TITLE

Single Dose Aromatase Inhibitor for Treating Infertility

FIELD OF THE INVENTION

This invention relates to the use of a single dose of aromatase inhibitors (AIs) for inducing and augmenting ovulation in females with anovulatory infertility or unexplained infertility. Also described is the use of AIs together with follicle stimulating hormone (FSH) for improving response to controlled ovarian hyperstimulation. Also disclosed are pharmaceutical formulations, which comprise the aromatase inhibitors and methods for administering them to females.

BACKGROUND OF THE INVENTION

In women with WHO type II anovulatory infertility such as polycystic ovary syndrome (PCOS), the treatment of first choice for the induction of ovulation is an anti-estrogen. The most commonly used drug is clomiphene citrate (CC). However, 20 to 25 percent of women do not ovulate with CC. In addition, clinical data reveal a discrepancy between ovulation and conception rates during CC treatment[1], and a higher than expected incidence of miscarriage in conception cycles[2]. These observations have been attributed to the anti-estrogenic mechanism of action of CC resulting in long-lasting estrogen receptor depletion. Thus, CC may have a negative effect on the quality and quantity of cervical mucus[3], on endometrial development[4], and on other as yet undetermined fertility factors since CC is accumulated in the body as a result of its long half-life[5].

In CC failures, gonadotropin preparations such as human menopausal gonadotropin (hMG) or pure follicle stimulating hormone (FSH) have been used as a second-line treatment for ovulation induction. In women with polycystic ovary syndrome, because of the high sensitivity of the ovaries to gonadotropin stimulation, treatment with hMG or pure FSH is difficult to control and characteristically induces multiple follicles. The result is a high frequency of multiple pregnancies and increased risk of ovarian hyperstimulation syndrome (OHSS)[6]. Therefore, a simple oral treatment that could be used without risk of hyperstimulation and with minimal monitoring is the preferred first line of therapy.

Additionally, although it has been established that pregnancy rates for women who take CC are less than expected based on ovulation rates, CC therapy is widely administered to women with unexplained infertility, often without ultrasound monitoring, in order to induce the development of multiple follicles[7]. The use of CC in these women may be unsuccessful because of antiestrogenic effects on endometrial development. A recent study has prospectively applied morphometric analysis of the endometrium, which is a quantitative and objective technique to study the effect of CC on the endometrium in a group of normal women. In this study, CC was found to have a deleterious effect on the endometrium, demonstrated by a reduction in glandular density and an increase in the number of vacuolated cells[8]. In some exceptional cases, normal ovulatory women may receive 6 to 12 cycles of CC before it is finally determined that the anti-estrogenic effects of CC on the endometrium are actually causing an anti-conception action. For these reasons, a simple,

inexpensive and safe alternative to CC for use in normally ovulatory women, in whom frequent cycle monitoring is difficult, is also required.

The induction of ovulation constitutes a vital part of infertility management. Unfortunately, most current therapeutic approaches for induction of ovulation have been empiric[9]. For over 40 years, clomiphene citrate (CC) has been the most commonly used treatment for the induction and augmentation of ovulation, accounting for about two thirds of the fertility drugs prescribed in the United States[10]. However, the mechanism(s) and site(s) of CC action have only been partially clarified despite extensive clinical research[11].

Mechanism of CC action

It is believed that the 2 isomers of CC exert either an anti-estrogenic effect (zu-clomiphene) or a weak estrogen agonist effect (en-clomiphene) at estrogen binding sites in the pituitary and hypothalamus, thus releasing the hypothalamic/pituitary axis from the inhibitory effect of the major circulating estrogen, estradiol (E_2)[12]. In women with PCOS, CC-induced ovulation was accompanied by increased secretion of LH and FSH with enhanced estrogen secretion. Increased LH pulse amplitude after CC, together with decreased pituitary sensitivity to a GnRH bolus, suggested that CC acted predominantly on the hypothalamus to cause release of larger pulses of GnRH into the pituitary-portal system[13]. Similar findings have been reported in normal ovulatory women[14]. Various mechanisms of CC action have also been suggested at the level of the pituitary and/or the ovary. In particular, the ovarian actions of CC have not been widely appreciated[15]. However, the overall mechanism of CC action may be the sum of its effects on the hypothalamus, pituitary and ovary as discussed by Adashi[16].

Approaches to improve pregnancy outcome with CC

In order to improve the outcome of CC treatment, various approaches have been suggested to overcome the antiestrogenic effect of CC. One approach has been to administer estrogen concomitantly during CC treatment to attain high estrogen levels to overcome the antiestrogenic effect of CC. Some investigators have reported success with this approach[17] while others have reported no benefit[18] or even a deleterious effect of estrogen administration[19]. Another approach to reduce adverse effects has been to administer CC earlier during the menstrual cycle rather than starting on day 5[20], in the hopes of allowing the anti-estrogenic effect to wear off to some extent. A third approach has been to combine another selective estrogen receptor modulator like tamoxifen, which has more estrogen agonistic effect on the endometrium with CC[21]. However, none of the above mentioned strategies have proved to be completely successful in avoiding the peripheral antiestrogenic effects of CC. In addition to a discrepancy between ovulation and pregnancy rates with CC treatment, 20% to 25% of anovulatory women are resistant to CC and fail to ovulate at doses up to 150 mg daily. In CC failures, gonadotropins have been used as a second-line treatment for ovulation induction. However, they are associated with higher risk of multiple pregnancy, and severe ovarian hyperstimulation syndrome, especially in women with PCOS. Therefore, a simple oral alternative to CC that could be

used without high risk and which requires minimal monitoring would be the preferred first line of therapy for ovulation induction.

Aromatase Inhibitor

A group of highly selective AIs has been approved for use in postmenopausal women with breast cancer to suppress estrogen production. These AIs have a relatively short half-life (approximately 48 hours) compared to CC, and therefore would be eliminated from the body rapidly[22]. In addition, since no estrogen receptor down-regulation occurs, no adverse effects on estrogen target tissues, as observed in CC treated cycles, would be expected.

Physiology of Aromatase Enzyme

Aromatase is a cytochrome P-450 hemoprotein-containing enzyme complex that catalyzes the rate-limiting step in the production of estrogens, i.e. the conversion of androstenedione and testosterone, via three hydroxylation steps, to estrone and estradiol[23]. Aromatase activity is present in many tissues, such as the ovaries, adipose tissue, muscle, liver, breast tissue, and in malignant breast tumors. The main sources of circulating estrogens are the ovaries in premenopausal women and adipose tissue in post-menopausal women [24]. Although aromatase has features in common with other steroidogenic P-450 enzymes, the heme-binding region has only 17.9±23.5% amino acids identical to those of other steroidogenic P-450 enzymes. This observation suggests that P-450arom belongs to a separate gene family which has been designated CYP19[25]. Aromatase catalyzes the conversion of androgens to estrone (E_1), which is further converted to the potent estrogen estradiol (E_2) by the enzyme 17ß-HSD type 1 in the granulosa cell.

Development of aromatase inhibitors

Aromatase is a good target for selective inhibition because estrogen production is a terminal step in the biosynthetic sequence. There are two types of aromatase inhibitors; steroidal (type I inhibitors) and non-steroidal inhibitors (type II inhibitors). Type I steroidal aromatase inhibitors are all derivatives of androstenedione that act as a false substrate and bind irreversibly to the androgen-binding site with continuing treatment. For this reason, they are also called suicide inhibitors. 4-hydroxyandrostenedione, the first selective steroidal aromatase inhibitor to be used clinically, has proved to be effective in tamoxifen-resistant breast cancer patients and is available in many countries worldwide [26]. Type II non-steroidal aromatase inhibitors exert their function through binding to the heme moiety of the cytochrome P450 enzyme. The first of these inhibitors to be used clinically was aminoglutethimide, which induces a medical adrenalectomy by inhibiting many other enzymes involved in steroid biosynthesis[27]. Although aminoglutethimide is an effective hormonal agent in postmenopausal breast cancer, its use is complicated by the need for concurrent corticosteroid replacement, in addition to side effects like lethargy, rashes, nausea and fever that results in 8–15% of patients stopping treatment. The lack of specificity and unfavorable toxicity profile of aminoglutethimide have led to the search for

more specific aromatase inhibitors. In addition, the above mentioned aromatase inhibitors were not able to completely inhibit aromatase activity in premenopausal patients[28].

Aromatase inhibitors such as anastrozole, ZN 1033, (Arimidex®), letrozole, CGS 20267, (Femara®) and vorozole (Rivizor®) are selective AIs, available for clinical use in North America and other parts of the world for treatment of postmenopausal breast cancer. These triazole (antifungal) derivatives are reversible, competitive AIs, which are highly potent and selective (104, 106)[29]. Their intrinsic potency is considerably greater than that of aminoglutethimide, and at doses of 1-5 mg/day, inhibit estrogen levels by 97% to >99%. This level of aromatase inhibition results in estradiol concentrations below detection by most sensitive immunoassays. The high affinity of AIs for aromatase is thought to reside in the N-4 nitrogen of the triazole ring that coordinates with the heme iron atom of the aromatase enzyme complex. AIs are completely absorbed after oral administration with mean terminal $t_{1/2}$ of approximately 50 hr (range, 30-60 hr). They are cleared from the systemic circulation mainly by the liver. Another AI available commercially is exemestane (Aromasin™).

In animal studies, letrozole resulted in increased FSH and LH when given to mature female rats and about a 30% increase in ovarian weight[30]. In the bonnet monkey, treatment with aromatase inhibitors to induce estradiol deficiency led to development of multiple normal Graafian follicles in vivo, and normal response of granulosa and theca cells to gonadotropins in vitro[31]. In vivo data describe a continuum of inhibition of aromatase, with aminoglutethimide (90%), vorozole (93%), anastrozole (97%), and letrozole (98.5%) displaying increasing potency and specificity[32]. Letrozole has an IC_{50} of 11.5 nM in vitro and ED_{50} of 1-3 μg/kg in vivo when given orally. The disposition of orally administered letrozole in healthy postmenopausal women is characterized by steady-state plasma concentrations in 4 to 8 hours, and a half-life of approximately 45 hours. The absolute systemic bioavailability of letrozole after oral administration was 100% compared with the same dose given intravenously[33]. Doses up to 30 mg have been well tolerated[34]. The lethal dose in mice and rats is approximately 2000 mg/kg. There is no experience in humans with an overdose of letrozole[35].

