Synthesis and Characterization of Process Related Impurities of Tegaserod Maleate

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ABSTRACT

Attempts to synthesize impurities of Gastro prokinetic drug tegaserod maleate, Three unknown impurities in tegaserod maleate bulk drug at level below 0.1% (ranging from 0.05 to 0.1 %) were detected by simple reverse phase high performance liquid chromatography (HPLC). These impurities were preliminarily identified with LCMS and by knowing the mass of the impurities, different experiments were conducted and finally synthesized and characterized as unknown impurities

Keywords: tegaserod, gastroprokinetic drug, ethyl acetate,

INTRODUCTION

Tegaserod maleate is known as 2-{(5-methoxy-1H-indole-3yl)methylene}-N-pentylhydrazine carboxidamide maleate. It is an oral medication for the treatment of constipation- predominate irritable bowel-syndrome in women, IBS is a chronic gastro intestinal disorder characterized by recurrent abdominal pain or discomfort and an altered bowel function which may be either constipation or diarrhea. Tegaserod anti diabetic compound, which is the drug of choice for non-insulin dependent diabetes mellitus (NIDDM). In the preparation of tegaserod maleate three unknown impurities were formed which were identified during analysis of different batches of tegaserod maleate whose percentage ranged from 0.05% to 0.1 %. A comphrensive study has been carried out to isolate or to prepare and characterize these impurities , the stringent requirement of customers that all the impurities >0.1% must identified and characterized. The paper aims at isolation or preparation and characterization of impurities

RESULTS AND DISCUSSIONS

In our approach by knowing the mass number of unknown impurities by mass spectrum we have proposed structures and for the preparation of the compound, we have designed different experiments, synthesized compounds and then characterized them. The isolated compounds RRT's are matching with unknown impurities. The same impurities, we tried to enrich from the filtrates of the isolated compounds, and by keeping compound stability at extreme temperatures or by keeping in basic and acidic condition.

