

## Synthesis and Biological Properties of New 5-Cyano-1,1-disubstituted Phthalans for the Treatment of Premature Ejaculation

Dong Sung Kim,<sup>†,‡</sup> Kyung Koo Kang,<sup>†</sup> Kyung Seok Lee,<sup>†</sup> Byoung Ok Ahn,<sup>†</sup> Moochi Yoo,<sup>†,\*</sup> and Seung Soo Yoon<sup>‡,\*</sup>

<sup>†</sup>Research Laboratory, Dong-A Pharmaceutical Company, Yongin, Gyeonggi 449-905, Korea. \*E-mail: moochi@donga.co.kr

<sup>‡</sup>Department of Chemistry, Sungkyunkwan University, Suwon, Gyeonggi 440-746, Korea. \*E-mail: ssooyoon@chem.skku.ac.kr

Received July 31, 2008

The synthesis of new 5-cyano-1,1-disubstituted phthalans having aromatic and aminoalkyl groups at C-1 position of phthalan ring and their biological evaluation are described. Most compounds exhibited comparable ejaculation-retarding effects to citalopram. Of these compounds, **3a, e** showed excellent efficacy in delaying ejaculation.

**Key Words** : Premature ejaculation, Phthalans, Efficacy

### Introduction

Premature ejaculation (PE)<sup>1</sup> is one of the most prevalent male sexual dysfunctions, with a prevalence rate of 30%, 3 times greater than that seen for erectile dysfunction.<sup>2</sup> Non-pharmacologically, behavioral methods (*e.g.* stop-start technique,<sup>3</sup> squeeze technique<sup>4</sup>) have been used for the treatment of PE. However they are difficult for patients to execute. Several pharmacologic and herbal treatments for PE are in use today. However, because none of these agents has yet been approved by the US FDA for this indication, they are being used investigationaly or off label. Pharmacological treatments have included the use of topical anesthetics,<sup>5</sup> tricyclic antidepressants (TCAs),<sup>6</sup> and selective serotonin reuptake inhibitors (SSRIs).<sup>7</sup> The use of topical anesthetics can produce the problem of local irritation and burning pain, and TCAs such as clomipramine have a high incidence of adverse effects. The introduction of the SSRIs, which have a benign adverse effect profile compared with TCAs, provided another option and SSRIs (paroxetine,<sup>8,10,12(a)</sup> fluoxetine,<sup>9,10</sup> fluvoxamine,<sup>10</sup> sertraline,<sup>11,8(d),9(c),10</sup> citalopram,<sup>12</sup> dapoxetine<sup>13</sup>) are reported to be effective for treating PE.

Citalopram is a potent and highly SSRIs antidepressant without much cardiotoxic, anticholinergic and sedating effects. It was suggested that citalopram's selectivity for the serotonergic system over other systems would cause considerable delay ejaculation.

Based on the importance of earlier findings, we carried out

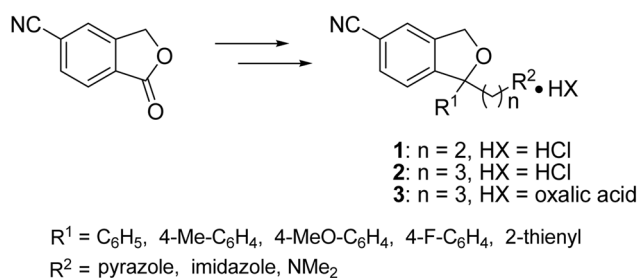


Figure 1.

the introduction of aromatics and aminoalkyl substitutes into 5-cyanophthalan nucleus in order to improve the activity for PE and safety like citalopram (Fig. 1) and the products showed good efficacy with delaying premature ejaculation.

