

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
21 December 2007 (21.12.2007)

PCT

(10) International Publication Number
WO 2007/145349 A2(51) International Patent Classification: **Not classified**

17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP).

(21) International Application Number:

PCT/JP2007/062194

(74) Agents: **TANAKA, Mitsuo** et al.; AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 5400001 (JP).

(22) International Filing Date: 12 June 2007 (12.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2006-163992 13 June 2006 (13.06.2006) JP(71) Applicant (for all designated States except US): **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka 5410045 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ITO, Mitsuhiro** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, Wadai, Tsukuba-shi, Ibaraki 3004293 (JP). **MATSUNAGA, Nobuyuki** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP). **YAMADA, Masami** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP). **HITAKA, Takenori** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP). **YAMAMOTO, Satoshi** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED,

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

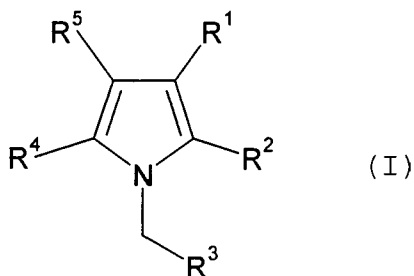
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PYRROLE DERIVATIVES

(57) Abstract: The present invention provides novel pyrrole derivatives represented by formula (I): wherein R₁ represents a hydrogen atom, cyano, optionally halogenated C₁-6#191 alkyl or an optionally substituted C₁-6#191 alkoxy-carbonyl; R₂ and R₄ may be the same or different and represent a hydrogen atom, C₁-6#191 alkyl, C₂-6#191 alkenyl substituted with an optionally substituted hydroxy, an optionally substituted or oxidized thiol, etc.; R₃ represents an optionally substituted thiazolyl, an optionally substituted pyrazolyl, an optionally substituted oxazolyl, etc.; and R₅ represents an optionally substituted phenyl having a cyano at the 4- or 3-position, and androgen receptor antagonists containing the same.

DESCRIPTION

SUBSTITUTED PYRROLE DERIVATIVES

Technical Field

5 The present invention relates to novel pyrrole derivatives and androgen receptor antagonists containing the same, and more particularly, to novel pyrrole derivatives which have preventive and/or therapeutic effects for diseases dependent on androgen by means of
10 inhibiting the androgen receptor (AR) that is a male hormone, and exert an androgen receptor antagonistic action free of the influence of mutation and the like, and androgen receptor antagonists containing the same.

15 Background Art

 Journal of Medicinal Chemistry (1986), 29(11), 2298-2315 discloses pyrrole derivatives having an androgen receptor binding inhibitory action. In addition, for example, WO 97/49709 and JP 11-255651A disclose a treatment
20 for benign prostatic hyperplasia and the like by an androgen receptor binding inhibitor.

 WO 03/57669 by the present applicant discloses an androgen receptor antagonist containing a pyrrole derivative, which is useful for prevention and treatment of
25 prostate cancer that is one of the most severe diseases among male hormone-dependent diseases, and treatment of prostate cancer in a hormone independent stage.

 WO 02/02524 discloses a pyrrole derivative useful as a therapeutic drug for AIDS.

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Disclosure of Invention

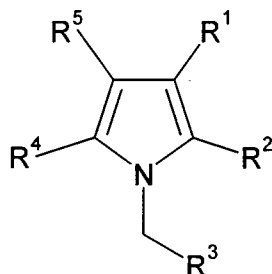
 A main object of the present invention is to provide pyrrole derivatives which are novel and exert an excellent androgen receptor antagonistic action, although they belong

to a category of the pyrrole derivative disclosed in WO 03/57669.

The present inventors have made various studies on pyrrole derivatives having an androgen receptor antagonistic action, and found that novel pyrrole derivatives having a substituted thiazolyl, a substituted pyrazolyl, a substituted oxazolyl, a substituted imidazo[1,2-a]pyridyl, a substituted 1,2,3-triazolyl, a substituted 1,2,4-triazolyl or a substituted tetrazolyl on the nitrogen atom of pyrrole ring, have unexpectedly an excellent androgen receptor antagonistic action, excellent pharmacokinetics and the like or the toxicity are alleviated, and thus the present invention has been completed.

That is, the present invention provides:

[1] A compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded (hereinafter, referred to as compound (I)), or a salt thereof;

[2] The compound according to the above-mentioned [1], wherein R¹ is (1) a hydrogen atom, (2) cyano or (3) an optionally halogenated C₁₋₆ alkyl;

[3] The compound according to the above-mentioned [1], wherein R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl optionally having hydroxy, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) cyano or (6) an acyl;

[4] The compound according to the above-mentioned [1], wherein R³ is (1) an optionally substituted pyrazolyl, (2) an optionally substituted oxazolyl, (3) an optionally substituted imidazo[1,2-a]pyridyl, (4) an optionally substituted 1,2,4-triazolyl or (5) an optionally substituted tetrazolyl;

[5] The compound according to the above-mentioned [1], wherein R³ is an optionally substituted thiazolyl;

[6] The compound according to the above-mentioned [1], wherein R³ is an optionally substituted 1,2,3-triazolyl;

[7] The compound according to the above-mentioned [1], wherein R⁵ is (1) 4-cyanophenyl, (2) 3-cyanophenyl, (3) 4-

cyano-3-(trifluoromethyl)phenyl, (4) 4-cyano-2-methylphenyl or (5) 3-chloro-4-cyanophenyl;

[8] (i) 4-(2,5-dimethyl-1-{{3-(trifluoromethyl)-1H-pyrazol-5-yl}methyl})-1H-pyrrol-3-yl)benzonitrile,

5 (ii) 3-(4-cyanophenyl)-5-methyl-1-{{3-(trifluoromethyl)-1H-pyrazol-5-yl}methyl})-1H-pyrrole-2-carbonitrile,

(iii) 5-{{3-(4-cyanophenyl)-5-ethyl-2-methyl-1H-pyrrol-1-yl}methyl})-1H-pyrazole-3-carbonitrile,

10 (iv) 4-[2-methyl-1-(1H-1,2,3-triazol-5-ylmethyl)-5-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile,

(v) 2-{{3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl}methyl})-1,3-thiazole-4-carbonitrile,

15 (vi) 4-(4-cyanophenyl)-2,5-dimethyl-1-{{4-(trifluoromethyl)-1,3-thiazol-2-yl}methyl})-1H-pyrrole-3-carbonitrile,

(vii) 2-{{3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl}methyl})-1,3-oxazole-4-carbonitrile,

(viii) 4-(4-cyanophenyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile, or

20 (ix) 4-(1-{{3-(1-hydroxy-1-methylethyl)-1H-pyrazol-4-yl}methyl})-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile, or a salt thereof;

[9] A prodrug of the compound according to the above-mentioned [1];

25 [10] A drug comprising compound (I) or a salt thereof or a prodrug thereof;

[11] The drug according to the above-mentioned [10], which is an androgen receptor antagonist;

30 [12] The drug according to the above-mentioned [11], wherein the androgen receptor is a normal androgen receptor and/or a mutant androgen receptor;

[13] The drug according to the above-mentioned [10], which is a preventive or therapeutic agent for hormone-sensitive cancer in an androgen dependent stage and/or independent stage;

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[14] The drug according to the above-mentioned [10], which is a preventive or therapeutic agent for prostate cancer;

[15] A method for antagonizing an androgen receptor, which comprises administering an effective amount of compound (I) or a salt thereof or a prodrug thereof to a mammal;

[16] A method for preventing or treating hormone sensitive cancer in an androgen dependent stage and/or an androgen independent stage, which comprises administering an effective amount of compound (I) or a salt thereof or a prodrug thereof to a mammal;

[17] A method for prevention or treatment of prostate cancer, which comprises administering an effective amount of compound (I) or a salt thereof or a prodrug thereof to a mammal;

[18] Use of compound (I) or a salt thereof or a prodrug thereof for the manufacture of an androgen receptor antagonistic agent;

[19] Use of compound (I) or a salt thereof or a prodrug thereof for the manufacture of a preventive or therapeutic agent for hormone sensitive cancer in an androgen dependent stage and/or an androgen independent stage;

[20] Use of compound (I) or a salt thereof or a prodrug thereof for the manufacture of a preventive or therapeutic agent for prostate cancer;

[21] The compound according to the above-mentioned [1], wherein R^1 is (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C_{1-6} alkyl or (4) an optionally substituted C_{1-6} alkoxy-carbonyl,

R^2 and R^4 are the same or different and each represents (1) a hydrogen atom, (2) a C_{1-6} alkyl, (3) a C_{3-6} cycloalkyl, (4) trifluoromethyl, (5) an amino- C_{1-6} alkyl, (6) a mono- or di-substituted amino- C_{1-6} alkyl, (7) an optionally halogenated C_{1-6} alkyl substituted with an optionally substituted hydroxy, (8) a C_{2-6} alkenyl substituted with an optionally substituted hydroxy, (9) a C_{1-6} alkyl substituted

with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R³ is (1) an optionally substituted pyrazolyl, (2) an optionally substituted oxazolyl, (3) an optionally substituted imidazo[1,2-a]pyridyl, (4) an optionally substituted 1,2,4-triazolyl or (5) an optionally substituted tetrazolyl, and

R⁵ is a phenyl which has a cyano at the 4- or 3-position and further may be substituted;

[22] The compound according to the above-mentioned [1], wherein R¹ is (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) a substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) 1,3-dioxolan-2-yl,

R³ is an optionally substituted thiazolyl, and

R⁵ is a phenyl which has a cyano at the 4- or 3-position and further may be substituted;

[23] The compound according to the above-mentioned [1], wherein R¹ is (1) a hydrogen atom, (2) an optionally halogenated C₁₋₆ alkyl or (3) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated

C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) 1,3-dioxolan-2-yl,

R³ is an optionally substituted 1,2,3-triazolyl, and

R⁵ is a phenyl which has a cyano at the 4- or 3-position and further may be substituted, or a salt thereof; and

further, the present invention provides,

[24] The compound according to the above-mentioned [1], wherein R¹ is (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl, or (4) a C₁₋₆ alkoxy-carbonyl optionally substituted with 1 to 5 substituents selected from substituent group A consisting of (1') oxo, (2') halogen atom, (3') C₁₋₃ alkylenedioxy, (4') nitro, (5') cyano, (6') C₂₋₆ alkenyl optionally having 1 to 3 halogen atoms, (7') carboxy C₂₋₆ alkenyl, (8') C₂₋₆ alkynyl optionally having 1 to 3 halogen atoms, (9') C₃₋₆ cycloalkyl optionally having 1 to 3 halogen atoms, (10') C₆₋₁₄ aryl, (11') C₁₋₈ alkoxy optionally having 1 to 3 halogen atoms, (12') C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkoxy, (13') hydroxy, (14') C₆₋₁₄ aryloxy, (15') C₇₋₁₆ aralkyloxy, (16') mercapto, (17') C₁₋₆ alkylthio optionally having 1 to 3 halogen atoms, (18') C₆₋₁₄ arylthio, (19') C₇₋₁₆ aralkylthio, (20') amino, (21') mono-C₁₋₆ alkylamino, (22') mono-C₆₋₁₄ arylamino, (23') di-C₁₋₆ alkylamino, (24') di-C₆₋₁₄ arylamino, (25') formyl, (26') carboxy, (27') C₁₋₆ alkyl-carbonyl, (28') C₃₋₆ cycloalkyl-carbonyl, (29') C₁₋₆ alkoxy-carbonyl, (30') C₆₋₁₄ aryl-carbonyl, (31') C₇₋₁₆ aralkyl-carbonyl, (32') C₆₋₁₄ aryloxy-carbonyl, (33') C₇₋₁₆ aralkyloxy-carbonyl, (34') 5- or 6-membered heterocyclic ring-carbonyl wherein said heterocyclic ring contains 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom, (35') carbamoyl,

(36') thiocarbamoyl, (37') mono- C_{1-6} alkyl-carbamoyl, (38') di- C_{1-6} alkyl-carbamoyl, (39') mono- or di- C_{6-14} aryl-carbamoyl, (40') mono- or di-5- or 6-membered heterocyclic ring-carbamoyl wherein said heterocyclic ring contains 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom, (41') C_{1-6} alkylsulfonyl, (42') C_{1-6} alkylsulfinyl, (43') C_{6-14} arylsulfonyl, (44') C_{6-14} arylsulfinyl, (45') formylamino, (46') C_{1-6} alkyl-carbonylamino, (47') C_{6-14} aryl-carbonylamino, (48') C_{1-6} alkoxy-carbonylamino, (49') C_{1-6} alkylsulfonylamino, (50') C_{6-14} arylsulfonylamino, (51') C_{1-6} alkyl-carbonyloxy, (52') C_{6-14} aryl-carbonyloxy, (53') C_{1-6} alkoxy-carbonyloxy, (54') mono- C_{1-6} alkyl-carbamoyloxy, (55') di- C_{1-6} alkyl-carbamoyloxy, (56') C_{6-14} aryl-carbamoyloxy, (57') nicotinoyloxy, (58') 5- to 7-membered saturated cyclic amino optionally having 1 to 3 substituents selected from the group consisting of (1") halogen atoms, (2") C_{1-6} alkyl optionally having 1 to 3 halogen atoms, (3") C_{3-6} cycloalkyl optionally having 1 to 3 halogen atoms, (4") C_{6-14} aryl and (5") C_{1-8} alkoxy optionally having 1 to 3 halogen atoms, (59') 5- to 10-membered aromatic heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom, and (60') sulfo,

R^2 and R^4 are the same or different and each represents (1) a hydrogen atom, (2) a C_{1-6} alkyl, (3) a C_{3-6} cycloalkyl, (4) trifluoromethyl, (5) an amino- C_{1-6} alkyl, (6) an amino- C_{1-6} alkyl wherein said amino is mono- or di-substituted with a substituent selected from the group consisting of C_{1-6} alkyl and C_{1-6} alkyl-carbonyl,

(7) an optionally halogenated C_{1-6} alkyl group substituted with a hydroxy which may be substituted with a substituent selected from substituent group B consisting of (a) C_{1-6} alkyl optionally substituted with 1 to 5 substituents

selected from substituent group A, (b) C₂₋₆ alkenyl optionally substituted with 1 to 5 substituents selected from substituent group A, (c) C₂₋₆ alkynyl optionally substituted with 1 to 5 substituents selected from substituent group A, (d) C₃₋₆ cycloalkyl optionally substituted with 1 to 5 substituents selected from substituent group A, (e) C₆₋₁₄ aryl optionally substituted with 1 to 5 substituents selected from substituent group A and (f) C₇₋₁₆ aralkyl optionally substituted with 1 to 5 substituents selected from substituent group A, (8) a C₂₋₆ alkenyl substituted with a hydroxy which may be substituted with a substituent selected from the substituent group B, (9) a C₁₋₆ alkyl substituted with 1 to 3 groups represented by formula: -S(O)_nR⁶ wherein R⁶ represents a hydrogen atom or a group selected from the substituent group B and n represents 0, 1 or 2, (10) cyano, (11) an acyl represented by formula: -COOR⁷, -CONR⁸R⁹, -COR¹⁰ or -(C=S)-NR¹¹R¹² wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² represent a hydrogen atom or a group selected from the substituent group B, respectively, and R⁸ and R⁹, and R¹¹ and R¹² may, together with the adjacent nitrogen atom, form a 5 or 6-membered heterocyclic group which contains 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atoms and may have a substituent selected from substituent group B, (12) an oxazolyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded), or (13) a 1,3-dioxolan-2-yl, R³ represents (1) a thiazolyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded) and substituent group B, (2) a pyrazolyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded) and substituent group B, (3) an oxazolyl optionally substituted with a substituent selected from

substituent group A (provided that oxo is excluded) and substituent group B, (4) imidazo[1,2-a]pyridyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded) and substituent group B, (5) a 1,2,3-triazolyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded) and substituent group B, (6) 1,2,4-triazolyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded) and substituent group B, or (7) a tetrazolyl optionally substituted with a substituent selected from substituent group A (provided that oxo is excluded) and substituent group B, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted with a substituent selected from substituent group A; and

[25] The compound according to the above-mentioned [1], wherein R¹ is (1) a hydrogen atom, (2) cyano or (3) a C₁₋₆ alkyl optionally having 1 to 3 halogen atoms,

R² is (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) a C₁₋₆ alkyl substituted with a hydroxy or (6) cyano,

R³ is (1) a thiazolyl optionally substituted with 1 or 2 substituents selected from the group consisting of (1') C₁₋₆ alkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen atom and hydroxy, (2') carbamoyl and (3') cyano, (2) a pyrazolyl optionally substituted with one substituent selected from the group consisting of (1') C₁₋₆ alkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen atom and hydroxy, (2') C₁₋₆ alkoxy-carbonyl, (3') carboxy, (4') carbamoyl, (5') mono-C₁₋₆ alkyl-carbamoyl and (6') cyano, (3) an oxazolyl optionally substituted with 1 or 2 substituents selected from the group consisting of (1') C₁₋₆ alkyl optionally

substituted with one hydroxy, (2') carbamoyl and (3') cyano, (4) imidazo[1,2-a]pyridyl, (5) a 1,2,3-triazolyl optionally substituted with one C₁₋₆ alkyl optionally having 1 to 3 halogen atoms, (6) a 1,2,4-triazolyl or (7) a tetrazolyl,

5 R⁴ is (1) a hydrogen atom, (2) a C₁₋₆ alkyl optionally substituted with one substituent selected from the group consisting of hydroxy and oxo, (3) trifluoromethyl or (4) cyano, and

10 R⁵ is a phenyl which has a cyano at the 4- or 3-position and further may be substituted with one substituent selected from the group consisting of (1) C₁₋₆ alkyl optionally having 1 to 3 halogen atoms and (2) a halogen atom.

15 In the case where the compound (I) or a salt thereof has an asymmetric carbon in the structure, both optically active compound and racemic compound are included in the scope of the present invention, and these compounds or a salt thereof may be either of a hydrate or an anhydride.

20 Compound (I) of the present invention or a salt thereof exhibits not only a potent antagonistic activity against natural type of androgen receptor but also a high antagonism against mutant androgen receptor, and these compounds can be administered orally, and are extremely low toxic, and thus are useful as a drug having an androgen
25 receptor antagonism that is effective against, for example, prostate cancer in the hormone independent stage.

In compound (I), R¹ represents (1) a hydrogen atom, 30 (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl.

Examples of the "optionally halogenated C₁₋₆ alkyl" include C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and hexyl) 35 optionally having 1 to 5, preferably 1 to 3, halogen atoms

(e.g., fluorine, chlorine, bromine and iodine), and specifically include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

Examples of the C₁₋₆ alkoxy-carbonyl of the "optionally substituted C₁₋₆ alkoxy-carbonyl" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.

The C₁₋₆ alkoxy-carbonyl may have 1 to 5, preferably 1 to 3, substituents selected from the following substituent group A at a substitutable position, and when the number of substituents is 2 or more, each substituent may be the same or different.

Substituent group A:

- (1) oxo,
- (2) halogen atom (e.g., fluorine, chlorine, bromine, iodine),
- (3) C₁₋₃ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.),
- (4) nitro,
- (5) cyano,
- (6) C₂₋₆ alkenyl (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine),
- (7) carboxy-C₂₋₆ alkenyl (e.g., 2-carboxyethenyl, 2-carboxy-2-methylethenyl, etc.),
- (8) C₂₋₆ alkynyl (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine),

- (9) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine),
- (10) C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.),
- (11) C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine),
- (12) C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkoxy (e.g., ethoxycarbonylmethoxy, etc.),
- (13) hydroxy,
- (14) C₆₋₁₄ aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy, etc.),
- (15) C₇₋₁₆ aralkyloxy (e.g., benzyloxy, phenethyloxy, etc.),
- (16) mercapto,
- (17) C₁₋₆ alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio, etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine),
- (18) C₆₋₁₄ arylthio (e.g., phenylthio, 1-naphthylthio, 2-naphthylthio, etc.),
- (19) C₇₋₁₆ aralkylthio (e.g., benzylthio, phenethylthio, etc.),
- (20) amino,
- (21) mono-C₁₋₆ alkylamino (e.g., methylamino, ethylamino, etc.),
- (22) mono-C₆₋₁₄ arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.),
- (23) di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino, ethylmethylamino, etc.),
- (24) di-C₆₋₁₄ arylamino (e.g., diphenylamino, etc.),
- (25) formyl,
- (26) carboxy,
- (27) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl, etc.),

- (28) C₃₋₆ cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.),
- (29) C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.),
- 5 (30) C₆₋₁₄ aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.),
- (31) C₇₋₁₆ aralkyl-carbonyl (e.g., phenylacetyl, 3-phenylpropionyl, etc.),
- (32) C₆₋₁₄ aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.),
- 10 (33) C₇₋₁₆ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.),
- (34) 5 or 6-membered heterocyclic ring-carbonyl wherein said heterocyclic ring contains 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom (e.g.,
- 15 nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.),
- (35) carbamoyl,
- 20 (36) thiocarbamoyl,
- (37) mono-C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.),
- (38) di-C₁₋₆ alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl, etc.),
- 25 (39) mono- or di-C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.),
- (40) mono- or di-5 or 6-membered heterocyclic ring-carbamoyl wherein said heterocyclic ring contains 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.),
- 30 (41) C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.),
- 35

- (42) C₁₋₆ alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, etc.),
- (43) C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.),
- 5 (44) C₆₋₁₄ arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl, etc.),
- (45) formylamino,
- (46) C₁₋₆ alkyl-carbonylamino (e.g., acetylamino, etc.),
- (47) C₆₋₁₄ aryl-carbonylamino (e.g., benzoylamino,
- 10 naphthoylamino, etc.),
- (48) C₁₋₆ alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, etc.),
- (49) C₁₋₆ alkylsulfonylamino (e.g., methylsulfonylamino,
- 15 ethylsulfonylamino, etc.),
- (50) C₆₋₁₄ arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.),
- (51) C₁₋₆ alkyl-carbonyloxy (e.g., acetoxy, propionyloxy, etc.),
- 20 (52) C₆₋₁₄ aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy, etc.),
- (53) C₁₋₆ alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.),
- 25 (54) mono-C₁₋₆ alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.),
- (55) di-C₁₋₆ alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.),
- (56) C₆₋₁₄ aryl-carbamoyloxy (e.g., phenylcarbamoyloxy,
- 30 naphthylcarbamoyloxy, etc.),
- (57) nicotinoyloxy,
- (58) 5 to 7-membered saturated cyclic amino optionally having 1 to 3 substituents selected from the group consisting of (1') halogen atom, (2') C₁₋₆ alkyl (e.g.,
- 35 methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-

butyl, tert-butyl, pentyl, hexyl, etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine and iodine), (3') C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), (4') C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl, etc.) and (5') C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine),

(59) 5 to 10-membered aromatic heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom (e.g., 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, 3-benzo[b]thienyl, 2-benzo[b]furanyl, 3-benzo[b]furanyl, etc.), and

(60) sulfo

R¹ is preferably (1) a hydrogen atom, (2) cyano or (3) an optionally halogenated C₁₋₆ alkyl, more preferably (1) a hydrogen atom, (2) cyano or (3) trifluoromethyl, and particularly preferably cyano.

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12)

an optionally substituted oxazolyl or (13) 1,3-dioxolan-2-yl.

Examples of the "C₁₋₆ alkyl" represented by R² and R⁴ include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, and the like.

Examples of the "C₃₋₆ cycloalkyl" represented by R² and R⁴ include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Examples of the "amino-C₁₋₆ alkyl" represented by R² and R⁴ include aminomethyl, aminoethyl, aminopropyl, aminobutyl, and the like.

Examples of the "mono- or di-substituted amino-C₁₋₆ alkyl" represented by R² and R⁴ include C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) substituted with an amino having 1 or 2 substituent(s) selected from the group consisting of C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) and C₁₋₆ alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, pentylcarbonyl, hexylcarbonyl, etc.).

Examples of the substituents for the "optionally substituted hydroxy" in the "optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy" represented by R² and R⁴ include (1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), (2) C₂₋₆ alkenyl (e.g., vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.), (3) C₂₋₆ alkynyl (e.g., ethynyl, propargyl, 1-butyne, 2-butyne, 3-butyne, 1-hexynyl, etc.), (4) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), (5) C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl, etc.) and (6) C₇₋₁₆ aralkyl (e.g.,

benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.). These substituents may have 1 to 5, preferably 1 to 3, substituents selected from
5 substituent group A at a substitutable position, and when the number of the substituents is 2 or more, each substituent may be the same or different.

In addition, examples of the "optionally halogenated C₁₋₆ alkyl" in the "optionally halogenated C₁₋₆ alkyl
10 substituted with an optionally substituted hydroxy" represented by R² and R⁴ include C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine,
15 bromine and iodine), and specifically include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-
20 butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl and the like.

The "optionally substituted hydroxy" in the "C₂₋₆ alkenyl substituted with an optionally substituted hydroxy" represented by R² and R⁴ is exemplified by those for the
25 "optionally substituted hydroxy" in the above-mentioned "optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy" represented by R² and R⁴, and examples of the "C₂₋₆ alkenyl" include vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl and the
30 like.

Examples of the "C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol" represented by R² and R⁴ include C₁₋₆ alkyl (e.g., methyl,
35 ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-

butyl, pentyl, hexyl, etc.) having 1 to 3 groups represented by formula $-S(O)_nR^6$ wherein R^6 represents (1) a hydrogen atom, (2) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (3) C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (4) C_{2-6} alkynyl (e.g., ethynyl, propargyl, 1-butyne, 2-butyne, 3-butyne, 1-hexyne, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (5) C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (6) C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, or (7) C_{7-16} aralkyl (e.g., benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, and n represents 0, 1 or 2.

Examples of the "acyl group" represented by R^2 and R^4 include a group represented by formula: $-COOR^7$, $-CONR^8R^9$, $-COR^{10}$ or $-(C=S)-NR^{11}R^{12}$, wherein R^7 , R^8 , R^9 , R^{10} , R^{11} and R^{12} represents (1) a hydrogen atom, (2) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) optionally having 1 to 5

(preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (3) C₂₋₆ alkenyl (e.g., vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (4) C₂₋₆ alkynyl (e.g., ethynyl, propargyl, 1-butyne, 2-butyne, 3-butyne, 1-hexynyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (5) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (6) C₆₋₁₄ aryl group (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, or (7) C₇₋₁₆ aralkyl (e.g., benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, or R⁸ and R⁹, and R¹¹ and R¹² may, together with the adjacent nitrogen atom, form a cyclic group (e.g., 5 or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom) optionally having 1 to 3 substituents selected from the group consisting of (1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (2) C₂₋₆ alkenyl (e.g., vinyl, allyl, isopropenyl,

1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (3) C₂₋₆ alkynyl (e.g., ethynyl, propargyl, 1-butyne, 2-butyne, 3-butyne, 1-hexynyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (4) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (5) C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (6) C₆₋₁₀ aryl-C₁₋₃ alkyl (e.g., benzyl, p-tolyl, phenylethyl, phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (7) C₆₋₁₀ aryl-C₂₋₄ alkenyl (e.g., α -styryl, β -styryl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position.

Specifically as the "acyl group" represented by R² and R⁴, C₁₋₇ alkanoyl (e.g., formyl, acetyl, propionyl, butyl, isobutyl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), C₃₋₇ alkenoyl (e.g., acryloyl, methacryloyl, crotonoyl, isocrotonoyl, etc.), C₄₋₇ cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), C₇₋₁₅ aroyl (e.g., benzoyl, p-toluoyl, 1-naphthoyl, 2-naphthoyl, etc.), C₆₋₁₀ aryl-C₂₋₄ alkanoyl (e.g., phenylacetyl, phenylpropionyl, hydroatropoyl, phenylbutyl, etc.), and C₆₋₁₀ aryl-C₃₋₅ alkenoyl (e.g., cinnamoyl, atropoyl, etc.) are exemplified.

As the substituent of the above-mentioned "optionally substituted oxazolyl", those wherein oxo is excluded from substituent group A are exemplified, and the oxazolyl may have 1 to 5 (preferably 1 to 3) substituents at a substitutable position, and when the number of the substituents is 2 or more, each substituent may be the same or different.

R^2 and R^4 are the same or different, and each is preferably a hydrogen atom, C_{1-6} alkyl optionally having hydroxy, C_{3-6} cycloalkyl, trifluoromethyl, cyano or acyl, and particularly preferably C_{1-6} alkyl, trifluoromethyl or cyano.

As R^2 , hydrogen atom, methyl, hydroxymethyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, cyano or acyl is preferred, and methyl, ethyl, trifluoromethyl or cyano is particularly preferred.

As R^4 , hydrogen atom, methyl, hydroxymethyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, cyano or acyl is preferred, and methyl or cyano is particularly preferred.

R^3 represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl.

Examples of the substituent in the "optionally substituted thiazolyl", "optionally substituted pyrazolyl", "optionally substituted oxazolyl", "optionally substituted imidazo[1,2-a]pyridyl", "optionally substituted 1,2,3-triazolyl", "optionally substituted 1,2,4-triazolyl" and "optionally substituted tetrazolyl" represented by R^3 include (1) a group wherein oxo is excluded from substituent group A, (2) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,

pentyl, hexyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (3) C₂₋₆ alkenyl (e.g., vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (4) C₂₋₆ alkynyl (e.g., ethynyl, propargyl, 1-butyne, 2-butyne, 3-butyne, 1-hexyne, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (5) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (6) C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, (7) C₆₋₁₀ aryl-C₁₋₃ alkyl group (e.g., benzyl, p-tolyl, phenylethyl, phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, and (8) C₆₋₁₀ aryl-C₂₋₄ alkenyl (e.g., α -styryl, β -styryl, etc.) optionally having 1 to 5 (preferably 1 to 3) substituents selected from substituent group A at a substitutable position, and 1 to 3 of these substituents may be possessed at substitutable positions, and when the number of the substituents is 2 or more, each substituent may be the same or different.

Among these, preferable substituents are methyl, hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, trifluoromethyl, carboxy, methoxycarbonyl, carbamoyl, N-methylcarbamoyl, cyano or formyl. Particularly preferable substituents are 1-hydroxy-1-methylethyl, trifluoromethyl

or cyano.

More specifically, particularly preferable R^3 includes 5-{3-(trifluoromethyl)}-1H-pyrazolyl, 5-(3-cyano)-1H-pyrazolyl, 5-1H-1,2,3-triazolyl, 2-(4-cyano)thiazolyl, 2-(4-trifluoromethyl)thiazolyl, 2-(4-cyano)oxazolyl, 4-{3-(1-hydroxy-1-methylethyl)}-1H-pyrazolyl and imidazo[1,2-a]pyridyl.

R^5 represents a phenyl which has cyano at the 4- or 3-position, and further may be substituted.

As the further substituent of the phenyl, those wherein oxo is excluded from substituent group A are exemplified.

As R^5 , 4-cyanophenyl, 3-cyanophenyl, 4-cyano-3-(trifluoromethyl)phenyl, 4-cyano-2-methylphenyl or 3-chloro-4-cyanophenyl is preferred, and 4-cyanophenyl, 3-cyanophenyl or 4-cyano-3-(trifluoromethyl)phenyl is particularly preferred.

As compound (I), the followings are preferred.

(Ia):

Compound (I) wherein R^1 is (1) hydrogen atom, (2) cyano, (3) an optionally halogenated C_{1-6} alkyl or (4) an optionally substituted C_{1-6} alkoxy-carbonyl, R^2 and R^4 are the same or different and each is (1) a hydrogen atom, (2) C_{1-6} alkyl, (3) C_{3-6} cycloalkyl, (4) trifluoromethyl, (5) amino- C_{1-6} alkyl, (6) mono- or di-substituted amino- C_{1-6} alkyl, (7) an optionally halogenated C_{1-6} alkyl substituted with an optionally substituted hydroxy, (8) C_{2-6} alkenyl substituted with an optionally substituted hydroxy, (9) C_{1-6} alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl, or (13) 1,3-dioxolan-2-yl, R^3 is (1) an optionally substituted pyrazolyl, (2) an optionally substituted oxazolyl, (3) an optionally substituted imidazo[1,2-a]pyridyl, (4) an optionally substituted 1,2,4-triazolyl or (5) an optionally

substituted tetrazolyl, and R⁵ is phenyl which has cyano at the 4- or 3-position and further may be substituted;

(Ib):

Compound (I) wherein R¹ is (1) hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) a C₁₋₆ alkoxy-carbonyl having a substituent, R² and R⁴ are the same or different and each is (1) a hydrogen atom, (2) C₁₋₆ alkyl, (3) C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) amino-C₁₋₆ alkyl, (6) mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl, or (13) 1,3-dioxolan-2-yl, R³ is an optionally substituted thiazolyl, and R⁵ is phenyl which has cyano at the 4- or 3-position and further may be substituted;

(Ic):

Compound (I) wherein R¹ is (1) hydrogen atom, (2) an optionally halogenated C₁₋₆ alkyl or (3) an optionally substituted C₁₋₆ alkoxy-carbonyl, R² and R⁴ are the same or different and each is (1) a hydrogen atom, (2) C₁₋₆ alkyl, (3) C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) amino-C₁₋₆ alkyl, (6) mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl, or (13) 1,3-dioxolan-2-yl, R³ is an optionally substituted 1,2,3-triazolyl, and R⁵ is phenyl which has cyano at the 4- or 3-position and further may be substituted;

(Id):

Compound (I) wherein R¹ is (1) hydrogen atom, (2) cyano or (3) an optionally halogenated C₁₋₆ alkyl, R² and R⁴ are the same or different and each is (i) a hydrogen atom, (ii) C₁₋₆ alkyl, (iii) C₃₋₆ cycloalkyl, (iv) trifluoromethyl, (v) amino-C₁₋₆ alkyl wherein said amino is mono- or di-substituted with C₁₋₆ alkyl, (vi) an optionally halogenated C₁₋₆ alkyl substituted with a hydroxy that may be substituted with C₁₋₆ alkyl, (vii) C₂₋₆ alkenyl substituted with a hydroxy, (viii) C₁₋₆ alkyl substituted with a thiol that may be substituted with C₁₋₆ alkyl and oxidized, (ix) cyano, (x) a C₁₋₆ alkanoyl, (xi) oxazolyl, or (xii) 1,3-dioxolan-2-yl, R³ is (i) an optionally substituted thiazolyl, (ii) an optionally substituted pyrazolyl, (iii) an optionally substituted oxazolyl, (iv) an optionally substituted imidazo[1,2-a]pyridyl, (v) an optionally substituted 1,2,3-triazolyl (vi) an optionally substituted 1,2,4-triazolyl or (vii) an optionally substituted tetrazolyl, and R⁵ is 4-cyanophenyl, 3-cyanophenyl, 4-cyano-3-(trifluoromethyl)phenyl, 4-cyano-2-methylphenyl or 3-chloro-4-cyanophenyl;

(Ie):

Compound (I) wherein R¹ is hydrogen atom, cyano or trifluoromethyl, R² and R⁴ are the same or different and each is hydrogen atom, C₁₋₆ alkyl optionally having hydroxy, C₃₋₆ cycloalkyl, trifluoromethyl, cyano or acyl, R³ is thiazolyl, pyrazolyl, oxazolyl, imidazo[1,2-a]pyridyl, 1,2,3-triazolyl, 1,2,4-triazolyl or tetrazolyl, each of which may have 1 to 3 substituents selected from the group consisting of (1) methyl, (2) hydroxymethyl, (3) 1-hydroxyethyl, (4) 1-hydroxy-1-methylethyl, (5) trifluoromethyl, (6) carboxy, (7) methoxycarbonyl, (8) carbamoyl, (9) N-methylcarbamoyl, (10) cyano and (11) formyl, and R⁵ is 4-cyanophenyl, 3-cyanophenyl, 4-cyano-3-(trifluoromethyl)phenyl, 4-cyano-2-methylphenyl or 3-chloro-4-cyanophenyl;

(If):

Compound (I) wherein R¹ is (1) hydrogen atom, (2) cyano or (3) C₁₋₆ alkyl optionally having 1 to 3 halogen atoms,

5 R² is (1) C₁₋₆ alkyl, (2) C₃₋₆ cycloalkyl, (3) trifluoromethyl, (4) C₁₋₆ alkyl substituted with one hydroxy, or (5) cyano,

R³ is (1) thiazolyl optionally substituted with 1 or 2 substituents selected from the group consisting of (1') C₁₋₆ alkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen atom and hydroxy, (2') carbamoyl and (3') cyano, (2) pyrazolyl optionally substituted with one substituent selected from the group consisting of (1') C₁₋₆ alkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen atom and hydroxy, (2') C₁₋₆ alkoxy-carbonyl, (3') carboxy, (4') carbamoyl, (5') mono-C₁₋₆ alkyl-carbamoyl and (6') cyano, (3) oxazolyl optionally substituted with 1 or 2 substituents selected from the group consisting of (1') C₁₋₆ alkyl substituted with one hydroxy, (2') carbamoyl and (3') cyano, (4) imidazo[1,2-
10 alpyridyl, (5) 1,2,3-triazolyl optionally substituted with one C₁₋₆ alkyl optionally having 1 to 3 halogen atoms, (6) 1,2,4-triazolyl or (7) tetrazolyl,

25 R⁴ is (1) C₁₋₆ alkyl optionally substituted with one substituent selected from the group consisting of hydroxy and oxo, (2) trifluoromethyl and (3) cyano, and

R⁵ is phenyl which has cyano at the 4- or 3-position and further may be substituted with one substituent selected from the group consisting of (1) C₁₋₆ alkyl optionally having 1 to 3 halogen atoms and (2) halogen atom;

(Ig):

Compound (I) wherein R¹ is hydrogen atom, cyano or a trifluoromethyl, R² is hydrogen atom, methyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, cyano or acyl, R³
35

is thiazolyl, pyrazolyl, oxazolyl, imidazo[1,2-a]pyridyl, 1,2,3-triazolyl, 1,2,4-triazolyl or tetrazolyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of (1) 1-hydroxy-1-methylethyl, (2) trifluoromethyl and (3) cyano, R⁴ is hydrogen atom, methyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, cyano or acyl, and R⁵ is 3-cyanophenyl, 4-cyano-3-(trifluoromethyl)phenyl, 3-chloro-4-cyanophenyl, 4-cyano-2-methylphenyl or 4-cyanophenyl;

- Specifically preferred is (i) 4-(2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl)benzonitrile,
(ii) 3-(4-cyanophenyl)-5-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-2-carbonitrile,
(iii) 5-([3-(4-cyanophenyl)-5-ethyl-2-methyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carbonitrile,
(iv) 4-[2-methyl-1-(1H-1,2,3-triazol-5-ylmethyl)-5-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile,
(v) 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carbonitrile,
(vi) 4-(4-cyanophenyl)-2,5-dimethyl-1-([4-(trifluoromethyl)-1,3-thiazol-2-yl]methyl)-1H-pyrrole-3-carbonitrile,
(vii) 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carbonitrile,
(viii) 4-(4-cyanophenyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile, or
(ix) 4-(1-([3-(1-hydroxy-1-methylethyl)-1H-pyrazol-4-yl]methyl)-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile, or a salt thereof.

As the salts of the compound (I) of the present invention, for example, metal salts, ammonium salt, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the

like are exemplified. Preferable examples of the metal salts include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt, magnesium salt and barium salt; aluminum salt and the like. Preferable examples of the salts with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N, N'-dibenzylethylenediamine and the like. Preferable examples of the salts with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salts with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salts with basic amino acid include salts with arginine, lysine, ornithine and the like, and preferable examples of the salts with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

Among these, pharmaceutically acceptable salts are preferred. For example, in case of having an acidic functional group in the compound, inorganic salts such as alkali metal salt (e.g., sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt, barium salt, etc.) and the like, and ammonium salt and the like are exemplified. In addition, in case of having a basic functional group in the compound, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid, or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid and p-

toluenesulfonic acid are exemplified.

The prodrug of compound (I) of the present invention refers to a compound that is converted into compound (I) by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, that is, a compound that is converted into compound (I) by an enzymatic oxidation, reduction, hydrolysis and the like, or a compound that is converted into compound (I) by hydrolysis with gastric acid or the like. Examples of the prodrug of compound (I) include a compound wherein amino of compound (I) is acylated, alkylated or phosphorylated (e.g., a compound wherein amino of compound (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated or tert-butylated, etc.); a compound wherein hydroxy of compound (I) is acylated, alkylated, phosphorylated or converted into borate (e.g., a compound wherein hydroxy of compound (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated, etc.); a compound wherein carboxy of compound (I) is esterified or amidated (e.g., a compound wherein carboxy of compound (I) is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified, methylamidated, etc.). These compounds can be produced from compound (I) according to a method known per se.

Also, the prodrug of compound (I) may be a compound which is converted into compound (I) under physiological conditions as described in "Development of Drugs", Volume 7, Molecular Design, Hirokawa Shoten, 1990; pages 163-198.

Hereinafter, a method for production of compound (I) or a salt thereof will be described.

In the following each production method, when alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, amidation reaction, etherification reaction, oxidation reaction, reduction reaction and the like are conducted, these reactions are carried out according to a per se known method. Examples of these methods include those described in ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC., published in 1989, Comprehensive Organic Transformations, VCH Publishers Inc., published in 1989, and the like.

Further, the product can be used as it is in the form of reaction solution, or can be used for the following reaction as a crude product, but also can be isolated from the reaction mixture according to a conventional method and easily produced by usual separation means (e.g., recrystallization, distillation, chromatography, etc.).

Compound (I) of the present invention or a salt thereof can be obtained by a known method or an analogous method thereto in addition to a method shown in the following reaction scheme 1 or an analogous method thereto. A compound represented by formula (IV) can be obtained by reacting a compound represented by formula (II) and a compound represented by formula (III). The compound represented by formula (IV) itself is included in the compound represented by formula (I).

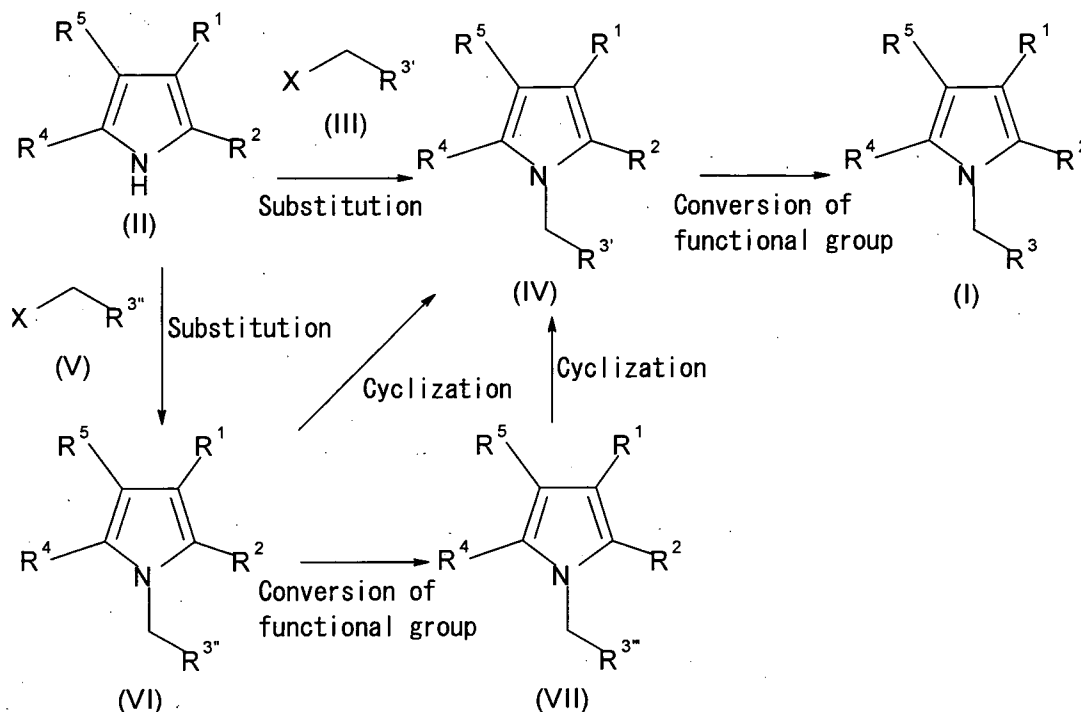
By converting the functional group of the compound represented by formula (IV) with a per se known method or an analogous method thereto (e.g., reduction reaction, catalytic hydrogenation reaction, acylation reaction, oxidation reaction, alkylation reaction, hydrolysis reaction, amidation reaction, dehydration reaction, decarboxylation reaction, dealkoxycarbonylation reaction,

sulfurization reaction, trifluoromethylation reaction, etc.), a compound included in formula (I) can be derived. In addition, when a protective group is attached to the compound represented by formula (IV), it can be removed by
5 a per se known method or an analogous method thereto to obtain a compound represented by formula (I).

A compound represented by formula (VI) or a salt thereof can be obtained by reacting a compound represented by formula (II) with a compound represented by formula (V),
10 and further by converting the functional group of the compound represented by formula (VI) with a known method or an analogous method thereto (e.g., reduction reaction, catalytic hydrogenation reaction, acylation reaction, oxidation reaction, alkylation reaction, hydrolysis
15 reaction, amidation reaction, dehydration reaction, decarboxylation reaction, dealkoxycarbonylation reaction, sulfurization reaction, trifluoromethylation reaction, etc.), a compound represented by formula (VII) or a salt thereof can be derived.

Furthermore, by subjecting a compound represented by formula (VII) or a compound represented by formula (VI) to a cyclization reaction with a method described in, for example, a document (Chem. Pharm. Bull. 1979, Vol. 27, pp793, Heterocycles 1987, Vol. 26, pp947, Tetrahedron 1994,
20 Vol. 60, pp901, and J. Am. Chem. Soc. 1982, Vol. 104, pp4461) or an analogous method thereto, a compound represented by formula (IV) can be obtained.

Reaction scheme 1



With respect to each symbol of the compound in the reaction scheme 1, X represents a leaving group such as halogen, $R^{3'}$ represents an optionally substituted thiazolyl, an optionally substituted pyrazolyl, an optionally substituted oxazolyl, an optionally substituted imidazo[1,2-a]pyridyl, an optionally substituted 1,2,3-triazolyl, an optionally substituted 1,2,4-triazolyl or an optionally substituted tetrazolyl, and as the "substituent" in the "optionally substituted thiazolyl", "optionally substituted pyrazolyl", "optionally substituted oxazolyl", "optionally substituted imidazo[1,2-a]pyridyl", "optionally substituted 1,2,3-triazolyl", "optionally substituted 1,2,4-triazolyl" and "optionally substituted tetrazolyl" in $R^{3'}$, substituents similar to those for the above-described R^3 are used.

$R^{3''}$ and $R^{3'''}$ represent a substituent that can be converted to R^3 by cyclization reaction such as optionally substituted C_{1-6} alkyl, formyl, optionally substituted acyl, optionally substituted carbamoyl, thiocarbamoyl and the like. As the "substituent" in the "optionally substituted

C₁₋₆ alkyl", "optionally substituted acyl" and "optionally substituted carbamoyl", substituents similar to those for the above-described R³ are used.

Others are as defined above, but they may be protected with a protective group or the like used generally in organic synthesis, if necessary. The compounds in the reaction scheme include the cases that a salt is formed, and examples of the salt include salts similar to those exemplified with respect to the salt of compound (I) and the like.

Compounds (II), (III) and (V) used as starting materials can be synthesized by a known method (for example, Japanese Patent No. 2003-252854) or an analogous method thereto, and, for example, can be produced by a method shown in Reference Examples described hereinafter. In addition, when commercially available, the commercial products can be used as it is.

In reaction scheme 1, compound (IV) or compound (VI) can be synthesized by reacting compound (II) with compound (III) or compound (V) in the presence of a base in accordance with a conventional method.

Examples of the base include alkali metal hydrides such as sodium hydride and potassium hydride, alkali metal amides such as sodium amide, potassium carbonate and the like. The amount of the base to be used is about 1.0 to about 10 moles based on 1.0 mole of compound (II). It is preferably about 1.0 to 2.0 moles.

The amount of compound (III) or compound (V) to be used is about 1.0 to about 10 moles based on 1.0 mole of compound (II). It is preferably about 1.0 to 2.0 moles.

The reaction temperature is usually about -70°C to about 100°C, and preferably about 0°C to about 50°C. The reaction time is usually about 5 min to about 48 hr, and preferably about 5 min to about 20 hr.

The present reaction is usually conducted in an

organic solvent having no adverse effect on the reaction. As the organic solvent having no adverse effect on the reaction, for example, ethers such as diethyl ether, dioxane and tetrahydrofuran (THF), saturated hydrocarbons
5 such as hexane and pentane, halogenated hydrocarbons such as dichloromethane and chloroform, amides such as N,N-dimethylformamide (DMF), aromatic hydrocarbons such as benzene and toluene and the like are used, and these solvents may be used alone or by mixing two or more at an
10 appropriate ratio.

