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Der Pharma Chemica, 2011, 3 (6):360-364
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

Identification and Synthesis of Impurities formed during Ilaprazole Preparation

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ABSTRACT

Ilaprazole, an anti-ulcer drug is used for the treatment for various acid related gastrointestinal (GI) disorders. During the laboratory optimization the formation of various impurities was observed. The impurities formed were monitored and their structures were tentatively assigned on the basis of their fragmentation pattern in LC-MS and other spectral data. Most of the impurities were synthesized and their assigned constitutions confirmed by co-injection in HPLC. We describe herein the formation, synthesis and characterization of these impurities.

Keywords:Regioselectivity, pyrrole, chloro ilaprazole, dialkyl products.

INTRODUCTION

Many compounds having benzimidazole structures, such as Omeprazole, can inhibit any stimulated acid secretion from gastric parietal cell, i.e. inhibit the last step of the delivery of gastric acid from gastric parietal cell to gastral cavity, and therefore are very effective for treating ulcer.

Prazoles (i.e. Proton pump inhibitors) can be used alone to treat various peptic ulcer, including multiple ulcer caused by gastrin, drug-induced ulcer caused by NSAIDs (non-steroidal anti-inflammatory drugs), and H₂ receptor antagonist (such as Cimetidine and Ranitidine) resistant refractory ulcer. Prazoles can be used in combination with two antibacterial agents, where Proton pump inhibitors (PPIs) can enhances the activity of the antibacterial agents, and as a result clearance of over 90% of Hp (*Helicobacter pylori*) may be achieved in two weeks.

Il-Yang Pharm. Co., Ltd., Korea has developed a Novel PPI, i.e. racemic 5-(1H-pyrrol-1-yl)-2-[[[(3-methyl-4-methoxy-2-Pyridyl)-methyl]sulfinyl]-benzimidazole[1,2], which shows superior anti-ulcer effects as compared to Omeprazole in the treatment of GORD(gastro-oesophageal reflux diseases), gastric ulcer and duodenal ulcer (KR 179,401 and US 5,703,097). Gastric and

duodenal ulcers are a gastrointestinal disease caused by various factors such as mental stress, dietary habit, intake of irritable food, and the like. The direct cause of peptic ulcers is damage to the gastric membrane due to excessive secretion of gastric acid.

MATERIALS AND METHODS

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Analytical TLC was performed on Merck precoated 60 F₂₅₄ Silica gel plates. IR spectra were recorded on a Perkin-Elmer One FT-IR Spectrometer in KBr Phase. ¹H and ¹³C NMR spectra were recorded in DMSO using Bruker 300 MHz Avance NMR instrument and mass Spectra were recorded on a Agilent 1100 series LC-MSD-TRAP-SL system.

General procedure for the preparation of Dialkyl Products, (4) and (5):

A mixture of 50 g of 5-(1H-pyrrol-1-yl)-1H-benzimidazole(1) and 45 g of 2-chloromethyl-4-Methoxy-3-Methyl pyridine hydrochloride (2) were stirred in 400 ml Methanol and slowly added sodium hydroxide solution (140 g in 280 ml water) to the reaction mixture in 30 -45 minutes at room temperature. Raised the reaction mass temperature to reflux and maintained for 10-15 hrs. Cooled the reaction mass temperature to 25-30⁰C and filtered the product (35g) which contained 74 % of compound (5). It was purified by recrystallization from 200 ml Methylene Dichloride and Toulene mixture (1: 1) to obtain 20 g of the pure compound (5). Distilled out Mother Liquor completely under vacuum which contained 77 % of Compound (4). It was purified by recrystallization from 60 ml Methylene dichloride and Toluene mixture (1: 1) to obtain 6 g of the pure compound (4)

1-(4-Methoxy-3-methyl-pyridin-2-ylmethyl)-2-(4-methoxy-3-methyl-pyridin-2-ylmethylsulfanyl)-6-pyrrol-1-yl-1H-benzoimidazole, (4) :

