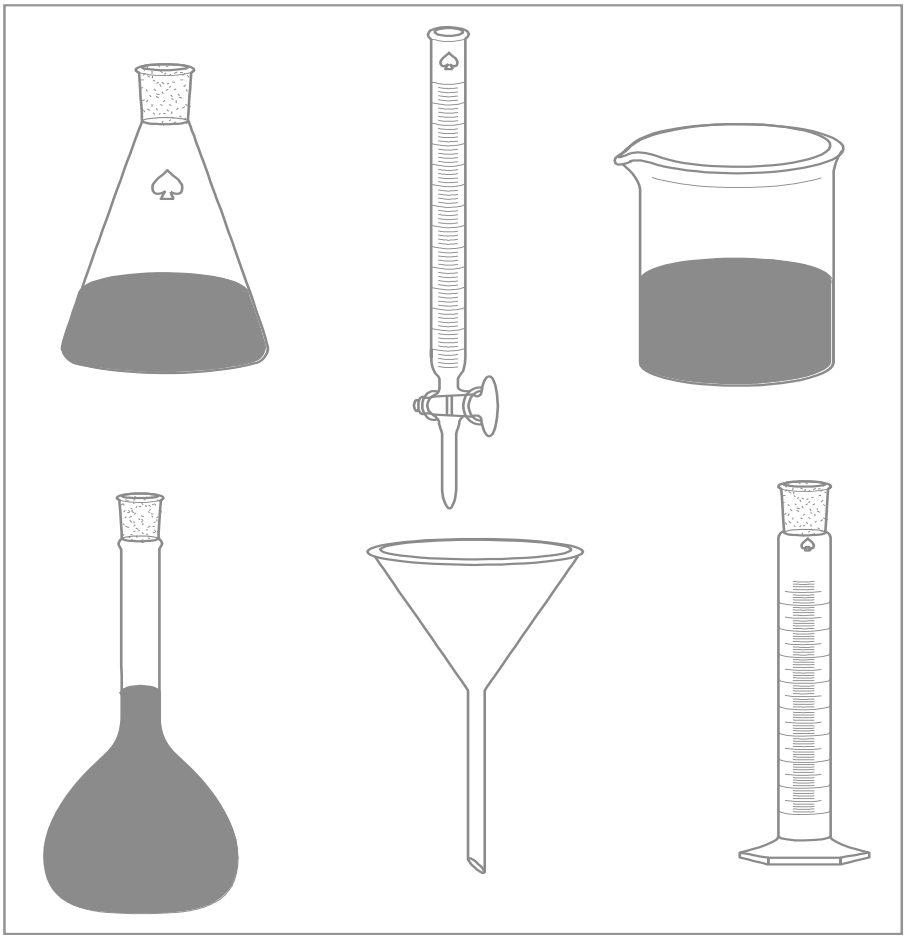
It prevent gastric acid ulceration caused by anti-inflammatory agents

6-Latanoprost (Xalatan^R)



It used as antiglaucoma, penetrated the cornea and slowly released into the anterior parts of the eye.

Practical Pharmaceutical Chemistry

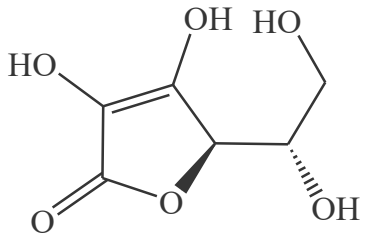


Contents

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Assay of Ascorbic acid (BP 2007)



$C_6H_8O_6$ **176.1**

Action and use

Used in the treatment of vitamin C deficiency.

Preparations

Ascorbic Acid Injection

Ascorbic Acid Tablets

Pediatric Vitamins A, C and D Oral Drops

Vitamins B and C Injection

DEFINITION

Ascorbic acid contains not less than 99.0 per cent and not more than the equivalent of 100.5 per cent of **(5R)-5-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one.**

CHARACTERS

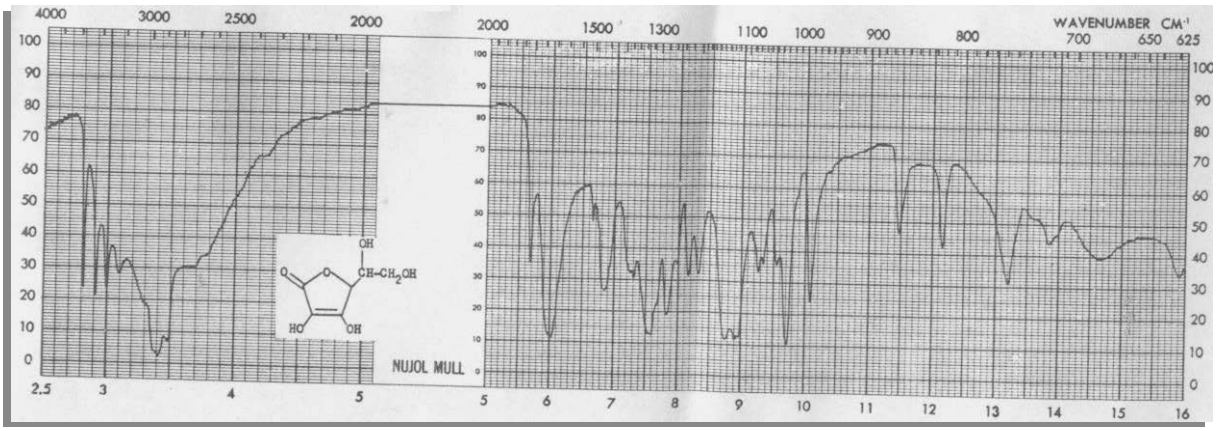
A white or almost white, crystalline powder or colorless crystals, becoming discolored on exposure to air and moisture, freely soluble in water, soluble in alcohol, practically insoluble in ether.

IDENTIFICATION

A) The pH of solution is 2.1 to 2.6.

B) Melting point : 190-192°.

C) Infrared absorption spectrophotometry



D) To 1 ml of solution add 0.2 ml of dilute nitric acid and 0.2 ml of silver nitrate solution. A grey precipitate is formed.

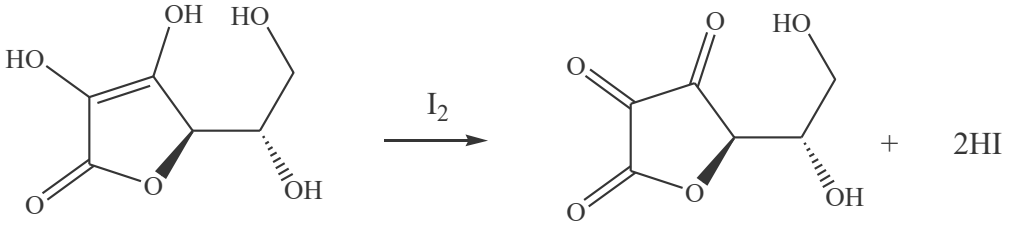
STORAGE

Store in a non-metallic container, protected from light.

ASSAY

Principle of assay

Idodometeric titration by titration against standard iodine solution in presence of starch as indicator. Iodine oxidize ascorbic acid into dehydroascorbic acid.



