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(54) **BICYCLIC, NITROGEN-CONTAINING HETEROCYCLES AND AROMATASE INHIBITORS**

(76) Inventors: **Peter Herold**, Basel (CH); **Robert Mah**, Muttenz (CH); **Vincenzo Tschinke**, Binningen (CH); **Christoph Schumacher**, Bettingen (CH); **Michael Quirmbach**, Basel (CH)

Correspondence Address:
WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W., SUITE 800
WASHINGTON, DC 20006-1021

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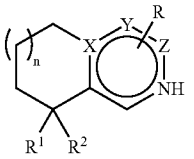
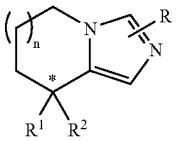
(57) **ABSTRACT**

The application relates to novel heterocyclic compounds of the general formula (I) (I*) in which R, R^1, R^2, X, Y, Z and n have the meanings defined in the description, to a process for their preparation and to the use of these compounds as medicaments, in particular as aromatase inhibitors.

(I)



(I*)

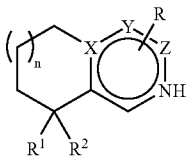


BICYCLIC, NITROGEN-CONTAINING HETEROCYCLES AND AROMATASE INHIBITORS

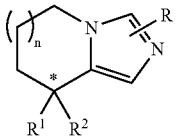
[0001] The invention relates to novel heterocyclic compounds, to a process for preparing the compounds, to pharmaceutical products containing them, and to their use as active pharmaceutical ingredients, in particular as aromatase inhibitors.

[0002] The present invention relates firstly to compounds of the general formulae

(I)



(I*)



in which,

[0003] X is C;

[0004] Y is C or N;

[0005] Z is C;

[0006] R

[0007] a) is hydrogen; or

[0008] b) is C_1-C_8-alkyl, C_1-C_8-alkoxy, halogen or trifluoromethyl;

[0009] R^1 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, aryl-C_0-C_4-alkyl or unsaturated heterocyclyl-C_0-C_4-alkyl, which radicals are unsubstituted or substituted by 1-4 C_1-C_8-alkoxy, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkyl, C_0-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, aryl-C_0-C_4-alkoxycarbonyl, aryl, cyano, halogen, heterocyclyl, oxo, trifluoromethoxy, trifluoromethyl or tri-C_1-C_4-alkylsilyl;

[0010] R^2

[0011] a) is hydrogen; or

[0012] b) is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, halogen, carboxy-C_1-C_4-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, C_0-C_4-alkylcarbonyl, aryl-C_0-C_4-alkyl or unsaturated heterocyclyl-C_1-C_4-alkyl, which radicals are unsubstituted or substituted by 1-4 C_1-C_8-alkoxy, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkyl, C_0-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, aryl-C_0-C_4-alkoxycarbonyl, aryl, cyano, halogen, heterocyclyl, oxo, trifluoromethoxy, trifluoromethyl or tri-C_1-C_4-alkylsilyl;

[0013] n is a number 0, 1 or 2;

[0014] * designates an asymmetric carbon atom

[0015] and the salts thereof, preferably the pharmaceutically usable salts thereof,

[0016] where, if X, Y and Z are C, R^1 is not an unsubstituted or alkoxy-substituted benzyl radical: or if R is methyl, R^1 is different from methyl.

[0017] The term aryl stands for an aromatic hydrocarbon radical which generally comprises 5-14, preferably 6-10, carbon atoms and is, for example, phenyl, indenyl, e.g. 2- or 4-indenyl, or naphthyl, e.g. 1- or 2-naphthyl. Aryl having 6-10 carbon atoms is preferred, especially phenyl or 1- or 2-naphthyl. Said radicals may be unsubstituted or substituted one or more times, e.g. once or twice, it being possible for the substituent to be in any position, e.g. in the o, m or p position of the phenyl radical or in the 3 or 4 position of the 1- or 2-naphthyl radical, and it also being possible for a plurality of identical or different substituents to be present.

[0018] Aryl-C_0-C_4-alkyl is, for example, phenyl, naphthyl or benzyl.

