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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Mohamed F.M. Robert F.	Mitwally Casper	Amherst, NY Toronto, Ontario, Canada

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max):

Use of Aromatase Inhibitors for Treatment of Ectopic Pregnancy

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ The address corresponding to Customer Number:

OR

☒ Firm or Individual Name ROHM & MONSANTO P.L.C

Address

12 Rathbone Place

City Grosse Pointe	State MI	Zip 48230
Country US	Telephone 313-886-1966	Fax 313-886-3130

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SIGNATURE Benita J. Rohm Date October 4, 2004

TYPED or PRINTED NAME Benita J. Rohm REGISTRATION NO. 28,664 *(if appropriate)*

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First Named Inventor	Mohamed F.M. Mitwally	Docket Number	RM. WSR

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Michael P.	Diamond	Grosse Pointe Shores, MI

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ATT'Y. DKT.	:	RM.WSR	)
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APPLICANT	:	Mohamed F.M. Mitwally, *et al.*	)
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I hereby certify that a Provisional Application Under 37 C.F.R. § 1.53(b)(2) in the names of inventor(s)Mohamed F.M. Mitwally, Robert F. Casper and Michael P. Diamond, including a Provisional Application Cover Sheet, Specification (63 pages); zero (0) sheets of drawings; and Form 2038 authorizing $80 to be charged to a credit card, are being deposited with the United States Postal Service under 37 C.F.R. § 1.10 as Express Mail Post Office to Addressee on the date indicated hereinabove and addressed to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Benita J. Rohm, Reg. No. 28,664
ROHM & MONSANTO, PLC
660 Woodward Avenue, Suite 1525
Detroit, MI 48226
(313) 965-1976

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Use Of Aromatase Inhibitors For Treatment Of Ectopic Pregnancy

by

Mohamed F.M. Mitwally, Robert F. Casper and Michael P. Diamond

Rohm & Monsanto, PLC
Attorneys at Law
660 WOODWARD AVENUE, SUITE 1525
DETROIT, MI 48226

TELEPHONE (313) 965-1976
TELECOPIER (313) 965-1951

Use of Aromatase Inhibitors for the Treatment of Ectopic Pregnancy

Field of the Invention

This invention relates to a method for medical treatment of ectopic pregnancy (pregnancy outside the normal intrauterine implantation site) in females. The invention involves administration of an aromatase inhibitor (AI) after ectopic pregnancy is diagnosed. Also disclosed are preparations and related uses.

Background of the Invention

Ectopic pregnancy is a major cause of maternal morbidity and mortality with increasing incidence worldwide (1-3). In the United States, the annual incidence of ectopic pregnancy has increased more than five times, from 0.37% of pregnancies in 1948 to 1.97% in 1992. Despite the continued rise in incidence, there was almost a 90% decline in the rate of death from ectopic pregnancy from 1979 to 1992 (4). However, ectopic pregnancy is still responsible for a significant proportion of maternal mortality as the third most common cause of maternal mortality in the United States, comprising about 9% of all such deaths (1).

Lawson Tait, (5) the father of gynecologic surgery, reported the first successful operation for ectopic pregnancy before the turn of this century. Until a little more than decade ago, little change had occurred in the diagnosis and management of ectopic pregnancy. The clinical use of sensitive pregnancy testing, ultrasonography, and diagnostic laparoscopy has had a major impact on the early diagnosis of this condition. The rate of ectopic rupture has declined, and the option of conservative surgical management of an unruptured fallopian tube is now a viable alternative.

1. Epidemiology of ectopic pregnancy:

Two entities must be differentiated in ectopic pregnancy epidemiology: ectopic pregnancy occurring in women without contraception (reproductive failure) and with contraception (contraceptive failure). These two entities differ on almost all issues. At the present time, the incidence of ectopic pregnancy with contraception goes on decreasing while the incidence of ectopic pregnancy without contraception is increasing (6).

The reported incidence of ectopic gestation in the United States increased from a total of 17,800 cases in 1970 to 70,000 cases in 1984 (7). In 1987, approximately 88,000 women were hospitalized in the United States for ectopic pregnancy, an increase of 19% over the number reported for 1986(8). Whether the higher reported incidence reflects a true

increase in the prevalence of the disease or is secondary to improved diagnostic techniques is unknown. Both factors probably play a role (9).

Of all ectopic pregnancies, 97% occur in the fallopian tube (tubal), 2.5% in the uterine cornu, and the remaining pregnancies occur in various other locations including the cervix, abdomen, and ovary. The majority of tubal pregnancies are located in the ampullary portion of the tube. Coexistence of an intrauterine and a tubal pregnancy (heterotopic) was initially reported to occur in 1:30,000 ectopic pregnancies, and the occurrence of bilateral ectopic pregnancy is even less frequent (10-12). With the increased use of ovulation induction, the reported incidence of heterotopic pregnancy has increased (13, 14).

1.1 Factors associated with increased ectopic pregnancy:
Several factors have been implicated in the increased incidence of ectopic gestation include pelvic inflammatory disease, complications of infections, the wide clinical use of reconstructive tubal surgery, widespread use of intrauterine devices, and the conservative surgical treatment of ectopic pregnancy itself (15-20).

The most important risk factor for ectopic pregnancy is a history of a previous ectopic gestation. This event confers a 10-fold increase in the likelihood of another ectopic pregnancy (121, 22). Ectopic pregnancy occurs in as many as 10% of recipients of embryo transfer during *in vitro* fertilization (23). Indeed, the first pregnancy reported in humans with this technique was an ectopic pregnancy (24). However, recently this incidence decreased significantly due to the increased application of assisted reproduction for non-tubal infertility indications as well as the increased tendency towards removal of diseased tubes before assisted reproduction cycles.

1.2 Mortality:
Despite the increased frequency of ectopic pregnancy, the case mortality rate has declined from 3.5 deaths per 1000 ectopic pregnancies in 1970 to 0.4 deaths per 1000 ectopic pregnancies in 1985. Although ectopic pregnancies accounted for only 1.5% of the total gestations in 1984 and 1985, they accounted for 14% of maternal deaths in 1984 and 11% in 1985 (25).
Ectopic pregnancy confers a greater risk of maternal mortality than either childbirth or legal abortion. This risk was found to be 50 times more likely to result in a maternal death than a first-trimester abortion and 10 times more likely than delivery in the third trimester (26).

The most frequent direct causes of death are hemorrhage, infection, and anesthetic complications. Of women dying from hemorrhage, 70% did not undergo surgery. In 50% of women, the condition was misdiagnosed or confused with other pathology. The site of implantation was also important, as interstitial and nontubal ectopic pregnancies account for only 5% to 10% of all ectopic pregnancies, but for 20% of all fatalities (27).

1.3 Economic impact of ectopic pregnancy

The costs associated with ectopic pregnancy were estimated to surpass $1 billion in 1990 in the United States (28). Efforts toward reducing morbidity and costs have rapidly changed the standard of care for surgically managed ectopic pregnancy from laparotomy to laparoscopy. A major driving force behind this change has been recent studies indicating a substantial cost reduction with laparoscopy.

Cost of Medical Versus Surgical Management

Laparoscopic salpingostomy, although well accepted as treatment for small-unruptured ectopic pregnancies, is associated with high costs related to operating room expense, anesthesia services, and surgeons' fees. Data on the medical management of ectopic pregnancy with methotrexate suggest that the efficacy of such an approach is equivalent to that of laparoscopic salpingostomy (29, 30). Assuming that both treatment strategies would result in identical clinical outcomes, Alexander and colleagues compared costs of methotrexate and laparoscopy in the treatment of ectopic pregnancy. Diagnostic costs were considered identical. Success rates for single-injection methotrexate ranged from 58% to 91% (31). Retreatment with additional methotrexate doses increased the overall nonsurgical success rate to 72% to 94%. Thus, 6% to 28% of patients initially treated with methotrexate ultimately require surgery to achieve resolution of ectopic pregnancy. For laparoscopic salpingostomy, the average initial success rate from 17 series with a total of 976 patients is 94.5% (range, 83% to 100%) (31, 32). Thus, up to 17% of patients require retreatment for persistent ectopic pregnancy, pain, or bleeding. When preservation of fertility is not an issue, salpingectomy can be performed, with initial cure rates approaching 100%. Using best-case and worst-case comparisons, Alexander and colleagues (31) demonstrated over a wide range of performance estimates that the initial use of methotrexate as opposed to laparoscopic salpingostomy would result in a substantial cost savings ($1124 to $2536 per patient) in the management of the small unruptured ectopic pregnancy. Based on an annual ectopic pregnancy rate of 88,000 and an estimate that 45% of all patients with ectopic pregnancy are eligible for initial treatment with methotrexate, (32) a potential annual direct cost savings of $43 to $97 million could be achieved when methotrexate is used as initial therapy in appropriate cases. Other authorities have estimated even greater annual savings (34).

2. Diagnosis:

Patients clinically suspected of having ectopic pregnancy fall into two major categories: those who have an acute abdomen and in whom immediate surgery is indicated, and those who are clinically stable and in whom adjunctive diagnostic procedures can be performed. Schermers (35) reviewed the symptoms in 3970 ectopic pregnancies reported in the literature and found pain to be the most common presenting symptom, occurring in 96.3% of the patients followed by irregular bleeding, occurring in 74.1% of the patients. Other symptoms included shoulder pain, gastrointestinal symptoms, and syncope. Adnexal tenderness has been reported as the second most common sign, occurring in 85% to 95% of patients. The irregular vaginal bleeding might not be a result only of a

breakdown of the endometrium, but of blood flowing from the fallopian tube into the uterine cavity and out the cervical os as well.

