INTRODUCTION
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Cardiovascular diseases such as angina pectoris, myocardial infarction, cardiac arrhythmias and congestive heart failure are a major cause of deaths worldwide, even surpassing deaths due to cancer. Of the various cardiovascular illness, hypertension is of particular concern, since elevated blood pressure for prolonged periods of time increase the risks of developing angina pectoris, myocardial infarction, cerebral hemorrhage, stroke, kidney failure, coronary and cerebral atherosclerosis. Implication of hypertension in the pathogenesis of coronary heart disease and stroke had made the health professionals to study and treat hypertension worldwide. As the blood pressure levels are continuously related to the risks of cardiovascular disease, the definition of hypertension is arbitrary. The World Health Organization-International Society of Hypertension (WHO-ISH) guidelines issued in 1999 for the management of hypertension, defines hypertension as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic blood pressure of 90 mm Hg or greater in subjects who are not taking antihypertensive medication.

Treatment strategy for hypertension includes non-pharmacological and pharmacological methods. The non-pharmacological strategy includes lifestyle changes such as cessation of smoking, moderation of alcohol intake, dietary changes, reduced salt intake and increased physical activity. Worldwide pharmacological strategy includes the use of mainly six drug classes for the control of blood pressure. They include diuretics, β-adrenoceptor blocking agents, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin II antagonists and α-adrenergic blockers.
It seems that the main benefits of treating hypertension are due to lowering of blood pressure per se rather than to any particular drug property. Although all available drug classes are suitable for the initiation and maintenance of antihypertensive therapy, the choice of drugs will be influenced by some of the following factors.

- Cardiovascular risk factor profile of the individual patient
- Presence of other cardiovascular diseases
- Side effects of the drugs
- Contra-indications if any present
- Dosing convenience
- Cost of the drug

β-Adrenoceptor blocking agents (β-adrenergic blocking agents, β-adrenergic blockers) are safe, cheap and effective for use as monotherapy or in combination with diuretics, dihydropyridine calcium antagonists and α-adrenergic blockers. Also β-adrenergic blocking agents are proven effective in reducing the symptoms of angina pectoris and in reducing morbidity and mortality after myocardial infarction. Moreover, recent clinical trial results support the beneficiary action of β-adrenergic blocking agents in patients with mild to moderate congestive heart failure. In addition to their usefulness in various cardiovascular diseases they are also used in the treatment of various non-cardiovascular disorders such as migraine, hyperthyroidism, anxiety, tremor and glaucoma.

The usefulness of β-adrenergic blocking agents in various cardiovascular and non-cardiovascular disorders prompted the present investigator to synthesize and
study some new β-adrenergic blocking agents. As the knowledge of mechanism of action, pharmacology, development, therapeutic applications and potential side effects of β-adrenergic blocking agents are important to the understanding and development of newer β-adrenergic blocking agents, it is in order to review the literature pertaining to β-adrenergic blocking agents in the following sections.

AUTONOMIC NERVOUS SYSTEM (ANS)

Before going into the literature of β-adrenergic blocking agents, a brief outline of autonomic nervous system with emphasis on β-adrenergic receptor is discussed to help in understanding the physiological consequences of blocking β-adrenergic receptors.

The autonomic nervous system (ANS) or involuntary nervous system is involved in the control of body functions that are not consciously controlled such as heart rate, regulation of body temperature, blood pressure, water balance, respiration, etc. The ANS could be divided into sympathetic and parasympathetic divisions. Both the systems have:

1. Preganglionic fiber that arise from central nervous system and synapse with ganglia.

2. Postganglionic fiber that arise from the ganglia and innervate an effector system.

Conduction of nerve impulse through the preganglionic / postganglionic fiber is of electrical nature while transmission of impulse across the postganglionic fiber and effector organ is of chemical nature. The chemical substance involved in the transmission of nerve impulse is called as neurotransmitter. The neurotransmitter
released by the preganglionic fibers of both sympathetic and parasympathetic system is acetylcholine (1). Also postsynaptic fibers of parasympathetic nervous system release acetylcholine (1). While postsynaptic fibers of sympathetic system mostly release norepinephrine (NE, 2). Postsynaptically released neurotransmitters act upon

![Formula 1](image1.png)

receptors present on the effector cell to produce the response. Thus the type of neurotransmitter released by postsynaptic fiber differentiates sympathetic and parasympathetic nervous system.

Preganglionically released acetylcholine (1) act upon nicotinic receptors. While postganglionically released acetylcholine (parasympathetic system) act upon nicotinic and muscarinic receptors and postganglionically released norepinephrine (2) (sympathetic system) act upon α- and β-receptors to elicit a response in the effector organ. Once the norepinephrine released by postganglionic nerve fiber act upon the receptors present on the effector organ to produce the desired response, norepinephrine is either enzymatically metabolized or reuptaken back into the nerve terminals, thus causing termination of action.

Parasympathetic system is concerned primarily with the conservation of energy and maintenance of function of organs during minimal activity. Stimulation of
parasympathetic system slows the heart rate, decreases blood pressure, stimulates gastrointestinal movements and secretions, aids in the absorption of nutrients, protects the retina from excessive light, and empties the urinary bladder and rectum. While sympathetic stimulation could help the body to cope with stressful situation by increasing heart rate, blood pressure, blood flow is shifted from skin and splanchnic region to the skeletal muscles, blood glucose rises, the bronchioles and pupils dilate; on the whole organism is better prepared for fight or flight. Many of these effects result primarily from, or are reinforced by, the actions of epinephrine (3), secreted by the adrenal medulla. Thus sympathetic and parasympathetic nervous system has contrasting functions in regulating the internal environment of the body.

ADRENERGIC NERVOUS SYSTEM AND β-ADRENERGIC RECEPTORS

Understanding the remarkably diverse effects of the sympathetic nervous system requires understanding of the classification and properties of the different type of adrenergic receptors. Ahlquist in 1948 proposed the existence of α- and β-adrenergic receptors after closely examining various related catecholamines. During his studies he had come across two different sets of order of potency in sympathomimetic amines on the tissues including cardiac and smooth muscle and various peripheral organ system. He gave the designation α and β for receptors present in smooth muscle where sympathomimetics produced excitatory and inhibitory responses, respectively. The rank order potency of agonist is isoprenaline >
epinephrine \geq \text{norepinephrine} \text{ for } \beta-\text{receptors and epinephrine} \geq \text{norepinephrine} \gg \text{isoprenaline} \text{ for } \alpha-\text{receptors.}

Activation of \alpha-\text{receptors results in vasoconstriction, increase in blood pressure, relax smooth muscle of intestine, increases carbohydrate metabolism and produce mydriasis. While activation of } \beta-\text{receptors result in stimulation of cardiac muscle and results in facilitation of myocardial conduction and leads to relaxation of muscles in skeletal blood vessels, bronchi, intestine and uterus, and increase glycolysis. Most sympathomimetic amines are able to combine with both types of receptors although there is usually a greater affinity for one type.}

Lands and his colleagues\textsuperscript{28-30} proposed that there were in fact two \beta-receptors, \(\beta_1\) and \(\beta_2\), based on his observation that in a series of catecholamines, some preferentially stimulate \(\beta\)-receptors in the heart, adipose tissue and small intestine, whereas other catecholamines stimulate those \(\beta\)-receptors in the vascular bed, bronchioles, uterus (rat) and diaphragm. \(\beta\)-Receptors in the first category are designated \(\beta_1\) and those in the second as \(\beta_2\). The rank order potency of the catecholamines are isoprenaline > epinephrine = norepinephrine at \(\beta_1\)-receptor and isoprenaline > epinephrine >> norepinephrine at \(\beta_2\)-receptor.

Recently with the help of molecular cloning techniques Emorine \textit{et al.}\textsuperscript{31} had isolated gene that encodes for a third type of \(\beta\)-adrenergic receptor, designated as \(\beta_3\). The rank order potency of agonists is isoprenaline = epinephrine > norepinephrine at \(\beta_3\).

Similar to \(\beta\)-adrenergic receptors, heterogeneity of \(\alpha\)-receptors is also appreciated\textsuperscript{32} Table 1 summarizes the type of adrenergic receptor subtypes present in various tissues and the effect produced in these tissues by adrenergic stimulation\textsuperscript{32}
Table 1: Adrenergic receptor subtypes present in various tissues and the effect produced in these tissues by adrenergic stimulation.32

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Receptor</th>
<th>Action of Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEART</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA node</td>
<td>$\beta_1 ; \beta_2$</td>
<td>increase in heart rate</td>
</tr>
<tr>
<td>AV node</td>
<td>$\beta_1 ; \beta_2$</td>
<td>increase in automaticity and conduction velocity</td>
</tr>
<tr>
<td>Atria</td>
<td>$\beta_1 ; \beta_2$</td>
<td>increase in contractility and conduction velocity</td>
</tr>
<tr>
<td>His-purkinje system</td>
<td>$\beta_1 , \beta_2$</td>
<td>increase in automaticity and conduction velocity</td>
</tr>
<tr>
<td>Ventricles</td>
<td>$\beta_1 , \beta_2$</td>
<td>increase in contractility, automaticity and conduction velocity</td>
</tr>
<tr>
<td><strong>ARTERIOLES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>$\alpha_1 ; \beta_2$</td>
<td>constriction ; dilatation</td>
</tr>
<tr>
<td>Skin and mucosa</td>
<td>$\alpha_1 $ ; $\alpha_2$</td>
<td>powerful constriction</td>
</tr>
<tr>
<td>Coronary</td>
<td>$\alpha_1 , \alpha_2 ; \beta_2$</td>
<td>constriction ; dilatation</td>
</tr>
<tr>
<td>Cerebral</td>
<td>$\alpha_1 $</td>
<td>slight constriction</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>$\alpha_1 , \beta_2$</td>
<td>constriction ; dilatation</td>
</tr>
<tr>
<td>Renal</td>
<td>$\alpha_1 , \alpha_2 ; \beta_1 , \beta_2$</td>
<td>constriction ; dilatation</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>$\alpha_1 , \alpha_2$</td>
<td>constriction</td>
</tr>
<tr>
<td><strong>VEINS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>$\alpha_1 , \alpha_2$ ; $\beta_2$</td>
<td>constriction ; dilatation</td>
</tr>
<tr>
<td><strong>LUNGS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal &amp; bronchial muscle</td>
<td>$\beta_2$</td>
<td>relaxation</td>
</tr>
<tr>
<td>Bronchial glands</td>
<td>$\alpha_1 ; \beta_2$</td>
<td>decrease secretion ; increase secretion</td>
</tr>
<tr>
<td><strong>STOMACH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motility &amp; tone</td>
<td>$\alpha_1 , \alpha_2 ; \beta_2$</td>
<td>decrease</td>
</tr>
<tr>
<td>Sphincter</td>
<td>$\alpha_1$</td>
<td>contraction</td>
</tr>
<tr>
<td><strong>INTESTINE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motility &amp; tone</td>
<td>$\alpha_1 , \alpha_2 ; \beta_1 , \beta_2$</td>
<td>decrease</td>
</tr>
<tr>
<td>Secretion</td>
<td>$\alpha_2$</td>
<td>Inhibition</td>
</tr>
<tr>
<td>Sphincter</td>
<td>$\alpha_3$</td>
<td>constriction</td>
</tr>
<tr>
<td><strong>LIVER</strong></td>
<td>$\alpha_1 ; \beta_2$</td>
<td>glycogenolysis and gluconeogenesis,</td>
</tr>
<tr>
<td><strong>UTERUS</strong></td>
<td>$\alpha_1 ; \beta_2$</td>
<td>contraction (pregnant) ; relaxation</td>
</tr>
</tbody>
</table>

<sup>a</sup> - *Table represents a summary of adrenergic receptor subtypes and their effects in various tissues.*
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Receptor</th>
<th>Action of Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKELETAL MUSCLE</td>
<td>$\beta_2$</td>
<td>glycogenolysis, increase contractility</td>
</tr>
<tr>
<td>ADIPOSE TISSUE$^b$</td>
<td>$\alpha_2$; $\beta_1$ ($\beta_2$)</td>
<td>lipolysis</td>
</tr>
<tr>
<td>SKIN</td>
<td>$\alpha_1$</td>
<td>contraction</td>
</tr>
<tr>
<td></td>
<td>$\alpha_1$</td>
<td>secretion</td>
</tr>
<tr>
<td>EYE</td>
<td>$\beta_2$</td>
<td>relaxation for far vision</td>
</tr>
<tr>
<td></td>
<td>$\alpha_1$</td>
<td>contraction (mydriasis)</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>$\alpha_1$</td>
<td>decrease; increase</td>
</tr>
<tr>
<td>URETER</td>
<td>$\alpha_1$</td>
<td>increase</td>
</tr>
<tr>
<td>PANCREAS</td>
<td>$\alpha_2$; $\beta_2$</td>
<td>decrease; increase</td>
</tr>
<tr>
<td>POSTERIOR PITUITARY</td>
<td>$\alpha_1$; $\beta_2$</td>
<td>antidiuretic hormone secretion</td>
</tr>
</tbody>
</table>

$^a$ Recent evidences indicated the presence of both $\beta_1$ & $\beta_2$ receptors$^{32}$

$^b$ $\beta_3$-adrenergic receptor may mediate lipolysis/thermogenesis in some species$^{32}$

The immediate consequence of Ahlquist's classification of sympathetic receptors is the evolution of alpha and beta receptor blocking agents, a term coined by Moran and Perkins$^{33}$ A true $\beta$-adrenergic blocking agent may be defined as a chemical which specifically blocks the effects of isoproterenol, blocks part of the response to epinephrine, and has no effect on the responses to phenylepinephrine.
MECHANISM OF β-ADRENERGIC RECEPTOR ACTIVATION AND ITS BIOCHEMICAL CONSEQUENCES

To understand how β-adrenergic blocking agents act, it is important to know the biochemical consequences of catecholamine binding to β-adrenergic receptors (β-ARs).

