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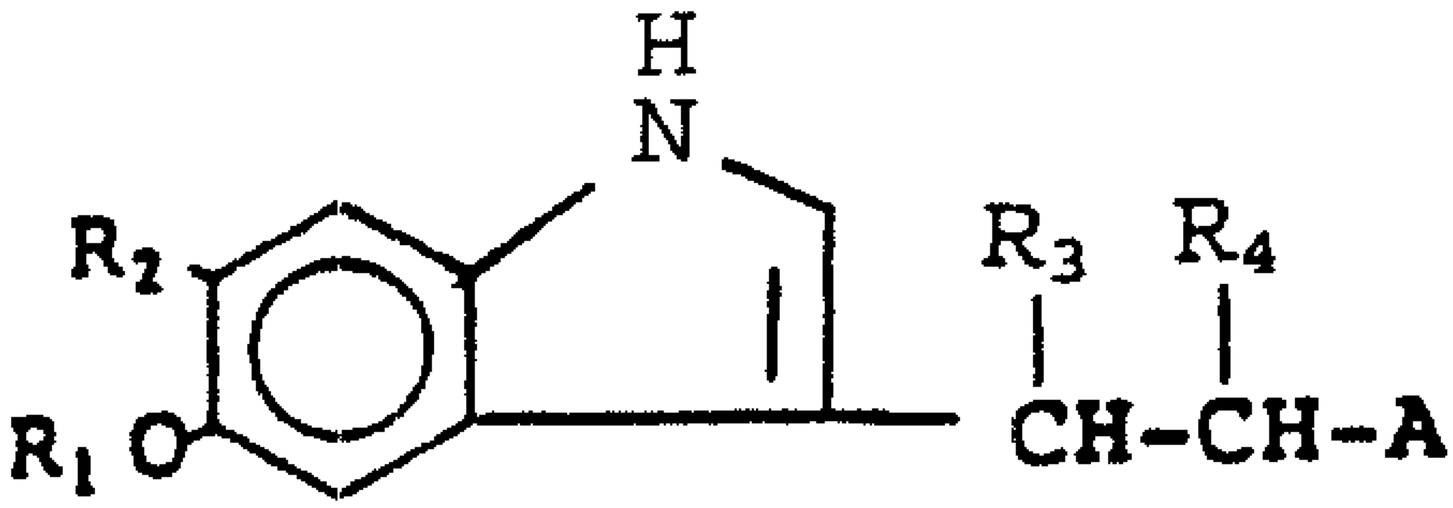


(57) Abrégé/Abstract:
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# COMPOSITIONS AND METHODS OF EFFECTING CONTRACEPTION

## Abstract of the Disclosure

A method of effecting contraception in human females comprises administering an ovulation-inhibiting amount of melatonin or an analog of melatonin. Optionally, the melatonin or melatonin analog is administered in combination with a progestogen and/or an estrogen.

# COMPOSITIONS AND METHODS OF EFFECTING CONTRACEPTION

## Field of the Invention

This invention relates to a method of inhibiting ovulation in human females. More particularly, the invention relates to a method of inhibiting ovulation by administering an ovulation-inhibiting amount of melatonin or an analog of melatonin. Optionally, the melatonin or melatonin analog is administered in combination with a progestational and/or estrogenic agent.

## Background of the Invention

Research and development in the field of contraception in humans has been in the areas of physical and chemical barriers to sperm transport, such as vaginal foams, diaphragms, intrauterine devices, and condoms, and in the area of oral contraceptives containing one or more steroid hormones. Oral contraceptives have been developed which are highly effective in preventing contraception, and today more than fifty million women

around the world use oral contraceptives. Typically, the oral contraceptives take the form of a combination of an estrogen and a progestogen (also known as progestin). In some of these regimens, known as combination regimens, a consistent dose of an estrogen and a progestogen is administered daily throughout the period of administration. In other regimens, referred to as sequential regimens, the amount of estrogen or progestogen or both is increased or decreased during the menstrual cycle. Some sequential regimens provide two-stage or bi-phasic control. (See, for example, USP 3,969,502). Others provide a three-stage or tri-phasic combination of components. (See, for example, USP 4,628,051; USP 4,390,531.) A third type of regimen also is known in which one or more progestogens is administered daily throughout the menstrual cycle.

The hormones in oral contraceptives act both within the central nervous system and in tissues of the urogenital tract to inhibit reproductive function. The principal sites of action are the hypothalamus and pituitary to prevent the midcycle surge of luetinizing hormone (LH) and hence to prevent ovulation. The basal concentrations of LH and follicle-stimulating hormone (FSH) and plasma levels of estradiol and progesterone are suppressed in users of oral contraceptives. In essence, these contraceptives work by causing changes in hormone levels that imitate those caused by pregnancy. This effect is dose dependent. These conventional oral contraceptives are administered for a minimum of 21 days of a woman's cycle, and in some instances for the entire 28-30 days of the cycle.