2.1 Current role of Culdocentesis:

Patients with a surgical abdomen are evaluated in the emergency room with rapid urine pregnancy tests and a culdocentesis. A positive culdocentesis in a patient with a positive pregnancy test result has been reported to correspond with ectopic pregnancy in 99.2% of cases (36). The results of a culdocentesis can be classified as negative, positive, or nondiagnostic. A negative culdocentesis is indicated by the presence of clear fluid. A positive result refers to the free flow of nonclotting blood. If no fluid is obtained, the test is considered nondiagnostic. When bloody fluid is obtained, a hematocrit of the aspirate is helpful. Ectopic pregnancies are generally associated with hematocrits of more than 15%. Lower hematocrits frequently indicate the presence of cystic fluid. Traditionally, culdocentesis was considered useful in the detection of a hemoperitoneum associated with a ruptured ectopic pregnancy. Romero, *et al.*, found ectopic pregnancy in 86% of all positive culdocentesis performed in the emergency room (36). Other causes of positive culdocentesis included ruptured ovarian cysts, retrograde menstruation, endometriosis, torsion of the fallopian tube, and bleeding of unknown etiology. It should be emphasized that a nondiagnostic culdocentesis should not lower the suspicion of an ectopic pregnancy. This is because in up to 16% of ectopic pregnancies cases culdocentesis was non-diagnostic and one quarter of these were ruptured at the time of operation. The authors suggested that patients who will benefit most from a culdocentesis are those in whom a clinical suspicion of ectopic pregnancy exists, and who present at a time when expeditious diagnosis is desired and when sophisticated diagnostic modalities, such as ultrasonography and sensitive human chorionic gonadotropin (hCG) assays, cannot be obtained without significant delay. Under these circumstances, culdocentesis is an inexpensive, rapid, and easily performed means of patient evaluation that often provides the impetus for immediate intervention. In clinically stable patients, a culdocentesis may be indicated when fluid is visualized in the cul-de-sac at the time of ultrasound examination of the pelvis. A positive culdocentesis dictates the need for a surgical diagnosis. The procedure should not be overlooked in patients without signs of peritoneal irritation, as up to 45% of patients with a positive culdocentesis did not have rebound tenderness (36).

The modern approach to the evaluation of clinically stable patients suspected of having an ectopic pregnancy is based on the combined use of sensitive pregnancy testing (or hCG testing), ultrasound examination, and laparoscopy. The hCG test is used to screen for pregnancy, and ultrasonography is employed to locate it (37).

2.2 Ultrasonography and Beta hCG assay:

Beta hCG levels and gestational sac visualization:
It has been established that the sac of a normal intrauterine pregnancy becomes visible with abdominal ultrasonography when the hCG titer is greater than 6500 mIU/mL. When levels are higher than this, the absence of a sac is associated with an ectopic pregnancy in 86% of cases. This criterion has a sensitivity of 100%, a specificity of 96%, and a negative predictive value of 100%. The clinical application of this criterion includes the fact that approximately 40% of women with an ectopic pregnancy possess titers in excess of 6500 mIU/mL (36). The absence of a sac at levels less than 6000 mIU/mL is a nondiagnostic finding and should not lower or raise the suspicion of ectopic pregnancy (38, 39). In 1974, the World Health Organization introduced a new standard that involved the use of a more highly purified preparation of hCG and subsequently established the International Reference Preparation (IRP). A decade earlier, the second International Standard had been introduced, but because of heterogeneity, it was often unsuitable for use in many immunoassays (40, 41). In comparing the two quantitative standards, clinicians should note that the serum hCG titers determined by the IRP approximately double the value calculated by the second International Standard. The hCG values stated in this review are based on the IRP standard unless otherwise specifically noted.

Pseudogestational sac:
Ectopic pregnancies can show a single-ring sac due to the presence of blood within the endometrial cavity in association with a significant decidual reaction. This appearance has been shown to occur in 10% to 20% of all cases (42-48). Nyberg and colleagues (49) and Bradley and associates have proposed morphologic criteria to distinguish the pseudogestational sac of ectopic pregnancy from the gestational sac of a normal intrauterine pregnancy. They have described the normal intrauterine gestational sac as having a double contour produced by the decidua capsularis and the decidua parietalis. The pseudogestational sac of an ectopic pregnancy has only a single ring. The researchers have reported that 98.3% of all patients with a double-ring sac had an intrauterine pregnancy and 64 of 68 patients with a single-ring sac had ectopic pregnancies.

Transvaginal ultrasonography:
Vaginal scanning has proved to be more accurate than abdominal scanning in detecting ectopic pregnancies (90% vs. 80%) and cul-de-sac fluid (77% vs. 46%) and in discerning whether the tubal pregnancy has ruptured (76% vs. 50%)(50). In the transvaginal ultrasonographic evaluation of pregnancy, Bernaschek and associates (51), using a 5-MHz transducer, proposed a "discriminatory zone" of an hCG titer of 750 mIU/mL (second International Standard) for the detection of an intrauterine gestational sac. Unfortunately, using this proposed criterion and similar ultrasonographic equipment, Fossum and associates (52) may have inadvertently surgically investigated several pregnancies that proved to be normal intrauterine gestations. If an hCG titer exceeds

2000 mIU/mL, we now expect to detect an intrauterine gestational sac using transvaginal ultrasonography.

Serial hCG measurement:
Even with the advent of transvaginal ultrasonography, the value of serial hCG determinations cannot be overemphasized. If hCG titers increase with time, it can be used to evaluate the normality of the increase. As a rule of thumb, the hCG titer should increase by at least 66% of the initial titer in a 48-hour period of observation (53). On the other hand, in asymptomatic women, declining hCG levels may be indicative of a nonviable, nondetectable intrauterine gestation. Serum progesterone values may prove a useful adjunct to hCG titers in distinguishing a viable intrauterine pregnancy from that of an ectopic or missed abortion. Accordingly, in two separate reports on 99 women, a progesterone value less than 15 ng/mL was always predictive either of an ectopic pregnancy or a nonviable intrauterine gestation (54). It should be emphasized that early intrauterine pregnancy failures may not have enough tissue to be detectable by routine pathologic examination, and therefore some patients with declining hCG titers will ultimately prove to have intrauterine pregnancy failures.

D&C:
The role of dilation and curettage (D&C) in the diagnosis of ectopic pregnancy has been abandoned by many authorities. Historically, when serum progesterone levels were lower than 5 ng/mL, or when the patient had abnormally rising serum hCG titers and no intrauterine pregnancy noted on transvaginal ultrasound, a D&C was performed to rule out the presence of villi. Because no villi were obtained in any patient with hCG titers greater than 2000 mIU/mL and an empty uterus or cardiac activity was seen in the adnexa by ultrasound, Stovall and colleagues no longer perform a D&C for diagnostic purposes in these patients and instead proceed directly to treatment (55).

3. Currently Available Treatments for Ectopic pregnancy:

Conservative surgical treatment of ectopic pregnancy is well established, and laparoscopic surgery seems to be feasible even in poor surgical candidates including morbidly obese patients (56). Laparoscopic salpingostomy is the preferred operative method in unruptured cases. Nonsurgical therapy for ectopic pregnancy, however, may prevent undesired postoperative adhesions that often result from surgical manipulation of the fallopian tubes (57).

3.1 Surgical management:

The ultimate decision regarding surgical management depends on a patient's desire for future fertility. If a patient is not interested in future fertility, the appropriate surgical procedure is salpingectomy. If a patient does desire future fertility, however, much data from the past few years support performing conservative surgery in a majority of these cases. One must always keep in mind and also inform the patient, though, that whatever procedure is performed, the pregnancy rate after an ectopic pregnancy is decreased by

40% to 70%. Conservative surgical options range from expression of a tubal abortion through the distal end of the tube to segmental resection and secondary anastomosis of an isthmic ectopic pregnancy (58).

Adjunctive therapy

The therapy used is the same as with reproductive surgery for chronic tubal disease. It includes prophylactic antibiotics; such as doxycycline 100 mg twice a day, and 200 mL of Hyskon hysteroscopy fluid (32% w/v dextran 70 in dextrose) instilled into the abdominal cavity either through the laparoscopic port or at the time the laparotomy incision is closed to prevent adhesion formation. Rh-negative patients should receive Rh_0 (D) immune globulin (RhoGAM) (59). Postoperatively, patients should be followed with a hysterosalpingogram 4 months after surgery and laparoscopy 1 year after surgery if pregnancy has not occurred (9).

Persistent ectopic pregnancy

To identify persistent ectopic pregnancy, all patients who undergo linear salpingostomy should be followed at least weekly by quantitative serum hCG levels until nonpregnant levels are attained. Residual trophoblastic tissue may continue to proliferate and lead to life-threatening hemorrhage resulting from tubal rupture (60, 61). The diagnosis of persistent ectopic pregnancy is made when serum hCG levels rise or decline by less than 20% between two consecutive measurements taken 3 days apart (62). If serum hCG levels continue to rise, however, three treatment options are available:

An additional conservative procedure may be considered, but there is a strong possibility that the remaining trophoblastic tissue will be extraluminal and a second operation may again be ineffective in removing all of the trophoblastic tissue.

A salpingectomy may be performed, but the potential fertility-sparing effects of the first procedure will be lost.

Systemic methotrexate is effective in treating persistent trophoblastic tissue and, despite the absence of large series confirming its efficacy; it may represent the best clinical option (9).

Adjuvant Methotrexate Therapy

Graczykowski and Mishell reported on a nonblinded randomized controlled series on the use of adjuvant methotrexate therapy in 116 patients undergoing conservative treatment of an unruptured ectopic pregnancy. The patients in the treatment arm received 1 mg/kg of methotrexate by intramuscular injection within 24 hours of the operative procedure. One of 54 patients (1.9%) in the methotrexate prophylaxis group and 9 of 62 (14.5%) in the control group had persistent ectopic pregnancies. The results were statistically significant ($P < 0.05$). The relative risk of developing persistent ectopic pregnancy after prophylactic methotrexate was 0.13 (95% confidence interval: 0.02 to 0.97). Three patients in the prophylaxis group reported side effects; one complained of mild stomatitis and two of mild gastroenteritis lasting 1 to 2 days. In all three, the side effects resolved spontaneously and did not require medical intervention. Patients undergoing

salpingectomy rarely have persistent trophoblastic activity. Routine postoperative measurement of serum hCG levels is not required (63).