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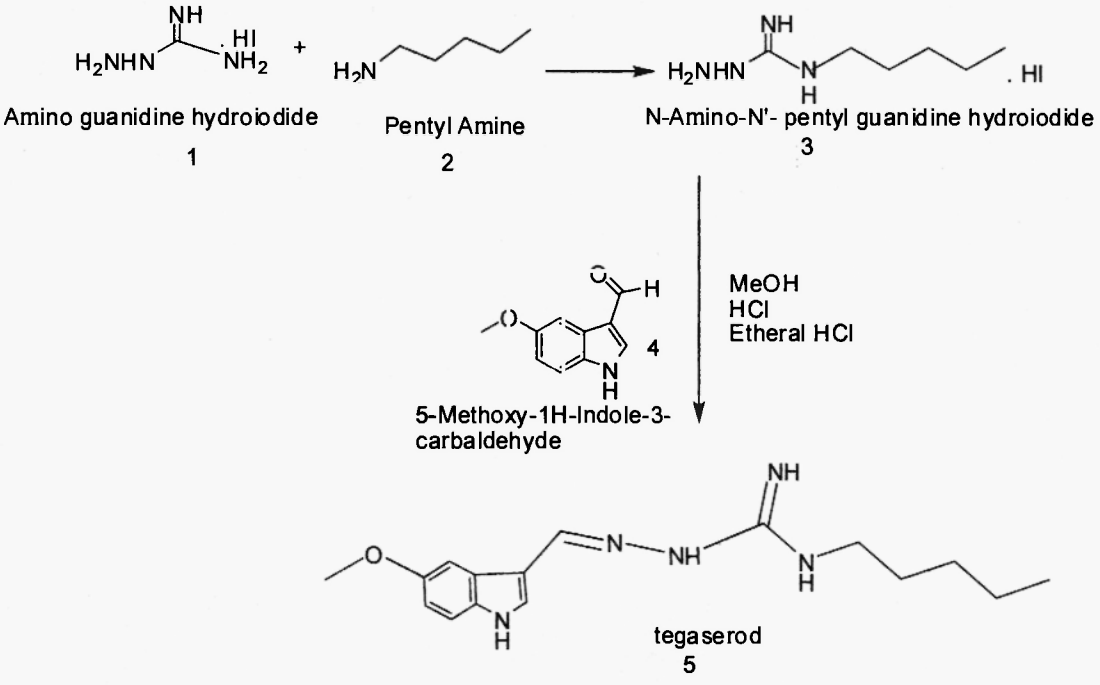
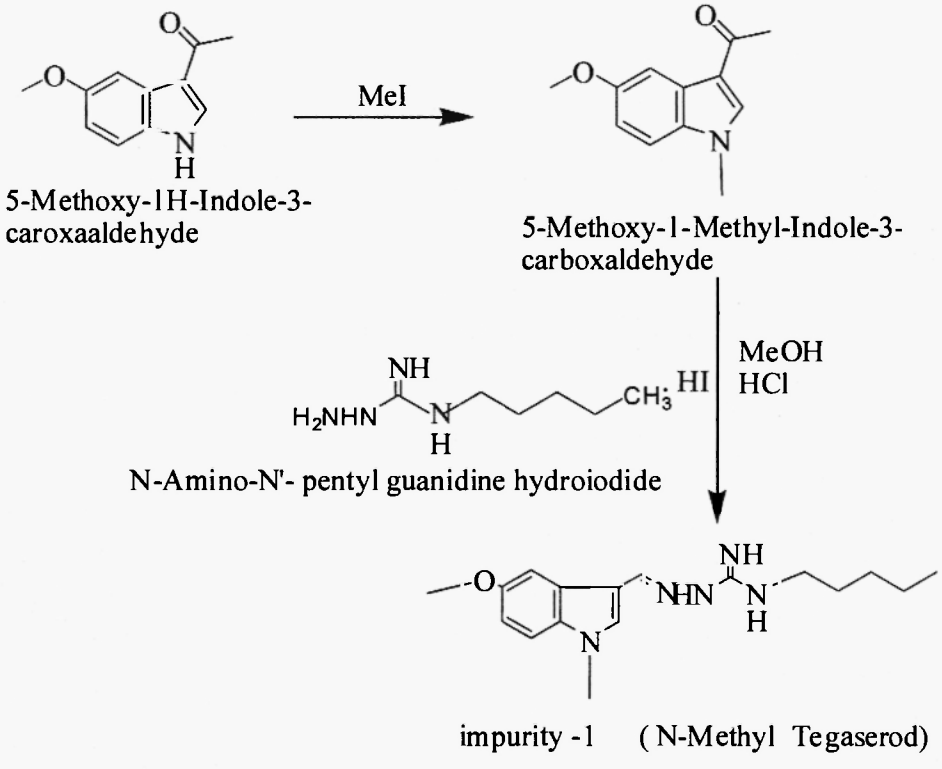
Synthetic scheme which has been followed is written below in **Scheme 1**, impurities which have been detected in HPLC for which process has been described and further it is confirmed by NMR, Mass spectral and IR data