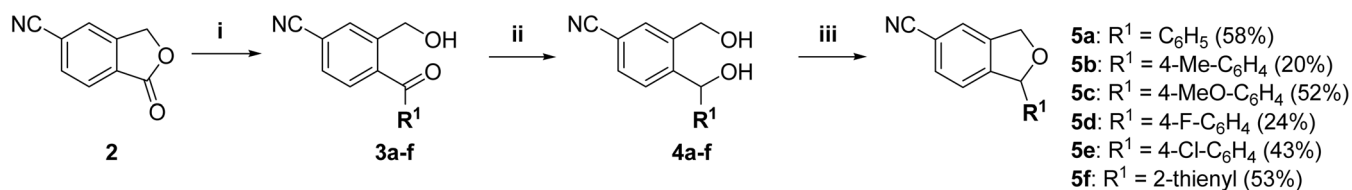
In this paper, we wish to describe synthesis of novel 5-cyanophthalans having aromatic and aminoalkyl group as C-1 side chains and biological evaluation for the compounds.

### Chemistry

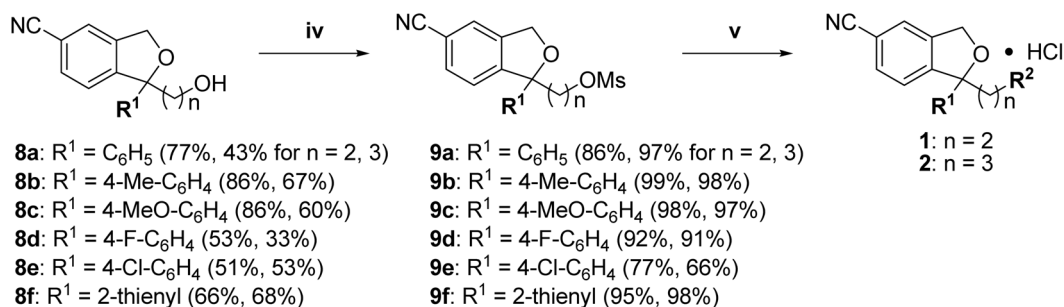
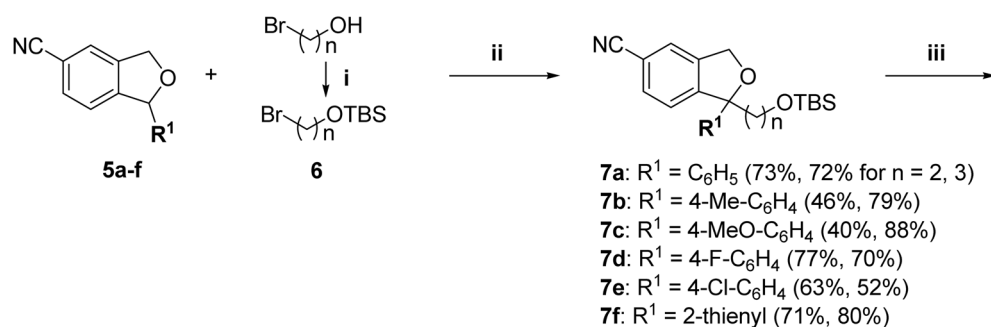
At first, we attempted the direct conversion 5-cyanophthalide (**2**)<sup>14</sup> into 3-(hydroxymethyl)-4-(1,1-disubstituted hydroxymethyl)benzimidazole using the two Grignard's reagents (ArMgBr then aminoalkyl MgBr) described Bogeso<sup>15</sup> however these conditions resulted in low yields (< 10%). So, 1-aryl-5-cyanophthalane **5a-f**, key intermediates, was prepared by the sequence outlined in Scheme 1.<sup>16</sup> The diol **4a-f** were prepared by Grignard's reaction of ArMgBr with 5-cyanophthalide (**2**) and subsequent reduction with NaBH<sub>4</sub>. The cyclization of diol **4a-f** with H<sub>3</sub>PO<sub>4</sub> in EtOAc afforded 1-aryl-5-cyanophthalane **5a-f**.

Introduction of the ethyl or propyl chain was performed by alkylation of phthalan **5a-f** with the corresponding bromo TBS protected alcohol **6** in the presence of NaH to yield the 1,1-disubstituted phthalan **7a-f** (Scheme 2). Deprotection of **7a-f** with tetrabutylammonium fluoride in THF provided the alcohol **8a-f**. Mesylation of hydroxyl group of **8a-f** followed by conversion of the resulting mesylate **9a-f** with amines such as pyrazole, imidazole, and dimethylamine in the presence of K<sub>2</sub>CO<sub>3</sub> gave amines, which upon saltation with HCl provided the desired target molecules **1** and **2**.

