Semester-IV

Sub Name-medicinal chemistry-I (sub code-BP-402T)

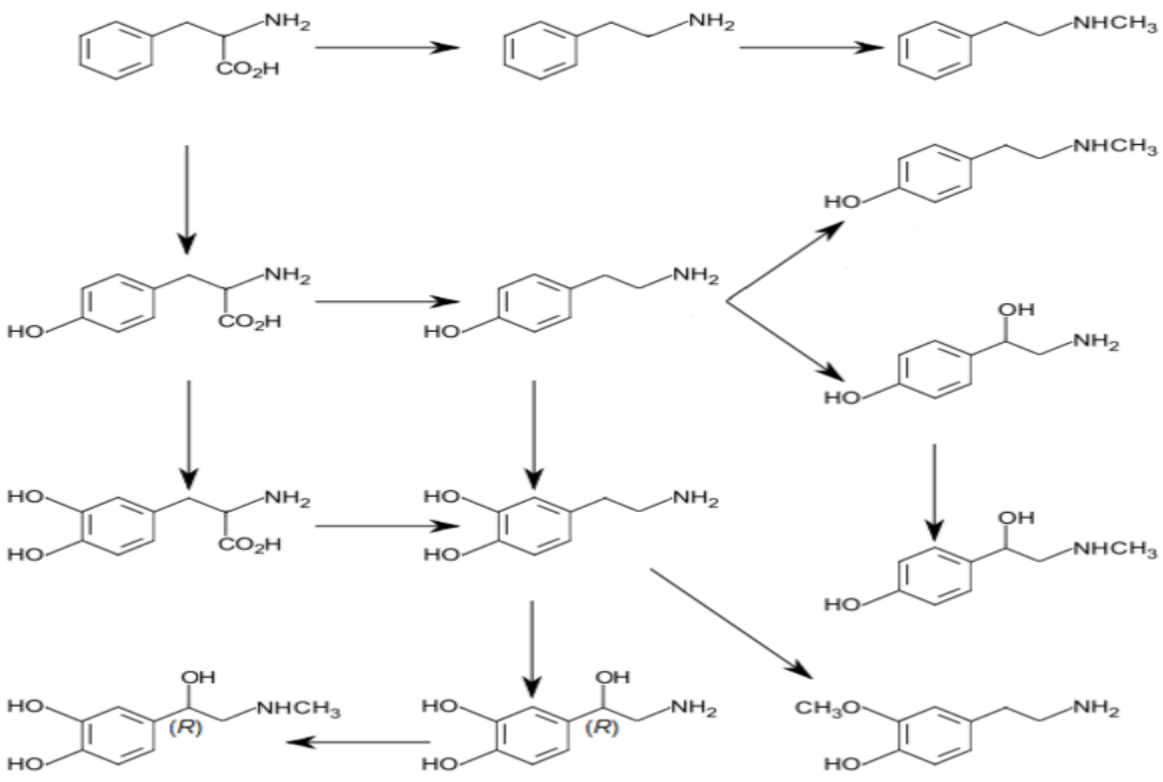
Objective

Drugs acting on Autonomic Nervous System
 Adrenergic Neurotransmitters: Biosynthesis and catabolism of catecholamine.
 Adrenergic receptors (Alpha and Beta) and their distribution.

Adrenergic Neurotransmitters

An adrenergic nerve fiber is a neuron for which the neurotransmitter is either adrenaline (epinephrine), noradrenaline or dopamine. These neurotransmitters are released at a location known as the synapse, which is a junction point between the axon of one nerve cell and the dendrite of another.

