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SYNTHESIS OF DEUTERATED MOSAPRIDE CITRATE

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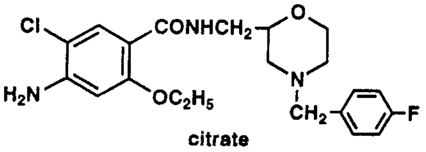
SUMMARY

The deuterium labeled form of mosapride citrate, a potential gastroprokinetic agent, was prepared *via* reduction of ethyl 4-(4-fluorobenzyl)-2-morpholinecarboxylate (**4**) with lithium borodeuteride.

Keywords: [$^2H_2$]-mosapride; gastroprokinetic agent;
5-HT_4 agonist; benzamide

INTRODUCTION

4-Amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide citrate (**1**, mosapride citrate) [1—3] is a potential gastroprokinetic agent without dopamine D_2 receptor antagonistic activity. The gastroprokinetic action is accepted to be correlated with agonistic activity at a new serotonin receptor subtype (5-HT_4) [4]. Mosapride citrate acts as a partial agonist for 5-HT_4 receptor and facilitates cholinergic transmission [5]. Clinical evaluations of **1** are ongoing. Metabolic studies required the synthesis of the deuterium labeled



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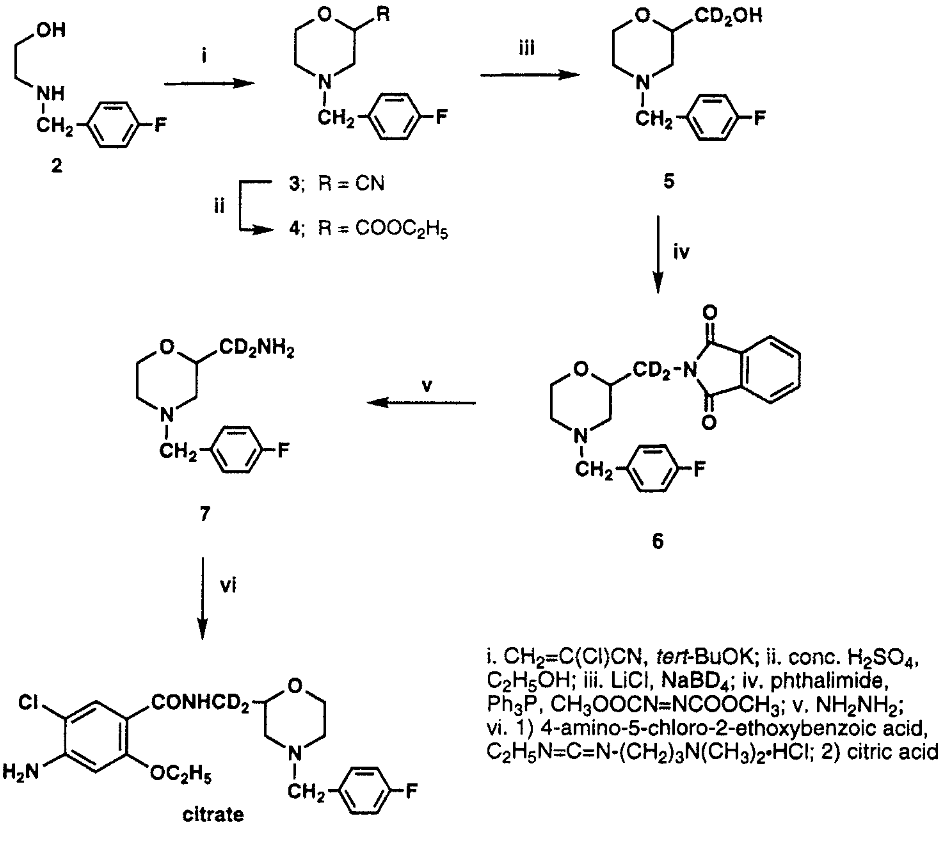
form of mosapride. In this paper, we describe the facile of [$^2H_2$]-mosapride citrate *via* reduction of ethyl 4-(4-fluorobenzyl)-2-morpholinecarboxylate (**4**) with lithium borodeuteride.