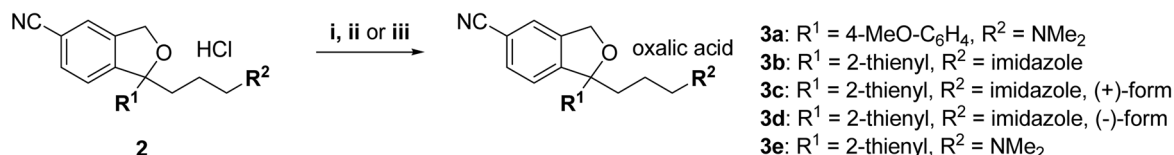
Selected compounds were performed trans saltation and chiral resolution by the sequence of reactions shown in Scheme 3. The salt exchange from HCl to oxalic acid to give oxalate **3a-e** gave the stable solids compared with HCl amorphous salts. The preparation of the single enantiomer **3c, d** carried out by the stereoselective crystallization of the diastereomeric salts of the **3b** with (-)/(+)-di-*p*-toloyltartaric acid.<sup>17</sup>



**Scheme 1.** Reagents and Reaction conditions: (i) R<sup>1</sup>MgBr, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to rt, 16 h; (ii) NaBH<sub>4</sub>, MeOH, 0 °C to rt, 3 h; (iii) 85% H<sub>3</sub>PO<sub>4</sub>, EtOAc, 80 °C, 3 h (20-58%, 3 steps).



**Scheme 2.** Reagents and Reaction conditions: (i) TBSCl, Imi, DMF, rt, 6 h (54% for n = 2, 36% for n = 3); (ii) NaH, DMSO, 80 °C, 24 h (40%-88%); (iii) TBAF, THF, rt, 2 h (33%-86%); (iv) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h (77%-99%); (v) amine, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 24 h then HCl/Et<sub>2</sub>O, Et<sub>2</sub>O, EtOAc, rt (31%-79%, 2 steps).



**Scheme 3.** Reagents and Reaction conditions: (i) aq. NaOH, THF; (ii) oxalic acid, EtOH (65% for **3a**, 81% for **3b**, 91% for **1e**, 2 steps); (iii) a) D-(–)-di-*p*-toluoyltartaric acid for **3c** or L-(+)-di-*p*-toluoyltartaric acid for **3d**, CH<sub>3</sub>CN, 70 °C, 1 h, b) 1 N NaOH, THF, rt, 0.5 h, then oxalic acid, EtOH (34% for **3c**, 33% for **3d**, 2 steps).

### Biological Properties

The title 5-cyano-1,1-disubstituted phthalans prepared above were evaluated for the efficacy on ejaculatory response by PCA (*p*-chloroamphetamine) induced ejaculation model<sup>18</sup> as shown in Table 1. Some compounds exhibited more potent activity for delaying ejaculation than control. With the exception of **2f**, 5-cyanophthalans having 3-dimethylaminopropyl group **2c**, **i**, **l**, **o**, **r** showed more potent delaying activity than those bearing 2-aminoethyl group. 2-Thienyl derivatives **2q**, **r** were as active as citalopram HCl (**2l**). The pyrazole derivatives showed lower activity than others. Among the compounds prepared, based on their efficacy on ejaculatory response, 3 compounds **2i**, **q**, **r** were selected and performed

trans saltation/chiral resolution (**3a-e**) for further evaluation.

Table 2 shows the efficacy on ejaculatory response of selected compounds **3a-e** together with citalopram as reference compound in a range of 50, 25, and 12.5 mg/kg dose. They showed excellent efficacy and dose-dependent response. Especially, the compounds **3a**, **e** had comparable activity to citalopram in delaying ejaculation at all dose range. The enantiomer **3c** showed more potent activity than (–)-form **3d** and was as active as racemic mixture **3b**.

In summary, the title 5-cyano-1,1-disubstituted phthalans bearing aromatic and aminoalkyl groups as C-1 side chains exhibited potent efficacy in delaying ejaculation by PCA induced ejaculation model in rat. In these series, **3a**, **e** exhibited excellent efficacy in delaying ejaculation.

