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(54) Titre : EMPLOI DE 17ALPHA-ESTERS EN C3-C10 DE LA 9,11-DESHYDROCORTEXOLONE AU TITRE D'AGENTS ANTI-GONADOTROPHIQUES

(54) Title: USE OF C3-C10 17ALFA-ESTERS OF 9,11-DEHYDROCORTEXOLONE AS ANTI-GONADOTROPHIC AGENTS

(57) Abrégé/Abstract:
The present invention relates to the use of C_3-C_{10} 17α-esters of 9,11- dehydrocortexolone as agents for inhibiting gonadotrophin secretion. The present invention therefore relates to the use of C_3-C_{10} 17 α-esters of 9,11- dehydrocortexolone for the preparation of a medicine for the treatment of disorders associated with the secretion of gonadotrophin and with the corresponding pharmaceutical compounds. The present invention relates specifically to the use of 9,11-dehydrocortexolone 17α-butyrate.

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(54) Title: USE OF C3-C10 17ALFA-ESTERS OF 9,11-DEHYDROCORTEXOLONE AS ANTI-GONADOTROPHIC AGENTS.

(57) Abstract: The present invention relates to the use of C_3-C_{10} 17α-esters of 9,11- dehydrocortexolone as agents for inhibiting gonadotrophin secretion. The present invention therefore relates to the use of C_3-C_{10} 17 α-esters of 9,11- dehydrocortexolone for the preparation of a medicine for the treatment of disorders associated with the secretion of gonadotrophin and with the corresponding pharmaceutical compounds. The present invention relates specifically to the use of 9,11-dehydrocortexolone 17α-butyrate.

Title

Use of c_3-c_{10} 17α-esters of 9,11-dehydrocortexolone as anti-gonadotrophic agents.

Description

The gonadotrophins (LH and FSH) are hormones produced in humans by the hypophysis (anterior pituitary gland), whose action is in turn controlled by the hypothalamus which releases gonadotrophin releasing hormone (GnRH) by pulsed secretion.

In turn, the gonadotrophins stimulate the male gonads to produce androgenic hormones, particularly testosterone.

Some skin diseases such as alopecia, hirsutism, seborrhoea, prostate diseases such as benign prostatic hypertrophy, prostate cancer, and other medical conditions such as polycystic ovary syndrome and precocious puberty are controlled by androgenic hormones and/or by gonadotrophins.

The treatment strategy for the aforesaid diseases is: i) to inhibit gonadotrophin secretion and consequently the production of androgenic hormones; ii) to block the conversion of androgens to their biologically active metabolites; iii) to interfere with the direct action of the androgens in the tissues (*Motta M., in: The Medical Management of Prostate Cancer, L. Denis (ed.), pp 19-35. Springer-Verlag, Berlin –1988).*

The first objective is normally achieved by using steroid hormones, or analogues and/or antagonists of the gonadotrophin releasing hormone (GnRH), both capable of suppressing gonadotrophin secretion and thus blocking the synthesis of hormones originating from the gonads.

The second objective is achieved by using androgen metabolism inhibitors which prevent the conversion of testosterone (T) to its principal metabolite, namely dihydrotestosterone (DHT). The third objective is achieved by the administration of substances, known as antiandrogens, which act as competitors at the receptors of the androgens, thus blocking the action of the androgens, regardless of their production site (testicles, ovaries, subrenal capsules).