The β-ARs form a part of a large super family of G-protein (guanine nucleotide binding protein) coupled, heptahelical, membrane localized receptors that are activated by the endogenous catecholamines, norepinephrine (2) and epinephrine (3). The G-protein coupled β-adrenergic receptor complex consists of β-adrenergic receptor, G-protein and adenylyl cyclase enzyme. Figure 1 shows the structure of G-protein coupled β-adrenergic receptor complex.

\[ \text{β-RECEPTOR} \quad \text{G}_{S}\text{-PROTEIN} \quad \text{EFFECCTOR} \]

FIG. 1
- **β-Adrenergic Receptor**: β-Adrenergic receptor is an integral membrane protein with seven hydrophobic stretches of amino acid sequence, which form transmembrane (TM) alpha helices and are connected by alternating extra and intracellular loops. The extracellular portion has a glycosylated amino (N) terminus and the intracellular portion has a carboxyl (C) terminal region.

- **Guanine Nucleotide Binding Protein (G-Protein)**: G-Protein is a heterotrimeric protein with α, β and γ subunits, which play a key role as transducers of signals between β-receptors and the effector adenylyl cyclase. Among the various Gα-proteins, Gαs- and Gαi-subtypes are involved most prominently in the β-adrenergic receptor signaling, and are coupled with the adenylyl cyclase enzyme in stimulatory and inhibitory fashion, respectively.

- **Adenylyl Cyclase Enzyme**: Adenylyl cyclase is the effector enzyme that catalyze the conversion of ATP (adenosine triphosphate) to cAMP (cyclic adenosine triphosphate), a ubiquitous second messenger that mediates diverse cellular responses.

  Binding of catecholamines to β-adrenergic receptor on the cell surface initiate a cascade of intracellular biochemical and molecular responses, leading ultimately to the stimulation of a number of cellular activities. When an agonist binds to the β-adrenergic receptor, it facilitates binding of GTP (guanosine triphosphate) to the αs subunit of G-protein. This leads to activation of G-protein followed by dissociation of αs-GTP complex from βγ-subunits. This αs-GTP complex stimulate adenylyl cyclase (AC) enzyme to synthesize the second messenger cAMP from ATP. The GTP bound to αs subunit is hydrolyzed to GDP (guanosine diphosphate) by intrinsic GTPase activity of α subunit, after which αs subunit combines with βγ-subunits and returns back to original inactive stage. The cascade of events progress...
as cAMP in turn activates certain protein kinase (PK) A, which then mediates phosphorylation of target proteins such as the cardiac L-type Ca\(^{2+}\) channels leading to various metabolic and physiological responses in the cells.

The traditional medicinal chemistry knowledge of β-adrenergic agonists and antagonists binding to β-adrenergic receptors coupled with site directed mutagenesis studies have helped in developing the “pharmacophore map” of the ligand binding site. 38 Both β-adrenergic agonists and antagonists are biogenic amines, and the basic amine moiety is the source of much of the binding energy of these compounds. Accordingly, it seems that there is an acidic group in the binding pocket of the receptor that would provide up to 10 Kcal / mol of binding energy. Likewise, the β-hydroxy group of the ligand is important for the stereoselective binding of both agonists and antagonists to the receptor, suggesting the existences of a hydrogen bond or acceptor in the binding site to interact with this moiety. The catechol ring of the agonist is critical for agonist binding and activation of the receptor, with both hydroxy groups of the catechol being essential for full agonist responsiveness. This requires a pair of hydrogen bond donors or acceptors in the receptor that can interact with the catechol hydroxyl groups, as well as some type of aromatic side chain to interact with the phenyl ring itself.

Molecular modeling and site directed mutagenesis studies have identified that the ligand binding site of β-receptor to be within the transmembrane domain and neither of the two receptor termini nor the hydrophilic loops are essential for ligand binding. 39 The amino acid residues essential for agonist binding are different from those that are important in their interaction with antagonist. 40, 41 The aromatic catechol moiety of β-agonists binds to a pocket involving residues in the 5th...
and 6th transmembrane (TM) helices of β-adrenergic receptors. The meta and para hydroxyl groups of the ligand form hydrogen bond with amino acid residue Ser 204 and Ser 207, while Phe 290 interacts with aromatic portion of the catechol moiety. The hydroxy side chain of Ser 165 in the 4th TM helix is ideally located to interact with the β-hydroxyl group on the ethanolamine chain of agonist. This β-hydroxyl group is critical for the stereoselective binding of agonist and antagonist to the β-receptor, with the R-isomer binding with 100 fold higher affinity than the S-isomer. The phenoxy oxygen of the antagonist (aryloxypropanolamines) appears to interact with the side chains of Asn 312 in helix seven. Only the Asp 113 amino acid in the third transmembrane helix forms a common point of interaction for both the agonist and antagonist. Asp 113 forms a hydrogen bond with the amine portion of the ligand and plays a role in ligand binding. Thus, it seems binding between agonist and receptors would be prevented by the formation of an ion pair between protonized nitrogen atom of β-adrenergic receptor blocker and carboxylic acid of Asp 113 of the 3rd TM helix.

CLASSIFICATION OF β-ADRENERGIC BLOCKING AGENTS

(1) Chemical classification:

Most β-adrenergic blocking agents belong to the following two structural classes.

(A) Arylethanolamines

(B) Aryloxypropanolamines

Both the classes have many structural features in common, but they vary in their potency and ancillary pharmacological properties. The only difference between these classes, A and B is the insertion of -OCH₂- (oxymethylene) group between the aryl component and the ethanolamine side chain (figure 2). Most of the clinically used
Figure 2. Four different classes of β-adrenergic blocking agents A (arylethanolamines), B (aryloxypropanolamines), C (MAOMM derivatives) and D (MOIMM derivatives). The spatial correspondence existing between molecular portions of these four drug classes: (a) Ar portion of class A; (b) Ar-O-CH₂- portion of class B; (c) MAOMM portion of class C and (d) MOIMM portion of class D β-adrenergic blocking agents, which may account for their bioisosteric relationship are shown above.
β-adrenergic blocking agents belong to aryloxypropanolamines, which generally have greater potency. To explain the similar pharmacological activity of the two classes of drugs, several hypotheses have been advanced about the mechanism through which the Ar-O-CH$_2$- portion of class B agents can substitute for the aromatic (Ar) portion of class A compounds in the drug receptor interaction. X-ray diffraction studies have shown the existence of spatial correspondence (figure 2) and theoretical calculations have found the presence of reactivity analogies between the aromatic (Ar) portion of type A compounds and Ar-O-CH$_2$- portion of type B compounds. These results suggest that the electronic distribution suitable for interaction with the β-receptor need not necessarily be generated by an aromatic structure. In view of these findings two more classes of β-adrenergic blocking agents without an aromatic portion were developed (figure 2).

(C) MAOMM ([(methyleneamino)oxy]methyl moiety) derivatives and
(D) MOIMM ([(methyloxy)imino]methyl moiety) derivatives

In MAOMM ([(methyleneamino)oxy]methyl moiety) derivatives (class C) the aromatic moiety of class A drug is replaced by the MAOMM moiety. The existence of bioisosterism between the aromatic and the MAOMM portions of class C β-adrenergic blocking agents are supported by comparison of the chemical reactivity of these groups.

Inversion of the atomic sequence >C=NOCH$_2$- of the MAOMM moiety leads to -CH$_2$ON=C<, MOIMM ([(methyloxy)imino]methyl moiety). MOIMM derivatives (class D), in E-configuration provides steric and electronic analogies with the aromatic (Ar) group of class A drugs.
(2) Pharmacological Classification

Accordingly to their pharmacological actions, β-adrenergic blocking agents may be divided into those (a) which are non-selective, (b) those which have a selective action on the β₁-receptors, and, (c) finally those which in addition possess other properties, such as α-receptor blocking action, vasodilator action, ultra short acting and diuretic action; they may be further divided into various groups according to the presence or absence of intrinsic sympathomimetic activity (ISA) and membrane stabilizing activity.

HISTORY AND DEVELOPMENT OF β-ADRENERGIC BLOCKING AGENTS

Cameron et al.⁵⁹, ⁶⁰ in 1938 described the pharmacology of a catecholamine named ethylnorepinephrine (4). It produced depressor action on intravenous administration in an intact cat and vasoconstriction when given into the artery of a cat leg. While repeated doses of 4 intravenously produced a response that changed from depressor to pressor effect. Explanation for this behaviour of 4 was offered in terms of adrenergic receptors that by repeated dosing the β-stimulant effect of 4 is abolished by the β-adrenergic blocking effect, causing the α-activating effect to predominate, leading to a pressor response. These investigations initiated the search for new drugs that possess β-adrenergic blocking activity.

\[
\text{(4)}
\]

\[\text{OH} \hspace{1cm} \text{NH}_2 \hspace{1cm} \text{CH}_3 \]

15
ARYLETHANOLAMINE DERIVATIVES

Dichloroisoproterenol And Its Modifications

The first β-adrenergic blocking agent dichloroisoproterenol (3,4-dichlorophenylisopropylaminoethanol, DCI, 5) came out from the research efforts of Lilly Research Laboratories, U.S.A. They were involved in the search for a specific, long acting bronchodilators for the treatment of asthma. While investigating a series of halogenated derivatives of isoproterenol (isoprenaline, IPA, 6), they have come across a compound isoprophenamine (7), which had an unusual activity in addition to its bronchodilatory activity. It blocked the inhibitory effects of adrenaline (3). This led to the study of structurally related candidate, of which the most active compound was dichloroisoproterenol (DCI, 5). Mills synthesized DCI, Powell and Slater investigated its pharmacological properties and found DCI to inhibit the β-adrenergic receptor effects. Moran and Perkins reported that DCI (5) inhibited positive inotropic and chronotropic effects produced by norepinephrine (2), epinephrine (3) and isoproterenol (6). Intravenous administration of small doses of DCI produced a
transient fall in blood pressure, and large doses showed persistent depressor response. It also showed intrinsic sympathomimetic activity (ISA). β-Adrenergic blocking activity and sympathomimetic activity both resides in the levo-isomer of DCI (5). Even though it was useful in certain cardiac conditions, it was not used clinically due to quick succession of other compounds with better pharmacological profiles.

Since the discovery of DCI (5) a number of compounds were synthesized and studied for β-adrenergic blocking activity and introduced into the market. Initial attempts were focused on the modifications of DCI structure.

The dichloro analogs (8, 9) of norepinephrine and epinephrine showed only

\[
\begin{align*}
(8) & = H \\
(9) & = CH_3
\end{align*}
\]

a temporary blockade, emphasizing the importance of \(N\)-isopropyl group of DCI for the potency and duration of β-adrenergic blocking activity.

Replacement of β-hydroxyl group with halogen produced α-receptor blocking agents. While α-methyl derivative (10) of DCI showed a decrease in potency of inhibition of the positive inotropic effect of IPA (6), but was equipotent to DCI (5) in blocking the IPA (6) induced vasodilatation effect.
Movement of the chlorine atom to 2,4-position or 2,5-position produced compounds, which blocked epinephrine (3) induced relaxation of the bronchospasm less than DCI and also showed a less intrinsic sympathomimetic activity.64

Replacement of halogens present in the phenyl ring of DCI (5) by alkyl or alkoxy group led to a variety of changes in the response.71-75 The dimethyl analogue (11) of DCI retained the β-adrenergic blocking activity, while the dimethoxy derivative (12) was inactive. The 2-chloro-4-methyl derivative of DCI was found to be a potent bronchodilator.76 From these studies it was concluded that 3,4-dihydroxyphenyl group of IPA (6) is involved in the interaction with β-adrenergic receptor as the 3,4-dichlorophenyl substitution afforded optimum β-adrenergic blocking activity.