**Table 1.** The efficacy of 5-cyano-1,1-disubstituted phthalans on ejaculatory response by PCA induced ejaculation model in rat<sup>a</sup>

	R <sup>1</sup>	R <sup>2</sup>	Yield	Efficacy <sup>b</sup>		R <sup>1</sup>	R <sup>2</sup>	Yield	efficacy
<b>1a</b>	C <sub>6</sub> H <sub>5</sub>	pyrazole	43%	N.T.	<b>2a</b>	C <sub>6</sub> H <sub>5</sub>	pyrazole	44%	N.T.
<b>1b</b>	C <sub>6</sub> H <sub>5</sub>	imidazole	36%	5/6	<b>2b</b>	C <sub>6</sub> H <sub>5</sub>	imidazole	53%	3/6
<b>1c</b>	C <sub>6</sub> H <sub>5</sub>	NMe <sub>2</sub>	66%	4/6	<b>2c</b>	C <sub>6</sub> H <sub>5</sub>	NMe <sub>2</sub>	61%	1/6*
<b>1d</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	pyrazole	43%	N.T.	<b>2d</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	pyrazole	70%	N.T.
<b>1e</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	imidazole	73%	N.T.	<b>2e</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	imidazole	59%	N.T.
<b>1f</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	52%	7/7	<b>2f</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	63%	7/8
<b>1g</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	pyrazole	36%	N.T.	<b>2g</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	pyrazole	68%	4/6
<b>1h</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	imidazole	59%	5/6	<b>2h</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	imidazole	73%	5/6
<b>1i</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	43%	N.T.	<b>2i</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	50%	1/6*
<b>1j</b>	4-F-C <sub>6</sub> H <sub>4</sub>	pyrazole	44%	6/6	<b>2j</b>	4-F-C <sub>6</sub> H <sub>4</sub>	pyrazole	45%	5/6
<b>1k</b>	4-F-C <sub>6</sub> H <sub>4</sub>	imidazole	38%	2/6	<b>2k</b>	4-F-C <sub>6</sub> H <sub>4</sub>	imidazole	64%	3/6
<b>1l</b>	4-F-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	51%	3/6	<b>2l</b>	4-F-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	40%	0/6*
<b>1m</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	pyrazole	54%	6/6	<b>2m</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	pyrazole	57%	6/6
<b>1n</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	imidazole	79%	4/6	<b>2n</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	imidazole	70%	5/7
<b>1o</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	36%	2/6	<b>2o</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	NMe <sub>2</sub>	62%	2/7*
<b>1p</b>	2-thienyl	pyrazole	66%	7/7	<b>2p</b>	2-thienyl	pyrazole	60%	7/7
<b>1q</b>	2-thienyl	imidazole	50%	5/7*	<b>2q</b>	2-thienyl	imidazole	55%	0/7*
<b>1r</b>	2-thienyl	NMe <sub>2</sub>	31%	5/7*	<b>2r</b>	2-thienyl	NMe <sub>2</sub>	63%	1/7*

N.T.: not tested; \**p* < 0.05, compared with PCA control. <sup>a</sup>Oral administration (50 mg/kg in 1% HPMC), before 80mins treating PCA. <sup>b</sup>Ejaculation ratio (the number of rats ejaculated/total rats tested, n/n), vehicle (7/7).

**Table 2.** The efficacy of **3a-e** on ejaculation in PCA induced model in rat<sup>a</sup>

Dose (mg/kg)	vehicle	<b>3a</b>	<b>3b</b>	<b>3c</b>	<b>3d</b>	<b>3e</b>	citalopram
50	17/18 <sup>b</sup> (653 ± 208) <sup>c</sup>	0/9* (N.D.)	2/9* (988 ± 047)	3/8* (811 ± 069)	4/8 (864 ± 142)	1/9* (719)	0/9* (N.D.)
25	15/18 (624 ± 207)	0/9* (N.D.)	1/9* (843)	1/8* (1067)	5/8 (801 ± 223)	2/9* (891 ± 018)	0/9* (N.D.)
12.5	16/18 (557 ± 162)	3/9* (537 ± 096)	5/9 (532 ± 190)	6/8 (670 ± 213)	4/8 (655 ± 294)	2/9* (577 ± 034)	1/9* (653)

