(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 September 2007 (07.09.2007)

PCT

(10) International Publication Number
WO 2007/099200 A1

(51) International Patent Classification:
C07C 255/60 (2006.01) *A61P 5/26* (2006.01)
A61K 31/277 (2006.01)

(21) International Application Number:
PCT/FI2007/000055

(22) International Filing Date: 2 March 2007 (02.03.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/778,417 3 March 2006 (03.03.2006) US

(71) Applicant *(for all designated States except US)*: **ORION CORPORATION** [FI/FI]; Orionintie 1, FI-02200 Espoo (FI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RATILAINEN, Jari** [FI/FI]; Kuurna-Kulhontie 93, FI-80910 Kulho (FI). **TÖRMÄKANGAS, Olli** [FI/FI]; Rossinpolku 2 D 4, FI-20380 Turku (FI). **KARJALAINEN, Arja** [FI/FI]; Iltatie 4 B 6, FI-02210 Espoo (FI). **HUHTALA, Paavo** [FI/FI]; Kuukausikuja 3 B 7, FI-02200 Espoo (FI).

(74) Agent: **ORION CORPORATION**; Intellectual Property Rights, P.O. Box 65, FI-02101 Espoo (FI).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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:
— *with international search 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.

WO 2007/099200 A1

(54) **Title:** SELECTIVE ANDROGEN RECEPTOR MODULATORS

(57) **Abstract:** A compound of formula (I) or an isomer, metabolite, or a pharmaceutically acceptable salt or ester thereof is disclosed. The compound of the invention possesses utility as a tissue-selective androgen receptor modulator (SARM) and is useful in hormonal therapy, e.g. in the treatment or prevention of hypogonadism, muscle wasting, osteoporosis, benign prostate hyperplasia, obesity associated with a metabolic syndrome, male and female sexual dysfunction and reduced libido, and androgen decline in aging male or female.

SELECTIVE ANDROGEN RECEPTOR MODULATORS

Technical field

The present invention relates to therapeutically active compounds that are useful in the treatment of androgen receptor (AR) dependent conditions. In particular, the invention discloses novel compounds having utility as tissue-selective androgen receptor modulators (SARM). The compounds of the invention, which possess AR agonist activity, are useful in hormonal therapy, especially in treatment or prevention of AR dependent conditions such as hypogonadism, muscle wasting, osteoporosis, benign prostate hyperplasia, obesity associated with a metabolic syndrome, male and female sexual dysfunction and reduced libido, and androgen decline in aging male or female.

Background of the invention

Non-steroidal propionanilides having AR modulating activity have been described e.g. in patent publications EP 100172, EP 253503, WO 98/53826 and WO 02/16310. The design of propionanilide structured AR modulators has concentrated on compounds where the anilide ring is substituted by two electron-withdrawing substituents, such as trifluoromethyl and nitro, since such substitution has been reported to enhance the androgen receptor binding affinity of the ligand. See e.g. Tucker, H. et al., J. Med. Chem., 1988, 31, 954-959.

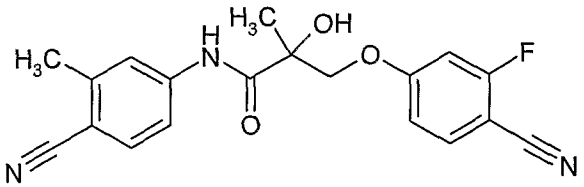
Recently, AR modulating compounds having the anilide ring substituted with an alkyl group were described in WO 2005/000794. However, there is still need for AR modulating compounds which have optimal combination of properties such as high affinity and activity in androgen receptor, tissue-selective androgenic or anabolic effects, high oral bioavailability, low potential for drug-drug interactions, lack of serious adverse effects and a favourable metabolic profile.

Summary of the invention

It has now been found that the compound of formula (I) or an isomer, metabolite, or a pharmaceutically acceptable salt or ester thereof, has high affinity and activity in androgen receptor, provides tissue-selective androgenic or anabolic

effects, good oral bioavailability and, at the same time, has low potential for drug-drug interactions, lacks serious adverse effects and has a favourable metabolic profile. Moreover, the compound of the present invention crystallizes easily and has little tendency to solvate formation. Therefore, the compound of the present invention is particularly useful as a tissue-selective androgen receptor modulator (SARM). The compound of the present invention is particularly suitable for use in hormonal therapy, especially in the treatment or prevention of AR dependent conditions, for example, but not limited to, in the treatment or prevention hypogonadism, muscle wasting, osteoporosis, benign prostate hyperplasia, obesity associated with a metabolic syndrome, male and female sexual dysfunction and reduced libido, and androgen decline in aging male or female. The beneficial androgenic or anabolic effects are obtained without concurrent harmful stimulation of the prostate.

