HETEROCYCLES, Vol. 62, 2004, pp. 807 - 813
Received, 22nd July, 2003, Accepted, 8th September, 2003, Published online, 27th October, 2003

AN EFFICIENT PREPARATIVE ROUTE TO 7-ETHYL-1*H*-FURO[2,3-*g*]INDAZOLE

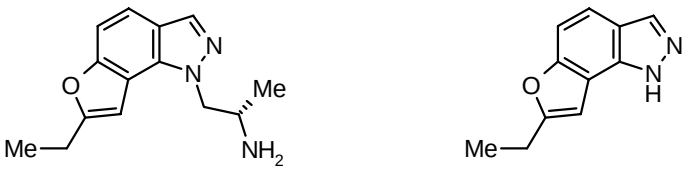
Itsuro Shimada,* Kyoichi Maeno, Tetsuya Kimizuka, Seiki Goto, Takumi Takahashi, Atsushi Nakamura, Akio Miyafuji, Shin-ichi Tsukamoto, and Shuichi Sakamoto

*Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21, Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

Abstract – A new and efficient route to 7-ethyl-1*H*-furo[2,3-*g*]indazole (**2**) has been developed. Treatment of 4,5-dihydro-7-(1-hydroxyethyl)indazole (**12**) with hydrochloric acid in ethanol resulted in a concomitant dehydration and aromatization to afford the title compound in good yield.

INTRODUCTION

The 5-HT_{2C} receptor, one of the serotonin receptors, has been implicated in a variety of disorders including schizophrenia, anxiety, depression and obesity,[1-4] and offers a target for the design of novel therapeutic drugs.[5] Our research was directed towards the synthesis of potent serotonin 5-HT_{2C} receptor agonists and (*S*)-2-(7-ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)-1-methylethylamine (YM348, **1**) was identified as a new and potent 5-HT_{2C} receptor agonist. To evaluate the pharmacological profile of **1**, a large-scale synthetic procedure was required. Structurally, this compound contains a novel hetero-tricyclic system, 7-ethyl-1*H*-furo[2,3-*g*]indazole (**2**). Few synthetic methods related to this system have been reported in the literature,[6] hence the development of an efficient synthetic route to this novel heterocyclic system (**2**) was required (Figure 1).