Oral contraceptives also exert a direct effect on the urogenital tract. They alter the structure and physical-chemical composition of the endometrium and the consistency of the cervical mucous, thus altering the uterine capacity for the ovum to implant.

Oral contraceptives have been shown to provide benefits other than the prevention of pregnancy. Compared to non-users, women who take oral contraceptives have been shown to have a lower risk of pelvic inflammatory disease (PID), ectopic pregnancy, endometrial cancer, and benign breast disease. Most significantly, the current combination-type contraceptives also are responsible for reducing the incidence of ovarian cancer. Oral contraceptives also can provide relief from common menstrual disorders, including irregular menses, premenstrual tension, excess blood loss and cramps.

Use of conventional oral contraceptives, however, also is attended by certain risks. These risks, which include a greater chance of suffering from venous thromboembolism, ischemic heart disease, cerebrovascular disease and hypertension, are believed to be largely due to the estrogen component (typically ethinyl estradiol or menstranol) in the contraceptives. The risk of suffering from any of these conditions has been found to be confined primarily to women over the age 35, especially to women over age 35 who smoke. Women who take estrogen also may suffer other negative side effects, including gastrointestinal disturbances, nausea and weight gain.

In an effort to avoid the negative side effects or possible side effects associated with oral contraceptives containing estrogen, oral contraceptives containing only one or more

progestogens as the active component have been developed. These contraceptives, however, generally have been found to be less effective than those containing both an estrogen and a progestogen. One common side effect suffered by women who take oral contraceptives which contain only progestogen is breakthrough bleeding during the menstrual cycle.

In view of the drawbacks and negative side effects of conventional oral contraceptives, new contraceptives are sought. Accordingly, it is an object of the present invention to provide a contraceptive method which is highly effective and provides the benefits and avoids the adverse effects associated with contraceptives currently used.

## Summary of the Invention

In accordance with the present invention there is disclosed a method for effecting contraception in human females of child-bearing age by administering an analog of melatonin in dosages effective to prevent ovulation. Optionally, the melatonin or melatonin analog is administered in combination with a progestogen and/or an estrogen. In a preferred embodiment, the contraceptives of this invention are administered in oral dosage form.

## Brief Description of the Figures

The graphs of Figures IA-D show the concentration of various hormones in a woman's blood stream for each day of her menstrual cycle, averaged over 5 cycles.

The graphs of Figures IIA-D, IIIA-D and IVA-D show the effects of melatonin administration on the

concentration of each of these hormones during each of three menstrual cycles.

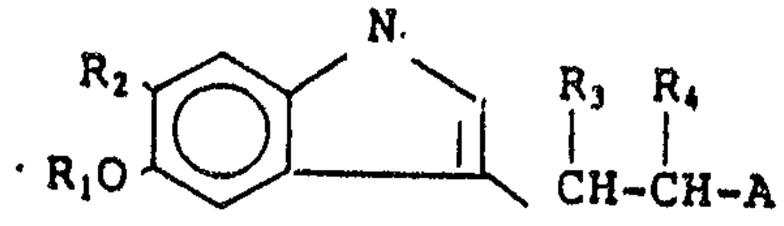
## Detailed Description of the Invention

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized and secreted by the pineal gland. The exact role of the hormone has not yet been determined. Studies have shown that the injection of melatonin into Syrian golden hamsters at certain specific times of the day has had an inhibitory effect on the development of the gonads, the weight of the testes in males and on ovulation in females. Female rats injected with melatonin at certain times of the day also showed an inhibition of ovulation. Melatonin thus has been shown to have a primary inhibitory effect on the gonads in various rodent species. A similar effect, however, has not been shown in other mammalian species injected with melatonin. Specifically, the administration of melatonin to sheep (Kenneway, D.J. et al., J. Reproductive Fertility 73:859 [1985]) and to primates (Reppert, S.M., et al., Endocrin. 104:295 [1979]) did not result in a direct alteration of their reproductive physiology. Exogenous melatonin administration in humans has been studied in conjunction with a hypothesis that an abnormal melatonin rhythm is associated with endogenous depression and for pharmokinetic purposes (Waldhauser, F., Neuroendocrinology 39:307, 313 [1984]) and in connection with sleep-wake rhythms and the phenomenon of "jet-lag" following airplane trips associated with a change in time zones.

The present invention is based on the discovery that pharmacological doses of melatonin administered

daily to a female selectively suppresses the normal mid-menstrual cycle surge in leutinizing hormone sufficient to prevent ovulation. The present invention is directed to a method of effecting contraception in human female of child-bearing years by daily administering to the female melatonin in dosages effective to prevent ovulation by suppressing the surge in leutinizing hormone which occurs prior to, and is required for, ovulation.

