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SYNTHESIS OF LANSOPRAZOLE IMPURITIES BY CONVENTIONAL METHOD

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ABSTRACT

The aim of this research was to synthesis Lansoprazole impurities N-Oxide Lanso Chloro, N-Oxide Lansoprazole Sulphide, N-oxide Lansoprazole by very conventional method. The proposed novel synthesis process for Lansoprazole impurities 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.

Keywords: Lansoprazole, Impurity, Synthesis.

INTRODUCTION

Lansoprazole is chemically (RS)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl]methylsulfinyl)-1H-benzo[d]imidazole. Lansoprazole is a proton pump inhibitor (PPIs) and inhibits the action of hydrogen/potassium adenosine tri-phosphatase (H⁺/K⁺ATPase) in parietal cells. It reduces the stomach acid by blocking the enzyme system responsible. Synthesis of related substances of Lansoprazole is official in IP, USP, BP and EP. [1,6-9].

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]. The IR spectra were recorded in the solid state as KBr Dispersion medium.

GENERAL PROCEDURE

Synthesis of impurity

General preparation of Lansoprazole involves (Scheme 1). 2-mercapto benzimidazole and Lanso-chloro [2-(Chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride] are condensed in presence of sodium hydroxide to get Lanso-sulphide which on oxidation with hydrogen peroxide gives Lansoprazole.

Synthetic path ways of impurities formation

The intermediate used in the preparation of Lansoprazole is Lanso-sulphide. Some amounts of Lanso-sulphide remains as unreacted with oxidizing reagent and carry forward for the next stage which results in the occurrence of impurity in the final stage. Sometimes during the oxidation of Lansoprazole, over oxidation takes place resulting in the formation of impurities like N-oxide Lanso-chloro, N-oxide Lanso-sulphide and N-oxide Lansoprazole.

Lanso-sulphide impurity is prepared by the condensation of Lanso-chloro and 2-mercapto benzimidazole in presence of aqueous sodium hydroxide at room temperature. N-oxide Lansoprazole impurity is prepared by oxidation of Lanso-chloro with peracetic acid to give N-oxide Lanso-chloro followed by condensation with 2-mercapto benzimidazole in presence of aqueous sodium hydroxide to give N-oxide Lanso-sulphide which is further oxidation with peracetic acid to give impurity N-oxide Lansoprazole.

Experimental details

Synthesis of Lanso-sulphide

Lanso-sulphide is a precursor of Lansoprazole which was prepared by condensation of 2-mercapto

benzimidazole 10 g with 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride 11 g by using sodium hydroxide 5 g, in presence of water at ambient temperature. The separated solid was filtered and dried to give 12.40g of Lanso-sulphide.

Synthesis of N-oxide Lanso - chloro

(N-oxide 2-chloromethyl-3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridine hydrochloride) 10 g of 2-chloromethyl-3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridine hydrochloride was dissolved in 150 g of acetic acid at ambient temperature. Reaction mass was slowly heated to 80-85°C and then 75 g of per acetic acid (4.0%) was added drop wise, reaction mass was maintained for 2-3h at 80-85°C. Reaction completion was checked on TLC. Distilled acetic acid and per acetic acid under vacuum to get yellowish colored semisolid compound of N-oxide Lanso-chloro 6.0 g (0.02 mol)

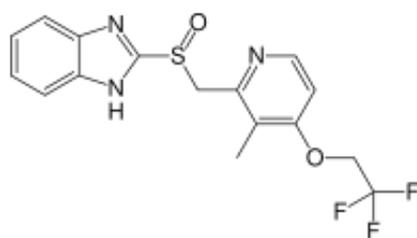
Synthesis of N-oxide Lanso-sulphide

10g of 2-mercapto benzimidazole was dissolved in solution of sodium hydroxide 5 g in 120 ml water at

ambient temperature. 11g N-oxide Lanso - chloro was added under stirring. Reaction mass was maintained for 1h. Completion of reaction was checked on TLC. Obtained solid was filtered and washed with water till neutral pH. Yield was 11.31g

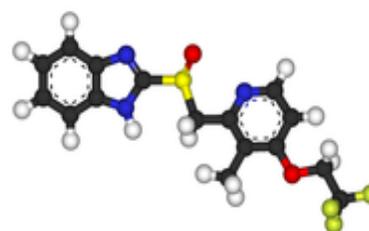
Synthesis of N-oxide Lansoprazole

5 g N-oxide Lanso-sulphide was dissolved in mixture of IPA and methanol [IPA 28g + methanol 3.6g]. Reaction mass was heated to 45-50°C, filtered hot and then cooled to 18 to 15°C. Catalyst solution (2.2 g water + 7.09g) H₂O₂ + 10.5 mg Vanadyl acetylacetonate) was added under stirring. Reaction was maintained for 2h. Completion of reaction was monitored on TLC. Chloroform was added to it and heated to 40 - 45°C and then chloroform layer was separated. Aqueous layer was charged into the reactor, cooled to 10 -15 °C and then 10 g, methanol was added dropwise for re-precipitation. White coloured solid was obtained which is filtered and washed with water and finally dried to obtain N-oxide Lansoprazole.



