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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2016 (24.11.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/184829 A1

(51) International Patent Classification:
A61K 31/5365 (2006.01) *A61K 31/4439* (2006.01)
A61K 31/40 (2006.01) *A61K 31/444* (2006.01)
A61K 31/436 (2006.01) *A61P 5/24* (2006.01)
A61K 31/4436 (2006.01)

(21) International Application Number:
PCT/EP2016/060945

(22) International Filing Date:
16 May 2016 (16.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/162,870 18 May 2015 (18.05.2015) US

(71) Applicant: **NERRE THERAPEUTICS LIMITED** [GB/GB]; Stevenage Bioscience Catalyst, Office F25 Incubator Building, Gunnels Wood Road, Stevenage, Herts SG1 2FX (GB).

(72) Inventor: **TROWER, Mike**; c/o NeRRe Therapeutics Limited Stevenage, Bioscience Cat. Incub. Bldg. Gunnels, Wood Road, Stevenage, Hertfordshire SG1 2FX (GB).

(74) Agent: **PEZZOLI, Anna**; Murgitroyd & Company, Piazza Borromeo 12, 20123 Milano (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2016/184829 A1

(54) Title: DUAL NK-1/NK-3 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF SEX-HORMONE-DEPENDENT DISEASES

(57) Abstract: This invention relates to new use of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof in the treatment of sex-hormone dependent diseases.

DUAL NK-1/NK-3 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF SEX-HORMONE-DEPENDENT DISEASES

FIELD OF THE INVENTION

This invention relates to a method of treatment of sex-hormone dependent diseases, in a mammal, for which gonadotropin suppression and/or androgen suppression is desired. Gonadotropin and /or androgen suppression is achieved according to this invention by administration of a dual neurokinin-1 (NK-1) receptor antagonist and neurokinin-3 (NK-3) receptor antagonist (herein called dual NK-1/NK-3 receptor antagonists). Suitable dual NK-1/NK-3 receptor antagonists useful in this invention are represented by the compounds described herein.

BACKGROUND OF THE INVENTION

Androgens are generally known as the male sex hormones. The androgenic hormones are steroids, which are produced in adult males by the testes and adult females by ovarian theca cells; and a lesser amount by the cortex of the adrenal gland or can be synthesized in the laboratory. Androgenic steroids play an important role in many physiologic processes, including the development and maintenance of male sexual characteristics such as muscle and bone mass, prostate growth, spermatogenesis, and the male hair pattern The endogenous steroidal androgens include testosterone and dihydrotestosterone ("DHT"). Testosterone is the principal steroid secreted by the testes and is the primary circulating androgen found in the plasma of adult males. Under normal physiological circumstances males produce much more testosterone than females. Testosterone is converted to DHT by the enzyme 5-alpha-reductase in many peripheral tissues. DHT is thus thought to serve as the intracellular mediator for most androgen actions.

The gonadotropin-releasing hormone (GnRH), also referred to as luteinizing hormone-releasing hormone (LHRH), is a decapeptide that plays a key role in human reproduction. The hormone is released from the hypothalamus and acts on the pituitary gland to stimulate the biosynthesis and secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH released from the pituitary gland is primarily responsible for the regulation of gonadal steroid production in both sexes, whereas FSH regulates spermatogenesis in males and follicular development in females.

It has been found that androgen and/or gonadotropin suppression or abrogation may result in beneficial effects, in a number of diseases and clinical applications, in males and in females.

In men these diseases or disorders, include, but are not limited to benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, breast cancer, testicular cancer, androgen dependent acne, hypertrichosis, seborrhoea, male pattern baldness and precocious puberty in boys.

In women, androgen and/or gonadotropin suppression or abrogation, has been shown to be therapeutic in clinical settings, such as, for example, in treating Polycystic Ovarian Syndrome (PCOS), endometriosis, adenomyosis, uterine fibroids, heavy menstrual bleeding, hirsutism, androgen dependent acne, seborrhoea, female androgenetic alopecia and hypertrichosis, gonadal steroid-dependent neoplasm (breast cancer, ovary cancer, etc.), gonadotropin-producing pituitary adenoma, premenstrual syndrome and sterility (e.g. assisted reproductive techniques such as in vitro fertilization). Other related conditions affecting women are pre-eclampsia and pregnancy prevention (contraception), and for both sexes, hidradenitis suppurativa and hot flushes.

As is the case in male and female subjects, however, gonadotropin and androgen suppression (also called androgen deprivation) is accompanied by a variety of undesirable clinical conditions and symptoms. For males receiving gonadotrophin releasing hormone (GnRH) agonists these initially cause a flare of increased androgen production that in patients with sex-hormone sensitive cancers may cause a short term increase in tumour growth and if the cancer has spread to the bone it may result in pain. These agents are also injected so there could be soreness, swelling and redness at the injection site. Other side effects that are also associated with GnRH antagonists are for example reduced or absent libido, impotence, shrinkage of testicles and penis, hot flushes, breast tenderness or growth of breasts, osteoporosis, anemia, cognitive reduction, muscle mass loss, weight gain, fatigue, elevated cholesterol and depression.