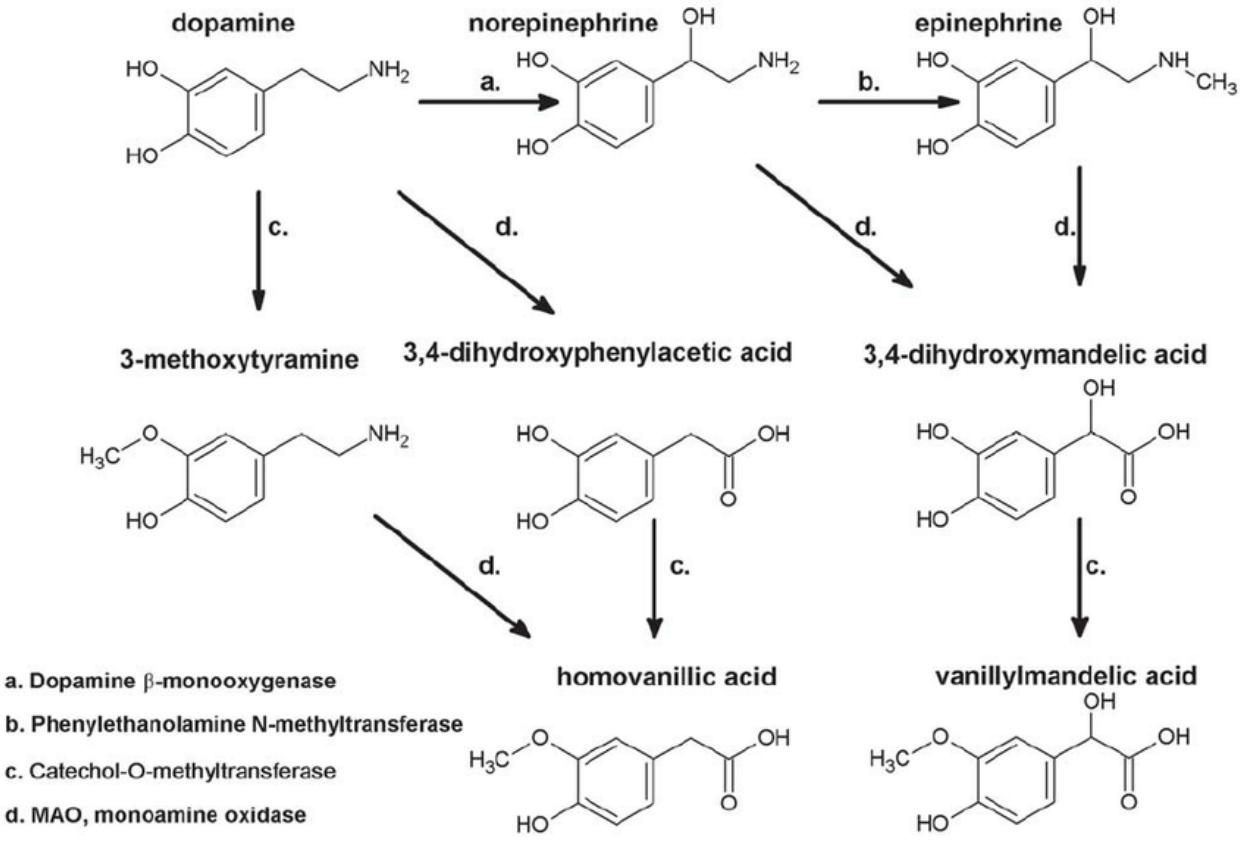
Biosynthesis of catecholamine



L-Phenylalanine is converted into L-tyrosine by an aromatic amino acid hydroxylase (AAAH) enzyme (phenylalanine 4-hydroxylase), with molecular oxygen (O_2) and tetrahydrobiopterin as cofactors. L-Tyrosine is converted into L-DOPA by another AAAH enzyme (tyrosine 3-hydroxylase) with tetrahydrobiopterin, O_2, and ferrous iron (Fe^{2+}) as

cofactors. L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC), with pyridoxal phosphate as the cofactor. Dopamine itself is also used as precursor in the synthesis of the neurotransmitters nor epinephrine and epinephrine. Dopamine is converted into nor epinephrine by the enzyme dopamine β-hydroxylase (DBH), with O_2 and L-ascorbic acid as cofactors. Nor epinephrine is converted into epinephrine by the enzyme phenyl ethanolamine *N*-methyltransferase (PNMT) with *S*-adenosyl-L-methionine as the cofactor.

Catabolism of catecholamine



Adrenergic receptors (Alpha and Beta) and their distribution

The **adrenergic receptors** or **adrenoceptors** are a class of G protein-coupled receptors that are targets of many catecholamines like norepinephrine (noradrenaline) and epinephrine (adrenaline) produced by the body, but also many medications like beta blockers, β_2 agonists and α_2 agonists, which are used to treat high blood pressure and asthma, for example.

Many cells have these receptors, and the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system (SNS). The SNS is responsible for the fight-or-flight response, which is triggered by experiences such as exercise or fear-causing situations.

