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(71) Applicant (for all designated States except US): **DONG-A PHARMACEUTICAL CO., LTD** [KR/KR]; 252 Yongdu-dong Dongdaemun-ku, Seoul 130-072 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LEE, Yeong Geon** [KR/KR]; #224-104 Chungmujugong Apt., Geumjeong-dong Gunpo-si, Gyeonggi-do 435-050 (KR). **CHOI, Soo-Jung** [KR/KR]; #201-1201 Jung-angheights Apt. 1282, Sanggye-dong Nowon-gu, Seoul 139-200 (KR). **KANG, Tae-Kyung** [KR/KR]; #1001-905 Cheong-solsharmang Apt. 676-23, Naebalsan-2dong Gangseo-gu, Seoul 157-282 (KR). **SEO, Mi-Jeong** [KR/KR]; 456-3 Sanggal-dong Giheung-gu Yongin-si, Gyeonggi-do 446-905 (KR). **SHIN, Chang-Yong** [KR/KR]; 9/5 354 Geumho-dong 1-ga Seongdong-gu, Seoul 133-091 (KR). **LEE, Kyung-Seok** [KR/KR]; #102-2002 Min-sokmaeulssangyong Apt., Bora-dong Giheung-gu Yongin-si, Gyeonggi-do 446-954 (KR). **AHN, Gook-Jun** [KR/KR]; #2702-406 Baekhyeonmaeuljugong Apt., Dongbaek-Dong Giheung-gu Yongin-si, Gyeonggi-do 446-911 (KR). **CHOI, Seul-Min** [KR/KR]; #149-1906 Hwanggoljugong Apt., Yeongtong-dong Yeongtong-gu Suwon-si, Gyeonggi-do 443-740 (KR). **KIM, Yong-Duck** [KR/KR]; #503-201 Sinnamusiljugong Apt. 964-5,

Yeongtong-dong Yeongtong-gu Suwon-si, Gyeonggi-do 443-470 (KR). **KIM, Dong-Hwan** [KR/KR]; #1-506 Samgak Apt. Hangangno-1ga Yongsan-gu, Seoul 140-011 (KR). **KANG, Kyung-Koo** [KR/KR]; #714-701 Donga Apt. Salgugol, Yeongtong-dong Yeongtong-gu Suwon-si, Gyeonggi-do 443-470 (KR). **SHIM, Hyun-Joo** [KR/KR]; #124-1902 Dongasolecity Apt., Bojeong-dong Giheung-gu Yongin-si, Gyeonggi-do 446-940 (KR). **KIM, Dong-Sung** [KR/KR]; #503-1009 Jugong Apt. Jamsil-dong Songpa-gu, Seoul 138-220 (KR). **AHN, Byoung-Ok** [KR/KR]; #102-201 Baemeuru-mael Apt. 555, Yeongmun-ri Pogok-eup Cheoin-gu Yongin-si, Gyeonggi-do 449-813 (KR). **YOO, Moo-Hi** [KR/KR]; #5-801 Woosung 3cha Apt. Gaepo-1dong Kangnam-gu, Seoul 135-241 (KR).

(74) Agent: **LEE, Won-Hee**; 8th Fl. Sung-ji Heights II 642-16, Yoksam-dong Kangnam-ku, Seoul 135-080 (KR).

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(54) Title: NOVEL 1,3-DIHYDRO-5-ISOBENZOFURANCARBONITRILE DERIVATIVES AND PHARMACEUTICAL COMPOSITION THEREOF FOR THE TREATMENT OF PREMATURE EJACULATION

(57) Abstract: Disclosed herein are novel 1,3-dihydro-5-isobenzofurancarbonitrile derivatives represented by Formula 1, or pharmaceutically acceptable salts thereof. Also disclosed is a pharmaceutical composition for treating or preventing premature ejaculation including the compound. The 1,3-dihydro-5-isobenzofurancarbonitrile derivatives have a short half-life and inhibit the ejaculation process by selectively inhibiting serotonin reuptake via a serotonin reuptake transporter present in a presynaptic neuron. Thus, the compounds are useful in the treatment and prevention of premature ejaculation.



WO 2009/057974 A2

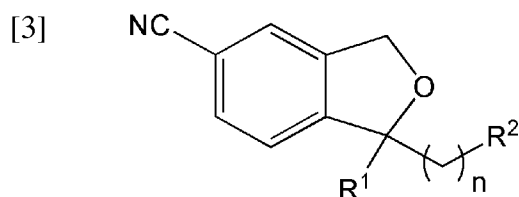
Description

NOVEL 1,3-DIHYDRO-5-ISOBENZOFURANCARBONITRILE DERIVATIVES AND PHARMACEUTICAL COMPOSITION THEREOF FOR THE TREATMENT OF PREMATURE EJACULATION

Technical Field

- [1] The present invention relates to 1,3-dihydro-5-isobenzofurancarbonitrile derivatives represented by Formula 1, below, or pharmaceutically acceptable salts thereof, and a pharmaceutical composition for treating or preventing premature ejaculation comprising the same as an effective ingredient.

[2] [Formula 1]



Background Art

- [4] There are various concepts with premature ejaculation. There lacks a universally acknowledged definition of premature ejaculation. According to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision), it defines premature ejaculation as the persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, during, or shortly after penetration and before the person wishes it.
- [5] Premature ejaculation is recognized to be the most common male sexual disorder, affecting approximately 30% of men. This prevalence rate is three times higher than that of erectile dysfunction (Int J Impot Res 2005 17:39-57). Erectile dysfunction is common in middle-aged men as well as in older men, whereas premature ejaculation occurs in men of all ages and has a deleterious impact on quality of life. Premature ejaculation is generally classified as either primary or secondary. Primary form applies to men who have had the condition since they became capable of functioning sexually (i.e., post-puberty). Primary premature ejaculation (PE) is associated with changes of neurotransmitters, which are involved in a variety of psychological actions. Secondary PE is considered when an individual has been able to control his ejaculation and faced no problem earlier but later is unable to do so due to mental stress, erectile dys-

function, prostatitis, urethritis or drug administration.

- [6] The two main causes contributing to premature ejaculation are biological and psychogenic factors. Biological factors include penile hypersensitivity, hyperexcitability of ejaculatory reflex, increased sexual arousability, endocrinopathy, genetic predisposition, and 5-HT receptor dysfunction. Psychogenic risk factors include anxiety, early sexual experiences, ejaculatory control techniques, and psychodynamics (J Sex Med 2004 1:58-65).
- [7] The ejaculatory process is mediated by a complex interplay of neurotransmitters, such as 5-hydroxytryptamine (5-HT) and dopamine. Cholinergic, adrenergic, GABAergic and oxytocinergic neurons have also been shown to be involved in the regulation of ejaculation. Of these, 5-HT has been known to play a major role in the regulation of ejaculation (Urology 2003 61:623-628). The overall role of serotonin (5-HT) on ejaculation has been shown to be inhibitory (Physiol Behav 2004 83:291-307). 5-HT released at L3-L5 spinal segments from terminals of axons descending from the rostral region of the paragigantocellular nucleus (nPGi) in the brainstem exerts an inhibitory role on ejaculation (Exp Brain Res 1992 88:313-320). Also, ejaculation is inhibited when 5-HT is released from serotonergic neurons in the medial preoptic area (MPOA), which is a hypothalamic brain area. (Eur J Pharmacol 1992 210:121-129). Serotonin is released from presynaptic neurons and acts on receptors on postsynaptic neurons in which 5-HT_{2C} receptor mediates the effects of serotonin on ejaculation. Presynaptic 5-HT_{1B} and somatodendritic 5-HT_{1A} autoreceptors induce a negative feedback control over 5-HT release and prevent overstimulation of postsynaptic 5-HT receptors to inhibit ejaculation. Then, 5-HT molecules present in the synapse are taken up again back into the presynaptic neuron via 5-HT transporter, which is located on the cell bodies of the presynaptic neuron. In this way, 5-HT is implicated in the control of ejaculation (European Urology 2006 50:454-466).
- [8] There are non-drug treatment and drug treatment for premature ejaculation.
- [9] Non-drug treatment for premature ejaculation is equally said behavioral therapies. The most popular methods are the squeeze technique developed by Masters & Johnson (1970) and the stop-start technique developed by Semans (1956). However, there are problems with the two techniques in terms that they are time-consuming and require the proper participation of his partner, leading to difficulty in practice and low success rates (Contemp Urol 2001 13:51-59).
- [10] No drug is approved by the American FDA for the treatment of premature

ejaculation. However, many studies have shown that topical anesthetics, off-label use of antidepressants, and the like are effective to treat premature ejaculation. The most commonly used topical anesthetic cream to desensitize the head of the penis is EMLA cream or spray that contains lidocaine and prilocaine. The lidocaine-prilocaine formulation has been shown to be in part effective in premature ejaculation and to improve sexual satisfaction when applied 30 minutes before sexual intercourse, but causes decreased penile sensation and vaginal numbness in a female partner (Int J Impot Res 2003 15:277-281). A domestically developed SS cream, which is prepared with an extract from nine Chinese herbal medicines, significantly increases intra vaginal ejaculation latency time (IVELT) in a clinical trial, but it is currently not marketed due to its low effectiveness and side effects including local burning and pain (Yonsei Med J 1997 38:91-95).

- [11] Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are currently used off-label. TCAs are less selective for inhibition of serotonin reuptake and have more side effects than SSRIs (Contemp Urol 2001 13:51-59).
- [12] SSRIs, such as Fluoxetine, paroxetine, sertraline, citalopram and fluvoxamine, have been shown to be effective in treating premature ejaculation. In particular, USP 4,136,193 discloses anti-depressive 1-dimethylaminopropyl-1-phenylphthalans, which comprise the citalopram compound that is similar to compounds according to the present invention. When various doses and administration schemes were tested, continuous daily administration of SSRI over a 2-wk period prolonged IVELT by 3-10 minutes and was thus more effective in premature ejaculation than a single dosing before intercourse (J Urol 1998 159:1935-1938).
- [13] However, the long-term use of SSRIs increases the incidence of side effects such as vomiting, dry mouth, drowsiness, reduced libido and anejaculation (J Sex Marital Ther 1999 25:89-101). With respect to effectiveness, SSRIs have another decisive drawback of having no indication for their use in premature ejaculation treatment. Moreover, SSRIs are intended for chronic use rather than on-demand use because they have a long half-life and a long T_{max}, which is the time to maximal plasma concentration, and it takes a long time for SSRIs to exert their therapeutic effects or efficacies, and these are difficult to predict.
- [14] When SSRI drugs are used in combination with monoamine oxidase inhibitors such as lithium, sumatriptan and tryptophan, there is an increased risk of serotonin syndrome with side effects including fever, delirium, coma, sweating and dizziness (N Eng J Med 2005 352:1112-1120).

- [15] In this regard, the inventors of the present application conducted intensive and thorough research in order to develop a compound that has a good ejaculation-delaying effect, an about three times shorter half-life and better safety and is thus suitable for on-demand use in premature ejaculation treatment. The research resulted in the findings that novel 1,3-dihydro-5-isobenzofurancarbonitrile derivatives or pharmaceutically acceptable salts thereof have a good ejaculation-delaying effect with a short half-life, thereby leading to the present invention.

Disclosure of Invention

Technical Problem

- [16] It is therefore an object of the present invention to provide novel 1,3-dihydro-5-isobenzofurancarbonitrile derivatives or pharmaceutically acceptable salts thereof and a method of preparing the same.
- [17] It is another object of the present invention to provide a pharmaceutical composition for treating or preventing premature ejaculation, the composition having a short half-life and a good ejaculation-delaying effect.

Technical Solution

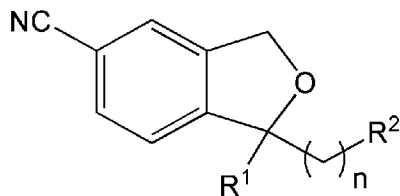
- [18] In order to accomplish the above objects, the present invention provides novel 1,3-dihydro-5-isobenzofurancarbonitrile derivatives or pharmaceutically acceptable salts thereof.

Advantageous Effects

- [19] In accordance with the present invention, the 1,3-dihydro-5-isobenzofurancarbonitrile derivatives have a short half-life and inhibit the ejaculation process by selectively inhibiting serotonin reuptake via a serotonin reuptake transporter present in a presynaptic neuron. Thus, the present invention is useful in the treatment or prevention of premature ejaculation.

Best Mode for Carrying Out the Invention

- [20] Hereinafter, the present invention will be described in detail.
- [21] In one aspect, the present invention provides 1,3-dihydro-5-isobenzofurancarbonitrile derivatives, represented by Formula 1, below, or pharmaceutically acceptable salts thereof:
- [22] [Formula 1]
- [23]



[24] The present invention comprises following derivatives.

[25] 1) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[26] R^1 is a substituted or unsubstituted phenyl; or heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl;

[27] R^2 is C_1 - C_6 dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[28] n is an integer from 1 to 3.

[29]

[30] 2) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[31] R^1 is a substituted or unsubstituted phenyl; or heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and in case that the R^1 contains a substituent, the substituent is C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, C_1 - C_6 dialkylamine or halogen;

[32] R^2 is C_1 - C_6 dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[33] n is an integer from 1 to 3.

[34]

[35] 3) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[36] R^1 is a substituted or unsubstituted phenyl; or heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl,

oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl;

[37] R² is C₁-C₆ dialkylamino, pyrazolyl, or imidazolyl; and

[38] n is an integer from 1 to 3.

[39]

[40] 4) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[41] R¹ is phenyl substituted with C₁-C₆ alkyloxy;

[42] R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[43] n is an integer from 1 to 3.

[44] In a preferred embodiment of the invention, the R¹ is methoxyphenyl;

[45] the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[46] the n is an integer from 1 to 3.

[47] In a more preferred embodiment of the invention, the R¹ is methoxyphenyl;

[48] the R² is dimethylamino, pyrazolyl, or imidazolyl; and

[49] the n is an integer from 1 to 3.