In reaction scheme 1, the deprotection reaction is carried out by treating compound (IV) with acid in the case where the protective group is t-butyl, triphenylmethyl, t-butoxycarbonyl, benzyloxycarbonyl, or the like, and
15 conducted in a solvent having no adverse effect on the reaction. Examples of the solvent include ethers, hydrocarbons, halogenated hydrocarbons, ketones, nitriles, amides, esters and organic acids. Preferable solvents are ethers, hydrocarbons and halogenated hydrocarbons. These
20 solvents may be used alone or by mixing two or more at an appropriate ratio.

As the acid, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and nitric acid, organic acids such as formic acid, acetic acid,
25 trifluoroacetic acid (TFA) and p-toluenesulfonic acid, Lewis acid such as boron tribromide and silica gel can be used, and these acids may be used alone or in combination of two or more.

The amount of the acid to be used is usually 1 to 100
30 moles, preferably 1 to 50 moles, based on 1.0 mole of compound (IV), but further excessive amount can also be used as a solvent.

The reaction temperature is usually -72°C to 100°C, and preferably 0°C to 60°C. The reaction time is usually
35 0.5 to 100 hr, and preferably 0.5 to 48 hr.

In the case where the protective group is benzyloxycarbonyl, benzyl or benzyloxymethyl, it is removed by carrying out a catalytic hydrogenation reaction under a condition similar to those described above. In addition
5 when the protective group is pivaloyloxymethyl and the like, it is removed by carrying out hydrolysis reaction, reduction reaction, and alkylation reaction to a carbonyl compound under a condition similar to those described above.

The reduction reaction is conducted by using a
10 reducing agent used generally in organic synthesis, for example, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, lithium borohydride and lithium aluminum hydride, and further a metal salt such as calcium chloride may be added. The amount of the reducing
15 agent to be used is about 1.0 to about 10 moles based on 1.0 mole of compound (IV) or (VI). It is preferably about 1.0 to 5.0 moles.

The reaction temperature is usually about -70°C to about 100°C , and preferably about 0°C to about 50°C . The
20 reaction time is usually about 30 min to about 50 hr, and preferably 30 min to about 20 hr.

The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction. As the organic solvent having no adverse effect on the
25 reaction, for example, alcohols such as methanol, ethanol and 2-propanol, ethers such as diethyl ether, dioxane and tetrahydrofuran (THF), saturated hydrocarbons such as hexane and pentane, and aromatic hydrocarbons such as benzene and toluene are used, and these solvents may be
30 used alone or by mixing two or more at an appropriate ratio.

The catalytic hydrogenation reaction is conducted by reacting with hydrogen in the presence of a metal catalyst used generally in organic synthesis, such as palladium-carbon and platinum-carbon, and further a mineral acid such
35 as hydrochloric acid and an organic acid such as acetic

acid may be added.

The amount of the metal catalyst to be used is usually about 0.01 to about 1 mole equivalent based on 1.0 mole of compound (IV) or (VI). It is preferably about 0.01 to 0.5 mole equivalent.

The reaction temperature is usually about -10°C to about 100°C , and preferably about 0°C to about 50°C . The reaction time is usually about 30 min to about 50 hr, and preferably 30 min to about 20 hr.

The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction. As the organic solvent having no adverse effect on the reaction, for example, alcohols such as methanol, ethanol and 2-propanol, ethers such as diethyl ether, dioxane and tetrahydrofuran (THF), saturated hydrocarbons such as hexane and pentane, and aromatic hydrocarbons such as benzene and toluene are used, and these solvents may be used alone or by mixing two or more at an appropriate ratio.

The acylation reaction can be carried out by a method used generally in organic synthesis, for example, using an acylating agent such as organic acid, acyl halide and acid anhydride, if necessary, in the presence of a base.

As the base, for example, alkali metal salts such as sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide and sodium hydroxide, and organic bases such as triethylamine, diisopropylethylamine and pyridine can be used.

The amount of the acylating agent to be used is usually 1 to 20 mole equivalent, and preferably 2 to 10 moles, based on 1.0 mole of compound (IV) or (VI). The amount of the base to be used is usually 1 to 10 moles, and preferably 1 to 5 mole equivalent, based on 1.0 mole of compound (IV) or (VI), and further excessive amount can be used as a solvent.

The reaction temperature is usually 0 to 120°C , and

preferably 20°C to 100°C. The reaction time is usually 0.5 to 100 hr, and preferably 1 to 48 hr.

The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction.

5 Examples of the organic solvent having no adverse effect on the reaction include ethers, hydrocarbons, halogenated hydrocarbons, ketones, nitriles, amides, esters, aromatic amines, heterocycles and the like. Preferable solvents are ethers, hydrocarbons, halogenated hydrocarbons, amides,
10 aromatic amines and heterocycles. These solvents may be used alone or by mixing two or more at an appropriate ratio.

The oxidation reaction is conducted by using oxidizing agent used generally in organic synthesis, for example, manganese compounds such as potassium permanganate and
15 manganese dioxide, chromium compounds such as chromic acid, cerium compounds such as di-ammonium cerium(IV) nitrate, and sulfur compounds such as dimethyl sulfoxide, in a solvent having no adverse effect on the reaction, if necessary, in the presence of an acid or a base. Examples
20 of the solvent include water, hydrocarbons, halogenated hydrocarbons, alcohols, ketones, organic acids, amides, esters and sulfoxides. Preferable solvents are water, hydrocarbons, halogenated hydrocarbons, ketones, organic acids, amides, esters and sulfoxides. These solvents may
25 be used alone or by mixing two or more at an appropriate ratio.

As the acid, for example, mineral acids such as sulfuric acid and organic acids such as acetic acid can be used. As the base, for example, alkali metal salts such as
30 potassium hydroxide and sodium hydroxide, and amines such as triethylamine, diisopropylethylamine and piperidine can be used. In addition, if necessary, a dehydrating agent such as dicyclohexylcarbodiimide, and oxalyl chloride, pyridine sulfur trioxide and the like can be added.

35 The amount of the oxidizing agent to be used is

usually 1 to 20 moles, preferably 1 to 10 moles, based on 1.0 mole of compound (IV) or (VI), and further excessive amount can be used as a solvent. The amount of the acid and the base to be used is usually 1 to 20 moles, preferably 1 to 10 moles, based on 1.0 mole compound (IV) or (VI). In addition, the amount of the additives is usually 1 to 20 moles, preferably 1 to 10 moles, based on 1.0 mole of compound (IV) or (VI).

The reaction temperature is usually -70 to 120°C, and preferably -70 to 100°C. The reaction time is usually 0.1 to 100 hr, and preferably 0.1 to 48 hr.

The alkylation reaction can be conducted by reacting compound (IV) or (VI) with compound (V) in the presence of a base according to a conventional method.

Examples of the base include alkali metal hydride compounds such as sodium hydride and potassium hydride, alkali metal amides such as sodium amide, potassium carbonate and the like. The amount of the base to be used is usually about 1.0 to about 10 moles, preferably about 1.0 to 2.0 moles, based on 1.0 mole of compound (IV) or (VI).

The amount of compound (V) to be used is about 1.0 to about 10 moles, preferably about 1.0 to 2.0 moles, based on 1.0 mol of compound (IV) or (VI).

The reaction temperature is usually about -70°C to about 100°C, preferably about 0°C to about 50°C. The reaction time is usually about 5 min to 48 hr, and preferably about 5 min to 20 hr.

The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction. As the organic solvent having no adverse effect on the reaction, for example, ethers such as diethyl ether, dioxane and tetrahydrofuran (THF), saturated hydrocarbons such as hexane and pentane, halogenated hydrocarbons such as dichloromethane and chloroform, amides such as DMF,

aromatic hydrocarbons such as benzene and toluene and the like are used, and these solvents may be used alone or by mixing two or more at an appropriate ratio.

5 The alkylation reaction to a carbonyl compound can be conducted by reacting carbonyl compound and alkylating agent in a solvent having no adverse effect on the reaction, if necessary, in the presence of an additive.

As the alkylating agent, for example, organic magnesium reagents such as alkylmagnesium halide and
10 organic lithium compounds such as alkyl lithium can be used.

Examples of the solvent include hydrocarbons such as hexane and ethers such as diethyl ether. These solvents may be used alone or by mixing two or more at an appropriate ratio.

15 The amount of the organic magnesium reagent or organic lithium reagent to be used is usually 1 to 20 moles, preferably 1 to 10 moles, based on 1.0 mole of compound (IV) or (VI).

20 The reaction temperature is usually about -70°C to about 100°C , preferably about -70°C to about 50°C . The reaction time is usually about 0.5 to about 24 hr.

The hydrolysis reaction is conducted by using an acid or base used generally in organic synthesis.

25 As the acid, for example, mineral acids such as hydrochloric acid, Lewis acids such as boron tribromide, combination of Lewis acid with thiols or sulfides, and organic acids such as TFA and p-toluenesulfonic acid can be used.

30 As the base, for example, metal hydroxides such as sodium hydroxide, potassium hydroxide and barium hydroxide, basic salts such as sodium carbonate and potassium carbonate, metal alkoxides such as sodium methoxide, sodium ethoxide and potassium tert-butoxide, organic bases such as triethylamine, imidazole and formamidine, and the like can
35 be used.

The amount of the acid and base to be used is usually 0.1 to about 50 moles, preferably about 1 to about 20 moles, based on 1.0 mole of compound (IV) or (VI).

5 The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction. As the organic solvent having no adverse effect on the reaction, for example, alcohols, ethers, aromatic hydrocarbons, aliphatic hydrocarbons, halogenated hydrocarbons, sulfoxides, water, or a mixture of two or
10 more of them are used.

The reaction time is usually about 10 min to about 50 hr, and preferably about 30 min to about 12 hr. The reaction temperature is usually about 0°C to about 200°C, and preferably about 20°C to about 120°C.

15 The amidation reaction can be conducted by activating a carboxylic acid derivative with a method used generally in organic synthesis, followed by reacting with an aromatic or aliphatic amine, if necessary, in the presence of a base or an additive. In addition, it can also be carried out by
20 reacting an ester derivative with an aromatic or aliphatic amine, if necessary, in the presence of a base or an additive.

As the activating agent, for example, chlorination agents used generally in organic synthesis such as thionyl chloride and oxalyl chloride, acylating agents used
25 generally in organic synthesis such as acid anhydride and acid chloride, condensing agents used generally in organic synthesis such as 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide and diethyl cyanophosphate, and the like can be used.
30

As the additive, for example, N-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be used.

As the base, organic bases such as diisopropylethylamine, triethylamine and pyridine, and the
35 like can be used.

The amount of the activating agent to be used is usually 1 to 10 moles, preferably 1 to 5 moles, based on 1.0 mole of compound (IV) or (VI). The amount of the additive to be used is usually 1 to 20 moles, preferably 2 to 10 moles, based on 1.0 mole of compound (IV) or (VI). The amount of the base to be used is usually 1 to 10 moles, preferably 1 to 5 moles, based 1.0 mole of compound (IV) or (VI), and further excessive amount can be used as a solvent.

The reaction time is usually about 10 min to about 50 hr, preferably about 30 min to about 12 hr. The reaction temperature is usually about 0°C to about 100°C, preferably about 20°C to about 80°C.

The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction. Examples of the organic solvent having no adverse effect on the reaction include ethers, hydrocarbons, halogenated hydrocarbons, ketones, nitriles, amides, heterocycles and the like. Preferable solvents are ethers, hydrocarbons, halogenated hydrocarbons and amides. These solvents may be used alone or by mixing two or more at an appropriate ratio.

The dehydration reaction can be conducted with a method used generally in organic synthesis, for example, using a dehydrating agent such as acyl halide and acid anhydride in a solvent having no adverse effect on the reaction, if necessary, in the presence of a base. Examples of the solvent include ethers, hydrocarbons, halogenated hydrocarbons, ketones, nitriles, amides, esters, aromatic amines and heterocycles. Preferable solvents are ethers, hydrocarbons, halogenated hydrocarbons, amides, aromatic amines and heterocycles. These solvents may be used alone or by mixing two or more at an appropriate ratio.

As the base, for example, alkali metal salts such as sodium hydride, potassium carbonate and sodium carbonate, and organic bases such as triethylamine, diisopropylethylamine and pyridine can be used.

The amount of the dehydrating agent to be used is usually 1 to 20 moles, preferably 1 to 10 moles, based on 1.0 mole of compound (IV) or (VI). The amount of the base to be used is usually 1 to 10 moles, preferably 1 to 5 moles, based on 1.0 mole of compound (IV) or (VI), and further excessive amount can be used as a solvent.

The reaction temperature is usually 0°C to 120°C, preferably 0°C to 100°C. The reaction time is usually 0.5 to 100 hr, and preferably 0.5 to 48 hr.

The decarboxylation reaction can be conducted by reacting compound (IV) or (VI) without solvent or in a solvent having no adverse effect on the reaction, if necessary, in the presence of an acid or a metal salt. Examples of the solvent include ethers, hydrocarbons, halogenated hydrocarbons, ketones, nitriles, amides, esters, organic acids and sulfonic acids. Preferable solvents are ethers, hydrocarbons, halogenated hydrocarbons and sulfonic acids. These solvents may be used alone or by mixing two or more at an appropriate ratio. As the acid, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and nitric acid, and organic acids such as acetic acid, TFA, pyridine hydrochloride and p-toluenesulfonic acid can be used. As the metal salt, for example, alkali metal salts such as sodium chloride can be used.

The amount of the acid to be used is usually 1 to 100 moles, preferably 1 to 50 moles, based on 1.0 mole of compound (IV) or (VI), and further excessive amount can be used as a solvent.

The amount of the metal salt to be used is usually 1 to 30 moles, preferably 1 to 10 moles, based 1.0 mole of compound (IV).

The reaction temperature is usually 0 to 200°C, and preferably 0 to 170°C. The reaction time is usually 0.5 to 100 hr, and preferably 0.5 to 48 hr.

The sulfurization reaction can be conducted by using, for example, phosphorus pentasulfide or Lawesson's reagent.

The present reaction can be conducted in a solvent having no adverse effect on the reaction. As the solvent, for example, ethers, aromatic hydrocarbons, aliphatic hydrocarbons, halogenated hydrocarbons or a mixture of two or more of them are used.

The amount of phosphorus pentasulfide or Lawesson's reagent to be used is usually 0.5 to 30 moles, and preferably 0.5 to 10 moles, based on 1.0 mole of compound (IV) or (VI).

The reaction temperature is usually about 0 to about 150°C, and preferably about 20 to about 120°C. The reaction time is usually 10 min to about 50 hr, and preferably about 30 min to about 12 hr.

The trifluoromethylation reaction can be conducted by reacting with a trifluoromethylating reagent in the presence of an aromatic iodide or bromide and a metal reagent, if necessary, under the coexistence of a base, with a method used generally in organic synthesis.

As the metal reagent, for example, copper reagents such as copper chloride, copper bromide, copper iodide and metal copper, and palladium reagents such as dichlorobis(triphenylphosphine)palladium can be used.

As the trifluoromethylating reagent, for example, silicone reagents such as triethyltrifluoromethylsilane, and ester derivatives such as ethyl chlorodifluoroacetate and methyl fluorosulfonyl(difluoro)acetate can be used.

As the base, for example, alkali metal salts such as potassium carbonate, sodium carbonate and potassium fluoride, and organic bases such as triethylamine, diisopropylethylamine and pyridine can be used.

The amount of the metal reagent to be used is usually 1 to 10 moles, and preferably 1 to 5 moles, based on 1.0 mole of compound (IV) or (VI). The amount of the

trifluoromethylating reagent to be used is usually 1 to 20 moles, preferably 2 to 10 moles, based on 1.0 mole of compound (IV) or (VI). The amount of the base to be used is usually 1 to 10 moles, and preferably 1 to 5 moles, based on 1.0 mole of compound (IV) or (VI), and further excessive amount can be used as a solvent.

The reaction time is usually about 10 min to about 50 hr, and preferably about 30 min to about 12 hr. The reaction temperature is usually about 0 to about 100°C, and preferably about 20 to about 80°C.

The present reaction is usually conducted in an organic solvent having no adverse effect on the reaction. Examples of the organic solvent having no adverse effect on the reaction include ethers, hydrocarbons, halogenated hydrocarbons, ketones, nitriles, amides, heterocycles and the like. Preferable solvents are ethers, hydrocarbons, halogenated hydrocarbons and amides. These solvents may be used alone or by mixing two or more at an appropriate ratio.

In the case where the objective product is obtained in a free form by the above reaction, it can be converted into a salt according to a conventional method, and in the case where it is obtained as a salt, it can be converted into a free form or other salts according to a conventional method.

Compound (I) or a salt thereof obtained by the above production method can be isolated and purified by known means, for example, extraction with solvent, liquid conversion, transfer dissolution, crystallization, recrystallization and chromatography.

When compound (I) or a salt thereof has optical isomers, stereoisomers, regioisomers or rotational isomers, they are also included in compound (I) or a salt thereof, and individual isomers can be obtained as a single compound by a synthetic method and/or separation method known per se, respectively. For example, when there are optical isomers in compound (I) or a salt thereof, the optical isomers

resolved from the compound is also included in compound (I) or a salt thereof.

Herein, an optical isomer can be prepared by a method known per se.

5 Compound (I) or a salt thereof may be a hydrate or a nonhydrate.

Compound (I) or a salt thereof may be labeled with an isotope (e.g., ^3H , ^{14}C and ^{35}S) and the like.

Compound (I) or a salt thereof may be a crystal.

10 A crystal of compound (I) or a salt thereof (hereafter, occasionally abbreviated as a crystal of the present invention) can be prepared by crystallizing with applying a crystallization method known per se to compound (I) or a salt thereof.

15 Since androgen receptor antagonists including compound (I) of the present invention or a salt thereof (hereafter, sometimes abbreviated as an androgen receptor antagonist of the present invention) have an excellent androgen receptor antagonism and are also low toxic and have less side
20 effects, they are useful as safe drugs and androgen receptor antagonists.

A pharmaceutical composition comprising the androgen receptor antagonist of the present invention exhibits an excellent androgen receptor antagonism and/or an inhibitory
25 action of production of prostate-specific antigen (PSA) to a mammal (for example, mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human, etc.), and has an excellent (oral) absorbability and (metabolic) stability, therefore it can be used as a preventive or therapeutic
30 agent for androgen receptor-related diseases, for example, hormone-sensitive diseases in an androgen dependent stage and/or androgen independent stage, in particular, hormone-sensitive cancer in an androgen dependent stage and/or androgen independent stage (e.g., prostate cancer (for
35 example, hormone-dependent prostate cancer, hormone-

independent prostate cancer, etc.), uterine cancer, breast cancer (including progressive breast cancer, for example, infiltrating duct carcinoma, noninfiltrating intraductal carcinoma, inflammatory breast cancer, etc.), pituitary tumor, liver cancer (for example, primary liver cancer, extrahepatic bile duct cancer, etc.) etc.), and sex hormone-sensitive diseases such as prostatic hypertrophy, endometriosis, uterine leiomyoma, precocious puberty, dysmenorrhea, amenorrhea, premenstrual syndrome and polycystic ovary syndrome, and as a contraceptive drug (or prevention or treatment of infertility in case that a rebound effect after cessation of the drug is utilized).

Particularly, since the compound (I) of the present invention or a salt thereof has an antagonistic action against a normal androgen receptor and/or a mutant receptor, it can exert an excellent preventive or therapeutic effect on hormone-sensitive cancer in an androgen dependent stage and/or androgen independent stage.

Among androgen receptor antagonists, drugs having an antagonism against a mutant androgen receptor or drugs having an antagonism against an androgen receptor with increased sensitivity are useful as a preventive or therapeutic for hormone-sensitive cancer in an androgen dependent stage and/or androgen independent stage.

A pharmaceutical composition comprising the androgen receptor antagonist of the present invention can be safely administered orally or parenterally (e.g., local, rectal, intravenous administration, etc.) by mixing and formulating the androgen receptor antagonist of the present invention with a pharmacologically acceptable carrier according to a known method into a pharmaceutical composition, for example, tablets (including sugar coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories or sustained release tablets. Injection can be administered

intravenously, intramuscularly, subcutaneously or intraorganically, or directly administered to the focus.

Examples of the pharmacologically acceptable carrier that can be used for the preparation of the pharmaceutical composition of the present invention include various organic or inorganic carriers conventionally used as a formulation material, for example, excipients, lubricants, binders and disintegrants in solid formulations, and solvents, solubilizing agents, suspending agents, isotonicity agents, buffering agents and soothing agents in liquid formulations. Furthermore, if necessary, usual additives such as antiseptics, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can be used appropriately with a suitable amount.

Examples of the excipient include lactose, white sugar, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic acid anhydride and the like.

Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Examples of the binder include crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methylcellulose, sodium carboxymethyl cellulose and the like.

Examples of the disintegrant include starch, carboxymethylcellulose, carboxymethylcellulose calcium, carboxymethyl starch sodium, L-hydroxypropyl cellulose, and the like.

Examples of the solvent include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, olive oil, and the like.

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the

like.

Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalconium chloride, benzethonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinylalcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose and the like.

Examples of the isotonicity agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like.

Examples of the buffering agent include phosphate, acetate, carbonate, citrate and the like.

Examples of the soothing agent include benzyl alcohol and the like.

Examples of the antiseptic include paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfite, ascorbic acid, α -tocopherol and the like.

The content of the androgen receptor antagonist of the present invention in the pharmaceutical composition of the present invention can be appropriately selected depending on the subject to be administered, route of administration, disease and the like. Although it differs depending on a form of preparation, the amount is usually, for example, about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, and more preferably about 0.5 to 20% by weight, based on the total amount of the preparation.

The content of the additives such as a carrier in the pharmaceutical composition of the present invention is usually, although it differs depending on a form of preparation, about 1 to 99.99% by weight, preferably about 10 to 90% by weight, based on the total amount of the

preparation.

The androgen receptor antagonist of the present invention has low toxicity, therefore it can be used safely. The dosage of the androgen receptor antagonist of the present invention differs depending on a kind of compound, age, body weight, symptom of the patient, dosage form, dosing method, and the like, however, for example, usually about 0.01 to about 1000 mg/kg, preferably about 0.01 to about 100 mg/kg, more preferably about 0.1 to about 100 mg/kg, particularly preferably about 0.1 to about 50 mg/kg, inter alia about 1.5 to about 30 mg/kg in terms of the androgen receptor antagonist of the present invention is intravenously administered daily in one to several divided doses to one patient suffering prostate cancer (adult, body weight: about 60 kg). As mentioned above, since the dosage varies depending on various conditions, less dosage may be enough in some cases, while dosage beyond the above range may be necessary in some cases.

As an example of a drug which can be used in combination with the androgen receptor antagonist of the present invention, a hormone therapeutic agent, anticancer agent (e.g., chemotherapeutic agent, immunotherapeutic agent (including vaccine), antibody, gene therapeutic agent, drugs that inhibit the action of cell growth factor and the receptor thereof, or drugs that inhibit angiogenesis) and the like (hereafter abbreviated as a concomitant drug) can be used in combination.

Although the compound of the present invention has a potent anticarcinoma activity when used as a single drug, the action can be more potentiated by further using in combination with one or more of the above-mentioned concomitant drug (combined use with multiple drug).

As the "hormone therapeutic agent", for example, fosfestrol, diethylstilbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate,

chlormadinone acetate, cyproterone acetate, danazol, dienogest, asoprisnil, allylestrenol, gestrinone, nomegestrol, tadenan, mepartricin, raloxifene, ormeloxifene, levormeloxifene, antiestrogen (e.g., tamoxifen citrate, 5 tremifene citrate, etc.), ER down regulator (e.g., fulvestrant etc.), human menopause gonadotropin, follicle-stimulating hormone, pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH derivatives (e.g., LH-RH agonist (e.g., goserelin acetate, buserelin, 10 leuprorelin, etc.), LH-RH antagonist), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitor (e.g., fadrozole hydrochloride, anastrozole, letrozole, exemestane, vorozole, formestane etc.), antiandrogen (e.g., flutamide, bicalutamide, nilutamide, 15 etc.), 5 α -reductase inhibitor (e.g., finasteride, dutasteride, epristeride, etc.), corticosteroid (e.g., dexamethasone, predonisolone, betamethasone, triamcinolone, etc.), androgen synthesis inhibitor (e.g., abiraterone, etc.), and retinoid and drugs that delays the metabolism of 20 retinoid (e.g., liarozole, etc.) are used.

As the "chemotherapeutic agent", for example, alkylating agents, antimetabolites, anticarcinogenic antibiotics, anticancer drugs derived from plant, and other chemotherapeutic agents are used.

25 As the "alkylating agent", for example, nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambucil, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, 30 ranimustine, sodium estramustine phosphate, triethylene melamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, 35 ribomustin, temozolomide, treosulfan, trophosphamide,

zinostatin stimalamer, adozelesin, cystemustine, bizelesin, and the like are used.

As the "antimetabolite", for example, mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmittefur, etc.), aminopterin, calcium leucovorin, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, tiazofurine, ambamustine, and the like are used.

As the "anticarcinogenic antibiotic", for example, actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, and the like are used.

As the "anticancer drug derived from plant", for example, etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, irinotecan, topotecan, and the like are used.

As the "other chemotherapeutic agent", for example, sobuzoxane, and the like are used.

As the "immunotherapeutic agent (BRM)", for example, Picibanil, krestin, sizofiran, lentinan, ubenimex, interferon, interleukin, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, Corynebacterium parvum, levamisole, polysaccharide K, procodazole, and the like are used. In addition, as the vaccine, BCG vaccine, PROVENGE,

Onyvax-P, PROSTVAC-VF, GVAX, DCVax-Prostate, SAPOIMMUNE, VPM-4-001, and the like are used.

As the "antibody", antibodies to EpiCAM, antibodies to PSCS and antibodies to PSMA are used.

5 As the "cell growth factor" in the "drugs that inhibit the action of cell growth factor and the receptor thereof", any substance can be used as long as it promotes the growth of cell. Usually, a factor that is a peptide having a molecular weight of 20,000 or less and exerts its action by
10 binding to a receptor at low concentration is used, and specific examples thereof include (1) EGF (epidermal growth factor) or a substance having substantially the same activity [e.g., EGF, heregulin, TGF- α , HB-EGF, etc.], (2) insulin or a substance having substantially the same
15 activity [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, etc.], (3) FGF (fibroblast growth factor) or a substance having substantially the same activity [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, etc.], (4) other cell growth factor [e.g., CSF
20 (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGF β (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor) etc.], and the like.

25 As the "receptor of cell growth factor", any receptor may be allowed as long as it has a binding ability to the above-mentioned cell growth factor, and specific examples thereof include HER2, HER3 and HER4 which are an EGF receptor and a receptor belonging to the same family,
30 insulin receptor, IGF receptor, FGF receptor-1, FGF receptor-2, and the like.

 Examples of the "drugs that inhibit the action of cell growth factor" include trastuzumab (Herceptin (trade mark); HER2 antibody), imatinib mesylate, ZD1839 or cetuximab,
35 gefitinib, erlotinib and the like.

As the "drugs that inhibit angiogenesis", antibodies to VEGF (e.g., bevacitumab), antibodies to VEGF receptor, VEGF receptor kinase inhibitor (e.g., SU11248 etc.), PDGF receptor kinase inhibitor, Tie2 kinase inhibitor, thalidomide, and the like are used.

In addition to the above-mentioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin cobalt complex, mercury hematoporphyrin sodium, differentiation inducer (e.g., retinoid, vitamin Ds, etc.), α -blocker (e.g., tamsulosin hydrochloride, naftopidil, urapidil, alfuzosin, terazosin, prazosin, silodosin, etc.), serine threonine kinase inhibitor, endothelin receptor antagonist (e.g., atrasentan, etc.), proteasome inhibitor (e.g., bortezomib etc.), Hsp90 inhibitor (e.g., 17-AAG etc.), spironolactone, minoxidil, 11α -hydroxyprogesterone, bone resorption inhibitor and antimetastatic agent (e.g., zoledronic acid, alendronic acid, pamidronic acid, etidronic acid, ibandronic acid, clodronic acid, etc.), and the like can also be used.

Among these, as a preferable concomitant drug, LH-RH derivatives and the like are exemplified.

Examples of the LH-RH derivative include a LH-RH derivative or a salt thereof which is effective for hormone dependent diseases, in particular, sex hormone-dependent cancer (e.g., prostate cancer, uterine cancer, breast cancer, pituitary tumor, liver cancer, etc.), sex hormone dependent diseases such as prostatic hypertrophy, endometriosis, uterine leiomyoma, precocious puberty, dysmenorrhea, amenorrhea, premenstrual syndrome and pleuritis ovarian syndrome, and contraception (or infertility in case that a rebound effect after cessation of the drug is utilized). In addition, a LH-RH derivative or a salt thereof which is effective for benign or malignant tumor or the like that is LH-RH sensitive but sex hormone independent, is exemplified.

Specific examples of the LH-RH derivative or a salt thereof include peptides described in, for example, Treatment with GnRH analogs: Controversies and perspectives (published by The Parthenon Publishing Group Ltd. in 1996),
5 JP-A H03-503165, JP-A H03-101695, JP-A H07-97334 and JP-A H08-259460.

As the LH-RH derivative, a LH-RH agonist or a LH-RH antagonist is exemplified. Examples of the LH-RH antagonist include physiologically active peptides
10 represented by formula

X-D2Nal-D4ClPhe-D3Pal-Ser-A-B-Leu-C-Pro-DAlaNH₂

wherein X represents N(4H₂-furoyl)Gly or NAc, A represents a residue selected from the group consisting of NMeTyr, Tyr, Aph(Atz) and NMeAph(Atz), B represents a residue selected
15 from the group consisting of DLys(Nic), DCit, DLys(AzaglyNic), DLys(AzaglyFur), DhArg(Et₂), DAph(Atz) and DhCi, and C represents Lys(Nisp), Arg or hArg(Et₂), respectively; or a salt thereof.

Examples of the LH-RH agonists include physiologically
20 active peptides represented by formula

5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z

wherein Y represents a residue selected from the group consisting of DLeu, DAla, DTrp, DSer(tBu), D2Nal and DHis(ImBzl), and Z represents NH-C₂H₅ or Gly-NH₂,
25 respectively, or a salt thereof. In particular, peptides wherein Y is DLeu and Z is NH-C₂H₅ (that is, peptides A represented by 5-oxo-Pro-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NH-C₂H₅; leuprorelin) or a salt thereof (e.g., acetate) is preferred.

The drug comprising a combination of the androgen receptor antagonist of the present invention and a concomitant drug (hereafter, referred to as a concomitant agent of the present invention) has low toxicity, and can be safely administered orally or parenterally (e.g., local,
35 rectal, intravenous administration, etc.) by mixing the

androgen receptor antagonist of the present invention or(and) the above-mentioned concomitant drug with a pharmacologically acceptable carrier and formulating according to a known method into a pharmaceutical composition, for example, tablets (including sugar coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories or sustained release tablets. Injection can be administered intravenously, intramuscularly, subcutaneously or intraorganically, or directly administered to the focus.

Examples of the pharmacologically acceptable carrier that can be used for the preparation of the concomitant agent of the present invention include various organic or inorganic carriers conventionally used as a formulation material, for example, excipients, lubricants, binders and disintegrants in solid formulations, and solvents, solubilizing agents, suspending agents, isotonicity agents, buffering agents and soothing agents in liquid formulations. Furthermore, if necessary, usual additives such as antiseptics, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can be used appropriately with a suitable amount.

Examples of the excipient include lactose, white sugar, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic acid anhydride and the like.

Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Examples of the binder include crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methylcellulose, sodium carboxymethyl cellulose and the like.

Examples of the disintegrant include starch, carboxymethylcellulose, carboxymethylcellulose calcium,

carboxymethyl starch sodium, L-hydroxypropyl cellulose, and the like.

Examples of the solvent include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil,
5 olive oil, and the like.

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the
10 like.

Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalconium chloride, benzethonium chloride, glycerin monostearate, etc.;
15 hydrophilic polymers such as polyvinylalcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose and the like.

Examples of the isotonicity agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the
20 like.

Examples of the buffering agent include phosphate, acetate, carbonate, citrate and the like.

Examples of the soothing agent include benzyl alcohol
25 and the like.

Examples of the antiseptic include paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfite, ascorbic
30 acid, α -tocopherol and the like.

The compounding ratio of the androgen receptor antagonist of the present invention to a concomitant drug in the concomitant agent of the present invention can be appropriately selected depending on the subject to be
35 administered, route of administration, disease and the like.

Although it differs depending on a form of preparation, the content of the androgen receptor antagonist of the present invention in the concomitant agent of the present invention is usually, for example, about 0.01 to 99.9% by weight, preferably about 0.1 to 50% by weight, and more preferably about 0.5 to 20% by weight, based on the total amount of the preparation.

The content of the concomitant drug in the concomitant agent of the present invention is, although it differs depending on a form of preparation, usually about 0.01 to 99.9% by weight, preferably about 0.1 to 50% by weight and more preferably about 0.5 to 20% by weight, based on the total amount of the preparation.

The content of the additives such as a carrier in the concomitant agent of the present invention is, although it differs depending on a form of preparation, usually about 1 to 99.98% by weight, preferably about 10 to 90% by weight, based on the total amount of preparation.

In addition, when the androgen receptor antagonist of the present invention and the concomitant drug are made into preparation separately, the same content may be applied.

These preparations can be produced by a method known per se that is conventionally used in a preparation producing process.

For example, the androgen receptor antagonist of the present invention or the concomitant drug can be formulated, together with a dispersing agent (e.g., Tween 80 (manufactured by ATRAS POWDER, USA), HCO 60 (manufactured by NIKKO CHEMICALS CO. LTD.), polyethylene glycol, carboxymethyl cellulose, sodium alginate, hydroxypropylmethylcellulose, dextrin, etc.), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, etc.), a surfactant (e.g., Polysorbate 80, Macrogol, etc.), a solubilizer (e.g., glycerin, ethanol, etc.), a buffering

agent (e.g., phosphoric acid and an alkali metal salt thereof, citric acid and an alkali metal salt thereof, etc.), an isotonicity agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose, etc.), a
5 pH adjuster (e.g., hydrochloric acid, sodium hydroxide, etc.), a preservative (e.g., ethyl paraoxybenzoate, benzoic acid, methylparabene, propylparabene, benzyl alcohol, etc.), a dissolving agent (e.g., concentrated glycerin, meglumine, etc.), a solubilizing agent (e.g., propylene glycol, white
10 sugar, etc.), a soothing agent (e.g., glucose, benzyl alcohol, etc.) and the like, into an aqueous injectable, or into an oil injectable by dissolving, suspending or emulsifying in a solubilizing agent such as vegetable oils such as olive oil, sesame oil, cotton oil and corn oil, and
15 propylene glycol to prepare an injectable.

In order to prepare a preparation for oral administration, an excipient (e.g., lactose, white sugar, starch, etc.), a disintegrant (e.g., starch, calcium carbonate, etc.), a binder (e.g., starch, gum arabic,
20 carboxymethyl cellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, etc.), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000, etc.) and the like are added to the androgen receptor antagonist of the present invention or the concomitant drug to compress and
25 mold with a method known per se, then if necessary, followed by coating according to a method known per se for the purpose of masking taste or providing enteric property or sustainability to give an oral preparation. As the coating agent, for example, hydroxypropylmethyl cellulose,
30 ethylcellulose, hydroxymethyl cellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit
35 (manufactured by ROHM CO. LTD., Germany, methacrylic acid-

acrylic acid copolymer), a coloring agent (e.g., colcothar, titanium dioxide, etc.) and the like are used. The oral preparation may be any one of a quick release preparation and a sustained release preparation.

5 For example, as for a suppository, the androgen receptor antagonist of the present invention or the concomitant drug is made into an oily or aqueous solid, semi-solid or liquid suppository according to a method known per se. Examples of the oil base used for the above
10 composition include glycerides of higher fatty acid (e.g., cacao butter, uitepsols (manufactured by DYNAMITE NOBEL CO., Germany), etc.), medium fatty acids (e.g., Migriols (manufactured by DYNAMITE NOBEL CO., Germany), etc.), vegetable oils (e.g., sesame oil, soybean oil, cotton oil,
15 etc.) and the like. In addition, examples of the aqueous base include polyethylene glycols and propylene glycol, and examples of the aqueous gel base include natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like.

20 Example of the sustained release preparation includes a sustained release microcapsule preparation.

 A method known per se can be employed to prepare a sustained release microcapsule, however, it is preferred to formulate into the sustained release preparation shown in
25 the following [2] to administer.

 The androgen receptor antagonist of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablets and capsules) or a preparation for rectal
30 administration such as a suppository. Particularly, an oral preparation is preferred.

 The concomitant drug can be made into the above-mentioned dosage form depending on a kind of the drug.

 Hereinafter, [1] an injectable of the androgen
35 receptor antagonist of the present invention or the

concomitant drug and the preparation of the same, [2] a sustained release preparation or quick release preparation of the androgen receptor antagonist of the present invention or the concomitant drug and the preparation of the same, and [3] a sublingual tablet, buccal or intraoral quick disintegrant of the androgen receptor antagonist or the concomitant drug of the present invention and the preparation of the same will be specifically described.

[1] Injectable and the preparation of the same

Preferred is an injectable wherein the androgen receptor antagonist of the present invention or the concomitant drug is dissolved in water. Benzoate and/or salicylate may be contained in the injectable.

The injectable can be obtained by dissolving the androgen receptor antagonist of the present invention or the concomitant drug and, if desired, benzoate and/or salicylate in water.

Examples of the salt of benzoic acid and salicylic acid include alkali metal salts such as sodium and potassium, alkaline earth metal salts such as calcium and magnesium, an ammonium salt, a meglumine salt and organic acid salts such as trometamol.

The concentration of the androgen receptor antagonist of the present invention or the concomitant drug in the injectable is about 0.5 to 50 w/v%, and preferably 3 to 20 w/v%. In addition, the concentration of benzoate and/or salicylate is 0.5 to 50 w/v%, and preferably 3 to 20 w/v%.

Further, additives conventionally used for an injectable can appropriately be blended to the injectable such as a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, etc.), a surfactant (e.g., Polysorbate 80, Macrogoal, etc.), a solubilizer (e.g., glycerin, ethanol, etc.), a buffering agent (e.g., phosphoric acid and a alkali metal salt thereof, citric acid and a alkali metal salt thereof, etc.), an isotonicity agent (e.g., sodium

chloride, potassium chloride, etc.), a dispersant (e.g., hydroxypropylmethylcellulose, dextrin, etc.), a pH adjuster (e.g., hydrochloric acid, sodium hydroxide, etc.), a preservative (e.g., ethyl paraoxybenzoate, benzoic acid, etc.), a dissolving agent (e.g., concentrated glycerin, meglumine, etc.), a solubilizing agent (e.g., propylene glycol, white sugar, etc.), a soothing agent (e.g., glucose, benzyl alcohol, etc.) and the like. These additives are blended at a ratio generally used for an injectable.

It is preferred to adjust the pH of the injectable to 2 to 12, preferably 2.5 to 8.0, by adding a pH adjuster.

The injectable can be obtained by dissolving the androgen receptor antagonist of the present invention or the concomitant drug and, if desired, benzoate and/or salicylate, and further if necessary, the above additives in water. These dissolution procedures may be conducted in any order, and can be appropriately carried out according to the same manner as a conventional production method for an injection.

An aqueous solution for injection is preferably warmed, and an injectable can be provided by subjecting to sterilization by filtration, high pressure thermal sterilization, or the like as the same way as in a usual injectable.

The aqueous solution for injection is preferably subjected to high pressure thermal sterilization under, for example, a condition of 100°C to 121°C for 5 to 30 min.

Furthermore, it can be a preparation wherein the solution is provided with antimicrobial activity so as to be used as a multiple divided administration preparation.

[2] Sustained release preparation or quick release preparation and the preparation of the same

Preferred is a sustained release preparation wherein a core comprising the androgen receptor antagonist of the present invention or the concomitant drug is coated with a

coating agent such as a water-insoluble substance, a swellable polymer or the like, if desired. For example, an once-daily dosing sustained release preparation for oral administration is preferred.

5 Examples of the water-insoluble substance used for the coating agent include cellulose ethers such as ethylcellulose, butylcellulose etc., cellulose esters such as cellulose acetate, cellulose propionate etc., polyvinyl esters such as polyvinyl acetate, polyvinyl butylate etc.,
10 acrylic acid polymers such as acrylic acid/methacrylic acid copolymer, methyl methacrylate copolymer, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymer, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide copolymer, poly(methyl
15 methacrylate), polymethacrylate, polymethacrylamide, aminoalkylmethacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymer, in particular, Eudragits (manufactured by ROHM PHARMA CO. LTD.) such as Eudragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO
20 (ethyl acrylate/methyl methacrylate/ chlorotrimethyl methacrylate/ammonium ethyl copolymer), Eudragit NE-30D (methyl methacrylate/ethyl acrylate copolymer) etc., hardened oils such as a hardened castor oil (e.g., Lovely Wax (Froint Inds.) etc.), waxes such as carnauba wax, fatty
25 acid glycerin ester, paraffin etc., and polyglycerin fatty acid ester, and the like.

As the swellable polymer, preferred is a polymer that has an acidic dissociable group and exhibits a pH-dependent swelling, that is, a polymer having an acidic dissociable
30 group wherein swelling is less at an acidic region such as in the stomach and large at a neutral region such as in the small intestine and large intestine is preferred.

Examples of the polymer that has an acidic dissociable group and exhibits a pH-dependent swelling include cross-
35 linking polyacrylic acid polymers such as Carbomer 934P,

940, 941, 974P, 980 and 1342, polycarbophil, calcium polycarbophil (each of them is manufactured by BF GOODRICH COM.), and High Bis Wako 103, 104, 105 and 304 (each of them is manufactured by WAKO-CHEM).

5 The coating agent used for the sustained release preparation may further contain a hydrophilic substance.

 Examples of the hydrophilic substance include polysaccharides optionally having a sulfuric acid group such as Pullulan, dextrin and alkali metal alginate,
10 polysaccharides having a hydroxyalkyl group or carboxy alkyl group such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose and sodium carboxymethyl cellulose, methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol and the like.

15 The content of the water-insoluble substance in the coating agent of the sustained release preparation is about 30 to about 90%(w/w), preferably about 35 to about 80%(w/w), and more preferably about 40 to 75%(w/w), and the content of the swellable polymer is about 3 to about 30%(w/w), and
20 preferably about 3 to about 15%(w/w). The coating agent may further contain a hydrophilic substance, and in that case, the content of the hydrophilic substance in the coating agent is about 50%(w/w) or less, preferably about 5 to about 40%(w/w), and more preferably about 5 to about
25 35%(w/w). Herein, the above %(w/w) denotes % by weight to the coating agent composition wherein the solvent (e.g., water, lower alcohols such as methanol, ethanol, etc.) is removed from the coating agent solution.

 The sustained release preparation can be produced by
30 preparing a core containing a drug, followed by coating the obtained core with a coating agent solution wherein a water-insoluble substance or a swellable polymer is dissolved by heating, or dissolved or dispersed in a solvent.

35 I. Preparation of core containing drug

The form of the core containing a drug to be coated with a coating agent (hereafter, sometimes simply referred to as a core) is not specifically limited, but it is preferably made into a granular form such as a granule or fine granule.

When the core is a granule or a fine granule, the average particle size is preferably about 150 to 2,000 μm , and more preferably about 500 to about 1,400 μm .

Preparation of the core can be conducted with a usual production method. For example, an adequate excipient, binder, disintegrant, lubricant, stabilizer and the like are mixed with a drug, followed by preparing the preparation by a wet extrusion granulation method or fluidized bed granulation method.

The content of the drug in the core is about 0.5 to about 95% (w/w), preferably about 5.0 to about 80% (w/w), and more preferably about 30 to about 70% (w/w).

As the excipient contained in the core, for example, saccharides such as white sugar, lactose, mannitol, glucose etc., starch, crystalline cellulose, calcium phosphate, cornstarch and the like are used. Among these, crystalline cellulose and cornstarch are preferred.

As the binder, for example, polyvinyl alcohol, hydroxypropyl cellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum arabic, gelatin, starch and the like are used. Preferable examples of the disintegrant include carboxymethylcellulose calcium (ECG505), croscarmellose sodium (Ac-Di-Sol), cross-linked polyvinyl pyrrolidone (Crospovidone), low substituted hydroxypropyl cellulose (L-HPC) and the like. Among these, hydroxypropyl cellulose, polyvinyl pyrrolidone and low substituted hydroxypropyl cellulose are preferred. As a glidant and an antiaggregant, for example, talc, magnesium stearate and an inorganic salt thereof are used, and as the lubricant, for example, polyethylene glycol and the like are used. As the

stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid and maleic acid are used.

In addition to the above production methods, the core can further be prepared by a rolling granulation method which is conducted by adding a drug or a mixture of the drug, excipient, glidant and the like little by little while spraying a binder dissolved in an adequate solvent such as water and lower alcohol (e.g., methanol, ethanol, etc.) onto an inert carrier particle to be a center of the core, a pan-coating method, fluidized bed coating method and melt granulation method. As the inert carrier particle, for example, those prepared from white sugar, lactose, starch, crystalline cellulose or waxes can be used, and the average particle size is preferably about 100 μm to about 1,500 μm .

In order to separate the drug contained in the core from the coating agent, the surface of the core may be coated with a protective agent. As the protective agent, for example, an above-described hydrophilic substance, a water-insoluble substance and the like are used. The protective agents are preferably polyethylene glycol and polysaccharides having a hydroxyalkyl group or carboxyalkyl group, and more preferably hydroxypropylmethyl cellulose and hydroxypropyl cellulose. The protective agent may contain an acid such as tartaric acid, citric acid, succinic acid, fumaric acid and maleic acid as a stabilizer, and a glidant such as talc. When a protective agent is used, the coating amount is about 1 to about 15% (w/w), preferably about 1 to about 10% (w/w), and more preferably about 2 to about 8% (w/w), based on the core.

The protective agent can be coated by a usual coating method, and specifically, it is coated by spray coating to the core with a fluidized bed coating method, pan-coating method or the like.

II. Coating of core by coating agent

A sustained release preparation can be produced by coating the core obtained in the above I with a coating agent solution wherein the above-mentioned water-insoluble substance, a pH-dependent swellable polymer and a hydrophilic substance are dissolved by heating or dissolved or dispersed in a solvent.

As a coating method for the core by a coating agent solution, a method of spray coating is exemplified.

The composition ratio of the water-insoluble substance, swellable polymer or hydrophilic substance in the coating agent solution is appropriately selected so as to make the content of the respective component in the coat to the above-mentioned content.

The coating amount of the coating agent is about 1 to about 90%(w/w), preferably about 5 to about 50%(w/w), and more preferably about 5 to about 35%(w/w), based on the core (not including the coating amount of the protective agent).

As the solvent for the coating agent solution, water or an organic solvent can be used alone or with a mixture thereof. When a mixture is used, the mixing ratio of water and an organic solvent (water/organic solvent: weight ratio) can be varied in a range of 1 to 100%, and it is preferably 1 to about 30%. The organic solvent is not specifically limited as long as it dissolves a water-insoluble substance, and lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and n-butyl alcohol, lower alkanones such as acetone, and acetonitrile, chloroform and dichloromethane are used. Among these, lower alcohols are preferred, and ethyl alcohol and isopropyl alcohol are particularly preferred. Water and a mixed solution of water and an organic solvent are preferably used as a solvent for a coating agent. At this time, acids such as tartaric acid, citric acid, succinic acid, fumaric acid and maleic acid may be added to the coating agent

solution, if necessary, so as to stabilize the coating agent solution.

The operation in case of coating by spray coating is conducted according to a usual coating method, and specifically, it is carried out by spray coating the coating agent solution onto the core by a fluidized bed coating method, pan-coating method or the like. At this time, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid or the like may be added as a glidant, and glycerin fatty acid ester, hardened castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol or the like may be added as a plasticizer.

After coating with coating agent, an antistatic agent such as talc may be mixed, if necessary.

The quick release preparation may be a liquid (solution, suspension, emulsion etc.) or solid (granule, pill, tablet etc.). Although an oral preparation and a parenteral preparation such as an injectable are used, an oral preparation is preferred.

The quick release preparation may usually contain, in addition to a drug as an active component, a carrier, additives and an excipient (hereafter, sometimes abbreviated as an excipient) that are conventionally used in a drug product field. An excipient used for the preparation is not particularly limited as long as it is commonly used as an excipient for drugs. Examples of the excipient for oral solid preparation include lactose, starch, cornstarch, crystalline cellulose (Avicel PH101, manufactured by ASAHI KASEI CORP.), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like, and preferably cornstarch, mannitol and the like. These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, about 4.5 to about 99.4 w/w%, preferably about 20 to about

98.5 w/w%, and more preferably about 30 to about 97 w/w%, based on the total amount of the quick release preparation.