As used herein, the term melatonin also encompasses melatonin analogs which have an ovulation inhibiting effect when administered to human females. Such melatonin analogs can have the general formula:



wherein $R_1$, $R_3$ and $R_4$, individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms, $R_2$ is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is either -OH or $-NH-\overset{\overset{O}{\|}}{C}-R_5$, wherein $R_5$ is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is $NH-\overset{\overset{O}{\|}}{C}-R_5$, and $R_1$ and $R_3$ are both methyl and $R_2$ is hydrogen, both of $R_3$ and $R_4$ are not hydrogen. Preferred compounds are those in which $R_2$ is hydrogen or methoxy, with hydrogen being most preferred. Melatonin analogs encompassed within this definition include N-acetyl serotonin, N-acetyl, 5-hydroxy, 6-methoxytryptamine, 6-hydroxy-melatonin, 5-hydroxytryptophol and 5-methoxytryptophol, with N-acetyl serotonin being preferred.

The melatonin is administered daily in dosages sufficient to suppress the user's normal surge in leutinizing hormone and thus prevent ovulation. Generally, the melatonin is administered in amounts ranging between about 2 mg and about 1000 mg per day per 70 kilograms body weight of the woman receiving the melatonin. Preferably about 30 mg to about 500 mg melatonin are administered daily.

The melatonin can be administered every day throughout a woman's cycle. It has been found, however, that administration of melatonin for only a 1 to about 7 day period in the cycle which immediately precedes the woman's normal day of ovulation is sufficient to achieve a contraceptive effect. Ovulation typically occurs on the fourteenth cycle day or alternatively between about the ninth and seventeenth day of a woman's cycle. This regimen is preferred for administering the melatonin. The type of regimen selected can affect the amount of melatonin administered daily. The amount provided in each daily dosage also can vary with the method of administration selected.

The melatonin can be administered to women either orally, parenterally or in the form of an implant. Administration is most convenient when the melatonin is in oral dosage form, such as capsules, tablets, suspensions or solutions. Capsules or tablets are preferred. Capsules can be prepared by mixing the compound with a pharmaceutically-acceptable excipient and then filling gelatin capsules with the mixture in accordance with conventional procedures. Alternatively, the melatonin can be mixed with one or more lubricants, such as stearic acid or magnesium stearate, flavor ameliorating agents, disintegrating

elements, including potato starch and alginic acid, binders, such as gelatin and corn starch, and/or tablet bases including lactose, corn starch and sucrose, and then pressed into tablets.

As an alternative to oral administration, the melatonin can be administered parenterally or in the form of a solid implant. For parenteral administration, the melatonin is provided in injectable doses of a solution or suspension of the hormone in a physiologically acceptable diluent with a pharmaceutical carrier. The carrier can comprise water or an oil and optionally also can contain a surfactant or other pharmaceutically acceptable adjuvant. Suitable oils include those of animal, vegetable, petroleum or synthetic origin, including peanut, soybean, corn, sesame, castor and mineral oil. Preferred liquid carriers include water, saline, aqueous sugar solutions, and glycols such as propylene glycol or polyethylene glycol.

The melatonin also can be administered in the form of an implant, which is formulated such that it will provide a sustained release of the melatonin over time. To make the implant, the melatonin can be compressed into small cylinders and placed inside a physiologically acceptable shell material such as a biodegradable or porous polymer in accordance with conventional implant technology. Similarly, the melatonin can be administered in the form of a vaginal suppository or depot, which also will provide for the sustained release of melatonin. The melatonin can be mixed with a conventional suppository or depot base, i.e., a physiologically acceptable material which is meltable at body temperature.

In a preferred embodiment of this invention, the melatonin is administered in combination with a progestogen. The progestogen is added to induce a cyclic bleeding resembling a cyclic menses bleeding and to provide the benefits currently associated with the administration of progestogens in conventional oral contraceptives. Any progestationally active compound is suitable for use as the progestogen component in the present invention. Suitable progestogens include progesterone and derivatives thereof. The presently preferred progestogen is norethindrone (i.e., 19-nor-17α-ethynyl-17ß-hydroxy-4-androsten-3-one) and norgestrel (13ß-ethyl-17α-ethynyl-17ß-hydroxygon-4-en-3-one). Other progestogens include the chlormadinone-acetate (6-chloro-17-hydroxy-pregna-4,6-diene-3,20-dione acetate), norethynodrel (17α-ethynyl-17-hydroxy-estr-5(10)-en), medroxyprogesterone acetate (17α-acetoxy-6α-methyl-pregn-4-ene-3,20-dione), megestrol acetate (17α-acetoxy-6-methyl-pregna-4,6-diene-3,20-dione), lynestrenol (17α-ethynyl-17ß-hydroxy-estr-4-ene), quingestrone (3-cyclopentyloxy-pregna-3,5-diene-20-one), norethindrone acetate (17ß-acetoxy-17α-ethnyl-estr-4-en-3-on), ethynodiol acetate (3ß,17ß-diacetoxy-17α-ethynyl-estr-4-ene), dimethisterone [17ß-hydroxy-6α-methyl-17(-1-propynyl)-androst-4-en-3-one], desogestrel and levonorgestrel.