N.D.: not detected; \**p* < 0.05, compared with PCA control. <sup>a</sup>Oral administration (in 1% HPMC), before 30 mins treating PCA. <sup>b</sup>Ejaculation ratio (the number of rats ejaculated/total rats tested, n/n). <sup>c</sup>Latency (time to ejaculation after PCA injection, mean ± SD, sec)

## Experimental

### PCA (*p*-chloroamphetamine) induced ejaculation model

**assay.** Male Wistar rats, 240-260 g, were used and anesthetized with ketamine 30 mg/kg, xylazine 8 mg/kg, and acepromazine 0.04 mg/kg (*I.M.*). Each compound was suspended in 1% HPMC solution (50, 25 and 12.5 mg/kg) and given orally in a volume of 5 mL/kg. The administration of compound and anesthesia were performed 80, 20 min before the administration of PCA (5 mg/mL saline/kg, *i.p.*). The ejaculatory response - rhythmic contraction of blubocavernous muscle and ejaculation of ejaculate - was observed for 30 min after PCA administration. The statistical significance of differences between groups in ejaculation ratio (the number of rats ejaculated/total rats tested) was analyzed with Fisher exact test and latency (time to ejaculation after PCA injection) was expressed as mean ± SD (not analyzed).

**1-(Thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile (**5f**).** To a solution of 5-cyanophthalide (**2**) (50.64 g, 318.18 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (500 mL) was added dropwise

2-thienyl magnesium bromide (1 M in THF, 350 mL, 350.0 mmol) at -78 °C under nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with 20% aq. NH<sub>4</sub>Cl and the organic layer was diluted with MeOH (100 mL). NaBH<sub>4</sub> (24.08 g, 636.42 mmol) was slowly added to the mixture at 0 °C and stirred for 3 h at room temperature. The mixture was quenched with 20% aq. NH<sub>4</sub>Cl and washed with brine. The organic layer was concentrated *in vacuo* to give diol compound **4f** as a yellow oil. To a solution of a compound **4f** in EtOAc (500 mL) was added 85% H<sub>3</sub>PO<sub>4</sub> (500 mL) at room temperature and heated to 80 °C. After being stirred for 3 h at the same temperature, the mixture was washed with water, sat. NaHCO<sub>3</sub> and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was treated with 2-propanol to provide a solid. This solid was filtered and washed with *n*-hexane to give 1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile (**5f**) (42.71 g, 59%, 3 steps) as a pale brown solid; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.86 (s, 1H), 7.75 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 7.50 (dd, *J* = 5.2 Hz, 1.4 Hz, 1H), 7.35 (d, *J* = 8.0

Hz, 1H), 7.18 (m, 1H), 7.02 (dd,  $J = 5.2$  Hz, 3.2 Hz, 1H), 6.53 (s, 1H), 5.20 and 5.09 (dd,  $J = 13.2$  Hz, 2.4 Hz, 2H).

**1-(3-*tert*-Butyldimethylsilyloxypropyl)-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile (7f).** To a solution of 5-cyanophthalne **5f** (42.70 g, 187.87 mmol) in DMSO (400 mL) was added NaH (60% in mineral oil, 9.02 g, 225.44 mmol) and stirred for 0.5 h at room temperature. 3-Bromo-1-(*tert*-butyldimethylsilyl)propanol (**6**) (71.37 g, 281.18 mmol) was added to the mixture at the same temperature and heated to 80 °C. After being stirred for 24 h, the mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4:1) to give coupling compound **7f** (60.28 g, 80%) as a yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.58 (d,  $J = 7.8$  Hz, 1H), 7.50 (s, 1H), 7.33 (d,  $J = 7.8$  Hz, 1H), 7.19 (d,  $J = 5.2$  Hz, 1H), 6.88-6.94 (m, 2H), 5.23 and 5.16 (m, 2H), 3.57 (m, 2H), 2.28 (m, 2H), 1.60 and 1.33 (m, 2H), 0.86 (s, 9H), -0.05 and -0.01 (s, 6H).

