Synthesis of Novel Piperidyl Spirofused Benzofurans/ Benzopyrans by Radical Cyclization

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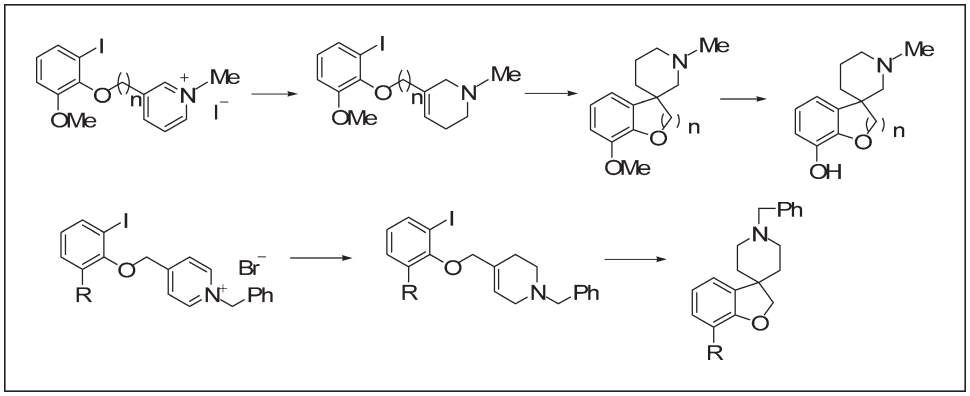

Several new piperidyl spirofused benzofurans and piperidyl spirofused benzopyrans were synthesized via an intramolecular radical cyclization as the key step. It was found that the yield of the formation of five-member ring was much higher than that of six-member ring. In addition, the substituent attached to the benzene ring had almost no effect on the cyclization.

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INTRODUCTION

In 1994, the fourth opioid receptor, opioid receptor-like 1 (ORL1), was discovered by homology cloning [1]. Subsequently, nociceptin, also named orphanin FQ (NC/OFQ), is a peptide consisting of 17-amino acids and was identified as an endogenous ligand for ORL1 in 1995 [2]. Pharmacological studies using NC/OFQ and ORL1-deficient mice showed that the NC/OFQ-ORL1 system might play important roles in pain regulation [3], learning and memory [4], food intake [5], anxiety [6], cardiovascular system [7], and locomotor activity [8]. These results prompted many industrial and academic researches to identify small molecules as potent and selective ORL1 agonists and antagonists [9].

Various structural classes of nonpeptide ligands for ORL1 have been reported [9c–9f], such as morphinan-based ligands, benzimidazopiperidines, spiropiperidines, aryl piperidines, and aminoquinolines. However, the development of new ORL1 ligands with high selectivity and bioavailability still remains an important challenge, especially for the extensive elucidation and control of the physiological role of the ORL1. Herein, we present the synthesis of new piperidyl spirofused benzofurans and piperidyl spirofused benzopyrans (Fig. 1) aiming at the development of new ORL1 ligands.

RESULTS AND DISCUSSION

The synthetic sequence for the new piperidyl spirofused benzofurans (benzopyrans) is outlined in Scheme 1. The preparation of the important intermediates **8** and **12** from substituted phenol **4** and pyridylalkyl alcohols **5** or **9** via three steps was previously reported from our laboratory [10]. Initially, Mitsunobu reaction of **4** and **5** or **9** gave pyridine derivatives **6** and **10**, respectively. Subsequent alkylation of compounds **6** and **10** followed by reduction with sodium borohydride afforded intermediates **8** and **12**. But, during the reduction of pyridinium salt **7a** ($n = 1$), a decoupling reaction encountered and the reaction gave **8a** in only 10% yield with substituted phenol **4a** as the major product. Fortunately, reduction of salts **8b** and **12** gave the desired products in moderate to good yields. Hence, to avoid the above mentioned decoupling reaction, in this text, we describe a new sequence for the preparation of intermediates **8a** and **12** as shown in Scheme 2. Compounds **15** and **16** were obtained smoothly in 83% and 90% yields by reduction of the corresponding pyridinium salts **13** and **14** resulted from alkylation of pyridylalkyl alcohols **5** and **9**, respectively [10]. Subsequent Mitsunobu reactions of **15**, **16** with substituted phenol **4** were effected