Chemical structure of Lansoprazole

Fig 1.



Lansoprazole 3D Structure

Fig 2. Synthesis of Lansoprazole

Scheme 1: Synthesis of Lansoprazole

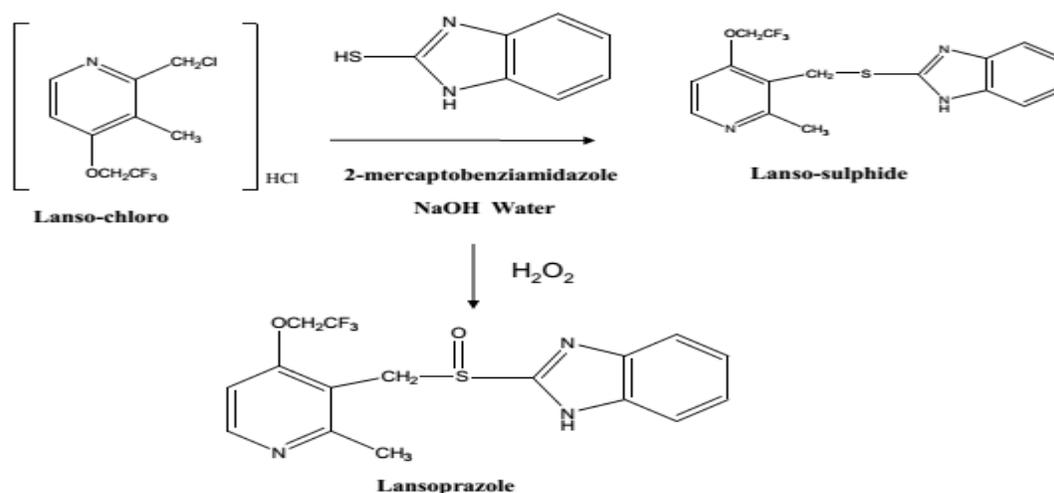


Fig 2: synthesis of Lansoprazole

Fig 3. Impurities of Lansoprazole
Lansoprazole impurities

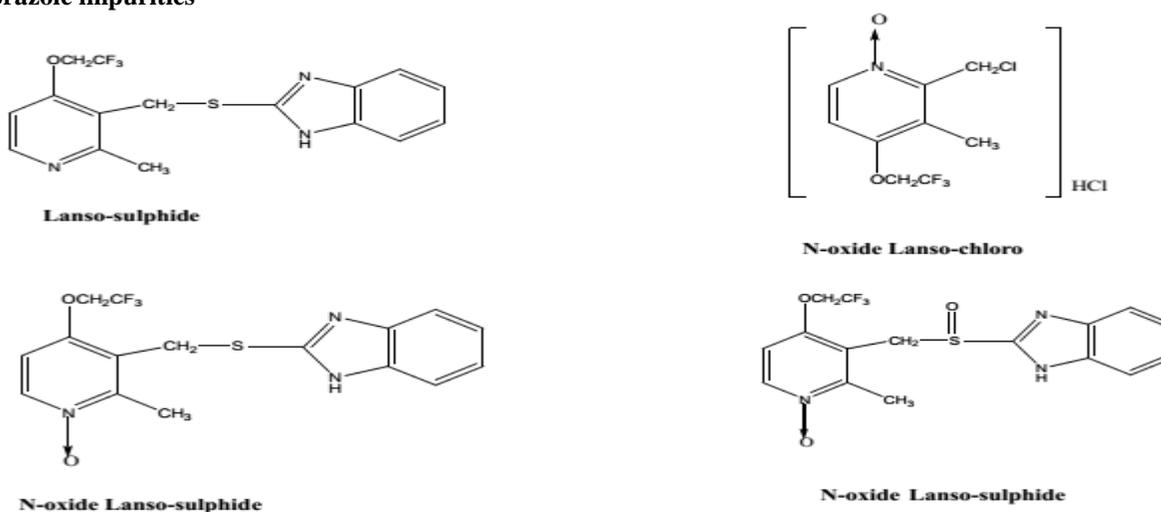


Fig 3: Impurities of Lansoprazole

Fig 4. Formation of Impurities

Scheme 2 :