Rh Factor

All Rh-negative, unsensitized women with ectopic pregnancies should receive Rh immunoglobulin at a dose of 50 μg if the gestation is of less than 12 weeks' duration and 300 μg otherwise. However, Grimes and associates (64) reported that, because hospitalization typically is unscheduled and not preceded by Rh screening, most Rh-negative women with ectopic pregnancies in the United States do not receive Rh(D) immunoglobulin. The magnitude of the risk of sensitization is unknown but is estimated to vary from no risk at one month to about 9% at three months' gestation. Because of the potential benefits and lack of risk, administration of Rh immunoglobulin should be undertaken in all Rh-negative unsensitized women with ectopic pregnancy (65).

3.2 Non-operative management:

Nonoperative management can be divided into observation/expectant care and medical therapy.

3.2.1 Observation

Some patients with ectopic pregnancies undergo spontaneous absorption and require no therapy (66). In 1955, Lund (67) reported on 119 women with unruptured tubal pregnancies who were treated with bed rest and frequent observation. Of these 119 patients, 68 (57%) were eventually discharged from the hospital without operation, but 60% required hospitalization for more than 1 month. The remainder required operative intervention for tubal rupture or worsening clinical course. More recently, several investigators have reported their experience with expectant management of unruptured ectopic pregnancy. In Maymon's (68) review of 8 series of patients (total of 81 patients) managed expectantly, 76% resolved spontaneously, 23% required laparotomy for rupture, and 79% demonstrated ipsilateral tubal patency on follow-up hysterosalpingogram. Whether a rigid and expensive hospital protocol that includes serial ultrasound examinations and hCG measurements results in better subsequent pregnancy rates than removing the ectopic pregnancy by salpingostomy at first laparoscopy has not been studied yet. At present, the consensus is that it is better to remove an unruptured ectopic pregnancy at the time of first laparoscopy to avoid the additional expense of hospitalization, serial hCG assays, and a second laparoscopy (69).
At this time, expectant management should be considered an option only for patients with extreme surgical risk, falling hCG titers, or in a research setting (9).

3.2.2 Medical treatment:

Nonsurgical therapy for ectopic pregnancy may prevent the undesired postoperative adhesions that often result from surgical manipulation of the fallopian tubes. The use of drug therapy for ectopic pregnancy was first reported in 1982, in a patient with an interstitial pregnancy who refused surgery (70). Since then, many investigators have

reported the successful treatment of selected patients using a variety of agents, including parenteral methotrexate, intratubal or intra-amniotic methotrexate, and intratubal osmotic agents (71-75). Observational studies in the mid-1980s used, with varying success, methotrexate, prostaglandins, dactinomycin, etoposide, hyperosmolar glucose, anti-hCG antibodies, potassium chloride, and mifepristone (RU 486) (76). Although treatments given systemically have proved practical, several of these agents also have been injected locally into the ectopic gestational sac under laparoscopic or ultrasound guidance or by hysteroscopic intratubal cannulation. However, to date, there have not been a significant number of reports of successful treatment of ectopic pregnancy using mifepristone (RU-486)(9), At this time, parenteral methotrexate seems to be the best-studied and most accepted agent for the medical treatment of ectopic pregnancy. Although surgical therapy will for now remain the mainstay of treatment for ectopic pregnancy, current evidence would support a shift toward treating carefully selected patients medically (77).

Criteria for surgical versus medical treatment:
Although operative laparoscopy is associated with substantially fewer complications than laparotomy, there remains an irreducible minimal degree of morbidity intrinsic to surgery and anesthesia. Although not yet standard treatment in many centers, medical therapy can greatly reduce this morbidity, and consequently there is increasing interest in its use. To supplant surgery, however, medical therapies must match the success rates, low complication rates, and subsequent reproductive potential achieved with laparoscopic operations. This appears to have happened (76).

With reliable early nonoperative diagnosis, choices for treatment include expectant, medical, or operative management. Factors influencing which choice to pursue depend on issues such as medical benefit, surgeon expertise, minimization of morbidity, costs for services, patient desire for future fertility, and efficacy rates for each approach (9).
In their recent meta-analysis, Canis, *et al.*, concluded that ectopic pregnancy treatment should be performed surgically if the patient is hemodynamically unstable. They also suggested that in cases when beta hCG is >10,000 mUI/mL, the ectopic pregnancy is > or = 4 cm in diameter, presence of a medical contraindication to methotrexate, and if the patient may not be followed adequately after treatment, surgical treatment should be done. Medical treatment should be preferred if the patient has undergone surgery many times previously, has extensive pelvic adhesion, a contraindication for general anesthesia, a cornual pregnancy, and after failure of a conservative laparoscopic treatment. Medical treatment is possible: if beta hCG is below 5,000 or 10,000 mUI/mL, if the ectopic pregnancy is less than 4 cm in diameter (78). Methotrexate is contraindicated in patients who are hemodynamically unstable and in those who have severe anemia, renal insufficiency, active liver disease, leukemia, bone marrow abnormalities, or allergy to methotrexate. Patients with white blood cell counts of less than 4000/mL, hematocrit less than 26%, bilirubin greater than 1.2 mg/dL, aspartate aminotransferase or alanine aminotransferase greater than 70 IU/dL, and serum creatinine levels of 1.4 mg/dL or greater should be excluded from such management (9).

Methotrexate

Methotrexate, a folic acid antagonist, inhibits dihydrofolate reductase, an enzyme necessary for nucleic acid synthesis, and thereby interferes with DNA synthesis and cell multiplication in actively dividing tissue. The efficacy of methotrexate in the treatment of gestational trophoblastic disease made it an attractive candidate for chemotherapeutic use in ectopic pregnancy. Patients treated with methotrexate should be counseled to refrain from alcohol consumption and intercourse and to avoid use of vitamin preparations containing folic acid until complete resolution of the ectopic pregnancy (9).

Systemic Methotrexate

The efficacy of methotrexate in the treatment of unruptured ectopic pregnancy using multiple-dose regimens had been well documented (79-81). In 1989, Stovall and associates (82) reported on the use of an individualized, multidose regimen in which 1 mg/kg of methotrexate was given intramuscularly on alternating days, with 0.1 mg/kg of leucovorin given on the intervening days until the β-hCG level had dropped by at least 15% in 48 hours or until four doses of methotrexate had been given. Using this regimen, 15% to 20% of patients required only a single methotrexate dose. In 1991, Stovall and colleagues reported on the efficacy of single-dose methotrexate in the treatment of ectopic pregnancy. Of 30 hemodynamically stable patients diagnosed with an unruptured ectopic pregnancy less than 3.5 cm in greatest dimension who desired future fertility, 29 (96.7%) were successfully treated with a single dose of methotrexate (50 mg/m^2 given intramuscularly) without leucovorin rescue. Mean time to resolution of ectopic pregnancy was 36 days. No patient experienced any chemotherapeutic side effects. Six of 30 (20%) reported an increase in lower abdominal pain between days 5 and 10, and 2 required hospitalization overnight for observation. Five of 6 (83%) ectopic pregnancies with cardiac activity were successfully treated with this protocol. The one treatment failure, a patient whose ectopic pregnancy had cardiac activity, required surgical intervention on day 6 because of tubal rupture. Cardiac activity can be identified much earlier in ectopic gestation because of recent advances in transvaginal ultrasonography; hence, the finding of adnexal cardiac activity is now considered a relative contraindication to medical therapy. Caution should be exercised when medically managing ectopic pregnancies with cardiac activity.

Methotrexate by Direct Injection

The advantages cited for the direct instillation of methotrexate, laparoscopically or transvaginally under ultrasound guidance, include higher local drug concentrations, less systemic distribution, a smaller therapeutic dose, and less toxicity. Despite the theoretical advantages of direct injection of methotrexate, success rates in practice appear unacceptably low, whereas other outcomes (tubal patency and subsequent fertility) are similar to those seen with systemic methotrexate (76).

Methotrexate by Tubal Cannulation

In a multicenter trial, Risquez and colleagues (83) reported resolution of 27 of 31 cases by the instillation of methotrexate using hysteroscopically directed tubal cannulation. The remaining four patients ultimately required surgery. Although encouraging, this approach appears to have no major advantage over other methods, except that methotrexate can be instilled into very small ectopic sacs without actually visualizing them.

Prostaglandins by direct injection

Prostaglandins cause strong tubal muscular contractions and local vasoconstriction. In 1987, Lindblom and associates (84) reported treating nine women with small unruptured tubal pregnancies with 0.5 to 1.5 mg of prostaglandin $F_{2\alpha}$ injected into the affected tube and corpus luteum. The preliminary experience was promising, but a larger study later failed to confirm the results. Moreover, cardiac arrhythmia, cardiopulmonary edema, and gastrointestinal symptoms have been reported after intratubal injection of prostaglandin (85).

Fertility after ectopic pregnancy treatment:

Conservative treatment can be carried out without lowering the chance of a subsequent intrauterine pregnancy or raising the incidence of an extrauterine pregnancy. DeCherney and Oelsner (86) reviewed 1630 cases treated radically and found a 41% intrauterine pregnancy rate and a 14% repeat extrauterine pregnancy rate. It is hoped that over time, with the use of modern microsurgical techniques, the intrauterine pregnancy rate will increase and the repeat ectopic pregnancy rate will decrease in these patients. Based on the similar findings in radically and conservatively treated patients, an important question is whether salpingostomy works at all. This begs the question that perhaps those patients who conceive are using the tube that was not operated on. This possibility has been reviewed, and the intrauterine pregnancy rate and the repeat ectopic pregnancy rate seem to be the same in patients who had salpingostomies performed on only one fallopian tube with an ectopic pregnancy for both the group receiving radical treatment and the group receiving conservative treatment (87). These statistics do not hold, however, for patients who have had two or more ectopic pregnancies. In these patients, the incidence of repeat ectopic pregnancy approximates that of a subsequent intrauterine gestation. An unanswered question at this point remains: How many conservative procedures for an ectopic pregnancy can a patient undergo before her reproductive future is compromised to the point where *in vitro* fertilization is the only viable alternative? (88, 89)

Although fewer data are available on methotrexate use, reported outcomes are similar, with a tubal patency rate of 81% and a pregnancy rate of 70%, but with a repeat ectopic pregnancy rate of 11%, less than that seen with laparoscopy (90, 91).