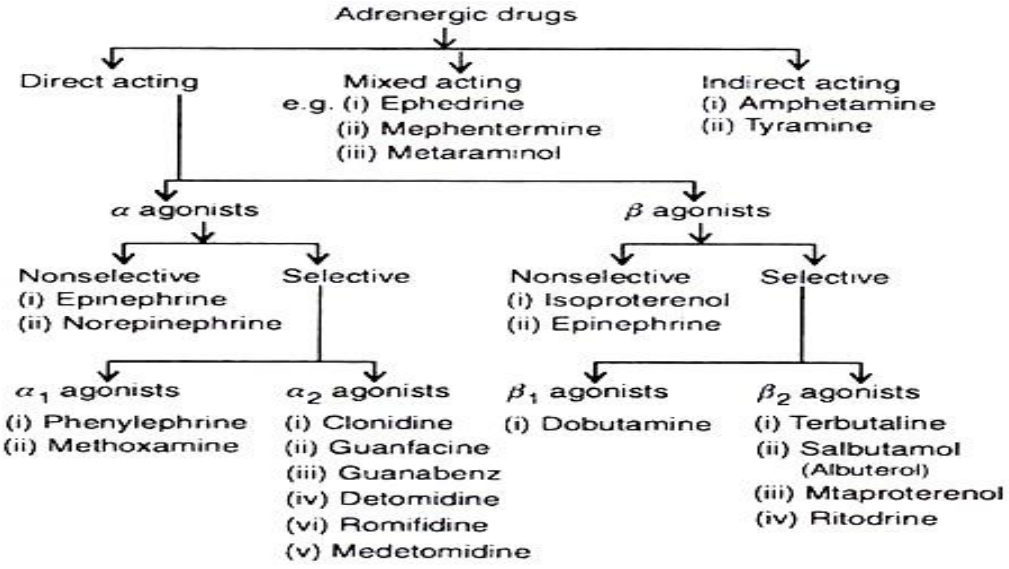
This response dilates pupils, increases heart rate, mobilizes energy, and diverts blood flow from non-essential organs to skeletal muscle. These effects together tend to increase physical performance momentarily.

RECEPTOR NAME	TYPICAL LOCATIONS
α1	Vascular smooth muscle, visceral smooth muscle, radial smooth muscle of iris, CNS neurons
α2	Some presynaptic terminals, pancreatic islets, platelets, ciliary epithelium, smooth muscles, CNS neurons
β1	Myocardium, JG cells, some presynaptic terminals, CNS neurons
β2	Visceral smooth muscle, vascular smooth muscle, liver, myocardium, skeletal muscle, some presynaptic terminals, CNS neurons

Sympathomimetic Agents:

Sympathomimetic drugs (also known as adrenergic drugs and adrenergic amines) are stimulant compounds which mimic the effects of endogenous agonists of the sympathetic nervous system. Sympathomimetic drugs are used to treat cardiac arrest and low blood pressure, or even delay premature labor, among other things.

