MEDICINAL CHEMISTRY

Cardiovascular Drugs

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1. Antianginal Drugs

Introduction
The word ‘angina’ derived from the Greek verb meaning to choke and is used to describe the pain or discomfort. Angina occurs when the blood supply to the heart is not able to meet the metabolic demands of the heart for oxygen. Angina pectoris, or ischemic heart diseases, is the name to the symptomatic oppressive pain resulting from myocardial ischemia.

An angina may have typical and variant forms, both of which may result in sudden, severe, pressing substantial pain, radiating to the left shoulder and along the flexor surface of the left arm. In typical angina the pain is generally induced by exercise, emotion, or eating. The variant (Prinzmetal’s) angina on the other hand is caused by vasospasm of the coronary vessels and may not be associated with severe atherosclerosis (Fig.1).

![CHEST PAIN Diagram]

The antianginal drugs are directed mainly to alleviating and preventing anginal attacks by dilating the coronary artery.

Classification of Antianginal drugs
1) Nitrates and nitrites
   a) Nitrates: e.g. Nitroglycerin (1), Erythritol tetranitrate (2), Trolnitrate phosphate (3), Isosorbide dinitrate (4), Pentaerythritol tetranitrate (5), Mannitol hexanitrate (6).
   
   b) Nitrites: e.g. Amyl nitrite (7), Sodium nitrite (8), Nitroprusside sodium (9).

2) Calcium Channel Blockers
   a) Aryl alkyl amine derivative: e.g. Verapamil (10)
   b) Benzothiazepine: e.g. Diltiazem (11)
c) Dihydropyridine derivative: e.g. Nifedipine (12), Nimodipine (13), Nitrendipine (14), Nicardipine (15), Amlodipine (16), Felodipine (17), Isradipine (18).

d) Newer second generation alkyl amine derivative: e.g. Bepridil (19)

3) \( \beta \)-Adrenergic Antagonist: e.g. Propranolol (see antihypertensives)

4) Miscellaneous Coronary Vasodilators: e.g. Dipyridamol (20), Cyclandelate (21), Papaverine (22)

Structures of some Anti-anginal Drugs

1 (a)

\[
\text{Nitroglycerin (1) } \quad \text{Erythritol tetranitrate (2)}
\]

\[
\text{Trolnitrate Phosphate (3) } \quad \text{Isosorbide dinitrate (4)}
\]

\[
\text{Pentaerythritol tetranitrate (5) } \quad \text{Mannitol hexanitrate (6)}
\]

1 (b)

\[
\text{Amyl nitrite (7) } \quad \text{Sodium Nitrite (8)}
\]

\[
\text{Nitroprusside sodium (9)}
\]
2 (d)

Bepridil (19)

Dipyridamole (20)

Chemistry: preparation of Dipyridamole:

Synthesis of Dipyridamole (20):

Papaverine (22)
**Mechanism of action of Nitrates and nitrates**
These act by the formation free radical nitric oxide (NO), which interact with and activate guanylate cyclase. Nitric oxide forms a reductive nitrothiol intermediate activate a soluble cytosolic form of the enzyme guanylate cyclase and cGMP formation is thereby increased. The guanylate cyclase increases the synthesis of guanosine 3’, 5’-monophosphate, which activates a protein kinase which mediates dephosphorylation of myosin responsible for the maintenance of the contractile state in smooth muscle.

**Mechanism of action of Calcium Channel Blockers**
These drugs acts by selectively inhibit calcium ion influx into heart muscle and inhibit calcium ion influx into vascular smooth muscle. It dilates the main coronary arterioles, and by inhibiting coronary artery spasm, they increase myocardial oxygen delivery in patients with Prinzmetal’s angina.

**Mechanism of action of β-Adrenergic Antagonist**
The β-Adrenergic Antagonist decreases sympathetic stimulation of the heart and thus reduces the heart rate and decreases myocardial contractibility. These effects in turn decrease the oxygen requirements of the myocardium, both during exercise and at rest.

**Official Drugs:**
**Concentrated Glycerol Trinitrate Solution, B. P.:** Concentrated glyceryl trinitrate solution is a 9-11 per cent solution of propane-1, 2, 3-triol trinitrate in ethanol (96 per cent). It is a clear, colorless to pale yellow solution. Glycerol trinitrate (nitroglycerin; nitro glycerol; trinitrin; trinitroglycerin) is the nitric acid ester of glycerin, and may be prepared by treating dehydrated glycerin with a mixture of fuming nitric acid and sulphuric acid. It is a white to pale yellow, thick, flammable, explosive liquid. It is slightly soluble in water.

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} \\
\text{CH}_2\text{OH} & \quad \text{H}_2\text{SO}_4 \\
3\text{HNO}_3 & \quad \rightarrow \\
\text{CH}_2\text{ONO}_2 & \quad \text{CH}_2\text{ONO}_2 \\
\text{CHONO}_2 & \quad + \text{3H}_2\text{O}
\end{align*}
\]

Glyceryl trinitrate is rapidly absorbed from the oral mucosa. It is also well absorbed from the gastrointestinal tract, but since it undergoes extensive first-pass metabolism in the liver its bioavailability is reduced. As it has short plasma half-life different long-acting formulations are available.

Glyceryl trinitrate is used for the prophylaxis and treatment of stable angina. It is also indicated for congestive heart failure and may have a role in the management of myocardial infarction.

**Preparation:** Glycerol Trinitrate Tablets, B.P. **Proprietary Names:** ANGISED; NITRO-BID; NITROSTAT

**Diluted Pentaerythritol Tetranitrate, I.P.**
Pentaerythritol tetranitrate, 2, 2-bis (hydroxymethyl) propane-1, 3- diol tetranitrate, is a white crystalline powder, practically insoluble in water. It is prepared by nitration of
pentaerythritol, and is supplied diluted with an inert substance such as lactose. The action of pentaerythritol tetranitrate is similar to glyceryl trinitrate but its duration of action is more prolonged. It is used in angina pectoris, usually in oral doses of 10 to 40 mg three or four times daily. It is given as tablets. Pentaerythritol trinitrate is an active metabolite of pentaerythritol tetranitrate which has been used clinically.  

*Preparation:* Pentaerythritol Tetranitrate Tablets, B.P., I.P.  
*Proprietary Names:* CARDIOCAP; MYOCARDOL; PERITRATE; PERITRATE-SA

**Diluted Isosorbide Dinitrate, B.P., I.P.**

Isosorbide dinitrate is 1, 4:3, 6-dianhydro-D-glucitol 2, 5-dinitrate. It is a white crystalline powder; slightly soluble in water. Diluted isosorbide dinitrate is a dry mixture of isosorbide dinitrate with lactose, mannitol or any other suitable inert excipient, which permits safe handling.

Isosorbide dinitrate is readily absorbed from the oral mucosa and gastrointestinal tract. Its major metabolites are isosorbide 2-mononitrate and isosorbide 5-mononitrate, both of which possess vasodilatory activity and may contribute to the activity of the parent compound. Isosorbide dinitrate is also absorbed through the skin from an ointment base. Isosorbide dinitrate is suitable for sublingual as well as oral administration. The usual dose in acute angina is 2.5 to 10 mg sublingually. The oral dosage is 30 to 120 mg daily in divided doses; preparations for sustained-release are available. It has been given in certain states by intravenous infusion. It has also been applied topically.

*Preparation:* Isosorbide Dinitrate Tablets, B.P., I.P.  
*Proprietary Names:* CARDICAP-TR; CEDOCARD; ISODRIL; SORBICHEW; SORBITRATE; VASCARDIN

### 2. Anticoagulants

**Introduction**

The phenomenon of blood coagulation is very complex. Thrombin and several blood clotting factors present in plasma and calcium ions are involved in the coagulation. The factors are precursor proteins or zymogens, and at each stage, a zymogen gets converted to an active protease (activated factor). The protease zymogens involved in coagulation include factor II (prothrombin), VII, IX, X, XI, and XII, and prekallikrein. In addition, there are nonenzymatic protein cofactors such as factor V and VIII. Thrombin cleaves factors V and VIII to yield activated factors (Va and VIIIa) that have at least fifty times the coagulant activity of the precursor form. Factors Va and VIIIa have no enzymatic activity themselves but serve as cofactors that increase the proteolytic efficiency of Xa and IXa, respectively (Fig. 2).

Another nonenzymatic cofactor is tissue factor, a lipoprotein that greatly enhances the proteolytic efficiency of VII and VIIa. High molecular weight kininogen is a plasma protein, which serves as a cofactor for XIIa when clotting is initiated *in vitro*. In the process of coagulation fibrinogen, a soluble plasma protein, gets converted to insoluble
Fibrin monomer by the action of thrombin (IIa) formed from its inert precursor prothrombin (II). These smaller peptides unite end to end and side to side to form insoluble strands of fibrin. These fibrins entangle blood cells and platelets to form the solid clot.

The conversion of prothrombin to thrombin is achieved by activated factor X (Xa) in the presence of Va, calcium ions and platelets or phospholipids. The formation of Xa may take place through two pathways. In the intrinsic pathway, clotting is initiated in vitro when XII, prekallikrein and kininogen interact with glass or any other surface to produce small amounts of XIIa. This is followed by activation of XI to Xla and IX to IXa. IXa then converts X to Xa with the help of VIIIa, calcium ions and phospholipids. The extrinsic pathway initiates coagulation in vivo. In this pathway activation of factor X to Xa is by VIIa in the presence of tissue factor and calcium ions. The Xa formed activates factor VII to VIIa. Factor VII itself possesses proteolytic activity, though less than 1% that of VIIa, and is sufficient to initiate coagulation in the presence of tissue factor. Tissue factor, which is available at the site of injury, accelerates the activation of factor X by VIIa (or VII), phospholipids and calcium ions about 30,000 fold. It is likely that tissue factor plays a major role in haemostasis during injury. The activated VII can also cause conversion of IX to IXa in the presence of tissue factor and calcium ions, supplementing the process by intrinsic pathway.

Blood clots are removed from the vascular system by breakdown of fibrin by proteolytic enzyme plasmin, which is formed from its inactive precursor plasminogen by the action
of streptokinase, urokinase and tissue plasminogen activator. The major reactions involved in blood coagulation and fibrinolysis are shown in the figure 2.

Coagulation normally does not occur within an intact blood vessel. It is prevented by several regulatory mechanisms requiring a normal vascular endothelium. Antithrombin, a plasma protein, inhibits coagulation factors. Prostacyclin (PGI2), synthesized by endothelial cells, inhibits platelet aggregation.

The drugs associated with phenomenon of blood coagulation may be discussed under anticoagulants, antiplatelet drugs and haemostatics. A heparin antagonist is also discussed under anticoagulants.

Anticoagulants are the drugs which prolong the coagulation time of blood. They are used in the treatment and prophylaxis of thrombo-embolic occlusive vascular diseases such as venous thrombosis, pulmonary embolism and cardiac infarction due to thrombosis of a coronary artery. They are also used to prevent thrombosis after operation or from other causes.

The retardation of coagulation may be accomplished by agents like heparin that acts through its action on anti-thrombin to inhibit the activity of thrombin and activated factor X. As heparin is not absorbed orally it is therefore, given parenterally. The other class of drugs is anticoagulants which act by depressing the synthesis of vitamin K-dependent coagulation factors.

**Classification of Anticoagulants**

**A. Heparin (26) and its Derivatives**

Heparin (named because of its abundance in liver) was discovered as a water-soluble mucopolysaccharide by W. H. Howell in 1922. Heparin is a complex anionic linear polysaccharide of mammalian origin with irregular sequence. It consists principally of alternating D-glucuronic acid (or its epimer L-iduronic acid) and D-glucosamine residues, most of which are sulphated. It may be described as a glucosaminoglycan. On complete hydrolysis, heparin releases D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulphuric acid. A pentasaccharide portion of heparin, which is involved in binding with antithrombin, is shown below.

![Heparin structure](image)

**Heparin (26):** (a = N-acetylglucosamine 6-O-sulphate; b = glucuronic acid; c = N-sulphated glucosamine 3, 6-O-disulphate; d = iduronic acid 2-O-sulphate; e = N-sulphated glucosamine 6-O-sulphate)
Heparin for therapeutic use is obtained from lung of ox or intestinal mucosa of ox, pigs or sheep. During the process of isolation the glucosaminoglycan chains become degraded to give a heterogeneous mixture of fragments with molecular weights ranging from 5,000 to 30,000 daltons. Low molecular weight heparins (less than 7,000 daltons) are fragments of heparin with anticoagulant activity. These are isolated from standard heparin by gel filtration chromatography or differential precipitation with ethanol.

Heparinoids are the compounds that have structural analogy to heparins. They are sulphuric acid esters of various polysaccharides. The heparinoids are in some respects more active than heparin in animals. Dextrans which are linear glucose polymers produced by Leuconostoc mesenteroides have been used as the sulphates as antithrombotic agents.

Heparin acts by increasing the rate of the thrombin-antithrombin reaction by serving as a catalytic template to which both the inhibitor and the protease get attached. Thus heparin exerts its anticoagulant effect by inhibiting the activity of thrombin. Other factors such as Xa are also inhibited. Heparin in high doses can also interfere with platelet aggregation which may prolong bleeding time. Heparin is used as heparin sodium and heparin calcium.

**Official Drugs**

**Heparin Sodium, B.P., I. P.:** Heparin sodium is a preparation containing the sodium salt of heparin. It is a white or greyish-white, moderately hygroscopic powder. It is freely soluble in water. Solutions are sterilized by filtration. It is stored in tightly-closed containers, sealed so as to exclude microorganisms, and kept in dry place. If the contents are intended to be used for the manufacture of injection, the container should be sterile and temper-evident. The source of the material should be stated on the label.

Heparin is not absorbed from the gastrointestinal tract. Following parenteral administration it is extensively bound to plasma proteins. It does not cross placenta or appear in the milk of nursing mother. Heparin inhibits clotting of blood both in vivo and in vitro. Heparin is used in the treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism as well as arterial thromboembolism. It is also used as an anticoagulant during haemodialysis, blood transfusion and collection.

Heparin sodium is given in doses of 20,000 to 50,000 Units daily by intravenous injection for the treatment. For prophylaxis it is given by subcutaneous injection, 10,000 to 15,000 Units daily, in divided doses.

**Preparation:** Heparin Sodium Injection, I.P. (Heparin Injection, B.P.); **Proprietary Names:** Liquaemin Sodium; Monoparin

**Heparin Calcium, B.P.:** It is a preparation containing the calcium salt of heparin. It is a white or almost white, moderately hygroscopic powder. It is freely soluble in water. Its conditions of storage, other requirements, actions and uses are similar to those of heparin sodium.

**Preparation:** Heparin Injection, B.P; **Proprietary Names:** Calciparine; Monoparin calcium
**Low-molecular-weight Heparins, B.P.** Low molecular-weight heparins are salts of sulphated glucosaminoglycan having a weight-average molecular weight less than 8,000 and for which at least 60% of the total weight has a molecular weight less than 8,000. Depending upon the method of production, the resulting low-molecular-weight heparins display different chemical structures at the reducing or the non-reducing end of the polysaccharide chain. Low-molecular weight heparins are obtained by fractionation or depolymerisation of heparin of natural origin. They occur as white or almost white powders, which are hygroscopic, and are freely soluble in water.

Low-molecular-weight heparins generally have a greater bioavailability after subcutaneous injection and longer half-life than heparin. Low-molecular-weight heparins are given parenterally for the treatment and prophylaxis of thrombo-embolic disorders. Their effects can be partially reversed by protamine sulphate. A possible decreased risk of bleeding complications compared with heparins has not been established. *Proprietary Names:* Fragmin; Fraxiparin; Sandoparine, Dalteparine sodium, Enoxaperine sodium, Medroparine calcium, Parnaparine sodium, Tinzaparine sodium.

**Heparin Antagonist**

Heparin can give rise to haemorrhage as a consequence of its action. If the haemorrhage is severe and is life-threatening, the effect of heparin can be reversed quickly by the intravenous infusion of protamine sulphate. The protamines are low-molecular-weight basic proteins isolated from the sperm or the mature testes of fish, usually species of family Salmonidae and Clupeidae. They combine with heparin to form a stable inactive complex. Protamine also has an anticoagulant effect of its own as it interacts with platelets, fibrinogen and other plasma proteins. Therefore, it should be given in minimal amount just to neutralize the heparin present in plasma.

**Official Drugs**

**Protamine Sulphate, B.P., I.P.:** Protamine sulphate is a mixture of the sulphates of basic peptides prepared from the sperm or mature testes of fish, usually species of Salmonidae and Clupeidae. It occurs as a white or almost white powder; hygroscopic. It is sparingly soluble in water. Protamine sulphate is kept in an airtight, temper-evident container. If the material is sterile the container should also be sterile.

