Synthesis of Ketoconazole Derivatives

Jae Chun Ryu, Kwang Jae Lee, and Sang Hee Lee*

Department of Chemistry, Kunsan National University, Kunsan, Chonbuk 573-701, Korea
Received January 20, 2003

For the drug master file (DMF) of ketoconazole, four impurities (**1-4**) contained in ketoconazole were synthesized. During the synthesis of **2**, a new synthetic method of 1,4-dihydropyrazine was established. To oxidize the aminoalcohol (**2j**) to the aminal (**2j-1**), the standard Swern oxidation condition was modified to mask the nucleophilicity of the amino group temporarily using one equivalent of acetic acid. Derivative **3** was synthesized *via* regioselective bromination at the 2 position of the 4-aminophenol derivative (**3a**) using Br_2 in the presence of *p*-TsOH. The etherification of aryl bromide with the phenol derivative (**1f**) was accomplished by a modification of the general Cu-mediated reaction condition using excess **1f** itself as a solvent at elevated temperature (190 °C).

Key Words : Drug master file (DMF), Ketoconazole, Impurities, 1,4-Dihydropyrazine

Introduction

In USA and European countries, a system of drug master files (DMF)[1,2] has been established to protect the confidential detailed information of third-party suppliers of a raw material. A DMF contains all the relevant details concerning the facilities, processes or articles used in the manufacturing, processing, packaging, and storing of human drugs or medical devices, and this is given to the authorities, *e.g.*, the FDA. Since dependency on imports from various countries of the raw materials is increasing, a DMF system will be established in Korea within the next few years.

Ketoconazole[3-7] is a potent, orally active, broad-spectrum antifungal agent, which was recently developed from imidazole derivatives. To export ketoconazole, advanced countries require a DMF that includes spectral data on all of the impurities that ketoconazole contains. As ketoconazole contains four impurities (less than 1%) that are difficult to isolate,[8] this study established synthetic procedures for the four impurities to obtain their spectral data.

Experimental Section

NMR spectra was recorded on a JEOL-ECP 500 spectrometer (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz), and chemical shifts was reported in ppm relative to TMS (δ 0.00) as a internal standard. The hydrogenation was performed using a PARR-3911 EA hydrogenation apparatus. Flash column chromotography was carried out using silicagel Merck 60 (230-400 mesh). Thin layer chromatography (TLC) was performed on Merck kieselgel 60, F254. Most chemicals were purchased from Aldrich and used without

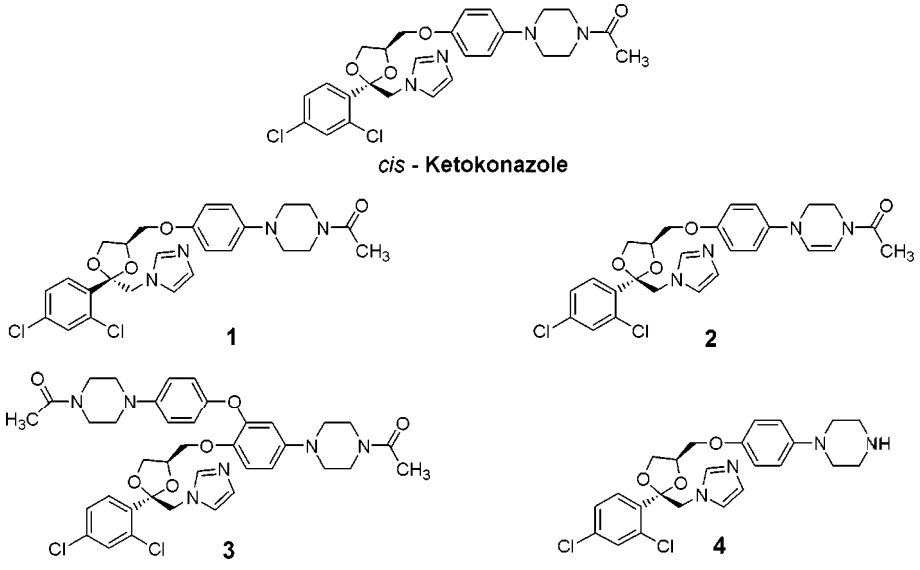


Figure 1. Structures of *cis*-ketoconazole and its derivatives.

*To whom all correspondence should be addressed. Phone: +82-63-469-4578, Fax: +82-63-469-4578, E-mail: leesh@kunsan.ac.kr

purification. *cis*-Ketokonazole and some intermediates (**1a**, **1f**, **2n**) were provided by Choongwae Pharma Corp (Korea). General workup procedure was followed that the reaction mixture was quenched by adding of water. The mixture was extracted with ethyl acetate, and the organic phase was dried over anhydrous Na_2SO_4 and concentrated.

2-Bromomethyl-2-(2,4-dichlorophenyl)-[1,3]-dioxolan-4-ylmethylbenzonate (1b). A solution of **1a** (6 g, 13.45 mmol) and dried *p*-TsOH (0.116 g, 0.67 mmol) in dried toluene (50 mL) was refluxed at 150 °C for 10 h. After workup, the residue was purified by column chromatography (SiO_2, *n*-hexane/toluene = 3/1) to give **1b** (2.07 g, 35%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 3.84-3.90 (m, 3H), 4.24 (dd, J = 11.9, 3.7 Hz, 1H), 4.43 (dd, J = 8.3, 6.5 Hz, 1H), 4.54 (dd, J = 12.4, 4.2 Hz, 1H), 4.76 (m, 1H), 7.13-7.70 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 36.8, 62.9, 67.5, 108.5, 127.5, 128.9, 130.0, 130.1, 131.7, 133.6, 133.8, 136.0.