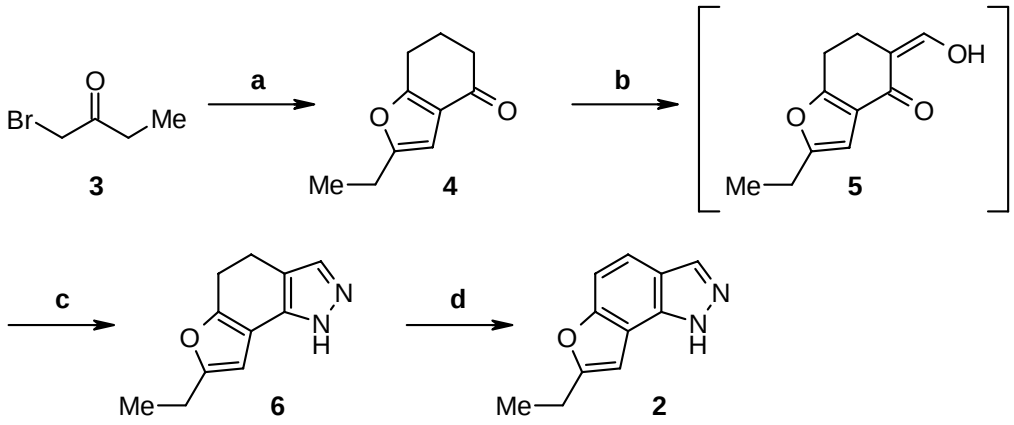
1 **2**

Figure 1

† Dedicated to Prof. Leo A. Paquette on the occasion of his 70th birthday

RESULTS AND DISCUSSION

A synthetic route to provide the desired hetero-tricyclic skeleton (**2),** for medicinal chemistry scale production (multi-gram) was developed (Scheme 1). In the first step, according to the procedure reported by Matsumoto and co-workers,[7] the condensation of 1-bromo-2-butanone (**3**) with 1,3-cyclohexanedione gave 2-ethyl-6,7-dihydrobenzofuran-4(5*H*)-one (**4**) in 50% yield based on **3**. Subsequent α-formylation of **4** was performed using ethyl formate and *t*-BuOK, followed by the addition of hydrazine[2] to afford 7-ethyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (**6**), in 80% yield from **4**. Finally, palladium(0)-catalyzed dehydration, in the presence of diethyl fumarate as a hydrogen scavenger, at 210°C provided the desired compound (**2**), in 79% yield.



Scheme 1

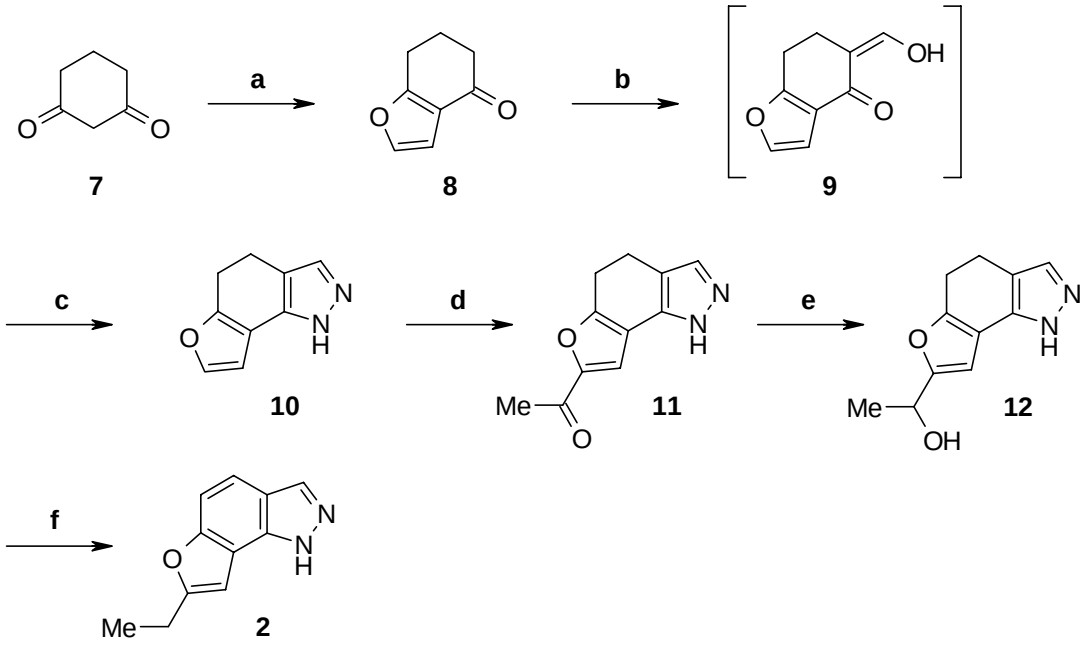
Reagents and conditions: (a) 1,3-cyclohexanedione, $NaHCO_3$, MeOH, H_2O, 0°C, then H_2SO_4, -20°C-rt (50%). (b) *t*-BuOK, HCO_2Et, THF, 0°C. (c) $H_2NNH_2 \cdot H_2O$, EtOH, rt (80% from **4**). (d) 10% Pd-C, diethyl fumarate, ethylene glycol, reflux (79%).

Although this route provided the desired hetero-tricyclic skeleton (**2**) on a multi-gram scale, there are two disadvantages for large-scale (multi-kilogram) synthesis. These are the use of 1-bromo-2-butanone (**3**), which is expensive and the high reaction temperatures (>200°C) required for the aromatization (step **d**). On this basis it was necessary to develop an alternative, efficient, scalable route for the synthesis of 7-ethyl-1*H*-furo[2,3-*g*]indazole (**2**).