The success of aromatase inhibition by letrozole in inducing ovulation in women with PCOS has been reported [36]. In a series of 10 patients with PCOS who either failed to ovulate (n=4) or ovulated with an endometrial thickness ≤ 5 mm (n=6) in response to CC administration, ovulation occurred in 7 of the 10 letrozole treated cycles (70%), with clinical pregnancy in 2 patients and chemical pregnancy in one patient. The mean number of mature follicles was 2.6, ranging from 1 to 4 follicles in the 7 ovulatory cycles. The mean level of estradiol on the day of hCG administration was 1076 pmol/L with mean estradiol per follicle of 378 pmol/L. This estradiol level allowed the growth of the endometrium to an adequate thickness that ranged from 0.7 cm to 0.9cm on the day of hCG administration, showing the absence of antiestrogenic effects as seen with CC.

In a second study, comparable success of letrozole in inducing ovulation in 12 women with PCOS women, in addition to success in augmenting ovulation in a group of 10 ovulatory women. Patients in both groups tried CC in prior treatment cycles with an inadequate response. With letrozole treatment, ovulation occurred in 9 of 12 cycles (75%) and pregnancy was achieved in 3 patients (25%) in the PCOS group. In the ovulatory group, letrozole resulted in a mean number of 2.3 mature follicles and a mean endometrial thickness of 0.8 cm. Pregnancy was achieved in one patient (10%)[37].

We have also studied the use of letrozole in conjunction with FSH for controlled ovarian super ovulation in both ovulatory women with unexplained infertility and anovulatory women with PCOS[38]. The use of letrozole was associated with a significantly lower FSH dose required for achievement of adequate ovarian super ovulation. The pregnancy rate and endometrial thickness with letrozole and FSH treatment was similar to FSH alone. We have also shown an improvement in ovarian response to FSH stimulation with the use of letrozole in low responders during ovarian stimulation[39].

In U.S. Patent No. 5,583,128 granted Dec. 10, 1996 to Bhatnagar, there is described the use of aromatase inhibitors for contraception in female primates of reproductive age without substantially affecting the menstrual cycle of the female primate. The contraceptive action of the aromatase inhibitors is reversible, that is to say once their use has been discontinued pregnancy can occur in the treated primates as early as the next cycle.

In U.S. Patent No. 5, 491, 136 granted Feb. 13, 1996 to Peet et al, the use of aromatase inhibitors in the treatment of breast cancer is described.

The disclosures of all references referred to herein are incorporated herein by reference.

SUMMARY OF THE INVENTION

The present invention mimics the action of CC, without depletion of estrogen receptors, by administration of an aromatase inhibitor (AI) in the early part of the menstrual cycle. This is believed to result in release of the hypothalamic/pituitary axis from estrogenic negative feedback, thereby increasing gonadotropin secretion and resulting in stimulation of ovarian follicles. In addition, a peripheral mechanism of action at the level of the ovary may also be present, secondary to prevention of androgen conversion to estrogen and an increase in intra-ovarian androgen concentration. In the primate ovary, androgen has been shown to increase granulosa cell FSH receptors[40],[41] thereby increasing ovarian responsiveness to FSH.

The present invention provides an improvement over the known multiple daily dose administration of aromatase inhibitor for treating infertility in females. The single dose provides a high initial dose of AI with a better or equal disappearance from the body as compared with the multiple dose treatment during the critical time for follicle recruitment and stimulation. Usually this encompasses a period of about 7 days at the beginning of the menstrual cycle. The single dose is more convenient and ensures better patient compliance. The amount of aromatase inhibitor that remains in the body in the single dose

form as compared with multiple dose form has been found to be about equivalent.

Thus the present invention provides a method of inducing ovulation in a female suffering from anovulatory infertility which comprises administering to such a female a single dose of at least one aromatase inhibitor (AI).

In another form the present invention provides a method for augmenting ovulation in an ovulating female suffering from unexplained infertility or another type of ovulatory infertility, which comprises administering to such a female, a single dose of at least one aromatase inhibitor (AI), early in one or more menstrual cycles.

In another aspect the invention provides a method of substantially reducing dosage levels of follicle stimulating hormone (FSH) for administration to a female undergoing infertility treatment which comprises administering a combination of a single dose of at least one aromatase inhibitor (AI) with a plurality of daily doses of follicle stimulating hormone (FSH). .

The invention also provides a method of increasing response to follicle stimulating hormone in a female who is a poor responder to follicle stimulation, which comprises administering a combination of a single dose of at least one aromatase inhibitor (AI) with a plurality of daily doses of follicle stimulating hormone (FSH).

In another aspect the invention provides a pharmaceutical preparation for treating infertility in a female comprising a single dose of an aromatase inhibitor for inducing or augmenting ovulation together with a pharmaceutically acceptable carrier

In another aspect the invention provides a two component pharmaceutical preparation for treating infertility in a female comprising a single dose of an aromatase inhibitor together with a pharmaceutically acceptable carrier in combination with a plurality of daily doses of follicle stimulating hormone together with a pharmaceutically acceptable carrier.

In another aspect the invention provides for the use of a single dose of an aromatase inhibitor for treating infertility in a female, each dose comprising an effective amount of an aromatase inhibitor for inducing or augmenting ovulation.

In another aspect the invention provides for the use of a single dose of an aromatase inhibitor in combination with a plurality of daily doses of follicle stimulating hormone for treating infertility in a female wherein the amount of follicle stimulating hormone is substantially reduced as compared with the use of follicle stimulating hormone on its own.

In another aspect the invention provides for the use a single dose of an aromatase inhibitor in combination with a plurality of daily doses of follicle stimulating hormone for treating a female who is a poor responder to follicle stimulation to increase follicle production.

In another aspect the invention provides for the use of a single dose of an aromatase inhibitor in the preparation of a medicament for the treatment of infertility in a female.

In another aspect the invention provides for the use of a single dose of an aromatase inhibitor in combination with a plurality of daily doses of follicle stimulating hormone in the preparation of a medicament for the treatment of infertility in a female.

DETAILED DESCRIPTION OF THE INVENTION

The daily doses required for the present invention depend entirely on the type of aromatase inhibitor that is used and the patient. Some inhibitors are more active than others and hence lower amounts of the former inhibitors may be used.

The aromatase inhibitor is selected from aromatase inhibitors having a half life of about 8 hours to about 4 days, more preferably from aromatase inhibitors having a half life of about 2 days. Most beneficial are those aromatase inhibitors selected from non-steroidal and reversible aromatase inhibitors. More detail on the types of aromatase inhibitors that may be used in the methods, uses and preparations of the present invention appears subsequently herein.

Aromatase Inhibitor

The aromatase inhibitors that have been found to be most useful of the commercially available forms are those in oral form. This form offers clear advantages over others, including convenience and patient compliance. Preferred aromatase inhibitors of those that are commercially available include anastrozole, letrozole, vorozole and exemestane. The AI exemestane is a steroidal inhibitor.

By "aromatase inhibitors" there are to be understood substances that inhibit the enzyme aromatase (estrogen synthetase), which is responsible for converting androgens to estrogens.

Aromatase inhibitors may have a non-steroidal or a steroidal chemical structure. According to the present invention, both non-steroidal aromatase inhibitors and steroidal aromatase inhibitors can be used.

By aromatase inhibitors there are to be understood especially those substances that in a determination of the in vitro inhibition of aromatase activity exhibit IC_{50} values of 10^{-5} M or lower, especially 10^{-6} M or lower, preferably 10^{-7} M or lower and most especially 10^{-8} M or lower.

The in vitro inhibition of aromatase activity can be demonstrated, for example, using the methods described in J. Biol. Chem. 249, 5364 (1974) or in J. Enzyme Inhib. 4, 169 (1990). In addition, IC_{50} values for aromatase inhibition can be obtained, for example, in vitro by a direct product isolation method relating to inhibition of the conversion of 4-^{14} C-androstenedione to 4-^{14} C-oestrone in human placental microsomes.

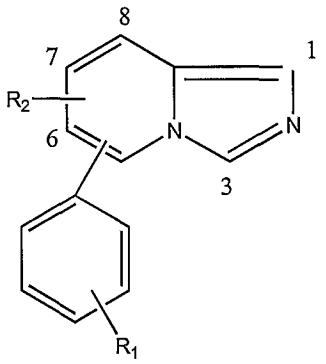
By aromatase inhibitors there are to be understood most especially substances for which the minimum effective dose in the case of in vivo aromatase inhibition is 10 mg/kg or less, especially 1 mg/kg or less, preferably 0.1 mg/kg or less and most especially 0.01 mg/kg or less.

In vivo aromatase inhibition can be determined, for example, by the following method [see J. Enzyme Inhib. 4, 179 (1990)]: androstenedione (30 mg/kg subcutaneously) is administered on its own or together with a compound of the invention (orally or subcutaneously) to sexually immature female rats for a period of 4 days. After the fourth administration, the rats are sacrificed and the uteri are isolated and weighed. The

aromatase inhibition is determined by the extent to which the hypertrophy of the uterus induced by the administration of androstenedione alone is suppressed or reduced by the simultaneous administration of the compound according to the invention.

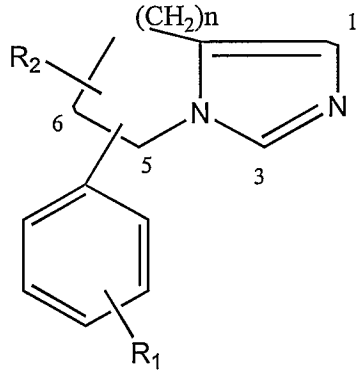
The following groups of compounds are listed as examples of aromatase inhibitors. Each individual group forms a group of aromatase inhibitors that can be used successfully in accordance with the present invention:

(a) The compounds of formulae I and I* as defined in EP-A-165 904. These are especially the compounds of formula I



(I)

wherein R_1 is hydrogen, lower alkyl; lower alkyl substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, halogen, sulfo, carboxy, lower alkoxycarbonyl, carbamoyl or by cyano; nitro, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, N-morpholino, N-thiomorpholino, N-piperazino that is unsubstituted or lower alkyl-substituted in the 4-position, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl, formyl; iminomethyl that is unsubstituted or substituted at the nitrogen atom by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or by amino; C_2 -C_7 alkanoyl, benzoyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, unsubstituted or lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl; and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; the 7,8-dihydro derivatives thereof; and the compounds of formula I*



(I*)

wherein n is 0, 1, 2, 3 or 4; and R_1 and R_2 are as defined above for formula I; it being possible for the phenyl ring in the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or by halogen; it being possible in a compound of formula I* for the two substituents $C_6 H_4$ --R_1 and R_2 to be linked to each of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or both to different carbon atoms, and pharmaceutically acceptable salts thereof.