Another compound that came up as a consequence of modification of DCI (5) is nifenalol (INPEA, 13).77 It has an electron withdrawing group in the para position of phenyl ring of IPA (6) and showed a comparable β-adrenergic blocking activity and weak direct sympathomimetic properties. Nifenalol was extensively studied in animals.78 The levo-isomer is about twice as active as the racemate in β-adrenergic blocking activity, but the dextro-isomer is inactive.79-81 The β-adrenergic blocking activity decrease on moving the nitro group from para to ortho or meta position. Also
two nitro groups in 2,4- or 3,5-positions decrease activity. Replacement of $p$-nitro group with $p$-amino or $p$-methyl sulphonyl groups in INPEA (13) leads to a decreased $\beta$-adrenergic blocking activity.\(^79\)

Larsen and Lish\(^{82}\) thought that the substitution of alky or aryl sulphonamido group in the phenyl ring of IPA (6) would mimic the phenolic hydroxyl groups present in the bioactive catecholamines with respect to its physicochemical properties and bond angles. This hypothesis led to the development of sotalol (MJ 1999, 14).\(^{83,84}\)

![Formula](image)

It was found to have $\beta$-adrenergic blocking activity six times more than DCI (5) and equipotent as that of pronethalol. The $\textit{levo}$-isomer of sotalol is about 14 times more potent than the $\textit{dextro}$-isomer as an $\beta$-adrenergic blocking agent in isolated guinea pig tracheal preparations.\(^{83}\) The $\textit{para}$-methylsulphonamido group when shifted to meta-position of the phenyl ring led to the loss of $\beta$-adrenergic blocking activity.\(^{82}\) Sotalol in addition possess class III antiarrhythmic properties and is found clinically useful in reentrant arrhythmias.\(^{85}\) It prolongs the action potential of cardiac purkinje and muscle fibers,\(^{86,87}\) moreover this effect was not specific to $\textit{dextro}$- or $\textit{levo}$-sotalol.\(^{85}\)

**Pronethalol and its Modifications**

Soon ICI pharmaceutical division joined the race to discover clinically useful $\beta$-adrenergic blocking agent. Professor J.W. Black, a pharmacologist suggested that $\beta$-adrenergic blocking agents could be used to protect the heart from an increased level of catecholamines in ischemic / anoxic cardiac tissue in patients suffering from angina pectoris.\(^{88}\) Following this an organic chemist, J.S. Stephenson reasoned that
3,4-dichloro substitution of DCI (5) could be replaced by a second phenyl ring fused to 3,4-position, which would provide a similar increase in electron density as did the two chlorine atoms in DCI. The validity of this reasoning was proved to be true and in 1962 Black and Stephenson published their work on pronethalol (2-isopropylamino-1-(2-naphthyl)ethanol, ICI 38147, 15). It showed less intrinsic sympathomimetic activity than DCI (5) and decreased cardiac force similar to DCI. It inhibited inotropic and chronotropic effects of epinephrine and isoproterenol. Also pronethalol was found to have local anaesthetic action better than procaine. Pronethalol proved clinically effective in the treatment of angina of efforts and certain forms of cardiac arrhythmias and also in the management of pheochromocytoma. But pronethalol was withdrawn following the reports that it produced thymic tumors in mice during toxicity studies.

In an effort to improve the activity of pronethalol (15), modifications were attempted at both the aromatic ring system and the side chain.

The effect of varying the substituents in the amino nitrogen is most extensively covered by Howe et al. who reported the synthesis of a series of N-substituted derivatives of 2-amino-1-(2-naphthyl)ethanols including pronethalol (15). They concluded that N, N-disubstitution of pronethalol led to a loss of β-adrenergic blocking activity, thus emphasizing the primary requirement of free amino hydrogen. Highest activity was associated with a branched alkyl chain in which the substituent on the α-carbon of the chain was methyl. Thus isopropyl, isobutyl and
*tert*-butyl analogs were approximately equipotent, while an ethyl group on the α-carbon atom appeared to be less beneficial.

The introduction of methylene group between the naphthalene ring and the aminoethanol side chain of pronethalol gave the compound 16, which showed moderate β-adrenergic blocking activity. Moving the side chain from β- to α-position of the naphthyl ring led to an improved β-adrenergic blocking activity.

Naphthalene ring of pronethalol (15) was replaced by various ring systems to give potent compounds. Replacement of 2-naphthyl ring of pronethalol, with 1-naphthyl, tetrahydro-2-naphthyl, 5-indanyl and various tricarbo cyclic groups led to compounds

![Chemical structures](17, 18, 19, 20)

with same level of β-adrenergic blocking activity. Chodnekar *et al.* had reported various heterocyclic analogs (17, 18, 19, 20) of pronethalol (15), which had similar level of potency.
Modifications of pronethalol led to butidrine (2-[(sec-butylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenemethanol, 21), which is a mixture of four isomers, and levo-isomers are about twice as active as the racemate. The racemate is slightly less potent and less toxic than pronethalol (15). It was found beneficial in the treatment of subvalvular obstruction, arrhythmias, and coronary diseases.

Another compound 6,7-dimethyl-2-(isopropylaminomethyl)-2-benzofuranmethanol (Ro 3-3528, 22), inhibited the positive chronotropic and inotropic effect of isoproterenol (6) on the isolated right and left atrium of guinea pig respectively.

In a series of 2-benzodioxinylaminoethanols, l-(l,4-benzodioxin-2-yl)-2-[l-(2-methoxyphenyl)piperazino]ethanol (23) was found to be most active and it lowered blood pressure when administered i/v at a dose of 2.5 Kg⁻¹.
ARYLOXYPROPANOLAMINE DERIVATIVES

Propranolol and its Modifications

During the investigations with arylethanolamines, various groups were inserted between the aryl moiety and the ethanolamine side chain, and their activity evaluated. In 1953, Petrov and Stephenson\textsuperscript{106} reported the synthesis of some aryloxypropane analogs of arylethanes. This idea of inserting an -OCH\textsubscript{2}- (oxymethylene) bridge between the aromatic nucleus and the ethanolamine side chain was exploited in \(\beta\)-adrenergic blocking series of pronethalol analogs.\textsuperscript{107} As a consequence various 1-amino-3-naphthoxy-2-propanols were synthesized and tested against the effects of IPA (6) in anaesthetized cat. They were found to be superior to 2-amino-1-(2-naphthyl)ethanol derivatives in their \(\beta\)-adrenergic blocking action. Moreover, moving the side from 2- to 1-position of the naphthyl ring gave compounds with better activity. One such compound propranolol (1-isopropylamino-3-(1-naphthoxy)-2-propanol, 24)\textsuperscript{108, 109} was found to be 20 times more potent than pronethalol (15). The effects of propranolol was studied in humans and animals and found to be a promising drug candidate.

Propranolol (24) is the prototype of the non-selective \(\beta\)-adrenergic blocking agents, i.e., it has equal affinity for \(\beta_1\) and \(\beta_2\)-receptors. It lacks intrinsic sympathomimetic activity and has a non-specific membrane stabilizing property.
Unlike pronethalol (15) it did not produce tumors on prolonged administration in mice. Propranolol is a highly lipophilic drug and is well absorbed after oral administration. But the systemic availability is limited as a result of extensive first-pass metabolism in the liver, with the most metabolites appearing in the urine. It has a plasma half-life of about 3-5 hrs, crosses both placental and blood brain barrier. Extensive metabolic studies in rat, dog and man have showed that propranolol is metabolized by several pathways, including oxidative N-dealkylation, aromatic hydroxylation and glucoridation. The major metabolite in humans is naphthoxy acetic acid (25). The ring hydroxylated metabolites of propranolol, particularly 4-hydroxypropranolol (26) has been demonstrated to be a potent β-adrenergic blocking agent with some intrinsic sympathomimetic activity and is believed to contribute to the activity of the drug in man.

4-Hydroxypropranolol (26) has been synthesized and found to be 100-1000 times less potent than propranolol as an β-adrenergic blocker in dog. The
β-adrenergic blocking activity and the direct vasodilating properties of seven isomeric monohydroxypropranolols have been described, and 6-hydroxypropranolol (27) found to be more potent than propranolol in its β-adrenergic blocking activity. \(^\text{122}\)

Presence of asymmetric center in the side chain of propranolol (24) gives rise to \(d\)- and \(l\)-stereoisomers. Resolution of both the enantiomers of DCI (5), pronethalol (15), propranolol (24) and other related β-adrenergic blocking agents have been reported by Howe and Rao.\(^\text{66}\) The \(l\)-isomer was in each case found to be more potent than the \(d\)-isomer. It has been reported that \(l\)-propranolol is cleared more slowly from the body than the \(d\)-isomer.\(^\text{123}\) Propranolol (24) was found to be useful in angina pectoris,\(^\text{124}\) arrhythmia,\(^\text{125}\) myocardial infarction\(^\text{126}\) and hypertension.\(^\text{127, 128}\) It is also used in the treatment of anxiety conditions,\(^\text{129}\) schizophrenia\(^\text{130}\) and for prophylaxis of migraine attacks.\(^\text{131}\)

Success of propranolol (24) as a clinically useful agent further increased the need for more potent and selective agents; hence modifications of propranolol structure were attempted. Structural modification both at the side chain and the aromatic nucleus were carried out. Introduction of methyl group at \(α\)-carbon atom of the side chain (28) of propranolol, led to an increased \(β_2\)-receptor selectivity of the compound. Similarly when the methyl group is placed at \(γ\)-carbon atom (29) of the side chain of propranolol, the compound showed a decreased activity, with selectivity towards \(β_2\)-receptors.\(^\text{132-134}\)
Modifications in the naphthalene nucleus led to the discovery of nadolol ((2R, 3S)-5-(3-tert-butlamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol, SQ 11725, 30). Condon and his colleagues\textsuperscript{135} have described a series of 3-amino-1-(5,6,7,8-tetrahydronaphthoxy)-2-propanols, of which nadolol (30) was a potent \( \beta \)-adrenergic blocking agent. It was found to be a non-selective \( \beta \)-adrenergic blocking agent without membrane stabilizing and intrinsic sympathomimetic activity.\textsuperscript{136, 137} Nadolol is not metabolized extensively and is largely excreted in urine as such.\textsuperscript{111} The distinguished feature of nadolol is its prolonged plasma half-life of about 20 hrs, which allows the drug to be administered once a day. It has been developed as an antianginal, antiarrhythmic and antihypertensive agent.\textsuperscript{138}

Schwender et al.\textsuperscript{139} had reported a number of compounds including bunolol (5-[3-tert-butlamino]-2-hydroxypropoxy]-3,4-dihydro-1(2\( H \))-naphthalenone, 31).

Bunolol was found to be 3 times more potent than propranolol when given i/v and 20-30 times when given orally.\textsuperscript{140} It showed a weak antiarrhythmic action against ouabain-induced arrhythmias. Similar to other \( \beta \)-adrenergic blocking agents the
-isomer (levobunolol) is the active isomer and is devoid of sympathomimetic activity.\textsuperscript{140} Levobunolol is used as topical agent in the treatment of glaucoma.\textsuperscript{25, 26}

The naphthyl ring of propranolol (24) was replaced by substituted phenyl ring systems by various workers to get active compounds.

Nakanishi et al.\textsuperscript{141} synthesized 1-aminoo-3-phenxy-2-propanol derivatives and tested them for β-adrenergic blocking activity. Out of this series bufetolol (1-\textit{tert}-butylamino-3-\[o-(tetrahydrofurfuryloxy)phenoxy\]-2-propanol, 32) was developed for clinical use.

The cyclopropylphenyl derivative porcinolol (1-[2-(cyclopropyl)]phenoxy-3-isopropylaminopropan-2-ol, 33) exhibited higher β-adrenergic blocking activity than propranolol (24). While the \textit{para} isomer is less active.\textsuperscript{142, 143}

\begin{center}
\includegraphics[width=0.5\textwidth]{image32}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{image33}
\end{center}

Alkenyl and alkenyloxy substituted phenoxypropanolamines also possess high levels of β-adrenergic blocking activity. This led to the development of both \textit{ortho}-allyl and \textit{ortho}-allyloxy analogs as alprenolol (1-(2-allylphenoxy)-3-isopropylaminopropan-2-ol, 34) and oxprenolol (1-(o-allyloxyphenoxy)-3-isopropylaminopropan-2-ol, 35), respectively. In some ways they may be regarded as
ring opened propranolol. Alprenolol has been extensively studied by Ablad et al., and found to be as potent as propranolol (24) in antagonizing the effects of IPA (6), with some agonistic activity. Alprenolol (34) is as potent as propranolol (24) in antagonizing the effects of IPA (6), with some agonistic activity. It is metabolized in the liver and its active metabolite is 4-hydroxyalprenolol.

While oxprenolol (35) is slightly less active than propranolol and possesses hypotensive, antiarrhythmic and chronotropic activity in man. It has central nervous system (CNS) stimulating activity and is metabolized by hydroxylation of the aromatic ring, by oxidation of propanolamine side chain and by glucuronidation. The 4'-hydroxyoxprenolol and 5'-hydroxyoxprenolol metabolites contribute to the pharmacological and therapeutic properties of oxprenolol in a way similar to that of propranolol (24) and alprenolol (34). Both metabolites are about 10 times less potent than oxprenolol. It is used to relieve anxiety in stressful situations.

Replacement of naphthalene ring of propranolol by a variety of heterocyclic ring systems produced compounds, which retained β-adrenergic blocking activity. Most compounds have the side chain attached to the benzenoid part of the heterocyclic system and the highest activity was observed when the side chain is attached at the α-position. Thus in the benzofuran series the 4-substituted analogue (36) is much more potent than the 5-substituted analogue (37). Similarly in benzothiophen series 38 was found to be more active than 39.