[50]

[51] 5) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[52] R¹ is unsubstituted phenyl or phenyl substituted with C₁-C₆ alkyl;

[53] R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[54] n is an integer from 1 to 3.

[55] In a preferred embodiment of the invention, the R¹ is unsubstituted phenyl or tolyl;

[56] the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl,

triazolyl, pyrrolyl and furyl; and

[57] the n is an integer from 1 to 3.

[58] In a more preferred embodiment of the invention, the R¹ is unsubstituted phenyl or tolyl;

[59] the R² is C₁-C₆ dialkylamino, pyrazolyl, or imidazolyl; and

[60] the n is an integer from 1 to 3.

[61]

[62] 6) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[63] R¹ is phenyl substituted with C₁-C₆ dialkylamino;

[64] R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[65] n is an integer from 1 to 3.

[66] In a preferred embodiment of the invention, the R¹ is dimethylaminophenyl;

[67] the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[68] the n is an integer from 1 to 3.

[69] In a more preferred embodiment of the invention, the R¹ is dimethylaminophenyl;

[70] the R² is dimethylamino, pyrazolyl, or imidazolyl; and

[71] the n is an integer from 1 to 3.

[72]

[73] 7) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[74] R¹ is thienyl;

[75] R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[76] the n is an integer from 1 to 3.

[77] In a preferred embodiment of the invention, the R¹ is thienyl;

[78] the R² is dimethylamino, pyrazolyl, or imidazolyl; and

[79] the n is an integer from 1 to 3.

[80]

[81] 8) A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[82] R¹ is phenyl substituted halogen;

[83] R² is a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

[84] n is an integer from 1 to 3.

[85] In a preferred embodiment of the invention, the R¹ is phenyl substituted halogen;

[86] the R² is pyrazolyl or imidazolyl; and

[87] the n is an integer from 1 to 3.

[88]

[89] The pharmaceutically acceptable salts of the compounds of Formula 1 include acid addition salts formed with an inorganic acid or an organic acid. Examples of inorganic acids include hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, and phosphoric acid. Examples of organic acids include p-toluenesulfonic acid, methane-sulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, and acetic acid. Examples of such pharmaceutically acceptable salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, chloride, dichloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylene-sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α -hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, and mandelate. Preferred pharmaceutically acceptable acid addition salts are those formed with inorganic acids, such as hydrochloric acid and hydrobromic acid, and those formed with organic acids, such as oxalic acid and maleic acid.

[90] Particularly preferred examples of the compound of Formula 1 according to the present invention include the following:

[91] 1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancar

- bonitrile;
- [92] 1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancar
bonitrile oxalate;
- [93] 1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancar
bonitrile hydrochloride;
- [94] 1-{3-(imidazole-1-yl)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancar
bonitrile;
- [95] 1-{3-(imidazole-1-yl)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancar
bonitrile hydrochloride;
- [96] 1-{2-(imidazole-1-yl)ethyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbo
nitrile;
- [97] 1-{2-(imidazole-1-yl)ethyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbo
nitrile hydrochloride;
- [98] 1-(4-methoxyphenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarb
onitrile;
- [99] 1-(4-methoxyphenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarb
onitrile hydrochloride;
- [100] 1-(4-methoxyphenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbon
itrile;
- [101] 1-(4-methoxyphenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbon
itrile hydrochloride;
- [102] 1-{3-(dimethylamino)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;
- [103] 1-{3-(dimethylamino)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hy-
drochloride;
- [104] 1-{2-(dimethylamino)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;
- [105] 1-{2-(dimethylamino)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hy-
drochloride;
- [106] 1-{3-(imidazole-1-yl)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;
- [107] 1-{3-(imidazole-1-yl)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hy-
drochloride;
- [108] 1-{2-(imidazole-1-yl)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;
- [109] 1-{2-(imidazole-1-yl)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hy-
drochloride;
- [110] 1-phenyl-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [111] 1-phenyl-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hy-

- drochloride;
- [112] 1-{3-(dimethylamino)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [113] 1-{3-(dimethylamino)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [114] 1-{2-(dimethylamino)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [115] 1-{2-(dimethylamino)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [116] 1-{3-(imidazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [117] 1-{3-(imidazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [118] 1-{2-(imidazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [119] 1-{2-(imidazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [120] 1-{3-(pyrazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [121] 1-{3-(pyrazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [122] 1-{2-(pyrazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [123] 1-{2-(pyrazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [124] 1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [125] 1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile oxalate;
- [126] 1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [127] 1-(4-dimethylaminophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [128] 1-(4-dimethylaminophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [129] 1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [130] 1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate;
- [131] 1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [132] 1-{2-(dimethylamino)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

- [133] 1-{2-(dimethylamino)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [134] 1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [135] 1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate;
- [136] 1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [137] 1-{2-(imidazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [138] 1-{2-(imidazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [139] 1-{3-(pyrazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [140] 1-{3-(pyrazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [141] 1-{2-(pyrazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;
- [142] 1-{2-(pyrazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [143] 1-(4-fluorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [144] 1-(4-fluorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [145] 1-(4-fluorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [146] 1-(4-fluorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [147] 1-(4-fluorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [148] 1-(4-fluorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [149] 1-(4-fluorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [150] 1-(4-fluorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;
- [151] 1-(4-chlorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;
- [152] 1-(4-chlorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

nitrile hydrochloride;

[153] 1-(4-chlorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

[154] 1-(4-chlorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

[155] 1-(4-chlorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

[156] 1-(4-chlorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

[157] 1-(4-chlorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile; and

[158] 1-(4-chlorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride.

[159]

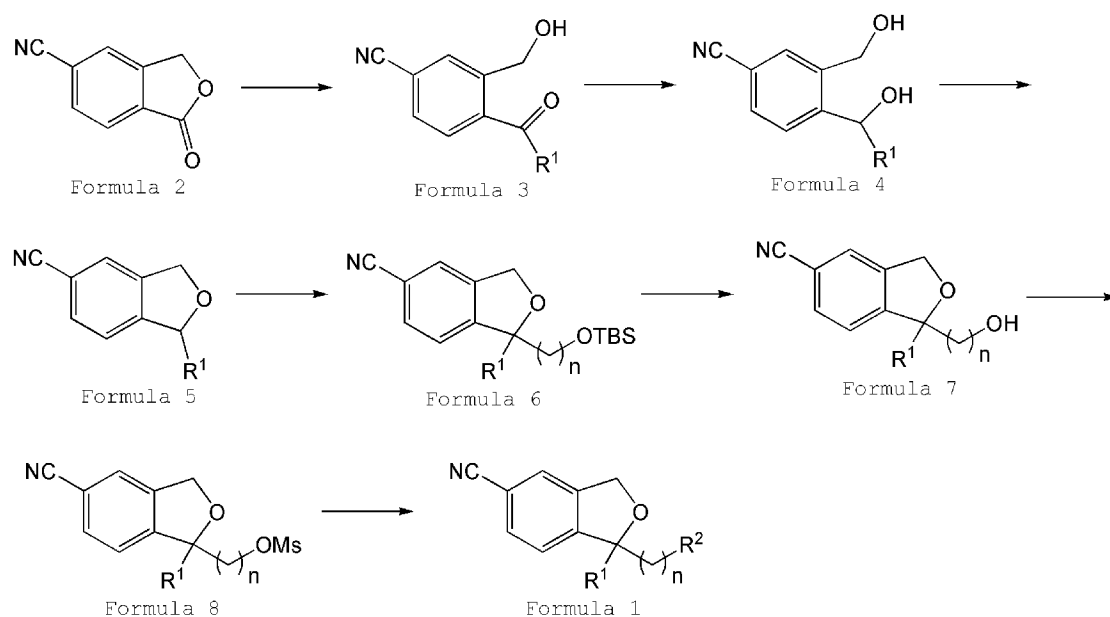
[160] In another aspect, the present invention provides a method of preparing the compound represented by Formula 1 or a pharmaceutically acceptable salt thereof.

[161] The present method is shown in Reaction Scheme 1, below.

[162]

[163] [Reaction Scheme 1]

[164]



[165] The compound of Formula 1 according to the present invention, as shown in Reaction Scheme 1, may be prepared through a series of steps from a 5-cyanophthalimide compound of Formula 2. In the Reaction Scheme 1, R¹, R² and n are the same as defined in Formula 1.

[166] The method comprises:

[167] 1) preparing a compound of Formula 3 by reacting 5-cyanophthalimide compound of Formula 2 with R^1MgBr (step 1);

[168] 2) preparing a compound of Formula 4 by reduction reaction of the compound of Formula 3 (step 2);

[169] 3) preparing a compound of Formula 5 by cyclization reaction of the compound of Formula 4 (step 3);

[170] 4) preparing a compound of Formula 6 by introducing an alkyl group into position 1 of the compound of Formula 5 (step 4);

[171] 5) preparing a compound of Formula 7 by deprotecting the compound of Formula 6 (step 5);

[172] 6) preparing a compound of Formula 8 by reacting the compound of Formula 7 with methanesulfonylchloride (step 6);

[173] 7) preparing a compound of Formula 1 by substitution reaction of the compound of Formula 8 with a R^2 group and saltation (with HCl or oxalic acid) (step 7).

[174] Each step of the method will be described in further detail below.

[175] The 5-cyanophthalimide of Formula 2 used as a starting compound at step 1 may be prepared using a known method (*Il Farmaco* 2001, 56, 715). At step 1, a Grignard's reaction is carried out with R^1MgBr . Examples of solvents useful in the reaction include tetrahydrofuran, 1,4-dioxane, diethylether, dimethoxyethane, and dichloromethane. Dichloromethane is preferred. The reaction is carried out at a temperature between 0°C and room temperature for 10 to 20 hours.

[176] At step 2, the reduction reaction may be carried out using sodium borohydride as a reducing reagent. The reducing reagent is used in an amount ranging from 0.5 to 3 equivalents, and preferably 2 equivalents.

[177] At step 3, the cyclization reaction of Formula 4 is carried out under an acidic condition. Examples of useful acids include hydrochloric acid, sulfuric acid, and phosphoric acid, phosphoric acid being preferred.

[178] At step 4, bases such as lithium diisopropyl amine, sodium hydride, n-butylamine, sodium methoxide and potassium t-butoxide may be used. Sodium hydride is preferred. Examples of suitable solvents include dimethylsulfoxide, dimethylformamide, N-methylpyrrolidine-2-one, tetrahydrofurane, and 1,4-dioxane. Dimethylsulfoxide is preferred. The reaction is carried out at 50°C to 110°C for 12 to 36 hours.

[179] At step 5, a protecting group of Formula 6 may be removed using hydrogen fluoride, potassium fluoride, tetrabutylammonium fluoride, hydrochloric acid, sulfuric acid, or

the like. Tetrabutylammonium fluoride is preferred. The deprotection reaction is carried out using tetrahydrofuran as a solvent at room temperature for about 1 hour.

[180] At step 6, the leaving group may be introduced into the compound of Formula 8 using methanesulfonylchloride, p-toluenesulfonylchloride, trichloromethanesulfonylchloride, or the like. Methanesulfonylchloride is preferred. The reaction is carried out in the presence of dichloromethane as a solvent at 0°C for about 1 hour.

[181] At step 7, bases suitable for use in the R² substitution reaction include carbonates, such as sodium carbonate, calcium carbonate, potassium carbonate and cesium carbonate, and hydroxides, such as sodium hydroxide, calcium hydroxide and potassium hydroxide. Potassium carbonate is preferred. Examples of solvents suitable for use in the reaction include dimethylsulfoxide, dimethylformamide, N-methylpyrrolidine-2-one, tetrahydrofuran, and 1,4-dioxane, and dimethylformamide being preferred. The reaction is carried out at 50°C to 110°C for 12 to 36 hours so as to obtain the target compound of Formula 1, a 1,3-dihydro-5-isobenzofurancarbonitrile derivative. Optionally, the compound is reacted with hydrochloric acid or oxalic acid for 10 to 60 minutes so as to obtain the 1,3-dihydro-5-isobenzofurancarbonitrile derivative in a salt form of hydrochloride or oxalate.

[182] In a further aspect, the present invention provides a pharmaceutical composition for treating or preventing premature ejaculation comprising the novel 1,3-dihydro-5-isobenzofurancarbonitrile derivative represented by Formula 1, below, or a pharmaceutically acceptable salt thereof as an effective ingredient, the composition having a short half-life and a good inhibitory effect on ejaculation.

[183] The 1,3-dihydro-5-isobenzofurancarbonitrile derivatives according to the present invention have a short half-life and inhibit the ejaculation process by selectively inhibiting serotonin reuptake via a serotonin reuptake transporter present in a presynaptic neuron. The present compounds are thus useful in the treatment and prevention of premature ejaculation.

[184] The pharmaceutical composition, comprising the novel 1,3-dihydro-5-isobenzofurancarbonitrile derivative according to the present invention or a pharmaceutically acceptable salt thereof as an effective ingredient, may be used in general pharmaceutical dosage forms. That is, the compounds of the present invention may be administered in a wide variety of oral and parenteral dosage forms upon clinical application, oral administration being preferred in the present invention. A formulation may be prepared with generally used diluents or excipients, such as fillers, thickeners, binders, humectants, disintegrators and surfactants.