Individual compounds that may be given special mention here are:

(1) 5-(p-cyanophenyl)imidazo[1,5-a]pyridine,
(2) 5-(p-ethoxycarbonylphenyl)imidazo[1,5-a]pyridine,
(3) 5-(p-carboxyphenyl)imidazo[1,5-a]pyridine,
(4) 5-(p-tert-butylaminocarbonylphenyl)imidazo[1,5-a]pyridine,
(5) 5-(p-ethoxycarbonylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(6) 5-(p-carboxyphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(7) 5-(p-carbamoylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(8) 5-(p-tolyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(9) 5-(p-hydroxymethylphenyl)imidazo[1,5-a]pyridine,
(10) 5-(p-cyanophenyl)-7,8-dihydroimidazo[1,5-a]pyridine,
(11) 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(12) 5-(p-hydroxymethylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(13) 5-(p-formylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(14) 5-(p-cyanophenyl)-5-methylthio-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(15) 5-(p-cyanophenyl)-5-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(16) 5-(p-aminophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(17) 5-(p-formylphenyl)imidazo[1,5-a]pyridine,
(18) 5-(p-carbamoylphenyl)imidazo[1,5-a]pyridine,
(19) 5H-5-(4-tert-butylaminocarbonylphenyl)-6,7-dihydropyrrolo[1,2-c]imidazole,
(20) 5H-5-(4-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]imidazole,
(21) 5H-5-(4-cyanophenyl)-6,7,8,9-tetrahydroimidazo[1,5-a]azepine,
(22) 5-(4-cyanophenyl)-6-ethoxycarbonylmethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(23) 5-(4-cyanophenyl)-6-carboxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine

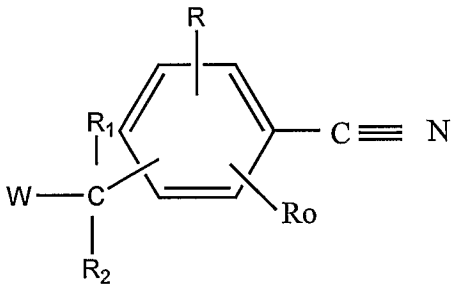
(24) 5-benzyl-5-(4-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,

(25) 7-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,

(26) 7-(p-carbamoylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,

(27) 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (=Fadrozol).

(b) The compounds of formula I as defined in EP-A 236 940. These are especially the compounds of formula I



(I)

wherein R and R_0, independently of one another, are each hydrogen or lower alkyl, or R and R_0 at adjacent carbon atoms, together with the benzene ting to which they are bonded, form a naphthalene or tetrahydronaphthalene ring; wherein R_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl or lower alkenyl; R_2 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio or lower alkenyl, or wherein R_1 and R_2 together are lower alkylidene or C_4 -C_6 alkylene; wherein W is 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl, 3-pyridyl or one of the mentioned heterocyclic radicals substituted by lower alkyl; and aryl within the context of the above definitions has the following meanings: phenyl that is unsubstituted or substituted by one or two substituents from the group lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; also thienyl, indolyl, pyridyl or furyl, or one of the four last-mentioned heterocyclic radicals monosubstituted by lower alkyl, lower alkoxy, cyano or by halogen; and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

(1) 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile,

(2) 4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile,

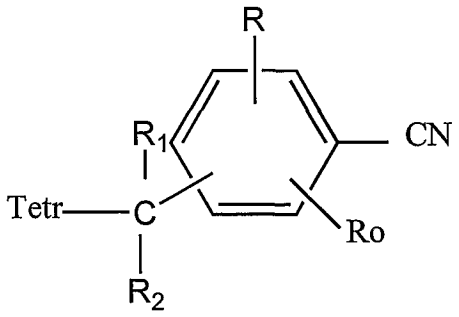
(3) 4-[alpha-(4-cyanobenzyl)-1-imidazolylmethyl]-benzonitrile,

(4) 1-(4-cyanophenyl)-1-(1-imidazolyl)-ethylene,

(5) 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile,

(6) 4-[alpha-(4-cyanophenyl)-3-pyridylmethyl]-benzonitrile.

(c) The compounds of formula I as defined in EP-A-408 509. These are especially the compounds of formula I



(I)

wherein Tetr is 1- or 2-tetrazolyl that is unsubstituted or substituted in the 5-position by lower alkyl, phenyl-lower alkyl or by lower alkanoyl; R and R_2, independently of one another, are each hydrogen; lower alkyl that is unsubstituted or substituted by hydroxy, lower alkoxy, halogen, carboxy, lower alkoxycarbonyl, (amino, lower alkylamino or di-lower alkylamino)-carbonyl or by cyano; lower alkenyl, aryl, heteroaryl, aryl-lower alkyl, C_3 -C_6 cycloalkyl, C_3 -C_6 cycloalkyl-lower alkyl, lower alkylthio, arylthio or aryl-lower alkylthio; or R_1 and R_2 together are straight-chained C_4 -C_6 alkylene that is unsubstituted or substituted by lower alkyl, or are a group --$(CH_2)_m$-1,2-phenylene-$(CH_2)_n$ -- wherein m and n, independently of one another, are each 1 or 2 and 1,2-phenylene is unsubstituted or substituted in the same way as phenyl in the definition of aryl below, or are lower alkylidene that is unsubstituted or mono- or di-substituted by aryl; and R and R_0, independently of one another, are each hydrogen or lower alkyl; or R and R_0 together, located at adjacent carbon atoms of the benzene ring, are a benzo group that is unsubstituted or substituted in the same way as phenyl in the definition of aryl below; aryl in the above definitions being phenyl that is unsubstituted or substituted by one or more substituents from the group consisting of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, carboxy, lower alkoxycarbonyl, (amino, lower alkylamino or di-lower alkylamino)-carbonyl, cyano, lower alkanoyl, benzoyl, lower alkylsulfonyl and (amino, lower alkylamino or di-lower alkylamino)-sulfonyl; heteroaryl in the above definitions being an aromatic heterocyclic radical from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, thienyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, triazinyl, indolyl, isoindolyl, benzimidazolyl, benzotriazolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, quinolyl and isoquinolyl that is unsubstituted or substituted in the same way as phenyl in the definition of aryl above; and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

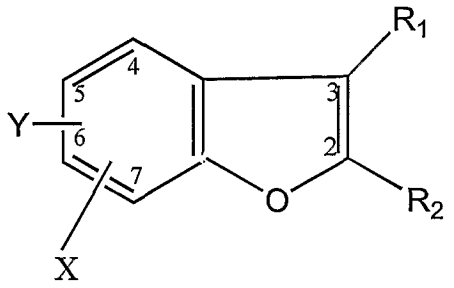
(1) 4-(2-tetrazolyl)methyl-benzonitrile,

(2) 4-[α-(4-cyanophenyl)-(2-tetrazolyl)methyl]-benzonitrile,

(3) 1-cyano-4-(1-tetrazolyl)methyl-naphthalene,

(4) 4-[α-(4-cyanophenyl)-(1-tetrazolyl)methyl]-benzonitrile.

(d) The compounds of formula I as defined in European Patent Application No. 91810110.6. These are especially the compounds of formula I



(I)

wherein X is halogen, cyano, carbamoyl, N-lower alkylcarbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy, wherein aryl is phenyl or naphthyl, each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen and/or by trifluoromethyl; Y is a group --CH_2 --A wherein A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-(1,2,5-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or Y is hydrogen, R_1 and R_1, independently of one another, are each hydrogen, lower alkyl or a group --CH_2 --A as defined for Y, or R_1 and R_2 together are --$(CH_2)_n$ -- wherein n is 3, 4 or 5, with the proviso that one of the radicals Y, R_1 and R_2 is a group --CH_2 --A, with the further proviso that in a group --CH_2 --A as a meaning of R_1 or R_2, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that in a group --$CH._2$ --A as a meaning of Y, A is other than 1-imidazolyl when X is halogen or lower alkoxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl, and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

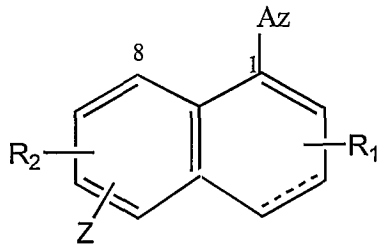
(1) 7-cyano-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran,

(2) 7-cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran,

(3) 7-carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran,

(4) 7-N-(cyclohexylmethyl)carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran.

(e) The compounds of formula I as defined in Swiss Patent Application 1339/90-7. These are especially the compounds of formula I



(I)

wherein the dotted line denotes an additional bond or no additional bond, Az is imidazolyl, triazolyl or tetrazolyl bonded via a ring nitrogen atom, each of those radicals being

unsubstituted or substituted at carbon atoms by lower alkyl or by aryl-lower alkyl, Z is carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, halogen, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkyl, trifluoromethyl or aryl-lower alkyl, and R_1 and R_2, independently of one another, are each hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen or trifluoromethyl; aryl being phenyl or naphthyl each of which is unsubstituted or substituted by one or two substituents from the group consisting of lower alkyl, lower alkoxy, hydroxy, halogen and trifluoromethyl; with the proviso that neither Z nor R_2 is hydroxy in the 8-position, and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

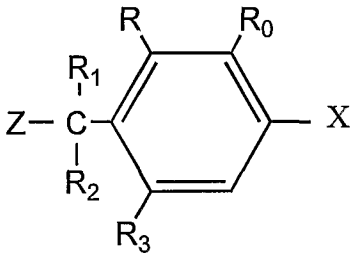
(1) 6-cyano-1-(1-imidazolyl)-3,4-dihydronaphthalene,

(2) 6-cyano-1-[1-(1,2,4-triazolyl)]-3,4-dihydronaphthalene,

(3) 6-chloro-1-(1-imidazolyl)-3,4-dihydronaphthalene,

(4) 6-bromo-1-(1-imidazolyl)-3,4-dihydronaphthalene.

(f) The compounds of formula I as defined in Swiss Patent Application 3014/90-0. These are especially the compounds of formula I



(I)

wherein Z is a five-membered nitrogen-containing heteroaromatic ting selected from the group 5-isothiazolyl, 5-thiazolyl, 5-isoxazolyl, 5-oxazolyl, 5-(1,2,3-thiadiazolyl), 5-(1,2,3-oxadiazolyl), 3-(1,2,5-thiadiazolyl), 3-(1,2,5-oxadiazolyl), 4-isothiazolyl, 4-isoxazolyl, 4-(1,2,3-thiadiazolyl), 4-(1,2,3-oxadiazolyl), 2-(1,3,4-thiadiazolyl), 2-(1,3,4-oxadiazolyl), 5-(1,2,4-thiadiazolyl) and 5-(1,2,4-oxadiazolyl); R and R_0 are hydrogen; or R and R_0 together are a benzo group that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; R_1 is hydrogen, hydroxy, chlorine or fluorine; R_3 is hydrogen; R_2 is hydrogen, lower alkyl or phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl or by cyano; or R_1 and R_2 together are methylidene; or R_2 and R_3 together are --$(CH_2)_3$ --; or R_1 and R_2 and R_3 together are a group =CH--$(CH_2)_2$ -- wherein the single bone is linked to the benzene ring; X is cyano; and X may also be halogen when R_2 and R_3 together are --$(CH_2)_3$ -- or R_1 and R_1 and R_3 together are a group =CH--$(CH_2)_2$ --; and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

(1) 4-[α-(4-cyanophenyl)-α-hydroxy-5-isothiazolylmethyl]-benzonitrile.