The content of the drug in a quick release preparation is appropriately selected from a range of about 0.5 to about 95%, and preferably about 1 to about 60%.

In the case where the quick release preparation is an oral solid preparation, it usually contains a disintegrant in addition to above-mentioned components. Examples of such a disintegrant include carboxymethylcellulose calcium (ECG-505, manufactured by GOTOKU CHEMICAL CO. LTD.), croscarmellose sodium (e.g., Ac-Di-Sol, manufactured by ASAHI KASEI CORP.), croscopidone (e.g., Kollidone CL, manufactured by BASF), low substituted hydroxypropylcellulose (manufactured by SHIN-ETSU CHEMICAL CO. LTD.), carboxymethyl starch (MATSUTANI CHEMICAL INDUSTRY CO. LTD.), carboxymethyl starch sodium (Explotab, manufactured by KIMURA SANGYO CO. LTD.), partial α -starch (PCS, manufactured by ASAHI KASEI CORP.), and those that disintegrate the granules by, for example, absorbing water, swelling or forming a channel between an active ingredient composing the core and the excipient as a result of contacting with water can be used. These disintegrants can be used alone or in combination of two or more. The compounding amount of the disintegrant is appropriately selected according to the kind or a blending quantity of the drug to be used and the releasing design of the preparation, however, it is about 0.05 to about 30 w/w%, and preferably about 0.5 to about 15 w/w%, based on the total amount of a quick release preparation.

When the quick release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, additives coventionally used for a solid preparation, if desired. Examples of such additives include a binder (e.g., sucrose, gelatin, gum arabic powder, methylcellulose, hydroxypropylcellulose,

hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin, etc.), a glidant (e.g., polyethylene glycol, magnesium stearate, talc, light anhydrous silicic acid (e.g., Aerosil (JAPAN AEROSIL CO. LTD.))), a surfactant (e.g., anion surfactants such as sodium alkylsulfate, nonionic surfactants such as polyoxyethylene fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives, etc.), a colorant (e.g., tar pigment, caramel, colcothar, titanium oxide and riboflavin), and if necessary, a masking agent (e.g., sweetener, perfume etc.), an adsorbent, an antiseptic, a wetting agent, an antistatic agent and the like. In addition, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like can be added as a stabilizer.

As the above binder, hydroxypropylcellulose, polyethylene glycol, polyvinylpyrrolidone and the like are preferably used.

The quick release preparation can be prepared by mixing each of the above components, kneading furthermore, if necessary, and molding them based on a usual drug production technique. The above mixing is conducted by a method used generally, for example, mixing, kneading and the like. Specifically, for example, when a quick release preparation is molded into a granule, the components are mixed with vertical granulator, universal kneader (manufactured by HATA IRON WORKS CO. LTD.), fluidized bed granulator FD-5S (manufactured by POWREX CORP.) or the like by a similar method to the preparation method for the core of the sustained release preparation, and then granulated by a wet extrusion granulation method, a fluidized bed granulation method or the like to prepare the granule.

The thus obtained quick release preparation and sustained release preparation are as it is or are separately formulated with excipients appropriately

according to a conventional method, and the resulting two preparations may be administered simultaneously or administered in combination with a given interval, or the both preparations are as it is or may be formulated with excipients or the like appropriately into a single oral preparation (e.g., granule, fine granule, tablet, capsule etc.). It is also possible that both preparations are formulated into granules or fine granules, and filled in a single capsule for an oral preparation.

[3] Sublingual tablet, buccal or intraoral quick disintegrant preparation and the preparation of the same

The sublingual tablet, buccal or intraoral quick disintegrant preparation may be a solid preparation such as tablet, or an oral mucosa film.

As the sublingual tablet, buccal or intraoral quick disintegrant preparation, a preparation containing the androgen receptor antagonist of the present invention or the concomitant drug and an excipient is preferred. In addition, it may contain auxiliary agents such as a glidant, isotonicity agent, hydrophilic carrier, water dispersible polymer and stabilizer. It also can contain β -cyclodextrin or β -cyclodextrin derivatives (e.g., hydroxypropyl- β -cyclodextrin etc.) so as to make absorption easier and increase bioavailability.

Examples of the above excipient include lactose, white sugar, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like. Examples of the glidant include magnesium stearate, calcium stearate, talc, colloidal silica and the like, and in particular, magnesium stearate and colloidal silica are preferred. Examples of the isotonicity agent include sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like, and in particular mannitol is preferred. Examples of the hydrophilic carrier include swellable hydrophilic carriers such as crystalline cellulose,

ethylcellulose, cross-linked polyvinylpyrrolidone, light anhydrous silic acid, silic acid, dicalcium phosphate, calcium carbonate and the like, and in particular crystalline cellulose (e.g., microcrystalline cellulose) is preferred. Examples of the water dispersible polymer include gum (e.g., tragacant, acacia gum, guar gum), alginic acid salt (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose), gelatin, water-soluble starch, polyacrylic acid (e.g., Carbomer), polymethacrylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbophil, a salt of ascorbic acid palmitic acid and the like, and hydroxypropylmethyl cellulose, polyacrylic acid, alginic acid salt, gelatin, carboxymethyl cellulose, polyvinyl pyrrolidone, polyethylene glycol and the like are preferred. Hydroxypropylmethyl cellulose is particularly preferred. Examples of the stabilizer include cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like, and in particular, citric acid and ascorbic acid are preferred.

The sublingual tablet, buccal or intraoral quick disintegrant preparation can be produced by mixing the androgen receptor antagonist of the present invention or the concomitant drug with an excipient by a method known per se. Furthermore, the auxiliary agents such as a glidant, isotonicity agent, hydrophilic carrier, water dispersible polymer, stabilizer, colorant, sweetener, antiseptic and the like may be mixed if desired. The components are mixed simultaneously or with some time intervals, followed by pressure tablet molding to obtain a sublingual tablet, a buccal tablet or an intraoral quick disintegrant tablet. In order to obtain an appropriate hardness, a solvent such as water and alcohol can be used

before or after tablet molding so as to give humidification or moistness, and the mixture can be dried after molding.

In the case of molding into a mucosa film, the androgen receptor antagonist of the present invention or the concomitant drug, the above-mentioned water dispersible polymer (preferably, hydroxypropyl cellulose, hydroxypropylmethyl cellulose), an excipient and the like are dissolved in a solvent such as water, and the obtained solution is cast to prepare a film. Further, additives such as plasticizer, stabilizer, antioxidant, preservative, colorant, buffering agent, sweetener and the like may be added. In order to provide a film with a proper elasticity, glycols such as polyethylene glycol and propylene glycol may be contained, and in order to increase adhesiveness of a film onto oral mucosa lining, a biological adhesive polymer (e.g., polycarbophil and Carbopol) may be contained. The casting is conducted by pouring a solution onto a non-adhesive surface, spreading it to a uniform thickness (preferably about 10 to 1000 micron) with an applicator such as a doctor blade, followed by drying the solution to prepare a film. The thus formed film is then dried at room temperature or under warm, and cut into an intended surface area.

As a preferable intraoral quick disintegrant preparation, a solid quick diffusion preparation is exemplified, which comprises a dictyosome of the androgen receptor antagonist of the present invention or the concomitant drug and a water-soluble or water diffusive carrier that is inert to the androgen receptor antagonist of the present invention or the concomitant drug. The dictyosome can be obtained by sublimation of a solvent from the solid composition which is composed of a solution wherein the androgen receptor antagonist of the present invention or the concomitant drug is dissolved in a suitable solvent.

In the composition of the intraoral quick disintegrant preparation, a matrix forming agent and a secondary component are preferably contained in addition to the androgen receptor antagonist of the present invention or the concomitant drug.

Examples of the matrix forming agent include gelatins, dextrans, and animal or vegetable proteins such as soy bean, wheat and psyllium; rubber substances such as gum arabic, guar gum, agar and xanthan; polysaccharide; alginic acids; carboxymethylcellulose; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; substances derived from gelatin-gum arabic complex and the like. In addition, saccharide such as mannitol, dextrose, lactose, galactose and trehalose; cyclic saccharide such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate; and amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxy proline, L-isoleucine, L-leucine, and L-phenylalanine are contained.

One or more of the matrix forming agent can be introduced into a solution or suspension before solidification. Such matrix forming agents may exist with or without a surfactant. The matrix forming agent can support maintaining the dispersed condition of the androgen receptor antagonist of the present invention or the concomitant drug in the solution or suspension, in addition to forming a matrix.

The composition may contain secondary components such as preservative, antioxidant, surfactant, thickener, colorant, pH adjustor, condiment, sweetener or taste-masking agent. Examples of the adequate colorant include red, black and yellow iron oxides, and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 manufactured by ELLIS AND EBERALD. Examples of the adequate condiment include mint, raspberry, licorice, orange, lemon,

grapefruit, caramel, vanilla, cherry, grape flavor and the combination thereof. Examples of the adequate pH adjustor include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the
5 adequate sweetener include aspartame, acesulfame K, thaumatin and the like. Examples of the adequate taste masking agent include sodium bicarbonate, ion-exchange resins, cyclodextrin clathrate compounds, absorptive substances and microcapsuled apomorphine.

10 The preparation contains usually about 0.1 to about 50% by weight, preferably about 0.1 to about 30% by weight of the androgen receptor antagonist of the present invention or the concomitant drug, and said preparation is preferably a preparation (the aforementioned sublingual
15 tablet, buccal etc.) in which 90% or more of the androgen receptor antagonist of the present invention or the concomitant drug can be dissolved (in water) within about 1 to about 60 min, preferably about 1 to about 15 min, and more preferably about 2 to about 5 min, and an intraoral
20 quick disintegrant preparation that disintegrates within 1 to 60 seconds, preferably 1 to 30 seconds, and more preferably 1 to 10 seconds once the preparation is put in the mouth.

The content of the above-mentioned excipient is about
25 10 to about 99% by weight, and preferably about 30 to about 90% by weight based on the total amount of the preparation. The content of β -cyclodextrin or β -cyclodextrin derivative is 0 to about 30% by weight based on the total amount of the preparation. The content of the glidant is about 0.01
30 to about 10% by weight, and preferably about 1 to about 5% by weight based on the total amount of the preparation. The content of the isotonicity agent is about 0.1 to about 90% by weight, and preferably about 10 to about 70% by weight based on the total amount of the preparation. The
35 content of the hydrophilic carrier is about 0.1 to about

50% by weight, and preferably about 10 to about 30% by weight based on the total amount of the preparation. The content of the water dispersible polymer is about 0.1 to about 30% by weight, and preferably about 10 to about 25% by weight based on the total amount of the preparation. The content of the stabilizer is about 0.1 to about 10% by weight, and preferably about 1 to about 5% by weight based on the total amount of the preparation. The preparation may further contain additives such as colorant, sweetener and antiseptic.

The dosage of the concomitant agent of the present invention differs depending on a kind of compound (I), age, body weight, symptom, dosage form, dosing method, dosing period and the like, however, for example, usually about 0.01 to about 1000 mg/kg, preferably about 0.01 to about 100 mg/kg, more preferably about 0.1 to about 100 mg/kg, particularly preferably about 0.1 to about 50 mg/kg, inter alia about 1.5 to about 30 mg/kg in terms of the androgen receptor antagonist of the present invention or the concomitant drug is intravenously administered daily in one to several divided doses to one patient suffering prostate cancer (adult, body weight: about 60 kg). As mentioned above, since the dosage varies depending on various conditions, less dosage may be enough in some cases, while dosage beyond the above range may be necessary in some cases.

The amount of the concomitant drug can be determined arbitrarily as long as no side effects become problematic. The daily dose as the concomitant drug differs depending on a degree of symptom, target age, sex, body weight, difference of sensitivity, dosing period, interval, properties of pharmaceutical preparation, preparation, kind, kind of active ingredient and the like, and is not particularly limited, however, it is usually about 0.001 to 2000 mg, preferably about 0.01 to 500 mg, and more

preferably about 0.1 to 100 mg per 1 kg body weight of a mammal in oral administration, and the amount is usually administered daily in 1 to 4 divided doses.

5 In case of administering the concomitant agent of the present invention, both preparations can be administered simultaneously, or after administering the concomitant drug first, the androgen receptor antagonist of the present invention may be administered, or after administering the androgen receptor antagonist of the present invention first,
10 the concomitant drug may be administered. When they are administered with some intervals, the time difference differs depending on an active ingredient to be administered, dosage form and administration method. For example, when the concomitant drug is administered first,
15 the androgen receptor antagonist of the present invention may be administered within 1 min to 3 days, preferably 10 min to 1 day, and more preferably 15 min to 1 hr after the concomitant drug is administered. When the androgen receptor antagonist of the present invention is
20 administered first, the concomitant drug may be administered within 1 min to 1 day, preferably 10 min to 6 hr, and more preferably 15 min to 1 hr after the androgen receptor antagonist of the present invention is administered.

25 As a preferable administration method, for example, about 0.001 to 200 mg/kg of the concomitant drug formulated into an oral preparation is orally administered, then after about 15 min, about 0.005 to 100 mg/kg as a daily dose of the androgen receptor antagonist of the present invention
30 formulated into an oral preparation is administered orally.

EXAMPLES

The present invention will be described in more detail by way of Reference Examples, Examples, Formulation
35 Examples and Test Examples, but is not limited thereto.

"Room temperature" usually means about 10 to about 35°C in Reference Examples. "%" denotes weight percentage unless otherwise specified. Provided that yield denotes mol/mol%.

5 NMR spectrum is proton NMR and was measured by a 200 MHz or 300 MHz spectrometer using tetramethylsilane as an internal standard, and the δ value was expressed by ppm.

In the present specification, the melting point means a melting point measured by a Micro melting point meter
10 (Model B-545, Buchi, manufactured by Yanaco Analytical Instruments Corp.) or differential scanning calorimeter (DSC, SEIKO, EXSTAR6000).

Generally, the melting point occasionally varies depending on measuring equipments and measuring conditions.
15 A crystal in the present specification may be a crystal which exhibits a melting point different from that described in the present specification if it is within a usual error range.

Other abbreviations used in the present specification
20 have the following meanings:

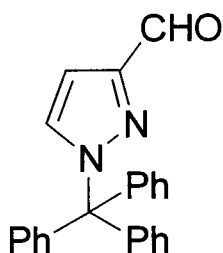
s: singlet
brs: broad singlet
d: doublet
t: triplet
25 q: quartet
dd: double doublet
ddd: double double doublet
dt: double triplet
td: triple doublet
30 m: multiplet
br: broad
CDCl₃: deuterated chloroform
DMSO-d₆: deuterated dimethyl sulfoxide
¹H-NMR: proton nuclear magnetic resonance
35 Me: methyl

Et: ethyl
i-Pr: isopropyl
boc: tert-butyloxycarbonyl
THF: tetrahydrofuran
5 TFA: trifluoroacetic acid
AIBN: 2,2'-azobis(isobutyronitrile)
DMF: N,N-dimethylformamide
NMP: N-methylpyrrolidone
NBS: N-bromosuccinimide

10

[Reference Example 1]

1-Trityl-1H-pyrazole-3-carboxyaldehyde

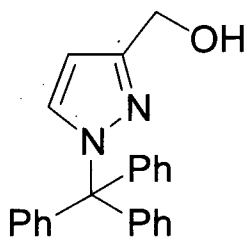


15 1H-Pyrazole-3-carboxyaldehyde (5.31 g) was dissolved
in DMF (50 ml) and potassium carbonate (13.8 g) and
triphenylchloromethane (15.62 g) were added thereto. The
reaction solution was stirred at room temperature for 40 hr,
diluted with water and extracted with ethyl acetate. The
organic layer was washed with water, then saturated brine,
20 dried over anhydrous magnesium sulfate, and concentrated.
The resulting residue was washed with diisopropylether to
obtain the titled compound (10.85 g) as colorless crystals.
¹H-NMR (CDCl₃) δ: 6.78 (1H, d), 7.11-7.35 (15H, m), 7.39
(1H, d), 9.97 (1H, s).

25

[Reference Example 2]

(1-Trityl-1H-pyrazol-3-yl)methanol

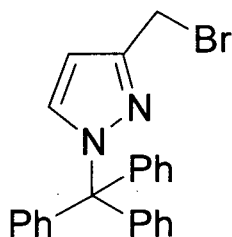


The compound (10.00 g) obtained in Reference Example 1 was suspended in methanol (100 ml) and THF (100 ml). The mixture was cooled to 0°C and sodium borohydride (1.10 g) was added thereto. The reaction solution was stirred at the same temperature for 30 min and concentrated, and then water was added to the residue. The precipitate was collected by filtration and then washed sequentially with water, 2-propanol and diisopropylether to obtain the titled compound (9.40 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.97 (1H, t), 4.69 (2H, d), 6.22 (1H, d), 7.11-7.32 (16H, m).

[Reference Example 3]

3-(Bromomethyl)-1-trityl-1H-pyrazole

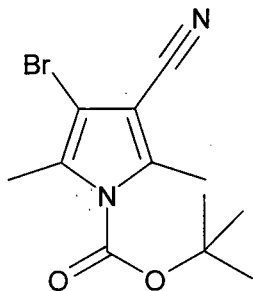


A mixture of the compound (2.72 g) obtained in Reference Example 2, triphenylphosphine (2.30 g) and dichloromethane (30 ml) was cooled with an ice bath and NBS (1.57 g) was added thereto. After the reaction mixture was stirred at room temperature for 30 min, saturated aqueous solution of sodium bicarbonate was added to the mixture and the dichloromethane layer was separated. The dichloromethane layer was purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (2.00 g).

¹H-NMR (CDCl₃) δ: 4.52 (2H, s), 6.30 (1H, d), 7.11-7.35 (16H, m).

[Reference Example 4]

tert-Butyl 3-bromo-4-cyano-2,5-dimethyl-1H-pyrrole-1-carboxylate

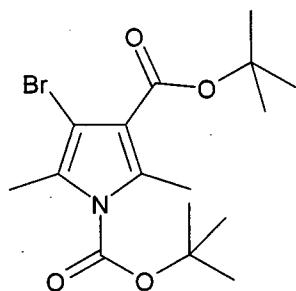


5 A solution of 3-bromo-4-cyano-2,5-dimethyl-1H-pyrrole (1.94 g), di-tert-butyl dicarbonate (1.61 ml) and 4-dimethylaminopyridine (0.86 g) in acetonitrile (12 ml) was stirred at room temperature for 20 hr. To the reaction mixture was added saturated brine (20 ml), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was crystallized from ether and ethyl acetate to obtain the objective product (2.76 g) as crystals.

15 ¹H-NMR (CDCl₃) δ: 1.62 (9H, s), 2.37 (3H, s), 2.56 (3H, s).

In the same manner as in Reference Example 4, the following compounds were obtained.

di-tert-Butyl 4-bromo-2,5-dimethyl-1H-pyrrole-1,3-dicarboxylate

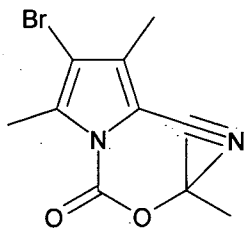


20

¹H-NMR (CDCl₃) δ: 1.57 (9H, s), 1.60 (9H, s), 2.36 (3H, s), 2.61 (3H, s).

tert-Butyl 3-bromo-5-cyano-2,4-dimethyl-1H-pyrrole-1-

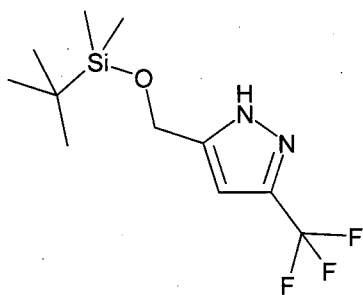
carboxylate



$^1\text{H-NMR}$ (CDCl_3) δ : 1.65 (9H, s), 2.20 (3H, s), 2.50 (3H, s).

[Reference Example 5]

5 5-([tert-Butyl(dimethyl)silyl]oxy)methyl)-3-(trifluoromethyl)-1H-pyrazole

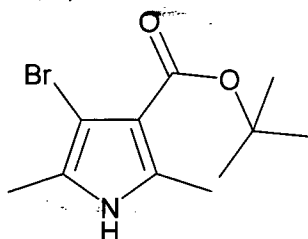


To a solution of [3-(trifluoromethyl)-1H-pyrazol-5-yl]methanol (19.1 g) synthesized by a known method in THF
 10 (230 ml) were added 4-dimethylaminopyridine (1.41 g), triethylamine (14.0 g) and tert-butyl(dimethyl)silyl chloride (18.2 g), and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The
 15 ethyl acetate layer was dried over anhydrous magnesium sulfate and then concentrated to obtain the objective product (35.9 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.13 (6 H, s), 0.93 (9 H, s), 4.81 (2 H, s), 6.35 (1H, s).

20 [Reference Example 6]

tert-Butyl 4-bromo-2,5-dimethyl-1H-pyrrole-3-carboxylate

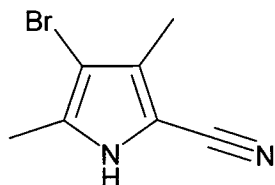


A solution of tert-butyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (9.65 g) and NBS (9.24 g) in DMF (50 ml) was stirred at room temperature for 2 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain the objective product (10.6 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.57 (9H, s), 2.18 (3H, s), 2.44 (3H, s), 8.20 (1H, s).

[Reference Example 7]

4-Bromo-3,5-dimethyl-1H-pyrrole-2-carbonitrile



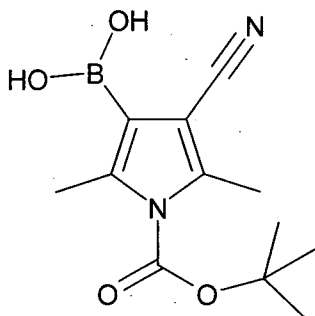
A solution of 4-bromo-3,5-dimethyl-1H-pyrrole-2-carboxylic acid (6.56 g) and N,N-carbonyldiimidazole (5.86 g) in THF (50 ml) was stirred at 0°C for 30 min, and ammonia water was added thereto, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into saturated brine (100 ml), and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. To a solution of the residue and pyridine (10 ml) in DMF (100 ml) was added oxalyl chloride (5.2 ml) under ice cooling, and the reaction mixture was stirred at room temperature for 1 hr. To the reaction

mixture were added ethyl acetate and sodium bicarbonate solution, and the layers were separated. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and then crystallized from diethylether to obtain the objective product (3.59 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.17 (3H, s), 2.26 (3H, s), 8.72 (1H, s).

[Reference Example 8]

[1-(tert-Butoxycarbonyl)-4-cyano-2,5-dimethyl-1H-pyrrol-3-yl]boronic acid



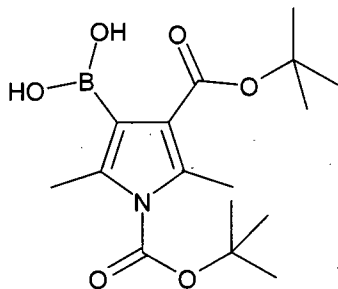
To a solution of tert-butyl 3-bromo-4-cyano-2,5-dimethyl-1H-pyrrole-1-carboxylate (5.0 g) in THF (75 ml) was added dropwise a solution of butyllithium in hexane (1.6 mol/l, 12.5 ml) at -78°C . The reaction mixture was stirred at the same temperature for 30 min, and a solution of trimethyl borate (20 ml) in THF (210 ml) was added thereto, and the mixture was stirred for 1 hr. To the reaction mixture was added a mixture of water (20 ml) and methanol (20 ml), and the mixture was allowed to warm to room temperature. To the reaction mixture was added saturated brine (100 ml), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from ether and ethyl acetate to obtain the objective product (4.93 g) as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.6-1.7 (2H, br s), 1.64 (9H, s), 2.54

(3H, s), 2.60 (3H, s).

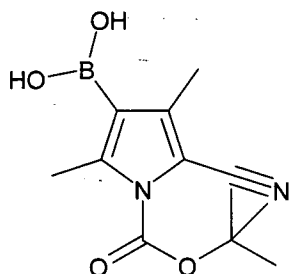
In the same manner as in Reference Example 8, the following compounds were obtained.

[1,4-Bis(tert-butoxycarbonyl)-2,5-dimethyl-1H-pyrrol-3-yl]boronic acid



¹H-NMR (CDCl₃) δ: 1.58 (9H, s), 1.62 (9H, s), 2.54 (3H, s), 2.58 (3H, s), 7.40 (2H, s).

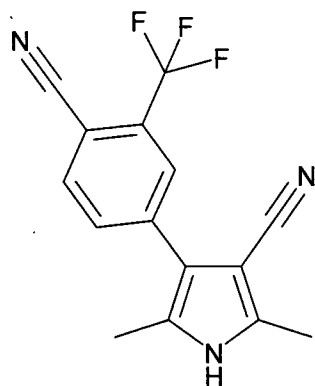
[1-(tert-Butoxycarbonyl)-5-cyano-2,4-dimethyl-1H-pyrrol-3-yl]boronic acid



¹H-NMR (CDCl₃) δ: 1.58 (9H, s), 2.19 (3H, s), 2.50 (3H, s), 7.93 (1H, s).

[Reference Example 9]

4-[4-Cyano-3-(trifluoromethyl)phenyl]-2,5-dimethyl-1H-pyrrole-3-carbonitrile

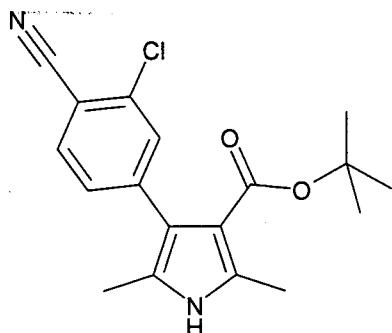


A mixture of [1-(tert-butoxycarbonyl)-4-cyano-2,5-dimethyl-1H-pyrrol-3-yl]boronic acid (6.0 g), 4-bromo-2-(trifluoromethyl)benzonitrile (5.68 g), potassium fluoride (4.62 g), tri-tert-butylphosphine (0.36 mol/l hexane solution, 3.2 ml), tris(dibenzylideneacetone)dipalladium (0.42 g) and THF (50 ml) was stirred at room temperature for 20 hr. To the reaction mixture was added saturated brine (100 ml), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain tert-butyl 3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-1-carboxylate (4.00 g) as crystals. A mixture of the obtained tert-butyl 3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-1-carboxylate (4.00 g), potassium carbonate (3.55 g), water (30 ml) and DMF (30 ml) was stirred at 70°C for 1 hr. The reaction mixture was combined with saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate to obtain the titled compound (2.74 g).

¹H-NMR (CDCl₃) δ: 2.34 (3H, s), 2.46 (3H, s), 7.7 - 7.8 (2H, m), 7.88 (1H, d), 8.25 (1H, br s).

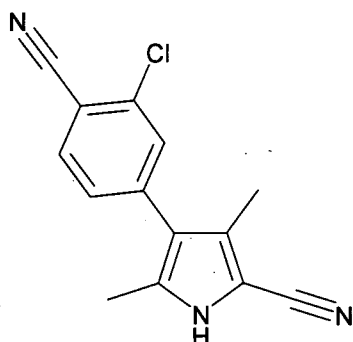
In the same manner as in Reference Example 9, the following compounds were obtained.

tert-Butyl 4-(3-chloro-4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate



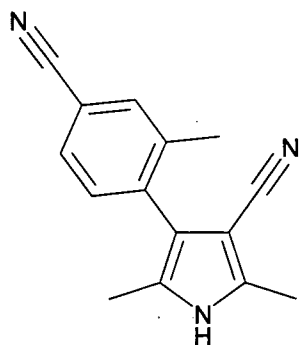
$^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (9H, s), 2.12 (3H, s), 2.50 (3H, s), 7.21 - 7.26 (1H, m), 7.39 (1H, d), 7.62 (1H, d), 8.08 (1H, s).

- 5 4-(3-Chloro-4-cyanophenyl)-3,5-dimethyl-1H-pyrrole-2-carbonitrile



$^1\text{H-NMR}$ (CDCl_3) δ : 2.20 (3H, s), 2.29 (3H, s), 7.33 - 7.40 (2H, m), 7.71 (1H, d), 8.60 (1H, s).

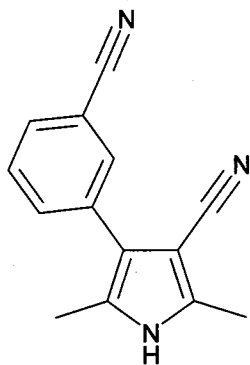
- 10 4-(4-Cyano-2-methylphenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile



$^1\text{H-NMR}$ (CDCl_3) δ : 2.07 (3H, s), 2.28 (3H, s), 2.44 (3H, s), 7.2-7.4 (1H, m), 7.4-7.55 (1H, m), 7.55-7.7 (1H, m), 8.20 (1H, s).

[Reference Example 10]

4-(3-Cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile

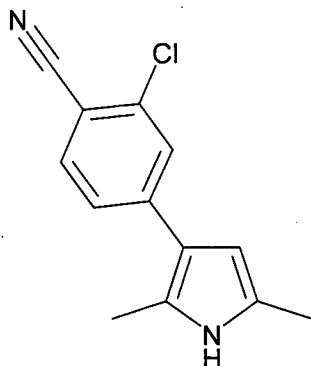


A mixture of 3-bromo-4-cyano-2,5-dimethyl-1H-pyrrole
5 (2.45 g), 3-cyanophenylboronic acid (2.16 g),
tetrakis(triphenylphosphine)palladium (0.60 g), anhydrous
potassium carbonate (3.90 g), DMF (90 ml) and water (12 ml)
was heated at 130°C for 20 hr, and then cooled to room
temperature. To the reaction mixture was added saturated
10 brine (100 ml), and the mixture was extracted with ethyl
acetate. The ethyl acetate layer was washed with saturated
brine, dried over anhydrous magnesium sulfate and
concentrated. The residue was purified by silica gel
column chromatography (ethyl acetate-hexane), and
15 crystallized from ethyl acetate to obtain the objective
product (0.91 g) as crystals.

¹H-NMR (CDCl₃) δ: 2.29 (3H, s), 2.41 (3H, s), 7.4-7.5 (2H,
m), 7.6-7.8 (2H, m), 8.30 (1H, br s).

[Reference Example 11]

20 2-Chloro-4-(2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile

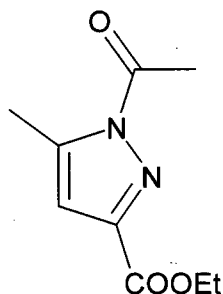


A mixture of tert-butyl 4-(3-chloro-4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (2.4 g) and TFA (10 ml) was stirred at room temperature for 4 hr. To the reaction solution were added an aqueous saturated sodium bicarbonate solution and ethyl acetate, and separated the layers. The organic layer was washed with saturated brine, dried over (anhydrous magnesium sulfate) and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (0.72 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.26 (3H, s), 2.40 (3H, s), 6.02 (1H, d), 7.34 (1H, dd), 7.50 (1H, d), 7.59 (1H, d), 7.83 (1H, s).

[Reference Example 12]

Ethyl 1-acetyl-5-methyl-1H-pyrazole-3-carboxylate

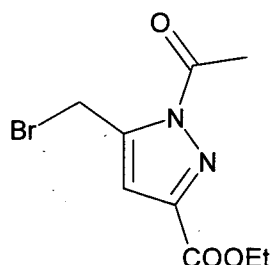


To a solution of ethyl 3-methyl-1H-pyrazole-5-carboxylate (3.08 g) in pyridine (40 ml) was added acetic anhydride (3.06 g), and the mixture was stirred at 60°C for 15 hr. After concentrating the reaction mixture, the residue was partitioned with ethyl acetate-water, and the organic layer was washed with diluted hydrochloric acid, an aqueous diluted solution of sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The crystals precipitated from the residue were pulverized in hexane and then filtered to obtain the objective product (2.51 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (3H, t), 2.61 (3H, d), 2.78 (3H, s), 4.22 (2H, q), 6.61 (1H, d).

[Reference Example 13]

Ethyl 1-acetyl-5-(bromomethyl)-1H-pyrazole-3-carboxylate

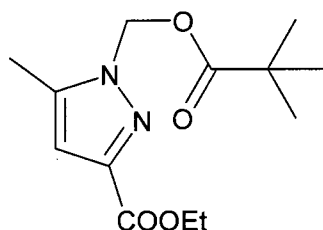


To a solution of ethyl 1-acetyl-5-methyl-1H-pyrazole-3-carboxylate (2.35 g) in carbon tetrachloride (72 ml) were added NBS (2.46 g) and AIBN (197 mg) and the mixture was refluxed for 13 hr. The precipitate was removed by filtration and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (2.23 g) as an amorphous powder.

¹H-NMR (CDCl₃) δ: 1.41 (3H, t), 2.81 (3H, s), 4.43 (2H, q), 4.82 (2H, s), 6.97 (1H, s).

[Reference Example 14]

Ethyl 1-[[[(2,2-dimethylpropanoyl)oxy]methyl]-5-methyl-1H-pyrazole-3-carboxylate



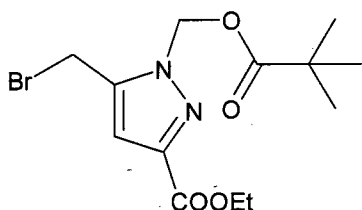
Under an argon atmosphere, to a solution of ethyl 3-methyl-1H-pyrazole-5-carboxylate (7.71 g) in dehydrated DMF (150 ml) was added sodium hydride (60% dispersion in oil, 2.3 g) under ice cooling, and the mixture was stirred for 30 min. Then, a solution of chloromethyl pivalate (8.66 g) in DMF (10 ml) was added to the mixture, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The

residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (9.2 g) as an oil.

¹H-NMR (CDCl₃) δ: 1.19 (9H, s), 1.39 (3H, t), 2.36 (3H, s),
 4.40 (2H, q), 6.04 (2H, s), 6.59 (1H, s).

[Reference Example 15]

Ethyl 5-(bromomethyl)-1-[[2,2-dimethylpropanoyl]oxy]methyl}-1H-pyrazole-3-carboxylate

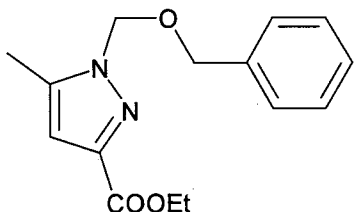


To a solution of ethyl 1-[[2,2-dimethylpropanoyl]oxy]methyl}-5-methyl-1H-pyrazole-3-carboxylate (4.03 g) in carbon tetrachloride (90 ml) were added NBS (3.07 g) and AIBN (246 mg), and the mixture was refluxed for 3 hr. The precipitate was removed by
 filtration, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (3.79 g) as an oil.

¹H-NMR (CDCl₃) δ: 1.20 (9H, s), 1.40 (3H, t), 4.41 (2H, q), 4.62 (2H, s), 6.15 (2H, s), 6.85 (1H, s).

[Reference Example 16]

Ethyl 1-[(benzyloxy)methyl]-5-methyl-1H-pyrazole-3-carboxylate

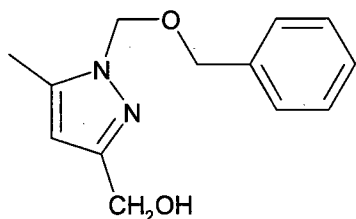


Under an argon atmosphere, to a solution of ethyl 3-methyl-1H-pyrazole-5-carboxylate (7.71 g) in dehydrated DMF (150 ml) was added sodium hydride (60% dispersion in oil, 2.3 g) under ice cooling, and the mixture was stirred for

30 min. Then, a solution of benzyl chloromethyl ether (9.0 g) in DMF (10 ml) was added to the mixture, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (5.2 g) as an oil.

¹H-NMR (CDCl₃) δ: 1.40 (3H, t), 2.38 (3H, s), 4.41 (2H, q), 4.51 (2H, s), 5.58 (2H, s), 6.61 (1H, s), 7.25-7.35 (5H, m).
[Reference Example 17]

{1-[(Benzyloxy)methyl]-5-methyl-1H-pyrazol-3-yl}methanol

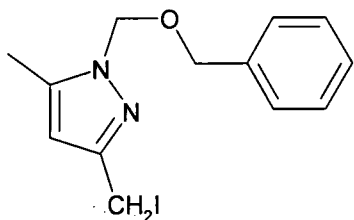


Under an argon atmosphere, to a suspension of lithium aluminum hydride (680 mg) in dehydrated THF (35.9 ml) was added a solution of ethyl 1-[(benzyloxy)methyl]-5-methyl-1H-pyrazole-3-carboxylate (4.92 g) in dehydrated THF (25 ml) at 10°C or lower under stirring and ice-cooling, and the mixture was stirred at the same temperature for 10 min and further at room temperature for 2.5 hr. After ice cooling again, the reaction was quenched by adding an aqueous saturated sodium sulfate solution. The reaction mixture was neutralized with 1N hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated to obtain the objective product (4.05 g) as an oil. The resulting product was used for the following process without further purification.

¹H-NMR (CDCl₃) δ: 2.26 (1H, t), 2.33 (3H, s), 4.50 (2H, s), 4.65 (2H, d), 5.44 (2H, s), 6.08 (1H, s), 7.25-7.37 (5H, m).

[Reference Example 18]

1-[(benzyloxy)methyl]-3-(iodomethyl)-5-methyl-1H-pyrazole

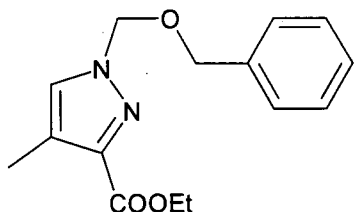


To a solution of {1-[(benzyloxy)methyl]-5-methyl-1H-pyrazol-3-yl}methanol (3.82 g) in ethyl acetate (164 ml) was added diisopropylethylamine (8.5 ml) under ice cooling and stirring, and methanesulfonyl chloride (2.55 ml) was added to the mixture, and the mixture was stirred for 1 hr. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. To a solution of the residue in acetone (164 ml) was added sodium iodide (24.64 g), and the mixture was refluxed for 1.5 hr. After concentrating the reaction mixture, the residue was partitioned with ethyl acetate-water, and the organic layer was washed with an aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain the objective product (5.55 g) as an oil. The resulting product was used for the following process without further purification.

¹H-NMR (CDCl₃) δ: 2.30 (3H, s), 4.37 (2H, s), 4.49 (2H, s), 5.42 (2H, s), 6.12 (1H, s), 7.24-7.40 (5H, m).

[Reference Example 19]

Ethyl 1-[(benzyloxy)methyl]-4-methyl-1H-pyrazole-3-carboxylate

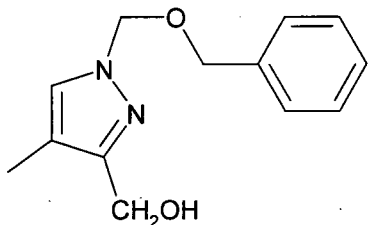


Under an argon atmosphere, to a solution of ethyl 4-methyl-1H-pyrazole-3-carboxylate (4.62 g) in dehydrated DMF (90 ml) was added sodium hydride (60% dispersion in oil, 1.38 g) under ice cooling, and the mixture was stirred for 30 min. Then, a solution of benzyl chloromethyl ether (5.4 g) in DMF (5 ml) was added thereto, and the mixture was stirred at room temperature for 2.5 hr. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over aqueous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (3.25 g) as an oil.

¹H-NMR (CDCl₃) δ: 1.42 (3H, t), 2.31 (3H, s), 4.42 (2H, q), 4.52 (2H, s), 5.52 (2H, s), 7.23-7.37 (5H, m), 7.42 (1H, s).

[Reference Example 20]

{1-[(Benzyloxy)methyl]-4-methyl-1H-pyrazol-3-yl}methanol



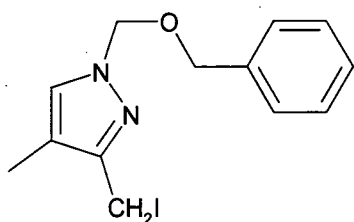
Under an argon atmosphere, to a suspension of lithium aluminum hydride (408 mg) in dehydrated THF (21.5 ml) was added a solution of ethyl 1-[(benzyloxy)methyl]-4-methyl-1H-pyrazole-3-carboxylate (2.95 g) in dehydrated THF (15 ml) at 10°C or below with stirring under ice cooling, and the mixture was stirred at the same temperature for 10 min and further at room temperature for 2 hr. After the reaction mixture was ice-cooled again, the reaction was quenched by adding an aqueous saturated sodium sulfate solution to the mixture, and the mixture was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over aqueous sodium sulfate, and concentrated to

obtain the objective product (2.56 g) as an oil. The resulting product was used for the following process without further purification.

¹H-NMR (CDCl₃) δ: 2.09 (3H, s), 2.10 (1H, br s), 4.51 (2H, s), 4.67 (2H, d), 5.40 (2H, s), 7.25-7.40 (6H, m).

[Reference Example 21]

1-[(Benzyloxy)methyl]-3-(iodomethyl)-4-methyl-1H-pyrazole

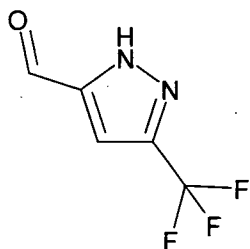


To a solution of {1-[(benzyloxy)methyl]-4-methyl-1H-pyrazol-3-yl}methanol (2.40 g) in ethyl acetate (103 ml) was added diisopropylethylamine (8.5 ml), and then methanesulfonyl chloride (2.55 ml) under ice cooling with stirring, the mixture was stirred for 1 hr. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. To a solution of the residue in acetone (103 ml) was added sodium iodide (15.48 g), and the mixture was refluxed for 1.5 hr. After concentrating the mixture, the residue was partitioned with ethyl acetate-water, and the organic layer was washed with an aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain the objective product (3.38 g) as an oil. The resulting product was used for the following process without further purification.

¹H-NMR (CDCl₃) δ: 2.05 (3H, s), 4.39 (2H, s), 4.49 (2H, s), 5.37 (2H, s), 7.24-7.39 (6H, m).

[Reference Example 22]

3-(Trifluoromethyl)-1H-pyrazole-5-carbaldehyde

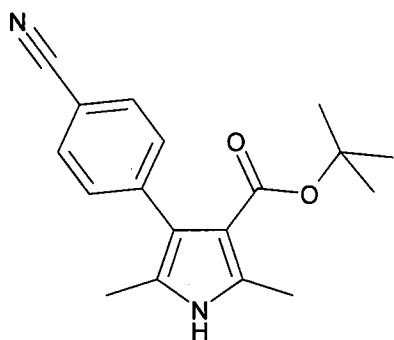


A mixture of [3-(trifluoromethyl)-1H-pyrazol-5-yl]methanol (15.0 g), manganese dioxide (150 g) and DMF (200 ml) was stirred at 60°C for 14 hr. To the reaction mixture was added saturated brine, and insolubles were removed by filtration. After extracting the filtrate with ethyl acetate, the extracted solution was washed with saturated brine, dried, and concentrated. The resulting residue was suspended in diisopropylether-hexane, and filtered to obtain the titled compound (9.75 g) as a colorless powder.

¹H NMR (DMSO-d₆) δ: 7.50 (1H, s), 9.88 (1H, s), 14.94 (1H, s).

[Reference Example 23]

tert-Butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate



A solution of potassium hydroxide (10.44 g) and tert-butyl acetoacetate (63.2 ml) in anhydrous THF (350 ml) was stirred at room temperature for 30 min, and 4-[(1E)-2-nitroprop-1-en-1-yl]benzonitrile (35.0 g) was added by several portions to the reaction solution under ice cooling with stirring over 30 min. After 30 min, the reaction solution was poured into saturated brine (200 ml), and

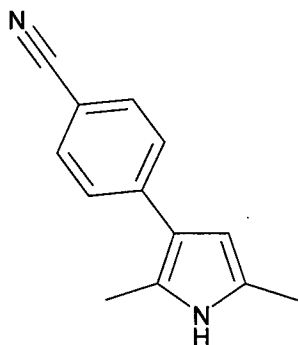
extracted with ethyl acetate (200 ml). The organic layer was washed with saturated brine (200 ml), and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was used

To the residue were added methanol (100 ml), water (14.2 ml) and TFA (14.2 ml), and the mixture was stirred at 75 to 78°C for 1 hr. The reaction solution was cooled to room temperature, and the solvent was distilled off under reduced pressure. The resulting residue was diluted with ethyl acetate (250 ml), and washed sequentially with water (300 ml), saturated aqueous sodium bicarbonate solution (200 ml $\times$ 2) and saturated brine (50 ml). After drying the solution over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure, and the objective product (23.7 g) was solidified as crystals. The product was filtered, washed with a small amount of diisopropylether, and dried.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.30(9H, s), 2.10(3H, s), 2.50(3H, s), 7.33(2H, d), 7.61(2H, d), 8.07(1H, s).

[Reference Example 24]

4-(2,5-Dimethyl-1H-pyrrol-3-yl)benzonitrile



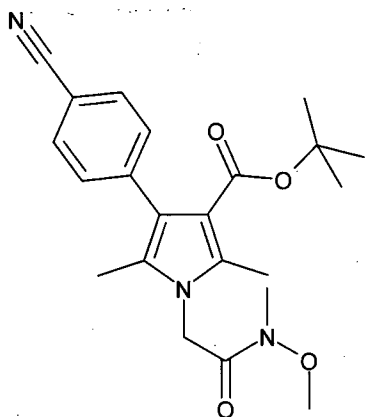
A mixture of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (20.1 g) and TFA (50 ml) was stirred at room temperature for 3 hr. The residue obtained by concentrating the reaction solution was diluted with ethyl acetate, washed with a sodium bicarbonate

solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (6.83 g) as crystals.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.27 (3H, s), 2.40 (3H, s), 6.04 (1H, d), 7.46 (2H, d), 7.61 (2H, d), 7.76 (1H, br s).

[Reference Example 25]

tert-Butyl 4-(4-cyanophenyl)-1-{2-[methoxy(methyl)amino]-2-oxoethyl}-2,5-dimethyl-1H-pyrrole-3-carboxylate



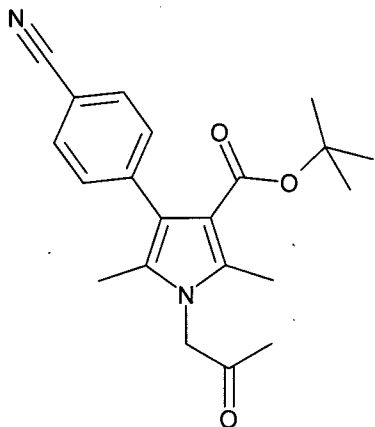
To a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (0.60 g) in DMF (15 ml) was added sodium hydride (60% dispersion in oil, 0.10 g) under ice cooling. The reaction mixture was stirred at room temperature for 30 min, and 2-chloro-N-methoxy-N-methylacetamide (0.33 g) was added to the mixture, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine, and extracted with ethyl acetate, and the ethyl acetate layer was dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective compound (637 mg) as a solid.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 2.01 (3H, s), 2.48 (3H, s), 3.25 (3H, s), 3.80 (3H, s), 4.76 (2 H, s), 7.34 (2 H, d), 7.61 (2 H, d).

[Reference Example 26]

tert-Butyl 2,5-dimethyl-1-(2-oxopropyl)-4-phenyl-1H-

pyrrole-3-carboxylate

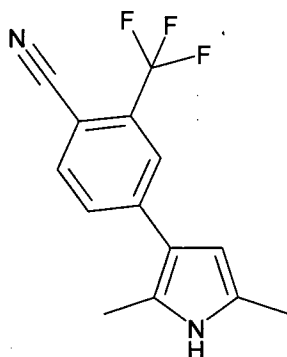


To a solution of tert-butyl 4-(4-cyanophenyl)-1-{2-[methoxy(methyl)amino]-2-oxoethyl}-2,5-dimethyl-1H-pyrrole-3-carboxylate (0.60 g) in THF (15 ml) was added dropwise methylmagnesium bromide (3 mol/l diethyl ether solution) under ice cooling, and the mixture was stirred at 0°C for 30 min and further at room temperature for 30 min. Then, the reaction mixture was added dropwise to ice water. To the reaction mixture was added citric acid, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective compound (637 mg) as a solid.

¹H-NMR (CDCl₃) δ: 1.96 (3H, s), 2.21 (3H, s), 2.44 (3H, s), 4.62 (2 H, s), 7.33 (2 H, d), 7.63 (2 H, d).

