Mechanism of action:-

Adrenergic Antagonists

UNIT-2 (Unit Topic 1)

-> Adrenergic antagonists, anti adrenergic agents, also called adrenergic blocking agents.

-> These are also called sympathoplytics.

-> These drugs are selectively inhibit certain responses of sympathetic stimulation or block the effects of produced by sympathomimetic agents.

->The antiadrenergic effect can be obtained by drugs with different modes and sites of action.

-> Adrenergic blocking agents refer to those drugs that reduce delivery of catechol amines to the adrenergic receptors by disrupting the CAs synthesis, storage & release.

-> These agents competitively antagonize the effect of the catecholamines at 'α' and or 'β' adrenergic receptors.

Classification of Adrenergic antagonists.

- **Alpha receptor antagonists**
  - non selective
    - phenoxy benzamine
    - phentolamine
  - α_1 selative
    - prazocine
    - terazocine
    - doxazocin
    - alfuzocin
    - tamsulosin
    - Sindoramin
  - α_2 selective
    - yohimbine
- **Beta receptor antagonists**
  - Non-selective
    - fist gen
    - nadalol
    - pindolol
    - propranolol
    - penbotalol
  - β_1 selective
    - 2nd gen
    - acebutolol
    - atenolol
    - bisoprolol
    - esmolol
    - metaprolol
  - nonselecti
    - 3rd
    - carteolol
    - carvedilol
    - bucindolol
    - labetolol
  - β_1
    - 3rd
    - betaxo
    - nebiv

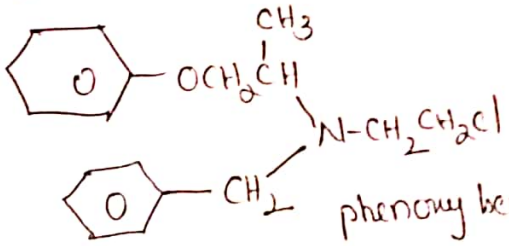
Classification:-

1. Adrenergic Alpha-Adrenoceptor Antagonists.

The drugs antagonises the effects produced by the drugs acting on α-receptors.

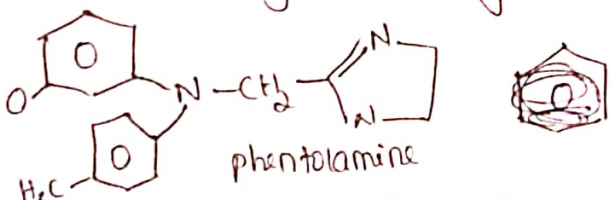
i) Non selective α-receptor antagonists.

a) Haloalkyl amines —eg: phenoxy benzamine.

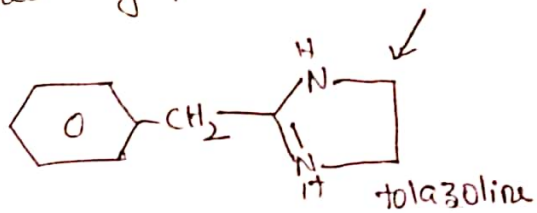


phenoxy benzamine.

b) Other types, including Imidazolines— eg: phentolamine, tolazoline

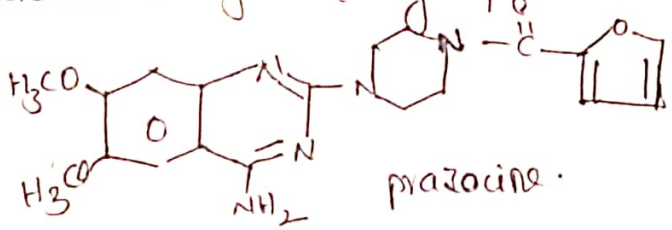


phentolamine



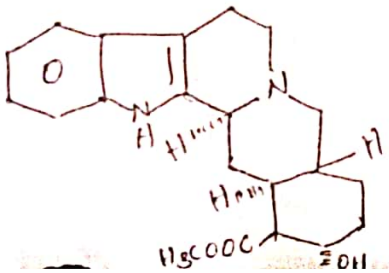
tolazoline

ii) α_1- Selective antagonists - eg: prazocin.



prazocine.