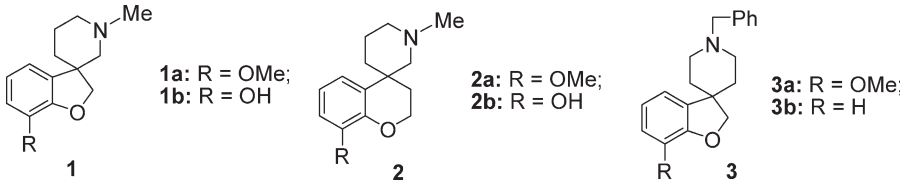


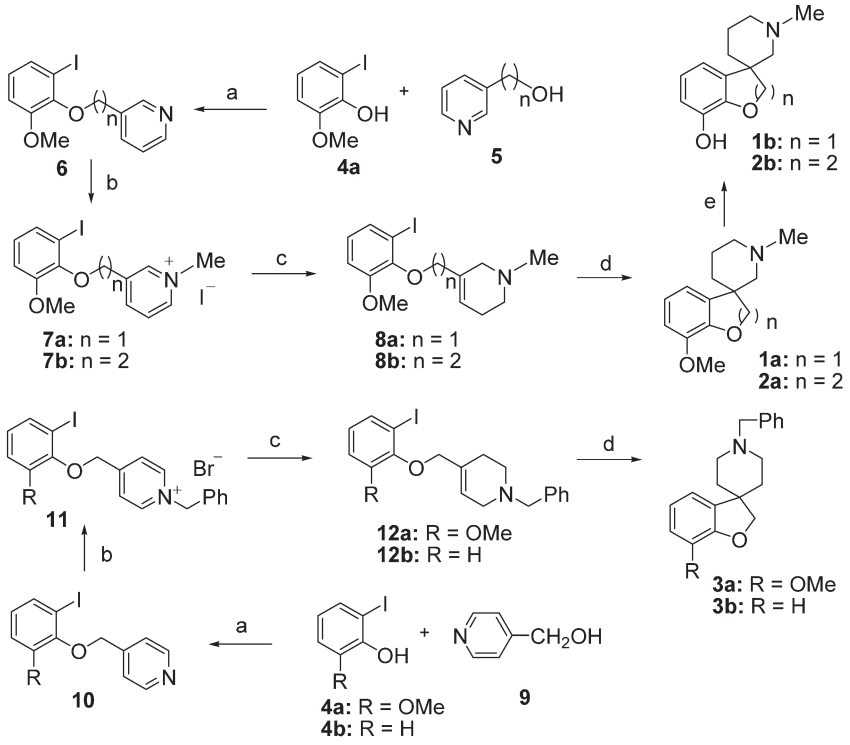
Figure 1. New piperidyl spirofused benzofurans/benzopyrans.

in the presence of PPh_3 and diethyl azodicarboxlate (DEAD) in dichloromethane at room temperature giving **8a** and **12** in 37–70% yields.

Finally, the cyclization of intermediates **8**, **12** to the title products would be achieved by free radical reaction with tributyltin hydide (Bu_3SnH) [11]. The reaction was ignited by azodiisobutyronitrile (AIBN, initiator) to produce the target compounds **1a**, **2a**, **3a–b** [12] in 39–85% yields (Scheme 1; Table 1). It can be clearly seen from the table, the reaction gave the five-member ring ($n = 1$) product in much higher yield than that of the six-member ring ($n = 2$) (entry 1 vs entry 2). Moreover, we observed that the free radical reaction of **8b** ($n = 2$) was slower than **8a** ($n = 1$), and not completed at the same condition. In addition, the R group attached to the benzene ring had almost no effect on the cyclization (entry 3 vs entry 4).

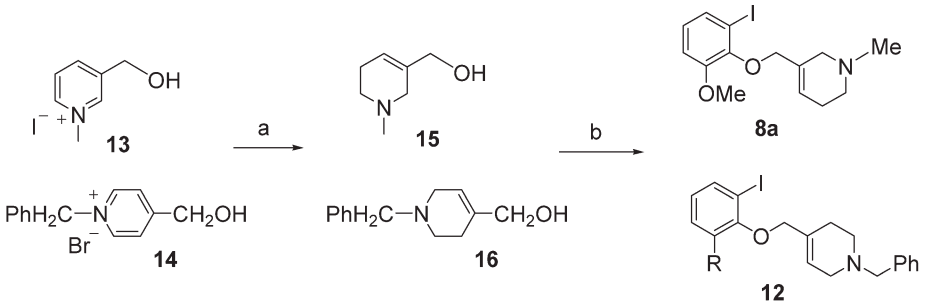
It should be further noted that the final products were usually contaminated by tin derivative, which made the

Scheme 1. Synthesis of piperidyl spirofused benzofurans (benzopyrans) **1**, **2**, and **3.**



Reagents and conditions: (a) DEAD (1.1 eq), PPh_3 (1.1 eq), CH_2Cl_2, rt, 8 h; (b) MeI or $PhCH_2Br$ (3-5eq), CH_2Cl_2, rt, 24 h; (c) $NaBH_4$ (3-5eq), MeOH, 0°C, 1 h, rt, 2 h; (d) Bu_3SnH (1.5 eq), AIBN, toluene, 95°C, 20 h. (e) For synthesis of **1b**: $BBr_3{\cdot}Sme_2$ (1.5 eq), CH_2Cl_2, - 60 to 0°C, 4 h; for synthesis of **2b**: HCl (10 N, 15 mL), 100°C, 12 h.