Ascorbic acid Dehydroascorbic acid

Procedure

Mix the powder of 20 tablets and to quantity powder containing 0.100 g of ascorbic acid, add 50 ml of distilled water and 10 ml of dilute sulfuric acid, and 1 ml of starch solution. Titrate with 0.05 M iodine until a persistent blue color is obtained.

Each 1 ml of 0.05 M iodine is equivalent to 8.81 mg of $C_6H_8O_6$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content
……
……
……
……

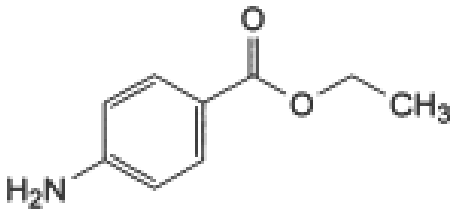
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……

Assay of Benzocaine Powder (BP 2007)



$C_9H_{11}NO_2$ **165.2**

Action and use

Local anesthetic.

DEFINITION

Benzocaine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of **ethyl 4-aminobenzoate**

CHARACTERS

A white, crystalline powder or colorless crystals, very slightly soluble in water, freely soluble in alcohol.

IDENTIFICATION

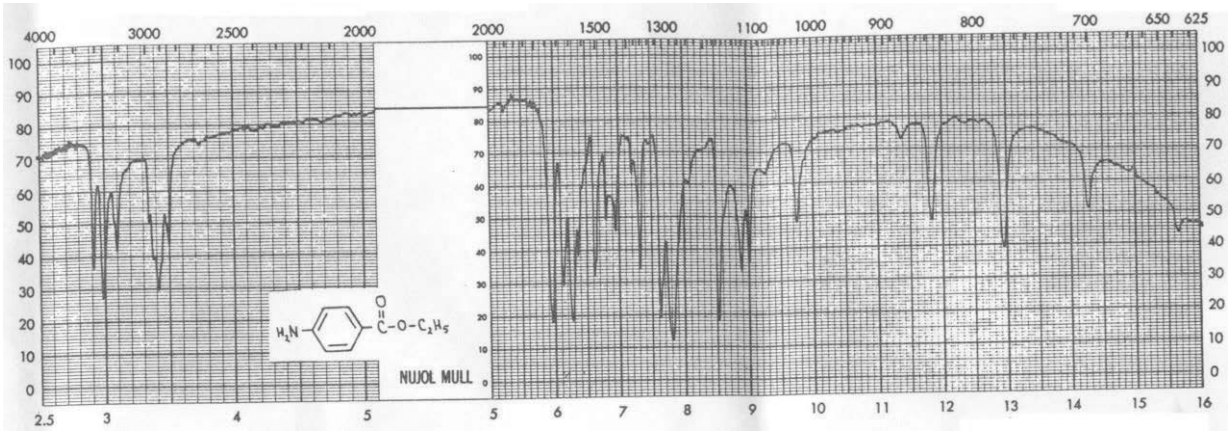
A) Melting point: 89 °C to 92 °C.

B) Infrared absorption spectrophotometry

D. The solution of benzocaine gives the reaction of primary aromatic amines (diazotization).

STORAGE

Store protected from light.



ASSAY

Principle of assay

The assay depends on diazonium salt formation with $NaNo_2$ in presence of acid and starch potassium iodide paper as indicator.

Procedure

Mix the powder of 20 tablets and to a quantity of the powder containing 0.2 g of benzocaine in a stoppered flask add 10 ml of 6M hydrochloric acid and 50 ml water, shake for 15 minutes and titrate with 0.1M sodium nitrite VS, using starch potassium iodide paper as indicator. Each 1 ml of 0.1 M sodium nitrite is equivalent to 16.52 mg of $C_9H_{11}NO_2$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content

……
……
……
……

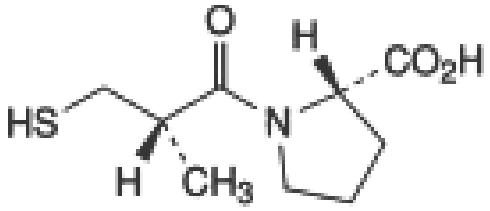
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Captopril Tablet (BP 2007)



$C_9H_{15}NO_3S$ **217.3**

Action and use

Angiotensin-converting enzyme inhibitor.

Preparation

Captopril Tablets

DEFINITION

It contains not less than 98.0 per cent and not more than the equivalent of 101.5 per cent of **(2S)-1-[(2S)-2-Methyl-3-sulphanylpropanoyl] pyrrolidine-2-carboxylic acid.**

CHARACTERS

White or almost white, crystalline powder. Freely soluble in water, in methylene chloride and in methanol. It dissolves in dilute solutions of alkali hydroxides.

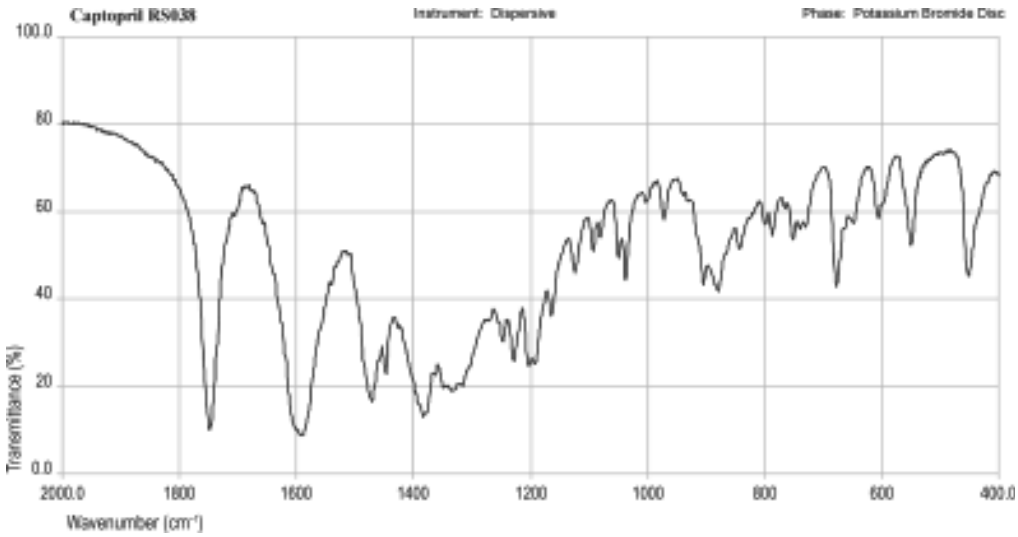
IDENTIFICATION

A) Melting point: 103 ^{O}C to 104 ^{O}C

B) Specific optical rotation (in ethanol)

The specific rotation is - 127 to - 132.

C) Infrared absorption spectroscopy.



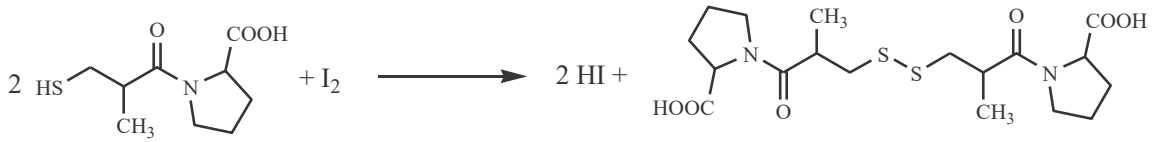
STORAGE

In an airtight container.