For male subjects administered 5-alpha-reductase inhibitors side effects are sexual in nature for example erectile dysfunction, decreased libido, reduced ejaculate and breast enlargement or tenderness. These drugs can also lower levels of Prostate-Specific Antigen (PSA) thereby interfering with the results of this analyte utilised to detect prostate cancer. Male and female subjects may also experience with spironolactone breast tenderness, menstrual irregularities (females only), fatigue, dizziness, confusion, nausea and vomiting, headache, hypotension, diarrhoea and possibly hyperkalemia. Cyproterone acetate can cause oligomenorrhea (females only), melasma, fluid retention, nausea and vomiting; this drug is also in rarer cases associated with liver hepatotoxicity and clotting disorders. Flutamide administration may lead to breast tenderness, gastrointestinal upset, hot flashes, and decreased libido; it has a serious potential side-effect of hepatotoxicity. Females taking combined oral contraceptives may experience metrorrhagia, nausea, vomiting, breast tenderness and headaches; and more rarely blood clots, myocardial infarctions, stroke, abnormal lipid indices, glucose intolerance and hypertension.

New innovative approaches are urgently needed at both the basic science and clinical levels to develop compositions and treatment regimens, which provide the beneficial effects of androgen and/or gonadotropins suppression or abrogation,

without the deleterious side-effects associated with the current treatments for sex-hormone dependent diseases.

Tachykinins belong to a family of short peptides that are widely distributed in the mammalian central and peripheral nervous system (Bertrand and Geppetti, Trends Pharmacol. Sci. 17: 255-259 (1996)). They share the common C-terminal sequence Phe-Xaa-Gly-Leu-Met-NH2. The three major tachykinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB) with preferential affinity for respectively three distinct receptor subtypes, termed NK-1, NK-2, and NK-3.

Compounds showing selective affinity simultaneously to both NK-1 and NK-3 receptors namely dual NK-1/NK-3 receptor antagonists are being developed for the treatment of both schizophrenia and substance abuse disorders.

Prior to the present invention, however it has not been disclosed or suggested that a dual NK-1/NK-3 receptor antagonist according to the present invention would be useful in the treatment of sex-hormone dependent diseases in which decreased levels of androgens and gonadotropins are desired.

SUMMARY OF THE INVENTION:

The present invention relates to the novel use of dual NK-1/NK-3 receptor antagonists to achieve gonadotropin and/or androgen suppression in mammals. According to this invention, dual NK-1/NK-3 receptor antagonists are administered for the treatment of diseases which are caused by abnormal levels of androgens, particularly testosterone. The compounds described herein by reference are particularly useful according to this invention.

Thus, the solution provided by the present invention is the use of dual NK-1/NK-3 receptor antagonists in the treatment of sex-hormone dependent diseases.

Specifically, in a first aspect, the invention provides a method of treatment of sex-hormone dependent diseases comprising administering to a human in need thereof an effective amount of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof.

In a further aspect thereof, the invention provides the use of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of sex-hormone dependent diseases.

In a yet further aspect thereof, the invention provides dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for use in the treatment of sex-hormone dependent diseases.

In a yet further aspect thereof, the invention provides a method for providing oral contraception, said method comprising administering to the patient an effective amount of dual NK-1/NK-3 receptor antagonists.

In a further aspect of the invention there is provided the use of dual NK-1/NK-3 receptor antagonists for the production of a drug for oral contraception.

DETAILED DESCRIPTION OF THE INVENTION

Surprisingly, it has now been found that dual NK-1/NK-3 receptor antagonists are effective in suppressing gonadotropin and/or androgen production/secretion, specifically in suppressing the production of LH and/or testosterone in mammals. Suppression of gonadotropin production/secretion results in the suppression of androgen production/secretion. Thus, the instant invention is in a method of treatment of sex-hormone dependent diseases which are affected, or exacerbated by, elevated and/or abnormal levels of gonadotropins and/or androgens. Specifically, the invention relates to a method of suppressing gonadotropin and/or androgen blood levels by administering an effective amount of a dual NK-1/NK-3 receptor antagonist. The compounds defined herein exhibit the ability to suppress gonadotropin and/or androgen production, and in particular, are effective in reversibly lowering blood levels of LH and the androgen testosterone.

DEFINITIONS

All numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term “about.”

It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components. It will be clear to one of ordinary skill in the art that the use of the singular includes the plural unless specifically stated otherwise.

The term “sex hormone-dependent disease” as used herein means a disease which is exacerbated by, or caused by, excessive, inappropriate or unregulated sex hormone production.

Example of such diseases in men include but are not limited to benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hypertrichosis, male pattern baldness and in boys precocious puberty. Example of such diseases in women include but not limited to endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, hormone-dependent cancers (ovarian cancer, breast cancer), hyperandrogenism, hirsutism, hypertrichosis, female androgenetic alopecia, androgen dependent acne, seborrhoea, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen concentrations (e.g. follicular maturation arrest, atresia, anovulation,

dysmenorrhea, dysfunctional uterine bleeding, infertility) and androgen-producing tumor (virilizing ovarian or adrenal tumor) and osteoporosis. In women other examples are pre-eclampsia and for both sexes, hidradenitis suppurativa and hot flushes.

As used herein “a dual NK-1/NK-3 receptor antagonist” refers to a compound that shows in a single molecule simultaneously affinity to both NK-1 and NK-3 receptors.

The term "androgen" is used herein to mean steroids that encourage the development of male sex characteristics and include the steroid derivatives of androstane including testosterone, dihydrotestosterone, androstenedione, and analogs.

As used herein, "gonadotropin suppression" refers to the reduction in the production or synthesis of one or more naturally occurring gonadotropins, including lutinizing hormone and follicle-stimulating hormone.

As used herein, "androgen suppression" refers to an effective amount of a dual NK-1/NK-3 receptor antagonist, which will cause a decrease in the in vivo levels of the androgen to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated androgen production.