- [185] Solid formulations for oral administration may include tablets, pills, powders, granules and capsules, and are prepared by mixing the 1,3-dihydro-5-isobenzofurancarbonitrile derivative or a pharmaceutically acceptable salt thereof with one or more excipients, such as starch, calcium carbonate, sucrose, lactose and gelatin. Also, the solid formulations may include, in addition to a simple excipient, a lubricant such as magnesium stearate or talc. Liquid formulations for oral administration may include suspensions, internal solutions, emulsions and syrups. The liquid formulations may include, in addition to commonly used simple diluents, such as water and liquid paraffin, various excipients, which are exemplified by humectants, sweeteners, aromatics and preservatives. Formulations for parenteral administration may include sterile aqueous solutions, non-aqueous solutions, suspensions, emulsions, lyophilized preparations, and suppositories. Non-aqueous solutions and suspensions may be prepared with propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable esters such as ethyl oleate. As a base for suppositories, Witepsol, macrogol, Tween 61, cacao oil, laurin oil and glycerinated gelatin may be used.
- [186] The dosage of the pharmaceutical composition of the present invention, comprising the 1,3-dihydro-5-isobenzofurancarbonitrile derivative or a pharmaceutically acceptable salt thereof as an effective ingredient, may vary depending on the patient's weight, age, gender and diet, the time and mode of administration, excretion rates, and the severity of illness. The present composition may be administered in an effective amount ranging from 0.1 to 1,000 mg, and preferably in a daily dosage of 10 to 50 mg. The daily dosage may be taken in a single dose or may be divided into several doses.

Mode for the Invention

- [187] A better understanding of the present invention may be obtained through the following examples which are set forth to illustrate, but are not to be construed as the limit of the present invention.
- [188] The molecular structure of the present compound of Formula 1 was identified through infrared spectroscopy, UV-visible spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy, and comparison of calculated and experimental values of elementary analysis of a representative compound.

[189]

[190] **EXAMPLE 1: Preparation of**

1-(4-methoxyphenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile (compound 1)

[191]

[192] Step 1: Preparation of 3-hydroxymethyl-4-(4-methoxybenzoyl)benzonitrile

[193] 200 g (125.6 mmol) of 5-cyanophthalimide was dissolved in 200 mL of anhydrous dichloromethane. The solution was cooled to -78°C, and 188 mL of 4-methoxyphenylmagnesium bromide (1 M in THF, 188 mmol) was added dropwise. The mixture was raised to room temperature and stirred for 16 hrs, followed by addition of a saturated ammonium chloride solution. An organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure, thereby yielding a yellow compound, represented by Formula 3. The compound thus obtained was used in the next reaction without further purification.

[194]

[195] ¹H NMR(400 MHz, CDCl₃) : 3.89(s, 3H), 4.60(d, J=6.0 Hz, 2H), 6.95(d, J=7.2 Hz, 2H), 7.48(d, J=7.6 Hz, 1H), 7.65(d, J=7.6 Hz, 1H), 7.75(d, J=7.2 Hz, 2H), 7.86(s, 1H).

[196]

[197] Step 2: Preparation of

4-{hydroxy(4-methoxyphenyl)methyl}-3-(hydroxymethyl)benzonitrile

[198] 33.6 g (125.6 mmol) of the 3-hydroxymethyl-4-(4-methoxybenzoyl)benzonitrile prepared in step 1 was dissolved in 200 mL of dichloromethane and 100 mL of methanol. The solution was cooled to 0°C, and 95 g (251.1 mmol) of sodium borohydride was slowly added.

[199] The mixture was raised to room temperature and stirred for 3 hrs, followed by addition of a saturated ammonium chloride solution. An organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure, thereby yielding a yellow compound represented by Formula 4. The compound thus obtained was used in the next reaction without further purification.

[200]

[201] ¹H NMR(400 MHz, DMSO-*d*₆) : 3.70(s, 3H), 4.28(dd, J=14.8 Hz, 5.4 Hz, 1H), 4.57(dd, J=14.8 Hz, 5.4 Hz, 1H), 5.37(t, J=5.4 Hz, 1H), 5.83(d, J=4.2 Hz, 1H), 5.94(d, J=4.2 Hz, 1H), 6.85(d, J=8.8 Hz, 2H), 7.15(d, J=8.8 Hz, 2H), 6.69-7.73(m, 2H), 7.75(s, 1H).

[202]

[203] Step 3: Preparation of 1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[204] 33.82 g (125.6 mmol) of the 4-{hydroxy(4-methoxyphenyl)methyl}-3-(hydroxymethyl)benzonitrile prepared in step 2 was dissolved in 150 mL of ethylacetate, and 150 mL of a 85% aqueous solution

of phosphoric acid was added at room temperature. The mixture was raised to 80°C and stirred for 3 hrs. The reaction mixture was then cooled again to room temperature, and washed with water and saturated NaCl solution. An organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure. The residue was treated with 2-propanol to afford 18.0 g of a white solid (yield: 57%).

[205]

[206] ^1H NMR(400 MHz, CDCl_3) : 2.73(s, 3H), 5.10(d, $J=13.0$ Hz, 1H), 5.27(dd, $J=13.0$ Hz, 1H), 6.17(s, 1H), 6.91(d, $J=8.4$ Hz, 2H), 7.17-7.24(m, 3H), 7.70(d, $J=8.0$ Hz, 1H), 7.87(s, 1H).

[207]

[208] Step 4: Preparation of
1-(3-tert-butyldimethylsilyloxypropyl)-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[209] 23.0 g (91.3 mmol) of the
1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbonitrile prepared in step 3 was dissolved in 200 mL of dimethylsulfoxide. 5.5 g (137.0 mmol) of sodium hydride was slowly added to the solution at room temperature. The solution was stirred for 0.5 hr. Then, to the mixture, 34.7 g (137.0 mmol) of bromo-1-(tert-butyldimethylsilyl)propane was added. The resulting mixture was raised to 80°C, stirred for 12 hrs, and cooled again to room temperature. The reaction mixture was mixed with water, extracted with ethylacetate, and washed with water and saturated NaCl solution. An organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure. The residue was purified using column chromatography to afford 34.1 g (yield: 88%) of the pale yellow target compound.

[210]

[211] ^1H NMR(400 MHz, CDCl_3) : 0.06(s, 6H), 0.89(s, 9H), 1.34(m, 1H), 1.52(m, 1H), 1.95(m, 1H), 2.21(m, 1H), 3.57(t, $J=6.2$ Hz, 1H), 3.65(t, $J=6.2$ Hz, 1H), 3.76(s, 3H), 5.16(m, 2H), 6.85(d, $J=8.2$ Hz, 2H), 7.33-7.35(m, 3H), 7.49(s, 1H), 7.57(d, $J=8.0$ Hz, 1H).

[212]

[213] Step 5: Preparation of
1-(3-hydroxypropyl)-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[214] 34.1 g (80.8 mmol) of the
1-(3-tert-butyldimethylsilyloxypropyl)-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofu

rancarbonitrile prepared in step 4 was dissolved in 200 mL of tetrahydrofuran. 121.1 mL (121.1 mmol) of 1 M tetrabutylammonium fluoride tetrahydrofuran was added dropwise to the solution at room temperature, and the mixture was stirred for 2 hrs. The reaction mixture was diluted in ethylacetate, and washed with water and saturated NaCl solution. An organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure. The residue was purified using column chromatography to afford 15.0 g of the pale yellow target compound (yield: 60%).

[215]

[216] ^1H NMR(400 MHz, CDCl_3) : 1.46(m, 1H), 1.55(m, 1H), 2.18(m, 1H), 2.30(m, 1H), 3.59(m, 2H), 3.76(s, 3H), 5.15(m, 2H), 6.83(d $J=8.8$ Hz, 2H), 7.31-7.38(m, 3H), 7.48(s, 1H), 7.57(d $J=8.0$ Hz, 1H).

[217]

[218] Step 6: Preparation of

1-(3-methanesulfonyloxypropyl)-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile

[219] 15.0 g (48.5 mmol) of the

1-(3-hydroxypropyl)-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile prepared in step 5 was dissolved in 200 mL of dichloromethane, and 7.4 g (72.7 mmol) of triethylamine and 6.7 g (58.2 mol) of methanesulfonylchloride were added dropwise at 0°C. The solution was then stirred for 1 hr. The reaction mixture was washed with water and saturated NaCl solution. An organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure to afford 18.2 g of the yellow target compound (yield: 79%). The compound thus obtained was used in the next reaction without further purification.

[220]

[221] ^1H NMR(400 MHz, CDCl_3) : 1.64(m, 1H), 1.71(m, 1H), 2.19(m, 1H), 2.30(m, 1H), 2.94(s, 3H), 3.76(s, 3H), 4.20(m, 2H), 5.15(m, 2H), 6.84(d $J=8.8$ Hz, 2H), 7.32(d $J=8.8$ Hz, 2H), 7.37(d $J=8.0$ Hz, 1H), 7.47(s, 1H), 7.57(d $J=8.0$ Hz, 1H).

[222]

[223] Step 7: Preparation of

1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile (compound 1)

[224] 18.2 g (47.0 mmol) of the

1-(3-methanesulfonyloxypropyl)-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile

rbonitrile prepared in step 6 was dissolved in 300 mL of dimethylformimide, and 13.0 g (94.0 mmol) of potassium carbonate and 94.0 mL (188.0 mmol) of 2 M dimethylamine in tetrahydrofuran were added at room temperature. The solution temperature was then raised to 80°C and stirred for 12 hrs. The reaction mixture was diluted in ethylacetate and washed with water and saturated NaCl solution. A resulting organic layer was dried over anhydrous magnesium sulfate, and filtered. After the solvent was evaporated under reduced pressure, the residue was purified with column chromatography to afford 8.3 g (yield: 53%) of a pale yellow compound, 1-(4-methoxyphenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile.

[225]

[226] ^1H NMR(400 MHz, CDCl_3) : 1.42(m, 1H), 1.55(m, 1H), 2.11-2.31(m, 7H), 2.42(m, 2H), 3.75(s, 3H), 4.20(m, 2H), 5.15(m, 2H), 6.83(d, $J=8.8$ Hz, 2H), 7.34(d, $J=8.8$ Hz, 2H), 7.40(d, $J=7.8$ Hz, 1H), 7.46(s, 1H), 7.59(d, $J=7.8$ Hz, 1H).

[227]

[228] **EXAMPLE 2: Preparation of**

1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate

[229]

[230] 8.3 g (24.7 mmol) of the 1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarbonitrile prepared in Example 1 was dissolved in 85 mL of ethanol, and 3.4 g (27.2 mmol) of oxalic acid was slowly added at room temperature. The solution was stirred at room temperature for 0.5 hr, and it was cooled to 0°C and further stirred for 1 hr. The solution was filtered to recover the precipitate. The precipitate was washed with hexane and dried to afford 7.1 g of the target compound as a white solid (yield: 67%).

[231]

[232] ^1H NMR(400 MHz, $\text{DMSO}-d_6$) : 1.41(m, 1H), 1.49(m, 1H), 2.18(m, 2H), 2.61(s, 6H), 2.95(t, $J=7.8$ Hz, 2H), 3.65(s, 3H), 5.19(d, $J=13.2$ Hz, 1H), 5.12(d, $J=13.2$ Hz, 1H), 6.88(d, $J=8.8$ Hz, 2H), 7.42(d, $J=8.8$ Hz, 2H), 7.68(d, $J=7.6$ Hz, 1H), 7.77(d, $J=7.6$ Hz, 1H), 7.78(s, 1H).

[233] ^{13}C NMR(100 MHz, $\text{DMSO}-d_6$) : 193, 369, 42.2, 55.0, 56.6, 70.9, 90.2, 110.2, 113.6, 118.6, 122.8, 125.5, 125.9, 131.8, 135.5, 139.6, 149.2, 158.1, 164.1.

[234]

[235] **EXAMPLE 3: Preparation of**

1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile hydrochloride

[236]

[237] 8.3 g (24.7 mmol) of the 1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile prepared in Example 1 was dissolved in 50 ml of dichloromethane, and 24.7 ml (494 mmol) of 2 M hydrochloric acid in diethyl ether was added dropwise at room temperature. The mixture was then stirred for 0.5 hr. After the solution was discarded, the precipitate was washed with diethylether and dried to afford 8.7 g of the pale yellow target compound (yield: 95%).

[238]

[239] ¹H NMR(400 MHz, DMSO-*d*₆) : 1.45(m, 1H), 1.56(m, 1H), 2.24(t, *J*=7.6 Hz, 2H), 2.59(s, 3H), 2.61(s, 3H), 2.98(m, 2H), 3.70(s, 3H), 5.12(d, *J*=13.2 Hz, 1H), 5.21(d, *J*=13.2 Hz, 1H), 6.87(d, *J*=8.4 Hz, 2H), 7.44(d, *J*=8.4 Hz, 2H), 7.70(d, *J*=7.6 Hz, 1H), 7.77(d, *J*=7.6 Hz, 1H), 7.78(s, 1H), 10.62(brs, 1H).

[240] ¹³C NMR(100 MHz, DMSO-*d*₆) : 190, 369, 41.8, 419, 55.0, 56.3, 70.6, 90.2, 110.2, 113.6, 118.6, 122.9, 125.5, 125.8, 131.7, 135.6, 139.6, 149.2, 158.1.

[241]

[242] According to the same method as described in Examples 1 to 3, the compounds of Examples 4 to 68, below, were prepared by using a Grignard reagent, amine and acid corresponding to each substituent of the compounds of Examples 4 to 68.

[243]

[244] **EXAMPLE 4: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile

[245]

[246] ¹H NMR(400 MHz, CDCl₃) : 1.69(m, 1H), 1.78(m, 1H), 1.98(m, 1H), 2.14(m, 1H), 3.72(s, 3H), 3.94(t, *J*=7.0 Hz, 2H), 5.13(m, 2H), 6.78-6.85(m, 3H), 7.05 (s, 1H), 7.23-7.29(m, 3H), 7.45(s, 1H), 7.54-7.57(m, 2H).

[247]

[248] **EXAMPLE 5: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile hydrochloride

[249]

[250] ¹H NMR(400 MHz, DMSO-*d*₆) : 1.67(m, 1H), 1.71(m, 1H), 2.14(m, 2H), 3.69(s,

3H), 4.17(t, $J=7.0$ Hz, 2H), 5.09(d $J=13.4$ Hz, 1H), 5.17(d $J=13.4$ Hz, 1H), 6.86(d $J=8.8$ Hz, 2H), 7.39(d $J=8.8$ Hz, 2H), 7.64-7.67(m, 2H), 7.73-7.77(m, 3H) 918(s, 1H).

