

Synthesis and Biological Activities of Metabolites of Mosapride, a New Gastroprokinetic Agent

Shiro KATO,* Toshiya MORIE, and Naoyuki YOSHIDA

Exploratory Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan. Received October 24, 1994; accepted December 8, 1994

In order to confirm the proposed structures of two metabolites **3** and **4** of the gastroprokinetic agent mosapride [4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide, **2**], the compounds were synthesized and their biological activity was examined. The structures of the metabolites were confirmed by means of comparison with the synthetic compounds. The serotonin 5-HT₄ receptor agonistic activities of the metabolites were found to be less than that of mosapride.

Key words mosapride; gastroprokinetic activity; metabolite; 4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide; serotonin 5-HT₄ receptor agonistic activity

We have previously reported the synthesis of 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxybenzamide (**1**) and its derivatives as potential gastroprokinetic agents without dopamine D₂ receptor antagonistic activity.¹⁾ Among them, 4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide (**2**, mosapride) was found to show the most potent gastroprokinetic activity and is presently under clinical study.²⁾ During the course of the metabolic studies of mosapride, two major metabolites were isolated from rat urine, and their structures were proposed to be the des-4-fluorobenzylated mosapride **3** and its oxo analogue **4** (Chart 1) on the basis of their MS and ¹H-NMR spectra.³⁾ The metabolites **3** and **4** were detected in the plasma and/or urine of mice, rats, dogs and/or monkeys, and the metabolite **3** has also been found in human plasma.⁴⁾

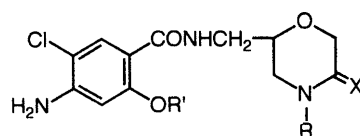
The present study was undertaken to confirm the structures of the two metabolites by chemical synthesis and to compare their biological activity with that of mosapride (**2**).

Synthesis of the Des-4-fluorobenzylated Mosapride 3
For the mild and selective *N*-debenzylation of tertiary amines, α -chloroethyl chloroformate is useful.⁵⁾ Thus, *N*-debenzylation of **2** using this reagent was first attempted. The treatment of **2** with α -chloroethyl chloroformate in 1,2-dichloroethane at 80 °C, followed by the decomposition of the resulting *N*-carbamate by MeOH gave a complex mixture, presumably because of the existence of the 4-amino group. We then tried the hydrogenolysis of **2**. Hydrogenation of **2** with 10% palladium-on-carbon in a mixture of 10% aqueous EtOH and acetic acid (AcOH) at ca. 50 °C caused not only debenzylation but also removal of the chlorine atom, thereby affording 4-amino-2-ethoxy-*N*-(2-morpholinylmethyl)benzamide (**5**) in an excellent yield. In this reaction, the dechlorination was faster than the debenzylation, and without acetic acid as a cosolvent the debenzylation was very slow. The reaction of **5** with acetic anhydride, followed by the chlorination of the resulting diacetyl derivative **6** with *N*-chlorosuccinimide (NCS) produced *N*-[(4-acetyl-2-morpholinyl)methyl]-4-(acetylamino)-5-chloro-2-ethoxybenzamide (**7**) as the precursor **3** of in a good yield. Compound **7** was finally hydrolyzed with 10% HCl to give compound **3** as its

hydrochloride (Chart 2).

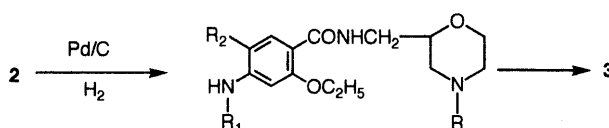
This synthetic compound was identical with the proposed metabolite **3**, on the basis of the MS, ¹H-NMR, and HPLC comparisons.

Synthesis of the Oxidized Metabolite 4 The synthetic route to the metabolite **4** from *N*-(2,3-epoxypropyl)phthalimide (**8**) via the amine **14** is shown in Chart 3. The reaction of **8** with dibenzylamine without solvent afforded the 2-aminoethanol derivative **9** in an excellent yield. The removal of the phthaloyl group of **9** by employing hydrazine afforded 1-amino-3-(dibenzylamino)-2-propanol (**10**) in a poor yield. On the other hand, the treatment of **9** with concentrated HCl gave the aminopropanol **10** in 84% yield. The ring closure reaction of **10** was achieved by using a method previously described⁶⁾; **10** was allowed to react with chloroacetyl chloride in a mixture of CHCl₃



