INTRODUCTION:

Anti-hypertensives are a class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.[1] There are many classes of antihypertensives, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers, and the angiotensin II receptor antagonists or ARBs. Table-4.1 lists wide range of available adrenergic drugs with classification and mechanism of action.

Beta blockers (β-blockers, beta-adrenergic blocking agents, beta antagonists, beta-adrenergic antagonists, beta-adrenoreceptor antagonists, or beta adrenergic receptor antagonists) are a class of drugs,
Table 4.1 (ADRENERGIC DRUGS)

<table>
<thead>
<tr>
<th>Receptor Ligands</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1)-adrenergic receptor ligands, Agonists</td>
<td>(\alpha_2)-adrenergic receptor ligands, Agonists</td>
<td>(\alpha_2)-adrenergic receptor ligands, Antagonists</td>
</tr>
<tr>
<td>(\beta)-adrenergic receptor ligands, Agonists</td>
<td>(\beta)-adrenergic receptor ligands, Antagonists</td>
<td></td>
</tr>
<tr>
<td>(\beta)-adrenergic receptor ligands, Antagonists</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reuptake Inhibitors**

|  |NorEpinephrine Transporter (NET) inhibitors (Selective norepinephrine reuptake inhibitors, Noradrenaline-dopamine reuptake inhibitors, Serotonin-norepinephrine reuptake inhibitor, Serotonin-norepinephrine-dopamine reuptake inhibitors, Tricyclic antidepressants, Tetracyclic antidepressants, Others) |
|  |Vesicular MonoAmine Transporter (VMAT) inhibitors|

**Releasing Agents**

|  |  |Anabolism (Phenylalanine hydroxylase (PAH) inhibitors, Tyrosine hydroxylase inhibitors, Aromatic L-amino acid decarboxylase (AAAD) inhibitors, Dopamine-beta-hydroxylase (DBH) inhibitors,Phenylethanolamine N-methyltransferase - (PNMT) inhibitors) |
|  |  |Catabolism (Monoamine oxidase (MAO) inhibitors: Nonselective, MAO-A selective, MAO-B selective) |
|  |  |Catechol-O-methyl transferase (COMT) inhibitors |
Beta blockers target the beta receptor. Beta receptors are found on cells of the heart muscles, smooth muscles, airways, arteries, kidneys and other tissues that are part of the sympathetic nervous system and lead to stress responses, especially when they are stimulated by epinephrine (adrenaline). Beta blockers interfere with the binding to the receptor of epinephrine and other stress hormones, and weaken the effects of stress hormones. They are particularly used for the management of cardiac arrhythmias, protecting the heart from a second heart attack (myocardial infarction) after a first heart attack (secondary prevention), and hypertension.

In 1962, Sir James W. Black found the first clinically significant beta blockers propranolol and pronethalol; it revolutionized the medical management of angina pectoris and is considered by many to be one of the most important contributions to clinical medicine and pharmacology of the 20th century.

Beta blockers block the action of endogenous catecholamine epinephrine (adrenaline) and nor epinephrine (nor adrenaline) in particular, on β-adrenergic receptors, part of the sympathetic nervous system, which mediates the fight-or-flight response. Three types of beta receptors are known, designated β₁, β₂ and β₃ receptors. β₁-adrenergic receptors are located mainly in the heart and in the kidneys. β₂-receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle and skeletal muscle. β₃-adrenergic receptors are located in fat cells.

Bisoprolol is a drug belonging to the group of beta blockers, a class of medicines used primarily in cardiovascular diseases. More specifically, it is a selective type β₁ adrenergic receptor blocker. The U.S. Food and Drug Administration (FDA) approved an application by Duramed Pharmaceutical for Zebeta Oral Tablets (Bisoprolol Fumarate) as a new molecular entity on July 31, 1992. It has since been approved by the FDA for manufacture by Teva, Mylan, Sandoz, and Mutual Pharmaceutical Companies.

| Others          | Precursors, Cofactors, Activity enhancers, Release blockers, Toxins |

Chapter - IV
Bisoprolol is beneficial in treatment for: high blood pressure (hypertension), reduced blood flow to the heart (cardiac ischemia); congestive heart failure, preventative treatment before and primary treatment after heart attacks decreasing the chances of recurrence.\[^{11}\] \(^{\text{[11]}}\) During hypertension there is an elevated blood pressure, which is what bisoprolol targets.\(^{12,13}\) \[^{\text{[12,13]}}\) While in cardiac ischemia the drug is used to reduce the activity of the heart muscle and therefore reduce oxygen and nutrient demand, so reduced blood supply can still transport sufficient amounts of oxygen and nutrients.\[^{14-16}\] \[^{\text{[14-16]}}\)

Many beta-blockers are now available (Table-4.2) and in general they are all equally effective. There are, however, differences between them which may affect choice in treating particular diseases or individual patients.

**Table-4.2 (Beta blockers)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta, nonselective</td>
<td>Alprenolol, Bopindolol, Bupranolol, Carteolol, Cloranolol, Mepindolol, Nadolol, Oxprenolol, Penbutolol, Pindolol, Propranolol, Sotalol, Tertatolol, Timolol</td>
</tr>
<tr>
<td>Beta(_1) selective</td>
<td>Acebutolol, <strong>Atenolol</strong>, Betaxolol, Bevantolol, <strong>Bisoprolol</strong>, Celiprolol, Epanolol, Esmolol, Nebivolol, <strong>Metoprolol</strong>, Practolol, S-atenolol, Talinolol</td>
</tr>
<tr>
<td>Alpha + beta</td>
<td>Carvedilol, Labetalol</td>
</tr>
<tr>
<td>Other/ungrouped</td>
<td>Butaxamine</td>
</tr>
</tbody>
</table>

Bisoprolol is cardio protective because it selectively and competitively blocks catecholamine (adrenalin) stimulation of β1 adrenergic receptors (adrenoreceptors), which are mainly found in the heart muscle cells and heart conduction tissue (cardio specific) but also found in juxtaglomerular cells in the kidney.\[^{14}\] \[^{\text{[14]}}\) Normally adrenalin and noradrenalin stimulation of the β1 adrenoreceptor activates a signalling cascade (Gs protein and cAMP) which ultimately lead to increased contractility and increased heart rate of the heart muscle and heart pacemaker respectively.\[^{17}\] \[^{\text{[17]}}\) Bisoprolol competitively blocks the activation of this cascade and therefore decreases the adrenergic tone/stimulation of the heart muscle and pacemaker cells. Decreased
adrenergic tone shows less contractility of heart muscle and lowered heart rate of heart pacemaker.\cite{18-20}

These are the favourable factors that are decreased and treat hypertension, heart attacks and ischemia. The decreases in contractility and heart rate are beneficial for hypertension because they reduce blood pressure\cite{12,15} but for preventive measures for heart attacks and cardiac ischemia these decreases in heart rate and contraction decrease the hearts demand for oxygen and nutrients; primary treatment post heart attacks is to prevent recurrence of the infarction.\cite{13,16,17}

Bisoprolol can be used to treat cardiovascular diseases such as hypertension, coronary heart disease, arrhythmias, ischemic heart diseases and treatment of myocardial infarction after the acute event. Patients with compensated congestive heart failure may be treated with bisoprolol as a co medication (usually together with an ACE inhibitor, a diuretic and a digitalis-glycoside, if indicated). In patients with congestive heart failure, it reduces the need for and the consumption of oxygen of the heart muscle. It is very important to start with low doses, as bisoprolol reduces also the muscular power of the heart, which is an undesired effect in congestive heart failure.

Bisoprolol has both lipid and water soluble properties making it a prime candidate over other $\beta$-blockers and even over other $\beta_1$-blockers, being water soluble it will have decreased incidence of central nervous system side effects (inability to diffuse into brain) compared to purely lipophilic compounds.\cite{18-19} Bisoprolol has an approximate half-life of 10-12 hours and when ingested has nearly complete absorption into the blood stream.\cite{19-20} The high absorption is indicative of high bioavailability (approx. 90\%).\cite{19-20} When being eliminated, the body evenly distributes it (50-50) between kidney excretion and liver biotransformation (then excreted).\cite{18-20}

These factors make it a convenient once/day dosage when it’s being administered.\cite{19-20}

Bisoprolol $\beta_1$-selectivity is especially important in comparison to other non-selective beta blockers. The effects of the drug are limited to areas containing $\beta_1$ adrenoreceptors which is
mainly the heart and a little bit of the kidney.\textsuperscript{[18-19]} Bisoprolol minimizes the side effects that might occur from administration of a non-specific beta blocker where blockage of the other adrenoreceptors (β2, β3, α1, α2) occurs. The other receptors elicit a variety of responses in the body and blockage of them could cause a wide range of reactions; but β1 adrenoreceptors are cardio specific for the most part, making bisoprolol ideal for treatment of cardiac events.\textsuperscript{[18-20]}

Bisoprolol has a higher degree of β1-selectivity compared to other β1-selective β-blockers such as atenolol, metoprolol and betaxolol.\textsuperscript{[18]}

Zebeta (bisoprolol fumarate) is a synthetic, β1-selective (cardioselective) adrenoceptor blocking agent. The chemical name for bisoprolol fumarate is $\text{(±)}-1\cdot[4\cdot[(1\text{-Methylethoxy})\text{-ethoxy}]\text{methyl}]\cdot\text{phenoxy}\cdot3\cdot[(1\text{-methylethyl})\text{amino}]\cdot2\cdot\text{propanol}(E)\cdot2\cdot\text{butenedioate (2:1) (salt)}$. It possesses an asymmetric carbon atom in its structure and is provided as a racemic mixture. The $S$-(-) enantiomer is responsible for most of the beta-blocking activity. Its empirical formula is $\text{(C_{18}H_{31}NO_{4})_2\cdotC_4H_4O_4}$ and its structure is:

\[
\begin{array}{c}
\text{N} \\
\text{O} \quad \text{H} \\
\text{O} \quad \text{O} \\
\text{H} \\
\text{O} \quad \text{O} \\
\text{O} \\
\text{C} \\
\text{H} \quad \text{C} \\
\text{O} \quad \text{H} \\
\end{array}
\]

Bisoprolol fumarate has a molecular weight of 766.97. It is a white crystalline powder which is approximately equally hydrophilic and lipophilic and is readily soluble in water, methanol, ethanol and chloroform. Zebeta (bisoprolol fumarate) is available as 5 and 10 mg tablets for oral administration.
Table 4.3

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Generic name</th>
<th>Systematic (IUPAC) name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bisoprolol (1)</td>
<td>(RS)-1-[4-[(2-isopropoxyethoxy)methyl]-phenoxy]-3-(isopropylamino)propan-2-ol</td>
<td><img src="image" alt="Structure of Bisoprolol" /></td>
</tr>
<tr>
<td>2</td>
<td>Metoprolol (2)</td>
<td>(RS)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol</td>
<td><img src="image" alt="Structure of Metoprolol" /></td>
</tr>
<tr>
<td>3</td>
<td>Atenolol (3)</td>
<td>(RS)-2-[[2-Hydroxy-3-(propan-2-ylamino)propoxy]phenyl]acetamide</td>
<td><img src="image" alt="Structure of Atenolol" /></td>
</tr>
<tr>
<td>4</td>
<td>Propranolol (4)</td>
<td>(RS)-1-[(1-methylethylamino)-3-(1-naphthyloxy)propan-2-ol</td>
<td><img src="image" alt="Structure of Propranolol" /></td>
</tr>
</tbody>
</table>

REVIEW OF LITERATURE:

Drugs belonging to the class of aryloxypropanolamine are useful beta blockers.\textsuperscript{[21]} Bisoprolol was first synthesized by Jonas et al.\textsuperscript{[22]} in 1978 (Scheme-4.1). Starting with 4-hydroxybenzyl alcohol 5 and heating to 150°C with 2-isopropoxyethanol 6 to give 4-[[2-(1-methylethoxy)-ethoxy]methyl]phenol 7, which is further reacted with epichlorohydrin 8 to give 2-[[2-(1-...
methylethoxy)ethoxy)methyl]phenoxy)methyl]oxirane 9. This is further reacted with isopropyl amine 10 to give Bisoprolol 1.