In particular, the inhibition of hypophysial secretion of gonadotrophin is an extremely important mechanism in the treatment of pathologies such as tumours of the prostate, polycystic ovary syndrome, endometriosis, gonadotrophin-

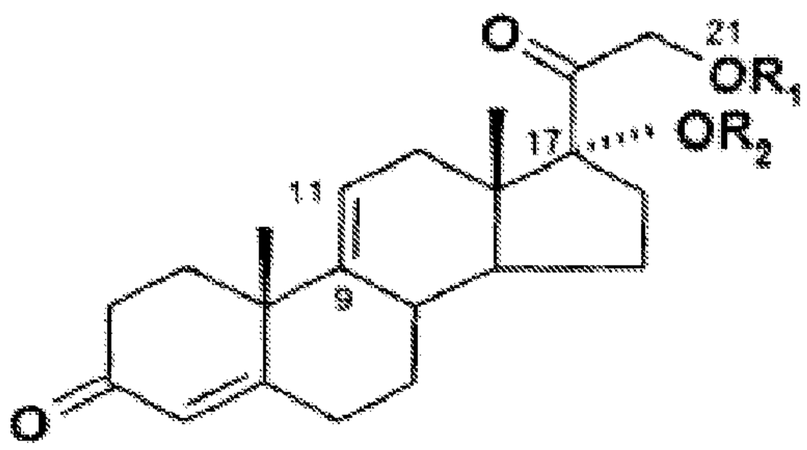
dependent precocious puberty, male contraception and aberrant sexual behaviour (*Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th Edition 1996, pp. 1379-1380. Ehrmann D.A., Polycystic ovary syndrome. N Engl J Med 2005; 352:1223-1236*) and/or in all medical practice which requires modulation of gonadotrophin secretion, for example in fertilization procedures used to prevent hot flushes in women, and in ovarian stimulation in assisted fertility treatment (*Ron-El A. et al., Induction of ovulation after GnRH antagonists. Human Reproduction Update 2000; 6:318-32*).

International patent application WO03/014141 describes compounds belonging to the family of steroids structurally related to cortexolone (11-deoxycortisone) as having high antiandrogenic activity.

These compounds, such as cortexolone 17α-propionate, act by blocking the conversion of androgens into their biologically active metabolites, and/or by interfering with the direct action of the androgenic hormones in the tissues, but are not found to have any inhibitory effect on gonadotrophin section.

U.S. patent 3,780,177 describes a process for obtaining new fluorinated steroids, mentioning some cortexolone derivatives such as 9,11-dehydrocortexonole 17α-butyrate (diagram B) as intermediates of the synthesis.

During the evaluation of new steroids structurally related to the cortexolone family, it was surprisingly found that, in accordance with the object of the present



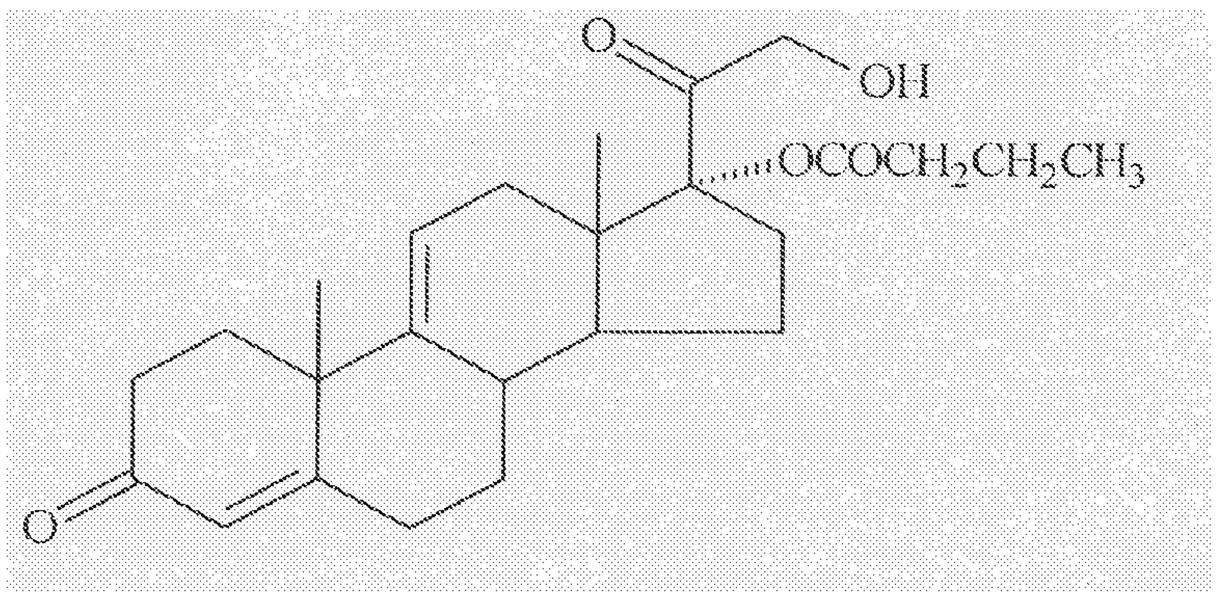
(I)