Protamine sulphate is used to neutralize the anticoagulant action of heparin in the treatment of haemorrhage resulting from severe heparin over dosage. It should be administered by slow intravenous injection over a period of ten minutes. Protamine sulphate has weak anticoagulant properties and if given in gross excess its anticoagulant effect could be significant. Protamine is also used to prolong the effects of insulin. *Preparation:* Protamine Sulphate Injection, B.P., I.P. *Proprietary Names:* Prosulf

**Protamine Hydrochloride, B.P.:** Protamine hydrochloride is a white or almost white powder; hygroscopic. It is soluble in water. The condition of storage, actions and uses are the same as for protamine sulphate.
Oral Anticoagulants

B. Dicoumarol (30) or Dicouman and other related derivatives
Orally active anticoagulant drugs belong to the chemical categories of coumarins and indanedione derivatives. In 1922, there appeared a report on a disease of cattle characterized by internal bleeding. It was traced to the ingestion of improperly cured sweet clover silage. In 1939, Campbell and Link identified the haemorrhagic agent as 3, 3’-methylenebis (4-hydroxycoumarin) (dicoumarol). It is also used as injection into cattle to prevent excessive and persistent bleeding (haemorrhage), and is used as a prophylactic against post-operative thrombosis and embolism. It retards the rate of coagulation by blocking the enzyme system responsible for the synthesis of prothrombin in the liver. Dicoumarol may be prepared from either methyl salicylate or malonic acid in the following way:

Warfarin (33): In 1948, another coumarin derivative called warfarin (an acronym derived from Wisconsin Alumni Research Foundation, plus coumarin) was synthesized, and was used as haemorrhagic rat poison. It was, however, not accepted as a therapeutic agent, partly due to the fear of its toxicity. In 1951, an army inductee who attempted suicide by taking massive doses of warfarin survived. This led to the acceptance of coumarins as orally effective anticoagulants for the prevention of thromboembolic disorders. Its alkali salts are water soluble and is used as rodenticide. Warfarin may be prepared by first synthesizing 4-hydroxycoumarin starting from methyl salicylate (27). The action of sodium on the methyl acetylsalicylate (28) yields the sodium derivative of 4-hydroxycoumarin. Acidification yields 4-hydroxycoumarin (29). Michael addition of the latter to benzalacetone gives warfarin (33).
Taking warfarin as a prototype, a number of derivatives of 4-hydroxycoumarin have been prepared where 3 and 4’-positions have been substituted by different substituents. Cyclocoumarol (35) may be prepared by passing HCl gas in methanolic solution of warfarin.

Nicoumalone (acenocoumarol) (34), phenprocoumon (36), coumachlor, snitrom and marcoumar are other examples. In all these compounds there is chiral centre. The enantiomers differ in anticoagulant potency. These are, therefore, used as racemic mixtures, and any advantage of administering a pure enantiomer has not yet been established. They are used in the form of alkali salts, also used as rodenticide.
Tromexan or Pelentan (Ethyl biscoumacetate) (40): Chemically ethyl-bis (4-hydroxycoumarin-3-yl)-acetate, is an analogue of dicoumarol. It is used as oral anticoagulant, and for quicker in action. It can be prepared by condensing 4-hydroxycoumarin (29) and glyoxalic acid (38) in the following way:
Warfarin and other coumarin derivatives are antagonists of vitamin K. Thus they act by depressing the vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX and X, and of the anticoagulant protein C and its protein cofactor protein S.

**Official Drugs**

**Warfarin Sodium, B.P., I.P.:** Warfarin sodium is the sodium salt of (RS)-4-hydroxy-3-(3-oxo-l-phenylbutyl)-coumarin. It is a white powder and hygroscopic. It is very soluble in water. It should be kept in an airtight container and protected from light. Warfarin sodium is readily absorbed from the gastrointestinal tract. It can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half-life is about 37 hours. Warfarin is transformed into inactive metabolites by the liver and kidneys. They are excreted in urine and stool. Warfarin is used in the prevention and treatment of deep-vein thrombosis or pulmonary embolism. It is equally effective either orally or intravenously. Warfarin should not be given to patients who are haemorrhaging. Warfarin sodium is used as a racemic mixture, and however the S-isomer is reported to be more potent. Usual dose of warfarin sodium is 10 mg daily by mouth for 2 days, but may be lower for patients with particular risk of haemorrhage. Subsequent maintenance doses usually range from 3 to 9 mg daily.

*Preparation:* Warfarin Tablets, B.P. *Proprietary Names:* COUMADIN; PANWARFIN

**Warfarin Sodium Clathrate, B.P., I.P.:** Warfarin sodium Clathrate is the Clathrate of the sodium salt of (RS)-4-hydroxy-3-(3-oxo-l-phenylbutyl)-coumarin with propan-2-ol. It consists of warfarin sodium and propan-2-ol in the molecular proportion of 2:1. It contains approximately 92% of warfarin sodium. It is a white powder and is very soluble in water. It should be kept in an airtight container and protected from light. It has actions and uses similar to those of warfarin sodium. *Preparation:* Warfarin Tablets, B.P.

**Acenocoumarin/Nicoumalone, B.P., I.P.:** Nicoumalone is (RS)-4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl] coumarin. It is a white to brownish white powder, practically insoluble in water. It is stored in light-resistant containers. Nicoumalone is readily absorbed when given by mouth. It is excreted chiefly in the urine mainly as metabolites. It is extensively bound to plasma proteins. Nicoumalone has actions and uses similar to those of warfarin sodium. It is administered orally. Though used as a racemic mixture, the R(+) enantiomer of nicoumalone is reported to be pharmacologically active component of nicoumalone. The initial dose of nicoumalone is 12 to 20 mg; subsequent doses are given in accordance with the needs of the patient.

*Preparation:* Nicoumalone Tablets, B.P., I.P. *Proprietary Name:* SINTHROME

**C. Indanedione**

Indanedione derivatives, such as phenindione and anisidione, were conceived as ring contracted analogues of coumarins. Like coumarins they also act as oral anticoagulants by inhibiting the synthesis of prothrombin and other factors VII, IX and X.
Mode of Action of Indanedione: The action of indanedione is similar to coumarin derivatives i.e., the synthesis of plasma prothrombin and other factors are inhibited, thereby lengthening the prothrombin time.

Official drugs

Phenindione (41), B.P., I.P. 2-Phenyldione-1, 3-dione. Phenindione may be prepared by heating phthalide with benzaldehyde in the presence of sodium ethoxide. Phenindione occurs as white or creamy-white crystals. It is sparingly soluble in water. It is stored in well-closed containers.

Phenindione (41), anisidione (42) and delphenadione (43) are absorbed from the gastrointestinal tract. Its metabolites are excreted in the urine; and the urine may become discoloured. Phenindione is an orally administered anticoagulant. However, it is generally more toxic than warfarin sodium. The initial dose of phenindione is 200 to 300 mg; subsequent doses are 25 to 100 mg daily, depending on the prothrombin activity of the blood.

Preparation: Phenindione Tablets, B.P., I.P. Proprietary Name: Dindevan; Pindione

D. Miscellaneous drugs:

1. Sodium citrate when taken orally, is metabolized in vivo to citrate ion, which is a soluble complex with Ca++, an agent required to convert prothrombin to thrombin and thus citric acid prevents the formation of clot.

2. Sulphanilamidoquinoxaline (47): It is very potent anticoagulant. Thrombodyn (48) is used for the treatment of thrombosis.
**Structure-activity Relationship**

All of the coumarin derivatives are water insoluble lactones. Though coumarin is a neutral compound, the clinically utilized derivatives are weakly acidic due to a 4-hydroxy substitution. Therefore, reaction of 4-hydroxycoumarin derivatives with an appropriate base yields water-soluble salts. Because of the acidity of the proton on the 4-hydroxy group of warfarin and the proximity of the side chain carbonyl six atoms away, the possibility of another ring closure exists. If the acidic 4-hydroxy proton is removed, the resulting oxyanion can act as a nucleophile and attack the electrophilic carbonyl carbon forming a hemiketal called cyclocoumarol, which is neutral.

Structure-activity relationship (SAR) requirements are typically based on substitution of the lactone ring, specifically, in positions 3 and 4. Initial investigation into the, anticoagulant activity requirements of coumarin derivatives led link to suggest that a 3-substituent, a 4-hydroxy group and a bis molecule were all necessary. Though a bis compound (bis-hydroxycoumarin, dicoumarol) fits these requirements, it is no longer used clinically. Additional studies have concluded that the methoxy group addition to position 8 increases anticoagulant activity. The conformation of warfarin has been studied by nuclear magnetic resonance spectroscopy. These studies suggest that there are three conformations of the drug in solution, two diastereomeric cyclic hemiketals and one open form. Since it has been suggested that vitamin K forms an active hemiketal in vivo, vitamin K antimetabolite compounds such as warfarin may well be active as the cyclic hemiketal

Warfarin is a chiral compound. Though the clinically utilized preparation is racemic, the enantiomers are not equipotent. In fact, (S)-warfarin is at least 4-fold more potent as an anticoagulant than the (R)-warfarin. The difference in the activities and metabolism of the enantiomers is the key to understanding several stereoselective drug interactions including those with zileuton, miconazole, sulfinpyrazone and cimetidine.

Derivatives of 1,3-indanedione are also known to cause anticoagulation through mechanisms similar to warfarin in that they inhibit the synthesis of active clotting factors VII, IX, X and plasma prothrombin.

**3. Anti-hypertensive Agents**

**Introduction**

Hypertension or High Blood Pressure is the name of a pathological condition in which blood pressure is persistently elevated (i.e. it stays high for a long period of time). The blood pressure is a measurement of the pressure of the blood against the blood vessel walls. The persistent high blood pressure puts undue stress on the heart, blood vessels and other organs. In fact, hypertension is a major public health problem of largely unknown cause. Unfortunately, at present, it is yet a great concern of modern medical practice due to its doubtful and uncertain etiology (even in the 90% of cases) and its faulty cure management. The people suffering from this disorder are not only at high risk of abnormally elevated blood pressure, but also they gradually come under the phenomena of secondary complications that may produce other vital-organ diseases. It is single
contributing factor and responsible for producing a number of Cardio-Vascular Diseases (CVD), which causes morbidity and premature deaths. According to a study, it affects 25% of most adult populations and is an important risk factor for death from stroke, myocardial infraction (MI), congestive heart failure (CHF) and renal failure. If, it is left untreated, hypertensive people may be further sufferer of more heart problems, kidney disease and stroke. It has been investigated that western type of life style, culture, diet and stress are more responsible for contributing the prevalence of hypertension than the rural mode of living in human beings.

The primary causes for this ailment may be environmental such as smoking, obesity, diabetes, hyperglycemia, continuous stress and strain, sudden shock, unachieved ambition etc. Recently, the genetic discovery reveals that human hypertension is caused by mutations in WNK kinases proteins. Researchers have identified the two genes, which encode WNK1 and WNK4 proteins. The mutation in the both proteins is the primary cause of pseudo-hypoaldosteronism type-II, a Mendelian trait featuring hypertension that increases renal salt re-absorption and impairs K$^+$ and H$^+$ excretion. It has been observed that both proteins are localized in distal nephron, a kidney segment and involve in K$^+$ salt and pH homeostasis.

Regarding the clinical control over this ailment, it is conventionally treated with diuretics along with β-blockers or vasodilators as the first line of management. The treatment may be further extended with a combination of β-blockers and other types of anti-hypertensive agents like α-blockers, ACE inhibitors and calcium channel blockers in the cases of severe to malignant hypertension.

**Physiological concept of BP regulation and control**

Blood pressure is a measure of the force of the blood pushing against the walls of the arteries (i.e. the blood vessels that carry blood from the heart to the rest of the body). It is determined by the amount of blood pumped by the heart, the pumping power of the heart, the condition of the heart valves and the size and condition of the arteries. Many other factors can affect blood pressure including the volume of water in the body, salt content of the body, condition of the kidneys, nervous system and the nature of blood vessels and levels of various hormones in the body.

**Systolic Blood Pressure (SBP):** When the heart contracts to pump out blood, pressure is highest. This measurement is called the systolic pressure.

**Diastolic Blood Pressure (DBP):** After pumping, the heart relaxes and pressure drops to its lowest point just before new beat starts. This measurement is called the diastolic pressure.

The measurement of an individual’s blood pressure is always expressed as systolic pressure over diastolic pressure. For example, normal blood pressure for adults is considered to be in the range of 120/80 millimeters of mercury. Generally, blood pressure above 140/90 mmHg is considered high for adults, and blood pressure under 90/60 mmHg is considered low for adults.
Mean Arterial Blood Pressure (MABP): The mean arterial pressure is calculated as:

\[ \text{MABP} = \frac{\text{Systolic} + (2 \times \text{diastolic})}{3} \]

According to WHO, the systolic and diastolic blood pressure in normal adult is equal to or below 140 mm Hg and 90 mm Hg. The blood pressure may be of three types.

- Mild hypertension - 90-104mmHg
- Moderate hypertension 105-114mmHg
- Severe hypertension above 115mmHg

Further, the hypertension has been divided into two categories.

I. General Classification of Hypertension

The widely accepted categorization of systemic hypertension for the basic research and in the field of clinical medicine was suggested by “Fein-Stein” as follows:

- **Category (1): Essential or primary hypertension:** It is a common form of HTN with no identifiable causes.
- **Category (2): Secondary hypertension:** It always occurs because of another disorder. Patients with HBP with diseases known to its cause are referred as suffering from secondary hypertension. It might be associated with end organ damage. The others unusual reasons for this type of HTN are coarctation of aorta, thyroid disorder, hyperparathyroidism, obstructive sleep apnea, drug-induced HTN and Liddle’s syndrome.
- **Category (3):** It may be consequences of either primary or secondary HTN manifestation due to anatomical changes in parenchymal organs such as left ventricular hypertrophy, hypertensive retinopathy or sclerosis of renal arteriolar with impaired kidney function (i.e. nephrosclerosis).
- **Category (4):** Patients with end organ changes from either type of HTN, subsequently, become normotensive with therapy or with counter-balancing comorbid diseases state and may still be considered to suffer from hypertensive disease of end organ.
- **Category (5): Malignant or accelerated hypertension:** It is complex and deadly forms of HTN related to circulatory and end-organ manifestations like encephalopathy heart failure, retinopathy and uremia. Other forms of malignant hypertension are diagnosed on the basis of patho-physiological criteria like arteriolar necrosis in kidney, elevated secretion of renin and secondary hyperaldosteronism.

II. Other kinds of Hypertension

- **Pulmonary hypertension:** It is defined as a pressure within the pulmonary arterial system, elevated above the normal range. It may be acute or chronic due to right ventricular (RV) failure. A variety of pathological disorders, which affect the pulmonary circulatory function, can elevate the pulmonary pressure. For example, polycythemia vera and increased pulmonary arteriolar resistance in a patient with
congenital heart disease, can cause chronic and severe pulmonary HTN while RV-failure and mitral stenosis can cause immediate pulmonary HTN. Approximately 2,00,000 death/annum in the world occurs from acute pulmonary embolism (a common cause of sudden onset of pulmonary HTN).

b. **Portal hypertension:** If the portal venous flow becomes obstructed, there is rise in BP because a collateral circulation develops; diverting the portal flow into systemic venous. It is reported that main cause of increased portal pressure is increased vascular resistance related to hepatic fibrosis, scaring regenerative nodules and increased blood flow. The causes of portal hypertension are categorized as prehepatic, intra-hepatic and post-hepatic which can be diagnosed by endoscopy and ultrasound (Lake, 2000).

c. **Childhood hypertension:** It is based on the normal distribution of systolic and diastolic BP in the general population for the children of comparable age, weight and height:

d. **Renal parenchymal hypertension:** It is associated with renal parenchymal disease and the most common form of secondary hypertension; 5% of all hypertensive patients have underlying renal disease. Among them 80% and 90 % are with pre-end-stage renal disease (pre-ESRD) and end-stage renal disease (ESRD) respectively.

e. **Reno-vascular hypertension:** Its presence is confirmed only by showing that HBP is improved or cured after correction of occlusion. It is resulted from the activation of renin-angiotensin-aldosterone axis mediated by ischemia. In 95% cases, the common cause for this type of HTN is atherosclerosis and fibromuscular dysplasia.

f. **Drug induced hypertension:** HTN related to medication is a disorder characterized by HBP caused by a response to using, or stopping the use of a chemical substance, drug or medication. It is a form of secondary hypertension caused by a response to medication. Examples include using substances such as alcohol or medications such as corticosteroids, cyclosporine, estrogen (including birth control pills), nasal decongestants, corticotropin or other hormones, sympathomimetic medications, which is found in many over-the-counter medications such as cough/cold medicines and medications for asthma or particularly when the cough/cold medicine is taken by a person who also takes tranylcypromine or tricyclic antidepressants. It can also be a result of stopping the use of antihypertensive medication such as clonidine. This is called rebound hypertension.

g. **Pseudo-hypertension:** It may occur in elderly patients with very stiff arteries. In such patients, sphygmomanometry may detect spurious blood pressure elevations because the cuff cannot completely occlude the sclerotic brachial artery (Osler's sign). It may be diagnosed when elderly patients treated for hypertension develop excessive fatigue or severe orthostasis.

Recently, scientific committee on high blood pressure has specified different levels of blood pressure and limited the range of high blood pressure in only 3 stages:
Table-1

<table>
<thead>
<tr>
<th>Level of BP</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High normal</td>
<td>130 - 139</td>
<td>85 - 89</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140 - 159</td>
<td>90 - 99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160 - 179</td>
<td>100 - 109</td>
</tr>
<tr>
<td>Stage 3</td>
<td>&gt; 180</td>
<td>&gt; 110</td>
</tr>
</tbody>
</table>

For diabetic subjects and/or in case of renal insufficiency, high blood pressure is defined by a blood pressure up to 130/85 mmHg (www.scientific committee/HTNgrade/htm.org 2003)

Treatment: pharmacological and non-pharmacological

Treatment is similar for elderly and younger patients in many ways. For both, blood pressure level and the presence of risk factors, target organ damage, and cardiovascular disease must be considered. However, for elderly patients, the greater potential for troublesome adverse effects from treatment must also be considered.

Patients whose systolic blood pressure increases usually with age but remains within the normal limits are not treated. However, without treatment, such patients are at higher risk of cardiovascular events: the greater the increase in systolic blood pressure, the higher the risk.

The generic and trade names of the common antihypertensive drugs and their dosage, frequency of administration, duration of action have been summarized in the table for the treatment.