2-(2,4-Dichlorophenyl)-2-imidazol-1-ylmethyl-[1,3]-dioxolan-4-ylmethylbenzonate (1c). A solution of **1b** (2.07 g, 4.64 mmol) and imidazole (2.52 g, 37.1 mmol) in dried pyrrolidinone (20 mL) was refluxed for 8 h . After workup, the residue was dissolved in diethyl ether and the resulting solid was filtered off. After addition of conc. HNO_3 (1 eq) to the filtrate, the resulting **1c** · HNO_3 was collected as a white solid (2.2 g, 96%). ^{1}H NMR ($CDCl_3$): δ3.73 (dd, J = 7.4, 7.4 Hz, 1H), 3.90 (dd, J = 8.2, 6.4 Hz, 1H), 4.08 (m, 1H), 4.12 (dd, J = 11.9, 4.0 Hz, 1H), 4.38 (s, 2H), 4.44 (dd, J = 12.0, 3.7 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 1H), 7.31-7.35 (m, 2H), 7.51-7.56 (m, 2H), 7.68 (d, J = 8.3 Hz, 2H).

2-(2,4-Dichlorophenyl)-2-imidazol-1-ylmethyl-[1,3]-dioxolan-4-ylmethyltoluene-4-sulfonate (1e). A solution of **1c** (1.67 g, 3.36 mmol) and NaOH (0.34 g, 8.42 mmol) in CH_3OH was stirred at room temperature for 40 min. After evaporation of methanol, water was added to the mixture to precipitate **1d** (0.86 g, 78%). To a solution of **1d** (0.86 g, 2.61 mmol) and triethylamine (0.73 mL, 5.23 mmol) in dried CH_2Cl_2 (15 mL) was added *p*-TsCl (0.65 g, 3.4 mmol) portion wise at 0 °C, and stirred at room temperature for 1h. After workup, the residue was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 15/1) to obtain **1e** as an oil (1.14 g, 70%). ^{1}H NMR ($CDCl_3$): δ 3.47 (m, 2H), 3.59 (dd, J = 6.9, 6.9 Hz, 2H), 3.84 (m, 2H), 4.37 (dd, J = 14.6, 14.6 Hz, 2H), 6.96 (s, 2H), 7.20 (dd, J = 8.3, 1.8 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.57 (d, J = 8.3Hz, 1H).

1-(4-4-[2-(2,4-Dichlorophenyl)-2-imidazol-1-ylmethyl-[1,3]-dioxolan-4-ylmethoxy]-phenylpiperazin-1-yl)ethanone (1). A solution of **1f** (0.35 g, 1.56 mmol), 60% sodium hydride (70 mg, 1.71 mmol), and **1e** (0.688 g, 1.42 mmol) in dried DMSO (10 mL) was stirred at 60 °C for 1 h. After workup, the residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 20/1) to give **1** (0.61 g, 82%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.1 (s, 3H), 3.01 (m, 4H), 3.5(d, J = 4.8 Hz, 2H), 3.74 (m, 4H), 3.86 (m, 2H), 4.12 (m, 1H), 4.37 (dd, J = 14.4, 14.8 Hz, 2H), 6.6 (d, J = 8.8 Hz, 2H), 6.8 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 5.2 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.49 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.3, 41.4, 46.3, 50.6, 51, 67.4, 67.5, 76, 76.6, 108, 115.1, 118.6, 126.94, 126.99, 129.3, 130.9, 132.7, 135.3, 135.52, 145.6, 152.7, 168.8. EIMS: m/z (%) 59 (100), 70 (21), 82 (25), 120 (37), 173 (49), 219 (57), 458 (85), 471 (82), 530 (56, M$^+$). HRMS (EI, M$^+$): Calcd for $C_{26}H_{28}Cl_2N_4O_3$ 530.1488, found 530.1491.

4-Aminophenyl acetate (2c). A solution of 4-nitrophenol **2a** (1.0 g, 7.19 mmol) and triethylamine (1.52 mL, 10.8 mmol) in CH_2Cl_2 (5 mL) was added to acetic anhydride (0.8 mL, 7.91 mmol) drop wise under ice bath. The mixture was stirred at room temperature for 15 min, and then CH_3OH was added to destroy the excess acetic anhydride followed by additional stirring of 30 min. After usual work up, **2b** (1.25 g, 6.88mmol) and 10% Pd/C (0.1 g) in CH_2Cl_2 (5 mL) was shaked at room temperature under H_2 (40 psi) for 1 h. The reaction mixture was filtered through celite and the filtrate was concentrated to give crude **2c** (0.97g, 93%). Since **2c** was unstable, it was immediately used in the next step without further purification.

***N,N*-Bis-(2-acetoxyethyl)acetamide (2e)**. To a solution of diethanolamine **2d** (20 g, 190.2 mmol) in pyridine (40 mL) was added acetic anhydride drop wise, and the reaction mixture was stirred for 2 h at 60 °C. After methanolysis of the excess acetic anhydride by adding of methanol (10 mL) and usual workup, the resulting **2e** (43 g, 98%) as a yellow oil was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 3H), 1.79 (s, 3H), 1.87 (s, 3H), 3.34 (m, 4H), 3.94 (m, 4H). ^{13}C NMR ($CDCl_3$): δ20.4, 20.5, 21.1, 45.1, 48.0, 61.6, 61.9, 170.3, 170.5, 171.2.