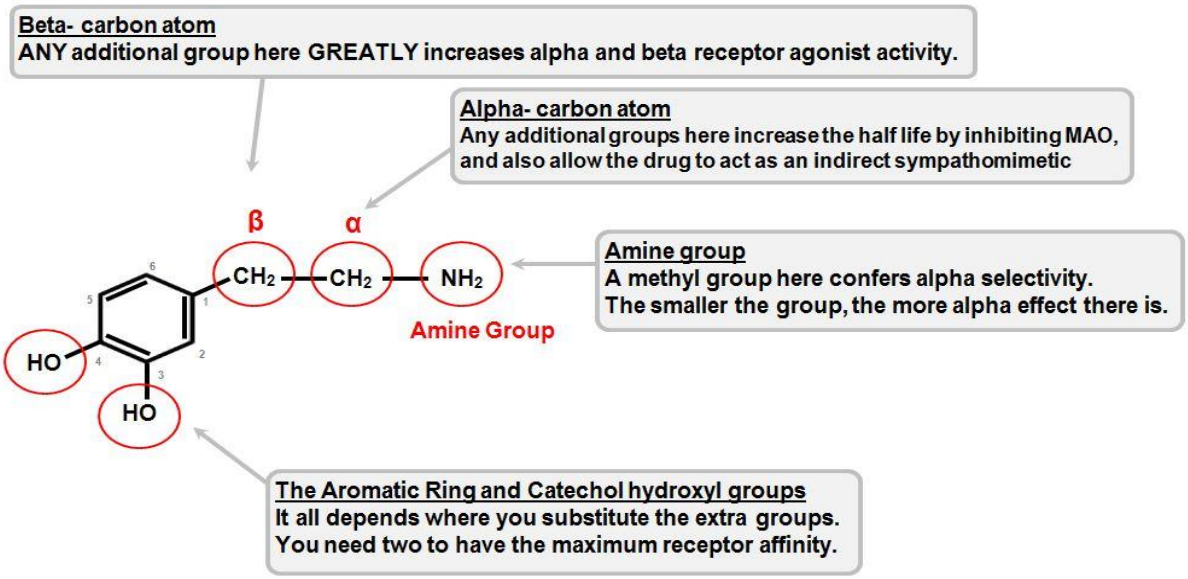
Classification



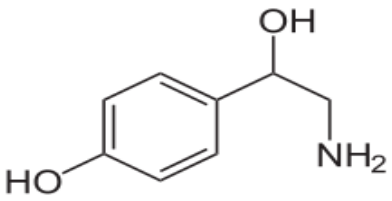
Mechanism of Action

Sympathomimetic drugs are agents which in general mimic responses due to stimulation of sympathetic nerves. These agents are able to directly activate adrenergic receptors or to indirectly activate them by increasing nor epinephrine and epinephrine (mediators of the sympathoadrenal system) levels.

