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

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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.

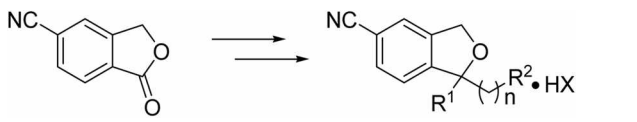
Key Words : Premature ejaculation, Phthalans, Efficacy

Introduction

Premature ejaculation (PE)[1] is one of the most prevalent male sexual dysfunctions, with a prevalence rate of 30%, 3 times greater than that seen for erectile dysfunction.[2] Non-pharmacologically, behavioral methods (*e.g.* stop-start technique,[3] squeeze technique[4]) 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 investigationally or off label. Pharmacological treatments have included the use of topical anesthetics,[5] tricyclic antidepressants (TCAs),[6] and selective serotonin reuptake inhibitors (SSRIs).[7] 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,[8,10,12(a)] fluoxetine,[9,10] fluvoxamine,[10] sertraline,[11,8(d),9(c),10] citalopram,[12] dapoxetine[13]) are reported to be effective for treating PE.

Citalopram is a potent and highly SSRIs antidepressant without much cardiotoxic, anticholinergenic 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 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.



1: n = 2, HX = HCl
2: n = 3, HX = HCl
3: n = 3, HX = oxalic acid

R^1 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 2-thienyl
R^2 = pyrazole, imidazole, NMe_2

Figure 1.

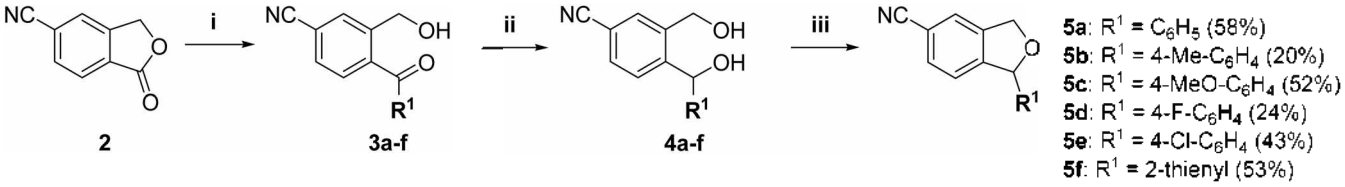
In this paper, we wish to describe synthesis of novel 5-cyanophthalans having aromatic and aminoalkyl group as C-1 side chains and biological evaluation for the compounds.

Chemistry

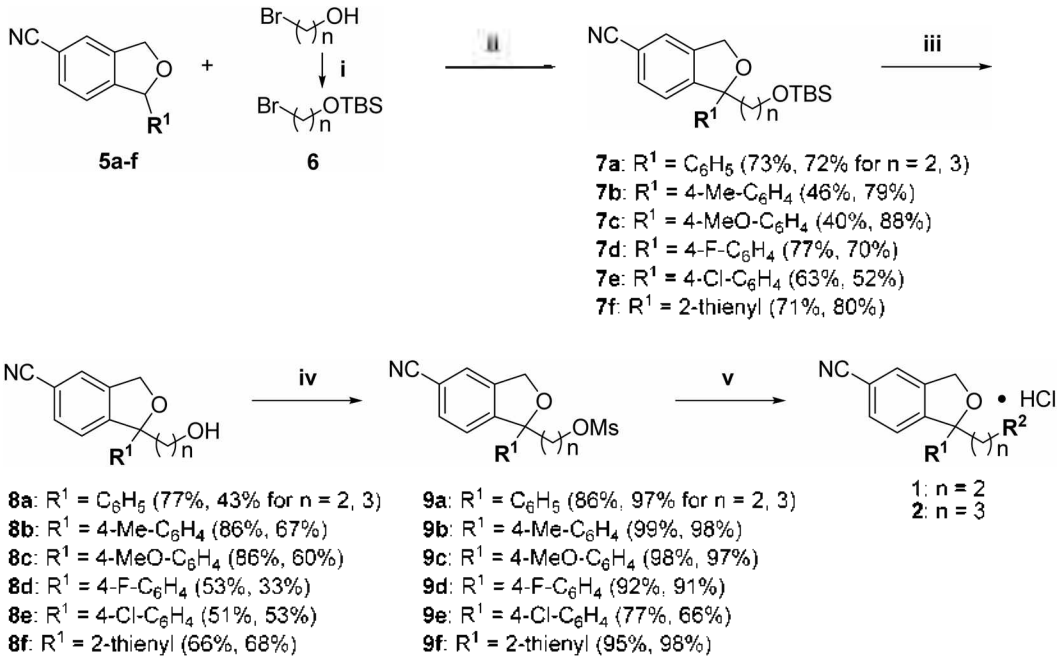
At first, we attempted the direct conversion 5-cyanophthalide (**2**)[14] into 3-(hydroxymethyl)-**4**-(1,1-disubstituted hydroxymethyl)benzonitril using the two Grignard's reagents (ArMgBr then aminoalkyl MgBr) described Bogeso[15] however these conditions resulted in low yields (< 10%). So, 1-aryl-5-cyanophthalane **5a-f**, key intermediates, was prepared by the sequence outlined in Scheme 1.[16] The diol **4a-f** were prepared by Grignard's reaction of ArMgBr with 5-cyanophthalide (**2**) and subsequent reduction with $NaBH_4$. The cyclization of diol **4a-f** with H_3PO_4 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 alchol **6** in the presence of NaH to yield the 1,1-disubstituted phtalan **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_2CO_3 gave amines, which upon saltation with HCl provided the desired target molecules **1** and **2**.