ASSAY

Principle of assay

Iodometric titration by titration against standard iodine solution in presence of starch as indicator. The sulfhydryl group of captopril reduce iodine into iodide.



Procedure

Mix the powder of 20 tablets and dissolve powder equivalent to 0.150 g in a mixture of 10 ml of dilute sulfuric acid and 50 ml of carbon dioxide-free water. Add 1 ml of starch solution. Titrate with 0.05 M iodine until a persistent blue color is obtained.

Each 1 ml of 0.05 M iodine is equivalent to 21.73 mg of $C_9H_{15}NO_3S$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content

……
……
……
……

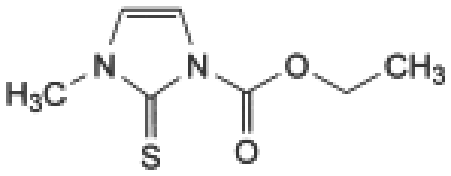
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Carbimazole Tablet (BP 2007)



$C_7H_{10}N_2O_2S$ **186.2**

Action and use

Antithyroid.

Preparation

Carbimazole Tablets

DEFINITION

It contains not less than 98.0 per cent and not more than the equivalent of 102.0 percent of **Ethyl 3-methyl-2-thioxo-2,3-dihydro-1H-imidazole-1-carboxylate.**

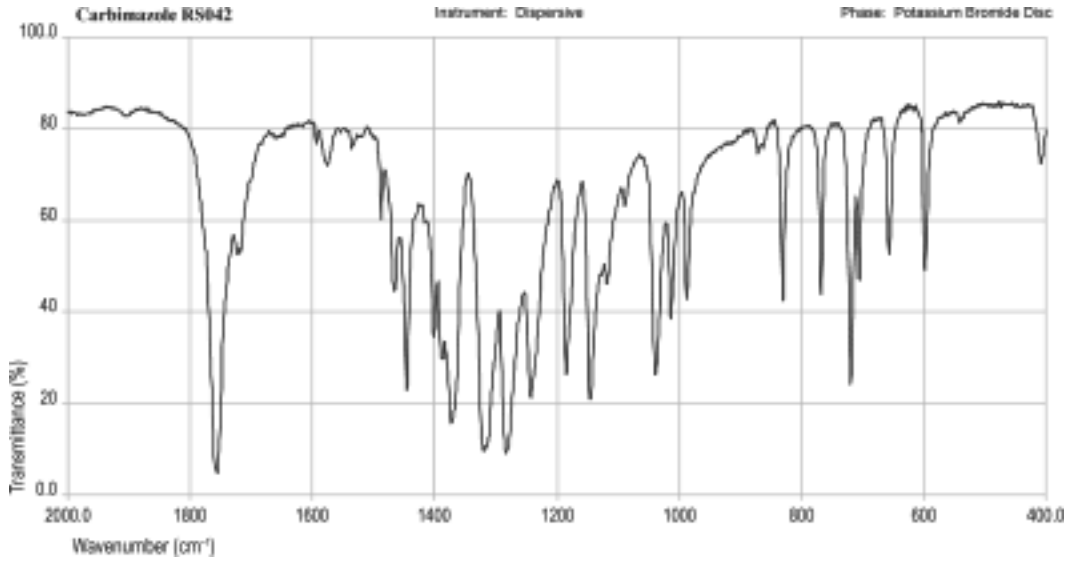
CHARACTERS

White or yellowish-white, crystalline powder. Slightly soluble in water, soluble in acetone and in alcohol.

IDENTIFICATION

A) Melting point: 122 °C to 125 °C.

B) Infrared absorption spectrophotometry.



C) Thin-layer chromatography.

D) To a small quantity of the powdered tablets add 0.05 ml of dilute potassium iodobismuthate solution. A scarlet color is produced.

ASSAY:

Principle of assay:

Spectrophotometric assay at λ_{max} 291 nm taking 557 as the value of $A^{1\%}_{1cm}$.

Procedure:

Mix the powder of 20 tablets and dissolve powder equivalent to 50.0 mg in 400 ml water and dilute to 500.0 ml with the same solvent. To 10.0 mL add 10 ml of dilute hydrochloric acid and dilute to 100.0 ml with water. Measure the absorbance at the maximum at 291 nm. Calculate the content of $C_7H_{10}N_2O_2S$ taking 557 as the value of $A^{1\%}_{1cm}$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

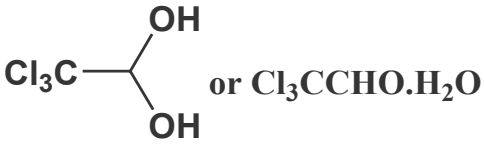
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Chloral hydrate solution (BP 2007)



or $Cl_3CCHO.H_2O$

$C_2H_3Cl_3O_2$ 165.4

Action and use

Hypnotic.

DEFINITION

Chloral hydrate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of **2,2,2-trichloroethane-1,1-diol.**

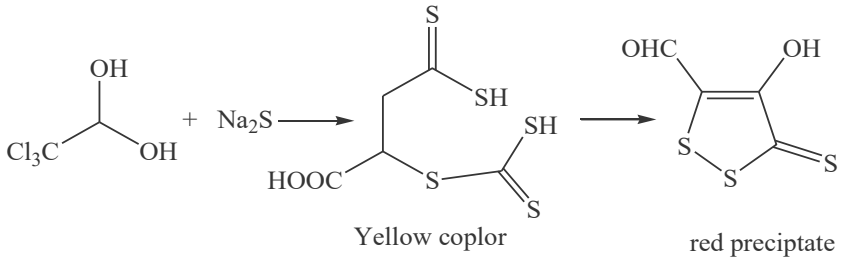
CHARACTERS

Colorless, transparent crystals, very soluble in water, freely soluble in alcohol.

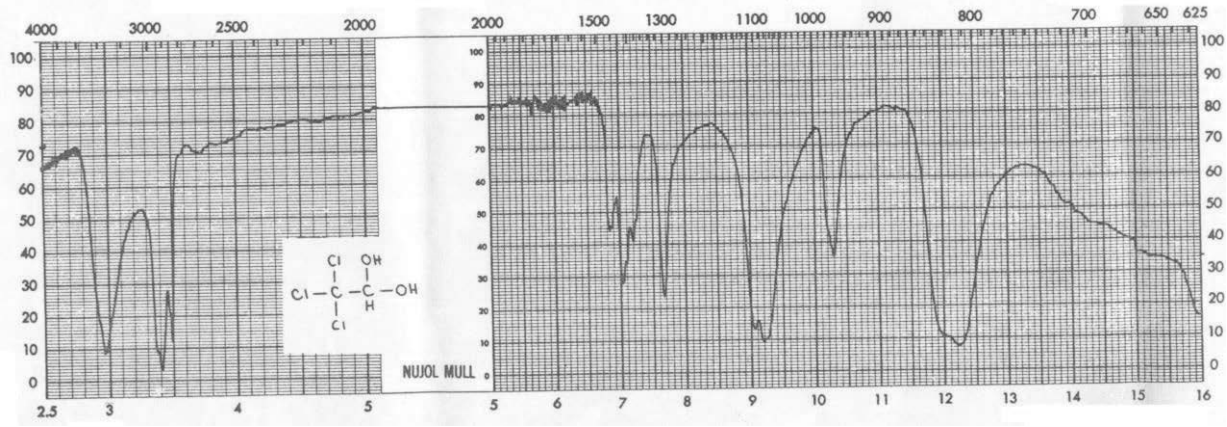
IDENTIFICATION

A) To 10 ml of solution (10%w/v), add 2 ml of dilute sodium hydroxide solution. The mixture becomes cloudy and, when heated, gives off an odour of chloroform.