In order to obviate the use of 1-bromo-2-butanone (**3**), chloroacetaldehyde was selected as an inexpensive starting material (Scheme 2). 1,3-Cyclohexanedione (**7**) was reacted with chloroacetaldehyde to give 6,7-dihydrobenzofuran-4(5*H*)-one (**8**), which was converted to 4,5-dihydro-1*H*-furo[2,3-*g*]indazole (**10**) in 52% yield from **7**, by utilizing the aforementioned synthetic methods with minor modifications. Acetylation of **10** using acetic anhydride under Friedel-Crafts conditions, in 80% yield, followed by reduction with sodium borohydride led to 1-(4,5-dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanol (**12**), in 93%

yield. It was expected that dehydration of the benzylic alcohol and subsequent aromatization would occur under acidic conditions to provide the desired 7-ethyl-1*H*-furo[2,3-*g*]indazole (**2**), so several acidic conditions were investigated (e.g. acetic acid, hydrochloric acid, sulfuric acid). The optimal conditions for dehydration and aromatization, were identified (one equivalent of concentrated hydrochloric acid in refluxing ethanol) and provided a 93% yield.

Therefore an efficient preparative route suitable for the multi-kilogram synthesis of 7-ethyl-1*H*-furo[2,3-*g*]indazole (**2**), in 36% overall yield from **7,** has been developed.



Scheme 2

Reagents and conditions: (a) chloroacetaldehyde, NaOH, $NaHCO_3$, H_2O, 0°C, then toluene, H_2SO_4, 0°C (92%). (b) *t*-BuOK, HCO_2Et, toluene, 0°C. (c) $H_2NNH_2 \cdot H_2O$, toluene, EtOH, rt (81% from **8**). (d) Ac_2O, MsOH, AcOH, 50°C (80%). (e) $NaBH_4$, MeOH, H_2O, rt (93%). (f) c. HCl, EtOH, reflux (93%).

EXPERIMENTAL

All melting points were determined on a Yanagimoto MP-3 melting point apparatus and without correction. ^{1}H NMR spectra were taken on a JEOL JNM-LA300 spectrometer or a JEOL JNM-A500 spectrometer. Chemical shifts are given in ppm relative to that of Me_4Si ($\delta = 0$) in $CDCl_3$ as an internal standard. IR spectra were measured in a HORIBA FT-720 spectrophotometer; the frequencies in the IR spectra are indicated in cm^{-1}. FAB-MS were obtained with a JEOL JMS-DX300 mass spectrometer or a JMS-LX2000 mass spectrometer. HR-MS were obtained with a Micromass Q-Tof Ultima API mass spectrometer. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N). Column chromatography was carried out on a silica gel (Kanto Silica gel 60N).

2-Ethyl-6,7-dihydro-1-benzofuran-4(5*H*)-one (4)

To a mixture of 1-bromobutan-2-one (**3**) (25.0 g, 166 mmol) and $NaHCO_3$ (55.8 g, 664 mmol) in MeOH (250 mL) and H_2O (500 mL), was added a solution of 1,3-cyclohexanedione (37.1 g, 332 mmol) in H_2O (500 mL) dropwise at 0°C. The resulting mixture was stirred at ambient temperature for 65 h. Subsequently, 1M aqueous HCl (500 mL) was added and the crude mixture extracted with chloroform. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. To the crude residue was added H_2SO_4 (150 mL) dropwise at -20°C. After stirring for 15 min at rt, the mixture was poured onto ice and extracted with AcOEt. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (hexane:AcOEt = 4:1) to afford **4** (13.6 g, 50%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.23 (3 H, t, *J* = 7.8 Hz), 2.10 - 2.21 (2 H, m), 2.43 – 2.51 (2 H, m), 2.63 (2 H, q, *J* = 7.8 Hz), 2.83 (2 H, t, *J* = 6.3 Hz), 6.25 (1 H, s). IR (neat) ν 2971, 2940, 2879, 1677, 1581, 1455, 1363, 1218, 1122, 1058, 1002, 933, 892, 813, 732. FAB-MS *m/z*: 165 $[M+H]^+$. HR-MS calcd for ($C_{10}H_{12}O_2$ + H) 165.0916, found 165.0921.

