ABSTRACT
The aim of this research was to synthesis Atenolol impurity G (Impurity G: 2-{4-[(2RS)-2-hydroxy-3-[(1-methyl-ethyl) amino] propoxy] phenyl] acetic acid, by very conventional method.

Keywords: Atenolol, Impurity, Synthesis.

INTRODUCTION
Atenolol is chemically (RS)-2-94-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl acetamide. Atenolol is a beta-adrenaceptor antagonist commonly known as beta blocker. Beta blockers are competitive inhibitors and interfere with the action of stimulating hormones on beta adrenergic receptors in nervous system. Atenolol works by competing for receptor site on cardiac muscle. This slows down the strength of heart’s contractions and reduces its oxygen requirements and volume of blood it has to pump. Hypertension may be treated with this drug because of their ability to increases the diameter of the blood vessels. Synthesis of related substances of Atenolol is official in IP, USP, BP and EP.1,6,8,9

EXPERIMENTAL
Purity of compound was monitored on silica gel 60 F254 purchased from Merck and solvents were procured from Aldrich Chemical Co. Ltd. Elemental analysis was performed using IR and HPLC analysis.4

Synthesis of Atenolol Impurity G: Impurity G is synthesized in 4 stages.

Stage-I: Synthesis of 4- Hydroxyl phenyl acetic acid to 4- hydroxyl phenyl acid methyl ester.
15 g of 4- hydroxyl phenyl acetic acid (a) was dissolved in 250 mL methanol. 0.8 mL of 98% sulphuric acid was added under stirring below 20°C and maintained for 4 hrs. Completion of reaction was monitored on TLC. After TLC complies, methanol was distilled out atmospherically and then under vacuum. Residue was cooled to get solid 4- hydroxyl phenyl acid methyl ester (b) (Ester Compound)2,3.

![Scheme-1](image)

Stage-II: 4- Hydroxyl phenyl acid methyl ester to Methyl- 2(4-(oxiran -2-ylmethoxy) phenyl) acetate
15.0 g of 4- hydroxyl phenyl acid methyl ester (b) was charged in lye solution (5.0 g of NaOH flask in 150 mL water) and 14.0 g of 1- Chloro-2, 3- epoxy-propane was added under stirring below 20 °C. Reaction mass was stirred for 1 hr, temperature was raised to 40-45°C and maintained for 6 hr.
Completion of reaction was monitored on TLC. Organic layer was separated from aqueous layer, washed with water till neutral pH to obtain methyl- 2(4-(oxiran -2-ylmethoxy)phenyl) acetate (e) (epoxide compound).

15 mL water was charged in round bottom flask, to it 60 mL mono Isopropyl amine was added below 20°C. 8.0 gm of methyl-2(4-(oxiran -2-ylmethoxy)phenyl) acetate (c) was added under stirring, maintained reaction mass for 1hr at 20°C and then raised the temperature to 40-45°C and maintained for 7 hr. Checked completion of reaction on TLC. After completion of reaction Mono isopropyl amine (MIPA) was distilled off under vacuum. 25 mL water was added which was distilled out with traces of MIPA under vacuum. Again 25 mL water was added and distilled out with traces of MIPA under vacuum. Solid obtained was dried under vacuum to get 2[4-(2-hydroxy-3[1-methyl ethyl amino]propoxy]phenyl] acetic acid methyl ester(d). (Amine compound).

Alcoholic NaOH (3.0 g of NaOH flask in 15 mL Methanol.) was charged in a reactor. 8.0 g of 2[4-(2-hydroxy-3[1-methyl ethyl amino] propoxy] phenyl] acetic acid methyl ester (d) was added under stirring. Reaction mass was refluxed under nitrogen blanker for 12 hr. Reaction completion was monitored on TLC. After completion of reaction, reaction mass was chilled 0 to 5°C under nitrogen blanket. Solid obtained was filtered under inert atmosphere under vacuum and was purified with MDC by hot and cold method under nitrogen blanket. Filtered to obtain white solid of 2[4-(2-hydroxy-3[1-methyl ethyl amino] propoxy] phenyl] acetic acid (e) i.e. Atenolol Impurity G.

RESULTS AND DISCUSSION
A Simple four stage of synthesis method was proposed for preparation of 2[4-(2-hydroxy-3[1-methyl ethyl amino] propoxy] phenyl] acetic acid. The target Impurity was synthesized in the Laboratory using the proposed method and was obtained in 80.3% yield. The product isolated was white crystalline powder was established using different characterization and structure elucidation techniques like physical date IR
Presented in Table-2 [Refer Fig.-1]. The purity of the compound was confirmed by HPLC analysis stated in Table-1 [Refer Figs.- 2-6].

Table-1: Specification

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Test</th>
<th>Standard specification</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Appearance</td>
<td>White to off white powder</td>
<td>White colored powder</td>
</tr>
<tr>
<td>2</td>
<td>Melting</td>
<td>174-176°C</td>
<td>173-175°C</td>
</tr>
<tr>
<td>3</td>
<td>Solubility</td>
<td>Soluble in methanol and Dimethyl sulphoxide. Insoluble in water.</td>
<td>Soluble in methanol and Dimethyl sulphoxide. Insoluble in water.</td>
</tr>
<tr>
<td>4</td>
<td>Purity by HPLC</td>
<td>98%-101%</td>
<td>99.92%</td>
</tr>
</tbody>
</table>

Fig.-1: IR of Impurity G

Fig.-2: Diluent
Fig.-3: Standard Impurity G Chromatogram

Fig.-4: Reference Standard Atenolol Graphs

Fig.-5: Impurity G chromatogram
CONCLUSIONS

The proposed novel synthesis process for Atenolol impurity G is well established in the Laboratory to achieve the expected yield and quality of the product. The process was observed to be short, simple. The synthesized impurity is confirmed by characterization and structural elucidation techniques. Synthesized impurity can be used as impurity standard, which can be further studied in various aspects.

ACKNOWLEDGEMENTS

I am thankful to Ultratech India Ltd. and D. G. Ruparel College for providing all the necessary analytical details of the compound, required support and co-operation for executing this project. I am also thankful to Mr. Deepak U. Shanbhag.

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[RJC-1039/2013]