**1-(3-Hydroxypropyl)-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile (8f).** To a solution of compound **7f** (60.28 g, 150.84 mmol) in THF (500 mL) was added tetrabutylammonium fluoride (1 M in THF, 226.3 mL, 226.3 mmol) at room temperature. After being stirred for 2 h, the mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1:1) to give alcohol **8f** (29.29 g, 68%) as a pale yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.59 (d,  $J = 7.4$  Hz, 1H), 7.51 (s, 1H), 7.36 (d,  $J = 7.4$  Hz, 1H), 7.19 (d,  $J = 5.2$  Hz, 1H), 6.89-6.94 (m, 2H), 5.24 and 5.18 (d,  $J = 13.0$  Hz, 2H), 3.62 (m, 2H), 2.39 and 2.27 (m, 2H), 1.64 and 1.50 (m, 2H).

**1-(3-Methanesulfonyloxypropyl)-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile (9f).** To a solution of compound **8f** (29.29 g, 102.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) were added Et<sub>3</sub>N (15.58 g, 153.96 mmol) and MsCl (14.10 g, 123.17 mmol) at 0 °C. After being stirred for 1 h at the same temperature, the mixture was washed with water and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to give methanesulfonate **9f** (36.56 g, 98%) as pale yellow oil. It was used to next reaction without further purification; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.61 (d,  $J = 8.0$  Hz, 1H), 7.51 (s, 1H), 7.37 (d,  $J = 8.0$  Hz, 1H), 7.20 (d,  $J = 5.2$  Hz, 1H), 6.94 (m, 1H), 6.90 (d,  $J = 3.3$  Hz, 1H), 5.23 and 5.17 (d,  $J = 12.8$  Hz, 2H), 4.22 (m, 2H), 2.96 (s, 3H), 2.39 and 2.62 (m, 2H), 1.81 and 1.71 (m, 2H).

**1-{3-(Imidazol-1-yl)propyl}-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile HCl (2q).** To a solution of mesylate **9f** (18.65 g, 51.31 mmol) in DMF (200 mL) were added K<sub>2</sub>CO<sub>3</sub> (28.36 g, 205.24 mmol) and imidazole (13.97 g, 205.24 mmol) at room temperature and heated to 80 °C. After being stirred for 24 h, the mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel column

chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 9:1) to give amine compound (9.04 g, 58%) as a pale yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.95 (s, 1H), 7.61 (d,  $J = 8.2$  Hz, 1H), 7.52 (s, 1H), 7.32 (d,  $J = 8.2$  Hz, 1H), 7.22 (m, 1H), 7.14 (s, 1H), 6.95 (m, 1H), 6.91 (s, 1H), 6.86 (m, 1H), 5.25 (d,  $J = 12.8$  Hz, 1H), 5.18 (d,  $J = 12.8$  Hz, 1H), 4.07 (t,  $J = 7.0$  Hz, 2H), 2.28 (m, 1H), 2.10 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H). It was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and treated HCl (2 M in Et<sub>2</sub>O, 27.0 mL, 54.0 mmol) at room temperature. The solution was decanted and washed with Et<sub>2</sub>O. The residue was dried to give HCl salt (9.46 g, 94%) as pale yellow foam; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  14.42 (br s, 1H), 9.09 (s, 1H), 7.83 (s, 1H), 7.81 (d,  $J = 7.8$  Hz, 1H), 7.72 (s, 1H), 7.65 (s, 1H), 7.63 (d,  $J = 7.8$  Hz, 1H), 7.39 (d,  $J = 4.8$  Hz, 1H), 7.08 (d,  $J = 3.6$  Hz, 1H), 6.98 (m, 1H), 5.20 (m, 2H), 4.02 (t,  $J = 7.0$  Hz, 2H), 2.21 (m, 2H), 1.79 and 1.61 (m, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  148.6, 148.0, 139.2, 134.9, 132.0, 127.3, 125.7, 124.8, 122.8, 122.7, 121.7, 119.5, 118.5, 110.7, 89.1, 71.4, 48.2, 37.3, 24.8.