The drawback of this process is that such a high temperature of 150°C is difficult to achieve on industrial scale and more over 4-hydroxybenzyl alcohol as well as 2-isoproxyethanol get self condensed and produces dimer impurities at this temperature.

Other schemes, to prepare Bisoprolol fumarate given in this patent are mentioned in Scheme-4.2 and Scheme-4.3.

Stewart[23] mentioned the selective etherification of 4-hydroxybenzyl alcohol by treating its solution in alcohol with a strong acid cation-exchange (especially "Zeo-Karb 225") resin at room temperature. But the limitations of this process were the low yield (60% in methanol and 37% in ethanol) and rapid polymerization of 4-hydroxybenzyl alcohol forming a resinous product.
Stein et al\cite{24} have described a process for the preparation of 7. In this process the solution of 4-hydroxybenzyl alcohol 5, and 2-isopropoxyethanol 6 in THF was passed over a bed of Amberlyst 15 in a fixed bed reactor loaded with ion exchanger leads. The obtained product mixture was passed through a second fixed bed reactor filled with weakly basic ion exchanger the Amberlyst A-21. The yield achieved was 72%. This process required a costly reactor loaded with ion exchanger leads and also the process was not feasible at industrial scale as it required to be passed through two ion exchangers. Thus the process was not commercially viable.

Mody et al\cite{25} have described the preparation of Bisoprolol and its pharmaceutically acceptable salt by reacting 4-[[2-(1-methylethoxy)ethoxy]methyl]-phenol 7 with 1,3-dichloro-2-hydroxy propane in the presence of phase transfer catalyst such as tri-n-butyl ammonium bromide to obtain 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]-phenoxy]-3-chloropropan-2-ol, which was further reacted with isopropyl amine in methanol in an autoclave at 100°C to get Bisoprolol. This process required a pressure reactor and high temperature making the process industrially uneconomical.

Liu et al\cite{26} used LSI-600 resin to prepare 7 from 5, where as Ramakrishnan et al,\cite{27} Peste et al\cite{28} used Amberlyst 15 resin and Zhang\cite{29} used strong acidic styrene type cation exchange resin at room temperature without solvent.

Kawada et al\cite{30,31} used transition metal complexes e.g. Yb(OSO₂Rf)₃ and RE(OTf)₃ for the etherification of 4-hydroxybenzyl alcohol 5 with 2-isopropoxyethanol 6 at 80°C for 18h to get 4-[[2-(1-methyl-ethoxy)ethoxy]methyl]-phenol 7 and reported 85% yield . Bhaskar et al\cite{32} have developed a method for the synthesis of benzyl ethers of alkyl, allyl and propargyl alcohols by direct coupling of alcohols in the presence of catalytic amount of InCl₃ under solvent free condition at 80°C for 3.25h and reported 87% product yield.

Zhang et al\cite{33} disclosed this etherification process using phosphoric acid as a catalyst in water at 60°C.
Jiang et al.\textsuperscript{[34]} reported preparation of 4-[[2-(1-methyl-ethoxy)ethoxy]methyl]-phenol, 7 as mentioned in the Scheme-4.4. 4-methylphenol 15 was acylated for hydroxy protection to obtain corresponding sulfonic acid 4-methylphenyl ester 17. The ester was brominated with bromine photochem. in CCl\(_4\) refluxed to obtain 18 with protected 4-hydroxy group. Subsequent reaction of 18 with sodium isopropoxyethoxide and reaction with hydrazine, ammonia for deprotection yielded 7. Overall yield of this multi-step synthesis was 68%.

Benzyl ether side chain was also introduced after synthesis of the aminopropanol group 21. Here the basic alcohol 21\textsuperscript{[35]} was protected by cyclization with diethyl carbonate 22 and subsequently chloromethylated in the 4-position to yield 24.\textsuperscript{[36]} Etherification with 2-isopropoxyethanol 6, resulted in the benzyl ether 25 which was saponified to 1 by alkaline hydrolysis (Scheme-4.5).
O’Neill et al\(^{[37]}\) have discussed the synthesis of 1, starting with isopropylaminopropanediol 26, which is detailed in the Scheme-4.6.

\[ \text{HO-} \bigg\| \text{O}\bigg\| \text{N} \bigg\| \text{H} \]

\[ \text{26} \]

Kitaori et al\(^{[38-39]}\) reported the first convenient synthesis of enantiopure Bisoprolol by use of glycidyl nosylate. They described the preparation of the generation of \(\beta\)-amino alcohol moiety involving of substituted phenol, the core of the \(\beta\)-blockers, in enantiopure form.

Yao et al\(^{[40,41]}\) reported the total synthesis of Bisoprolol starting from 4-[[2-(1-methylethoxy)ethoxy]-methyl]phenol 7 which was further reacted with R-epichlorohydrin R-8 to give 2-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxymethyl]oxirane R-9. This was further reacted with isopropyl amine 10 to give Bisoprolol 1 in 61% yield and 92% enantiomeric excess. (Scheme-4.7)

\[ \text{OH} \]

\[ \text{7} \]
Chapter - IV

PRESENT WORK:

The object of the present work was to uncover and overcome the many disadvantages of the prior work. Present work details the journey towards development of a simple, safe, productive, eco-friendly and easy to handle commercial process for preparing Bisoprolol. Hence, we have developed and optimized the process, impurities formed in the process were identified, prepared and characterized. Additionally, force degradation study of Bisoprolol was also investigated. A mechanistic rationale for the formation of the various process impurities and degradation products has also been provided.

RESULTS AND DISCUSSION:

Three synthetic approaches are described herein, among which approach A deals with the total synthesis of Bisoprolol and its analogs. It also includes process development of Bisoprolol. Approach B discloses numerous common impurities, formed in the process for the preparation of Bisoprolol, Metoprolol, Atenolol and Propranolol. Approach C specifically deals with the formation of Bisoprolol homolog related substance which originates in Bisoprolol synthesis, was prepared synthetically in four chemical steps.

APPROACH A:

Bisoprolol 1 was first synthesized by Jonas et al in 1978.[22] Starting with 4-hydroxybenzyl alcohol 5 and heating to 150°C with 2-isopropoxyethanol 6 to give 4-[[2-(1-methylethoxy)ethoxy]methyl]phenol 7 which was further reacted with epichlorohydrin 8 to give 2-[[2-(1-methylethoxy)ethoxy]-methyl]phenoxy-methyl]-oxirane 9. This was further reacted with isopropyl amine 10 to give Bisoprolol 1.

The most difficult step in the industrial manufacturing of bisoprolol fumarate, an important beta-blocker agent, was the synthesis of 4-[[2-(1-methyl-ethoxy)ethoxy]methyl]-phenol 7, which was influenced by three main parameters: 2-isopropoxyethanol/4-hydroxybenzyl alcohol molar ratio, reaction time and temperature. Preparation of the simple p-(and o-)alkoxymethyl-
phenols has generally been attended by difficulties on account of their strong tendency to resinify on heating, particularly in the presence of acids or bases to produce a complex phenol-formaldehyde resin Bakelite (Scheme-4.8).\textsuperscript{[42]}

\[ \text{Scheme-4.8} \]

The process described above for the preparation of 4-[[2-(1-methylethoxy)ethoxy]methyl]-phenol 7 using resins rare earth metal complexes or at higher temperature cannot be the commercial process and not feasible to be used at industrial scale. Parallel to this process, we have developed and optimized a process avoiding these reagents/elevated temperatures for preparation of 7 (Scheme-4.9).

\[ \text{Scheme-4.9} \]
PROCESS DEVELOPMENT AND IMPURITY PROFILE:

Preparation of benzyl ether: Accordingly, the present invention relates to an improved process for the preparation of 4-[[2-(1-methylethoxy)ethoxy]methyl]-phenol 7 from 4-hydroxybenzyl alcohol 5 and 2-isopropanol 6, using acid in catalytic amount in the presence or absence of solvent.

The acid used can be organic acid or inorganic acid such as sulfonic acids for example p-toluenesulfonic acid, methanesulfonic acid, benzenesulfonic acid, naphthalenesulfonic acid; halo acids such as hydrochloric acid, hydrobromic acid; sulfuric acid, phosphoric acid and the like or mixture thereof, preferred being sulfonic acids and most preferred being p-toluenesulfonic acid.

The amount of catalyst played an important role on the rate of the reaction. If amount of catalyst was increased the reaction was faster. The catalyst was used in an amount of 2-10 % to the weight of the 4-hydroxybenzyl alcohol 5, preferably in an amount of 1-5 %.

The solvent used in the present condensation reaction was selected from hydrocarbons, halogenated hydrocarbons, ethers, ketones, nitrites, amides, sulfoxides and the like or mixtures thereof.

In one of the embodiments of the present invention, the reaction was carried out in the absence of solvent.

Usually, condensation reaction was carried out at a temperature between 0 to 100°C and preferably 10 to 40°C and most preferably the reaction was carried out at 15 to 30°C.

When the reaction was carried out in the absence of solvent, on completion of reaction, the reaction mass was diluted with the inert solvent exemplified above and neutralized with a base or washed with water until the pH of the washings was 4.5-7.0 and preferably between 5.0-5.8.
When the reaction was conducted in the presence of solvent, after completion of reaction, the organic layer was washed with water or base until the pH of the washings was 4.5-7.0 and preferably 5.0-5.8.

This washing was essential to remove any traces of acid, which if present, lead to degradation during isolation of product. The bases, which can be used, were dilute aqueous solutions of alkali metal hydroxides, bicarbonates, carbonates or aqueous ammonium hydroxide solution. Thereafter, the organic layer was concentrated and crude product obtained was purified by distillation under reduced pressure to obtain the compound of Formula 7 in high yield and having purity greater than 98 % by HPLC.

By LCMS study, following impurities were observed in the isolated product.

The compound of Formula 7 was isolated and converted to Bisoprolol by the method which comprise, reacting compound of Formula 7 with epichlorohydrin 8 in the presence of a base, such as sodium hydroxide or potassium hydroxide at a temperature of 30-60°C to prepare epoxy benzyl ether 9, treating epoxy benzyl ether of Formula 9 with isopropyl amine 10 in hydroxylated solvents such as by the method reported in the prior art. Specifically the reaction was conducted in alcohols such as ethanol, methanol, isopropyl alcohol and the like, to prepare Bisoprolol of high purity. Bisoprolol thus prepared was further converted to its fumarate salt by treating with fumaric acid.
Major advantages realized in the present investigation were the use of catalytic amount of acid under mild condition, to prepare 4-(2-isopropoxyethoxymethyl)phenol of Formula 7 in high yield and purity without using any ion exchange resin and expensive reagents.

**Preparation of epoxy benzyl ether:** It was well known in literature that phenyl group react with epichlorohydrin in presence of base. Therefore, we carried out the reaction by heating 7, epichlorohydrin (1.5 m. eq.) and sodium hydroxide (1.1 m. eq.) in methanol at 40-45°C. The reaction was monitored by qualitative HPLC. It was observed that a number of impurities were formed, one of them was 20-30%.

One experiment was carried out by preparing sodium salt of 7 and adding 4 times epichlorohydrin, at 50°C in one hour. After 5 h, Bisoprolol phenol 7 left unreacted was 1.76% and product formation was only 48.65%, while one major impurity was formed (~40%). Later this ~40% impurity was identified to be 37 (by LC Mass) and its likely formation was shown in Scheme-4.10.

![Scheme-4.10](image)

In another reaction Bisoprolol phenol 7 was reacted with sodium hydroxide (1.1 m.eq.) in epichlorohydrin at 30-33°C. The reaction was monitored by qualitative HPLC analysis, which after 5 h 30 min showed presence of Bisoprolol phenol 7.66%, while the product formation was 77.06%.

In another experiment, toluene was tried in place of methanol and monitored by qualitative HPLC, which showed that after 3 h 45 min, product formation was 50.25% and the 7 left unreacted was 15.28%. This experiment also showed formation of ~28% impurity. This
impurity was later identified to be dimer and was formed by the reaction of Bisoprolol phenol 7 with Bisoprolol epoxide 9 as described in Scheme-4.11.