(2) 4-[α-(4-cyanophenyl)-5-isothiazolylmethyl]-benzonitrile,

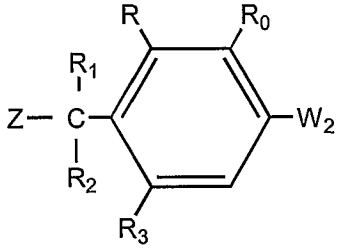
(3) 4-[α-(4-cyanophenyl)-5-thiazolylmethyl]-benzonitrile,

(4) 1-(4-cyanophenyl)-1-(5-thiazolyl)-ethylene,

(5) 6-cyano-1-(5-isothiazolyl)-3,4-dihydronaphthalene,

(6) 6-cyano-1-(5-thiazolyl)-3,4-dihydronaphthalene.

(g) The compounds of formula VI as defined in Swiss Patent Application 3014/90-0. These are especially the compounds of formula VI



(VI)

wherein Z is a five-membered nitrogen-containing heteroaromatic ring selected from the group 5-isothiazolyl, 5-thiazolyl, 5-isoxazolyl, 5-oxazolyl, 5-(1,2,3-thiadiazolyl). 5-(1,2,3-oxadiazolyl) 3-(1,2,5-thiadiazolyl), 3-(1,2,5-oxadiazolyl), 4-isothiazolyl. 4-isoxazolyl, 4-(1,2,3-thiadiazolyl), 4-(1,2,3-oxadiazolyl), 2-(1,3,4-thiadiazolyl), 2-(1,3,4-oxadiazolyl), 5-(1,2,4-thiadiazolyl) and 5-(1,2,4-oxadiazolyl); R and R_0 are each hydrogen; or R and R_0 together are a benzo group that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; R_1 is hydrogen, hydroxy, chlorine or fluorine; R_3 is hydrogen; R_2 is hydrogen, lower alkyl or phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, aryl-lower alkoxy or by aryloxy; or R_1 and R_2 together are methylidene, and W_2 is halogen, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy; aryl in each case being phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

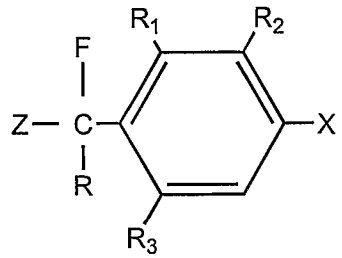
(1) bis(4,4'-bromophenyl)-(5-isothiazolyl)methanol,

(2) bis(4,4'-bromophenyl)-(5-isothiazolyl)methane,

(3) bis(4,4'-bromophenyl)-(5-thiazolyl)methanol,

(4) bis(4,4'-bromophenyl)-(5-thiazolyl)methane,

(h) The compounds of formula I as defined in Swiss Patent Application 3923/90-4. These are especially the compounds of formula I



(I)

wherein Z is imidazolyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl. triazinyl, quinolinyl or isoquinolinyl, all those radicals being bonded via their heterocyclic rings and all those radicals being unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen or by trifluoromethyl: R_1 and R_2, independently of one another, are each hydrogen or lower alkyl; or R_1 and R_2 together are C_3 -C_4 alkylene, or a benzo group that is unsubstituted or substituted as indicated below for aryl; R is hydrogen, lower alkyl, aryl or heteroaryl, and X is cyano, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylenecarbamoyl; N,N-lower alkylenecarbamoyl interrupted by --O--, --S-- or --NR"--, wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-cycloalkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-carbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-aryl-lower alkylcarbamoyl, N-arylcarbamoyl, N-hydroxycarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy; and wherein X is also halogen when Z is imidazolyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl or benzotriazolyl; wherein aryl is phenyl or naphthyl, these radicals being unsubstituted or substituted by from 1 to 4 substituents from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower alkylene (linked to two adjacent carbon atoms), C_3 -C_8 cycloalkyl, phenyl-lower alkyl, phenyl; lower alkyl that is substituted in turn by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy; lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenoxy, lower alkenyloxy, halo-lower alkenyloxy, lower alkynyloxy, lower alkylenedioxy (linked to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3 -C_8 cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino; lower alkyleneamino or lower alkyleneamino interrupted by --O--, --S-- or --NR"-- (wherein R" is hydrogen, lower alkyl or lower alkanoyl); lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylenecarbamoyl; N,N-lower alkylenecarbamoyl interrupted by --O--, --S-- or --NR"--, wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-cycloalkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-carbamoyl, N-cycloalkyl-lower alkylcarbamoyl,

N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenyl-lower alkylcarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkoxysulfonyl, sulfamoyl, N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl; the phenyl groups

occurring in the substituents of phenyl and naphthyl in turn being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; wherein heteroaryl is indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzo[b]furanyl, benzo[b]thienyl, benzoxazolyl or benzothiazolyl, those radicals being unsubstituted or substituted by from 1 to 3 identical or different substituents selected from lower alkyl, hydroxy, lower alkoxy, halogen, cyano and trifluoromethyl; and pharmaceutically acceptable salts thereof.

Those compounds are especially the compounds of formula I whereto Z is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl, 2-tetrazolyl, 3-pyridyl, 4-pyridyl, 4-pyrimidyl, 5-pyrimidinyl or 2-pyrazinyl; R_1 and R_2, independently of one another, are each hydrogen or lower alkyl; or R_1 and R_2 together are 1,4-butylene or a benzo group; R is lower alkyl; phenyl that is unsubstituted or substituted by cyano, carbamoyl, halogen, lower alkyl, trifluoromethyl, hydroxy, lower alkoxy or by phenoxy; or benzotriazolyl or benzo[b]furanyl, the last two radicals being unsubstituted or substituted by from 1 to 3 identical or different substituents selected from lower alkyl, halogen and cyano; and X is cyano or carbamoyl; and wherein X is also halogen when Z is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl 2-tetrazolyl; and pharmaceutically acceptable salts thereof.

Individual compounds that may be given special mention here are:

(1) 4-[α-4-cyanophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-benzonitrile,

(2) 4-[α-(4-cyanophenyl)-α-fluoro-(2-tetrazolyl)methyl]-benzonitrile,

(3) 4-[α-(4-cyanophenyl)-α-fluoro-(1-tetrazolyl)methyl]-benzonitrile,

(4) 4-[α-(4-cyanophenyl)-α-fluoro-(1-imidazolyl)methyl]-benzonitrile,

(5) 1-methyl-6-[α-(4-chlorophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-benzotriazole,

(6) 4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,3-triazolyl)methyl]-benzo nitrile,

(7) 7-cyano-4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzo[b]furan,

(8) 4-[α-(4-bromophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-benzo nitrile,

(9) 4-[α-(4-cyanophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,

(10) 4-[α-(4-bromophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,

(11) 4-[α-(4-cyanophenyl)-α-fluoro-(3-pyridyl)methyl]-benzonitrile,

(12) 7-bromo-4-[α-(4-cyanophenyl)-α-fluoro-(1-imidazolyl)methyl]-2,3-dimethylbenzo[b]furan,

(13) 7-bromo-4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzo[b]furan,

(14) 4-[α-(4-cyanophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,

(15) 4-[α-(4-bromophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,

(16) 4-[α-(4-cyanophenyl)-1-(1,2,3-triazolyl)methyl]-benzonitrile,

(17) 2,3-dimethyl-4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-7-cyano-benzo[b]furan,

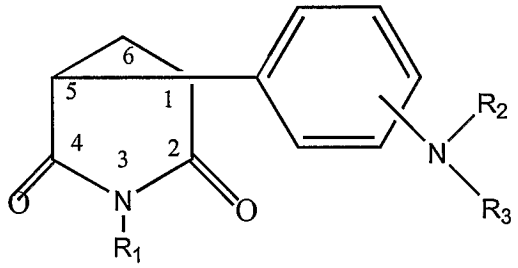
(18) 4-[α-(4-cyanophenyl)-(5-pyrimidyl)methyl]-benzonitrile,

(19) 4-[α-(4-bromophenyl)-(5-pyrimidyl)methyl]-benzonitrile,

(20) 2,3-dimethyl-4-[α-(4-cyanophenyl)-(1-imidazolyl)methyl]-7-bromo-benzo[b]furan,

(21) 2,3-dimethyl-4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-7-bromo-benzo-[b]furan.

(i) The compounds of formula I as defined in EP-A-114 033. These are especially the compounds of formula I



wherein R_1 is hydrogen, R_2 is hydrogen, sulfo, C_1 -C_7 alkanoyl or C_1 -C_7 alkanesulfonyl and R_3 is hydrogen, or wherein R_1 is C_1 -C_{12} alkyl, $C_{.2}$ -C_{12} alkenyl, C_2 -C_7 alkynyl, C_3 -C_{10} cycloalkyl, C_3 -$C_{.10}$ cycloalkenyl, $C_{.3}$ 3 -C_6 cycloalkyl-C_1 -C_4 alkyl, C_3 -C_6 cycloalkyl-$C_{.2}$ -C_4 alkenyl or C_3 -C_6 cycloalkenyl-C_1 -C_4 alkyl, R_2 is hydrogen, C_1 -C_7 alkyl, sulfo, C_1 -C_7 alkanoyl or C_1 -C_7 alkanesulfonyl and R_3 is hydrogen or C_1 -C_7 alkyl, and salts of those compounds.

