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

Dong Sung Kim,†‡ Kyung Koo Kang,† Kyung Seok Lee,† Byoung Ok Ahn,† Moohi Yoo,†,* and Seung Soo Yoon†,*

†Research Laboratory, Dong-A Pharmaceutical Company, Yongin, Gyeonggi 449-905, Korea. E-mail: moohi@donga.co.kr
‡Department of Chemistry, Sangkyunkwan University, Suwon, Gyeonggi 440-746, Korea. E-mail: ssyoon@chem.sku.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) is one of the most prevalent male sexual dysfunctions, with a prevalence rate of 30%, 3 times greater than that seen for erectile dysfunction. Non-pharmacologically, behavioral methods (e.g. stop-start technique, squeeze technique) 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 investigational or off label. Pharmacological treatments have included the use of topical anesthetics, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs). 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. 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-cyano phthalan 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-cyano phthalans 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) into 3-(hydroxymethyl)-4-(1,1-disubstituted hydroxymethyl)benzonitril using the two Grignard’s reagents (ArMgBr then aminoalkyl MgBr) described Bogeso however these conditions resulted in low yields (<10%). So, 1aryl-5-cyanophthalane 5a-f, key intermediates, was prepared by the sequence outlined in Scheme 1. The diol 4a-f were prepared by Grignard’s reaction of ArMgBr with 5-cyanophthalide (2) and subsequent reduction with NaBH4. The cyclization of diol 4a-f with H3PO4 in EtOAc afforded 1aryl-5-cyanophthalane 5a-f.

Introduction of the ethyl or propyl chain was performed by alkylation of phthalan 5a-f with the corresponding bromo alcohols protected alkalol 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 K2CO3 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.
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 as shown in Table 1. Some compounds exhibited more potent activity for delaying ejaculation than control. With the exception of 2f, 5-cyano phthalans 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 in delaying ejaculation 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.
**Experimental**

**PCA (p-chloramphetamine) 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-cyanophthalalide (2) (50.64 g, 318.18 mmol) in anhydrous CH2Cl2 (500 mL) was added dropwise 2-thieryl 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. NH4Cl and the organic layer was diluted with MeOH (100 mL). NaBH4 (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. NH4Cl 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% H3PO4 (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. NaHCO3 and brine. The organic layer was dried over anhydrous MgSO4 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; 1H NMR (400 MHz, DMSO-d6) 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, 2H).

---

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

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

N.D.: not detected; *p < 0.05, compared with PCA control. *Oral administration (in 1% HPMC), before 30 mins treating PCA. **Ejaculation ratio (the number of rats ejaculated/total rats tested, n/n). 3Latency (time to ejaculation after PCA injection, mean ± SD, sec)
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-cyanophthalanth 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. After being stirred for 2 h, the mixture was added with EtOAc and washed with water and brine. The organic layer was dried over anhydrous MgSO₄ 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; ⁱH NMR (400 MHz, CDCl₃) δ 7.59 (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 MgSO₄ 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; ⁱH NMR (400 MHz, CDCl₃) 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 CHCl₃ (300 mL) were added Et₃N (15.58 g, 153.96 mmol) and MsCl (14.10 g, 71.37 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. After being stirred for 2 h, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 9:1) to give amine compound (9.04 g, 58%) as a pale yellow oil; ⁱH NMR (400 MHz, CDCl₃) 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), 0.86 (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, 2H), 1.90 (m, 1H), 1.78 (m, 1H). It was dissolved in CH₂Cl₂ (50 mL) and treated HCl (2 M in EtO, 27.0 mL, 540 mmol) at room temperature. The solution was decanted and washed with Et₂O. The residue was dried to give HCl salt (9.46 g, 94%) as pale yellow foam; ¹³C NMR (100 MHz, DMSO-d₆) 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); ¹³C NMR (100 MHz, DMSO-d₆) 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, 18.76 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 MgSO₄ 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; ¹³C NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (100 MHz, DMSO-d₆) 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-isobenzofurancarbonitrile-nitro (6.97 g, 20.8 mmol) in CH₂CN (85 mL) was added D-(-)-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 MgSO₄ 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: [α] = +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

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”.