Scheme 2. Synthesis of **8a** and **12**.



Reagents and conditions: (a) $NaBH_4$ (3-5eq), MeOH, 0°C, 1 h, rt, 2 h; (b) **4** (1 eq), DEAD (1.1 eq), PPh_3 (1.1 eq), CH_2Cl_2, rt, 8 h.

purification very difficult. We found an effective work-up process for the purification by initially eliminating the tin derivative. This needed to form the corresponding salts of the spirofused piperidines by adding HCl to ethyl acetate solution of the crude products. Afterwards, the separated aqueous layer was neutralized with saturated Na_2CO_3 solution and extracted with dichloromethane.

As pointed out in the literature, within the group of opioid ligands with a morphinan structure the phenolic group in the 3-position was historically regarded as a requirement for high affinity interaction with a respective H-bond accepting site of the opioid receptor [13]. We thus decided to convert the methoxyl group connected with the benzene ring in compounds **1a**, **2a** into hydroxyl group. The goal was accomplished by demethylation of the methoxyl group with BBr_3 or HCl. Reaction of compound **1a** with BBr_3 in dichloromethane at room temperature gave the desired product **1b** in 60% yield (entry 5), while to our surprised, very low yield was obtained for compound **2a**. We then used HCl as demethylation reagent, the desired product **2a** was obtained in 77% yield (entry 6) when the reaction was performed at 100°C.

In summary, we have synthesized several new piperidyl spirofused benzofurans and piperidyl spirofused benzopyrans via an important intramolecular radical cyclization. It was found that the yield of the formation of five-member ring was much higher than that of six-member ring. In addition, the R group attached to the benzene ring had almost no effect on the cyclization.

Table 1

The results of the synthesis of compounds **1**, **2**, and **3**.

Entry	R	*n*	Product	Yield/%
1	**OMe**	**1**	**1a**	85
2	**OMe**	**2**	**2a**	40
3	**OMe**	–	**3a**	41
4	**H**	–	**3b**	39
5	**OH**	**1**	**1b**	60
6	**OH**	**2**	**2b**	77

EXPERIMENTAL

All solvents were dried by standard procedure. Infrared spectra were recorded on a PE-2000 FT-IR. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX 200-MHz sonde QNP (H, C, F, P) and Bruker Avance 400-MHz sonde H-BB with gradient Z spectrometer. Chemical shifts (δ) are given in ppm relative to Me_4Si (0, ^1H) or $CDCl_3$ (77.0, ^{13}C). Mass spectra were obtained with Thermo Finnigan LCQ Advantage spectrometer. Elemental analysis was measured on PE 2400 II CHNS instrument. Thin-layer chromatography (TLC) was run on precoated silica gel phates (Merck $60F_{254}$). Column chromatography was carried out using flash silica gel.

General procedure for the preparation of 8 and 12. ***Method A (for preparation 8b, 12a,b)*** See ref. 10 for the preparation of 8b, 12a,b.

Method B (for preparation 8a, 12a,b). To a 100-mL, three-neck flask with a stirring bar, 3.61 g of 2-iodo-6-methoxyphenol **4a** (14.4 mmol, 1 eq), 4.17 g of PPh_3 (16 mmol, 1.1 eq), alcohol **15** (24 mmol, 1.7 eq), and 50 mL of dry CH_2Cl_2 were added under argon. Then, a solution of DEAD (16 mmol, 2.9 mL, 1.1 eq) in 10 mL CH_2Cl_2 was added dropwise at room temperature. After the addition was completed, the mixture was stirred for an additional 8 h at the same temperature. The solvent was removed under reduced pressure, and the residue was subjected to chromatography to afford **8a** in 37% yield (2.0 g).**12a**: Yield: 67% (Method B). **12b**: Yield: 70% (Method B). ^1H NMR and ^{13}C NMR of **8a–b**, **12a–b** see ref. 10.