The present invention provides a compound of formula (I)



(I)

or an isomer, metabolite, or a pharmaceutically acceptable salt or ester thereof.

Particularly preferred compound of formula (I) is the S-enantiomer of the compound of formula (I), namely (2*S*)-3-(4-cyano-3-fluorophenoxy)-N-(4-cyano-3-methylphenyl)-2-hydroxy-2-methylpropionamide.

Particularly preferred metabolites of a compound of formula (I) are those which are useful in the treatment or prevention of androgen receptor (AR) dependent conditions. Such preferred metabolites include

2-cyano-5-[(S)-3-(4-cyano-3-fluorophenoxy)-2-hydroxy-2-methylpropionyl-amino]benzoic acid,

(S)-3-(4-cyano-3-fluorophenoxy)-N-(4-cyano-3-hydroxymethylphenyl)-2-hydroxy-2-methylpropionamide, and

(S)-3-(4-cyano-3-fluorophenoxy)-N-(4-cyano-3-formylphenyl)-2-hydroxy-2-methylpropionamide.

Pharmaceutically acceptable salts or esters of the above metabolites are also useful in the treatment or prevention of androgen receptor (AR) dependent conditions.

The present invention provides further a method of hormonal therapy, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or its isomer, metabolite or a pharmaceutically acceptable salt or ester thereof.

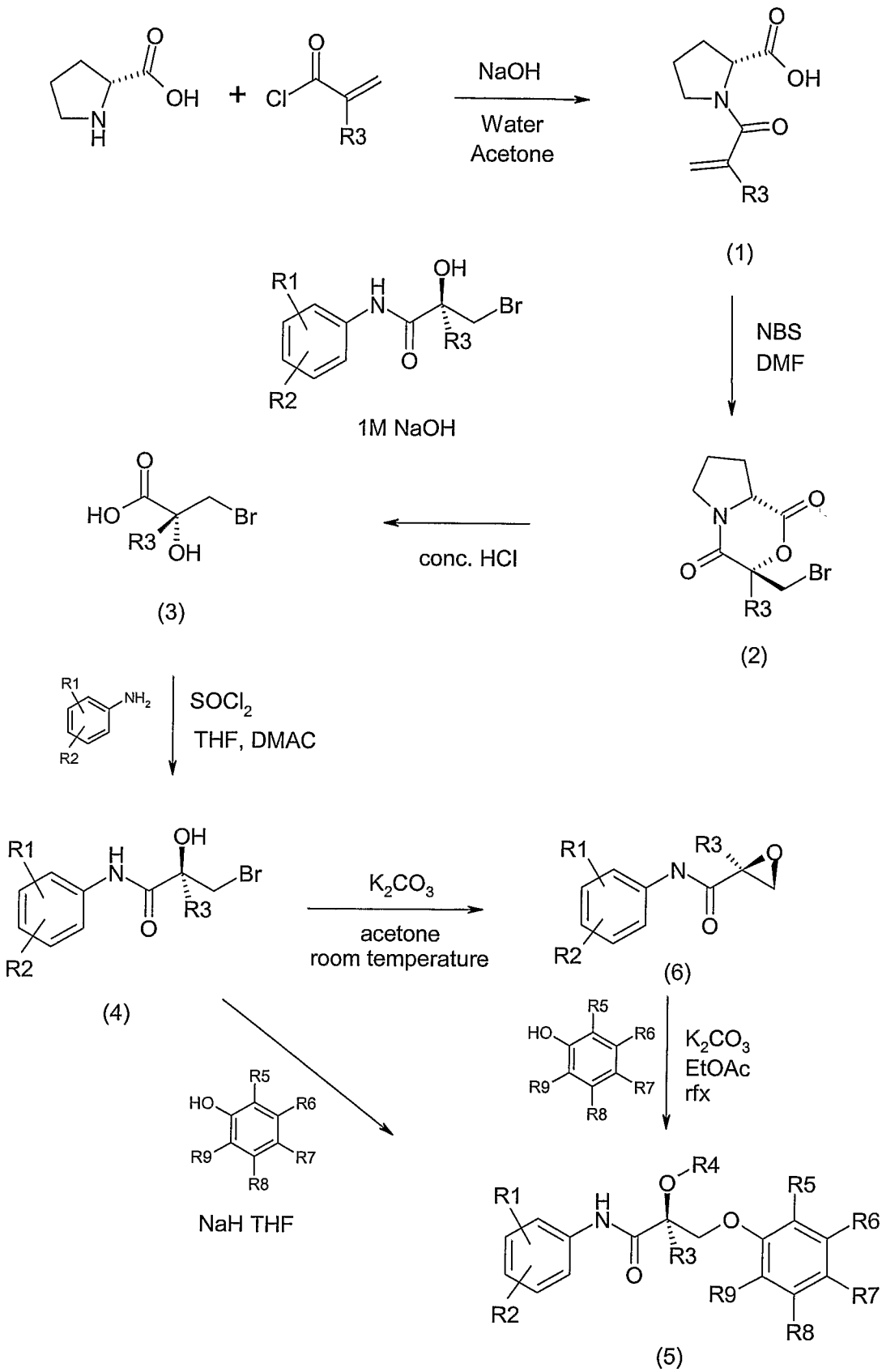
The present invention provides further a method for the treatment or prevention of androgen receptor (AR) dependent conditions, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or its isomer, metabolite or a pharmaceutically acceptable salt or ester thereof.