As used herein, the term "hot flushes” is interchangeable with the term “hot flashes” and with the term “vasomotor symptoms” and intended to have the same meaning.

As used herein, the terms "treatment," "treating," and the like, refer to obtaining a desired pharmacologic, physiologic, dermatologic or cosmetic effect. The effect may be prophylactic in terms of completely or partially preventing a condition or disease or disorder or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a condition or disease or disorder and/or adverse symptom or effect attributable to the condition or disease or disorder.

"Treatment," thus, for example, covers any treatment of a condition or disease in a mammal, particularly in a human, and includes: (a) preventing the condition or disease, disorder or symptom thereof from occurring in a subject which may be predisposed to the condition or disease or disorder but has not yet been diagnosed as having it; (b) inhibiting the condition or disease, disorder or symptom thereof, such as, arresting its development; and (c) relieving, alleviating or ameliorating the condition or disease or disorder or symptom thereof, such as, for example, causing regression of the condition or disease or disorder or symptom thereof.

As used herein, the term “effective amount” means that amount of a drug or a therapeutic agent or a pharmaceutical agent that will elicit the biological or

medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher, clinician or veterinarian.

As used herein, "pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must of course be pharmaceutically-acceptable e.g. of sufficiently high purity.

As used herein "pharmaceutically acceptable salts" means salts suitable for medical applications having a pharmaceutically acceptable anion or cation.

In one embodiment, the invention provides a method of treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, abnormal puberty, uterine fibrosis, ovarian cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian or adrenal tumor, or osteoporosis, comprising administering to a human in need thereof an effective amount of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof.

In one embodiment, the invention provides a method of treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis, or pre-eclampsia comprising administering to a human in need thereof an effective amount of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for use in the

treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, abnormal puberty, uterine fibrosis, ovarian cancer, breast cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian or adrenal tumor, or osteoporosis, comprising administering to a human in need thereof an effective amount of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for use in the treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, breast cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis, or pre-eclampsia.

In a further aspect thereof, the invention provides the use of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, abnormal puberty, uterine fibrosis, ovarian cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian or adrenal tumor, or osteoporosis.

In a further aspect thereof, the invention provides the use of a dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness,

female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, , hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis, or pre-eclampsia.

In one embodiment, the sex-hormone dependent diseases according to the invention are selected from hirsutism, endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes.

Compounds for use herein include dual NK-1/NK-3 receptor antagonists as described in, and made according to WO2004056799, WO2004056805, WO2005002577, WO2005097794, WO2006013050, WO2007028654, WO2008128891, WO2011131571 or WO2011023733 which are incorporated herein by reference in their entirety.

Preferred pyridine derivatives of WO2006013050 for use herein are as follows:

- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-ethoxy)-pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-l-hydroxymethyl-ethoxy)-pyridin-3-yl]-N-methyl-isobutyramide;
- (S)-2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(pyrrolidin-2-ylmethoxy)-pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(2-hydroxy-ethylsulfanyl)-pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-[2,3']bipyridinyl- 5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-oxy-[2,3']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(3-hydroxymethyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-5'-hydroxymethyl-[2,3']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-2'-hydroxymethyl-[2,4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2)4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- (RS)-2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',4',5',6'-hexahydro-[2,3']bipyridinyl-5-yl]-N-methyl-isobutyramide;

- (RS)-N-[1'-acetyl-4-(4-fluoro-2-methyl-phenyl)-1',2',3',4',5',6'-hexahydro-[2,3']bipyridinyl-5-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3,6-dihydro-2H-thiopyran-4-yl)-4-(4-fluoro- 2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1,2,3,6-tetrahydro-1λ^6thiopyran-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide**;**

or pharmaceutically acceptable salts thereof.

Preferred pyrrolidine derivatives of WO2008128891 for use herein are as follows:

- rac-2-(3,5-bis-trifluoromethyl-phenyl)-N-[(3S,4R)-4-(4-chloro-phenyl)-1-(morpholine- 4-carbonyl)-pyrrolidin-3-yl]-N-methyl-isobutyramide;
- rac-2-(3,5-dichloro-phenyl)-N-[(3S,4R)-4-(4-fluoro-phenyl)-1-(morpholine-4-carbonyl)-pyrrolidin-3-yl]-N-methyl-isobutyramide;
- rac-2-(3,5-bis-trifluoromethyl-phenyl)-N-[(3S,4R)-4-(4-fluoro-2-methyl-phenyl)-1-(morpholine-4-carbonyl) -pyrrolidin-3-yl]-N-methyl-isobutyramide**;**
- rac-2-(3,5-bis-trifluoromethyl-phenyl)-N-[(3S,4R)-4-(4-fluoro-phenyl)-l-(4-methanesulfonyl-piperazine-1-carbonyl) -pyrrolidin-3-yl]-N-methyl-isobutyramide;
- rac-N-[(3S,4R)-1-(4-acetyl-piperazine-1-carbonyl)-4-(4-fluoro-phenyl) -pyrrolidin-3yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide;
- rac-2-(3,5-bis-trifluoromethyl-phenyl)-N-[(3S,4R)-l-(4-methanesulfonyl-piperazine-1-carbonyl)-4-phenyl-pyrrolidin-3-yl] -N-methyl-isobutyramide;
- rac-2-(3,5-dichloro-phenyl)-N-[(3S,4R)-4-(4-fluoro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl) -pyrrolidin-3-yl]-N-methyl-isobutyramide;
- rac-2-(3,5-bis-trifluoromethyl-phenyl)-N-[(3S,4R)-4-(4-fluoro-2-methyl-phenyl)-1-(4- methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl] -N-methyl-isobutyramide;
- rac-N-[(3S,4R) -4-(4-chloro-phenyl) -1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl] -2-(3,5-dichloro-phenyl)-N-methyl-isobutyramide;
- rac-(3S,4R)-3-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl- amino}-4-(4-fluoro-phenyl)-pyrrolidine-1-carboxylic acid bis-(2-hydroxy-ethyl)–amide;
- rac-(3S,4R)-3-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl] -methyl- amino}-4-(4-fluoro-phenyl)-pyrrolidine-1-carboxylic acid (2-hydroxy-ethyl)–amide;

or pharmaceutically acceptable salts thereof.