[251] ^{13}C NMR(100 MHz, DMSO- d_6) : 249, 36.7, 48.3, 55.0, 709, 90.1, 110.2, 113.6, 118.0, 119.5, 121.7, 122.9, 125.4, 125.8, 131.7, 134.9, 135.5, 139.6, 149.1, 158.1.

[252]

[253] **EXAMPLE 6: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarboxonitrile

[254]

[255] ^1H NMR(400 MHz, CDCl_3) : 2.62(m, 1H), 2.77(m, 1H), 3.77(s, 3H), 4.00(t, $J=7.8$ Hz, 2H), 5.17(m, 2H), 6.84-6.88(m, 3H), 7.05(s, 1H), 7.36(d $J=7.2$ Hz, 2H), 7.45(d $J=8.0$ Hz, 1H), 7.50(s, 1H), 7.59(d $J=8.0$ Hz, 1H), 7.92(s, 1H).

[256]

[257] **EXAMPLE 7: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofurancarboxonitrile hydrochloride

[258]

[259] ^1H NMR(400 MHz, DMSO- d_6) : 2.85(m, 2H), 3.71(s, 3H), 4.10(m, 2H), 5.13(d $J=13.4$ Hz, 1H), 5.22(d $J=13.4$ Hz, 1H), 6.89(d $J=8.2$ Hz, 2H), 7.44(d $J=8.2$ Hz, 2H), 7.56(s, 1H), 7.65-7.75(m, 3H), 7.79(s, 1H), 8.95(s, 1H), 14.23(brs, 1H).

[260] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.1, 44.7, 55.1, 71.1, 89.1, 110.4, 113.7, 118.5, 119.3, 121.8, 122.8, 125.5, 125.7, 131.8, 135.0, 135.1, 139.3, 148.2, 158.2.

[261]

[262] **EXAMPLE 8: Preparation of**

1-(4-methoxyphenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarboxonitrile

[263]

[264] ^1H NMR(400 MHz, CDCl_3) : 1.74(m, 1H), 1.85(m, 1H), 2.03(m, 1H), 2.15(m, 1H), 3.74(s, 3H), 4.09(m, 2H), 5.12(m, 2H), 6.20(s, 1H), 6.34(s, 1H), 6.81(d $J=7.6$ Hz, 2H), 7.23-7.29(m, 3H), 7.45(s, 1H), 7.53(d $J=7.6$ Hz, 1H), 7.61(s, 1H).

[265]

[266] **EXAMPLE 9: Preparation of**

1-(4-methoxyphenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarboxonitrile hydrochloride

[267]

[268] ^1H NMR(400 MHz, DMSO- d_6) : 1.54(m, 1H), 1.63(m, 1H), 2.09(m, 2H), 3.69(s, 3H), 4.04(t, $J=7.0$ Hz, 2H), 5.07(d, $J=13.6$ Hz, 1H), 5.14(d, $J=13.6$ Hz, 1H), 6.16(m, 1H), 6.29(m, 1H), 6.85(d, $J=8.8$ Hz, 2H), 7.36(d, $J=8.8$ Hz, 2H), 7.59-7.75(m, 4H).

[269] ^{13}C NMR(100 MHz, DMSO- d_6) : 25.3, 37.2, 50.9, 55.1, 70.9, 90.3, 105.1, 110.2, 113.6, 118.7, 122.9, 125.5, 125.9, 130.3, 131.8, 135.7, 137.6, 139.7, 149.4, 158.1.

[270]

[271] **EXAMPLE 10: Preparation of**

1-(4-methoxyphenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[272]

[273] ^1H NMR(400 MHz, CDCl_3) : 2.78(m, 2H), 4.14(m, 2H), 5.18(m, 2H), 6.10(s, 1H), 6.84(d, $J=8.8$ Hz, 2H), 7.16(s, 1H), 7.34-7.37(m, 3H), 7.44-7.46(m, 2H), 7.52(d, $J=8.0$ Hz, 1H).

[274]

[275] **EXAMPLE 11: Preparation of**

1-(4-methoxyphenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[276]

[277] ^1H NMR(400 MHz, DMSO- d_6) : 2.72(m, 2H), 3.71(s, 3H), 3.97(m, 2H), 5.15(d, $J=13.4$ Hz, 1H), 5.25(d, $J=13.4$ Hz, 1H), 6.11(s, 1H), 6.88(d, $J=7.6$ Hz, 2H), 7.32(s, 1H), 7.47(d, $J=7.6$ Hz, 2H), 7.59(s, 1H), 7.68-7.74(m, 2H), 7.78(s, 1H), 11.82(brs, 1H).

[278] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.4, 47.1, 55.1, 71.2, 89.2, 105.0, 110.3, 113.7, 118.6, 122.9, 125.5, 125.8, 130.2, 131.8, 135.3, 137.7, 139.4, 148.6, 158.2

[279]

[280] **EXAMPLE 12: Preparation of**

1-{3-(dimethylamino)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile

[281]

[282] ^1H NMR(400 MHz, CDCl_3) : 1.40(m, 1H), 1.52(m, 1H), 2.10-2.48(m, 10H), 5.17(m, 2H), 7.22-7.33(m, 4H), 7.43-7.47(m, 3H), 7.57(d, $J=8.0$ Hz, 1H).

[283]

[284] **EXAMPLE 13: Preparation of**

1-{3-(dimethylamino)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[285]

[286] ^1H NMR(400 MHz, DMSO- d_6) : 1.43(m, 1H), 1.52(m, 1H), 2.25(m, 2H), 2.56(s, 6H), 2.96(m, 2H), 5.16(m, 2H), 7.20(m, 1H), 7.29(m, 2H), 7.53(m, 2H), 7.65-7.85(m, 3H), 10.69(brs, 1H).

[287] ^{13}C NMR(100 MHz, DMSO- d_6) : 18.8, 36.8, 41.7, 41.8, 56.1, 71.0, 90.2, 110.1, 118.3, 122.8, 124.3, 125.3, 126.8, 128.0, 131.6, 139.3, 143.3, 148.5.

[288]

[289] **EXAMPLE 14: Preparation of**

1-{2-(dimethylamino)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile

[290]

[291] ^1H NMR(400 MHz, CDCl_3) : 2.22(s, 6H), 2.29(m, 2H), 2.41(m, 2H), 5.14(m, 2H), 7.23-7.42(m, 6H), 7.47(s, 1H), 7.57(d $J=7.8$ Hz, 1H).

[292]

[293] **EXAMPLE 15: Preparation of**

1-{2-(dimethylamino)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[294]

[295] ^1H NMR(400 MHz, DMSO- d_6) : 2.66-2.70(m, 4H), 2.71(s, 3H), 2.87(s, 3H), 5.17(d $J=13.4$ Hz, 1H), 5.24(d $J=13.4$ Hz, 1H), 7.27(m, 1H), 7.36(m, 2H), 7.57(d $J=7.6$ Hz, 2H), 7.77-7.82(m, 2H), 7.94(s, 1H), 10.75(brs, 1H).

[296] ^{13}C NMR(100 MHz, DMSO- d_6) : 35.0, 42.8, 42.9, 53.4, 72.2, 80.1, 111.5, 119.3, 123.9, 125.3, 126.6, 128.3, 129.3, 132.9, 140.2, 143.6, 148.7.

[297]

[298] **EXAMPLE 16: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile

[299]

[300] ^1H NMR(400 MHz, CDCl_3) : 1.68(m, 1H), 1.70(m, 1H), 2.03(m, 1H), 2.16(m, 1H), 3.91(m, 2H), 5.28(m, 2H), 6.80(s, 1H), 7.02(s, 1H), 7.23-7.39(m, 6H), 7.47(s, 1H), 7.59(d $J=8.0$ Hz, 1H), 7.99(s, 1H).

[301]

[302] **EXAMPLE 17: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[303]

[304] ^1H NMR(400 MHz, DMSO- d_6) : 1.62(m, 1H), 1.70(m, 1H), 2.17(t, $J=7.4$ Hz, 2H), 4.15(t, $J=7.2$ Hz, 2H), 5.13(d $J=13.4$ Hz, 1H), 5.19(d $J=13.4$ Hz, 1H), 7.21-7.34(m,

3H), 7.51(d, $J=8.0$ Hz, 2H), 7.64(s, 1H), 7.71-7.79(m, 4H), 9.08(s, 1H), 14.44(bris, 1H).

[305] ^{13}C NMR(100 MHz, DMSO- d_6) : 24.1, 36.0, 47.9, 70.6, 89.3, 109.2, 117.5, 118.9, 121.3, 122.4, 123.7, 124.8, 126.2, 127.5, 131.1, 134.3, 138.5, 142.5, 147.6.

[306]

[307] **EXAMPLE 18: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile

[308]

[309] ^1H NMR(400 MHz, CDCl_3) : 2.69(m, 1H), 2.79(m, 1H), 4.02(m, 2H), 5.16(d, $J=12.8$ Hz, 1H), 5.23(d, $J=12.8$ Hz, 1H), 6.86(s, 1H), 7.08(s, 1H), 7.32(d, $J=8.4$ Hz, 2H), 7.42-7.44(m, 3H), 7.51(s, 1H), 7.54(d, $J=7.8$ Hz, 1H), 7.61(d, $J=7.8$ Hz, 1H), 8.29(s, 1H).

[310]

[311] **EXAMPLE 19: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[312]

[313] ^1H NMR(400 MHz, DMSO- d_6) : 2.80(m, 1H), 2.93(m, 1H), 4.22(m, 2H), 5.17(d, $J=13.4$ Hz, 1H), 5.26(d, $J=13.4$ Hz, 1H), 7.41(d, $J=8.4$ Hz, 2H), 7.56-7.61(m, 3H), 7.68-7.78(m, 4H), 7.82(s, 1H), 9.00(s, 1H), 14.80(bris, 1H).

[314] ^{13}C NMR(100 MHz, DMSO- d_6) : 38.1, 44.5, 71.3, 88.9, 110.7, 118.4, 119.2, 121.8, 122.9, 125.6, 126.4, 128.3, 131.9, 132.0, 135.0, 139.3, 142.3, 147.3.

[315]

[316] **EXAMPLE 20: Preparation of**

1-phenyl-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[317]

[318] ^1H NMR(400 MHz, CDCl_3) : 2.74(t, $J=6.8$ Hz, 2H), 4.10(t, $J=6.8$ Hz, 2H), 5.15(d, $J=13.0$ Hz, 1H), 5.23(d, $J=13.0$ Hz, 1H), 6.06(s, 1H), 7.12(s, 1H), 7.27(d, $J=8.0$ Hz, 2H), 7.32-7.40(m, 5H), 7.46(s, 1H), 7.51(d, $J=7.6$ Hz, 1H).

[319]

[320] **EXAMPLE 21: Preparation of**

1-phenyl-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[321]

[322] ^1H NMR(400 MHz, DMSO- d_6) : 2.75(m, 2H), 3.99(t, $J=7.6$ Hz, 2H), 5.18(d, $J=13.4$

Hz, 1H), 5.28(d $J=13.4$ Hz, 1H), 6.11(s, 1H), 7.25(m, 1H), 7.32-7.36(m, 3H), 7.58-7.60(m, 3H), 7.74-7.78(m, 3H), 12.00(brs, 1H).

[323]

[324] **EXAMPLE 22: Preparation of**

1-{3-(dimethylamino)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[325]

[326] ^1H NMR(400 MHz, CDCl_3) : 1.51(m, 1H), 1.64(m, 1H), 2.17(m, 1H), 2.29(s, 3H), 2.32(m, 1H), 2.37(s, 6H), 2.56(s, 2H), 5.14(d $J=13.2$ Hz, 1H), 5.19(d $J=13.2$ Hz, 1H), 7.12(d $J=7.6$ Hz, 2H), 7.33(d $J=7.6$ Hz, 2H), 7.43-7.46(m, 2H), 7.56(d $J=8.4$ Hz, 1H).

[327]

[328] **EXAMPLE 23: Preparation of**

1-{3-(dimethylamino)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[329]

[330] ^1H NMR(400 MHz, $\text{DMSO}-d_6$) : 1.46(m, 1H), 1.55(m, 1H), 2.14-2.31(m, 5H), 2.59(s, 6H), 2.99(m, 2H), 5.12(d $J=13.0$ Hz, 1H), 5.21(d $J=13.0$ Hz, 1H), 7.12(d $J=7.6$ Hz, 2H), 7.42(d $J=7.6$ Hz, 2H), 7.70-7.77(m, 3H), 10.82(brs, 1H).

[331] ^{13}C NMR(100 MHz, $\text{DMSO}-d_6$) : 19.0, 20.5, 36.9, 41.8, 56.2, 71.0, 90.4, 110.2, 118.6, 122.9, 124.5, 125.4, 128.8, 131.7, 136.1, 139.5, 140.6, 149.1.

[332]

[333] **EXAMPLE 24: Preparation of**

1-{2-(dimethylamino)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[334]

[335] ^1H NMR(400 MHz, CDCl_3) : 2.26(s, 6H), 2.29(s, 3H), 2.32-2.50(m, 4H), 5.13(d $J=12.8$ Hz, 1H), 5.17(d $J=12.8$ Hz, 1H), 7.13(d $J=8.0$ Hz, 2H), 7.32(d $J=8.0$ Hz, 2H), 7.43(d $J=8.0$ Hz, 1H), 7.47(s, 1H), 7.57(d $J=8.0$ Hz, 1H).

[336]

[337] **EXAMPLE 25: Preparation of**

1-{2-(dimethylamino)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[338]

[339] ^1H NMR(400 MHz, $\text{DMSO}-d_6$) : 2.24(s, 3H), 2.67(s, 6H), 2.70-2.87(m, 4H), 5.15(d $J=13.2$ Hz, 1H), 5.23(d $J=13.2$ Hz, 1H), 7.16(d $J=8.4$ Hz, 2H), 7.45(d $J=8.4$ Hz, 2H), 7.74-7.81(m, 3H), 11.13(brs, 1H).