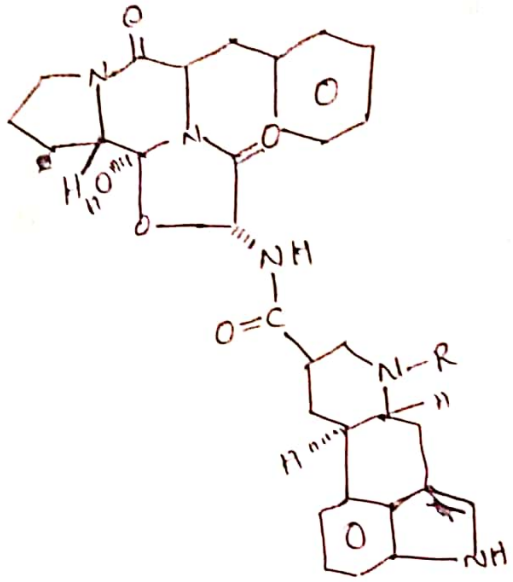
iii) α_2 - selective antagonists - eg: yohimbine, idazoxan.



yohimbine.

Mechanism of action:-

iv) Ergot alkaloids:- Eg: Dihydroergotamine, methylsergide.



11. Beta adrenergic blockers:-

These inhibit the actions of catecholamines at the β-adrenergic receptors competetively.

classified into 2 main types.

i) Aryloxy propylamines : eg: propranalol, Nadolol, metaprolol.

ii) Aryl ethanol amines: Eg Isoproterenol, pronethalol.

a) The first generation β-blockers are non selective, they block both β_1 & β_2 eg: propranolol, Timolol pindolol.

b) The second generation β-blockers are cardio selective that they are selective for β_1 adreno receptor Eg: Atenolol, Acebutalol, metaprolol, Esmolol.

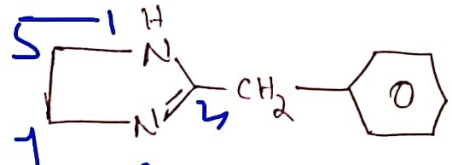
c. The second generation β-blockers are mixed α_1/β_1 blockers. They are used as vasodilators. Eg: clonidine, guanabenz.

Alpha adrenergic blocking agents:-

effects - Reduced blood pressure, causes nasal congestion.
enhances venous capacitance.
produces miosis and interference with ejaculation.
Red secretion of renin, tachycardia palpitations.

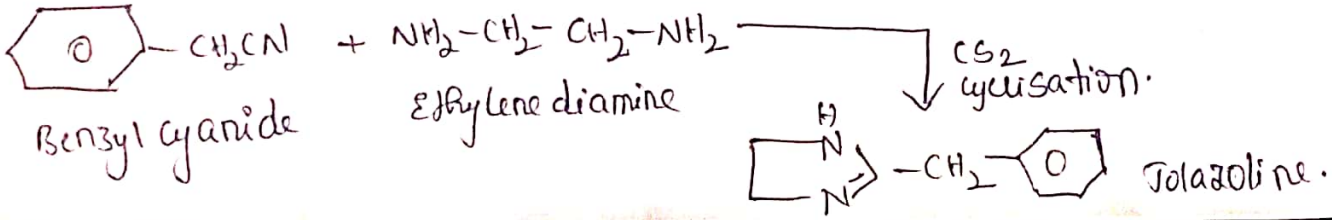
1) Tolazoline *
2) phentolamine
3) phenoxybenzamine
4) prazocin
5) Dihydroergotamine
6) Methysergide.

① Tolazoline:-



4,5-dihydro-2-(phenylmethyl)-1H-imidazole.

Synthesis:-



Benzyl cyanide
Ethylene diamine
Tolazoline.

mechanism of action:-

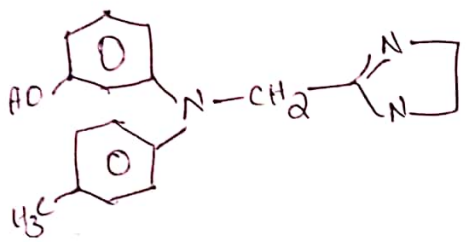
-> It is a competetive inhibitor of α-receptor.