B) To 1 ml of solution add 2 ml of sodium sulphide solution. A yellow color develops which quickly becomes reddish-brown. On standing for a short time, a red precipitate may be formed.



C) Infrared absorption spectrophotometry.



STORAGE

Store in an airtight container.

ASSAY

Principle of assay

Depends on the hydrolysis of the chloral hydrate with 1M NaOH

$$CCl_3CH(OH)_2 + \text{xss NaOH} \longrightarrow CHCl_3 + HCOONa + H_2O$$

The excess NaOH is back titrated with 0.5M H_2SO_4 using ph.ph. as indicator. Due to the presence excess NaOH a small part of chloroform will be hydrolyzed to offered sodium chloride and sodium formate, this will use some NaOH that include to the consuming by the hydrolyses of chloral hydrate. So, correction should be making to overcome this problem. Correction will be done by determine the NaOH consumed by side reaction through determine the formed sodium chloride by Mohr's method using 0.1 M $AgNO_3$ as titrant and $KCrO_4$ as indicator.

$$CCl_3CH(OH)_2 + \text{xss NaOH} \longrightarrow CHCl_3 + HCOONa + H_2O$$

$$3NaCl + 3AgNO_3 \longrightarrow 3AgCl + 3NaNO_3$$

$$K_2CrO_4 + \text{xss } AgNO_3 \longrightarrow Ag_2CrO_4 + KNO_3$$

Procedure

Dissolve 2.00 g of chloral hydrate in 10 ml of water and add 20.0 ml of 1 M sodium hydroxide. Allow to stand for exactly 2 min and titrate with 0.5 M sulfuric acid, using 0.1 ml of phenolphthalein solution as indicator. Titrate the neutralized solution with 0.1 M silver nitrate, using 0.2 ml of potassium chromate solution as indicator. Calculate the number of milliliters of 1 M sodium hydroxide used by deducting from the volume of 1 M sodium hydroxide, added at the beginning of the titration, the volume of 0.5 M sulfuric acid used in the first titration and two-fifteenths of the volume of 0.1 M silver nitrate used in the second titration.

Each 1 ml of 1 M sodium hydroxide is equivalent to 0.1654 g of $C_2H_3Cl_3O_2$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

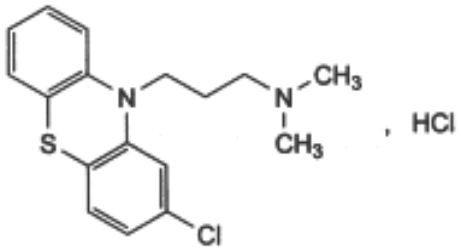
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Chlorpromazine hydrochloride (BP 2007)



$C_{17}H_{19}ClN_2S$, HCl **355.3**

Action and use

Antipsychotic; antiemetic.

Preparations

Chlorpromazine Injection

Chlorpromazine Oral Solution

Chlorpromazine Tablets

DEFINITION

Chlorpromazine hydrochloride contain not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of **3-(2-Chloro-10H-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine hydrochloride**.

CHARACTERS

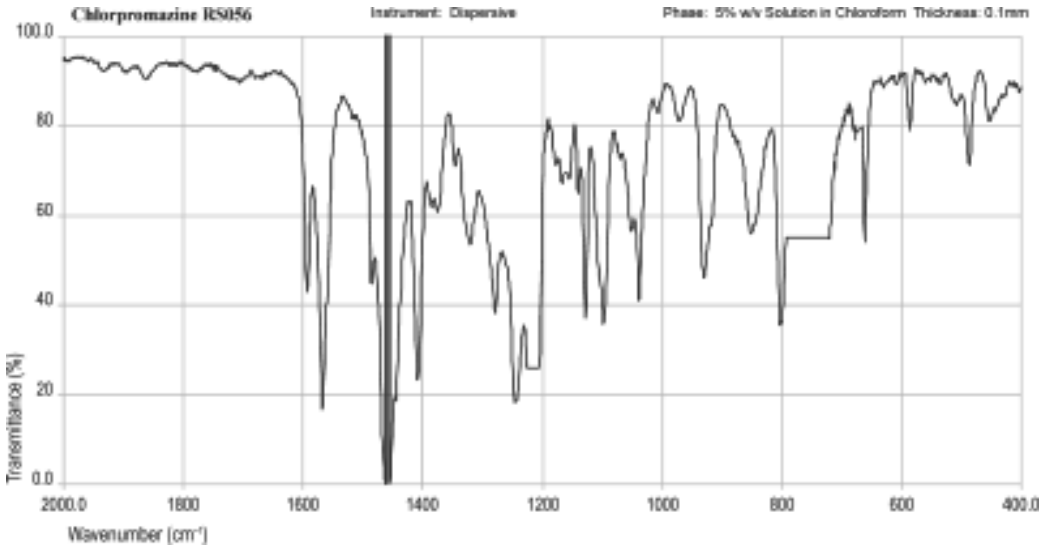
White crystalline powder. Very soluble in water, freely soluble in ethanol (96 per cent). It decomposes on exposure to air and light.

IDENTIFICATION

A) Melting point: About 196 °C.

B) Ultraviolet absorption spectrophotometry.

C) Infrared absorption spectrophotometry



D) It gives reaction of chlorides ion with $AgNO_3$ solution.

STORAGE

In an airtight container, protected from light.

ASSAY

Principle of assay

Spectrophotometric assay at λ_{max} 254 nm taking 915 as the value of $A^{1\%}_{1\ cm}$.

Procedure

Carry out the following procedure protected from light. Triturate the powder of 10 tablets with 10 ml of absolute ethanol, add about 300 ml of 0.1M hydrochloric acid and shake for 15 minutes. Add sufficient 0.1M hydrochloric acid to produce 500 ml, filter, dilute a volume of the filtrate containing 5 mg of chlorpromazine hydrochloride to 100 ml with 0.1M hydrochloric acid and further dilute 10 ml to 100 ml with the same solvent. Measure the absorbance of the resulting solution at λ_{max} 254 nm. Calculate the content of $C_{17}H_{19}ClN_2S$, HCl taking 915 as the value of $A^{1\%}_{1\ cm}$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

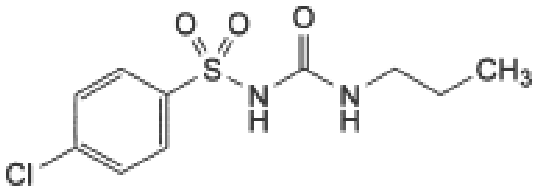
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Chlorpropamide Tablet **(BP 2007)**



$C_{10}H_{13}ClN_2O_3S$ **276.74**

Action and use

Oral hypoglycemic.