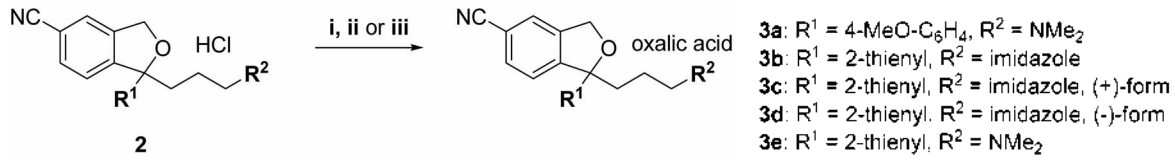
Selected compounds were performed trans saltation and chiral resolution by the sequence of reactions shown in Scheme 3. The salt exchange from HCl to oxalic acid to give oxalate **3a-e** gave the stable solids compared with HCl amorphous salts. The preparation of the single enantiomer **3c**, **d** carried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



Scheme 1. *Reagents and Reaction conditions*: (i) R^1MgBr, CH_2Cl_2, −78 °C to rt, 16 h; (ii) $NaBH_4$, MeOH, 0 °C to rt, 3 h; (iii) 85% H_3PO_4, 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_3N, CH_2Cl_2, 0 °C, 1 h (77%-99%); (v) amine, K_2CO_3, DMF, 80 °C, 24 h then HCl/Et_2O, Et_2O, 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_3CN, 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[18] 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[a]

	R^1	R^2	Yield	Efficacy[b]		R^1	R^2	Yield	efficacy
1a	C_6H_5	pyrazole	43%	N.T.	**2a**	C_6H_5	pyrazole	44%	N.T.
1b	C_6H_5	imidazole	36%	5/6	**2b**	C_6H_5	imidazole	53%	3/6
1c	C_6H_5	NMe_2	66%	4/6	**2c**	C_6H_5	NMe_2	61%	1/6*
1d	4-Me-C_6H_4	pyrazole	43%	N.T.	**2d**	4-Me-C_6H_4	pyrazole	70%	N.T.
1e	4-Me-C_6H_4	imidazole	73%	N.T.	**2e**	4-Me-C_6H_4	imidazole	59%	N.T.
1f	4-Me-C_6H_4	NMe_2	52%	7/7	**2f**	4-Me-C_6H_4	NMe_2	63%	7/8
1g	4-MeO-C_6H_4	pyrazole	36%	N.T.	**2g**	4-MeO-C_6H_4	pyrazole	68%	4/6
1h	4-MeO-C_6H_4	imidazole	59%	5/6	**2h**	4-MeO-C_6H_4	imidazole	73%	5/6
1i	4-MeO-C_6H_4	NMe_2	43%	N.T.	**2i**	4-MeO-C_6H_4	NMe_2	50%	1/6*
1j	4-F-C_6H_4	pyrazole	44%	6/6	**2j**	4-F-C_6H_4	pyrazole	45%	5/6
1k	4-F-C_6H_4	imidazole	38%	2/6	**2k**	4-F-C_6H_4	imidazole	64%	3/6
1l	4-F-C_6H_4	NMe_2	51%	3/6	**2l**	4-F-C_6H_4	NMe_2	40%	0/6*
1m	4-Cl-C_6H_4	pyrazole	54%	6/6	**2m**	4-Cl-C_6H_4	pyrazole	57%	6/6
1n	4-Cl-C_6H_4	imidazole	79%	4/6	**2n**	4-Cl-C_6H_4	imidazole	70%	5/7
1o	4-Cl-C_6H_4	NMe_2	36%	2/6	**2o**	4-Cl-C_6H_4	NMe_2	62%	2/7*
1p	2-thienyl	pyrazole	66%	7/7	**2p**	2-thienyl	pyrazole	60%	7/7
1q	2-thienyl	imidazole	50%	5/7*	**2q**	2-thienyl	imidazole	55%	0/7*
1r	2-thienyl	NMe_2	31%	5/7*	**2r**	2-thienyl	NMe_2	63%	1/7*

N.T.: not tested; *$p < 0.05$, compared with PCA control. [a]Oral administration (50 mg/kg in 1% HPMC), before 80mins treating PCA. [b]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[a]

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

N.D.: not detected; *$p < 0.05$, compared with PCA control. [a]Oral administration (in 1% HPMC), before 30 mins treating PCA. [b]Ejaculation ratio (the number of rats ejaculated/total rats tested, n/n). [c]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_2Cl_2 (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_4Cl and the organic layer was diluted with MeOH (100 mL). $NaBH_4$ (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_4Cl 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_3PO_4 (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. $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ 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-2yl)-1,3-dihydro-5-isobenzofurancarbonitrile (**5f**) (42.71 g, 59%, 3 steps) as a pale brown solid; ^{1}H NMR (400 MHz, DMSO-d_6) 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 $MgSO_4$ 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 $MgSO_4$ 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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_2Cl_2 (300 mL) were added Et_3N (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 $MgSO_4$ 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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_2CO_3 (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 $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 9:1) to give amine compound (9.04 g, 58%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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_2Cl_2 (50 mL) and treated HCl (2 M in Et_2O, 27.0 mL, 54.0 mmol) at room temperature. The solution was decanted and washed with Et_2O. The residue was dried to give HCl salt (9.46 g, 94%) as pale yellow foam; ^{1}H NMR (400 MHz, DMSO-d_6) δ 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); ^{13}C NMR (100 MHz, DMSO-d_6) δ 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 $MgSO_4$ 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; ^{1}H NMR (400 MHz, DMSO-d_6) δ 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); ^{13}C NMR (100 MHz, DMSO-d_6) δ 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-isobenzofurancarbo-nitrile (6.97 g, 20.8 mmol) in CH_3CN (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 $MgSO_4$ 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 ºC, 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 ºC, MeOH, c = 0.1).

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

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1. 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".
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