Table-2: Common antihypertensive drugs in ambulatory treatment of hypertension

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name (Manufacturer)</th>
<th>Adult maintenance dose (in mg/day)</th>
<th>Frequency of administration (Times/day)</th>
<th>Duration of action (in hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adrenergic inhibitors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Central α-1 agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catapres (Boehringer-Ingelheim)</td>
<td>0.2 - 0.6</td>
<td>2</td>
<td>6-12</td>
</tr>
<tr>
<td>Clonidine Patch</td>
<td>Catapres –TTS (0.1, 0.2, 0.3 mg)</td>
<td>1 Patch</td>
<td>weekly</td>
<td>7 days</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>wytensin (wyth-Ayerst)</td>
<td>8-64</td>
<td>2</td>
<td>8-12</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Tenex (Robins)</td>
<td>1-3</td>
<td>1</td>
<td>12 – 24</td>
</tr>
<tr>
<td>Methyl dopa</td>
<td>Aldomet (Merck)</td>
<td>500-2000</td>
<td>2</td>
<td>6-12</td>
</tr>
<tr>
<td>(b) β-Adrenergic blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Sectral (Wyeth-Ayerst)</td>
<td>400-1200</td>
<td>1 or 2</td>
<td>12 – 24</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin (Zeneca)</td>
<td>50 - 100</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Carteolol</td>
<td>Cartrol (Abbott)</td>
<td>2.5 – 10</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>
### Adrenergic blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaxolol</td>
<td>Kerlonie(Searle)</td>
<td>10-20</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Zebeta(Lederle)</td>
<td>2.5 – 20</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Lopressor (Novartis)</td>
<td>100 – 450</td>
<td>1 or 2</td>
<td>12</td>
</tr>
<tr>
<td>Metoprolol SR</td>
<td>Toprol XL (Astra)</td>
<td>50 – 400</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Generic (Mylan)</td>
<td>40 – 320</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>Levatol(Schwarz Pharma)</td>
<td>20</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Generic</td>
<td>10 - 60</td>
<td>2</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Inderal (Wyeth- Ayerst)</td>
<td>40 - 640</td>
<td>2</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Propranolol SR</td>
<td>Inderal LA (Wyeth- Ayerst)</td>
<td>80 – 640</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Timolol</td>
<td>Blowcadren(Merck)</td>
<td>20 - 60</td>
<td>2</td>
<td>6 – 12</td>
</tr>
</tbody>
</table>

(c) α₁-Adrenergic blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin</td>
<td>Cardora (Pfizer)</td>
<td>2 –16</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Minipress (Pfizer)</td>
<td>2.5 – 20</td>
<td>2 or 3</td>
<td>3- 6</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Hytrin (Abbott)</td>
<td>1 – 20</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

(d) Mixed α and β-adrenergic blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>Coreg (Smith-Kline)</td>
<td>12.5 - 50</td>
<td>2</td>
<td>7 -10</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Normodyne (Schering)</td>
<td>200 - 2400</td>
<td>2</td>
<td>3 – 6</td>
</tr>
</tbody>
</table>

### Diuretics

(a) Thiazides and related sulfonamides

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>Hygroton (Rhone-Poulenc Rorer)</td>
<td>12.5 - 100</td>
<td>1</td>
<td>24 –72</td>
</tr>
<tr>
<td></td>
<td>Thalitone (Monarch)</td>
<td>15 – 50</td>
<td>1</td>
<td>24 -72</td>
</tr>
<tr>
<td>Hydro-chlorothiazide</td>
<td>Hydro-DIURIL (Merck)</td>
<td>12.5 – 50</td>
<td>1 or 2</td>
<td>12 – 18</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Lozol (Rhone-Poulenc Rorer)</td>
<td>1.25 - 5</td>
<td>1</td>
<td>18 – 24</td>
</tr>
<tr>
<td>Metolazone</td>
<td>Mykrox (Medeva)</td>
<td>0.5 – 1</td>
<td>1 - 2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Zaroxolyn (Medeva)</td>
<td>2.5 - 5</td>
<td>1 - 2</td>
<td>12 - 24</td>
</tr>
</tbody>
</table>

(b) Loop Diuretics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>Generic (Mylan)</td>
<td>0.5 - 2</td>
<td>2</td>
<td>1 - 4</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>Edecrin (Merck)</td>
<td>50 – 400</td>
<td>2</td>
<td>3 - 6</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix (Hoechst Marion)</td>
<td>80 – 600</td>
<td>2</td>
<td>3 - 6</td>
</tr>
<tr>
<td>Torsimide</td>
<td>Demadax (Boehringer)</td>
<td>5 - 10</td>
<td>1</td>
<td>8 – 12</td>
</tr>
</tbody>
</table>

(c) Potassium-sparing Diuretic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>Midamor (Merck)</td>
<td>5 - 20</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone (Searle)</td>
<td>50 – 400</td>
<td>1 - 2</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Dyrenium (Smith-Kline)</td>
<td>50 – 300</td>
<td>1 - 2</td>
<td>3 –6</td>
</tr>
</tbody>
</table>

### ACE inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Frequency</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>Lotensin (Novartis)</td>
<td>10- 80</td>
<td>1 or 2</td>
<td>12 –24</td>
</tr>
<tr>
<td>Captopril</td>
<td>Generis (Mylan)</td>
<td>75 – 450</td>
<td>2- 3</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vascotec (Merck)</td>
<td>5 – 40</td>
<td>1 or 2</td>
<td>12 –24</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril (Bristol Myers Squibb)</td>
<td>10 - 80</td>
<td>1 or 2</td>
<td>12 –24</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil (Merck) Zestril (Zeneca)</td>
<td>10 –40</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Mexopril</td>
<td>Univase (Schwarz Pharma)</td>
<td>7.5 – 30</td>
<td>1 or 2</td>
<td>12 - 24</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril (Parke-Davis)</td>
<td>10 –80</td>
<td>1 or 2</td>
<td>12 –24</td>
</tr>
<tr>
<td>Drug</td>
<td>Brand Name</td>
<td>Dosage (mg)</td>
<td>Duration</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace (Hoechst-Marion)</td>
<td>2.5 – 20</td>
<td>1 or 2</td>
<td>12 –24</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Mavik (Knoll)</td>
<td>1 - 4</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

### 4. Angiotensin- II Antagonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dosage (mg)</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Atacand (Astra)</td>
<td>8 – 32</td>
<td>1 or 2</td>
<td>24</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro (Sanobil)</td>
<td>75 – 300</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozaar (Merk)</td>
<td>25 – 100</td>
<td>1 or 2</td>
<td>12 –24</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis (Boehringer)</td>
<td>40 - 80</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan (Novartis)</td>
<td>80 - 320</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

### Calcium Channel Antagonist

#### (i) Dihydro pyridines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dosage (mg)</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Norvasc (Pfizer)</td>
<td>2.5 – 10</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Plendil (Astra)</td>
<td>2.5 – 10</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Isradipine</td>
<td>DynaCirc (Novartis)</td>
<td>5 – 20</td>
<td>2</td>
<td>3 - 6</td>
</tr>
<tr>
<td></td>
<td>DynaCirc CR (Novartis)</td>
<td>5 – 20</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Procardia XL (Pfizer)</td>
<td>30 –90</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Adalat CC (Bayer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Generic</td>
<td>60 –120</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Sular (Zeneca)</td>
<td>20 - 60</td>
<td>1</td>
<td>12 –24</td>
</tr>
</tbody>
</table>

#### (ii) Non –Dihydropyridines

##### (a) Phenylalkyl amine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dosage (mg)</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Calan SR(Searle)</td>
<td>120 –480</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Covera HS (Searle)</td>
<td>180 –480</td>
<td>1(at bed time)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Isoptin SR (Knoll)</td>
<td>120 – 480</td>
<td>1 or 2</td>
<td>12-24</td>
</tr>
<tr>
<td></td>
<td>Verelan (lederle)</td>
<td>120 - 480</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

##### (b) Benzothiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dosage (mg)</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Cardizem SR (Hoechst)</td>
<td>120-360</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Cardizem CR (Hoechst)</td>
<td>120 –360</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Dilacor XR (Watson)</td>
<td>120 – 540</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Tiazac (Forest)</td>
<td>120 - 540</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>


### Classification of Antihypertensives agents and their Chemistry

Antihypertensives are those agents which are used to reduce high blood pressure.

#### (A) Adrenoceptor Blocking Agents:

1. **α - Adrenergic Antagonist**
   1. Piperazinylnquinazoline derivatives e.g. Prazosin, Terazosin
   2. Imidazoline derivatives e.g. Tolazoline, Phentolamine
2. **β - adrenoceptor antagonists** e.g. Propranolol, Atenolol, Metoprolol
3. **α, β - adrenoceptor antagonists** e.g. Labetalol
4. **Centrally Acting Agents** e.g. Methyldopa, Clonidine, Guanabenz, Guanfacine
5. **Agents Depleting Neurotransmitter Stores** e.g. Reserpine, Guanethidine, Guandrel Sulfate
6. **Gaglionic Blocking Agents** e.g. Pentolinium, Trimethaphan, Mecamylamine HCl
(B) Agents Acting on Renin-angiotensin system:
1) Angiotensin Converting Enzyme (ACE) Inhibitors e.g. Captopril, Lisinopril, Enalapril
2) Angiotensin Receptor Antagonist e.g. Losartan, Saralasin

(C) Vasodilators
1) Directly Acting Vasodilators
   a) Arterial dilators: e.g. Hydralazine, Dihydralazine, Sodium nitroprusside
   b) Potassium Channel agonist: e.g. Minoxidil (91), Diazoxide (90)
2) Calcium Channel Blockers
   a) Alkylamines: e.g. Verapamil
   b) Benzothiazepines: e.g. Diltiazem
   c) Dihydropyrimidines: e.g. Nifedipine, Felodipine, Amlodipine, Nimodipine

(D) Diuretics
1) Thiazides: e.g Hydrochlorothiazide
2) Loop Diuretics: e.g. Furosemide
3) Potassium Sparing Diuretics: e.g. Triamterene, Spironolactone

(E) 5HT Antagonists e.g. Ketanserine

A (1). α - Adrenergic Antagonist: Prazosin (49) is a piperazinylquinazoline and selective α₁ antagonist. The affinity of prazosin for α₁ receptors is about 1000 fold greater than for α₂ receptors. It has close structural relation to that of terazosin (50) is less potent than prazosin but retains its specificity for α₁ receptors.

Tolazoline (51) and Phentolamine (52) both are nonselective α- adrenergic antagonist. Both stimulate gastrointestinal smooth muscle and also increase gastric acid secretion.
Official drugs:
Prazosin Hydrochloride, B.P. 2-[4{2-Furoyl}-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine hydrochloride. It is a white or almost white powder and is very slightly soluble in water.

Prazosin is well absorbed from the gastrointestinal tract; the bioavailability is about 70%. On oral administration the peak concentrations in plasma are reached within 1 to 3 hours. Prazosin is extensively metabolized in the liver.

Prazosin hydrochloride is used in the treatment of all grades of hypertension usually as a second step agent in conjunction with a diuretic or other antihypertensive agent. The dose of the drug is 500 µg given 2 to 4 times daily.

Preparation: Prazosin Tablets, B.P. Proprietary Names: HYPOVASE; MINIPRESS; PRAZOPRESS

A (2). β-Adrenoceptor antagonists: Propranolol (53) is an aryloxypropranolamine and non-selective β-adrenergic antagonist. In aqueous solution propranolol decomposes with oxidation of the isopropylamino side chain, leading to discoloration of the solution. Solutions are most stable at pH 3 decomposes rapidly when alkaline. It is highly lipophilic and completely absorbed from the gastrointestinal tract. It is extensively metabolized in liver. The major metabolite is 4-hydroxypropranolol (54) which possesses some β-adrenergic blocking activity.

The (-) - enantiomers of propranolol and other β - blockers are the active forms of the drugs.

Synthesis of Propranolol:
Official drugs:
Propranolol Hydrochloride, B.P., I.P. (RS)-1-Isopropylamino-3-(1-naphthyloxy)-propan-2-ol hydrochloride. Propranolol hydrochloride is a white or almost white powder. It is soluble in water.

Propranolol is highly lipophilic and is almost completely absorbed from the gastrointestinal tract. Propranolol is extensively metabolized in the liver with most metabolites appearing in the urine. The major metabolite is the carboxylic acid. One product of hepatic metabolism is 4- hydroxy propranolol (54) which possesses some adrenergic blocking activity.

Propranolol is used in the treatment of hypertension, to improve the tolerance to exercise in patients with angina pectoris, and has been given for the prevention of re-infarction in patient who has suffered an acute myocardial infarction. It is also used in the treatment of cardiac arrhythmias. It is often effective in supraventricular tachyarrhythmia. The dose of the drug is 20 mg to 2 g daily, in divided doses, the initial daily dose not to exceed 40 mg; and by slow intravenous injection the dose is 3 to 10 mg.

Preparations: Propranolol Injection, B.P. Propranolol Tablets, B.P., I.P. Proprietary Names: CARDIOLONG; INDERAL; IPRAN

A (3). α, β - adrenoceptor antagonists: e.g. Labetalol

\[
\text{CH}_2\text{-CH}_2\text{-CH-NH-CH}_2\text{-CH}_3\text{CONH}_2\text{OH} \quad \text{Labetalol (60)}
\]

It possesses two chiral centers and therefore is administered as a mixture of four stereoisomers, of which R(CH₃), R(OH) is the active β-blocker and the S(CH₃), R(OH) diastereomer is predominantly an α₁-blocker.

- R, R diastereomer of labetalol also known as dilevalol.
- S(CH₃), S(OH) and R(CH₃), S(OH) diastereomer are both inactive

Official drug:
Labetalol Hydrochloride, B.P. all-rac-2-Hydroxy-5[1-Hydroxy-2-(1--methyl-3-phenylpropylanmo)- ethyl]-benzamide hydrochloride. Labetalol hydrochloride forms white powder or granules. It is sparingly soluble a water. Labetalol is readily absorbed from the gastrointestinal tract. The metabolites are excreted in the urine along with only small amounts of unchanged Labetalol.

Labetalol is a nonselective β-blocker that acts as a competitive antagonist at both α₁- and β-adrenergic receptors. Labetalol decreases blood pressure more rapidly than other β-blockers. Labetalol hydrochloride is usually given by mouth in the
treatment of hypertension, the dosage varying from 200 mg to 2.4 g daily in divided doses.

Preparations: Labetalol Injection, B.P. Labetalol Tablets, B.P. Proprietary Names: NORMADATE; NORMODYNE; TRANDATE,

A (4). Centrally Acting Agents

\[
\text{HO} \quad \text{CH}_2 \quad \text{C} \quad \text{COOH} \quad \text{NH}_2
\]

\[
\text{HO} \quad \text{CH}_2 \quad \text{N}-\text{C} \quad \text{NH} \quad \text{NH}_2
\]

\[
\text{HO} \quad \text{CH}_2 \quad \text{N} \quad \text{Cl}
\]

\[
\text{HO} \quad \text{CH}_2 \quad \text{N}-\text{C} \quad \text{NH} \quad \text{NH}_2
\]

\[
\text{HO} \quad \text{CH}_2 \quad \text{N} \quad \text{OH}
\]

α-Methyldopa (61) is converted into α-methyl noradrenaline which acts as a false neurotransmitter which activates central α-receptor and produce fall in blood pressure. Clonidine (62) originally developed as nasal decongestant. It is also used in the treatment of all grades of hypertension. There are two major metabolites of clonidine are p-hydroxyclonidine (65) and its O-glucuronide.

Synthesis of Methyldopa:
Official Drugs

Methyldopa, B.P., I.P. 3-(3, 4-Dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate. It is a white to yellowish-white, fine powder which may contain friable lumps. It is sparingly soluble in water. When administered orally methyldopa is absorbed by an amino acid active transport system. Peak concentrations in plasma occur after 2 to 3 hours. It is eliminated with half-life of about 2 hours. It is extensively metabolized and is excreted in urine as unchanged drug and O-sulphate conjugate.

Methyldopa is used in the treatment of moderate to severe hypertension in conjunction with a diuretic. The side effects and toxicity limit its usefulness.

Preparation: Methyldopa Tablets, B.P., I.P. Proprietary Names: ALDOMET; DOPAMET

A (5). Agents Depleting Neurotransmitter Stores

Synthesis of Guanethidine:
Official Drugs

Reserpine B.P., I.P. Methyl 11,17a-dimethoxy-18β-(3, 4, 5- trimethoxybenzoyloxy) -3β, 20α- yohimbane-16β-carboxylate. Reserpine forms white or pale buff to slightly yellowish, crystalline powder. It is practically insoluble in water. Reserpine is absorbed from the gastrointestinal tract. Reserpine is metabolized by the liver and intestine to methyl reserpate and 3, 4, 5-trimethoxybenzoic acid.

Reserpine is used in mild to moderate hypertension. It has been used in chronic psychoses. In psychiatric states 1 to 5 mg daily, in divided doses, are given orally, and in the treatment of hypertension the dose is 0.5 mg daily. Reserpine has also been given by intravenous and intramuscular injection. 
Preparations: Reserpine Injection, I.P. Reserpine Tablets, I.P. Proprietary Name: SERPASIL

Guanethidine Sulphate, I. P. Guanethidine Monosulphate, B.P. 1-[2-(Perhydroazocin-1-yl)-ethyl guanidine sulphate. It may be prepared by interaction of 1-(2-aminoethyl) perhydroazocine with S-methyl isothiourea and conversion of the product to the sulphate. Guanethidine sulphate is a white or almost white, crystalline powder. It is freely soluble in water. Guanethidine is variably and incompletely absorbed from the gastrointestinal tract with less than 50% of the dose reaching the systemic circulation. It is excreted in the urine as metabolites and unchanged drug. It has a terminal half-life of about 5 days.