Repeat Ectopic Pregnancy

The rate of repeat ectopic pregnancy after a single ectopic pregnancy ranges from 8% to 20%, with a mean of 15%. Only about one of three nulliparous women who have an

ectopic pregnancy ever conceives again (35%), and about one third have another ectopic pregnancy (13%). After two ectopic pregnancies, infertility rates as high as 90% have been reported (92). In 1987, DeCherney and Diamond (93) reported on a series of 79 patients with ampullary tubal ectopic pregnancies managed with laparoscopic linear salpingostomy. Follow-up revealed that, of 69 patients actively trying to conceive, 43 (62%) conceived. Seven (16%) of these were repeat ectopic pregnancies—four contralateral and three ipsilateral to the previous ectopic pregnancy. Ten (23%) of 43 patients aborted. The viable pregnancy rate was 38% (26 of 69), comparable to that seen after other techniques.

4. Problems associated with methotrexate therapy

The availability of newer and more sophisticated diagnostic tools allows ectopic pregnancy to be diagnosed early, before tubal rupture, without the use of laparoscopy. The subsequent use of methotrexate therapy in selected women offers a nonsurgical approach to the treatment of ectopic pregnancy. Increasing knowledge of the natural history of ectopic pregnancy after methotrexate therapy has facilitated the identification of both appropriate candidates for nonsurgical therapy and the potential complications of therapy. However there are several problems associated with methotrexate therapy including: serious side effects, contraindications in certain medical conditions, high failure rates when beta hCG and progesterone levels are high (>10,000 IU/ml) and most notably, the significantly long period to resolution with the occasional need for repeat administration of methotrexate that count for most of the cost of medical treatment due to the long follow up.

4.1 Side effects and contraindications for Methotrexate Therapy

Systemic methotrexate therapy is contraindicated in patients who are hemodynamically unstable or have signs of bone marrow depression or liver or renal dysfunction, as evidenced by leukopenia and/or thrombocytopenia, elevated liver enzymes, or elevated serum creatinine, respectively. After methotrexate therapy, abdominal pain commonly increases, presumably as a result of either tubal abortion or stretching of the tube by hematomas (94). The pain is generally self-limiting and usually controlled with orally administered nonsteroidal anti-inflammatory drugs. If such drugs do not relieve the pain, reevaluation is indicated for possible need for surgical therapy is necessary (94).

In a study of 258 consecutive women with ectopic pregnancies who were treated with single-dose methotrexate, women with severe pain who were hemodynamically stable were admitted and observed with serial measurement of the hematocrit and selective transvaginal ultrasonography (94). Twenty-seven of 34 patients (79%) who were hospitalized for severe, unremitting pain did not require surgery.

After treatment with methotrexate, up to 56 percent of ectopic gestational masses that are monitored ultrasonographically increase in size (95). Although masses of 7 to 8 cm have been noted, most of the women with masses of this size are asymptomatic. These masses

may persist after serum chorionic gonadotropin levels have decreased to less than 15 mIU per milliliter; with long time to resolution up to 108 days (95).

4.2 Increased failure rates with methotrexate treatment associated with high beta hCG and progesterone:

Women most likely to respond to methotrexate therapy are thought to be those with small gestational sacs, lower serum concentrations of hCG and progesterone, and the absence of blood in the peritoneal cavity and fetal heart activity. However, a retrospective review of 360 consecutive cases of ectopic pregnancies treated with methotrexate revealed that neither the size of the gestation nor the presence of hemoperitoneum had any effect on the success rate. But high serum levels of serum chorionic gonadotropin (>10,000 IU/l) or progesterone (≥10 ng/ml) and the presence of fetal cardiac activity were associated with higher rates of failure of methotrexate therapy. The single most important factor associated with failure of treatment with a single-dose methotrexate protocol was high serum concentration of human chorionic gonadotropin (96).

4.3 Significantly long interval to resolution associated with methotrexate therapy:

Methotrexate treatment is associated with a long interval until resolution (more than three weeks in most of the patients). Moreover, in almost up to a quarter of patients, a second dose of methotrexate was required (97-106).

In addition to the obvious impact on the cost of treatment, prolonged follow up period associated with methotrexate treatment is results in several negative effects on the patients' quality of life. +In a multicenter, randomized clinical trial conducted in the Netherlands, Nieuwkerk, *et al.* found that patients treated with systemic methotrexate had more limitations in physical functioning, role functioning, and social functioning. They also had worse health perceptions, less energy, more pain, more physical symptoms, and a worse overall quality of life; furthermore, they were more depressed than surgically treated patients. This persistently more negative impact on patients' health-related quality of life may be explained by both the long-term persistence of the ectopic pregnancy and the prolonged treatment associated with the medical therapy (107).

From the above-mentioned data, it seems that there might be a room for improving medical treatment of ectopic pregnancy. Recently, Rozenberg, *et al.* (108), suggested that improving the efficacy of medical management can prevent potentially serious events such as tubal rupture through two different strategies: first by restricting medical treatment to the least developed ectopic pregnancies as reflected by low serum β-hCG and progesterone levels. The second strategy is to increase the efficacy of methotrexate by medical treatment with another drug. The authors suggested that a potential candidate would be mifepristone. However, although in a non-randomized phase II study (109), the failure rate was significantly more reduced in patients treated with mifepristone and methotrexate than in patients previously treated by methotrexate alone and in a randomized controlled trial (110), unruptured ectopic pregnancy appeared to resolve

significantly faster with the combination of methotrexate and mifepristone when compared to methotrexate alone, as assessed by the interval to resolution of β-hCG levels, the authors did not find supporting results in their most recent multicenter randomized clinical trial. Rozenberg, *et al.* found no significant difference in the success rate of medical treatment between the methotrexate–mifepristone (n = 113) and the methotrexate–placebo group (n = 99): 79.6% (90/113) versus 74.2% (72/97) respectively, RR (95% CI): 1.07 (0.92–1.25), P = 0.41, non-significant. The authors concluded that their study failed to demonstrate any benefit of the addition of mifepristone to methotrexate.

However, there remains a need for a medication that can add to the efficacy of methotrexate treatment of ectopic pregnancy by increasing the success rate, especially in patients with initial high beta hCG and progesterone levels, and that can shorten the interval to recovery, which would reduce the cost of treatment and improve the quality of life of the patients.

5. Role of estrogen in establishing and maintaining early pregnancy

In the following section, we will discuss the role of estrogen in the establishment and maintenance of early pregnancy. Although most of the data come from studies involving intrauterine pregnancy, extrapolation of these data towards ectopic pregnancy seems appropriate. This is supported by the available data on placentation in ectopic pregnancy (111), as well as recent data on steroidogenesis in ectopic pregnancy (112) and apopotosis in extravillous trophoblast cells (113). These data provide strong evidence for similarities between intra and extrauterine pregnancy as regards steroidogenesis and comparable roles for estrogen and progesterone in the support of early pregnancy phase.

5.1 Role of hormones in the establishment of early pregnancy:

To establish and successfully maintain a human pregnancy requires the coordinated secretion of hormones within and between the fetus, mother, and placenta. The placenta synthesizes and secretes steroid and peptide hormones that regulate hormonogenesis by endocrine glands in both the mother and the fetus. Placental hormones also act in a paracrine and/or autocrine manner to regulate growth and differentiation of placental cytotrophoblast and syncytiotrophoblast, growth and maturation of the placental vascular tree, and uterine endovascular invasion by extravillous cytotrophoblast. Moreover, the placenta metabolizes the large quantities of steroid hormones produced by the maternal endocrine glands to protect the fetus and to orchestrate the timing and development of fetal organ systems, the fetal pituitary-adrenocortical axis in particular. Clearly, placental hormonogenesis and metabolism are among the most important determinants of a successful pregnancy (114)

There is controversy in the literature regarding the role of estrogens in the establishment and maintenance of early pregnancy. Three findings may be behind such controversy:

-First: experiments that found that progesterone only was needed to rescue pregnancy after corpus luteum removal without the need for a concomitant estrogen administration (115);
-Second: successful pregnancies in conditions associated with very low estrogen levels such as aromatase deficiency (116, 117, 118); and
-Third: failure to consistently demonstrate estrogen receptors in the trophoblast and early pregnancy placenta (119).

Despite the above-mentioned evidence against an important role for estrogen in the establishment and maintenance of early pregnancy, we believe that estrogen has a major role and that disruption of estrogen formation and/or function would result in the failure of early pregnancy leading to pregnancy loss.

Regarding the first finding:
It is known that the corpus luteum is the main source of estrogen and progesterone in early pregnancy until the establishment of the placenta. In their experiments (115), the authors found progesterone supplementation only (without estrogen) to be necessary for the maintenance of pregnancy after removal of the corpus luteum. However, they did not consider the non-corpus luteum sources of estrogen production , *i.e.*, the embryo as well as the early developing placenta (120). We believe that estrogen plays its role in early pregnancy, indirectly, by two mechanisms: the first through priming for progesterone action by upregulating progesterone receptors (121, 122), and the second by enhancing progesterone production by the placenta and corpus luteum (123, 124, 125) through various mechanisms including increase in receptor-mediated LDL uptake (126) and LDL receptor (127) and P450scc (128) mRNA expression in placental trophoblasts.

