A SYNTHESIS OF CHOLINE SALTS OF PRAZOLE DERIVATIVES

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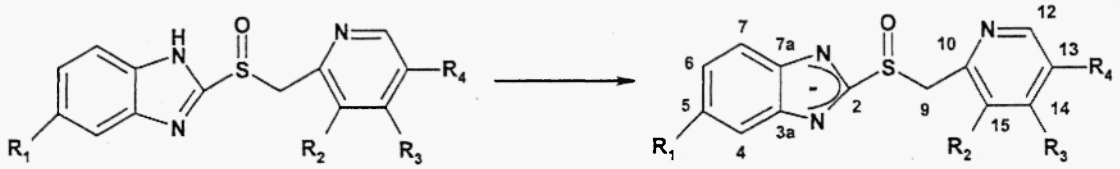
Abstract: Synthesis of new choline salt of prazole derivatives was described starting from sodium salts with choline chloride.
Keywords: Choline salts, prazole derivatives, synthesis.

Compounds of common name omeprazole[1], pantoprazole[2] and lansoprazole[3] of the chemical structural formula **(1a)-(1c)** (Scheme-1), respectively, are known as highly potent acid gastric secretion inhibitor[4], and are prescribed clinically for the prevention and treatment of gastrointestinal inflammatory diseases in mammals. They serve also as therapeutic agents for digestive ulcers[5]. These compounds, however, have poor stability. In solid state, they are susceptible to heat, moisture and light. In aqueous solution or suspension, their stability decreases with decreasing pH. In pharmaceutical compositions they are present in an inorganic salt form with lithium, sodium, potassium, magnesium, calcium or titanium[6] as counterion.



(1a) R_1, R_3=OCH_3; R_2, R_4=CH_3
(1b) R_1=CHF_2; R_2, R_3=OCH_3; R_4=H
(1c) R_1, R_4=H; R_2=CH_3; R_3=OCH_2CF_3

(2a) R_1, R_3=OCH_3; R_2, R_4=CH_3
(2b) R_1=CHF_2; R_2, R_3=OCH_3; R_4=H
(2c) R_1, R_4=H; R_2=CH_3; R_3=OCH_2CF_3

Scheme-1

In this communication, we report on a simple and convenient method of preparation of a new salts of prazole derivatives in the form of choline salts. This form of prazole derivative can be uses as drug delivering vehicles, and it is expected to be well tolerated by mammal digestive systems and to have much improved stability. The choline salt was prepared by transferring commercial prazole derivatives into sodium salt if necessary, and by quantitative addition choline chloride. As a solvent, absolute ethanol was used. Precipitated by-product, sodium chloride, was removed *via* filtration. All products were obtained as solids with 93-94% yield.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini (200 MHz) instruments. Chemical shifts are expressed in ppm (δ) referred to TMS, coupling constants (*J*) are in Hz. IR and UV spectra were recorded on Perkin Elmer Paragon 1000 and Hewlett Packard 8453 instruments, respectively. Mass spectra was obtained on an AMD-604 spectrometer.

Omeprazole and lansoprazole were submitted by Cipla Ltd., Mumbai Central India, pantoprazole sodium sesquihydrate was submitted by Ramjay Impex Pvt Ltd. Bangalore India, choline chloride was purchased from the Fluka Chemical Co.

Solvents were distilled and dried, if required, other materials were commercial.

General Procedure: Powdered sodium hydroxide (0.028 mole) was dissolved in absolute ethyl alcohol (60 cm^3), followed by addition of omeprazole **1a** or lansoprazole **1c** (0.028 mole) while stirring at room temperature. After, the reaction mixture become homogenous, the choline chloride (0.028 mole) was added. Reaction mixture was stirred for 24 h, then precipitate was filtered off, filtrate were evaporated to dryness. Residue, a slightly yellow oil, was dissolved in anhydrous acetone (60-70 cm^3), cooled to +4° C, and additional precipitate (sodium chloride) was filtered off. Solvent was evaporated and residue dried under vacuum to afford solid pure choline salt. Yield was 94% for both products **2a** and **2c**.

In the case of pantoprazole **1b**, which was supplied as a sodium sesquihydrate, to the solution of pantoprazole sodium sesquihydrate (3 mmol) in absolute ethyl alcohol (15 cm^3), choline chloride (3 mmol) was added. After standard work-up, the product **2b** was obtained as a solid with 93% yield.

Choline salt of 5-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-ylmethanesulfinyl)-1*H*-benzoimidazole, (2a):

^{1}H-NMR($CDCl_3$): 2.14 (s, 3H, C**H**$_3$); 2.15 (s, 3H, C**H**$_3$); 2.77 (s, 9H, 3xC**H**$_3$); 3.0 (m, 2H, C**H**$_2$OH); 3.64 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.7-3.8 (m, 2H, NC**H**$_2$CH$_2$); 4.53 and 4.78 (2d, 2H, *J*=13.12, SC**H**$_2$); 5.8 (br.s, 1H, O**H**); 6.75 (dd, 1H, *J*=2.24 and 8.8, H-6); 7.05 (d, 1H, *J*=2.24, H-7); 7.45 (d, 1H, *J*=8.8, H-4); 8.10 (s, 1H, H-12).