Guanethidine sulphate is used in the treatment of hypertension when other drugs have proved inadequate. Initial dose is 10 to 20 mg daily with the subsequent doses, increasing at week intervals to a maximum of 300 mg daily, is accordance with the need of the patient.
Preparation: Guanethidine Tablets, B.P, I.P. Proprietary Name: ISMELIN

A(6). Gaglionic Blocking Agents
Synthesis of Mecamylamine:

\[
\text{Camphene (77)} + \text{Hydrocyanic Acid} \xrightarrow{\text{Strong Acid}} \text{3-formamidoisocamphane (78)}
\]

Mecamylamine (76)

Official Drug

**Mecamylamine Hydrochloride, I.P.** Methyl-2, 3, 3-trimethylbicyclo-[2, 3, 3]-hept-2-yl-amine hydrochloride. Mecamylamine hydrochloride is a white crystalline powder. It is soluble in water. It is almost completely absorbed from the gastrointestinal tract. It is excreted slowly by the kidney in unchanged form and has a relatively long duration of action. Mecamylamine hydrochloride may be indicated in severe or malignant hypertension. It is available as tablets for oral administration. The initial dosage is 5 mg daily, in divided doses; the subsequent doses are in accordance with the needs of the patients.

*Proprietary Name:* INVERSIVE

**B(1). Angiotensin Converting Enzyme (ACE) Inhibitors:** Captopril (79), Enalapril (80) is prodrug that is not itself highly active and it must be hydrolyzed to enalaprilate. Lisinopril (81) is the lysine analogue of enalaprilate and is itself active.
B (2). Angiotensin Receptor Antagonist

Sar-Arg-Val-Tyr-Val-His-Pro-Ala

Saralasin (82)

Losartan (83)

C(1)a. Directly Acting Vasodilators:

Hydralazine (84)

Nitroprusside sodium (85)

Synthesis of Hydralazine:
Official drugs:

**Sodium Nitroprusside, B.P.** Sodium nitrosylpentacyanoferrate (III) dihydrate. It forms reddish-brown crystals or powder; freely soluble, nitroprusside should be kept in a well-closed container and protected from light.

Sodium nitroprusside is a short-acting hypotensive agent with duration of action of 1 to 10 minutes. It may be used in the treatment of hypertensive crises. It may also be employed to produce controlled hypotension during general anesthesia. It is given by continuous infusion of a solution containing 50 to 200 g per ml.

*Preparation:* Sodium Nitroprusside Intravenous, Infusion, B.P. *Proprietary Names:* NIPRIDE; NITROPRESS

**C(1)b. Potassium Channel agonist:**

**Synthesis of Diazoxide:**

**Minoxidil (91)**

```
H2N-NH2
\[\text{Hydrazine} \quad \text{lactim-form (88)}\]
```

```
NN
Cl
\[\text{Hydralazine (84)}\]
```

```
NN
Cl
\[\text{chloro derivative (89)}\]
```
Official drugs:
**Diazoxide, B.P.** 7-Chloro-3-methyl-2H-1, 2, 4- benzothiadiazine 1,1-dioxide. It is a white or almost white, crystalline powder; practically insoluble in water. Diazoxide is readily absorbed from the gastrointestinal tract. About 20 to 25% of the drug is eliminated as such by the kidney, and the remaining is metabolized in the liver to the 3- hydroxy methyl and 3-carboxy derivatives. Diazoxide is given intravenously for the treatment of hypertensive emergencies. The parenteral dose is 1 to 3 mg per kg body weight within 30 seconds, up to a maximum of 150 mg and repeated after 5 to 15 minutes, if required. Diazoxide is given by mouth in the treatment of intractable hypoglycemia. The initial dose is 5 mg per kg daily in 2-3 divided doses.

*Preparations:* Diazoxide Injection, B.P. Diazoxide Tablets, B.P.*

**Proprietary Names:** EUDEMINE; HYPERSTAT I.V.

**C (2) Calcium Channel Blockers**

Verapamil (10)

Diltiazem (11)

Nifedipine (12)
D. Diuretics:

Nimodipine (13)

Amlodipine (16)

D. Diuretics:

Hydrochlorothiazide (97)

Furosemide (98)

Spironolactone (99)

Triamterene (100)

Official Drug

Spironolactone, B.P., I.P. Spirolactone. 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone. Spironolactone is a white to cream powder; odorless or with a slight odour of thioacetic acid. It is practically insoluble in water. It should be protected from light. The onset of action of spironolactone is relatively slow. The maximum effect appears in 2 or 3 days. On discontinuation of the drug the action again takes 2 or 3 days to taper off. Spironolactone is employed in the treatment of refractory edema associated with congestive heart failure, cirrhosis of the liver, or the nephrotic syndrome, and in malignant ascites. It has also been used in the treatment of essential hypertension. It is used in conjunction with other diuretic agents to prevent excessive loss of potassium ions. The dose is 100-200 mg daily, increased to 400 mg if required. It may be given in doses of 400 mg per day as diagnostic test for primary hyperaldosteronism.

Preparation: Spironolactone Tablets, B.P., I.P. Proprietary Names: ALDACTONE; LACTONE; SPIROCTAN

Structure Activity Relationship (SAR) of Antihypertensives: The Structure Activity Relationship (SAR) of some important classes of antihypertensives have been given in the following pages.
Structure-activity Relationships of ACE inhibitors:
Angiotensin converting enzyme is a stereoselective drug target. Since currently approved ACE inhibitors act as either di- or tripeptide substrate analogs, they must contain a stereochemistry that is consistent with the L-amino acids present in the natural substrates. This was established very early in the development of ACE inhibitors when compounds with carboxyl-terminal D-amino acids were discovered to be very poor inhibitors. It was reported that a 100 to 1000 fold loss in inhibitor activity whenever the configuration of either the carboxylate or the R, substituent was altered. The S, SS configuration seen in enalapril and dicarboxylate inhibitors meets the above stated criteria and provides for optimum enzyme inhibition.

Physicochemical Properties: Captopril (79) and fosinopril are acidic drugs, while all other ACE inhibitors are amphoteric. The carboxylic acid attached to the N-ring is a common structural feature in all ACE inhibitors. It has a pKa in the range of 2.5-3.5 and will be primarily ionized at physiologic pH. As discussed above with enalapril, the pKa and ionization of the secondary amine present in the dicarboxylate series depends upon whether the adjacent functional group is in the prodrug or active form. In the prodrug form, the amine is adjacent to an ester, is less basic, and is primarily unionized at physiologic pH. Following bioactivation, the amine is adjacent to an ionized carboxylic acid, which enhances both the basicity and ionization of the amine. Similarly, the basic nitrogen enhances the acidity of the adjacent carboxylic acid such that it usually has a lower pKa than the carboxylic acid attached to the N-ring. As an example, the pKa values of enalapril are 3.39 and 2.30. These values correspond to the carboxylic acid on the N-ring and the carboxylic acid adjacent to the amine, respectively.

Structure-activity Relationship of ACE Inhibitors

![Structure-activity Relationship of ACE Inhibitors](image)

a. The N-ring must contain a carboxylic acid to mimic the C-terminal carboxylate of ACE substrates.
b. Large hydrophobic heterocyclic rings in the ~N-ring increase potency and alter pharmacokinetic parameters.
c. Groups A, B, or C can serve as zinc binding groups.
d. The sulfhydryl group shows superior binding to zinc (Phe in carboxylate and phosphinic acid side chain compensates for sulfhydryl group).
e. Sulfhydryl-containing compounds produce high incidence of skin rash and taste disturbances.
f. Sulfhydryl-containing compounds can form disulfides, which may shorten duration of action.
g. Binding to zinc through either a carboxylate or phosphinate mimics the peptide hydrolysis transition state.

h. Esterification of the carboxylate or phosphinate produces an orally bioavailable prodrug.

i. X is usually methyl to mimic the side chain of alanine. Within the dicarboxylate series, when X equals n-butylamine (lysine side chain) this produces a compound, which is orally active without being a prodrug.

j. Optimum activity occurs when stereochemistry of inhibitor is consistent with L-amino acid stereochemistry.

Analogous values for these functional groups in lisinopril are 3.3 and 1.7. The enalaprilat and lisinopril, all of the compounds possess good lipid solubility. Compounds which contain hydrophobic bicyclic ring systems are more lipid soluble than those which contain proline. A comparison of the log P values of benazepril, perindopril, quinapril, ramipril, and trandolapril to those for captopril and enalapril illustrates this fact. As previously discussed, enalaprilat is much more hydrophilic than its ester prodrug and is currently the only ACE inhibitor marked for intravenous administration. In terms of solubility, lisinopril is probably the most interesting compound in that it is the most hydrophilic inhibitor, yet unlike enalaprilat, it is orally active. One possible explanation for this phenomenon is that in the duodenum, lisinopril will exist as a di-zwitterion in which the ionized groups can internally bind to one another. In this manner, lisinopril may be able to pass through the lipid bilayer with an overall net neutral charge.

**Structure-activity Relationships of angiotensin II antagonists:**

All commercially available angiotensin II antagonists are analogs of the following general structure:

1) The "acidic group" is thought to mimic either the Tyr₄ phenol or the A-sp, carboxylate of angiotensin II. Groups capable of such a role include the carboxylic acid (A), a phenyl tetrazole (B), or a phenyl carboxylate (C).

2) In the biphenyl series, the tetrazole and carboxylate groups must be in the ortho position for optimal activity (the tetrazole group is superior in terms of metabolic stability, lipophilicity, and oral bioavailability).

3) The n-butyl group of the model compound provides hydrophobic binding and most likely mimics the side chain of Ile₅, of angiotensin II. As seen with candesartan and telmisartan, this n-butyl group can be replaced with a substituted benzimidazole ring.

4) The imidazole ring, or an isosteric equivalent, is required to mimic the His₁₁, side chain of angiotensin II.

5) Substitution with a variety of R groups including a carboxylic acid, methyl alcohol, ether, or an alkyl chain is required to mimic the Phe, of angiotensin II. All of these groups are thought to interact with the AT₁ receptor, some through ionic or ion-dipole bonds and others through hydrophobic interactions.
Structure activity Relationships of calcium channel blockers:
The structure-activity relationships for 1, 4-DHP derivatives indicate that the following structural features are important for activity:

1) A substituted phenyl ring at the C₄ position optimizes activity (heteroaromatic rings, such as pyridine, produce similar therapeutic effects; but are not used due to observed animal toxicity). C₄ substitution with a small nonplanar alkyl or cycloalkyl group decreases activity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>CH₂OH₂CH₂NH₂</td>
<td>CO₂CH₂CH₃</td>
<td>CO₂CH₃</td>
<td>2-Cl</td>
</tr>
<tr>
<td>2-Felodipine</td>
<td>CH₃</td>
<td>CO₂CH₂CH₃</td>
<td>CO₂CH₃</td>
<td>2,3-Cl₂</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>CH₃</td>
<td>CO₂(CH₂)₂-NH(Me)CH₂-Ph</td>
<td>CO₂CH₃</td>
<td>3-NO₂</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>CH₃</td>
<td>CO₂CH₂CH₃</td>
<td>CO₂CH₃</td>
<td>2-NO₂</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>CH₃</td>
<td>CO₂CH₂CH₂OCH₃</td>
<td>CO₂CH(CH₃)₂</td>
<td>3-NO₂</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>CH</td>
<td>CO₂CH₂CH(CH₃)₂</td>
<td>CO₂CH₃</td>
<td>2-NO₂</td>
</tr>
</tbody>
</table>
2) Phenyl ring substitution (X) is important for size and position rather than for electronic nature. Compounds with ortho or meta substitutions possess optimal activity, while those which are unsubstituted or contain a para-substitution show a significant decrease in activity. Electron withdrawing ortho or meta-substituents or electron donating groups demonstrated good activity. The importance of the ortho and meta-substituents is to provide sufficient bulk to "lock" the conformation of the 1, 4-DHP such that the C₄ aromatic ring is perpendicular to the 1, 4-dihydropyridine ring. This perpendicular conformation has been proposed to be essential for the activity of the 1, 4DHPs.

3) The 1, 4-dihydropyridine ring is essential for activity. Substitution at the N₁ position or the use of oxidized (piperidine) or reduced (pyridine) ring systems greatly decreases or abolishes activity.

4) Ester groups at the C₃ and C₅ positions optimize activity. Other electron withdrawing groups show decreased antagonist activity and may even show agonist activity. For example, the replacement of the C₃ ester of isradipine with a NO₂ group produces a calcium channel activator, or agonist (Fig.). Thus the term, calcium channel modulators, is a more appropriate classification for the 1, 4-DHPs.

5) When the esters at C₃ and C₅ are nonidentical, the C₄ carbon becomes chiral and stereoselectivity between the enantiomers is observed. Additionally, there is evidence that the C₃ and C₅, positions of the dihydropyridine ring are not equivalent positions. Crystal structures of Nifedipine, a symmetrical 1, 4-DHP, have shown that the C₃ carbonyl is synplanar to the C₂-C₃ bond, but that the C₅, carbonyl is antiplanar to the C₅-C₆ bond. Asymmetrical compounds have shown enhanced selectivity for specific blood vessels and are preferentially being developed. Nifedipine, the first 1, 4-DHP to be marketed, is the only symmetrical compound in this chemical class.

6) With the exception of amlodipine, all 1, 4-DHPs have C₂, and C₆ methyl groups. The enhanced potency of amlodipine (vs. Nifedipine) suggests that the 1, 4-DHP receptor can tolerate larger substituents at this position and that enhanced activity can be obtained by altering these groups.

---

**Fig.** Conformation of the C₃ and C₅, esters of nifedipine (Ar = 2-nitrophenyl). The C₃ carbonyl is synplanar to the C₂-C₃ bond, and the C₅ carbonyl antiperiplanar to the C₅-C₆ bond.
Structure-activity Relationships of β-adrenergic antagonist

Shortly thereafter, a major innovation in drug development for the β-adrenergic antagonists was introduced when it was discovered that an oxymethylene bridge, OCH₂, could be inserted into the arylethanolamine structure of pronethalol to afford propranolol (53), an aryl-substituted phenyloxypropanolamines and the first clinically successful practolol, which selectively inhibited sympathetic β-blocker. Note that, along with the introduction of the Oxymethylene Bridge, the side chain has been moved from C₂ of the naphthyl group to the C₁ position.

In general, aryloxypropanolamines are more potent β-blockers than the corresponding arylethanolamines and most of β-blockers currently used clinically are aryloxypropanolamines. β-blockers have found wide use in treating hypertension.

4. Cardiac Glycosides

Introduction

The cardiac glycosides are an important class of naturally occurring drugs whose actions include both beneficial and toxic effects on the heart. Their desirable cardiotonic action is of particular benefit in the treatment of congestive heart failure and associated edema and their preparations have been used as medicinal agents as well as poisons since 1500 B.C. This dual application serves to highlight the toxic potential for this class of life-saving drugs.

The cardio active steroids and their glycosides are widely distributed in nature and have characteristic actions on contractility and electrophysiology of heart. Their discovery is an example of folk lore medicine, known to ancient people like Romans and Egyptians. Most glycosides are obtained from leaves of the foxglove, *Digitalis purpurea* or *Digitalis lanata*. William Withering (1785) was the first to notice their effects on heart; cardiac glycosides are the combination of an aglycone or genin, and one to four sugars. The steroidal aglycone of the glycosides is responsible for cardiac activity and sugars provide favorable solubility and distribution, and thus, affect its potency and duration of action. Now these glycosides are used less frequently. Patients are generally treated with calcium channel blockers (verapamil), Acetyl Choline Esterase Inhibitors (ACEIs) and diuretics.

Classification of Cardiac Glycosides
1. Cardenolides (107)
2. Bufadenolides (108)
## Selected natural cardiac glycosides and their sources

<table>
<thead>
<tr>
<th>Source</th>
<th>Glycosides</th>
<th>Aglycone</th>
<th>General Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Digitalis lanata</em> (Leaf)</td>
<td>Lanatoside A (Digilanide A)</td>
<td>Digitoxigenin (107)</td>
<td>Glucose-3-acetyldigitoxose-digitoxose,-aglycone</td>
</tr>
<tr>
<td></td>
<td>Lanatoside B (Digilanide B)</td>
<td>Gitoxigenin (112)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lanatoside C (Digilanide C)</td>
<td>Digoxigenin (111)</td>
<td></td>
</tr>
<tr>
<td><em>Digitalis purpurea</em> (Leaf)</td>
<td>Purpurea glycoside A (desacetyl digilanide A)</td>
<td>Digitoxigenin (107)</td>
<td>Glucos-digitoxose,-aglycone</td>
</tr>
<tr>
<td></td>
<td>Purpurea glycoside B (desacetyl digilanide B)</td>
<td>Gitoxigenin (112)</td>
<td></td>
</tr>
<tr>
<td><em>Strophanthus gratus</em> (Seed)</td>
<td>g-Strophanthin</td>
<td>Oubagenin (113)</td>
<td>Rhamnose-aglycone</td>
</tr>
<tr>
<td><em>Strophanthus kombe’</em> (Seed)</td>
<td>k-Strophanthoside</td>
<td>Strophanthidine (114)</td>
<td>Glucose-glucose-cymarose-aglycone</td>
</tr>
</tbody>
</table>

### The Cardenolides and Bufadienolides

- **Cardenolide Prototype**
  - Digitoxigenin (107)

- **Bufadienolide Prototype**
  - Bufalin (108)

- **5β, 14β−** (cis, cis) (109)

- **5β, 14β−** (cis, cis) (110)
In most cases, the cardiac glycosides of plant origin, the cardenolides, possess a five-membered α, β-unsaturated lactone ring, whereas those derived from animal origin, the bufadienolides, possess a six-membered lactone ring with two conjugated double bonds (generally referred to as α-pyrone). Bufadienolides are commonly known as toad poison because several are found in the skin secretion of toad species.
The cardiac glycosides occur mainly in plants and in rare cases in animals, such as poisonous toads. The most important glycosides are as follows:

- **Digitalis purpurea** - Digitoxin, Digoxin
- **Digitalis lanata** - Digoxin, lanatosides, Deslanoside
- **Strophanthus gratus** - Ouabain

**Chemistry of the Cardiac Glycosides**

Cardiac glycosides and similar other glycosides are composed of sugar and the non-sugar (aglycone) moieties.