In brief, it seems that the role of estrogen in maintaining early pregnancy is mediated by progesterone. Hence, it is obvious that administering progesterone alone would be enough to rescue pregnancy after corpus luteum removal without the need for estrogen administration. Moreover, estrogen administration alone would not result in maintenance of pregnancy after removal of the corpus luteum, due to the absence of the main machinery for the production of progesterone at that stage of pregnancy. Another important point not to be missed is the theoretical possibility of conversion of administered progesterone to estrogens but not the reverse. Looking at the steroidogenesis cascade, estrogens are terminal products while progesterone is an early product in the steroidogenesis cascade.

Regarding the second finding:
Although pregnancy is maintained in most women having low estrogen levels resulting from deficiencies in various placental enzymes (117, 118), interestingly, in those cases, although maternal estradiol levels are markedly reduced, concentrations are found to be close to 0.45 ng/mL, or 10^{-9} mol/L, a concentration that approximates the dissociation constant for estradiol binding to its receptor (129). Differences in the outcome of

pregnancy in various women with estrogen deficiency suggest that the important biologic effects of estradiol can be achieved with available receptor and concentrations of estrogen sufficient to interact with it. It would appear that in both human and nonhuman primate pregnancy, estrogen is produced in considerable excess. In the baboon, when two estrogen antagonists were administered in early pregnancy to study the effect of estrogen deprivation on progesterone production, a depression in plasma progesterone indicating a placental requirement for estrogen in progesterone product was found with the pure estrogen antagonist, MER-25, while with the other antagonist, trioxifene mesylate, no such effect was found apparently due to an inherent estrogenicity of trioxifene (124). This would indicate that even such minimal estrogenic activity is still enough to exert its role in early pregnancy.

In females with aromatase deficiency, the placenta would be unaffected because it would carry a complement of genes from the father as well, and would therefore produce estrogen.

Regarding the third finding:
Despite their failure to detect the estrogen receptor in the human trophoblast, the authors concluded that their finding does not entirely preclude the presence of this receptor in human trophoblasts, but might be attributed to a relatively low number and density of ER on these cells. Alternatively, a different type of estrogen receptor may mediate estrogen action on the placenta, such as by a non-classical membrane-bound receptor. In addition, most recently, Bukovsky, *et al.* reported the expression and localization of estrogen receptor-alpha protein in normal and abnormal term placentae and stimulation of trophoblast differentiation by estradiol (130).

5.2 Evidence supporting the major role of estrogen in establishment and maintenance of early pregnancy:
We believe that estrogen plays a pivotal role in the establishment and maintenance of early pregnancy as evidenced by the following facts:

-First: Existence of estrogen synthase enzyme (aromatase and 17 HSD1) and estrogen production by the corpus luteum, embryo and trophoblast. Normal estrogen production is associated with healthy development of early pregnancy.

-Second: Presence of estrogen receptors in the trophoblastic tissues mediating its actions on trophoblastic differentiation and invasion

-Third: Significant role of estrogen in progesterone action through both an effect on progesterone receptors upregulation and an effect on progesterone production early in pregnancy

-Fourth: Disruption of estrogen function is associated with defective early pregnancy development

5.2.1 First: Existence of estrogen synthesis enzymes and estrogen production by the corpus luteum, embryo and trophoblast

The human placenta is a unique organ for the maintenance of pregnancy. Its important functions include hormone supply for the maternal body and fetal development. In addition to the synthesis of placenta-specific hormones, such as human chorionic gonadotropin and placental lactogen (131, 132), the placenta plays a critical role in producing progesterone and estrogens throughout gestation (133). Trophoblast cells secrete progesterone; the production of which can be doubled *in vitro* in the presence of pure HCG (134).

Both P450arom and 17HSD1 are abundantly expressed in syncytiotrophoblast cells, in line with the role of syncytiotrophoblast cells in endocrine function. Cytosolic 17HSD1 has been found in the nuclei of syncytiotrophoblast (135, 136). Cultured cytotrophoblast cells purified from first-trimester placenta express both P450arom and 17HSD1 and are capable of converting dehydroepiandrosterone and A-dione to E_2 (137).

During human pregnancy, the production of 17-beta-estradiol rises eighty fold, from 0.75 nM preovulatory peak to 60 nM at term (138-141), and estrogens influence various aspects of placental function and fetal development in humans and primates (142-148). The corpus luteum is the main source of estrogen and progesterone during early stages of pregnancy during which, hCG is responsible for corpus luteum hormonal rescue and maintenance of luteal estradiol and progesterone production (149, 150). Estradiol has been found also to be produced from embryonic and endometrial sources suggesting a permissive role in embryo implantation (120). In addition, the blastocyst actively participates in the process of implantation (151). Mechanisms that enable the blastocyst to initiate implantation (a process termed activation) include catecholestrogens, a class of estrogen metabolites (152).

Most recently, Li, *et al.* (112) studied the expression pattern of P450arom and 17HSD1 at the fetal–maternal interface, particularly in various trophoblast cells, in tubal pregnancy. Using *in situ* hybridization, P450arom mRNA was localized in syncytiotrophoblast cells, which are mainly responsible for hormone production during pregnancy. In addition, 17HSD1 was found in epithelial cells of the fallopian tube. Interestingly, the authors found that the expression level of 17HSD1 in fallopian tube epithelium during tubal pregnancy was significantly higher than that during normal cycle. This study provided the first evidence that normal and tubal pregnancies possess identical expression of P450arom and 17HSD1 in syncytiotrophoblast cells and therefore, similar estradiol production in the placenta. The authors suggested that the association of 17HSD1 with extravillous cytotrophoblast cells indicates that 17HSD1 perhaps play a role in

trophoblast invasion. Moreover, increased expression of 17HSD1 in epithelial cells of fallopian tube may lead to a local estradiol supply sufficient for the maintenance of tubal pregnancy.

Estradiol levels are known to be low in abnormal pregnancies including ectopic pregnancy and abortion. In women with threatened first-trimester abortion, abnormal estradiol concentrations are highly associated with a subsequent pregnancy loss (153).

The fall in estradiol concentrations was seen in ectopic pregnancies with an abnormal doubling time for HCG and in all abortions. When the ectopic pregnancy had a normal doubling time, estradiol and progesterone concentrations were normal. These findings suggest that corpus luteum function particularly in ectopic pregnancy depends on an adequate doubling time of HCG more than an absolute value, and with normal trophoblastic tissue the site of implantation does not affect corpus luteum function. In abortions, the fall in estradiol and progesterone concentrations was less influenced by the doubling time of HCG (154). These findings suggest that the function of the corpus luteum in ectopic pregnancy is expected to be defective due to the lower levels of hCG produced in ectopic pregnancy which indicates a crucial role for steroidogenesis by the developing trophoblast in maintaining ectopic pregnancy.

5.2.2 Second: Presence of estrogen receptors in the trophoblastic tissues mediating its actions on trophoblastic differentiation and invasion

Several previous studies have shown that human placenta binds estradiol (155-157). However, more recent immunohistochemical studies on paraffin-embedded or snap frozen sections as well as other techniques (RT-PCR for ER-alpha mRNA) failed to demonstrate estrogen receptor alpha in human placentae during pregnancy or in cultures of dispersed placental cells (158, 159). However, it has been indicated that the failure to detect the estrogen receptor α does not entirely preclude the presence of this receptor in human trophoblast cells, but might be attributed to a relatively low number and density on these cells (159). On the other hand, Billiar, *et al.* reported identification of the estrogen receptor α in the nuclei of cultured human placental syncytiotrophoblast (160). None of the above mentioned studies applied western blot analysis of placental ERα expression until recently when Bukovsky, *et al.* (130), using western blot analysis, found that in normal placentae, nuclear estrogen receptor α expression was confined to villous cytotrophoblast cells. In abnormal placentae, they found no cytotrophoblast expressing estrogen estrogen receptor α was detected. The authors concluded that placental estrogen receptor α expression *in vivo* is high in normal placentae and barely detectable in abnormal placentae. The significant increase of estrogen production occurring with pregnancy advancement may play a role, via the ERα, in the stimulation of terminal differentiation of mononucleated trophoblast cells into syncytial aggregates and promote

placental function. This mechanism, however, may not operate in abnormal placentae, which show a lack of estrogen receptor α expression.

5.2.3 Third: Significant role of estrogen in progesterone action both an effect on progesterone receptors upregulation and an effect on progesterone production early in pregnancy

Estrogen and progesterone play pivotal roles during the implantation process and the establishment and maintenance of pregnancy. Progesterone, which is secreted initially by the corpus luteum and later by the placenta, is essential in maintaining an ongoing pregnancy (120). Without progesterone support, the embryo is expelled by a prostaglandin-mediated mechanism. Clinically, preventing its synthesis or blocking its action at the receptor can accomplish inhibition of progesterone effects. Epostane, a 3β-hydroxysteroid dehydrogenase inhibitor, prevents synthesis of progesterone but requires dosing every 6 hours for 7 days to effect abortion (161-163).

Interaction between estrogen and progesterone receptors:
Estrogenic and progestational actions on target cells are mediated through estrogen receptors and progesterone receptors, respectively. Both progesterone and estrogen receptors are members of the steroid-retinoid receptor superfamily, and function as steroid-modulated transcription factors (164).

The levels of progesterone receptor and estrogen receptors are thought to be critical in determining cell responsiveness to steroids, and thus receptor regulation has been studied extensively. Progesterone receptor is one of most well documented estrogen-regulated genes. In many target tissues, both normal and neoplastic, progesterone receptor is induced by estrogen and is widely recognized as a marker for estrogen action (165). In vitro studies have shown that human, rat and rabbit progesterone receptors are induced through binding of the occupied estrogen receptor to multiple estrogen-responsive regions in the 5'-region of progesterone receptor gene (166-168). In many species, estrogen up-regulates progesterone receptor in almost all uterine cell types including the epithelium (169-171). These reports are consistent with a model of estrogen regulation of progesterone receptor in which occupied estrogen receptor binds to the progesterone receptor promoter and activates transcription of the progesterone receptor gene.

The expression of progesterone receptor, and therefore sensitivity to progestins, is under the control of estrogen, which increases, and progesterone, which decreases progesterone receptor expression in most target tissues. progesterone receptor protein is increased during proestrus or by exogenous estrogen administration in the mammalian uterus (172-178).