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{NaOH, 40-45°C} \]

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad 38 \]

…..Scheme-4.11

Attempts were made to minimise the impurity formation and to limit \( 7 \leq 1.0\% \). Another similar experiment was repeated using two times epichlorohydrin and 1.03 m.eq. sodium hydroxide based on 7. The reaction temperature was maintained at 40-45°C. This reaction resulted in the formation of \( \sim 16.86\% \) dimer 38 after 4 h. An additional experiment was carried out using 3 times of epichlorohydrin based on 7 at 40-45°C. After 4 h, Bisoprolol phenol left unreacted was 0.44%, while the product and dimer formation were 79.52% and 9.79% respectively.

Based on these observations, it was concluded that dimer impurity decreases with increase in the amount of epichlorohydrin in reaction. Another experiment was carried out using 5 times epichlorohydrin based on 7. After 1 h 45 min unreacted Bisoprolol phenol 7 was 0.67% while product was \( \sim 91.93\% \) with the dimer formation 5.15%. Same experiment was repeated at 45-50°C temperature range. After 2 h 30 min, starting material i.e. 7 was absent with 92.38% formation of 9 while the impurity 38 formed was 5.03%.

After completion of reaction, reaction mass was washed with DM water at 15-20°C to 7.0±0.5 pH to remove excess of sodium hydroxide and by product sodium chloride and then concentrated to yield Bisoprolol epoxide 9 having HPLC purity 90-92%, the major impurity being the dimer 38 with several other impurities. These impurities were further identified by LC mass as under.
The examination of results obtained from above experiments led to conclusion that heating of Bisoprolol phenol in 5 times epichlorohydrin in presence of 1.05 sodium hydroxide at 40-50°C resulted in completion of reaction (≤0.5% unreacted) and inevitably about 5% of the dimer impurity formed.

The oxidation of benzylic hydroxy methyl group of 4-hydroxybenzyl alcohol present in Bisoprolol phenol had also been restricted by adding an antioxidant butylated hydroxytoluene in reaction and another two experiments were carried out as discussed above. The purity of isolated product was >91% by qualitative HPLC. Results of these batches are given in Table-4.4.
Table-4.4

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Bisoprolol phenol</th>
<th>Bisoprolol epoxide</th>
<th>Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK(321)120</td>
<td>Not detected</td>
<td>91.83%</td>
<td>4.11%</td>
</tr>
<tr>
<td>MK(321)137</td>
<td>Not detected</td>
<td>94.02%</td>
<td>4.11%</td>
</tr>
</tbody>
</table>

Preparation of Bisoprolol: It is well documented in literature that oxirane on reaction with amines gave β-amino alcohols. Following this view, initially one reaction has been carried out by reacting Bisoprolol epoxide 9 with 7 m. eq. isopropylamine in ethanol (absolute alcohol, 2 times) at 10-15°C which require 27 h to achieve Bisoprolol epoxide in 0.79% level by qualitative HPLC analysis, with the formation of 84.45% Bisoprolol. Subsequent to this, in another experiment, sodium hydroxide (1 m. eq.) was used to reduce the reaction time but formation of number of impurities was observed in reaction.

In another experiment, which was carried out using 6 m. eq. mono isopropylamine 10 and 3.3 time isopropyl alcohol based on 9 at 58-62°C, the reaction was completed within two hours. The formation of product was 94.43% by qualitative HPLC, whereas the largest impurity formation was 3.56%, which was identified as Bisoprolol dimer diastereoisomers, originated from the reaction of 9 with Bisoprolol base as given in Scheme-4.12.

![Scheme-4.12](image)

The other impurity from Bisoprolol epoxides remain in ~5% was 38. Hence we attempted to minimize the formation of 46. In one experiment, Bisoprolol epoxide 9 was treated with
monoisopropyl amine 10, 10 m. eq. and isopropyl alcohol 5 times at 58-62°C. After 2 h 15 min the starting material i.e. 9 was 0.09% with the product Bisoprolol 91.36%. The Bisoprolol dimer diastereoisomer 46 formed was only 1.48%. Subsequent to this, another reaction was repeated in which formation of 46 was 1.22% observed.

After concentration, the product was extracted with dilute hydrochloric acid and thereafter washed with organic solvent to remove 38 and 46 partially and other non salt forming impurities. The obtained Bisoprolol base was analysed by LC mass spectroscopy, which showed the presence of following impurities:

\[ 47 \]
\( (2RS)-1-[4-(HYDROXYMETHYL)PHENOXY]-3-[(1-METHYLETHYL)AMINO]-2-PROPANOL \)
\[ 48 \]
\( (2RS)-1-[4-(FORMYL)PHENOXY]-3-[(1-METHYLETHYL)AMINO]-2-PROPANOL \)
\[ 49 \]
\( (2RS)-1-[4-(METHYL)PHENOXY]-3-[(1-METHYLETHYL)AMINO]-2-PROPANOL \)
\[ 50 \]
\( (2RS)-1-[4-[[2-ISOPROPOXYETHOXY]-METHOXY]METHYL]PHENOXY]-3-[(1-METHYLETHYL)AMINO]-2-PROPANOL \)
\[ 46 \]
\( N,N-Bis[3-[4-[[2-(1-METHYLETHOXY)ETHOXY]METHYL]PHENOXY]-\]
\( (2RS)-2-HYDROXYPROPYL]ISOPROPYLAMINE \)

Chapter - IV
Among these impurities, Bisoprolol carbinol 47 and Methyl bisoprolol 49 originate from 7, (raw material impurities 5 and 15) carried through the synthesis and contaminate the final product, while Bisoprolol aldehyde 48 was formed by stepwise oxidation of 7 (Scheme-4.13). Bisoprolol carbinol and Methyl bisoprolol were the potential impurities and could carry through up to Bisoprolol fumarate.

To understand the behaviour of these impurities, one experiment was designed in which 4-hydroxybenzyl alcohol 5 and p-cresol 15 were added in 0.5% w/w level, based on Bisoprolol phenol during Bisoprolol epoxide formation. The obtained product was used to prepare Bisoprolol base, which showed the formation of 0.61% Bisoprolol carbinol and 0.68% methyl bisoprolol. After normal distillation, the Bisoprolol carbinol 47 was increased to 0.73 while methyl bisoprolol 49 was remained almost constant at 0.62%. Further, in fumarate preparation, 47 get decreased to 0.33% while 49 enriched to 0.73%.

So there was a need to control 4-hydroxybenzyl alcohol 5 and p-cresol 15 in 7. Some unknown impurities remained in residue during distillation. Fractional distillation of Bisoprolol base led to decrease 49. Being a low boiler methyl bisoprolol 49 distils initially in first fraction. In another experiment, 1 having 47 (0.2%), Bisoprolol aldehyde 48 (0.2%), Methyl bisoprolol 49 (0.2%), Bisoprolol homologue 50 (0.2%) and Bisoprolol dimer diastereoisomer 46 (0.5%) were subjected to high vacuum distillation. The results of this batch are given in Table-4.5.
Table-4.5

<table>
<thead>
<tr>
<th></th>
<th>Before distillation</th>
<th>After distillation (Without fractionations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol carbinol</td>
<td>0.29%</td>
<td>0.31%</td>
</tr>
<tr>
<td>Bisoprolol aldehyde</td>
<td>0.24%</td>
<td>Not detected</td>
</tr>
<tr>
<td>Methyl Bisoprolol</td>
<td>0.20%</td>
<td>0.15%</td>
</tr>
<tr>
<td>Bisoprolol homologue</td>
<td>0.22%</td>
<td>0.18%</td>
</tr>
<tr>
<td>Bisoprolol dimer, diastereoisomer</td>
<td>0.59%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

It was evident that fractional distillation under reduced pressure was required to meet the product quality. In order to restrict the impurities in Bisoprolol fumarate, there was a need to purify Bisoprolol fumarate at base stage itself, as Bisoprolol fumarate re-crystallization was not effective to remove most of the impurities. At the end of distillation, Bisoprolol aldehyde 48 and impurity were presents at RRT (0.92) remain in the residue, while Methyl Bisoprolol 49 could be eliminated by removing forerun during high vacuum distillation.

Direct conversion of Bisoprolol to Bisoprolol fumarate (2:1) was carried out using crude Bisoprolol base Table-4.6 and distilled Bisoprolol base Table-4.7 to know the impurity behaviour in distillation as well as in fumarate preparation.

Table-4.6

<table>
<thead>
<tr>
<th></th>
<th>47</th>
<th>48</th>
<th>49</th>
<th>50</th>
<th>46</th>
<th>RRT (0.92)</th>
<th>Chromato -graphic Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Input</strong></td>
<td>0.15%</td>
<td>0.03%</td>
<td>0.11%</td>
<td>0.18%</td>
<td>0.78%</td>
<td>0.15%</td>
<td>98.05%</td>
</tr>
<tr>
<td><strong>Fumarate</strong></td>
<td>0.08%</td>
<td>0.03%</td>
<td>0.08%</td>
<td>0.16%</td>
<td>0.03%</td>
<td>0.29%</td>
<td>99.33%</td>
</tr>
<tr>
<td><strong>Recrystal- lisation</strong></td>
<td>0.07%</td>
<td>0.03%</td>
<td>0.08%</td>
<td>0.14%</td>
<td>Not detected</td>
<td>0.31%</td>
<td>99.34%</td>
</tr>
</tbody>
</table>
Table-4.7

<table>
<thead>
<tr>
<th></th>
<th>47</th>
<th>48</th>
<th>49</th>
<th>50</th>
<th>46</th>
<th>RRT (0.92)</th>
<th>Chromatographic Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td>0.15%</td>
<td>0.03%</td>
<td>0.11%</td>
<td>0.18%</td>
<td>0.78%</td>
<td>0.15%</td>
<td>98.05%</td>
</tr>
<tr>
<td>Fraction-I</td>
<td>0.23%</td>
<td>Not detected</td>
<td>1.13%</td>
<td>0.06%</td>
<td>0.01%</td>
<td>Not detected</td>
<td>98.16%</td>
</tr>
<tr>
<td>Fraction-II</td>
<td>0.13%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.15%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>99.39%</td>
</tr>
<tr>
<td>Fumarate</td>
<td>0.07%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.10%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>99.77%</td>
</tr>
<tr>
<td>Recrystallisation</td>
<td>0.07%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.11%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>99.77%</td>
</tr>
</tbody>
</table>

Above experiment clearly indicated that fractional distillation was able to remove the impurity before preparation of its fumarate salt. Some more experiments were repeated to establish advantages of the fractional distillation in obtaining pure base and its use in fumarate preparation Table-4.8, 4.9 and 4.10.

Table-4.8

<table>
<thead>
<tr>
<th>Batch No. MK(321)129</th>
<th>47</th>
<th>48</th>
<th>49</th>
<th>50</th>
<th>46</th>
<th>RRT 0.92</th>
<th>Chromatographic purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td>0.15%</td>
<td>0.03%</td>
<td>0.11%</td>
<td>0.18%</td>
<td>0.78%</td>
<td>0.15%</td>
<td>98.05%</td>
</tr>
<tr>
<td>Fr-I</td>
<td>0.18%</td>
<td>Not detected</td>
<td>1.21%</td>
<td>0.06%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>98.08%</td>
</tr>
<tr>
<td>Fr-II</td>
<td>0.13%</td>
<td>Not detected</td>
<td>0.02%</td>
<td>0.16%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>99.33%</td>
</tr>
</tbody>
</table>
Table-4.9

<table>
<thead>
<tr>
<th>Batch No. MK(321)141</th>
<th>47</th>
<th>48</th>
<th>49</th>
<th>50</th>
<th>46</th>
<th>RRT 0.92</th>
<th>Chromatographic purity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base input</strong></td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.04%</td>
<td>0.11%</td>
<td>0.86%</td>
<td>0.42%</td>
<td>97.65%</td>
</tr>
<tr>
<td><strong>Distilled</strong></td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.14%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>99.53%</td>
</tr>
<tr>
<td><strong>Fumarate</strong></td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.11%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>99.88%</td>
</tr>
</tbody>
</table>

Table-4.10

<table>
<thead>
<tr>
<th>Batch No. MK(321)146</th>
<th>47</th>
<th>48</th>
<th>49</th>
<th>50</th>
<th>46</th>
<th>RRT 0.92</th>
<th>Chromatographic purity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base input</strong></td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.14%</td>
<td>0.08%</td>
<td>3.31%</td>
<td>0.40%</td>
<td>91.22%</td>
</tr>
<tr>
<td><strong>Distilled</strong></td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.14%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>97.16%</td>
</tr>
<tr>
<td><strong>Fumarate</strong></td>
<td>0.03%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.10%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>98.82%</td>
</tr>
</tbody>
</table>

The experimentation of foregoing distillation confirm the utility of fractional distillation which can remove Methyl bisoprolol and other light molecular weight impurities.