General procedure for the synthesis of 1a–3a, 3b. Argon was bubbled into a solution of **8a** (1.0 g, 28 mmol, 1 eq) in dry toluene (75 mL) in a round bottle with a stirring bar and a condenser for 15 min. Then, tributyl hydride (1.13 mL, 42 mmol, 1.5 eq), and AIBN (260 mg) were added. The mixture was heated at 95°C for 20 h. The resulting mixture was evaporated under reduced pressure to give crude product. The crude was diluted with AcOEt and added HCl to form the corresponding salt of the spirofused piperidine, and separated. The aqueous layer was neutralized with saturated Na_2CO_3 solution, and extracted with dichloromethane (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, evaporated to

give the crude, which was then subjected to flash chromatography on silica gel giving product **1a** (0.55 g, 85%).

1′-Methylspiro[7-methoxybenzofuran-2(3H),3′-piperidine] 1a. Yield: 85%, viscous oil; IR (film): 3020, 2940, 2854, 1711, 1621, 1593, 1492, 1466, 1289. 1270, 1216, 1101, 1064, 755, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.55–1.80 (m, 4H), 1.98 (td, 1H, J = 11.0 Hz, J = 3.9 Hz), 2.10 (dd, 1H, J = 11.0 Hz, J = 1.0 Hz), 2.25 (s, 3H, NCH_3), 2.70 (d, 1H, J = 11.0 Hz), 2.75–2.85 (m, 1H), 3.86 (s, 3H, OCH_3), 4.38 (dd, 1H, J = 9.0 Hz, J = 1.3 Hz), 4.69 (d, 1H, J = 9.0 Hz), 6.71–6.86 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.94, 34.00, 46.57, 46.83, 55.40, 55.84, 64.82, 81.72, 111.60, 115.33, 120.77, 134.44, 144.57, 147.92; MS(EI, 70ev) m/z (%) = 233 (10) [M^+], 161 (7), 117 (5), 91 (10), 71(60), 58 (100); Anal. Calcd. for $C_{14}H_{19}NO_2$: C 72.07; H 8.21; N 6.00. Found: C 71.94; H 8.26; N 5.96.

1′-Methylspiro[8-methoxybenzopyran-3(4H),3′-piperidine] 2a. Yield 40% (0.11 g), viscous oil; IR [(film): 3020, 2940, 1711, 1600, 1419, 1363, 1216, 1089, 767, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz]: δ 1.54–1.69 (m, 2H), 1.75–2.03 (m, 4H), 2.16 (d, 1H, J = 11.5 Hz), 2.22(s, 3H, NCH_3), 2.37 (dq, 1H, J = 14.0 Hz, J = 3.2 Hz), 2.67 (dt, 1H, J = 11.6 Hz, J = 1.3 Hz), 2.81–2.89 (m, 1H), 3.85 (s, 3H, OCH_3), 4.12–4.32 (m, 2H), 6.72 (dd, 1H, ArH, J = 7.9 Hz, J = 1.6 Hz), 6.83 (t, 1H, ArH, J = 7.9 Hz), 6.98 (dd, 1H, ArH, J = 7.9 Hz, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.66, 30.97, 34.24, 35.92, 46.66, 55.70, 56.09, 63.25, 66.29, 108.91, 118.88, 119.36, 129.77, 144.25, 148.27; MS(EI, 70ev) m/z (%) = 247 (15) [M^+], 176 (12), 161 (8), 105 (7), 91 (10), 71 (80), 58 (100); Anal. Calcd. for $C_{15}H_{21}NO_2$: C 72.84; H 8.56; N 5.66. Found: C 72.60; H 8.52; N 5.63.

1′-Benzylspiro[7-methoxybenzofuran-2(3H),4′-piperidine] 3a [12]. Yield: 41% (0.25 g), colorless oil; IR (film): 3023, 2950, 2860, 1712, 1598, 1486, 1365, 1214, 1088, 764, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.66–1.77 (m, 2H), 1.92–2.08 (m, 4H), 2.97–3.85 (m, 2H), 3.54 (s, 2H), 3.87 (s, 3H, OCH_3), 4.43 (s, 2H), 6.72–6.89 (m, 3H, ArH), 7.23–7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.44 (2C), 45.11, 50.90 (2C), 55.85, 63.38, 80.94, 111.31, 115.14, 121.13, 127.01, 128.17 (2C), 129.08 (2C), 136.21, 138.13, 144.54, 147.50; Anal. Calcd. for $C_{20}H_{23}NO_2$: C 77.64; H 7.49; N 4.53. Found: C 77.22; H 7.53; N 4.51.