The progestogen component of these contraceptives generally is administered in the range of about 7.5 µg to about 2500 µg per day, preferably in the range of about 7.5 to about 600 µg per day. Most preferably, the progestogen is administered in the range of about 7.5 µg to about 250 µg per day. The actual amount of progestogen provided in each daily dosage will depend

upon the particular progestogen chosen, its relative potency, and the method of administration selected. For example, a lesser quantity of a more potent progestogen may achieve the same results as a larger quantity of a less potent progestogen. As noted above, the amount of progestogen also can vary with the mode of administration, with lower doses typically needed for administration of an implant or intravenous injection than for oral administration.

A number of regimens are suitable for administering a combination of melatonin and a progestogen. For example, assuming a 28 day cycle, both the melatonin and progestogen can be administered for about 21 days, followed by administration of the melatonin without the progestogen for about 7 days. In a second regimen the melatonin and progestogen are administered for about 21 days, and then both are withheld for about 7 days. If desired, the melatonin and progestogen alternatively can be administered each day continuously throughout the woman's cycle for a total of about 28 days.

In a fourth suggested regimen, a combination of melatonin and progestogen is administered for about thirteen days, typically from about day 5 through day 17 of a woman's cycle, then both the melatonin and progestogen are withheld for the remainder of her cycle.

In an alternative regimen, a combination of melatonin and progestogen are administered for about 10 or eleven days, during the follicular phase of a woman's cycle, at dosages of about 300 micrograms of progestogen and about 75 mg melatonin. Then, a second combination of melatonin and progestogen are administered for the next ten to eleven days, during

the luteal phase of her cycle, for a total of about twenty-one days, at dosages of about 750 micrograms progestogen and about 75 mg. melatonin. In this regimen, a smaller dosage of progestogen is administered during the first half of the woman's cycle because an insufficient amount of estrogen has been formed endogenously (due to slow follicular growth resulting from the melatonin administration) and the administration of relatively high amounts of a progestogen can lead to break-through bleeding. By the second half of the cycle, however, there has been a significant level of estrogen production. Break-through bleeding can occur during this half of the cycle as a result of estrogen production peaking and then withdrawing. Increasing the amount of progestogen in each daily dose administered during this portion of the woman's cycle will prevent this cause of break-through bleeding.

In another regimen, the melatonin is administered for about 5-14 days, followed by administration of either a combination of melatonin and progestogen or progestogen alone for about 7-14 days for a combined total of about 24, preferably about 21, days. Neither the melatonin nor the progestogen is administered for the remaining 7 days of the cycle. A seventh regimen comprises administering a placebo for the first 5 days, then administering melatonin for about 3-7 days, followed by administration of the progestogen through the twenty-first day of the medication. Again, neither melatonin nor the progestogen is administered for the remaining 7 days of the cycle.

In another regimen, a progestogen is administered for about 21 to about 28 days. Melatonin is administered in combination with the progestogen for

about 1-13 days (preferably to about 3-5 days) at mid-cycle (e.g., days 5-17 of the cycle), just prior to the user's normal day of ovulation. If the progestogen is administered for less than the full 28 days of the cycle, no medication is administered for the remaining days. As noted above, the conventional 21-28 daily dose progestogen-only contraceptives have not been very effective. The addition of melatonin overcomes the inefficacy of administering progestogen alone.

In any of the suggested regimens set forth above, on those days in which both melatonin and a progestogen are administered, the two active components conveniently are combined and administered together, although they also can be administered separately.

In an alternative embodiment of the present invention, a small amount of an estrogen can be added to any of the melatonin or melatonin-progestogen regimens set forth above. The estrogen can be added, if desired, to stabilize the melatonin by preventing any escape ovulation that might possibly occur if the melatonin is administered in the absence of an estrogen. Any conventional estrogen can be employed as a suitable component of the contraceptive compositions of the present invention. The presently preferred estrogens are ethinyl estradiol (i.e. 17α-ethynyl-3,17ß-dihydroxy-estra-1,3,5(10)-triene) and mestranol (17α-ethynyl-17ß-hydroxy-3-methoxy-estra-1,3,5(10)triene). Other suitable estrogens include estradiol (3,17ß-dihydroxy-estra-1,3,5(10-triene), estradiol(3,-16α,17ß-trihydroxy-estera-1,3,5(10)-triene, estrone (3,hydroxy-estra-1,3,5(10)-triene-17-one), diethylstilbestrol, quinestradiol (3-