- 1: R = C₆H₅CH₂, R' = CH₃, X = H₂
- 2: R = 4-FC₆H₄CH₂, R' = C₂H₅, X = H₂
(mosapride)
- 3: R = H, R' = C₂H₅, X = H₂
- 4: R = H, R' = C₂H₅, X = O

Chart 1



- 5: R = R₁ = R₂ = H
- 6: R = R₁ = COCH₃, R₂ = H
- 7: R = R₁ = COCH₃, R₂ = Cl

Chart 2

* To whom correspondence should be addressed.

consumed (ca. 4 h). The catalyst was filtered off, and the filtrate was concentrated to dryness. The residual oil was dissolved in water and then basified with 10% NaOH. The resulting precipitates were collected by filtration, washed with water, and dried to give 6.2 g (94%) of **5**, mp 209–210 °C (MeOH). ¹H-NMR [dimethyl sulfoxide (DMSO)-*d*₆] δ: 1.41 (3H, t, *J* = 7.0, OCH₂CH₃), 2.3–3.8 (10H, m), 4.05 (2H, q, *J* = 7.0, OCH₂CH₃), 5.70 (2H, s, NH₂), 6.17 (1H, dd, *J* = 2.0, 8.5, arom. 5-H), 6.21 (1H, d, *J* = 2.0, arom. 3-H), 8.05 (1H, d, *J* = 8.5, arom. 6-H), 8.08 (1H, brt, *J* = 5.5, CONH). SIMS *m/z*: 280 (MH⁺), 206. IR ν_{cm}⁻¹: 3360, 3150, 1650. Anal. Calcd for C₁₄H₂₁N₃O₃: C, 60.20; H, 7.58; N, 15.04. Found: C, 60.08; H, 7.67; N, 14.75.

***N*-[4-(Acetyl-2-morpholinyl)methyl]-4-(acetyl-amino)-2-ethoxybenzamide (6)** A mixture of **5** (4.0 g, 14 mmol), acetic anhydride (3.2 g, 31 mmol), MeOH (200 ml), and CHCl₃ (50 ml) was stirred at room temperature for 4 h. The solvent was evaporated, then the residue was taken up in CHCl₃ and the solution was washed successively with 10% NaOH, water, and brine. The solvent was evaporated to give a solid, which was recrystallized from iso-PrOH-*n*-hexane to afford 4.7 g (90%) of **6**, mp 154–156 °C. ¹H-NMR (CDCl₃) δ: 1.50 (3H, t, *J* = 7.0, OCH₂CH₃), 2.09 (3H, s, NCOCH₃), 2.19 (3H, s, NHCOCCH₃), 3.35–4.05 (9H, m), 4.19 (2H, q, *J* = 7.0, OCH₂CH₃), 6.77 (1H, dd, *J* = 8.5, 2.0, arom. 5-H), 7.84 (1H, d, *J* = 2.0, arom. 3-H), 8.02 (1H, brs, NHCO), 8.09 (1H, d, *J* = 8.5, arom. 6-H), 8.43 (1H, brs, CONH). EIMS *m/z*: 363 (M⁺), 320 (M⁺ – COCH₃). IR ν_{cm}⁻¹: 3370, 3290, 1680, 1620. Anal. Calcd for C₁₈H₂₅N₃O₅: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.24; H, 6.99; N, 11.47.

***N*-[4-(Acetyl-2-morpholinyl)methyl]-4-(acetyl-amino)-5-chloro-2-ethoxybenzamide (7)** A solution of **6** (60.0 g, 0.17 mol) and NCS (24.3 g, 0.18 mol) in *N,N*-dimethylformamide (DMF, 300 ml) was heated at 70 °C for 1 h. The reaction mixture was concentrated to dryness. The residue was triturated with water, and the resulting precipitates were collected by filtration and then recrystallized from MeOH to give 59.9 g (91%) of **7**, mp 204–205 °C. ¹H-NMR (CDCl₃) δ: 1.52 (3H, t, *J* = 7.0, OCH₂CH₃), 2.10 (3H, s, NCOCH₃), 2.26 (3H, s, NHCOCCH₃), 2.5–4.05 (9H, m), 4.22 (2H, q, *J* = 7.0, OCH₂CH₃), 7.78 (1H, br s, NHCO), 8.22 (1H, s, arom. 3-H), 8.30 (1H, s, arom. 6-H), 8.37 (1H, brs, CONH). CIMS *m/z*: 398 (MH⁺), 354 (M⁺ – COCH₃), 240. IR ν_{cm}⁻¹: 3380, 3260, 1690, 1665, 1635. Anal. Calcd for C₁₈H₂₄ClN₃O₅: C, 54.34; H, 6.08; Cl, 8.91; N, 10.56. Found: C, 54.15; H, 6.05; Cl, 9.07; N, 10.49.