***N,N*-Bis-(2-hydroxyethyl)acetamide (2f)**. A solution of compound **2e** (44 g, 190 mmol) and NaOH (16 g, 380 mmol) in CH_3OH (50 mL) was stirred at room temperature for 1 h. After workup, the residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 10/1) to give compound **2f** (21 g, 75%) as an oil. ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H), 3.47 (t, J = 5.1 Hz, 2H), 3.51 (t, J = 5.1 Hz, 2H), 3.76 (t, J = 5.5 Hz, 2H), 3.80 (t, J = 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 50.4, 53.2, 60.5, 61.0, 173.2. EIMS: m/z (%) 43 (76), 56 (34), 74 (100), 104 (34), 116 (24), 129 (15), 147 (6, M$^+$).

***N*-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-*N*-(2-hydroxyethyl)acetamide (2g)**. To a solution of **2f** (11 g, 74.76 mmol) and imidazole (9 g, 149.52 mmol) in DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (TBSCl) (12.4 g, 82.24 mmole), and stirred at room temperature for 30min. After workup, the residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 1/1 → CH_2Cl_2/ CH_3OH = 15/1) to give **2g** (7.8 g, 40%) as an oil. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.86 (s, 9H), 2.10 (s, 1.2H), 2.13 (s, 1.8H), 3.43-3.51 (m, 4H), 3.72 (t, J = 5.5 Hz, 3H), 3.84 (t, J = 5.5 Hz, 1H).

***N*-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-*N*-(2-oxoethyl)acetamide (2h)**. To a solution of oxalyl chloride (2.29 mL, 25.70 mmol) and DMSO (3.84 mL, 53.55 mmol) in dried CH_2Cl_2 (30 mL) under N_2 atmosphere were added **2g** (5.6 g, 21.42 mmol) and triethylamine (15.08 mL, 107.10

mmol) at −78 °C, and the reaction mixture was stirred at room temperature for 10min. After workup, **2h** (5.4 g, 97%) as a oil was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 0.03 (s, 9H), 0.86 (s, 6H), 2.19 (s, 3H), 3.49 (t, J = 5.0 Hz, 2H), 3.70 (t, J = 5.0 Hz), 5.25-5.33 (m, 2H), 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −5.5, −3.5, 18.2, 21.2, 25.9, 52.4, 61.7, 171.9, 198.3. EIMS: m/z (%) 43 (100), 58 (18), 130 (29), 146 (28), 160 (30), 202 (20), 259 (3, M$^+$).

***N*-[2-*N*'-(4-Acetoxyphenyl)aminoethyl]-*N*-(2-hydroxyethyl)acetamide (2j)**. A solution of **2h** (5.4 g, 20.82 mmol) and **2c** (4.09 g, 27.06 mmol) in EtOH (20 mL) was shaked under H_2 (40 psi) in the presence of 10% Pd/C (30 mg) for 10h, and then the reaction mixture was filtered through celite. To a resulting crude **2i** in EtOH was added 1 N HCl (33 mmol), and the reaction mixture was stirred at rt for 1h. After workup, the residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 30/1 → 20/1) to give compound **2j** (2.0 g, 34%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 1.3H), 2.16 (s, 1.7H), 2.24 (s, 1.7H), 2.25 (s, 1.3H), 3.29 (t, J = 6.0 Hz, 1H), 3.33 (t, J = 6.0 Hz, 1H), 3.42 (t, J = 5.5 Hz, 1H), 3.52 (m, 2H), 3.59 (t, J = 6.0 Hz, 1H), 3.71 (t, J = 5.1 Hz, 1H), 3.76 (t, J = 5.1 Hz, 1H), 6.57 (m, 2 H), 6.86 (m, 2H).

***N*-Acetyl-*N*'-(4-acetoxyphenyl)-1,2,3,4-tetrahydropyrazine (2l)**. To a solution of oxalyl chloride (0.76 mL, 8.57 mmol) and DMSO (1.28 mL, 17.86 mmol) in dried CH_2Cl_2 (20 mL) under N_2 atmosphere were added **2j** (2 g, 7.14 mmol), acetic acid (0.41 mg, 7.14 mmol) and triethylamine (5 mL, 35.72 mmol) at −78 °C, and the reaction mixture was stirred at room temperature for 10 min. After workup, the residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate/CH_2Cl_2 = 1/1/1) to give **2l** (0.98 g, 53%) as a white solid. ^{1}H NMR (CD_3OD): δ 2.15 (s, 1H), 2.18 (s, 2H), 2.23 (s, 3H), 3.63 (dd, J = 5.5, 5.5 Hz, 1.3H), 3.85 (m, 2H), 6.03 (d, J = 6.5, 0.7H), 6.19 (d, J = 6.8 Hz, 0.7H), 6.26 (d, J = 6.9 Hz, 0.3H), 6.46 (d, J = 6.9 Hz), 6.96-7.01 (m, 4H). ^{13}C NMR (CD_3OD): δ 19.5, 19.6, 19.7, 38.8, 43.7, 44.2, 44.3, 102.7, 113.8, 115.1, 115.2, 122.1, 143.3, 144.4, 167.0, 167.4, 170.3. EIMS: m/z (%) 43 (100), 176 (64), 218 (49), 260 (25, M$^+$).