Preparation

Chlorpropamide Tablets

DEFINITION

Chlorpropamide contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of **1-[(4-chlorophenyl)sulphonyl]-3-propylurea.**

CHARACTERS

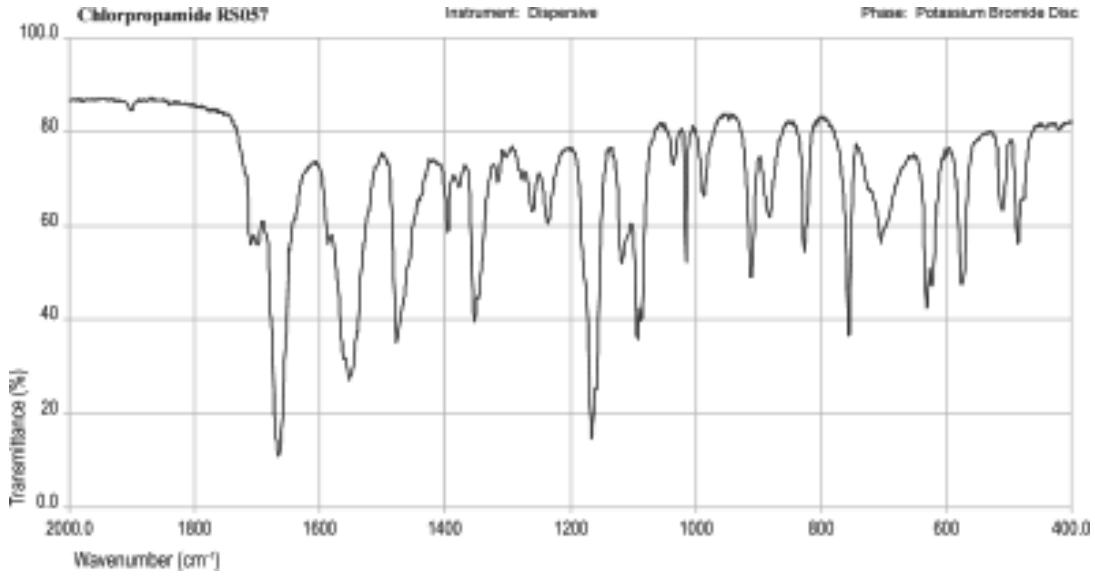
A white, crystalline powder, practically insoluble in water, freely soluble in acetone and in methylene chloride, soluble in alcohol.

IDENTIFICATION

A) Melting point: 126 °C to 130 °C.

B) Heat 0.1 g with 2 g of anhydrous sodium carbonate until a dull red color appears for 10 min. Allow to cool, extract the residue with about 5 ml of water, dilute to 10 ml with water and filter. The solution gives the reaction of chloride ion.

C) Infrared absorption spectrophotometry



STORAGE

Store protected from light.

ASSAY

Principle of Assay

Spectrophotometric assay at λ_{max} 232 nm taking 598 as the value of $A^{1\%}_{1\ cm}$.

Procedure

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.25 g of Chlorpropamide with 40 ml of *methanol* for 20 minutes, add sufficient *methanol* to produce 50 ml, mix, and filter and dilute 5 ml of the filtrate to 100 ml with 0.1M hydrochloric *acid*. Dilute 10 ml of this solution to 250 ml with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at λ_{max} 232 nm.

Calculate the content of $C_{10}H_{13}ClN_2O_3S$ taking 598 as the value of $A^{1\%}_{1\ cm}$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title: Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

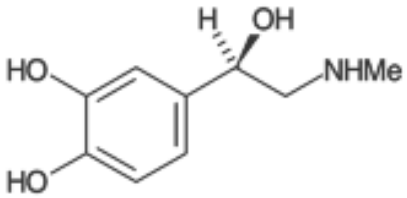
3- Results of Analyses:

	Exper. 1	Exper. 2	Exper. 3
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Epinephrine powder (USP 2007)



$C_9H_{13}NO_3$ **183.2**

Action and use

β-adrenoceptor agonist; used in treatment of glaucoma.

Preparations

Adrenaline Eye Drops (0.1% w/v of Adrenaline)

Dilute Adrenaline Injection (1 in 10,000)

DEFINITION

Adrenaline contains not less than 98.5% and not more than the equivalent of 101.0% of **(R)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol**.

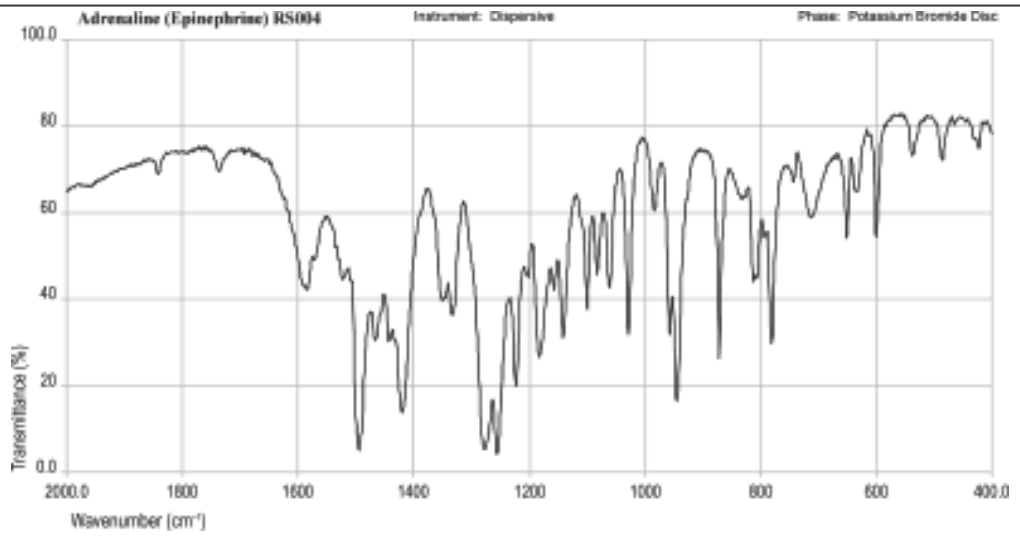
CHARACTERISTICS

A white or creamy white, sphero-crystalline powder. It darkens in color on exposure to air and light. Sparingly soluble in water, practically insoluble in ethanol (96%) and in ether. It dissolves in solutions of mineral acids, potassium hydroxide and sodium hydroxide, but not in solutions of ammonia or of the alkali carbonates.

It is not stable in neutral or alkaline solutions, which rapidly become red on exposure to air.

IDENTIFICATION

A) The infrared absorption spectrum



B. Specific optical rotation (in 1M hydrochloric acid),

The specific rotation is -50 to -53, calculated with reference to the dried substance.

STORAGE

Adrenaline should be kept in a well-closed container, which is preferably filled with nitrogen, and protected from light.

ASSAY

Principle

Non-aqueous titration, using perchloric acid in glacial acetic acid as a titrant & crystal violet solution as indicator.