1′-Benzylspiro[benzofuran-2(3H),4′-piperidine] 3b [12]. Yield: 39% (0.14 g), m.p. > 260°C (decomp.); IR (KBr): 3019, 2936, 1711, 1599, 1480, 1421, 1364, 1215, 1098, 766, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.68–1.76 (m, 2H), 1.94–2.12 (m, 4H), 2.86–2.98 (m, 2H), 3.55 (s, 2H), 4.37 (s, 2H), 6.79 (d, 1H, ArH, J = 7.6 Hz), 6.88 (t, 1H, ArH, J = 7.3 Hz), 7.13 (t, 2H, ArH, J = 7.7 Hz), 7.24–7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.59 (2C), 44.45, 50.97 (2C), 63.45, 80.40, 109.68, 120.53, 123.04, 127.13, 128.27 (3C), 129.18 (2C), 135.05, 138.15, 159.47; MS(EI, 70ev) m/z (%) = 279 (25) [M^+], 253 (10), 202 (8), 185 (10), 160 (5), 146 (15), 105 96), 91 (100), 77 (10), 56 925); Anal. Calcd. for $C_{19}H_{21}NO$: C 81.68; H 7.58; N 5.01. Found: C 81.32; H 7.55; N 4.99.

Synthesis of 1′-Methylspiro[7-hydroxybenzofuran-2(3H),3′-piperidine] 1b. To a solution of **1a** (0.26 g, 1 mmol, 1 eq) in dry dichloromethane (10 mL) was added $BBr_3.SMe_2$ (1.5 eq, 1.5 mmol, 1.7 mL) (1. M in CH_2Cl_2) at −60°C. The solution was allowed to warm to 0°C and stirred for 4 h. A saturated $NaHCO_3$ solution was added to neutralize the mixture followed by extracting with CH_2Cl_2 (3 × 20 mL). The collected organic layers were dried over Na_2SO_4 and evaporated. The crude was then subjected to flash chromatography on silica gel giving product **1b** (0.14 g, 60%).

IR (KBr): 3403, 3020, 2940, 2856, 1711, 1606, 1476, 1420, 1363, 1215, 1085, 1062, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.57–1.81 (m, 4H), 1.99 (td, 1H, J = 11.1 Hz, J = 3.8 Hz), 2.11 (dd, 1H, J = 11.5 Hz, J = 1.0 Hz), 2.27 (s, 3H, NCH_3), 2.76 (d, 1H, J = 11.0 Hz), 2.81–2.86 (m, 1H), 4.40 (dd, 1H, J = 8.8 Hz, J = 1.3 Hz), 4.70 (d, 1H, J = 8.8 Hz), 6.46–6.78 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.67, 33.75, 45.83, 46.76, 55.05, 64.51, 80.87, 114.07, 115.61, 120.64, 134.68, 141.49, 147.10; MS(EI, 70ev) m/z (%) = 219 (5) [M^+], 161 (5), 147 (6), 105 (4), 91 (8), 71 (20), 58 (100); Anal. Calcd. for $C_{13}H_{17}NO_2$: C 71.21; H 7.81; N 6.39. Found: C 71.60; H 7.77; N 6.36.

Synthesis of 1′-Methylspiro[8-hydroxybenzopyran-3(4H),3′-piperidine] 2b. Compound **2a** (0.11 g, 0.44 mmol) and HCl (10 *N*, 15 mL) were mixed together, sealed, and heated at 100°C for 12 h. After cooling, the solution was neutralized with Na_2CO_3 solution, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude was subjected to flash chromatography on silica gel giving product **2b** (80 mg, 77%).

IR (KBr): 3330, 3019, 2942, 1711, 1600, 1475, 1428, 1362, 1216, 1084, 760, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.51–170 (m, 2H), 1.75–2.02 (m, 4H), 2.16 (d, 1H, J = 11.7 Hz), 2.24 (s, 3H, NCH_3), 2.39 (dq, 1H, J = 14.0 Hz, J = 3.3 Hz), 2.69 (dt, 1H, J = 11.6 Hz, J = 1.4 Hz), 2.85–2.90 (m, 1H), 4.11–4.31 (m, 2H), 6.72–6.91 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.57, 31.08, 34.18, 35.68, 46.62, 56.06, 63.45, 66.05, 112.19, 117.78, 120.07, 129.26, 141.80, 144.87; MS(EI, 70 ev) m/z (%) = 233 (7) [M^+], 161 (8), 105 (15), 91 (15), 71 (30), 58 (100); Anal. Calcd. for $C_{14}H_{19}NO_2$: C 72.07; H 8.21; N 6.00. Found: C 71.62; H 8.17; 5.97.

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