Bisoprolol base was dissolved in aqueous acetone, a Class 3 solvent, and treated with fumaric acid (0.5 m. eq.) to make Bisoprolol fumarate (2:1). This fumarate salt does not involve any complexity and proceeds smoothly. Bisoprolol base input with the requisite impurity profile was required to obtain Bisoprolol fumarate having more than 99.5% purity. No new impurity formation has been observed during preparation of Bisoprolol fumarate.
Nevertheless, a number of solvents have been tried to make Bisoprolol fumarate eg. ethyl acetate, ethylacetate-methanol, ethylacetate-ethanol, acetone, methylene chloride-acetone, acetone-water, but all of them gave the Bisoprolol fumarate having same infrared and XRD. No polymorph has also been reported in literature.

We also observed that Bisoprolol forms only (2:1) salt with fumaric acid. In one experiment fumaric acid 1.05 m.eq. was added to Bisoprolol base in acetone to prepare 1:1 salt. But 

\[ ^{1}HNMR \] shows that, obtained product was Bisoprolol fumarate (2:1) salt.

Drying of the product should be carried out at 65-70°C under reduced pressure (~20 mm Hg) to obtain a single endotherm between 95°C and 105°C in DSC. If DSC profiles show an additional minor endotherm between 70°C and 85°C, drying was continued at 65-70°C until the minor endotherm disappears.

Following the same process as discussed for the preparation of Bisoprolol, 12 analogs were prepared as shown in Scheme-4.14.

Where R is:
APPROACH B:

Common impurities which are observed in Atenolol, Bisoprolol, Metoprolol and Propranolol also prepared. These impurities are identified as diol, chlorohydrin, dimer and dimer diastereoisomer as shown in Scheme-4.15 to 4.18.
The hydrolysis of epoxides is a convenient method for the preparation of vicinal-diols. The reaction is catalyzed by acids or bases. Among acid catalysts, perchloric acid leads to minimal side reactions,\textsuperscript{[43]} and 10% Bu₄NHSO₄ in water is effective.\textsuperscript{[44]} Water reacts with epoxides in the presence of β-cyclodextrin to give the corresponding diol.\textsuperscript{[45]} Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.\textsuperscript{[46]} We also prepared diols 40 by alkaline hydrolysis of epoxides 9 (\textit{Scheme-4.15}).

Chlorohydrin can be prepared by treating epoxides with triphenyl phosphine and chlorine,\textsuperscript{[47]} TiCl₄-LiCl\textsuperscript{[48]} and SiCl₄.\textsuperscript{[49-50]} We have prepared these impurities 37 by using aqueous hydrochloric acid in methylene chloride medium at temperature below 10°C (\textit{Scheme-4.16}).

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=east] {\textbf{9}};
\node at (2,0) [anchor=west] {\textbf{37}};
\node at (2,2) {\begin{tikzpicture}
\node at (0,0) [anchor=west] {\textbf{ATENOLOL}};
\node at (0,2) [anchor=west] {\textbf{BISOPROLOL}};
\node at (0,4) [anchor=west] {\textbf{METOPROLOL}};
\node at (0,6) [anchor=west] {\textbf{PROPRANOLOL}};
\end{tikzpicture}};
\node at (0,2) [anchor=west] {\begin{tikzpicture}
\node at (0,0) [anchor=west] {A. R- :};
\node at (0,2) [anchor=west] {B. R- :};
\node at (0,4) [anchor=west] {C. R- :};
\end{tikzpicture}};
\end{tikzpicture}
\end{center}

Alcoholysis of epoxides is analogous to hydrolysis of diols. It may be acid (including lewis acids),\textsuperscript{[51-54]} base, or alumine\textsuperscript{[55]} catalyzed, occur with electrolysis,\textsuperscript{[56]} and may occur by either an S₅₁ or S₅₂ mechanism. We have prepared dimer 38, by reacting 9 and 7 in aqueous alkaline solution at 45-50°C (\textit{Scheme-4.17}).
Studies on the synthesis of anti-hypertensive drug, Bisoprolol and analogs

### Scheme 4.17

A. R- : 
\[
\text{H}_2\text{N} - \text{O} - \text{C} - \text{O} - \text{OH}
\]
(ATENOLOL)

B. R- : 
\[
\text{O} - \text{O} - \text{C} - \text{O} - \text{OH}
\]
(BISOPROLOL)

C. R- : 
\[
\text{O} - \text{C} - \text{O} - \text{OH}
\]
(METOPROLOL)

### Scheme 4.18

A. R- : 
\[
\text{H}_2\text{N} - \text{O} - \text{C} - \text{O} - \text{OH}
\]
(ATENOLOL)

B. R- : 
\[
\text{O} - \text{O} - \text{C} - \text{O} - \text{OH}
\]
(BISOPROLOL)

C. R- : 
\[
\text{O} - \text{C} - \text{O} - \text{OH}
\]
(METOPROLOL)
The reaction between epoxides and amine^{57-58} is a general and useful method for the preparation of β-hydroxylamine. Primary and secondary amines give, respectively, secondary and tertiary amines (Scheme-4.18).

**APPROACH C:**

Preparation of Bisoprolol Homolog 50 is nowhere reported in the literature. We think its forming due to presence of formaldehyde in etherification reaction. This impurity is chemically similar to Bisoprolol and very difficult to remove. Preparation of this impurity is schematically given in Scheme-4.19. Experimental details can be found in experimental section.

**CONCLUSION:**

In the present work, we detailed the journey towards development of a simple, safe, productive, eco-friendly and easy to handle commercial process for preparing Bisoprolol. Hence, we have developed and optimized the process, impurities formed in the process were identified, prepared and characterized. Additionally, force degradation study of Bisoprolol was also investigated. A mechanistic rationale for the formation of the various process impurities and degradation products has also been provided.
EXPERIMENTAL:

4-(2-Isopropoxyethoxymethyl)Phenol (Bisoprolol Phenol, 7)

To mixture of 4-hydroxybenzyl alcohol 5 (150 g, 1.21 mol) and 2-isopropoxyethanol 6 (540 g, 5.2 mol) was added p-toluenesulfonic acid monohydrate (4.5 g, 3% w/w) at 25-35°C. The reaction mass was stirred at 25-35°C until unreacted 4-hydroxybenzyl alcohol is ≤ 2.5% which was evidenced by HPLC analysis. After completion of the reaction, reaction mass was cooled to 10-15°C and added 5% w/w aqueous sodium bicarbonate solution (~ 40 ml) to adjust the pH to 6.0±0.3 at temperature below 20°C. Added DM water (300 ml) and product was extracted in methylene chloride (960 ml). The organic layer was separated and extracted the aqueous layer with methylene chloride (90 ml). Combined organic extracts were washed with DM water till pH of final washing was 5.8±0.5. Subsequently methylene chloride and unreacted 2-isopropoxyethanol were distilled under reduced pressure at 30-55°C, to obtain crude product 225 g (88%) with a chromatographic purity of 90.44% which was distilled under reduced pressure and collected the fraction distilling at (b.p. 120-150°C/0.5 mm) to yield 175 g (70%) of the title compound having purity of 96.11 % by HPLC. The main impurity observed after fractional distillation was 5, which was eliminated by dissolving the product in methylene chloride and washing with water. Chromatographic purity of the pure product: 98.71% by HPLC and assay ~96.4% w/w. Molecular Formula: \( \text{C}_{12}\text{H}_{18}\text{O}_{3} \); Molecular Weight: 210; Mass (ESI, in -ve ion mode): 209.1 \([\text{M}-\text{H}]^-\); IR (KBr, cm\(^{-1}\)): 3326, 3068, 2973, 2932, 2869, 1615, 1597, 1517, 1447, 1381, 1369, 1337, 1268, 1215, 1082, 827. 'H-NMR (300 MHz) in DMSO-\(d_6\): \(\delta\) (ppm) 1.07 (d, 6H, 2CH\(_3\)); 3.47 (s, 4H, 2CH\(_2\)); 3.55 (m, 1H, CH); 4.34 (s, 2H, CH\(_2\)); 6.74 (d, 2H, Ar-H); 7.12 (d, 2H, Ar-H); 9.36 (s, 1H, OH).

4-(2-Isopropoxyethoxymethyl)Phenol (Bisoprolol Phenol, 7)

4-Hydroxybenzyl alcohol (100 g, 0.80 mol) was added to 2-isopropoxyethanol (361g, 3.47 mol) and then added p-toluenesulfonic acid monohydrate (2 g, 2% w/w). The reaction was continued till unreacted 4-hydroxybenzyl alcohol was 2.6% as evidenced by HPLC analysis. After
completion of reaction, the product was extracted in methylene chloride (700 ml) and washed the reaction mass with DM water, till pH of final washing was 5.66. The solvent and unreacted 2-isopropoxyethanol were distilled under reduced pressure to obtain 142 g of crude product, which was purified by distillation under reduced pressure (b.p. 140-150°C/0.5 mm) to yield pure title product having purity 95.18% by HPLC.

4-(2-Isopropoxyethoxymethyl)Phenol (Bisoprolol Phenol, 7)

4-Hydroxybenzyl alcohol (10 g, 0.08 mol) was added to 2-isopropoxyethanol (54.18 g, 0.52 mol), followed by p-toluenesulfonic acid monohydrate (0.5 g, 5% w/w) at 25-30°C. Reaction mass was stirred at ambient temperature and monitored by qualitative HPLC analysis. After 5.5 h, when unreacted 4-hydroxybenzyl alcohol on qualitative HPLC was 1.7%, added 50 ml of methylene chloride and washed the reaction mass with DM water (2x50 ml). Distilled out methylene chloride and unreacted 2-isopropoxyethanol under reduced pressure (500-5 mm Hg) / 30-55°C, to get 16.5 g of crude product with a purity of 86.33%, which was further purified to get 13.54 g of pure product having purity 98.91% by HPLC.

4-(2-Isopropoxyethoxymethyl)Phenol (Bisoprolol Phenol, 7)

Methanesulphonic acid (0.1 g, 2%w/w) was added to a mixture of 4-hydroxybenzyl alcohol (5 g, 0.04 mol) and of 2-isopropoxyethanol (27.09 g, 0.26 mol) and the reaction mass was stirred at ambient temperature. After completion of reaction the reaction was worked up in a similar manner as given in Example 1, to yield 5.9 g of the title compound.

4-(2-Isopropoxyethoxymethyl)Phenol (Bisoprolol Phenol, 7)

To a mixture of 4-hydroxybenzyl alcohol (5 g, 0.04 mol) and of 2-isopropoxyethanol (27.09 g, 0.26 mol), sulfuric acid (0.1 g, 2% w/w) was added and the reaction mass was stirred at ambient temperature. After completion of the reaction, the reaction was worked up in a similar manner as given in Example 1, to yield 5.7 g of the title compound.
4-(2-Isopropoxyethoxymethyl)Phenol (*Bisoprolol Phenol, 7*)

To a mixture of 4-hydroxybenzyl alcohol (5 g, 0.04 mol) and of 2-isopropoxyethanol (27.09 g, 0.26 mol) was added 35% w/w hydrochloric acid (0.1 g, 2% w/w) and stirred the reaction mass at ambient temperature. After completion of the reaction, the reaction mass was worked up in similar manner as given in Example 1, to yield 4.1 g of the title compound.