It is well known that estradiol increases the concentration of its own receptor as well as that of progesterone receptor in normal endometrium (121, 122) at the same time

progesterone in adequate amounts counteracts these estrogenic effects. Moreover, unoccupied progesterone receptor also plays a role in the control of progesterone receptor biosynthesis in primate endometrium as suggested by Chwalisz, *et al.* (179). Anti-estrogen also counteracts such estrogenic effects/action (180). Treatment with anti-estrogen CDRI-85/287 was found to decrease the amount of both receptors suggesting that anti-estrogens may have decidualization inhibitory activity in primate endometrium (181).

Role of estrogen in progesterone production during pregnancy:
Estrogen has been shown to play an important role in progesterone production by the trophoblast. During rat and rabbit pregnancy, estrogen is the major luteotropic stimulus that maintains the corpus luteum and progesterone production (182-184). Estrogen stimulates the uptake of high-density lipoprotein cholesterol substrate (185) and P450scc expression in the rat (186) and rabbit (187) corpus luteum, thereby promoting progesterone production. During mid- to late primate pregnancy, when the placenta is the principal source of progesterone, estrogen has a similar regulatory role within trophoblasts (188, 189). Placental progesterone formation and serum progesterone concentrations are decreased by administration of the estrogen receptor antagonist ethamoxytriphetol (190,191) in baboons, an effect that can be reversed by diethylstilbestrol (192). Moreover, placental progesterone production by human trophoblasts in culture is inhibited by treatment with an aromatase inhibitor and restored by estradiol (193). The increase in receptor-mediated LDL uptake (126) and LDL receptor (127) and P450scc (128) mRNA expression in placental trophoblasts observed during the second half of baboon pregnancy when estrogen levels rise, can be suppressed by blocking the action or formation of estrogen (129, 191, 194, 195). In contrast, placental 3β-HSD and adrenodoxin mRNA expression and 3β-HSD activity are not developmentally regulated or altered by antiestrogen treatment in baboons (128, 196). Therefore, inhibiting the action or levels of estrogen specifically blocks the developmental increase in placental LDL cholesterol uptake and expression of the P450scc enzyme essential for the metabolism of cholesterol to pregnenolone in baboons.

5.2.4 Fourth: Disruption of estrogen function is associated with defective early pregnancy development

Strong evidence is accumulating supporting the crucial role of estrogen in the establishment and maintenance of early pregnancy. A 50% spontaneous abortion rate has been observed among women having a mutation in the amino terminal region of the estrogen receptor involved in transcription (197). In the baboon, reduction of maternal estrogen levels to less than 0.1 ng/mL by daily administration of an inhibitor of placental estrogen synthesis resulted in a 66% incidence of abortion during early gestation that was prevented by treatment with exogenous estradiol (198). Derfoul, *et al.*, (199) suggested that trophoblast Ca^{+} handling functions are endocrinally modulated, and that their alteration by estrogen disruptors constitutes a possible pathway of the harmful effects on fetal development.

6. Aromatase Inhibitors

Aromatase is a microsomal member of the cytochrome P450 hemoprotein-containing enzyme complex superfamily (P450arom, the product of the CYP19 gene) that catalyzes the rate-limiting step in the production of estrogens, that is, the conversion of androstenedione and testosterone via three hydroxylation steps to estrone and estradiol respectively (200, 201). Aromatase activity is present in many tissues, such as the ovaries, the brain, 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 postmenopausal women (202, 203).

6.1 The development of aromatase inhibitors

Aromatase is a good target for selective inhibition because estrogen production is a terminal step in the biosynthetic sequence. A large number of aromatase inhibitors have been developed and utilized in clinical studies over the last 20 years. The most successful, third generation aromatase inhibitors are now being licensed mainly for breast cancer treatment (204, 205). Aromatase inhibitors have been classified in a number of different ways, including first-, second-, and third-generation; steroidal and nonsteroidal; reversible (ionic binding), and irreversible (suicide inhibitor, covalent binding) (206, 207).

The first aromatase inhibitor to be used clinically was aminoglutethimide, which induces a medical adrenalectomy by inhibiting many other enzymes involved in steroid biosynthesis (208). Although aminoglutethimide is an effective hormonal agent in postmenopausal breast cancer, its use is complicated by the need for concurrent corticosteroid replacement. In addition side effects, like lethargy, rashes, nausea and fever, result in 8–15% of patients stopping the aminioglutethimide treatment (209, 210). The lack of specificity and unfavorable toxicity profile of aminoglutethimide has led to a search for more specific aromatase inhibitors. In addition, the earlier aromatase inhibitors were not able to completely inhibit aromatase activity in premenopausal patients.

6.2 Third generation aromatase inhibitors

The third-generation anti-aromatase agents commercially available include two nonsteroidal preparations, anastrozole and letrozole, and a steroidal agent, exemestane (211-214). Anastrozole, ZN 1033, (Arimidex®) and letrozole, CGS 20267, (Femara®) are selective aromatase inhibitors, available for clinical use in North America, Europe and other parts of the world for treatment of postmenopausal breast cancer. These triazole (antifungal) derivatives are reversible, competitive aromatase inhibitors, which are highly potent and selective. 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 aromatase inhibitors for aromatase is thought to reside in the –4 nitrogen of the triazole ring that coordinates with the heme iron atom of the aromatase enzyme complex. Aromatase inhibitors are completely

absorbed after oral administration with mean terminal $t_{1/2}$ of approximately 45 hr (range, 30-60 hr). They are cleared from the systemic circulation mainly by the liver. Gastrointestinal disturbances account for most of the adverse events, although these have seldom limited therapy. Other adverse effects are asthenia, hot flashes, headache, and back pain (212-215).

Summary of the Present Invention

The present invention involves the use of an aromatase inhibitor, alone or in combination with other aromatase inhibitors and/or other medications, including but not exclusive to methotrexate, for treatment of ectopic pregnancy, and more specifically for prevention of the establishment and/or continuation of an ectopic pregnancy.

The administration of the aromatase inhibitor, alone or in combination with other medication(s), may be given as a single dose for one day or multiple days, or as multiple doses for one day or multiple days. Other medications may be started before, concurrent with, or subsequent to starting the administration of the aromatase inhibitor(s). Administration of the aromatase inhibitor(s) alone, or in conjunction with other medications, can start immediately after the diagnosis of ectopic pregnancy, or can be started several days after conservative management or can be started concomitantly with surgical management as an adjuvant therapy. The administration of the aromatase inhibitor(s) alone or in combination together, or in conjunction with other medications or other therapies, can be done orally, parenterally or through other known routes of pharmacologic administration of medications such as but not exclusive to transvaginal and transrectal routes of administration, and through the skin or mucous membranes.

Although not wishing to be bound by theory, there are several possible mechanisms that explain the success of aromatase inhibitors in preventing establishment and/or the continuation of pregnancy. The main hypothesis is the prevention of the establishment of early ectopic pregnancy by inducing atrophy and death of the trophoblastic tissues secondary to estrogen deprivation leading to inhibition of progesterone action. Both estrogen and progesterone are necessary for the maintenance of pregnancy. Progesterone receptors are dependant on estrogen priming. Moreover, estrogen is required to enhance progesterone production during pregnancy. We hypothesize that the use of an aromatase inhibitor results in suppression of estrogen production leading to estrogen deprivation, which will interfere with progesterone action indirectly through suppression of progesterone receptors as a result of estrogen depletion, as well as suppression of progesterone production. Thus, we propose that the prevention of the establishment of ectopic pregnancy and destruction of the early trophoblastic tissue by aromatase inhibition is the result of two mechanisms: first, a direct mechanism involving local estrogen withdrawal by inhibition of blastocyst and trophoblastic aromatase and local estrogen production, and second, by a direct or indirect intraovarian effect resulting from steroid precursor substrate failure (*i.e.*, androgens and progestins) to be converted to

estrogens by reduced aromatase levels induced by the AI resulting in a drop in circulating estrogen levels.

Both "estrogen withdrawal" actions are expected to result in a cascade of events resulting in the disruption of trophoblastic integrity leading to its breakdown and the induction of ectopic pregnancy atrophy and destruction. Therefore, trophoblastic disruption will occur, regardless of the gestational age of the ectopic pregnancy in which the aromatase inhibitor is given.

The use of an aromatase inhibitor alone may be an effective alternative modality for medical management of ectopic pregnancy. This has the advantages of significantly higher safety as well as less cost, and the convenience of oral administration. In another embodiment, administering an aromatase inhibitor in conjunction with methotrexate therapy would improve the outcome of methotrexate treatment, which is presently the current standard for medical management of ectopic pregnancy.

By improved outcome we mean:
-Lowering the failure rate
-Decreasing the need for a repeat second or more doses of methotrexate.
-Shortening the interval between initiation of treatment and the complete resolution (negative ßhCG).
-Reducing the methotrexate dose required for achieving complete resolution
-Reducing the adverse effects of methotrexate

Other significant advantages include the excellent safety profile of third generation aromatase inhibitors and their high tolerability. Specifically, third generation aromatase inhibitors lack the significant contraindications that have limited the success, or even the use of, methotrexate in some women with medical contraindications.

In addition, the third generation aromatase inhibitors are administered orally without known significant allergic reactions, drug interactions or contraindications. The use of the aromatase inhibitors, therefore, would reduce significantly the cost of medical treatment of ectopic pregnancy, reduce the interval to compete resolution, and shorten the follow-up period, as well as reducing the failure rate of the currently available medical treatment. This would also have a significant positive impact on the quality of life for patients with ectopic pregnancy.

Other avenues for the use of aromatase inhibitors in indications similar to ectopic pregnancy:
The success of aromatase inhibitors in preventing the establishment and maintenance of early pregnancy in ectopic pregnancy would make this class of medication and the use of aromatase inhibition a valid novel approach for medical termination of pregnancy. This would be of great benefit especially for women with significant medical problems

contraindicating surgical termination of pregnancy or the use of the currently available methods of medical termination of pregnancy. Those women might benefit from the wide safety profile of such class of medications.