^{13}C-NMR (25 MHz)($CDCl_3$):11.46 and 13.24 (2xCH_3); 54.05 (C-9); 55.55 and 55.73 (3xC-16); 59.82 (2xOCH_3); 67.99 (C-17); 99.15 (C-4); 111.28 (C-13); 117.89 (C-15); 125.73 (C-7) and 126.75 (C-5); 140.27 (C-7a); 145.69 (C-2); 149.19 (C-3a) and 150.53 (C-12); 155.14 (C-10); 159.55 (C-6); 164.08 (C-14).

IR (KBr)(cm^{-1}), ν: 3370 (OH); 1607; 1566; 1475; 1358; 1152; 1028; 836.

UV(EtOH)(nm)(c=0.52mg/10cm^3), λ_{max}: 213 (ε=20300); 302 (ε=11100).

MS-ESI/TOF(%): 713 (100, $[2(M\text{-}C_5H_{13}N)+Na]^+$); 368 (12, $[(M\text{-}C_5H_{13}N)+Na]^+$); 346 (30, $[(M\text{-}C_5H_{13}N)+H]^+$).

HR-MS for m/z = $C_{17}H_{19}N_3O_3NaS$: calcd. 368.1039; found 368.1045.

Choline salt of 5-difluoromethoxy-2-(3,4-dimethoxypyridin-2-ylmethanesulfinyl)-1*H*-benzoimidazole, (2b):

^{1}H-NMR ($CDCl_3$): 2.70 (s, 9H, 3xCH_3), 3.00 (br.s, 2H, CH_2OH); 3.76 (s, 6H, 2xOCH_3); 3.80 (br.s. 2H, CH_2OH); 3.82 (s, 1H, CHF_2); 4.65 (2d, 2H, *J*=12.80, SCH_2); 5.30 (br.s, 1H, OH), 6.68 (d, 1H, *J*=5.60, H-13); 6.85 (m, 1H, arom); 7.35 (m, 1H, arom); 7.50 (m, 1H, arom); 8.05 (d, 1H, *J*=5.60, H-12).

^{13}C-NMR (25 MHz)($CDCl_3$): 54.03 (3x C-16), 55.48 (C-9), 55.70 and 56.81 (2xOCH_3); 61.27 (C-17); 68.01 (C-18); 107.58 (CHF_2), 108.16 (C-13); 113.49 (C-6); 116.91 and 118.02 (C-4, C-7); 143.72 (C-12), 144.84 (C-15), 145.43 and 145.73 (C-3a, C-7a), 146.12 (C-2); 158.68 (C-5, C-14); 162.49 (C-10).

IR (KBr)(cm^{-1}), ν: 3401 (OH); 1587; 1491; 1361; 1304;1030; 828.

UV(EtOH)(nm)(c=0.21mg/10cm^3), λ_{max}: 214(ε=59400); 289 (ε=29600).

MS-ESI/TOF(%): 789 (45, $[2(M\text{-}C_5H_{13}N)+Na]^+$); 406 (100, $[(M\text{-}C_5H_{13}N)+Na]^+$); 384 (42, $[(M\text{-}C_5H_{13}N)+H]^+$).

HR-MS for m/z = $C_{16}H_{15}N_3O_4F_2NaS$: calcd. 406.0644; found 406.0654.

Choline salt of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-ylmethanesulfinyl)-1*H*-benzoimidazole, (2c):

^{1}H-NMR ($CDCl_3$): 2.13 (s, 3H, CH_3); 2.59 (s, 9H, 3xCH_3); 2.85 (br.s, 2H, CH_2OH); 3.68 (br.s, 2H, NCH_2); 4.23 (q, 2H, *J*=7.8, CH_2CF_3); 4.65 (2d, 2H, *J*=13.37, SCH_2); 5.80 (br.s, 1H, OH); 6.48 (d, 1H, *J*=5.78, NCHCH); 7.10 (m, 2H, arom); 7.65 (m, 2H, arom); 8.10 (d, 1H, *J*=5.78, NCHCH).

^{13}C-NMR (25 MHz)($CDCl_3$): 10.84 (CH_3); 53.85 (C-16); 55.40 (C-9); 59.74 (C-18); 65.80 (OCH_2); 67.82 (C-17); 105.72 (C-13) 117.60 (C-4,C-7) and 120.41 (C-5,C-6); 122.86 (C-15); 145.56 (CF_3); 148.03(C-2); 152.12 (C-12); 160.55 (C-10) and 161.55 (C-14).

IR (KBr)(cm^{-1}), ν: 3401 (OH); 1583; 1475; 1373; 1265; 1169; 751.

UV(EtOH)(nm)(c=0.40mg/10cm^3), λ_{max}: 216 (ε=42000); 285 (ε=24500).

MS-ESI/TOF(%): 761 (100, $[2(M-C_5H_{13}N)+Na]^+$); 392 (65, $[(M-C_5H_{13}N)+Na]^+$).

HR-MS for m/z = $C_{16}H_{14}N_3O_2F_3NaS$: calcd. 392.0651; found 392.0662.

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