[0019] The term heterocyclyl stands for a saturated, partially saturated or unsaturated, 4-8-membered, particularly preferably 5-membered, monocyclic ring system, for a saturated, partially saturated or unsaturated, 7-12-membered, particularly preferably 9-10-membered, bicyclic ring system and also for a saturated, partially saturated or unsaturated, 7-12-membered tricyclic ring system, in each case comprising an N, O or S atom in at least one ring, it also being possible for an additional N, O or S atom to be present in one ring. Said radicals may be unsubstituted or substituted one or more times, e.g. once or twice, it also being possible for a plurality of identical or different substituents to be present.

[0020] Unsaturated monocyclic heterocyclyl-C_0-C_4-alkyl is, for example, pyrrolyl, thiophenyl, thiazolyl or oxazolyl. Unsubstituted pyridinyl is less preferred.

[0021] Unsaturated bicyclic heterocyclyl-C_0-C_4-alkyl is for example benzofuranyl, benzothiophenyl, indazolyl, indolyl, isoquinolinyl or quinolinyl.

[0022] Partially saturated bicyclic heterocyclyl-C_0-C_4-alkyl is for example 4, 5, 6, 7-tetrahydrobenzofuranyl or 4,5,6,7-tetrahydrobenzothiazolyl.

[0023] C_3-C_8-Cycloalkyl is preferably 3-, 5- or 6-membered cycloalkyl, such as cyclopropyl, cyclopentyl or cyclohexyl.

[0024] C_1-C_8-Alkyl may be straight-chain or branched and/or bridged and is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl, tertiary butyl, or a pentyl, hexyl or heptyl group.

[0025] C_2-C_8-Alkenyl is, for example, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, secondary butenyl, tertiary butenyl, or a pentenyl, hexenyl or heptenyl group.

[0026] C_2-C_8-Alkynyl is, for example, ethynyl, propynyl, butynyl, or a pentynyl, hexynyl or heptynyl group.

[0027] C_1-C_8-Alkoxy is, for example, C_1-C_5-alkoxy such as methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, secondary butyloxy, tertiary butyloxy or pentyloxy, but may also be a hexyloxy or heptyloxy group.

[0028] C_1-C_8-Alkoxycarbonyl is preferably C_1-C_4-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, secondary butyloxycarbonyl or tertiary butyloxycarbonyl.

[0029] C_0-C_8-Alkylcarbonyl is, for example, formyl, acetyl, propionyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, secondary butylcarbonyl or tertiary butylcarbonyl.

[0030] C_1-C_4-Alkoxycarbonyl-C_1-C_4-alkyl is, for example, methoxycarbonyl- or ethoxycarbonylmethyl, 2-methoxycarbonyl- or 2-ethoxycarbonylethyl, 3-methoxycarbonyl- or 3-ethoxycarbonylpropyl or 4-ethoxycarbonylbutyl.

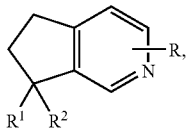
[0031] Halogen is, for example, fluorine, chlorine, bromine or iodine.

[0032] Carboxy-C_1-C_4-alkyl is, for example, carboxymethyl, 2-carboxyethyl, 2- or 3-carboxypropyl, 2-carboxy-2-methylpropyl, 2-carboxy-2-ethylbutyl or 4-carboxybutyl, in particular carboxymethyl.

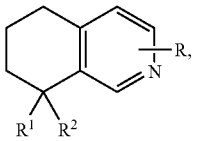
[0033] The compound groups mentioned below are not to be regarded as closed; on the contrary, parts of these compound groups may be replaced by one another or by the definitions given above, or be omitted, in a meaningful way, e.g. to replace general by more specific definitions.

[0034] Preferred compounds of the formula (I) or (I*) are compounds of the general formulae

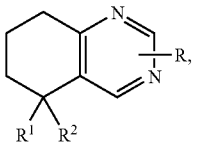
(Ia)



(Ib)



(Ic)



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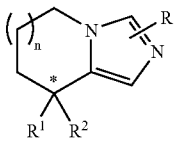


where the meanings of R, R^1, R^2 and n are as indicated for compounds of the formula (I) or (I*).

[0035] R is preferably hydrogen or C_1-C_8-alkyl, particularly preferably hydrogen or methyl.

[0036] R^1 is preferably aryl or unsaturated heterocyclyl, very particularly preferably optionally mono- or di-substituted benzofuranyl, benzothiophenyl, indazolyl, indolyl, phenyl, pyrrolyl, thiazolyl, thiophenyl or oxazolyl.