**Sugars:** The hydroxyl group at C-3 of the aglycone portion is usually conjugated to a monosaccharide or a polysaccharide with β-1, 4-glucosidic linkages. The number and identity of sugars vary from one glycoside to another as detailed subsequently. The most commonly found sugars in the cardiac glycosides are D-glucose, D-digitoxose, L-rhamnose, and D-Cymarose.

At a time, the aglycone portion may combine with 1-4 molecule of sugar. The attached sugar through glycosidic linkage may be mono-, di-, tri-, or tetra-saccharides.

All aglycones represent similar set of pharmacological action. It is the sugar moieties attached to the aglycone play an important role in governing duration of action, partition coefficient, absolute potency, and protein binding properties of glycosides. It also inhibits an enzyme induced metabolic change in the aglycone configuration.

Sugars predominately exist in the cardiac glycosides in the β-conformation. In some cases, the sugars exist in the acetylated form. The presence of an O-acetyl group on a sugar greatly affects the lipophilic character and pharmacokinetics of the entire glycoside.

Cardiac glycosides are the cardiotonic that increase the contractile force of the heart and exert important actions on cardiac excitability automaticity conduction velocity and
refractory periods. These are mainly used for CHF, arterial fibrillation, arterial flutter and paroxysmal arterial

Chemistry of aglycone part
Aglycone portion of the cardiac glycosides is a steroid nucleus with a unique set of fused rings, which makes these agents easily distinguished from the other steroids. Rings A-B and C-D are cis fused, while rings B-C have a trans fusion. Such ring fusion gives the aglycone nucleus of cardiac glycosides the characteristic "U" shape as shown in the figure. The steroid nucleus also carries, in most cases, two angular methyl groups at C-10 and C-13. Hydroxyl groups are located at C-3, the site of the sugar attachment, and at C-14. The C-14 hydroxyl is normally unsubstituted. However, additional hydroxyl groups may be found at C-12 and C-16, the presence or absence of which distinguishes the important genins: digitoxigenin, digoxigenin, oubagenin and gitoxigenin (107, 111-113).

The lactone ring at C-17 is another major structural feature of the cardiac aglycones. The size and degree of unsaturation of the lactone ring varies with the source of the glycoside.

(i) In digitalis glycosides: The anellation of the A - B and C - D rings is cis (Z), the 3-OH is axial and all of these steroids carry a 14β-OH group. The C-17 side chain is an unsaturated lactone ring. The sugar part, binding to the 3-OH, is a tri or tetrasaccharide consisting mainly of digitoxose and glucose.

(ii) Strophanthin aglycone has a 5β-OH group in addition to other hydroxyls, up to a maximum of 6 in ouabain. The 19-CH₃ is replaced by a CHO or primary alcohol and the sugars are the unusual rhamnose cymarose.

(iii) The squill aglycones carry a six-membered lactone ring with two double bonds. None is used because of high toxicity.

(iv) The lactone ring is not essential. The coplanar Compounds with marginal activity: where side-chains instead of a ring have even higher activity.

(v) The activity of a compound depends to a great extent on the position of the 23rd carbonyl oxygen, which is held quite rigidly by ring D and the double bond.

(vi) Removal of the sugar portion allows epimerization of the 3β-OH group, with a decrease in activity and an increase in toxicity due to changes in polarity.

The lactone ring at C-17 is another major structural feature of the cardiac aglycones. The size and degree of unsaturation of the lactone ring varies with the source of the glycoside.

Mechanism of action
Cardiac glycosides exert positive inotropic effect on heart. At the cellular level, digitalis inhibits membrane-bound Na⁺, K⁺-activated adenosine triphosphatase. This inhibition increases intracellular Na⁺. This Na⁺ in turn exchanges with extra cellular Ca²⁺, thus increasing intracellular Ca²⁺ levels. Inhibition of the enzyme also decreases outward pumping of both Na⁺. The net effect is an increase in the Ca²⁺ pool available for excitation-contraction coupling.

Official drugs:
Digoxin, B.P., I.P. 3β-[(O-2, 6-Dideoxy-β-D-ribo-hexopyranosyl-(1-4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1-4)-O-2, 6-dideoxy-β-D-ribo-hexopyranosyl)-oxy]- 12β,14-dihydroxy-5 β, 14β-card-20(22)-enolide. It has the aglycone digoxigenin and
the sugar part is composed of three molecules of D-digitoxose. Digoxin form colorless crystals or a white or almost white powder. It is practically insoluble in water.

The absorption of digoxin from the gastrointestinal tract is variable depending upon the formulation used. Digoxin is mainly excreted unchanged in the urine. Digoxin is used in the treatment of congestive heart failure with arterial fibrillation although the beneficial effect of long-term treatment in sinus rhythm is questioned.

The initial dose for oral administration of digoxin is 1 to 1.5 mg, with maintenance dose of 0.25 mg, once or twice daily. The initial dose by intravenous injection is 0.5 to 1 mg.

Preparations: Digoxin Injection, B.P., I.P., Digoxin Tablets, B.P., I.P., Pediatric Digoxin Injection, B.P. Pediatric Digoxin Oral Solution, B.P. Proprietary Name: LANOXIN

Digitoxin, B.P., I.P. 3β-O-2, 6-Dideoxy-β-D-ribo-hexopyranosyl (1-4)-O-2, 6-dideoxy-β-D-ribo-hexopyranosyl-(1-4)-O-2, 6-dideoxy-β-D-ribo-hexopyranosyl-oxy]-14-hydroxy-5 β, 14β-card-20(22)-enolide. Digitoxin occurs as white or almost white powder. It is practically insoluble in water. Digitoxin is readily and completely absorbed from the gastrointestinal tract. Digitoxin is extensively bound to plasma protein. It is very slowly eliminated from the body and is metabolized in the liver, the major active metabolite being digoxin. Digitoxin has an elimination half-life up to 7 days or more.

It is the most potent of the digitalis glycosides and is the most cumulative in action. The onset of action is slower than that of other cardiac glycosides. Its effects persist for about 3 weeks. It is given orally and may also be given by slow intravenous injection. The initial dose is 1 to 1.5 mg, divided over twenty-four to twenty-eight hours, with maintenance of 0.05 to 0.2 mg daily.

Preparation: Digitoxin Tablets, B.P., I.P. Proprietary Name: CRYSTODIGIN

Deslanoside, B.P., I.P. Deacetyl-lanatoside C; Desacetyl-lanatoside C. 3β[(O-β-D-glucopranosyl (1-4)-O-2, 6-dideoxy-β-D-ribo-hexopyranosyl(1-4)-O-2, 6-dideoxy-β-D-ribo-hexopyranosyl(1-4)-O-2, 6-dideoxy-β-D-ribo-hexopyranosyl-oxy]12β, 14-dihydroxy-5β,14β-card-20(22)-enolide. Deslanoside forms white crystals or a white crystalline powder and is hygroscopic. It is practically insoluble in water. Deslanoside is a derivative of lanatoside C. It has actions and uses similar to those of digoxin. Usually it is reserved for treatment of emergencies, although digoxin is generally preferred. It has half-life of about 33 hours and its effects persist for 2 to 5 days. It is given by intravenous injection and has also been given intramuscularly. By intravenous or intramuscular injection, the initial dose is 0.8 to 1.2 mg, with maintenance dose of 0.4 mg given at intervals of two to four hours.

Preparation: Deslanoside Injection, I.P.
Structure - Activity Relationship: Since cardiac glycosides comprise of:
1. A genin or aglycone portion and
2. A sugar portion, the SAR studies of these agents are based on the separate SAR investigations on these portions.

(1) Genin or aglycone portion
(A) C-17 Side chain: The substitutions at C-17 of the genin portion cardiac glycosides are generally of two types

\[ \text{CH} = \text{CH} - \text{C} (R) = \text{A} \]

(120)

Where A may be oxygen or nitrogen.

(a) A five or six-membered lactone ring. In both these types of C-17 substituent, there is a double bond conjugated with carbonyl oxygen.

(b) Reduction of C-17 side chain double bond results into decreased activity.

(c) The compounds having -CH = CH- CH = NH, side chain (A=N) at C-17, exhibit higher activity.

(d) If the conjugation system in C-17 side chain is extended (i.e. - CH = CH – CH = CH CH = A), activity abolishes.

(e) Since H-boning (which takes place between the side-chain and K⁺ -binding site of Na⁺, K⁺ -ATPase enzyme) determines the degree of Na⁺, K⁺ -ATPase inhibition, the molecule's dipole is an important parameter.

(B) Steroid nucleus
(a) Lactone ring at C-1 7, essential for activity.

(b) Since some compounds, not having C-14 hydroxyl group, have not shown activity, therefore, C-14 hydroxyl group is not essential for activity.

(2) Sugar Portion
 Though the sugars are not directly involved in cardiotonic activity, their attachment to the steroid (at C₃₃) contributes greatly to both the pharmacodynamic and pharmacokinetic
parameters of the cardiac glycosides. Since the free genins are more rapidly absorbed and
more widely distributed than the corresponding glycosides, this leads to their rapid
metabolism to give less active 3-epimers, followed by rapid excretion via sulphates and
glucuronides formation at free C-3 OH group. The free genins therefore are quite
unstable as therapeutic agents.

Pharmacodynamically, the genins are usually less potent than their glycosidic forms and
show rapid onset and reversal of enzyme inhibitions. In contrast to this the glycosides
form very stable complexes with Na\(^+\), K\(^+\) ATPase enzyme. Replacement of the sugar
moieties with nitrogen containing side chains gives potent analogs of digitalis e.g. N-(4'-
amino- n-butyl) - 3- amino acetyl derivative of strophanthidine has about 60 times greater
affinity towards Na\(^+\), K\(^+\) -ATPase enzyme than the parent genin. H- bonding is the
principal interaction involved between sugar and enzyme. Particularly 3-OH and 5-CH\(_3\)
groups seem to be binding group in 2, 6-desoxy sugars.

5. Vasodilators

There are certain drugs having cerebral and peripheral vasodilating effects. Mainly
under these category arterial vasodilators and arterial and venous dilatators are
included. Others are smooth muscle relaxants, and there are some which act by
simulating the effects of beta-adrenoceptor stimulation.

Classification
a. Arterial vasodilators: This group of antihypertensive drugs directly releases arteriolar
smooth muscle and thus, decreases peripheral vascular resistance and arterial blood
pressure. These drugs often cause salt and water retention and thus expansion of the
extra-cellular fluid and plasma volume. Therefore, these drugs should be used in
conjunction with diuretic and \(\beta\)-blocker. Some of the important drugs are described here.

Hydralazine Hydrochloride (Apresoline): 1-Hydrizinophthalazine \((123)\).

Synthesis: It can be prepared by condensing 2-formyl benzoic acid \((86)\) and hydrazine in
the following way:
Hydralazine is a direct relaxant of vascular smooth muscle for the treatment of moderate to severe hypertension. It causes reflex tachycardia and fluid retention; therefore, it should always be given in combination with a \( \beta \)-adrenergic receptor blocker and a diuretic. Nitric oxide can be generated from hydralazine; therefore, its action is similar in mechanism to sodium nitroprusside and organic nitrates. Headache, palpitations, and GI disturbances are the most frequent adverse effects. The major metabolite is hydralazine pyruvic acid hydrazone. Dose: 25 to 100 mg oral twice daily; 20 to 40 mg i. v. in emergency.

**Minoxidil** (Loniten): 6-(1-Piperidinyl)-2, 4-pyrimidine diamine 3-oxide (91)

**Synthesis:** It can be prepared starting from ethylcyanoc acetate in the following way:

It occurs as a white, crystalline solid soluble in water. Minoxidil (91), a piperidino pyrimidine derivative directly relaxes arterial smooth muscle and is indicated for patients with severe hypertension who do not respond to other drugs. It causes considerable \( \text{Na}^{+} \) retention and tachycardia, which necessitate concomitant use of diuretic and \( \beta \)-adrenergic blocking agents. It is biotransformed to an active metabolite, minoxidil \( \text{N} \rightarrow \text{O} \) sulfate, which releases vascular smooth muscles and increases the permeability of the cell membrane to \( \text{K}^{+} \), resultant hyperpolarization. Minoxidil (91) also causes hirsutism, a side effect that has prompted its development as a treatment (Rogaine 2% solution) for baldness. Dose: Initial 5 mg; can be increased to 40 mg/ day.

**Diazoxide** (Hyperstat): 7-Chloro-3-methyl-2H-1, 2, 4-benzothiadiazine- 1, 1 –dioxide (90).

**Synthesis:** It can be prepared by condensing 2, 4- dichloro nitrobenzene (128) and benzylthiol in the following way:
Diazoxide (90) is chemically similar to thiazide diuretics. Paradoxically though, it causes Na\(^+\) retention. This may be due to its lack of sulfonamido group. It is used as an antihypertensive drug in emergencies. It has rapid onset of action (3-5 minutes) and when administered intravenously it lowers blood pressure. It also produces hyperglycemia, and can cause severe hypotension. Diazoxide (90) hyperpolarizes arterial smooth muscle cells by activating ATP-sensitive K\(^+\) channels; this causes relaxation of the vascular smooth muscle. It is metabolized to the 3-hydroxymethyl (133) and 3-carboxy (134) derivatives.

Dose: 1 mg. kg every 10 minutes.

(b) Arterial and venous dilatators

**Sodium Nitroprusside (Nipride):** Nitroprusside (137) is used for short term, rapid reduction of blood pressure in hypertensive emergencies. Onset of action occurs within 1 minute of intravenous administration, and effects cease within 5 minutes of stopping on infusion. In the vascular endothelium it forms an active nitrosothiol with glutathione that increases cyclic GMPI, thereby causing vasodilatation. The nitroso moiety of sodium nitroprusside (9) decomposes to nitric oxide. Endogenously sodium nitroprusside is a non-selective vasodilator. Hypotension, nausea, headache can occur. A metabolic product of nitroprusside is cyanide, which is quickly metabolized to thiocyanate.

Dose: 1 mg/kg/min by I.V. infusion.
Official Drugs

Hydralazine Hydrochloride, I.P. Hydralazine Hydrochloride, B.P. 1-Hydrazinophthalazine hydrochloride; phthalazin-1-ylhydrazine hydrochloride. It is a white or almost white crystalline powder; soluble in water. In plasma hydralazine is chiefly present as a hydrazone with pyruvic acid. Hydralazine hydrochloride is used for the treatment of moderate, severe hypertension usually in conjunction with a beta-blocker and a thiazide diuretic. The oral dose is 10 mg four times a day, gradually increased up to 50 mg four times a day. It may be given by slow intravenous injection or by intravenous infusion for hypertensive emergencies; the dose range is 20 to 40 mg, repeated as may be necessary. It has also been given by intramuscular injection.

Preparations: Hydralazine Injection, B.P. Hydralazine Tablets, B.P. Proprietary Name: APRESOLINE

Diazoxide, B.P. 7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide. It is a white or almost white, crystalline powder; practically insoluble in water. Diazoxide is readily absorbed from the gastrointestinal tract. About 20 to 25% of the drug is eliminated as such by the kidney, and the remaining is metabolized in the liver to the 3-hydroxymethyl and 3-carboxy derivatives. Diazoxide is given intravenously for the treatment of hypertensive emergencies. The parenteral dose is 1 to 3 mg per kg body weight within 30 seconds, up to a maximum of 150 mg and repeated after 5 to 15 minutes, if required. Diazoxide is given by mouth in the treatment of intractable hypoglycemia. The initial dose is 5 mg per kg daily in 2-3 divided doses. The hyperglycemic effect normally lasts for up to 8 hours.

Preparations: Diazoxide Injection, B.P. Diazoxide Tablets, B.P. Proprietary Names: EUDEMINE; HYPERSTAT I.V.
6. Anti-arrhythmic Agents

Introduction
Certain disease and the effect of some drugs are usually responsible affecting the rhythm and the normal heart rate. These cardiac arrhythmia may be caused from disorders in the normal mechanical activity of the heart depends upon a specific sequence of electrical activation for all myocardial cells during each beat, beginning first at the SA node and ending with depolarization of the ventricle. Thus arrhythmia may arise due to alteration in, Conduction Automaticity Refractory period of the myocardial cells.

Antiarrhythmic drugs may be defined as drugs that are capable of reverting any irregular cardiac rhythm or rate to normal. Antiarrhythmic agents are also termed as antidysrhythmic drugs or antifibrillatory drugs. The 'ideal' antiarrhythmic drug should have the following properties:

(i) High efficiency in controlling symptoms and improving survival in both supraventricular and ventricular arrhythmias.
(ii) No negative effect.
(iii) Favourable effect on myocardial oxygen consumption.
(iv) Both oral and intravenous activity.
(v) Wide therapeutic range.

Classification of Antiarrhythmic drugs
Vaughan Williams & Singh gave four class systems for Antiarrhythmic agents and further proposed modified sub-grouping of class I drug was done by D.C. Harrison.

Class I: Membrane stabilizing agents (Na⁺ channel blockers). These classes of drugs are found to interfere directly with depolarization of the cardiac membrane.

Class IA: Prolongs action potential duration e.g. Quinidine, Procainamide, Disopyramide and moricizine.

Class IB: Shortens action potential duration e.g. Lidocaine, Phenytoin, Tocainide and Mexiletine.

Class IC: Have no effect on action potential duration (i.e., slow phase O depolarization), e.g. Encainide, Flecaainide, Indecainide and propaferone.

Class II: β- adrenergic Blockers e.g. Propranolol, Metoprolol

Class III: Drugs that prolongs the action potential duration. e.g. Amiodaron, Bretylium tosylate.