Compounds were synthesized containing features of both arylethanolamines.
and aryloxypropanolamines, one such compound $R,R$-racemate of 1-(1,4-benzodioxan-2-yl)-2-tert-butylaminoethanol (40) was the most potent $\beta$-adrenergic blocking agent of the series and was found to be 5-10 times more potent than propranolol (24).  

$$
\begin{align*}
\text{(36)} & \\
\text{(37)} & \\
\text{(38)} & \\
\text{(39)} & \\
R = O\text{CH}_3
\end{align*}
$$

Timolol (1-tert-butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol, 41) was developed from a series of 3-(3-substituted-amino-2-hydroxypropoxy)-1,2,5-thiadiazoles. It was found to be a nonselective $\beta$-adrenergic blocking agent with intrinsic sympathomimetic activity and membrane stabilizing activity. It is well absorbed from stomach and metabolized by the liver. It is used in the management of myocardial infarction and glaucoma. Adverse effects can occur in patients with asthma or congestive heart failure (CHF).
Another compound pindolol (1-(indol-4-yloxy)-3-isopropylaminopropan-2-ol, 42) was found to be 20-40 times more potent than propranolol (24) in blocking \( \beta \)-adrenergic receptors. It has intrinsic sympathomimetic activity and membrane stabilizing activity. It is almost completely absorbed after oral administration and has a half-life of 3-4 hrs. It is metabolized in the liver; principal metabolites are hydroxylated derivatives and are excreted through urine after conjugation with glucuronides or sulfates. It is used in the treatment of hypertension and glaucoma.\(^\text{156, 157}\)

Nakagawa et al.\(^\text{158}\) reported a series of (3-substituted amino-2-hydroxy)propoxy-3,4-dihydrocarbostyril derivatives, of which carteolol (5-(3-\text{tert}-butylamino-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1H)-one, 43) was found to have potency similar to that of pindolol (42) and approximately 10 times more potent than that of propranolol. Compared to pindolol (42) and propranolol (24), it has a longer duration of action.
CARDIOSELECTIVE β-ADRENERGIC BLOCKING AGENTS

The β-adrenergic blocking agents so far discussed have no selectivity to β₁- or β₂-adrenergic receptors, they block both β₁- and β₂-adrenergic receptors to the same extent. One physiological consequence of blocking β₂-adrenergic receptor is the constriction of bronchial smooth muscle and hence increases in airway resistance. Thus non-selective β-adrenergic blocking agents were contraindicated for use in patients suffering from asthma and other bronchial disease, as this may lead to precipitation of acute bronchoconstriction. Moreover, propranolol, which is a highly lipid soluble drug, allows it to penetrate nerve tissue and exert a cardiodepressant effect in addition to β-adrenergic blocking activity. To avoid this cardiodepressant side effect, substitution of aryl moiety with polar groups were considered. The hydrophilic nature of methylsulphonamido derivatives of isopropylaminophenylethanolamines led Crowther *et al.* to study the corresponding acetamido derivatives. The synthesis of several derivatives of (3-amino-2-hydroxypropoxy)acetyl-anilides, and their evaluation in animals led to the discovery of practolol (44) of optimal potency without cardiodepressant activity. Further studies have shown that practolol was also relatively weak in counteracting isoprenaline (6)
as a bronchodilator,\textsuperscript{161} i.e., it is a cardioselective agent and hence it could be used in patients suffering from asthma. Practolol (44) is a partial agonist, but unlike propranolol (24) does not have membrane stabilizing properties.\textsuperscript{162} Practolol is associated with a serious adverse effect, “oculomucocutaneous syndrome” hence withdrawn from clinical use in the U.K. in 1975.\textsuperscript{163}

Following the discovery of practolol (44) with cardioselective action, numerous attempts were made by various researchers to develop β-adrenergic blocking agents with cardioselective activity. All these efforts led to the conclusion that significant cardioselectivity could be achieved either by an appropriate substitution in the 4-position of the phenyl ring by a group with a suitably positioned heteroatom, either oxygen or nitrogen or by appropriate substitution of the amino group.

Thus, systematic modification of the lead compound practolol (44) was attempted to develop more potent cardioselective agents. Movement of the acylamino group to 3- or 2-position caused a loss of potency.\textsuperscript{160}

Addition of methylene bridge between a carbamoyl moiety and the aromatic ring

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{OH} \\
\text{NH}_2 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{K} \\
\text{OH} \\
\end{array}
\]

\textbf{(45)}

of aryloxypropanolamine gave atenolol (45), which was found to be a potent cardioselective agent without membrane stabilizing and partial agonistic action.\textsuperscript{164} It
is as active as propranolol (24) in antagonizing the positive chronotropic response to isoproterenol (6) in cats and dogs.\textsuperscript{164} Atenolol is completely absorbed from the gastrointestinal tract. It has a plasma half-life of about 6-7 hours. It undergoes little or no hepatic metabolism; the absorbed portion is excreted in urine and the unabsorbed portion excreted unchanged in the faces.\textsuperscript{165}

Basil \textit{et al.}\textsuperscript{166} have reported a series of 1-(2-acyl-4-acylaminophenoxy)-3-isopropylaminopropan-2-ols (46), where the relative $\beta_1$- and $\beta_2$-adrenergic responses were observed to vary with the nature of substituents in the aromatic ring. The activities have been correlated quantitatively with partition coefficient and steric substituent constants. Their results are consistent with the proposal that the vascular receptor is situated in a more lipophilic environment than that of the cardiac receptor. One of the compound described in which $R = A_1-C_3H_7$ and $R' = CH_3$ has been marketed as acebutolol and was found to be less cardioselective than metoprolol and atenolol. Diacetolol, its metabolite accounts for most of its action. Acebutolol is used in the management of hypertension.\textsuperscript{167,168}

\begin{center}
\begin{align*}
\text{HN R1 = CH}_3, \text{C}_2H_5, n/i-C_3H_7, n/i-C_4H_9 \\
\text{R = CH}_3, \text{C}_2H_5, n-C_3H_7
\end{align*}
\end{center}

\textbf{(46)}

Cetamolol (2-{O-[3-(tert-butylamino)-2-hydroxypropoxy-phenoxy]}-N-methylacetamide, 47), a cardioselective $\beta$-adrenergic blocking agent was reported to possess intrinsic
sympathomimetic activity, but without membrane stabilizing action. The cardioselectivity is greater than that of metoprolol, but less than atenolol. It could be used as once daily dose β-adrenergic blocking agent.169,170

Smith171 investigated a series of (1-amino-2-hydroxypropoxy)benzamides (48) in which the aryl residue has a para-substituted carbamoyl group together with an ortho substituent. It was found that replacement of acylamino (-NHCO-) group by carbamoyl

\[
\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{CH}_2\text{CH}=\text{CH}_2
\]

\[
\text{R}' = \text{H}, \text{Br}, \text{Cl}, \text{NO}_2, \text{CH}_2\text{CH}=\text{CH}_2
\]

\[
\text{R}^2 = \text{i-C}_3\text{H}_7, \text{t-C}_4\text{H}_9
\]

(-CONH-) moiety resulted in retention of cardioselectivity but with a decrease in overall potency. It was found that tert-butyl group is intrinsically more potent than the isopropyl group. The ortho substituent, R², was noted to be playing an important role in the potency of the compounds. Electron withdrawing groups in this position were found to increase the potency. The lipophilic contribution from the groups R, R¹ and R² was observed to be additive and produced a marked effect.
As a further modification of the lead compound practolol (44), 1-substituted-ureidophenoxy-3-amino-2-propanols (49) were synthesized in which the acylamino moiety was replaced by ureido moiety. Many of these compounds were found to be potent cardioselective β-adrenergic blocking agents. It was difficult to correlate the selectivity of action with the substituents $R_1$, $R_1'$, and $R_2$, as this property is randomly distributed throughout the series. While the potency of the compounds were found to be dependant on the substituents.

$$
\begin{align*}
R &= \text{H, CH}_3, \text{C}_2\text{H}_5, \text{n/i-C}_3\text{H}_7, \text{n-C}_4\text{H}_9 \\
R_1 &= \text{H, Br, Cl, CH}_3, \text{C}_2\text{H}_5, \text{CH}_2\text{CH=CH}_2 \\
R_2 &= \text{i-C}_3\text{H}_7, \text{t-C}_4\text{H}_9
\end{align*}

(49)

Smith has reported a series of compounds that have a methylene or ethylene bridge interposed between the aromatic ring and an acylamino (50) or ureido (51) moiety.

$$
\begin{align*}
R &= \text{CH}_3, \text{C}_2\text{H}_5 \\
R_1 &= \text{H, Br, Cl, OCH}_3, \text{CH}_2\text{CH=CH}_2 \\
R_2 &= \text{i-C}_3\text{H}_7, \text{t-C}_4\text{H}_9 \\
x &= 1 \text{ or } 2
\end{align*}

(50) (51)

Smith has reported a series of compounds that have a methylene or ethylene bridge interposed between the aromatic ring and an acylamino (50) or ureido (51) moiety.
moiety. The potency and selectivity of action found throughout the series was, in general, of a lower order than that observed with parent acylamino and ureido analogs. Many of these agents were devoid of partial agonist activity similar to atenolol (45). The ortho substituent (R^1) favors potency and correlates well with \( \pi \) value of the substituent. Thus as the lipophilicity of R^2 increases, the potency increases independent of steric bulk, while selectivity of action decreased. The substituent on the para amidic moiety (R) is however, sensitive to steric bulk with small groups preferred for maximal potency. A similar reduction in potency can also be seen by increasing the length of the methylene bridge. These findings suggest that there is limited accommodation at the \( \beta \)-adrenergic receptor site for para substituents on the aryl ring.

Celiprolol (52) is a \( \beta_1 \)-selective adrenergic blocking agent with \( \beta_2 \)-selective agonism as well as possessing a vasodilator action of uncertain mechanism.\(^{174}\)

Shtacher et al.\(^{175}\) had investigated open chain and lactam type (53) benzamido analogs of practolol. All the compounds displayed competitive blocking activity both on vascular and myocardial \( \beta \)-adrenergic receptors. Since all the test compounds share
similar lipohydrophilic character, it was suggested that their ability to selectively block either myocardial or vascular receptors depends primarily on electronic and steric factors. Iakovou et al.\textsuperscript{176} had recently reported a series of oxypropanolamine derivatives of 3,4-dihydro-2\textsubscript{H}-1,4-benzoxazine and found that compound 54 to possess high $\beta_1/\beta_2$

![Chemical Structure](image1.png)

receptor selectivity in receptor binding studies. Some of the compounds in this series possessed chronotropic and vasodilating activities.

In 1973 reports appeared featuring non-amidic cardioselective $\beta$-adrenergic blocking agents,\textsuperscript{177, 178} para analog (55) of oxprenolol and metoprolol (56), which differ from the already known cardioselective $\beta$-adrenergic blocking agents in that they possessed oxygen atom in the form of ether linkage at the para position of phenoxypropanolamine. Following these report many investigators have observed that cardioselectivity could be achieved not only by the introduction of properly positioned nitrogen atom (amidic function) in the para position of the aryloxypropanolamines, but

37
also by the introduction of oxygen atom at the para position. Thus a number of compounds were also reported with an oxygen atom, particularly in the form of ether linkage at the para position.

Metoprolol (56), bisoprolol (57) and betaxolol (58) are some of the drugs from this group to be introduced into the market for various clinical applications and all of them possess varying degree of cardioselectivity.

Metoprolol (56) is a cardioselective β-adrenergic blocking agent with little membrane stabilizing activity, but without any intrinsic sympathomimetic action. It is extensively metabolized in humans and rats, via oxidative pathways, which include O-demethylation and N-dealkylation processes. Metoprolol is used in the treatment of hypertension and ischemic heart disease. Bisoprolol (57) is also a cardioselective β-adrenergic blocking agent without intrinsic sympathomimetic action. Betaxolol (58) is used for hypertension and glaucoma, and is less likely to produce
bronchoconstriction than other ophthalmic preparations of nonselective β-adrenergic blocking agents such as timolol and levobunolol.\textsuperscript{111, 183, 184}

The phenylethanolamine analog (59) of metoprolol was found to possess less affinity for β\textsubscript{1}- and β\textsubscript{2}-receptor in comparison to metoprolol (56).\textsuperscript{185}

![Chemical Structure](image)

(59)

A series of phenoxypropanolamines substituted in the 4-position by groups incorporating diazole and triazole rings were reported by Machin,\textsuperscript{186} to support the claims that a heteroatom suitably placed in a 4-substituent is necessary to produce both potent and cardioselective β-adrenergic blockade.\textsuperscript{187} 1-[4-[(4-Chloropyrazol-1-yl)methoxy]phenoxy]-3-(isopropylamino)-2-propanol (60) and 4-(2H-1,2,3-triazol-2-yl)methoxy analog (61) showed β\textsubscript{1}-blockade in the rat with a selectivity ratio in excess of 100:1.

Louis \textit{et al.}\textsuperscript{188} had synthesized a series of 25 \textit{para}-substituted \textit{N}-isopropylphenoxypropanolamines (62) and carried out Comparative Molecular Field Analysis (CoMFA) studies on this series. They have found that the \textit{para} substitution led to
β₁-selective compound with a reduced potency at both β₁ and β₂-adrenergic receptors. CoMFA results suggest that the steric factor of the para-substituent are more important but the phenyl ring charge also governs the potency and selectivity of the compounds.

Augenstein et al.\textsuperscript{189} reported derivatives of 1-aryloxy-3-(aryloxyalkylamino)propan-2-ols which showed selectivity for cardiac receptors. The cardiac depressant activity was less than that for propranolol (24). One of the compound tolamolol (4-[2-(2-hydroxy-3-o-tolyloxypropylamino)ethoxy]benzamide, 63) exhibited selectivity for myocardial β-receptors in man.\textsuperscript{190} The levo-isomer was more potent than the dextro-isomer of tolamolol.\textsuperscript{189} It was withdrawn from the market as it caused cancer.\textsuperscript{191} Following this report that cardioselectivity could be conferred on to aryloxypropanolamine type compounds by replacing isopropyl / tert-butyl groups with certain arylalkyl groups as the amino substituent, led various workers to investigate similar compounds having cardioselective β-adrenergic blocking activity.
Smith and Tucker replaced the isopropyl / tert-butyl groups with a variety of non-amidic substituted aryloxyalkyl or alkyl substituents to study the effect on potency and selectivity. Many of the synthesized 1-phenoxy-3-phenoxyalkylamino-2-propanols (64) and 1-alkoxyalkylamino-3-phenoxy-2-propanols (65) showed cardioselectivity (R & R^1 are non-amidic substituents). They concluded that the oxygen atom of the ethyleneoxy-linking group between the nitrogen atom and the aryl ring plays a major role in the determination of selectivity in this series of compounds.