***N*-Acetyl-*N*'-(4-hydroxyphenyl)-1,4-diydropyrazine (2m)**. To a solution of **2l** (0.47 g, 1.8 mmol) in CH_3OH (5 mL) was added 1 N NaOH (2.0 mmol), and the reaction mixture was stirred at room temperature for 10min. Before extraction of **2m** with ethyl acetate, methanol was evaporated and the reaction mixture was neutralized using phosphate buffer (pH 7). After workup the resulting **2m** as a yellow solid (0.38 g, 97%) was used in the next step without further purification. ^{1}H NMR (CD_3OD): δ 2.13 (s, 1H), 2.16 (s, 2H), 3.56 (m, 1.3H), 3.62 (m, 0.7H), 3.82 (m, 2H), 5.92 (d, J = 6.4 Hz, 0.7H) 6.08 (d, J = 6.9 Hz, 0.7H), 6.14 (d, J = 6.9 Hz, 0.3H), 6.36 (d, J = 6.4 Hz, 0.3H), 6.71-6.74 (m, 2H), 6.81-6.84 (m, 2H). ^{13}C NMR (CD_3OD): δ 19.6, 19.7, 38.8, 43.8, 45.2, 101.2, 102.1, 115.6, 117.1, 118.0, 139.1, 151.6, 167.2. EIMS: m/z (%) 43 (100), 65 (22), 120 (22), 147 (21), 175 (45), 218 (34, M$^+$).

1-Acetyl-4-[4-[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1,2,3,4-tetrahydropyrazine (2). A solution of **2m** (0.37 g, 1.70 mmol), 60% sodium hydride (0.1 g, 2.54 mmol), **2n** (0.9 g, 1.87 mmol) in dried DMSO (10 mL) was stirred at 80 °C for 1h. After workup, the residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 50/1) to give **2** as a yellow solid (0.83 g, 93%). ^{1}H NMR (CD_3OD): δ 2.14 (s, 1H), 2.16 (s, 2H), 3.30 (m, 1H), 3.40 (s, 1H), 3.43 (dd, J = 10.1, 6.0 Hz, 1H), 3.57 (m, 1H), 3.64 (dd, J = 9.7, 5.5 Hz, 1H), 3.73 (dd, J = 8.3, 4.6 Hz, 1H), 3.82 (dd, J = 9.6, 5.1 Hz, 1H), 3.87 (dd, J = 8.3, 6.9 Hz, 1H), 4.34 (m, 1H), 4.57 (d, J = 15.6 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 6.79 (d, J = 9.2 Hz, 2H), 6.9 (m, 3H), 7.08 (s, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.63 (m, 2H). ^{13}C NMR (CD_3OD): δ 19.6, 38.8, 43.7, 44.8, 51.0, 66.9, 67.9, 75.0, 101.8, 102.8, 108.0, 115.3, 116.3, 117.2, 121.6, 126.8, 127.0, 129.9, 130.8, 1332.0, 135.0, 135.5, 140.2, 153.0, 166.8, 167.3. EIMS: m/z (%) 69 (100), 78 (82), 148 (22), 175 (40), 217 (26), 485 (24), 528 (55, M$^+$). HRMS (EI, M$^+$): Calcd for $C_{26}H_{26}Cl_2N_4O_4$ 528.1331, found 528.1339.

***N*-Acetyl-*N*'-(3-bromo-4-acetyloxyphenyl)piperazine (3b)**. To a solution of **1f** (1.0 g, 4.55 mmol) and triethylamine (1.27 mL, 9.1 mmol) in THF (20 mL) was added acetyl chloride (0.39 mL, 5.45 mmol) and the reaction mixture was stirred at room temperature for 30 min. After usual workup, the resulting **3a** (1.19 g, 4.54 mmol) and *p*-TsOH (0.82 g, 4.76 mmol) were dissolved in acetonitrile (10 mL) and a solution of Br_2 (0.76 g, 4.76 mmol) in acetonitrile (1 mL) was added drop wise at 0 °C and then the reaction mixture was stirred at rt for 3 h. After usual workup, the residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 1/4) to give **3b** (1.0 g, 92%) as an oil. ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H), 2.23 (s, 3H), 2.91 (dd, J = 4.7, 4.7 Hz, 2H), 2.94 (dd, J = 5.1, 5.1 Hz, 2H), 3.57 (dd, J = 4.7, 4.7 Hz, 2H), 3.73 (s, 2H), 6.97 (m, 2H), 7.3 (d, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.0, 21.5, 41.7, 46.6, 51.5, 52.1, 120.0, 121.2, 121.5, 127.0, 146.7, 147.8, 169.2, 169.3. EIMS: m/z (%) 148 (50), 212 (67), 259 (100), 297 (15), 340 (5, M-1), 342 (6, M+1).

***N*-Acetyl-*N*'-(3-bromo-4-hydroxyphenyl)piperazine (3c)**. A solution of compound **3b** (0.4 g, 1.12 mmol) and NaOH (44.8 mg, 1.12 mmol) in CH_3OH (5 mL) was stirred at room temperature for 10 min. After workup, the residue was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 10/1) to give compound **3c** (0.32 g, 96%) as a solid. ^{1}H NMR (CD_3OD): δ 2.12 (s, 3H), 2.86 (dd, J = 5.0, 4.6 Hz, 2H), 2.91 (dd, J = 5.0, 4.6 Hz, 2H), 3.65 (dd, J = 5.1, 4.6 Hz, 1H), 3.70 (s, 1H), 6.73 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H).

***N*-Acetyl-*N*'-(4-benzyloxy-3-bromophenyl)piperazine (3d)**. To a solution of compound **3c** (0.3 g, 1.0 mmol) and 60% sodium hydride (60 mg, 1.5 mmol) in DMF was added benzyl bromide (0.12 mL, 1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min. After workup, the resulting **3d** (0.377 g, 97%) as a yellow solid was used in the next step without further purification. ^{1}H

NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.90 (m, 4H), 3.59 (t, J = 4.1 Hz, 4H), 4.99 (s, 2H), 6.86-6.94 (m, 2H), 7.24-7.40 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 14.3, 21.1, 21.4, 41.5, 41.7, 46.1, 46.6, 50.4, 50.8, 51.5, 60.5, 70.5, 107.4, 109.0, 118.5, 119.3, 120.3, 127.6, 128.1, 128.6, 136.5, 136.8, 147.2, 150.8, 151.3, 155.4, 169.0, 169.1, 171.2. EIMS: m/z (%) 79 (100), 108 (100), 297 (22), 299 (17), 388 (11, M-1), 390 (10, M+1).