Preferred pyrazolopyridine derivatives of WO2011131571 for use herein are as follows:

- 2-(3,5-bis-trifluoromethyl-phenyl)-N-(1-ethyl-4-o-tolyl-1H-pyrazolo [3 ,4-b]pyridin-5-yl)-N-methyl-isobutyramide;

- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-ethyl-4-(4-fluoro-2-methyl-phenyl)-1 H-pyrazolo [3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-l-ethyl-1-H-pyrazolo [3, 4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(3,4-dichloro-phenyl)-1-ethyl-1H-pyrazolo [3 ,4-]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-(2,2-difluoro-ethyl)-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo [3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)- 1 -methyl-1H-pyrazolo [3 ,4- b]pyridin-5-yl] -N-methyl-isobutyramide;
- N-[1-benzyl-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide;
- 2-(3 ,5-bis-trifluoromethyl-phenyl)-N-[1 -ethyl-4-(4-fluoro-2-methoxy-phenyl)-1H-pyrazo lo [3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-3-fluoro-phenyl)-1-ethyl-1 H-pyrazolo [3,4-b]pyridin-5 -yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2,3-dichloro-phenyl)-1-ethyl-lH-pyrazolo[3,4-b]pyridin-5 yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-4-fluoro-phenyl)-1-ethyl-1 H-pyrazolo[3,4-b]pyridin-5 -yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-5-hydroxymethyl-phenyl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- N-[1-acetyl-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1-(2-methoxy-acetyl)-1H-pyrazolo [3 ,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[l-cyclopropanecarbonyl-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo [3 ,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1 -methanesulfonyl-1H-pyrazolo[3,4-b]pyridin-5 -yl] -N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-dimethylsulfamoyl-4-(4-fluoro-2-methyl-phenyl)-1H- pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1-methanesulfonylmethyl-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-ethyl-4-(4-methyl-thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;

- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-thiophen-3-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3-fluoro-5-trifloromethyl-phenyl)-N-[1-ethyl-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4- b]pyridin-5-yl]-N-methyl-isobutyramide ;or
- 2-(3,5-dichloro-phenyl)-N-[1-ethyl-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;

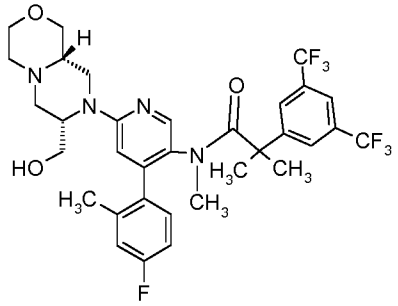
or pharmaceutically acceptable salts thereof.

Particularly preferred compounds for use herein are

- 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxylmethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide;
- (2R,3S)-2-(3,5-bis-trifluoromethylphenyl)- N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydrox ymethyl- pyrrolidin-1-yl) -pyridin-3-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2)4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1,2,3,6-tetrahydro-1λ^6thiopyran-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide;
- rac-N-[(3S,4R)-4-(4-chloro-phenyl) -1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-2-(3,5-dichloro-phenyl)-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-(2,2-difluoro-ethyl)-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1-methanesulfonylmethyl-1H-pyrazolo[3,4-b]pyridin-5 -yl]-N-methyl-isobutyramide; or pharmaceutically acceptable salts thereof.

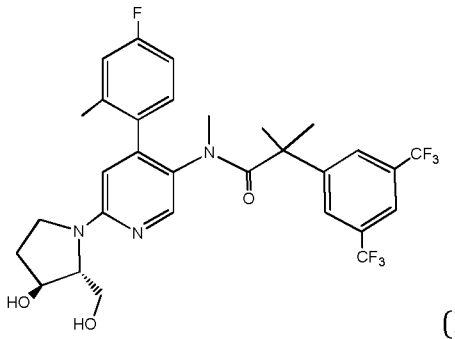
Particularly preferred compounds according to the invention are

- 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (formula A);



(A)

- (2R,3S)-2-(3,5-bis-trifluoromethylphenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide (formula B);



(B)

or pharmaceutically acceptable.salt or crystalline forms thereof.

Methods for preparing compound of formula A, salts thereof and its crystalline forms are described in WO2007028654 and WO2011023733 respectively, which methods are incorporated herein by reference.

Specifically WO2011023733 discloses compound of formula A in a crystalline anhydrate form (Form 1), having certain characteristic 2 theta angles occurring at 4.3±0.1, 7.9±0.1, 9.8±0.1, 10.7±0.1, 10.8±0.1, 13.3±0.1, 14.0±0.1, 15.1±0.1degrees, which correspond respectively to d-spacing at 20.4, 11.1, 9.0, 8.3, 8.2, 6.6, 6.3 and 5.9 Angstroms (Å).

Methods for preparing the compound of formula B or salt thereof are described in WO2005002577, which methods are incorporated herein by reference.