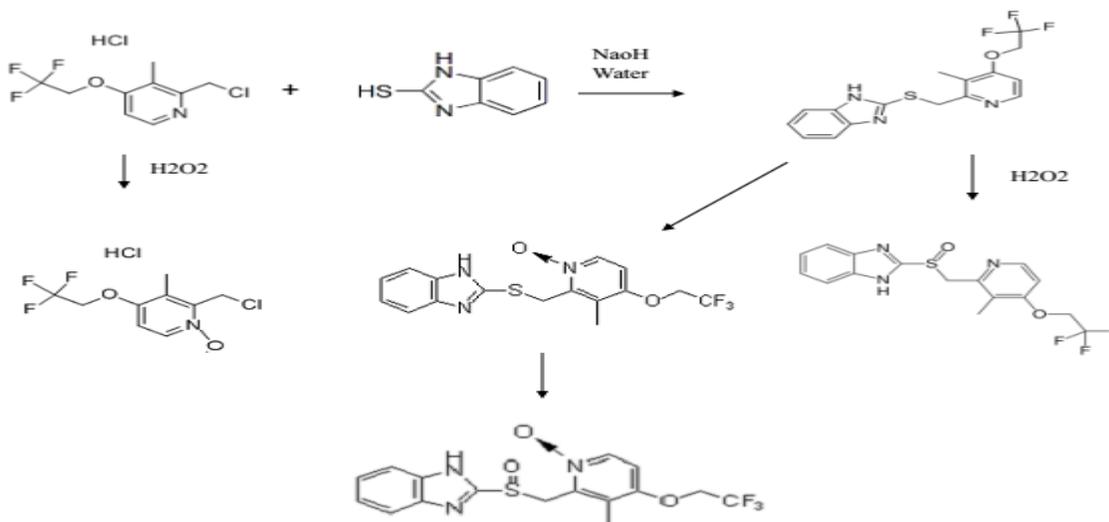


Fig 4: Formation of Impurities

Fig 5. Synthesis of Lansoprazole impurities by conventional method

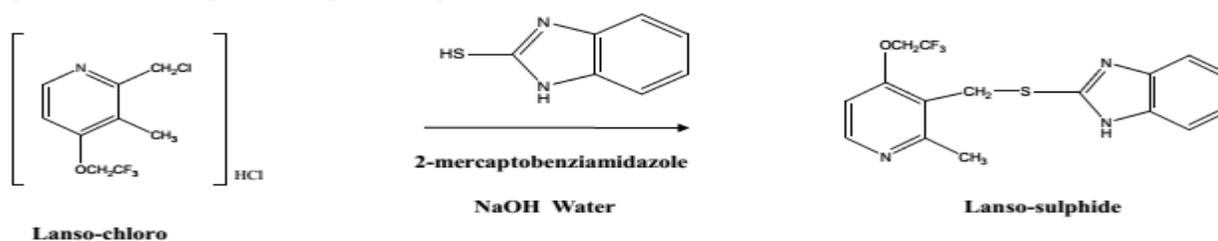


Fig 5: Synthesis of Lanso-sulphide

Scheme II

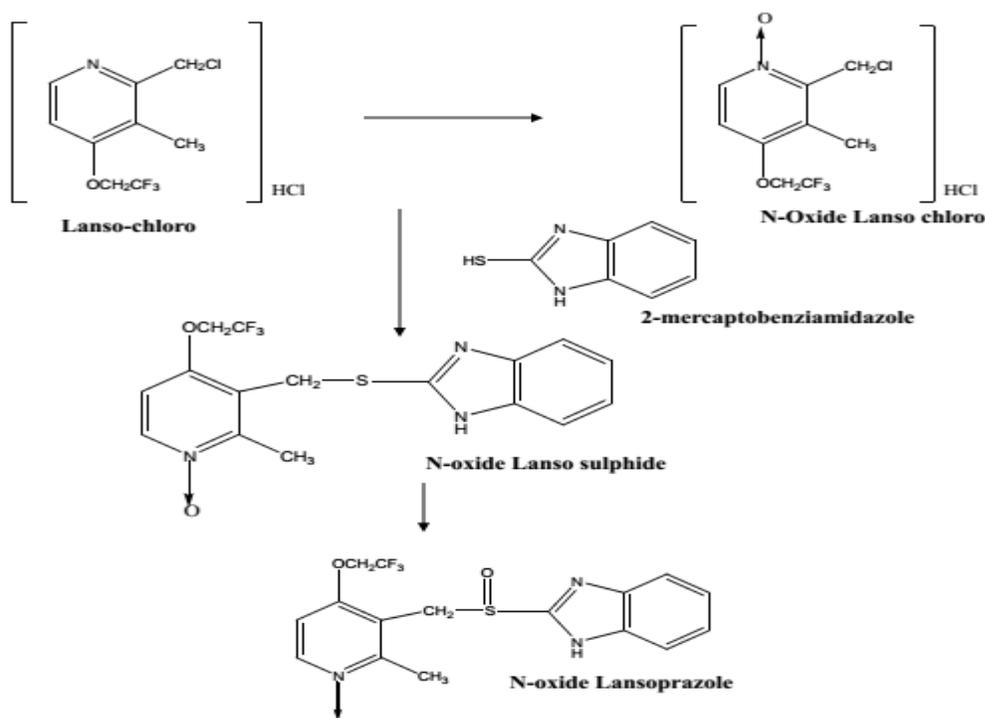


Fig 6: Synthesis of Lansoprazole impurities by conventional method

Table 1. Lansoprazole impurity Mass spectra

Name of Impurity	Molecular Wt	Melting Pt °C	Molecular formula	Mass	Yield in %
Lanso-sulphide	353.22	142-144	C ₁₆ H ₁₄ N ₃ OSF ₃	354	80.00%
N-oxide Lanso-chloro	255.58	209-212	C ₉ H ₉ NO ₂ F ₃	256	76.52%
N-oxide Lanso-sulphide	369.31	213-215	C ₁₆ H ₁₄ N ₃ O ₂ SF ₃	370	78.08%
N-oxide Lansoprazole	385.30	163-164	C ₁₆ H ₁₄ N ₃ O ₃ SF ₃	386	69.63%

Table 2. Lansoprazole impurity IR spectra

Name of Impurity	IR
Lanso-sulphide	3571.92(N-H str), 2977.89(C-H str), 2136.98(C-N str), 1758.96(C-O str), 1658.67(C=C Ar str), 1110.92(C-F str)
N-oxide Lanso-chloro	3224.76(N-H str), 2993.37 -CH str), 1612.38(-C=C Ar), 1265.22 (C-O-C), 1116.64 (C-F str), 709.76 (C-Cl str)
N-oxide Lanso-sulphide	3155.33(N-H str), 2985.60 (N-H str), 2877.60(C-H str), 1674.10(C=O str), 1627.81(C=C Ar str), 1512.09(H-C-H str), 1357.79(C-O-C str), 1180.35(C-F str)
