WO 2003/022835, WO 2003/033487, WO 2004/046111, WO 2004/060488, WO 2004/110459, WO 2005/032527, and WO 2005/084295.

WO2004/085457 discloses steroidal compounds capable of inhibiting 17β-hydroxysteroid dehydrogenase. WO2006/003012 discloses 2-substituted D-homo-estriene derivatives suitable for the treatment of estrogen-dependent diseases that can be influenced by the inhibition of the 17β-hydroxysteroid dehydrogenase type 1. Similarly WO2006/003013 presents 2-substituted estratrienones usable for preventing and treating estrogen-dependent diseases influenced by inhibiting 17β-hydroxysteroid dehydrogenase type 1.

15-substituted estradiol analogues acting as locally active estrogens are presented in WO2004/085345. WO2006/027347 discloses 15b-substituted estradiol derivatives having selective estrogenic activity for the treatment or prevention of estrogen receptor-related diseases and physiological conditions. Further, WO2005/047303 discloses 3, 15 substituted estrone derivatives capable of inhibiting the 17β-hydroxysteroid dehydrogenase type 1.

International application WO2008/034796 relates to estratrien triazoles suitable for use in treatment and prevention of steroid hormone dependent diseases or disorders requiring the inhibition of a 17β-hydroxysteroid dehydrogenases such as 17β-HSD type 1, type 2 or type 3 enzyme. Inhibitors of 17β-HSD type 3 enzyme have been disclosed in WO99/46279.

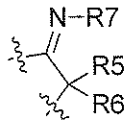
BRIEF DESCRIPTION

An object of the present disclosure is to provide compounds useful in treating disorders and diseases associated with increased level of estradiol and/or treatable by inhibition of 17β-HSD1 enzyme. It is further an object of the present disclosure to provide compounds that show little or no inhibitory effect on 17β-HSD2 enzyme.

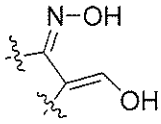
One of the problems associated with the known 17β-HSD1 inhibitors is the disposition, in particular the metabolic stability, of the compounds. It is therefore yet a further object of the present disclosure to provide compounds with improved metabolic stability.

In one aspect of the present disclosure, there is provided a novel compound of formula (I)

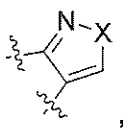
(ii-b) R5 and R6 and =NR7 form together with the carbons they are attached to a structure



, which is selected from



and



,

wherein X is O or NH;

or a pharmaceutically acceptable salt thereof.

Compounds of the present disclosure may be useful in therapy, especially in the treatment or prevention of steroid hormone dependent diseases or disorders requiring the lowering of the endogenous estradiol concentration or the inhibition of 17β-HSD enzymes, in animals, in particular mammals, and humans. In particular, compounds of formula (I) represent inhibitors of the 17β-HSD1 enzyme, possessing pharmacological properties for the treatment and/or prophylaxis of malignant steroid dependent diseases or disorders such as breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer and endometrial hyperplasia, but also for the treatment and/or prophylaxis of benign steroid dependent diseases or disorders such as endometriosis, uterine fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prostadynia, benign prostatic hyperplasia, urinary dysfunction, polycystic ovarian syndrome or lower urinary tract syndrome. Further estrogen-dependent diseases which may be treated and/or prevented with an effective amount of a compound of the present disclosure include multiple sclerosis, obesity, rheumatoid arthritis, colon cancer, tissue wounds, skin wrinkles and cataracts. The compounds of the present disclosure typically have an inhibitory activity at the 17-β-HSD1 enzyme in the IC50 range of 0.1 nM to 1 µM. The inhibitory activity can be measured as explained in context of the experimental examples.

The present disclosure also relates to pharmaceutical compositions comprising an effective amount of one or more compound(s) of formula (I).

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising an effective amount of one or more compounds disclosed herein, together with one or more pharmaceutically acceptable excipient(s).

Further the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a medicament.

The present disclosure also relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of estradiol dependent malign or benign diseases and disorders.

In another aspect of the present disclosure, there is provided a compound disclosed herein, for use as a medicament.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treatment or prevention of a steroid hormone dependent malign or benign disease or disorder.

In a further aspect of the present disclosure, there is a provided a compound disclosed herein for use in treatment or prevention of a disease or disorder requiring the inhibition of 17β-HSD enzyme.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treatment or prevention of a disease or disorder selected from the group consisting of breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer, endometrial hyperplasia, endometriosis, uterine fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prostadynia, benign prostatic hyperplasia, urinary dysfunction, polycystic ovarian syndrome, lower urinary tract syndrome, multiple sclerosis, obesity, rheumatoid arthritis, colon cancer, tissue wounds, skin wrinkles and cataracts.

In a further aspect of the present disclosure, there is provided a use of one or more compounds disclosed herein for the manufacture of a medicament for use in treatment of a steroid hormone dependent malign or benign disease or disorder.

In another aspect of the present disclosure, there is provided a use of one or more compounds disclosed herein for the manufacture of a medicament for use in treatment of a steroid hormone dependent malign or benign disease or disorder selected from the group consisting of breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer, endometrial hyperplasia, endometriosis, uterine fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prostadynia, benign prostatic

hyperplasia, urinary dysfunction, polycystic ovarian syndrome, lower urinary tract syndrome, multiple sclerosis, obesity, rheumatoid arthritis, colon cancer, tissue wounds, skin wrinkles and cataracts.

Finally the present disclosure provides a method for the preparation of compounds of formula (I).

wherein said disease or disorder is an estradiol dependent disease or disorder.

22. A compound as claimed in any one of claims 1 to 18 for use in treatment or prevention of a disease or disorder requiring the inhibition of 17β-HSD enzyme.

23. A compound as claimed in any one of claims 1 to 18 for use in treatment or prevention of a disease or disorder selected from the group consisting of breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer, endometrial hyperplasia, endometriosis, uterine fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prostadynia, benign prostatic hyperplasia, urinary dysfunction, polycystic ovarian syndrome, lower urinary tract syndrome, multiple sclerosis, obesity, rheumatoid arthritis, colon cancer, tissue wounds, skin wrinkles and cataracts.

24. A pharmaceutical composition comprising an effective amount of one or more compounds as claimed in any one of claims 1 to 18, together with one or more pharmaceutically acceptable excipient(s).

25. A pharmaceutical composition as claimed in claim 24 comprising one or more compounds as claimed in any one of claims 1 to 18 in combination with one or more other active ingredients.

26. Use of one or more compounds as claimed in any one of claims 1 to 18 for the manufacture of a medicament for use in treatment of a steroid hormone dependent malign or benign disease or disorder.

27. Use of one or more compounds as claimed in any one of claims 1 to 18 for the manufacture of a medicament for use in treatment of a steroid hormone dependent malign or benign disease or disorder selected from the