invention, C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone having the formula (I) in which R_1 is hydrogen and R_2 is a linear or branched C_3-C_{10} acyl group show a powerful hypophysial activity, in addition to the characteristic antiandrogenic activity of the aforesaid family of substances; in fact, they act by significantly

inhibiting gonadotrophin secretion. The present invention therefore relates to the novel use of C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone as anti-gonadotrophic agents.

The use of C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone according to the present invention is specifically intended for the preparation of compounds for the treatment of disorders closely related to excess gonadotrophin production, such as prostate tumour, polycystic ovary and gonadotrophin-dependent precocious puberty, for the control of aberrant sexual behaviour, for male contraception, and/or in all medical practice requiring modulation of gonadotrophin secretion, for example in the fertilization procedure used to prevent premature hot flushes in women and ovarian stimulation in assisted fertilization methods.

The present invention relates specifically to the use of 9,11-dehydrocortexolone 17α-butyrate of formula (II), corresponding to the compound of formula (I) in which R_1 is hydrogen and R_2 is a linear C_4 acyl,



(II)

as an anti-gonadotrophic agent capable of inhibiting gonadotrophin secretion.

The present invention therefore also proposes the pharmaceutical compounds containing as their active principle a compound belonging to the family of the C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone, particularly 9,11-dehydrocortexolone 17α-butyrate, in association with pharmacologically acceptable excipients and, optionally, any other active principles having a synergistic action.

The compounds of the invention can be formulated as injectable liquid pharmaceutical compounds such as monobasic or polyphase solutions and/or suspensions in solvents, or as solid pharmaceutical compounds such as tablets,

capsules, pellets or liquid and/or semi-solid oral and/or topical pharmaceutical compounds such as solutions or suspensions, suppositories, globuli, vaginal suppositories, creams, ointments, lotions and/or gels, transdermal patches and sprays for cutaneous or nasal administration.

According to the present invention, the C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone, and particularly 9,11-dehydrocortexolone 17α-butyrate, can be administered systematically in quantities varying from 0.1 to 1000 mg per unit dose, and preferably from 0.5 to 500 mg. According to the present invention, the term "unit dose" refers to a single form of administration, such as a tablet, a capsule and/or an injection.

According to the present invention, the C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone, and particularly 9,11-dehydrocortexolone 17α-butyrate, can also be administered topically in quantities varying from 0.01 to 25%, and preferably from 0.01 to 2%, of the total weight of the formulation (cream, ointment, lotion, gel, transdermal patch and/or cutaneous spray).

The anti-gonadotrophic action was evaluated in an animal model by evaluation of the hypersecretion of the gonads induced by castration in parabiotic rats (*Shipley E.G., in: Methods in Hormone Research, R.I. Dorfman (ed.), vol. 2, pp 179-274. Academic Press, New York and London,* 1962). The results of the inhibitory action of 9-dehydrocortexolone 17α-butyrate on the gonads are shown below in Table 1.