-> Its structure is similar to that of α-agonist so, it bind reversibly with the α-receptor (in place of α-agonist) and blocks the effects of α-receptors.

Uses:-

1. It is used in persistent pulmonary hypertension of new bond when supportive measures are not successful.
2. It has histamine like effect and causes stimulation of the gastric acid secretion.
3. It is mainly used as a vasodilator with direct vasodilator action.
4. It is also used to antagonize the overdoses of clonidine.

2 phentolamine:-



3-[N-(2-Imidazolin-2ylmethyl)-4-toluidino]phenol.

Mechanism of action:-

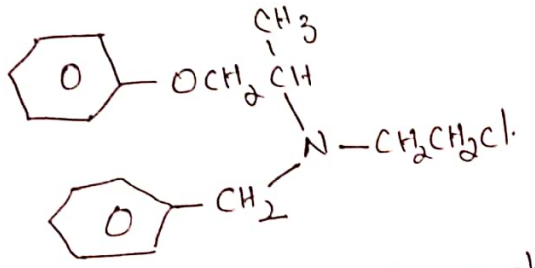
-> It is a competetive α-adrenergic antagonist and has similar affinity for both α_1 & α_2-receptors.

Uses:-

① It is used to control hypertensive conditions in patients with pheocytochroma.

② It is also used as a vasodilatory as it inhibits vaso constriction caused by catecholamines.

3. phenoxybenzamine:-



(RS) - Benzyl (2-chloroethyl) (1-methyl-2-phenoxyethyl)amine.

Mechanism of action:-

-> It is an irreversible α-blocker and blocks both α_1 & α_2-receptors

It gets covalently conjugated with α-receptors.

uses:-

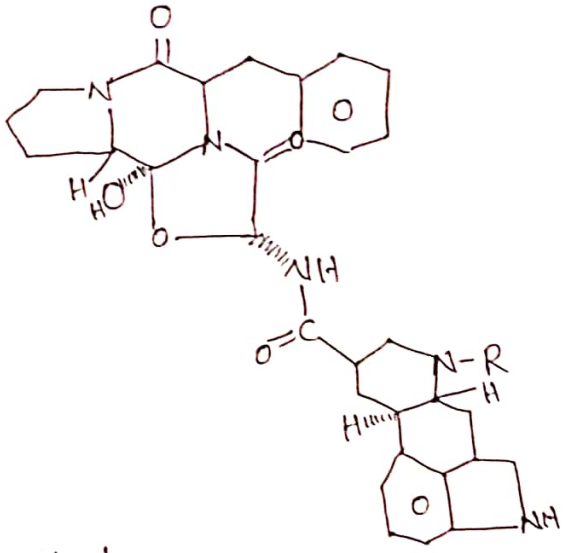
1. It is used in the treatment of hypertension caused by pheochromocytoma
2. It is used in urinary retention.
3. used in the treatment of peripheral vascular disease like Raynoud's syndrome.

Ergot Alkaloids :-

-> These are the amide der. of lysergic acid.

-> These are antagonist of adrenergic, tryptaminergic and dopaminergic receptors.

Dihydroergotamine :-



(5'α)-9,10-dihydro-12-hydroxy-2'-methyl-5'-(phenylmethyl)-ergotaman-3,6,18 trione.

Mechanism of action :-

-> It is an antagonist of α adrenergic receptors.

Uses :- 1) It is used in the treatment of migraine.

2) also used in treatment of medication overdose headache.

3) It is used in combination with heparin in prophylaxis of post-operative deep vein thrombosis.

4) It is also used as a vasoconstrictor.

Uses:—

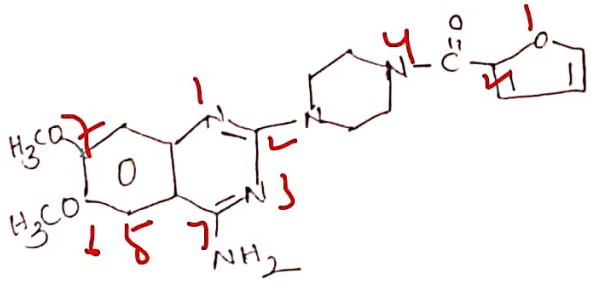
1. It is used to control hypertensive conditions in patients with pheochromocytoma
2. It is also used as vasodilatory as it inhibits vasoconstriction caused by catecholamines.