Procedure

Take 0.2 gm of epinephrine in about 10mL glacial acetic acid and titrate against 0.1M perchloric acid and using crystal violet solution as indicator. Each ml of 0.1M perchloric acid VS is equivalent to 18.32 mg of $C_9H_{13}NO_3$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

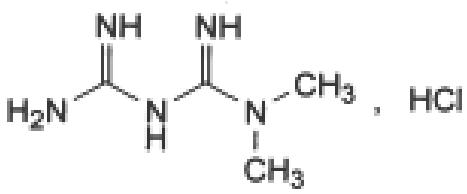
Sample specification
1- Laboratory Content: ……
2- Sample weight (or volume): ……
3- Drug content
……
……
3- Results of Analyses: ……

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Metformin hydrochloride Tablet (BP 2007)



$C_4H_{12}ClN_5$ **165.6**

Action and use

Oral hypoglycemic.

Preparation

Metformin Tablets

DEFINITION

Metformin hydrochloride contain not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of **1,1-dimethylbiguanide hydrochloride**.

CHARACTERS

White crystals, freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

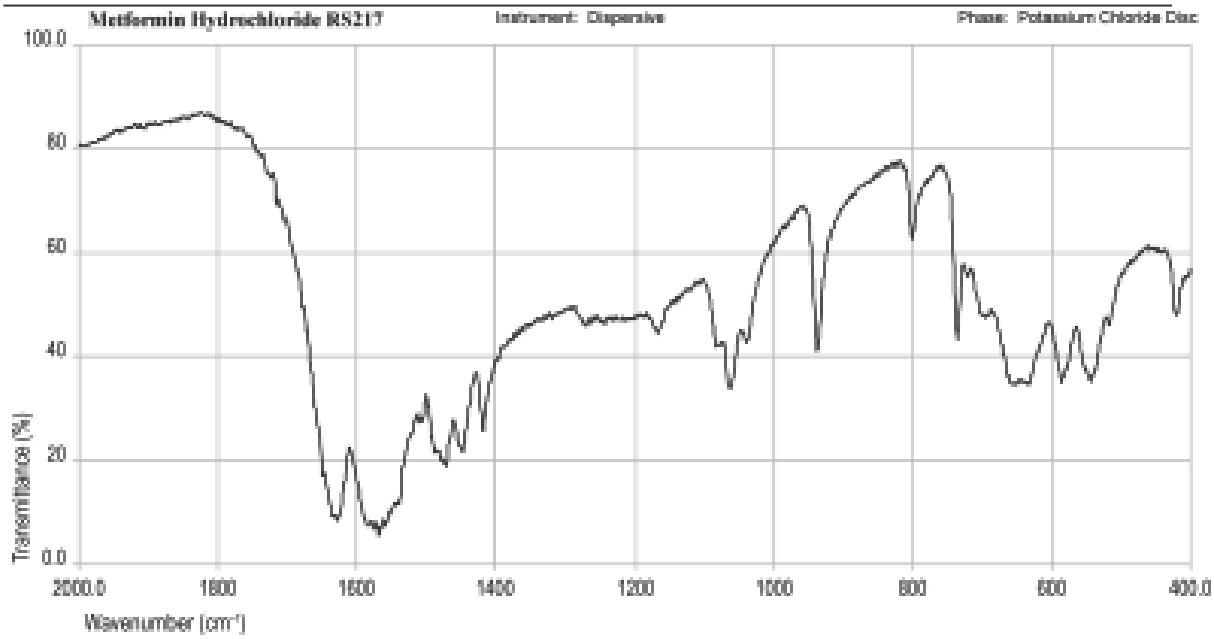
IDENTIFICATION

A) Melting point: 222 °C to 226 °C.

B) Infrared absorption spectrophotometry.

C. Thin-layer chromatography.

D) The solution gives reaction with $AgNo_3$ solution for chloride ion.



ASSAY

Principle of assay

Spectrophotometric assay at λ_{max} 232 nm taking 798 as the value of $A^{1\%}_{1\ cm}$.

Procedure

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Metformin hydrochloride with 70 ml of *water* for 15 minutes, dilute to 100 ml with *water* and filter, discarding the first 20 ml. Dilute 10 ml of the filtrate to 100 ml with *water* and dilute 10 ml of the resulting solution to 100 ml with *water* . Measure the *absorbance* of the resulting solution at λ_{max} 232 nm. Calculate the content of the $C_4H_{11}N_5$, HCl taking 798 as the value of $A^{1\%}_{1cm}$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

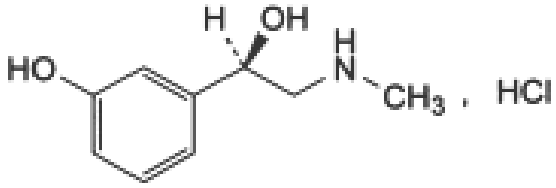
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Phenylephrine injection (USP 2007)



$C_9H_{13}NO_2$, HCl **203.7**

Action and use

Sympathomimetic.

Preparations

Phenylephrine Eye Drops

Phenylephrine Injection

DEFINITION

Phenylephrine hydrochloride contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of **(1*R*)-1-(3-hydroxyphenyl) -2-(methylamino)ethanol hydrochloride.**

CHARACTERS

A white or almost white, crystalline powder, freely soluble in water and in alcohol.

IDENTIFICATION

A) Melting point: 143 °C (free base 171 °C to 176 °C.)

B) Infrared absorption spectrophotometry

C) Dissolve about 10 mg in 1 ml of *water* and add 0.05 ml of a 125 g/l solution of *copper sulphate* and 1 ml of a 200 g/l solution of *sodium hydroxide*. A violet color is produced. Add 1 ml of *ether* and shake; the ether layer remains colorless.

D) It gives reaction of chloride ion with $AgNO_3$.

STORAGE

Phenylephrine Injection should be protected from light.

ASSAY

Principle of assay

Bromination of the phenolic moiety of the phenylephrine with standard bromine, and the excess bromine will liberate the iodine from 10% potassium iodide solution, that subsequently titrated against standard sodium thiosulfate in presence of starch as indicator

Procedure

In stoppered conical flask, talk a quantity solution containing 50 mg of Phenylephrine Hydrochloride. Add 25 ml 0.1N *bromine*, and 5ml *hydrochloric acid* and immediately insert the stoppered. Shake the flask and stand for 15 min. introduce quickly 10 ml of 10% potassium iodide solution and allow to stand for 5 min with thoroughly shake. Titrate the liberated iodine with 0.1 N sodium thiosulfate till straw yellow color. Add 3ml starch reagent and complete the titration till colorless. Each 1 ml of 0.1N *bromine* is equivalent to 3.395 mg $C_9H_{13}NO_2$.HCl

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

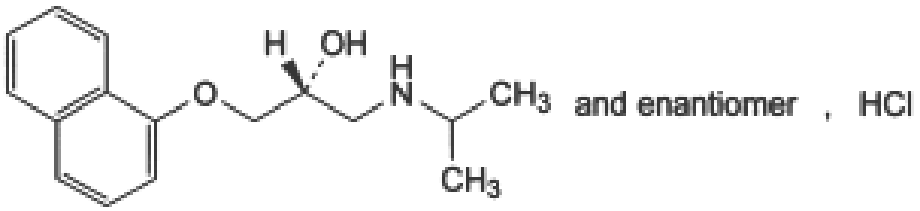
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Propranolol hydrochloride Tablet (BP 2007)



$C_{16}H_{21}NO_2$, HCl **295.8**

Action and use

Beta-adrenoceptor antagonist.