Individual compounds from that group that may be given special mention are:

(1) 1-(4-aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione,

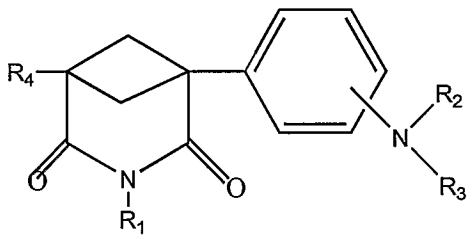
(2) 1-(4-aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione,

(3) 1-(4-aminophenyl)-3-isobutyl-3-azabicyclo[3.1.0]hexane-2,4-dione,

(4) 1-(4-aminophenyl)-3-n-heptyl-3-azabicyclo[3.1.0]hexane-2,4-dione,

(5) 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

(j) The compounds of formula I as defined in EP-A-166 692. These are especially the compounds of formula I



(I)

wherein R_1 is hydrogen, alkyl having from 1 to 12 carbon atoms, alkenyl having from 2 to 12 carbon atoms, lower alkynyl, cycloalkyl or cycloalkenyl each having from 3 to 10 carbon atoms, cycloalkyl-lower alkyl having from 4 to 10 carbon atoms, cycloalkyl-lower alkenyl having from 5 to 10 carbon atoms, cycloalkenyl-lower alkyl having from 4 to 10 carbon

atoms, or aryl having from 6 to 12 carbon atoms or aryl-lower alkyl having from 7 to 15 carbon atoms, each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, acyloxy, amino, lower alkylamino, di-lower alkylamino, acylamino amino or by halogen, R_2 is hydrogen, lower alkyl, sulfo, lower alkanoyl or lower alkanesulfonyl, sulfonyl, R_3 is hydrogen or lower alkyl and R_4 is hydrogen, lower alkyl, phenyl or phenyl substituted by --$N(R_2)(R_3)$, and salts thereof, radicals described as "lower" containing up to and including 7 carbon atoms.

Individual compounds from that group that may be given special mention are:

(1) 1-(4-aminophenyl)-3-n-propyl-3-azabicyclo[3.1.1]heptane-2,4-dione,

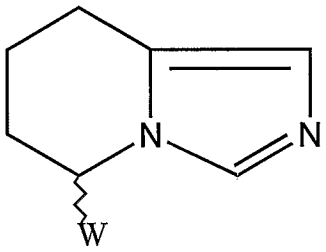
(2) 1-(4-aminophenyl)-3-methyl-3-azabicyclo[3.1.1]heptane-2,4-dione,

(3) 1-(4-aminophenyl)-3-n-decyl-3-azabicyclo[3.1.1]heptane-2,4-dione,

(4) 1-(4-aminophenyl)-3-cyclohexyl-3-azabicyclo[3.1.1]heptane-2,4-dione,

(5) 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.1]heptane-2,4-dione.

(k) The compounds of formula I as defined in EP-A-356 673. These are especially the compounds of formula I



(I)

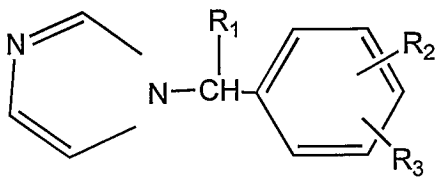
wherein W (α) is a 2-naphthyl or 1-anthryl radical, wherein each benzene ring is unsubstituted or substituted by a substituent selected from halogen, hydroxy, carboxy, cyano and nitro; or (.beta.) is 4-pyridyl, 2-pyrimidyl or 2-pyrazinyl, each of those radicals being unsubstituted or substituted by a substituent selected from halogen, cyano, nitro, C_1 - C_4 alkoxy and C_2 -C_5 alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Individual compounds from that group that may be given special mention are:

(1) 5-(2'-naphthyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,

(2) 5-(4'-pyridyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine.

(l) The compounds of formula I or Ia as defined in EP-A-337 929. These are especially the compounds of formula I/Ia



(I/Ia)

wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, R_2 is benzyloxy, 3-bromo-, 4-bromo-, 4-chloro-, 2,3-, 2,4-, 4,5- or 4,6-dichloro-benzyloxy, and R_3 is cyano; C_2 -C_{10} alkanoyl that is unsubstituted or mono- or poly-substituted by halogen, methoxy, amino, hydroxy and/or by cyano; benzoyl that is unsubstituted or substituted by one or more substituents from the group halogen, C_1 -C_4 alkyl, methoxy, amino, hydroxy and cyano; carboxy, (methoxy, ethoxy or butoxy)-carbonyl, carbamoyl, N-isopropylcarbamoyl, N-phenylcarbamoyl, N-pyrrolidylcarbonyl, nitro or amino; and salts thereof.

Individual compounds from that group that may be given special mention are:

(1) 4-(2,4-dichlorobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzonitrile,

(2) (4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-phenyl pentyl ketone,

(3) 4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzanilide,

(4) 4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzoic acid,

(5) 3-(2,4-dichlorobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzonitrile,

(6) 3-(2,4-dichlorobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzoic acid methyl ester,

(7) 3-(2,4-dichlorobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzoic acid,

(8) 3-(3-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzonitrile,

(9) 4-(3-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzonitrile,

(10) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzoic acid,

(11) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzanilide,

(12) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-phenyl pentyl ketone,

(13) 4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzonitrile,

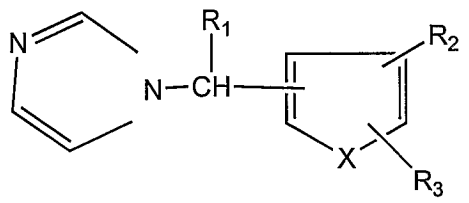
(14) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzonitrile,

(15) 4-nitro-2-[1-(1-imidazolyl)-butyl]-phenyl-(2,4-dichlorobenzyl) ether,

(16) 4-amino-2-[1-(1-imidazolyl)-butyl]-phenyl-(2,4-dichlorobenzyl) ether,

(17) (2,4-dichlorobenzyl)-[2-(1-imidazolyl-methyl)-4-nitrophenyl]ether.

(m) The compounds of formula I as defined in EP-A-337 928. These are especially the compounds of formula I



(I)

wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, R_2 is hydrogen, halogen, cyano, methyl, hydroxymethyl, cyanomethyl, methoxymethyl, pyrrolidinylmethyl, carboxy, (methoxy, ethoxy or butoxy)-carbonyl, carbamoyl, N-isopropylcarbamoyl, N-phenylcarbamoyl, N-pyrrolidylcarbonyl; C_2 -C_{10} alkanoyl that is

unsubstituted or mono- or poly-substituted by halogen, methoxy, ethoxy, amino, hydroxy and/or by cyano; or benzoyl that is unsubstituted or substituted by one or more substituents from the group halogen, C_1 -C_4 alkyl, methoxy, ethoxy, amino, hydroxy and cyano, R_3 is hydrogen, benzyloxy, 3-bromo-, 4-bromo-, 4-chloro-, 2,3-, 2,4-, 4,5- or 4,6-dichlorobenzyloxy, and X is --CH=N--; --CH=N(--O)--or --S--; and salts thereof.

Individual compounds from that group that may be given special mention are:

(1) 5-[1-(1-imidazolyl)-butyl]-thiophene-2-carbonitrile,

(2) 2-[1-(1-imidazolyl)-butyl]-thiophene-4-carbonitrile,

(3) 2-[1-(1-imidazolyl)-butyl]-4-bromo-thiophene,

(4) 2-[1-(1-imidazolyl)-butyl]-5-bromo-thiophene,

(5) 5-[1-(1-imidazolyl)-butyl]-2-thienyl pentyl ketone,

(6) 5-[1-(1-imidazolyl)-butyl]-2-thienyl ethyl ketone,

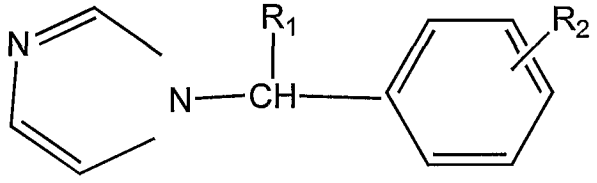
(7) 5-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine-2-carbonitrile,

(8) 3-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine-2-carbonitrile,

(9) 3-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine-N-oxide,

(10) 3-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine.

(n) The compounds of formula I as defined in EP-A-340 153. These are especially the compounds of formula I



(I)

wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, and R_2 is a radical from the group methyl, ethyl, propyl, benzyl, phenyl and ethenyl that is substituted by hydroxy, cyano, methoxy, butoxy, phenoxy, amino, pyrrolidinyl, carboxy, lower alkoxycarbonyl or by carbamoyl; or R_2 is formyl or derivatised formyl that can be obtained by reaction of the formyl group with an amine or amine derivative from the group hydroxylamine, O-methylhydroxylamine, O-ethylhydroxylamine, O-allylhydroxylamine, O-benzylhydroxylamine, O-4-nitrobenzyloxyhydroxylamine, O-2,3,4,5,6-pentafluorobenzyloxyhydroxylamine, semicarbazide, thiosemicarbazide, ethylamine and aniline; acetyl, propionyl, butyryl, valeryl, caproyl; benzoyl that is unsubstituted or substituted by one or more substituents from the group halogen, C_1 -C_4 -alkyl, methoxy, amino, hydroxy and cyano; carboxy, (methoxy, ethoxy or butoxy)carbonyl, carbamoyl, N-isopropylcarbamoyl, N-phenylcarbamoyl or N-pyrrolidylcarbonyl; and salts thereof.

Individual compounds from that group that may be given special mention are:

(1) 4-(1-(1-imidazolyl)-butyl)-benzoic acid methyl ester,

(2) 4-(1-(1-imidazolyl)-butyl)-benzoic acid butyl ester,

(3) 4-(1-(1-imidazolyl)-butyl)-phenyl-acetonitrile,

(4) 4-(1-(1-imidazolyl)-butyl)-benzaldehyde,

(5) 4-(1-(1-imidazolyl)-butyl)-benzyl alcohol,

(6) {4-[1-(1-imidazolyl)-butyl]-phenyl }-2-propyl ketone,

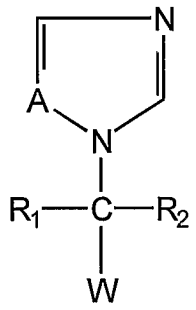
(7) 4-[1-(1-imidazolyl)-butyl]-phenyl propyl ketone,

(8) 4-[1-(1-imidazolyl)-butyl]-phenyl butyl ketone,

(9) 4-[1-(1-imidazolyl)-butyl]-phenyl pentyl ketone,

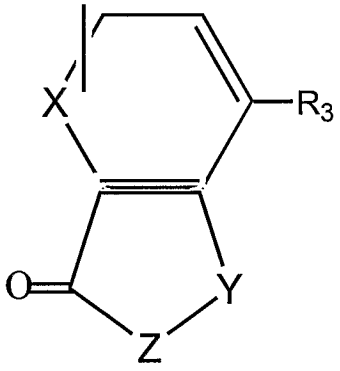
(10) 4-[1-(1-imidazolyl)-butyl]-phenyl hexyl ketone.