4-(2-Isopropoxyethoxymethyl)Phenol (*Bisoprolol Phenol, 7*)

Phosphoric acid (0.1 g, 2% w/w) was added to a mixture of 4-hydroxybenzyl alcohol (5 g, 0.04 mol) and of 2-isopropoxyethanol (27.09 g, 0.26 mol) and stirred at ambient temperature. After completion of the reaction, the reaction mass was worked up in a similar manner as given in Example 1, to yield 5.8 g of the title compound.

4-(2-Isopropoxyethoxymethyl)Phenol (*Bisoprolol Phenol, 7*)

4-Hydroxybenzyl alcohol (5 g, 0.04 mol) and 2-isopropoxyethanol (9.03 g, 0.08 mol) were taken in 25 ml of tetrahydrofuran, and to this mixture was added p-toluenesulfonic acid monohydrate (1 g, 2% w/w). The reaction mass was stirred at ambient temperature and after completion of the reaction, reaction mass was washed with DM water (25 ml) to remove p-toluenesulfonic acid. The organic layer was concentrated to obtain 7.75 g of crude product, which was purified in a similar manner as given in Example 1.

**7A:** HPLC purity: 98.74%; $^1$HNMR (DMSO-$d_6$, 300 MHz, $\delta$ ppm): 3.22 (s, 2H, CH$_2$), 6.67 & 7.03 (2d, 4H, Ar-H), 6.79 & 7.33 (2s, 2H, CONH$_2$), 9.20 (s, 1H, OH). MF: C$_8$H$_9$NO$_2$; Exact Mass ($m/z$, 151.06); Observed: (in –ve ion mode) $m/z$; 150.0 [(M’–H)$^-$].

**7B:** HPLC purity: 97.32%; IR (KBr, cm$^{-1}$): 3320, 2936, 2867, 1617, 1597, 1517, 1450, 1235, 1110, 1098, 832. $^1$HNMR (CDCl$_3$, 300 MHz, $\delta$ ppm): 2.85 (t, 2H, CH$_2$), 3.41 (s, 3H, CH$_3$), 3.64 (t, 2H, CH$_2$), 6.74 & 7.09 (2d, 4H, Ar-H), 6.41 (brs, 1H, OH). MF: C$_9$H$_{12}$O$_2$; Exact Mass ($m/z$, 152.08); Observed: (in –ve ion mode) $m/z$; 151.3 [(M’–H)$^-$].
7C: HPLC purity: 99.26%; \( ^1 \)HNMR (DMSO-d\(_6\), 300 MHz, \( \delta \) ppm): 6.90 (dd, 1H, Ar-H), 7.33 (m, 2H, Ar-H), 7.46 (m, 2H, Ar-H), 7.82 \& 8.15 (2dd, 2H, Ar-H), 10.12 (s, 1H, OH). MF: C\(_{10}\)H\(_8\)O; Exact Mass (m/z, 144.06); Observed: (in –ve ion mode) m/z; 143.0 [(M+H)\(^+\)].

7H: HPLC purity: 99.21%; IR (KBr, cm\(^{-1}\)): 3224, 1889, 1612, 1597, 1445, 1364, 1345, 1316, 1249, 1233, 1210, 1172, 1121, 1081, 1016, 853, 834, 825. \( ^1 \)HNMR (CDCl\(_3\), 300 MHz, \( \delta \) ppm): 3.11 (t, 2H, CH\(_2\)), 3.55 (t, 2H, CH\(_2\)), 6.82 \& 7.10 (2d, 4H, Ar-H). MF: C\(_8\)H\(_{10}\)O\(_2\); Exact Mass (m/z, 138.34); Observed: (in –ve ion mode) m/z; 137.4 [(M+H)\(^+\)].

2-[4-(2-Isopropoxyethoxy)methyl]Phenoxymethyl]Oxirane (Epoxy Benzyl Ether 'or' Bisoprolol Epoxide, 9)

To a mixture of 4-(2-isopropoxyethoxymethyl)phenol, 7 (150 g, 0.71 mol) in 860 ml epichlorohydryn, sodium hydroxide (30 g, 0.75 mol) was added in lots and stirred at 40-45°C. After completion of the reaction, which is monitored by HPLC, the reaction mixture was cooled to 15-20°C and diluted with DM water (540 ml). Separated the lower organic layer and washed it with precooled DM water (2x230 ml) to pH of the washing to be neutral. The organic layer was concentrated at 40-60°C under reduced pressure to obtain 186 g (97%) of the title compound having 93.31% purity by HPLC. Molecular Formula: C\(_{15}\)H\(_{22}\)O\(_4\); Molecular Weight: 266; Mass (ESI, in +ve ion mode): 289.1 [(M+Na)\(^+\)]; IR (KBr, cm\(^{-1}\)): 2972, 2928, 2865, 1613, 1587, 1513, 1456, 1381, 1368, 1300, 1244, 1176, 1091, 1037, 916, 848. \( ^1 \)H-NMR (300 MHz) in DMSO-d\(_6\): \( \delta \) (ppm) 1.09 (d, 6H, 2CH\(_3\)); 2.71 & 2.84 (2m, 1H each, CH\(_3\)); 3.33 (m, 1H, CH); 3.49 (s, 4H, 2CH\(_2\)); 3.54 (m, 1H, CH); 3.82 \& 4.30 (2dd, 1H each, CH\(_2\)); 4.41 (s, 2H, CH\(_2\)); 6.94 \& 7.26 (2d, 2H each, Ar-H). Following same procedure, below compounds were prepared.

9A: HPLC purity: 92.52%; \( ^1 \)HNMR (DMSO-d\(_6\), 300 MHz, \( \delta \) ppm): 2.70 (m, 1H, CH\(_2\)), 2.83 (m, 1H, CH\(_2\)), 3.28 (s, 2H, CH\(_2\)), 3.31 (m, 1H, CH), 3.78 (m, 1H, CH\(_2\)), 4.28 (m, 1H, CH\(_2\)), 6.87 \& 7.17 (2d, 4H, Ar-H), 6.83 \& 7.39 (2s, 2H, CONH\(_2\)). MF: C\(_{11}\)H\(_{13}\)NO\(_3\); Exact Mass (m/z, 207.09); Observed: (in +ve ion mode) m/z; 208.2 [(MH)\(^+\)].
9C: HPLC purity: 85.62%; $^1$H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 2.84 (m, 1H, CH$_2$), 2.92 (m, 1H, CH$_2$), 3.50 (m, 1H, CH), 4.05 (m, 1H, CH$_2$), 4.52 (m, 1H, CH$_2$), 6.98 (m, 1H, Ar-H), 7.39 (m, 2H, Ar-H), 7.55 (m, 2H, Ar-H), 7.89 & 8.20 (2dd, 2H, Ar-H). MF: C$_{18}$H$_{31}$NO$_4$; Exact Mass (m/z, 200.08); Observed: (in +ve ion mode) m/z; 201.3 [(MH)$^+$].

**(RS)-1-[(2-Isopropoxyethoxy)Methyl]-Phenoxy]-3-(Isopropylamino)Propan-2-ol**

**(Bisoprolol, I)**

2-[(4-Isopropoxyethoxy)phenoxy]methyl]oxirane, 9 (150 g, 0.56 mol) was added to the mixture of isopropylamine (325 g, 5.51 mol) and isopropyl alcohol 450 ml precooled to 15-20°C. Reaction mass was heated to 55-60°C and monitored by qualitative HPLC analysis. After completion of reaction, excess of isopropylamine / isopropyl alcohol was removed from reaction mass at 35-50°C under reduced pressure. To the residue, ethyl acetate (600 ml) and DM water (450 ml) was added and was cooled to 15-20°C. pH was adjusted to 1.8±0.2 using 15% w/w hydrochloric acid (125 ml). The layers were separated and the aqueous layer, containing Bisoprolol hydrochloride washed with ethyl acetate (250 ml). Ethyl acetate (600 ml) was added to aqueous layer and adjusted the pH to 11.8±0.2 at 15-20°C with 20% w/w aqueous sodium hydroxide solution (~110 ml). Thereafter, the reaction mixture was extracted with ethyl acetate (2x125 ml) and the combined organic layer was washed with 15% w/w aqueous sodium chloride solution (1x150 ml) at 20-30°C. The organic layer was concentrated at 40-60°C under reduced pressure to obtain 150 g (82%) of the title compound having 97.69% purity by HPLC. This was purified by distillation under reduced pressure and collected the forerun (~6 g) fraction to remove low boiler impurities and then fraction distilling at (b.p. 135-175°C/0.5 mm) to yield 135 g (74%) of the title compound having purity of 99.52% by HPLC. **Molecular Formula:** C$_{18}$H$_{31}$NO$_4$; **Molecular Weight:** 325.23; **Mass (ESI, in +ve ion mode):** 326.3 [(MH)$^+$]; IR (KBr, cm$^{-1}$): 3409, 3304, 3129, 3068, 3036, 2970, 2929, 2866, 1612, 1586, 1513, 1468, 1381, 1368, 1336, 1301, 1246, 1175, 1153, 1093, 1040, 972, 886, 824. **H-NMR (300 MHz) in DMSO-d$_6$: δ (ppm)** 0.97 (d, 6H, 2CH$_3$); 1.07 (d, 6H, 2CH$_3$); 1.50 (bvs, 1H, NH); 2.52 & 2.68 (2m, 2H each, CH$_2$); 2.70 (m, 1H, CH); 3.48 (s, 4H, CH$_2$); 3.54 (m, 1H, CH); 3.87 (m, 2H, CH$_2$); 3.95 (m, 1H,
CH); 4.39 (s, 2H, CH₂); 4.99 (brs, 1H, OH); 6.80 (d, 2H, Ar-H); 7.22 (d, 2H, Ar-H); Following same procedure, I(A-L) was prepared, see (Table-4.1) for characterization data.

### Table-4.1

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Compound</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1A</td>
<td>HPLC purity: 99.74%; IR (KBr, cm⁻¹): 3368, 3198, 3179, 3071, 2966, 2924, 2870, 1666, 1649, 1638, 1584, 1516, 1460, 1417, 1382, 1340, 1302, 1244, 1180, 1103, 1076, 919, 828. 'H-NMR (300 MHz) in CDCl₃: δ (ppm) 0.97 (d, 6H, 2CH₃); 1.50 (brs, 1H, NH); 2.54 &amp; 2.68 (2m, 2H each, CH₂); 2.70 (m, 1H, CH); 3.84 (m, 2H, CH₂); 3.91 (m, 1H, CH); 5.00 (brs, 1H, OH); 6.85 &amp; 7.16 (2d, 4H, Ar-H); 6.85 &amp; 7.41 (2brs, 2H, CONH₂). Molecular Formula: C₁₄H₂₂N₂O₃; Molecular Weight: 266.16; Mass (ESI, in +ve ion mode): 267.3 [(MH)⁺].</td>
</tr>
<tr>
<td>2</td>
<td>1B</td>
<td>HPLC purity: 99.18%; IR (KBr, cm⁻¹): 3301, 3120, 3007, 2969, 2910, 2864, 2842, 2807, 2734, 2628, 2554, 1614, 1584, 1514, 1474, 1458, 1429, 1383, 1370, 1339, 1299, 1248, 1217, 1177, 1109, 1028, 931. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 0.97 (d, 6H, 2CH₃); 1.50 (brs, 1H, NH); 2.53 &amp; 2.75 (m, 5H, 2CH₂ &amp; CH); 3.23 (s, 3H, CH₃); 3.47 (t, 2H, CH₂); 3.82-3.92 (m, 3H, CH₂ &amp; CH); 4.90 (brs, 1H, OH); 6.83 &amp; 7.11 (2d, 4H, Ar-H). Molecular Formula: C₁₅H₂₅NO₃; Molecular Weight: 267.18; Mass (ESI, in +ve ion mode): 268.2 [(MH)⁺].</td>
</tr>
<tr>
<td>3</td>
<td>1C</td>
<td>HPLC purity: 99.05%; IR (KBr, cm⁻¹): 3322, 3277, 2963, 2930, 2923, 2854, 2807, 2710, 2531, 2503, 2490, 1590, 1579, 1510, 1457, 1400, 1384, 1368, 1351, 1323, 1268, 1241, 1179, 1157, 1107, 1031, 1018, 961, 901. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 0.99 (2d, 6H, 2CH₃); 1.50 (brs, 1H, NH); 2.66-2.81 (m, 3H, CH₂ &amp; CH); 4.01 (m, 1H, CH); 4.04-4.14 (m, 2H, CH₂); 5.10 (brs, 1H, OH); 6.95 (d, 1H, Ar-H); 7.37-7.53 (m, 4H, Ar-H); 7.86 &amp; 8.23 (2d, 2H, Ar-H). Molecular Formula: C₁₆H₂₁NO₂; Molecular Weight: 259.34; Mass (ESI, in +ve ion mode): 260.4 [(MH)⁺].</td>
</tr>
<tr>
<td>4</td>
<td>1E</td>
<td>HPLC purity: 96.47%; 'HNMR (D₂O, 300 MHz, δ ppm): 1.24 (s, 6H, 2CH₃), 2.32 (m, 2H, CH₂), 3.48 (s, 2H, CH₂), 4.01 (m, 2H, CH₂), 4.15 (m, 1H, CH), 6.88 (m, 2H, Ar-H), 7.16 (m, 2H, Ar-H). MF: C₁₄H₂₃NO₄; Exact Mass (m/z, 267.15); Observed: (in +ve ion mode) m/z: 268.1 [(MH)⁺].</td>
</tr>
<tr>
<td>5</td>
<td>1F</td>
<td>HPLC purity: 99.25%; IR (KBr, cm⁻¹): 3291, 3075, 2966, 2919, 2901, 2866, 2825, 2797, 2733, 2633, 1689, 1653, 1603, 1578, 1510, 1473, 1451, 1386, 1373, 1341, 1328, 1313, 1267, 1236, 1217, 1158, 1146, 1126, 1110, 1097, 1014, 926, 905. 'H-NMR (300 MHz) in CDCl₃: δ (ppm) 1.15 (d, 6H, 2CH₃); 1.51 (brs, 2H, NH &amp; OH); 2.70-2.94 (m, 3H, CH₂ &amp; CH); 4.01-4.06 (m, 3H, CH₂ &amp; CH); 7.04 &amp; 7.84 (2d, 4H, Ar-H); 9.89 (s, 1H, CHO). Molecular Formula: C₁₃H₁₈NO₂; Molecular Weight: 237.14; Mass (ESI, in +ve ion mode): 237.9 [(MH)⁺].</td>
</tr>
</tbody>
</table>
Chapter IV