Preparations

Prolonged-release Propranolol Capsules

Propranolol Injection

Propranolol Tablets

DEFINITION

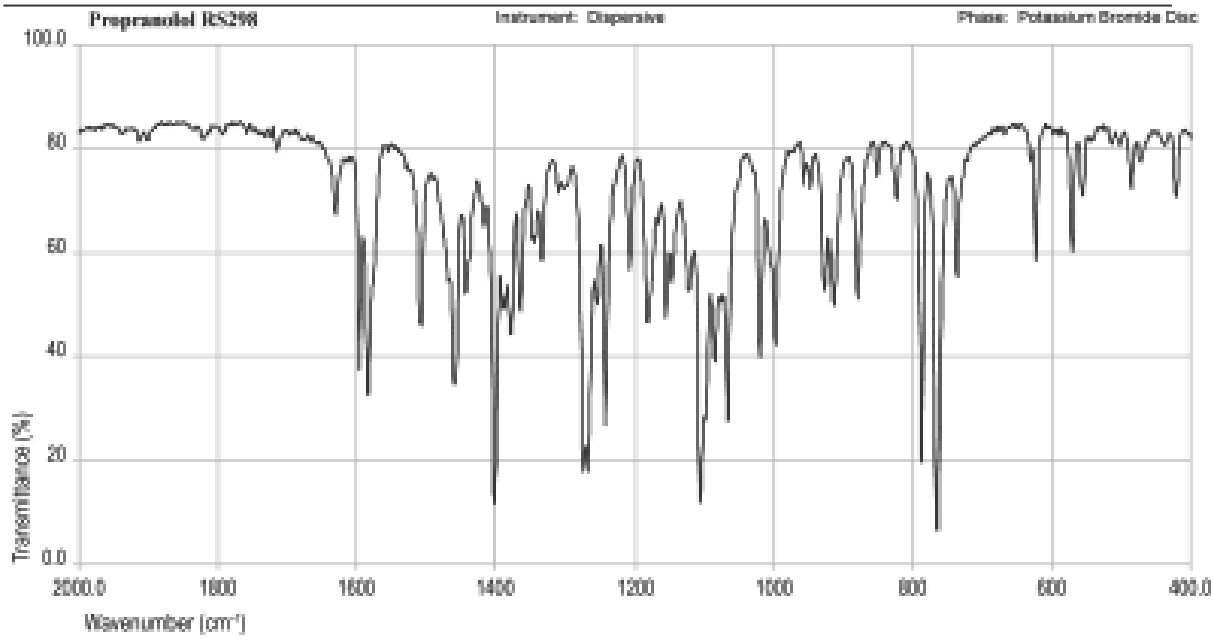
Propranolol hydrochloride contains not less than 99.0 per cent and not more than 101.0 per cent the equivalent of **(2RS)-1-[(1-methylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride**.

CHARACTERS

A white or almost white powder, soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A) Infrared absorption spectrophotometry.



B) Melting point: 163 °C to 166 °C (M.P. of Propranolol free base 94°).

C) Thin-layer chromatography.

d) It gives reaction of chloride with $AgNO_3$ solution.

ASSAY

Principle of assay:

Spectrophotometric assay at λ_{max} 290 nm taking 206 as the value of $A^{1\%}_{1\ cm}$.

Procedure:

Weigh and powder 20 tablets. Shake a quantity of the powder containing 20 mg of Propranolol Hydrochloride with 20 ml of water for 10 minutes. Add 50 ml of methanol, shake for a further 10 minutes, add sufficient methanol to produce 100 ml and filter. Dilute 10 ml of the filtrate to 50 ml with methanol and measure the absorbance of the resulting solution at λ_{max} 290 nm. Calculate the content of $C_{16}H_{21}NO_2$, HCl taking 206 as the value of $A^{1\%}_{1\ cm}$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

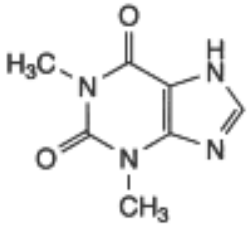
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Theophylline powder (BP 2007)



$C_7H_8N_4O_2$ **180.2**

Action and use

Xanthine bronchodilator.

Preparations

Aminophylline Injection

Prolonged-release Theophylline Tablets

DEFINITION

Theophylline contain not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of **1,3-Dimethyl-3,7-dihydro-1H-purine-2,6-dione.**

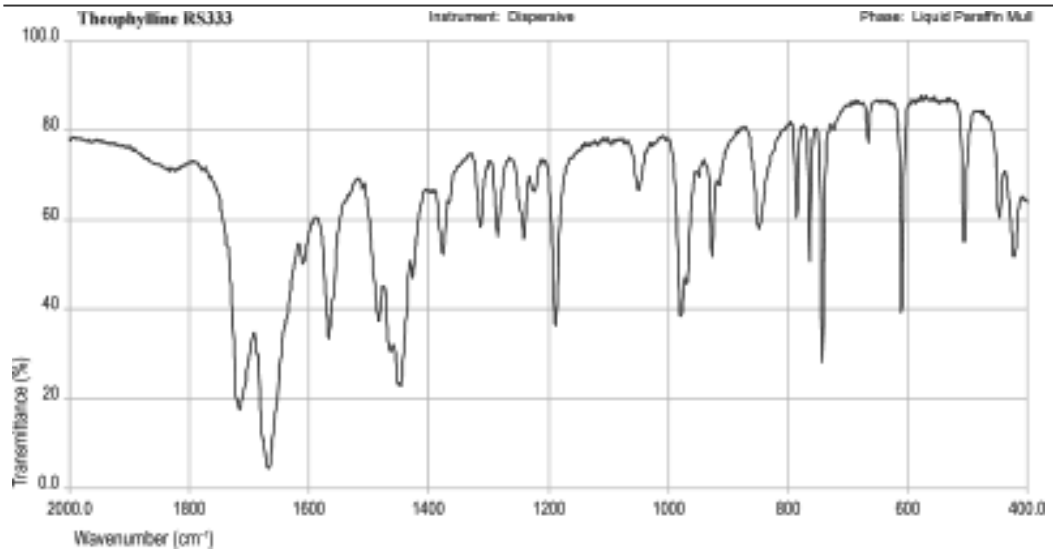
CHARACTERS

White, crystalline powder. Slightly soluble in water, sparingly soluble in ethanol. It dissolves in solutions of alkali hydroxides, in ammonia and in mineral acids.