(o) The compounds of formula I as defined in DE-A-4 014 006. These are especially the compounds of formula I



(I)

wherein A is an N-atom or a CH radical and W is a radical of the formula



wherein X is an oxygen or a sulfur atom or a --CH=CH-- group and Y is a methylene group, an oxygen or a sulfur atom and Z is a $--(CH_2)_n--$ group wherein n=1, 2 or 3 and either

a) R_3 in W is a hydrogen atom and R_1 and R_2, independently of one another, are each a hydrogen atom, a C_1 -- to C_{10} alkyl group or a C_3 -- to C_7 cycloalkyl group, or

b) R_2 is as defined under a) and R_1 together with R_3 forms a $--(CH_2)_m--$ group wherein m=2, 3, or 4, and their pharmaceutically acceptable addition salts with acids.

Individual compounds from that group that may be given special mention are:

(1) 5-[1-(1-imidazolyl)-butyl]-1-indanone,

(2) 7-[1-(1-imidazolyl)-butyl]-1-indanone,

(3) 6-[1-(1-imidazolyl)-butyl]-1-indanone,

(4) 6-(1-imidazolyl)-6,7,8,9-tetrahydro-1H-benz[e]inden-3(2H)-one,

(5) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6-oxo-cyclopenta[b]-thiophene,

(6) 6-[1-(1-imidazolyl)-butyl]-3,4-dihydro-2H-naphthalen-1-one,

(7) 2-[1-(1-imidazolyl)-butyl]-6,7-dihydro-5H-benzo[b]thiophen-4-one,

(8) 6-[1-(1-imidazolyl)-butyl]-2H-benzo[b]furan-3-one,

(9) 5-[cyclohexyl-(1-imidazolyl)-methyl]-1-indanone,

(10) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6H-benzo[b]thiophen-7-one,

(11) 5-[1-(1-imidazolyl)-1-propyl-butyl]-1-indanone,

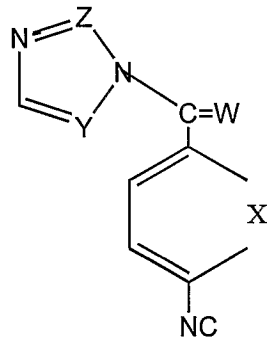
(12) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6H-benzo[b]thiophen-7-one,

(13) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6-oxo-cyclopenta[b]-thiophene,

(14) 5-(1-imidazolylmethyl)-1-indanone,

(15) 5-[1-(1,2,4-triazolyl)-methyl]-1-indanone.

(p) The compounds of formula I as disclosed in DE-A-3 926 365. These are especially the compounds of formula I



(I)

wherein W' is a cyclopentylidene, cyclohexylidene, cycloheptylidene or 2-adamantylidene radical, X is the grouping --CH=CH--, an oxygen or a sulfur atom, and Y and Z, independently of one another, are each a methine group (CH) or a nitrogen atom, and their pharmaceutically acceptable addition salts with acids.

Individual compounds from that group that may be given special mention are:

(1) 4-[1-cyclohexylidene-1-(imidazolyl)-methyl]-benzonitrile,

(2) 4-[1-cyclopentylidene-1-(imidazolyl)-methyl]-benzonitrile,

(3) 4-[1-cycloheptylidene-1-(imidazolyl)-methyl]-benzonitrile,

(4) 4-[2-adamantylidene-1-(imidazolyl)-methyl]-benzonitrile,

(5) 4-[1-cyclohexylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,

(6) 4-[1-cyclopentylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,

(7) 4-[1-cycloheptylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,

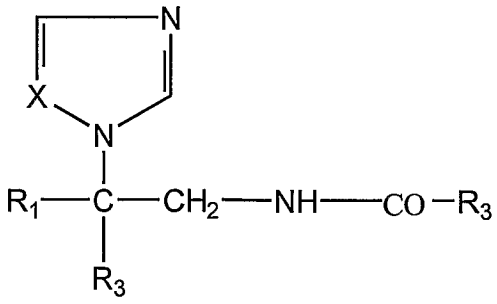
(8) 4-[2-adamantylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,

(9) 4-[1-cyclohexylidene-1-(1,2,3-triazolyl)-methyl]-benzonitrile,

(10) 4-[1-cyclopentylidene-1-(1,2,3-triazolyl)-methyl]-benzonitrile,

(11) 5-[cyclohexylidene-1-imidazolylmethyl]-thiophene-2-carbonitrile.

(q) The compounds of formula I as defined in DE-A-3 740 125. These are especially the compounds of formula I



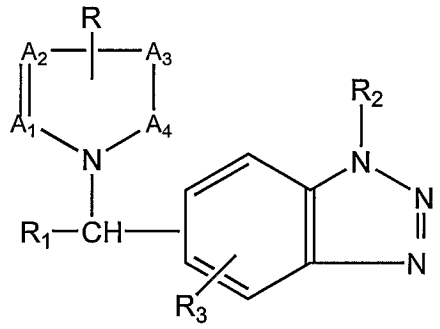
(I)

wherein X is CH or N, R_1 and R_2 are identical or different and are each phenyl or halophenyl, and R_3 is C_1 -C_4 alkyl; C_1 -C_4 alkyl substituted by CN, C_1 -C_4 alkoxy, benzyloxy or by C_1 -C_4 alkoxy-(mono-, di- or tri-)ethyleneoxy; C_1 -C_4 alkoxy, phenyl; phenyl that is substituted by halogen or by cyano; a C_5 -C_7 cycloalkyl group that is optionally condensed by benzene, or is thienyl, pyridyl or 2- or 3-indolyl; and acid addition salts thereof.

An individual compound from that group that may be given special mention is:

(1) 2,2-bis(4-chlorophenyl)-2-(1H-imidazol-1-yl)-1-(4-chlorobenzoyl-amino) ethane.

(r) The compounds of formula I as defined in EP-A-293 978. These are especially the compounds of formula I



(I)

pharmaceutically acceptable salts and stereochemically isomeric forms thereof, wherein -- A_1 =A_2 --A_3 =A_4 -- is a divalent radical selected from --CH=N--CH=CH--, --CH=N--CH=N-- and --CH=N--N=CH--, R is hydrogen or C_1 -C_6 alkyl; R_1 is hydrogen, C_1 -C_{10} alkyl, C_3 -C_7 cycloalkyl, Ar_1, Ar_2 -C_1`-C_6 alkyl, C_2 -C_6 alkenyl or C_2 -C_6 alkynyl: R_2 is hydrogen; C_1 -C_{10} alkyl that is unsubstituted or substituted by Ar_1 ; C_3 -C_7 cycloalkyl, hydroxy, C_1 -C_6 alkoxy, Ar_1, C_2 -C_6 alkenyl, C_2 -C_6 alkynyl, C_3 -C_7 cycloalkyl, bicyclo[2.2.1]heptan-2-yl, 2,3-dihydro-1H-indenyl, 1,2,3,4-tetrahydronaphthyl, hydroxy; C_2 -C_6 alkenyloxy that is unsubstituted or substituted by Ar_2 ; C_2 -C_6 alkynyloxy; pyrimidyloxy; di(Ar_2)methoxy, (1-C_1 -C_4 alkyl-4-piperidinyl)oxy, C_1 -C_{10} alkoxy; or C_1 -C_{10} alkoxy that is substituted by halogen, hydroxy, C_1 -C_6 alkyloxy, amino, mono- or di-(C_1 -C_6 alkyl)amino, trifluoromethyl, carboxy, C_1 -C_6 alkoxycarbonyl, Ar.sub.l, Ar_2 --O--, Ar_2 --S--, C_3 -C_7 cycloalkyl, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_1 -C_4 alkyl-substituted 1H-benzimidazolyl, (1,1'-

biphenyl)-4-yl or by 2,3-dihydro-2-oxo-1H-benzimidazolyl; and R_3 is hydrogen, nitro, amino, mono- or di-(C_1 -C_6 alkyl)amino, halogen, C_1 -C_6 alkyl, hydroxy or C_1 -C_6 alkoxy; wherein Ar_1 is phenyl, substituted phenyl, naphthyl, pyridyl, aminopyridyl, imidazolyl, triazolyl, thienyl, halothienyl, furanyl, C_1 -C_6 alkylfuranyl, halofuranyl or thiazolyl; wherein Ar_2 is phenyl, substituted phenyl or pyridyl; and wherein "substituted phenyl" is phenyl that is substituted by up to 3 substituents in each case selected independently of one another from the group consisting of halogen, hydroxy, hydroxymethyl, trifluoromethyl, C_1 -C_6 alkyl, C_1 -C_6 alkoxy, C_1 -C_6 alkoxycarbonyl, carboxy, formyl, hydroxyiminomethyl, cyano, amino, mono- and di-(C_1 -C_6 alkyl)amino and nitro.

Individual compounds from that group that may be given special mention are:

(1) 6-[(1H-imidazol-1-yl)-phenylmethyl]-1-methyl-1H-benzotriazole,

(2) 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole.

(s) The compounds of formula II as defined in EP-A-250 198, especially

(1) 2-(4-chlorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,

(2) 2-(4-fluorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,

(3) 2-(2-fluoro-4-trifluoromethylphenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,

(4) 2-(2,4-dichlorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,

(5) 2-(4-chlorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)-ethanol,

(6) 2-(4-fluorophenyl)-1,1-di(1,2,4-triazol-1-yl-methyl)ethanol.

(t) The compounds of formula I as defined in EP-A-281 283, especially

(1) (1R*2R*)-6-fluoro-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazo l-1-yl-methyl)naphthalene,

(2) (1 R *,2R *)-6-fluoro-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-imidazolylmethyl)-naphthalene,

(3) (1R*,2R*)- and (1R*,2S*)-2-(4-fluorophenyl)-l,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)naphthalene-6-carbonitrile,

(4) (1R*,2R*)- and (1R*,2S*)-2-(4-fluorophenyl)-l,2,3,4-tetrahydro-1-(1H-imidazolylmethyl)naphthalene-6-carbonitrile,

(5) (1R*,2R*)- and (1R*,2S*)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)-naphthalene-2,6-dicarbonitrile,

(6) (1R*,2R*)- and (1R*,2S*)-1,2,3,4-tetrahydro-1-(1H-imidazol-1-ylmethyl)naphthalene-2,6-dicarbonitrile,

(7) (1R*,2S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(5-methyl-1H-imidazolyl-methyl)naphthalene-6-carbonitrile.

(u) The compounds of formula I as defined in EP-A-296 749, especially

(1) 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]di(2-methylpropiononitrile),

(2) 2,2'-[5-(imidazol-1-ylmethyl)-1,3-phenylene]di(2 methylpropiononitrile),

(3) 2-[3-(1-hydroxy-1-methylethyl)-5-(5H-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropiononitrile,

(4) 2,2'-[5-dideuterio(1H-1,2,4-triazol-1-yl)methyl-1,3-phenylene]di(2-trideuteriomethyl-3,3,3-trideuteriopropiononitrile),

(5) 2,2'-[5-dideuterio(1H-1,2,4-triazol-1-yl)methyl-3-phenylene]di(2methylpropiononitrile).