The present invention provides further a method the treatment or prevention of androgen deficiency, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or its isomer, metabolite or a pharmaceutically acceptable salt or ester thereof.

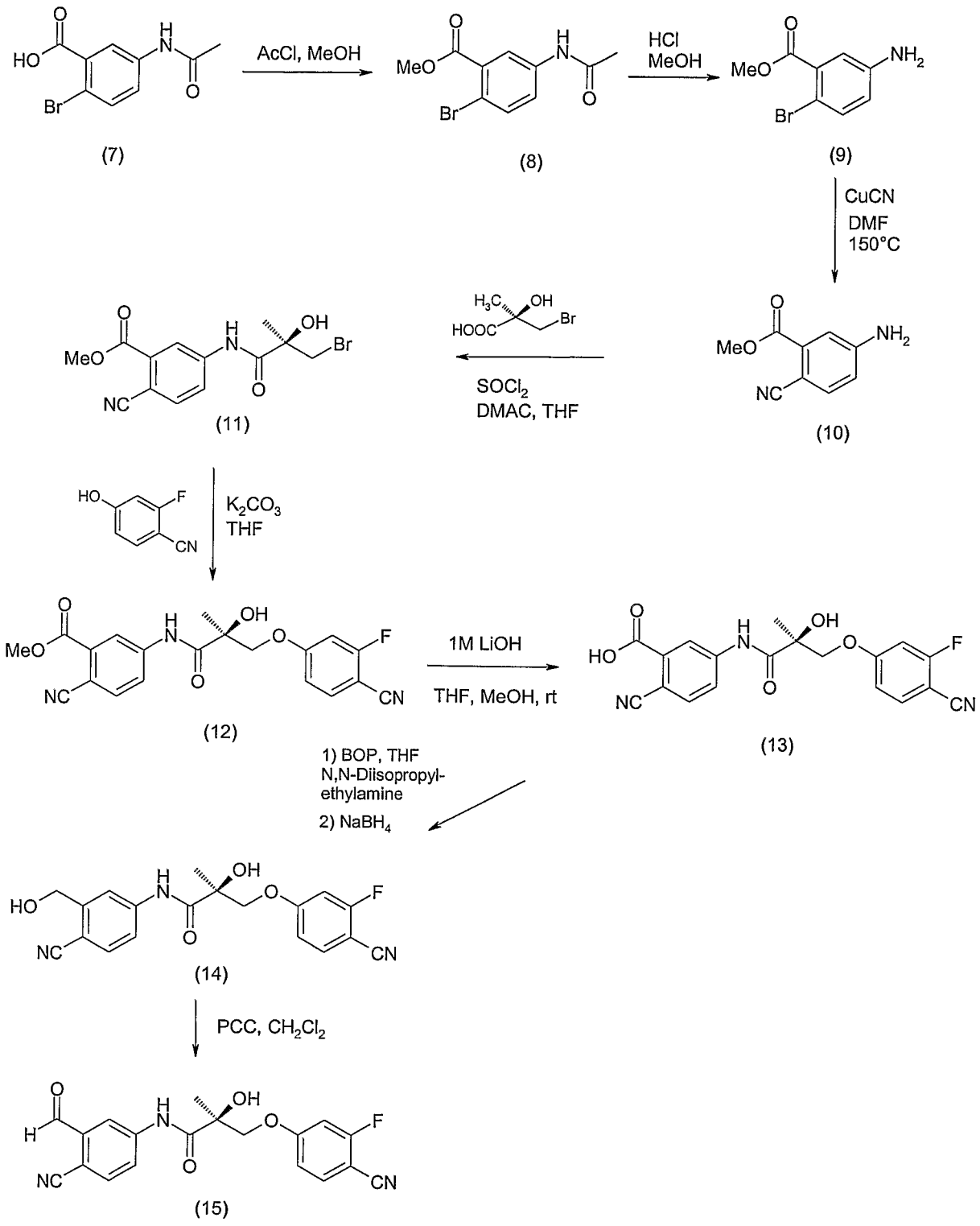
The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or its isomer, metabolite or a pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable carrier.