[0037] R^2 is preferably hydrogen, halogen, C_1-C_8-alkyl or aryl-C_1-C_4-alkyl.

[0038] n is preferably a number 0 or 1. n is particularly preferred the number 1 for compounds of formula (I*).

[0039] Preferred substituents for aryl or unsaturated heterocyclyl are halogen, cyano, trifluoromethyl, heterocyclyl or C_1-C_8-alkylcarbonyl. Very particularly preferred substituents for aryl or unsaturated heterocyclyl are bromine, cyano, thiophenyl, thiazolyl, oxazolyl or acetyl.

[0040] Particularly preferred compounds of the formula (I) or (I*) are compounds of the general formulae (Ia), (Ib), (Ic) or (I*) where R^1 is aryl, preferably mono- or di-substituted phenyl, or unsaturated heterocyclyl, preferably mono- or di-substituted benzofuranyl, benzothiophenyl, indazolyl or indolyl.

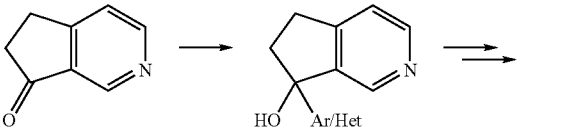
[0041] With regard to the compounds of formula (I*) per se (but not to their use or any composition containing said compounds), the compound, wherein R and R^2 are H, R^1 is p-cyanophenyl and n is 1, is less preferred.

[0042] The compounds of the formula (I) which have at least one asymmetric carbon atom can exist in the form of optically pure enantiomers, mixtures of enantiomers or as racemates. Compounds having a second asymmetric carbon atom can exist in the form of optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates or as meso compounds. The invention includes all these forms. Mixtures of enantiomers, racemates, mixtures of diastereomers, diastereomeric racemates or mixtures of diastereomeric racemates can be fractionated by conventional methods, e.g. by racemate resolution, column chromatography, thin-layer chromatography, HPLC and the like.

[0043] The compounds of formula (I*) have at least one asymmetric carbon atom designated as *. Said compounds are to be understood as a single compound having a specific configuration at said asymmetric carbon atom. In case of using a method of preparation leading to racemic compounds, separation of the enantiomers is carried out in a conventional manner, for example using a chiral HPLC-column. Details are found in the examples. Compounds of formula (I*) according to the current invention show a pronounced aromatase inhibiting activity. Said activity may conveniently be determined by using a commercial Cyp19 enzyme inhibition kit, preferably the Cyp19/Methoxy-4-trifluoromethyl-coumarin (MFC) high throughput inhibition kit (Becton Dickinson Biosciences, San Jose, Calif., USA as described hereafter. Compounds of formula (I*) having the opposite configuration at the asymmetric carbon atom designated * show an activity in such a test system which is at least 20-fold, preferably 40-fold, less than the current compounds of formula (I*)."

[0044] The term "pharmaceutically usable salts" includes salts with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like. Salts of compounds having salt-forming groups are, in particular, acid addition salts, salts with bases or, if a plurality of salt-forming groups is present, optionally also mixed salts or inner salts.

[0045] The compounds of the formula (I) or (I*) can be prepared in a manner analogous to preparation processes disclosed in the literature (scheme).



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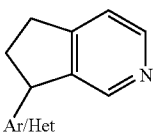
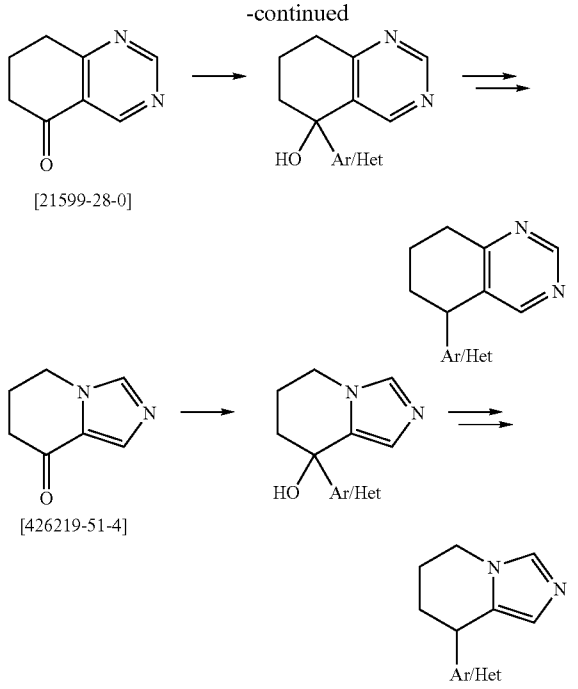




[0046] Details of the specific preparation variants can be found in the examples.