In a further embodiment, the invention provides

- 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or
- (2R,3S)-2-(3,5-bis-trifluoromethylphenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide; pharmaceutically acceptable salts or crystalline forms thereof for use for the treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, breast cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation,

dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis, or pre-eclampsia.

In a further embodiment, the invention provides a method of treatment of sex-hormone dependent diseases selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, breast cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis or pre-eclampsia which comprises administering to a human in need thereof an effective amount of the compounds:

- 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide;
- (2R,3S)-2-(3,5-bis-trifluoromethylphenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-yl]-N-methyl isobutyramide; or pharmaceutically acceptable salts or crystalline forms thereof.

In a further embodiment, the invention provides a method of treatment of sex-hormone dependent diseases selected from the group consisting of androgen dependent hirsutism, female androgenetic , endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes, which comprises administering to a human in need thereof an effective amount comprising administering to a human in need thereof an effective amount of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof.

In a further embodiment, the invention provides a method of treatment of sex-hormone dependent diseases selected from the group consisting of androgen dependent hirsutism, female androgenetic endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes, which comprises administering to a human in need thereof an effective amount of 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide;

(2R,3S)-2-(3,5-bis-trifluoromethylphenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide;or pharmaceutically acceptable salts thereof.

In one embodiment, the compound according to the invention is 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or crystalline anhydrate forms thereof for use in the treatment of hirsutism, endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes.

In a yet further embodiment, the compound according to the invention is 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide as anhydrous crystalline Form 1 for use in the treatment of endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes.

In a yet further embodiment, the compound according to the invention is 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide as anhydrous crystalline Form 1 for use in the treatment of hot flushes.

Owing to their activity on the gonadotropin-releasing hormone (GnRH) pathway, dual NK-1/NK-3 receptor antagonists can be used alone or in combination with estrogen and progestin as contraceptives.

Thus, in a further aspect, the present invention provides a method for providing oral contraception, said method comprising administering to the patient an effective amount of dual NK-1/NK-3 receptor antagonists.

In a further aspect of the invention there is provided the use of dual NK-1/NK-3 receptor antagonists for the production of a drug for oral contraception.

Compounds for use for oral contraception include dual NK-1/NK-3 receptor antagonists as described in, and made according to WO2004056799, WO2004056805, WO2005002577, WO2005097794, WO2006013050, WO2007028654, WO2008128891, WO2011131571, WO2011023733 which are incorporated herein by reference in their entirety.

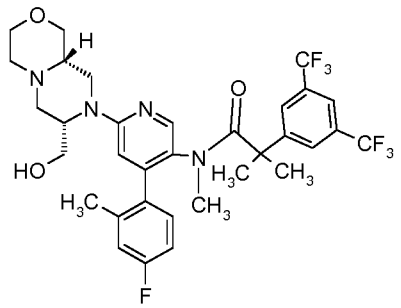
Preferred pyridine derivatives of WO2006013050 for use for oral contraception are those disclosed on pages 8 and 9, lines 10-45 and lines 1-15 respectively of the present specification.

Preferred pyrrolidine derivatives of WO2008128891 for use for oral contraception are those disclosed on page 9, lines 15-43 of the present specification.

Preferred pyrazolopyridine derivatives of WO201131571 for use for oral contraception are those disclosed from page 9, line 47 to page 11, line 6 of the present specification.

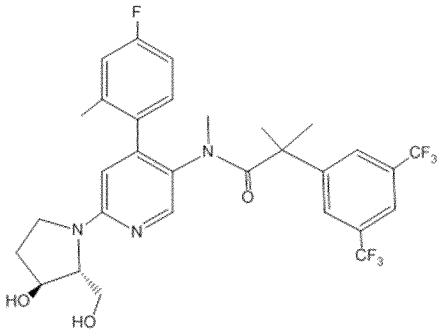
Particularly preferred compounds for use for oral contraception are

- 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide(Formula A);



(A)

- (2R,3S)-2-(3,5-bis-trifluoromethylphenyl)- N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide (Formula B);



(B)

or pharmaceutically acceptable salt or crystalline forms thereof.

The present invention further provides a pharmaceutical composition comprising a dual NK-1/NK-3 receptor antagonist or a compound described above, a pharmaceutically acceptable salt or crystalline forms thereof, and a pharmaceutically acceptable carrier.

Thus, in one embodiment, the invention provides a pharmaceutical composition comprising a dual NK-1/NK-3 receptor antagonist or a

pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for use in the treatment of sex hormone-dependent diseases.

In a further embodiment, the invention provides a pharmaceutical composition comprising 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide or crystalline anhydrate forms thereof and a pharmaceutically acceptable carrier for use in the treatment of of sex hormone-dependent diseases.

In a further embodiment, the invention provides a pharmaceutical composition comprising 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide or crystalline anhydrate forms thereof and a pharmaceutically acceptable carrier for use in the treatment hirsutism, endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes.

In a further embodiment, the present invention provides a drug containing a dual NK-1/NK-3 receptor antagonist and a pharmaceutically acceptable carrier.

In a yet further embodiment, the present invention provides a drug containing 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)yl]-3-pyridinyl}-N,2-dimethylpropanamide or a pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate pharmaceutically acceptable carrier. It may contain a diluent, binder, filler, disintegrant, flavoring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarian fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage.

Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release ofthe active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatine, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk.

Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatine containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatine, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavoring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They

may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e. g. sterile pyrogenic-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives.

Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronized compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilizing a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

The manufacture of the pharmaceutical compositions according to the present subject matter may be performed according to methods known in the art. Commonly known and used pharmaceutically acceptable auxiliaries as well as further suitable diluents, flavourings, sweetening agents, colouring agents etc. may be used, depending on the intended mode of administration as well as particular characteristics of the active compound to be used, such as solubility, bioavailability etc.

Any non-toxic, inert, and effective topical, oral, etc. pharmaceutically acceptable carrier may be used to formulate the compositions described herein.

Well-known carriers used to formulate other topical therapeutic compositions for administration to humans are useful in these compositions. Examples of these components that are well known to those of skill in the art are described in *The Merck Index*, Thirteenth Edition, Budavari et al., Eds., Merck & Co., Inc., Rahway, N.J. (2001); the CTFA (Cosmetic, Toiletry, and Fragrance Association) *International Cosmetic Ingredient Dictionary and Handbook*, Tenth Edition (2004);

and the "Inactive Ingredient Guide", U.S. Food and Drug Administration (FDA) Center for Drug.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. An effective dose will generally contain from 1 mg to 250 mg and preferably will contain from 10 mg to 220 mg, in particular 30 mg to 200 mg.

The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 30 mg to 200 mg.

Alternatively the unit dose will contain from 10 to 100 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily doses.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The compounds of the invention or pharmaceutically acceptable salts thereof and the other pharmaceutically active agent(s) may be administered together in a fix combination or separately (i.e. non fix combination).

When administered separately, this may occur separately or sequentially in any order and treatment regimens in which the agents are not necessarily administered by the same route of administration may also occur. The amounts of the compound inventions or pharmaceutically acceptable salts thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Examples of suitable therapeutic agents which may be used in combination of the compounds of the invention or pharmaceutically acceptable salts thereof include agonists of Gonadotropin-releasing hormone (GnRH) such as nafarelin, buserelin, goserelin and leuprorelin; antagonists of the Gonadotropin-releasing hormone (GnRH) such as degarelix, ganirelix, cetrorelix, abarelix and elagolix; 5-alpha-reductase inhibitors such as dutasteride and finasteride; combined androgen receptor antagonists/ 5-alpha-reductase inhibitors such as spironolactone; anti-androgens such as cyproterone acetate and flutamide; combined (estrogen with a progestin) oral contraceptives such as estrogen with either norgestimate, or norethindrone, or drospirenone; progesterone receptor modulators such as ulipristal acetate.

BIOLOGICAL DATA

The anti-androgenic effects of the compounds useful herein are determined bythe following clinical studies on human volunteers which demonstrate testosterone lowering effects.

Example 1

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-

N,2-dimethylpropanamide(hereinafter Compound A) was administered both as single and repeat ascending doses in male human volunteers (HV) and the effect of Compound A on the levels of testosterone was assessed

1. Single ascending dose studies

Male HVs received in a single-blinded, randomised fashion, single ascending oral doses of placebo or Compound A ranging from 10 to 250 mg as suspensions.

Free and total testosterone serum levels were measured at Day-1, then 24 hours after each dose and at follow-up (7-14 days after Compound A dose). Resulting HV serum testosterone levels (free and total) were determined as described in Table 1.

Table 1. Free and total testosterone levels in HVs from single ascending dose study

Treatment	Timepoint	n	Free testosterone (pmol/L)			Total testosterone (nmol/L)		
			Mean	SD	Mean % change from baseline	Mean	SD	Mean % change from baseline
Placebo	Day 1 pre-dose	12	48.5	15.0		23.5	6.8	
	24 h post dose	12	51.4	11.3	6.0	24.3	6.6	3.4
10 mg	Day 1 pre-dose	2	51.0	4.4		18.4	6.3	
	24 h post dose	2	46.3	18.8	-9.2	21.0	10.3	14.1
30 mg	Day 1 pre-dose	3	42.2	5.5		15.9	2.0	
	24 h post dose	3	50.4	10.0	19.4	16.7	4.4	5.0
60 mg	Day 1 pre-dose	10	44.3	17.7		22.0	7.1	
	24 h post dose	10	43.9	14.5	-0.9	23.7	5.8	7.7
120 mg	Day 1 pre-dose	10	41.7	12.3		23.1	6.1	
	24 h post dose	10	38.0	17.9	-8.9	18.9	7.9	-18.2
160 mg	Day 1 pre-dose	9	49.2	14.3		22.6	6.9	
	24 h post dose	9	31.1	13.0	-36.8	14.6	8.5	-35.4
Individualized dose 160-250 mg	Day 1 pre-dose	8	47.2	9.1		20.9	5.7	
	24 h post dose	8	26.9	15.7	-43.0	12.9	7.2	-38.3

Key: SD =standard deviation

As shown in Table 1 clinically relevant reductions in free and total testosterone levels are evident within 24 h following administration of Compound A. At doses of ≥160 mg the decreases range from between 35% and 43%. Testosterone levels recovered to baseline levels at follow-up (7-14 days after the last dose of Compound A).

2. Repeat ascending dose of Compound A

Part A of this study comprised 3 cohorts that investigated the safety, tolerability and PK of escalating multiple daily doses of Compound A. Information on these cohorts is as follows:

- Cohorts 1 and 2 received Compound A for 14 days; with a follow-up 7 to 14 days after their last dose. Testosterone levels in both cohorts were measured pre-dose on Day 1, on Day 15 and at follow-up.
- Cohort 3 also received Compound A over a repeat treatment period of 14 days; with a follow-up 7-14 days after their last dose. Testosterone levels were measured in this cohort pre-dose on Day-1 and pre-dose on Day 14, and at follow-up.