N-oxide Lansoprazole	3857.37(N-H str), 2854.45 -C-H str), 1334..05 (N-O str), 1134.07 (C-F str) .1095.49 (S=O str)

Table 3. Lansoprazole impurity NMR spectra

Name of Impurity	NMR (DMSO)
Lanso-sulphide	8.67-6.84(d, 2H, pyridine), 2.32(s, 3H, CH ₃), 4.46 (m, 3H, CH ₃), 4.52(s, 2H, CH ₂ -S), 5.0(s, 1H, NH), 7.70-7.26 (m, 4H H-Ar)
N-oxide Lanso-chloro	8.18-6.74(d, 2H, pyridine), 2.35(s, 3H, CH ₃), 4.64(s, 2H, CH ₂ Cl)
N-oxide Lanso-sulphide	8.67-6.84(d, 2H, pyridine), 2.35(s, 3H, CH ₃), 4.46 (2, 2H, CH ₂ -CF ₃), 4.19(s, 2H, CH ₂ -S), 5.0(s, 1H, NH), 7.50-7.26 (m, 4H H-Ar)
N-oxide Lansoprazole	8.18-6.74(d, 2H, pyridine), 2.35(s, 3H, CH ₃), 4.46 (2, 2H, CH ₂ -CF ₃), 3.83(s, 2H, CH ₂ -S=O), 5.0(s, 1H, NH), 7.70-7.26 (m, 4H H-Ar)

RESULTS

A Simple synthesis method was proposed for preparation of Lansoprazole impurities. The target Impurity was synthesized in the Laboratory using the proposed method and was obtained in good yield. Impurities structure was established using different characterization and structure elucidation techniques like physical data IR & Mass The purity of the compound was confirmed by HPLC analysis.

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