Detailed description of the invention

The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. In particular, the compounds of the invention can be prepared analogously to the general methods described in WO 2005/000794. For example, a compound of formula (I), including optically active enantiomers thereof, can be prepared according to the following reaction scheme, wherein R1 and R3 are methyl, R4 is hydrogen, R2 and R7 are cyano, R6 is fluoro, and R5, R8 and R9 are hydrogen:


NaOH
Water
Acetone
(1)
NBS
DMF
1M NaOH
conc. HCl
(3)
(2)
$SOCl_2$
THF, DMAC
(4)
K_2CO_3
acetone
room temperature
(6)
K_2CO_3
EtOAc
rfx
NaH THF
(5)

Metabolites of the compound of formula (I) can be suitably prepared e.g. according to the following reaction scheme:



Pharmaceutically acceptable salts, e.g. acid addition salts with both organic and inorganic acids are well known in the field of pharmaceuticals. Non-limiting examples of these salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl esters. Phosphate esters and carbonate esters, are also within the scope of the invention.

The definition of formula (I) above is inclusive of all the possible stereo-isomers of the compounds, including geometric isomers, e.g. *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers, and all prodrug esters, e.g. phosphate esters and carbonate esters. Furthermore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures.

In one embodiment, the term "isomer" is meant to encompass optical isomers of the compounds of the invention. It will be appreciated by those skilled in the art that the compounds of the present invention contain at least one chiral center. Accordingly, the compounds of the invention may exist in optically active or racemic forms. It is to be understood that the present invention encompasses any racemic or optically active form, or mixtures thereof. In one embodiment, the compounds of the invention are the pure (R)-isomers. In another embodiment, the compounds of the invention are the pure (S)-isomers. In another embodiment, the compounds of the invention are a mixture of the (R) and the (S) isomers. In another embodiment, the compounds of the invention are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

As defined herein, the term "metabolite of a compound of formula (I)" means a biologically active agent which is formed in-vivo from a compound of formula (I).

According to the present invention, preferred are metabolites of a compound of formula (I) which are useful in the treatment or prevention of androgen receptor (AR) dependent conditions. Such preferred metabolites include

2-cyano-5-[(S)-3-(4-cyano-3-fluorophenoxy)-2-hydroxy-2-methylpropionyl-amino]benzoic acid,

(S)-3-(4-cyano-3-fluorophenoxy)-N-(4-cyano-3-hydroxymethylphenyl)-2-hydroxy-2-methylpropionamide, and

(S)-3-(4-cyano-3-fluorophenoxy)-N-(4-cyano-3-formylphenyl)-2-hydroxy-2-methylpropionamide.

Pharmaceutically acceptable salts or esters of the above metabolites are also useful in the treatment or prevention of androgen receptor (AR) dependent conditions.

For the treatment or prevention of androgen receptor (AR) dependent conditions a particularly preferred compound of formula (I) is the (S) isomer of the compound of formula (I), namely (2*S*)-3-(4-cyano-3-fluorophenoxy)-N-(4-cyano-3-methylphenyl)-2-hydroxy-2-methylpropionamide.

Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 0.1 to about 1000 mg per day depending on the age, weight, ethnic group, condition of the patient, condition to be treated, administration route and the androgen (AR) modulator used. The compounds of the invention can be formulated into dosage forms using the principles known in the art. It can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories, emulsions, suspensions or solutions. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The compositions containing the active compound can be given enterally or parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about

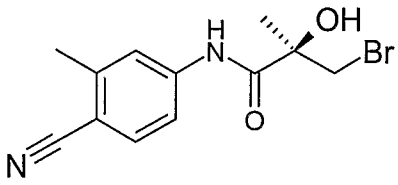
0.5 to 100 %, preferably from about 0.5 to about 20 %, per weight of the total composition.