[0047] The compounds of the formula (I) can also be prepared in optically pure form. Separation into antipodes is possible by methods known per se, either preferably at an early stage of the synthesis by salt formation with an optically active acid such as, for example, (+)- or (−)-mandelic acid and separation of the diastereomeric salts by fractional crystallization or preferably at a rather late stage by derivatization with a chiral auxiliary component such as, for example, (+)- or (−)-camphanyl chloride, and separation of the diastereomeric products by chromatography and/or crystallization and subsequent cleavage of the linkage to the chiral auxiliary. The pure diastereomeric salts and derivatives can be analyzed to determine the absolute configuration of the contained compound using conventional spectroscopic methods, a particularly suitable method being single-crystal X-ray spectroscopy.

[0048] Salts are primarily the pharmaceutically usable or nontoxic salts of compounds of the formula (I) or (I*). Such salts are formed for example by compounds of the formula (I) or (I*) having an acidic group, e.g. a carboxy or sulpho group, and are, for example, salts thereof with suitable bases, such as nontoxic metal salts derived from metals of group Ia, Ib, IIa and IIb of the Periodic Table of Elements, e.g. alkali metal, in particular lithium, sodium or potassium salts, alkaline earth metal salts, for example magnesium or calcium salts, also zinc salts or ammonium salts, and those salts formed with organic amines such as optionally hydroxy-substituted mono-, di- or trialkylamines, in particular mono-, di- or tri-lower-alkylamines, or with quaternary ammonium bases, e.g. methyl-, ethyl-, diethyl- or triethylamine, mono-, bis- or tris(2-hydroxy-lower-alkyl)amines such as ethanol-, diethanol- or triethanolamine, tris(hydroxymethyl)methylamine or 2-hydroxy-tertiary-butylamine, N,N-di-lower-alkyl-N-(hydroxy-lower-alkyl)amine, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or N-methyl-D-glucamine, or quaternary ammonium hydroxides such as tetrabutylammonium hydroxide. The compounds of the formula (I) or (I*) having a basic group, e.g. an amino group, can form acid addition salts, e.g. with suitable inorganic acids, e.g. hydrohalic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid with replacement of one or both protons, phosphoric acid with replacement of one or more protons, e.g. orthophosphoric acid or metaphosphoric acid, or pyrophosphoric acid with replacement of one or more protons, or with organic carboxylic, sulphonic or phosphonic acids or N-substituted sulphamic acids, e.g. acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid, isonicotinic acid, also amino acids such as, for example, the abovementioned α-amino acids, and methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, ethane-1,2-disulphonic acid, benzenesulphonic acid, 4-toluenesulphonic acid, naphthalene-2-sulphonic acid, 2- or 3-phosphoglycerate, glucose 6-phosphate, N-cyclohexylsulphamic acid (to form cyclamates) or with other acidic organic compounds such as ascorbic acids. Compounds of the formula (I) or (I*) having acidic and basic groups can also form inner salts.

[0049] Pharmaceutically unsuitable salts can also be used for isolation and purification.

[0050] The compounds of the formula (I) or (I*) also include compounds in which one or more atoms are replaced by their stable, nonradioactive isotopes; for example a hydrogen atom by deuterium.

[0051] Prodrug derivatives of the compounds described above are derivatives thereof which on use in vivo release the original compound through a chemical or physiological process. A prodrug may be converted into the original compound for example when a physiological pH is reached or by enzymatic conversion. Examples of possible prodrug derivatives are esters of freely available carboxylic acids, S- and O-acyl derivatives of thiols, alcohols or phenols, where the acyl group is as defined above. Preference is given to pharmaceutically usable ester derivatives which are converted by solvolysis in physiological medium into the original carboxylic acid, such as, for example, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or disubstituted lower alkyl esters, such as lower ω-(amino, mono- or dialkylamino, carboxy, lower alkoxycarbonyl)-alkyl esters or such as lower α-(alkanoyloxy, alkoxycarbonyl or dialkylaminocarbonyl)-alkyl esters; pivaloyloxymethyl esters and similar esters are conventionally used as such.