4-Amino-5-chloro-2-ethoxy-*N*-(2-morpholinylmethyl)benzamide Hydrochloride (3) A suspension of **7** (25.0 g, 63 mmol) in 10% HCl (170 ml) was heated to reflux for 3 h and then cooled to ca. 5 °C. The resulting precipitates were collected by filtration and recrystallized from EtOH to give 16.3 g (83%) of **3** as slightly hygroscopic crystals, mp 220–222 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.40 (3H, t, *J* = 7.0, OCH₂CH₃), 2.76 (1H, t-like, *J* = 12.0, 3-H_{ax}), 2.95 (1H, td, *J* = 12.0, 4.0, 5-H_{ax}), 3.1–4.1 (7H, m), 3.3 (s, H₂O), 4.08 (2H, q, *J* = 7.0, OCH₂CH₃), 5.99 (2H, s, NH₂), 6.49 (1H, s, arom. 3-H), 7.70 (1H, s, arom. 6-H), 8.09 (1H, t, *J* = 5.5, CONH), 9.45 (2H, brs, NH₂⁺Cl⁻). SIMS *m/z*: 314 (MH⁺). IR ν_{cm}⁻¹: 3360, 1625. Anal. Calcd for C₁₄H₂₀ClN₃O₃·HCl·1/4H₂O: C, 47.40; H, 6.11; Cl, 19.99; N, 11.84. Found: C, 47.35; H, 6.06; Cl, 19.80; N, 11.73.

1-(Dibenzylamino)-3-phthalimido-2-propanol (9) A mixture of 98% *N*-(2,3-epoxypropyl)phthalimide (**8**, 149.4 g, 0.72 mol) and dibenzylamine (145.2 g, 0.74 mol) was heated at 80 °C for 20 h and then cooled to room temperature. The resulting solid was recrystallized from EtOH to give 284.3 g (95%) of **9**, mp 115–117 °C. ¹H-NMR (CDCl₃) δ: 1.58 (1H, s, OH), 2.56 (2H, d, *J* = 6.5, (PhCH₂)₂NCH₂), 3.45 (2H, d, *J* = 13.5, PhCH₂ × 2), 3.59 (1H, d, *J* = 7.0, CH₂N(CO)₂), 3.66 (1H, d, *J* = 7.0, CH₂N(CO)₂), 3.74 (2H, d, *J* = 13.5, PhCH₂ × 2), 4.05 (1H, m), 7.15–7.45 (10H, m), 7.65–7.8, 7.8–7.9 (4H, m). SIMS *m/z*: 401 (MH⁺), 210 [CH₂N(CH₂Ph)₂]⁺. IR ν_{cm}⁻¹: 3450, 1695. Anal. Calcd for C₂₅H₂₄N₂O₃: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.76; H, 5.97; N, 6.93.

1-Amino-3-(dibenzylamino)-2-propanol (10) A mixture of **9** (55.9 g, 0.14 mol) and concentrated HCl (300 ml) was heated to reflux for 24 h and then cooled to 0 °C. The resulting precipitates were filtered off, and the filtrate was washed with CHCl₃ and then basified with 30% aqueous NaOH. The resulting precipitates were collected by filtration, washed with water, and recrystallized from toluene-*n*-hexane to give 31.7 g (84%) of **10**, mp 90–92 °C. ¹H-NMR (CDCl₃) δ: 1.95 (3H, brs, NH₂, OH), 2.35–2.8 (4H, m), 3.47 (2H, d, *J* = 13.5, PhCH₂ × 2), 3.77 (2H, d, *J* = 13.5, PhCH₂ × 2), 3.7 (1H, m), 7.15–7.45 (10H, m). CIMS *m/z*: 271 (MH⁺), 210. Anal. Calcd for C₁₇H₂₂N₂O: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.53; H, 8.29; N, 10.29.