Aromatase inhibitors have not been used in women of the reproductive age group until recently. We have found that estrogen levels following induction or augmentation of ovulation with aromatase inhibitors were significantly lower (especially serum E2 concentration/mature follicle) when compared with conventional stimulation protocols.

Thus, the present invention provides a method for preventing the establishment and/or maintenance of ectopic pregnancy in females by oral administration of an aromatase inhibitor and the consequent blockade of estrogen synthesis.

Method of administration:
While one aromatase inhibitor is preferred for use in the present invention, combinations of aromatase inhibitors, and especially those aromatase inhibitors having different half-lives, are within the contemplation of the invention. The aromatase inhibitor is preferably 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 details on the types of aromatase inhibitors that may be used in the methods, uses and preparations of the present invention appear subsequently herein.

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 other forms, including convenience and patient compliance. Preferred aromatase inhibitors of those that are presently commercially available, include anastrozole, letrozole, vorozole and exemestane. Exemestane (Aromasin™) is an example of a steroidal, non-reversible aromatase inhibitor that may be used in the present invention.

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

Typically, the amount of aromatase inhibitor for preventing the achievement and/or establishment and/or maintenance of pregnancy in females exposed to unprotected sexual encounter that may lead to pregnancy may be selected from amounts that lower estrogen levels resulting in disruption of endometrial integrity leading to shedding of the endometrium and induced menstruation or at least destroying the integrity of the endometrial structure that will be unfavorable for the implantation of a fertilized oocyte or maintenance of early pregnancy.

Examples of preferred dosages are as follows. When the aromatase inhibitor is letrozole, it is preferably administered in a daily dose of from about 2.5 mg to about 30 mg. When the aromatase inhibitor is anastrozole, preferably, it is administered in a daily dose of from about 1 mg to about 30 mg. When the aromatase inhibitor is vorozole, the preferred daily dose is from about 4 to about 30 mg. Exemestane is preferably administered in a daily dose of about 25 to 200 mg. Preferred are 1 to 10 daily doses of the aromatase inhibitor with administration starting on any of days 1 to 10 after exposure to unprotected intercourse, for 1-10 days. Most preferably the daily doses of the aromatase inhibitor comprise five daily doses.

In another preferred form of the invention, a single dose of AI is administered in place of the multiple daily doses described above. The aromatase inhibitor is preferably administered in a single dose selected from amounts in the range of from about 5 mg to 60 mg of letrozole or arimidex to about 500 to 2000 mg of exemestane.

Aromatase Inhibitors

As used herein, the term "aromatase inhibitors" is to be understood as substances that inhibit the enzyme aromatase (= estrogen synthetase), which is responsible for converting androgens to oestrogens.

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, by using the methods described in *J. Biol. Chem.*, Vol. 249, page 5364 (1974) or in *J. Enzyme Inhib.*, Vol. 4, page 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.

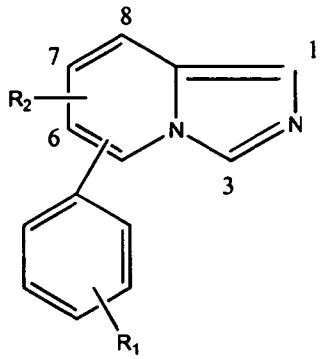
By "aromatase inhibitors" there are to be understood most especially substances for which the minimum effective dose in the case of *in vivo* aromatase inhibition is 10 mg/kg or less, especially 1 mg/kg or less, preferably 0.1 mg/kg or less and most especially 0.01 mg/kg or less.

In vivo aromatase inhibition can be determined, for example, by the following method [see, *J. Enzyme Inhib.*, Vol. 4, page179 (1990)]: androstenedione (30 mg/kg

subcutaneously) is administered on its own or together with an aromatase inhibitor (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 aromatase inhibitor.

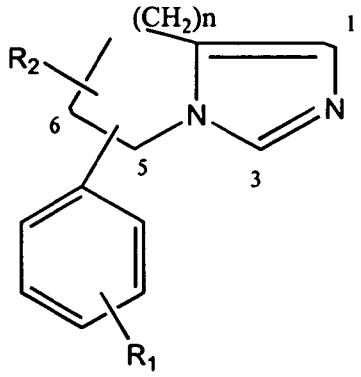
The following groups of compounds are listed as examples of aromatase inhibitors. Each individual group forms a group of aromatase inhibitors that can be used successfully in accordance with the present invention:

(a) The compounds of formulae I and I* as defined in European Patent Publication No. 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, –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*)

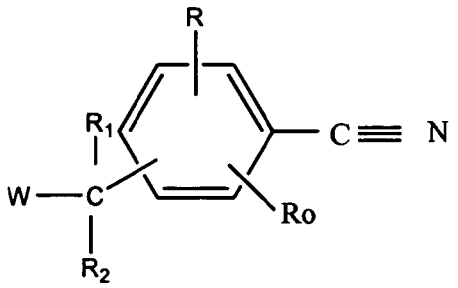
wherein n is 0, 1, 2, 3 or 4; and R_1 and R_2 are as defined above for Formula I; it being possible for the phenyl ring in the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy 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 European Patent Publication No. EP-A 236 940. These are especially the compounds of Formula I



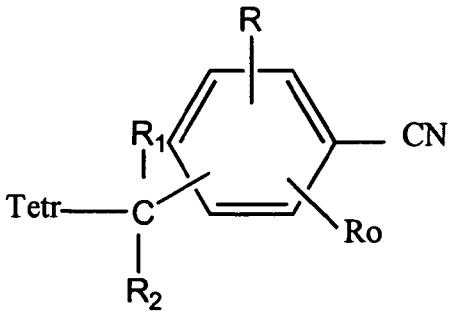
(I)

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 ring 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 European Patent Publication No. EP-A-408 509. These are especially the compounds of Formula I

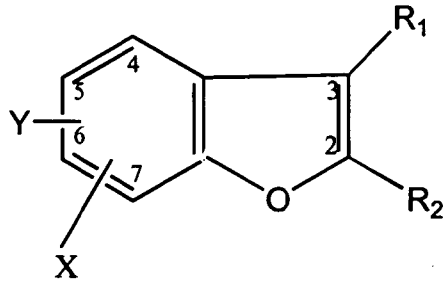


(I)

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-[a-(4-cyanophenyl)-(2-tetrazolyl)methyl]-benzonitrile,
(3) 1-cyano-4-(1-tetrazolyl)methyl-naphthalene,
(4) 4-[a-(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

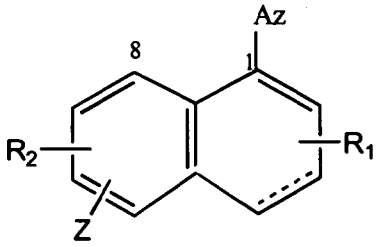


(I)

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 No. 1339/90-7. These are especially the compounds of Formula I

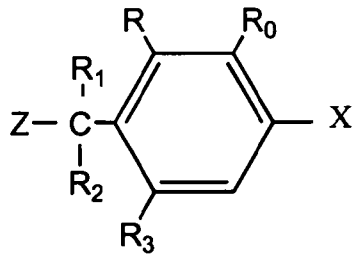


(I)

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 No. 3014/90-0. These are especially the compounds of Formula I



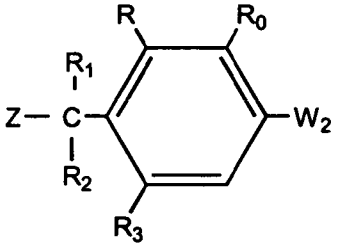
(I)

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-[a-(4-cyanophenyl)-a-hydroxy-5-isothiazolylmethyl]-benzonitrile.
(2) 4-[a-(4-cyanophenyl)-5-isothiazolylmethyl]-benzonitrile,
(3) 4-[a-(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.

The compounds of formula VI as defined in Swiss Patent Application No. 3014/90-0. These are especially the compounds of formula VI



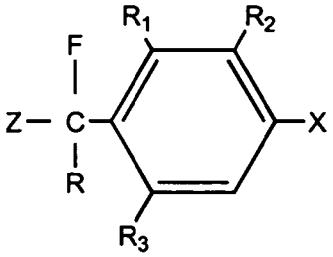
(VI)

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 No. 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, –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

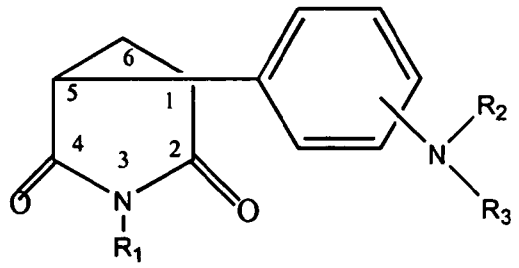
two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, 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, –cycloalkyl-lower alkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenyl-lower alkylcarbamoyl, –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-[a-4-cyanophenyl)-a-fluoro-1-(1,2,4-triazolyl)methyl]-benzonitrile,
(2) 4-[a-(4-cyanophenyl)-a-fluoro-(2-tetrazolyl)methyl]-benzonitrile,
(3) 4-[a-(4-cyanophenyl)-a-fluoro-(1-tetrazolyl)methyl]-benzonitrile,
(4) 4-[a-(4-cyanophenyl)-a-fluoro-(1-imidazolyl)methyl]-benzonitrile,
(5) 1-methyl-6-[a-(4-chlorophenyl)-a-fluoro-1-(1,2,4-triazolyl)methyl]-benzotriazole,

(6) 4-[a-(4-cyanophenyl)-a-fluoro-1-(1,2,3-triazolyl)methyl]-benzo nitrile,
(7) 7-cyano-4-[a-(4-cyanophenyl)-a-fluoro-1-(1,2,4-triazolyl)methy l]-2,3-dimethylbenzo[b]furan,
(8) 4-[a-(4-bromophenyl)-a-fluoro-1-(1,2,4-triazolyl)methyl]-benzo nitrile,
(9) 4-[a-(4-cyanophenyl)-a-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(10) 4-[a-(4-bromophenyl)-a-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(11) 4-[a-(4-cyanophenyl)-a-fluoro-(3-pyridyl)methyl]-benzonitrile,
(12) 7-bromo-4-[a-(4-cyanophenyl)-a-fluoro-(1-imidazolyl)methyl]-2, 3-dimethylbenzo[b]furan,
(13) 7-bromo-4-[a-(4-cyanophenyl)-a-fluoro-1-(1,2,4-triazolyl)methy l]-2,3-dimethylbenzo[b]furan,
(14) 4-[a-(4-cyanophenyl)-a-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(15) 4-[a-(4-bromophenyl)-a-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(16) 4-[a-(4-cyanophenyl)-1-(1,2,3-triazolyl)methyl]-benzonitrile,
(17) 2,3-dimethyl-4-[a-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-7-cyano -benzo[b]furan,
(18) 4-[a-(4-cyanophenyl)-(5-pyrimidyl)methyl]-benzonitrile,
(19) 4-[a-(4-bromophenyl)-(5-pyrimidyl)methyl]-benzonitrile,
(20) 2,3-dimethyl-4-[a-(4-cyanophenyl)-(1-imidazolyl)methyl]-7-bromo-benzo[b]furan,
(21) 2,3-dimethyl-4-[a-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-7-bromo-benzo-[b]furan.

