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SYNTHESIS OF ANTIULCER DRUG ESOMEPRAZOLE

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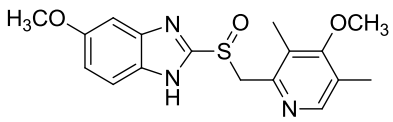
Abstract

Esomeprazole (Nexium®), the (*S*)-isomer of Omeprazole, is the first proton-pump inhibitor developed as a single isomer for the treatment of acid-related diseases. It is used for the treatment of peptic ulcers, gastroesophagal reflux disease, and erosive esophagitis. Herein, we report our synthetic study of esomeprazole sodium salt from the starting 2-mercapto-5-methoxybenzimidazole and 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine hydrochloride reagents. The Esomeprazole sodium salt was obtained from enantioselectivesulfoxidation reaction in moderate yield with high enantioselectivity.

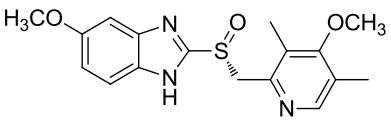
Keywords. Peptic Ulcer, Proton Pump Inhibitor, Omeprazole, Esomeprazole.

1. INTRODUCTION

Peptic ulcer is one of the most common diseases in modern society. For the treatment of ulcer, proton pump inhibitors (PPIs) are the most important group of drugs because their activity is inhibiting the H^+/K^+-ATPase enzyme system of gastric parietal cells and decreasing the amount of acid produced in the stomach.Omeprazole, a racemic mixture, was the first PPI drug in 1987 and has been the best-selling drug on the market [1].



Omeprazole



Esomeprazole

Esomeprazole, the (*S*)-enantiomer of Omeprazole, provides better acid control than current racemic PPIs and has a favorable pharmacokinetic profile relative to Omeprazole [2]. Esomeprazole became commercially available as the first single-optical-isomer PPI in 2001. Sales of Esomeprazole reached nearly 4 billion US dollars in 2013, and it is one of the top 20 best-selling drugs.Thus, the preparation of esomeprazole has attracted much attention in both academia and industry. The synthesis of Esomeprazole was reported by several groups [3-9].

Herein, we report our preliminary synthetic study of Esomeprazole sodium salt from the starting 2-mercapto-5-methoxybenzimidazole and 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine hydrochloride reagents. The Esomeprazole sodium salt was obtained from enantioselectivesulfoxidation reactions in moderate yield with high enantioselectivity.

2. MATERIALS AND METHODS

All chemicals were used as received from commercial sources without further purification. ^1H and ^{13}C NMR spectra were recorded on a BrukerAvance 500 (500 MHz, ^1H; 125 MHz ^{13}C) spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or the internal solvent signal of deuterated solvents (^{13}C and ^1H). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants *J* are reported in Hertz. The mass spectra were recorded with aAgilent 1260LC/MS instrument. For thin layer chromatography, analytical TLC plates (70-230 mesh silica gel

(Merck) were used. Visualization was accomplished with UV (254nm).

Preparation of sulfide 3 (5-methoxy-2-[3,5-dimethyl-4-methoxypyridinyl) methylthio]-1H-benzimidazole)