[0052] Because of the close relatioship between a free compound, a prodrug derivative and a salt compound, a defined compound in this invention also includes its prodrug derivative and salt form where this is possible and appropriate.

[0053] The naturally occuring estrogens 17β-estradiol (E2), estrone (E1) and estriol (E3) are C18 steroids derived from cholesterol. After binding to lipoprotein receptors, cholesterol is taken up by steroidogenic cells, stored and moved to the sites of steroid synthesis. Aromatization of the A-ring in the steroid scaffold is the last step in the formation

of estrogen. This reaction is catalyzed by the P450 aromatase monooxygenase enzyme complex (Cyp19) that is present in the smooth endoplasmic reticulum and functions as a demethylase. In three consecutive hydroxylating reactions, estrone and estradiol are formed from their obligatory precursors androstenedione and testosterone, respectively.

[0054] The primary sources of estradiol in woman are the theca and granulose cells of the ovaries and the luteinized derivatives of these cells. According to the "two-cell" theory of estrogen synthesis, the theca cells secrete androgens that diffuse to the granulose cells to be aromatized to estrogens. There is, however, evidence that both cell types are enabled to form both androgens and estrogens. Estrone and estriol are primarily formed in the liver from estradiol. Aromatase activity has also been detected in muscle, fat, nervous tissue and the Leydig cells of the testes. The level of estrogen synthesis in extragonadal tissues increases as a function of age and body weight.

[0055] In the serum, estradiol reversibly binds to sex-hormone-binding globulin, a β-globulin, and with lesser affinity to albumin; about 2-3 percent is unbound. Estrogens are metabolized by sulfation or glucuronidation, and the conjugates are excreted into the bile or urine. Hydrolysis of these conjugates by the intestinal flora and subsequent reabsorption of the estrogens results in enterohepatic circulation.

[0056] Estrogens stimulate growth, blood flow and water retention in sexual organs and are also involved in causing breast cancer and endometrial tumors. In the liver, estrogens increase the expression of lipoprotein receptors that results in a decrease in serum concentrations of low-density lipoprotein cholesterol. Estrogens also increase the potential for coagulation by stimulating the production of coagulation factors in the liver. In bone, both osteoclasts and osteoblasts are direct targets of estrogens, but overall, estrogens are classified as anti-resorptive agents.

[0057] In breast tissue, estrogens stimulate the growth and differentiation of the ductal epithelium, induce mitotic activity of ductal cylindric cells and stimulate the growth of connective tissue. Estrogens stimulate the growth of breast cancer cells. In postmenopausal women with breast cancer, the tumor concentration of estradiol is high caused by in situ aromatization, despite the presence of low serum estradiol concentrations.

[0058] The compounds described in the present invention have useful pharmacological properties as they selectively inhibit the enzyme aromatase (Cyp19) in mammals, including humans. As a result, the metabolic conversion of androgens into estrogens is inhibited. The compounds are therefore suitable, for example, for the treatment of estrogen-dependent diseases, including estrogen-dependent breast cancer, particularly in postmenopausal women. They are also useful, for example, in the treatment of gynaecomastia, that is to say the development of breasts in men, as the aromatization of steroids can be inhibited by the described compounds.

[0059] These effects are demonstrable in in vitro assay tests using cell-free and cellular systems.

[0060] The in vitro inhibition of aromatase activity of the compounds of the present invention can be demonstrated by using a commercial Cyp19 enzyme inhibition kit. The Cyp19/Methoxy-4-trifluoromethyl-coumarin (MFC) high throughput inhibition kit (Becton Dickinson Biosciences, San Jose, Calif., USA), for example, is designed to screen for potential inhibitors of Cyp19 catalytic activity in a 96-well format. The kit includes recombinant human Cyp19 enzyme in the form of supersomes, a fluorescent P450 substrate, an NADPH regenerating system, a reaction buffer and a stop reagent. MFC, the fluorogenic substrate is rapidly converted by Cyp19 supersomes to the highly fluorescent product 7-hydroxy-4-trifluoromethyl coumarin (7-HFC). The execution of the assay in the presence of various concentrations of inhibitor compounds ranging from 0.2 nanomolar to 20 millimolar occurs according to the manufacturer's instructions.