(b) α_1 - Selective antagonist :—

Prazosin belongs to a class of piperizinyl quinazolines, a selective α_1- adrenergic antagonist.

It has affinity for α_1- receptors which is 1000 times more than that for α_2- receptors.

Prazosin :—



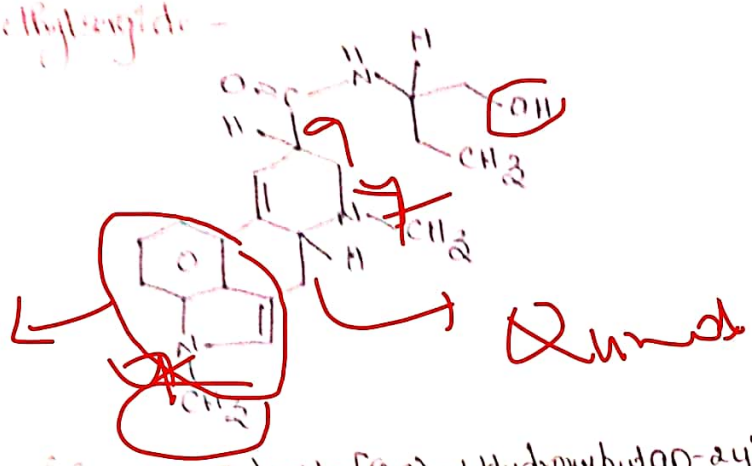
2-[4-(2-Furoyl)piperazin-1-yl]-6,7-dimethoxy-quinazolin-4-ylamine.

Mechanism of action :—

-> α_1- adrenergic antagonist

Uses :— 1) used in management of hypertension.
2) used in treatment of heart failure.
3) used in " " Raynaud's syndrome.
4) It is used as an adjunct in the symptomatic treatment of urinary obstruction caused prostatic hypertrophy.

Methylergotide -



(6aR,9R)-N-[(2S)-1-Hydroxybutan-2-yl]-4,7-dimethyl-6,6a,8,9-tetrahydroindolo[4,3-fg]quinoline-9-carboxamide.

Mechanism of action:-

--> It is an antagonist of α-adrenergic receptors. It is a potent Serotonin antagonist.

Uses:-

1. It is used as a prophylactic in the treatment of severe recurrent migraine.
2. It has weak vasoconstrictive and oxytocic effects.

β-adrenergic blockers

Beta (β) blockers are competetive inhibitors of the effects produced by catecholamines at β-receptor site.

The β adrenergic blockers can be classified as -

1) β_1 selective
2) β_2 selective
3) Non selective (Blocks with β_1 & β_2).

Drugs:-

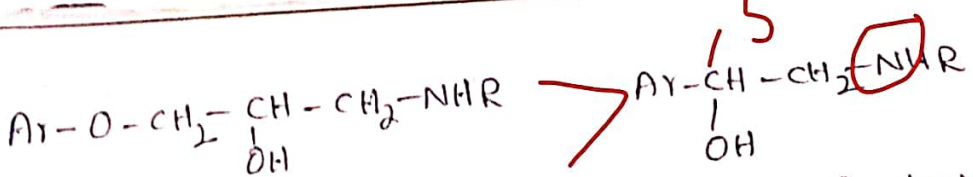
propranolol *
Metibranolol
Atenolol
Betazolol
Bisoprolol
metoprolol
Labetolol
Carvedilol.

SAR of β-blockers:-

-> β blockers are structurally similar to β-agonist. The catechol ring can be replaced by a variety of ring system without loss of antagonistic activity.

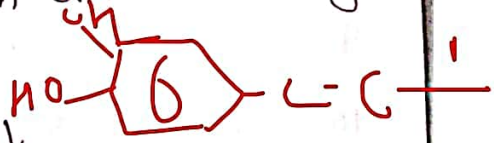
-> Aryl oxy propanol amines are more potent β-blockers than aryl ethanol amine

-> Most of the currently clinically used β-blockers are aryl oxy propanol amine derivatives.



Aryloxy Ethanolamines.

1. Replacement of catechol hydroxyl group with chlorine or phenyl ring system retains β-blocking activity



eg: pronethalol, dichloro isoproterenol.