(v) The compounds of formula I as defined in EP-A-299 683, especially

(1) (Z)-α-(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,

(2) (Z)-4'-chloro-α-(1,2,4-triazol-1-ylmethyl)stilbene-4-carbonitrile,

(3) (Z)-α-(1,2,4-triazol-1-ylmethyl)-4'-(trifluoromethyl)stilbene-4-carbonitrile,

(4) (E)-.beta.-fluoro-α-(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,

(5) (Z)-4'-fluoro-α-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,

(6) (Z)-2', 4'-dichloro-α-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,

(7) (Z)-4'-chloro-α-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,

(8) (Z)-α-(imidazol-1-ylmethyl)stilbene-4,4'dicarbonitrile,

(9) (Z)-α-(5-methylimidazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,

(10) (Z)-2-[2-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)propenyl]pyridine-5-carbonitrile.

(w) The compounds of formula I as defined in EP-A-299 684, especially

(1) 2-(4-chlorobenzyl)-2-fluoro-1,3-di(1,2,4-triazol-1-yl)propane,

(2) 2-fluoro-2-(2-fluoro-4-chlorobenzyl)-1,3-di(1,2,4-triazol-1-yl)propane,

(3) 2-fluoro-2-(2-fluoro-4-trifluoromethylbenzyl)-1,3-di(1,2,4-triazol-1-yl)propane,

(4) 3-(4-chlorophenyl)-1-(1,2,4-triazol-1-yl)-2-(1,2,4-triazol-1-ylmethyl)butan-2-ol,

(5) 2-(4-chloro-α-fluorobenzyl)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol,

(6) 2-(4-chlorobenzyl)-1,3-bis(1,2,4-triazol-1-yl)propane,

(7) 4-[2-(4-chlorophenyl)-1,3-di(1,2,4-triazol-1-ylmethyl)ethoxymethyl]-benzonitrile,

(8) 1-(4-fluorobenzyl)-2-(2fluoro-4-trifluoromethylphenyl)-1,3-di(1,2,4-triazol-1-yl)-propan-2-ol,

(9) 2-(4-chlorophenyl)-1-(4-fluorophenoxy)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol,

(10) 1-(4-cyanobenzyl)-2-(2,4-difluorophenyl)-1,3di(1,2,4-triazol-1-yl)propan-2-ol,

(11) 2-(4-chlorophenyl)-1-phenyl-1,3-di(1,2,4-triazol-1-yl)propan-2-ol.

(x) The compounds as defined in claim 1 of EP-A-316 097, especially

(1) 1,1-dimethyl-8-(1H-1,2,4-triazol-1-ylmethyl)-2(1H)-naphtho[2,1-b]furanone,

(2) 1,2-dihydro1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-1-ylmethyl)naphtho[2,1-b]-furan-7-carbonitrile,

(3) 1,2-dihydro-1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-1-ylmethyl)naphtho[2,1-b]-furan-7-carboxamide,

(4) 1,2-dihydro-1,1-dimethyl-2-oxo-8-[di(1H-1,2,4-triazol-1-yl)methyl]naphtho[2,1-b]-furan-7-carbonitrile.

(y) The compounds of formula I as defined in EP-A-354 689, especially

(1) 4-[2-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)propyl]benzonitrile,

(2) 4-[1-(4-chlorobenzyl)-2-(1,2,4-triazol-1-yl)ethyl]benzonitrile,

(3) 4-[2-(1,2,4-triazol-1-yl)-1-(4-trifluoromethyl]benzyl)ethyl]benzonitrile,

(4) 4-[2-(1,2,4-triazol-1-yl)-1-(4-[trifluoromethoxy]benzyl)ethyl]benzonitrile .

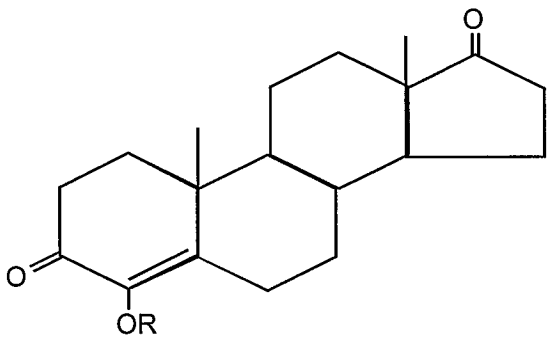
(z) The compounds of formula (1) as defined in EP-A-354 683, especially

(1) 6-[2-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)-propyl]nicotinonitrile,

(2) 4-[1-(1,2,4-triazol-1-yl-methyl)-2-(5-[trifluoromethyl]pyrid-2-yl)ethyl]benzonitrile.

Examples of steroidal aromatase inhibitors that may be mentioned are:

(aa) The compounds of formula I as defined in EP-A-181 287. These are especially the compounds of formula I



(I)

wherein R is hydrogen, acetyl, heptanoyl or benzoyl. An individual compound from that group that may be given special mention is:

(1) 4-hydroxy-4-androstene-3,17-dione.

(ab) The compounds as defined in the claims of U.S. Pat. No. 4,322,416, especially 10-(2-propynyl)-oestr-4-ene-3,17-dione.

(ac) The compounds as defined in the claims of DE-A-3 622 841, especially 6-methyleneandrosta-1,4-diene-3,17-dione.

(ad) The compounds as defined in the claims of GB-A-2 17 1100, especially 4-amino-androsta-1,4,6-triene-3,17-dione.

Also: (ae) androsta-1,4,6-triene-3,17-dione.

The content of the patent applications mentioned under (a) to (z) and (aa) to (ad), especially the subgroups of compounds disclosed therein and the individual compounds disclosed therein as examples, have been incorporated by reference into the disclosure of the present application.

The general terms used hereinbefore and hereinafter to define the compounds have the following meanings:

Organic radicals designated by the term "lower" contain up to and including 7, preferably up to and including 4, carbon atoms.

Acyl is especially lower alkanoyl.

Aryl is, for example, phenyl or 1- or 2-naphthyl, each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino or by halogen.

Pharmaceutically acceptable salts of the above-mentioned compounds are, for example, pharmaceutically acceptable acid addition salts or pharmaceutically acceptable metal or ammonium salts.

Pharmaceutically acceptable acid addition salts are especially those with suitable inorganic or organic acids, for example strong mineral acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or organic acids, especially aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, propionic, succinic, glycolic, lactic, hydroxysuccinic, tartaric, citric, maleic, fumaric, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, gluconic, nicotinic, methanesulfonic, ethanesulfonic, halobenzenesulfonic, p-toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; or with other acidic organic substances, for example ascorbic acid. Pharmaceutically acceptable salts may also be formed, for example, with amino acids, such as arginine or lysine.

Compounds containing acid groups, for example a free carboxy or sulfo group, can also form pharmaceutically acceptable metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, also ammonium salts derived from ammonia or suitable organic amines. Them come into consideration especially aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic primary, secondary or tertiary mono-, di- or poly-amines, such as lower alkylamines, for example di- or tri-ethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis(2-hydroxyethyl)amine or tris(2-hydroxyethyl)amine, basic aliphatic esters or carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, benzylamines, for example N,N'-dibenzylethylenediamine; also heterocyclic bases, for example of the pyridine type, for example pyridine, collidine or quinoline. If several acidic or basic groups are present, mono- or poly-salts can be formed. Compounds according to the invention having an acidic and a basic group may also be in the form of internal salts, i.e. in the form of zwitterions and another part of the molecule in the form of a normal salt.

In the case of the above-mentioned individual compounds the pharmaceutically acceptable salts are included in each case insofar as the individual compound is capable of salt formation.

The compounds listed, including the individual compounds mentioned, both in free form and in salt form, may also be in the form of hydrates, or their crystals may include, for example, the solvent used for crystallisation. The present invention relates also to all those forms.

Many of the above-mentioned compounds, including the individual compounds mentioned, contain at least one asymmetric carbon atom. They can therefore occur in the form of R- or S-enantiomers and as enantiomeric mixtures thereof, for example in the form of a racemate. The present invention relates to the use of all those forms and to the use of all further isomers, and of mixtures of at least 2 isomers, for example mixtures of diastereoisomers or enantiomers which can occur when there are one or more further asymmetric centres in the molecule. Also included are, for example, all geometric isomers,

for example cis- and trans-isomers, that can occur when the compounds contain one or more double bonds.

The doses required for the present invention depend entirely on the type of aromatase inhibitor that is used. Some inhibitors are more active than others and hence lower amounts of the former inhibitors could be used. The dosage levels do depend on the patient also.

Typically, the amount of aromatase inhibitor may be selected from amounts that lower estrogen levels to post-menopausal levels in a female. For example the amount of aromatase inhibitor may be selected from amounts that lower the level of estrogen to at or about 100 pmoles/litre or less as measured by standard immunoassay techniques.

The aromatase inhibitor is administered in a single dose in amounts preferably selected from amounts in the range of from at or about 5 mg to at or about 500 mg and the daily doses of follicle stimulating hormone range from at or about 25 to at or about 600 units or an equivalent dosage in another form of administration.

It may be said that the amount of aromatase inhibitor is selected from amounts that lower estrogen levels to post-menopausal levels in a female. For example, the amount of aromatase inhibitor may be selected from amounts that lower estrogen levels to about 100 pmol/L or less as measured by standard immunoassay techniques. Typically the aromatase inhibitor may be administered in a single dose selected from amounts comprising 10 mg, 20 mg, 25 mg or 30 mg.

Examples of preferred dosages for the single doses are when the aromatase inhibitor is letrozole the single dose administered is from at or about 5 mg to at or about 100 mg. When the AI is anastrozole, it may be administered in a single dose of from at or about 5 mg to at or about 50 mg. When the AI is vorozole, the single dose may be from at or about 10 mg to at or about 200 mg. Exemestane is preferably administered in a daily dose of from at or about 50 to at or about 500mg. Preferred is for administration of the single dose to be administered on any of days 1 to 5 of the menstrual cycle. The separate doses AI and FSH may be administered simultaneously, sequentially, separately, or consecutively, with or without a gap.

A "**POOR RESPONDER**" is considered to be a patient who fails to ovulate or who fails to develop an adequate number of pre-ovulatory ovarian follicles after at least one cycle of FSH alone or FSH plus LH at an average daily dose of up to the typical maximum doses, for example, 600 I.U. of F.S.H. for an assisted reproductive technology as described below.

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

Assisted reproductive technologies (ART) includes, for example, the following techniques:

***In vitro* fertilization (IVF)**, in which oocytes are aspirated from pre-ovulatory follicles, combined with sperm *in vitro* and viable embryos are selected and placed in the uterus.