**1-{3-(Imidazol-1-yl)propyl}-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalic acid (3b).** To a solution of HCl salt **2q** (6.95 g, 18.69 mmol) in THF (140 mL) was added 2 N-NaOH (11.2 mL, 22.4 mmol) at 0 °C and stirred for 0.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with water and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub> and treated with charcoal. The solution was filtered on celite pad and the filtrate was evaporated *in vacuo* to give free amine (5.72 g, 91%) as a pale yellow oil. The solution of free amine in EtOH (70 mL) was added oxalic acid (2.36 g, 18.76 mmol) at room temperature and stirred for 0.5 h. The mixture was cooled to 0 °C and stirred for 1 h. The white precipitate was filtered and washed with *n*-hexane to give **3b** (6.46 g, 89%) as white solid: mp = 160.7 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.34 (s, 1H), 7.81 (s, 1H), 7.80 (d,  $J = 8.0$  Hz, 1H), 7.60 (d,  $J = 7.8$  Hz, 1H), 7.41 (s, 1H), 7.38 (d,  $J = 4.8$  Hz, 1H), 7.25 (s, 1H), 7.06 (d,  $J = 3.2$  Hz, 1H), 6.98 (m, 1H), 5.16 (m, 2H), 4.05 (t,  $J = 7.0$  Hz, 2H), 2.18 (m, 2H), 1.75 and 1.55 (m, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  162.7, 148.7, 148.1, 139.2, 136.0, 132.0, 127.3, 125.7, 124.8, 123.8, 122.7, 122.6, 120.4, 118.5, 110.7, 89.2, 71.4, 47.0, 37.6, 25.3.

**(+)-1-{3-(Imidazol-1-yl)propyl}-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalic acid (3c).** To a solution of 1-{3-(imidazol-1-yl)propyl}-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile (6.97 g, 20.8 mmol) in CH<sub>3</sub>CN (85 mL) was added D-(−)-di-*p*-toluoyltartaric acid (8.03 g, 20.8 mmol) at room temperature. After being stirred for 20 min, the mixture was heated to 60 °C and stirred for 1 h. MeOH (6.8 mL) was added to the mixture at the same temperature and stirred for 1 h. The white solid was filtered and dried to give DPPTA salt (5.48 g, 34%). To a solution of (+)-1-{3-(Imidazol-1-yl)propyl}-1-(thien-2-yl)-1,3-dihydro-5-isobenzofurancarbonitrile D-(−)-DPPTA salt (5.48 g, 7.85 mmol) in THF (100 mL) was added 1 N NaOH (10 mL, 10 mmol) at room temperature and stirred for 0.5 h. The mixture was concentrated *in vacuo*. The residue was treated

with EtOAc and water. The organic layer was dried over anhydrous MgSO<sub>4</sub> and evaporated under reduced pressure to give free amine (1.41 g, 54%) as a pale yellow oil. The oil was dissolved with EtOH (14 mL) and oxalic acid (0.58 g, 4.6 mmol) was added to the mixture. After being stirred for 1 h at 0 °C, the precipitate was filtered and washed with *n*-hexane to give oxalic acid salt **3c** (1.45 g, 81%) as a white solid:  $[\alpha] = +6.02$  deg (Na 589 nm, 24.9 °C, MeOH, *c* = 0.1).