Class IV: Calcium Channel Blockers e.g Verapamil, Diltiazem, Nifedipine

Class I Antiarrhythmic Drugs: Class I drugs are generally local anesthetics acting on nerve and myocardial membranes to slow conduction by inhibiting phase 0 of the action potential. Myocardial membranes show the greatest sensitivity. Class I drugs decrease the maximal rate of depolarization without changing the resting potential. They also increase the threshold of excitability; increase the effective refractory period, decrease
conduction velocity, and decrease spontaneous diastolic depolarization in pacemaker cells. The decrease in diastolic depolarization tends to suppress ectopic foci activity. Prolongation of the refractory period tends to abolish reentry arrhythmias. This class is further subclassified into class IA, IB, and IC based on the primary pharmacologic effect.

**Class IA Antiarrhythmic Drugs**

**Quinidine** (138) is a d-isomer of quinine. It is obtained from bark of various species of cinchona and from *Remijia pendunculata*. Quinidine has a direct myocardial depressant action. It increases refractory period, depresses contractility, depresses excitability and slows speed of conduction in cardiac muscle.

**Synthesis of Procainamide (139)**

**Procainamide** (p-Amino-N-[2-diethylamino)-ethyl] benzamide hydrochloride) (139) differs from local anaesthetic procaine in that the ester linkage of procaine is replaced by an amide linkage. This difference had distinct advantages as an antiarrhythmic drug, that is, greater stability from enzymatic hydrolysis and fewer CNS effects of procaine. Procainamide is so similar in its action to quinidine that the two drugs can be used interchangeably. It is particularly effective in promptly abolishing ventricular premature depolarization and paroxysmal ventricular tachycardia. Acute glaucoma and urinary retention is observed. Procainamide analogs with electron-donating groups (OH, NH₂,
NHCOCH₃) on the aromatic ring possess more antiarrhythmic activity than the analog with an electron-withdrawing group (NO₂).

Disopyramide (144)

Moricizine (145)

**Synthesis of Disopyramide (144)**

Disopyramide Phosphate (α-[2-(Diisopropylamino) ethyl]-x-phenyl-2-pyridine acetamide phosphate) is approved for oral administration in the treatment of ventricular arrhythmias as an alternative to quinidine and procainamide. It has both direct and indirect actions of the heart, which resemble those of quinidine. Disopyramide is administered as a racemic mixture, but its antiarrhythmic activity resides primarily in the S-enantiomer. It is metabolised by mono-N-desalkylation with loss of one Nitroisopropyl group. This metabolite is responsible for its anticholinergic actions.

Moricizine Hydrochloride (Ethyl 10-(3-morpholino nothiazine-2-carbamate hydrochloride) (145). It causes frequency-dependent inhibition of the fast sodium ion current during the action potential. It also shows conduction throughout the heart. It has in particularly useful in patients with impaired cardiac function. Therefore, it is contraindicated to patients with glaucoma, myasthenia gravis, or urinary retention.
Synthesis of Moricizine:

Structure activity relationship
(1) Substitution at the ortho position improved the biological activity. Ethyl group is optimal.
(2) Replacement of pyridyl group with acyclic amines gave good compounds. Cyclohexyl group gave equally potent compound. Pentenamide showed a longer duration of action than disopyramide.
(3) 2-Pyridyl is more potent than other isomers.
(4) Variation in the amino group only di-isopropylamine and 2, 6dimethylpiperidine were the most suitable groups.
(5) A correlation between n values and ventricular arrhythmias was obtained.

Class IB Antiarrhythmic Drugs

Lidocaine (154) is similar to procaine, is an effective, clinically used local. Its cardiac effects, however, are distinctly different from those of procainamide or quinidine. Lidocaine is normally reserved for the treatment of ventricular arrhythmias and is, in fact, usually the drug of choice for emergency treatment of ventricular arrhythmias. Its utility in these situations is due to the rapid onset of antiarrhythmic effects on intravenous infusion. In addition, these effects cease soon after the infusion is terminated. Thus, lidocaine therapy may be rapidly modified in response to changes in the patient's status.
Lidocaine is effective as an antiarrhythmic only when given parenterally, and the intravenous route is the most common. Antiarrhythmic activity is not observed after oral administration because of the rapid and efficient first-pass metabolism by the liver.

**Phenytoin (155)** is most useful in treating ventricular arrhythmias associated with digitalis toxicity or acute myocardial infarction. CNS side effects are the most common problems encountered with phenytoin and include vertigo, loss of mental acuity.

\[
\begin{align*}
\text{Mexiletine (156)} & \quad \text{Tocainide (157)} \\
\text{(158)} & \quad \text{(159)} \\
\text{(160)} & \quad \text{(156)} \\
\text{Mexiletine Hydrochloride:} & \quad (\pm) \ 1\text{-Methyl-2-(2, 6-xylyloxy) ethylamine hydrochloride (156) is most useful in suppressing symptomatic ventricular arrhythmias. It is very similar to lidocaine in its action. It differs from lidocaine in its suitability for oral administration, high systemic availability (90%) after ingestion and is metabolized by hepatic route. It is administered with food and antacid. The major adverse effects of mexiletine are neurologic and include tremors, ataxia and confusion. It is metabolized by N-methylation and p-hydroxylation to inactive metabolites}
\end{align*}
\]

**Synthesis of Mexiletine:**

\[
\begin{align*}
\text{(158)} & \quad \text{(159)} \\
\text{Mexiletine (156)} & \quad \text{HCl}
\end{align*}
\]

**Synthesis of Tocainide:**

\[
\begin{align*}
\text{(161)} & \quad \text{(162)} \\
\text{Tocainide (157)} & \quad \text{NH}_2
\end{align*}
\]
**Tocainide Hydrochloride** (±)-2-Amino-N-(2,6-dimethyl-phenyl) propionamide hydrochloride (157) is another lidocaine congener, similar to mexiletine its electrophysiologic properties and antiarrhythmic action; A low incidence of bone marrow depression has caused this drug to be used less frequently than mexiletine.

**Class IC Antiarrhythmic Drugs**

![Chemical structures of Class IC Antiarrhythmic Drugs]

### Synthesis of Flecainide (163):

![Synthesis of Flecainide (163)]

**Flecainide Acetate**: (±)-N-(2-piperidinylmethyl)-2, 5bis(2,2,2-trifluoroethoxy) benzamide (163) represents the first fluorine containing newer group of antiarrhythmic drugs. It is indicated for use in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. It is able at precipitate cardiac arrest. Other side effects include headache, dizziness and nausea. The major metabolites, meta-O-dealkyl flecainide and meta-O-dealkyl flecainide lactam are inactive. The most potent compounds were having two trifluoroethoxy groups, one of which was ortho to the carboxamide function. The parasubstituted derivatives were less active. Replacement of trifluoro-ethoxy group with 5-CH3, 5-Cl, 5-F resulted in loss of activity. A two-carbon link between amide and amine nitrogen atoms appears to be optimal. Branching at the positions adjacent to the basic nitro-en is responsible for prolonged elimination half-life due to reduced N-dealkylation.
**Encainide Hydrochloride**: 4-Methoxy-2'-[2-(1-methyl-2-piperidyl) ethyl] benzanilide hydrochloride (164) is similar pharmacologically to flecainide. However, its action after long-term therapy seems to be affected by at least two active metabolites, O-demethylencainide (half-life 5 hours) and 3-methoxy-O-demethyl encainide. It is 12 times more active than quinidine. The benzanilido group seems to be essential for activity. Replacement of 4-methoxy group by 4-OH, 4-OAc, or 4-NH$_2$ increases activity dramatically. Introduction of additional methoxy groups, or substitution of methylthio or chloro for 4-methoxy have decreased activity.

**Indecainide** (165) is structurally similar to aprindine and disopyramide. It has shown to be highly efficacious and well treated antiarrhythmic drug for the suppression of ventricular tachycardias. The principal metabolite of indecaainide, N-desisopropylindecaainide, has double half-life (18 hours) than the parent drug and has substantial antiarrhythmic activity. The activity is retained of the 9-carboxamido group is placed by a hydroxyl group.

**Synthesis of Propafenone** (169):

\[
\begin{align*}
\text{Epichlorohydrin} & \rightarrow (170) \\
& \rightarrow (171) \\
& \rightarrow \text{Propafenone (169)}
\end{align*}
\]

**Propafenone Hydrochloride**: 2'-((2-Hydroxy-3-propyl amino proproxy)-3-phenylpropiophenone hydrochloride (169) is useful in supraventricular and ventricular tachycardias and tachyarrhythmias. It resembles the β-adrenoceptor blockers of aryloxypropanolamines. It is administered as a racemic mixture, wherein the R-enantiomer possesses the antiarrhythmic activity and the S-enantiomer is a non-selective β-adrenergic antagonist. These complexities suggest that the drug should be used by only expert cardiologists. It is metabolised to a 5-hydroxyl group attached to propiophenone aryl ring and N-desalkylpropafenone. Introdution of substituents in the β-phenyl ring (4-CH$_3$O, and (CH$_3$)$_2$N, 4-Cl) increases potency.

**Class II-Antiarrhythmic Drugs: β-Receptor antagonists** (See antihypertensive agents) Class II antiarrhythmic drugs are, β-adrenergic receptor blocking agents, which blocks the role of the sympathetic nervous system in the genesis of certain cardiac arrhythmias. Their dominant electrophysiological effect is to depress adrenergically enhanced calcium...
influx through β-receptor blockade. Drugs in this class decrease neurologically induced automaticity at normal therapeutic doses. At higher doses, these drugs may also exhibit anesthetic properties, which cause decreased excitability, decreased conduction velocity, and a prolonged effective refractory period. In normal therapeutic situations, the β-blocking effects are more important than any local anesthetic effects these drugs may have. Propranolol is the prototype β-adrenergic blocker drug for class II.

β-Receptor antagonists exert their antiarrhythmic activity through their selective blockade of β-receptors. They depress automaticity, prolong A.V. conduction, reduce heart rate, and also decrease contractility. These drugs are primarily effective in treatment of tachyarrhythmias caused by increased sympathetic activity.

**Propranolol** is primarily given orally for long-term treatment of cardiac arrhythmias. It is useful in ventricular arrhythmias that are due to enhanced adrenergic stimulation (from emotional stress, exercise).

**Acebutolol** is a β₁-selective adrenergic receptor blocker and is used chiefly for controlling ventricular pressure beats. The principal metabolite is N-acetylacebutolol (diacetolol) which is more potent and selective for β₁-receptors than the parent drug.

**Esmolol** is particularly useful because of its very brief action (half-life 9 minutes) for the treatment of supraventricular tachyarrhythmias.

**Sotalol** is effective against both supraventricular and ventricular arrhythmias. It is a much safer drug than amiodarone. It has a long half-life (about 15 hours).

**Class III Antiarrhythmic Drugs**

Class III drugs cause a homogeneous prolongation of the duration of the action potential. This results in a prolongation of the effective refractory period. It is believed that most of Class III antiarrhythmic agents act through phase 3 of the action potential by blocking potassium channels.

**Bretylium Tosylate**: N-(2-Bromobenzyl)-N-ethyl-N,N-dimethyl ammonium p-toluene sulfonate (172), chemically, bretylium belongs to the class of quaternary ammonium compounds and simultaneously prolongs the action potential and the effective refractory period. Bretylium is reserved for life-threatening ventricular arrhythmias that are refractory to other therapy. Its use is confined to intensive care units. Oral absorption of bretylium is poor. Its elimination half-time is approximately 6-10 hours.
Amiodarone Hydrochloride: 2-Butyl-3-benzofuranyl][4-(diethylamino) ethoxy]-3, 5-diiodophenyl methenone (173) is an iodinated benzofuran derivative. Amiodarone suppresses premature ventricular contractions and ventricular tachycardia. Its use is reserved for the treatment of life threatening ventricular arrhythmias refractory to other treatment. Amiodarone is highly lipid-soluble and its half-life is 20-100 days. The precise mechanism of its action is not known. A depressant effect of the drug on inactivated sodium channels has been observed. It is also possible that its antiarrhythmic effects are mediated partly by selectively inhibiting thyroxine action on the heart. Desethylamiodarone is the only metabolite identified. Adverse effects include, pulmonary fibrosis, photosensitivity, corneal microdeposits, thyroid disorders and gray skin discoloration('gray man syndrome').

Iodine can be replaced by bromine and methyl and the benzofuran ring by the benzothiophene ring without losing activity. Substitution of indolizine for the benzofuran ring in amiiodarone gave butoprozine with higher antiarrhythmic activity.

Class IV Antiarrhythmic Drugs: Calcium-channel Blockers
Class IV antiarrhythmic drugs comprise a group of agents which selectively block the slow inward current carried by calcium, i.e., calcium channel blockers. The slow inward current in cardiac cells has been shown to be of importance for the normal action potential in pacemaker cells. It has also been suggested that this inward current is involved in the genesis of certain types of cardiac arrhythmias. Administration of a Class IV drug causes a prolongation of the refractory period in the AV node and the atria, a decrease in atrioventricular conduction, and a decrease in spontaneous diastolic depolarization. These effects block conduction of premature impulses at the AV node and thus are very effective in treating supraventricular arrhythmias. Verapamir is the prototype drug for this class.

Verapamir is considered the drug of choice for supraventricular tachycardia. It is also useful for patients with atrial fibrillation. Not yet approved, but 60-90 mg of diltiazem can be given every 6 hours for prophylactic control against paroxysmal supraventricular tachycardia.

Class V Antiarrhythmic Drugs: Anion antagonists
Alinidine: 2-N-allyl-N-(2, 6-dichlorophenyl) amino-2imidazolidine (174) is an elective bradycardiac agent. It might restrict anionic membrane currents.

Adenosinen (175) does not'fit' into any of the classes of antiarhythmic agents described above. It is used to treat paroxysmal supraventricular tachy-arrhythmias, including those associated with bypass pathways. The adverse effects include headache and hypotension.
Official Drugs:

**Quinidine Sulphate, B.P., I.P.** Quinidine sulphate is the dihydrate of \((8R,9S)-6'\)-methoxycinchonan-9-ol sulphate. Quinidine sulphate forms white, needle-like crystals. It is sparingly soluble in water. Quinidine is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations being achieved about 1.5 hours after oral administration of quinidine sulphate. Quinidine and its salts are used to maintain sinus rhythm after cardioversion of atrial fibrillation, and for the prevention and treatment of supraventricular and ventricular arrhythmias. However, other drugs are generally preferred. Quinidine may be used, as an alternative to quinine in the treatment of malaria when quinine is not immediately available. In the prophylaxis of cardiac arrhythmias the oral dose is 0.2 g three or four times daily. In the treatment of atrial fibrillation, 0.2 to 0.4 g dose is given every two to four hours to a total dose of 3 g daily.

_Preparation I:_ Quinidine Tablets, (Quinidine Sulphate Tablets, B.P.) _Proprietary Name:_ CIN-QUIN

**Procainamide Hydrochloride, B.P., I.P.** 4- Am i no-N-(2-diethylaminoethy l)benzamide hydrochloride. Procainamide may be prepared by interaction between p-nitrobenzoyl chloride and NN-diethylthelyenediamine, followed by catalytic reduction of the nitro group of the product. Procainamide hydrochloride occurs as a white to yellowish-white crystalline powder. It is hygroscopic. It is very soluble in water. Procainamide hydrochloride is given for the treatment of ventricular arrhythmias particularly those which are resistant to lignocaine and those following myocardial infarction. It is also employed to maintain sinus rhythm after cardioversion of atrial fibrillation and has been used for prevention of supraventricular and ventricular arrhythmias. In case oral route is not suitable procainamide hydrochloride may be given intramuscularly. The dose is stated to be 0.5 to 1.5 g.

_Preparations:_ Procainamide Injection, B.P., I.P. Procainamide Tablets, B.P. _Proprietary Names:_ PROCAINAMIDE DURULES; PRONESTYL

**Disopyramide, B.P.** 4-Diisopropylamino-2- phenyl-2-(2-pyridyl)butyramide. It is a white powder, which is slightly soluble in water.
Disopyramide Phosphate, B.P. 4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide dihydrogen orthophosphate. It is a white powder which is soluble in water. Disopyramide is readily and almost completely absorbed from the gastrointestinal tract. The major metabolite is mono-N-dealkylated disopyramide which retains some antiarrhythmic and antimuscarinic activity. Disopyramide is mainly used for the prevention and treatment of ventricular arrhythmias. It is also used for the treatment of supraventricular arrhythmias. It may be given by mouth as either the base or the phosphate, the dose being generally expressed in terms of the base. A dose of 100 to 150 mg is given every 6 hours adjusted according to the patient's response.

Preparation: Disopyramide Phosphate Capsules, B.P. Proprietary Names: NAPAMIDE; NORPACE; RYTHMODAN

7. Anti-hyperlipidemic Agents

Introduction
The pharmacological agents which reduce the concentration of plasma lipids are called hypocholesterolemic agents or antihyperlipidemic agents or lipid Lowering Agents.

An increase in plasmalipids, particularly cholesterol, is a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischaemic heart diseases myocardial infarction and cerebral vascular accidents. These conditions are responsible for one third of all deaths from disease in industrial nations. Lipids are insoluble in water, and they are transported in the plasma as lipoproteins. An increase in the plasma concentration of these substances is termed hyperlipidemia (or hyperlipoproteinaeinia).

Lipoproteins consist of a central core of hydrophobic lipid (triglycerides or cholesteryl esters) encased in a more hydrophilic coat of polar substances-phospholipids, free cholesterol and associated proteins (apoproteins). There are four main classes of lipoprotein, differing in the relative proportion of the core lipids and in the type of apoprotein.

(i) High Density Lipoproteins (HDL): This is a group of heterogeneous lipoproteins having low lipid content. A further subclassification in HDL is based upon density value of these particles. HDL apparently enhances the removal of cholesterol from the arterial wall. Hence chances of development of atherosclerotic lesions are more when HDL value falls below normal. While the elevated levels of VLDL, IDL and LDL are always correlated with increased risk of atherosclerosis.