[Reference Example 27]

4-(2,5-Dimethyl-1H-pyrrol-3-yl)-2-(trifluoromethyl)benzonitrile

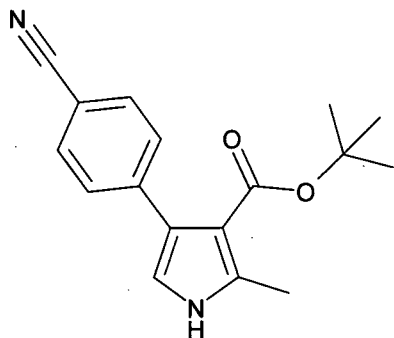


A mixture of [1,4-bis(tert-butoxycarbonyl)-2,5-dimethyl-1H-pyrrol-3-yl]boronic acid (7.7 g), 4-bromo-2-(trifluoromethyl)benzonitrile (7.38 g), potassium fluoride (4.62 g), tri-tert-butylphosphine (0.36 mol/l hexane solution, 3.2 ml), tris(dibenzylideneacetone)dipalladium (0.42 g) and THF (50 ml) was stirred at room temperature for 20 hr. To the reaction mixture was added saturated brine (100 ml). After extracting with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. A mixture of the residue and TFA (10 ml) was stirred at room temperature for 6 hr. To the reaction solution, aqueous saturated sodium bicarbonate solution and ethyl acetate were added, and the layers were separated. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (148 mg) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.27 (3H, s), 2.42 (3H, s), 6.07 (1H, d), 7.59 - 7.67 (1H, m), 7.72 - 7.80 (2H, m), 7.85 (1H, s).

[Reference Example 28]

tert-Butyl 4-(4-cyanophenyl)-2-methyl-1H-pyrrole-3-carboxylate

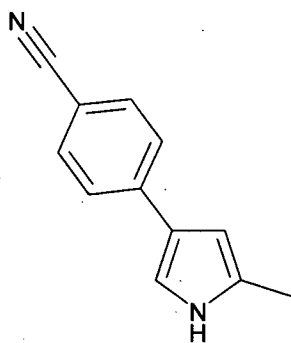


To a solution of 4-[(E)-2-nitrovinyl]benzonitrile (11.47 g) synthesized by a known method and tert-butyl acetoacetate (11.47 ml) in methanol (18 ml) was added sodium methoxide (918 mg), and the mixture was stirred at room temperature for 20 min. To the reaction solution, a 2M ammonia-methanol solution (180 ml) was added, and the mixture was stirred at room temperature for 20 hr. The reaction solution was concentrated, and the residue was partitioned with ethyl acetate and an aqueous 10% citric acid solution. The organic layer was washed with an aqueous 10% citric acid solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was washed with diisopropyl ether to obtain the objective product (4.49 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (9H, s), 2.53 (3H, s), 6.60-6.61 (1H, m), 7.45-7.48 (2H, m), 7.58-7.61 (2H, m), 8.33 (1H, s).

[Reference Example 29]

4-(4-Cyanophenyl)-2-methyl-1H-pyrrole



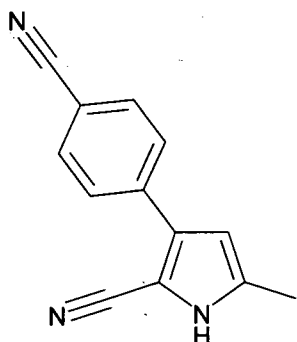
To tert-butyl 4-(4-cyanophenyl)-2-methyl-1H-pyrrole-3-carboxylate (327 mg) was added TFA (1.1 ml), and the mixture was stirred at room temperature for 1 hr. After

the reaction solution was concentrated under reduced pressure, the residue was poured into a mixed THF-ethyl acetate-saturated sodium bicarbonate solution, and separated. The organic layer was washed with saturated sodium bicarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was washed with diisopropyl ether to obtain the objective product (172 mg) as a solid.

¹H-NMR (DMSO-d₆) δ: 2.19 (3H, s), 6.22 (1H, s), 7.27 (1H, t), 7.66 (4H, dd), 10.93 (1H, s).

[Reference Example 30]

3-(4-Cyanophenyl)-5-methyl-1H-pyrrole-2-carbonitrile

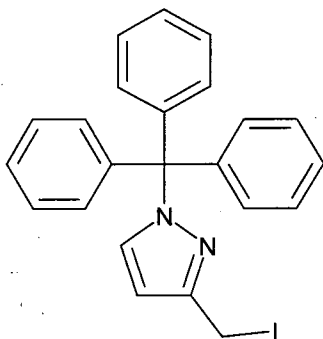


To a mixture of 4-(4-cyanophenyl)-2-methyl-1H-pyrrole (3.07 g), DMF (3.1 ml) and acetonitrile (12 ml) was added dropwise a mixture of chlorosulfonyl isocyanate (1.6 ml) and acetonitrile (6 ml) at 0°C. After stirring at 0°C for 30 min, the mixture was poured into a sodium bicarbonate solution, and extracted with ethyl acetate. The extracted solution was washed with saturated brine, and purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (1.49 g) as crystals.

¹H-NMR (CDCl₃) δ: 2.36 (3H, s), 6.27 (1H, dd), 7.59 (2H, d), 7.76 (2H, d), 8.74 (1H, s).

[Reference Example 31]

3-(Iodomethyl)-1-trityl-1H-pyrazole

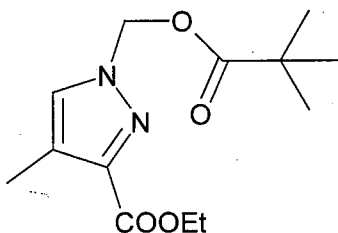


A mixture of (1-trityl-1H-pyrazol-3-yl)methanol (1.16 g), triphenylphosphine (1.07 g), iodine (1.04 g), imidazole (0.28 g) and THF (20 ml) was stirred at room temperature for 20 hr. To the reaction solution were added an aqueous saturated sodium bicarbonate solution and ethyl acetate, and the layers were separated. Then, the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was suspended in diethyl ether, and filtered to obtain the objective product (1.00 g) as crystals.

¹H-NMR (CDCl₃) δ: 4.44 (2H, s), 6.26 (1H, d), 7.1-7.2 (6 H, m), 7.24 (1H, s), 7.31 (9 H, m).

[Reference Example 32]

Ethyl 1-{[(2,2-dimethylpropanoyl)oxy]methyl}-4-methyl-1H-pyrazole-3-carboxylate



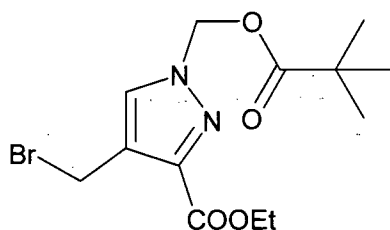
Under an argon atmosphere, to a solution of ethyl 4-methyl-1H-pyrazole-3-carboxylate (7.71 g) in dehydrated DMF (150 ml) was added sodium hydride (60% dispersion in oil, 2.3 g) under ice cooling, and the mixture was stirred for 30 min. Then, a solution of chloromethyl pivalate (8.66 g) in DMF (7.5 ml) was added to the mixture, and the mixture was stirred at room temperature for 2 hr. The reaction

mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate-hexane to obtain the objective product (12.7 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.17 (9H, s), 1.41 (3H, t), 2.27 (3H, s), 4.41 (2H, q), 5.99 (2H, s), 7.47 (1H, s).

[Reference Example 33]

Ethyl 4-(bromomethyl)-1-[[(2,2-dimethylpropanoyl)oxy]methyl]-1H-pyrazole-3-carboxylate

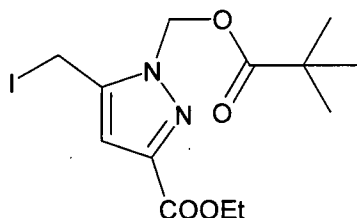


To a solution of 1-[[(2,2-dimethylpropanoyl)oxy]methyl]-4-methyl-1H-pyrazole-3-carboxylate (8.05 g) in carbon tetrachloride (180 ml) were added NBS (6.14 g) and AIBN (492 mg), and the mixture was refluxed for 3 hr. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (5.88 g) as an oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.18 (9H, s), 1.44 (3H, t), 4.46 (2H, q), 4.68 (2H, s), 6.02 (2H, s), 7.80 (1H, s).

[Reference Example 34]

Ethyl 1-[[(2,2-dimethylpropanoyl)oxy]methyl]-5-(iodomethyl)-1H-pyrazole-3-carboxylate

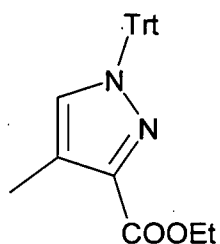


To a solution of ethyl 5-(bromomethyl)-1-[(2,2-dimethylpropanoyl)oxy]methyl}-1H-pyrazole-3-carboxylate (2.39 g) in acetone (68.8 ml) was added sodium iodide (10.3 g), and refluxed for 1.5 hr. After concentrating the reaction mixture, the residue was partitioned with ethyl acetate-water, and the organic layer was washed with an aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain the objective product (2.74 g) as a crystalline powder. The resulting product was used in the following process without further purification.

¹H-NMR (CDCl₃) δ: 1.20 (9H, s), 1.39 (3H, t), 4.41 (2H, q), 4.53 (2H, s), 6.12 (2H, s), 6.83 (1H, s).

[Reference Example 35]

Ethyl 4-methyl-1-trityl-1H-pyrazole-3-carboxylate



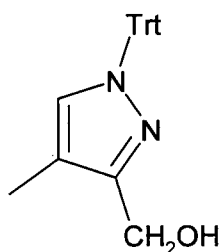
To a solution of ethyl 4-methyl-1H-pyrazole-3-carboxylate (1.0 g) in dehydrated DMF (19.5 ml) were added triethylamine (1.09 ml), triphenylchloromethane (2.17 g) and dimethylaminopyridine (79 mg) under ice cooling, and the mixture was stirred at room temperature for 4 days. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane), and

crystallized from ethyl acetate to obtain the objective product (1.19 g) as crystals.

¹H-NMR (CDCl₃) δ: 1.35 (3H, t), 2.23 (3H, s), 4.33 (2H, q), 7.05 (1H, s), 7.11-7.15 (6H, m), 7.27-7.31 (9H, m).

5 [Reference Example 36]

(4-Methyl-1-trityl-1H-pyrazol-3-yl)methanol

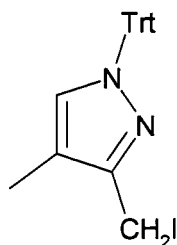


A mixture of sodium borohydride (525 mg), calcium chloride (770 mg), THF (27.7 ml) and ethanol (13.8 ml) was stirred at room temperature for 30 min, and ethyl 4-methyl-1-trityl-1H-pyrazole-3-carboxylate (1.1 g) was added to the mixture, and the mixture was stirred at room temperature for 22 hr. After the reaction mixture was poured into ice water, 1N hydrochloric acid (13.9 ml) was added thereto. THF-ethanol was distilled off, and the residue was partitioned with ethyl acetate-water. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate, concentrated, and the crystals precipitated from the residue were filtered to obtain the objective product (900 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.92 (1, t), 2.03 (3H, s), 4.63 (2H, d), 7.04 (1H, s), 7.11-7.16 (6H, m), 7.25-7.31 (9H, m).

[Reference Example 37]

3-(Iodomethyl)-4-methyl-1-trityl-1H-pyrazole

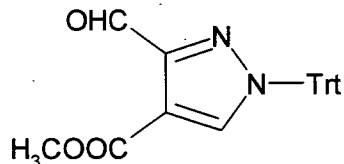


To a solution of {4-methyl-1-trityl-1H-pyrazol-3-yl}methanol (0.9 g) in dichloromethane (90 ml) were added imidazole (190 mg), triphenylphosphine (730 mg) and iodine (707 mg) under ice cooling with stirring, and the mixture was stirred at the same temperature for 1.5 hr. Insolubles were removed by filtration, and the filtrate was washed with aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (760 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.99 (3H, s), 4.41 (2H, s), 7.00 (1H, s), 7.12-7.15 (6H, m), 7.26-7.32 (9H, m).

[Reference Example 38]

Methyl 3-formyl-1-trityl-1H-pyrazole-4-carboxylate

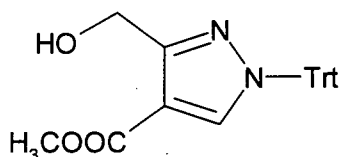


To a solution of methyl 3-formyl-1H-pyrazole-4-carboxylate (1.18 g) in dehydrated DMF (53.6 ml) were added triethylamine (1.35 ml) and triphenylchloromethane (2.24 g) under ice cooling, and stirred at room temperature for 63 hr. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (1.97 g) as crystals.

¹H-NMR (CDCl₃) δ: 3.85 (3H, s), 7.10-7.14 (6H, m), 7.31-7.36 (9H, m), 7.92 (1H, s), 10.34 (1H, s).

[Reference Example 39]

Methyl 3-(hydroxymethyl)-1-trityl-1H-pyrazole-4-carboxylate

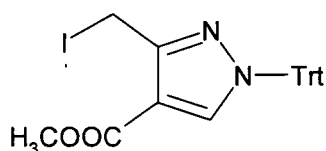


To a solution of methyl 3-formyl-1-trityl-1H-pyrazole-4-carboxylate (1.74 g) in a methanol-THF mixture (1:1, 70 ml) was added sodium borohydride (182 mg) under ice cooling with stirring, and the mixture was stirred for 30 min. To the reaction mixture, ice water and 0.1N hydrochloric acid (48 ml) were added, and the mixture was concentrated. The residue was partitioned with ethyl acetate-water, and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was crystallized from ethyl acetate to obtain the objective product (1.7 g) as crystals.

¹H-NMR (CDCl₃) δ: 3.79 (3H, s), 4.05 (1H, t), 4.79 (2H, d), 7.10-7.15 (6H, m), 7.25-7.34 (9H, m), 7.80 (1H, s).

[Reference Example 40]

Methyl 3-(iodomethyl)-1-trityl-1H-pyrazole-4-carboxylate

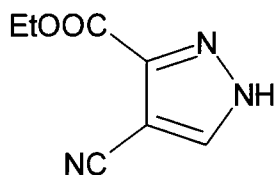


To a solution of methyl 3-(hydroxymethyl)-1-trityl-1H-pyrazole-4-carboxylate (1.7 g) in dichloromethane (90 ml) were added imidazole (336 mg), triphenylphosphine (1.29 g) and iodine (1.25 g) under ice cooling with stirring, and the mixture was stirred at the same temperature for 2 hr. Insolubles were removed by filtration, and the filtrate was washed with aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (1.06 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.82 (3H, s), 4.67 (2H, s), 7.10-7.13 (6H, m), 7.28-7.34 (9H, m), 7.78 (1H, s).

[Reference Example 41]

Ethyl 4-cyano-1H-pyrazole-3-carboxylate

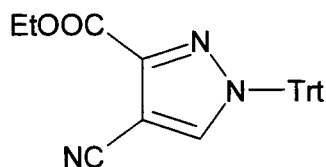


To a solution of ethyl 4-formyl-1H-pyrazole-3-carboxylate (505 mg) in NMP (6 ml) was added hydroxyl amine hydrochloride (219 mg), and the mixture was stirred at 100°C for 6 hr. Then, the reaction mixture was ice-cooled, and thionyl chloride (1.08 g) was added thereto. After stirring at room temperature for 1 hr, the mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was crystallized from ethyl acetate to obtain the objective product (356 mg) as crystals.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.31 (3H, t), 4.35 (2H, q), 8.69 (1H, s).

[Reference Example 42]

Ethyl 4-cyano-1-trityl-1H-pyrazole-3-carboxylate



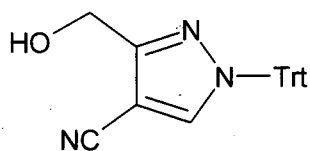
Under an argon atmosphere, to a solution of ethyl 4-cyano-1H-pyrazole-3-carboxylate (1.94 g) in DMF (117 ml) was added sodium hydride (60% dispersion in oil, 517 mg) under ice cooling, and the mixture was stirred for 1 hr. A solution of triphenylchloromethane (3.43 g) in DMF (20 ml) was added thereto, and stirred at room temperature for 3 hr. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed

with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel chromatography (ethyl acetate-hexane) to obtain the objective product (4.09 g) as an amorphous powder.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (3H, t), 4.43 (2H, q), 7.06-7.10 (6H, m), 7.30-7.37 (9H, m), 7.77 (1H, s).

[Reference Example 43]

3-(Hydroxymethyl)-1-trityl-1H-pyrazole-4-carbonitrile

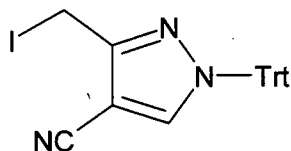


10 Under an argon atmosphere, a mixture of sodium borohydride (1.89 g), calcium chloride (2.78 g), THF (100 ml) and ethanol (50 ml) was stirred at room temperature for 30 min, and ethyl 4-cyano-1-trityl-1H-pyrazole-3-carboxylate (4.07 g) was added thereto, and the mixture was
15 stirred at room temperature for 14 hr. To the reaction mixture were added ice-water and 1N hydrochloric acid (45 ml), and the mixture was concentrated. The residue was partitioned with ethyl acetate-water, and the ethyl acetate layer was washed with saturated brine, dried over anhydrous
20 magnesium sulfate, and concentrated. Then, the residue was crystallized from ethyl acetate to obtain the objective product (3.26 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.18 (1H, br s), 4.79 (2H, s), 7.07-7.10 (6H, m), 7.31-7.36 (9H, m), 7.73 (1H, s).

25 [Reference Example 44]

3-(Iodomethyl)-1-trityl-1H-pyrazole-4-carbonitrile



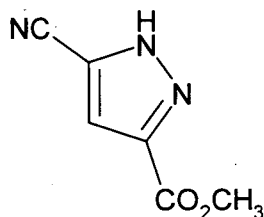
To a solution of 3-(hydroxymethyl)-1-trityl-1H-pyrazole-4-carbonitrile (2 g) in dichloromethane (110 ml)

were added imidazole (410 mg), triphenylphosphine (1.58 g) and iodine (1.53 g) under ice cooling with stirring, and the mixture was stirred at the same temperature for 2 hr. Insolubles were removed by filtration, and the filtrate was washed with aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (1.89 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.44 (2H, s), 7.07-7.14 (6H, m), 7.28-7.37 (9H, m), 7.68 (1H, s).

[Reference Example 45]

Methyl 5-cyano-1H-pyrazole-3-carboxylate

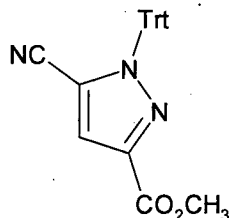


To a solution of methyl 5-formyl-1H-pyrazole-3-carboxylate (14.79 g) in NMP (192 ml) was added hydroxylamine hydrochloride (7.0 g), and the mixture was stirred at 100°C for 6 hr. Then, the reaction mixture was ice-cooled, and thionyl chloride (34.53 g) was added thereto. After stirring at room temperature for 1 hr, the mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (12.42 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.99 (3H, s), 7.21 (1H, s), 11.61 (1H, br s).

[Reference Example 46]

Methyl 5-cyano-1-trityl-1H-pyrazole-3-carboxylate

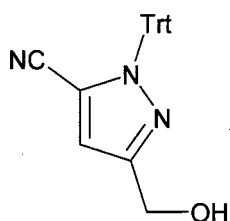


Under an argon atmosphere, to a solution of methyl 5-cyano-1H-pyrazole-3-carboxylate (9.07 g) in DMF (300 ml) was added sodium hydride (60% dispersion in oil, 2.64 g) under ice cooling, and stirred for 1 hr. A solution of triphenylchloromethane (17.56 g) in DMF (100 ml) was added thereto, and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The crystals deposited from the residue were pulverized in ethyl acetate, and filtrated to obtain the objective product (18.57 g) as crystals.

¹H-NMR (CDCl₃) δ: 3.08 (3H, s), 7.03-7.16 (6H, m), 7.27-7.37 (9H, m), 7.42 (1H, s).

[Reference Example 47]

3-(Hydroxymethyl)-1-trityl-1H-pyrazole-5-carbonitrile



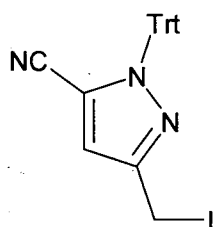
Under an argon atmosphere, a mixture of sodium borohydride (4.73 g), calcium chloride (6.94 g), THF (250 ml) and ethanol (125 ml) was stirred at room temperature for 30 min, and methyl 5-cyano-1-trityl-1H-pyrazole-3-carboxylate (9.84 g) was added thereto, and the mixture was stirred at room temperature for 22 hr. To the reaction mixture were added ice-water and 1N hydrochloric acid (100 ml), and the mixture was concentrated. The residue was partitioned with ethyl acetate-water, and the ethyl acetate

layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was crystallized from ethyl acetate to obtain the objective product (9.74 g) as crystals.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.94 (1H, t), 4.68 (2H, d), 6.94 (1H, s), 7.12-7.17 (6H, m), 7.29-7.35 (9H, m).

[Reference Example 48]

3-(Iodomethyl)-1-trityl-1H-pyrazole-5-carbonitrile

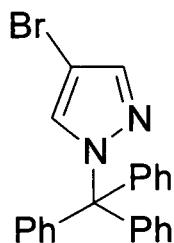


10 To a solution of 3-(hydroxymethyl)-1-trityl-1H-pyrazole-5-carbonitrile (7.31 g) in dichloromethane solution (150 ml) were added imidazole (1.50 g), triphenylphosphine (5.77 g) and iodine (5.58 g) under ice cooling with stirring, and the mixture was stirred at the
15 same temperature for 2 hr. Insolubles were removed by filtration, and the filtrate was washed with aqueous sodium thiosulfate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to
20 obtain the objective product (7.36 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.34 (2H, s), 6.95 (1H, s), 7.13-7.16 (6H, m), 7.31-7.34 (9H, m).

[Reference Example 49]

25 4-Bromo-1-trityl-1H-pyrazole



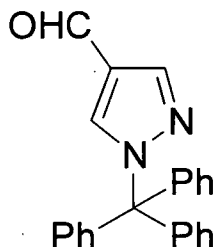
Using 4-bromo-1H-pyrazole (19.8 g), the same reaction

as in Reference Example 1 was conducted to obtain the titled compound (40.2 g) as colorless crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.10-7.39 (16H, m), 7.62 (1H, s).

[Reference Example 50]

5 1-Trityl-1H-pyrazole-4-carboxyaldehyde

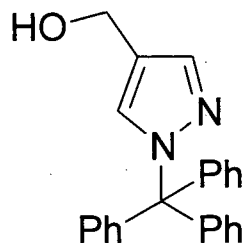


A solution of the compound (11.7 g) obtained in Reference Example 49 in THF (110 ml) was cooled to -78°C , and a solution of n-butyllithium in hexane (1.6 mol/l, 19.5 ml) was added dropwise thereto. After the reaction mixture was stirred at the same temperature for 1 hr, DMF (4.7 ml) was added thereto, and the mixture was stirred for 1 hr. To the reaction mixture, an aqueous ammonium chloride solution was added and, after warming to room temperature, the solution was diluted with water. The precipitate was collected by filtration, washed sequentially with water, ethanol and diethyl ether, and dried to obtain the titled compound (7.9 g) as colorless crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.11-7.37 (15H, m), 7.97 (1H, s), 8.12 (1H, s), 9.85 (1H, s).

[Reference Example 51]

(1-Trityl-1H-pyrazol-4-yl)methanol



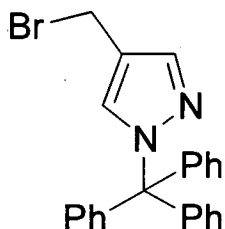
Using the compound (5.3 g) obtained in Reference Example 50, the same reaction and purification operation as

in Reference Example 2 were conducted to obtain the titled compound (4.8 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.43 (1H, t), 4.56 (2H, d), 7.10-7.36 (15H, m), 7.39 (1H, s), 7.67 (1H, s).

5 [Reference Example 52]

4-(Bromomethyl)-1-trityl-1H-pyrazole

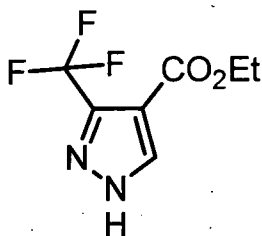


Using the compound (1.4 g) obtained in Reference Example 51, the same reaction and purification operation as in Reference Example 3 were conducted to obtain the titled compound (1.1 g) as a colorless amorphous solid.

¹H-NMR (CDCl₃) δ: 4.43 (2H, s), 7.10-7.48 (16H, m), 7.69 (1H, s).

[Reference Example 53]

15 Ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate

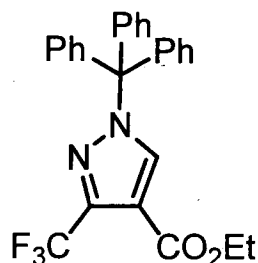


Ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrates (4.80 g) was dissolved in ethanol (50 ml), and hydrazine monohydrate (1.20 g) was added thereto. The reaction mixture was heated under reflux for 16 hr, and concentrated. After the residue was dissolved in an aqueous ammonium chloride solution and ethyl acetate, the ethyl acetate layer was separated, dried over anhydrous magnesium sulfate, and concentrated to obtain the titled compound (3.80 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.38 (3H, t), 4.36 (2H, q), 8.23 (1H, s).

[Reference Example 54]

Ethyl 3-(trifluoromethyl)-1-trityl-1H-pyrazole-4-carboxylate

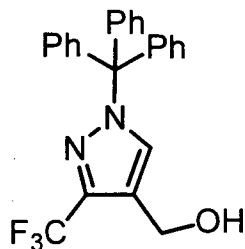


The compound (3.80 g) obtained in Reference Example 53 was dissolved in DMF (40 ml), and triethylamine (3.1 ml) and triphenylchloromethane (5.36 g) were added thereto. The reaction solution was stirred at room temperature for 16 hr, diluted with water, and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The resulting residue was washed with diisopropyl ether to obtain the titled compound (4.12 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.32 (3H, t), 4.29 (2H, q), 7.07-7.38 (15H, m), 7.92 (1H, s).

[Reference Example 55]

[3-(Trifluoromethyl)-1-trityl-1H-pyrazol-4-yl]methanol



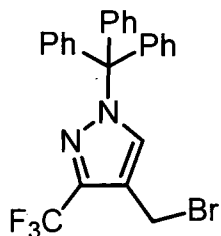
Lithium aluminum hydride (0.34 g) was suspended in THF (50 ml) and cooled to 0°C. To the suspension, a solution of the compound (4.00 g) obtained in Reference Example 54 in THF (120 ml) was added dropwise. The reaction solution was stirred at room temperature for 16 hr and cooled in an ice bath, and water (0.34 ml) was carefully added thereto, and also an aqueous 15% sodium hydroxide solution (0.34 ml)

and water (1.0 ml) were added thereto. The precipitate was filtered and the filtrate was concentrated to obtain the titled compound (3.80 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.65 (1H, t), 4.64 (2H, d), 7.08-7.13 (6H, m), 7.27-7.34 (9H, m), 7.38 (1H, s).

[Reference Example 56]

4-(Bromomethyl)-3-(trifluoromethyl)-1-trityl-1H-pyrazole

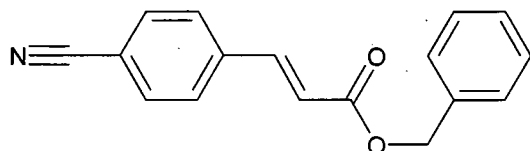


Using the compound (3.80 g) obtained in Reference Example 55, the same reaction and purification operation as in Reference Example 3 were conducted to obtain the titled compound (1.62 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 4.42 (2H, s), 7.06-7.11 (6H, m), 7.28-7.35 (9H, m), 7.41 (1H, s).

[Reference Example 57]

Benzyl (2E)-3-(4-cyanophenyl)acrylate

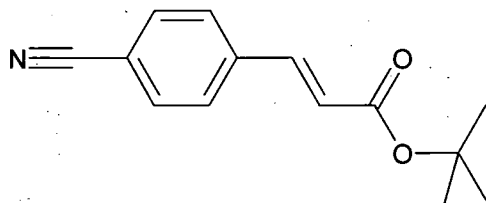


To a suspension of sodium hydride (60% dispersion in oil, 3.1 g) in THF (120 ml) was added dropwise a solution of benzyl (dimethoxyphosphoryl)acetate (20.0 g) and p-cyanobenzaldehyde (10.0 g) in THF (90 ml) under ice cooling, and the mixture was stirred at room temperature for 4 hr. After the reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was crystallized from diethyl ether to obtain the objective product (20.0 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 5.27 (2H, s), 6.56 (1H, d), 7.33 - 7.46 (5H, m), 7.58 - 7.73 (5H, m).

In the same manner as in Reference Example 57, the following compounds were obtained.

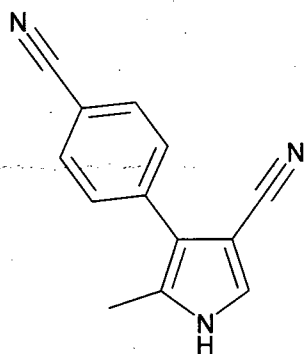
5 tert-Butyl (2E)-3-(4-cyanophenyl)acrylate



$^1\text{H-NMR}$ (CDCl_3) δ : 1.54 (9H, s), 6.45 (1H, d), 7.5 - 7.7 (5H, m).

[Reference Example 58]

10 4-(4-Cyanophenyl)-5-methyl-1H-pyrrole-3-carbonitrile

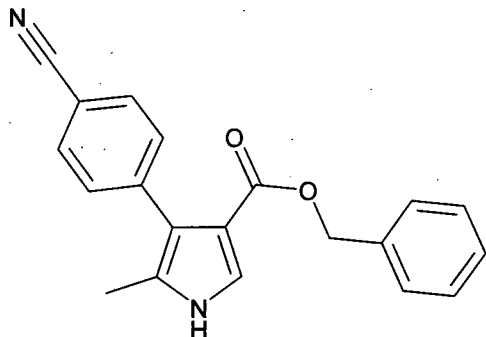


To a suspension of sodium hydride (60% dispersion in oil, 0.48 g) in THF (20 ml) was added dropwise a solution of 4-[(E)-2-cyanovinyl]benzonitrile (1.54 g) and 1-[(1-isocyanoethyl)sulfonyl]-4-methylbenzene (2.09 g) in THF (50 ml) under ice cooling, and the mixture was stirred at the same temperature for 2 hr. After the reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate, concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ether to obtain the objective product (0.60 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.37 (3H, s), 7.29 (1H, d), 7.55 (2H, d), 7.72 (2H, d), 8.63 (1H, br s).

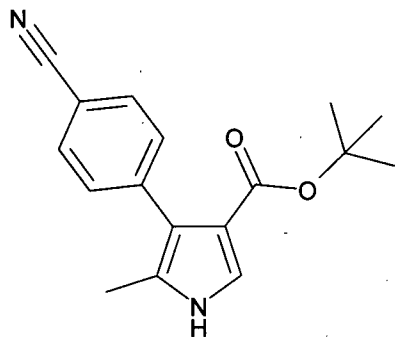
In the same manner as in Reference Example 58, the following compounds were obtained.

5 Benzyl 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylate



$^1\text{H-NMR}$ (CDCl_3) δ : 2.18 (3H, s), 5.14 (2H, s), 7.20 (2H, dd), 7.28 - 7.34 (3H, m), 7.38 (2H, d), 7.44 (1H, d), 7.57 (2H, d), 8.41 (1H, s).

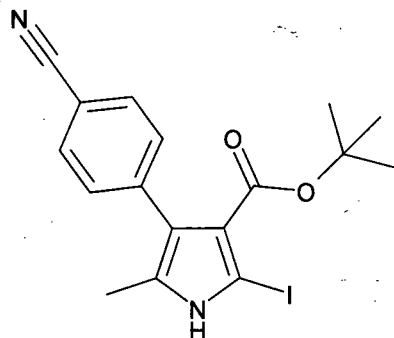
10 tert-Butyl 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylate



$^1\text{H-NMR}$ (CDCl_3) δ : 1.37 (9H, s), 2.18 (3H, s), 7.34 (1H, d), 7.41 (2H, d), 7.65 (2H, d), 8.39 (1H, s).

15 [Reference Example 59]

tert-Butyl 4-(4-cyanophenyl)-2-iodo-5-methyl-1H-pyrrole-3-carboxylate

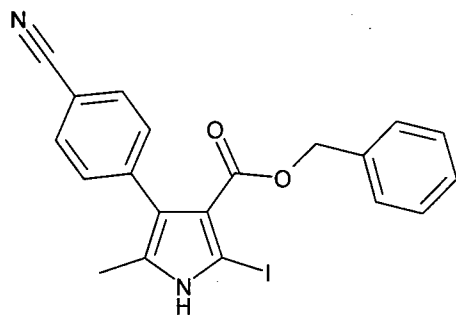


A solution of tert-butyl 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylate (4.79 g) and N-iodosuccinimide (4.21 g) in DMF (50 ml) was stirred at room temperature for 2 hr. After the reaction mixture was poured into saturated brine (200 ml) and extracted with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (5.83 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.31 (9H, m), 2.15 (3H, s), 7.30 - 7.35 (2H, m), 7.61 - 7.67 (2H, m), 8.49 (1H, s).

In the same manner as in Reference Example 59, the following compounds were obtained.

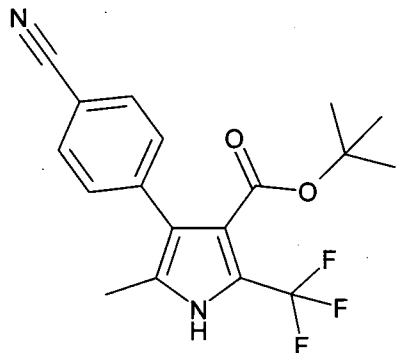
Benzyl 4-(4-cyanophenyl)-2-iodo-5-methyl-1H-pyrrole-3-carboxylate



$^1\text{H-NMR}$ (CDCl_3) δ : 2.27 (3H, s), 2.31 (3H, s), 7.45 (2H, d), 7.67 (2H, d), 8.10 (1H, s).

[Reference Example 60]

tert-Butyl 4-(4-cyanophenyl)-5-methyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxylate

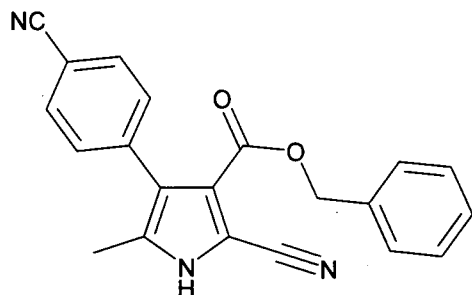


A solution of tert-butyl 4-(4-cyanophenyl)-2-iodo-5-methyl-1H-pyrrole-3-carboxylate (1.06 g), methyl fluorosulfonyl(difluoro)acetate (0.99 ml) and copper iodide
5 (0.55 g) in DMF (15 ml) was stirred at 80°C for 14 hr. After the reaction mixture was poured into saturated brine (20 ml) and extracted with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated, and then the residue
10 was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from ethyl acetate to obtain the objective product (0.65 g) as crystals.

¹H-NMR (CDCl₃) δ: 1.39 (9H, s), 2.18 (3H, s), 7.37 (2H, d), 7.67 (2H, d), 8.77 (1H, br s).

15 [Reference Example 61]

Benzyl 2-cyano-4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylate



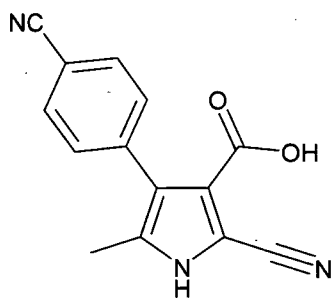
To a mixture of benzyl 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylate (3.09 g), DMF (2.25 ml) and
20 acetonitrile (15 ml) was added dropwise a mixture of chlorosulfonyl isocyanate (1.01 ml) and acetonitrile (5 ml)

at 0°C. After stirring at 0°C for 30 min, the mixture was poured into an aqueous sodium bicarbonate solution, and extracted with ethyl acetate. The extract solution was washed with saturated brine, and purified by silica gel column chromatography (ethyl acetate) to obtain the objective product (2.70 g) as crystals.

¹H-NMR (CDCl₃) δ: 2.14 (3H, s), 5.15 (2 H, s), 7.17 (2 H, dd), 7.26 - 7.33 (3H, m), 7.44 (2 H, d), 7.75 (2 H, d), 13.17 (1H, s).

10 [Reference Example 62]

2-Cyano-4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylic acid

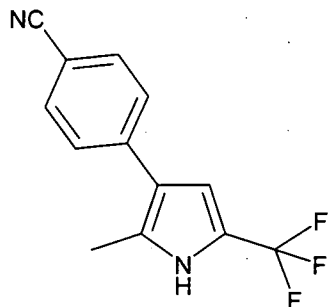


A mixture of benzyl 4-(4-cyanophenyl)-5-methyl-2-cyano-1H-pyrrole-3-carboxylate (2.50 g), 10% palladium carbon (water content of 50%, 250 mg), THF (10 ml) and methanol (10 ml) was stirred at room temperature for 3 hr under a hydrogen atmosphere. The catalyst was removed by filtration through celite, followed by washing with methanol. The wash and the mother liquor were combined, concentrated and then washed with ethyl acetate to obtain the objective product (1.47 g) as crystals.

¹H-NMR (DMSO-d₆) δ: 2.14 (3H, s), 7.47 (2 H, d), 7.81 (2 H, d), 8.62 (1H, s).

25 [Reference Example 63]

4-[2-Methyl-5-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile

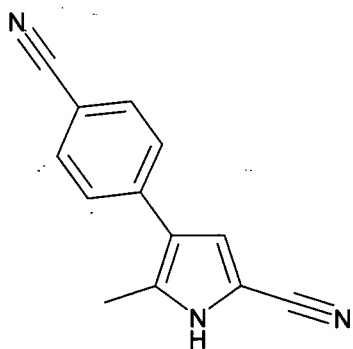


A mixture of tert-butyl 4-(4-cyanophenyl)-5-methyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxylate (267 mg), sodium chloride (90 mg) and dimethyl sulfoxide (2 ml) was stirred at 170°C for 48 hr. The catalyst was removed by filtration through celite, followed by washing with methanol. The wash and the mother liquor were combined, concentrated and then washed with ethyl acetate to obtain the objective product (1.47 g) as crystals. After the reaction mixture was poured into saturated brine (20 ml) and extracted with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain the objective product (41 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.45 (3H, s), 6.71 (1H, d), 7.45 - 7.51 (2 H, m), 7.61 - 7.72 (2 H, m), 8.43 (1H, s).

Using the compound of Reference Example 62, the following compounds were obtained in the same manner as in Reference Example 63.

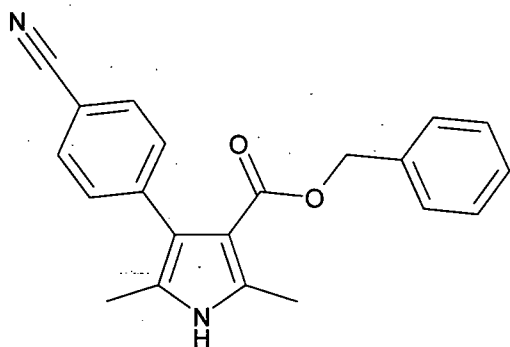
4-(4-Cyanophenyl)-5-methyl-1H-pyrrole-2-carbonitrile



$^1\text{H-NMR}$ (CDCl_3) δ : 2.46 (3H, s), 6.97 (1H, d), 7.46 (2 H, d), 7.69 (2 H, d), 8.75 (1H, s).

[Reference Example 64]

5 Benzyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate



A mixture of benzyl acetoacetate (152.8 g), potassium hydroxide (14.8 g) and THF (495 ml) was stirred at room temperature for 20 min and cooled to 0°C. 4-[(1E)-2-nitroprop-1-en-1-yl]benzonitrile (50 g) was added thereto and the mixture was stirred at 0°C for 1 hr. The mixture was poured into saturated brine and extracted with ethyl acetate. The extract solution was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated to obtain an oil. A mixture of the oil, methanol (13.9 ml), water (13.9 ml) and hydrochloric acid (13.9 ml) was stirred at 75°C for 2 hr. The reaction solution was cooled to room temperature and concentrated, and then the residue was partitioned between ethyl acetate and water. The organic layer was washed with an aqueous

10

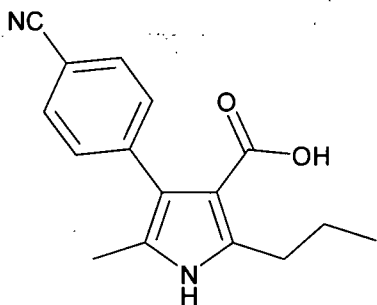
15

20

sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The precipitated crystals were filtered and then washed with a small amount of diisopropylether to obtain benzyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (34.1 g).
5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.10 (3H, s), 2.53 (3H, s), 5.07 (2H, s), 7.03-7.06 (2H, m), 7.22-7.29 (5H, m), 7.47 (2H, d), 8.01 (1H, s).

[Reference Example 65]

10 4-(4-Cyanophenyl)-5-methyl-2-propyl-1H-pyrrole-3-carboxylic acid



A mixture of benzyl 3-oxohexanoate (6.40 g) synthesized by a known method, potassium hydroxide (776 mg) and THF (50 ml) was stirred at room temperature for 20 min and cooled to 0°C. 4-(2-nitroprop-1-en-1-yl)benzonitrile (2.60 g) synthesized by a known method was added and to the mixture, and the mixture was stirred at 0°C for 1 hr. The mixture was poured into saturated brine and extracted with ethyl acetate. The extract solution was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated to obtain an oil. A mixture of the oil, methanol (10 ml), water (1 ml) and hydrochloric acid (1 ml) was stirred at 75°C for 2 hr. The reaction solution was cooled to room temperature and concentrated, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with an aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The

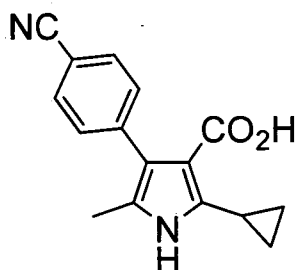
residue was subjected to silica gel column chromatography (ethyl acetate-hexane) to obtain benzyl 4-(4-cyanophenyl)-5-methyl-2-propyl-1H-pyrrole-3-carboxylate. The resulting compound was used in the following reaction without being purified furthermore.

A mixture of benzyl 4-(4-cyanophenyl)-5-methyl-2-propyl-1H-pyrrole-3-carboxylate, 10% palladium carbon (water content of 50%, 294 mg), THF (105 ml) and methanol (35 ml) was stirred at room temperature for 3 hr under hydrogen atmosphere. The catalyst was removed by filtration through celite, followed by washing with methanol. The wash and the mother liquor were combined, concentrated and then washed with ethyl acetate to obtain the objective product (2.42 g) as crystals.

¹H-NMR (DMSO-d₆) δ: 0.90 (3H, t), 1.54-1.66 (2H, m), 2.05 (3H, s), 2.80 (2H, t), 7.35 (2H, d), 7.70 (2H, d), 11.14 (1H, s), 11.35 (1H, br.s).

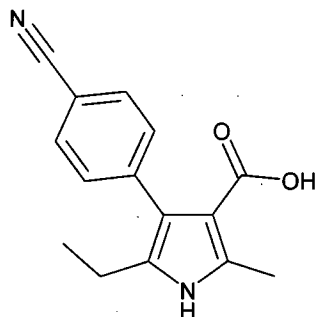
In the same manner as in Reference Example 65, the following compounds were obtained.

4-(4-Cyanophenyl)-2-cyclopropyl-5-methyl-1H-pyrrole-3-carboxylic acid



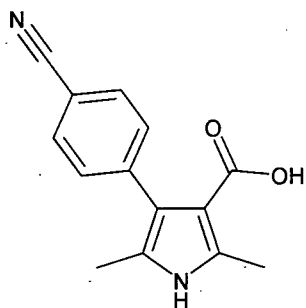
¹H-NMR (DMSO-d₆) δ: 0.78-0.83 (2H, m), 0.89-0.95 (2H, m), 2.02 (3H, s), 2.65-2.74 (1H, m), 7.35 (2H, d), 7.73 (2H, d), 10.63 (1H, s).

4-(4-Cyanophenyl)-5-ethyl-2-methyl-1H-pyrrole-3-carboxylic acid



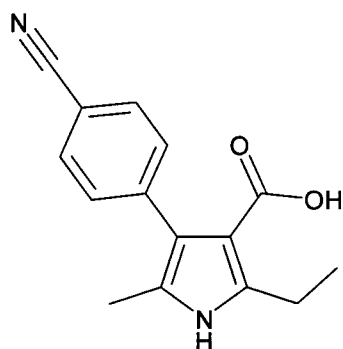
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.07 (3H, t), 2.37 (2H, q), 2.41 (3H, s), 7.34 (2H, d), 7.72 (2H, d), 10.98 (1H, s), 11.19 (1H, s).

5 4-(4-Cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid



$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.05 (3H, s), 2.39 (3H, s), 7.35 (2H, d), 7.71 (2H, d), 11.22 (1H, s), 11.43 (1H, s).

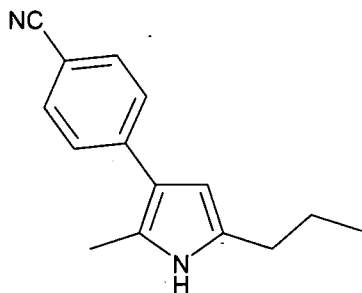
10 4-(4-Cyanophenyl)-2-ethyl-5-methyl-1H-pyrrole-3-carboxylic acid



$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.17 (3H, t), 2.06 (3H, s), 2.84 (2H, q), 7.37 (2H, d), 7.73 (2H, d), 11.19 (1H, s).

[Reference Example 66]

15 4-(2-Methyl-5-propyl-1H-pyrrol-3-yl)benzonitrile

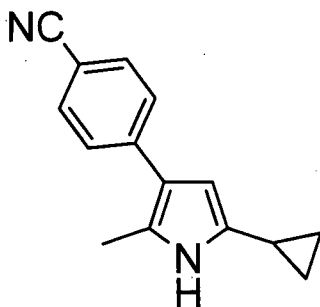


A mixture of 4-(4-cyanophenyl)-5-methyl-2-propyl-1H-pyrrole-3-carboxylic acid (2.42 g) and TFA (5 ml) was stirred at room temperature for 40 min. The residue obtained by concentrating the reaction solution was diluted with ethyl acetate, washed with an aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the objective product (1.97 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (3H, t), 1.66 (2H, sextet), 2.40 (3H, s), 2.55 (2H, t), 6.05 (1H, d), 7.44-7.48 (2H, m), 7.57-7.61 (2H, m), 7.78 (1H, br.s).

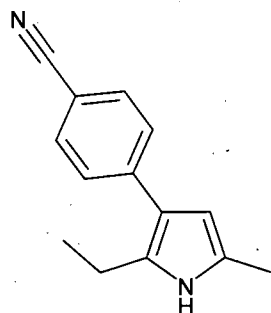
In the same manner as in Reference Example 66, the following compounds were obtained.

4-(5-Cyclopropyl-2-methyl-1H-pyrrol-3-yl)benzonitrile

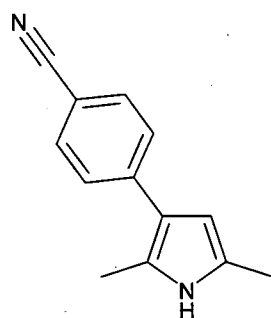


$^1\text{H-NMR}$ (CDCl_3) δ : 0.61-0.67 (2H, m), 0.82-0.88 (2H, m), 1.75-1.82 (1H, m), 2.39 (3H, s), 5.99 (1H, d), 7.45 (2H, d), 7.60 (2H, d), 7.89 (1H, s).

4-(2-Ethyl-5-methyl-1H-pyrrol-3-yl)benzonitrile

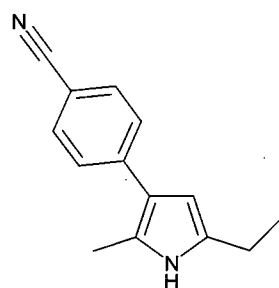


$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.18 (3H, t), 2.59 (3H, s), 2.69 (2H, q), 5.94 (1H, d), 7.45 (2H, d), 7.71 (2H, d), 10.64 (1H, s).
4-(2,5-Dimethyl-1H-pyrrol-3-yl)benzonitrile



5

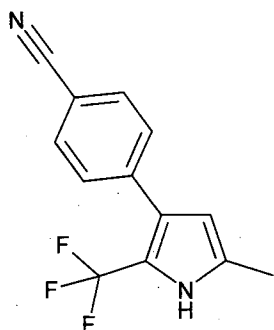
$^1\text{H-NMR}$ (CDCl_3) δ : 2.27 (3H, s), 2.40 (3H, s), 6.04 (1H, d), 7.46 (2H, d), 7.61 (2H, d), 7.76 (1H, br s).
4-(5-Ethyl-2-methyl-1H-pyrrol-3-yl)benzonitrile



10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t), 2.41 (3H, s), 2.62 (2H, q), 6.06 (1H, d), 7.46-7.49 (2H, m), 7.59-7.62 (2H, m), 7.80 (1H, br.s).