[0061] The inhibition curve is generated by fitting a 4-parameter logistic function to the raw data of the samples using the least squares approach. The function is described as follows:

$$Y=(d-a)/((1+(x/c)^{-b}))+a$$

where:

[0062] a=minimal data values

[0063] b=slope

[0064] c=IC50

[0065] d=maximal data values

[0066] x=inhibitor concentrations

[0067] The compounds described in the present invention show Cyp19 inhibitory properties at minimal concentrations between 10^{-3} to 10^{-10} mol/l.

[0068] The Cyp19 inhibitory properties of compounds described in the present invention can also be demonstrated in a cellular assay. The NCl-H295R human adrenocortical carcinoma cell line has been characterized in detail in the literature and shown to express most of the key enzymes necessary for steroidogenesis. These include Cyp11A (cholesterol side-chain cleavage), Cyp11B1 (steroid 11β-hydroxylase), Cyp11B2 (aldosterone synthetase), Cyp17 (steroid 17α-hydroxylase and/or 17,20 lyase), Cyp19 (aromatase), Cyp21B2 (steroid 21-hydroxylase) and 3β-HSD (hydroxysteroid dehydrogenase). The cells have the physiological characteristics of zonally undifferentiated human fetal adrenal cells, with the ability to produce the steroid hormones of each of the three phenotypically distinct zones found in the adult adrenal cortex.

[0069] Th NCl-295R cells (American Type Culture Collection, ATCC, Rockville, Md., USA) are cultured in Dulbecco's Modified Eagle'Ham F-12 medium (DME/F12) that is supplemented with Ultroser SF serum (Soprachem, Cergy-Saint-Christophe, France) as well as insulin, transferrin, selenit (I-T-S, Becton Dickinson Biosiences, Franklin Lakes, N.J., USA) and antibiotics in 75 cm^2 cell culture flasks at a temperature of 37° C. and a 95% air/5% CO2 humidified atmosphere. The cells are subsequently transferred in a 24-well plate and seeded in presence of DME/F12 medium that is supplemented with 0.1% bovine serum albumin instead of Ultroser SF serum. The experiment is initiated by incubating the cells for 72 hours in DME/F12 medium supplemented with 0.1% bovine serum albumin and test compounds in the presence or absence of cell stimulatory agents. The test compound is added in a concentration range of 0.2 nanomolar to 20 millimolar. As cell-stimulatory agents, angiotensin-II (at 10 or 100 nanomolar concentration), potassium ions (at 16 millimolar), forskolin (at 10 micromolar) or a combination of two agents are used. The cellular secretion of estrone, estradiol, dihydroepiandrostendione, aldosterone, corticosterone and/or cortisol into the cell culture medium can be quantitatively assessed with

commercially available immuno-assays and specific monoclonal antibodies according to the manufacturer's instructions. The degree of secretion of a selective steroid is used as a measure of enzyme activity, respectively enzyme inhibition in the presence of absence of a test compound. The dose-dependent enzyme inhibitory activity of a compound is reflected in a inhibition curve that is characterized by an IC50 value.

[0070] The inhibition curve is generated by fitting a 4-parameter logistic function to the raw data of the samples using the least squares approach. The function is described as follows:

$$Y=(d-a)/((1+(x/c)^{-b}))+a$$

where:

[0071] a=minimal data values

[0072] b=slope

[0073] c=IC50

[0074] d=maximum

[0075] x=inhibitor concentrations

[0076] The compounds described in the present invention show Cyp19 inhibitory properties at minimal concentrations between 10^{-3} to 10^{-10} mol/l.

[0077] The aromatase inhibitory effects of described compounds can be also demonstrated in vivo using advantageous mammalian animal models such as e.g. guinea pigs, mice, rats, cats, dogs, or monkeys.