7-Ethyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (6)

To a suspension of *t*-BuOK (35.3 g, 314 mmol) in THF (400 mL) was added a solution of 2-ethyl-6,7-dihydro-1-benzofuran-4(5*H*)-one (**4**) (25.8 g, 157 mmol) and ethyl formate (50.6 mL, 628 mmol) in THF (300 mL) dropwise at 0 °C. Subsequently, the mixture was stirred at this temperature for an additional 1.5 h. 1M Aqueous HCl (350 mL) was then added and the crude mixture extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **5** (30 g). The residue, without further purification, was dissolved in EtOH (600 mL). This solution was added dropwise to a solution of hydrazine monohydrate (98%, 9.08 mL, 187 mmol) in EtOH (600 mL), over a period of 1 h and then stirred at rt for an additional 17 h. The reaction mixture was evaporated and the residue diluted with AcOEt and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (hexane:AcOEt = 4:1) to give **6** (23.5 g, 80%) as a pale yellow solid.

mp 96 – 98 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (3 H, t, *J* = 7.5 Hz), 2.66 (2 H, q, *J* = 7.5 Hz), 2.88 - 2.94 (4 H, m), 6.27 (1 H, s), 7.27 (1 H, s). IR (KBr) ν 3162, 3110, 3048, 2967, 2931, 2842, 1629, 1577, 1448, 1388, 1332, 1241, 1189, 1101, 1051, 1002, 933, 802. FAB-MS *m/z*: 189 $[M+H]^+$. *Anal* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.01; H, 6.58; N, 14.92.

7-Ethyl-1*H*-furo[2,3-*g*]indazole (2) from 6

To a solution of 7-ethyl-4,5-dihydro-1*H*-furo[2,3-*g*]indazole (**6**) (500 mg, 2.66 mmol) in ethylene glycol (5 mL) were added diethyl fumarate (0.44 mL, 2.66 mmol) and 5% Pd/C (50 mg). After 5 h at reflux, to the cooled mixture was added MeOH (50 mL). The catalyst was removed by filtration and washed with MeOH. The filtrate was concentrated *in vacuo* and then brine was added to the residue. The resulting aqueous solution was extracted with AcOEt - toluene (1:3), the organic layer dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (hexane:AcOEt = 5:1) to give **2** (391 mg, 79%) as a white solid.

mp 130 – 131 °C. ^{1}H NMR ($CDCl_3$) δ: 1.37 (3 H, t, *J* = 7.5 Hz), 2.87 (2 H, dq, *J* = 0.9 Hz, 7.5 Hz), 6.60 (1 H, d, *J* = 0.9 Hz), 7.32 (1 H, dd, *J* = 0.9 Hz, 8.7 Hz), 7.54 (1 H, d, *J* = 8.7 Hz), 8.15 (1 H, s), 10.85 (1 H, br). IR (KBr) ν 3168, 3120, 3058, 2964, 2931, 2813, 1644, 1585, 1409, 1369, 1245, 1172, 1060, 948, 848, 796, 757, 661. FAB-MS *m/z*: 187 $[M+H]^+$. *Anal* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.94; H, 5.43; N, 15.06.

6,7-Dihydro-1-benzofuran-4(5*H*)-one (8)

To a solution of 1,3-cyclohexanedione (**7**) (32.0 kg, 285 mol), NaOH (10.3 kg, 258 mol) and $NaHCO_3$ (7.18 kg, 85.5 mol) in water (220 L) was added a solution of chloroacetaldehyde (64.6 kg, 342 mol, 41.5% in water), whilst maintaining the temperature below 0°C. After stirring for 1 h below 0°C, toluene (160 L) and H_2SO_4 (18.7 kg) were added and the mixture was stirred for a further 16 h below 0°C. The precipitate was removed by filtration and the aqueous filtrate was extracted with toluene (64 L). The combined organic phases were washed with saturated aqueous $NaHCO_3$, brine and then concentrated to give **8** (24.8 kg, 64%) as a pale yellow oil, which was 98.4% purity by HPLC analysis using YMC ODS-A A-302 (20% CH_3CN / 80% water with 0.02M perchloric acid) with UV detection at a wavelength of 254 nm.