[Reference Example 67]

3-(4-Cyanophenyl)-5-methyl-2-(trifluoromethyl)-1H-pyrrole

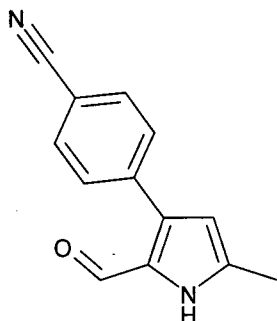


A solution of 4-(4-cyanophenyl)-2-methyl-1H-pyrrole (1.01 g) and N-iodosuccinimide (1.31 g) in DMF (25 ml) at room temperature for 1 hr. The reaction solution was diluted with ethyl acetate, washed with water and saturated brine, dried over anhydrous magnesium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain 3-(4-cyanophenyl)-5-methyl-2-iodo-1H-pyrrole (1.17 g) as a mixture with by-product. To a solution of the mixture (700 mg) in DMF (12 ml), copper iodide (476 mg) and methyl fluorosulfonyl(difluoro)acetate (1.92 ml) were added, and the mixture was heated at 100°C for 1 hr. The reaction solution was cooled to room temperature, poured into water and then extracted with ethyl acetate (50 ml). The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diisopropyl ether-hexane to obtain the objective product (92 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.34 (3H, s), 6.09-6.10 (1H, m), 7.53 (2H, d), 7.65 (2H, d), 8.40 (1H, s).

[Reference Example 68]

3-(4-Cyanophenyl)-5-methyl-2-formyl-1H-pyrrole

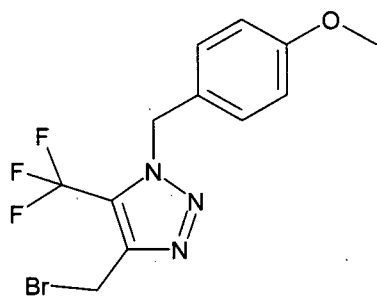


To a solution of 4-(4-cyanophenyl)-2-methyl-1H-pyrrole (200 mg) in DMF (3.0 ml), a Vilsmeier reagent (337 mg) was added by several portions under ice cooling, and the mixture was stirred at room temperature for 4 hr. The reaction solution was poured into saturated aqueous sodium bicarbonate solution (20 ml) and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-diisopropyl ether to obtain the objective product (148 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.42 (3H, s), 6.21 (1H, d), 7.58 (2H, d), 7.72 (2H, d), 9.50 (1H, s), 10.07 (1H, s).

[Reference Example 69]

4-(Bromomethyl)-1-(4-methoxybenzyl)-5-(trifluoromethyl)-1H-1,2,3-triazole



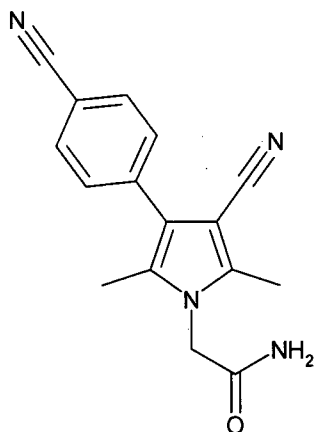
A mixture of p-methoxybenzylazide (3.35 g), ethyl 4,4,4-trifluorobut-2-ynoate (2.90 g) and toluene (30 ml) was stirred at 100°C for 20 hr. The reaction mixture was poured into saturated brine and extracted with ethyl

acetate, and the ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain a yellow oil (5.53 g). A mixture of sodium borohydride (1.27 g), calcium chloride (2.80 g), THF (40 ml) and ethanol (20 ml) was stirred at room temperature for 30 min and the resulting oil (5.53 g) was added thereto, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate, and the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain a colorless oil (3.11 g). A mixture of the resulting oil (2.11 g), NBS (1.57 g), triphenylphosphine (2.31 g) and THF (20 ml) was stirred at room temperature for 2 hr. The reaction mixture was poured into saturated brine, extracted with ethyl acetate, and the ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the titled compound (1.92 g) as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.80 (3H, s), 4.59 (2H, s), 5.57 (2H, s), 6.88 (2H, d), 7.25 (2H, d).

[Reference Example 70]

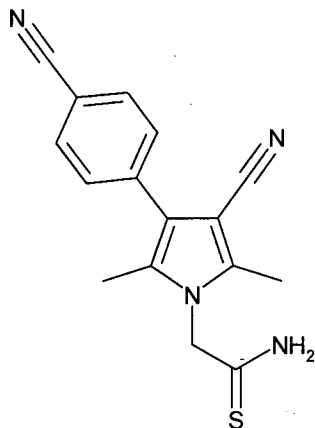
2-[3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]acetoamide



A solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (20.0 g), iodoacetamide (84.0 g) and potassium carbonate (62.5 g) in DMF (150 ml) was stirred at 120°C for 20 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate, and then the ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain the objective product (18.8 g) as crystals.

¹H-NMR (DMSO-d₆) δ: 2.12 (3H, s), 2.25 (3H, s), 4.55 (2H, s), 7.34 (1H, s), 7.48 (2H, d), 7.65 (1H, s), 7.86 (2H, d).
[Reference Example 71]

2-[3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]ethanethioamide



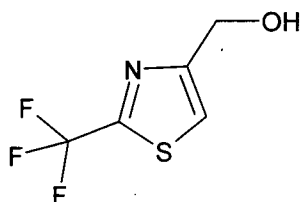
A solution of 2-[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]acetamide (8.0 g) and Lawesson's reagent (7.5 g) in THF (250 ml) was stirred at 80°C for 2 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate, and then the ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate and diethylether to obtain the objective product (6.35 g) as crystals.

¹H-NMR (CDCl₃) δ: 2.26 (3H, s), 2.42 (3H, s), 4.95 (2H, s),

6.56 (1H, s), 7.2-7.4 (3H, m), 7.72 (2H, d).

[Reference Example 72]

[2-(Trifluoromethyl)-1,3-thiazol-4-yl]methanol

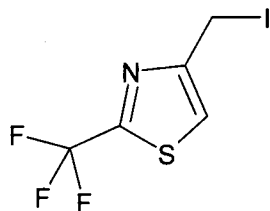


5 Under an argon atmosphere, to a solution of lithium aluminum hydride (441 mg) in dehydrated THF (116 ml), a solution of ethyl 2-(trifluoromethyl)-1,3-thiazole-4-carboxylate (2.62 g) in dehydrated THF (5 ml) was added under ice cooling with stirring at 10°C or lower, and the
10 mixture was stirred at the same temperature for 20 min and further stirred at room temperature for 1 hr. After ice cooling again, the reaction was quenched by adding an aqueous saturated sodium sulfate solution to the mixture, and the mixture was neutralized with 1N hydrochloric acid
15 and then extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated to obtain the objective product (about 2.6 g). The resulting product
20 was used in the following process without being purified furthermore.

¹H-NMR (CDCl₃) δ: 2.02 (1H, br s), 4.97 (2H, s), 7.82 (1H, s).

[Reference Example 73]

4-(Iodomethyl)-2-(trifluoromethyl)-1,3-thiazole



25

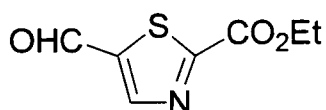
To a solution of [2-(trifluoromethyl)-1,3-thiazol-4-yl]methanol (2.6 g) in ethyl acetate (116 ml),

diisopropylethylamine (4.81 ml) was added under ice cooling with stirring and a solution of methanesulfonyl chloride (2.65 g) in ethyl acetate (11 ml) was added thereto, and the mixture was stirring for 1 hr. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. To a solution of the residue in acetone (174 ml), sodium iodide (17.4 g) was added, and the mixture was refluxed for 1.5 hr. After concentrating the reaction mixture, the residue was partitioned with ethyl acetate-water and the organic layer was washed with an aqueous thiosodium sulfate solution and saturated brine, dried over anhydrous sodium sulfate and concentrated to obtain the objective product (2.96 g). The resulting product was used in the following process without being purified furthermore.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.66 (2H, s), 7.89 (1H, s).

[Reference Example 74]

Ethyl 5-formyl-1,3-thiazole-2-carboxylate

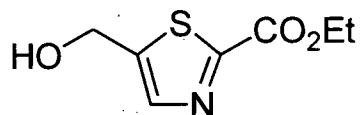


Ethylamino(thioxo)acetate (31.6 g) was dissolved in 1,2-dimethoxyethane (450 ml) and bromomalonaldehyde (35.8 g) was added thereto. The reaction mixture was stirred at room temperature for 68 hr and concentrated, and then the residue was dissolved in ethyl acetate and an aqueous saturated sodium bicarbonate solution. The ethyl acetate layer was separated and, after drying over anhydrous magnesium sulfate and concentrating, the residue was purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (6.90 g) as an oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (3H, t), 4.52 (2H, q), 8.56 (1H, s), 10.13 (1H, s).

[Reference Example 75]

Ethyl 5-(hydroxymethyl)-1,3-thiazole-2-carboxylate

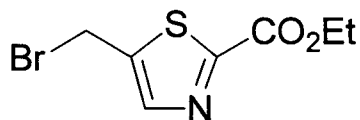


A solution of the compound (6.90 g) obtained in Reference Example 74 in ethanol (200 ml) was cooled to 0°C and sodium borohydride (0.71 g) was added thereto. The reaction solution was stirred at the same temperature for 30 min and concentrated, and then the residue was dissolved in ethyl acetate and water. The ethyl acetate layer was separated, dried over anhydrous magnesium sulfate and concentrated, and then the residue was purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (3.78 g) as an oil.

¹H-NMR (CDCl₃) δ: 1.44 (3H, t), 2.13 (1H, t), 4.48 (2H, q), 4.96 (2H, d), 7.88 (1H, s).

[Reference Example 76]

Ethyl 5-(bromomethyl)-1,3-thiazole-2-carboxylate

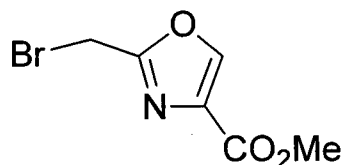


Using the compound (1.87 g) obtained in Reference Example 75, the same reaction and purification operation as in Reference Example 3 were conducted to obtain the titled compound (1.87 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.44 (3H, t), 4.47 (2H, q), 4.71 (2H, s), 7.94 (1H, s).

[Reference Example 77]

Methyl 2-(bromomethyl)-1,3-oxazole-4-carboxylate



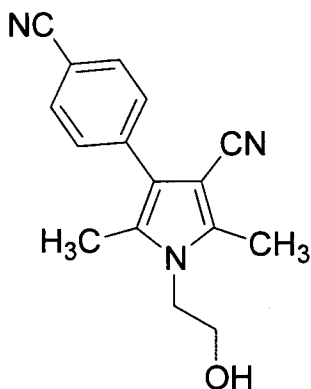
A mixture of methyl 2-methyl-1,3-oxazole-4-carboxylate [1.83 g, synthesized by the method described in Tetrahedron

Lett., 38, 331, (1997)], NBS (6.90 g), 2,2'-azobis(isobutyronitrile) (0.40 g) and carbon tetrachloride (40 ml) was heated under reflux for 14 hr, diluted with an aqueous saturated sodium bicarbonate solution and then
5 extracted with ethyl acetate. The extracted ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated, and then the residue was purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (1.17 g) as colorless crystals.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 3.93 (3H, s), 4.48 (2H, s), 8.25 (1H, s).

[Reference Example 78]

4-(4-Cyanophenyl)-1-(2-hydroxyethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile

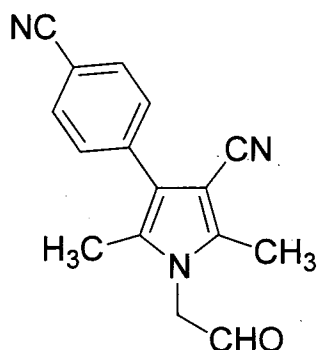


15 A suspension of sodium hydride (60% dispersion in oil, 0.44 g) in DMF (15 ml) was cooled in an ice bath and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.99 g) was added thereto. The reaction mixture was stirred at the same temperature for 30 min and 2-bromoethyl acetate
20 (1.1 ml) was added thereto, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was poured into water and extracted with ethyl acetate, and then the ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate and concentrated. The
25 residue was dissolved in methanol (50 ml) and potassium carbonate (2.60 g) was added thereto, and then the reaction solution was stirred at room temperature for 2 hr and concentrated. The residue was dissolved in ethyl acetate

and water and the ethyl acetate layer was separated, followed by drying over anhydrous magnesium sulfate and further concentration. The residue was purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (0.90 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.72 (1H, br), 2.31 (3H, s), 2.46 (3H, s), 3.88-3.94 (2H, m), 4.04 (2H, t), 7.49 (2H, d), 7.70 (2H, d). [Reference Example 79]

4-(4-Cyanophenyl)-2,5-dimethyl-1-(2-oxoethyl)-1H-pyrrole-3-carbonitrile

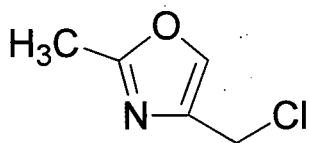


A solution of oxalyl chloride (0.068 ml) in dichloromethane (1 ml) was cooled to -70°C and dimethyl sulfoxide (0.12 ml) was added thereto. The reaction mixture was stirred at the same temperature for 20 min and a solution of the compound (88 mg) obtained in Reference Example 78 in dichloromethane (1 ml) was added thereto, and then dimethyl sulfoxide (0.50 ml) was added thereto. The reaction mixture was slowly heated to -30°C and cooled again to -70°C. To the reaction mixture, triethylamine (0.32 ml) was added and, and the mixture was heated to 0°C and stirred at the same temperature for 1 hr, water and ethyl acetate were added to the reaction solution. The ethyl acetate layer was separated, washed with water, dried over anhydrous magnesium sulfate and concentrated to obtain the crude titled compound (90 mg) as an amorphous solid.

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.34 (3H, s), 4.79 (2H, s), 7.50 (2H, d), 7.70 (2H, d), 9.75 (1H, s).

[Reference Example 80]

4-(Chloromethyl)-2-methyl-1,3-oxazole

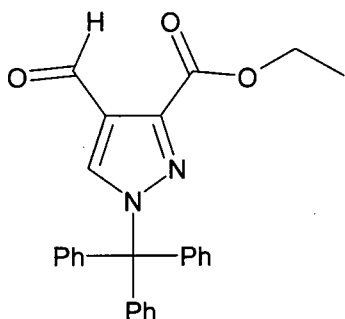


A mixture of acetamide (60.0 g) and 1,3-dichloro-2-propanone (26.0 g) was heated at 100°C for 2 hr. The reaction mixture was poured into an aqueous saturated sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated, and then the residue was distilled (100 to 130°C/40 to 60 mmHg). The resulting crude titled compound was further purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (3.34 g) as a colorless oil.

¹H-NMR (CDCl₃) δ: 2.47 (3H, s), 4.48 (2H, s), 7.54 (1H, s).

[Reference Example 81]

Ethyl 4-formyl-1-trityl-1H-pyrazole-3-carboxylate

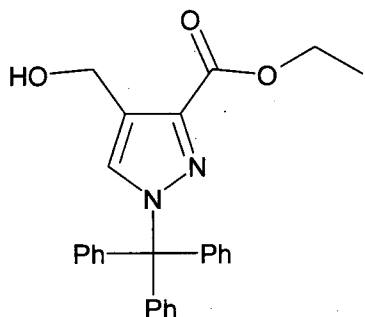


A mixture of ethyl 4-formyl-1H-pyrazole-3-carboxylate (5.00 g) synthesized by a known method, triphenylchloromethane (8.71 g), triethylamine (6.2 ml), 4-dimethylaminopyridine (0.38 g) and dichloromethane (50 ml) was stirred at room temperature for 3 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain the titled compound (7.01 g).

¹H-NMR (CDCl₃) δ: 1.39 (3H, t), 4.42 (2H, q), 7.08 - 7.15 (6H, m), 7.31 (1H, s), 7.32 - 7.37 (8 H, m), 7.96 (1H, s), 10.39 (1H, s).

[Reference Example 82]

5 Ethyl 4-(hydroxymethyl)-1-trityl-1H-pyrazole-3-carboxylate

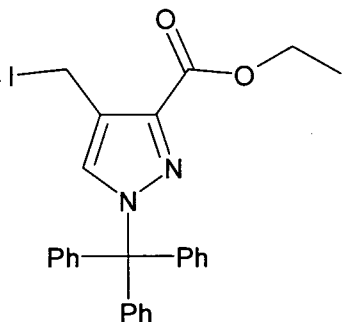


A mixture of the compound (4.0 g) synthesized in Reference Example 81, sodium borohydride (0.45 g), THF (20 ml) and methanol (20 ml) was stirred at 0°C for 1 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain the titled compound as a colorless solid (4.26 g).

15 ¹H-NMR (CDCl₃) δ: 1.37 (3H, t), 3.75 (1H, t), 4.38 (2H, q), 4.62 (2H, d), 7.10 - 7.16 (6H, m), 7.24 (1H, s), 7.32 (9H, td).

[Reference Example 83]

Ethyl 4-(iodomethyl)-1-trityl-1H-pyrazole-3-carboxylate



20

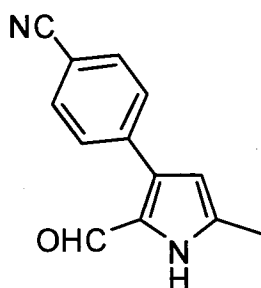
A mixture of the compound (2.30 g) synthesized in Reference Example 82, triphenylphosphine (1.61 g), iodine (1.56 g), imidazole (0.42 g) and dichloromethane (20 ml)

was stirred at room temperature for 4 hr. To the reaction solution, an aqueous saturated sodium bicarbonate solution and ethyl acetate were added, and the mixture was separated into an aqueous layer and an organic layer. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and then concentrated. The residue was suspended in diethylether and filtered to obtain the titled compound (1.12 g) as a colorless solid.

¹H-NMR (CDCl₃) δ: 1.40 (3H, t), 4.39 (2H, q), 4.59 (2H, s), 7.08 - 7.15 (6H, m), 7.32 (9H, td), 7.37 (1H, s).

[Reference Example 84]

4-(2-Formyl-5-methyl-1H-pyrrol-3-yl)benzonitrile

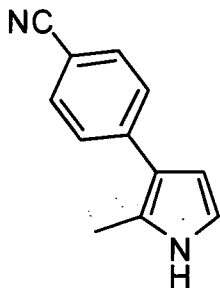


Vilsmeier reagent (1.72 g) was dissolved in DMF (17 ml), and 4-(4-cyanophenyl)-2-methyl-1H-pyrrole (1.02 g) was added thereto by small portions over 20 min under ice-cooling. The reaction mixture was stirred at room temperature for 10 min, water (1 ml) was added thereto, and the mixture was stirred further for 45 min. The reaction mixture was poured into an aqueous sodium bicarbonate solution, and extracted with ethyl acetate three times. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the titled compound (884.1 mg).

¹H-NMR (CDCl₃) δ: 2.39 (3H, s), 6.20 (1H, d), 7.57 (2H, d), 7.72 (2H, d), 9.41 (1H, brs), 9.51 (1H, s).

[Reference Example 85]

4-(2-Methyl-1H-pyrrol-3-yl)benzonitrile

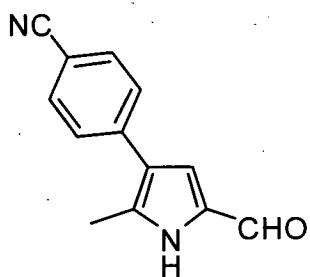


TFA (7.3 ml) was added to tert-butyl 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carboxylate (409.3 mg), and the mixture was stirred at room temperature for 3 hr.

5 The reaction solution was diluted with toluene, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the titled compound (122.8 mg).
¹H-NMR (CDCl₃) δ: 2.44 (3H, s), 6.38 (1H, t), 6.73 (1H, t),
10 7.50 (2H, d), 7.63 (2H, d), 8.07 (1H, brs).

[Reference Example 86]

4-(5-Formyl-2-methyl-1H-pyrrol-3-yl)benzonitrile



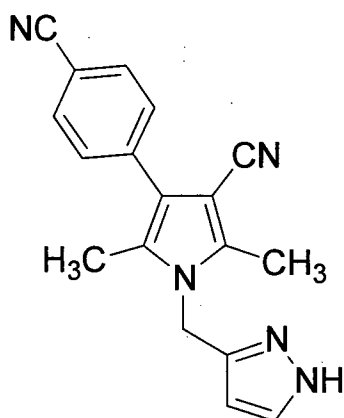
4-(2-Methyl-1H-pyrrol-3-yl)benzonitrile (144.7 mg) was
15 dissolved in DMF (1.6 ml), and Vilsmeier reagent (203.52 mg) was added thereto by small portions under ice-cooling. The reaction solution was stirred for 45 min at room temperature, poured into an aqueous sodium bicarbonate solution (3 ml), and further stirred for 15 min. The
20 solution was extracted with ethyl acetate four times. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column
25 chromatography (ethyl acetate-hexane) to obtain the titled

compound (130.1 mg) as white crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.50 (3H, s), 7.08 (1H, d), 7.50 (2H, d), 7.69 (2H, d), 9.48 (1H, s).

[Example 1]

5 4-(4-Cyanophenyl)-2,5-dimethyl-1-(1H-pyrazol-3-ylmethyl)-
1H-pyrrole-3-carbonitrile



A suspension of sodium hydride (60% dispersion in oil, 400 mg) in DMF (13 ml) was cooled in an ice bath and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.30 g) was added thereto. The reaction mixture was stirred at the same temperature for 30 min and the compound (2.00 g) obtained in Reference Example 3 was added thereto, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into water and extracted with ethyl acetate, and then the ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane-ethyl acetate) to obtain 4-(4-cyanophenyl)-2,5-dimethyl-1-[(1-trityl-1H-pyrazol-3-yl)methyl]-1H-pyrrole-3-carbonitrile (2.27 g) as crystals.

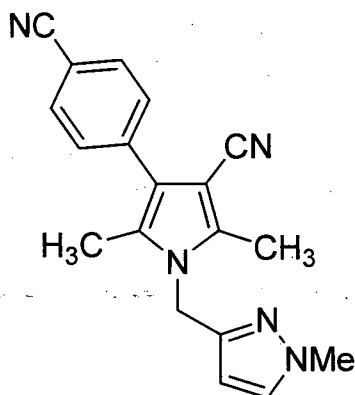
A mixture of 4-(4-cyanophenyl)-2,5-dimethyl-1-[(1-trityl-1H-pyrazol-3-yl)methyl]-1H-pyrrole-3-carbonitrile (2.27 g), pyridine hydrochloride (1.00 g) and methanol/THF (3/1, 70 ml) was heated at 80°C for 4 hr and concentrated, and then ethyl acetate and water were added to the residue. The ethyl acetate layer was separated, dried over anhydrous

magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane-ethyl acetate) and crystallized from ethyl acetate to obtain the titled compound (0.85 g) as colorless crystals.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.31 (3H, s), 2.47 (3H, s), 5.11 (2H, s), 6.08 (1H, d), 7.51 (2H, d), 7.56 (1H, d), 7.69 (2H, d), 10.08 (1H, s).

[Example 2]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[(1-methyl-1H-pyrazol-3-yl)methyl]-1H-pyrrole-3-carbonitrile
10

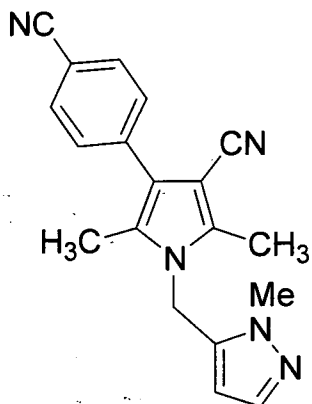


To a mixture of the compound (0.49 g) obtained in Example 1, potassium carbonate (0.45 g) and DMF (4 ml), methyl iodide (0.10 ml) was added. The reaction mixture
15 was stirred at room temperature for 14 hr, diluted with water and then extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane-ethyl acetate $\rightarrow$ ethyl acetate-methanol) to obtain the titled compound (0.35 g) as
20 colorless crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.31 (3H, s), 2.48 (3H, s), 3.88 (3H, s), 5.04 (2H, s), 5.90 (1H, d), 7.30 (1H, d), 7.50 (2H, d), 7.69 (2H, d).

25 [Example 3]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[(1-methyl-1H-pyrazol-5-yl)methyl]-1H-pyrrole-3-carbonitrile

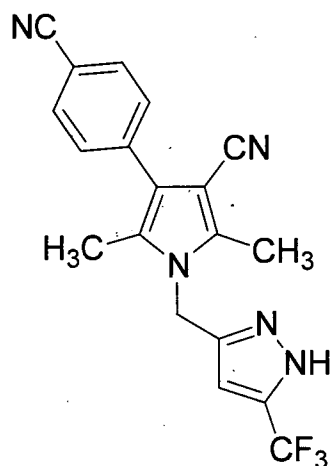


The reaction operation of Example 2 was conducted and purified by column chromatography to obtain the titled compound (0.10 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.22 (3H, s), 2.37 (3H, s), 3.89 (3H, s), 5.06 (2H, s), 5.66 (1H, d), 7.40 (1H, d), 7.51 (2H, d), 7.72 (2H, d).

[Example 4]

4-(4-Cyanophenyl)-2,5-dimethyl-1-([5-(trifluoromethyl)-1H-pyrazol-3-yl]methyl)-1H-pyrrole-3-carbonitrile



To a solution of 5-([tert-butyl(dimethyl)silyl]oxy)methyl)-3-(trifluoromethyl)-1H-pyrazole (33.0 g) in DMF (318 ml), sodium hydride (60% dispersion in oil, 4.87 g) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and benzyloxymethyl chloride (19.1 g) was added thereto, and the mixture was stirred at room temperature for 6 hr.

The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain an oil (34.38 g). The oil (4.80 g) obtained by the above reaction was dissolved in THF (50 ml) and tetrabutylammonium fluoride (3.38 g) was added thereto. The reaction solution was stirred at room temperature for 30 min and concentrated. Then ethyl acetate and water were added to the residue. The ethyl acetate layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and then concentrated to obtain a colorless oil (3.80 g).

A mixture of the resulting oil (3.80 g), triphenylphosphine (3.66 g) and dichloromethane (20 ml) was cooled in an ice bath and NBS (2.49 g) was added thereto. After the reaction mixture was stirred at room temperature for 30 min, an aqueous saturated sodium bicarbonate solution was added to the mixture and the dichloromethane layer was separated. The dichloromethane layer was purified by column chromatography (hexane-ethyl acetate) to obtain a mixture of 1-[(benzyloxy)methyl]-3-(bromomethyl)-5-(trifluoromethyl)-1H-pyrazole and 1-[(benzyloxy)methyl]-5-(bromomethyl)-3-(trifluoromethyl)-1H-pyrazole (about 1:1) as a colorless oil (3.70 g).

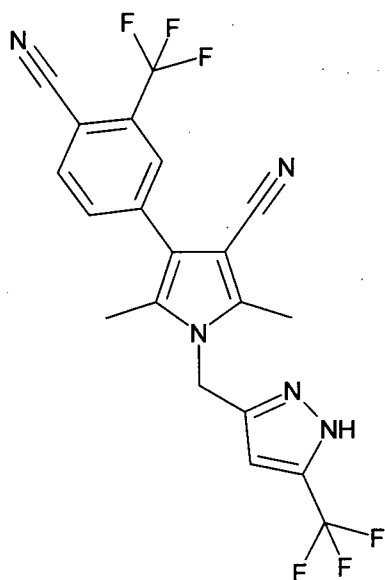
Using the resulting oil (3.70 g), sodium hydride (60% dispersion in oil, 0.52 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (2.21 g), the same reaction and purification operation as in Example 1 were conducted to obtain a mixture of 1-[[1-[(benzyloxy)methyl]-5-(trifluoromethyl)-1H-pyrazol-3-yl]methyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile and 1-[[1-[(benzyloxy)methyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (about 1:1, 3.83 g) as colorless crystals.

The resulting colorless crystals (3.44 g) were dissolved in methanol/THF (5:1, 60 ml) and 10% palladium carbon (1.00 g) was added thereto, and the mixture was stirred at room temperature for 2 hr under a hydrogen atmosphere. After the catalyst was removed by filtration, the filtrate was concentrated and the resulting residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with an aqueous 10% sodium hydrogen phosphate solution, dried over anhydrous magnesium sulfate and then concentrated. The residue was purified by column chromatography (hexane-ethyl acetate) to obtain the titled compound (0.22 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.45 (3H, s), 5.15 (2H, s), 6.36 (1H, s), 7.50 (2H, d), 7.71 (2H, d), 10.30-10.50 (1H, br s).

[Example 5]

4-[4-Cyano-3-(trifluoromethyl)phenyl]-2,5-dimethyl-1-[[5-(trifluoromethyl)-1H-pyrazol-3-yl]methyl]-1H-pyrrole-3-carbonitrile



To a solution of 4-[4-cyano-3-(trifluoromethyl)phenyl]-2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.45 g) in DMF (5 ml), sodium hydride (60% dispersion in oil, 0.085 g) was added under ice cooling.

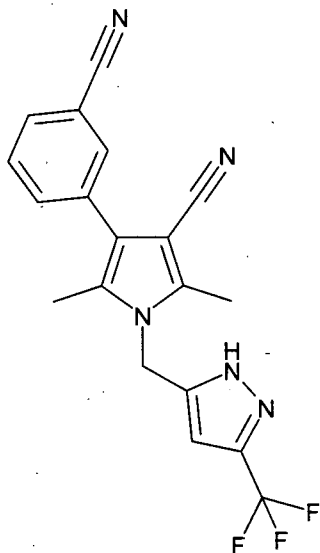
After the reaction mixture was stirred at room temperature for 30 min, a mixture (0.58 g) of 1-[(benzyloxy)methyl]-5-(bromomethyl)-3-(trifluoromethyl)-1H-pyrazole and 1-[(benzyloxy)methyl]-3-(bromomethyl)-5-(trifluoromethyl)-1H-pyrazole was added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain a mixture (3.65 g) of 1-[[1-[(benzyloxy)methyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile and 1-[[1-[(benzyloxy)methyl]-5-(trifluoromethyl)-1H-pyrazol-3-yl]methyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile.

To a mixture of a mixture of above two isomers (0.70 g) and dichloromethane (20 ml), a 2 mol/l boron tribromide dichloromethane solution (2.2 ml) was added at 0°C. After stirring at room temperature for 2 hr, the reaction mixture was poured into an aqueous saturated sodium bicarbonate solution (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. Then, the residue was purified by basic silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethylether to obtain the titled compound (0.42 g) as crystals.

¹H NMR (CDCl₃) δ: 2.30 (3H, s), 2.46 (3H, s), 5.17 (2H, s), 6.37 (1H, s), 7.70 - 7.82 (2H, m), 7.89 (1H, d), 10.79 (1H, s).

[Example 6]

4-(3-Cyanophenyl)-2,5-dimethyl-1-[[3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl]-1H-pyrrole-3-carbonitrile

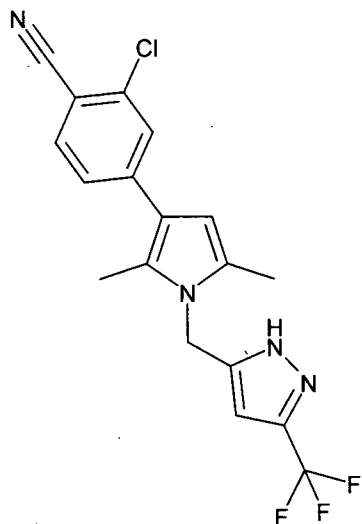


Using 4-(3-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile as a material, the titled compound was obtained in the same manner as in Example 5.

¹H-NMR (CDCl₃) δ: 2.25 (3H, s), 2.44 (3H, s), 5.16 (2H, s), 6.37 (1H, s), 7.53 - 7.68 (4 H, m), 10.58 (1H, s).

[Example 7]

2-Chloro-4-(2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl)benzonitrile



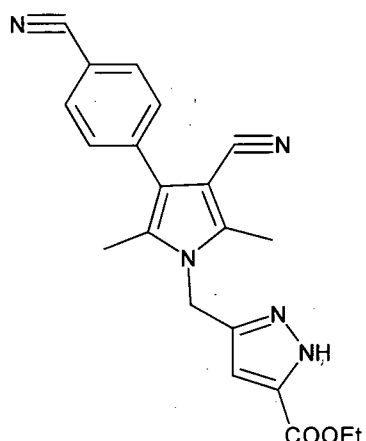
Using 2-chloro-4-(2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile as a material, the titled compound was obtained in the same manner as in Example 5.

¹H-NMR (CDCl₃) δ: 2.24 (3H, s), 2.32 (3H, s), 5.14 (2H, s),

6.13 (1H, s), 6.36 (1H, s), 7.33 (1H, dd), 7.48 (1H, d),
7.63 (1H, d).

[Example 8]

Ethyl 3-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-
1-yl]methyl)-1H-pyrazole-5-carboxylate

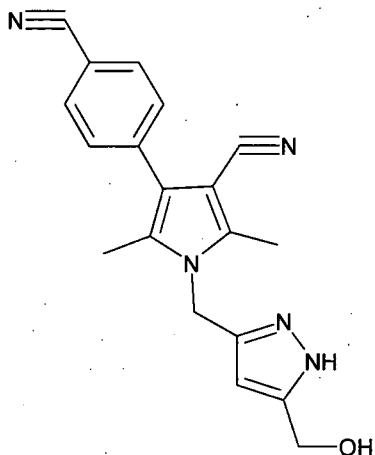


Under an argon atmosphere, to a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.45 g) in dehydrated-DMF (19.6 ml), sodium hydride (60% dispersion in oil, 300 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of ethyl 1-acetyl-5-(bromomethyl)-1H-pyrazole-3-carboxylate (2.07 g) in dehydrated-DMF (3 ml) was added to the mixture, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-ether to obtain the titled compound (169 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.39 (3H, t), 2.31 (3H, s), 2.37 (3H, s), 4.39 (2H, q), 5.11 (2H, s), 6.54 (1H, s), 7.51 (2H, d), 7.70 (2H, d), 10.80 (1H, s).

[Example 9]

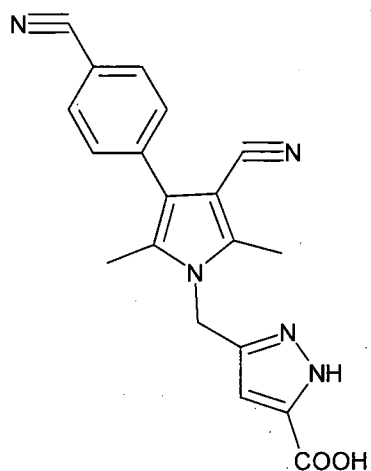
4-(4-Cyanophenyl)-1-([5-(hydroxymethyl)-1H-pyrazol-3-yl]methyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile



A mixture of sodium borohydride (120 mg), calcium chloride (175 mg), THF (12.6 ml) and ethanol (6.3 ml) was stirred at room temperature for 30 min and ethyl 3-
5 cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-5-carboxylate (235 mg) was added thereto, and the mixture was stirred at room temperature for 17 hr. The reaction mixture was poured into ice water and 1N hydrochloric acid (3.14 ml) was added thereto. The
10 reaction mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-
15 ether to obtain the titled compound (50 mg) as crystals
¹H-NMR (DMSO-d₆) δ: 2.31 (3H, s), 2.44 (3H, s), 4.42 (2H, d), 5.09 (2H, s), 5.24 (1H, t), 6.02 (1H, s), 7.52 (2H, d), 7.89 (2H, d), 12.66 (1H, s).

[Example 10]

20 3-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-5-carboxylic acid



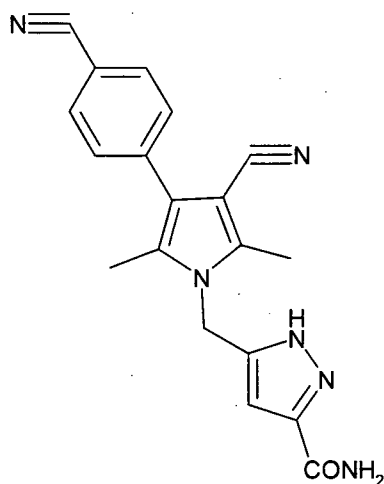
Under an argon atmosphere, to a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.77 g) in dehydrated-DMF (24 ml), sodium hydride (60% dispersion in oil, 368 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of ethyl 5-(bromomethyl)-1-[(2,2-dimethylpropanoyl)oxy]methyl}-1H-pyrazole-3-carboxylate (3.20 g) in dehydrated-DMF (5 ml) was added to the mixture, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain ethyl 5-[[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl]-1-[[[(2,2-dimethylpropanoyl)oxy]methyl]-1H-pyrazole-3-carboxylate (3.12 g) as a crystalline powder.

To a solution of ethyl 5-[[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl]-1-[[[(2,2-dimethylpropanoyl)oxy]methyl]-1H-pyrazole-3-carboxylate (1.05 g) in THF (9.7 ml), an aqueous 1N sodium hydroxide solution (6.45 ml) was added and also methanol (9.7 ml) was added, and the mixture was stirred at room temperature for 26 hr. After methanol and THF were distilled off, the residue was diluted with water and neutralized by adding 1N

hydrochloric acid (6.45 ml). After extracting with ethyl acetate, the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The precipitated crystals were filtered, washed with ether and dried to obtain the titled compound (517 mg).

¹H-NMR (DMSO-d₆) δ: 2.29 (3H, s), 2.43 (3H, s), 3.81 (1H, s), 5.20 (2H, s), 6.64 (1H, s), 7.55 (2H, d), 7.90 (2H, d).
[Example 11]

5-{{[3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-3-carboxamide

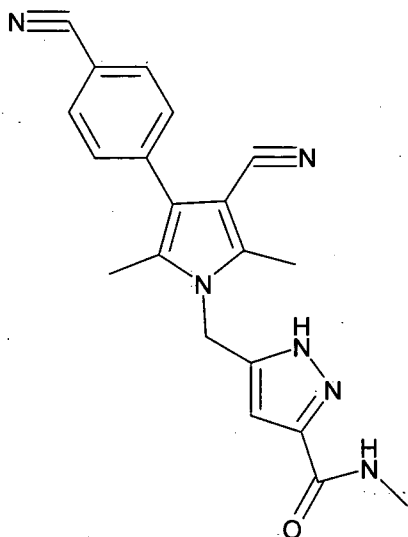


To a solution of 3-{{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-5-carboxylic acid (204 mg) in dehydrated THF solution (1.8 ml), oxazolyl chloride (225 mg) was added and also DMF (one drop) was added under ice cooling with stirring, and the reaction temperature was returned to room temperature and further the mixture was stirred for 2 hr. After concentration, an acid chloride dissolved in THF again was added to a mixed solution of concentrated ammonia water (2.5 ml) and THF (1.25 ml) under ice cooling with stirring, and the reaction temperature was returned to room temperature and further the mixture was stirred for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue

was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-methanol to obtain the titled compound (65 mg) as crystals.
¹H-NMR (DMSO-d₆) δ: 2.29 (3H, s), 2.44 (3H, s), 5.18 (2H, s), 6.65 (1H, s), 7.42 (1H, br s), 7.53 (2H, d), 7.81 (1H, br s), 7.89 (2H, d), 13.45 (1H, br s).

[Example 12]

5-{{[3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-N-methyl-1H-pyrazole-3-carboxamide



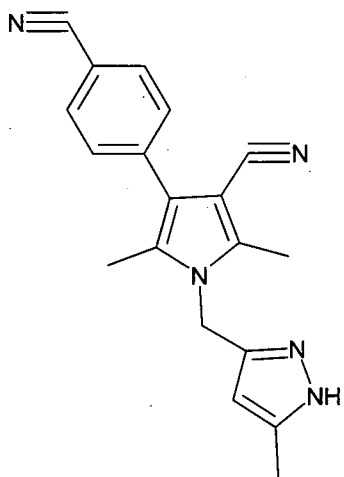
To a solution of 3-{{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-5-carboxylic acid (204 mg) in dehydrated THF (1.8 ml), oxazolyl chloride (225 mg) was added and also DMF (one drop) was added under ice cooling with stirring, the reaction temperature was returned to room temperature and further the mixture was stirred for 2 hr. After concentration, an acid chloride dissolved in THF again was added to a solution of 2M-methylamine in THF (10 ml) under ice cooling with stirring, the reaction temperature was returned to room temperature and the mixture was further stirred for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column

chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-methanol to obtain the titled compound (64 mg) as crystals.

¹H-NMR (DMSO-d₆) δ: 2.28 (3H, s), 2.43 (3H, s), 2.72 (3H, d), 5.19 (2H, s), 6.59 (1H, s), 7.54 (2H, d), 7.89 (2H, d), 8.31 (1H, br s), 13.47 (1H, br s).

[Example 13]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[(5-methyl-1H-pyrazol-3-yl)methyl]-1H-pyrrole-3-carbonitrile



Under an argon atmosphere, to a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.11 g) in dehydrated-DMF (15 ml), sodium hydride (60% dispersion in oil, 230 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 1-[(benzyloxy)methyl]-3-(iodomethyl)-5-methyl-1H-pyrazole (1.97 g) in dehydrated-DMF (3 ml) was added to the mixture, and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane) and also the effluent was purified by silica gel column chromatography (ethyl acetate-hexane) and recrystallized from ethyl acetate-methanol to obtain 1-({1-

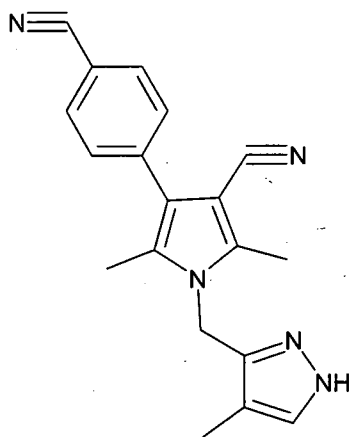
[(benzyloxy)methyl]-5-methyl-1H-pyrazol-3-yl)methyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.87 g).

To a solution of 1-({1-[(benzyloxy)methyl]-5-methyl-1H-pyrazol-3-yl)methyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.31 g) in dichloromethane (30 ml), a solution of 2M-boron tribromide in dichloromethane (5.25 ml) was added under ice cooling with stirring, and the mixture was stirred for 2 hr. The reaction mixture was poured into ice water, neutralized with an aqueous saturated sodium bicarbonate solution and then partitioned. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated. Crystals obtained from the residue was refined with methanol, filtered, purified by NH-silica gel column chromatography (ethyl acetate-hexane) and then crystallized from ethyl acetate to obtain the titled compound (159 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.30 (6H, s), 2.46 (3H, s), 5.02 (2H, s), 5.76 (1H, s), 7.49 (2H, d), 7.68 (2H, d), 9.63 (1H, br s).

[Example 14]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[(4-methyl-1H-pyrazol-3-yl)methyl]-1H-pyrrole-3-carbonitrile



Under an argon atmosphere, to a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.11 g) in dehydrated-DMF (15 ml), sodium hydride (60%

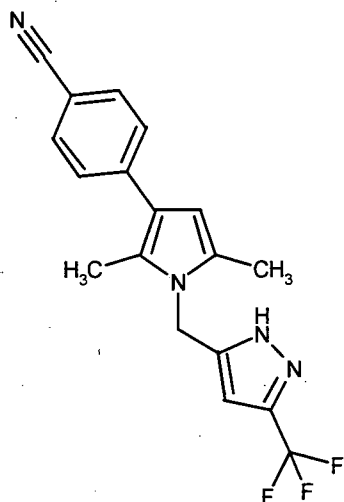
dispersion in oil, 230 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 1-[(benzyloxy)methyl]-3-(iodomethyl)-4-methyl-1H-pyrazole (1.97 g) in dehydrated-DMF (3 ml) was added to the mixture, and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane), and then the effluent was further purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-methanol to obtain 1-({1-[(benzyloxy)methyl]-4-methyl-1H-pyrazol-3-yl)methyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.83 g).

To a solution of 1-({1-[(benzyloxy)methyl]-4-methyl-1H-pyrazol-3-yl)methyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.62 g) in dichloromethane (37.2 ml), a solution of 2M-boron tribromide in dichloromethane (6.51 ml) was added under ice cooling with stirring, and the mixture was stirred for 3 hr. The reaction mixture was poured into ice water, neutralized with saturated sodium bicarbonate water and then partitioned with. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-hexane to obtain the titled compound (245 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.99 (3H, s), 2.26 (3H, s), 2.43 (3H, s), 5.04 (2H, s), 7.32 (1H, s), 7.49 (2H, d), 7.67 (2H, d), 9.96 (1H, br s).

[Example 15]

4-(2,5-Dimethyl-1-{{3-(trifluoromethyl)-1H-pyrazol-5-yl)methyl}-1H-pyrrol-3-yl)benzonitrile



Synthesis method 1: A mixture of 3-(trifluoromethyl)-1H-pyrazole-5-carbaldehyde (9.75 g), triphenylchloromethane (16.6 g), triethylamine (12.2 ml), 4-dimethylaminopyridine (0.55 g) and dichloromethane (300 ml) was stirred at room temperature for 24 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain a colorless solid (21.92 g). A mixture of the solid (21.58 g), sodium borohydride (4.05 g), THF (300 ml) and methanol (300 ml) was stirred at 0°C for 1 hr, and then stirred at room temperature for 3 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain a colorless solid (21.72 g). The solid (11.67 g) obtained by the above reaction was dissolved in dichloromethane (250 ml), and imidazole (2.15 g), triphenylphosphine (8.26 g) and iodine (8.00 g) were added thereto, and the mixture was stirred at 0°C for 3 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by

silica gel column chromatography (ethyl acetate-hexane) to obtain a mixture (14.32 g) of 5-(iodomethyl)-3-(trifluoromethyl)-1-trityl-1H-pyrazole and 3-(iodomethyl)-5-(trifluoromethyl)-1-trityl-1H-pyrazole as a solid. To a solution of 3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole (360 mg) in DMF (10 ml), sodium hydride (60% dispersion in oil, 88 mg) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and the above-mentioned mixture (0.95 g) of 5-(iodomethyl)-3-(trifluoromethyl)-1-trityl-1H-pyrazole and 3-(iodomethyl)-5-(trifluoromethyl)-1-trityl-1H-pyrazole was added, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain a mixture (310 mg) of 4-(2,5-dimethyl-1-([3-(trifluoromethyl)-1-trityl-1H-pyrazol-5-yl]methyl)-1H-pyrrole-3-yl)benzonitrile and 4-(2,5-dimethyl-1-([5-(trifluoromethyl)-1-trityl-1H-pyrazol-3-yl]methyl)-1H-pyrrole-3-yl)benzonitrile as a solid.

The mixture (293 mg) was dissolved in TFA (2 ml), and the mixture was stirred at room temperature for 10 min. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was separated into an aqueous layer and an organic layer. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethylether to obtain the titled compound (116 mg) as crystals.

Synthesis method 2: A mixture of tert-butyl 2,5-dimethyl-1-(2-oxopropyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carboxylate (350 mg) and sodium methoxide (28% methanol solution, 0.24

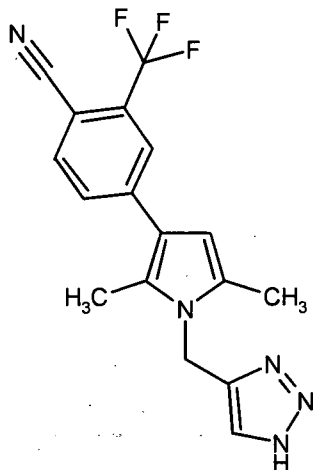
ml) and 1,2-dimethoxyethane (3 ml) was stirred at room temperature for 30 min and ethyl trifluoroacetate (0.14 ml) was added, followed by stirring at room temperature for 20 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in acetic acid (3 ml) and hydrazine monohydrate (0.25 ml) was added thereto, and the mixture was stirred at 80°C for 30 min. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was separated an aqueous layer and an organic layer. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. As a result of crystallization from the residue using diethylether, tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-3-carboxylate (276 mg) was obtained as crystals. To a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-3-carboxylate (223 mg) in ethyl acetate (2.5 ml), a 4N hydrogen chloride/ethyl acetate was added, and the mixture was stirred at 40°C for 14 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethylether to obtain the titled compound (150 mg) as crystals.