cyclopentyloxy-16α,17ß-dihydroxy-estra-1,3,5-(10)-triene) and estrone sulfate. The estrogen can be administered daily throughout 21 days of the 28 day cycle in any of the regimens set forth above, but preferably it is administered only prior to the normal day of ovulation. The estrogen generally is administered in the range of about 2 µg to about 100 µg per day and preferably in the range of about 10 µg to about 50 µg per day. As with the progestogen, the actual amount of estrogen used in a daily dosage will depend upon the particular estrogen selected and its relative potency. Ethinyl estradiol, for example, has twice the biological potency as mestranol. Given the deleterious side effects of estrogen, desirably only the minimum amount of estrogen needed to stabilize the melatonin is used. The estrogen can be combined with the melatonin and/or progestogen in any of the regimens suggested above. In an alternative regimen, an estrogen is administered at the beginning of a woman's cycle for about 5-13 days, followed by the administration of melatonin for about 1-7 days (preferably for about 3-5 days) prior to her normal day of ovulation, then a progestogen is administered through about the twenty-first day of her medication.

In another embodiment of this invention, melatonin can be administered as a "morning after" pill, either by itself or in combination with an estrogen and or progestogen. In this embodiment, the melatonin is administered in daily doses of about 100 mg. to about 10,000 mg., preferably a dose of at least 2000 mg., over a 1-5 day post-coital period. If the melatonin is administered in combination with a progestogen and/or an estrogen, the progestogen preferably is administered in a daily amount ranging

between about 10 mg and 20 mg, and the estrogen is administered in a daily amount ranging between about 2.5 and 25 mg.

In the preferred embodiment of this invention, the contraceptive compositions of this invention are administered in oral dosage form, preferably in the form of pills or capsules. The pills or capsules can be packaged in any manner suitable for proper delivery and use. Preferably, they are packaged in the form of a pharmaceutical kit or package in which the daily unit dosage forms are provided or arranged in a contiguous, sequential order which will enable the women taking the pills to take the proper formulation at the appropriate time in her reproductive cycle. Suitable kits or packages include the conventional bubble plastic package containing individual bubbles for either 21 or 28 pills, depending upon the regimen selected, in a sheet of flexible plastic. The bubbles are sealed by a sheet of plastic which can break and release a pill when the bubble is pressed. On the first day of her medication, which is generally the first day after the cessation of bleeding from her last menstrual period the first pills in the sequence, whether it contains the contraceptive or a placebo, is removed from its individual slot and taken. The next pills in the sequence is taken the next day and so on thereafter until the dispenser is empty. A new dispenser is begun on day seven of her next cycle. Appropriate notations or instructions can be placed on the dispensing kit to guide or instruct the user in the proper use of the oral contraceptives.

The present invention is further described and illustrated by the following examples, which are

provided for informational purposes and are not to be construed as limiting.

Example I

The contraceptive effectiveness of melatonin was studied in a patient, referred to herein by the initials S.B., born September 21, 1950. In figures IA, IB, IC and ID, respectively, are shown the concentration in her blood of leutinizing hormone (LH), follicle stimulating hormone (FSH), progestrone and estradiol for each day of her cycle, averaged over 5 consecutive cycles. As shown in the figures, this patient had a normal LH preovulatory surge and an FSH peak followed by a post-ovulatory progestrone rise. In the figures, the legend PHC stands for plasma hormone concentration.

For each of three cycles the patient was given intravenously 300 mg of melatonin in a physiological solution of glucose in saline from day 9 of her cycle for 6 consecutive days. Figures IIA, IIB, IIC and IID show the effects of the melatonin administration during the first cycle (January, 1983). The figures show an anovulatory cycle following the injections. Figures IIIA-IIID show the results of melatonin administration in the second cycle (May, 1983) and Figures IVA-IVD show the results of melatonin administration in the third cycle (November, 1984). These figures also show an anovulatory cycle following melatonin injection.

The data show three cycles wherein the administration of melatonin resulted in a suppression of the patient's normal pre-ovulatory surge of LH. The data also illustrates that there was a marginal

suppression of FSH and pre-ovulatory estradiol and a significant reduction in progestrone levels. The LH suppression is a sufficient indication that the patient did not ovulate in any of the three months if which melatonin was administered.

Example II

The concentrations of LH, FSH, progestrone and estradiolin a patient's plasma were measured daily throughout three of the patient's menstrual cycles. The average concentration of each hormone for each day of the cycle was determined. The average concentration of the patient's LH peak was 295 ng/ml and the average of her FSH peak was 410 ng/ml. Her average progestrone level at the peak of the leuteal phase of her cycle was 14.5 ng/ml, and the average concentration of her estradiol peak was 0.6 ng/ml. The patient's peak in LH occurred on the fifteenth day of her cycle.

The patient was given an intravenous injection of 500 mg melatonin in a glucose in saline solution on each of days 7 through 12 of her cycle. The concentration of the four hormones in her plasma was measured throughout this cycle as before. The administration of melatonin was found to affect the hormone concentrations as follows:

peak PHC LH 110 ng/ml
FSH 295 ng/ml
estradiol .4 ng/ml
progestrone .3 ng/ml

These data indicate that the patient did not ovulate during this cycle; studies have shown that a

peak of LH concentration of at least 250 ng/ml is necessary for ovulation.