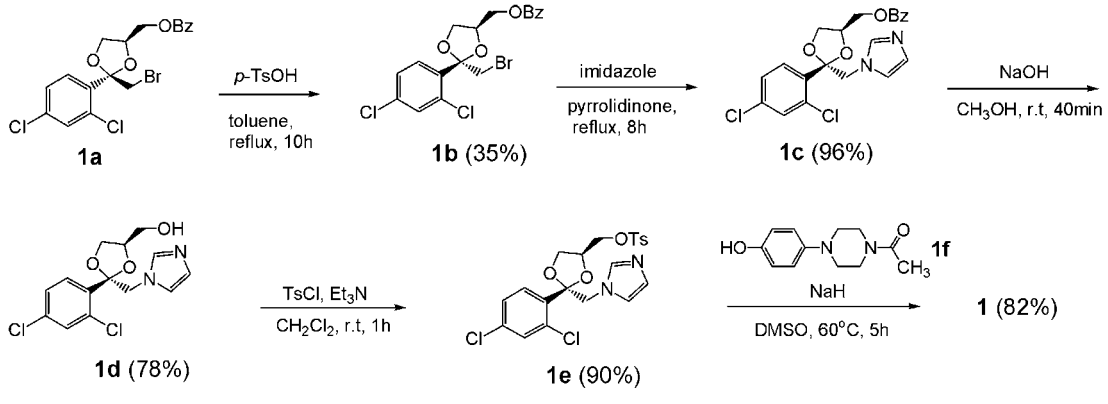
***N*-Acetyl-*N'*-3-[4-(4-acetylpiperazin-1-yl)phenoxy]-4-benzyloxyphenylpiperazine (3f).** **3e** was prepared from a solution of **1f** (23 g, 104.55 mmol) and NaOH (3.76 g, 94.99 mmol) in CH_3OH (60 mL). A mixture of **3d** (10.47 g, 26.92 mmol), **1f** (17.75 g, 80.55 mmol), **3e** (19.54 g, 80.75 mmol) and 50% active Cu (0.68 g, 5.38 mmol) was heated up to 190 °C for 4 h. DMSO (30 mL) was added to the reaction mixture at 150 °C and then the reaction mixture was cooled to room temperature. The mixture was extracted with CH_2Cl_2 and washed with 1 N NaOH to remove excess **1f**. Organic layer was dried, concentrated and purified by column chromatography (SiO_2, CH_2Cl_2/ethyl acetate = 1/3 → CH_2Cl_2/CH_3OH = 20/1) to give compound **3f** (4.97 g, 35%) as a yellow solid. ^1H NMR ($CDCl_3$): δ 2.15 (d, J = 16 Hz, 6H), 3.1 (m, 8H), 3.64 (m, 8H), 4.94 (s, 2H), 6.52 (d, J = 4.2 Hz, 1H), 6.67 (m, 1H), 6.9 (m, 5H), 7.35 (s, 5H). EIMS: m/z (%) 91 (27), 112 (16), 217 (13), 437 (100), 528 (54, M^+).

1-(4-3-[4-(4-Acetylpiperazin-1-yl)phenoxy]-4-[2-(2,4-dichlorophenyl)-2-imidazole-1-ylmethyl-[1,3]-dioxolan-4-ylmethoxy]phenylpiperazin-1-yl)ethanone (3). A solution of **3f** (1.3 g, 2.46 mmol) in acetic acid (10 mL) was stirred under H_2 (15 psi) and 10% Pd/C (0.26 g) at room temperature for 8h, and then the mixture was filtered through celite. The filtrate was concentrated and recrystallized from *n*-hexane-CH_2Cl_2-CH_3OH to obtain **3g** (1.06 g, 98%) as a pale yellow solid. A solution of **3g** (1.06 g, 2.42 mmol), 60% sodium hydride (87 mg, 3.63 mmol), and **2n** (1.167 g, 2.42 mmol) in dried DMSO (10 mL) was stirred at 60 °C for 1 h. After workup, the residue was purified by column chromatography (SiO_2, ethyl acetate → CH_2Cl_2 / CH_3OH = 30/1 → 20/1) to give compound **3** (1.52 g, 95%) as a yellow solid. ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H), 2.14 (s, 3H), 2.98 (m, 4H), 3.1 (m, 4H), 3.2 (m, 1H), 3.63 (m, 5H), 3.78 (dd, J = 4.8, 5.2 Hz, 2H), 3.83 (dd, J = 8.4, 6.0 Hz, 1H), 4.3 (m, 1H), 4.37 (d, J = 14.8 Hz, 1H), 4.48 (d, J = 14.8 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 6.92 (s, 8H), 7.24 (dd, J 8.8, 2.0 Hz, 1H), 7.45 (d, J = 2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H). ^{13}C NMR (CD_3OD): δ 21.4, 30.9, 41.4, 41.7, 46.3, 46.6, 50.3, 50.6, 50.7, 51.3, 67.4, 67.5, 74.6, 107.2, 107.9, 108.4, 118.3, 119.12, 120.1, 127.1, 129.4, 131.2, 132.8, 134.3, 135.8, 136.7, 147, 150.6, 150.9, 154.5, 168.8. EIMS: m/z (%) 82 (51), 173 (92), 217 (27), 255 (20), 531 (13), 559 (100), 743 (14, M^+). HRMS (EI, M^+): Calcd for $C_{38}H_{43}Cl_2N_6O_3$ 748.2543, found 748.2551.