4,5-Dihydro-1*H*-furo[2,3-*g*]indazole (10)

To a solution of 6,7-dihydro-1-benzofuran-4(5*H*)-one (**8**) (24.8 kg, 182 mol) and ethyl formate (54.0 kg, 729 mol) in toluene (120 L), was added a mixture of *t*-BuOK (40.9 kg, 364 mol) in THF (150 L), and then stirred for 0.5 h below 0°C. Following the addition of water (120 L), to the mixture conc. aqueous HCl was added in order to adjust the pH of the aqueous layer to 5. The aqueous phase was extracted with toluene (50 L), the combined organic phases were washed with water (2 x 98 L) and concentrated to give the crude **9** (30.1 kg) in 99.0% purity (HPLC). The residue, without further purification, was dissolved in toluene (60 L) and EtOH (190 L). To this solution was added hydrazine monohydrate (80.35%, 12.6 kg, 202 mmol) and the mixture was stirred below 45 °C for 22 h. The reaction mixture was evaporated, and to the residue was added water (180 L). The crystals were removed by filtration to afford **10** (23.7 kg, 81%)

as a brown solid, which was 99.0% purity by HPLC analysis using YMC ODS-A A-302 (40% CH_3CN / 60% water) with UV detection at a wavelength of 254 nm.

mp 135 – 137 °C. ^{1}H NMR ($CDCl_3$) δ: 2.94 (4 H, s), 6.69 (1 H, d, *J* = 2.1 Hz), 7.30 (1 H, s), 7.35 (1 H, d, *J* = 2.1 Hz). IR (KBr) ν 3137, 3099, 3035, 2915, 1625, 1531, 1492, 1388, 1334, 1230, 1168, 1130, 1087, 1045, 983, 894, 827, 744, 595, 449. FAB-MS *m/z*: 161 $[M+H]^+$. *Anal* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.64; H, 5.06; N, 17.57.

1-(4,5-Dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanone (11)

To a solution of 4,5-dihydro-1*H*-furo[2,3-*g*]indazole (**10**) (23.6 kg, 147 mol) in acetic acid (49 kg) were added methanesulfonic acid (70.6 kg, 735 mol) and acetic anhydride (45.0 kg, 441 mol) and the solution stirred for 1 h at 40~50°C. Following the addition of 2-propanol (120 L), the solution was stirred for 1 h at 20~40°C, and the precipitate removed by filtration. After the addition of water (230 L) to the precipitate, a solution of NaOH (5.88 kg, 147 mol) in water (54 L) was added whilst cooling. The crystals were removed by filtration to afford **11** (23.8 kg, 80%) as a brown solid, which was 98.1% purity by HPLC analysis using TOSOH TSKgel ODS-80TM (50% CH_3CN / 50% water with 0.01M potassium dihydrogenphosphate) with UV detection at a wavelength of 254 nm.

mp 230 – 232 °C. ^{1}H NMR ($CDCl_3$) δ: 2.05 (3 H, s), 2.96 – 3.06 (4 H, m), 7.36 (1 H, s), 7.46 (1 H, s). IR (KBr) ν 3305, 3168, 3083, 2942, 1166, 1644, 1508, 1446, 1392, 1307, 1174, 1108, 1051, 1004, 931, 811, 744. FAB-MS *m/z*: 203 $[M+H]^+$. *Anal* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.11; H, 4.89; N, 13.81.