[340] ^{13}C NMR(100 MHz, DMSO- d_6) : 20.6, 34.1, 41.8, 52.5, 71.1, 89.0, 110.6, 118.5, 122.9, 124.4, 125.6, 129.0, 131.9, 136.6, 139.3, 139.7, 148.2

[341]

[342] **EXAMPLE 26: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[343]

[344] ^1H NMR(400 MHz, CDCl_3) : 1.72(m, 1H), 1.77(m, 1H), 1.99(m, 1H), 2.16(m, 1H), 2.29(s, 3H), 3.97(t, $J=7.0$ Hz, 2H), 5.14(m, 2H), 6.84(s, 1H), 7.07(s, 1H), 7.11(d, $J=8.4$ Hz, 2H), 7.25(d, $J=8.4$ Hz, 2H), 7.32(d, $J=7.8$ Hz, 1H), 7.46(s, 1H), 7.55(d, $J=7.8$ Hz, 1H), 7.69(s, 1H).

[345]

[346] **EXAMPLE 27: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[347]

[348] ^1H NMR(400 MHz, DMSO- d_6) : 1.61(m, 1H), 1.70(m, 1H), 2.16(m, 2H), 2.20(s, 3H), 4.19(m, 2H), 5.09(d, $J=13.0$ Hz, 1H), 5.18(d, $J=13.0$ Hz, 1H), 7.10(d, $J=7.6$ Hz, 2H), 7.37(d, $J=7.6$ Hz, 2H), 7.64-7.93(m, 5H), 9.24(s, 1H), 15.17(brs, 1H).

[349] ^{13}C NMR(100 MHz, DMSO- d_6) : 20.7, 25.1, 36.9, 48.5, 71.1, 90.4, 110.4, 118.7, 119.6, 121.9, 123.1, 124.6, 125.6, 129.0, 131.9, 135.0, 136.3, 139.8, 140.7, 149.2

[350]

[351] **EXAMPLE 28: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[352]

[353] ^1H NMR(400 MHz, CDCl_3) : 2.31(s, 3H), 2.57(m, 1H), 2.74(m, 1H), 3.96(m, 2H), 5.16(d, $J=13.2$ Hz, 1H), 5.21(d, $J=13.2$ Hz, 1H), 6.82(s, 1H), 7.02(s, 1H), 7.15(d, $J=8.0$ Hz, 2H), 7.33(d, $J=8.0$ Hz, 2H), 7.44(d, $J=8.0$ Hz, 1H), 7.49(s, 1H), 7.58(d, $J=8.0$ Hz, 1H), 7.69(s, 1H).

[354]

[355] **EXAMPLE 29: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[356]

[357] ^1H NMR(400 MHz, DMSO- d_6) : 2.23(s, 3H), 2.80(m, 1H), 2.95(m, 1H), 4.11(m, 2H), 5.15(d, $J=13.4$ Hz, 1H), 5.25(d, $J=13.4$ Hz, 1H), 7.13(d, $J=7.2$ Hz, 2H), 7.44(d, J

=7.2 Hz, 2H), 7.57(s, 1H), 7.70-7.77(m, 3H), 7.78(s, 1H), 9.08(s, 1H), 14.89(brs, 1H).

[358] ^{13}C NMR(100 MHz, DMSO- d_6) : 20.6, 40.1, 44.7, 71.2, 89.2, 110.4, 118.6, 119.2, 121.8, 122.9, 124.3, 125.5, 128.9, 131.8, 134.9, 136.5, 139.4, 140.2, 148.1.

[359]

[360] **EXAMPLE 30: Preparation of**

1-{3-(pyrazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[361]

[362] ^1H NMR(400 MHz, CDCl_3) : 1.79(m, 1H), 1.88(m, 1H), 2.05(m, 1H), 2.20(m, 1H), 2.28(s, 3H), 4.20(t, $J=6.8$ Hz, 2H), 5.14(m, 2H), 6.26(s, 1H), 7.11(d, $J=8.0$ Hz, 2H), 7.23-7.35(m, 4H), 7.45(s, 1H), 7.52-7.56(m, 2H).

[363]

[364] **EXAMPLE 31: Preparation of**

1-{3-(pyrazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[365]

[366] ^1H NMR(400 MHz, DMSO- d_6) : 1.57(m, 1H), 1.66(m, 1H), 2.09(m, 2H), 2.18(s, 3H), 4.13(m, 2H), 5.06(d, $J=13.2$ Hz, 1H), 5.13(d, $J=13.2$ Hz, 1H), 6.29(s, 1H), 7.07(d, $J=7.4$ Hz, 2H), 7.33(d, $J=7.4$ Hz, 2H), 7.58-7.70(m, 4H), 7.79(s, 1H), 13.47(brs, 1H).

[367] ^{13}C NMR(100 MHz, DMSO- d_6) : 20.6, 25.2, 37.1, 50.9, 70.9, 90.4, 105.3, 110.2, 118.7, 122.9, 124.5, 125.4, 128.8, 130.8, 131.8, 136.1, 137.3, 139.7, 140.7, 149.2.

[368]

[369] **EXAMPLE 32: Preparation of**

1-{2-(pyrazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[370]

[371] ^1H NMR(400 MHz, CDCl_3) : 2.29(s, 3H), 2.79(m, 2H), 4.15(m, 2H), 5.19(m, 2H), 6.11(s, 1H), 7.13(d, $J=8.4$ Hz, 2H), 7.17(s, 1H), 7.34(d, $J=8.4$ Hz, 2H), 7.39(d, $J=7.6$ Hz, 1H), 7.45-7.53(m, 3H).

[372]

[373] **EXAMPLE 33: Preparation of**

1-{2-(pyrazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[374]

[375] ^1H NMR(400 MHz, DMSO- d_6) : 2.21(s, 3H), 2.77(m, 2H), 4.05(m, 2H), 5.13(d, $J=12.8$ Hz, 1H), 5.24(d, $J=12.8$ Hz, 1H), 6.18(s, 1H), 7.12(d, $J=7.0$ Hz, 2H), 7.43(d, $J=7.0$ Hz, 2H), 7.51(s, 1H), 7.60-7.80(m, 4H), 11.81(brs, 1H).

[376] ^{13}C NMR(100 MHz, DMSO- d_6) : 20.6, 40.2, 47.1, 71.2, 89.3, 105.2, 110.3, 118.6, 122.9, 124.4, 125.4, 128.9, 130.6, 131.8, 136.3, 137.4, 139.4, 140.4, 148.4.

[377]

[378] **EXAMPLE 34: Preparation of**

1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[379]

[380] ^1H NMR(400 MHz, CDCl_3) : 1.32(m, 1H), 1.50(m, 1H), 2.08-2.27(m, 10H), 2.91(s, 6H), 5.29(m, 2H), 6.66(d, $J=7.2$ Hz, 2H), 7.27(d, $J=7.2$ Hz, 2H), 7.35(d, $J=8.0$ Hz, 1H), 7.47(s, 1H), 7.55(d, $J=8.0$ Hz, 1H).

[381]

[382] **EXAMPLE 35: Preparation of**

1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile oxalate

[383]

[384] ^1H NMR(400 MHz, DMSO- d_6) : 1.41(m, 1H), 1.53(m, 1H), 2.14(m, 2H), 2.62(s, 6H), 2.83(s, 6H), 2.97(t, $J=8.0$ Hz, 2H), 5.08(d, $J=13.6$ Hz, 1H), 5.17(d, $J=13.6$ Hz, 1H), 6.65(d, $J=8.0$ Hz, 2H), 7.28(d, $J=8.0$ Hz, 2H), 7.62(d, $J=7.6$ Hz, 1H), 7.75(d, $J=7.6$ Hz, 1H), 7.77(s, 1H).

[385] ^{13}C NMR (100 MHz, DMSO- d_6) : 19.3, 30.7, 36.8, 42.1, 56.6, 70.8, 90.3, 110.0, 112.0, 118.7, 122.8, 125.3, 125.4, 130.9, 131.7, 139.6, 149.3, 149.7, 164.1.

[386]

[387] **EXAMPLE 36: Preparation of**

1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[388]

[389] ^1H NMR(400 MHz, DMSO- d_6) : 1.44(m, 1H), 1.52(m, 1H), 2.23(t, $J=7.2$ Hz, 2H), 2.69(s, 3H), 2.70(s, 3H), 2.94(s, 6H), 3.00(m, 2H), 5.13(d, $J=13.4$ Hz, 1H), 5.21(d, $J=13.4$ Hz, 1H), 6.64(d, $J=7.8$ Hz, 2H), 7.25(d, $J=7.8$ Hz, 2H), 7.70-7.80(m, 3H), 9.1(brs, 1H).

[390] ^{13}C NMR (100 MHz, DMSO- d_6) : 19.3, 36.8, 41.8, 41.9, 56.2, 71.2, 90.2, 110.5, 112.0, 118.6, 122.9, 125.6, 126.0, 130.9, 131.9, 139.6, 148.4, 149.3.

[391]

[392] **EXAMPLE 37: Preparation of**

1-(4-dimethylaminophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile

urancarbonitrile

[393]

[394] ^1H NMR(400 MHz, CDCl_3) : 1.69(m, 1H), 1.80(m, 1H), 2.01(m, 1H), 2.17(m, 1H), 2.92(s, 6H), 3.92(m, 2H), 5.30(m, 2H), 6.66(d $J=7.4$ Hz, 2H), 6.83(s, 1H), 7.04(s, 1H), 7.19-7.23(m, 3H), 7.41(s, 1H), 7.48(s, 1H), 7.56(d $J=7.6$ Hz, 1H).

[395]

[396] **EXAMPLE 38: Preparation of****1-(4-dimethylaminophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride**

[397]

[398] ^1H NMR(400 MHz, $\text{DMSO}-d_6$) : 1.62(m, 1H), 1.72(m, 1H), 2.12(m, 2H), 2.88(s, 6H), 4.15(t, $J=7.0$ Hz, 2H), 5.09(d $J=13.6$ Hz, 1H), 5.15(d $J=13.6$ Hz, 1H), 6.82(d $J=8.2$ Hz, 2H), 7.34(d $J=8.2$ Hz, 2H), 7.62-7.94(m, 5H), 9.08(s, 1H).

[399]

[400] **EXAMPLE 39: Preparation of****1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile**

[401]

[402] ^1H NMR(400 MHz, CDCl_3) : 1.56(m, 1H), 1.73(m, 1H), 2.25(m, 1H), 2.35-2.50(m, 7H), 2.62(m, 2H), 5.19(d $J=13.2$ Hz, 1H), 5.24(d $J=13.2$ Hz, 1H), 6.92-6.95(m, 2H), 7.19(m, 1H), 7.41(d $J=7.6$ Hz, 1H), 7.50(s, 1H), 7.60(d $J=7.6$ Hz, 1H).

[403]

[404] **EXAMPLE 40: Preparation of****1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate**

[405]

[406] ^1H NMR(400 MHz, $\text{DMSO}-d_6$) : 1.41(m, 1H), 1.59(m, 1H), 2.26(t, $J=7.6$ Hz, 2H), 2.62(s, 6H), 2.97(t, $J=7.8$ Hz, 2H), 5.16(d $J=13.2$ Hz, 1H), 5.21(d $J=13.2$ Hz, 1H), 6.99(m, 1H), 7.12(d $J=3.6$ Hz, 1H), 7.40(d $J=5.2$ Hz, 1H), 7.64(d $J=7.8$ Hz, 1H), 7.80(d $J=7.8$ Hz, 1H), 7.83(s, 1H).

[407] ^{13}C NMR(100 MHz, $\text{DMSO}-d_6$) : 192, 37.5, 42.1, 56.4, 71.4, 89.2, 110.7, 118.6, 122.7, 122.8, 124.9, 125.7, 127.4, 132.0, 139.3, 148.1, 148.7, 164.3.

[408]

[409] **EXAMPLE 41: Preparation of**

1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[410]

[411] ^1H NMR(400 MHz, DMSO- d_6) : 1.45(m, 1H), 1.56(m, 1H), 2.29(t, $J=7.6$ Hz, 2H), 2.64(s, 3H), 2.65(s, 3H), 3.01(m, 2H), 5.17(d $J=13.2$ Hz, 1H), 5.22(d $J=13.2$ Hz, 1H), 7.00(m, 1H), 7.13(d $J=3.6$ Hz, 1H), 7.40(d $J=5.2$ Hz, 1H), 7.67(d $J=7.6$ Hz, 1H), 7.82(d $J=8.2$ Hz, 1H), 7.85(s, 1H), 9.2(brs, 1H).

[412] ^{13}C NMR(100 MHz, DMSO- d_6) : 189, 37.5, 41.7, 41.8, 56.1, 71.4, 89.2, 110.7, 118.5, 122.7, 122.8, 124.8, 125.7, 127.3, 132.0, 139.2, 148.1, 148.7.

[413]

[414] **EXAMPLE 42: Preparation of**

1-{2-(dimethylamino)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[415]

[416] ^1H NMR(400 MHz, CDCl_3) : 2.58-2.70(m, 8H), 2.80(m, 2H), 5.19(d $J=13.0$ Hz, 1H), 5.24(d $J=13.0$ Hz, 1H), 6.92-7.00(m, 2H), 7.22(m, 1H), 7.47-7.52(m, 2H), 7.63(d $J=8.0$ Hz, 1H).

[417]

[418] **EXAMPLE 43: Preparation of**

1-{2-(dimethylamino)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[419]

[420] ^1H NMR(400 MHz, DMSO- d_6) : 2.60-2.78(m, 8H), 2.82(m, 2H), 5.18(d $J=13.4$ Hz, 1H), 5.23(d $J=13.4$ Hz, 1H), 7.02(m, 1H), 7.25(d $J=2.8$ Hz, 1H), 7.42(d $J=4.4$ Hz, 1H), 7.69(d $J=7.6$ Hz, 1H), 7.82-7.85(m, 2H), 11.21(brs, 1H).