1-[(Chloroacetyl)amino]-3-(dibenzylamino)-2-propanol (11) A solu-

tion of chloroacetyl chloride (5.0 g, 44 mmol) in CHCl₂ (20 ml) was added dropwise to a mixture of **10** (10.0 g, 37 mmol), 3% aqueous NaOH (100 ml), and CHCl₃ (80 ml) at such a rate that the temperature did not rise above 5 °C (about 15 min). The mixture was vigorously stirred at the same temperature for 1 h and then at room temperature for an additional 3 h. The organic layer was separated and washed successively with water and brine. The solvent was evaporated to leave a crude oil, which was chromatographed on silica gel with AcOEt:CHCl₃ = 1:1 to give 11.1 g (86%) of **11** as an oil. ¹H-NMR (CDCl₃) δ: 1.6 (1H, brs, OH), 2.48 (2H, d, *J* = 6.5, (PhCH₂)₂NCH₂), 3.14 (1H, dt, *J* = 14.0, 6.0, CH₂NH), 3.3–3.7 (2H, m), 3.82 (2H, s, CH₂COCl), 3.90 (2H, d, *J* = 13.5, PhCH₂ × 2), 3.93 (2H, d, *J* = 13.5, PhCH₂ × 2), 6.75 (1H, brs, CONH), 7.15–7.6 (10H, m). SIMS *m/z*: 347 (MH⁺), 210. IR (neat) ν_{cm}⁻¹: 3400, 3300, 1665.

2-[(Dibenzylamino)methyl]-5-oxomorpholine (12) A solution of **11** (10.5 g, 30 mmol) and potassium *tert*-butoxide (4.1 g, 37 mmol) in EtOH (200 ml) was heated to reflux for 10 h. The reaction mixture was concentrated to give a residue, which was chromatographed on silica gel with AcOEt:*n*-hexane = 1:1 to 2:1 to afford 1-[(ethoxyacetyl)amino]-3-(dibenzylamino)-2-propanol (**13**, 2.4 g, 22%) as an oil and **12** (5.0 g, 53%) as a solid in that order. Compound **12** was recrystallized from toluene.

Compound **12**: mp 111–112 °C. ¹H-NMR (CDCl₃) δ: 2.58 (1H, dd, *J* = 6.5, 13.5, 3-H_{ax}), 2.68 (1H, dd, *J* = 5.5, 13.5, 3-H_{eq}), 3.08 (1H, dd, *J* = 10.5, 12.0, CH₂N), 3.30 (1H, dt, *J* = 12.0, 3.5, CH₂N(CH₂Ph)₂), 3.52 (2H, d, *J* = 13.5, CH₂Ph × 2), 3.75 (2H, d, *J* = 13.5, CH₂Ph × 2), 3.7 (1H, m, 2-H), 4.04 (1H, d, *J* = 17.0, 6-H_{ax}), 4.21 (1H, d, *J* = 17.0, 6-H_{eq}), 6.15 (1H, brs, NH), 7.1–7.4 (10H, m). SIMS *m/z*: 311 (MH⁺), 210. IR ν_{cm}⁻¹: 3175, 3060, 2850, 2820, 1680. Anal. Calcd for C₁₉H₂₂N₂O₂: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.33; H, 7.19; N, 8.98.

Compound **13**: ¹H-NMR (CDCl₃) δ: 1.17 (3H, t, *J* = 7.0, OCH₂CH₃), 1.6 (1H, brs, OH), 2.48 (2H, d, *J* = 6.5, (PhCH₂)₂NCH₂), 3.12 (1H, dt, *J* = 14.0, 6.0, CH₂NH), 3.2–3.7 (4H, m), 3.80 (2H, s, OCH₂CO), 3.83 (2H, d, *J* = 13.5, PhCH₂ × 2), 3.85 (2H, d, *J* = 13.5, PhCH₂ × 2), 6.82 (1H, brs, CONH), 7.1–7.5 (10H, m). SIMS *m/z*: 357 (MH⁺), 210. IR (neat) ν_{cm}⁻¹: 3400, 3300, 1665.

2-(Aminomethyl)-5-oxomorpholine (14) A solution of **12** (3.3 g, 11 mmol) in EtOH (150 ml) was hydrogenated over 10% palladium hydroxide-on-carbon (3.0 g) at room temperature and atmospheric pressure. After the theoretical amount of hydrogen was absorbed, the catalyst was filtered off. Then ca. 30% HCl in EtOH (1.9 g) was added to the filtrate, and the solvent was evaporated. The residual solid was recrystallized from iso-PrOH-Et₂O to give 1.4 g (79%) of **14**·HCl, mp 275–276 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.75–3.45 (4H, m), 4.0 (1H, m), 3.99 (1H, d, *J* = 16.0, 6-H_{ax}), 4.15 (1H, d, *J* = 16.0, 6-H_{eq}), 8.10 (1H, d, *J* = 4.0, CONH). EIMS *m/z*: 130 (M⁺), 101. IR ν_{cm}⁻¹: 3170, 1650. Anal. Calcd for C₅H₁₀N₂O₂·HCl: C, 36.05; H, 6.66; Cl, 21.28; N, 16.81. Found: C, 36.10; H, 6.67; Cl, 21.19; N, 16.66.