The present invention will be explained in more detail by the following examples. The examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

EXAMPLES:

Example 1.

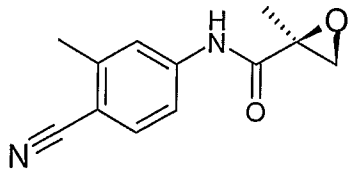
a) (2*R*)-3-Bromo-N-(4-cyano-3-methylphenyl)-2-hydroxy-2-methylpropion-amide



(2*R*)-3-Bromo-2-hydroxy-2-methylpropionic acid (1.52 g, 8.3 mmol) was dissolved in 35 ml of dry THF and 0.5 ml of dry DMA was added. Solution was cooled to 0°C and thionyl chloride (0.8 ml; 10.8 mmol) was added dropwise. The solution was allowed to heat up to room temperature and stirred for 2 hours at room temperature. 4-Cyano-3-methylaniline (1.07 g, 8.1 mmol) was added in 5 ml of dry THF and reaction refluxed for 2 hours. THF was evaporated, the residue dissolved in 40 ml of CH_2Cl_2 and washed with 50 ml of 1% $NaHCO_3$ and then with 4 x 25 ml of water. The organic phase was evaporated and residue was dried under reduced pressure at 40°C overnight to give 2.24 g of crude product which was crystallized from 5 ml of toluene (75°C then cooled to room temperature and to 0°C), filtered and washed with 5 ml of ice cold toluene. The precipitate was dried under reduced pressure overnight at 40°C to give 1.54 g of the product.

^{1}H NMR (DMSO-d_6): 1.48 (3H, s), 2.45 (3H, s), 3.59 (1H, d, J=10.3 Hz), 3.83 (1H, d, J=10.3 Hz), 6.32 (1H, bs), 7.70 (1H, d, J=8.5 Hz), 7.78 (1H, dd, J=8.6 Hz, J=1.9 Hz), 7.92 (1H, d, J=1.4 Hz), 9.97 (1H, bs).

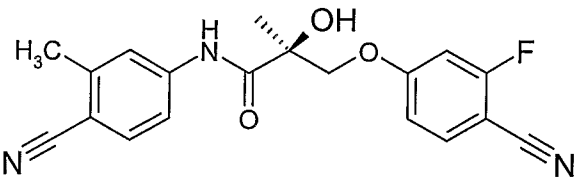
b) (2*R*)-2-Methyloxirane-2-carboxylicacid-(4-cyano-3-methylphenyl)amide



(2*R*)-3-Bromo-2-hydroxy-2-methyl-N-(4-cyano-3-methylphenyl)propionamide (1.54 g, 5.2 mmol) was dissolved in 50 ml of toluene and stirred for 5 minutes with 15 ml of 1M NaOH at room temperature. Organic layer was separated and washed with 2 x 25 ml of water. Toluene was filtered and evaporated to give 0.905 g of the product.

^{1}H NMR (DMSO-d_6): 1.54 (3H, s), 2,43 (3H, s), 2.99 (1H, d, J=5.1 Hz), 3.04 (1H, d, J=5.1 Hz), 7.65-7.75 (2H, m), 7.82 (1H, d, J=0.6 Hz), 9.77 (1H, bs).

c) (2*S*)-3-(4-Cyano-3-fluorophenoxy)-N-(4-cyano-3-methylphenyl)-2-hydroxy-2-methylpropionamide

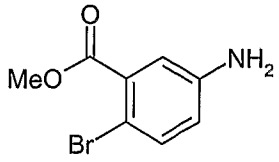


2-Fluoro-4-hydroxy benzonitrile (0.81 g, 5.9 mmol) and (2*R*)-2-methyl-oxirane-2-carboxylicacid-(4-cyano-3-methylphenyl)amide (0.905 g, 4.2 mmol) were dissolved in 17.6 ml of EtOAc. Anhydrous K_2CO_3 (0.29 g; 2.1 mmol) was added and the mixture heated to 50°C and stirred for 25.5 hours. The mixture was cooled to room temperature, 30 ml of EtOAc added and washed first with 2 x 24 ml of 1M Na_2CO_3 and then 2 x 24 ml of water. Organic layer was dried over Na_2SO_4, filtered and evaporated to give 1.05 g of crude product.