Yield: 6 g (12% w/w); HPLC Purity : > 94%; IR (KBr): 612, 636, 1297, 1377, 1438, 1465, 1501, 1583, 1624, 2925, 2839, and 3042 cm⁻¹; ¹H NMR (300 MHz, DMSO-D₆) : δ 2.23&2.16 (s, 6H), δ 3.85 (s, 6H), δ 4.68 (s, 2H), δ 5.50 (s, 2H), δ 6.23(s, 2H), δ 6.90&6.95 (d(5.7)&d(5.7), 2H), δ 7.27 (s, 2H), δ 7.57 (d(1.5), 1H), δ 7.64 (d(8.4), 1H), δ 8.22&8.06 (d(5.7) & d(5.7), 2H).
Mass : m/z 486 (M+H)⁺ ; m/z 508 (M+Na)⁺.

1-(4-Methoxy-3-methyl-pyridin-2-ylmethyl)-2-(4-methoxy-3-methyl-pyridin-2-ylmethylsulfanyl)-5-pyrrol -1-yl-1H-benzoimidazole, (5) :

Yield: 20 g (40% w/w); HPLC Purity: > 94%; IR (KBr) : 611, 1293, 1334, 1347, 1428, 1463, 1501, 1582, 2918, 2941, and 3093 cm⁻¹; ¹H NMR (300 MHz, DMSO-D₆) : δ 2.22&2.17 (s, 6H), δ 3.85 (s, 6H), δ 4.71 (s, 2H), δ 5.48 (s, 2H), δ 6.24(s, 2H), δ 6.91&6.95 (d(5.7)&d(5.4), 2H), δ 7.30-7.37 (m, 1H), δ 7.30-7.37 (m, 1H), δ 7.76 (s, 1H), δ 8.22&8.06 (d(5.7) & d(5.4), 2H); Mass : m/z 486 (M+H)⁺ ; m/z 508 (M+Na)⁺.

General procedure for the preparation of Chloro Ilaprazole, (7)

A mixture of 30 g Ilaprazole (6) and sodium hydroxide solution (6.5 g in 130 ml water) were stirred in 600 ml Acetonitrile and slowly added sodium hypochlorite solution(10%) 305 g to the reaction mixture in 30-45 minutes at room temperature. Maintained the reaction mass for 90 minutes. Separated the layers and Distilled out Acetonitrile layer under vacuum completely. The Obtained Crude (28 g) was subjected to silica gel column

chromotography using (9:1) by volume mixture of Ethylacetate and methanol as the eluent, to give the compound (7).

5-(2-Chloro-pyrrol-1-yl)-2-(4-methoxy-3-methyl-pyridin-2-ylmethanesulfinyl)-1H-benzoimidazole, (7):

Yield : 3.0g (10% w/w); HPLC Purity: > 88%; IR (KBr) : 612, 679, 818, 1253, 1273, 1297, 1396, 1478, 1582, 1623, 1632, 2938, 2978, and 3434 cm^{-1} ; ^1H NMR (300 MHz, DMSO- D_6) : δ 2.15 (s, 3H), δ 3.87 (s, 3H), δ 4.74 (d(13.8), 1H), δ 4.82 (d(13.8), 1H), δ 6.26-6.31(m, 1H), δ 6.26-6.31(m, 1H), δ 6.99 (d(5.7), 1H), δ 7.09-7.10 (m, 1H), δ 7.31-7.35 (dd(8.4,1.8), 1H), δ 7.66-7.78 (m, 1H), δ 7.66-7.78 (m, 1H), δ 8.25 (d(5.7), 1H), δ 13.82 (br,s, 1H); Mass : m/z 401 (M+H) $^+$; m/z 423 (M+Na) $^+$