6  IG

HPLC purity: 99.52%; IR (KBr, cm⁻¹): 3316, 3061, 2971, 2958, 2927, 2869, 2838, 2739, 1599, 1585, 1492, 1470, 1448, 1382, 1343, 1333, 1322, 1297, 1254, 1243, 1181, 1174, 1111, 1086, 1035, 1020, 927, 895. 'H-NMR (300 MHz) in CDCl₃: δ (ppm) 1.11 (d, 6H, 2CH₃); 2.70-2.92 (m, 5H, CH₂, CH, NH & OH); 3.98 (m, 2H, CH₂); 4.06 (m, 1H, CH); 6.92-7.32 (2m, 5H, Ar-H). Molecular Formula: C₁₂H₁₉NO₂; Molecular Weight: 209.14; Mass (ESI, in +ve ion mode): 210.1 [(MH)⁺].

7  IH

HPLC purity: 91.12%; IR (KBr, cm⁻¹): 3353, 3072, 2985, 2926, 2874, 2570, 2527, 2458, 2418, 1631, 1611, 1575, 1512, 1473, 1389, 1343, 1333, 1311, 1297, 1254, 1243, 1181, 1156, 1113, 1092, 1054, 1025, 929, 823. 'H-NMR (300 MHz) in CDCl₃: δ (ppm) 1.11-1.13 (d, 3H each, 2CH₃); 2.79 (t, 2H, CH₂); 3.00 & 3.09 (ABq, 1H each, CH₂); 3.23 (m, 1H, CH); 3.81 (t, 2H, CH₂); 3.92 & 4.04 (ABq, 1H each, CH₂); 4.35 (m, 1H, CH); 6.84 & 7.13 (2d, 2H each, Ar-H). Molecular Formula: C₁₄H₂₃NO₃; Molecular Weight: 253.17; Mass (ESI, in +ve ion mode): 254.1 [(MH)⁺].

8  IJ

HPLC purity: 98.62%; IR (KBr, cm⁻¹): 3336, 3287, 3162, 2974, 2952, 2927, 2831, 2743, 2657, 1615, 1584, 1559, 1519, 1481, 1423, 1396, 1385, 1342, 1311, 1300, 1257, 1176, 1141, 1114, 1102, 1083, 1033, 1018, 1009, 929, 852. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 0.99 (d, 6H, 2CH₃); 1.70 (brs, 1H, NH); 2.22 (s, 3H, CH₃); 2.54-2.73 (m, 2H, CH₂ & CH); 3.80-3.93 (m, 3H, CH₂ & CH); 4.41 (s, 2H, CH₂); 6.88 & 7.13 (2d, 2H, Ar-H). Molecular Formula: C₁₃H₂₁NO₃; Molecular Weight: 239.15; Mass (ESI, in +ve ion mode): 240.1 [(MH)⁺].

9  IL

HPLC purity: 99.18%; IR (KBr, cm⁻¹): 3309, 3056, 3028, 2977, 2964, 2923, 2877, 2776, 1615, 1583, 1514, 1472, 1460, 1439, 1403, 1384, 1362, 1348, 1338, 1288, 1268, 1247, 1178, 1118, 1090, 1024, 897, 844. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 0.97 (d, 6H, 2CH₃); 1.00 (d, 12H, 4CH₂); 2.54-2.73 (m, 2H, CH₂ & CH); 3.80-3.93 (m, 3H, CH₂ & CH); 4.41 (s, 2H, CH₂); 5.00 (brs, 1H, OH); 6.81 & 7.06 (2d, 2H each, Ar-H). Molecular Formula: C₁₃H₂₁NO₂; Molecular Weight: 223.16; Mass (ESI, in +ve ion mode): 224.1 [(MH)⁺].

10  IL

HPLC purity: 67.56%; IR (KBr, cm⁻¹): 3417, 3162, 2976, 2934, 2869, 2814, 2758, 2729, 2590, 2512, 2468, 1718, 1606, 1571, 1511, 1479, 1438, 1422, 1376, 1347, 1318, 1280, 1253, 1222, 1172, 1148, 1124, 1105, 1092, 1042, 982. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 1.08-1.11 (2d, 12H, 4CH₃); 2.77 & 2.89 (2m, 1H each, CH₂); 3.00 (m, 1H, CH); 3.60 (m, 1H, CH); 3.67 (m, 2H, CH₂); 4.03 (m, 3H, CH & CH₂); 4.31 (m, 2H, CH₂); 7.06 & 7.90 (2d, 2H each, Ar-H). Molecular Formula: C₁₃H₂₉NO₅; Molecular Weight: 339.20; Mass (ESI, in +ve ion mode): 340.0 [(MH)⁺].

Bisoprolol Fumarate

A mixture of acetone (450 ml) and DM water (10 ml) was added to the Bisoprolol base (100 g, 0.31 mol) and heated the reaction mass to 40-45°C. To this fumaric acid (17.84 g, 0.15 mol)
was added and stirred the reaction mass at 50°C, till the clear solution was obtained. The reaction mass was cooled slowly to 8-12°C and was stirred for 3 hrs to complete the crystallization. Product was filtered, washed with chilled acetone (2x50 ml) and dried at 65-70°C under reduced pressure to obtain 103 g of the title compound.

(RS)-1-[(4-[(2-Isopropoxyethoxy)Methyl]-Phenoxy]-3-chloropropan-2-ol (Chlorohydrin impurity, 37)

2-[(4-Isopropoxyethoxy)phenoxymethyl]oxirane, 9 (115 g, 0.43 mol) was dissolved in chloroform (230 ml) and added to aqueous hydrochloric acid (230 ml) at below 10°C. Reaction mass was maintained at 10-15°C and monitored by qualitative HPLC analysis. After completion of reaction, layers were separated and the organic layer was washed with water (230 ml) at 20-25°C, dried on sodium sulphate and was concentrated at 40-50°C under reduced pressure to obtain 130 g (99%) of the title compound having 99.34% purity by HPLC. Molecular Formula: C_{15}H_{23}ClO_{4}; Molecular Weight: 302.13; Mass (ESI, in +ve ion mode): 325.4 [(M+Na)^+]; 'H-NMR (300 MHz) in DMSO-d_6: δ (ppm) 1.07 (d, 6H, 2CH_3); 3.49 (s, 4H, 2CH_2); 3.53 (m, 1H, CH); 3.66 & 3.73 (2m, 1H each, CH_2); 3.97 (m, 1H, CH); 4.03 (m, 2H, CH_2); 4.40 (s, 2H, CH_2); 5.55 (d, 1H, OH); 6.92 (d, 2H, Ar-H); 7.23 (d, 2H, Ar-H). Following same procedure, 37(A and B) were prepared.

37A: Molecular Formula: C_{11}H_{14}ClNO_3; Molecular Weight: 243.07; Mass (ESI, in +ve ion mode): 244.1 [(MH)^+]; 'H-NMR (300 MHz) in DMSO-d_6: δ (ppm) 3.28 (s, 2H, CH_2); 3.63-3.77 (ABq, 2H, CH_2); 3.94 (d, 2H, CH_2); 4.02 (m, 1H, CH); 5.51 (brs, 1H, OH); 6.87 & 7.16 (2d, 2H each, Ar-H); 6.83 & 7.39 (2brs, 2H, CONH_2).

37B: Molecular Formula: C_{12}H_{17}ClO_3; Molecular Weight: 244.09; Mass (GCMS): m/z 244; IR (neat, cm^-1): 3401, 3033, 2932, 2872, 2829, 2741, 1613, 1584, 1513, 1462, 1434, 1384, 1299, 1244, 1179, 1114, 1045, 998, 959, 830. 'H-NMR (500 MHz) in DMSO-d_6: δ (ppm) 2.72 (t, 2H, CH_2); 3.22 (s, 3H, CH_3); 3.47 (t, 2H, CH_2); 3.66-3.75 (ABq, 2H, CH_2); 3.94 (d, 2H, CH_2); 4.02 (m, 1H, CH); 5.51 (d, 1H, OH); 6.85 & 7.13 (2d, 2H each, Ar-H).
Sodium hydroxide (9.52 g) was added to a mixture of Bisoprolol phenol, 7 (50 g, 0.24 mol) and of Bisoprolol epoxide, 9 (63.3 g, 0.24 mol) in water (50 ml) and slowly heated to 50-55°C. After completion of reaction, ethyl acetate (1000 ml) was added and washed with water (2x250 ml) at 20-25°C, dried on sodium sulphate and was concentrated at 40-50°C under reduced pressure to obtain 110 g (97%) of the title compound having 85% purity by HPLC. Thereafter, desired impurity, 38 was purified by flash chromatography, (by eluting with ethyl acetate and methylene chloride). Yield 72 g (63%) of the title compound having purity of 99.5% by HPLC.

**Molecular Formula:** C_{27}H_{40}O_{7}; **Molecular Weight:** 476.28; **Mass (ESI, in +ve ion mode):** 494.5 [(M+NH_4)^+]; **IR (KBr, cm^{-1}):** 3458, 2972, 2919, 2870, 1612, 1587, 1513, 1474, 1457, 1425, 1382, 1368, 1354, 1337, 1303, 1241, 1175, 1154, 1090, 1041, 1025, 973, 831. **'H-NMR (300 MHz) in DMSO-d_6:** δ (ppm) 1.07 (d, 12H, 4CH_3); 3.48 (s, 8H, 4CH_2); 3.54 (m, 2H, 2CH); 4.04 (m, 5H, 2CH_2 & CH); 4.40 (s, 4H, 2CH_2); 4.40 (s, 4H, 2CH_2). Following same procedure, 38(A and C) were prepared.