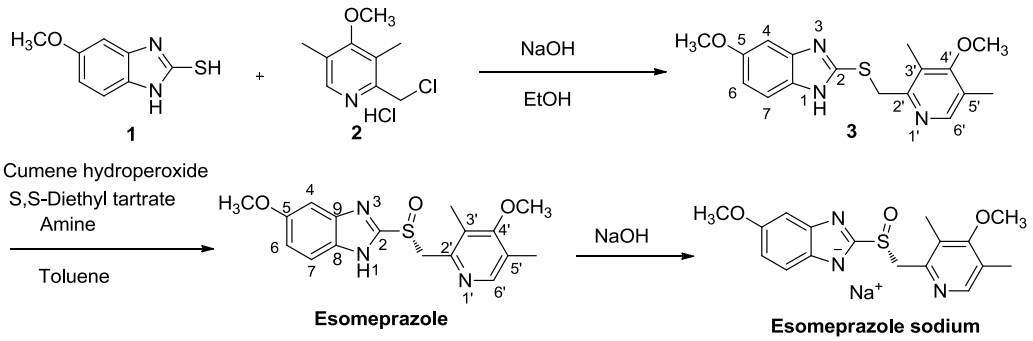
To a stirred solution of 2-mercapto-5-methoxybenzimidazole (3.6 g, 20 mmol) and Na_2CO_3(4.62 g, 44 mmol) in EtOH (90 mL) was added 2-chloromethyl-3,5-dimethyl-4-methoxy pyridinehydrochloride (4.44g, 20 mmol) and the reaction mixture was refluxed for 4 hours. Reaction was cooled down and water was then added at room temperature, wherein the of 5-methoxy-2-[3,5-dimethyl-4-methoxypyridinyl)methylthio]-1H-benzimidazole precipitated. The white product was separated, washed with water and dried in a vacuum. Product (6.12 g) was obtained with 93 % yield. Mp: 48-51 ^oC.^{1}H-NMR (500 MHz, DMSO-d_6) δ(ppm): 2.27 (s, 3H, C$\underline{H}_3$), 2.31 (s, 3H, C$\underline{H}_3$), 3.78 (s, 3H, OC$\underline{H}_3$), 3.84 (s, 3H, OC$\underline{H}_3$), 4.34 (s, 2H, C$\underline{H}_2$S), 6.81 (dd, *J* = 2.5 Hz và *J* = 8.5 Hz, 1H, H-6), 7.03 (brs, 1H, H-4), 7.40 (brs, 1H, H-7), 8.26 (s, 1H, H-6').^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 11.3 (C$\underline{H}_3$), 13.4 (C$\underline{H}_3$), 35.0 (C$\underline{H}_2$S), 55.8 (OC$\underline{H}_3$), 60.0 (OC$\underline{H}_3$), 97.2 (C-7), 111.0 (C-6), 115.3 (C-4), 125.4 (C-5'), 126.3 (C-3'), 134.2 (C-8), 140.0 (C-9), 148.3 (C-2), 149.4 (C-6'), 155.9 (C-2'), 156.0 (C-5), 165.1 (C-4'). ESI-MS: m/z 330 $[M+H]^+$.

Synthesis of Esomeprazole

To a stirred solution of sulfide **3** (1 g, 3 mmol) in toluene (6 mL) was added (*S*,*S*)-diethyl tartrate (371 mg, 1.8mmol) and titanium tetraisopropoxide (0.27 mL, 0.9mmol) and the mixture was stirred for 1 h at 55°C. The reaction temperature was cooled to 30°C and subsequently*N*,*N*-diisopropylethylamine (0.14 mL, 0.9mmol) and cumenehydroperoxide (80 % in cumene, 0.46 mL, 3mmol) were added. After 1 hour at 30°C the reaction mixture was extracted three times with aqueousammonium hydroxide (12.5% of NH_3,3×6 mL). Then combined aqueous extracts were adjusted to pH =8 with aceticacid, extracted with methyl isobutyl ketone (2 x 3mL). A portion of organic extract was concentrated and purified by chromatography to give Esomeprazole as an oil. ^{1}H-NMR (500 MHz,DMSO-d_6) δ(ppm): 2.16 (s, 3H, C$\underline{H}_3$); 2.19 (s, 3H, C$\underline{H}_3$); 3.67 (s, 3H, OC$\underline{H}_3$); 3.80 (s, 3H, OC$\underline{H}_3$); 4.67 (d, *J* = 13.5 Hz, 1H, C$\underline{H}_2$S); 4,75 (d, *J* = 13.5 Hz, 1H, C$\underline{H}_2$S); 6.92 (d, *J* = 9.0 Hz, 1$\underline{H}$, H-6); 7.09 (brs, 1H, H-4); 7.53 (d, *J* = 7.5 Hz, 1H, H-7); 8.17 (s, 1H, H-6').^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 11.1 (C$\underline{H}_3$), 12.9 (C$\underline{H}_3$), 55.5 (OC$\underline{H}_3$), 59.8 (C$\underline{H}_2$S), 60.0 (OC$\underline{H}_3$), 100.4 (C-7), 111.5 (C-6), 116.0 (C-4), 125.6 (C-5'), 126.5 (C-3'), 131.0 (C-8), 139.8 (C-9), 149.1 (C-2), 149.6 (C-6'), 157.5 (C-2'), 158.0 (C-5), 163.6 (C-4'). ESI-MS: m/z 346 $[M+H]^+$.