2. N,N- Disubstitution decreases β-blocking activity. Activity is maintained when phenyl ethyl, hydroxy phenyl ethyl or methoxy phenyl ethyl groups are added to amine as a part of the molecule.

3. The two carbon chain is essential for activity.

4. Introduction of $-OCH_2-$ group into the molecule b/n the aromatic ring and the ethylamine side chain provides β-blocking agents

eg: propranalol.

5. Nitrogen atom should be 2° amine for optimum β-blocking activity.

6. β-blockers exhibits a high degree of stereoselectivity in the production of their β-blocking effect, the carbon side chain bearing hydroxyl group must be (S) configuration for optimal affinity to the β-receptor

eg: Levobunolol, Timolol.

07 W

7> Replacement of ethereal oxygen in aryl oxy propanol amine with S, CH_2 or $-N-CH_3$ ↓es the β-blocking activity.

8. Most effective substitution at amino group of the aryl oxy propanol amine β blockers is tert-butyl or isopropyl group.

9. N methyl group at side chain ↓es the activity.

10. The activity ↓es if aromatic portion is converted to phenanthrene or Anthracene ring.

Classification of β-blockers.

2 main types.

1) Aryloxy propyl amines Eg: propranolol, Nadolol, practolol, metaprolol.

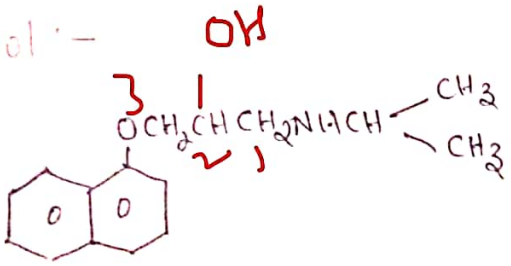
2) Aryl ethanol amines Eg: isoproterenol, Dichloro isoproterenol, pronethalol.

1st gen:- (non selective) → Eg: propranalol, timolol, pindolol.

2nd gen:- (cardio selective) → Eg: Atenolol, Acebutolol, metoprolol, esmolol.

2nd gen:- mixed (α_1/β_1) → Eg: clonidine, Guanabenz.

Propranolol :-



(RS) - 1- isopropylamino - 3- (1-naphthyloxy) propan-2-ol

Mechanism of action:-

-> It is a non-cardioselective β-adrenergic blocker.

-> It has some membrane stabilizing properties.

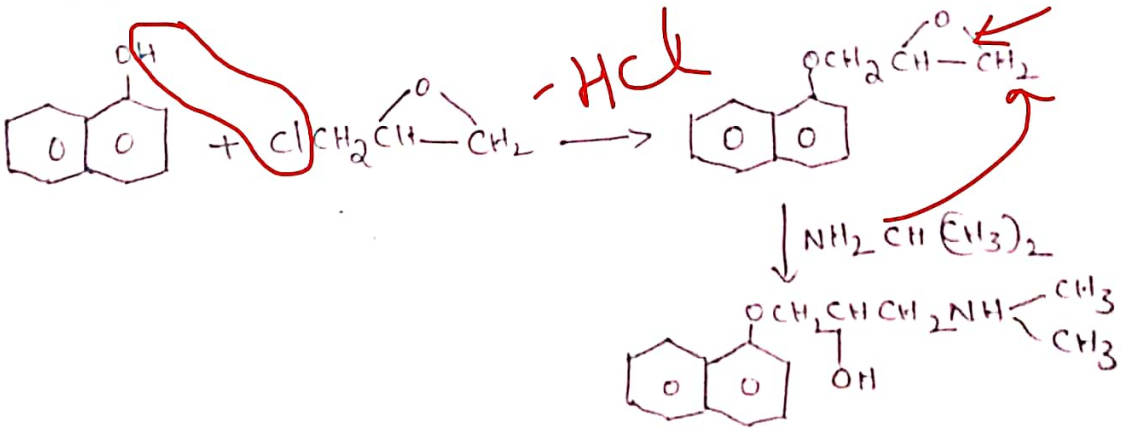
-> Its mop due to

a) Red renin release

b) Reduced cardiac out put

c) Red peripheral resistance.

Synthesis:-



propranolol.