Melting point 147-149°C

¹H NMR (CDCl₃) δ: 2.24 (3H, s), 2.31 (3H, s), 5.14 (2H, s), 6.13 (1H, s), 6.35 (1H, s), 7.43 (2H, d), 7.63 (2H, d), 10.40 (1H, s).

[Example 16]

4-[2,5-Dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]-2-(trifluoromethyl)benzonitrile



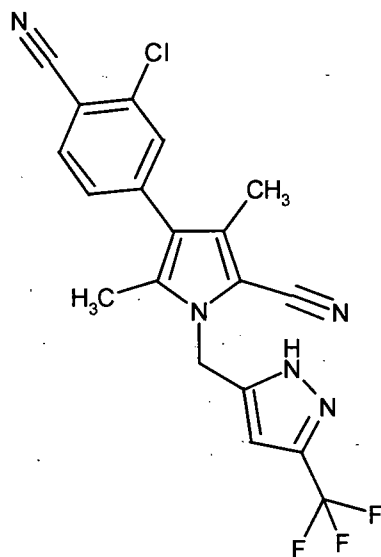
A mixture of ethyl 1H-1,2,3-triazole-4-carboxylate
5 (20.2 g) synthesized by a known method, triphenylchloromethane (40 g), triethylamine (24 ml) and DMF (140 ml) was stirred at room temperature for 20 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate
10 layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain a colorless solid (52.1 g). A mixture of sodium borohydride (6.9 g), calcium chloride (15 g), THF (120 ml) and ethanol (60 ml) was stirred at room temperature for 30 min. The solid (35
15 g) obtained by the above reaction was added to the mixture, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over
20 anhydrous magnesium sulfate and concentrated to obtain a colorless solid (31.0 g). The solid (24.0 g) obtained by the above reaction was dissolved in DMF (300 ml), and NBS (13.1 g) and triphenylphosphine (19.4 g) were added thereto, and the mixture was stirred at room temperature for 2 hr.
25 The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain a mixture (21.1 g) of bromomethyltriazole derivatives as a solid. The resulting product is a mixture of two kinds of isomers and was used in the following reaction without being purified furthermore. Using 3-[4-cyano-3-(trifluoromethyl)phenyl]-2,5-dimethyl-1H-pyrrole as a material, the titled compound was obtained in the same manner as in the synthesis method 1 of Example 15.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.30 (3H, s), 2.39 (3H, s), 5.18 (2H, s), 6.12 (1H, s), 7.42 (1H, s), 7.60 (1H, d), 7.71 - 7.84 (2H, m), 11.91 (1H, s).

[Example 17]

4-(3-Chloro-4-cyanophenyl)-3,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-2-carbonitrile

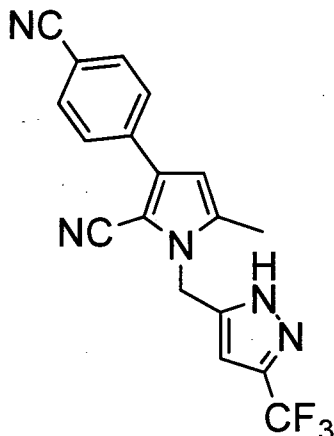


Using 4-(3-chloro-4-cyanophenyl)-3,5-dimethyl-1H-pyrrole-2-carbonitrile and 5-(iodomethyl)-3-(trifluoromethyl)-1-trityl-1H-pyrazole as materials, the titled compound was obtained in the same manner as in the synthesis method 1 of Example 15.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.20 (3H, s), 2.30 (3H, s), 7.23 (1H, dd), 7.38 (1H, d), 7.71 (1H, d), 8.59 (1H, s).

[Example 18]

3-(4-Cyanophenyl)-5-methyl-1-{{3-(trifluoromethyl)-1H-pyrazol-5-yl}methyl}-1H-pyrrole-2-carbonitrile



To a solution of sodium hydride (60% dispersion in oil, 0.03 g) in DMF (3.0 ml), 3-(4-cyanophenyl)-5-methyl-1H-pyrrole-2-carbonitrile (0.14 g) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and a solution of a mixture (0.26 g) of 1-[(benzyloxy)methyl]-5-(bromomethyl)-3-(trifluoromethyl)-1H-pyrazole and 1-[(benzyloxy)methyl]-3-(bromomethyl)-5-(trifluoromethyl)-1H-pyrazole described in Example 5 in DMF (1.0 ml) was added to the mixture, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from hexane to obtain an intermediate (316 mg) as crystals.

Subsequently, to a solution of the compound (308 mg) obtained above in dichloromethane (10 ml), a solution of boron tribromide (1.0 M) in dichloromethane (2.27 ml) was

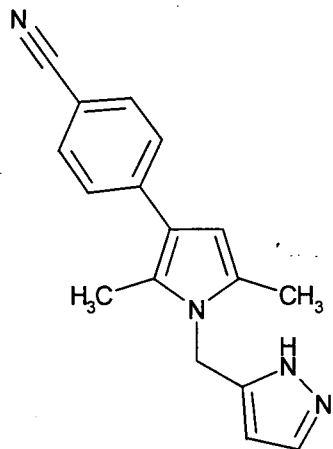
added dropwise under ice cooling, and the mixture was stirred for 1 hr. Water and aqueous saturated sodium bicarbonate solution were poured into the reaction solution, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and then the resulting titled compound was subsequently purified by basic silica gel column chromatography (ethyl acetate) and crystallized from ethyl acetate-diisopropylether to obtain the titled compound (48 mg) as crystals.

Melting point: 189-190°C

¹H-NMR (DMSO-d₆) δ: 2.32 (3H, s), 5.40 (2H, s), 6.55 (1H, s), 6.59 (1H, s), 7.85 (2H, d), 7.93 (2H, d).

[Example 19]

4-[2,5-Dimethyl-1-(1H-pyrazol-5-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



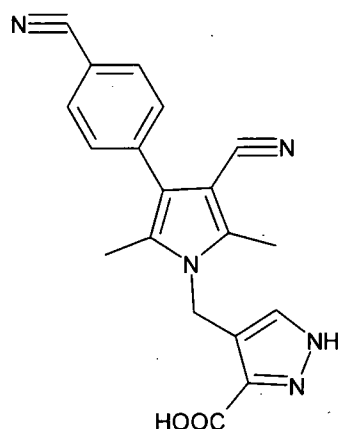
To a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (440 mg) in DMF (10 ml), sodium hydride (60% dispersion in oil, 98 mg) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and 5-(iodomethyl)-1-trityl-1H-pyrazole (0.73 g) was added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction

mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in TFA (10 ml), and the mixture was stirred at room temperature for 4 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from diethylether to obtain the titled compound (12 mg) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.28 (3H, s), 2.36 (3H, s), 5.09 (2H, s), 6.03 (1H, s), 6.08 (1H, s), 7.30 (1H, s), 7.45 (2H, d), 7.51 (1H, d), 7.60 (2H, d).

[Example 20]

4-{[3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-3-carboxylic acid



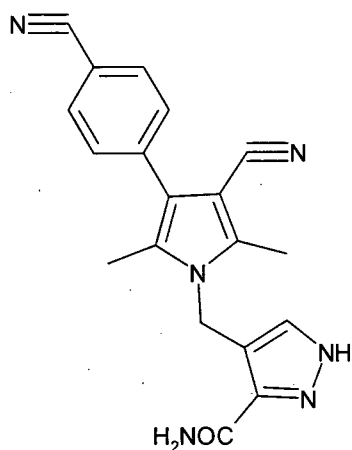
Under an argon atmosphere, to a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.77 g) in dehydrated-DMF (24 ml), sodium hydride (60% dispersion in oil, 368 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of ethyl 4-(bromomethyl)-1-[(2,2-dimethylpropanoyl)oxy]methyl}-1H-pyrazole-3-carboxylate (3.81 g, purity: 84%) in dehydrated-DMF (5 ml) was added to

the mixture, the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain ethyl 4-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1-([(2,2-dimethylpropanoyl)oxy]methyl)-1H-pyrazole-3-carboxylate (1.86 g) as a crystalline powder.

To a solution of ethyl 4-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1-([(2,2-dimethylpropanoyl)oxy]methyl)-1H-pyrazole-3-carboxylate (1.06 g) in THF (9.7 ml), an aqueous 1 N sodium hydroxide solution (6.45 ml) and methanol (9.7 ml) were added, and the mixture was stirred at room temperature for 26 hr. After methanol and THF were distilled off, the residue was diluted with water and neutralized by adding 1N hydrochloric acid (6.45 ml). After extracting with ethyl acetate, the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The crystalline powder was filtered, washed with ether and then dried to obtain the titled compound (489 mg). ¹H-NMR (DMSO-d₆) δ: 2.20 (3H, s), 2.35 (3H, s), 5.29 (2H, s), 7.29 (1H, s), 7.58 (2H, d), 7.93 (2H, d).

[Example 21]

4-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carboxamide

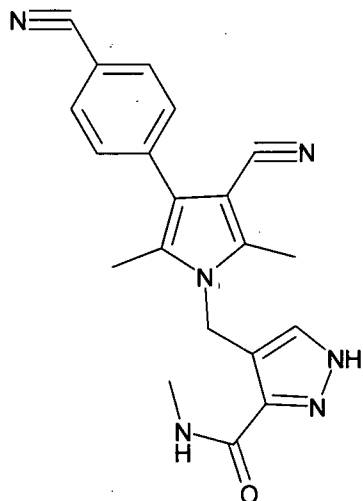


To a solution of 4-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carboxylic acid (216 mg) in dehydrated THF (1.9 ml), oxalyl chloride (245 mg) was added and also DMF (one drop) was added under ice cooling with stirring, the reaction temperature was returned to room temperature and the reaction mixture was further stirred for 2 hr. After concentration, an acid chloride dissolved in THF again was added to a mixed solution of concentrated ammonia water (2.5 ml) and THF (1.25 ml) under ice cooling with stirring, the reaction temperature was returned to room temperature and the reaction mixture was further stirred for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate-methanol to obtain the titled compound (59 mg) as crystals.

¹H-NMR (DMSO-d₆) δ: 2.19 (3H, s), 2.34 (3H, s), 5.33 (2H, s), 7.24 (1H, s), 7.33 (1H, br s), 7.56 (2H, d), 7.70 (0.5H, br s), 7.90 (2H, d), 7.97 (0.5H, br s), 13.23 (1H, br s).

[Example 22]

4-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-N-methyl-1H-pyrazole-3-carboxamide

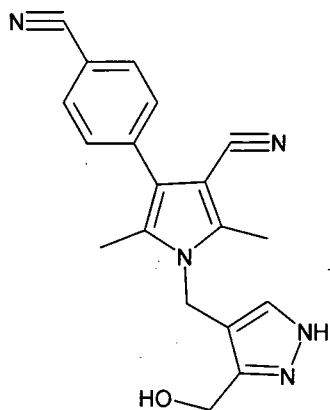


To a solution of 4-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carboxylic acid (216 mg) in dehydrated THF solution (1.9 ml), oxazolyl chloride (245 mg) was added and also DMF (one drop) was added under ice cooling with stirring, the reaction temperature was returned to room temperature and the reaction mixture was further stirred for 2 hr. After concentration, an acid chloride dissolved in THF again was added to a solution of 2M-methylamine in THF (10 ml) under ice cooling with stirring, the reaction temperature was returned to room temperature and the reaction mixture was further stirred for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-methanol to obtain the titled compound (118 mg) as crystals.

¹H-NMR (DMSO-d₆) δ: 2.20 (3H, s), 2.34 (3H, s), 2.76 (3H, d), 5.35 (2H, s), 7.27 (1H, s), 7.56 (2H, d), 7.90 (2H, d), 8.19 (1H, q), 13.22 (1H, br s).

[Example 23]

4-(4-Cyanophenyl)-1-([3-(hydroxymethyl)-1H-pyrazol-4-yl]methyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile

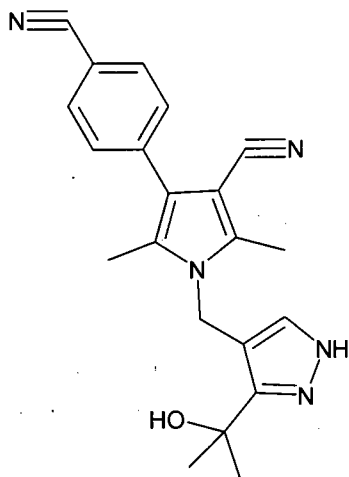


A mixture of sodium borohydride (272 mg), calcium chloride (400 mg), THF (14.4 ml) and ethanol (7.2 ml) was stirred at room temperature for 30 min and ethyl 4-{{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1-{{[(2,2-dimethylpropanoyl)oxy]methyl}-1H-pyrazole-3-carboxylate (704 mg) was added thereto, and the mixture was stirred at room temperature for 13.5 hr. The reaction mixture was poured into ice water and 1N hydrochloric acid (7.2 ml) was added thereto. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from ethyl acetate-methanol to obtain the titled compound (338 mg) as crystals.

¹H-NMR (DMSO-d₆+TFA) δ: 2.25 (3H, s), 2.39 (3H, s), 4.50 (2H, s), 5.10 (2H, s), 7.27 (1H, s), 7.57 (2H, d), 7.91 (2H, d).

[Example 24]

4-(4-Cyanophenyl)-1-{{[3-(1-hydroxy-1-methylethyl)-1H-pyrazol-4-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carbonitrile

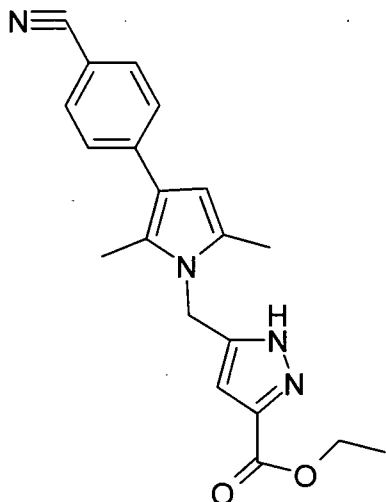


Under an argon atmosphere, to a solution of ethyl 4-
 {[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-
 yl]methyl}-1-[[2,2-dimethylpropanoyl]oxy]methyl}-1H-
 5 pyrazole-3-carboxylate (521 mg) in dehydrated THF (5.21 ml),
 a solution of 1M-methylmagnesium bromide in THF (3.18 ml)
 was added at -70°C . The reaction mixture was allowed to
 stand at the same temperature for 30 min, and at room
 temperature for 3 hr. To the reaction mixture, an aqueous
 10 saturated ammonium chloride solution was added, and the
 mixture was extracted with ethyl acetate. The organic
 layer was washed with saturated brine, dried over anhydrous
 magnesium sulfate and concentrated. The residue was
 purified by silica gel column chromatography (ethyl
 15 acetate-hexane) and the effluent was further purified by
 NH-silica gel (manufactured by Fuji Silysia Chemical Ltd.)
 column chromatography (ethyl acetate-hexane) and
 recrystallized from ethyl acetate-ether to obtain the
 titled compound (171 mg).

20 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.49 (9H, s), 2.21 (3H, s), 2.34 (3H,
 s), 5.19 (2H, s), 5.10-5.30 (1H, br s), 6.76 (1H, s), 7.59
 (2H, d), 7.92 (2H, d), 12.37 (1H, br s).

[Example 25]

Ethyl 5-[[3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-
 25 yl]methyl}-1H-pyrazole-3-carboxylate



Under an argon atmosphere, to a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (297 mg) in dehydrated-DMF (5 ml), sodium hydride (60% dispersion in oil, 44 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of ethyl 1-{[(2,2-dimethylpropanoyl)oxy]methyl}-5-(iodomethyl)-1H-pyrazole-3-carboxylate (475 mg) in dehydrated-DMF (5 ml) was added to the mixture, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain, as an amorphous powder, ethyl 5-[[3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl]-1-[(2,2-dimethylpropanoyl)oxy]methyl}-1H-pyrazole-3-carboxylate (126 mg).

A mixture of sodium borohydride (74 mg), calcium chloride (108 mg), THF (3.9 ml) and ethanol (1.95 ml) was stirred at room temperature for 30 min and ethyl 5-{[3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1-{[(2,2-dimethylpropanoyl)oxy]methyl}-1H-pyrazole-3-carboxylate (222 mg) was added thereto, and

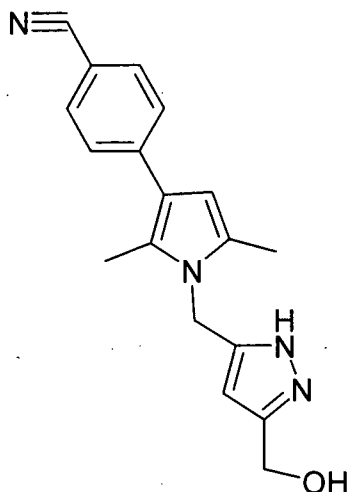
the mixture was stirred at room temperature for 20 hr. To the reaction mixture, 1N hydrochloric acid (1.95 ml) was added and, after extracting with ethyl acetate, the ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. Then, the residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane) to obtain ethyl 5-{{[3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-3-carboxylate (97 mg) and tert-butyl 4-(4-cyanophenyl)-1-{{[3-(hydroxymethyl)-1H-pyrazol-5-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carboxylate (40 mg) as an amorphous powder.

Ethyl 5-{{[3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-3-carboxylate (15 mg) was dissolved in TFA (0.3 ml), and the mixture was stirred at room temperature for 3 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-hexane to obtain the titled compound (8 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.37 (3H, t), 2.28 (3H, s), 2.36 (3H, s), 4.36 (2H, q), 5.10 (2H, s), 6.09 (1H, s), 6.49 (1H, s), 7.45 (2H, d), 7.61 (2H, d).

[Example 26]

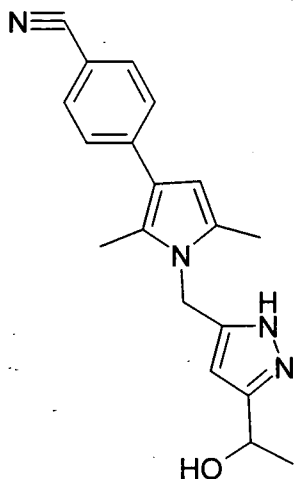
4-(1-{{[3-(Hydroxymethyl)-1H-pyrazol-5-yl]methyl}-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile



Tert-butyl 4-(4-cyanophenyl)-1-([3-(hydroxymethyl)-1H-pyrazol-5-yl]methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (33 mg) was dissolved in TFA (0.5 ml), and the mixture was stirred at room temperature for 2.5 hr. To the reaction mixture, dichloromethane and sodium bicarbonate water were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane) and crystallized from dichloromethane-methanol to obtain the titled compound (8 mg) as crystals. ¹H-NMR (CDCl₃) δ: 2.25 (3H, s), 2.34 (3H, s), 4.68 (2H, s), 5.04 (2H, s), 5.88 (1H, s), 6.06 (1H, s), 7.42 (2H, d), 7.59 (2H, d).

[Example 27]

4-(1-([3-(1-Hydroxyethyl)-1H-pyrazol-5-yl]methyl)-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile



To a solution of tert-butyl 4-(4-cyanophenyl)-1-[(3-(hydroxymethyl)-1H-pyrazol-5-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (186 mg) in dichloromethane (18.3 ml), manganese dioxide (794 mg) was added, and the mixture was stirred at room temperature for 22 hr. Insolubles were removed by filtration through celite, followed by washing with dichloromethane. The filtrate and the wash were concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain tert-butyl 4-(4-cyanophenyl)-1-[(3-formyl-1H-pyrazol-5-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (90 mg) as a crystalline powder.

To a solution of tert-butyl 4-(4-cyanophenyl)-1-[(3-formyl-1H-pyrazol-5-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (79 mg) in dehydrated THF (2.9 ml), a solution of 1M-methylmagnesium bromide in THF (0.7 ml) was added at -70°C. After the temperature was returned to room temperature, the mixture was allowed to stand at the same temperature for 30 min, and at room temperature for 1 hr. To the reaction mixture, an aqueous saturated ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain

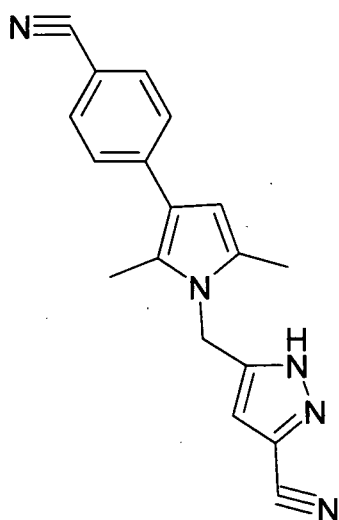
tert-butyl 4-(4-cyanophenyl)-1-{[3-(1-hydroxyethyl)-1H-pyrazol-5-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carboxylate (28 mg) as a crystalline powder.

5 Tert-butyl 4-(4-cyanophenyl)-1-{[3-(1-hydroxyethyl)-1H-pyrazol-5-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carboxylate (43 mg) was dissolved in TFA (0.157 ml), and the mixture was stirred at room temperature for 1.5 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the mixture was
10 partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain the titled
15 compound (15 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.52 (3H, d), 2.28 (3H, s), 2.36 (3H, s), 4.96 (1H, q), 5.04 (2H, s), 5.82 (1H, s), 6.07 (1H, s), 7.44 (2H, d), 7.60 (2H, d).

[Example 28]

20 5-{[3-(4-Cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-3-carbonitrile



To a solution of tert-butyl 4-(4-cyanophenyl)-1-[(3-formyl-1H-pyrazol-5-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-
25 carboxylate (138 mg) in NMP (3.4 ml), hydroxylamine

hydrochloride (28.4 mg) was added, and the mixture was stirred at 100°C for 2 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain tert-butyl 4-(4-cyanophenyl)-1-((3-[(E)-(hydroxyimino)methyl]-1H-pyrazol-5-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (116 mg) as an amorphous powder.

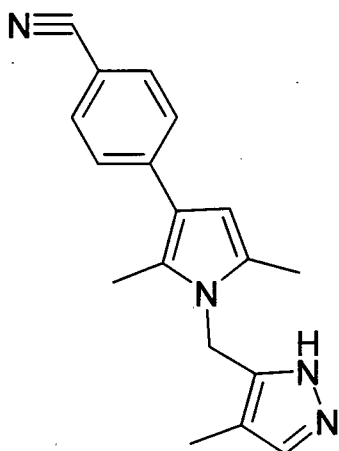
To a solution of tert-butyl 4-(4-cyanophenyl)-1-((3-[(E)-(hydroxyimino)methyl]-1H-pyrazol-5-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (83 mg) in dioxane (11.84 ml), pyridine (155 mg) and cyanuric chloride (109 mg) were added, and the mixture was stirred at room temperature for 2.5 hr. The precipitate was removed by filtration, followed by washing with dioxane. The filtrate and the wash were partitioned with ethyl acetate-saturated brine. The organic layer was dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain tert-butyl 4-(4-cyanophenyl)-1-[(3-cyano-1H-pyrazol-5-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (37 mg) as a crystalline powder.

Tert-butyl 4-(4-cyanophenyl)-1-[(3-cyano-1H-pyrazol-5-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (36 mg) was dissolved in TFA (0.139 ml), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain the titled compound (9 mg) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (3H, s), 2.30 (3H, s), 5.15 (2H, s), 6.14 (1H, s), 6.51 (1H, s), 7.43 (2H, d), 7.63 (2H, d), 10.50 (1H, s).

[Example 29]

- 5 4-{2,5-Dimethyl-1-[(4-methyl-1H-pyrazol-5-yl)methyl]-1H-pyrrol-3-yl}benzonitrile



Under an argon atmosphere, to a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate
10 (208 mg) in dehydrated-DMF (5 ml), sodium hydride (60% dispersion in oil, 30 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 3-(iodomethyl)-4-methyl-1-trityl-1H-pyrazole (330 mg) in dehydrated-THF (5 ml) was added to the mixture,
15 and the mixture was stirred at room temperature for 17 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel
20 column chromatography (ethyl acetate-hexane) to obtain tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1-({4-methyl-1-trityl-1H-pyrazol-3-yl)methyl}-1H-pyrrole-3-carboxylate (392 mg) as an amorphous powder.

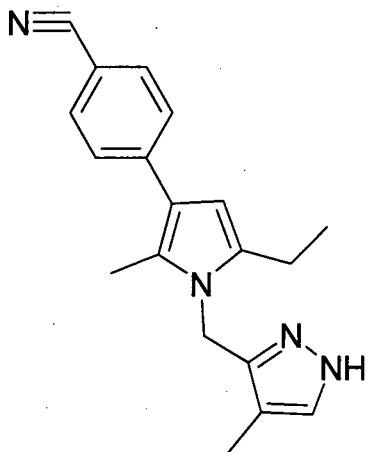
tert-Butyl 4-(4-cyanophenyl)-2,5-dimethyl-1-({4-methyl-1-trityl-1H-pyrazol-3-yl)methyl}-1H-pyrrole-3-
25 carboxylate (390 mg) was dissolved in TFA (4.74 ml), and

the mixture was stirred at room temperature for 4 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated
5 brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-ether to obtain the titled compound (16 mg) as crystals.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.94 (3H, s), 2.25 (3H, s), 2.32 (3H, s), 5.03 (2H, s), 6.07 (1H, s), 7.30 (1H, s), 7.43 (2H, d), 7.59 (2H, d).

[Example 30]

4-{5-Ethyl-2-methyl-1-[(4-methyl-1H-pyrazol-3-yl)methyl]-
15 1H-pyrrol-3-yl}benzonitrile



Under an argon atmosphere, to a solution of tert-butyl 4-(4-cyanophenyl)-2-ethyl-5-methyl-1H-pyrrole-3-carboxylate (217 mg) in dehydrated-DMF (5 ml), sodium hydride (60%
20 dispersion in oil, 30 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 3-(iodomethyl)-4-methyl-1-trityl-1H-pyrazole (330 mg) in dehydrated-THF (5 ml) was added to the mixture, and the mixture was stirred at room temperature for 17 hr.
25 The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with

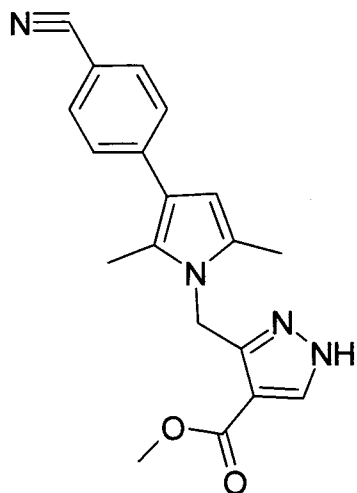
saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane) to obtain
5 tert-butyl 4-(4-cyanophenyl)-2-ethyl-5-methyl-1-({4-methyl-
1-trityl-1H-pyrazol-3-yl)methyl}-1H-pyrrole-3-carboxylate
(370 mg) as an amorphous powder.

tert-Butyl 4-(4-cyanophenyl)-2-ethyl-5-methyl-1-({4-methyl-1-trityl-1H-pyrazol-3-yl)methyl}-1H-pyrrole-3-
carboxylate (365 mg) was dissolved in TFA (4.31 ml), and
10 the mixture was stirred at room temperature for 4 hr. To
the reaction mixture, dichloromethane and an aqueous sodium
bicarbonate solution were added, and the mixture was
partitioned. The organic layer was washed with saturated
brine, dried over anhydrous sodium sulfate and then
15 concentrated. The residue was purified by silica gel
column chromatography (ethyl acetate-hexane) and
crystallized from methanol-ether to obtain the titled
compound (80 mg) as crystals.

¹H-NMR (CDCl₃) δ: 1.26 (3H, t), 1.93 (3H, s), 2.32 (3H, s),
20 2.57 (2H, q), 5.04 (2H, s), 6.09 (1H, s), 7.29 (1H, s),
7.45 (2H, d), 7.59 (2H, d).

[Example 31]

Methyl 3-{[3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1H-pyrazole-4-carboxylate



Under an argon atmosphere, to a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (581 mg) in dehydrated-DMF (15 ml), sodium hydride (60% dispersion in oil, 83 mg) was added, and the mixture was stirred under ice cooling for 30 min. Furthermore, a solution of methyl 3-(iodomethyl)-1-trityl-1H-pyrazole-4-carboxylate (1.05 g) in dehydrated-DMF (35 ml) was added to the mixture, and the mixture was stirred at room temperature for 21 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain methyl 3-([3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1-trityl-1H-pyrazole-4-carboxylate (1.11 g) as crystals.

To a solution of methyl 3-([3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1-trityl-1H-pyrazole-4-carboxylate (1.1 g) in dichloromethane (16.2 ml), a solution of 1M-TFA in dichloromethane (24.3 ml) was added by three portions under ice cooling with stirring, and the mixture was stirred at the same temperature for 4 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain methyl 3-([3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-4-carboxylate (598 mg) as an amorphous powder.

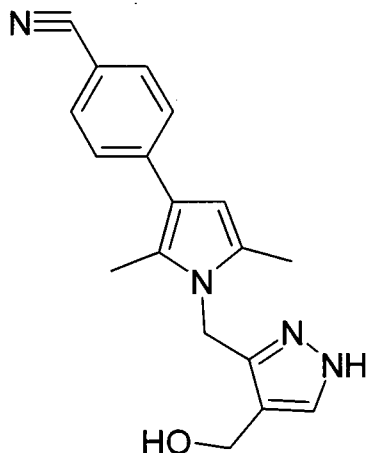
Methyl 3-([3-(tert-butoxycarbonyl)-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-4-

carboxylate (541 mg) was dissolved in TFA (0.96 ml), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from methanol to obtain the titled compound (300 mg) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.22 (3H, s), 2.29 (3H, s), 3.90 (3H, s), 5.37 (2H, s), 6.13 (1H, s), 7.45 (2H, d), 7.61 (2H, d), 9.86 (1H, br s).

[Example 32]

4-(1-([4-(Hydroxymethyl)-1H-pyrazol-3-yl]methyl)-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile



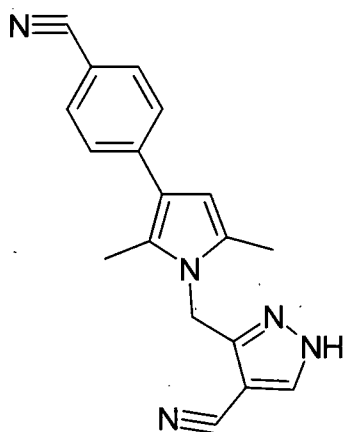
A mixture of sodium borohydride (170 mg), calcium chloride (252 mg), THF (9 ml) and ethanol (4.5 ml) was stirred at room temperature for 30 min and methyl 3-([3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-4-carboxylate (100 mg) was added thereto, and the mixture was stirred at room temperature for 5 days. The reaction mixture was poured into ice water and 1N hydrochloric acid (4.5 ml) was added thereto, and extracted with ethyl acetate. The ethyl acetate layer was washed

with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the titled compound (4 mg) as a crystalline powder.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.26 (3H, s), 2.32 (3H, s), 4.43 (2H, s), 5.17 (2H, s), 6.11 (1H, s), 7.44 (2H, d), 7.53 (1H, s), 7.61 (2H, d).

[Example 33]

3-([3-(4-Cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-
10 1H-pyrazole-4-carbonitrile



Under an argon atmosphere, to a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (462 mg) in dehydrated-DMF (11.7 ml), sodium hydride (60% dispersion in oil, 66 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 3-(iodomethyl)-1-trityl-1H-pyrazole-4-carbonitrile (817 mg) in dehydrated-DMF (15 ml) was added to the mixture, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain tert-butyl 4-(4-cyanophenyl)-1-((4-cyano-1-trityl-1H-pyrazol-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-

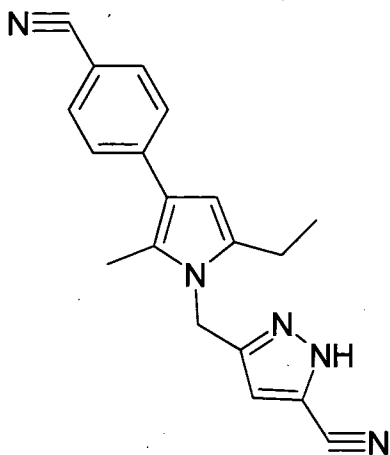
carboxylate (1.0 g) as crystals.

To a solution of tert-butyl 4-(4-cyanophenyl)-1-({4-cyano-1-trityl-1H-pyrazol-3-yl)methyl}-2,5-dimethyl-1H-pyrrole-3-carboxylate (1.0 g) in dichloromethane (15.5 ml),
5 a solution of 1M-TFA in dichloromethane (23.25 ml) was added by three portions under ice cooling with stirring, and the mixture was stirred at the same temperature for 4 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the
10 mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and
crystallized from ethyl acetate-hexane to obtain tert-butyl
15 4-(4-cyanophenyl)-1-[(4-cyano-1H-pyrazol-3-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (231 mg) as crystals.

tert-Butyl 4-(4-cyanophenyl)-1-[(4-cyano-1H-pyrazol-3-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (230 mg)
was dissolved in TFA (0.66 ml), and the mixture was stirred
20 at room temperature for 1.5 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was
25 purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from dichloromethane-methanol to obtain the titled compound (113 mg) as crystals.
¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.36 (3H, s), 5.18 (2H, s), 6.11 (1H, s), 7.43 (2H, d), 7.60 (2H, d), 7.94 (1H, s),
30 10.32 (1H, br s).

[Example 34]

3-{{[3-(4-Cyanophenyl)-5-ethyl-2-methyl-1H-pyrrol-1-yl)methyl]-1H-pyrazole-5-carbonitrile



Under an argon atmosphere, to a solution of tert-butyl 4-(4-cyanophenyl)-2-ethyl-5-methyl-1H-pyrrole-3-carboxylate (1.55 g) in dehydrated-DMF (37.5 ml), sodium hydride (60% dispersion in oil, 220 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 3-(iodomethyl)-1-trityl-1H-pyrazole-5-carbonitrile (2.66 g) in dehydrated-DMF (15 ml) was added to the mixture, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. To the residue, ethyl acetate and ether were added and the crystals were refined, followed by filtration, washing with ether and further drying to obtain tert-butyl 4-(4-cyanophenyl)-1-((5-cyano-1-trityl-1H-pyrazol-3-yl)methyl)-2-ethyl-5-methyl-1H-pyrrole-3-carboxylate (2.78 g) as crystals.

To a solution of tert-butyl 4-(4-cyanophenyl)-1-((5-cyano-1-trityl-1H-pyrazol-3-yl)methyl)-2-ethyl-5-methyl-1H-pyrrole-3-carboxylate (987 mg) in dichloromethane (15 ml), 1M-TFA of a dichloromethane solution (22.5 ml) was added by three portions under ice cooling with stirring, and the mixture was stirred at the same temperature for 2.5 hr. To the reaction mixture, dichloromethane and an aqueous sodium bicarbonate solution were added, and the mixture was

partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and
5 crystallized from ethyl acetate to obtain tert-butyl 4-(4-cyanophenyl)-1-[(5-cyano-1H-pyrazol-3-yl)methyl]-2-ethyl-5-methyl-1H-pyrrole-3-carboxylate (422 mg) as crystals.

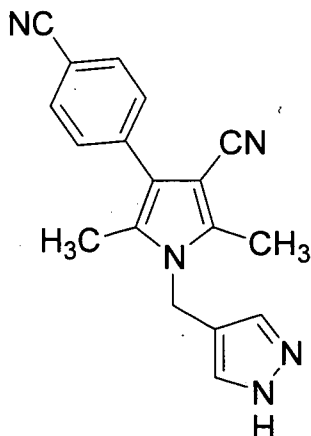
A solution of tert-butyl 4-(4-cyanophenyl)-1-[(5-cyano-1H-pyrazol-3-yl)methyl]-2-ethyl-5-methyl-1H-pyrrole-
10 3-carboxylate (323 mg) in 4N hydrogen chloride of ethyl acetate (7.78 ml) was stirred at room temperature for 4.5 hr. The reaction mixture was poured into an aqueous saturated sodium bicarbonate solution, neutralized and extracted with ethyl acetate. The organic layer was washed
15 with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethanol to obtain the titled compound (75 mg) as crystals.

20 Melting point: 159-160°C

¹H-NMR (CDCl₃) δ: 1.27 (3H, t), 2.29 (3H, s), 2.53 (2H, q), 5.15 (2H, s), 6.15 (1H, s), 6.51 (1H, s), 7.45 (2H, d), 7.63 (2H, d), 10.02 (1H, br s).

[Example 35]

25 4-(4-Cyanophenyl)-2,5-dimethyl-1-(1H-pyrazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile



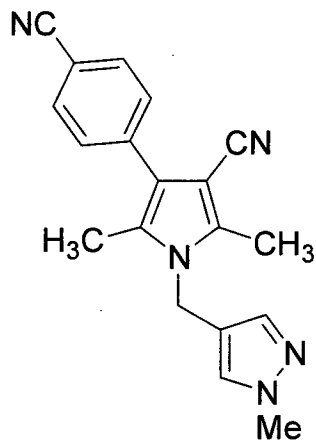
Using the compound (1.10 g) obtained in Reference Example 52, sodium hydride (60% dispersion in oil, 0.20 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.66 g), the same reaction and purification operation as in Example 1 were conducted to obtain 4-(4-cyanophenyl)-2,5-dimethyl-1-(1-trityl-1H-pyrazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile (0.51 g) as a colorless amorphous solid.

Using the resulting solid (0.51 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound as colorless crystals (0.24 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.28 (3H, s), 2.44 (3H, s), 5.01 (2H, s), 7.37 (2H, s), 7.49 (2H, d), 7.69 ((2H, d).

[Example 36]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-pyrrole-3-carbonitrile



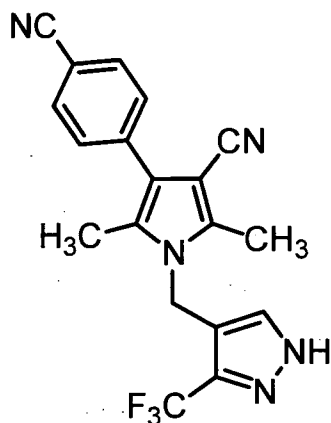
Using the compound (133 mg) obtained in Example 35, the same reaction and purification operation as in Example 2 were conducted to obtain the titled compound as colorless crystals (113 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.28 (3H, s), 2.44 (3H, s), 3.88 (3H, s), 4.95 (2H, s), 7.07 (1H, s), 7.30 (1H, s), 7.50 (2H, d), 7.70 (2H, d).

[Example 37]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[[3-(trifluoromethyl)-1H-

pyrazol-4-yl)methyl}-1H-pyrrole-3-carbonitrile



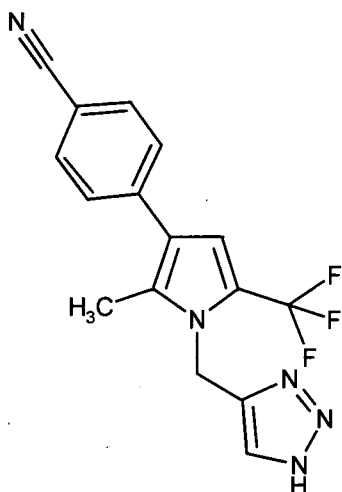
Using the compound (1.41 g) obtained in Reference Example 56, sodium hydride (60% dispersion in oil, 0.14 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.66 g), the same reaction and purification operation as in Example 1 were conducted to obtain 4-(4-cyanophenyl)-2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl]-1H-pyrrole-3-carbonitrile (1.69 g) as colorless crystals.

Using 4-(4-cyanophenyl)-2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl]-1H-pyrrole-3-carbonitrile (1.64 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound (0.75 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.24 (3H, s), 2.40 (3H, s), 5.08 (2H, s), 6.95 (1H, s), 7.50 (2H, d), 7.71 (2H, d), 10.43 (1H, brs).

[Example 38]

4-[2-Methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-5-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile



To a solution of 4-[2-methyl-5-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile (284 mg) in DMF (10 ml), sodium hydride (60% dispersion in oil, 68 mg) was added under ice cooling. After the reaction mixture was stirred at room temperature for 30 min, a mixture (550 mg) of bromomethyltriazole derivatives synthesized by the method described in Example 16 was added to the mixture, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in methanol (5 ml) and THF (5 ml), and p-toluenesulfonic acid monohydrate (0.43 g) was added thereto, and the mixture was stirred at 60°C for 2 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain the titled compound (290 mg) as crystals.

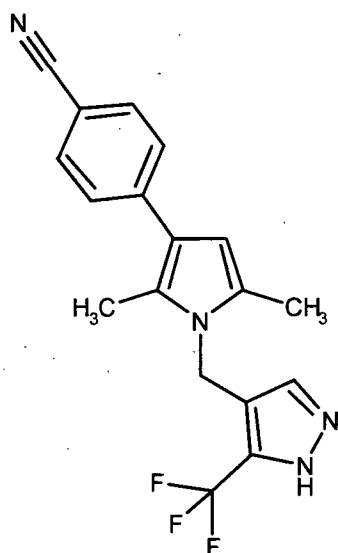
Melting point: 135-137°C

¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 5.34 (2H, s), 6.75 (1H, s),

7.43 (2H, d), 7.52 (1H, s), 7.66 (2H, d), 11.81 (1H, s).

[Example 39]

4-(2,5-Dimethyl-1-([5-(trifluoromethyl)-1H-pyrazol-4-yl]methyl)-1H-pyrrol-3-yl)benzonitrile



5

To a solution of 3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole (86 mg) in DMF (10 ml), sodium hydride (60% dispersion in oil, 26 mg) was added under ice cooling. After the reaction mixture was stirred at room temperature for 30 min, 4-(iodomethyl)-5-(trifluoromethyl)-1-trityl-1H-pyrazole (0.21 g) was added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in methanol (10 ml) and THF (10 ml) and p-toluenesulfonic acid monohydrate (0.17 g) was added thereto, and the mixture was stirred at 60°C for 2 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and

10

15

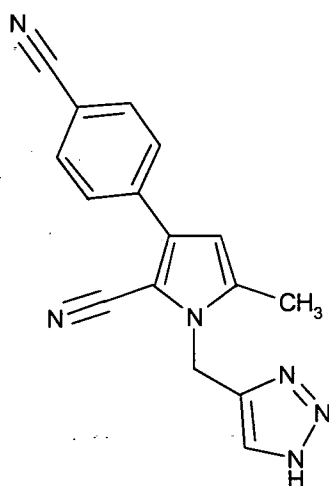
20

crystallized from diethylether to obtain the titled compound (32 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.21 (3H, s), 2.30 (3H, s), 5.03 (2H, s), 6.10 (1H, s), 6.88 (1H, s), 7.45 (2H, d), 7.63 (2H, d), 10.64 (1H, s).

[Example 40]

3-(4-Cyanophenyl)-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-2-carbonitrile

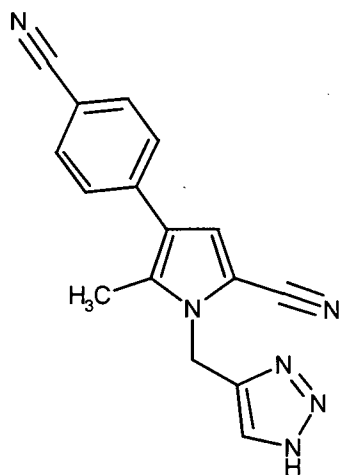


Using 3-(4-cyanophenyl)-5-methyl-1H-pyrrole-2-carbonitrile and a mixture of bromomethyltriazole derivatives described in Example 16 as materials, the titled compound was obtained in the same manner as in Example 39.

¹H-NMR (CDCl₃) δ: 2.42 (3H, s), 5.36 (2H, s), 6.27 (1H, s), 7.66 - 7.71 (2H, m), 7.72 - 7.77 (3H, m).

[Example 41]

4-(4-Cyanophenyl)-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-2-carbonitrile

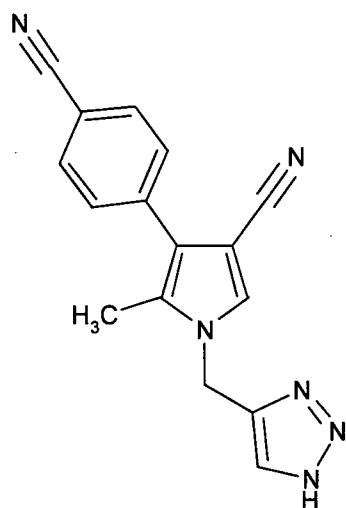


Using 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-2-carbonitrile and a mixture of bromomethyltriazole derivatives described in Example 16 as materials, the
 5 titled compound was obtained in the same manner as in Example 39.

¹H-NMR (CDCl₃) δ: 2.48 (3H, s), 5.39 (2H, s), 6.94 (1H, s), 7.41 (2H, d), 7.68 (2H, d), 7.76 (1H, s), 11.97 (1H, s).

[Example 42]

10 4-(4-Cyanophenyl)-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile



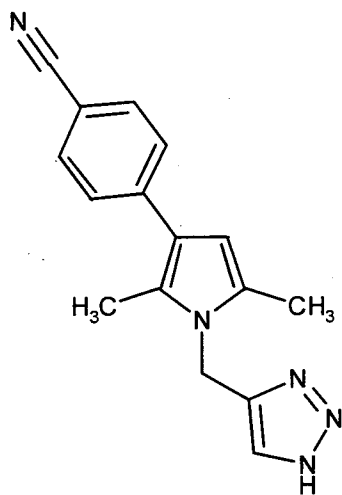
Using 4-(4-cyanophenyl)-5-methyl-1H-pyrrole-3-carbonitrile and a mixture of bromomethyltriazole derivatives described in Example 16 as materials, the
 15 titled compound was obtained in the same manner as in

Example 39.

¹H-NMR (CDCl₃) δ: 2.30 (3H, s), 5.34 (2H, s), 7.56 (2H, d), 7.82 (1H, s), 7.92 (2H, d), 15.12 (1H, s).

[Example 43]

5 4-[2,5-Dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile

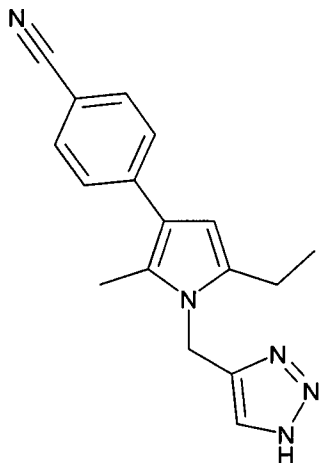


Using 3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole and a mixture of bromomethyltriazole derivatives described in
10 Example 16 as materials, the titled compound was obtained in the same manner as in Example 39.

¹H-NMR (CDCl₃) δ: 2.23 (3H, s), 2.31 (3H, s), 5.14 (2H, s), 6.13 (1H, s), 6.35 (1H, s), 7.44 (2H, d), 7.63 (2H, d), 10.54 (1H, s).

15 [Example 44]

4-[5-Ethyl-2-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



To a mixture of 4-(4-cyanophenyl)-5-ethyl-2-methyl-1H-pyrrole (200 mg) and DMF (4 ml), sodium hydride (60% dispersion in oil, 57 mg) was added at room temperature.

5 After the reaction mixture was stirred for 10 min, 4-(bromomethyl)-N-trityl-1H-1,2,3-triazole (461 mg) was added thereto, and the mixture was stirred at room temperature for 30 min. After the reaction mixture was poured into saturated brine and extracted with ethyl acetate, the
10 organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain an oil.

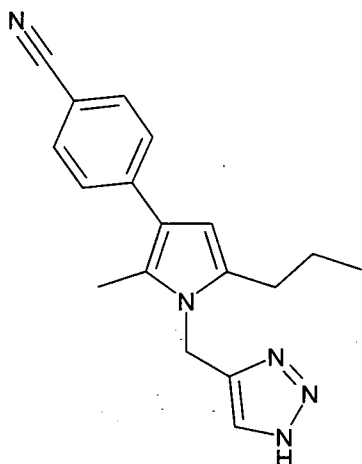
A mixture of the oil, p-toluenesulfonic acid monohydrate (272 mg), THF (4 ml) and methanol (4 ml) was
15 stirred at 60°C for 1.5 hr. The reaction mixture was cooled to room temperature, poured into an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed in turn with
20 an aqueous saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain the titled compound (45 mg) as a solid.