EXPERIMENTAL SECTION

Effect of 9,11-dehydrocortexolone on the hypersecretion of gonadotrophin in the parabiotic rat

Wistar rats of both sexes with body weights of 50-60 g were used. The males were castrated and, on the next day, were surgically united along the lateral body wall with intact females (parabiosis). In this experimental procedure, the castration of the males induces in them an immediate hypersecretion of gonadotrophin, which, on reaching the female via the parabiotic union, stimulates ovarian growth. Starting on the day after parabiosis, 9,11-dehydrocortexolone 17α-butyrate and its analogue, cortexolone 17α-propionate, were injected daily subcutaneously into

the males in doses of 1 and 5 mg. Progesterone was used as a positive control and was administered by the same procedure, in doses of 0.5 and 2 mg.

Additional groups of pairs including intact males/intact females and castrated males/intact females were treated with the vehicle only and used as a control.

At the end of the treatment period, the pairs were killed and autopsies performed.

The ovaries and uteruses of each female rate were isolated and weighed.

The inhibitory action causing hypersecretion of gonadotrophin due to castration was evaluated via the capacity of the tested compound to oppose the increase of weight of the ovaries.

Table 1

Effect of 9,11-dehydrocortexolone 17α-butyrate on the hypersecretion of gonadotrophin in the parabiotic rat

Treatment	Daily dose (mg)	Inhibition of ovarian weight (%)
9,11-dehydrocortexolone 17α-butyrate	1	59 [a]
	5	96 [a]
cortexolone 17α-propionate	1	5
	5	5
progesterone	0.5	38 [b]
	2	66 [a]

[a] = P <0.01 [b] = P <0.05 against control*

* an analysis of variance (ANOVA) was performed for each test and a value of P < 0.05 was selected as the limit for statistical significance.

RESULTS

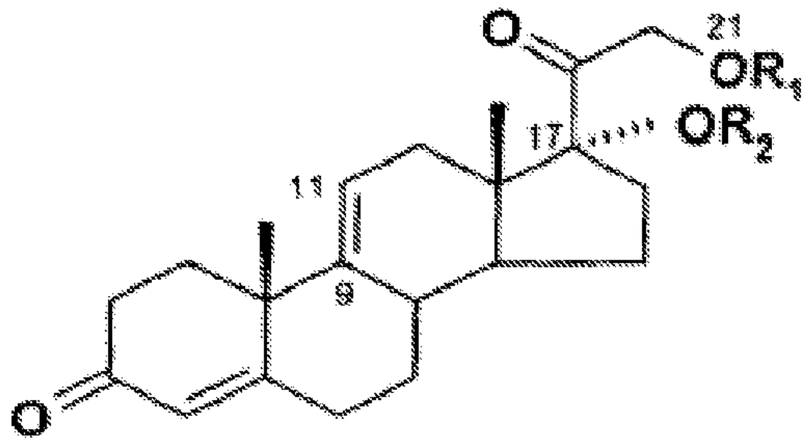
Table 1 above shows that 9,11-dehydrocortexolone 17α-butyrate has a strong and significant dose-correlated inhibitory effect on gonadotrophin secretion. This effect is evident from the percentage decrease in weight of the ovaries of females in parabiotic union, which decreases by 59% when 1 mg of the trial compound is administered, and by 96% when 5 mg of the same compound is administered.

The anti-gonadotrophic effect of 9,11-dehydrocortexolone 17α-butyrate is comparable to that shown by comparable doses of progesterone.

On the other hand, cortexolone 17α-propionate has no anti-gonadotrophic action at all.

CLAIMS

1. Use of C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone having the formula



(I)

in which R_1 is hydrogen and R_2 is C_3-C_{10} acyl, for the preparation of a medicine with anti-gonadotrophic action.

2. Use according to Claim 1, in which R_1 is hydrogen and R_2 is linear or branched C_4 acyl.

3. Use according to Claim 1, in which R_1 is hydrogen and R_2 is $COCH_2CH_2CH_3$.

4. Use according to the preceding claims, in which the said medicine is used for the treatment of disorders associated with gonadotrophin secretion.