(ii) Very low density lipoproteins (VLDL): These are globular particles synthesized in the liver having diameter of 30-80 nm. They contain apoproteins B, C and E. They are involved in the transport of endogenous lipid from liver to the plasma.
(iii) **Intermediate density lipoproteins (IDL):** These are the lipoproteins obtained when the triglyceride content of VLDL are partially digested in capillaries by the action of extrahepatic lipoprotein lipase. They have a diameter of 20 - 35 nm.

(iv) **Low Density Lipoproteins (LDL):** Due to further action of lipoprotein lipase on IDL in the circulation, most of the remaining triglyceride content of IDL is digested resulting into the loss of apoproteins C and E from their structure. The density of particle is increased and diameter is brought down to 18 - 28 nm. These particles are now termed as LDL which consist of cholesterol, phospholipids and apoprotein B-100. LDL also contains B-74 and B-26. They have longest plasma half-life of about 1.5 days amongst the lipoproteins.

LDL Particles are finally delivered to hepatic and certain extrahepatic tissues for further lysosomal degradation to release the cholesterol, which can be utilised in cell membrane formation.

(v) **Chylomicrons:** These are the largest species of triglyceride rich lipoproteins, which are involved in the, transportation of dietary fat from gut. These are secreted into the lymph and contain apoprotein A and B-48.

Lipid Lowering Agents act either by reducing the production of lipoprotein or by increasing their removal from blood. The main aim is to decrease plasma cholesterol. The risk of atherosclerosis is associated with an increased plasma cholesterol, and a high LDL:HDL ratio.

There are several mechanisms by which pharmacological agents can affect the metabolism of cholesterol and the relative levels of various cholesterol carrying lipoproteins in the plasma.

(i) Inhibit synthesis of cholesterol (e.g. HMG-CoA reductase inhibition; Lovastatin).
(ii) Alter the relative levels of different plasma lipoproteins e.g. clofibrate, gemfibrozil, nicotinic acid and possibly probucol, thyroid hormone, androgens.
(iii) Sequester bile acids in the intestine, e.g. cholestyramine and colestipol.
(iv) Inhibit cholesterol absorption in the intestine, e.g. neomycin and plant steroids, such as β-sitosterol.

**Classification of antihyperlipidemic agents**

(i) HMG-CoA-reductase Inhibitor: e.g. Lovastatin, Simvastatin, Pravastatin
(ii) Fibric acid derivatives: e.g. Clofibrate, Fenofibrate, Ciprofibrate, Bezafibrate, Gemfibrozil
(iii) Bile-acid sequestrants: e.g. Cholestyramine, colestipol
(iv) Inhibition of LDL oxidation: e.g. Probucol
(v) Miscellaneous Agents: e.g. Nicotinic acid, Neomycin, β-Sitosterol, Acipimox, Metformin, Dextrothyroxine
(i) **HMG CoA-reductase Inhibitors**: A new class of fungal derived compounds are potent inhibitors of the enzyme β-Hydro-β-methyl-glutaryl-CoA reductase (HMG-CoA reductase) (176) and includes compactin and mevinolin. This enzyme is the rate determining step in the endogenous synthesis of cholesterol. These enzymes are often referred to collectively as statins' - a new class of lipid lowering agents. Compactin was first isolated from the cultures of Penicillium species in 1976 by Endo while mevinolin (or monacolin K) was isolated from the cultures of Aspergillus and Monascus species. These drugs bring about specific, reversible and competitive blockage of HMG-CoA reductase leading to decreased hepatic cholesterol synthesis. This induces an increased rate of hepatic uptake and catabolism of circulating LDL. Thus the levels of total and LDL-cholesterol are significantly reduced.

![HMG CoA (176)](image)

Three statins, lovastatin (177), simvastatin (178) and pravastatin (179), have been extensively studied. Simvastatin is a prodrug. The eliminating half-life of which is relatively short,(1-3 hrs), but duration of enzyme inhibition is much longer.

![Lovastatin (177): R₁ = CH₃ ; R₂ = H][Simvastatin (178): R₁ = CH₃ ; R₂ = CH₃][Pravastatin (179): R₁ = OH ; R₂ = H][Fluvastatin (180)](image)

The first drug of this class, mevastatin (1976) was isolated in Japan from Pencillium species. But the first drug to be marketed from this class was lovastatin (1987) which was isolated from cultures of *Aspergillus and Monascus*. The success of lovastatin, therefore, has prompted the development of additional synthetic HMGRI's resulting in the marketing of pravastatin (epstatin) and simvastatin (synvinolin). Pravastatin was isolated from Absidiacoerulea. The structures of these agents have been shown in the figures.
Structure-activity Relationship

Mevastatin and lovastatin served as lead compounds in the development of additional HMGRIS. The lactone and bicyclic rings as well as the ethylene bridge between them responsible for the activity of HMGRIs. Additionally, it was found that the bicyclic ring could be replaced with other lipophilic rings and that the size and shape of these other ring systems were important to the overall activity of the compounds. Minor modifications of the bicyclic ring and side chain ester of lovastatin produced simvastatin and pravastatin. Pravastatin, a ring-opened dihydroxyacid with a 6’-hydroxyl group, is much more hydrophilic than either lovastatin or simvastatin. Proposed advantages of this enhanced hydrophilicity are minimal penetration into the lipophilic membranes of peripheral cells, better selectivity for hepatic tissues, and a reduction in the incidence of side effects seen with lovastatin and simvastatin.

The initial rationale centered on a desire to simplify the structures of mevastatin and lovastatin. The 2, 4-dichlorophenyl analog (compound 181) shown below was one of the first compounds to demonstrate that this type of substitution was possible. The replacement of the bicyclic ring with various substituted, aromatic ring systems led to the development of fluvastatin (180), atorvastatin (182), and cerivastatin.

However, compound (181) was considerably less potent than mevastatin. Subsequent research investigated a variety of aromatic substitutions and heterocyclic ring systems in order to optimize HMGRI activity. The substituted pyrrole (compound 183) shown below retained 30% of the activity of mevastatin and was a key intermediate in the substitutions and the addition of spacer groups, have produced a number of active compounds.
(ii) **Fibric Acid Derivatives:** A series of aryloxy-isobutyric acids was effective in reducing plasma concentrations of triglyceride and cholesterol. Clofibrate (184), the first compound of this class was clinically effective for the treatment of hypertriglyceridemia. Several chemical analogs, congeners and homologs, collectively referred to as fibric acids have been prepared with lesser toxicity. One of these, Gemfibrozil, has been widely used.

![Structure of Clofibrate and Fenofibrate](image)

**Stibnification:**

![Synthesis of Clofibrate](image)

**Structure-activity Relationships**

Fibrates can be chemically classified as analogs of phenoxyisobutyric acid. The SAR for this class of drugs is sparse; however, all compounds are analogs of the following general structure (190).

![General Structure of Fibrates](image)

The isobutyric acid group is essential for activity. Compounds containing an ester, such as clofibrate and fenofibrate, are pro-drugs and require in vivo hydrolysis. Stibnification at the para position of the aromatic ring with a chloro group or chlorine containing isopropyl ring produces compounds with significantly longer half-lives. While most compounds contain a phenoxyisobutyric acid, the addition of an m-propyl spacer, as seen in gemfibrozil, results in an active drug.

(iii) **Bile-acid sequestrants:** Bile acids are secreted by the liver into intestine where they aid in the dissolution and absorption of lipids. Bile acids are the metabolic end-products of cholesterol which are released into the intestine. Major fraction (about 98%) of bile acids released into the gut is reabsorbed through the enterohepatic circulation and suppresses the microsomal hydroxylase enzyme involved in the conversion of cholesterol.
to the bile acids. Thus due to enterohepatic reabsorption of the bile acids further of cholesterol is suppressed.

Cholestyramine (191) and colestipol (192) are the examples of bile acid-binding resins which form a sort of non-absorbable complex with bile acids due to the presence of quaternary nitrogen in their structure. Thus these drugs promote their elimination from the gut and inhibit their reabsorption into the circulation. The fecal excretion of bile acids in fact, has been shown to increase 30 folds by these drugs.

Cholestyramine and colestipol are the examples of anion exchange resins and remain undigested and nonabsorbable in the GIT. Hence the drugs are considered safest antilipidemic agents due to the lack of systemic effects. They are used only in the patients who have elevated LDL levels. In the treatment of familial hypercholesterolemia, usually a combination of cholestyramine and nicotinic acid gives better results. Besides bile acids, these resins also bind with other drugs due to their anionic nature. Thus absorption of thyroxine, vitamin C, digitalis glycosides, iron, and warfarin is reported to be impaired by these resins. Colestipol appears to similar to cholestyramine in mechanism of action.

**Structure-activity Relationships**

Cholestyramine is a copolymer consisting primarily of polystyrene with a small amount of divinylbenzene as the cross-linking agent. These positively charged Cholestyramine and colestipol are not orally absorbed groups function as binding sites for anions. Virtually all of and are not metabolized by gastrointestinal enzymes. They these sites are accessible by bile acids. Increasing the amount of divinylbenzene from 2% to 4% to 8% increases the cross linkage and reduces the porosity of the resin acids. This prevents binding of bile acids to interior sites and decreases the efficacy of the compound.

Colestipol is a copolymer of tetraethylenepentamine and epichlorohydrin and is commercially marked as its hydrochloride salt. The key functional groups on colestipol are the basic secondary and tertiary amines. Although the total nitrogen content of colestipol is greater than that of cholestyramine, the functional anion exchange capacity of the resin depends upon intestinal pH and may be less than cholestyramine. Quaternization of colestipol with methyl iodide increases the capacity in vitro for glycocholate

(iv) Inhibition of LDL oxidation: Oxidised LDL is taken by macrophages to convert it into foam cell. Groups of these foam cells constitute the earliest hallmark of
atherosclerosis. The antioxidant effects of agents of this group inhibit the oxidantion of LDL, thereby, preventing its uptake by macrophages. This may help pi-event development of atherosclerosis.

Probucol [4,4’-(Isopropylidendithio)-bis[2,6-ditertiarybutyl phenol] (193) is the most potent cholesterol lowering agent of a series of alklylenedithibisphenols. It is an antioxidant that partitions into lipophilic media Such as LDL particles, where it can prevent or terminate the oxidative process. Probucol has been shown to lower LDL cholesterol levels apparently through stimulation of non-receptor mediated clearance pathways.

![Probucol (193)]

**Synthesis**

![Synthesis](image)

(v) **Miscellaneous Agents:**

(a) **Nicotinic acid (206):** Used in the treatment of hyperlipoproteinemia. It brings about hypolipidemic action by decreasing lipolysis and by promoting hepatic storage of lipids. It also enhances the activity of lipoprotein lipase resulting into low circulating VLDL level. Since VLDL acts as the precursor for most of the circulating LDL, the low VLDL level results into low level of circulating LDL. Nicotinamide, however, lacks hypolipidemic activity. In many cases, nicotinic acid is coadministered along with bile acid binding resin to get better results. In body, nicotinic acid (196) undergoes extensive metabolism resulting into formation of various metabolites, such as nicotinamide, nicotine uric acid, methyl nicotinamide, N- methyl 2-pyridone-3-carboxamide and N-methyl-2 pyridone-5-carboxamide. These metabolites are mainly excreted in the urine along with some unchanged nicotinic acid.

![Nicotinic acid (206)]

(b) **β – Sitotsterol (197):** It is a plant sterol. Due to the structural similarity with cholesterol, this agent impedes the absorption of dietary cholesterol and produces a
moderate reduction in cholesterol level. Its low efficacy and high cost decrease its popularity as lipid lowering agent.

(c) Acipimox: Acipimox is a synthetic derivative of nicotinic acid and like nicotinic acid; it acts by inhibiting adipose tissue lipolysis (hydrolysis of lipid esters). It appears to produce less flushing and GI-intolerance than nicotinic acid. It is about 20 times more active than nicotinic acid.

(d) Neomycin: It is an amino glycoside antibiotic. It exerts hypolipidemic activity only in oral administration while if given parenterally, neomycin does not reduce the plasma level of LDL. The poor absorption upon oral administration of neomycin indicates that its site of action is in GIT. The adverse effects like, otoxicity, nephrotoxicity seen during parenteral administration of neomycin, are not reported to occur with oral use of the drug.

(e) Metformin: Chemically it is N, N-dimethyl biguanidine. It has no effect on cholesterol biosynthesis but it affects the lipoprotein composition. It produces about 50% reduction in the serum triglyceride level. It is also a hypoglycemic agent and lowers blood glucose level.

(f) Dextrothyroxine: There exist an inversely proportional relationship between plasma levels of cholesterol and thyroxine (198). It increases the hepatic catabolism of LDL and thus lowers the plasma concentration of LDL particles.

(g) Other agents having hypolipidemic activity include sucrose polymers, eicosapentaenoic acid, propranolol and pindolol. Similarly estrogens also interfere in the fat metabolism resulting into a decrease in plasma LDL concentration and an increase in plasma HDL concentration. These metabolic effects of estrogens are partly opposed by progestin.
Official Drug:
Clofibrate, B.P., I.P. Ethyl 2-(4-chlorophenoxy)-2-methylpropionate. It may be prepared by refluxing p-chlorophenol, acetone and chloroform in presence of alkali, processing, and esterification of the carboxylic acid. Clofibrate is a clear, colourless to pale-yellow liquid, which is practically insoluble in water. Clofibrate is readily absorbed from gastrointestinal tract and is rapidly hydrolysed to active metabolite chlorophenoxyisobutyric acid (clofibric acid). Clofibrate is used, in conjunction with dietary modification, in the treatment of type III hyperlipoproteinaemia and severe hypertriglyceridaemia. The dosage is up to 2 g daily, in divided doses. It is no more used for long-term prophylaxis of ischaemic heart disease since such use is associated with serious toxicity.

Preparation: Clofibrate Capsules, B.P., I.P. Proprietary Name: ATROMID-S

8. Hypoglycemic Agents

Introduction
Hypoglycemic agents are those, which are used to lower the blood sugar and are used to treat the symptoms of diabetes mellitus. There are three peptide hormones secreted by the pancreas play a major role in the regulation of metabolism of carbohydrates, lipids & amino acids. These are insulating glucagons & somatostatin.

The normal blood glucose level in human’s ranges between 70 - 90 mg per 100ml. Hyperglycemia is characterized by more than normal concentration of the blood sugar and hypoglycemia develops when the blood sugar level falls below the normal range. Diabetes mellitus is the condition arising due to abnormal metabolism of carbohydrates, fats and proteins. It is characterized mainly by an unusually high sugar level in the blood (hyperglycemia) and the presence of sugar in the urine (glucosuria). The ancient Greek and Roman physicians used the term *Diabetes* to mean large urine volume. The adjective melitus, a Latin word (meaning, honey). The large urine volume is due to the large amounts of glucose and urea in the urine (osmotic diuresis). Because the biochemical basis of diabetes is still not clear, the disease is usually defined by its symptoms. These include, hyperglycemia, hyperlipemia, glucosuria, polyuria (loss of water and salts), polydipsia (increase in thirst), polyphagia (excessive hunger), ketonemia (ketone bodies and fatty acids in the blood), ketonuria (ketone bodies In the urine), azoturia (increased production and excretion of ammonia), poor wound healing and infection. Sometimes, the disease eventually causes serious complications. like, kidney damage degeneration, premature atheroscler (heart disease, neuro-logical dysfunction a predisposition to gangrene.

Types of Diabetes:
Under current clinical terms, diabetes mellitus can be categorised as under:
(i) Insulin - dependent, type I (IDDM or juvenile or brittle or unstable diabetes),
(ii) Non-insulin dependent type, type II (NIDDM or adult onset or maturity onset diabetes)
(iii) Other types:
(a) Insulin receptor abnormalities
(b) Hormonal etiology e.g., acromegaly
(c) Pancreatic disease
(d) Genetically related abnormalities
(e) Drug-induced conditions.

Another term 'diabetes insipidius' is sometimes used in which the urine of the patient remains tasteless. Now-a-days, the term 'diabetes insipidius' is reserved for the conditions produced by the disorders of the pituitary gland and the term, diabetes mellitus is used to describe the actual diabetes.

(i) Insulin dependent diabetes mellitus (IDDM): This condition results when there is under production of insulin in childhood or adolescence. The principal derangement is the failure of cells to produce insulin in full capacity. The insignificant amounts of insulin fail to properly utilise and metabolise carbohydrate as the available source of energy. To overcome the shortage in energy production, body attempts to find out other alternative pathways. To meet the demand of energy, fat and protein metabolism gets accelerated. These metabolic alterations are symptomized by the presence of increased amounts of ketone bodies and nitrogenous waste material both in the blood and in the urine. In severe ketosis, coma follows. In less severe cases, poor wound healing, infection, nausea, vomiting, restlessness and drowsiness constitute as main symptoms. Evidences are gathering to suggest that juvenile diabetes may have a viral origin. Scattered reports support this proposal. The communicable nature of this type of diabetes adds to the evidence. The persons having genetic susceptibility to get affected by virus easily get diabetes. Recently 'encephalomyocarditis' virus was reported to produce diabetes when injected into mice. It is proposed that a viral attack may trigger an autoimmune reaction which destroys some of the pancreatic β-cells and thus cuts off partially the source of insulin. Though there is marked reduction in the number of β-cells, the number of α, D and PP cells appears to be unaffected. The decreased number of β-cells may get decreased due to the patients exposure to certain chemicals. These chemicals selectively destroy pancreatic β-cells and reduce the secretion of insulin. Such agents include, alloxan, uric acid, dehydroascorbic acid, quinolones and streptozocin.