Resulting HV serum testosterone levels (free and total) were determined as described in Table 2.

Table 2. Free and total testosterone levels in HVs from repeat dose study

Treatment	Timepoint	n	Free testosterone (pmol/L)			Total testosterone (nmol/L)		
			Mean	SD	Mean % change from baseline	Mean	SD	Mean % change from baseline
Placebo (Cohorts 1 & 2) N=5	Day 1 (PD)	5	49.2	20.7		18.0	5.1	
	Day 15	5	56.4	10.8	14.6	18.9	3.3	5.0
30 mg N=5	Day 1 (PD)	5	48.6	6.9		22.6	5.5	
	Day 15	5	53.4	15.4	9.9	21.6	3.4	-4.4
90 mg N=9*	Day 1 (PD)	7	48.7	10.4		19.9	5.6	
	Day 15	7	55.0	13.0	12.9	20.0	6.1	0.5
Placebo (Cohort 3) N=3	Day-1	3	62.8	7.0		23.4	1.7	
	Day 14 (PD)	3	52.1	16.6	-17.0	19.8	1.0	-15.4
200 mg N=15**	Day-1	13	46.0	12.1		22.3	4.6	
	Day 14 (PD)	13	25.4	9.8	-44.8	12.7	4.0	-43.0

Key: SD = standard deviation; * two subjects in the 90 mg dose arm were dose reduced between baseline and Day 5 and have been removed from the analysis to avoid confounding the data; ** two subjects in the 200 mg dose arm were dose-reduced between baseline and Day 14 (data removed)

Clinically relevant reductions in free and total testosterone levels were again evident after repeat dosing with Compound A. At doses of 200 mg after 14 days; the decreases ranged from between 43% and 45%; consistent with the values observed after 24 hours in the single ascending dose study. Testosterone levels recovered to baseline levels at follow-up (7-14 days after the last dose of 200 mg Compound A).

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the

preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

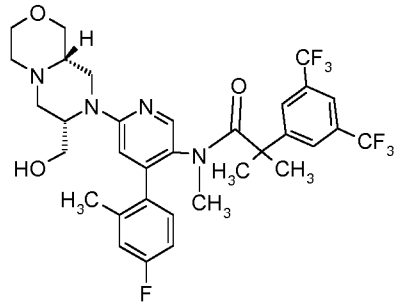
CLAIMS

1. Dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for use in the treatment of sex-hormone dependent diseases.

2. Use of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of sex-hormone dependent diseases.

3. Use according to claims 1 or 2, wherein the dual NK-1/NK-3 receptor antagonist is selected from:
   - 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxylmethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide;
   - (2R,3S)-2-(3,5-bis-trifluoromethylphenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide;
   - 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2)4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
   - 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
   - 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1,2,3,6-tetrahydro-1λ^6thiopyran-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide;
   - rac-N-[(3S,4R)-4-(4-chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-2-(3,5-dichloro-phenyl)-N-methyl-isobutyramide;
   - 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-(2,2-difluoro-ethyl)-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
   - 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1-methanesulfonylmethyl-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide; or pharmaceutically acceptable salts thereof.

4. Use according to any one of claims 1 to 3, wherein the dual NK-1/NK-3 receptor antagonist is 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide of formula (A) or crystalline anhydrate forms thereof.



A

5. Use according to any one of claims 1 to 4, wherein the dual NK-1/NK-3 receptor antagonist is 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino [2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide as crystalline anhydrate Form 1.

6. Use according to any one of claims 1 to 5, wherein the sex-hormone dependent disease is selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis, or pre-eclampsia.

7. Use according to any one of claims 1 to 6, wherein the sex-hormone dependent disease is endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS), or hot flushes.

8. A method of treatment of sex-hormone dependent diseases comprising administering to a human in need thereof an effective amount of dual NK-1/NK-3 receptor antagonists or a pharmaceutically acceptable salt thereof.

9. A method according to claim 8, wherein the dual NK-1/NK-3 receptor antagonist is selected from:
   - 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxylmethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide;
   - 2R,3S)-2-(3,5-bis-trifluoromethylphenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6–(3-hydroxy-2-hydrox ymethyl-pyrrolidin-1-yl) -pyridin-3-yl]-N-methyl-isobutyramide;

- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2)4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1'-methanesulfonyl-1',2',3'4',5',6'-hexahydro-[2,4']bipyridinyl-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1,2,3,6-tetrahydro-1λ^6thiopyran-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide;
- rac-N-[(3S,4R)-4-(4-chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-2-(3,5-dichloro-phenyl)-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[1-(2,2-difluoro-ethyl)-4-(4-fluoro-2-methyl-phenyl)-1H-pyrazolo [3,4-b]pyridin-5-yl]-N-methyl-isobutyramide;
- 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-1-methanesulfonylmethyl-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-isobutyramide; or pharmaceutically acceptable salts thereof.

10. A method according to claims 8 or 9, wherein the dual NK-1/NK-3 receptor antagonist is 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide of formula (A) or crystalline anhydrate forms thereof.

11. A method according to any one of claims 8 to 10, wherein the dual NK-1/NK-3 receptor antagonist is 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide of formula (A) as crystalline anhydrate Form1.

12. A method according to any one of claims 8 to 11, wherein the sex-hormone dependent disease is selected from the group consisting of benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhoea, hirsutism, hypertrichosis, male pattern baldness, female androgenetic alopecia, endometriosis, adenomyosis, abnormal puberty, uterine fibrosis, heavy menstrual bleeding, ovarian cancer, hyperandrogenism, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome, ovarian hyperthecosis, hidradenitis suppurativa, hot flushes and precocious puberty in boys, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility virilizing ovarian, adrenal tumor, osteoporosis, or pre-eclampsia.