^{1}H NMR (DMSO-d_6): 1.43 (3H, s), 2,44 (3H, s), 4.10 (1H, d, J=10.0 Hz), 4.36 (1H, d, J=10.0 Hz), 6.29 (1H, bs), 6.96 (1H, dd, J=8.8 Hz, J=2.3 Hz), 7.18 (1H, dd, J=11.9 Hz, J=2.3 Hz), 7.70 (1H, d, J=8.54 Hz), 7.76-7.83 (2H, m), 7.92 (1H, d, J=1.6 Hz), 10.05 (1H, bs).

Example 2.

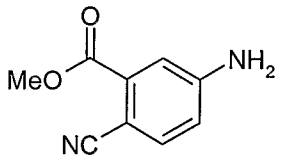
a) 5-Amino-2-bromobenzoic acid methyl ester



Acetyl chloride (29.2 ml, 32.2 g, 410.7 mmol) was added dropwise to methanol (210 ml) at 0-10 °C under nitrogen atmosphere and the solution was stirred for 30 min at 0 °C. After addition of 5-acetamido-2-bromobenzoic acid (21.2 g, 82.1 mmol) in methanol at 0 °C the solution was stirred for 3 h at 55 °C. After evaporation of methanol ethyl acetate (160 ml) was added and stirring was continued for 1 h at room temperature. The precipitation was filtered off and it was dissolved in water. pH was adjusted to 8 with $NaHCO_3$. The mixture was extracted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under vacuum.

^{1}H NMR (400 MHz, DMSO-d_6): 3.38 (3H, s), 5.57 (2H, broad s), 6.64 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.9 Hz), 6.95 (1H, d, ^4J = 2.8 Hz), 7.30 (1H, d, ^3J = 8.6 Hz).

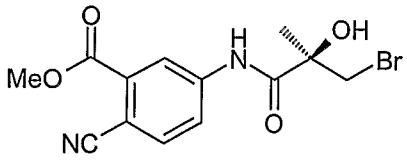
b) 5-Amino-2-cyanobenzoic acid methyl ester



The mixture of 5-amino-2-bromobenzoic acid methyl ester (14.27 g, 62.0 mmol) and CuCN (6.11 g, 68.2 mmol) in DMF (130 ml) was heated at 150 °C for 1h 10 min under nitrogen atmosphere. The mixture was cooled to 70 °C and poured into the mixture of water (250 ml) and 12.5 % NH_3 (500 ml). The product was extracted into ethyl acetate (3 x 250 ml). The organic phase was washed several times with 12.5 % NH_3 and water, dried over Na_2SO_4 and concentrated under vacuum.

^{1}H NMR (400 MHz, DMSO-d_6): 3.86 (3H, s), 6.46 (2H, broad s), 6.80 (1H, dd, ^3J = 8.5 Hz, ^4J = 2.4 Hz), 7.23 (1H, d, ^4J = 2.3 Hz), 7.51 (1H, d, ^3J = 8.5 Hz).

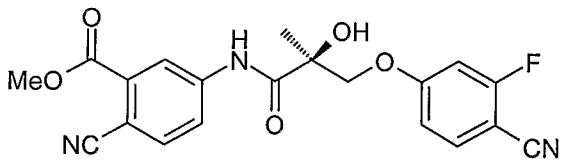
c) 5-((R)-3-Bromo-2-hydroxy-2-methylpropionylamino)-2-cyanobenzoic acid methyl ester



Thionyl chloride (3.9 ml, 5.3 mmol) was added dropwise to a solution of (2R)-3-bromo-2-hydroxy-2-methylpropionic acid (8.19 g, 44.8 mmol, prepared as described in WO 2005/000794) in 190 ml of THF and 5.8 ml of N,N-dimethyl-acetamide (DMAC) at 5 °C under nitrogen atmosphere. The solution was stirred for 3 h at room temperature. A solution of 5-amino-2-cyanobenzoic acid methyl ester (7.50 g, 4.3 mmol) in 75 ml of THF was added and the reaction mixture was maintained at 50 °C for 3 h and at room temperature for 16 h. The mixture was poured into water, extracted with ethyl acetate, washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was stirred in toluene and filtration afforded the purified compound.

^{1}H NMR (400 MHz, DMSO-d_6): 1.48 (3H, s), 3.58 (1H, d, $^2J_{gem}$ = 10.3 Hz), 3.82 (1H, d, $^2J_{gem}$ = 10.3 Hz), 3.92 (3sH,s), 6.35 (1H, s, -OH), 7.95 (1H, d, ^3J = 8.5 Hz), 8.16 (1H, dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz), 8.73 (1H, d, ^4J = 2.2 Hz), 10.40 (1H, s, -NHCO-).