Example III

A woman having a normal menstrual cycle of 28 days with 3-5 days of moderate menstrual bleeding (±50 ml. blood loss) was given intravenous injections of 350 mg melatonin in a glucose in saline solution for seven consecutive days, beginning on day 8 of her cycle. On days 14-28 of her cycle she was administered orally 0.75 mg norethindrone per day. The concentration of LH, FSH, progestrone and estradiol in her blood was measured daily throughout her cycle. She did not ovulate during this cycle (peak PHC LH was 115 ng/ml). She had a minimal menstrual blood loss (±15 ml).

Example IV

A woman having a normal menstrual cycle of 30 days (12th day ovulator) was given intravenous injections of 200 mg melatonin in a glucose in saline solution on each of days 7-10 of her cycle. She did not ovulate in his cycle, although the level of LH in her blood was found to be not uniformly suppressed but rather erratic with levels between 50 ng/ml and 180 ng/ml during the cycle. Her FSH PHC during this cycle was normal for her, her progesterone PHC was somewhat depressed, and her estradiol PHC throughout the cycle was normal.

Example V

In an ongoing study, four women are taking melatonin in gelatin capsules. The melatonin is being administered in daily doses ranging from 30 mg. to 1000 mg. A preliminary evaluation indicates a satisfactory uptake of the melatonin from the gastrointestinal tract without negative side effects (such as diarrhea or nausea).

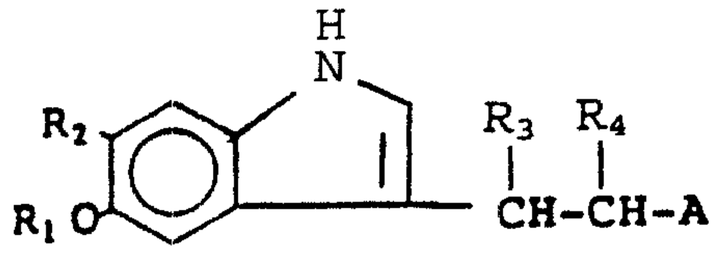
Example VI

A woman having a normal menstrual cycle of 30 days (12th day ovulator) is given oral doses of a combination of 200 mg N-acetyl serotonin (5-hydroxy-N-acetyltryptamine) and 7.5 µg norethisterone on each of days 7-30 of her cycle. The dosage is found to effectively block ovulation, as evidenced by measuring the concentration of LH and FSH in her blood on each day of her cycle.

Similar results are obtained when each of 5-hydroxytryptophol, 5-methoxytryptophol, 6-hydroxymelatonin and N-acetyl, 5-hydroxy, 6-methoxytryptamine are administered with norethisterone at the dosage levels and in accordance with cyclic schedule set forth above.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method of effecting contraception which comprises the administration of a melatonin analog having an ovulation-inhibiting effect in human females to a human female of child-bearing years on a schedule and at dose levels sufficient to prevent ovulation wherein the analog has the general formula



wherein $R_1$, $R_3$ and $R_4$, individually are hydrogen or an alkyl group having 1 to 4 carbon atoms, $R_2$ is hydrogen, hydroxy or an alkoxy group having from 1 to 4 carbon atoms, and A is selected from hydroxy and $NH-\overset{\overset{O}{\|}}{C}-R_5$,

wherein $R_5$ is either hydrogen or an alkyl group having from 1 to 4 carbon atoms, provided, however, that if A is $NH-\overset{\overset{O}{\|}}{C}-R_5$,

$R_2$ is hydrogen and $R_1$ and $R_5$ are both methyl, both of $R_3$ and $R_4$ are not hydrogen.

2. The method of claim 1, wherein $R_2$ is selected from hydrogen and methoxy.

3. The method of claim 2, wherein $R_2$ is hydrogen.

4. The method of claim 3, wherein A is -OH.

5. The method of claim 4, wherein the analog is 5-hydroxytryptophol.

6. The method of claim 4, wherein the analog is 5-methoxytryptophol.

7. The method of claim 1, wherein A is $-NH-\overset{\overset{O}{\|}}{C}-R_5$.

8. The method of claim 7, wherein the analog is N-acetylserotonin.

9. The method of claim 7, wherein the analog is N-acetyl-5-hydroxy-6-methoxytryptamine.

10. The method of claim 7, wherein the analog is 6-hydroxymelatonin.

11. The method of claim 1 wherein the daily dosage level of melatonin analog ranges from 2 mg to 1000 mg per 70 kg body weight of the female.