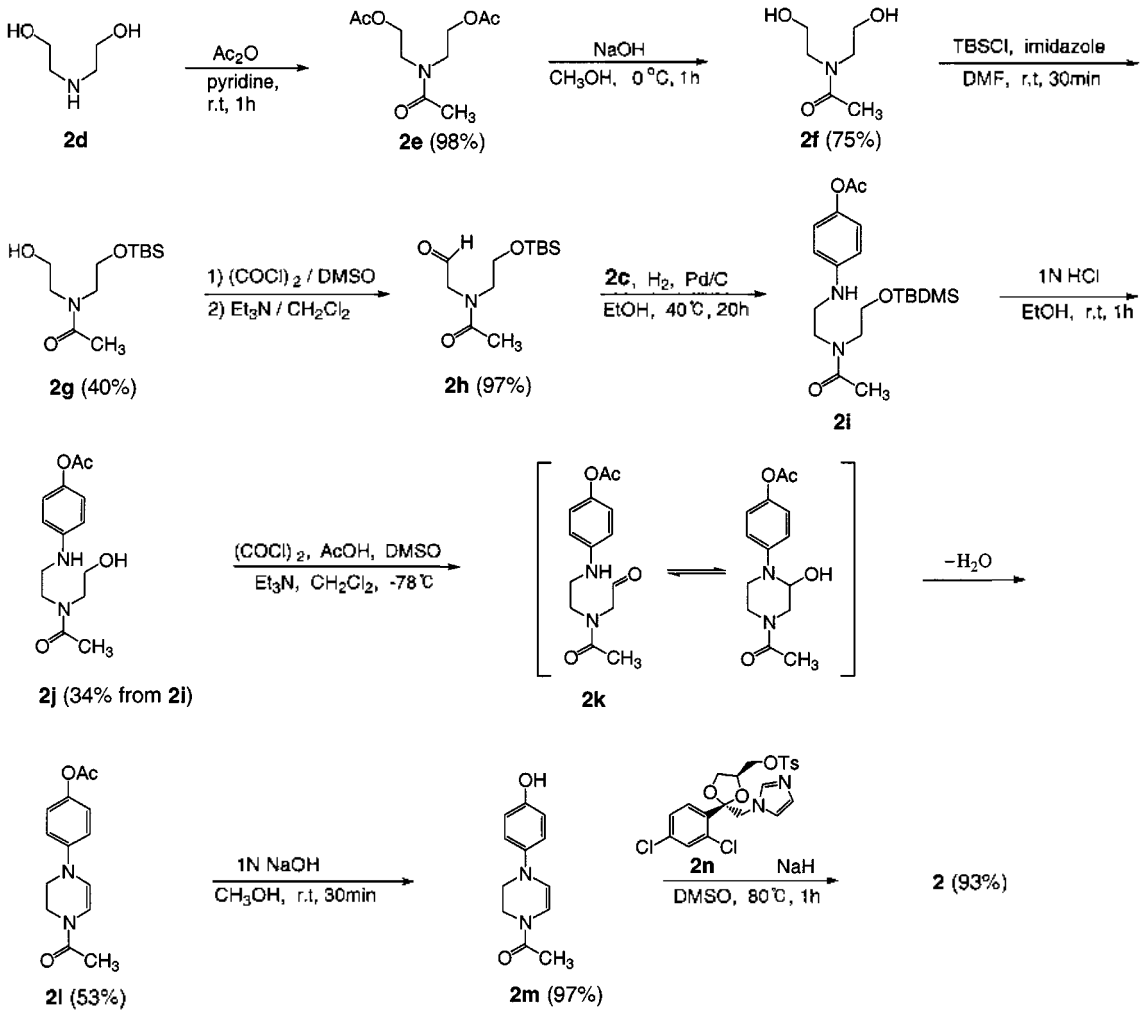
1-4-[2-(2,4-Dichlorophenyl)-2-imidazol-1-ylmethyl-[1,3]-dioxolan-4-ylmethoxy]phenyl-piperazine (4). A solution of *cis*-ketoconazole (2.0 g, 3.76 mmol) and KOH (0.63 g, 11.3 mmol) in DMSO (20 mL)-H_2O (10 mL) was stirred at 100 °C for 5h. The mixture was solidified by adding of excess water. The resulting solid was collected to give derivative **4** (1.55 g, 84.2%) as a brownish solid. ^1H NMR ($CDCl_3$): δ 3.05 (s, 8H), 3.31 (dd, J = 9.2, 6.8 Hz, 1H), 3.72 (dd, J = 8.4, 4.8, 2H), 3.87 (dd, J = 6.8, 6.8 Hz, 1H), 4.34 (m, 1H), 4.40 (dd, J = 14.4, 1.0 Hz, 2H), 6.75 (d, J = 9.2 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 11.2 Hz, 2H), 7.24 (s, 1H), 7.48 (d, J = 16.8 Hz, 2H), 7.57 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 46.1, 51.3, 51.6, 67.6, 67.7, 74.8, 107.9, 115, 118.1, 121, 127.1, 128.5, 129.4, 131.3, 132.9, 134.5, 135.7, 138.7, 146.5, 152.2. EIMS: m/z (%) 82 (63), 120 (47), 136 (36), 177 (61), 255 (9), 446 (66), 459 (100), 488 (24, M^+). HRMS (EI, M^+): Calcd for $C_{24}H_{26}Cl_2N_4O_3$ 488.1382, found 488.1388.