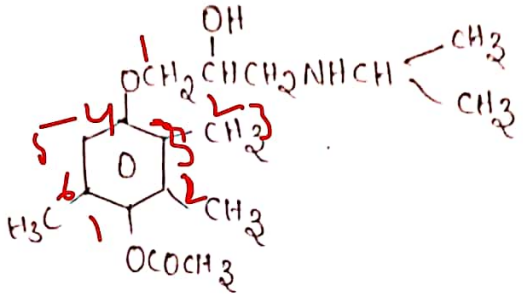
Uses:-

-> It is used in the treatment of hypertension.

-> It is used for the prevention of re-infraction in patients with acute myocardial infraction.

-> It is used in the treatment of coordiac arrhythmia.

2. Metipranolol :-



(RS) -4-(2-Hydroxy-3-isopropylaminopropoxy)-2,3,6-trimethyl phenylacetate.

Mechanism of action:-

-> It is a non-cardio selective beta blocker.

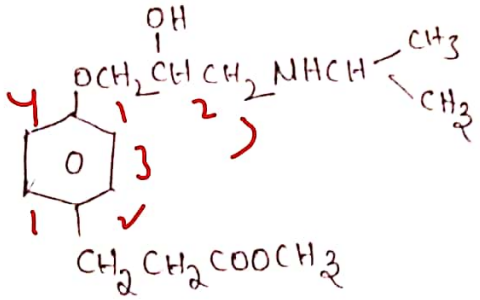
-> It lacks intrinsic sympathomimetic activity & membrane stabilising properties.

Uses:-

-> It is used in eye drops in the treatment of glaucoma.

-> It works by decreasing the pressure in the eye.

3 Atenolol :-



(RS) -4(-2-hydroxy-3-isopropylamino propoxy)-phenyl acetamide.

Mechanism of action:-

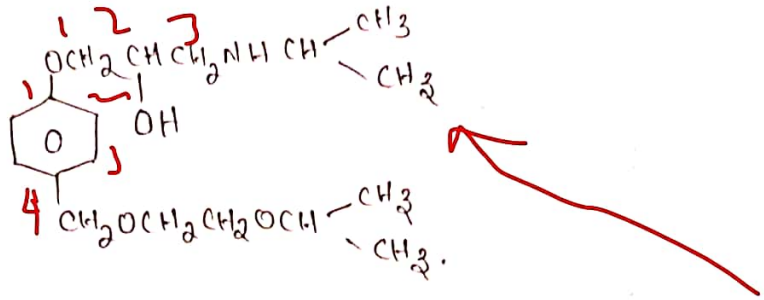
-> Atenolol is β_1-selective antagonist. It lacks intrinsic sympathomimetic activity and membrane stabilising properties.

Uses:-

-> It is used in the management of hypertension and angina pectoris.

-> It is also given in the emergency treatment of cardiac arrhythmias.

4. ~~Bisoprolol~~:- Bisoprolol:-



(RS) -1-{4-[2-isopropoxymethoxy)methyl]phenoxy}-3-(isopropylamino) propan-2-ol.

Mechanism of action:-

-> It is β-selective adrenergic blocker and lacks intrinsic sympathomimetic activity and membrane stabilizing prop's.

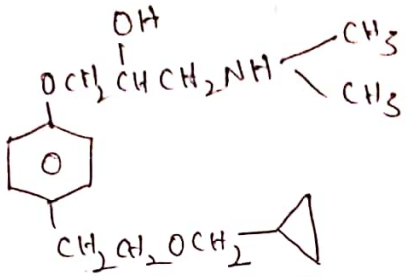
Uses:-

-> It is useful in the treatment of high blood pressure.

-> Also used in the management of cardiac ischaemia i.e reduced blood flow to the heart.

-> It is used to reduce the activity of the heart muscle, so reduces oxygen and nutrient demand.

5) Betaxalol :-



(RS) -1[4-{2-cyclopropyl ethoxy) ethyl} phenoxy]-3-[(1-methyl ethyl) amino] propan-2-ol.