Gamete Intrafallopian Transfer Procedure (GIFT), in which oocytes and sperm are combined in a catheter, and placed in the fallopian tube, so that conception occurs in the fallopian tube.

Zygote Intrafallopian Transfer Procedure (ZIFT), in which the collected oocytes are combined with sperm, and fertilized embryos are transferred to the fallopian tube.

Intracytoplasmic Sperm Injection (ICSI), in which each oocyte is directly injected with a single sperm via a microscopic needle, and viable embryos are selected for placement in the uterus or the fallopian tube.

Intrauterine insemination (IUI). Intrauterine insemination (IUI) is a fertility procedure in which motile sperm are washed, concentrated, and injected directly into a woman's uterus.

Therapeutic Donor insemination (TDI) involves the use of timed insemination of sperm from a donor rather than from the husband.

Controlled ovarian Hyperstimulation (COH) for timed intercourse, for IUI or for other ART procedures such as IVF encompasses the concept of deliberate and regulated induction of superovulation, but also refers to production of a hormonal response intended to lead to the production of multiple eggs in the woman's ovaries and to favor implantation of the embryo into the endometrium.

The female in need of treatment is a preferably a human being, but females of other species could benefit from the treatment of the invention and hence the invention encompasses such applications where applicable.

Pharmaceutical Formulations

The pharmaceutical compositions that can be prepared according to the invention are compositions for enteral, such as peroral or rectal administration, also for transdermal or sublingual administration, and for parenteral, for example intravenous, subcutaneous and intramuscular, administration. Suitable unit dose forms, especially for peroral and/or sublingual administration, for example dragees, tablets or capsules, comprise preferably from approximately 0.01 mg to approximately 20 mg, especially from approximately 0.1 mg to approximately 10 mg, of one of the above-mentioned compounds or of a pharmaceutically acceptable salt thereof, together with pharmaceutically acceptable carriers. The preferred form of administration is oral. The proportion of active ingredient in such pharmaceutical compositions may range from approximately 0.001% to approximately 60%, preferably from approximately 0.1% to approximately 20%.

Suitable excipients for pharmaceutical compositions for oral administration are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starches, for example corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or hydroxypropylcellulose, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate,

and/or cellulose, for example in the form of crystals, especially in the form of microcrystals, and/or flow regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, cellulose and/or polyethylene glycol.

Dragee cores can be provided with suitable, optionally enteric, coatings, there being used inter alia concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate.

Other orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers and/or anti-bacterial agents may also be added. There may also be used capsules that are easily bitten through, in order to achieve by means of the sublingual ingestion of the active ingredient that takes place as rapid an action as possible.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. There may also be used gelatin rectal capsules, which contain a combination of the active ingredient with a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable formulations for transdermal administration comprise the active ingredient together with a carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents that serve to facilitate the passage through the skin of the host. Transdermal systems are usually in the form of a bandage that comprises a support, a supply container containing the active ingredient, if necessary together with carriers, optionally a separating device that releases the active ingredient onto the skin of the host at a controlled and established rate over a relatively long period of time, and means for securing the system to the skin.

Suitable for parenteral administration are especially aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also suspensions of active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate, or triglycerides, or aqueous

injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, optionally, stabilisers.

Dyes or pigments may be added to the pharmaceutical compositions, especially to the tablets or dragee coatings, for example for identification purposes or to indicate different doses of active ingredient.

The pharmaceutical compositions of the present invention can be prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture, and processing the mixture or granules, if desired or necessary after the addition of suitable excipients, to form tablets or dragee cores.

The invention that is claimed is described in detail in the following Example, which is intended merely to illustrate the invention, and in no way to represent a limitation thereof.

EXAMPLE

Seven infertile patients (3 with PCOS and 4 with unexplained infertility) undergoing ovarian stimulation and cycle monitoring for intrauterine insemination, received letrozole as a single 20 mg dose on day 3 of the menstrual cycle for 9 treatment cycles. HCG 10,000 IU was given to trigger ovulation. Follicular development was monitored by transvaginal ultrasound and hormonal assays of estrogen and LH. Various parameters of the single dose treatment cycles have been compared with a historical control group which included 105-treatment cycles in which letrozole was administered in a dose of 2.5mg/day, from day 3 to 7 of the menstrual cycle.

Ovulation occurred in 8 out of the 9 single-dose treatment cycles and pregnancy was achieved in one patient. In the historical control group (33 PCOS patients underwent 42 treatment cycles and 51 patients with unexplained infertility underwent 63 cycles), ovulation rate was 83.7% in the PCOS group and pregnancy rate was 13.3 % (14% in the PCOS group and 12.7% in the unexplained infertility group). There was no significant difference in the various characteristics of the single dose treatment cycles from the 5-day treatment cycles of letrozole.

The aromatase inhibitor letrozole has been shown to be effective in stimulating ovarian follicular development. This is believed to be due to decreasing estrogen synthesis without having a direct anti-estrogenic effect, which leads to release of the estrogen negative feedback on the pituitary and/or hypothalamus resulting in an increase in gonadotropin secretion. Administering letrozole as a single dose on day three of the menstrual cycle has the advantage of allowing rapid clearance of the letrozole from the body due to its short half-life (around two days). This leads to negligible levels of letrozole in the body around the ovulation and early embryogenesis period. Besides the increased safety of the single dose administration, it is more convenient.

Table 1		
	Letrozole single-dose cycles	**Letrozole 5 days cycle**
Day of hCG administration	12.9 (2.9)	13.2 (2.5)
Endometrial thickness on hCG day (cm)	0.9 (0.11)	0.9 (0.2)
Follicles>1.5cm	2.29 (1.3)	1.9 (0.2)
Estradiol on hCG day (pmol/L)	831 (359)	919 (782)
Estradiol/mature follicle (pmol/L)	390 (74)	462 (257)
LH (IU/L)	19.1 (12.7)	18.2 (16.2)

While the invention has been described with particular reference to certain embodiments thereof, it will be understood that changes and modifications may be made by those of ordinary skill in the art within the scope and spirit of the following claims.

In the claims, the word "comprising" means "including the following elements (in the body), but not excluding others"; the phrase "consisting of" means "excluding more than traces of other than the recited ingredients"; and the phrase "consisting essentially of" means "excluding unspecified ingredients which materially affect the basic characteristics of the composition".

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CLAIMS

1. Use of an aromatase inhibitor selected form letrozole, anastrozole and vorozole for the preparation of a medicament for inducing ovulation in a female suffering from anovulatory infertility, wherein the medicament is for administration as a single dose of at least one aromatase inhibitor on any one of days 1 to 5 of the menstrual cycle, wherein the dose of the aromatase inhibitor is effective to reduce serum estradiol levels to post-menopausal levels.

2. Use of an aromatase inhibitor selected from letrozole, anastrozole and vorozole for the preparation of a medicament for augmenting ovulation in an ovulating female suffering from unexplained infertility or other types of ovulatory infertility, wherein the medicament is for administration to said female as a single dose of at least one aromatase inhibitor on any one of days 1 to 5 of one or more menstrual cycles, and wherein the dose of the aromatase inhibitor is effective to reduce serum estradiol levels to post-menopausal levels.

3. Use of claim 1, wherein the medicament is for use with follicle stimulating hormone (FSH).

4. Use of a single dose of an aromatase inhibitor selected from letrozole, anastrozole and vorozole for the preparation of a medicament for use with follicle stimulating hormone (FSH) in the treatment of a female for infertility, wherein the female is considered to be a poor responder to FSH, and wherein the medication is for administration as a single dose on any one of days 1 to 5 of the menstrual cycle, and wherein the dose of the aromatase inhibitor is effective to reduce serum estradiol levels to post-menopausal levels.

5. Use of any Claims 3-4, wherein the doses of the aromatase inhbitor and FSH are for simultaneous, separate or sequential administration.

6. Use of any of Claims 1-2, wherein the aromatase inhibitor is for administration in a single dose selected from amounts in the range of from at or about 5 mg to at or about 500 mg, preferably from amounts comprising 5 mg, 10 mg, 20 mg, 25 mg or 30 mg.

7. Use of any of Claims 1-3, wherein the aromatase inhibitor is

- letrozole and is for administration in a single dose of from at or about 5 mg to at or about 100 mg,
- anastrozole and is for administration in a single dose of from at or about 5 mg to at or about 100 mg, preferably from at or about 5 mg to at or about 50 mg, or
- vorozole and is for administration in a single dose of from at or about 10 mg to at or about 200 mg or from at or about 5 mg to at or about 100 mg.

8. Use of any of Claims 3-5, wherein the aromatase inhibitor is for administration in a dose selected from amounts in the range of from at or about 5 mg to at or about 500 mg, preferably from amounts comprising 5 mg, 10 mg, 20 mg, 25 mg or 30 mg, and wherein the daily doses of follicle stimulating hormone ranges from at or about 25 to at or about 600 units or an equivalent dosage in another form of administration.

9. Use of any of Claims 3-6 or 8, wherein the aromatase inhibitor is

- letrozole and is for administration in a single dose of from at or about 5 mg to at or about 100 mg,
- anastrozole and is for administration in a single dose of from at or about 5 mg to at or about 100 mg,
- vorozole and is for administration in a single dose of from at or about 10 mg to at or about 200 mg or from at or about 5 mg to at or about 100 mg,

and wherein the daily doses of follicle stimulating hormone ranges from at or about 25 to at or about 600 units or an equivalent dosage in another form of administration.

10. Use of any of Claims 1-9, wherein the aromatase inhibitor is for oral administration.

11. Use of any of Claims 1-10, wherein the amount of aromatase inhibitor is selected from amounts that lower estrogen levels to at or about 100 pmol/L or less as measured by standard immunoassay techniques.

12. The use of any of Claims 1-11, wherein the medicament is for administration on day 3 of the menstrual cycle.

13. A kit for treating infertility in a female comprising a single dose of an aromatase inhibitor selected form letrozole, anastrozole and vorozole together with a pharmaceutical acceptable carrier in combination with a plurality of daily doses of follicle stimulating hormone together with a pharmaceutically acceptable carrier, wherein the dose of the aromatase inhibitor is effective to reduce serum estradiol levels to post-menopausal levels.

14. A pharmaceutical package, comprising a single dose of an aromatase inhibitor selected from letrozole, anastrozole and vorozole, and instructions for its use in ovulation induction, wherein the dose of the aromatase inhibitor is effective to reduce serum estradiol levels to post-menopausal levels.

15. The pharmaceutical package of claim 14, further comprising a plurality of doses of FSH.

16. A pharmaceutical package according to claim 15, wherein the female patient is a poor responder to FSH.