To verify these findings a series of compounds (66) were synthesized and tested where, X = S or SO. They exhibited good cardioselectivity, but the compounds having X = S were less potent than the corresponding oxygen analog indicating that the nature of X group plays an important role in determining both the potency and cardioselectivity. It
was proposed that the cardioselectivity in these agents were due to interaction between the oxygen or sulphur atom and a complementary site on the \( \beta_1 \)-receptor.\(^{193}\)

To further explore the requirements of \( X \) group, both the ether \((X = O)\) and thioether \((X = S)\) groups were replaced with various amidic functions \((X = \text{NHCO, CONH, NHCONH and NHSO}_2)\) in arylethanamine series\(^{194}\) (67) and aryloxypropanolamine series\(^{195}\) (68), which led to cardioselective compounds. Epanolol (68: \( R = o\)-CN; \( R^1 = p\)-hydroxyphenyl, \( X = \text{NHCOCH}_2 \)) a member of this series was found to be a potent cardioselective \( \beta \)-adrenergic blocking agent.\(^{196}\)

Large and smith\(^{197}\) have investigated a series of 1-(aryloxy)-3-\{[(amido)alkyl]amino\}propan-2-ols where either the aryl moiety is heterocyclic (69) or the amidic group is substituted with heterocycle (70) and they concluded that such substitution can lead to potent and in some cases cardioselective \( \beta \)-adrenergic blocking agents.

Hoefle et al.\(^{198}\) studied the effect of various amino substituents on the
β-adrenergic blocking activity and cardioselectivity in a series of 1-amino-3-(m-tolyloxy)-2-propanols and found that 1-[(3,4-dimethoxy-phenylethyl)amino]-3-(m-tolyloxy)-2-propanol (bevantolol, 71) to have cardioselective β-adrenergic blocking action and selected it for clinical trials. Bevantolol is reported to be lacking in significant intrinsic sympathomimetic activity, has membrane stabilizing action and also has vasodilator action.\textsuperscript{199}

As a continuation to their findings that use of 3,4-dimethoxyphenylethyl moiety as amino substituent lead to potent cardioselective agents, Hoefle \textit{et al.}\textsuperscript{198} also incorporated this moiety into several known β-adrenergic blocking agents with the aim of
increasing cardioselectivity and found that the practolol analog (72) showed highest cardioselectivity compared to other agents studied.

![](image1)

(72)

Working on these lines Rzeszotarski et al. had synthesized a series of 1-[(3,4-dimethoxyphenylethyl)amino]-3-(aryloxy)propan-2-ols. The compound

![](image2)

(73)

1-[(3,4-dimethoxyphenylethyl)amino]-3-(caproamidophenoxy)propan-2-ol (73) showed highest cardioselectivity in this series. An increase in size of the 4-substituent led to a substantially higher affinity for the β₁-adrenergic receptor of rat ventricular muscle in the presence of 3,4-dimethoxyphenylethyl moiety.
In addition to these standard manipulations at para-position or at the amino function of aryloxypropanolamines to obtain cardioselective β-adrenergic blocking agents, other ways of achieving cardioselectivity has been reported in literature.

Thus Vo et al.\textsuperscript{201} investigated whether a 5-quinolyl or 5-isoquinolyl ring system was a suitable bioisostere for the aryl moiety of aryloxypropanolamines. The quinolyl compounds exhibited potent and cardioselective β\textsubscript{1}-adrenergic blocking activities superior to that of metoprolol (56). The quinolyl derivatives (74) were more potent than the isoquinolyl derivatives (75). Shifting the oxypropanolamine side chain from 5-position to 4-position of quinoline ring led to a 100-fold decrease in β-adrenergic blocking activity.\textsuperscript{202}

Introduction of second 2-hydroxy-3-isopropylaminopropoxy group (76) in various aromatic systems resulted in compounds with reduced affinity for tracheal and cardiac β-adrenergic receptors \textsuperscript{203, 204}

Kierstead \textit{et al.}\textsuperscript{205} has reported binary aryloxypropanolamines, of which compound 77 was found to be a potent cardioselective β-adrenergic blocking agent

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{figure.png}};
\end{tikzpicture}
\end{center}
with short duration of action. Replacement of one of the oxypropanolamine side chain by substituents such as hydrogen, halogen or alkyl group resulted in more potent cardioselective β-adrenergic blocking agents, e.g., flusoxalol (78). 187

Nebivolol, \((\pm)-\alpha, \alpha\)-[iminobis(methylene)bis(6-fluro-3,4-dihydro-2\(H\)-1-benzopyran-2-methanol (79), contains two cyclized aryloxypropanolamine moieties.

\[
(76)
\]

\[
(77) \quad R = R^1 = O\CH_3
\]

\[
(78) \quad R = O\CH_3, \quad R^1 = F
\]

\[
(79)
\]

Ten stereoisomers are possible for this compound. It is a cardioselective β-adrenergic blocking agent without partial agonistic activity. The active \((S,R, R,R)\) enantiomer and racemic mixture produce equal reduction in blood pressure. It is also reported to have vasodilating activity. 206-208
β-ADRENERGIC BLOCKING AGENTS WITH DUAL ACTIVITY

A major problem often faced in the treatment of hypertension is the complex and heterogeneous pathogenesis and in many instances, treatment with a single drug do not adequately control blood pressure. Combinations of drugs with different pharmaco-therapeutic effects such as diuretics, β-adrenergic blocking agents, vasodilators, angiotensin converting enzyme inhibitors, calcium channel blockers and α-blockers are used to adequately control hypertension. The principle of combination therapy can be achieved by either using concomitant administration of two or more single active drugs or by drugs exhibiting both of the desired pharmacological actions combined in one molecule, so called hybrid molecules. These hybrid molecules often consist of different pharmacophoric groups, which are linked to each other via spacers.

The advantages of dual acting hybrid drugs over fixed-ratio drug combinations in one dosage form would be that hybrid drugs are absorbed, distributed, metabolized and excreted at one rate, implying that the concentration of the drug during the entire course remains in balance. While concomitantly applied drugs compete with each other for plasma protein binding sites and thus influence each other’s bioavailability, the total plasma protein binding fraction and the free drug concentration remain the same for hybrid drugs. In some of the β-adrenergic blocking agent discussed below with a dual activity it is often very difficult to distinguish the pharmacophoric groups responsible for the different pharmacological actions.

While most of the fortuitously discovered hybrids molecules have coinciding or overlapping pharmacophoric groups, in most of the designed hybrid molecules the pharmacophoric groups are linked to each other via spacers. Combinations of
different pharmacophoric groups do not automatically lead to successful hybrid drugs. The following example illustrates the failure of combination of two pharmacophoric groups. Willard et al.\textsuperscript{213} in 1981 reported the synthesis of a hybrid molecule 80 based on a benzodioxane $\beta$-adrenergic blocking agent 40 and the diuretic quinca rbate. However, the designed tricyclic amino alcohol appeared to be inactive as a diuretic or as an $\beta$-adrenergic blocking agent.

**$\beta$-ADRENERGIC BLOCKING AGENTS WITH $\alpha$-ADRENERGIC BLOCKING ACTIVITY**

$\alpha_1$-Adrenergic blocking agent prazosin is useful in the treatment of hypertension.\textsuperscript{14} Blockade of $\alpha$-adrenergic receptors inhibits vasoconstriction causing vasodilation in both arterioles and veins resulting fall in blood pressure.\textsuperscript{111} But use of $\alpha_1$-adrenergic blocker is associated with reflux tachycardia, postural hypotension and sexual dysfunction.\textsuperscript{16} It has been suggested that use of properly balanced combination of $\alpha$- and $\beta$-blocking agents to overcome the problems associated with either class of the drugs in the treatment of hypertension\textsuperscript{214, 215} Hybrid compounds have been designed, synthesized and evaluated for both $\alpha$- and $\beta$-adrenergic blocking activity by various workers.

The first compound to come into clinical practice from these research programmes was labetalol (81), which was found to be effective in reducing high
blood pressure with minimal side effect. Labetalol contains two chiral centers and therefore consists of four stereoisomers. The individual enantiomers of labetalol were synthesized and resolved by Clifton et al. and Gold et al. to correlate the biological activity with stereochemical structure. Although racemic labetalol exhibits $\alpha_1$, $\beta_1$, and $\beta_2$-adrenergic blocking activities, the $\alpha_1$-blocking activity mainly resides in the ($S$, $R$) isomer, and is 10 times more active than any other isomer. While $\beta$-adrenergic blocking activity resides almost entirely in the ($R$, $R$) isomer called dilevalol. The ($R$, $S$) isomer is almost devoid of both $\alpha$- and $\beta$-receptor blocking activity. While the ($S$, $S$) isomer is devoid of $\beta$-receptor activity. As the $\alpha$- and $\beta$-receptor blockade are present in different enantiomers they are actually considered as pseudohybrid molecules.
Other phenylethanolamines possessing a dual action were also reported, one such compound is medroxalol (82). It blocks both α- and β-adrenergic responses. Modification of medroxalol (82) led to various compounds with varying degree of α- and β-receptor blocking property.

Sulfinalol\textsuperscript{222, 223} (83) and amosulalol\textsuperscript{224} (84) are antagonists of both α- and β-receptors. Amosulalol is an antihypertensive with α\textsubscript{1}-receptor selectivity.

Kriehbaum \textit{et al.}\textsuperscript{225} has synthesized a series out of which bucindolol (85) was found to induce peripheral vasodilation by α-receptor blockade and also possesses non-selective β-receptor blockade.\textsuperscript{226}
Carvedilol (86) is a mixed α- and β-receptor antagonist. It induces peripheral vasodilatation, which is mediated partly by α₁-receptor blocking activity. It is comparable to propranolol in potency at β₁- and β₂-receptors. The 2-methoxyphenyl component provides affinity for the α-receptor. The S-enantiomer possesses 50-fold higher affinity than the R-enantiomer for the β-receptor.

Kubo et al. had described KF-4317 (87) possessing a chemical structure common to labetalol (81) and atenolol (45), and was found to possess selective β-receptor blocking activity and α-receptor blocking activity.

Khouili et al. had investigated a series of 2,3-dihydro-1,4-benzodioxin derivatives and they found that the compound 88 in which the oxypropanolamine chain is attached to 7-position to have potent β₁-receptor blocking activity and α-receptor blocking activity. All the four isomers of 88 were also synthesized and tested.

\[ \text{(86)} \]

\[ \text{(87)} \]

\[ \text{(88)} \]
β-ADRENERGIC BLOCKING AGENTS WITH VASODILATOR PROPERTIES

Vasodilators such as sodium nitroprusside,233 hydralazine,234 minoxidil235 and diazoxide236 have been used in the treatment of moderate to severe hypertension. They lower blood pressure by decreasing peripheral resistance through direct relaxation of the vascular smooth muscle. Common clinical problems associated with the use of vasodilators include reflux increase in sympathomimetic tone, followed by increase in heart rate, cardiac output and plasma rennin activity, which attenuate the antihypertensive effect.237, 238 It was reported that these undesirable effects of vasodilators could be eliminated by simultaneous treatment with β-adrenergic blocking agents, and at the same time, that the possible increase in peripheral vascular resistance induced by β-adrenergic blocking agents was eliminated by concomitant use of vasodilators.239, 240 Keeping this in view hybrid molecules were developed possessing both β-adrenergic blocking activity and vasodilating properties.

Baldwin et al.241 in 1979 reported the S-2-[p-[3-(/cV-butylamino)-2-hydroxypropoxy]phenyl]-4-trifluromethylimidazole (89) to lower arterial blood pressure in spontaneously hypertensive (SH) rats and exhibited vasodilation and β-adrenergic blocking properties. The vasodilation was assumed to be mainly due to
β₂-adrenergic agonist activity. Further modifications of 89 have led to the synthesis of highly cardioselective compounds 90 and 91 with antihypertensive activity.242

Also Baldwin et al.243 have reported S-2-[(3-([t]er-butylamino)-2-hydroxypropoxy)-3-cyanopyridine (92) to be a potent nonselective β-adrenergic blocking agent that lowered blood pressure in SH rats. Isoelectronic analogs of 92, including thiazole (93) and isothiazoles (94) and (95) were also reported by them. The compounds 93, 94 and 95 effectively reduced mean arterial blood pressure in SH rats and exhibited β-adrenergic blocking activity in dog.244

Extensive efforts to combine both the β-adrenergic blocking and vasodilation properties in a single molecule led to the emergence of prizidilol (SK&F-92657, 96),245 which is a combination of vasodilator hydralazine and a β-adrenergic blocking agent. Prizidilol was found to be potent antihypertensive,246, 247 but further
investigations were stopped after long-term toxicity studies showed unfavorable results.\textsuperscript{212} The hydrazine group was found responsible for toxicity effects, and hence, the hydrazinopyridazine moiety was replaced by 4,5-dihydro-3(2H)-pyridazinone moieties resulting in SK&F-95018 (97).\textsuperscript{245} It is moderately active $\beta_1$-antagonist with a prolonged antihypertensive action without baroreflex induced sympathomimetic activity.\textsuperscript{248} The four stereoisomers of 97 have been synthesized and evaluated for their different pharmacological profile.\textsuperscript{249}

Other compounds with a hydrazinopyridazine moiety were synthesized and tested. TZC 8159 (98) was found to possess long lasting hypotensive and $\beta$-adrenergic blocking activity. If the hydrazinopyridazinyl moiety was shifted to meta or para position of the phenyl ring both the activities were lost.\textsuperscript{250}

Another compound TZC 1370 (99) was found to possess hypotensive activity equal to hydralazine, and its $\beta$-adrenergic blocking activity 3 times more potent than
that of propranolol. The $S$-isomer was about 40 times more potent in terms of $P$-adrenergic blocking activity than that of the $R$-isomer, while their hypotensive activities were equipotent with that of the racemic compound.