**Acknowledgments.** This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A080062).

### References

- Premature ejaculation (PE) is defined by the diagnostic and statistical manual of mental disorders (DSM-IV-TR, revision IV) as “persistent or recurrent onset of orgasm and ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it,” which causes “marked distress or interpersonal difficulty”.
- (a) Laumann, E. O.; Paik, A.; Rosen, R. C. *JAMA*. **1999**, *281*, 537. (b) Laumann, E. O.; Nicolosi, A.; Glasser, D. B. *Int. J. Impot. Res.* **2005**, *17*, 39.
- Semans, J. H. *South. Med. J.* **1956**, *49*, 353.
- Masters, W.; Johnson, V. *Human Sexual Inadequacy*; Little, Brown: Boston, Mass., 1970.
- (a) Berkovitch, M.; Keresteci, A. G.; Koren, G. *J. Urol.* **1995**, *154*, 1360. (b) Xin, Z. C.; Choi, Y. D.; Lee, S. H. *Yonsei Med. J.* **1997**, *38*, 277.
- Goodman, R. E. *J. Int. Med. Res.* **1977**, *5*, 78.
- (a) Rosen, R. C.; Lane, R. M.; Menza, M. *J. Clin. Psychopharmacol.* **1999**, *19*, 67. (b) Waldinger, M. D.; Zwinderman, A. H.; Schweitzer, D. H.; Olivier, B. *Int. J. Impot. Res.* **2004**, *16*, 369. (c) Moreland, A. J.; Makela, E. H. *Ann. Pharmacother.* **2005**, *39*, 1296.
- (a) Waldinger, M. D.; Hengeveld, M. W.; Zwinderman, A. H. *Am. J. Psychiatry* **1994**, *151*, 1377. (b) Waldinger, M. D.; Hengeveld, M. W.; Zwinderman, A. H. *Br. J. Urol.* **1997**, *79*, 592. (c) McMahon, C. G.; Touma, K. *J. Urol.* **1999**, *161*, 1826. (d) Waldinger, M. D.; Zwinderman, A. H.; Olivier, B. *J. Clin. Psychopharmacol.* **2001**, *21*, 293.
- (a) Kara, H.; Aydin, S.; Yucel, M.; Agargum, M. Y.; Odabas, O.; Yilmaz, Y. *J. Urol.* **1996**, *156*, 1631. (b) Lee, H. S.; Song, D. H.; Kim, C. H.; Choi, H. K. *J. Clin. Psychopharmacol.* **1996**, *16*, 379. (c) Kim, S. C.; Seo, K. K. *J. Urol.* **1998**, *159*, 425.
- Waldinger, M. D.; Hengeveld, M. W.; Zwinderman, A. H.; Olivier, B. *J. Clin. Psychopharmacol.* **1998**, *18*, 274.
- (a) Mendels, J.; Camera, A.; Sikes, C. *J. Clin. Psychopharmacol.* **1995**, *15*, 341. (b) Balbay, M. D.; Yildiz, M.; Salvarci, A.; Ozsar, O.; Ozbek, E. *Int. Urol. Nephrol.* **1998**, *30*, 81. (c) Biri, H.; Isen, K.; Sinik, Z.; Onaran, M.; Kupeli, B.; Bozkirli, I. *Int. Urol. Nephrol.* **1998**, *30*, 611. (d) Kim, S. W.; Paick, J. S. *Urology* **1999**, *54*, 544.
- (a) Waldinger, M. D.; Zwinderman, A. H.; Olivier, B. *J. Clin. Psychopharmacol.* **2001**, *21*, 556. (b) Atmaca, M.; Kuloglu, M.; Tezcan, E.; Semercioz, A. *Int. J. Impot. Res.* **2002**, *14*, 502. (c) Atmaca, M.; Kuloglu, M.; Tezcan, E.; Semercioz, A. *Br. J. Urol. Int.* **2003**, *91*, 252. (d) Safarinehad, M. R.; Hosseini, S. Y. *Int. J. Impot. Res.* **2005**, *17*, 1. (e) de Jong, T. R.; Pattij, T.; Veening, J. G.; Dederen, P. J. W. C.; Waldinger, M. D.; Cools, A. R.; Olivier, B. *Eur. J. Pharmacol.* **2005**, *509*, 49.
- (a) Anon, N. Z. *Drugs R&D.* **2005**, *6*, 307. (b) Andersson, K. E.; Mulhall, J. P.; Wyllie, M. G. *Br. J. Urol. Int.* **2006**, *97*, 311. (c) Giuliano, F.; Bernabe, J.; Gengo, P.; Alexandre, L.; Clement, P. *J. Urol.* **2007**, *177*, 386.
- Micheli, F.; Crippa, L.; Donati, D.; Fabio, R. D.; Leslie, C. *Il Farmaco* **2001**, *56*, 715.
- Bogeso, K. P.; Toft, A. S. *U.S. Patent 4136193*, 1979.
- Petersen, H.; Ahmadian, H.; Rock, M. H. *U.S. Patent 6420574*, 2002.
- Bogeso, K. P.; Perregaard, J. *U.S. Patent 4943590*, 1979.
- (a) Fuller, R. W. *Neurochem. Res.* **1992**, *17*, 119. (b) Yonezawa, A.; Watanabe, C.; Ando, R.; Furuta, S.; Sakurada, S.; Yoshimura, H.; Iwanaga, T.; Kimura, Y. *Life Sciences* **2000**, *67*, 3031.