Results and Discussion

Impurity **1** was synthesized as shown in Scheme 1. Although it was thought that **1b** can be synthesized using the same procedure as is used to synthesize **1a**,[9] we prepared **1b** by isomerization of **1a**, which was provided by Choongwae Pharma Co. In the isomerization reaction, the acetal ring was opened and closed in the presence of anhydrous *p*-TsOH, resulting in equilibration between **1a** and **1b** in a roughly 1 : 1 ratio. Since **1b** differs from **1a** in the R_f (**1a** : 0.5, **1b** : 0.4) on TLC (SiO_2, hexane/ethyl acetate = 9/1), **1b** was isolated by column chromatography. **1** was synthesized from **1b** following the same synthetic procedure[9] as used to obtain



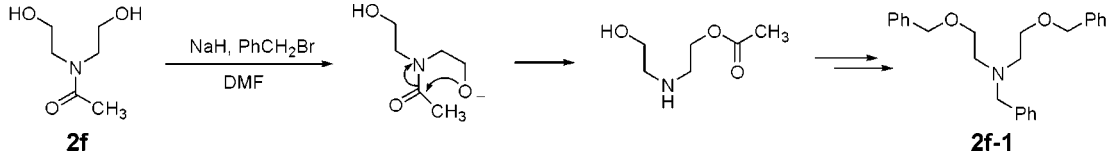
Scheme 1



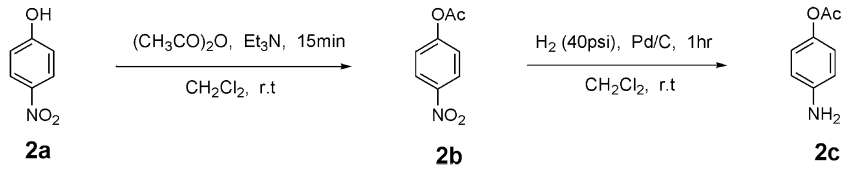
Scheme 2

ketoconazole from **1a**. The bromide of **1b** was converted to the imidazole to get **1c** which was hydrolyzed to **1d**. The hydroxyl group of **1d** was tosylated and coupled with **1f** to obtain **1**.

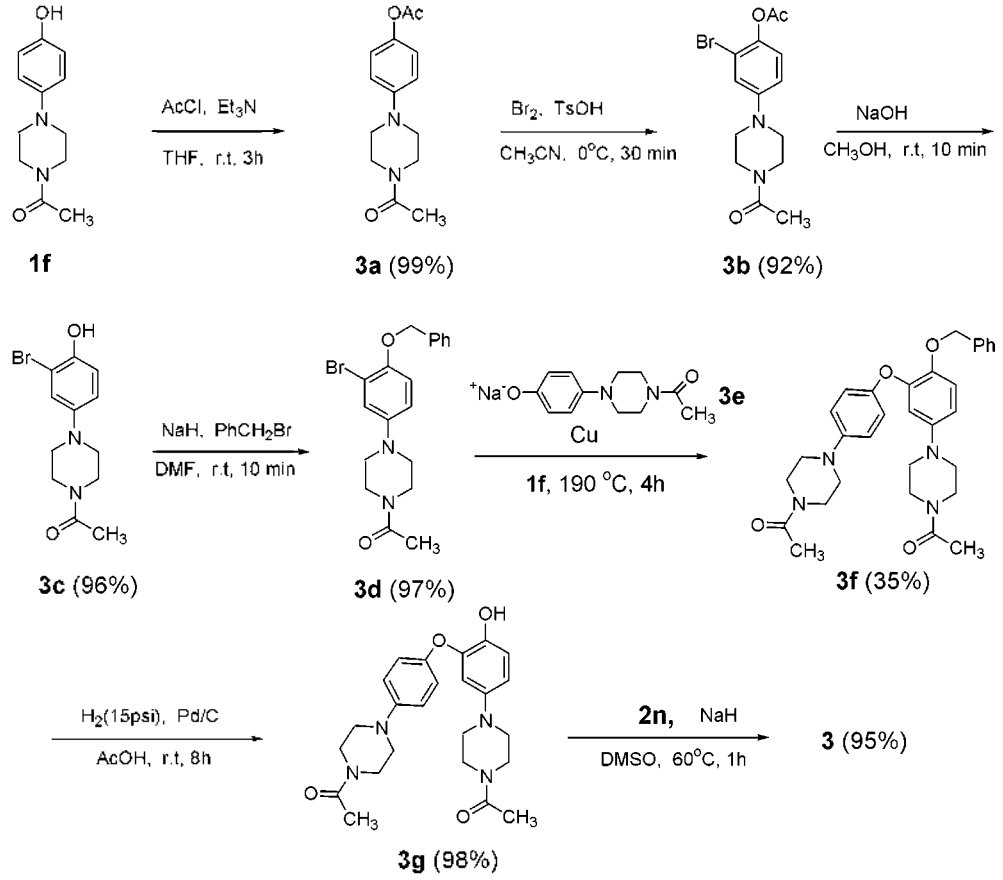
Impurity **2** contains a 1,4-dihydropyrazine ring instead of the piperazine in ketoconazole. Therefore, the oxidation of **3a** to **2k** was first tried using a rhodium catalyst[10] or photooxidation[11] in the presence of photosensitizer. These methods failed, so **2k** was synthesized from the diethanolamine (**2d**), as shown in Scheme 2. The hydroxyl and amine groups of **2d** were acetylated using acetic anhydride, and then two *O*-acetyl groups were removed by partial hydrolysis. In the hydrolysis reaction, when more than 2 eq. of NaOH was used, the *N*-acetyl group was also hydrolyzed very easily at rt. The instability of the amide bond is thought to be due to an intramolecular acyl-transfer reaction involving the alkoxide. Therefore, the hydrolysis reaction should be performed carefully at 0 °C using less than 2 eq. of NaOH. This phenomenon was also observed in the step used to protect the hydroxyl group of **2f** with benzyl bromide, as shown in Scheme 3, in which the major product was *N*-benzylated **2f-1**. Without using a strong base, the hydroxyl group of **2f** could be protected with TBS to obtain **2g**. Swern oxidation of **2g** followed by reductive amination with aniline derivative **2c** gave **2i**, which was converted to **2j** by acidic hydrolysis of the TBS group. **2c** was obtained from *p*-nitrophenol (**2a**) by acetylation and hydrogenation, as shown in Scheme 4. In the Swern oxidation of **2j**, the standard conditions[12] did not work, because of the nucleophilicity[13] of the amine of aminoalcohol **2j**. The addition of one equivalent of acetic acid was crucial to temporarily mask the nucleophilicity of the amine. The resulting aldehyde **2k**



