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## **Synthesis of Ketoconazole Impurity by novel method**

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### **ABSTRACT**

*The aim of the work was to synthesize 1-[4-[[[(2RS, 4SR)-2-(2, 4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl) -1, 3-dioxolan-4-yl] methoxy] phenyl] piperazine, i.e. impurity D of Ketoconazole which is an antifungal drug. Impurity was synthesized in a very conventional method and Elemental analysis was done by Mass spectroscopy and Proton NMR.*

**Key words:** Hydrolysis, Ketoconazole, Antifungal agents.

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### **INTRODUCTION**

Control of pharmaceutical impurities is currently a problem to pharmaceutical industry but the most critical issue is to know the impurity (Chemical structure), thus International conference on Harmonization (ICH) [1-5] has formulated a workable guideline regarding the control of impurities. The presence of unwanted chemicals even in small amount may influence the efficacy and safety of pharmaceutical product [6].

Impurity profiling i.e. identification as well as the quantitation of impurity in the pharmaceutical industry is now gaining importance thus current research paper explains synthesis of impurity D of Ketoconazole by hydrolysis.

### **EXPERIMENTAL SECTION**

Purity of compound was monitored on silica gel 60 F<sub>254</sub>, purchased from Merck and solvents which were procured from Aldrich Chemical Co. Ltd. Anhydrous silica gel 60 was used as solid

support after dehydration is oven at 100°C for 5 mins. Elemental analysis was performed using Mass spectroscopy and Proton NMR [8].

### General Procedure for the synthesis of compound:

*Preparation of 1-[4-[[[(2RS, 4SR)-2-(2, 4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1, 3-dioxolan-4-yl] methoxy] phenyl] piperazine*

10% solution of caustic soda was prepared at RT i.e. (10gm in 100ml water), to it 50gm of Ketoconazole (API) and 200ml of Methanol was added. Mixture was heated to reflux on heating mantle and maintained for 10hrs. Completion of reaction was checked on T.L.C. Mobile phase used was chloroform and methanol, single spot other than the starting compound was observed, reaction mass was cooled to room temperature and then chilled to 10°C, solid precipitated out was filtered. Solid was re-purified in methanol by hot and cool method and filtered [7].

Dried solid at 65-70°C for 5 hrs

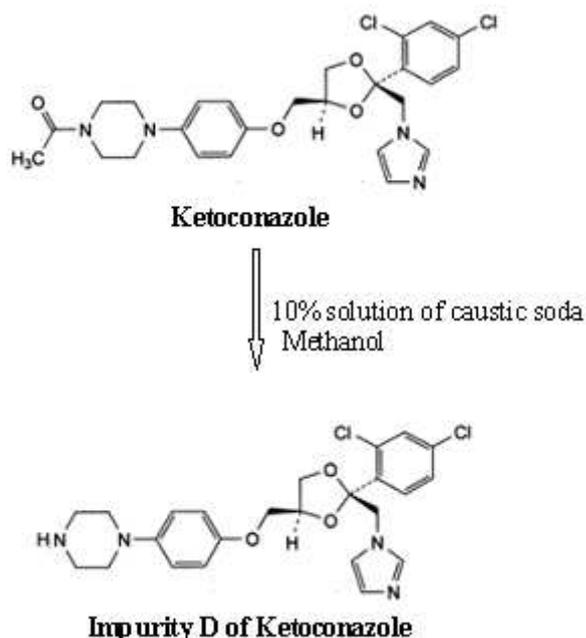
Dry weight up to 44.0gm.

**Melting point:** 170-173°C

**Assay:** by potentiometric titration with perchloric acid was 99.46%.

## RESULTS AND DISCUSSION

Reaction of Ketoconazole with caustic soda in presence of methanol results into hydrolysis.



Elemental Analysis was carried out to match the standard impurity D of Ketoconazole by Proton NMR, [Fig. 1], C-NMR [Fig. 2] and Mass spectroscopy [Fig. 3]. H.P.L.C. analysis was also carried out by BP 2008 [4] method to check the retention time [Fig. 4-10].

## CONCLUSION

Synthesized compound can be used as a impurity standard of Ketoconazole, which can be further studied in various aspects [3].

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