Preparation of Esomeprazole sodium salt

To the combined methyl *iso*-butyl ketone extracts were added an aqueous solution of sodium hydroxide 50% (168 mg, 2.1mol) and acetonitrile (12mL). The solution was concentrated during which the product gradually precipitated. Esomeprazole sodium (528 mg, 48% in overall yield) was obtained as a white solid. $[\alpha]_D^{20}$ = +30 (*c* 1.0, H_2O); *ee* > 99% (measured by HPLC on AD-H column, hexane-*iso*-propanol-acetic acid (50: 50: 0.1) as the eluent, flow rate: 0.6 mL/min, wavelength 300 nm). ^{1}H-NMR (500 MHz,DMSO-d_6) δ(ppm): 2.16 (s, 3H, C$\underline{H}_3$); 2.21 (s, 3H, C$\underline{H}_3$); 3.70 (s, 3H, OC$\underline{H}_3$); 3.75 (s, 3H, OC$\underline{H}_3$); 4.46 (d, *J* = 13.0 Hz, 1H, C$\underline{H}_2$S); 4.72 (d, *J* = 13.0 Hz, 1H, C$\underline{H}_2$S); 6.60 (d, *J* = 8.5 Hz,2.5 Hz, 1$\underline{H}$, H-6); 7.02 (d, *J* = 2.5 Hz, 1H, H-4); 7.37 (d, *J* = 8.5 Hz, 1H, H-7); 8.25 (s, 1H, H-6').^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 11.3 (C$\underline{H}_3$), 12.9 (C$\underline{H}_3$), 55.2 (OC$\underline{H}_3$), 58.6 (C$\underline{H}_2$S),59.7 (OC$\underline{H}_3$), 99.4 (C-7), 109.0 (C-6), 117.5 (C-4), 124.9 (C-5'), 126.5 (C-3'), 141.6 (C-8), 147.0 (C-9), 149.1 (C-2), 151.9 (C-6'), 153.7 (C-2'), 161.8 (C-5), 163.4 (C-4').ESI-MS: m/z 344 $[M-Na]^-$



3. RESULTS AND DISCUSSION

Esomeprazole was prepared from starting 2-mercapto-5-methoxybenzimidazole and 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine hydrochloride reagents. Firstly, the reaction of two above compounds was heated in the presence of sodium carbonate (2.2 eq) in EtOH to give the sulfide product in excellent yield, up to 90-95 % [10]. The structure of sulfide **3** was confirmed by NMR and MS spectroscopic data. The ^{1}H-NMR shows the signals of protons of benzimidazole ring at δ_H 6.81 (dd, J = 2.5 Hz and J = 8.5 Hz, 1H, H-6); 7.03 (brs, 1H, H-4); 7.40 (brs, 1H, H-7). A signal of H-6 of pyridine unit appears at δ_H 8.26 ppm. Methyl group and methoxy group signals are found at δ_H 2.27, 2.31 and 3.78, 3.81 ppm, respectively. And a methylen group signal (CH_2S) appears at 4.34 ppm. The molecular ion peak $[M+H]^+$ was found at 330 in the ESI-MS spectrum. These spectroscopic data was identical with previously reported studies [10].