IDENTIFICATION

A. Melting point: 270 °C to 274 °C.

B. Infrared absorption spectrophotometry



C. Heat 10 mg with 1.0 ml of a 360 g/l solution of potassium hydroxide in a water-bath at 90 °C for 3 min, then add 1.0 ml of diazotized sulphanilic acid solution. A red color slowly develops

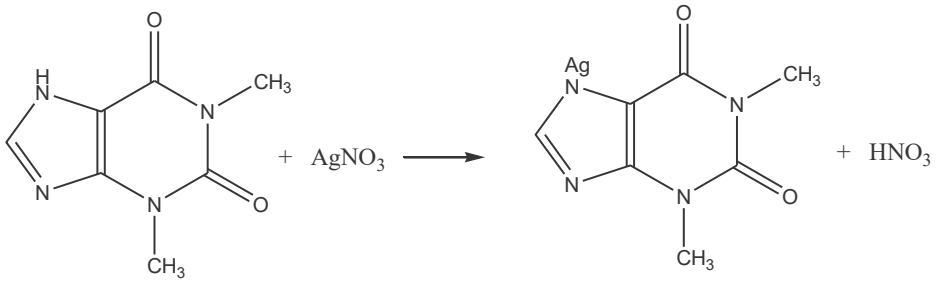
D. It gives the reaction of xanthines.

To a few milligrams powder add 0.1 ml of strong hydrogen peroxide solution and 0.3 ml of dilute hydrochloric acid. Heat to dryness on a water-bath until a yellowish-red residue is obtained. Add 0.1 ml of dilute ammonia. The color of the residue changes to violet-red.

ASSAY

Principle of assay:

Depend on, theophylline reacts with silver nitrate solution to offered HNO_3 that can be titrated against 0.1 M NaOH in presence of bromothymol blue solution as indicator



Theophylline

Procedure

Dissolve 0.150 g in 100 ml of water, add 20 ml of 0.1 M silver nitrate and shake. Add 1 ml of bromothymol blue solution. Titrate with 0.1 M sodium hydroxide.

Each 1 ml of 0.1 M sodium hydroxide is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

Assay of Aminophylline Injection

For Theophylline

To a volume containing the equivalent of 0.1 g of aminophylline add sufficient 0.01M sodium hydroxide to produce 250 ml, dilute 5 ml to 250 ml with 0.01M sodium hydroxide and measure the absorbance of the resulting solution at the maximum at 275 nm. Calculate the content of $C_7H_8N_4O_2$ taking 650 as the value of A (1%, 1 cm) at the maximum at 275 nm.

For ethylenediamine

To a volume containing the equivalent of 0.5 g of aminophylline add sufficient water to produce 20 ml and titrate with 0.05M sulphuric acid VS, using bromocresol green solution as indicator, until the color changes from blue to green. Each ml of 0.05M sulphuric acid VS is equivalent to 3.005 mg of $C_2H_8N_2$. Calculate the weight of $C_2H_8N_2$ present for each g of $C_7H_8N_4O_2$ found.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

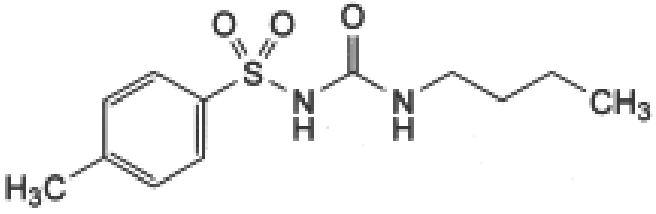
3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……

Assay of Tolbutamide tablet (BP 2007)



$C_{12}H_{18}N_2O_3S$ **270.3**

Action and use

Oral hypoglycemic.

Preparation

Tolbutamide Tablets

DEFINITION

Tolbutamide contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of **1-butyl-3-[(4-methylphenyl) sulphonyl]urea**.

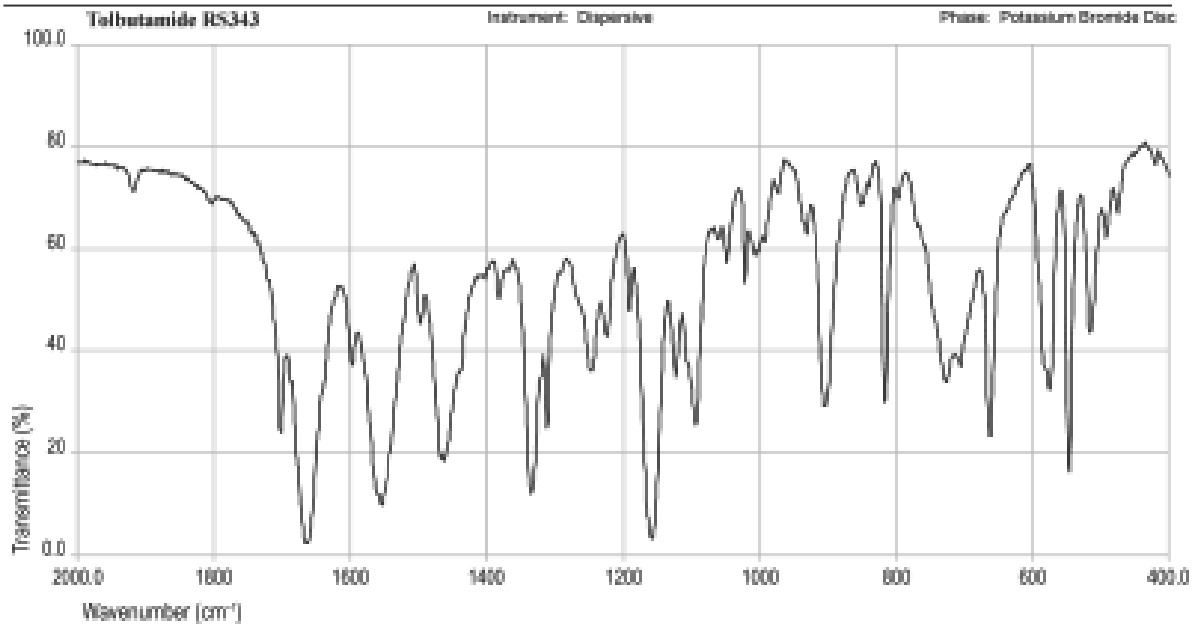
CHARACTERS

A white, crystalline powder, practically insoluble in water, soluble in acetone and in alcohol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Melting point (2.2.14): 126 °C to 130 °C.

B. Infrared absorption spectrophotometry.



C. To 0.2 g powder add 8 ml of a 50% aqueous sulfuric acid (*W/V*), heat under a reflux condenser for 30 min, and allow to cool. Crystals are formed which, after recrystallisation from hot water and drying at 100 °C to 105 °C, melt at 135 °C to 140 °C.

ASSAY

Principle of assay

Acid-base titration against standard alkali in presence of phenolphthalein as indicator, depend on the acidity of NH urea group adjacent to the 4-toluenesulfonyl moiety.

Procedure:

Weigh and powder 20 tablets. To a quantity of the powder containing 0.5 g of tolbutamide add 50 ml of ethanol (96%) previously neutralized to phenolphthalein, warm to dissolve, add 25 ml of water and titrate with 0.1M sodium hydroxide VS using phenolphthalein solution as indicator. Each ml of 0.1M sodium hydroxide VS is equivalent to 27.03 mg of $C_{12}H_{18}N_2O_3S$.

Menoufia University
Faculty of Pharmacy
Pharm. Chem. Dep. **3rd year**

Section No.:

Title Assay of ……

Sample specification
1- Sample weight (or volume): ……
2- Laboratory Content:
……
……
……
……

3- Results of Analyses:

	Exper. 1	**Exper. 2**	**Exper. 3**
End point (or absorbance)			

Calculation:

……
……
……
……
……
……
……
……
……
……
……
……
……
……
……