Nipradilol (K-351, 100) is a nonselective $P$-adrenergic blocking agent with vasodilating properties without ISA. The nitrate ester is important for vasodilation as was shown by the compound desnitro K-351 (hydroxyl group instead of a nitrate ester function) which had no relaxant effects on $K^+$ depolarization induced contractions in isolated canine blood vessels. Furthermore, nipradilol has also $\alpha_1$- and $\alpha_2$-adrenergic blocking activities.

Hybrid compounds 101 having nitric oxide donor furoxan substructure

linked to a $\beta$-adrenergic blocking agent was reported by Boschi et al. They have
found some of the compound from this series to have NO-dependent vasodilating and β-adrenergic blocking properties in the same concentration range.

**β-ADRENERGIC BLOCKING AGENTS WITH CALCIUM CHANNEL BLOCKING ACTION**

Dual acting compounds were designed using a combination of structural features of 1,4-dihydropyridines and β-adrenergic blocking agent, which could be used for the treatment of hypertension.

Baldwin et al. have synthesized hybrid molecules (102) combining a 1,4-dihydropyridine (1,4-DHP) calcium channel blocker with an aryloxypropanolamine.

![Chemical structure of compound 102](image)

Both the ortho and para isomers were devoid of potent β₂-adrenergic receptor activity but the compounds exhibited antihypertensive property.

Shibasaki et al. had shown that YM 430 (103) might be of value in the treatment of various types of angina pectoris such as variant and stable angina.
YM 430 was found to possess calcium entry blocking and β-adrenergic blocking activities on in vitro testing.

Other compounds such as YM-16151-4 (104) and YM-15430-1 (105) were also synthesized and tested.

Yamamoto et al. had reported that FR-172516 (106) has a potent and long-lasting antihypertensive effects without activating sympathetic tone by calcium blocking and β-adrenergic blocking actions.
Recently, another compound labedipinedilol-A (107) was reported to possess calcium channel, α-adrenergic and β-adrenergic blocking actions. It demonstrated long acting antihypertensive effects without tachycardia and may be useful as monotherapy in the treatment of hypertension.60

β-ADRENERGIC BLOCKING AGENTS WITH DIURETIC ACTION

The most important first line drug therapies for essential hypertension are diuretics and β-adrenergic blocking agents.261 In many instances, neither of these drugs alone adequately controls blood pressure, and as a result, combination of β-adrenergic blocking agents and diuretics has been subjected to extensive clinical trials with encouraging results.262-264 Certain adverse effects associated with diuretic therapy alone such as potassium sparing action and blockade of the renin release are ameliorated by β-adrenergic blocking agents.212,265 An attractive alternative to this combination therapy could be a hybrid molecule exhibiting both of the desired pharmacological actions.

Bouley et al.266 had reported 2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-5-[(2-thienylcarbonyl)amino]benzoate (108) to possess good diuretic and β-adrenergic blocking activity in the same species and at the same dosage after oral administration.
Kau et al.\textsuperscript{267} have synthesized ICI 147,798 (109) based on propranolol and a slightly modified diuretic amiloride derivative. The natriuretic activity of ICI 147,798 is about 65\% of the value of hydrochlo-thiazide, while the \( \beta \)-adrenergic blocking activity is equipotent to propranolol (24) in several animal studies.

Cecchetti et al.\textsuperscript{268} have designed hybrid molecules combining \( \beta \)-adrenergic blocking agents with the diuretic hydrochlo-thiazide resulting in 110. It was found to inhibit isoprenaline (6) induced tachycardia in the same concentration range as propranolol, and had 3-fold lower affinity for \( \beta_1 \)-receptors than propranolol (24).
Compounds 111 and 112 were synthesized to investigate the influence of the chain connecting the two pharmacophoric groups. The modifications carried out on the \( \text{R} \) connecting bridge did not affect the \( \beta_1 \)-adrenergic blocking activity, while the diuretic activity was improved by 2-fold.\(^{269}\)

\[ \text{Compounds 111 and 112.} \]

\( \text{R} = \) \( \text{O} \) \( \text{OH} \) \( \text{NH} \) \( \text{SO}_2 \text{NH}_2 \) \( \text{SO} \) \( \text{Cl} \)

**\( \beta \)-ADRENERGIC BLOCKING AGENTS WITH OTHER PROPERTIES**

As a part of synthetic programme aimed at the development of hybrid molecules with \( \beta \)-adrenergic blocking activity, many other compounds were synthesized. Some of them were designed so as to exhibit novel activity profile other than vasodilating, \( \alpha \)-blocking or diuretic activity.

Barraclough et al.\(^{270}\) synthesized two hybrid molecules based on the structure of sulmazole and isomazole (positive inotropic agents with phosphodiesterase (PDE) III inhibitory activity). Compound 113 is inactive as an inotropic agent but was a weak \( \beta \)-blocker, while 114 is a weak inotropic agent and was devoid of \( \beta \)-blocking activity.
Reentrant ventricular arrhythmias are one of the major contributors to sudden cardiac death. As no single agent is effective against all types of arrhythmias, hybrid drugs have been developed combining class II (β-blocking) and class III (K^+ channel blocking) antiarrhythmic activity. Class III antiarrhythmic agents prolong action potential duration and are effective against reentrant arrhythmias. Class II antiarrhythmic agents reduce sympathomimetic activity, which is thought to be involved in the generation of reentrant arrhythmias. The standard class II / III agent Sotalol (14), originally developed as a β-adrenergic blocking agent also appeared to possess K^+ channel blocking activity.

Lis et al. prepared several hybrid molecules combining the structures of sematilide (K^+ channel blocker) with the structure of β-adrenergic blocking agent, one of the compound prepared is 115. Morgan et al. reported another compound 116, which was found to possess both class II (β1-selective) and class III antiarrhythmic activity and was effective in preventing arrhythmias. It was found to be orally active and to have profile similar to that of sotalol (14).
A hybrid molecule RWA-575C (117), combining angiotensin converting enzyme (ACE) inhibitor activity and β-adrenergic blocking activity were developed. It is designed from pindolol (42) and the ACE inhibitor enalapril. It is 50 times less potent than pindolol as β₁-adrenergic blocker in vitro, while the ACE inhibitor activity is equipotent with that of enalapril.

**ULTRA SHORT ACTING β-ADRENERGIC BLOCKING AGENTS**

The use of β-adrenergic blocking agents after myocardial infarction to control dysrhythmia has been limited because of the potential problem of long-lasting depression associated with β-blockade therapy. It was suggested that use of β-adrenergic blocking agents with an ultrashort duration of action as i/v infusion could overcome this problem, as the undesirable effects of drug would rapidly dissipate upon termination of the infusion. Moreover, i/v infusion of ultrashort acting β-adrenergic blocking agents will allow rapid achievements of the desired effect in a dose-titration manner. It could be useful for testing the patient response.
and tolerance to the therapy before using a long acting compound. The ideal ultrashort acting β-adrenergic blocking agents should have a duration of action of 10-30 min., the metabolites should be inactive and should not be toxic even at a high concentration and should be at least as potent as propranolol (24)\textsuperscript{280}.

The design of ultrashort acting β-adrenergic blocking agents involved "inactive metabolite" approach, where incorporation into the skeleton of the β-adrenergic blocking agents a "metabolically unstable" ester function that on breakdown \textit{in vivo} by esterase would lead to products that are devoid of β-adrenergic blocking activity. Esterase are widely distributed in body fluids and tissues.\textsuperscript{279}

The first ultrashort acting β-adrenergic blocking agent to be available for clinical use came from the studies of Erhardt and coworkers.\textsuperscript{281} They have prepared several derivatives (118) with the ester function incorporated on the amino nitrogen of the aryloxypropanolamines, where potency was found to be greater for \textit{ortho} compounds than that of \textit{meta} or \textit{para} substituted compounds.

In another series of compounds investigated,\textsuperscript{282} where ester function is attached to the aromatic ring, they have reported esmolol (119), as a moderately cardioselective and short acting drug with $t_{1/2}$ of 10 min. It possesses intrinsic sympathomimetic activity and membrane stabilizing properties. It is rapidly hydrolyzed by esterase in the blood cells and is excreted as de-esterified metabolites
in urine. Esmolol (119) is used for the acute, temporary control of ventricular rates in certain supraventricular arrhythmias such as sinus tachycardia and atrial flutter and/or fibrillation in the perioperative, postoperative or emergency setting.  

\[
\text{(119)}
\]

Kam et al.\textsuperscript{280} had reported a series of [(arylcarbonyl)oxy]propanolamines, where the ester function is incorporated between the ring and the nitrogen. Of the compounds studied flestolol (120) was found to be as potent as propranolol (24) and had duration of action of about 21 min., in dog. It is non-selective \(\beta\)-adrenergic blocking agent without intrinsic sympathomimetic activity.

The “inactive metabolite” approach was also successfully applied by other workers to develop soft \(\beta\)-adrenergic blocking agents for systemic and ophthalmic use. Bodor et al.\textsuperscript{285} had modified the major inactive metabolite (121) of metoprolol to obtain adaprolol (122), which was found to be a potential topical antiglaucoma agent. It produces prolonged and significant reduction of intraocular pressure but rapidly hydrolyzes in human blood (\(t_{1/2} = 7\) min.). It thus produces a significant separation of
local activity and undesired systemic cardiovascular, pulmonary activity, a characteristic much sought after for antiglaucoma therapy. The enantiomers of adaprolol were synthesized and both $R$- and $S$-enantiomers were found to possess ocular hypotensive effect. Recently Yang et al. developed methylthiomethyl \textsuperscript{(123)} and related esters \textsuperscript{(124, 125)} and were found to be ultrashort acting.

ONO-1101 \textsuperscript{(126)}, a highly cardioselective ultrashort acting $\beta$-adrenergic blocking agent was developed by Iguchi \textit{et al.} \textsuperscript{(288)} and investigated. It was 9 times more potent \textit{in vivo} $\beta$-adrenergic blocking activity and 8 times more selective \textit{in vitro} $\beta_1/\beta_2$ cardioselectivity than esmolol.\textsuperscript{(288)}

Vasmolol \textsuperscript{(127)}, a novel vanilloid type ultrashort acting $\beta_1$-receptor antagonist with a vasorelaxant activity, which is devoid of intrinsic sympathomimetic
activity is reported. As with other ultrashort acting β-adrenergic blocking agents, vasomolol (127) infusion led to a rapid onset of action and a rapid recovery from blockade after discontinuation of the infusion.290

CH₃
O
CH₃

(127)

OXIME ETHER DERIVATIVES AS β-ADRENERGIC BLOCKING AGENTS

To achieve better potency and selectivity variations in the aromatic substituents or aromatic nucleus were carried out. Modifications of the side chain were also attempted. Leclerc et al.191 has reported one such series, where carbon-nitrogen double bond (>C=N-) was inserted into the side chain of β-adrenergic blocking agents. One of the compound in this series of aromatic oxime ethers is IPS 339 (128), which showed 155 times more activity on the trachea than on the atria of guinea pig in vitro test. It increased blood pressure of spontaneously hypertensive rats. This and further studies had led to the development of β-adrenergic blocking agents without an aromatic ring.
This was exemplified by the development of cyclopropyl analogue falitolol (129),

![Image of compound 129]

which has been found useful in the clinical treatment of glaucoma. Various aliphatic oxime ethers were also reported to possess \(\beta\)-adrenergic blocking activity. The \(\beta\)-adrenergic blocking activity of these class of compounds with a MAOMM (\(\text{\(>\)}\text{C}=\text{NOCH}_2-, [(methylenamino)oxy]methyl moiety) substituent is by theoretical studies, showing the existence of bioisosterism between the Ar and the MAOMM. It was thought that the formal inversion of MAOMM atomic sequence to MOIMM (\(-\text{CH}_2\text{ON=C<, [(methyloxy)imino]methyl moiety}\)) could better imitate the steric and electronic analogies of Ar group. Compounds of MOIMM type (130) were synthesized and tested for their \(\beta\)-adrenergic receptor binding affinity and blocking activity.

In order to rationalize the similar pharmacological properties of the MOIMM and MAOMM derivatives, their conformational and electronic characteristics were
evaluated by means of theoretical studies. It was shown that both possess very similar conformational profiles. Analyses of molecular electrostatic potential (MEP) of both the class of compounds did not show much difference in their chemical reactivity. A thorough review on the subject of MOIMM oxime ether derivatives has appeared recently.

STRUCTURE-ACTIVITY RELATIONSHIPS

As β-adrenergic blocking agents have structural resemblance with that of naturally occurring catecholamines, it will be in order to outline the salient structural features of catecholamines responsible for the β-adrenergic receptor affinity and agonistic efficacy. Many reviews have focused on the structure-activity relationships of agonist and antagonist for the β-adrenergic receptors.