13. A method according to any one of claims 8 to 12, wherein the disease is selected from the group consisting of hirsutism, endometriosis, adenomyosis, uterine fibrosis, heavy menstrual bleeding, polycystic ovary syndrome (PCOS) and hot flushes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/060945

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5365 A61K31/40 A61K31/436 A61K31/4436 A61K31/4439
A61K31/444 A61P5/24
ADD.
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)
A61K

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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 02/089802 A2 (SCHERING CORP [US]) 14 November 2002 (2002-11-14) abstract page 1, line 20 - line 39 page 4, line 11 - page 6, line 27 page 9, line 25 - line 31 page 28, line 31 - page 31, line 36 claims 1-22 -----	1,2,6-8, 12,13 3-5,9-11
X Y	WO 2005/097774 A1 (JANSSEN PHARMACEUTICA NV [BE]; JANSSENS FRANS EDUARD [BE]; SOMMEN FRAN) 20 October 2005 (2005-10-20) abstract page 1, line 5 - line 15 page 28, line 31 - page 29, line 2 page 64, Table 8, compound 8 claim 14 ----- -/--	1,2,6,8 3-5,9-13

[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent 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
23 June 2016	29/06/2016

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, Fax: (+31-70) 340-3016	Taylor, Mark

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/023733 A1 (GLAXOSMITHKLINE LLC [US]; CRAIG ANDREW SIMON [GB]; ISMAIL SALIMA ZARAH) 3 March 2011 (2011-03-03) cited in the application abstract page 1, line 5 - line 19 page 2, line 205 - page 21 claims 1-13	3-5,9-13
Y	WO 2005/002577 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN TORSTEN [DE]; KOBLET ANDREAS [CH]; PE) 13 January 2005 (2005-01-13) cited in the application abstract page 4, line 10 - line 13 page 105, Example 155 example 155	3,5,9, 12,13
A	CATERINA BISSANTZ ET AL: "Identification of a Crucial Amino Acid in the Helix Position 6.51 of Human Tachykinin Neurokinin 1 and 3 Receptors Contributing to the Insurmountable Mode of Antagonism by Dual NK 1 /NK 3 Antagonists", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 11, 14 June 2012 (2012-06-14) , pages 5061-5076, XP055234123, US ISSN: 0022-2623, DOI: 10.1021/jm2017072 the whole document	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/060945

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02089802 A2	14-11-2002	AU 2002259147 A1	18-11-2002
		US 2003092602 A1	15-05-2003
		WO 02089802 A2	14-11-2002
WO 2005097774 A1	20-10-2005	AR 048532 A1	03-05-2006
		AT 396185 T	15-06-2008
		AU 2005231986 A1	20-10-2005
		BR PI0509720 A	25-09-2007
		CA 2561967 A1	20-10-2005
		CN 1938291 A	28-03-2007
		EA 200601880 A1	27-02-2007
		EP 1737838 A1	03-01-2007
		ES 2307169 T3	16-11-2008
		JO 2525 B	17-03-2010
		JP 2007532516 A	15-11-2007
		KR 20070007347 A	15-01-2007
		MY 142773 A	31-12-2010
		NZ 550098 A	30-10-2009
		PA 8628901 A1	08-09-2006
		TW I358298 B	21-02-2012
		US 2007213346 A1	13-09-2007
		WO 2005097774 A1	20-10-2005
		ZA 200608356 A	30-07-2008
WO 2011023733 A1	03-03-2011	AU 2010288502 A1	23-02-2012
		BR 112012003435 A2	23-02-2016
		CA 2772168 A1	03-03-2011
		CN 102639536 A	15-08-2012
		DK 2470545 T3	13-01-2014
		EA 201270302 A1	30-07-2012
		EP 2470545 A1	04-07-2012
		ES 2440938 T3	31-01-2014
		JP 2013503134 A	31-01-2013
		JP 2016000739 A	07-01-2016
		KR 20120056258 A	01-06-2012
		SG 178231 A1	29-03-2012
		US 2012157450 A1	21-06-2012
		WO 2011023733 A1	03-03-2011
WO 2005002577 A1	13-01-2005	AR 044974 A1	12-10-2005
		AT 371451 T	15-09-2007
		AU 2004253267 A1	13-01-2005
		BR PI0412291 A	19-09-2006
		CA 2530886 A1	13-01-2005
		CN 1852712 A	25-10-2006
		CO 5650234 A2	30-06-2006
		DE 602004008631 T2	10-07-2008
		DK 1643998 T3	27-12-2007
		EP 1643998 A1	12-04-2006
		ES 2291891 T3	01-03-2008
		HR P20070471 T3	30-11-2007
		IL 172614 A	30-12-2010
		JP 4490421 B2	23-06-2010
		JP 2009500290 A	08-01-2009
		KR 20060030893 A	11-04-2006
		MX PA06000192 A	11-04-2006
		MY 137156 A	31-12-2008
		NZ 544244 A	31-10-2008

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/060945

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		PT 1643998 E	21-11-2007
		RU 2347777 C2	27-02-2009
		SI 1643998 T1	31-12-2007
		US 2005090533 A1	28-04-2005
		US 2009137806 A1	28-05-2009
		US 2011178055 A1	21-07-2011
		WO 2005002577 A1	13-01-2005
		ZA 200510453 A	31-01-2007