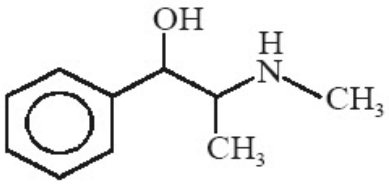
SAR of Sympathomimetic Agents



1. Nor-epinephrine

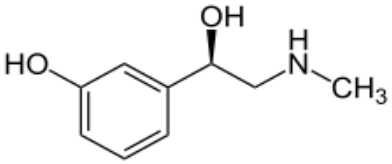


2. Epinephrine

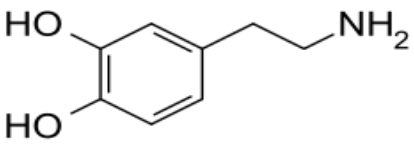


Ephedrine

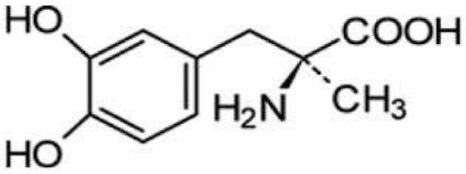
3. Phenylephrine



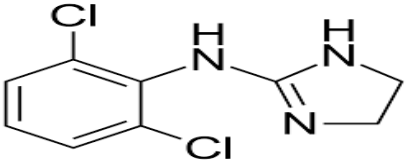
4. Dopamine



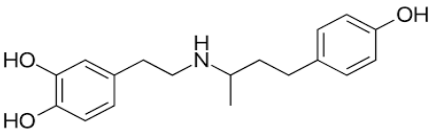
5. Methyldopa



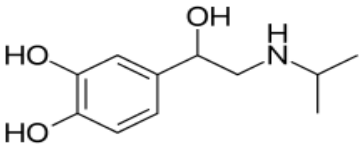
6. Clonidine



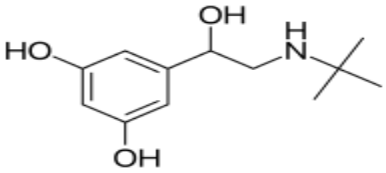
7. Dobutamine



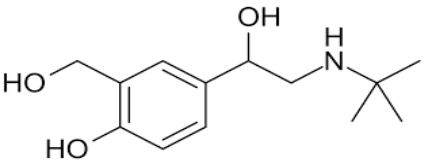
8. Isoproterenol



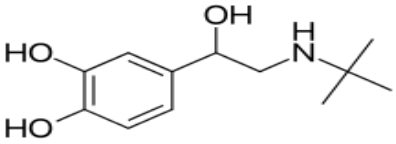
9. Terbutaline



10. Salbutamol

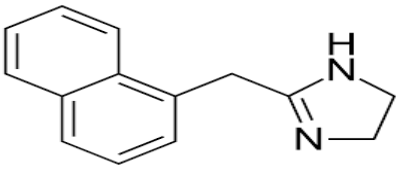


11. Bitolterol

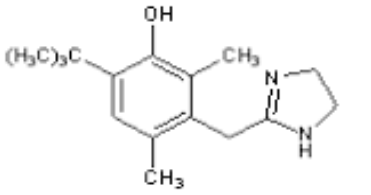


12. Naphazoline

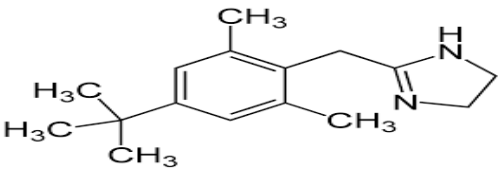
13. Oxymetazoline



14. Xylometazoline

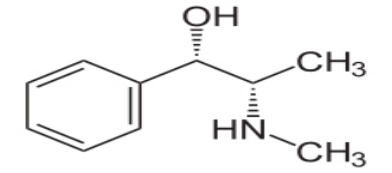


15. Hydroxyamphetamine

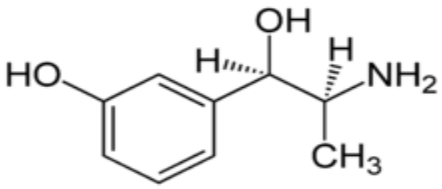


16. Pseudoephedrine

17. Propylhexedrine



18. Metaraminol



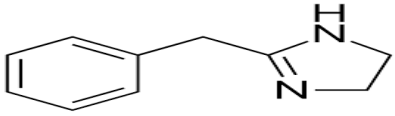
Adrenergic Antagonists

An **adrenergic antagonist** is a drug that inhibits the function of adrenergic receptors. There are five adrenergic receptors, which are divided into two groups. The first group of receptors are the beta (β) adrenergic receptors. There are β_1, β_2, and β_3 receptors. The second group contains the alpha (α) adrenoreceptors. There are only α_1 and α_2 receptors. Adrenergic receptors are located near the heart, kidneys, lungs, and gastrointestinal tract. There are also α-adreno receptors that are located on vascular smooth muscle.

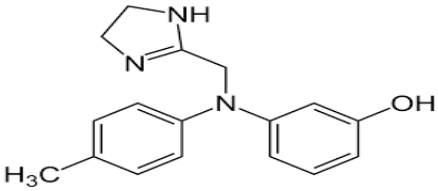
Mechanism of action

Adrenergic antagonists have inhibitory or opposing effects on the receptors in the adrenergic system. Administration of an adrenergic antagonist that specifically targets the beta receptors, results in this decrease in blood pressure by slowing or reducing cardiac output.

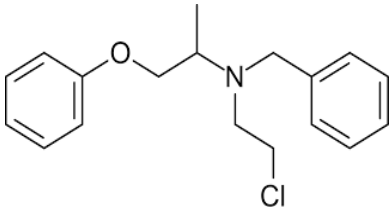
19. Tolazoline



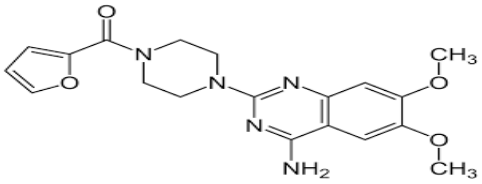
20. Phentolamine



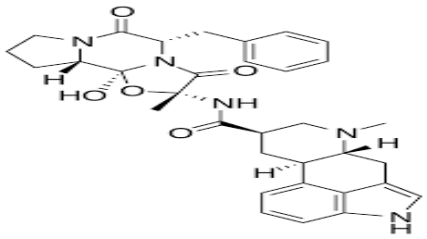
21. Phenoxybenzamine



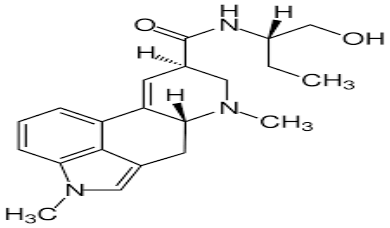
22. Prazosin



23. Dihydroergotamine



24. Methysergide



Uses of Adrenergic Antagonists

- Adrenergic antagonists are mostly used for cardiovascular disease.
- The adrenergic antagonists are widely used for lowering blood pressure and relieving hypertension.
- These antagonists have a been proven to relieve the pain caused by myocardial infarction, and also the infarction size, which correlates with heart rate.