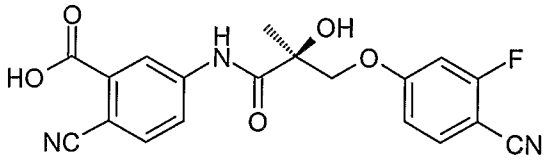
d) 2-Cyano-5-[(S)-3-(4-cyano-3-fluorophenoxy)-2-hydroxy-2-methyl-propionylamino]benzoic acid methyl ester



A mixture of 2-fluoro-4-hydroxybenzonitrile (4.80 g, 35.0 mmol), 5-((R)-3-Bromo-2-hydroxy-2-methylpropionylamino)-2-cyanobenzoic acid methyl ester (8.41 g, 24.7 mmol) and K_2CO_3 (8.51 g, 61.6 mmol) in THF (150 ml) was heated at 65 °C for 5 hours under nitrogen atmosphere. The mixture was cooled to room temperature and water was added. The product was extracted into ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate 7:3-6:4).

^{1}H NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 3.91 (3H, s), 4.12 (1H, d, $^2J_{gem}$ = 10.1 Hz), 4.38 (1H, d, $^2J_{gem}$ = 10.1 Hz), 6.33 (1H, s, -OH), 6.96 (1H, dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.19 (1H, dd, $^3J_{H,F}$ = 11.9 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.80 (1H, t, $^3J_{H,H}$ = $^4J_{H,F}$ = 8.4 Hz), 7.95 (1H, d, ^3J = 8.5 Hz), 8.17 (1H, dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz), 8.73 (1H, d, ^4J = 2.1 Hz), 10.47 (1H, s, -NHCO-).

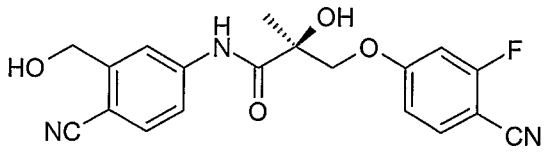
e) 2-Cyano-5-[(S)-3-(4-cyano-3-fluorophenoxy)-2-hydroxy-2-methyl-propionylamino]benzoic acid



1 M LiOH (34 ml) was added to a solution of 2-cyano-5-[(S)-3-(4-cyano-3-fluorophenoxy)-2-hydroxy-2-methylpropionylamino]benzoic acid methyl ester (4.52 g, 11.4 mmol) in THF (50 ml) and methanol (6 ml) at 16-18 °C. The resulting solution was stirred at room temperature for 2.5 h. The solvents were evaporated and pH was adjusted to 2 with HCl solution. The product was extracted into ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (eluent: CH_2Cl_2/MeOH 98:2). Trituration in hot CH_2Cl_2, cooling to room temperature and filteration yielded the title compound.

^{1}H NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 4.11 (1H, d, $^2J_{gem}$ = 10.1 Hz), 4.37 (1H, d, $^2J_{gem}$ = 10.1 Hz), 6.32 (1H, s, -OH), 6.96 (1H, dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.4 Hz), 7.20 (1H, dd, $^3J_{H,F}$ = 11.9 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.80 (1H, t, $^3J_{H,H}$ = $^4J_{H,F}$ = 8.4 Hz), 7.91 (1H, d, ^3J = 8.5 Hz), 8.14 (1H, dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz), 8.67 (1H, d, ^4J = 2.1 Hz), 10.41 (1H, s, -NHCO-), 13.84 (1H, broad s, COOH).

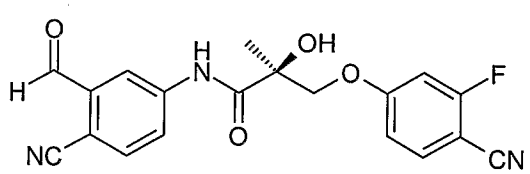
f) (S)-3-(4-Cyano-3-fluorophenoxy)-N-(4-cyano-3-hydroxymethylphenyl)-2-hydroxy-2-methylpropionamide



(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexaflurophosphate (BOP, 335 mg, 0.757 mmol) was added to a solution of 2-cyano-5-[(S)-3-(4-cyano-3-fluorophenoxy)-2-hydroxy-2-methylpropionylamino]benzoic acid (250 mg, 0.652 mmol) in anhydrous THF (8 ml) under nitrogen. N,N-diisopropylethylamine (0.14 ml, 0.803 mmol) was added to a mixture and it was stirred at room temperature for 10 min. Then $NaBH_4$ (30 mg, 0.793 mmol) was added, and the mixture was stirred at room temperature for 50 min. The solvent was removed under reduced pressure, and the residue was dissolved into ethyl acetate. The organic phase was washed with 0.5 M HCl, concentrated $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on siliga gel using dichloromethane/methanol (95:5) as the eluent to provide the desired alcohol.