1-(4,5-Dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanol (12)

To a solution of 1-(4,5-dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanone (**11**) (5.50 g, 27.2 mmol) in MeOH (110 mL) below 0°C, was added sodium borohydride (1.03 g, 27.2 mmol) and the mixture stirred for 0.5 h at rt. After the addition of water (50 mL) the mixture was concentrated to ~50 mL and stirred for 0.5 h at rt, followed by a further 1 h at 0°C. The crystals were isolated by filtration to afford **12** (5.19 g, 93%) as a pale yellow solid, which was 98.8% purity by HPLC analysis using TOSOH TSKgel ODS-80TM (60% CH_3CN / 40% water with 0.01M ammonium acetate) with UV detection at a wavelength of 254 nm.

mp 113 – 115 °C. ^{1}H NMR ($CDCl_3$) δ: 1.55 (3 H, d, *J* = 6.6 Hz), 2.90 (4 H, s), 4.87 (2 H, q, *J* = 6.6 Hz), 6.49 (1 H, s), 7.27 (1 H, s). IR (KBr) ν 3201, 2940, 1631, 1577, 1535,1421, 1332, 1301, 1216, 1182, 1078, 1002, 939, 879, 750. FAB-MS *m/z*: 205 $[M+H]^+$. *Anal* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.43; H, 5.83; N, 13.72.

7-Ethyl-1*H*-furo[2,3-*g*]indazole (2) from 12

To a solution of 1-(4,5-dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanol (**12**) (6.18 g, 30.3 mmol) in EtOH (62 mL) was added conc. aqueous HCl (2.5 mL). The mixture was refluxed for 7 h and cooled to rt. Following the addition of 10% aqueous NaOH solution (12.7 mL) and water (50 mL), the mixture was concentrated and 6M aqueous HCl (15 mL) was added. This mixture was stirred for 0.5 h at rt and the resulting crystals removed by filtration, rinsed with 1M aqueous HCl and water. Subsequently, the crystals were dissolved in MeOH (25 mL), 10% aqueous NaOH solution (13.3 mL) was added and the mixture stirred for 15 min at rt. Water (40 mL) was added, and the mixture stirred for a further 1 h at 0 ^{o}C. The resulting crystals were isolated by filtration and rinsed with water to afford **2** (5.26 g, 93%) as a pale yellow solid, which was 97.4% purity by HPLC analysis using TOSOH TSKgel ODS-80TM (60% CH_3CN / 40% water with 0.01M ammonium acetate) with UV detection at a wavelength of 254 nm.

7-Ethyl-1*H*-furo[2,3-*g*]indazole (2). One-Pot Procedure from 11

To a solution of 1-(4,5-Dihydro-1*H*-furo[2,3-*g*]indazol-7-yl)ethanone (**11**) (23.6 kg, 117 mol) in EtOH (240 L) was added sodium borohydride (2.21 kg, 58.4 mol) and the whole was stirred for 4 h at rt. After the addition of conc. aqueous HCl (16.5 kg, 176 mol) the mixture was refluxed for 7 h. The mixture was concentrated, conc. aqueous HCl (33.2 kg, 354 mol) and water (90 L) were then added and the resulting precipitate isolated by filtration. The precipitate was dissolved in MeOH (180 L), and then 10% aqueous NaOH solution (52.2 kg, 129 mol) and water (310 L) were added. The resulting solid was removed by filtration to afford **2** (19.7 kg, 106 mol, 91%) as a pale yellow solid, which was 98.1% purity by HPLC analysis using TOSOH TSKgel ODS-80TM (60% CH_3CN / 40% water with 0.01M potassium dihydrogenphosphate) with UV detection at a wavelength of 254 nm.

REFERENCES

(*) Corresponding author, e-mail: shimadai@yamanouchi.co.jp

1. G. A. Kennett, *Curr. Opin. Invest. Drugs*, 1993, **2**, 317.
2. C. T. Dourish, *Obes. Res.*, 1995, **3**, 449S.
3. G. R. Martin and P. P. A. Humphrey, *Neuropharmacology*, 1994, **33**, 261.
4. D. Leysen and J. Kelder, *Trends in Drug Res Ⅱ.*, 49.
5. M. Issac, *Drugs Future*, 2001, **26**, 383.
6. N. P. Peet and M. E. LeTourneau, *Heterocycles*, 1991, **32**, 41.
7. M. Matsumoto and N. Watanabe, *Heterocycles*, 1994, **22**, 2313.
8. J. M. Schaus, D. L. Huser, and R. D. Titus, *Synth. Commun.*, 1990, **20**, 3553.