[421] ^{13}C NMR(100 MHz, DMSO- d_6) : 34.5, 41.8, 41.9, 52.3, 71.4, 87.8, 111.0, 118.4, 122.8, 123.0, 125.3, 125.8, 127.5, 132.2, 138.9, 147.4, 147.3.

[422]

[423] **EXAMPLE 44: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[424]

[425] ^1H NMR(400 MHz, CDCl_3) : 1.78(m, 1H), 1.92(m, 1H), 2.10(m, 1H), 2.28(m, 1H), 4.07(t, $J=7.0$ Hz, 2H), 5.18(d $J=12.8$ Hz, 1H), 5.25(d $J=12.8$ Hz, 1H), 6.86(m, 1H), 6.91(s, 1H), 6.95(m, 1H), 7.14(s, 1H), 7.22(m, 1H), 7.32(d $J=8.2$ Hz, 1H), 7.52(s, 1H), 7.61(d $J=8.2$ Hz, 1H), 7.95(s, 1H).

[426]

[427] **EXAMPLE 45: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate

[428]

[429] ^1H NMR(400 MHz, DMSO- d_6) : 1.55(m, 1H), 1.75(m, 1H), 2.18(m, 2H), 4.05(t, J =7.0 Hz, 2H), 5.16(m, 2H), 6.98(m, 1H), 7.06(d, J =3.2 Hz, 1H), 7.25(s, 1H), 7.38(d, J =4.8 Hz, 1H), 7.41(s, 1H), 7.60(d, J =7.8 Hz, 1H), 7.80(d, J =8.0 Hz, 1H), 7.81(s, 1H), 8.34(s, 1H).

[430] ^{13}C NMR(100 MHz, DMSO- d_6) : 25.3, 37.6, 47.0, 71.4, 89.2, 110.7, 118.5, 120.4, 122.6, 122.7, 123.8, 124.8, 125.7, 127.3, 132.0, 136.0, 139.2, 148.1, 148.7, 162.7.

[431]

[432] **EXAMPLE 46: Preparation of**

1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[433]

[434] ^1H NMR(400 MHz, DMSO- d_6) : 1.61(m, 1H), 1.79(m, 1H), 2.21(m, 2H), 4.02(t, J =7.0 Hz, 2H), 5.20(m, 2H), 6.98(m, 1H), 7.08(d, J =3.6 Hz, 1H), 7.39(d, J =4.8 Hz, 1H), 7.63(d, J =7.8 Hz, 1H), 7.65(s, 1H), 7.72(s, 1H), 7.81(d, J =7.8 Hz, 1H), 7.83(s, 1H), 9.09(s, 1H), 14.42(brs, 1H).

[435] ^{13}C NMR(100 MHz, DMSO- d_6) : 24.8, 37.3, 48.2, 71.4, 89.1, 110.7, 118.5, 119.5, 121.7, 122.7, 122.8, 124.8, 125.7, 127.3, 132.0, 134.9, 139.2, 148.0, 148.6.

[436]

[437] **EXAMPLE 47: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[438]

[439] ^1H NMR(400 MHz, CDCl_3) : 2.66(m, 1H), 2.84(m, 1H), 4.07(m, 2H), 5.22(d, J =13.2 Hz, 1H), 5.28(d, J =13.2 Hz, 1H), 6.88(s, 1H), 6.96-6.99(m, 2H), 7.07(s, 1H), 7.25(m, 1H), 7.43(d, J =8.0 Hz, 1H), 7.55(s, 1H), 7.63(d, J =8.0 Hz, 1H), 7.90(s, 1H).

[440]

[441] **EXAMPLE 48: Preparation of**

1-{2-(imidazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[442]

[443] ^1H NMR(400 MHz, DMSO- d_6) : 2.95(m, 2H), 4.16(m, 2H), 5.21(m, 2H), 7.00(m,

1H), 7.22(d, $J=24$ Hz, 1H), 7.41(d, $J=4.4$ Hz, 1H), 7.57-7.75(m, 5H), 9.12(s, 1H), 14.94(brs, 1H).

[444] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.1, 44.5, 71.5, 88.0, 110.8, 118.5, 119.1, 121.8, 122.8, 123.0, 125.1, 125.8, 127.5, 132.0, 134.9, 139.0, 147.2, 148.0.

[445]

[446] **EXAMPLE 49: Preparation of**
1-{3-(pyrazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[447]

[448] ^1H NMR(400 MHz, CDCl_3) : 1.82(m, 1H), 1.99(m, 1H), 2.14(m, 1H), 2.29(m, 1H), 4.26(t, $J=7.0$ Hz, 2H), 5.18(d, $J=13.0$ Hz, 1H), 5.24(d, $J=13.0$ Hz, 1H), 6.30(s, 1H), 6.86(s, 1H), 6.93(m, 1H), 7.20(m, 1H), 7.32(d, $J=8.0$ Hz, 1H), 7.40(s, 1H), 7.51(s, 1H), 7.57-7.61(m, 2H).

[449]

[450] **EXAMPLE 50: Preparation of**
1-{3-(pyrazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile
hydrochloride

[451]

[452] ^1H NMR(400 MHz, DMSO- d_6) : 1.56(m, 1H), 1.74(m, 1H), 2.16(m, 2H), 4.14(m, 2H), 5.13(m, 2H), 6.26(s, 1H), 6.94(s, 1H), 7.03(s, 1H), 7.33(s, 1H), 7.53-7.57(m, 2H), 7.73-7.79(m, 2H), 8.27(s, 1H), 13.64(brs, 1H).

[453] ^{13}C NMR(100 MHz, DMSO- d_6) : 25.1, 37.8, 50.8, 71.4, 89.3, 105.3, 110.9, 118.6, 122.6, 122.7, 124.8, 125.7, 127.3, 130.7, 132.0, 137.4, 139.3, 148.2, 148.8.

[454]

[455] **EXAMPLE 51: Preparation of**
1-{2-(pyrazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile

[456]

[457] ^1H NMR(400 MHz, CDCl_3) : 2.87(m, 2H), 4.22(m, 2H), 5.26(m, 2H), 6.13(s, 1H), 6.92-6.96(m, 2H), 7.19-7.22(m, 2H), 7.34(d, $J=7.6$ Hz, 1H), 7.47(s, 1H), 7.51(s, 1H), 7.55(d, $J=7.6$ Hz, 1H).

[458]

[459] **EXAMPLE 52: Preparation of**
1-{2-(pyrazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile
hydrochloride

[460]

[461] ^1H NMR(400 MHz, DMSO- d_6) : 2.83(m, 2H), 4.11(m, 2H), 5.20(m, 2H), 6.19(s,

1H), 695(s, 1H), 7.15(s, 1H), 7.36(s, 1H), 7.50-7.59(m, 2H), 7.68-7.76(m, 2H), 8.23(s, 1H), 14.18(brs, 1H).

[462] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.5, 469, 71.7, 88.1, 105.4, 110.7, 118.6, 122.8, 122.9, 125.0, 125.7, 127.5, 131.1, 1320, 133.3, 1390, 147.5, 148.4.

[463]

[464] **EXAMPLE 53: Preparation of**
1-(4-fluorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[465]

[466] ^1H NMR(400 MHz, CDCl_3) : 1.68(m, 1H), 1.76(m, 1H), 1.99(m, 1H), 2.14(m, 1H), 3.96(t, $J=6.8$ Hz, 2H), 5.12(m, 2H), 6.82(s, 1H), 6.98(m, 2H), 7.05(s, 1H), 7.28-7.38(m, 3H), 7.48(s, 1H), 7.57(d $J=8.0$ Hz, 1H), 7.64(s, 1H).

[467]

[468] **EXAMPLE 54: Preparation of**
1-(4-fluorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[469]

[470] ^1H NMR(400 MHz, DMSO- d_6) : 1.62(m, 1H), 1.70(m, 1H), 2.17(m, 2H), 4.15(t, $J=7.0$ Hz, 2H), 5.13(d $J=13.6$ Hz, 1H), 5.19(d $J=13.6$ Hz, 1H), 7.15(m, 2H), 7.55(m, 2H), 7.64-7.80(m, 5H), 9.09(s, 1H).

[471] ^{13}C NMR(100 MHz, DMSO- d_6) : 249, 36.8, 48.3, 71.0, 90.1, 110.4, 115.0(d $^2J_{CF}=21$ Hz), 118.5, 119.5, 121.7, 123.0, 125.5, 126.7(d $^3J_{CF}=8$ Hz), 131.9, 134.9, 139.6, 139.7, 148.5, 161.0(d $^1J_{CF}=242$ Hz).

[472]

[473] **EXAMPLE 55: Preparation of**
1-(4-fluorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[474]

[475] ^1H NMR(400 MHz, CDCl_3) : 2.79(m, 1H), 2.91(m, 1H), 4.13(m, 2H), 5.15(d $J=13.0$ Hz, 1H), 5.23(d $J=13.0$ Hz, 1H), 6.93(s, 1H), 7.03(m, 2H), 7.18(s, 1H), 7.48-7.51(m, 3H), 7.61-7.68(m, 2H), 9.03(s, 1H).

[476]

[477] **EXAMPLE 56: Preparation of**
1-(4-fluorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[478]

[479] ^1H NMR(400 MHz, DMSO- d_6) : 2.81(m, 1H), 2.90(m, 1H), 4.10(m, 2H), 5.17(d J =13.4 Hz, 1H), 5.25(d J =13.4 Hz, 1H), 7.18(m, 2H), 7.56-7.62(m, 3H), 7.76-7.78(m, 3H), 7.81(s, 1H), 8.95(s, 1H), 14.00(brs, 1H).

[480] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.1, 44.6, 71.3, 89.0, 110.6, 115.1(d $^2J_{\text{CF}}$ =21 Hz), 118.5, 119.2, 121.8, 122.9, 125.6, 126.6(d $3J_{\text{CF}}$ =8 Hz), 131.9, 135.0, 139.3, 147.6, 162.2(d $^1J_{\text{CF}}$ =242 Hz).

[481]

[482] **EXAMPLE 57: Preparation of**
1-(4-fluorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[483]

[484] ^1H NMR(400 MHz, CDCl_3) : 1.74(m, 1H), 1.90(m, 1H), 2.04(m, 1H), 2.15(m, 1H), 4.09(m, 2H), 5.10(d J =13.0 Hz, 1H), 5.16(d J =13.0 Hz, 1H), 6.20(s, 1H), 6.39(s, 1H), 6.97(m, 2H), 7.23-7.35(m, 4H), 7.46(s, 1H), 7.55(d J =7.6 Hz, 1H).

[485]

[486] **EXAMPLE 58: Preparation of**
1-(4-fluorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[487]

[488] ^1H NMR(400 MHz, DMSO- d_6) : 1.55(m, 1H), 1.62(m, 1H), 2.12(t, J =7.6 Hz, 2H), 4.05(t, J =7.2 Hz, 2H), 5.10(d J =13.4 Hz, 1H), 5.16(d J =13.4 Hz, 1H), 6.17(m, 1H), 6.38(m, 1H), 7.14(m, 2H), 7.37(m, 1H), 7.52(m, 2H), 7.63-7.78(m, 3H).

[489]

[490] **EXAMPLE 59: Preparation of**
1-(4-fluorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[491]

[492] ^1H NMR(400 MHz, CDCl_3) : 2.76(m, 2H), 4.12(m, 2H), 5.16(d J =12.8 Hz, 1H), 5.23(d J =12.8 Hz, 1H), 6.08(s, 1H), 7.00(m, 2H), 7.14(s, 1H), 7.35(d J =7.6 Hz, 1H), 7.40-7.44(m, 3H), 7.48(s, 1H), 7.53(d J =7.6 Hz, 1H).

[493]

[494] **EXAMPLE 60: Preparation of**
1-(4-fluorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[495]

[496] ^1H NMR(400 MHz, DMSO- d_6) : 2.77(m, 2H), 4.02(d $J=7.0$ Hz, 2H), 5.17(d $J=13.4$ Hz, 1H), 5.25(d $J=13.4$ Hz, 1H), 6.15(s, 1H), 7.14(m, 2H), 7.43(s, 1H), 7.59-7.65(m, 3H), 7.73-7.77(m, 3H), 12.03(brs, 1H).

[497] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.4, 47.0, 71.3, 89.1, 105.0, 110.5, 115.1 (d $^2J_{CF}=20$ Hz), 118.6, 123.0, 125.5, 126.7 (d $^3J_{CF}=8$ Hz), 130.1, 131.9, 137.8, 139.4, 139.6 (d $^4J_{CF}=3$ Hz), 148.1, 161.1 (d $^1J_{CF}=242$ Hz).

[498]

[499] **EXAMPLE 61: Preparation of**
1-(4-chlorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[500]

[501] ^1H NMR(400 MHz, CDCl_3) : 1.72(m, 2H), 2.00(m, 1H), 2.11(m, 1H), 3.97(t, $J=7.0$ Hz, 2H), 5.14(m, 2H), 6.83(s, 1H), 7.06(s, 1H), 7.24-7.32(m, 5H), 7.48(s, 1H), 7.57(d $J=8.0$ Hz, 1H), 7.66(s, 1H).

[502]

[503] **EXAMPLE 62: Preparation of**
1-(4-chlorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride

[504]

[505] ^1H NMR(400 MHz, DMSO- d_6) : 1.62(m, 2H), 2.16(m, 2H), 4.14(t, $J=7.0$ Hz, 2H), 5.13(d $J=13.6$ Hz, 1H), 5.19(d $J=13.6$ Hz, 1H), 7.39(d $J=8.6$ Hz, 2H), 7.54(d $J=8.6$ Hz, 2H), 7.64(s, 1H), 7.71-7.80(m, 4H), 9.08(s, 1H).

[506] ^{13}C NMR(100 MHz, DMSO- d_6) : 24.8, 36.6, 48.3, 71.1, 90.0, 110.5, 118.5, 119.5, 121.7, 123.0, 125.6, 126.6, 128.2, 131.8, 131.9, 134.9, 139.6, 142.5, 148.3.