12. The method of claim 11 wherein the daily dosage level is from 30 mg to 500 mg per 70 kg body weight.

13. The method of claim 1, wherein a progestogen is administered in combination with the melatonin analog.

14. The method of claim 13 wherein the dosage level of meltonin analog is from 2 mg to 1000 mg per 70 kg body weight and the dosage level of the progestogen is from 7.5 µg to 2500 µg per 70 kg body weight on each day of administration.

15. The method of claim 14, wherein the dosage level of progestogen is from 7.5 µg to 600 µg per 70 kg body weight on each day of administration.

16. The method of claim 15 wherein the progestogen is selected from the group consisting of norethindrone, norgestrel, chlormadinone-acetate, norethynodrel, medroxyprogesterone acetate, megestrolacetate lynestrenol, quingestrone, norethindrone acetate, ethynodiol acetate, levonorgestrel, desogestral and dimethisterone.

17. The method of claim 1, wherein an estrogen is administered in combination with the melatonin analog.

18. The method of claim 17 wherein the dosage level of melatonin analog is from 2 mg to 1000 mg per 70 kg of body weight of the female and the dosage level of estrogen is 2 µg to 100 µg per 70 kg of body weight on each day of administration.

19. The method of claim 18 wherein the dosage level of melatonin analog is from 30 mg to 500 mg per 70 kg of body weight and the dosage level of estrogen is 10 µg to 50 µg per 70 kg of body weight on each day of administration.

20. The method of claim 17, wherein a progestogen is administered in combination with the melatonin analog and the estrogen.

21. The method of claim 20 wherein the dosage level of melatonin analog is from 2 mg to 1000 mg per 70 kg body weight, the dosage level of progestogen is 7.5 µg to 2500 µg per 70 kg body weight, and the dosage level of estrogen is 2 µg to 100 µg per 70 kg body weight on each day of administration.

22. The method of claim 17 or 20 wherein the estrogen is selected from the group consisting of ethinyl estradiol, mestranol, estradiol, estrone, estriol, diethylstilbestrol, quinestradiol and estrone sulfate.

23. The method of claim 1 wherein the method of administration is oral.

24. The method of claim 1 wherein the method of administration is by intravenous injection in a physiologically suitable carrier.

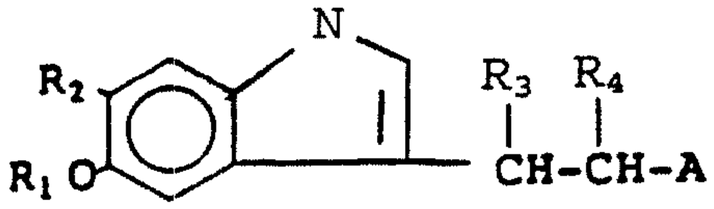
25. The method of claim 1 wherein the method of administration is by implant.

26. A composition for effecting contraception in a human female of child-bearing age which comprises a contraceptively effective combination of an analog of melatonin having ovulation-inhibiting effects in human females and a progestogen, wherein the analog has the general formula

wherein $R_1$, $R_3$ and $R_4$, individually are hydrogen or an alkyl group having 1 to 4 carbon atoms, $R_2$ is hydrogen, hydroxy or an alkoxy group having from 1 to 4 carbon atoms, and A is selected from hydroxy and $NH-\overset{\overset{O}{\|}}{C}-R_5$,

wherein $R_5$ is either hydrogen or an alkyl group having from 1 to 4 carbon atoms, provided, however, that if A is $NH-\overset{\overset{O}{\|}}{C}-R_5$, $R_2$ is hydrogen and $R_1$ and $R_5$ are both methyl, both of $R_3$ and $R_4$ are not hydrogen.

27. A composition for effecting contraception in a human female of child-bearing age which comprises a contraceptively effective combination of an analog of melatonin having an ovulation-inhibiting effect in human females and an estrogen, wherein the analog has the general formula

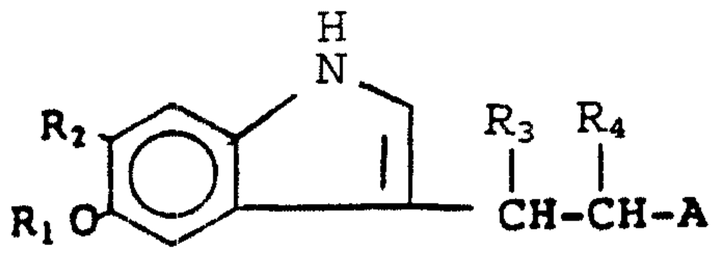


wherein $R_1$, $R_3$ and $R_4$, individually are hydrogen or an alkyl group having 1 to 4 carbon atoms, $R_2$ is hydrogen, hydroxy or an alkoxy group having from 1 to 4 carbon atoms, and A is selected from hydroxy and $NH-\overset{\overset{O}{\|}}{C}-R_5$,

wherein $R_5$ is either hydrogen or an alkyl group having from 1 to 4 carbon atoms, provided, however, that if A is $NH-\overset{\overset{O}{\|}}{C}-R_5$,

$R_2$ is hydrogen and $R_1$ and $R_5$ are both methyl, both of $R_3$ and $R_4$ are not hydrogen.