RESULTS AND DISCUSSION

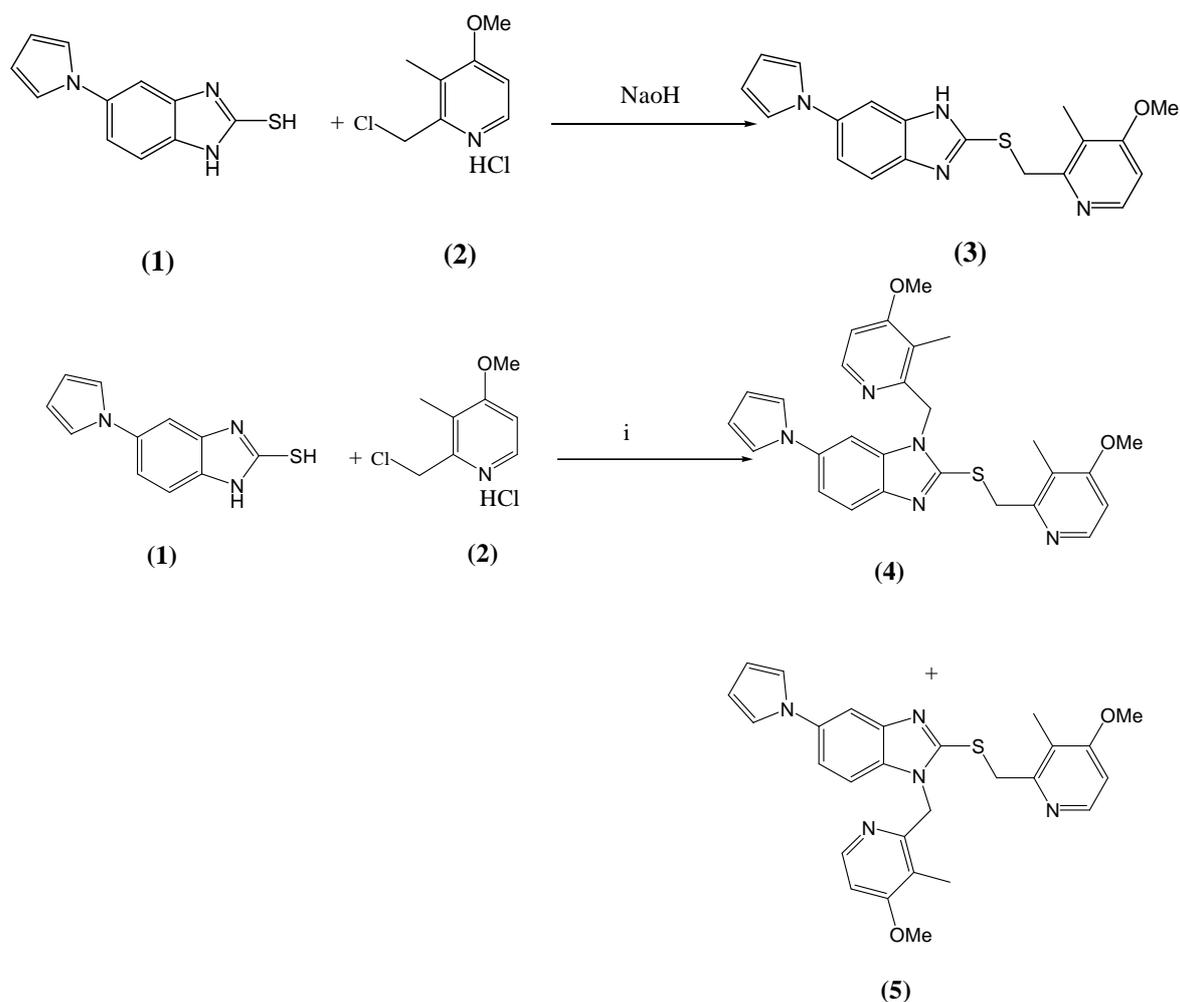
Recently impurity profiles of the drug substances became more important than the purity of the compound. Identification of impurities can help to minimize the formation. The present communication describes the isolation and identification of three important impurities which are hitherto unreported in the manufacture of Ilaprazole an important anti ulcer compound.