The naturally occurring catecholamines, norepinephrine (2) and epinephrine (3) are the prototype agonists for both α- and β-adrenergic receptors. SAR studies by various workers have led to some generalized observations regarding the structural requirements for β-adrenergic receptor affinity and agonistic efficacy. The following structural features (131) are found to be essential for agonist efficacy: (i) presence of phenolic hydroxy groups, essential for β-adrenergic stimulation. If any one of the hydroxyl group is removed there is a decrease in agonistic activity at β-adrenergic receptor, (ii) phenyl ring is essential for β-adrenergic receptor agonistic activity.
(iii) benzylic β-hydroxyl group with the proper stereochemistry is the prerequisite for β-sympathomimetic activity. The *levo*-epinephrine is forty times more potent than the respective *dextro* isomer and (iv) the nitrogen atom with at least one hydrogen is essential structural feature for the binding to β-adrenergic receptors.

According to Easson-Stedman hypothesis, the catechol hydroxyl, the benzylic β-hydroxyl group and the aliphatic amino nitrogen group have been implicated by three point attachment between these drugs and the adrenergic receptors.

Norepinephrine (2) is a potent agonist at α-receptors and has relatively little action on β-receptors in most tissues except for the heart and intestine, while epinephrine (3) has dualistic action at α- and β-receptors. Increasing the bulk at the amino nitrogen by addition of isopropyl group gave isoprenaline (IPA, 6), which stimulates β-receptors and has essentially no α-stimulant activity. This compound is a prototype of the β-adrenergic sympathomimetic and used for assessing β-adrenergic blocking activity.

**SAR of arylethanolamines**

Replacement of phenolic hydroxyl group of isoprenaline (6) with chlorine atoms in 3- and 4-position afforded the first β-adrenergic blocking agent dichloroisoproterenol (DCI, 5). This was followed by many compounds with β-adrenergic blocking activity. The general observations related to the structure activity relationship for the arylethanolamines (132) could be summarized as follows:

1. Aromatic ring substitution such as CH₃, Cl and CH₃O group at 3,4- or 4-position gave the most active compounds of arylethanolamines, e.g., DCI 4-NO₂ or 4-CH₃SO₂NH₂ group led to active compounds such as INPEA (13) and sotalol (14), respectively.
Moving these groups to meta position decreased activity. Fused benzene ring in place of chlorine atom in DCI, produced pronethanol (15), which was the first beta blocker to be used clinically.

2. *N*, *N*-Disubstitution leads to inactive compounds.

3. Replacement of secondary alcoholic hydroxyl group on the 2-aminoethanol side chain by a chlorine atom leads to α-receptor blocking action. Removal of this hydroxyl group generally eliminates β-adrenergic blocking activity.

On the basis of these observations, the structural features required for optimum β-adrenergic blocking activity in this series are: (i) a substituted phenyl ring (ii) a 2-aminoethanol side chain with no substitution (iii) a secondary amino nitrogen bearing hydrophobic group, such as isopropyl or tert-butyl group (iv) a benzylic hydroxyl group in the *R*-(I)-configuration.

**SAR of aryloxypropanolamines**

Introduction of -OCH₂- (oxymethylene) group between the naphthalene moiety and the ethanolamine side chain led to compounds with a sharp rise in β-adrenergic blocking activity, e.g., propranolol (24). This new class of compounds are known as aryloxypropanolamines. This class of drugs in general have greater potency by an order of magnitude. With a few exceptions most of the β-adrenergic blocking agents belong to aryloxypropanolamines. The structural requirement of aryloxypropanolamines (133) could be summarized as follows:
1. An aromatic ring, which may be benzenoid, heterocyclic or benzoheterocyclic. Various substituents such as ethyl, nitro, alkoxy, allyl and allyloxy group substituents in 2- and 3- position of phenyl ring were of interest, e.g., alprenolol (34)\textsuperscript{144, 145} and oxyprenolol (35)\textsuperscript{147, 148} The ortho substituted benzenoid analogs are more potent than the corresponding meta or para analogs. Shifting the allyloxy group of oxprenolol from ortho to para position led to cardioselective $\beta$-adrenergic blocking agents.\textsuperscript{178}

2. $N, N$-Disubstitution leads to inactive compounds similar to arylethanolamines. Highest activity is seen in secondary amino compounds with alkyl chain in which $\alpha$-carbon bears a methyl group, and is of three to four carbon atoms, e.g., isopropyl, sec-butyl or tert-butyl group.

3. Presence of secondary alcoholic hydroxyl group on the oxypropanolamine side chain is essential for activity. Unlike the arylethanolamines (S)-(I)-aryloxypropanolamines are active biologically.

Cardioselective aryloxypropanolamines could be obtained by: (i) introduction of polar substituent such as amidic group in the para-position\textsuperscript{160, 166, 171}, (R\textsuperscript{1}) of 1-[(aralkyl of alkyl)amino]-3-(aryloxy)propa-2-ol (134), (ii) substitution of side chain amino moiety with some aralkyl or alkyl group.\textsuperscript{189, 198} Skillful manipulation of R, R\textsuperscript{1} and R\textsuperscript{2} group gave highest cardioselective agents. It has been suggested that
cardioselectivity of these agents may be due to their ability to bind to an additional site in the $\beta_1$-receptor.

$\beta$-Adrenergic blocking agents of the both classes have been studied to determine the conformational preference, charge distribution, inter and intra molecular interaction.\textsuperscript{305, 306} X-ray crystallography and quantum mechanical calculation studies have shown that the preferred conformation for hydroxyl and amino group is gauche to each other in both the classes of $\beta$-adrenergic blocking agents.\textsuperscript{305,308} $^1$H NMR spectroscopic studies have reached the same conclusion,\textsuperscript{309,310} and also postulated the presence of hydrogen bond interaction between the two groups.\textsuperscript{309,311} The high pKa values indicate that the protonised form of the $\beta$-adrenergic blocking agents to be responsible for the activity.\textsuperscript{203}

Zaagsma\textsuperscript{312} has investigated the intermolecular interaction of toliprolol (135) and its position isomer (136) to determine the biological significance of these interaction using NMR and IR spectral methods. He concludes that the halide anion is intermolecularly bound to the hydroxyl and amino function so as to form a seven membered ring structure, which can play a role in binding the drug to the receptor.

**CHIRAL ASPECTS OF $\beta$-ADRENERGIC BLOCKING AGENTS**

The $R$- and $S$-nomenclature according to Cahn, Ingold and Prelog (CIP) priority rules defines the absolute configuration of a steriogenic center.\textsuperscript{311} On the
other hand, the prefixes \( d \)- and \( l \)- as well as the (+)- and (-)-nomenclature give information according to rotation of polarized light to the right or to the left, and therefore, merely describe these physiochemical properties of the enantiomers.

All the \( \beta \)-adrenergic blocking agents are structurally related to the \( \beta \)-adrenergic agonists epinephrine and nor-epinephrine. As a common feature, these catecholamines and all \( \beta \)-adrenergic blocking agents that are currently available for clinical use possess an amino-alkanol side chain with an asymmetric carbon atom resulting in the existence of a pair of enantiomers which are mirror images.\(^{314}\) Effects of agonists as well as antagonists on \( \beta \)-adrenergic receptors are highly stereoselective with the \( l \)-enantiomers being markedly more potent than the respective \( d \)-forms.\(^{315}\) In the arylenethanolamine series (137) such as sotalol, \( R \)-sotalol (equivalent to \( l \)-sotalol) is much more effective as \( \beta \)-adrenergic blocking agent than \( S \)-sotalol (equivalent to \( d \)-sotalol).\(^{316}\) While in the arylenepropanolamines (138) type compounds the \( d \)-enantiomer shows \( R \)-configuration, and the \( l \)-enantiomer show the \( S \)-configuration.

\[(137) R \text{-arylenethanolamine} \quad (138) S \text{-arylenepropanolamine}\]

\( S \)-enantiomer is more potent in blocking adrenergic \( \beta \)-receptors than the respective \( R \)-form. Because of the insertion of an oxygen atom in the side chain of the arylenepropanolamines, the priority (numbers shown) of the substituents around the asymmetric carbon changes, and the isomer with the required spatial arrangement now has the \( S \)-configuration. This is an effect of nomenclature rules and the groups still have the same spatial arrangement.
The β-adrenergic blocking effects of d- and l-enantiomers of propranolol (24),317 atenolol (45),318 metoprolol (56),319 sotalol (14)\textsuperscript{320} and carvedilol (86)\textsuperscript{321} have been compared; the results reveal that the l-enantiomers are markedly more effective than the respective d-form. But still most β-adrenergic blocking agents except a few are still are used as racemic mixture (equal parts of both d- and l-enantiomers) in clinical practice.

During recent years a number of studies reported highly specific effects such as antiarrhythmic class I effects\textsuperscript{322} and inhibition of the conversion of triiodothyronin\textsuperscript{323} by d-propranolol, or antiarrhythmic class III effects of d-sotalol. In addition, there are marked pharmacokinetic differences between d- and l-enantiomers.\textsuperscript{316} Recent clinical trial SWORD\textsuperscript{324} study showed that optically pure d-sotalol increased mortality in patients with myocardial infarction by 65% compared with placebo, emphasizing the potential harm that may be caused by a non β-blocking d-enantiomer of a currently used racemic β-adrenergic blocking agent. Thus it is unequivocally clear that the d- and l-enantiomers of all β-adrenergic blocking agent that are currently used in clinical practice may have different pharmacodynamic and pharmacokinetic properties. Therefore, the optically pure enantiomers should be recognized as distinct drugs, and hence should perform the so called “chiral switch”, i.e., to replace the currently used racemic β-adrenergic blocking agents with the optically pure l-enantiomers in order to avoid potential harm to patients that might be derived from the non β-adrenergic blocking d-enantiomers. Moreover use of l-enantiomers for therapy uses only half dose of optically pure l-enantiomer to obtain the full effect of the currently used racemic mixture. Many workers have reported the asymmetric synthesis of various β-adrenergic blocking agents, even on an industrial scale and at low costs.\textsuperscript{316}
PHARMACOKINETICS

Although the β-adrenergic blocking agents as a group have a similar therapeutic effects, their pharmacokinetic properties are markedly different.\textsuperscript{325, 326} Their varied aromatic ring structures lead to differences in completeness of gastrointestinal absorption, amount of first-pass hepatic metabolism, lipid solubility, protein binding, extent of distribution in the body, penetration into the brain, concentration in the heart, rate of hepatic biotransformation, pharmacological activity of metabolites, and renal clearance of the drugs and its metabolites, which may influence the clinical usefulness of these drugs in some patients.\textsuperscript{325-327} The β-adrenergic blocking agents can be divided by their pharmacokinetic properties into two broad categories: those eliminated by hepatic metabolism, which tend to have relatively short plasma half-life, and those eliminated unchanged by the kidney, which tend to have longer half-life.\textsuperscript{327}

Lipid soluble drugs such as propranolol (24), metoprolol (56), and alprenolol (34), are almost completely absorbed by the small intestine, and are largely metabolized by the liver. They tend to have relatively short plasma half-life making them suitable for once or twice daily administration.\textsuperscript{327} In contrast, agents which are water soluble such as atenolol (45), sotalol (14) and nadolol (30) are incompletely absorbed through the gut and are eliminated unchanged by the kidney. They have longer half-lives making them suitable for once a day administration.\textsuperscript{328, 329} Hepatic detoxification mechanism includes glucuronide conjugation of the parent molecule with or without prior ring or side chain hydroxylation, \textit{O}- or \textit{N}-dealkylation and/or oxidative deamination.\textsuperscript{330} When drugs with extensive first-pass metabolism are taken by mouth, they undergo so much hepatic
biotransformation that relatively little drug reaches the systemic circulation\textsuperscript{325,327} Some β-adrenergic blocking agents are biotransferred to active metabolites, and hence the pharmacological effect depends on the amount of drug administered and its active metabolite\textsuperscript{326}. Characteristics of lipid-solubility in a β-adrenergic blocking agent have been associated with the ability of the drug to concentrate in the brain\textsuperscript{325,327} and many side effects of these drugs have been clearly related to their actions on the central nervous system, such as lethargy, mental depression, and hallucinations\textsuperscript{327,329}.