28. A composition for effecting contraception in a human female of child-bearing age which comprises a contraceptively effective combination of an analog of melatonin having ovulation-inhibiting effects in human females, a progestogen and an estrogen, wherein the analog has the general formula



wherein $R_1$, $R_3$ and $R_4$, individually are hydrogen or an alkyl group having 1 to 4 carbon atoms, $R_2$ is hydrogen, hydroxy or an alkoxy group having from 1 to 4 carbon atoms, and A is selected from hydroxy and $NH-\overset{\overset{O}{\|}}{C}-R_5$, wherein $R_5$ is either hydrogen or an alkyl group having from 1 to 4 carbon atoms, provided, however, that if A is $NH-\overset{\overset{O}{\|}}{C}-R_5$,

$R_2$ is hydrogen and $R_1$ and $R_5$ are both methyl, both of $R_3$ and $R_4$ are not hydrogen.

29. The composition of claim 26 or 28 wherein the progestogen is selected from the group consisting of norethindrone, norestrel, chlormadinone-acetate, norethynodrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, norethindrone acetate, ethynodiol acetate, levonorgestrel, desogestrel and dimethisterone.

30. The composition of claim 27 or 28 wherein the estrogen is selected from the group consisting of ethinyl estradiol, mestranol, estradiol, estrone, estriol, diethylstilbestrol, quinestradiol and estrone sulfate.

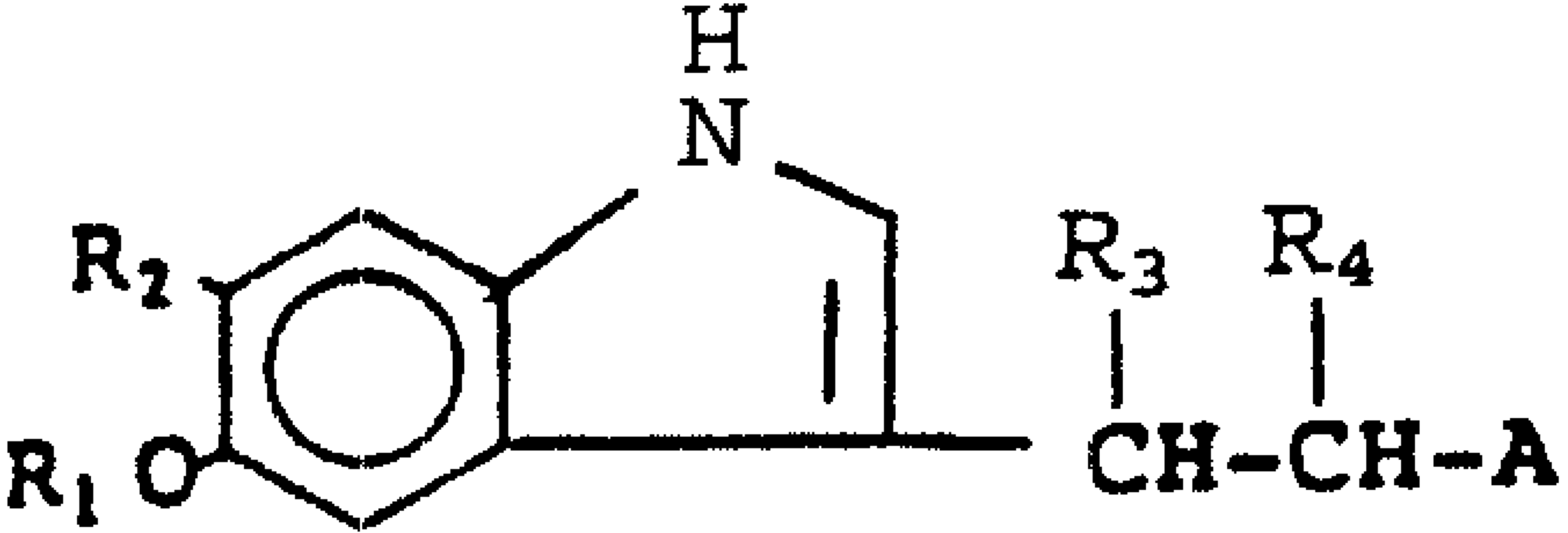
31. The composition of claim 30, wherein the melatonin analog is N-acetyl serotonin.

32. The composition of claim 30, wherein the melatonin analog is 5-hydroxytryptophol.

33. The composition of claim 30, wherein the melatonin analog is 5-methoxytryptophol.

34. The composition of claim 30, wherein the melatonin analog is 6-hydroxymelatonin.

35. The composition of claim 30, wherein the melatonin analog is N-acetyl-5-hydroxy-6-methoxytryptamine.


H
N
R2
R1
O
R3
R4
CH-CH-A