^{1}H NMR (400 MHz, DMSO-d_6): 1.42 (3H, s), 4.09 (1H, d, $^2J_{gem}$ = 10.0 Hz), 4.35 (1H, d, $^2J_{gem}$ = 10.1 Hz), 4.59 (2H, d, ^3J = 5.6 Hz), 5.52 (1H, t, ^3J = 5.5 Hz, -$CH_2O\underline{H}$), 6.23 (1H, s, -OH), 6.94 (1H, d, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.16 (1H, dd, $^3J_{H,F}$ = 11.9 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.70 (1H, d, ^3J = 8.4 Hz), 7.78 (2H, m), 8.14 (1H, d, ^4J = 1.5 Hz), 10.09 (1H, s, -NHCO-).

g) (S)-3-(4-Cyano-3-fluorophenoxy)-N-(4-cyano-3-formylphenyl)-2-hydroxy-2-methylpropionamide



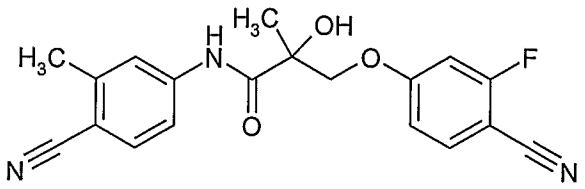
(S)-3-(4-Cyano-3-fluorophenoxy)-N-(4-cyano-3-hydroxymethylphenyl)-2-hydroxy-2-methylpropionamide (170 mg, 0.460 mmol) and pyridinium chlorochromate (150 mg, 0.696 mmol) in anhydrous CH_2Cl_2 (10 ml) were stirred for 1h 45 min at room temperature. Then the solvent was evaporated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4) to afford (S)-3-(4-Cyano-3-fluorophenoxy)-N-(4-cyano-3-formylphenyl)-2-hydroxy-2-methylpropionamide.

^{1}H NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 4.11 (1H, d, $^2J_{gem}$ = 10.1 Hz), 4.37 (1H, d, $^2J_{gem}$ = 10.0 Hz), 6.32 (1H, broad s, -OH), 6.94 (1H, dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.2 Hz), 7.16 (1H, dd, $^3J_{H,F}$ = 11.9 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.78 (1H, t, $^3J_{H,H}$ =

$^{4}J_{H,F}$ = 8.3 Hz), 7.97 (1H, d, ^{3}J = 8.5 Hz), 8.18 (1H, dd, ^{3}J = 8.5 Hz, ^{4}J = 2.2 Hz), 8.61 (1H, d, ^{4}J = 1.9 Hz), 10.05 (1H, d, ^{4}J = 0.4 Hz , -CHO), 10.46 (1H, broad s, -NHCO-).

Claims

1. A compound of formula (I)



(I)

or an isomer, metabolite, or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, which is (2*S*)-3-(4-cyano-3-fluoro-phenoxy)-N-(4-cyano-3-methylphenyl)-2-hydroxy-2-methylpropionamide.

3. A pharmaceutical composition comprising a compound according to claim 1 or 2, together with a pharmaceutically acceptable carrier.

4. A method for the treatment or prevention of androgen receptor dependent conditions, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 1 or 2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/FI2007/000055

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C255/60 A61K31/277 A61P5/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/000794 A (ORION CORP [FI]; RATILAINEN JARI [FI]; MOILANEN ANU [FI]; TOERMAEKANGA) 6 January 2005 (2005-01-06) cited in the application examples 41-43,51,66 abstract	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2007	16/05/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fitz, Wolfgang

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2007/000055

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/FI2007/000055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005000794 A	06-01-2005	AU 2004251900 A1	06-01-2005
		BR PI0411939 A	15-08-2006
		CA 2529464 A1	06-01-2005
		EP 1641745 A1	05-04-2006
		HR 20060036 A2	31-03-2006
		IS 8256 A	23-01-2006
		KR 20060035629 A	26-04-2006
		MX PA05013619 A	10-03-2006