[0078] The compound-mediated in vivo inhibition of aromatase activity can be tested by monitoring plasma steroid level changes as described in the following protocol: cycling female rats are injected subcutaneously 5-times on alternate days with 100 IU of pregnant mare's serum gonadotropin (PMSG, Sigma) in 0.1 ml sterile saline. Twenty-four hours after the last injection, the animals are treated orally with test compound at doses ranging from 0.01 to 10 mg/kg. Twenty-four hours after treatment, the animals are subjected to a terminal bleed. Heparinized plasma is stored at −20° C. until analysis. Plasma levels of steroid (17beta-estradiol, estrone, estriol, progesterone, testosterone, aldosterone and cortiocosterone) are determined by commercially available radioimmunoassay kits, according to the manufacturer's instructions. A purification and concentration step is needed to measure plasma testosterone in female rats: four volumes of diethyl ether are added to the samples, mixed by gentle inversion for 15 minutes and then centrifuged for 5 minutes at 2000 rpm. The aqueous phase is frozen in dry ice and the organic phase is recovered and evaporated to dryness under a nitrogen stream. The dried extract is reconstituted in the assay buffer.

[0079] The compound-mediated in vivo inhibition of aromatase activity can be tested by monitoring the ovary estrogen content as follows: twenty-one day old female rats are injected subcutaneously with 10 IU pregnant mare serum gonadotropin (PMSG, Sigma). Two days later, the same rats are injected subcutaneously with 30 IU human chorionic gonadotropin (hCG, Sigma). On the day following the hCG treatment, the rats are injected subcutaneously with either propylene glycol (0.2 ml) or with various doses of the test compound. One hour later, all the rats are treated with 2.25 mg 4-androstene-3,17-dione in 0.1 ml oil, subcutaneously. Four hours after the injection of androstenedione, the rats are killed and their ovaries removed and trimmed free of adhering tissue and stored in pairs at −50° C. To determine the total estrogen content of the ovaries, 1.5 ml of 0.05 M aqueous potassium phosphate buffer (pH 7.4) and 0.2 ml of 0.1 N aqueous NaOH are added to the tissues which are then homogenized. The homogenate is extracted with 15 ml of diethyl ether—5 ml aliquots are radioimmunoassayed with antiserum having 100% cross-reactivity with estrone, estradiol and estriol. The results are expressed as ng estrogen/pair of ovaries.

[0080] The anti-tumor activity, especially in estrogen-dependent tumors, can be demonstrated in vivo e.g. in dimethylbenzanthracene (DMBA)-induced mammary tumors in female Sprague-Dawley rats (see Proc. Soc. Exp. Biol. Med. 160, 296-301, 1979). Compounds of the invention cause regression of existing tumors and suppress the appearence of new tumors at daily doses of about 1 to about 20 mg/kg p.o or less.

[0081] In order to achieve the desired effects in a patient to be treated, the compounds of the present invention can be administered orally or enterally, such as, for example, intravenously, intraperitoneally, intramuscularly, rectally, subcutaneously or else by direct injection of the active substance locally in tissues or tumours. The term patient encompasses warm-blooded species and mammals such as, for example, human, primate, bovine, dog, cat, horse, sheep, mouse, rat and pig. The compounds can be administered as pharmaceutical product or be incorporated into an administration device which ensures permanent release of the compound. The amount of substance to be administered can vary over a wide range and represent every effective dose. Depending on the patient to be treated or the condition to be treated and mode of administration, the dose of the effective substance each day can be between about 0.005 and 50 milligrams per kilogram of body weight, but is preferably between about 0.05 and 5 milligrams per kilogram of body weight each day.

[0082] For oral administration, the compounds can be formulated in solid or liquid pharmaceutical forms such as, for example, as capsules, pills, tablets, coated tablets, granules, powders, solutions, suspensions or emulsions. The dose of a solid pharmaceutical form can be one usual hard gelatin capsule which may be filled with active ingredients and excipients such as lubricants and fillers, such as, for example, lactose, sucrose and maize starch. Another form of administration may be represented by tableting of the active substance of the present invention. The tableting can take place with conventional tableting excipients such as, for example, lactose, sucrose, maize starch, combined with binder from gum acacia, maize starch or gelatin, disintegrants such as potato starch or crosslinked polyvinylpyrrolidone (PVPP) and lubricants such as stearic acid or magnesium stearate.

[0083] Examples of excipients suitable for soft gelatin capsules are vegetable oils, waxes, fats, semisolid and liquid polyols etc.