25 ¹H-NMR (CDCl₃) δ: 1.26 (3H, t), 2.36 (3H, s), 2.61 (2H, q), 5.19 (2H, s), 6.09 (1H, s), 7.38 (1H, s), 7.43-7.46 (2H, m),

7.58-7.62 (2H, m), 12.6-13.6 (1H, br s).

[Example 45]

4-[2-Methyl-5-propyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



5

To a mixture of 4-(4-cyanophenyl)-2-methyl-5-propyl-1H-pyrrole (50 mg) and DMF (1 ml), sodium hydride (60% dispersion in oil, 13 mg) was added at room temperature. After the reaction mixture was stirred for 10 min, 4-(bromomethyl)-N-trityl-1H-1,2,3-triazole (94 mg) was added thereto, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain an oil.

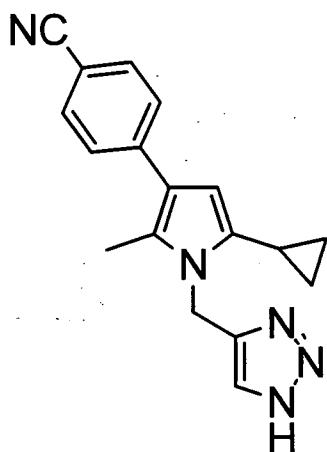
A mixture of the oil, p-toluenesulfonic acid monohydrate (64 mg), THF (1 ml) and methanol (1 ml) was stirred at 60°C for 2 hr. The reaction mixture was cooled to room temperature, poured into an aqueous saturated sodium bicarbonate solution and then extracted with ethyl acetate. The organic layer was washed in turn with an aqueous saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel

column chromatography (ethyl acetate-hexane) to obtain the titled compound (45 mg) as an amorphous.

¹H-NMR (CDCl₃) δ: 1.00 (3H, t), 1.66 (2H, sextet), 2.35 (3H, s), 2.56 (2H, t), 5.19 (2H, s), 6.09 (1H, s), 7.36 (1H, s),
5 7.43-7.46 (2H, m), 7.59-7.62 (2H, m).

[Example 46]

4-[5-Cyclopropyl-2-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-
1H-pyrrol-3-yl]benzonitrile



10 To a solution of sodium hydride (60% dispersion in oil, 0.08 g) in DMF (8.0 ml), 4-(5-cyclopropyl-2-methyl-1H-pyrrol-3-yl)benzonitrile (0.35 g) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and 4-(bromomethyl)-N-trityl-1H-
15 1,2,3-triazole (0.67 g) was added thereto, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and
20 concentrated. The resulting residue was dissolved in a methanol-THF mixed solution (1:1, 4.0 ml) and tosylic acid monohydrate (0.6 g) was added thereto, and the mixture was stirred at 60°C for 1 hr. After the solvent in the reaction solution was distilled off under reduced pressure,
25 the residue was diluted with ethyl acetate, washed with an aqueous saturated sodium bicarbonate solution and saturated

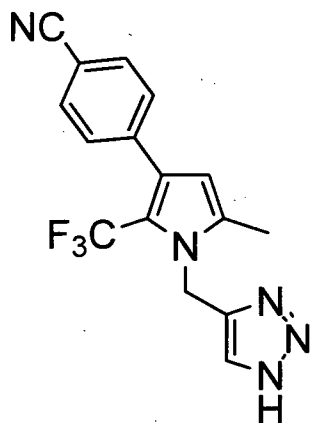
brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diisopropyl ether-hexane to obtain the

¹H-NMR (CDCl₃) δ: 0.60-0.65 (2H, m), 0.83-0.89 (2H, m), 1.16-1.73 (1H, m), 2.36 (3H, s), 5.37 (2H, s), 5.99 (1H, s), 7.41 (1H, s), 7.42 (2H, d), 7.60 (2H, d), 12.02 (1H, br s).

In the same manner as in Example 46, the following compounds were obtained.

[Example 47]

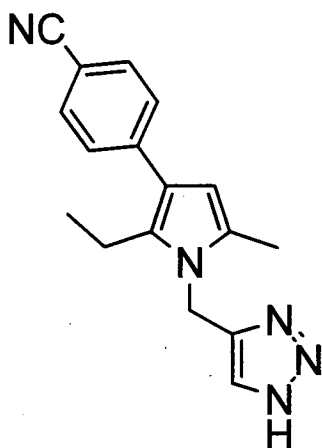
4-[5-Methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-2-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile



¹H-NMR (CDCl₃) δ: 2.33 (3H, s), 5.33 (2H, s), 5.99 (1H, s), 7.43 (2H, d), 7.52 (1H, d), 7.63 (2H, d), 11.91 (1H, br s).

[Example 48]

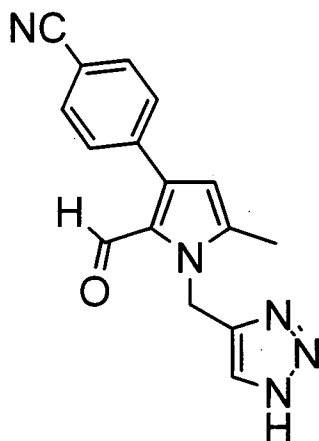
4-[2-Ethyl-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



$^1\text{H-NMR}$ (CDCl_3) δ : 1.20 (3H, t), 2.24 (3H, s), 2.74 (2H, q), 5.19 (2H, s), 6.10 (1H, s), 7.35 (1H, s), 7.45 (2H, d), 7.62 (2H, d), 12.05 (1H, br s).

5 [Example 49]

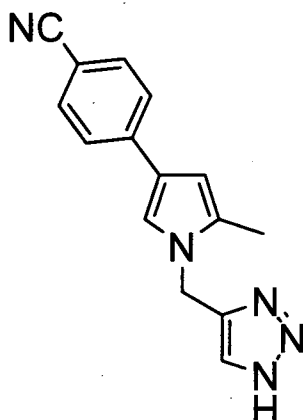
4-[2-Formyl-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



10 $^1\text{H-NMR}$ (CDCl_3) δ : 2.50 (3H, s), 5.72 (2H, s), 6.16 (1H, s), 7.49 (2H, d), 7.69 (2H, d), 7.76 (1H, s), 9.50 (1H, s), 12.27 (1H, br s).

[Example 50]

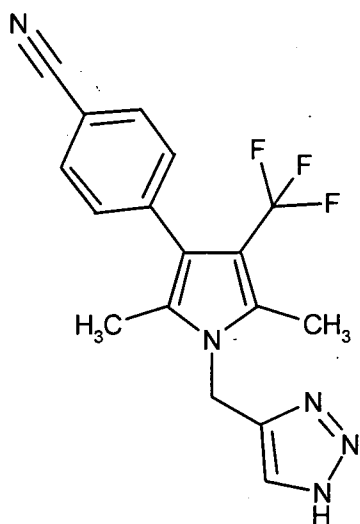
4-[5-Methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.32 (3H, s), 5.17 (2H, s), 6.29 (1H, s), 7.41 (2H, d), 7.61 (2H, d), 7.68 (2H, d), 7.78 (1H, s).

[Example 51]

5 4-[2,5-Dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-4-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile



To a solution of 4-(4-iodo-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile (250 mg) in DMF (5 ml), sodium hydride (60% dispersion in oil, 28 mg) was added under ice cooling. The
 10 reaction mixture was stirred at room temperature for 30 min and a mixture (350 mg) of bromomethyltriazole derivatives described in Example 8 was added thereto, and the mixture was stirred at room temperature for 4 hr. The reaction
 15 mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue

was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain 4-{4-iodo-2,5-dimethyl-1-[(1-trityl-1H-1,2,3-triazol-4-yl)methyl]-1H-pyrrol-3-yl}benzonitrile (440 mg) as a solid.

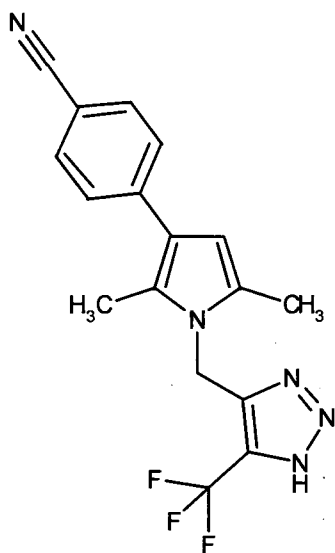
5 A mixture of 4-{4-iodo-2,5-dimethyl-1-[(1-trityl-1H-1,2,3-triazol-4-yl)methyl]-1H-pyrrol-3-yl}benzonitrile (343 mg), methyl fluorosulfonyl(difluoro)acetate (302 mg) and copper (I) iodide (111 mg) was stirred at 80°C for 14 hr. To the reaction mixture, ethyl acetate and an aqueous
10 sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and
15 crystallized from diethylether to obtain 4-{2,5-dimethyl-4-(trifluoromethyl)-1-[(1-trityl-1H-1,2,3-triazol-4-yl)methyl]-1H-pyrrol-3-yl}benzonitrile (130 mg) as a solid.

4-{2,5-dimethyl-4-(trifluoromethyl)-1-[(1-trityl-1H-1,2,3-triazol-4-yl)methyl]-1H-pyrrol-3-yl}benzonitrile
20 (130.0 mg) was dissolved in methanol (2 ml) and THF (2 ml) and pyridine hydrochloride (51 mg) was added thereto, and the mixture was stirred at 60°C for 2 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The
25 organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain the titled compound (51 mg) as crystals.

30 ¹H-NMR (CDCl₃) δ: 2.14 (3H, s), 2.42 (3H, s), 5.19 (2H, s), 7.36 (2H, d), 7.47 (1H, s), 7.64 (2 H, d), 11.85 (1H, s).

[Example 52]

4-(2,5-Dimethyl-1-{[5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methyl]-1H-pyrrol-3-yl}benzonitrile



To a solution of benzyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (600 mg) in DMF (10 ml), sodium hydride (60% dispersion in oil, 100 mg) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and 4-(bromomethyl)-1-(4-methoxybenzyl)-5-(trifluoromethyl)-1H-1,2,3-triazole (0.64 g) was added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain benzyl 4-(4-cyanophenyl)-1-([1-(4-methoxybenzyl)-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl]methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (599 mg) as a solid.

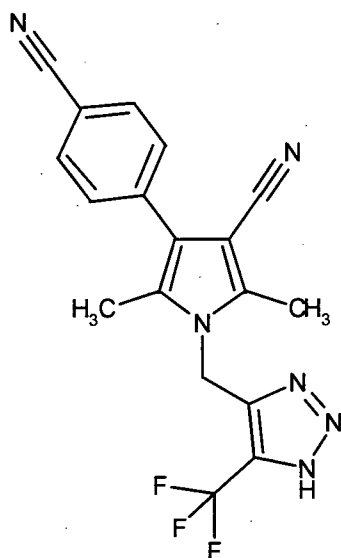
Benzyl 4-(4-cyanophenyl)-1-([1-(4-methoxybenzyl)-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl]methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (350 mg) was dissolved in TFA (3 ml), and the mixture was stirred at 60°C for 3 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then

concentrated. The residue was dissolved in methanol and palladium-carbon (0.1 g) was added thereto, and the mixture was stirred at room temperature for 3 hr under a hydrogen atmosphere. After removal of insolubles by filtration and concentration, the residue was dissolved in TFA (3 ml), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain the titled compound (56 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.25 (3H, s), 2.32 (3H, s), 5.22 (2H, s), 6.13 (1H, s), 7.45 (2H, d), 7.61 (2H, d), 11.97 (1H, s).

[Example 53]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[[5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl]methyl]-1H-pyrrole-3-carbonitrile



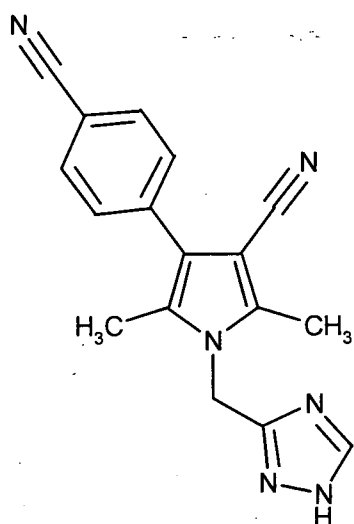
To a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (250 mg) in DMF (3 ml), sodium hydride (60% dispersion in oil, 68 mg) was added under ice cooling. After the reaction mixture was stirred at room

temperature for 30 min, 4-(bromomethyl)-1-(4-methoxybenzyl)-5-(trifluoromethyl)-1H-1,2,3-triazole (0.21 g) was added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured
5 into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in TFA (3 ml), and the mixture was stirred at 60°C for 3 hr. To the reaction mixture, ethyl acetate and an aqueous sodium
10 bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and
15 crystallized from diethyl ether to obtain the titled compound (357 mg) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.26 (3H, s), 2.44 (3H, s), 5.24 (2H, s), 7.51 (2H, d), 7.70 (2H, d), 12.53 (1H, s).

[Example 54]

20 4-(4-Cyanophenyl)-2,5-dimethyl-1-(1H-1,2,4-triazole-3-ylmethyl)-1H-pyrrole-3-carbonitrile



A mixture of ethyl 1H-1,2,4-triazole-5-carboxylate (4.00 g), triphenylchloromethane (8.77 g), triethylamine
25 (5.2 ml) and DMF (30 ml) was stirred at room temperature

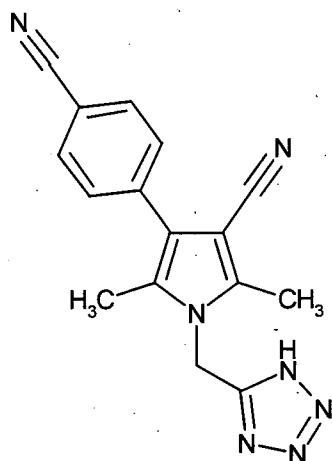
for 14 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain Intermediate 1 (10.40 g). A mixture of sodium borohydride (2.06 g), calcium chloride (4.52 g), THF (80 ml) and ethanol (40 ml) was stirred at room temperature for 30 min. Intermediate 1 (10.02 g) was added to the mixture, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain Intermediate 2 (8.61 g). The resulting Intermediate 2 (2.05 g) was dissolved in dichloromethane (20 ml), and methanesulfonyl chloride (0.56 ml) and triethylamine (1.25 ml) were added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in acetone (20 ml) and sodium iodide (1.80 g) was added thereto, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from diethyl ether to obtain a iodomethyltriazole derivative (0.94 g) as a solid. The product is a mixture of two kinds of isomers and was used in the following reaction without being purified furthermore. Using the above iodomethyltriazole derivative and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile as starting materials and using pyridine

hydrochloride as an acid, the titled compound was obtained in the same manner as in Example 39.

¹H-NMR (CDCl₃) δ: 2.33 (3H, s), 2.48 (3H, s), 5.25 (2H, s), 7.53 (2H, d), 7.90 (2H, d), 8.47 (1H, s), 14.05 (1H, s).

5 [Example 55]

4-[2,5-Dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



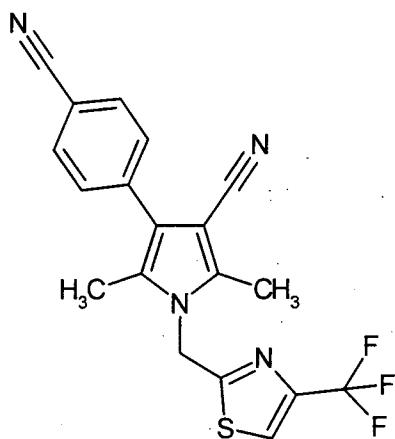
A mixture of an ethyl 1H-tetrazole-5-carboxylate sodium salt (5.28 g), triphenylchloromethane (8.97 g) and DMF (30 ml) was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain ethyl 1-trityl-1H-tetrazole-5-carboxylate (10.15 g). A mixture of sodium borohydride (1.89 g), calcium chloride (4.15 g), THF (80 ml) and ethanol (40 ml) was stirred at room temperature for 30 min. Ethyl 1-trityl-1H-tetrazole-5-carboxylate (9.58 g) was added to the mixture, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to obtain (1-trityl-1H-tetrazole-5-yl)methanol (7.76 g). The resulting (1-trityl-1H-

tetrazole-5-yl)methanol (2.06 g) was dissolved in dichloromethane (20 ml), and methanesulfonyl chloride (0.56 ml) and triethylamine (1.25 ml) were added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in acetone (20 ml) and sodium iodide (1.80 g) was added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into saturated brine (100 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from diethyl ether to obtain 5-(iodomethyl)-1-trityl-1H-tetrazole (2.25 g) as a solid. Using 5-(iodomethyl)-1-trityl-1H-tetrazole and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile obtained in the above reaction as materials and using pyridine hydrochloride as an acid, the titled compound was obtained in the same manner as in Example 39.

¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.45 (3H, s), 5.59 (2H, s), 7.55 (2H, d), 7.92 (2H, d).

[Example 56]

4-(4-Cyanophenyl)-2,5-dimethyl-1-([4-(trifluoromethyl)-1,3-thiazole-2-yl]methyl)-1H-pyrrole-3-carbonitrile



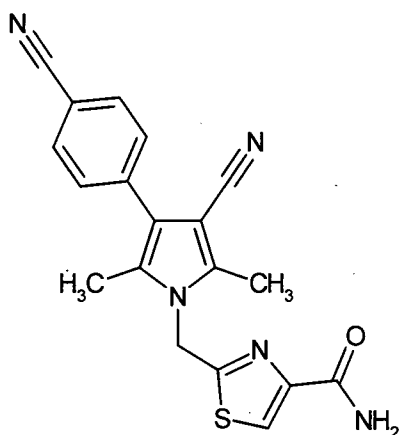
A solution of 2-[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]ethanethioamide (1.5 g) and 3-bromo-1,1,1-trifluoroacetone (0.79 ml) in acetonitrile (30 ml) was stirred at 80°C for 1 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain the titled compound (355 mg) as crystals.

Melting point: 180-182°C

¹H NMR (CDCl₃) δ: 2.32 (3H, s), 2.49 (3H, s), 5.38 (2H, s), 7.31 (2H, d), 7.72 (2H, d), 7.79 (1H, s).

[Example 57]

2-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carboxamide

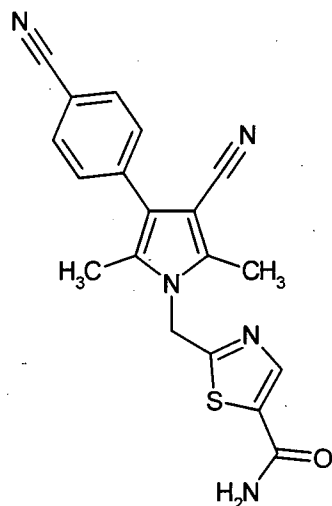


To a mixture of 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carboxylic acid (360 mg) prepared from 2-[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]ethanethioamide and bromopyruvic acid in the same manner as in Example 56, THF (10 ml) and DMF (two drops), oxalyl chloride (0.43 ml) was added under ice cooling, and the mixture was stirred at room temperature for 30 min. The reaction mixture was added dropwise to ammonia water (10 ml) under ice cooling and the mixture was stirred at room temperature for 2 hr. Ethyl acetate and saturated brine were added to the mixture, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate to obtain the titled compound (255 mg) as crystals.

^1H NMR (CDCl_3) δ : 2.32 (3H, s), 2.50 (3H, s), 5.34 (2H, s), 5.78 (1H, s), 7.01 (1H, s), 7.51 (2H, d), 7.72 (2H, d), 8.16 (1H, s).

[Example 58]

2-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-5-carboxamide



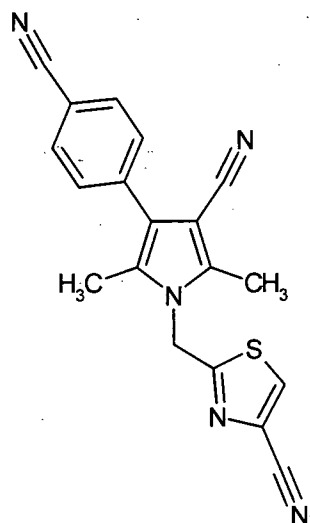
A solution of 2-[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]ethanethioamide (1.00 g), potassium 1-chloro-1-(ethoxycarbonyl)-2-oxoethanide (0.68 g) and
5 acetic acid (0.23 ml) in ethanol (5 ml) was stirred at 80°C for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel
10 column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain ethyl 2-{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-5-carboxylate (589 mg) as crystals. A solution of ethyl 2-{[3-cyano-4-(4-cyanophenyl)-2,5-
15 dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-5-carboxylate (380 mg) and an aqueous 1N sodium hydroxide solution (2 ml) in ethanol (2 ml) was stirred at 50°C for 1 hr. The reaction mixture was poured into 1N hydrochloric acid (4 ml) and extracted with ethyl acetate, and then the ethyl
20 acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from ethyl acetate to obtain 2-{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-5-carboxylic acid (310 mg) as crystals. Using 2-{[3-cyano-4-(4-
25 cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-

thiazole-5-carboxylic acid, the titled compound was obtained in the same manner as in Example 57.

^1H NMR (CDCl_3) δ : 2.31 (3H, s), 2.48 (3H, s), 5.34 (2H, s), 5.81 (2H, s), 7.51 (2H, d), 7.72 (2H, d), 8.11 (1H, s).

5 [Example 59]

2-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carbonitrile



Synthesis method 1: To a solution of 4-(4-cyanophenyl)-
10 2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.6 g) in DMF (15 ml), sodium hydride (60% dispersion in oil, 0.16 g) was added under ice cooling. The reaction mixture was stirred at room temperature for 30 min and 2-(bromomethyl)-1,3-thiazole-4-carbonitrile (1.0 g) was added thereto, and the
15 mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column
20 chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain the titled compound (230 mg) as crystals.

Synthesis method 2: To a solution of the compound (8.7 g) of Example 57 and pyridine (3.9 ml) in DMF (100 ml), oxalyl
25 chloride (2.47 ml) was added under ice cooling, and the

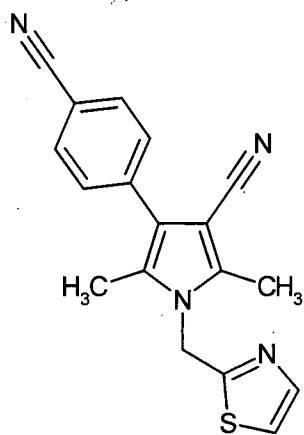
reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain the titled compound (6.26 g) as crystals.

Melting point: 183-185°C

¹H NMR (CDCl₃) δ: 2.31 (3H, s), 2.48 (3H, s), 5.37 (2H, s), 7.55 (2H, d), 7.72 (2H, d), 8.03 (1H, s).

[Example 60]

4-(4-Cyanophenyl)-2,5-dimethyl-1-(1,3-thiazole-2-ylmethyl)-1H-pyrrole-3-carbonitrile

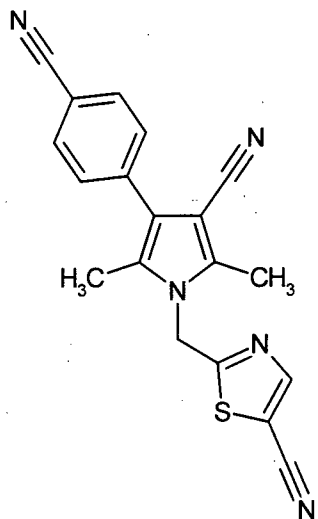


Using 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile and 2-(bromomethyl)-1,3-thiazole as materials and using THF as a solvent, the titled compound was obtained in the same manner as in the synthesis method 1 of Example 59.

¹H NMR (CDCl₃) δ: 2.31 (3H, s), 2.48 (3H, s), 5.37 (2H, s), 7.55 (2H, d), 7.72 (2H, d), 8.03 (1H, s).

[Example 61]

2-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-5-carbonitrile

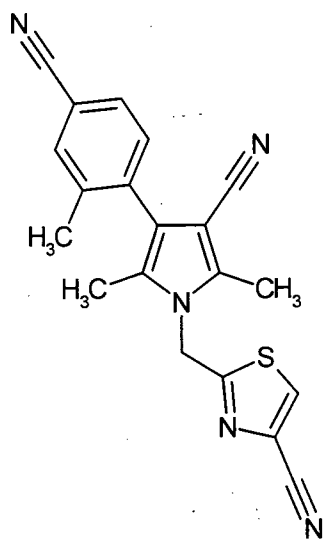


Using the compound of Example 58, the titled compound was obtained in the same manner as in the synthesis method 2 of Example 59.

5 ^1H NMR (CDCl_3) δ : 2.30 (3H, s), 2.48 (3H, s), 5.39 (2H, s), 7.51 (2H, d), 7.73 (2H, d), 8.25 (1H, s).

[Example 62]

2-([3-Cyano-4-(4-cyano-2-methylphenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carbonitrile



10

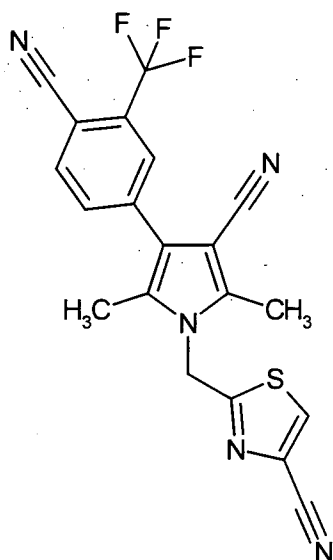
Using 4-(4-cyano-2-methylphenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile, the titled compound was obtained in the same manner as in the synthesis method 1 of Example 59.

^1H NMR (CDCl_3) δ : 2.06 (3H, s), 2.26 (3H, s), 2.46 (3H, s),

5.36 (2H, s), 7.1-7.3 (1H, m), 7.4-7.7 (2H, m), 8.02 (1H, s).

[Example 63]

2-({3-Cyano-4-[4-cyano-3-(trifluoromethyl)phenyl]-2,5-dimethyl-1H-pyrrole-1-yl)methyl)-1,3-thiazole-4-carbonitrile

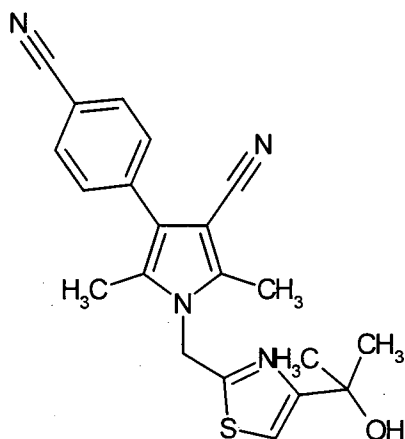


Using 4-[4-cyano-3-(trifluoromethyl)phenyl]-2,5-dimethyl-1H-pyrrole-3-carbonitrile, the titled compound was obtained in the same manner as in the synthesis method 1 of Example 59.

^1H NMR (CDCl_3) δ : 2.33 (3H, s), 2.50 (3H, s), 5.38 (2H, s), 7.7-7.8 (2H, m), 7.90 (1H, d), 8.03 (1H, s).

[Example 64]

4-(4-Cyanophenyl)-1-{{[4-(1-hydroxy-1-methylethyl)-1,3-thiazole-2-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carbonitrile

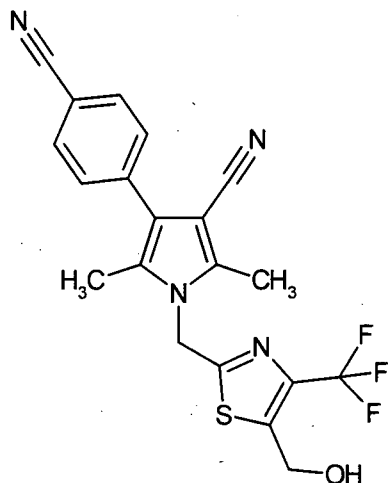


To a solution of ethyl 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carboxylate (150 mg) prepared from 2-[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]ethanethioamide and ethyl bromopyruvate in the same manner as in Example 56 in THF (5 ml), methylmagnesium bromide (3M diethylether solution, 0.63 ml) was added under ice cooling, and the mixture was stirred at room temperature for 30 min. To the reaction mixture, ethyl acetate and an aqueous citric acid solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and crystallized from diethyl ether to obtain the titled compound (98 mg) as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.61 (6H, s), 2.33 (3H, s), 2.48 (1H, s), 2.50 (3H, s), 5.32 (2H, s), 7.13 (1H, s), 7.51 (2H, d), 7.71 (2H, d).

[Example 65]

4-(4-Cyanophenyl)-1-([5-(hydroxymethyl)-4-(trifluoromethyl)-1,3-thiazole-2-yl]methyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile



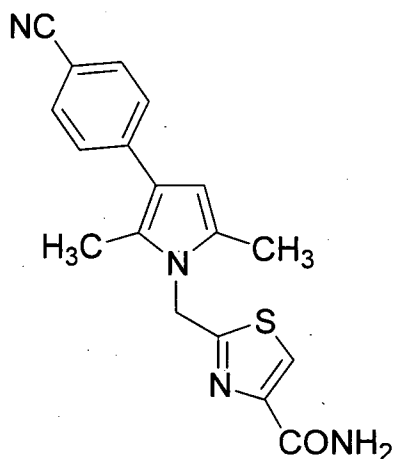
A solution of 2-[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]ethanethioamide (1.07 g), ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate (0.87 g),
5 triethylamine (0.8 ml) and thionyl chloride (0.32 ml) in acetonitrile (15 ml) was stirred at 80°C for 1 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated.
10 The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethylether to obtain ethyl 2-[[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl]-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate (397 mg) as crystals. A mixture
15 of sodium borohydride (66 mg), calcium chloride (130 mg), THF (6 ml) and ethanol (3 ml) was stirred at room temperature for 30 min and ethyl 2-[[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl]-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate (254 mg) was
20 added thereto, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into an aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and
25 concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and

crystallized from ethanol to obtain the titled compound (211 mg) as a solid.

¹H-NMR (CDCl₃) δ: 2.32 (3H, s), 2.49 (3H, s), 5.01 (2H, s), 5.31 (2H, s), 7.50 (2H, d), 7.71 (2H, d).

5 [Example 66]

2-([3-(4-Cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carboxamide



Using ethyl 2-(bromomethyl)-1,3-thiazole-4-carboxylate
10 (3.00 g), sodium hydride (60% dispersion in oil, 0.52 g)
and benzyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-
carboxylate (4.29 g), the same reaction and purification
operation as in Example 1 were conducted to obtain ethyl 2-
15 {[3-[(benzyloxy)carbonyl]-4-(4-cyanophenyl)-2,5-dimethyl-
1H-pyrrol-1-yl]methyl}-1,3-thiazole-4-carboxylate (4.51 g)
as crystals. A mixture of ethyl 2-([3-
[(benzyloxy)carbonyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-
pyrrol-1-yl]methyl)-1,3-thiazole-4-carboxylate (4.45 g),
ethanol (200 ml) and 2N sodium hydroxide (100 ml) was
20 stirred at room temperature for 1.5 hr and then
concentrated. The pH of the residue was adjusted to 1 by
adding 3N hydrochloric acid, and the mixture was extracted
with ethyl acetate. The extracted layer was dried over
anhydrous magnesium sulfate and concentrated to obtain 2-
25 {[3-[(benzyloxy)carbonyl]-4-(4-cyanophenyl)-2,5-dimethyl-
1H-pyrrol-1-yl]methyl}-1,3-thiazole-4-carboxylic acid (4.27

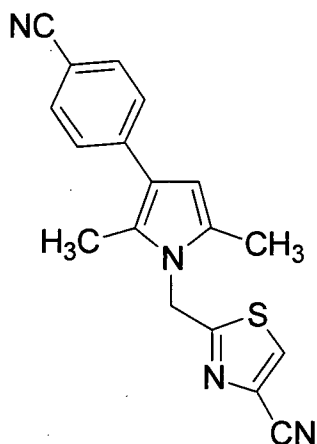
g) as crystals. 2-([3-[(benzyloxy)carbonyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl)methyl]-1,3-thiazole-4-carboxylic acid (4.25 g) was suspended in THF (70 ml) and oxalyl chloride (2.6 ml) was added dropwise thereto. After the reaction mixture was stirred at room temperature for 30 min, the solvent was distilled off under reduced pressure. The residue was dissolved in THF (40 ml) and the solution was added dropwise to a mixture of 28% ammonia water (100 ml) and THF (50 ml). The reaction mixture was stirred at room temperature for 1 hr and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated to obtain benzyl 1-([4-(aminocarbonyl)-1,3-thiazole-2-yl)methyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (4.25 g) as an amorphous solid. To a solution of benzyl 1-([4-(aminocarbonyl)-1,3-thiazole-2-yl)methyl]-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (4.20 g) and pyridine (2.2 ml) in DMF (20 ml), oxalyl chloride (2.0 ml) was added dropwise under ice cooling. After stirring at the same temperature for 0.5 hr, the reaction mixture was diluted with water and extracted with ethyl acetate. The extracted layer was washed in turn with 1N hydrochloric acid, water and an aqueous saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane-ethyl acetate) to obtain benzyl 4-(4-cyanophenyl)-1-([4-cyano-1,3-thiazole-2-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (3.30 g) as crystals. A solution of benzyl 4-(4-cyanophenyl)-1-([4-cyano-1,3-thiazole-2-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (2.80 g) in dichloromethane (30 ml) was cooled in an ice bath and a 2N boron tribromide dichloromethane solution (8.3 ml) was added dropwise thereto. After the reaction mixture was stirred at room temperature for 30 min, the reaction mixture was poured into ice water and

extracted with ethyl acetate. The ethyl acetate layer was extracted with 2N sodium hydroxide and the pH of the sodium hydroxide extracted layer was adjusted to 1 with concentrated hydrochloric acid, followed by extraction with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated, and then the residue was purified by column chromatography (hexane-ethyl acetate → ethyl acetate-methanol) to obtain 1-{{[4-(aminocarbonyl)-1,3-thiazole-2-yl]methyl}-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid (1.07 g) as a colorless amorphous solid. 1-{{[4-(aminocarbonyl)-1,3-thiazole-2-yl]methyl}-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid (0.90 g) was dissolved in TFA (10 ml), and the mixture was stirred at room temperature for 2 hr and further concentration. To the residue, ethyl acetate and an aqueous saturated sodium bicarbonate solution were added, and the mixture was separated. The ethyl acetate layer was dried over anhydrous magnesium sulfate and further concentrated to obtain the titled compound (0.60 g) as a powder.

¹H-NMR (CDCl₃) δ: 2.29 (3H, s), 2.37 (3H, s), 5.29 (2H, s), 5.65 (1H, br s), 6.13 (1H, s), 7.07 (1H, br s), 7.45 (2H, d), 7.63 (2H, d), 8.09 (1H, s).

[Example 67]

2-{{[3-(4-Cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-4-carbonitrile

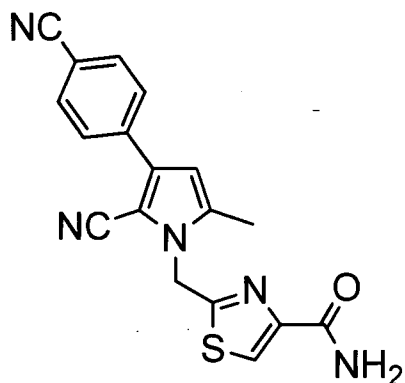


Using the compound (0.53 g) obtained in Example 66, the same reaction and purification operation as in the synthesis method 2 of Example 59 to obtain the titled compound (0.30 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.34 (3H, s), 5.32 (2H, s), 6.13 (1H, s), 7.44 (2H, d), 7.62 (2H, d), 7.93 (1H, s).

[Example 68]

2-([2-Cyano-3-(4-cyanophenyl)-5-methyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carboxamide



To a solution of sodium hydride (60% dispersion in oil, 0.03 g) in DMF (3.0 ml), 3-(4-cyanophenyl)-5-methyl-1H-pyrrole-2-carbonitrile (0.14 g) was added under ice cooling. After the reaction mixture was stirred at room temperature for 30 min, a solution of 2-(bromomethyl)-1,3-thiazole-4-carbonitrile (0.19 g) in DMF (1.0 ml) was added thereto, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice water and

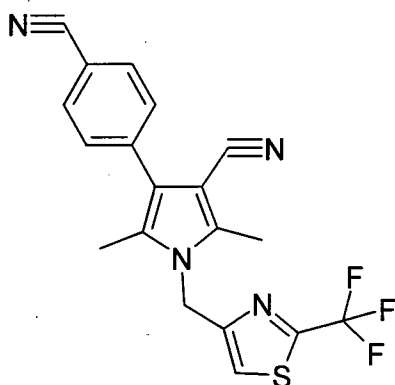
extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain an intermediate (217 mg).

Subsequently, to a solution of the compound (125 mg) obtained above in THF (2.5 ml), 28% ammonia water (5.0 ml) was added, and the mixture was stirred at room temperature for 88 hr. The reaction solution was poured into water and extracted with an ethyl acetate-THF mixed solution. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from ethyl acetate to obtain the titled compound (76 mg) as crystals.

¹H-NMR (DMSO-d₆) δ: 2.38 (3H, s), 5.65 (2H, s), 6.62 (1H, s), 7.62 (2H, br d), 7.84 (2H, d), 7.92 (2H, d), 8.24 (1H, s).

[Example 69]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[[2-(trifluoromethyl)-1,3-thiazol-4-yl]methyl]-1H-pyrrole-3-carbonitrile



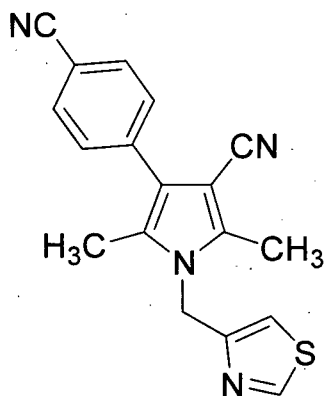
Under an argon atmosphere, to a solution of 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (443 mg) in dehydrated-DMF (20 ml), sodium hydride (60% dispersion in oil, 120 mg) was added under ice cooling, and the mixture was stirred for 30 min. Furthermore, a solution of 4-(iodomethyl)-2-(trifluoromethyl)-1,3-thiazole (880 mg) in dehydrated-DMF (2 ml) was added to the mixture,

and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by NH-silica gel column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-isopropyl ether to obtain the titled compound (332 mg) as crystals.

¹H-NMR (CDCl₃) δ: 2.31 (3H, s), 2.48 (3H, s), 5.32 (2H, s), 7.50 (2H, d), 7.69 (1H, s), 7.72 (2H, d).

[Example 70]

4-(4-Cyanophenyl)-2,5-dimethyl-1-(1,3-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile



4-chloromethyl-1,3-thiazole (2.00 g) was dissolved in acetone (100 ml) and sodium iodide (5.00 g) was added thereto. After the reaction mixture was stirred at room temperature for 16 hr and concentrated, the residue was dissolved in ethyl acetate and an aqueous saturated sodium bicarbonate solution. The ethyl acetate layer was separated, dried over anhydrous magnesium sulfate and concentrated to obtain 4-iodomethyl-1,3-thiazole.

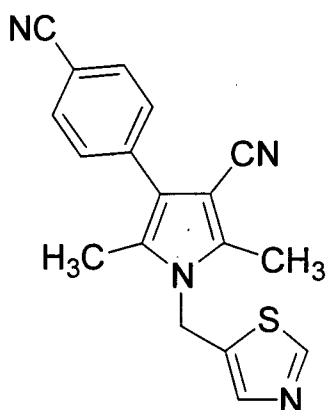
Using 4-iodomethyl-1,3-thiazole (1.00 g), sodium hydride (60% dispersion in oil, 0.28 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.00 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound

(1.17 g) as colorless crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.30 (3H, s), 2.47 (3H, s), 5.24 (2H, s), 6.88 (1H, d), 7.51 (2H, d), 7.70 (2H, d), 8.84 (1H, d).

[Example 71]

5 4-(4-Cyanophenyl)-2,5-dimethyl-1-(1,3-thiazole-5-ylmethyl)-1H-pyrrole-3-carbonitrile



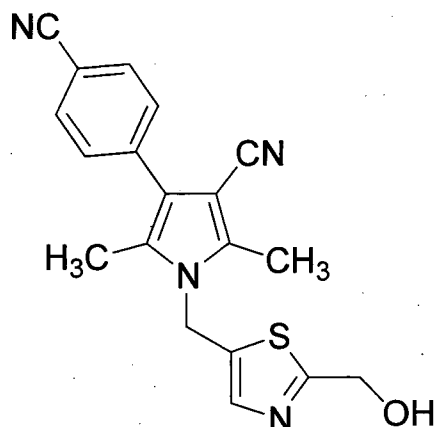
Using 5-chloromethyl-1,3-thiazole, 5-iodomethyl-1,3-thiazole was obtained by the same reaction as in Example 67.

10 Using 5-iodomethyl-1,3-thiazole (1.13 g), sodium hydride (60% dispersion in oil, 0.17 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.60 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound
15 (0.22 g) as colorless crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.31 (3H, s), 2.48 (3H, s), 5.28 (2H, s), 7.49 (2H, d), 7.65 (1H, s), 7.71 (2H, d), 8.81 (1H, s).

[Example 72]

4-(4-Cyanophenyl)-1-{[2-(hydroxymethyl)-1,3-thiazole-5-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carbonitrile
20



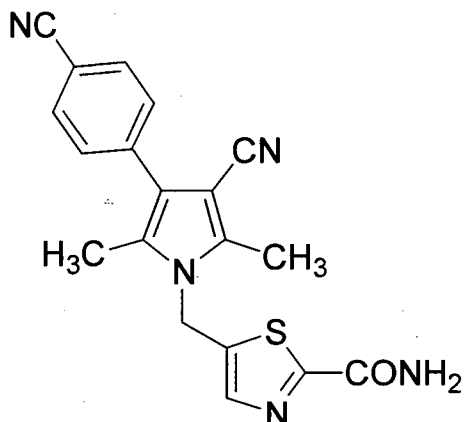
Using the compound (1.87 g) obtained in Reference Example 76, sodium hydride (60% dispersion in oil, 0.44 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (2.21 g), the same reaction and purification operation as in Example 1 were conducted to obtain ethyl 5-
5 { [3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl }-1,3-thiazole-2-carboxylate (1.32 g) as colorless crystals.

10 A solution of ethyl 5- { [3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl }-1,3-thiazole-2-carboxylate (0.50 g) in THF (14 ml) was cooled to 0°C and calcium chloride (0.33 g) and sodium borohydride (0.11 g) were added thereto, and then ethanol (7 ml) was added dropwise
15 thereto. The reaction mixture was stirred at room temperature for 16 hr, diluted with water and extracted with ethyl acetate. The extracted ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (ethyl
20 acetate-methanol) to obtain the titled compound (0.37 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.31 (3H, s), 2.47 (3H, s), 3.11 (1H, br s), 4.91 (2H, s), 5.23 (2H, s), 7.46 (1H, s), 7.48 (2H, d), 7.70 (2H, d).

25 [Example 73]

5- { [3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl }-1,3-thiazole-2-carboxamide



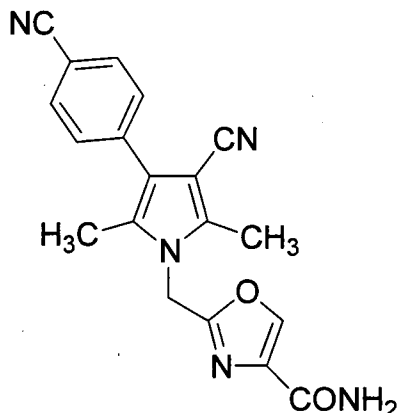
Using ethyl 5-{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-2-carboxylate (0.50 g), the same reaction and purification operation as
 5 in Example 66 were conducted to obtain 5-{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-2-carboxylic acid (0.43 g) as colorless crystals.

To a mixture of 5-{[3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-thiazole-2-carboxylic
 10 acid (50 mg), ammonium chloride (30 mg), diethyl cyanophosphate (0.14 ml) and DMF (1 ml), triethylamine (0.14 ml) was added. The reaction mixture was stirred at room temperature for 7 hr, poured into water and then extracted with ethyl acetate. The ethyl acetate layer was
 15 washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was suspended in ethyl acetate and filtered to obtain the titled compound (29 mg) as crystals.

¹H-NMR (CDCl₃+DMSO-d₆) δ: 2.30 (3H, s), 2.45 (3H, s), 5.30
 20 (2H, s), 6.62 (1H, br s), 7.19 (1H, br s), 7.49 (2H, d), 7.55 (1H, s), 7.71 (2H, d).

[Example 74]

2-{[3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl}-1,3-oxazole-4-carboxamide



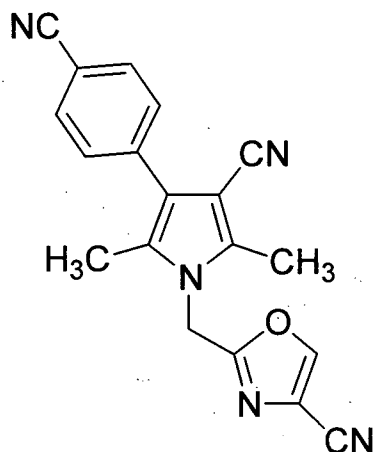
Using the compound (1.05 g) obtained in Reference Example 77, sodium hydride (60% dispersion in oil, 0.20 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.06 g), the same reaction and purification operation as in Example 1 were conducted to obtain methyl 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carboxylate (1.30 g) as colorless crystals. Using methyl 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carboxylate (1.15 g), the same reaction and purification operation as in Example 66 were conducted to obtain 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carboxylic acid (1.05 g) as colorless crystals.

Using 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carboxylic acid (0.85 g), the same reaction and purification operation as in Example 57 were conducted to obtain the titled compound (0.62 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.36 (3H, s), 2.54 (3H, s), 3.16 (2H, s), 5.55 (1H, br s), 6.70 (1H, br s), 7.49 (2H, d), 7.71 (2H, d), 8.23 (1H, s).

[Example 75]

2-([3-Cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carbonitrile



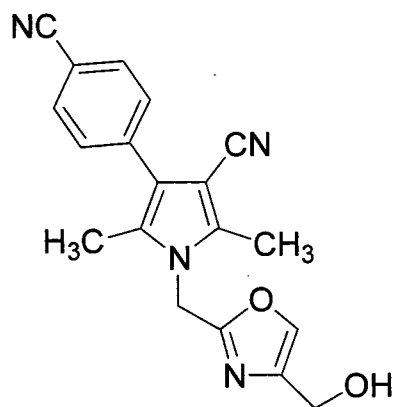
Using the compound (0.42 g) obtained in Example 74, the same reaction and purification operation as in the synthesis method 2 of Example 59 were conducted to obtain the titled compound (0.38 g) as crystals.

Melting point: 188-189°C

$^1\text{H-NMR}$ (CDCl_3) δ : 2.35 (3H, s), 2.53 (3H, s), 5.19 (2H, s), 7.47 (2H, d), 7.70 (2H, d), 8.18 (1H, s).

[Example 76]

4-(4-Cyanophenyl)-1-{[4-(hydroxymethyl)-1,3-oxazole-2-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carbonitrile

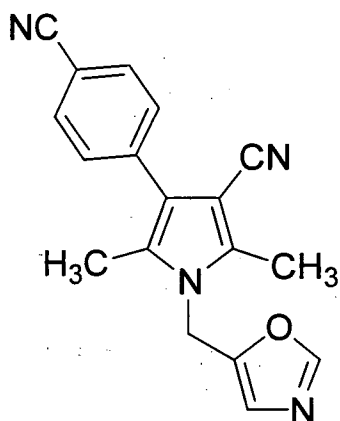


Using the compound (0.28 g) obtained in Reference Example 77, the same reaction and purification operation as in Example 72 were conducted to obtain the titled compound (0.16 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.35 (3H, s), 2.51 (3H, s), 4.56 (2H, s), 5.14 (2H, s), 7.48 (2H, d), 7.61 (1H, s), 7.68 (2H, d).