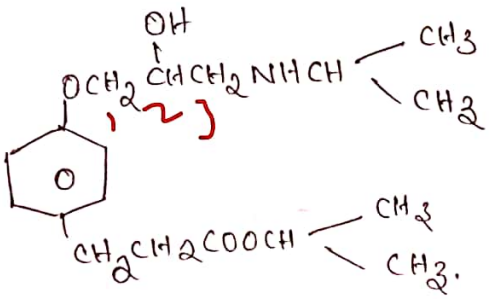
mechanism of action :-

-> It is cardioselective β_1-blocker and lacks intrinsic sympatho mimetic activity but has some membrane stabilising activity.

Uses :-

1. It is used in the treatment of hypertension.
2. As eye drops it is used in the management of glaucoma.
3. It act as a neuroprotector in glaucoma treatment.

6). Esmolol-



Methyl- 3-[4-[2-hydroxy 3-propan-2-ylamino) propoxyl] phenyl propanoate.

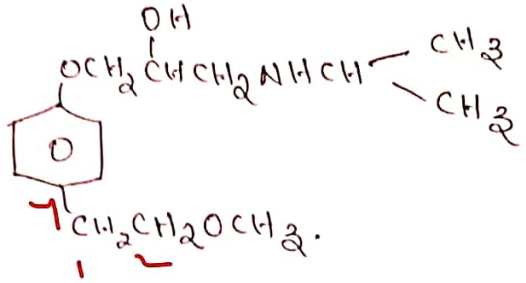
Mechanism of action:-

--> It is a selective β_1- blocker and lacks intrinsic sympathomimetic and membrane stabilizing activity.

Uses:-

- It is used in supraventricular tachycardia.
- In the management of atrial fibrillation.
- In the treatment of high bp during and after cardiac surgery.
- It is also used in the early treatment of myocardial infraction.

7 Metoprolol:-



(Rs) -1- Isopropylamino- 3-[4-2-methoxyethyl) phenoxy] - propan-2-ol.

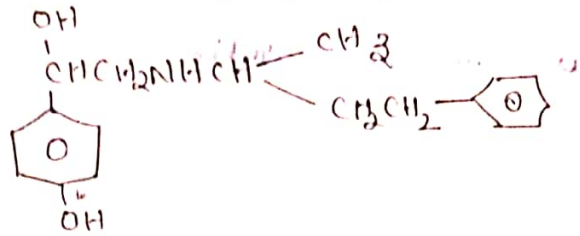
Mechanism of action:-

--> It is a selective β_1- adrenergic antagonist and lacks intrinsic sympathomimetic activity. It has little & no membrane stabilising activity.

Uses:- It is used orally in the treatment of hypertension.

- It is also used in the management of cardiac arythmia & angino pectoris.
- used in acute M.I.
- used in treatment of heart failure.
- Used as a adjunct in the treatment of hyperthyroidism.

8) Labetalol :-



(RS) -2-Hydroxy-5-[1-hydroxy-2-(1-methyl-3-phenyl propylamino) ethyl] benzamide.

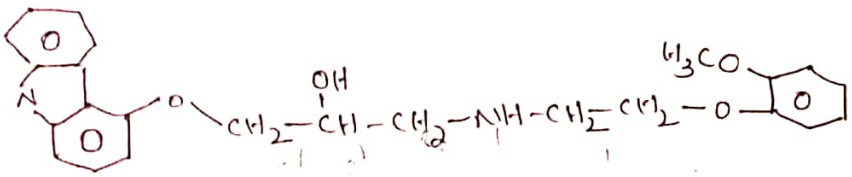
mechanism of action :-

- non selective (cardio) β-blocker and acts as a competitive blocker on both α_1 & β-receptors.
- Being α_1-blockers it decreases peripheral vasular resistance

Uses :-

1. It is given orally in the treatment of hypertension.
2. mainly used in the treatment of pregnancy-induced hypertension.
3. It is given intravenously in severe hypertension.

9) Carvedilol :



-[3(9H-carbazol-4yloxy)-2-hydroxypropyl][2-(2-methoxy-phenoxy)ethyl]amine.

mechanism of action :-

non-selective β-blocker

It acts on both α_1 & β blocker.

Due to α_1-blockage it relaxes blood vessels, dilates them and lower b.p.

Uses :- used in congestive heart failure.

- used in hypertension & reduces risk of mortality.
- It is used alone / in combination with other anti-hypertensive drugs.