<table>
<thead>
<tr>
<th>Table 4: Insulin dependent versus non-insulin dependent forms of diabetes mellitus</th>
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<tbody>
<tr>
<td><strong>IDDM</strong></td>
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<tr>
<td>1. Lacks the ability to synthesize and release insulin due to destruction of some β-cells</td>
</tr>
<tr>
<td>2. Obesity is not the common factor.</td>
</tr>
<tr>
<td>3. Occurs at an early age</td>
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<tr>
<td>4. May be of viral origin.</td>
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<tr>
<td>5. Equally affects male and female.</td>
</tr>
<tr>
<td>6. The mass of α, D and PP cells remain unchanged.</td>
</tr>
<tr>
<td>7. Characterized by decreased secretion of insulin.</td>
</tr>
<tr>
<td>8. Insulin therapy is the only answer.</td>
</tr>
</tbody>
</table>
(ii) Non-Insulin dependent diabetes mellitus (NIDDM) : This type has more definite genetic and hereditary characteristics. This disease type announces its presence quite late. More often this is a disease of affluent and old aged people and is more common in women than in men. The patient retains a considerable number of functioning cells making insulin deficiency less severe. However the population of \( \alpha \)-cells is increased without major changes in D or PP cells. Ketosis does not occur and wasting is not a common feature. This indicates that this type may not need any treatment except a strict dietary restriction.

The Hypoglycemic agents are classified into 2 categories:-

(1)Insulin & Insulin preparations- used parentally only.
Insulin synthesized by (-cells of the islets of langerhans of the pancreas in the form of proinsulin. It is a single peptide chain. Human proinsulin consists of 76 amino acids residues & on its conversion to human insulin four basic amino acids & the remaining peptide chain called c-peptide are removed by proteolysis.

Insulin consists of two peptide chain A & B which are converted by disulphide bonds. Chain A- has 21 Amino acid & one intra chain Disulphide bond. And Chain B- has 30 Amino acid.

Bovine insulin has 2 Amino acid in the middle of the chain A and one at the end of chain B that are different from human insulin. Bovine insulin differs only by the presence of alanine as the last amino acid in the chain B, where the human insulin has threonine.

Insulin occurs as haxamer containing two zinc atoms and in the system (in blood) dissociates into monomers is the most likely biologically active form of the insulin. Semi synthetic human insulin is produced by the enzymatic modifications of insulin obtained from the procaine e pancreas.

The duration of actions of insulin may be prolonged- Firstly by forming a complex of insulin with a protein from which it is slowly released. e.g. Protamine zinc insulin, Isophane insulin, Globin zinc insulin. Secondly by modification of the particle size, e.g. Insulin zinc suspension.

Insulin Preparations
(a) Short - acting Insulin preparations: As the plasma half-life of intravenously injected insulin is not enough to meet the requirements, one has to search for such insulin preparations, having quick onset and prolong duration of action. Presently, available insulin preparations differ only with respect to onset and duration of action. First clinically used form was amorphous insulin which was highly soluble in body fluids. This leads to its rapid excretion and hence it was to be replaced by other insulin preparations. In early 1940's came 'Regular insulin' which is a buffered solution of crystalline zinc insulin. Duration of action of this preparation still needs improvement. Chemically pure zinc insulin has physiologic action essentially identical to that of regular
non-crystalline insulin as far as onset, duration and rate of blood sugar reduction are concerned.

(b) Intermediate and long-acting Insulin preparations
   (i) Protamine- Insulin preparations: The longer duration of action is due to protamine, a basic protein that leaves the site of injection more slowly.

   (ii) Protamine zinc insulin preparations: Prolonged duration of action of insulin, a long time objective, was finally achieved with protamine zinc insulin. Developed in 1936, these suspensions were proved to be better than 'prolamine insuline' duration of action. This is prepared by complexing insulin with zinc and protamine. The products are available with 40 – 80 units/ml.

   (iii) Globin zinc Insulin preparation: Developed in 1939, its duration of action (12 - 18 hours) is less than protamine zinc insulin preparations (24 - 36 hours).

   (iv) Isophane Insulin suspensions: Developed in 1946, these suspensions contain protamine, zinc and insulin. It differs from protamine zinc insulin' in the method of preparation and contains less prolamine than protamine zinc insulin'. This preparation has time activity' best adopted to the requirements of majority of diabetic patients. This has a blood sugar lowering effect usually lasting over 24 hours.

   (v) Lante Insulins : The solubility pattern of insulin (and hence its absorption) is mainly governed by its physical state. For example, large crystals of insulin with high zinc content will be less soluble in body fluids and naturally produce long duration of action due to slow absorption. Such preparations are known as ultralante insulin. This concept was utilized to develop such preparations which do not need a protein modifier (e.g., protamine or globin) to prolong their action. Stretching the same concept ahead, amorphous insulin exhibits rapid absorption and hence rapid onset of action. Such insulin cells zinc suspension I known as semilante insulin. A proper combination of ultralante insulin (7 parts) and semilante insulin (3 parts) will naturally constitute a preparation having a rapid onset and intermediate duration of action; both the properties desirable for well clinical acceptance of the preparation.

(c) Very long- acting Insulin preparations: Attempts to formulate insulin preparations with very long duration of action are made. The solubility of insulin at physiological pH 7.4 is mainly controlled by the amount of ZnCl₂ which is increased to 5 - 10 times than normally required to prepare 'soluble zinc insulin'. The increased concentration of zinc ions form low solubility complexes with insulin molecules if the buffer is changed from phosphate to acetate. Such suspensions are reported in U.S.P.

SAR studies
The structure of animal insulin has minor but potentially important differences from human insulin: Porcine insulin differs by one amino acid (alanine instead of threonine at the carboxyterminal of the B-chain, i.e., position B 30), and beef insulin differs by two additional alterations in the sequence of the A - chain (instead of threonine and isoleucine
on positions A 8 and A 10, are alanine and valine). Thus, there is nearly a complete homology between human insulin and porcine insulin in the amino acid sequence. The natural sources of insulin are mainly porcine and bovine pancreatic tissues. In comparison to synthetic insulin, natural is cheaper and is readily obtained in large amounts. SAR studies carried out on insulin revealed the following points:

(1) There exist a definite relationship between the conformation of insulin molecule and its activity. Any attempt to change this conformation leads to decrease in activity.

(2) Disturbance in the sequence of amino acids in chain A reduces the activity while amino acids from one to six and 28 to 30 can be removed from chain B, without significantly affecting the activity.

(3) Reduction of either chains, abolishes the activity.

(4) Any modification of the side-chain carboxyl groups or the tyrosine residues tend to decrease the activity.

It may be concluded that chemical modifications in the insulin structure fail to potentiate the hormone activity. Some analogs have been prepared but are of limited use to study insulin receptors.

The therapeutic importance of zinc and chromium in the treatment of diabetes is recently reviewed. Zinc, being an integral part of the insulin structure, is also found to affect carbohydrate metabolism while chromium activates insulin at its receptor sites and is found to increase both, the affinity and intrinsic activity of insulin.

**Mechanism of Action**

(i) Cyclic-AMP plays an important role in phosphorylation of various protein kinase involved in the metabolism of carbohydrate, proteins and fat. Various hormones affect the blood glucose level by influencing the concentration of c-AMP. For example, hormones like epinephrine, glucagon and ACTH tend to increase intracellular c-AMP concentration. Similar effects are also exerted by secretin, thyroxine and TSH. While insulin, melatonin, PGF$_2$ tend to lower down intracellular c-AMP concentration. Thus insulin promotes dephosphorylation of activated protein kinases.

(ii) Triglyceride lipase is involved in lipolysis insulin process. It is activated by c-AMP through phosphorylation. Insulin exerts antilipolytic effect by catalysing dephosphorylation process. Similarly by dephosphorylation of pyruvate dehydrogenase, the conversion of pyruvate to glucose is inhibited by insulin. Hence pyruvate has to get converted to fat.

(2) Oral Hypoglycemic agents

a) Guanidine derivatives: e.g. Phenformin, Metformin, other biguanides

**Biguanides**
The parent lead compound of this series, guanidine was reported to lower blood glucose levels in animals in 1918. High toxicities associated with its use necessitated the search
for better drug in this series. Subsequently, phenformin was reported which is comparatively more safe, nontoxic biguanide. It was soon followed by metformin, another biguanide. These biguanides are usually represented by following general formula.

\[
\begin{align*}
\text{R}_1 \text{NH} & \text{H} \text{NH} \text{R}_3 \\
\text{R}_2 & \text{C} \text{N} \text{NH} \text{C} \text{N} \\
\text{R}_4
\end{align*}
\]

General formula for biguanides (199)

Biguanide derivatives lower the blood sugar in the absence of pancreatic islet cells; they act in pancreatectomize animals and man but do not appreciably lower the blood sugar level in normal subjects. Peripheral utilization of glucose is increased. Biguanides may inhibit oxidative phosphorylation by inhibiting such oxidative enzymes as succinic dehydrogenase. Respiratory enzyme inhibition results in cellular hypoxia; subsequently, glucose uptake by the peripheral muscles increases and anaerobic glycolysis follows. Owing to decrease in oxidation of adipose tissue, lipogenesis is also decreased. Because of these differences in action, applications and usefulness these preparations differ from those of the sulfonylurea compounds. They often lower the blood sugar content in patients resistant to sulfonylurea compounds.

Phenformin (200) and Metformin (201) are similar in their in actions. The normal therapeutic dose for both these biguanides ranges from 25 - 150 mg/day. They do not stimulate insulin release but remain ineffective in the absence of insulin. Because of lactic acidosis associated with the use of phenformin, it was withdrawn from the market.

Phenformin (Phenethyl Biguanide) \(200\)  
Metformin (N, N-dimethylBiguanide) \(201\)

The possible mechanisms of action of these hypoglycemic biguanides include:

(a) Inhibition of intestinal transport and absorption of sugars.
(b) Potentiation of the action of insulin on glucose transfer processes into the cell.
(c) Inhibition of hepatic gluconeogenesis and
(d) Enhancement of glucose utilization processes and / or inhibition of oxidative phosphorylation in the peripheral tissues.

Diguanidines
The two diguanidines i.e. synthaline A (202) and B (203) were reported to lower blood glucose level in diabetic patients. High toxicity, failure to offer advantages over insulin and a number of fatalities (renal and hepatic damages), associated with these drugs lead to their clinical termination.
Biguanides also reduce the GIT absorption of amino acids and other ingredients of dietary energy value. They also lower the plasma levels of triglycerides and cholesterol. In the treatment of maturity onset diabetes, biguanides thus offer two fold advantage. They induce weight loss and reduce obesity along with their hypoglycemic action.

In patients with cardiac (myocardial infarction) or renal disease, phenformin treatment was found to increase blood lactic acid level. This lactic acidosis sometimes induces severe fatalities in patients. Lactic acidosis is characterized by dehydration, acidosis and a bicarbonate deficiency. This complication demands contraindication of phenformin in patients having liver, heart and kidney diseases. Along with acidosis, prolonged use of phenformin is found to induce malabsorption of cyanocobalamin. On the creditable sides, biguanides sometime have been used in combination with insulin preparation for smoother control of brittle diabetes in some patients. They are also used in combination with sulfonylureas, in cases where treatment with either agent alone, fails.

**Mechanism of Action:** The mechanism of action include-
- Inhibition of intestinal transport and absorption of sugars.
- Inhibition of hepatic gluconeogenesis potentiation of action of insulin on glucose transport process into cell.
- Enhancement of glucose utilisation process.
  e.g. Synthalin A; Decamethylene (H=10)
  Synthalin B: Dodecamethylene (H=12)

**b) First, Second and Third Generation Sulfonylureas**

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd Generation</th>
<th>3rd Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolbutamide</td>
<td>Glyburide (Glibenclamide)</td>
<td>Glybormuride</td>
</tr>
<tr>
<td>Chloropropamide</td>
<td>Glipizide</td>
<td>Glypizide</td>
</tr>
<tr>
<td>Tolazamide</td>
<td></td>
<td>Glimepirides</td>
</tr>
<tr>
<td>Acetohexamide</td>
<td></td>
<td>Repaglinide</td>
</tr>
</tbody>
</table>

The clinically used sulfonylureas are represented above. In all effective compounds, a substituted aryl sulfonyl moiety is attached to N1 of urea molecule. These derivatives are structurally similar and bear essentially the similar properties. They differ in their duration of action and chemically in the nature of the substituent at para position (-X-) and R. The substitution of aliphatic side-chain present in the first generation hypoglycemic sulfonylurea by cyclopentyl or cyclohexyl group and addition of yet another ring structure to the aromatic nucleus resulted into development of more potent second generation series.
### Key to general structure

<table>
<thead>
<tr>
<th>Name</th>
<th>$X$</th>
<th>$Y$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Generation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide (205)</td>
<td>CH$_3$</td>
<td>-(CH$_2$)$_3$-CH$_3$</td>
</tr>
<tr>
<td>Chlorpropamide (206)</td>
<td>Cl</td>
<td>-(CH$_2$)$_3$-CH$_3$</td>
</tr>
<tr>
<td>Acetohexamide (207)</td>
<td>CH$_3$C=O</td>
<td></td>
</tr>
<tr>
<td>Tolazamide (208)</td>
<td>CH$_3$</td>
<td></td>
</tr>
<tr>
<td>Carbutamide (209)</td>
<td>NH$_2$</td>
<td>-(CH$_2$)$_2$-CH$_3$</td>
</tr>
<tr>
<td><strong>2nd Generation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide (210)</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>Glymide (211)</td>
<td></td>
<td>CH$_2$-CH$_2$OCH$_3$</td>
</tr>
<tr>
<td>Glypentide (212)</td>
<td>CONHCH$_2$CH$_2$</td>
<td></td>
</tr>
<tr>
<td>Glycodiazine (213)</td>
<td>SO$_2$NH</td>
<td>OCH$_2$CH$_2$OCH$_3$</td>
</tr>
</tbody>
</table>
**Mechanism of Action:** Sulfonyl ureas affect various plasma factors that influence the insulin release.

(i) Sulfonyl ureas are found to be effective only in patients who retain functioning of islet \(\beta\)-cells or in non-insulin-dependent diabetic patients. Hence the principal mechanism of action is to stimulate the production and secretion of insulin by the \(\beta\)-cells of pancreas. Glucose also stimulates insulin release but mechanism at molecular level differs from that of sulfonyl ureas.

(ii) These drugs may lower down the output of glucose from the liver by insulin independent mechanism.

(iii) Extrapancreatic effects: These effects could be linked to the hypoglycemic activity of sulfonyl ureas. These effects include inhibition of lipolysis, inhibition of platelet aggregation, suppression of hepatic glucose output and enhancement of glucagon secretion by the \(\alpha\)-cells.

SAR Studies

There must be reasonable bulk on the urea nitrogen; methyl and ethyl compounds are not active. Usually, there is only one (normally substituent para) on the sulfonyl aromatic ring. Many simple substituents are active, and the p-(P-arylcarboxamidoethyl) grouping seen in second generation compounds is consistent with high potency. Among these compounds, it is thought that the spatial relationship between the amide nitrogen of the substituent and the sulfonamide nitrogen is important.

SAR can be summarized into following points:

(i) Certain substituents when placed at para position in benzene ring tend to potentiate the activity, e.g. halogens, amino, acetyl, methyl, methylthio and trifluoromethyl groups.

(ii) The size of terminal nitrogen along with its aliphatic substituent \(R\), determines lipophilic properties of the molecule. Optimum activity results when \(R\) consists of 3 to 6 carbon atoms.

(iii) The nature of para substituents in benzene ring (-X-) appears to govern the duration of action of the compound.

(iv) Aliphatic substituents (\(R\)) at the terminal nitrogen may also be replaced by an alicyclic or heterocyclic ring.

(iv) Hypoglycemic activity can be related to the nature of sulfonyl grouping.
Official Drugs:

Insulin, B.P. It is the natural antidiabetic hormone obtained from the pancreas of either the pig or the ox and purified. Insulin is a white or almost white powder; practically insoluble in water. When thawed, insulin should be stored at a temperature of 2° to 8° and used for the manufacture of preparations within a short period of time.

Glibenclamide, B.P., I.P. Glybenclamide; Glyburide. 1-(4-[2-(5-Chloro-2-methoxybenz-amido)ethyl]benzenesulphonyl)-3-cyclohexyl-urea. It is a white or almost white crystalline powder; practically insoluble in water. Glibenclamide has a half-life of about 10 hours. It is metabolised almost completely in the liver. Glibenclamide has a duration of action of up to 24 hours. The dose of glibenclamide is 2.5 to 20 mg once daily, after food.

Preparation: Glibenclamide Tablets, B.P., I.P. Proprietary Names: DAONIL; DIA BETA; EUGLUCON; MICRONASE

Glipizide, B.P. I-Cyclohexyl-3-(4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzene sulphonyl)urea. Glipizide is a white or almost white crystalline powder; practically insoluble in water. Glipizide has a half-life of approximately 3 to 4 hours. Its hypoglycaemic effect may persist for up to 24 hours. The usual dose of glipizide is 2.5 to 5 mg daily given as a single dose 15 to 30 minutes before breakfast.

Preparation: Glipizide Tablets, B.P. Proprietary Names: GLIBENESE; GLUCOTROL; MINODIAB

Phenformin Hydrochloride I.P. 1-Phenethylbiguanide hydrochloride. It is a white or almost white crystalline powder; freely soluble in water. Phenformin is not recommended for patients with renal failure and in patients with severe hepatic and cardiovascular disease because it causes lactic acidosis. The usual dose of phenformin hydrochloride by is 50 to 200 mg daily, in divided doses.

Preparation: Phenformin Tablets, B.P. Proprietary Name: DBI

Metformin Hydrochloride, B.P., I.P. 1, 1- Dimethylbiguanide. It is a white crystalline powder; hygroscopic. It is freely soluble in water. It is stored in tightly closed containers. Metformin is only partially absorbed from the gastrointestinal tract. It has a half-life of 1.5 to 3 hours, and is eliminated entirely by renal excretion. It should not be used in renal failure patients. The dose of metformin hydrochloride is 0.5 to 2 g daily, in divided doses.

Preparation: Metformin Tablets, B.P., I.P. Proprietary Names: GLUCOPHAGE; GLYCIPHAGE; ORABET

Suggested Readings