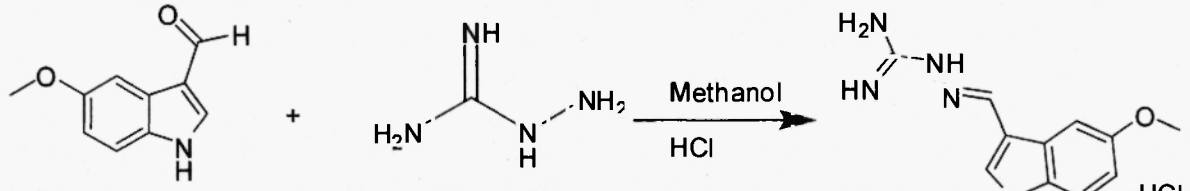
Scheme 1



Scheme 2



Scheme 3



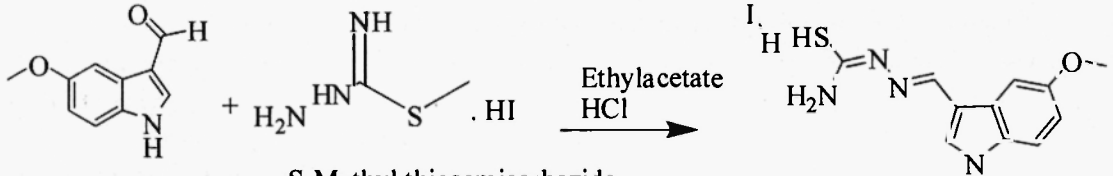
5-Methoxy-1H-Indole-3-carboxaaldehyde

Aminoguanidine

impurity-3

[(5-methoxy-1 H--indole-3yl)-methylene-amino]-guanidine HCl

Scheme 4



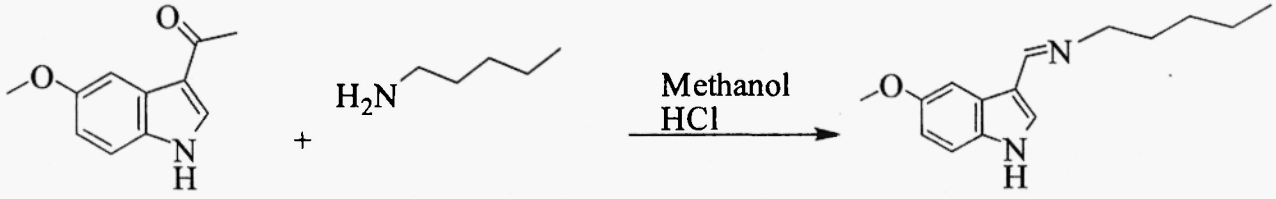
5-Methoxy-1H-Indole-3-carboxaaldehyde

S-Methyl thiosemicarbazide hydroiodie

impurity 4

1- [(5-methoxy-1 H--indole-3yl)-methylene-amino] - iso thio urea Hydro iodide

Scheme 5



5-Methoxy-1H-Indole-3-carboxaldehyde

Pentylamine

impurity-4
(pentyl amine impurity)

Experimental section:

The proton NMR were measured in CDCl3 and DMSO using 200 and 50 MHz respectively on Varian Gemini 200 MHz, FT NMR spectrometer the chemical shifts were reported in delta ppm relative to TMS, the FT-IR spectra were recorded in the solid state as KBR dispersion using perkin -Elmer 1650 FT-IR spectrometer. The mass spectrum (70 ev) was recorded in HP-5989 A LC-MS spectrometer. the solvents and reagent were used without further purification's

Preparation of 2-[(5-methoxy-N-methyl)-indole-3yl)-methylene]-N-pentyl hydrazine carboxidamide (impurity 1)

Charged 5-methoxy indole 3-carboxyaldehyde,(0.1143 mole), K_2CO_3(0.4571 moles) & methanol (1.0 Lit) into the dry RBF . Stirred for 10 to 15 min. added methyl iodide slowly. Heated to reflux and maintained for 5-6 hrs., at reflux . Then distilled off the solvent completely under reduced pressure. Added ethyl acetate 200 ml to the residue. Cool to 0-5°C. Stirred for 30-45 min. Filtered the solid and washed with ethyl acetate 30ml, 50%yield obtained, charged above material 0.105 moles and methanol 400 ml into the RBF Stirred the Rm. for 5 to minutes. Added N - pentyl N -amino guanidine hydro iodide. Adjusted the PH to 1-2 with HCl. Solution for 5-6hours.distilled off the solvent partially (70 to 80%). Cooled the reaction mass to 0-5°C , Filtered the solid and wash with methanol 30 ml. Taken the wet material in a RBF. Charged 280ml of water. Adjusted the PH to 11to 12 with 20% NaOH solution filtered the solid and wash with 50 ml of the water 60% yield.

Mass spectrum APCI+ Ve shows M/Z 316 and IR spectrum shows 3459 NH (amine) stretching, 2927 CH (CH3) stretching, 2869.53 CH (CH2) stretching, 1584.77 NH(sec amine)bending,1687.0 C=C stretching, 1257 C-0 (aryl) stretching, and 1072 C-0 (alkyl) stretching, Proton NMR Shows 8.0-8.2 (s)1H,6.7-7.3 (d)2H,7.5-7.6(s) 2H, 1.0-2.0(m) (6H)

Preparation of [(5-methoxy-1 H--indole-3yl)-methylene-amino]-guanidine.HCl. (impurity 2)

Charged 5-methoxy--indole-3 carboxaldehyde (0.02857 moles) and methanol 100 ml into the dry RBF Stirr for 5-10 minutes. Adjusted the PH to 3-4 with HCl solution. Maintained for 4 to 5 hours at 25-35°C. Distilled off the solvent partially (about 60 to 70%) to cool the residue to 0-5°C. Filtered the solid and washed with methanol,