Adverse effects of Adrenergic Antagonists

- Cold feet and hands.
- Fatigue.
- Nausea, weakness, and dizziness.
- Dry mouth, skin, and eyes.
- Slow heartbeat.

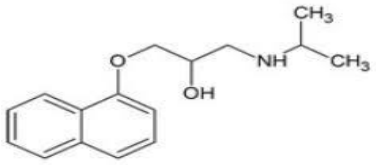
Beta- adrenergic blockers

Beta adrenergic blocking agents: A class of drugs, also called beta blockers, that block beta-adrenergic substances such as adrenaline (epinephrine), a key agent in the "sympathetic" portion of the autonomic (involuntary) nervous system. Beta blockers can serve to treat abnormal heart rhythms (cardiac arrhythmias).

Mechanism of action

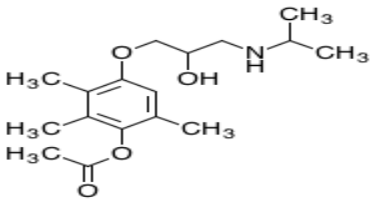
Beta blockers, also known as beta-adrenergic blocking agents, are medications that reduce your blood pressure. Beta blockers work by blocking the effects of the hormone epinephrine, also known as adrenaline. Beta blockers cause your heart to beat more slowly and with less force, which lowers blood pressure.

25. Propranolol

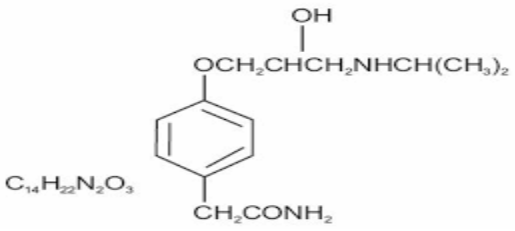


Propranolol

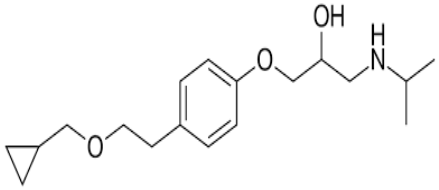
26. Metibranolol



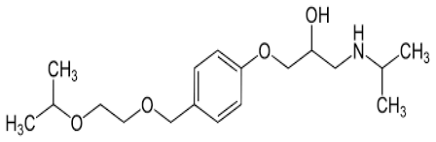
27. Atenolol



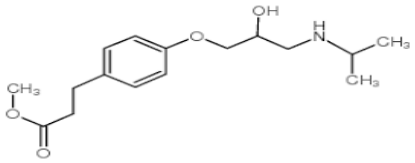
28. Betazolol



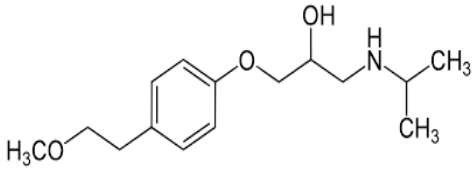
29. Bisoprolol



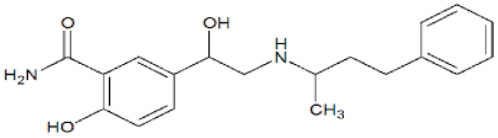
30. Esmolol



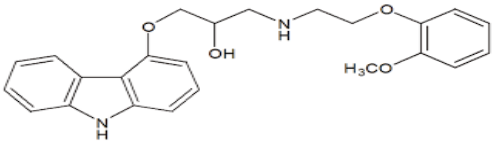
31. Metoprolol



32. Labetolol



33. Carvedilol



Uses of Beta- adrenergic blockers

- Beta blockers can serve to treat abnormal heart rhythms (cardiac arrhythmias).
- They are used specifically to prevent abnormally fast heart rates (tachycardias) or irregular heart rhythms such as premature ventricular beats.

Adverse effects of Beta- adrenergic blockers

- cold feet and hands.
- fatigue.
- nausea, weakness, and dizziness.

- dry mouth, skin, and eyes.
- slow heartbeat.
- swelling of the hands and feet.
- weight gain.

Learning Outcomes

- Understand the Biosynthesis, Catabolism ,structure activity relationship (SAR) and therapeutic values of drugs.