**38A: Molecular Formula:** C_{19}H_{22}N_2O_5; **Molecular Weight:** 358.15; **Mass (ESI, in +ve ion mode):** 359.0 [(MH)^+]; **'H-NMR (300 MHz) in DMSO-d_6:** δ (ppm) 3.28 (s, 4H, 2CH_2); 3.95-4.06 (m, 4H, 2CH_2); 4.12 (m, 1H, CH); 6.87 & 7.16 (2d, 2H each, Ar-H); 6.83 & 7.39 (2 brs, 1H, OH); 6.92 & 7.24 (2 d, 4H each, Ar-H).

**38C: Molecular Formula:** C_{23}H_{20}O_3; **Molecular Weight:** 344.14; **Mass (ESI, in +ve ion mode):** 345.3 [(MH)^+]; **IR (neat, cm^{-1}):** 3574, 3565, 3402, 3054, 3012, 2930, 2875, 1729, 1629, 1596, 1580, 1509, 1461, 1398, 1349, 1318, 1269, 1240, 1215, 1179, 1157, 1102, 1071, 1021, 1004, 983, 951, 898, 873, 791, 769. **'H-NMR (300 MHz) in DMSO-d_6:** δ (ppm) 4.32-4.42 (m, 4H, 2CH_2); 4.50 (m, 1H, CH); 5.64 (d, 1H, OH); 7.03 (d, 2H, Ar-H); 7.38-7.54 (m, 8H, Ar-H); 7.87 (d, 2H, Ar-H); 8.26 (d, 2H, Ar-H).
2-[[4-Hydroxymethyl]Phenoxy methyl]Oxirane (39)

To a mixture of 4-hydroxybenzyl alcohol, 5 (100 g, 0.81 mol) in 500 ml epichlorohydrin, sodium hydroxide (33.87 g, 0.85 mol) was added in lots and stirred at 40-45°C. After completion of the reaction, which is monitored by HPLC, the reaction mixture was cooled to 15-20°C and diluted with DM water (300 ml). Separated the lower organic layer and washed it with precooled DM water (2x160 ml) to pH of the washing to be neutral. The organic layer was concentrated at 40-60°C under reduced pressure. Ethyl acetate (400 ml) was added at 40-45°C and obtained slurry was cooled to 5-10°C, filtered washed and dried to obtain 98 g (67%) of the title compound having 98.31% purity by HPLC. Molecular Formula: C_{10}H_{12}O_{3}; Molecular Weight: 180.08; Mass (ESI, in +ve ion mode): 198.1 [(M+NH_{4})^{+}]; IR (KBr, cm^{-1}): 3343, 3065, 3006, 2930, 2870, 1612, 1585, 1512, 1456, 1430, 1363, 1346, 1304, 1246, 1220, 1172, 1139, 1131, 1113, 1033, 1014, 1005, 971, 912, 866, 845, 814. 'H-NMR (300 MHz) in DMSO-d_{6}: δ (ppm) 2.70 & 2.84 (2m, 1H each, CH_{2}); 3.34 (m, 1H, CH); 3.80 & 4.28 (2dd, 1H each, CH_{2}); 4.41 (d, 2H, CH_{2}); 5.05 (t, 1H, OH); 6.90 (dd, 2H, Ar-H); 7.23 (d, 2H, Ar-H).

(RS)-1-[[4-[(2-Isopropoxyethoxy)Methyl]-Phenoxy]-3-hydroxypropan-2-ol (Diol impurity, 40)

To a mixture of 2-[[4-Isopropoxyethoxy]phenoxy methyl]oxirane, 9 (100 g, 0.38 mol) in 500 ml DM water, sodium hydroxide (18 g, 0.45 mol) was added in lots and stirred at 40-45°C. Added DMSO (100 ml) and heated to reflux for 12hr. After completion of the reaction, which is monitored by HPLC, the reaction mixture was cooled to 15-20°C and product was extracted in ethyl acetate and concentrated at 40-60°C under reduced pressure. This was purified by column chromatography, and crystallized with Ethyl acetate and hexane to obtain 15 g (14%) of the title compound having 93.31% purity by HPLC. Following same procedure, 40(A, B and C) were prepared.

40A: Molecular Formula: C_{11}H_{13}NO_{4}; Molecular Weight: 225.10; Mass (ESI, in +ve ion mode): 226.1 [(MH)^{+}]; 'H-NMR (300 MHz) in DMSO-d_{6}: δ (ppm) 3.28 (s, 2H, CH_{2}); 3.43 (s, 2H, CH_{2});
3.83 (m, 2H, CH₂); 3.95 (m, 1H, CH); 4.66 & 4.93 (2brs, 1H each, OH); 6.87 & 7.16 (2d, 2H each, Ar-H); 6.83 & 7.39 (2brs, 2H, CONH₂).

40B: Molecular Formula: C₁₂H₁₈O₄; Molecular Weight: 226.12; Mass (GCMS): m/z 226; IR (KBr, cm⁻¹): 3403, 3034, 2926, 2872, 1613, 1584, 1514, 1460, 1384, 1299, 1246, 1179, 1115, 1047, 1003, 935. 'H-NMR (300 MHz) in CDCl₃: δ (ppm) 2.60 (brs, 2H, 2OH); 2.84 (t, 2H, CH₂); 3.36 (s, 3H, CH₃); 3.58 (t, 2H, CH₂); 3.74 & 3.83 (ABq, 2H, CH₂); 4.01-4.03 (m, 2H, CH₂); 4.09 (m, 1H, CH); 6.85 & 7.14 (2d, 4H, Ar-H).

40C: Molecular Formula: C₁₃H₁₄O₃; Molecular Weight: 218.09; Mass (ESI, in +ve ion mode): 219.3 [(MH)+]; IR (KBr, cm⁻¹): 3287, 3054, 2950, 2937, 2877, 2641, 2509, 1629, 1596, 1582, 1540, 1509, 1466, 1455, 1441, 1394, 1350, 1272, 1242, 1214, 1180, 1156, 1128, 1106, 1076, 1045, 1018, 988, 893. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 3.57 (s, 2H, CH₂); 3.95 (s, 1H, CH); 4.03-4.19 (ABq, 2H, CH₂); 4.73 & 5.08 (2brs, 1H each, OH); 6.95 (d, 1H, Ar-H); 7.38-7.54 (m, 4H, Ar-H); 7.86 (m, 1H, Ar-H); 8.23 (m, 1H, Ar-H).

N,N-Bis[3-{4-[(2-Isopropoxyethoxy)Phenoxy]-Methyl}-Phenoxy]-(2RS)-2-hydroxypropylisopropylamine (Dimer diastereoisomer impurity, 46)

2-[[4-Isopropoxyethoxy]phenoxyethyl]oxirane, 9 (112.78 g, 0.42 mol) and (RS)-1-{4-[(2-Isopropoxyethoxy)Methyl]-Phenoxy}-3-(Isopropylamino)Propan-2-ol, 1 (106 g, 0.33 mol) was added to isopropyl alcohol 250 ml at 25-30°C. Reaction mass was heated to 55-60°C and monitored by qualitative HPLC analysis. After completion of reaction, excess of solvent was removed from reaction mass at 55-60°C under reduced pressure. To the residue, added water (700 ml) and adjusted pH 0.5 using concentrated hydrochloric acid at 25-30°C. Reaction mass was washed with isopropyl ether (2x150 ml). Added ethyl acetate (500 ml) and was cooled to 15-20°C. pH was adjusted to 12 using 15% w/w aqueous sodium hydroxide. The layers were separated and the aqueous layer more extracted with ethyl acetate (150 ml). The combined organic layer was washed with brine and concentrated at 50-60°C under reduced pressure to obtain 188 g (97%) of the title compound having 82% purity by HPLC. Molecular Formula:
C$_{33}$H$_{53}$NO$_8$; **Molecular Weight:** 591.38; **Mass (ESI, in +ve ion mode):** 592.4 [(MH)$^+$]; IR (KBr, cm$^{-1}$): 3422, 3034, 2971, 2930, 2868, 1739, 1612, 1586, 1513, 1465, 1424, 1369, 1334, 1300, 1247, 1174, 1153, 1092, 1043, 970, 939, 919, 885, 848, 824. $^1$H-NMR (300 MHz) in DMSO-d$_6$: δ (ppm) 0.90-0.94 (m, 6H, 2CH$_3$); 1.07 (d, 12H, 4CH$_3$); 2.45-2.60 (m, 4H, 2CH$_2$); 2.95 (m, 1H, CH); 3.48 (s, 8H, 4CH$_2$); 3.55 (m, 2H, 2CH); 3.83 (m, 4H, 2CH$_2$); 3.95 (m, 2H, 2CH); 4.38 (s, 4H, 2CH$_2$); 4.84 (brs, 2H, OH); 6.85 & 7.20 (2m, 4H each, Ar-H). Following same procedure, **46(A, B and C)** were prepared.

**46A:** **Molecular Formula:** C$_{25}$H$_{36}$N$_3$O$_6$; **Molecular Weight:** 473.25; **Mass (ESI, in +ve ion mode):** 474.1 [(MH)$^+$]; $^1$H-NMR (300 MHz) in DMSO-d$_6$: δ (ppm) 0.92 (m, 6H, 2CH$_3$); 2.42 (m, 2H, CH$_3$); 2.59 (m, 2H, CH$_2$); 2.90 (m, 1H, CH); 3.27 (s, 4H, CH$_2$); 3.82 (m, 2H each, CH$_2$); 3.92 (m, 1H each, CH); 4.85 (brs, 2H each, OH); 6.89 & 7.14 (2d, 4H each, Ar-H); 6.78 & 7.41 (2brs, 2H each, CONH$_2$).

**46B:** **Molecular Formula:** C$_{27}$H$_{41}$NO$_6$; **Molecular Weight:** 475.29; **Mass (ESI, in +ve ion mode):** 476.4 [(MH)$^+$]; IR (KBr, cm$^{-1}$): 3338, 3237, 3086, 3028, 2978, 2932, 2870, 2825, 2805, 1688, 1612, 1583, 1514, 1464, 1456, 1431, 1385, 1365, 1340, 1302, 1256, 1239, 1180, 1159, 1113, 1087, 1042, 973, 955. $^1$H-NMR (300 MHz) in CDCl$_3$: δ (ppm) 1.47 (m, 6H, 2CH$_3$); 2.82 (t, 4H, 2CH$_3$); 3.35 (s, 6H, 2CH$_3$); 3.49 (m, 1H, CH); 3.56 (t, 4H, 2CH$_2$); 3.30 & 3.92-4.75 (m, 10H, 4CH$_2$ & 2CH); 6.82 & 7.14 (2d, 8H, Ar-H).