(I) The compounds of Formula I as defined in European Patent Publication No. EP-A-114 033. These are especially the compounds of Formula I

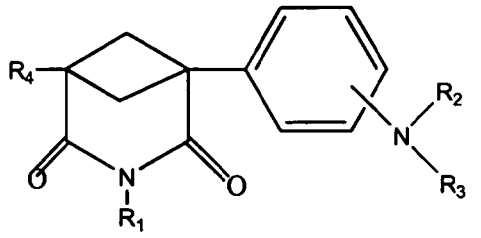


wherein R_1 is hydrogen, R_2 is hydrogen, sulfo, C_1 -C_7 alkanoyl or C_1 -C_7 alkanesulfonyl and R_3 is hydrogen, or wherein R_1 is C_1 -C_{12} alkyl, C_2 -C_{12} alkenyl, C_2 -C_7 alkynyl, C_3 -C_{10} cycloalkyl, C_3 -C_{10} cycloalkenyl, C_3 -C_6 cycloalkyl-C_1 -C_4 alkyl, C_3 -C_6 cycloalkyl-C_2 -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 European Patent Publication No. EP-A-166 692. These are especially the compounds of Formula I



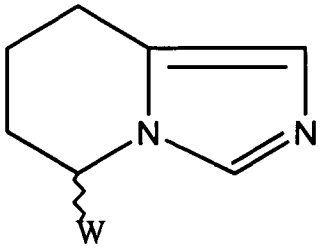
(I)

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 European Patent Publication No. EP-A-356 673. These are especially the compounds of Formula I



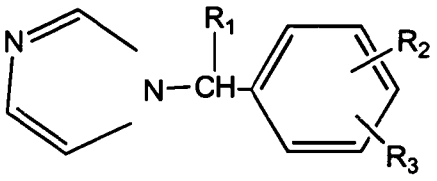
(I)

wherein W (a) 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 European Patent Publication No. EP-A-337 929. These are especially the compounds of Formula I/Ia

(I/Ia)

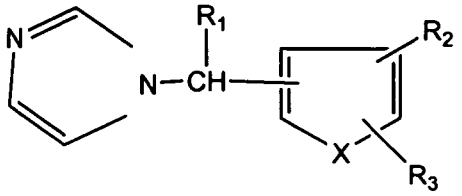


wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, R_2 is benzyloxy, 3-bromo-, 4-bromo-, 4-chloro-, 2,3-, 2,4-, 4,5- or 4,6-dichloro-benzyloxy, and R_3 is cyano; C_2 -C_{10} alkanoyl 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 European Patent Publication No. EP-A-337 928. These are especially the compounds of Formula I



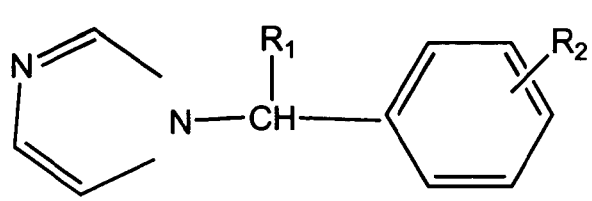
(I)

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, –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=—; --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 European Patent Publication No. EP-A-340 153. These are especially the compounds of Formula I

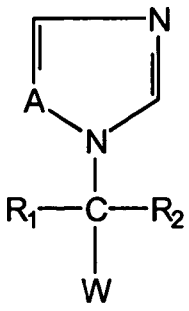


(I)

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.

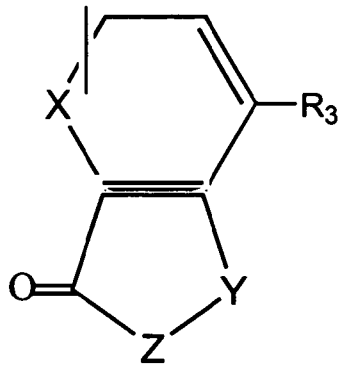
Individual compounds from that group that may be given special mention are:
(1) 4-(1-(1-imidazolyl)-butyl)-benzoic acid methyl ester,
(2) 4-(1-(1-imidazolyl)-butyl)-benzoic acid butyl ester,
(3) 4-(1-(1-imidazolyl)-butyl)-phenyl-acetonitrile,
(4) 4-(1-(1-imidazolyl)-butyl)-benzaldehyde,
(5) 4-(1-(1-imidazolyl)-butyl)-benzyl 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 German Patent Application No. 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

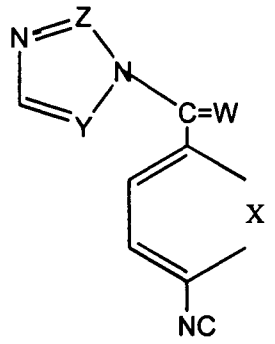
b) R_2 is as defined under a) and R_1 together with R_3 forms a --$(CH_2)_m$—group wherein m=2, 3, or 4, and their pharmaceutically acceptable addition salts with acids.

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 German Patent Application No. DE-A-3 926 365. These are especially the compounds of Formula I

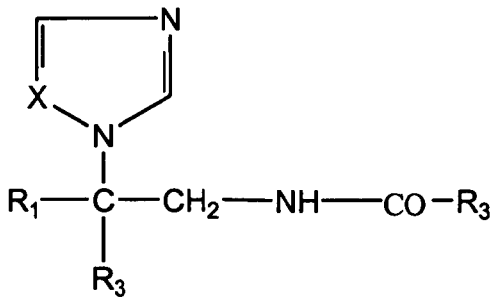


(I)

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

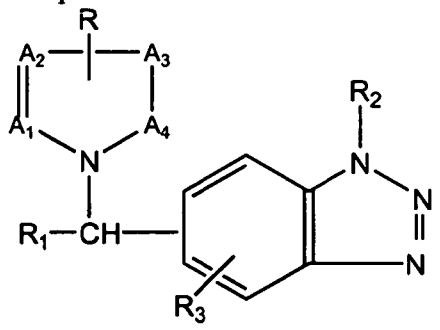


(I)

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.

®) 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 European Patent Publication No. 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 European Patent Publication No. 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 European Patent Publication No. 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 European Patent Publication No. EP-A-299 683, especially
(1) (Z)-a-(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,
(2) (Z)-4'-chloro-a-(1,2,4-triazol-1-ylmethyl)stilbene-4-carbonitrile,
(3) (Z)-a-(1,2,4-triazol-1-ylmethyl)-4'-(trifluoromethyl)stilbene-4-carbonitrile,
(4) (E)-.beta.-fluoro-a-(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,
(5) (Z)-4'-fluoro-a-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,
(6) (Z)-2', 4'-dichloro-a-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,
(7) (Z)-4'-chloro-a-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,
(8) (Z)-a-(imidazol-1-ylmethyl)stilbene-4,4'dicarbonitrile,
(9) (Z)-a-(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 European Patent Publication No. 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-a-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.

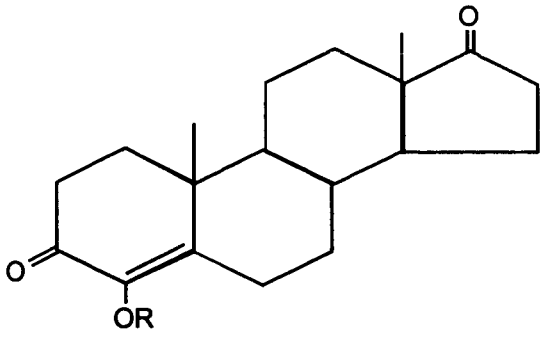
(x) The compounds as defined in claim 1 of European Patent Publication No. EP-A-316 097, especially
(1) 1,1-dimethyl-8-(1H-1,2,4-triazol-1-ylmethyl)-2(1H)-naphtho[2,1-b]furanone,

(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 European Patent Publication No. 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 European Patent Publication No. 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 European Patent Publication No. 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 German Patent Application No. DE-A-3 622 841, especially 6-methyleneandrosta-1,4-diene-3,17-dione.

(ad) The compounds as defined in the claims of Published British Patent Application No. GB-A-2 17 1100, especially 4-amino-androsta-1,4,6-triene-3,17-dione.

(ae) The compound 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, are 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 a 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, or ammonium salts derived from ammonia or suitable organic amines. Also under consideration are 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.

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 or more of the above-mentioned compounds, or of pharmaceutically acceptable salts thereof, together with pharmaceutically acceptable carriers. The particularly preferred form of administration is oral.

The proportion of active ingredient in such pharmaceutical compositions is generally 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 or transvaginally 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.

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