4-(Acetyl-amino)-5-chloro-2-ethoxy-*N*-(5-oxo-2-morpholinyl)methyl-benzamide (16) A mixture of 4-(acetyl-amino)-5-chloro-2-ethoxybenzoic acid^{2a)} (1.7 g, 6.6 mmol), thionyl chloride (2.4 g, 20 mmol), DMF (2 drops), and toluene (70 ml) was heated at 80 °C for 2 h. The solvent was evaporated, and the residue including 4-(acetyl-amino)-5-chloro-2-ethoxybenzoyl chloride (**15**) was dissolved in CHCl₃ (50 ml). To this solution was added dropwise a mixture of **14**·HCl (1.1 g, 6.6 mmol), Et₃N (2.8 g, 28 mmol), and CHCl₃ (100 ml) at 5 °C. The reaction mixture was stirred at room temperature for 5 h, then the solvent was evaporated, and the residue was triturated with water. The resulting precipitates were collected by filtration and recrystallized from MeOH to afford 1.7 g (70%) of **16**, mp 249–251 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.40 (3H, t, *J* = 7.0, OCH₂CH₃), 2.15 (3H, s, COCH₃), 3.05–3.45 (3H, m), 3.5 (1H, m), 3.8 (1H, m), 4.07 (2H, s, 6-H), 4.12 (2H, q, *J* = 7.0, OCH₂CH₃), 7.79 (1H, s, arom. 3-H), 7.84 (1H, s, arom. 6-H), 8.01 (1H, d, *J* = 4.0, 4-NH), 8.30 (1H, t, *J* = 5.0, CONH), 9.56 (1H, s, NHCOCCH₃). SIMS *m/z*: 370 (MH⁺), 240. IR ν_{cm}⁻¹: 3360, 3260, 1668, 1628. Anal. Calcd for C₁₆H₂₀ClN₃O₅: C, 51.97; H, 5.45; Cl, 9.59; N, 11.36. Found: C, 51.73; H, 5.39; Cl, 9.30; N, 11.24.

4-Amino-5-chloro-2-ethoxy-*N*-(5-oxo-2-morpholinyl)methyl-benzamide (4) A mixture of **16** (1.1 g, 3.0 mmol), ca. 30% HCl in EtOH (20 ml), and 10% aqueous EtOH (50 ml) was heated to reflux for 1.5 h. The solvent was evaporated, and ca. 28% NH₄OH (10 ml) was added to the residue. The resulting precipitates were collected by filtration, washed with water, and recrystallized from MeOH to give 0.5 g (51%) of **4**, mp 212–214 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.39 (3H, t, *J* = 7.0,

OCH₂CH₃), 3.0–3.4 (3H, m), 3.6 (1H, m), 3.8 (1H, m), 4.05 (2H, s, 6-H), 4.07 (2H, q, $J=7.0$, OCH₂CH₃), 5.96 (2H, s, NH₂), 6.48 (1H, s, arom. 3-H), 7.71 (1H, s, arom. 6-H), 7.99 (1H, d, $J=4.0$, 4-NH), 8.10 (1H, t, $J=5.0$, CONH). SIMS m/z : 328 (MH⁺), 198. IR $\nu_{\text{cm}^{-1}}$: 3345, 3340, 3200, 1670, 1620. Anal. Calcd for C₁₄H₁₈ClN₃O₄: C, 51.30; H, 5.54; Cl, 10.82; N, 12.82. Found: C, 51.15; H, 5.50; Cl, 10.58; N, 12.63.

B) A solution of 4-amino-5-chloro-2-ethoxybenzoic acid^{2a)} (1.0 g, 4.6 mmol) and *N,N'*-carbonyldiimidazole (0.83 g, 5.6 mmol) in tetrahydrofuran (THF, 50 ml) was stirred at room temperature for 2 h. This reaction mixture was added to a suspension of **14**·HCl (0.77 g, 4.8 mmol), Et₃N (0.7 g, 5.9 mmol), THF (20 ml), and DMF (5 ml) at room temperature. The whole was stirred at room temperature for 18 h. The solvent was evaporated, and the residue was triturated with 10% HCl. The resulting precipitates were collected by filtration, washed with water and dried to afford a solid, which was recrystallized from MeOH to give 1.0 g (77%) of **4**. This compound was confirmed to be identical with the sample obtained from A), on the basis of TLC, IR, ¹H-NMR comparisons.