**THERAPEUTIC USES OF β-ADRENERGIC BLOCKING AGENTS**

β-Adrenergic blocking agents, which constitute a major pharmacotherapeutic advance, were conceived initially for the treatment of patients of angina pectoris and arrhythmias. After the clinical introduction of propranolol (24) for angina pectoris and arrhythmias in 1963, it was proposed that β-adrenergic blocking agents might favorably influence the acute and long-term course of patients with myocardial infarction. Since then, a wide range of β-adrenergic blocking agents were synthesized and clinically tested for various effects. β-Adrenergic blocking agents have therapeutic effects in many other clinical disorders including systemic hypertension, hypertrophic cardiomyopathy, supraventricular tachycardia, mitral valve prolapse, silent myocardial ischemia, migraine, glaucoma, essential tremor, and thyrotoxicosis\textsuperscript{325,327,330}. All β-adrenergic blocking agents block β-adrenergic receptors and this action is responsible for their use in various clinical conditions\textsuperscript{331}. Various β-adrenergic blocking agents with concomitant properties such as, cardioselectivity, intrinsic sympathomimetic activity, membrane stabilizing activity and
α-adrenergic blocking activity have been found useful in various disorders depending on the concomitant conditions. The clinical aspects of β-adrenergic blocking agents are extensively reviewed.265, 297, 327, 330, 332, 333

**HYPERTENSION**

β-Adrenergic blocking agents have been used for over 25 years in the treatment of hypertension and have an established record of safety and efficacy. The original observation that β-adrenergic blocking agents lowered blood pressure was made with pronethalol334 (15). All β-adrenergic blocking agents are equally effective as antihypertensive agents regardless of the presence or absence associated properties, cardioselectivity, intrinsic sympathomimetic activity and membrane stabilizing effect. They can be used in all grades of hypertension, mild, moderated and severe, alone or in combination with other antihypertensives.335 β-Adrenergic blocking agents are especially suitable for the chronic treatment of hypertension because of their relative freedom from the troublesome side effects such as postural hypotension, sedation and sexual dysfunction.336 While the exact mechanism of antihypertensive action of β-adrenergic blocking agents is not yet known, a number of mechanism has been put forward to explain its antihypertensive action, including a reduction in myocardial contractility and cardiac output caused by beta blockade. Decreased renin secretion caused by blockade of β-adrenergic receptors, leads to a fall in the levels of angiotensin II and aldosterone, also contributes to the antihypertensive action of β-adrenergic blocking agents.7, 337 Other mechanisms have also been proposed to account for the blood pressure lowering effect of β-adrenergic blocking agents, including alteration of the control of the sympathetic
nervous system at the level of CNS, a change in baroreceptor sensitivity, an alteration in peripheral neuron function by presynaptic actions of β-adrenergic blocking agents, and an increase in prostaglandin biosynthesis.\textsuperscript{7, 337} The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) from the National High Blood Pressure Education Programme of the National Heart, Lung and Blood Institute, U.S.A., has recommended that β-adrenergic blocking agents as appropriate alternatives as first-line treatment for hypertension.\textsuperscript{261} These recommendations are based on the reductions in morbidity and mortality when these drugs are used in large clinical trials. Thirteen orally active β-adrenergic blocking agents are approved in the United States for the treatment of hypertension. In addition, intravenous labetalol is approved for the management of hypertensive emergencies.\textsuperscript{330}

**ANGINA PECTORIS**

Angina pectoris occurs when oxygen demand exceeds supply, as when coronary blood flow is restricted by coronary atherosclerosis. As increased sympathetic activity was known to be a precipitating factor for effort angina, it was thought that blockade of β-adrenergic receptors would relieve angina. On this basis the early clinical studies with β-adrenergic blocking agents in patients with angina pectoris were initiated.\textsuperscript{88} Reduction in heart rate by β-adrenergic blocking agents has two consequences. (i) a decrease in blood pressure-heart rate product (cardiac work), which reduces myocardial oxygen demand, and (ii) a longer diastolic filling time associated with a slower heart rate, which allows for increased coronary perfusion.\textsuperscript{338} They are effective in reducing severity and frequency of attacks of exertional angina. In contrast they are not useful in vasospastic
angina and, if used in isolation may worsen the condition. They are also used in combination with other drugs such as nitrates and calcium channel blockers for the treatment of angina. Combination therapy of nitrates and β-adrenergic blocking agents, ensures that the reflex increase in heart rate caused by nitrate administration is blocked by β-adrenergic blocker therapy and hence more effective than either of the individual therapy.338

MYOCARDIAL INFARCTION

β-Adrenergic blocking agents are used in the hyper-acute phase of a myocardial infarction339 and also in the prevention of recurrences in patients,340 who have survived an initial attack. Following an acute myocardial infarction, treatment with β-adrenergic blocking agents demonstrated a favorable effect on total mortality, cardiovascular mortality, including sudden death, and the incidence of non-fatal reinfarction.340 These beneficial effects with β-adrenergic blocking agents can be explained by both the antiarrhythmic and anti-ischemic effects of the drugs330. It has also been proposed that β-adrenergic blocking agents could reduce the risk of atherosclerotic plaque fissure and subsequent thrombosis.330 Metoprolol (56), propranolol (24) and timolol (41) decrease the mortality rate when started 5 to 28 days after an infarction. While atenolol (45) or metoprolol (56) when administered intravenously during the early phases of an acute attack, may decrease the mortality by 15%,339 an effect that may be improved upon when thrombolytic therapy is co-administered.330
CARDIAC ARRHYTHMIAS

β-Adrenergic blocking agents have become an important treatment modality for various cardiac arrhythmias. These are effective in the treatment of supraventricular arrhythmias such as atrial fibrillation and flutter, and also in the treatment of ventricular arrhythmias such as ventricular tachycardia and fibrillation. The major mechanism through which β-adrenergic blocking agents act as antiarrhythmic is by decreased automaticity of sinus node and ectopic pacemakers by a decrease in phase 4 depolarization. Also the “quinidine like” or local anaesthetic action of β-adrenergic blocking agents reduce the rate of increase in intracardial action potential, which leads to elevated threshold of excitability, delay of conduction velocity and a significant increase in refractory period. Among β-Adrenergic blocking agents, sotalol is unique in that it possesses class III antiarrhythmic properties, causing prolongation of action potential period and thereby delaying repolarization. Intravenous esmolol (119), a short acting cardioselective β-adrenergic blocking agent is useful in controlling rapidly conducted atrial fibrillation.

HEART FAILURE

Even though β-adrenergic blocking agents were once contraindicated in congestive heart failure as it was thought that the negative inotropic effects could precipitate heart failure, recent randomized controlled clinical trials have shown that β-adrenergic blocking agents decrease the mortality in mild to moderate heart failure. Administration of β-adrenergic blocking agents improve long term haemodynamics and LV ejection fraction and reduce the ventricular volumes, filling pressure and left
ventricular mass thereby preventing the progression of the disease. Substantial amount of evidence has accumulated over the last 20 years supporting the use of β-adrenergic blocking agents in patients with congestive heart failure due to systolic left ventricular dysfunction. The major mechanism by which β-adrenergic blocking agents produce these beneficial action seems to be from the blockade of β-adrenergic signal transduction, thereby preventing the heart from excessive exposure to adrenergic activity which is present on congestive heart failure. Presently carvedilol, bisoprolol, metoprolol and bucindolol has been shown by clinical trials to be beneficial in congestive heart failure, but only carvedilol is approved now for use in mild to moderate congestive heart failure. Use of β-adrenergic blocking agents in severe congestive heart failure is still unwarranted as this may worsen the symptoms.

GLAUCOMA

Use of β-adrenergic blocking agents in glaucoma began following the initial discovery that propranolol lowered intraocular pressure in glaucoma patients, but the mild local anaesthetic property of propranolol precluded its use for treating glaucoma. This was followed by discovery that β-adrenergic blocking agents such as timolol, betaxolol, levobunolol and carteolol to reduce intra-ocular pressure and are used as topical preparation for the treatment of glaucoma. It seems that the decrease in intraocular pressure following the administration of β-adrenergic blocking agents are due to a decrease in production of aqueous humor by the ciliary body. Caution is required in patients who are at risk of developing adverse systemic effects to β-adrenergic blocking agents as systemic absorption via nasolacrimal system have been
β-Adrenergic blocking agents are mainstay in glaucoma treatment and have been employed as first line therapy if there are no contraindications such as asthma. They can also be used in combination with dorzolamide, a carbonic anhydrase inhibitor or with latanoprost, a prostaglandin for the effective treatment of glaucoma.

ANXIETY

Since anxiety is known to be associated with excessive sympathetic nervous system discharge, it was investigated in anxiety conditions. It was demonstrated to be effective in generalized anxiety, situational anxiety such as public speaking and examination stress. β-Adrenergic blocking agents relieve the somatic symptoms more significantly than the psychic symptoms associated with anxiety. Thus they decrease symptoms such as tachycardia, palpitation, sweating, muscle tremor and other symptoms that arise from an increased sympathetic activity. Studies have demonstrated that benzodiazepines are more effective than β-adrenergic blocking agents in relieving anxiety, but they are not liable to produce any kind of dependence unlike benzodiazepines. The exact mechanism of anxiolytic action of β-adrenergic blocking agents is debatable with contribution from both the central and peripheral β-adrenergic receptor blockade contributing for their observed action.

TREMOR

Marsden et al. first reported that β-adrenergic blocking agents are useful to reduce tremors in various conditions such as parkinsonism, thyrotoxicosis and anxiety. Essential tremor is a condition of unknown etiology. β-Adrenergic blocking agents are found to be effective in treating essential tremor, but it is not clear whether this is a
consequence of blocking peripheral or central $\beta_1$ or $\beta_2$-receptors. Also controversy exists whether cardioselective or non-selective $\beta$-adrenergic blocking agents are preferable for essential tremor.\(^{355}\) Propranolol is mainly used for the treatment of tremors.\(^{24}\)

**HYPERTHYROIDISM**

Hyperthyroidism is characterized by an excessive release of thyroid hormone into circulation due to hyperactivity of the thyroid gland. The symptomatic and physical manifestations of thyrotoxicosis resemble those produced by sympathetic nervous system.\(^{357}\) $\beta$-Adrenergic blocking agents are capable of alleviating the sympathomimetic manifestations of the thyrotoxic state, such as sweating, tachycardia, palpitation, tremor and anxiety.\(^{358}\) Although the largest experience is with propranolol, other $\beta$-adrenergic blocking agents with and without cardioselectivity have also proven useful.\(^{355}\) The exact mechanism of $\beta$-adrenergic blocking agents benefit in hyperthyroidism is not fully defined. It is not resolved whether the effects are mediated by adrenergic blockade or by blocking the peripheral conversion of $T_4$ to $T_3$.\(^{359}\) They are mainly used as an adjuvant to more specific antithyroid therapy.

**MIGRAINE**

Propranolol was first found to have a beneficial effect on migraine.\(^{260}\) Following this report many other $\beta$-adrenergic blocking agents were found to be of value in the prophylaxis of migraine. Propranolol (24), timolol (41) and atenolol (45) have proven to be of value in the prophylaxis of migraine, while pindolol (42), acebutolol, oxprenolol (35) and alprenolol (34), which have intrinsic sympathomimetic activity, are of no use.\(^{20,355}\) Moreover they are not useful in relieving an acute migraine attack.\(^{111}\) As the
pathophysiology of migraine is not fully understood, the exact mechanism by which 
β-adrenergic blocking agents produce its prophylactic effect is not well defined.

SCHIZOPHRENIA

Propranolol (24) was found to have antipsychotic effect in some patients who 
were also receiving neuroleptics. It is speculated that the beneficial effects are due to 
increase in bioavailability of chlorpromazine. But no consistency has been found in the 
therapeutic benefit of this drug class.

β-Adrenergic blocking agents are also reported to be useful in other conditions 
such as pheochromocytoma and in the treatment of alcohol withdrawal syndrome.

ADVERSE EFFECTS OF β-ADRENERGIC BLOCKING AGENTS AND PRECAUTIONS

β-Adrenergic blocking agents are remarkably safe drugs with a good therapeutic 
index. The major adverse effects are the pharmacological consequence of beta-blockade. 
The most serious of side effects are heart failure and acute exacerbation of asthma.

Among the CVS side effects the possibility of β-adrenergic blocking agents to 
induce congestive heart failure in susceptible patients is of particular concern. Even 
though carvedilol is approved for use in mild to moderate congestive heart failure, 
use of β-adrenergic blocking agents in patients with compensated heart failure may lead 
to worsening of symptoms as the patient is dependant on the sympathetic activity for the 
functioning of the heart. It may also cause life-threatening bradyarrhythmias in patients 
with partial or complete atrioventricular conduction block. Hypotension and 
bradycardia are also reported following β-adrenergic blocking agents administration.
Moreover there may be increased incidence of angina, coronary spasm, and myocardial infarction on abrupt withdrawal of the β-adrenergic blocking agents after long term treatment of patients with ischemic heart disease and hence withdrawal of therapy should be gradual.364

Various central nervous system side effects such as dreams, hallucination, insomnia, depression and confusion are reported and these side effects seems to be more common with lipid soluble β-adrenergic blocking agents, which better penetrate the central nervous system than the water soluble ones.359

Propranolol and other nonselective β-adrenergic blocking agents may cause life-threatening increase in narrowing of asthmatic bronchial airway. The selective β1-adrenergic blocking agents may be of some value in such patients.159

Many metabolic abnormalities have been observed after administration of β-adrenergic blocking agents. They may mask the warning signs of hypoglycemia in diabetic patients on insulin, and hence there is a need for great care when a diabetic patient is taking β-adrenergic blocking agent.111,359,365 Also β-adrenergic blocking agents have an adverse effect on the plasma lipids such as an increase serum triglycerides and reduction in high density lipoprotein (HDL) cholesterol levels. It seems that these negative metabolic effects are less with selective or vasodilating β-adrenergic blocking agents.2

OVERDOSAGE

The manifestation of poisoning with β-adrenergic blocking agents depends on the pharmacological characteristics of the ingested drug.366 Bradycardia associated with
overdosage is normally treated with atropine, but a cardiac pacemaker may often be required, and the hypotension with isoproterenol or an α-adrenoceptor agonist. In case where bronchoconstriction is a problem, aminophylline may be used.\textsuperscript{111}

**DRUG INTERACTIONS**

Both pharmacokinetic and pharmacodynamic interactions have been found between β-adrenergic blocking agents and other drugs.\textsuperscript{367} Drugs such as cholestyramine and colestipol decrease the absorption of β-adrenergic blocking agents from stomach. While drugs such as phenytoin, rifampin and phenobarbital decrease plasma concentration of β-adrenergic blocking agents, by increasing their hepatic biotransformation On the other hand hydralazine and cimetidine increase the bioavailability of propranolol and metoprolol by increasing hepatic blood flow. Pharmacodynamic interactions between β-adrenergic blocking agents and other drugs are often sought in the treatment of hypertension.\textsuperscript{111, 325}