Mass spectrum APCI+ Ve shows M/Z 232,IR absorption spectra shows peaks 3469.66 NH (amine) stretching,2978 CH stretching,1582 NH(sec amine),1296 C-N stretching, 1238 C-O (aryl) stretching ,1021.92 C-0 (alkyl) stretching, NMR shows 6-7 (d) 2H,7.2-7.5 (s) 2H,7.8-8.4 (s) 1H

Preparation of 1- [(5-methoxy-1 H--indole-3yl)-methylene-amino] - iso thio urea Hydro iodide. (impurity 3)

Charged ethyl acetate 100 ml, 5-methoxy indole 3-carboxaldehyde (0.0285 moles) and S- methyl thio semi carbazide hydro iodide dry RBF. Stirred for 5-to10 min. Adjusted the PH with HCl to 1.0 to 2.0. Stirred for 1.0 hour. Filtered the solid wash with ethyl acetate (10 ml). Dried the compound at 50-60°C yield: 90%

Mass spectrum APCI+ Ve shows M/Z 173.0,ir spectrum shows absorption at:

IR spectrum 3320.0 NH (amine) stretching, 1630.2 C=C stretching, , proton NMR shows 6.8-7.0 (d) 2H, 7.2-7.6 (s)2H, 7.9-8.2 (s) 1H, 2.3-2.4 (s)3H

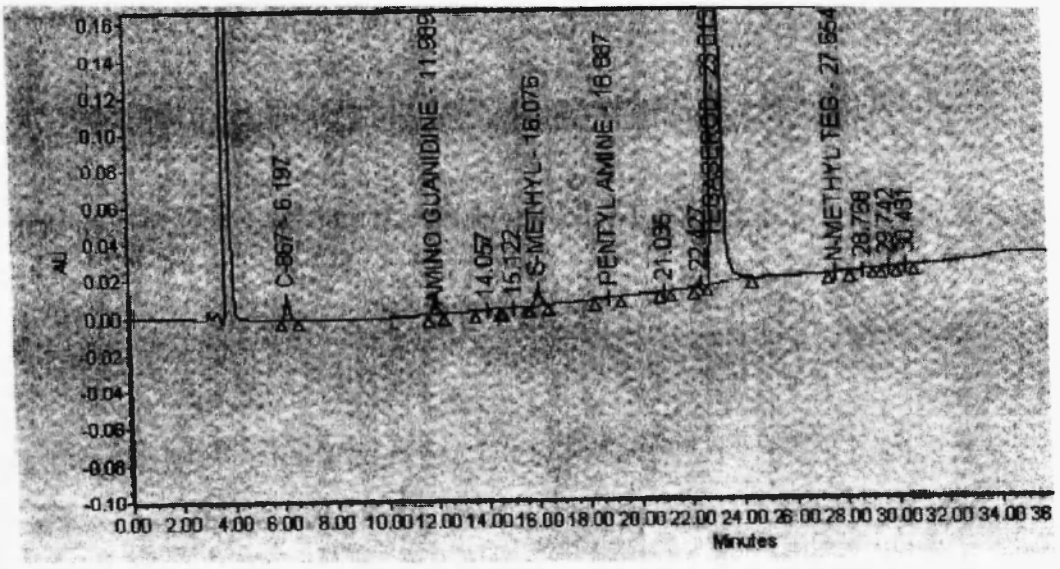
Preparation of (5-Methoxy-1H-indol-3-ylmethylene)-pentyl-amine. (impurity 4)

Charged 5-methoxy indole-3carboxaldehyde (0.1142 moles) acetonitrile (400 ml) and pentyl amine (0.1379 moles) into the RBF. Adjusted the PH to 2-3 with HCl. Maintained for 5-6 hours. Distilled off the solvent partially (about 80%). Cooled to ambient temperature . Filtered the solid and washed with acetonitrile (15 ml) . Solid kept aside. Taken filtrates mls and distill off under reduced pressure. (Residue) yield 80 %

Mass spectrum APCI+ Ve shows M/Z 245.0,

IR spectrum shows absorption at 3394.64 NH (amine) stretching,1655 C=C stretching ,1255 C-O (aryl)stretching, C-0 1027 (alkyl) stretching,, Proton NMR shows 6-7 (d) 2H,7.4-7.6 (s) 2H,7.8-8.4 (s) 1H,0.9(t) 3H,1.1-1.3 (m) 6H,3.8-4.0(s) 3H,

Blend HPLC chromatogram



CONCLUSION

In conclusion we have synthesized and characterized the unknown impurities

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