5. Use according to Claim 4, in which the said disorders are chosen from: prostate tumour, polycystic ovary and gonadotrophin-dependent precocious puberty, control of aberrant sexual behaviour, male contraception, hot flushes in women and/or in ovarian stimulation in assisted fertilization methods.

6. Use according to one of the preceding claims, in which the said medicine can be administered systematically.

7. Use according to Claim 6, in which the said systematic method is chosen from: injectable solutions and/or suspensions, tablets, capsules, pellets oral solutions and/or suspensions, globuli, nasal sprays, vaginal suppositories, and other suppositories.

8. Use according to Claim 6 and 7, in which the said medicine is administered in quantities varying from 0.1 to 1000 mg per unit dose.

9. Use according to Claim, in which the said medicine is administered in quantities varying from 0.5 to 500 mg per unit dose.

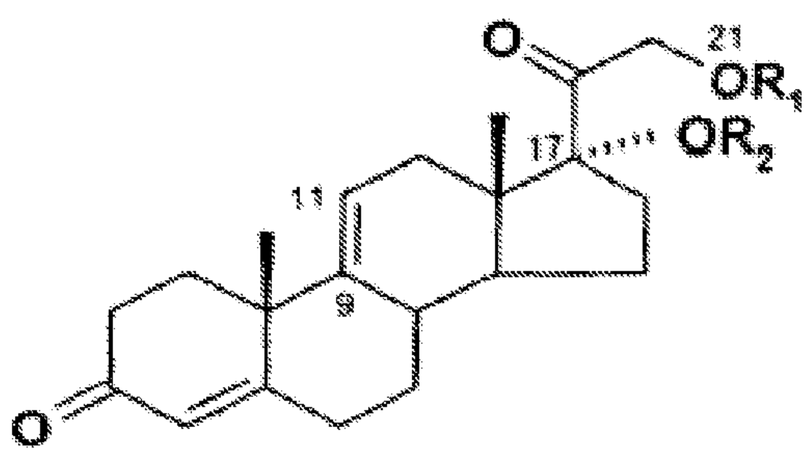
10. Use according to Claims 1-5, in which the said medicine can be administered topically.

11. Use according to Claim 10, in which the said topical method is chosen from: creams, ointments, lotions, gels, cutaneous sprays, and/or transdermal patches.

12. Use according to Claims 10 and 11, in which the said medicine is administered in quantities varying from 0.01 to 25% by weight.

13. Use according to Claim 12, in which the said medicine is administered in quantities varying from 0.01 to 2% by weight.

14. Pharmaceutical compounds containing as their active principle C_3-C_{10} 17α-esters of 9,11-dehydrocortexolone, having the formula



(I)

in which R_1 is hydrogen and R_2 is C_3-C_{10} acyl, in association with pharmacologically acceptable excipients.

15. Pharmaceutical compounds according to Claim 14, in which R_1 is hydrogen and R_2 is linear or branched C_4 acyl.

16. Pharmaceutical compounds according to Claim 14, in which R_1 is hydrogen and R_2 is $COCH_2CH_2CH_3$.

17. Pharmaceutical compounds according to the preceding claims for the treatment of disorders associated with gonadotrophin secretion.

18. Pharmaceutical compounds according to Claim 17, in which the said disorders are chosen from: prostate tumour, polycystic ovary, gonadotrophin-dependent precocious puberty, control of aberrant sexual behaviour, male contraception, hot flushes in women and/or in ovarian stimulation in assisted fertilization methods.

19. Pharmaceutical compounds according to the preceding claims, in the form

of injectable solutions and/or suspensions, tablets, capsules, pellets oral solutions and/or suspensions, transdermal patches, suppositories, globuli, vaginal suppositories, creams, ointments, lotions, cutaneous and/or nasal sprays and/or gels.