[Example 77]

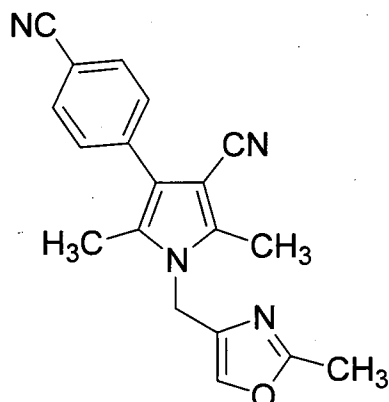
4-(4-Cyanophenyl)-2,5-dimethyl-1-(1,3-oxazole-5-ylmethyl)-
1H-pyrrole-3-carbonitrile



5 The compound (90 mg) obtained in Example 78 was
dissolved in methanol (4 ml), and potassium carbonate (97
mg) and p-toluenesulfonylmethyl isocyanide (70 mg) were
added thereto, and then the mixture was heated at reflux
for 1 hr. After the reaction mixture was concentrated, the
10 residue was dissolved in ethyl acetate and water. The
ethyl acetate layer was separated, dried over anhydrous
magnesium sulfate and concentrated. The residue was
purified by column chromatography (ethyl acetate-methanol)
to obtain the titled compound (54 mg) as colorless crystals.
15 ¹H-NMR (CDCl₃) δ: 2.34 (3H, s), 2.51 (3H, s), 5.09 (2H, s),
7.02 (1H, s), 7.48 (2H, d), 7.68 (2H, d), 7.87 (1H, s).

[Example 78]

4-(4-Cyanophenyl)-2,5-dimethyl-1-[(2-methyl-1,3-oxazole-4-
yl)methyl]-1H-pyrrole-3-carbonitrile



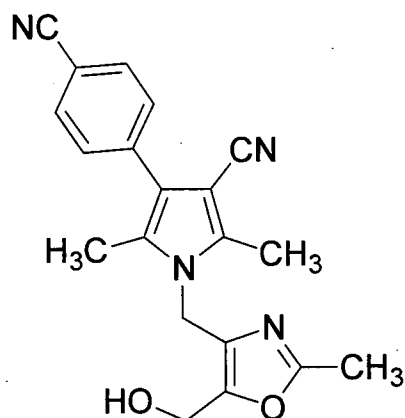
Using the compound (0.92 g) obtained in Reference Example 80, 2-methyl-4-iodomethyl-1,3-oxazole (1.43 g) was obtained in the same manner as in Reference Example 31.

5 Using 2-methyl-4-iodomethyl-1,3-oxazole (1.13 g), sodium hydride (60% dispersion in oil, 0.24 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.89 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound
10 (0.98 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.33 (3H, s), 2.45 (3H, s), 2.49 (3H, s), 4.91 (2H, s), 7.26 (1H, s), 7.50 (2H, d), 7.70 (2H, d).

[Example 79]

15 4-(4-Cyanophenyl)-1-{[5-(hydroxymethyl)-2-methyl-1,3-oxazole-4-yl]methyl}-2,5-dimethyl-1H-pyrrole-3-carbonitrile



A solution of the compound (221 mg) obtained in Example 78 in THF (6 ml) was cooled to -78°C and a solution of n-butyllithium in hexane (1.6 mol/l, 0.44 ml) was added

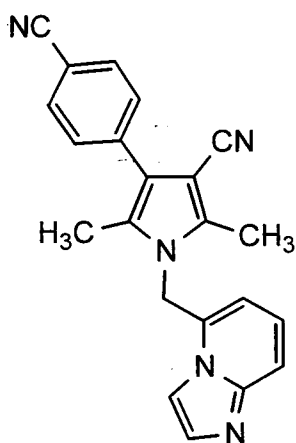
dropwise thereto. The reaction mixture was stirred at the same temperature for 15 min, and DMF (0.40 ml) was added thereto and stirred at the same temperature for 1 hr and at room temperature for 2 hr. To the reaction mixture, water and ethyl acetate were added. The ethyl acetate layer was separated, dried over anhydrous magnesium sulfate and further concentrated. The residue was purified by column chromatography (ethyl acetate-methanol) to obtain 4-(4-cyanophenyl)-1-[(5-formyl-2-methyl-1,3-oxazole-4-yl)methyl]-2,5-dimethyl-1H-pyrrole-3-carbonitrile as a colorless amorphous solid (75 mg).

Using this colorless solid (75 mg), the same reaction and purification operation as in Reference Example 75 were conducted to obtain the titled compound (35 mg) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.73 (1H, t), 2.34 (3H, s), 2.42 (3H, s), 2.50 (3H, s), 4.41 (2H, d), 4.94 (2H, s), 7.50 (2H, d), 7.69 (2H, d).

[Example 80]

4-(4-Cyanophenyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile



Imidazo[1,2-a]pyridin-5-ylmethanol (0.76 g) was suspended in THF (20 ml) and thionyl chloride (1.2 ml) were added thereto. The reaction mixture was stirred at room temperature for 1.5 hr and concentrated. The residue was suspended in ethyl acetate and filtered to obtain 5-

(chloromethyl)imidazo[1,2-a]pyridine hydrochloride (1.00 g).

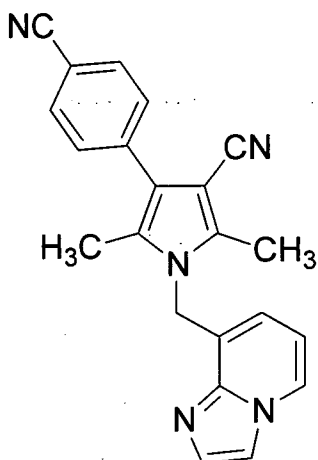
Using 5-(chloromethyl)imidazo[1,2-a]pyridine hydrochloride (0.33 g), sodium hydride (60% dispersion in oil, 0.14 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (0.29 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound (0.19 g) as crystals.

Melting point: 276-278°C

¹H-NMR (CDCl₃) δ: 2.23 (3H, s), 2.40 (3H, s), 5.21 (2H, s), 5.92 (1H, d), 7.19 (1H, dd), 7.56-7.58 (3H, m), 7.68-7.76 (3H, m), 7.86 (1H, s).

[Example 81]

4-(4-Cyanophenyl)-1-(imidazo[1,2-a]pyridin-8-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile



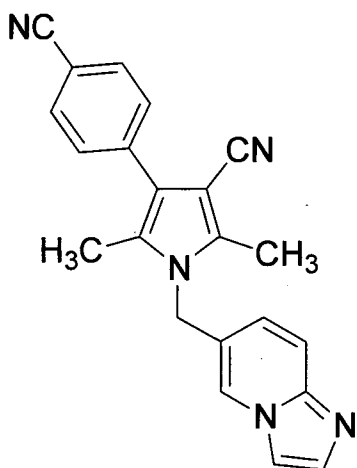
Imidazo[1,2-a]pyridin-8-ylmethanol (0.89 g) was suspended in THF (20 ml) and thionyl chloride (1.3 ml) was added thereto. The reaction mixture was stirred at room temperature for 2 hr and concentrated to obtain 8-(chloromethyl)imidazo[1,2-a]pyridine hydrochloride (1.20 g).

Using 8-(chloromethyl)imidazo[1,2-a]pyridine hydrochloride (1.20 g), sodium hydride (60% dispersion in oil, 0.72 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.00 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound (0.50 g) as crystals.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (3H, s), 2.39 (3H, s), 5.50 (2H, s), 6.21 (1H, d), 6.75 (1H, d), 7.56 (2H, d), 7.70-7.75 (4H, m), 8.13 (1H, d).

[Example 82]

5 4-(4-Cyanophenyl)-1-(imidazo[1,2-a]pyridin-6-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile



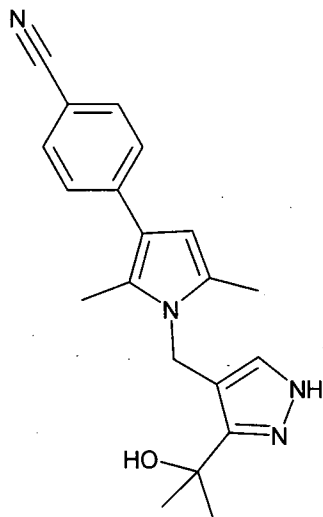
Imidazo[1,2-a]pyridin-6-ylmethanol (0.74 g) was suspended in THF (14 ml) and thionyl chloride (1.1 ml) was added thereto. The reaction mixture was stirred at room temperature for 2 hr and concentrated. The residue was suspended in diisopropyl ether and filtered to obtain 6-(chloromethyl)imidazo[1,2-a]pyridine hydrochloride (1.00 g).

Using 6-(chloromethyl)imidazo[1,2-a]pyridine hydrochloride (1.00 g), sodium hydride (60% dispersion in oil, 0.60 g) and 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile (1.00 g), the same reaction and purification operation as in Example 1 were conducted to obtain the titled compound (1.07 g) as colorless crystals.

20 $^1\text{H-NMR}$ (CDCl_3) δ : 2.27 (3H, s), 2.44 (3H, s), 5.13 (2H, s), 6.93 (1H, d), 7.48-7.75 (8H, m).

[Example 83]

4-(1-([3-(1-Hydroxy-1-methylethyl)-1H-pyrazol-4-yl]methyl))-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile



To a solution of tert-butyl 4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (0.60 g) in DMF (10 ml), sodium hydride (60% dispersion in oil, 0.12 g) was added under ice cooling. After the reaction mixture was stirred at room temperature for 30 min, ethyl 4-(iodomethyl)-1-trityl-1H-pyrazole-3-carboxylate (1.11 g) was added to the mixture, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated to obtain a colorless solid (793 mg). The resulting colorless solid (0.76 g) was dissolved in TFA (5 ml), and the mixture was stirred at room temperature for 3 hr. To the reaction mixture, ethyl acetate and an aqueous sodium bicarbonate solution were added, and the mixture was partitioned. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diethyl ether to obtain ethyl 4-([3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carboxylate (246 mg) as crystals.

To a solution of ethyl 4-([3-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carboxylate

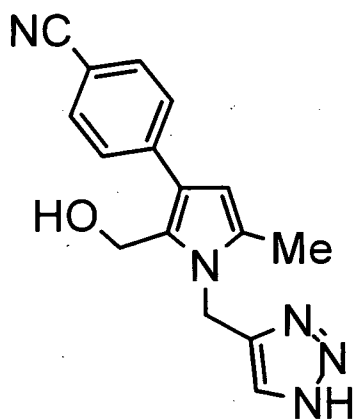
(69.4 mg) in THF (3 ml), a solution of 3M-methylmagnesium bromide in diethyl ether (0.3 ml) was added at 0°C. The mixture was allowed to stand at the same temperature for 1 hr. To the reaction mixture, an aqueous saturated citric acid solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane), and then the effluent was further purified by NH-silica gel (manufactured by Fuji Silysia Chemical Ltd.) column chromatography (ethyl acetate-hexane) and recrystallized from ethyl acetate-ether to obtain the titled compound (30 mg).

Melting point: 164-166°C

¹H-NMR (CDCl₃) δ: 1.68 (6H, s), 2.21 (3H, s), 2.30 (3H, s), 5.06 (2H, s), 6.09 (1H, s), 6.67 (1H, s), 7.45 (2H, d), 7.61 (2H, d).

[Example 84]

4-[2-(Hydroxymethyl)-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile



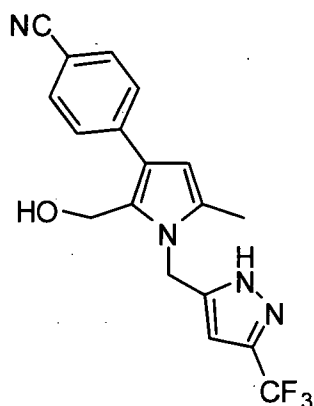
Ethanol (2.0 ml) was added to a solution of sodium borohydride (31 mg) and calcium chloride (46 mg) in THF (2.0 ml), and the mixture was stirred for 20 min. 4-[2-Formyl-5-methyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrol-3-yl]benzonitrile (80 mg) was added to the mixture, and the

mixture was stirred at room temperature for 5 hr. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The obtained residue was crystallized from ethyl acetate-diisopropyl ether to obtain the titled compound as a pale yellow solid (37 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.27 (3H, s), 4.53 (2H, s), 5.28 (2H, s), 6.08 (1H, s), 7.61 (2H, d), 7.78 (2H, d).

[Example 85]

4-(2-(Hydroxymethyl)-5-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl]benzonitrile



4-(2-Formyl-5-methyl-1H-pyrrol-3-yl)benzonitrile

(767.9 mg) was dissolved in DMF (12.2 ml), and sodium hydride (60% dispersion in oil, 210.2 mg) was added thereto under ice-cooling. The reaction mixture was stirred at the same temperature for 30 min, and 5-(iodomethyl)-3-(trifluoromethyl)-1-trityl-1H-pyrazole (2.08 g) was added thereto. The reaction mixture was stirred at room temperature for 30 min, poured into water, and extracted three times with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane). The obtained oil was crystallized by the addition of diethyl ether, and the

crystals were washed with diethyl ether to obtain 4-(2-formyl-5-methyl-1-([3-(trifluoromethyl)-1-trityl-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl]benzonitrile (2.98 g) as colorless crystals.

5 The obtained 4-(2-formyl-5-methyl-1-([3-(trifluoromethyl)-1-trityl-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl]benzonitrile (1.65 g) was dissolved in acetonitrile, and 1M solution of TFA in acetonitrile prepared in other way was added thereto under ice-cooling
10 and under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 25 min, poured into an aqueous saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium
15 sulfate, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate-hexane) to obtain a mixture of 4-(2-formyl-5-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl]benzonitrile and 4-[9-hydroxy-6-methyl-2-(trifluoromethyl)-4H,9H-pyrazolo[1,5-a]pyrrolo[1,2-
20 d]pyrazin-8-yl]benzonitrile (694.1 mg).

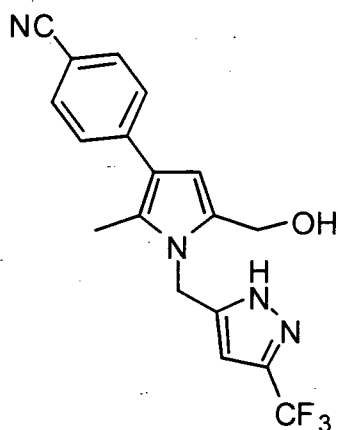
 The obtained mixture (649.1 mg) was dissolved in methanol (9.7 ml), and sodium borohydride (87.9 mg) was added thereto under ice-cooling. The reaction mixture was
25 stirred at the same temperature for 20 min, poured into an aqueous saturated ammonium chloride solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was
30 successively purified by silica gel column chromatography (ethyl acetate-hexane), and recrystallized from ethyl acetate-heptane to obtain the titled compound (first crystals: 306.8 mg, second crystals: 56.5 mg) as colorless crystals.

35 ¹H-NMR (DMSO-d₆) δ : 2.18 (3H, s), 4.48 (2H, s), 5.29 (2H,

s), 6.13 (1H, s), 6.40 (1H, s), 7.62 (2H, d), 7.80 (2H, d).

[Example 86]

4-(5-(Hydroxymethyl)-2-methyl-1-{[3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl}-1H-pyrrol-3-yl]benzonitrile



5

4-(5-Formyl-2-methyl-1H-pyrrol-3-yl)benzonitrile

(130.1 mg) was dissolved in DMF (2.1 ml), and sodium hydride (60% dispersion in oil, 35.7 mg) was added thereto under ice-cooling. The reaction mixture was stirred at the same temperature for 15 min, and 5-(iodomethyl)-3-(trifluoromethyl)-1-trityl-1H-pyrazole (352.8 mg) was added thereto. The reaction mixture was stirred at room temperature for 20 min, poured into water, and extracted twice with diethyl ether. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane). The obtained oil was crystallized from diethyl ether, and the crystals were washed with diethyl ether to obtain 4-(5-formyl-2-methyl-1-{[3-(trifluoromethyl)-1-trityl-1H-pyrazol-5-yl]methyl}-1H-pyrrol-3-yl]benzonitrile (269.1 mg) as colorless crystals.

10

15

20

The obtained 4-(5-formyl-2-methyl-1-{[3-(trifluoromethyl)-1-trityl-1H-pyrazol-5-yl]methyl}-1H-

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pyrrol-3-yl]benzonitrile (141.9 mg) was dissolved in acetonitrile, and 1M TFA solution in acetonitrile prepared in other way was added thereto under ice-cooling and under

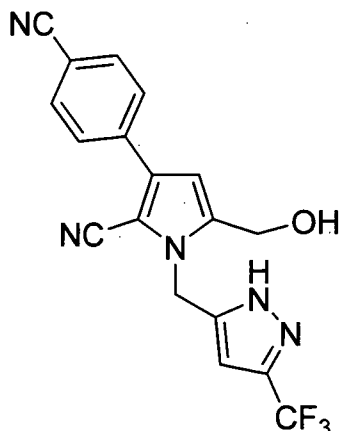
nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 20 min, poured into an aqueous saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was washed with an aqueous saturated sodium bicarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to obtain 4-(5-formyl-2-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl]benzonitrile (77.5 mg).

The obtained 4-(5-formyl-2-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl]benzonitrile (56.4 mg) was suspended in methanol (9.7 ml), and sodium borohydride (11.9 mg) was added thereto under ice-cooling. The reaction mixture was stirred at the same temperature for 15 min, poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was successively purified by silica gel column chromatography (ethyl acetate-hexane) and recrystallized from ethyl acetate-hexane to obtain the titled compound (first crystals: 20.3 mg, second crystals: 4.6 mg) as pale yellow crystals.

¹H-NMR (DMSO-d₆) δ : 2.31 (3H, s), 4.47 (2H, s), 5.30 (2H, s), 6.30 (1H, s), 6.45 (1H, s), 7.53 (2H, d), 7.77 (2H, d).

[Example 87]

3-(4-Cyanophenyl)-5-(hydroxymethyl)-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-2-carbonitrile

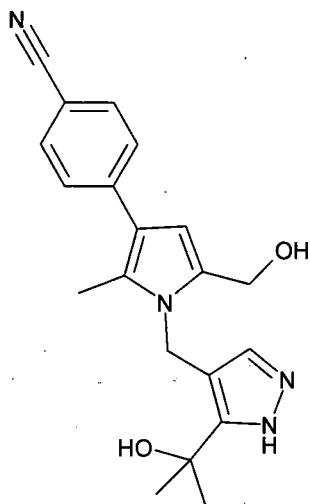


Ammonium cerium(IV) nitrate (2.74 g) was added to a solution of 3-(4-cyanophenyl)-5-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-2-carbonitrile (0.36 g) in acetonitrile (30 ml) and water (5 ml) at room temperature. The reaction mixture was stirred at the same temperature for 3 hr, poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain a brown solid (0.20 g). The brown solid (0.18 g) was suspended in THF (2 ml) and ethanol (2 ml), and sodium borohydride (80 mg) was added thereto at room temperature. The reaction mixture was stirred at the same temperature for 3 hr, poured into an aqueous saturated citric acid solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was crystallized from ethyl acetate-diethyl ether to obtain the titled compound (113.5 mg) as a colorless solid.

¹H-NMR (DMSO-d₆) δ : 4.55 (2H, s), 5.48 (2H, s), 6.56 (1H, s), 6.74 (1H, s), 7.86 (2H, d), 7.94 (2H, d).

[Example 88]

4-(5-(Hydroxymethyl)-1-([5-(1-hydroxy-1-methylethyl)-1H-pyrazol-4-yl]methyl)-2-methyl-1H-pyrrol-3-yl)benzonitrile



Sodium hydride (60 % dispersion in oil, 87 mg) was added to a solution of the compound synthesized in Reference Example 86 (381.3 mg) in DMF (10 ml). The reaction mixture was stirred at room temperature for 30 min and ethyl 4-(iodomethyl)-1-trityl-1H-pyrazole-3-carboxylate (1.04 g) was added thereto. The reaction mixture was stirred at room temperature for 14 hr, poured into saturated brine and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated to obtain a colorless solid (1.01 g). The obtained colorless solid (1.00 g) was dissolved in acetonitrile (25 ml) and TFA (0.63 ml) was added thereto. The reaction mixture was stirred at room temperature for 24 hr, poured into an aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) and crystallized from diisopropyl ether to obtain ethyl 4-([3-(4-cyanophenyl)-5-formyl-2-methyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-5-carboxylate (292 mg) as crystals.

Sodium borohydride (25.2 mg) was added to a solution of ethyl 4-([3-(4-cyanophenyl)-5-formyl-2-methyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-5-carboxylate (200.6 mg) in

ethanol (5 ml) at 0°C. The reaction mixture was stirred at the same temperature for 3 hr. The reaction mixture was combined with an aqueous saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether and filtered to obtain ethyl 4-[[3-(4-cyanophenyl)-5-(hydroxymethyl)-2-methyl-1H-pyrrol-1-yl]methyl]-1H-pyrazole-5-carboxylate (198.5 mg).

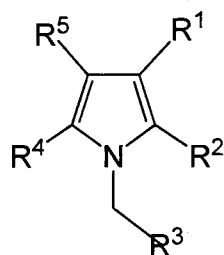
A solution of 3M methylmagnesium bromide in diethyl ether (0.82 ml) was added to a solution of ethyl 4-[[3-(4-cyanophenyl)-5-(hydroxymethyl)-2-methyl-1H-pyrrol-1-yl]methyl]-1H-pyrazole-5-carboxylate (90.1 mg) in THF (10 ml) and the mixture was stirred at room temperature for 5 hr. The reaction mixture was combined with an aqueous saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-methanol) and crystallized from ethyl acetate-diethyl ether to obtain the titled compound (46.5 mg).

Melting point: 167-168 °C

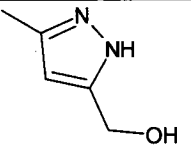
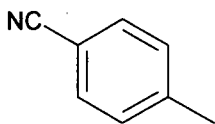
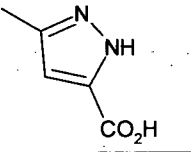
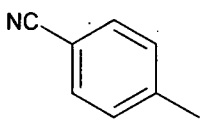
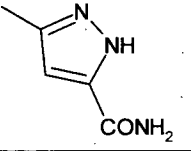
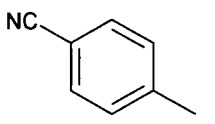
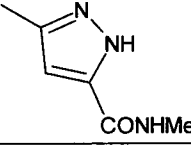
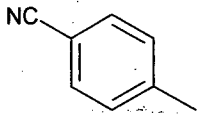
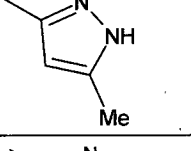
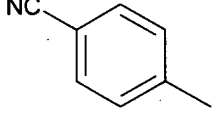
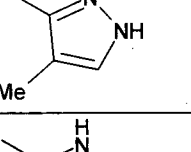
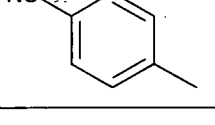
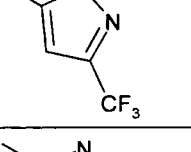
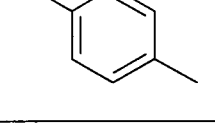
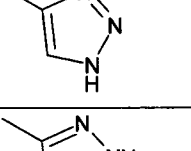
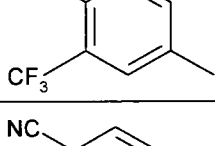
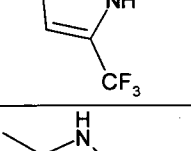
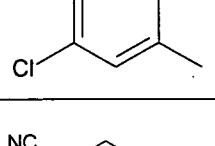
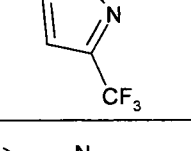
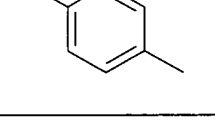
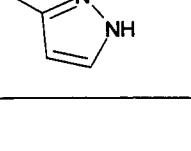
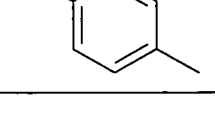
¹H-NMR (DMSO-d₆) δ: 1.50 (6H, s), 2.27 (3H, s), 4.35 (2H, d), 4.94 (1H, s), 5.02 (1H, s), 5.22 (2H, s), 6.29 (1H, s), 6.57 (1H, s), 7.55 (2H, d), 7.77 (2H, d), 12.18 (1H, s).

The compounds obtained in the above Examples are summarized in table 1 below.

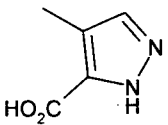
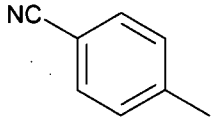
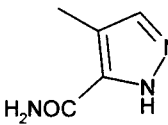
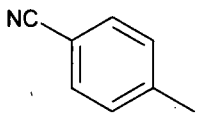
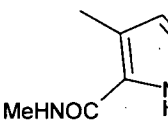
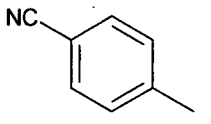
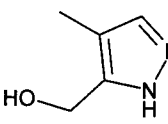
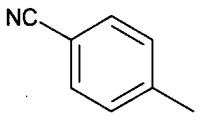
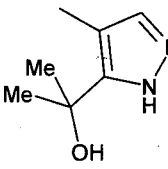
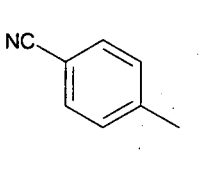
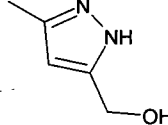
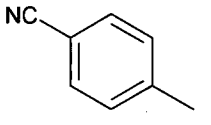
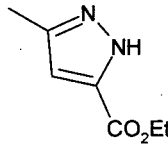
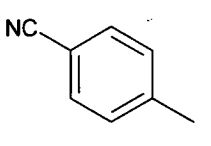
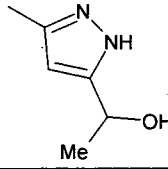
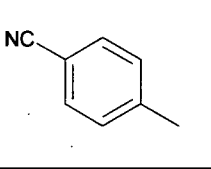
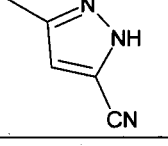
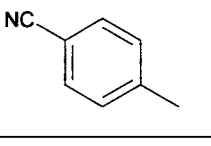
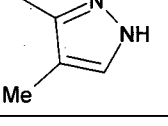
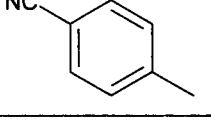
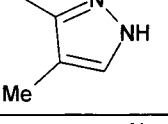
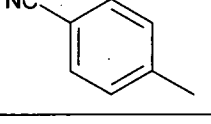
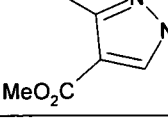
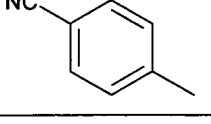
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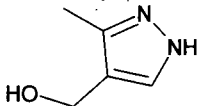
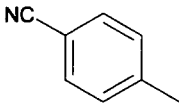
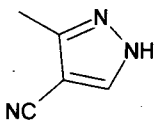
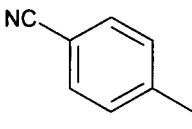
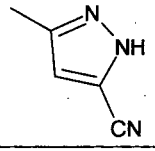
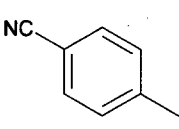
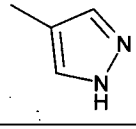
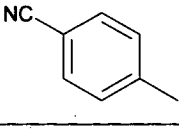
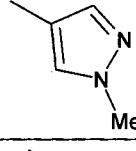
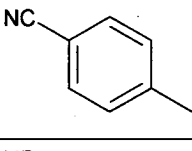
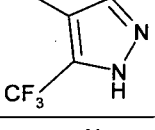
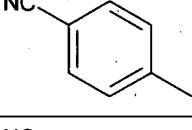
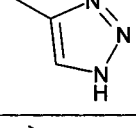
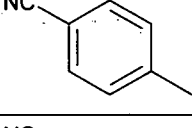
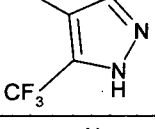
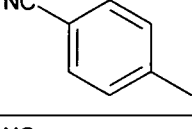
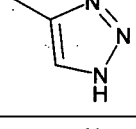
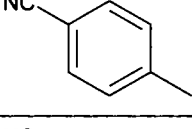
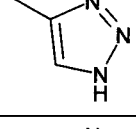
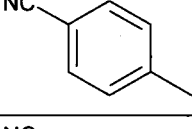
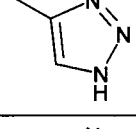
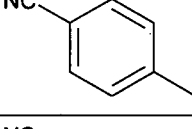
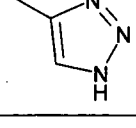
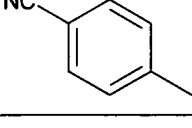


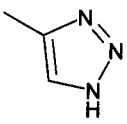
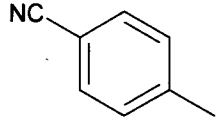
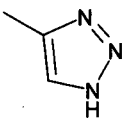
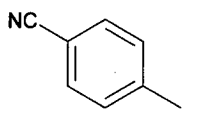
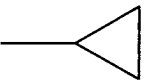
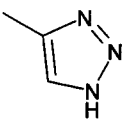
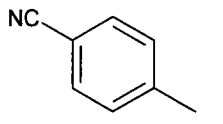
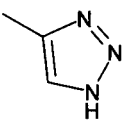
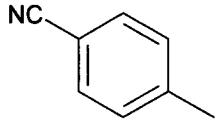
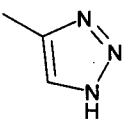
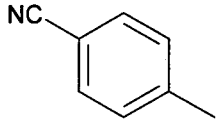
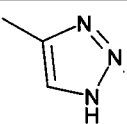
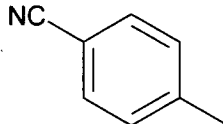
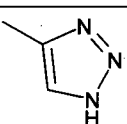
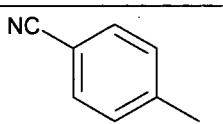
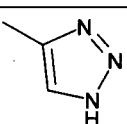
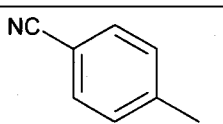
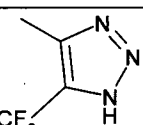
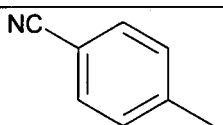
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵
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2	CN	Me		Me	
3	CN	Me		Me	
4	CN	Me		Me	
5	CN	Me		Me	
6	CN	Me		Me	
7	H	Me		Me	
8	CN	Me		Me	

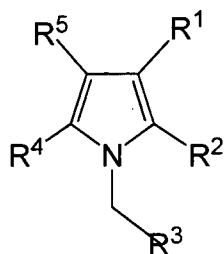
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10	CN	Me		Me	
11	CN	Me		Me	
12	CN	Me		Me	
13	CN	Me		Me	
14	CN	Me		Me	
15	H	Me		Me	
16	H	Me		Me	
17	Me	CN		Me	
18	H	Me		CN	
19	H	Me		Me	

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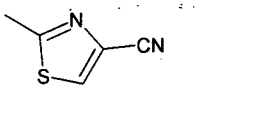
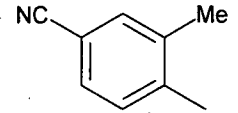
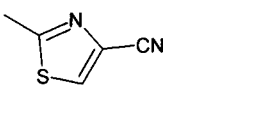
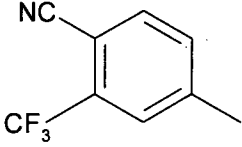
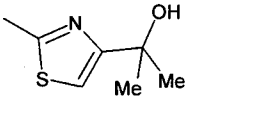
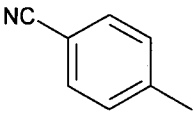
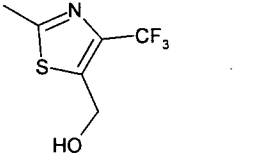
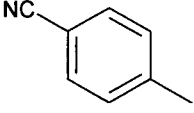
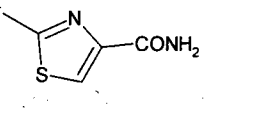
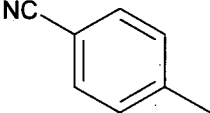
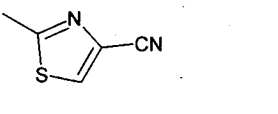
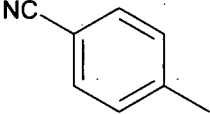
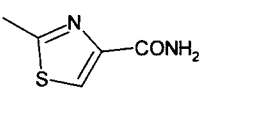
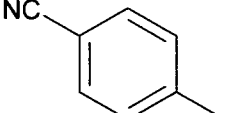
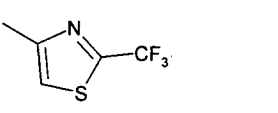
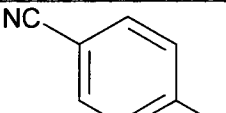
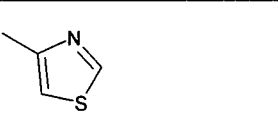
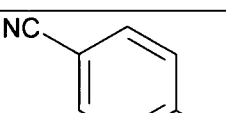
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21	CN	Me		Me	
22	CN	Me		Me	
23	CN	Me		Me	
24	CN	Me		Me	
25	H	Me		Me	
26	H	Me		Me	
27	H	Me		Me	
28	H	Me		Me	
29	H	Me		Me	
30	H	Et		Me	
31	H	Me		Me	

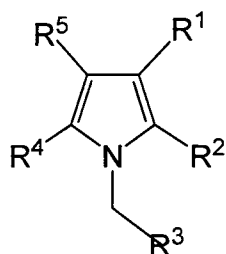
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36	CN	Me		Me	
37	CN	Me		Me	
38	H	CF3		Me	
39	H	Me		Me	
40	H	Me		CN	
41	H	CN		Me	
42	CN	H		Me	
43	H	Me		Me	

44	H	Et		Me	
45	H	Pr		Me	
46	H			Me	
47	H	Me		CF ₃	
48	H	Me		Et	
49	H	Me		CHO	
50	H	Me		H	
51	CF ₃	Me		Me	
52	H	Me		Me	

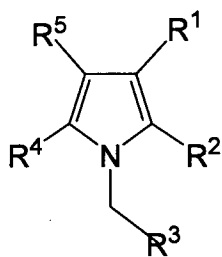


Example No.	R ¹	R ²	R ³	R ⁴	R ⁵
53	CN	Me		Me	
54	CN	Me		Me	
55	CN	Me		Me	
56	CN	Me		Me	
57	CN	Me		Me	
58	CN	Me		Me	
59	CN	Me		Me	
60	CN	Me		Me	
61	CN	Me		Me	

62	CN	Me		Me	
63	CN	Me		Me	
64	CN	Me		Me	
65	CN	Me		Me	
66	H	Me		Me	
67	H	Me		Me	
68	H	Me		CN	
69	CN	Me		Me	
70	CN	Me		Me	



Example No.	R ¹	R ²	R ³	R ⁴	R ⁵
71	CN	Me		Me	
72	CN	Me		Me	
73	CN	Me		Me	
74	CN	Me		Me	
75	CN	Me		Me	
76	CN	Me		Me	
77	CN	Me		Me	
78	CN	Me		Me	
79	CN	Me		Me	



Example No.	R ¹	R ²	R ³	R ⁴	R ⁵
80	CN	Me		Me	
81	CN	Me		Me	
82	CN	Me		Me	
83	H	Me		Me	
84	H	Me		CH ₂ OH	
85	H	Me		CH ₂ OH	
86	H	CH ₂ OH		Me	
87	H	CH ₂ OH		CN	
88	H	CH ₂ OH		Me	

[Preparation Example 1]

	(1) Compound of Example 9	50 mg
	(2) Lactose	34 mg
	(3) Cornstarch	10.6 mg
5	(4) Cornstarch (pasty)	5 mg
	(5) Magnesium stearate	0.4 mg
	(6) Calcium carboxymethylcellulose	20 mg
	Total	120 mg

10 According to a conventional method, the above ingredients (1) to (6) were mixed and compressed using a tablet machine to obtain tablets.

[Preparation Example 2]

	(1) Compound of Example 41	50 mg
	(2) Lactose	34 mg
15	(3) Cornstarch	10.6 mg
	(4) Cornstarch (pasty)	5 mg
	(5) Magnesium stearate	0.4 mg
	(6) Calcium carboxymethylcellulose	20 mg
	Total	120 mg

20 According to a conventional method, the above ingredients (1) to (6) were mixed and compressed using a tablet machine to obtain tablets.

[Preparation Example 3]

	(1) Compound of Example 80	50 mg
25	(2) Lactose	34 mg
	(3) Cornstarch	10.6 mg
	(4) Cornstarch (pasty)	5 mg
	(5) Magnesium stearate	0.4 mg
	(6) Calcium carboxymethylcellulose	20 mg
30	Total	120 mg

According to a conventional method, the above ingredients (1) to (6) were mixed and compressed using a tablet machine to obtain tablets.

35 Test Example 1: AR binding inhibitory test (wild type,

LNCaP type)

To a solution containing an androgen receptor (AR) having a wild type or LNCaP type mutation, 3 nM radio-labeled mibolerone and a 1 μ M compound were added and, after the solution was incubated at 4°C for 3 hr, B (Bound)/F (Free) separation was conducted by a dextran/charcoal method. A label count of B was measured and an inhibitory ratio of each compound was calculated. The results are shown in Table A.

Table A Inhibitory ratio at 1 μ M

Compound No.	Wild type	LNCaP type
1	97	94
4	96	92
14	101	101
34	89	95
43	93	96
56	99	94
59	97	94
60	93	88
70	100	94
71	90	86
75	99	93
80	89	80
Bicalutamide	88	63

As is apparent from the results shown in Table A, the compounds of the present invention exhibit strong affinity against both wild type and LNCaP type mutant androgen receptors.

Test Example 2: Prostate Specific Antigen (PSA) Production Inhibitory Test by Compounds of the Present Application in various (including mutation) Prostate Cancer Cells

Human prostate cancer cells LNCaP-FGC were inoculated in 96-hole plates at 5000 cells/100 μ L/well. The next day testosterone having a final concentration 1 ng/mL and a 1 μ M compound were added thereto. Three days after the addition, the concentration of PSA in the culture

supernatant was measured by ELISA and a PSA production inhibitory ratio was calculated assumed that the inhibitory ratio of the group (no addition of testosterone) is 100% and that of the group (addition of testosterone) is 0%.

5 The results are shown in Table B.

Table B Inhibitory ratio at 1 μ M

Compound No.	Inhibitory ratio (%)
1	90
15	90
18	91
34	99
38	97
43	99
56	98
59	98
60	91
71	95
Bicalutamide	51

As is apparent from Table B, the compounds of the present invention exhibit strong PSA production inhibitory activity.

Test Example 3: AR Transcription Inhibitory Test

In a flask, 5,000,000 cells of Cos-7 were inoculated and cultured in a culture broth (DMEM+10% Dextran Charcoal (DCC)-Fetal Bovine Serum (FBS)+2 mM glutamine) for 24 hr. Then, a vector DNA into which mutant type AR (W741C) was inserted, and a vector DNA in which a luciferase gene was bound to the downstream of an androgen response promoter were transfected by a liposome method. After 2 hr, the media was exchanged. After culturing for 3 hr culture, DHT dihydrotestosterone) having a final concentration of 0.04 μ M and a test compound having a final concentration 0.1 μ M, were added thereto. After culturing for 24 hr, luciferase activity was measured and transcription inhibitory activity of AR by the test compound was examined. The results are shown in Table C by way of an inhibitory ratio (%) against

a control.

Table C Inhibitory ratio at 0.1 μ M

Compound No.	Inhibitory ratio (%)
1	42
4	51
9	39
14	60
15	29
34	47
38	23
56	29
60	33
70	43
75	51
80	29
Bicalutamide	-72

As is apparent from the results shown in Table C, bicalutamide scarcely exhibited transcription inhibitory activity against mutant type AR (W741C), while the compounds of the present application exhibit excellent transcription inhibitory activity.

Test Example 4: Rat Prostate Weight Reduction Test

After castration, 1.5 mg/kg of testosterone propionate was subcutaneously administered to each of three-week-old male rats and 50 mg/kg/day of a compound (also in case of bicalutamide, 50 mg/kg/day) was orally administered for 7 days. The day after the completion of administration, the prostate weight was measured. A prostate weight reduction rate was measured assumed that the weight reduction rate measured upon no addition of a drug is 0% and that measured upon castration is 100%. The results are shown in Table D.

Table D

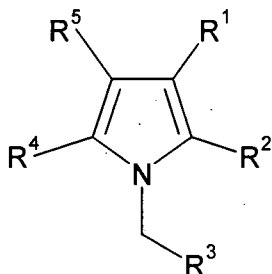
Compound No.	Reduction rate (%)
56	79
59	89
75	84
Bicalutamide	78

INDUSTRIAL APPLICABILITY

The compounds (I) of the present invention or salts thereof have excellent antagonism against a normal androgen receptor and/or a mutant androgen receptor, and are useful
5 as a preventive and/or a remedy for hormone-sensitive cancers in an androgen dependent stage and/or an androgen independent stage.

CLAIMS

1. A compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3)
 5 an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1)
 a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4)
 trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-
 10 substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10)
 15 cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R³ represents (1) an optionally substituted thiazolyl, (2)
 an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted
 20 imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-
 position and further may be substituted,

25 provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-
 30 1H-pyrrole-3-carbonitrile are excluded, or a salt thereof.

2. The compound according to claim 1, wherein R^1 is a hydrogen atom, cyano or an optionally halogenated C_{1-6} alkyl.

3. The compound according to claim 1, wherein R^2 and R^4 are the same or different and each represents (1) a hydrogen atom, (2) a C_{1-6} alkyl optionally having hydroxy, (3) a C_{3-6} cycloalkyl, (4) trifluoromethyl, (5) cyano or (6) an acyl.

4. The compound according to claim 1, wherein R^3 is (1) an optionally substituted pyrazolyl, (2) an optionally substituted oxazolyl, (3) an optionally substituted imidazo[1,2-a]pyridyl, (4) an optionally substituted 1,2,4-triazolyl or (5) an optionally substituted tetrazolyl.

5. The compound according to claim 1, wherein R^3 is an optionally substituted thiazolyl.

6. The compound according to claim 1, wherein R^3 is an optionally substituted 1,2,3-triazolyl.

7. The compound according to claim 1, wherein R^5 is 4-cyanophenyl, 3-cyanophenyl, 4-cyano-3-(trifluoromethyl)phenyl, 4-cyano-2-methylphenyl or 3-chloro-4-cyanophenyl.

8. (i) 4-(2,5-dimethyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrol-3-yl)benzonitrile,

(ii) 3-(4-cyanophenyl)-5-methyl-1-([3-(trifluoromethyl)-1H-pyrazol-5-yl]methyl)-1H-pyrrole-2-carbonitrile,

(iii) 5-([3-(4-cyanophenyl)-5-ethyl-2-methyl-1H-pyrrol-1-yl]methyl)-1H-pyrazole-3-carbonitrile,

(iv) 4-[2-methyl-1-(1H-1,2,3-triazol-5-ylmethyl)-5-(trifluoromethyl)-1H-pyrrol-3-yl]benzonitrile,

(v) 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-thiazole-4-carbonitrile,

(vi) 4-(4-cyanophenyl)-2,5-dimethyl-1-([4-(trifluoromethyl)-1,3-thiazol-2-yl]methyl)-1H-pyrrole-3-carbonitrile,

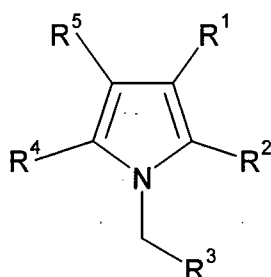
(vii) 2-([3-cyano-4-(4-cyanophenyl)-2,5-dimethyl-1H-pyrrol-1-yl]methyl)-1,3-oxazole-4-carbonitrile,

(viii) 4-(4-cyanophenyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carbonitrile, or

(ix) 4-(1-{{3-(1-hydroxy-1-methylethyl)-1H-pyrazol-4-yl}methyl}-2,5-dimethyl-1H-pyrrol-3-yl)benzonitrile, or a salt thereof.

9. A prodrug of the compound according to claim 1.

10. A drug comprising a compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof.

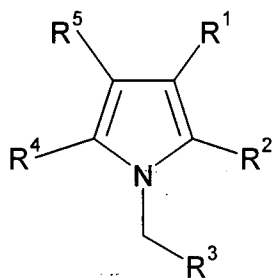
11. The drug according to claim 10, which is an androgen receptor antagonist.

12. The drug according to claim 11, wherein the androgen receptor is a normal androgen receptor and/or a mutant androgen receptor.

13. The drug according to claim 10, which is a preventive or therapeutic agent for hormone-sensitive cancer in an androgen dependent stage and/or independent stage.

14. The drug according to claim 10, which is a preventive or therapeutic agent for prostate cancer.

15. A method for antagonizing an androgen receptor, which comprises administering an effective amount of a compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally

substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

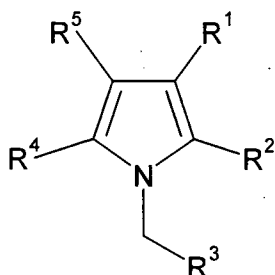
5 R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or
10 (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate,

15 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof to a mammal.

20 16. A method for preventing or treating hormone sensitive cancer in an androgen dependent stage and/or independent stage, which comprises administering an effective amount of a compound represented by formula (I):



25 wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4)
30 trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-

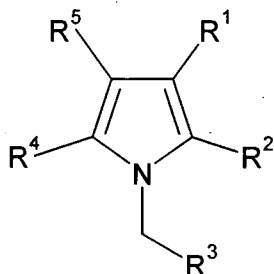
substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof to a mammal.

17. A method for preventing or treating prostate cancer, which comprises administering an effective amount of a compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1)

a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

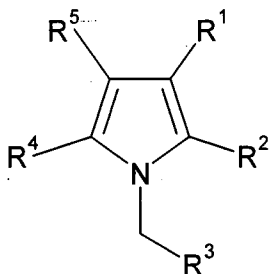
R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate,

4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof to a mammal.

18. Use of a compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1)

a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

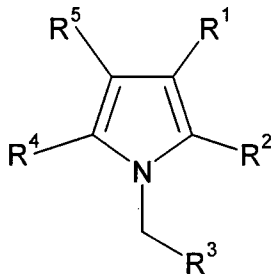
R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate,

4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl)-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof for the manufacture of an androgen receptor antagonistic agent.

19. Use of a compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

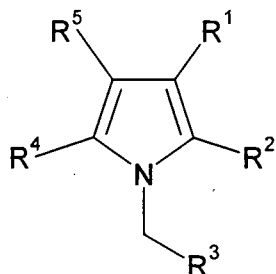
R^2 and R^4 are the same or different and each represents (1) a hydrogen atom, (2) a C_{1-6} alkyl, (3) a C_{3-6} cycloalkyl, (4) trifluoromethyl, (5) an amino- C_{1-6} alkyl, (6) a mono- or di-substituted amino- C_{1-6} alkyl, (7) an optionally halogenated C_{1-6} alkyl substituted with an optionally substituted hydroxy, (8) a C_{2-6} alkenyl substituted with an optionally substituted hydroxy, (9) a C_{1-6} alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R^3 represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R^5 represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-triazol-4-yl)methyl-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof for the manufacture of a preventive or therapeutic agent for hormone sensitive cancer in an androgen dependent stage and/or an androgen independent stage.

20. Use of a compound represented by formula (I):



wherein R¹ represents (1) a hydrogen atom, (2) cyano, (3) an optionally halogenated C₁₋₆ alkyl or (4) an optionally substituted C₁₋₆ alkoxy-carbonyl,

R² and R⁴ are the same or different and each represents (1) a hydrogen atom, (2) a C₁₋₆ alkyl, (3) a C₃₋₆ cycloalkyl, (4) trifluoromethyl, (5) an amino-C₁₋₆ alkyl, (6) a mono- or di-substituted amino-C₁₋₆ alkyl, (7) an optionally halogenated C₁₋₆ alkyl substituted with an optionally substituted hydroxy, (8) a C₂₋₆ alkenyl substituted with an optionally substituted hydroxy, (9) a C₁₋₆ alkyl substituted with an optionally substituted and optionally oxidized thiol, (10) cyano, (11) an acyl, (12) an optionally substituted oxazolyl or (13) a 1,3-dioxolan-2-yl,

R³ represents (1) an optionally substituted thiazolyl, (2) an optionally substituted pyrazolyl, (3) an optionally substituted oxazolyl, (4) an optionally substituted imidazo[1,2-a]pyridyl, (5) an optionally substituted 1,2,3-triazolyl, (6) an optionally substituted 1,2,4-triazolyl or (7) an optionally substituted tetrazolyl, and

R⁵ represents a phenyl which has a cyano at the 4- or 3-position and further may be substituted,

provided that methyl 4-(4-cyanophenyl)-1-((4-cyano-1,3-thiazol-2-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, 4-(4-cyanophenyl)-2,5-dimethyl-1-((1-trityl-1H-1,2,3-

triazol-4-yl)methyl-1H-pyrrole-3-carbonitrile and 4-(4-cyanophenyl)-2,5-dimethyl-1-(1H-1,2,3-triazol-4-ylmethyl)-1H-pyrrole-3-carbonitrile are excluded, or a salt thereof or a prodrug thereof for the manufacture of a preventive or therapeutic agent for prostate cancer.