**46C:** **Molecular Formula:** C$_{29}$H$_{33}$NO$_4$; **Molecular Weight:** 459.24; **Mass (ESI, in +ve ion mode):** 460.5 [(MH)$^+$]; IR (KBr, cm$^{-1}$): 3272, 3053, 2981, 2934, 2876, 2636, 2109, 1732, 1628, 1595, 1580, 1509, 1461, 1441, 1398, 1349, 1269, 1241, 1215, 1179, 1157, 1103, 1069, 1020, 1002, 961, 912, 873, 795, 771. $^1$H-NMR (300 MHz) in DMSO-d$_6$: δ (ppm) 1.39 (d, 6H, 2CH$_3$); 3.40-3.68 (m, 4H, 2CH$_3$); 3.99 (m, 1H, CH); 4.20 (m, 4H, 2CH$_2$); 4.66 (m, 2H, 2CH); 6.13-6.25 (m, 2H, OH); 6.99 (d, 2H, Ar-H); 7.40-7.56 (m, 8H, Ar-H); 7.88 (m, 2H, Ar-H); 8.30 (m, 2H, Ar-H).
Studies on the synthesis of anti-hypertensive drug, Bisoprolol and analogs

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(2RS)-1-{4-(Hydroxymethyl)-Phenoxy}-3-(Isopropylamino)Propan-2-ol (Bisoprolol carbinol, 47/1I)

2-[(4-Hydroxymethyl]Phenoxy]Oxirane, 39 (115 g, 0.64 mol) was added to the mixture of isopropylamine (370 g, 6.26 mol) and isopropyl alcohol 345 ml precooled to 15-20°C. Reaction mass was heated to 55-60°C and monitored by qualitative HPLC analysis. After completion of reaction, excess of isopropylamine / isopropyl alcohol was removed from reaction mass at 35-50°C under reduced pressure. To the residue, ethyl acetate (600 ml) and DM water (450 ml) was added and was cooled to 15-20°C. pH was adjusted to 1.8±0.2 using 15% w/w hydrochloric acid (125 ml). The layers were separated and the aqueous layer, containing Bisoprolol hydrochloride washed with ethyl acetate (250 ml). Ethyl acetate (600 ml) was added to aqueous layer and adjusted the pH to 11.8±0.2 at 15-20°C with 20% w/w aqueous sodium hydroxide solution (~110 ml). Thereafter, the reaction mixture was extracted with ethyl acetate (2x125 ml) and the combined organic layer was washed with 15% w/w aqueous sodium chloride solution (1x150 ml) at 20-30°C. The organic layer was concentrated at 40-60°C under reduced pressure, Hexanes (200 ml) was added and stirred at 25-30°C to obtain 120 g (78%) of the title compound having 91.19% purity by HPLC. This was purified by making fumarate salt having purity of 95.36 % by HPLC. IR (KBr, cm⁻¹): 3336, 3287, 3106, 2974, 2952, 2927, 2831, 2743, 2657, 1615, 1584, 1559, 1519, 1481, 1423, 1396, 1385, 1342, 1311, 1300, 1257, 1176, 1141, 1114, 1102, 1083, 1033, 1018, 1009, 929, 852. 'H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 0.99 (d, 6H, 2CH₃); 2.57-2.75 (m, 3H, CH₂ & CH); 3.84-3.93 (m, 3H, CH₂ & CH); 4.41 (s, 2H, CH₂); 6.88 & 7.21(2d, 4H, Ar-H). Molecular Formula: C₁₃H₂₁NO₃; Molecular Weight: 239.15; Mass (ESI, in +ve ion mode): 240.1 [(MH)⁺].

(2RS)-1-{4-(Formyl)-Phenoxy}-3-(Isopropylamino)Propan-2-ol (Bisoprolol aldehyde, 48/1F)

To a mixture of 4-hydroxybenzaldehyde, 31 (50 g, 0.41 mol) in 380 ml epichlorohydrin, potassium carbonate (85 g, 0.62 mol) was added in lots and stirred at 25-35°C. Heated to 70-75°C and after completion of the reaction, which is monitored by HPLC, the reaction mixture
was cooled to 15-20°C and insoluble salts were filtered. Filtrate was concentrated at 85-90°C under reduced pressure, dissolved in methylene chloride (800 ml) and washed with 4% aqueous sodium hydroxide solution (400 ml) followed by DM water (400 ml). The organic layer was concentrated at 40-60°C under reduced pressure. Methylene chloride (200 ml) and DM water (400 ml) was added, adjusted pH to 1.5 using hydrochloric acid. Separated aqueous layer and extracted the product with methylene chloride (200 ml) at 25-30°C. The organic layer was concentrated at 35-40°C under reduced pressure to obtain 64 g of the intermediate compound.

Concentrated mass (64 g) was added to the mixture of isopropylamine (87 g, 0.98 mol) and isopropyl alcohol 600 ml precooled to 15-20°C. Reaction mass was heated to 55-60°C and monitored by qualitative HPLC analysis. After completion of reaction, excess of isopropylamine / isopropyl alcohol was removed from reaction mass at 35-50°C under reduced pressure. To the residue, methylene chloride (600 ml) and DM water (800 ml) was added and was cooled to 15-20°C. pH was adjusted to 1.8±0.2 using 15% w/w hydrochloric acid (100 ml). The layers were separated and the aqueous layer, containing Bisoprolol aldehyde washed with methylene chloride (2x250 ml). Methylene chloride (600 ml) was added to aqueous layer and adjusted the pH to 9.6±0.2 at 15-20°C with 20% w/w aqueous sodium hydroxide solution (~70 ml). Thereafter, the reaction mixture was extracted with methylene chloride (2x625 ml) and the combined organic layer was washed with 15% w/w aqueous sodium chloride solution (1x150 ml) at 20-30°C. The organic layer was concentrated at 40-60°C under reduced pressure, Isopropyl ether (450 ml) was added and stirred at 25-30°C to obtain 40 g of the title compound having 99.29% purity by HPLC. IR (KBr, cm⁻¹): 3291, 3075, 2966, 2919, 2901, 2866, 2825, 2797, 2733, 2633, 1689, 1653, 1603, 1578, 1510, 1473, 1451, 1386, 1373, 1341, 1328, 1313, 1267, 1236, 1217, 1158, 1146, 1126, 1110, 1097, 1014, 926, 905. 'H-NMR (300 MHz) in CDCl₃: δ (ppm) 1.15 (d, 6H, 2CH₃); 1.51 (brs, 2H, NH & OH); 2.70-2.94 (m, 3H, CH₂ & CH); 4.01-4.06 (m, 3H, CH₂ & CH); 7.04 & 7.84 (2d, 4H, Ar-H); 9.89 (s, 1H, CHO). Molecular Formula: C₁₃H₁₉NO₃; Molecular Weight: 237.14; Mass (ESI, in +ve ion mode): 237.9 [(MH)⁺].
Followed same operating process as described for the synthesis of 48. p-Cresol, 15 (10 g, 0.09 mol) used in place of 4-hydroxybenzaldehyde, 31 to obtain 11.52 g of the title compound having 99.29% purity by HPLC. IR (KBr, cm⁻¹): 3309, 3056, 3028, 2977, 2964, 2923, 2877, 2776, 1615, 1583, 1514, 1472, 1460, 1439, 1403, 1384, 1362, 1348, 1338, 1288, 1268, 1247, 1178, 1118, 1090, 1024, 897, 844. H-NMR (300 MHz) in DMSO-d₆: δ (ppm) 0.97 (d, 6H, 2CH₃); 1.70 (brs, 1H, NH); 2.22 (s, 3H, CH₃); 2.54-2.73 (m, 3H, CH₂ & CH); 3.80-3.93 (m, 3H, CH₂ & CH); 5.00 (brs, 1H, OH); 6.81 & 7.06 (2d each, Ar-H). Molecular Formula: C₁₃H₂₁NO₂; Molecular Weight: 223.16; Mass (ESI, in +ve ion mode): 224.1 [(MH)⁺].

(2RS)-1-4-(Methyl)-Phenoxy]-3-(Isopropylamino)Propan-2-ol (Methyl Bisoprolol, 49/1J)

(2RS)-1-{4-(Methyl)-Phenoxy]-3-(Isopropylamino)Propan-2-ol (Methyl Bisoprolol, 49/1J)

(2RS)-1-4-[(2-Isopropoxyethoxy)methoxy]Methyl]-Phenoxy]-3-(Isopropylamino)Propan-2-ol (Bisoprolol homologue, 50)

2-[(4-[(2-Isopropoxyethoxy)methoxy]methyl]Phenoxy methyl]Oxirane, 53 (165 g, 0.56 mol) was added to the mixture of isopropylamine (322 g, 5.46 mol) and isopropyl alcohol 495 ml precooled to 15-20°C. Reaction mass was heated to 55-60°C and monitored by qualitative HPLC analysis. After completion of reaction, excess of isopropylamine / isopropyl alcohol was removed from reaction mass at 35-50°C under reduced pressure. To the residue, ethyl acetate (600 ml) and DM water (450 ml) was added and was cooled to 15-20°C. pH was adjusted to 1.8±0.2 using 15% w/w hydrochloric acid (125 ml). The layers were separated and the aqueous layer, containing Bisoprolol hydrochloride washed with ethyl acetate (250 ml). Ethyl acetate (600 ml) was added to aqueous layer and adjusted the pH to 11.8±0.2 at 15-20°C with 20% w/w aqueous sodium hydroxide solution (~110 ml). Thereafter, the reaction mixture was extracted with ethyl acetate (2x125 ml) and the combined organic layer was washed with 15% w/w aqueous sodium chloride solution (1x150 ml) at 20-30°C. The organic layer was concentrated at 40-60°C under reduced pressure to obtain 97 g (50%) of the title compound having 85.65% purity by HPLC. This was purified by making its fumarate salt to yield 87 g (85%) of the title compound having purity of 95.5% by HPLC. Molecular Formula: C₁₉H₂₉NO₅; Molecular Weight: 355.24; Mass (ESI, in +ve ion mode): 356.3 [(MH)⁺]; IR (KBr, cm⁻¹): 3570, 2974,
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2928, 2873, 2730, 2595, 2478, 1652, 1615, 1574, 1516, 1495, 1464, 1431, 1383, 1369, 1351, 1315, 1241, 1166, 1150, 1128, 1096, 1050, 976, 953. ‘H-NMR (300 MHz) in DMSO-d$_6$: δ (ppm) 1.08 (d, 6H, 2CH$_3$); 1.11 (d, 6H, 2CH$_3$); 2.76 & 2.88 (2m, 1H each, CH$_2$); 3.02 (m, 1H, CH); 3.48-3.60 (m, 5H, 2CH$_2$, CH); 3.92 (m, 2H, CH$_2$); 4.00 (m, 1H, CH); 4.46 (s, 2H, CH$_2$); 4.67 (s, 2H, CH$_2$); 6.92 (d, 2H, Ar-H); 7.25 (d, 2H, Ar-H).

(2-Isopropoxyethoxy)Methyl chloride (52)

To 2-isopropoxy ethanol, 6 (102 g, 0.98 mol) paraformaldehyde, 51 (31.2 g, 1.04 mol) was added and stirred at 25-35°C. Thionyl chloride (128.38 g, 1.08 mol) was added over 1 hour at 25-35°C. Heated to 45-48°C and after completion of the reaction, which is monitored by TLC, the reaction mixture was concentrated at 70-80°C under reduced pressure to obtain 115 g of the oily compound.


2-[[4-Hydroxymethyl]Phenoxy]methyl]Oxirane, 39 (100 g, 0.55 mol) was added to dry tetrahydrofuran 800 ml under nitrogen atmosphere and cooled to -20±3°C. n-Butyl lithium (370 ml, 0.58 mol, ~15% in hexane) was added during 1 hour at -15±2°C and then (2-Isopropoxyethoxy)Methyl chloride, 52 (93.2 g, 0.61 mol) and monitored progress of reaction by qualitative HPLC analysis. After completion of reaction, quenched the reaction mass with DM water (200 ml) and concentrated at 25-35°C under reduced pressure. To the residue, methylene chloride (400 ml) was added and the layers were separated. Aqueous layer, more extracted with methylene chloride (400 ml) and combined washed with 2% sodium bi carbonate, dried on sodium sulphate and concentrated at 35-50°C under reduced pressure, to obtain 184 g (99%) of the title compound having 88.25 % purity by HPLC.
SPECTRA:

.....IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 7
.....IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 9

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IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 1
……IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 1B
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.....^1^H NMR AND MASS SPECTRUM OF COMPOUND 1C

.....^1^H NMR SPECTRUM OF COMPOUND 1E
.....IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 1F

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IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 1G
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.....IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 1H
IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND II

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.....IR AND $^1$H NMR SPECTRUM OF COMPOUND 1J
IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 1L
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.....$^1$H NMR SPECTRUM OF COMPOUND 37A

.....$^1$H NMR AND MASS SPECTRUM OF COMPOUND 37B
IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 38
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IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 38C
IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 39
IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 40B
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......$^1$H NMR AND MASS SPECTRUM OF COMPOUND 40A

......IR SPECTRUM OF COMPOUND 40C
…..\textsuperscript{1}H NMR SPECTRUM OF COMPOUND 40C

…..\textsuperscript{1}H NMR AND MASS SPECTRUM OF COMPOUND 46A
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IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 46
.....IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 46B

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.....IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 46C

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…..IR, $^1$H NMR AND MASS SPECTRUM OF COMPOUND 50
REFERENCES:


10. "Bisoprolol Official FDA information, side effects and uses." drugs.com


40. Yao, J.; Song, W.; Zhu, J. [P]. *CN 101323580*. Dec. 17, **2008**. (assigned to Hebei University of Science and Technology).