RESULTS AND DISCUSSION



i. $CH_2=C(Cl)CN$, *tert*-BuOK; ii. conc. H_2SO_4,
C_2H_5OH; iii. LiCl, $NaBD_4$; iv. phthalimide,
Ph_3P, $CH_3OOCN=NCOOCH_3$; v. NH_2NH_2;
vi. 1) 4-amino-5-chloro-2-ethoxybenzoic acid,
$C_2H_5N=C=N-(CH_2)_3N(CH_3)_2\cdot HCl$; 2) citric acid

Scheme 1

The synthetic route is shown in Scheme 1. This route comprises the reduction of ethyl 4-(4-fluorobenzyl)-2-morpholinecarboxylate (**4**) with lithium borodeuteride. Beecham group reported that the reaction of 2-(benzylamino)ethanol with 2-chloroacrylonitrile gave 4-benzyl-2-morpholinecarbonitrile [6]. This method was applied for the morpholine ring synthesis; the treatment of 2-[(4-fluorobenzyl)amino]ethanol (**2**) with 2-chloroacrylonitrile afforded the corresponding 2-cyanomorpholine **3**, which was converted to the intermediate ethyl morpholine-2-carboxylate **4** in a moderate yield. The reduction of **4** with sodium borodeuteride and lithium chloride in C_2H_5OH furnished $[2\text{-}^2H_2]$-4-(4-fluorobenzyl)-2-hydroxymethylmorpholine (**5**) in an excellent yield. Compound **5** was transformed into the phthalimide **6** using the Mitsunobu reaction [7]. The resultant **6** was treated with hydrazine to give the amine **7** in a good yield. Finally, the reaction of **7** with 4-amino-5-chloro-2-ethoxybenzoic acid [1] in the presence of 1-ethyl-3-[(3-dimethylamino)propyl]carbodiimide hydrochloride as a coupling agent, followed by the treatment of citric acid, afforded the desired $[^2H_2]$-mosapride citrate.

EXPERIMENTAL SECTION

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi 260-10 spectrometer. Electron ionization (EI) and secondary ion (SI) mass spectra (abbreviated as EIMS and SIMS, respectively) were obtained on a JEOL JMS D-300 spectrometer or a Hitachi M-80B spectrometer. ^{1}H-NMR spectra were taken at 200 MHz with a Varian GEMINI-200 spectrometer. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in Hz. Organic extracts were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. Merck silica gel 60 (70—230 mesh) was used for column chromatography.

Ethyl 4-(4-fluorobenzyl)-2-morpholinecarboxylate (4) A solution of 2-[(4-fluorobenzyl)amino]ethanol [8] (**2**, 17.0 g, 0.10 mol) and 2-chloroacrylonitrile (9.7 ml, 0.12 mol) in $(C_2H_5)_2O$ (100 ml) was stirred at room temperature for 5 days. The solvent was evaporated to leave an oily residue, which was dissolved in 1,2-dimethoxyethane (300 ml). To the cooled solution was added potassium *tert*-butoxide (11.3 g, 0.10 mol). The mixture was stirred at room temperature for 2 h and then heated to reflux for 1h. After cooled to room temperature, saturated aqueous $NaHCO_3$ (100 ml) was added. The solution was extracted with $(C_2H_5)_2O$ and the extract was washed with brine. The solvent was evaporated to give a pale yellow oil, which was chromatographed on silica gel with $CHCl_3/CH_3OH$ = 50/1 to afford 13.6 g (62%) of 4-(4-fluorobenzyl)-2-morpholinecarbonitrile (**3**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (1H, ddd, *J* = 3.0, 9.0, 12.0, 5-H_{ax}), 2.47—2.70 (2H, m), 2.76 (1H, ddd, *J* = 1.5, 4.0, 12.0, 3-H_{eq}), 3.49 (1H, d, *J* = 13.0, $C\underline{H}_2C_6H_4F$), 3.57 (1H, d, *J* = 13.0, $C\underline{H}_2C_6H_4F$), 3.77 (1H, td, *J* = 3.5, 11.8, 6-H_{eq}), 4.02 (1H, ddd, *J* = 3.0, 9.0, 11.8, 6-H_{ax}), 4.60 (1H, t, *J* = 3.5, 2-H), 6.95—7.10 (2H, m, arom H), 7.25—7.40 (2H, m, arom H). SIMS *m/z*: 221, 220 (M^+), 219. IR (neat) ν cm^{-1}: 2230 (CN).