[507]

[508] **EXAMPLE 63: Preparation of**
1-(4-chlorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile

[509]

[510] ^1H NMR(400 MHz, CDCl_3) : 2.60(m, 1H), 2.71(m, 1H), 3.96(m, 2H), 5.15(d $J=13.0$ Hz, 1H), 5.22(d $J=13.0$ Hz, 1H), 6.81(s, 1H), 7.01(s, 1H), 7.30-7.41(m, 4H), 7.45(d $J=8.4$ Hz, 1H), 7.51(s, 1H), 7.60(d $J=8.4$ Hz, 1H), 7.74(s, 1H).

[511]

[512] **EXAMPLE 64: Preparation of**

1-(4-chlorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbo nitrile hydrochloride

[513]

[514] ^1H NMR(400 MHz, DMSO- d_6) : 2.81(m, 1H), 2.91(m, 1H), 4.12(m, 2H), 5.17(d J =13.4 Hz, 1H), 5.25(d J =13.4 Hz, 1H), 7.42(d J =7.2 Hz, 2H), 7.57-7.61(m, 3H), 7.68-7.78(m, 3H), 7.82(s, 1H), 8.97(s, 1H), 14.00(brs, 1H).

[515] ^{13}C NMR(100 MHz, DMSO- d_6) : 40.1, 44.6, 71.4, 89.0, 110.7, 118.5, 119.2, 121.8, 122.9, 125.6, 126.5, 128.3, 131.9, 132.1, 135.0, 139.3, 142.1, 147.3.

[516]

[517] **EXAMPLE 65: Preparation of**

1-(4-chlorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbo nitrile

[518]

[519] ^1H NMR(400 MHz, CDCl_3) : 1.74(m, 1H), 1.83(m, 1H), 2.03(m, 1H), 2.15(m, 1H), 4.10(m, 2H), 5.10(d J =13.0 Hz, 1H), 5.15(d J =13.0 Hz, 1H), 6.20(s, 1H), 7.24-7.32(m, 5H), 7.45-7.46(m, 2H), 7.55(d J =8.0 Hz, 1H), 7.73(s, 1H).

[520]

[521] **EXAMPLE 66: Preparation of**

1-(4-chlorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbo nitrile hydrochloride

[522]

[523] ^1H NMR(400 MHz, DMSO- d_6) : 1.59(m, 2H), 2.12(m, 2H), 4.05(d J =7.2 Hz, 2H), 5.11(d J =13.4 Hz, 1H), 5.17(d J =13.4 Hz, 1H), 6.17(m, 1H), 7.35-7.38(m, 3H), 7.52(d J =8.4 Hz, 2H), 7.63-7.69(m, 2H), 7.76-7.78(m, 2H).

[524] ^{13}C NMR(100 MHz, DMSO- d_6) : 25.2, 37.1, 50.8, 71.1, 90.2, 105.0, 110.5, 118.6, 122.9, 125.6, 126.6, 128.2, 130.1, 131.9, 133.3, 137.8, 139.6, 142.7, 148.5.

[525]

[526] **EXAMPLE 67: Preparation of**

1-(4-chlorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarboni trile

[527]

[528] ^1H NMR(400 MHz, CDCl_3) : 2.78(m, 2H), 4.14(t, J =7.6 Hz, 2H), 5.16(d J =13.2 Hz, 1H), 5.23(d J =13.2 Hz, 1H), 6.09(s, 1H), 7.14(s, 1H), 7.27-7.43(m, 5H), 7.44(s, 1H), 7.47(s, 1H), 7.53(s, 1H).

[529]

- [530] **EXAMPLE 68: Preparation of**
 1-(4-chlorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarboni
 trile hydrochloride
- [531]
- [532] ¹H NMR(400 MHz, DMSO-*d*₆) : 2.75(m, 2H), 3.98(m, 2H), 5.18(d, *J*=14.0 Hz, 1H),
 5.28(d, *J*=14.0 Hz, 1H), 6.10(m, 1H), 7.33-7.41(m, 3H), 7.58-7.63(m, 3H),
 7.52-7.79(m, 3H).
- [533] ¹³C NMR(100 MHz, DMSO-*d*₆) : 40.3, 46.9, 71.4, 89.1, 104.9, 110.6, 118.6, 122.9,
 125.5, 126.5, 128.3, 129, 131.9, 137.9, 139.4, 142.4, 143.8, 147.8.
- [534]
- [535] The structures of the examples 1 to 68 are described in Tables 1 and 2, below.
- [536] Table 1

[Table 1]

[Table]

Example	R ¹	n	R ²	salt
1	4-methoxyphenyl	3	dimethylamino	
2	〃	3	〃	Oxalic acid salt
3	〃	3	〃	HCl salt
4	〃	3	1-imidazolyl	
5	〃	3	〃	HCl salt
6	〃	2	〃	
7	〃	2	〃	HCl salt
8	〃	3	1-pyrazolyl	
9	〃	3	〃	HCl salt
10	〃	2	〃	
11	〃	2	〃	HCl salt
12	phenyl	3	dimethylamino	
13	〃	3	〃	HCl salt
14	〃	2	〃	
15	〃	2	〃	HCl salt
16	〃	3	1-imidazolyl	
17	〃	3	〃	HCl salt
18	〃	2	〃	
19	〃	2	〃	HCl salt
20	〃	2	1-pyrazolyl	
21	〃	2	〃	HCl salt
22	4-tolyl	3	dimethylamino	
23	〃	3	〃	HCl salt
24	〃	2	〃	
25	〃	2	〃	HCl salt
26	〃	3	1-imidazolyl	

27	〃	3	〃	HCl salt
28	〃	2	〃	
29	〃	2	〃	HCl salt
30	〃	3	1-pyrazolyl	
31	〃	3	〃	HCl salt
32	〃	2	〃	
33	〃	2	〃	HCl salt

[537]

[538] Table 2

[Table 2]

[Table]

Example	R ¹	n	R ²	salt
34	4-dimethylaminophenyl	3	dimethylamino	
35	1	3	〃	Oxalic acid salt
36	〃	3	〃	HCl salt
37	〃	3	1-imidazolyl	
38	〃	3	〃	HCl salt
39	2-thienyl	3	dimethylamino	
40	〃	3	〃	Oxalic acid salt
41	〃	3	〃	HCl salt
42	〃	2	〃	
43	〃	2	〃	HCl salt
44	〃	3	1-imidazolyl	
45	〃	3	〃	Oxalic acid salt
46	〃	3	〃	HCl salt
47	〃	2	〃	
48	〃	2	〃	HCl salt
49	〃	3	1-pyrazolyl	
50	〃	3	〃	HCl salt
51	〃	2	〃	
52	〃	2	〃	HCl salt
53	4-fluorophenyl	3	1-imidazolyl	
54	〃	3	〃	HCl salt
55	〃	2	〃	
56	〃	2	〃	HCl salt
57	〃	3	1-pyrazolyl	
58	〃	3	〃	HCl salt

59	〃	2	〃	
60	〃	2	〃	HCl salt
61	4-chlorophenyl	3	1-imidazolyl	
62	〃	3	〃	HCl salt
63	〃	2	〃	
64	〃	2	〃	HCl salt
65	〃	3	1-pyrazolyl	
66	〃	3	〃	HCl salt
67	〃	2	〃	
68	〃	2	〃	HCl salt

[539]

[540] **TEST EXAMPLE 1: Evaluation of ejaculation-delaying effect**

[541] The compounds prepared in the above examples were evaluated to determine whether they have an effect of delaying ejaculation. The evaluation was carried out using an animal model according to a method described in Yonezawa et al., Life Sci. 2000, 67(25) p3031-9 Male Wistar rats weighing 240-260 g were used. Each compound was suspended in 1% HPMC, and then administered orally to each animal. After 60 min, the animals were anesthetized and fixed. 20 min later, para-chloroamphetamine (p-PCA) was intraperitoneally administered in a dose of 5 mg/kg in order to induce ejaculation. Then, the ejaculatory response to p-PCA was observed in anesthetized rats over 30 min. An ejaculatory response was considered to be elicited when rhythmic contraction of bulbocavernosus muscles and semen discharge occurs. Six or more animals were used for each compound. A Fisher's exact test was performed for the comparison of the proportion of responding rats (ejaculated rats) to determine significance of difference between a treatment group and a vehicle control. The time to reach ejaculation was expressed as mean±standard deviation.

[542] The compounds prepared in Examples 1 to 68 were found to have good inhibitory effects on ejaculation. The ejaculation-inhibiting effects of representative compounds are given in Table 3, below. Each test compound was administered at a dose of 50 mg/kg. Ejaculation was elicited in all seven animals of a control group. In contrast, the administration of the compounds prepared in Examples 1 to 68 significantly reduced the number of responding rats. These results indicated that the present compounds are very

effective in inhibiting ejaculation. Citalopram, which is conventional SSRI drug known to have ejaculation-delaying effects, was used as control compound.

[543] Table 3

[Table 3]

[Table]

Compound	Ratio	Latency	Compound	Ratio	Latency
Control	7/7	778±344	Ex. 35	0/9	ND
Ex. 1	5/9	1024±256	Ex. 36	2/6	554±77
Ex. 2	0/9	ND	Ex. 37	4/7	950±241
Ex. 3	1/6	1234	Ex. 38	4/7	764±304
Ex. 4	4/9	1300±124	Ex. 39	5/9	854±287
Ex. 5	3/7	986±342	Ex. 40	3/9	876±110
Ex. 6	4/7	889±284	Ex. 41	1/7	702
Ex. 7	5/9	963±304	Ex. 42	4/9	906±275
Ex. 8	4/9	1230±421	Ex. 43	3/7	888±275
Ex. 9	4/7	950±245	Ex. 44	4/7	904±350
Ex. 10	4/9	889±360	Ex. 45	2/9	676±10
Ex. 11	3/7	974±289	Ex. 46	0/7	ND
Ex. 12	4/9	1025±189	Ex. 47	4/7	814±278
Ex. 13	1/6	327	Ex. 48	3/7	904±321
Ex. 14	3/7	1032±451	Ex. 49	5/9	807±301
Ex. 15	4/9	1345±510	Ex. 50	3/7	979±347
Ex. 16	4/9	856±365	Ex. 51	4/7	1042±451
Ex. 17	3/6	949±330	Ex. 52	3/7	869±274
Ex. 18	3/7	691±361	Ex. 53	4/9	1054±320
Ex. 19	5/9	954±275	Ex. 54	5/9	1247±352
Ex. 20	3/7	978±378	Ex. 55	4/7	1450±671
Ex. 21	4/7	799±387	Ex. 56	2/6	606±130
Ex. 22	3/7	830±287	Ex. 57	4/9	951±342
Ex. 23	4/7	967±274	Ex. 58	4/9	850±362
Ex. 24	3/7	1021±367	Ex. 59	3/7	954±287
Ex. 25	4/9	841±254	Ex. 60	4/9	1010±400

Ex. 26	4/7	904±304	Ex. 61	3/7	930±247
Ex. 27	3/7	864±257	Ex. 62	4/7	888±284
Ex. 28	3/7	734±451	Ex. 63	3/7	904±307
Ex. 29	5/9	1054±287	Ex. 64	4/7	1032±299
Ex. 30	3/7	876±300	Ex. 65	5/9	801±401
Ex. 31	3/9	754±401	Ex. 66	4/7	960±350
Ex. 32	4/9	1000±401	Ex. 67	3/7	853±352
Ex. 33	3/7	698±374	Ex. 68	4/9	908±274
Ex. 34	4/9	807±304			
Ratio : Number fo responding animals / total animal number Latency : Time (sec) to display the ejaculatory response ND : not determined					

[544]

[545] **TEST EXAMPLE 2: Determination of half-lives of the compounds in rats.**

[546] The half-lives of present compounds were determined as follows. Each compound was administered orally to male Sprague-Dawley rats weighing approximately 270 g at a dose of 10 mg/kg. 5 mg/kg of each compound was suspended in 0.5% methyl-cellulose and then administered to rats. Blood samples were collected 0.017, 0.083, 0.25, 0.5, 1, 2, 3, 5, 7 and 24 hours after administration, and centrifuged at 1,000 rpm for 3 min to separate plasma. The concentration of each compound in plasma was determined using high performance liquid chromatography, which was performed with a mobile phase of 10 mM ammonium formate (pH 3.0) and acetonitrile (50:50), an atlanis dC18 column (2.1×100 mm, 3 μm) and a flow rate of 0.2 ml/min.

[547] The results are given in Table 4, below. The present compounds displayed Tmax (time to reach maximal plasma concentration) values similar to that of citalopram, which is conventional SSRI drug known to have ejaculation-delaying effects, but showed half-lives three times shorter than that of citalopram. These results indicated that the present compounds are rapidly absorbed into the body and quickly excreted outside the body and thus have a lower risk of incidence of side effects and improved safety.

[548] Table 4

[Table 4]

[Table]

	Citalopram	Ex. 2	Ex. 35	Ex. 40	Ex. 45
T _{1/2} (hr)	3.24	1.28	3.51	1.26	1.06
T _{max} (hr)	0.33	0.33	0.25	0.25	0.25

[549]

[550] **TEST EXAMPLE 3: Evaluation of mechanism of the present compounds**

[551] The mechanism of the present derivatives was investigated by assessing their inhibitory effects on neurotransmitters and ligand binding affinity to serotonin receptors.

[552] First, the effects of the present compounds on cellular uptake of dopamine, norepinephrine and serotonin were evaluated with human-derived CHO-1, MDCK and HEK-293 cell lines. Each cell line was dosed with 10⁻⁵ μM to 10⁴ μM of the compounds of Examples 2, 35, 40 and 45, and then incubated with [³H]dopamine, [³H]norepinephrine and [³H]serotonin in buffer. After 10 min, the amount of each neurotransmitter taken up into cells was determined by counting radioactivity using a liquid scintillation counter (LSC).

[553] The results are given in Table 5, below. The present compound was found to be not involved in dopamine or norepinephrine reuptake, but was found to act selectively for serotonin to inhibit its reuptake.