Two main process steps in the preparation of ilaprazole consist of alkylation of pyrrole mercapto benzimidazole and finally oxidation of sulfide to sulfoxide. Process Optimization studies reveals one equivalent of the alkylating agent is required to give desired sulfide in 90% yield. However it was observed that two additional compounds were formed to the extent of 1%. Based on the spectral data (Mass, NMR) the compounds were identified as dialkyl products (4) & (5). HPLC analysis reveals that these two products are in 1: 3 ratio.

Theoretically two regio dialkyl isomer products can be formed because of the presence of pyrrole substitution. As expected reaction using more than two equivalent of alkylating agent increase the yields of dialkylated compounds (30%). The two isomers were separated and purified by crystallization. It is interesting to observe the regioselectivity of the above reaction giving two alkyl products in different portions which may be attributed to the presence of pyrrole group.

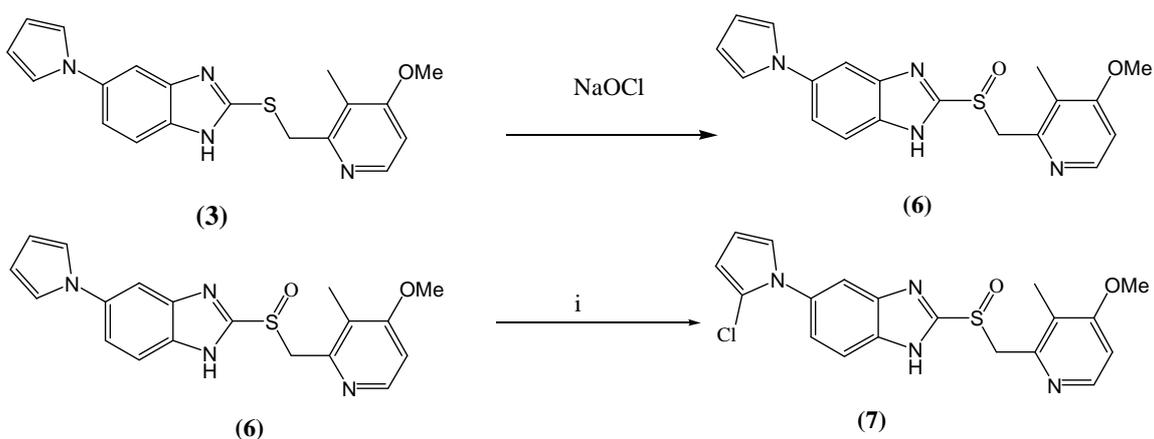
The API formation involves the conversion of sulfide to sulfoxide. Interestingly the use of hypochlorite has resulted in the reduction of sulphone formation to a greater extent compare to that of MCPBA (meta chloro per benzoic acid). However we have observed the formation of another impurity which is formed to the extent of 0.5%. The compound was isolated by column chromatography. The impurity was identified as the halogenated ilaprazole by NMR & Mass. Isolation of the impurity by column chromatography which was identified as 5-(2-Chloro-pyrrol-1-yl)-2-(4-methoxy-3-methyl-pyridin-2-ylmethanesulfinyl)-1H-benzoimidazole (7).

This observation is of interest in view of chloro methyl formation in pantoprazole[3] (WO 2004111029). This is the first report on the identification of Chloro Ilaprazole.



Reagents and conditions: i) a) NaOH (excess), Methanol water, reflux; b) purification with toluene + Methylene chloride mixture

Scheme I - Synthesis of Dialkyl products 4 and 5.



Reagent and Conditions: i) (a) 10 % NaOCl, acetonitrile, 20% NaOH, 25-30°C, (b) Column Chromatography

Scheme II - Synthesis Chloro Ilaprazole (3)

CONCLUSION

The three process impurities in the manufacture of ilaprazole were identified for the first time. Reaction of (2) with marcapto benzimidazole[4] has resulted two regio isomeric dialkyl products. Reaction (6) with hypochlorite has afforded chloro ilaprazole (7). Formation of (7) and the absence of the chloromethyl compound observed in the related prazole (Ex: Pantoprazole) is noteworthy.

Acknowledgement

The authors wish to thank Matrix Laboratories Limited for supporting this work and also authorities of Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500 085.

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