Scheme 3



Scheme 4



Scheme 5

was transformed to **2l** *via* spontaneous cyclization and dehydration. ^{1}H and ^{13}C NMR spectra showed that **2l** is a mixture of two rotomers in a 2 : 1 ratio. These rotomers were thought to result from steric hindrance between the methyl proton of the acetyl group and the vinyl proton. To confirm the structure of **2l**, it was hydrogenated to **3a** in the presence of Pd/C. Due to the instability of **2m** under acidic conditions, after basic hydrolysis of **2l**, the reaction mixture was neutralized using phosphate buffer (pH 7) for extraction. **2m** was coupled with **2n** to obtain **2**, which is also a mixture of two rotomers according to the ^{1}H and ^{13}C NMR spectra.

The synthetic procedure for **3** is outlined in Scheme 5. Since direct bromination of **1f** gave side products, it was first acetylated to **3a**. The selective bromination at the ortho position of the phenolic oxygen was accomplished by protonation of the anilinic nitrogen with *p*-TsOH during bromination using Br_2. The acetyl-protecting group of **3b** was replaced by a benzyl group, due to the instability of the ester under next harsh condition. For the diaryl ether coupling of **3d** with **3e**, several procedures, such as Pd[14]- or Cu-mediated coupling in toluene[15] or CH_3CN[16] solvent were tried. However, these procedures were not effective. Replacement of these solvents by phenol derivative **1f** and increasing the reaction temperature to 190 °C gave **3f** in 35% yield. After debenzylation of **3f** by hydrogenolysis, the resulting **3g** was coupled with **2n** to obtain **3**.

Finally, derivative **4** was obtained by deacetylation from ketoconazole using an aqueous KOH-DMSO system.

Conclusion

For DMF of ketoconazole, four impurities (**1**-**4**) contained in ketoconazole were synthesized. During the synthesis of **2**, a new synthetic method for 1,4-dihydropyrazine was established. To oxidize the aminoalcohol (**2j**) to the aminal (**2k**), standard Swern oxidation condition was modified to temporarily mask the nucleophilicity of the amino group of **2j** using one equivalent of acetic acid. Derivative **3** was

synthesized *via* regioselective bromination at the 2 position of the 4-aminophenol derivative (**3a**) using Br_2 in the presence of *p*-TsOH. The etherification of the aryl bromide with the phenol derivative (**3e**) was accomplished by modifying the general Cu-mediated reaction using the phenol derivative itself as the solvent at 190 °C.

References

1. The Rules Governing Medicinal Products in the European Union. Quality Guidelines *European Drug Master File Procedure for Active Substances*; 1998; Vol. 3A.
2. Bendix, D. *Polymer Degradation and Stability* **1998**, *59*, 129.
3. Heel, R. C.; Brogden, R. N.; Carmine, A.; Morley, P. A.; Speight, T. M.; Avery, G. S. *Drugs* **1982**, *23*, 1.
4. Vanden Bossche, H.; Willemsens, G.; Cools, W.; Cornelissen, F.; Lauwers, W.; Van Cutsem, J. M. *Antimicrob. Agents Chemother.* **1980**, *17*, 922.
5. Kraemer, F. B.; Pont, A. *Am. J. Med.* **1986**, *80*, 616.
6. Ballard, S. A.; Lodola, A.; Tarbit, M. H. *Biochem. Pharmacol.* **1988**, *37*, 4643.
7. Shepherd, F. A.; Hoffert, B.; Evans, W. K.; Emery, G.; Trachtenberg, J. *Arch. Intern. Med.* **1985**, *145*, 863.
8. Camps, P.; Farres, X. *Tetrahedron: Asymmetry* **1995**, *6*, 1283.
9. Heeres, J.; Backx, L. J.; Mostmans, J. H.; Van Cutsem, J. *J. Med. Chem.* **1979**, *22*, 1003.
10. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Letters* **1997**, *38*, 7565.
11. Kallinayer, H. J.; Petesch, N. *Pharm. Acta Helv.* **1991**, *66*, 178.
12. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
13. Keirs, D.; Overton, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1660.
14. Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.
15. Marcoux, J. F.; Doye, S.; Buchwald, S. *J. Am. Chem. Soc.* **1997**, *119*, 10539.
16. Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J. *J. Org. Chem.* **1998**, *63*, 6338.