Biological Method Male guinea pigs of the Hartley strain (Nihon Animals Co.) weighing 300–500 g were used. The guinea pigs were killed by a blow on the head. The distal ileum was removed at least 10 cm proximal to the cecum, and the longitudinal muscles with the mesenteric plexus (2–3 cm) were prepared according to the method of Craig and Clarke.⁸⁾ Each preparation was mounted between two parallel platinum wire electrodes in a 10 cm organ bath containing Krebs–Henseleit solution (NaCl 118 mM, KCl 4.75 mM, CaCl₂ 2.5 mM, KH₂PO₄ 1.2 mM, MgSO₄ 1.2 mM, NaHCO₃ 2.5 mM, and glucose 10 mM). The solution was maintained at 37°C and saturated with 95% O₂ and 5% CO₂. A resting tension of 1 g was applied, and the response was recorded isometrically through a force displacement transducer. The strips were equilibrated for 60 min. The strips were then stimulated through two parallel platinum electrodes with square-wave pulses (1 ms duration, supramaximal voltage, 0.2 Hz frequency) from an electrical stimulator. Therefore, the strips were treated with phenoxybenzamine (3×10^{-7} M) for 30 min. After washing out of the phenoxybenzamine several times, the stimulus voltage was adjusted to a submaximal voltage inducing approximately 50% of the maximal contractile response. Mosapride (**2**, as its citrate) and the

metabolites **3** and **4**, dissolved in deionized water containing 1% lactic acid, were cumulatively applied.

Acknowledgment We thank Dr. J. Matsumoto for his encouragement throughout this work. We are grateful to the staff of the Analytical Chemistry Division of the Laboratories for elemental analyses and spectral measurements.

References

- 1) Kato S., Morie T., Hino K., Kon T., Naruto S., Yoshida N., Karasawa T., Matsumoto J., *J. Med. Chem.*, **33**, 1406 (1990).
- 2) a) Kato S., Morie T., Kon T., Yoshida N., Karasawa T., Matsumoto J., *ibid.*, **34**, 616 (1991); b) Yoshida N., Kato S., Ito T., *Drugs Future*, **18**, 513 (1993).
- 3) Matsumoto S., Yoshida K., Itokawa A., Tagawa M., Fujii T., Miyazaki H., Sekine Y., *Arzeim.-Forsch./Drug Res.*, **43**, 1095 (1993).
- 4) Sakashita M., Yamaguchi T., Miyazaki H., Sekine Y., Nomiyama T., Tanaka S., Miwa T., Harasawa S., *Arzeim.-Forsch./Drug Res.*, **43**, 867 (1993).
- 5) a) Olofson R. A., Martz J. T., Senet J.-P., Piteau M., Malfroot T., *J. Org. Chem.*, **49**, 2081 (1984); b) DeShong P., Kell D. A., *Tetrahedron Lett.*, **27**, 3979 (1986); c) Olofson R. A., *Pure Appl. Chem.*, **60**, 1715 (1988); d) Gubert S., Braojos C., Sacristan A., Ortiz J. A., *Synthesis*, **1991**, 318; e) Yang B. V., O'Rourke D., Li J., *Synlett*, **1993**, 195.
- 6) a) Greenwood D. T., Mallion K. B., Todd A. H., Turner R. W., *J. Med. Chem.*, **18**, 573 (1975); b) Picciòla G., *Boll. Chim. Farm.*, **119**, 141 (1980); c) Brown G. R., Foubister A. J., Wright B., *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2577.
- 7) a) Pearlman W. M., *Tetrahedron Lett.*, **1967**, 1663; b) Yoshida K., Nakajima S., Wakamatsu T., Ban Y., Shibasaki M., *Heterocycles*, **27**, 1167 (1988).
- 8) Craig D. A., Clarke D. C., *J. Pharmacol. Exp. Ther.*, **252**, 1378 (1990).
- 9) Yoshida N., Omoya H., Kato S., Ito T., *Arzeim.-Forsch./Drug Res.*, **43**, 1078 (1993).