A mixture of **3** (1.0 g, 4.5 mmol), concentrated H_2SO_4 (1.3 ml), and C_2H_5OH (8 ml) was heated to reflux for 20 h and then cooled to room temperature. The solvent was evaporated to leave a residue, which was dissolved in water. The aqueous solution was basified with 20% aqueous K_2CO_3 and extracted with $(C_2H_5)_2O$. The extract was washed with brine. The solvent was evaporated to afford an oily residue, which was chromatographed on silica gel with ethyl acetate to give 1.2 g (98%) of **4** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$), 2.23—2.43 (2H, m), 2.57 (1H, m), 2.91 (1H, ddd, *J* = 1.3, 3.0, 10.0, 3-H_{eq}), 3.45 (1H, d, *J* = 13.2, $C\underline{H}_2C_6H_4F$), 3.54 (1H, d, *J* = 13.2, $C\underline{H}_2C_6H_4F$), 3.69 (1H, ddd, *J* = 3.0, 9.5, 12.0, 6-H_{ax}), 4.02 (1H, td, *J* = 3.5, 12.0, 6-H_{eq}), 4.20 (1H, m), 4.22 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$), 6.95—7.08 (2H, m, arom H), 7.20—7.35 (2H, m, arom H). SIMS *m/z*: 268 (MH^+), 266. IR (neat) ν cm^{-1}: 1725 (COOEt).

[2-$^2H_2$]-4-(4-Fluorobenzyl)-2-hydroxymethylmorpholine (5) To a mixture of **4** (1.2 g, 4.5 mmol), lithium chloride (0.38 g, 9.0 mmol), sodium borodeuteride (0.38 g, 9.0 mmol), and anhydrous tetrahydrofuran (THF, 10 ml) was added dropwise anhydrous C_2H_5OH (10 ml) at room temperature. The mixture was stirred at the same temperature for 15 h and concentrated to dryness. The residue was dissolved in water and then extracted with $CHCl_3$, and the extract was washed with brine. The solvent was evaporated to give a pale yellow oil, which was chromatographed on silica gel with ethyl acetate to afford 1.0 g (98%) of **5** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (1H, t-like, *J* = 10.0, 3-H_{ax}), 2.19 (1H, dt, *J* = 3.5, 11.3, 5-H_{ax}), 2.68—2.76 (2H, m), 3.43 (1H, d, *J* = 13.0, $C\underline{H}_2C_6H_4F$), 3.52 (1H, d, *J* = 13.0, $C\underline{H}_2C_6H_4F$), 3.65 (1H, dd, *J* = 2.0, 10.0, 2-H), 3.71 (1H, dt, *J* = 2.2, 11.3, 6-H_{ax}), 3.90 (1H, ddd, *J* = 1.5, 3.5, 11.3, 6-H_{eq}), 6.92—7.10 (2H, m, arom H), 7.21—7.36 (2H, m, arom H). EIMS *m/z*: 227 (M^+), 164, 109.

[2-$^2H_2$]-*N*-[[4-(4-Fluorobenzyl)-2-morpholinyl]methyl]phthalimide (6) Dimethyl azodicarboxylate (0.64 g, 4.4 mmol) in anhydrous THF (3 ml) was added portionwise to a solution of **5** (1.0 g, 4.4 mmol), triphenylphosphine (1.2 g, 4.4 mmol), and phthalimide (0.65 g, 4.4 mmol) in THF (20 ml) at 0°C. The mixture was stirred at room temperature for 15 h and concentrated to dryness. The residue was dissolved in $CHCl_3$ and washed successively with water and brine. The solvent was evaporated to leave a solid, which was recrystallized from CH_3OH to give 1.5 g (96%) of **6**, mp 151—152°C. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (1H, t-like, *J* =