Next, the oxidation reaction of sulfide to Esomeprazole was studied. Among numerous catalysts for enantioselective oxidation of sulfide, those applied in the preparation of esomeprazole include titanium/diethyltartrate [3], titanium/chiral diol [4], titanium/tartramide [5, 6], the condition of titanium/diethyltartrate is the most important one for application.Thus, the reaction condition was chosen as followed: sulfide **3** 3 mmol, titanium tetraisopropoxide 0.9mmol, (*S*,*S*)-diethyl tartrate 1.8mmol, *N*,*N*-diisopropylethylamine 0.9 mmol and cumenehydroperoxide 3 mmol. A small amount of product Esomeprazole was purified to confirm the chemical structure.

Table 1:^{1}H, ^{13}C- NMR data of Esomeprazole, Esomeprazole sodium salt.

	^{1}H-NMR (δ) ppm				^{13}C-NMR (δ) ppm		
	Esomeprazole	Esomeprazole sodium	Esomeprazole sodium [a,][3, 7]		Esomeprazole	Esomeprazole sodium	Esomeprazole sodium [a][7]
H-6'	8.17 (s)	8.25 (s)	8.24 (s)	C-4'	163.6	163.4	163.3
H-7	7.54 (brs)	7.37 (d)	7.35 (d)	C-5	158.0	161.8	161.1
H-4	7.09 (brs)	7.02 (d)	7.00 (d)	C-2'	157.5	153.7	153.5
H-6	6.81(dd)	6.60 (dd)	6.57 (dd)	C-6'	149.6	151.9	151.6
$C\underline{H}_2S$	4.67(d) and 4.75(d)	4.46 (d) and 4.72 (d)	4.41 (d) and 4.60 (d)	C-2	149.1	149.1	148.9
OCH_3	3.80 (s)	3.75 (s)	3.72 (s)	C-9	139.8	147.0	146.7
OCH_3	3.67(s)	3.70 (s)	3.68 (s)	C-8	131.0	141.6	141.3
CH_3	2.19 (s)	2.21 (s)	2.21 (s)	C-3'	126.5	126.5	126.3
CH_3	2.16 (s)	2.16 (s)	2.16 (s)	C-5'	125.6	124.9	124.9
				C-4	116.0	117.5	117.3
				C-6	111.5	109.0	108.9
				C-7	100.4	99.4	99.3
				OCH_3	60.0	59.7	60.4
				OCH_3	55.5	55.2	55.1
				CH_2S	59.8	58.6	59.6
				CH_3	12.9	12.9	12.8
				CH_3	11.1	11.3	11.2

[a]^{1}H,^{13}C spectra were recorded in DMSO-d_6, 400 MHz.

The NMR spectra show similar signals to that of sulfide compound, except the signals of methylene group attached to S=O. Two proton signals of methylene group, that appeared as the singlet at 4.34 ppm, was found at 4.67 and 4.75 ppm as 2 doublets. In the ^{13}C-NMR, the signal of CH_2S=O moved to 59.8 ppm from 35.0 ppm in the spectrum of sulfide **3**. The molecular ion peak $[M+H]^+$ was found at 346 in the ESI-MS, hence the chemical formula is $C_{17}H_{19}N_3O_3S$.

Esomeprazole was converted to its more stable salt using reaction with sodium hydroxide in acetonitrile. The sodium salt was crystallized and

obtained with high enantioselectivity (*ee* > 99 %) in moderate overall yield (48 %).

4. CONCLUSION

In summary, a proton pump inhibitor, esomeprazolesodium,was obtained from 2-mercapto-5-methoxybenzimidazole and 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride in 3 steps with 44 % overall yield. Further works on optimization of reaction condition and amplification of synthetic scale are under investigation and will be reported in due course.

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