[554] In addition, ligand binding to 5HT1A, 5-HT1B and 5-HT2C receptors and 5-HT transporter was evaluated with human-derived recombinant CHO cells, Wistar rat-derived cerebral cortical cells, human-derived recombinant CHO-K1 cells, and human-derived recombinant HEK-293 cells. Each cell line was dosed with 10⁻⁵ μM to 10⁴ μM of the compounds of Examples 2, 35, 40 and 45, and then incubated with a radio-labeled ligand for competitive binding. Ligands used were [³H]8-OH-DPAT, [¹²⁵I]Cyanopindolol, [³H]Mesulergine and [³H]Paroxetine, respectively. The competitive binding assay was carried out in 50 mM Tris-HCl buffer at 25°C or 37°C, for 60 to 90 min.

[555] The radioligand assay revealed that the present compound is highly associated with 5-HT2C receptor and 5-HT transporter. These results indicate that the 1,3-dihydro-5-isobenzofurancarbonitrile derivatives inhibit the ejaculatory response by selectively inhibiting the serotonin reuptake via a serotonin reuptake transporter present in a presynaptic neuron, one among several mechanisms of the central nervous

system involved in ejaculation.

[556] Table 5

[Table 5]

[Table]

Test	Receptors	IC50 (micromole)			
		Ex. 2	Ex. 35	Ex. 40	Ex. 45
Radioligand assay	5-HT1A	805	1120	967	898
	5-HT1B	>1000	>1000	>1000	>1000
	5-HT2C	7.12	898	10.12	8.88
	5-HT transporter	$<0.1 \times 10^{-3}$	1×10^{-3}	12.5×10^{-3}	8.7×10^{-3}
Cellularreuptake assay	Dopamine	85.7	100.2	123.5	94.2
	Norepinephrine	36.5	53.2	691	67.3
	Serotonin	0.304	0.425	0.531	0.465

[557]

[558] **TEST EXAMPLE 4: Acute toxicity test**

[559] To evaluate the safety of the present derivatives in comparison with control drug, an acute toxicity test was conducted with 5-week-old Sprague-Dawley (SD) rats. The present derivatives and citalopram were individually administered orally and intravenously to SD rats at a single dose. Then, the rats were observed for mortality. The results are given in Table 6, below.

[560] Table 6

[Table 6]

[Table]

	Citalopram		Ex. 2		Ex. 35		Ex. 40		Ex. 45	
	female	male	female	male	female	male	female	male	female	male
Intravenously	30	30	70	70	50	50	50	50	50	50
Orally	650	650	1000	1000	1000	1000	800	800	1000	1000

[561] As being shown in Table 6, the minimum lethal doses of the compounds of examples

2, 35, 40 and 45 were higher than that of citalopram. It means the compounds of examples 2, 35, 40 and 45 are safer than citalopram. Specially, it was found that the compound of example 2 was over twice safer than citalopram.

[562]

[563] **TEST EXAMPLE 5: Cardiotoxicity test**

[564] To evaluate the safety of the present derivatives in comparison with control drug, conducted was hERG (human Ether-a-go-go Related Gene) assay which is a representative test of safety medical test. This test was requested to trial institute MDS Pharma., which conducted this test. The results are given in Table 7, below.

[565] Table 7

[Table 7]

[Table]

Compounds	Results (IC ₅₀ , μ M)
Citalopram	49
Ex. 2	194
Ex. 35	12.2
Ex. 40	8.7
Ex. 45	10.6

[566]

[567] As shown in Table 7, IC₅₀ value of example 3 is about four times higher than that of citalopram. It means the potassium channel inhibition activities of the present derivatives are very low, so the possibility causing cardiotoxicity such as arrhythmia is very small. Therefore, the present derivatives are much safer than citalopram.

[568]

[569] **TEST EXAMPLE 6: Mutagenicity test**

[570] To evaluate the safety of the present derivatives, mutagenicity test was conducted. Ames test and chromosome aberration test were conducted with the examples 2, 35, 40 and 45. The results are given in Table 8, below.

[571] Table 8

[Table 8]

[Table]

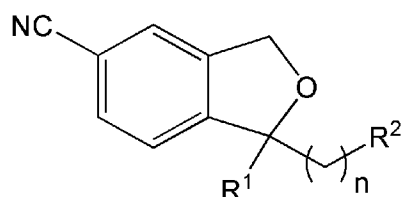
Tests	Tester strains	Concentrations	Results
ames test	Five strains(<i>Salmonella typhimurium</i> TA98, 100, 1535, 1537, E.coli WP2 uvrA)	8, 40, 200, 1000, 2500, 5000 $\mu\text{g}/\text{plate}$ (in the presence/absence of a metabolic activation system)	negative
chromosome aberration test	CHL (Chinese Hamster Lung) cell	75, 150, 300 $\mu\text{g}/\text{ml}$ (in the presence of a metabolic activation system) 20, 40, 80 $\mu\text{g}/\text{ml}$ (in the absence of a metabolic activation system)	negative

[572] As shown in Table 8, the results of the examples 2, 35, 40 and 45 were negative. On the other hand, it was reported the result of citalopram was positive in the same test, so it was found the present derivatives are safer than citalopram.

Claims

- [1] A derivative represented by Formula 1 or a pharmaceutically acceptable salt thereof:

[Formula 1]



wherein, R^1 is a substituted or unsubstituted phenyl; or heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl;

R^2 is C_1 - C_6 dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

n is an integer from 1 to 3.

- [2] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R^1 is a substituted or unsubstituted phenyl; or heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and in case that the R^1 contains a substituent, the substituent is C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, C_1 - C_6 dialkylamino or halogen; the R^2 is C_1 - C_6 dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and the n is an integer from 1 to 3.

- [3] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R^1 is a substituted or unsubstituted phenyl; or heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and

furyl;

the R² is C₁-C₆ dialkylamino, pyrazolyl, or imidazolyl; and

the n is an integer from 1 to 3.

- [4] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R¹ is phenyl substituted with C₁-C₆ alkyloxy;

the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

the n is an integer from 1 to 3.

- [5] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 4, wherein, the R¹ is methoxyphenyl;

the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

the n is an integer from 1 to 3.

- [6] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 5, wherein, the R¹ is methoxyphenyl;

the R² is dimethylamino, pyrazolyl, or imidazolyl; and

the n is an integer from 1 to 3.

- [7] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R¹ is unsubstituted phenyl or phenyl substituted with C₁-C₆ alkyl;

the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

the n is an integer from 1 to 3.

- [8] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 7, wherein, the R¹ is unsubstituted phenyl or tolyl;

the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, im-

idazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and
the n is an integer from 1 to 3.

- [9] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 8, wherein, the R¹ is unsubstituted phenyl or tolyl; the R² is C₁-C₆ dialkylamino, pyrazolyl, or imidazolyl; and the n is an integer from 1 to 3.
- [10] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R¹ is phenyl substituted with C₁-C₆ dialkylamino;
the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and the n is an integer from 1 to 3.
- [11] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 10, wherein, the R¹ is dimethylaminophenyl;
the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and the n is an integer from 1 to 3.
- [12] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 11, wherein, the R¹ is dimethylaminophenyl;
the R² is dimethylamino, pyrazolyl, or imidazolyl; and the n is an integer from 1 to 3.
- [13] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R¹ is thienyl;
the R² is C₁-C₆ dialkylamino, or a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and the n is an integer from 1 to 3.
- [14] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 13, wherein, the R¹ is thienyl;
the R² is dimethylamino, pyrazolyl, or imidazolyl; and

the n is an integer from 1 to 3.

- [15] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 1, wherein, the R¹ is phenyl substituted halogen; the R² is a substituted or unsubstituted heterocyclyl selected from pyridinyl, isoxazolyl, thiazolyl, pyrimidinyl, indanyl, benzthiazolyl, pyrazolyl, thiadiazolyl, oxazolyl, piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, thienyl, triazolyl, pyrrolyl and furyl; and

the n is an integer from 1 to 3.

- [16] The derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof according to claim 15, wherein, the R¹ is phenyl substituted halogen; the R² is pyrazolyl or imidazolyl; and
- the n is an integer from 1 to 3.

- [17] The pharmaceutically acceptable salt of the derivative represented by Formula 1 according to claim 1, wherein the salt is formed with hydrochloric acid or oxalic acid.

- [18] The derivative or the pharmaceutically acceptable salt thereof according to claim 1, which is selected from the group consisting of the following compounds:

1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile;

1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile oxalate;

1-{3-(dimethylamino)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrochloride;

1-{3-(imidazole-1-yl)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile;

1-{3-(imidazole-1-yl)propyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrochloride;

1-{2-(imidazole-1-yl)ethyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile;

1-{2-(imidazole-1-yl)ethyl}-1-(4-methoxyphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrochloride;

1-(4-methoxyphenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofuran carbonitrile;

1-(4-methoxyphenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofuran carbonitrile hydrochloride;

1-(4-methoxyphenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-methoxyphenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(dimethylamino)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(dimethylamino)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(dimethylamino)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(dimethylamino)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(imidazole-1-yl)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(imidazole-1-yl)propyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(imidazole-1-yl)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(imidazole-1-yl)ethyl}-1-phenyl-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-phenyl-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-phenyl-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(dimethylamino)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(dimethylamino)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(dimethylamino)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(dimethylamino)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(imidazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(imidazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(imidazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(imidazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(pyrazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(pyrazole-1-yl)propyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

hydrochloride;

1-{2-(pyrazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(pyrazole-1-yl)ethyl}-1-(4-tolyl)-1,3-dihydro-5-isobenzofurancarbonitrile

hydrochloride;

1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile oxalate;

1-(4-dimethylaminophenyl)-1-{3-(dimethylamino)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-dimethylaminophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-dimethylaminophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate;

1-{3-(dimethylamino)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(dimethylamino)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(dimethylamino)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate;

1-{3-(imidazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(imidazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile;

1-{2-(imidazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{3-(pyrazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile

le;

1-{3-(pyrazole-1-yl)propyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-{2-(pyrazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile ;

1-{2-(pyrazole-1-yl)ethyl}-1-(2-thienyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-fluorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-fluorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-fluorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-fluorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-fluorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-fluorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-fluorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-fluorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-chlorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-chlorophenyl)-1-{3-(imidazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-chlorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

1-(4-chlorophenyl)-1-{2-(imidazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-chlorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile;

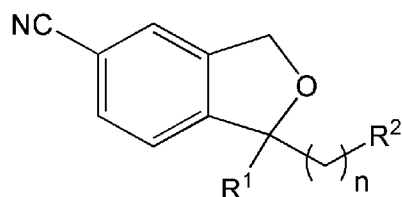
1-(4-chlorophenyl)-1-{3-(pyrazole-1-yl)propyl}-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride;

1-(4-chlorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbo-
nitrile; and

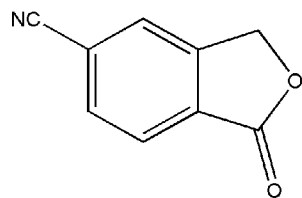
1-(4-chlorophenyl)-1-{2-(pyrazole-1-yl)ethyl}-1,3-dihydro-5-isobenzofurancarbo-
nitrile hydrochloride.

- [19] A pharmaceutical composition comprising the derivative as claimed in any one
of claims 1 to 18 and a pharmaceutically acceptable carrier.
- [20] A method for treating or preventing premature ejaculation, comprising admin-
istering to a patient in need of such treatment or prevention a therapeutically
effective amount of the derivative as claimed in any one of claims 1 to 18 or
pharmaceutically acceptable salts thereof.
- [21] A process of preparing the derivative as claimed in any one of claims 1 to 18,
comprising:
- 1) preparing a compound of Formula 3 by reacting 5-cyanophthalimide
compound of Formula 2 with R^1MgBr (step 1);
 - 2) preparing a compound of Formula 4 by reduction reaction of the compound of
Formula 3 (step 2);
 - 3) preparing a compound of Formula 5 by cyclization reaction of the compound
of Formula 4 (step 3);
 - 4) preparing a compound of Formula 6 by introducing an alkyl group into
position 1 of the compound of Formula 5 (step 4);
 - 5) preparing a compound of Formula 7 by deprotecting the compound of
Formula 6 (step 5);
 - 6) preparing a compound of Formula 8 by reacting the compound of Formula 7
with methanesulfonylchloride (step 6);
 - 7) preparing a compound of Formula 1 by substitution reaction of the compound
of Formula 8 with a R^2 group and saltation (step 7):

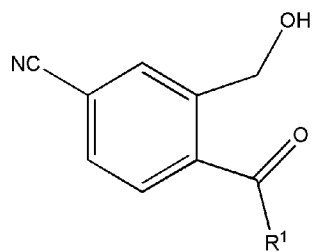
[Formula 1]



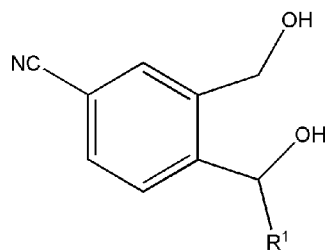
[Formula 2]



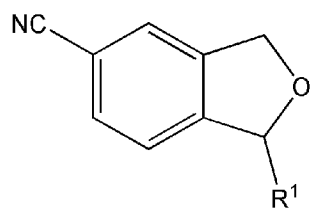
[Formula 3]



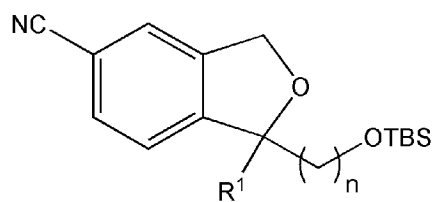
[Formula 4]



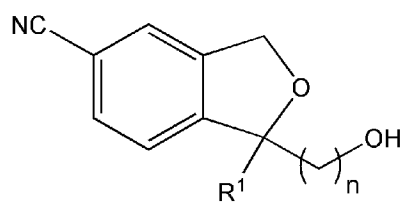
[Formula 5]



[Formula 6]



[Formula 7]



[Formula 8]