11.0, 3-H_{ax}), 2.21 (1H, t, *J* = 10.0, 5-H_{ax}), 2.57 (1H, d, *J* = 11.0, 5-H_{eq}), 2.78 (1H, d, *J* = 10.0, 3-H_{eq}), 3.3—3.7 (3H, m, $C\underline{H}_2C_6H_4F$, 2-H), 3.8—4.0 (2H, m), 6.95—7.1 (2H, m, arom H), 7.2—7.4 (2H, m, arom H), 7.67—7.8 (2H, m, arom H), 7.8—7.93 (2H, m, arom H). SIMS *m/z*: 357 (MH^+), 313, 208, 136, 109. IR (KBr) ν cm^{-1}: 1755, 1700 [$N(CO)_2$]. *Anal.* Calcd for $C_{20}H_{17}D_2FN_2O_3$: C, 67.40; H, 4.81; D, 1.13; F, 5.33; N, 7.86. Found: C, 67.41; H, 4.70; D, 1.07; F, 5.50; N, 7.83.

[2-$^2H_2$]-2-(Aminomethyl)-4-(4-fluorobenzyl)morpholine (7) The mixture of **6** (1.5 mmol), 100% hydrazine monohydrate (0.32 g, 6.4 mmol), and C_2H_5OH (15 ml) was heated to reflux for 4 h and cooled to room temperature. After the reaction mixture was diluted with $CHCl_3$, the insoluble materials were filtered off. The filtrate was washed successively with a small amount of water and brine. The solvent was evaporated to leave 0.92 g of **7** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (2H, br. s, NH_2), 1.85 (1H, dd, *J* = 10.0, 11.3, 3-H_{ax}), 2.15 (1H, dd, *J* = 3.5, 11.3, 5-H_{ax}), 2.58—2.76 (2H, m), 3.45 (2H, s, $C\underline{H}_2C_6H_4F$), 3.49 (1H, dd, *J* = 2.0, 10.0, 2-H), 3.67 (1H, dt, *J* = 2.5, 11.3, 6-H_{ax}), 3.87 (1H, ddd, *J* = 1.5, 3.5, 11.3, 6-H_{eq}), 6.92—7.07 (2H, m, arom H), 7.20—7.36 (2H, m, arom H). SIMS *m/z*: 227 (MH^+), 194, 109.

[$^2H_2$]-Mosapride citrate The mixture of 4-amino-5-chloro-2-ethoxybenzoic acid [1] (0.86 g, 4.0 mmol), **7** (0.9 g, 4.0 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.84 g, 4.4 mmol), CH_2Cl_2 (30 ml) was stirred at room temperature for 4 h. The reaction mixture was washed successively with water, 10% aqueous NaOH, water, and brine. The solvent was evaporated to give a pale yellow oil, which was chromatographed on silica gel with $CHCl_3/CH_3OH$ = 12/1 to furnish 1.6 g (93%) of [$^2H_2$]-mosapride as a colorless oil. Mosapride was converted to the citrate in the usual manner. Mp 131.5—132.5°C (CH_3OH—C_2H_5OH). ^{1}H-NMR (DMSO-d_6) δ: 1.38 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$), 1.96 (1H, t-like, *J* = 11.0, 3-H_{ax}), 2.15 (1H, dt, *J* = 2.0, 11.0, 5-H_{ax}), 2.64 (2H, d, *J* = 15.5, citric acid), 2.73 (2H, *J* = 15.5, citric acid), 3.15—3.65 (2H, m), 3.54 (2H, s, $C\underline{H}_2C_6H_4F$), 3.84 (1H, d, *J* = 11.5, 6-H), 4.05 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$), 5.94 (2H, s, NH_2), 6.46 (1H, s, arom 3-H), 7.1—7.23 (2H, m, arom H), 7.28—7.4 (2H, m, arom H), 7.70 (1H, s, arom 6-H), 8.04 (1H, s, CONH). SIMS *m/z*: 424 (MH^+). IR (KBr) ν cm^{-1}: 3360, 1720, 1630, 1580, 1540. *Anal.* Calcd for $C_{21}H_{23}ClD_2FN_3O_3 \cdot C_6H_8O_7$: C, 52.64; H, 5.07; Cl, 5.75; D, 0.65; F, 3.08; N, 6.82. Found: C, 52.39; H, 4.99; Cl, 5.52; D, 0.84; F, 3.08; N, 6.75.

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