[0084] Examples of excipients suitable for producing solutions and syrups are water, polyols, sucrose, invert sugar, glucose etc.

[0085] For rectal administration, the compounds can be formulated in solid or liquid pharmaceutical forms such as, for example, suppositories. Examples of excipients suitable for suppositories are natural or hardened oils, waxes, fats, semiliquid or liquid polyols etc.

[0086] For parenteral administration, the compounds can be formulated as injectable dosage of the active ingredient in a liquid or suspension. The preparations usually comprise a physiologically tolerated sterile solvent which may com-

prise a water-in-oil emulsion, with or without surfactant, and other pharmaceutically acceptable excipients. Oils which can be used for such preparations are paraffins and triglycerides of vegetable, animal or synthetic origin, such as, for example, peanut oil, soya oil and mineral oil. Injectable solutions generally comprise liquid carriers such as, preferably, water, saline, dextrose or related sugar solutions, ethanol and glycols such as propylene glycol or polyethylene glycol.

[0087] The substances may be administered as transdermal patch system, as depot injection or implant if the formulation makes sustained delivery of the active ingredient possible. The active substance can be compressed as granules or to narrow cylinders and be administered subcutaneously or intramuscularly as depot injection or implant.

[0088] The pharmaceutical products may in addition also comprise preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, aromatizing agents, salts to change the osmotic pressure, buffers, coating agents or antioxidants. They may also comprise other therapeutically valuable substances too.

[0089] The present invention further provides the use of the compounds of the formula (I) or (I*) and the pharmaceutically usable salts thereof in the treatment or prevention of a disease or conditions which responds to aromatase inhibition, in particular a proliferative disease such as breast cancer or similar soft tissue endocrine-sensitive cancer, most preferably estrogen-dependent conditions like gynecomastia, mammary and endometrial tumors, endometrioisis and premature labor. The compounds are also useful for the treatment or prevention of locally advanced or metastatic breast cancer in postmenopausal women with hormone receptor positive or unknown.

[0090] The compounds of the formula (I) or (I*) and the pharmaceutically usable salts thereof may also be administered in combination with one or more agents having anti-neoplastic actions, such as anti-oestrogenic activity as described for example for exemestane, toremifene, fulvestrant, tamoxifen; such as bone resorption inhibititory activity as described for example for pamidronate, zoledronic acid, such as alkylating activity as described for busulfan, temozolomide, melphalan, chlorambucil, mechlorethalamine, such as nucleotide base intercalating activity as described for example for adriamycin, daunorubicin, dactinomcyin, doxorubicin, epirubicin, idarubicin; such as anti-metabolite activity as described for example for cytarabine, fludarabine, cladrbine, mercaptopurine, thioguanine, capecitabine; such as anti-androgenic activity as described for example for abarelix, bicalutamide; such as androgenic activity as described for example for nilutamide, methyltestosterone; such as gonadotropin releasing hormone activity as described for example for leuprolide, triptorelin, goserelin; such as progestogenic activity as described for example for medroxyprogesterone, such as nucleoside analogue activity as described for example for gemcitarabine; such as topoisomerase I inhibitory activity as described for example for topotecan, irinotecan; such as kinase inhibitory activity as described for example for imatinib; such as growth factor inhibitory activity as described for example for gefitinib, trastuzumab; such as growth hormone activity as described for example for epoetin alfa, sargramostim, filgastrim, pegfilgastrim, oprelvekin, interferon alpha 2b; such as miscellaneous anti-tumor activity as described for example for pemetrexed, dacarbazine, procarbazine, oxaliplatin, asparaginase, pegaspargase, altetamine, gemtuzumab, vinorelbine, mitoxantrone, denileukin, rituximab, alitretinoin, arsenic trioxide, bortezomib, tretinoin, docetaxel; such as antiemetic activity as described for example for dolasetron, palonosetron, aprepitant, ganisetron, dronabinol, odansetron.

[0091] The compounds described in the present invention may be used as follows:

[0092] As therapeutic combination in form of a preparation or a kit that is composed of individual components, including a herein described compound of the formula (I) or (I*) and the pharmaceutically usable salts thereof and at least one medication with anti-neoplastic activity that can be administered either simultaneously or sequentially. The preparation or the kit may contain instructions of usage.

[0093] The dose may vary within wide limits and has of course to be adapted to the individual circumstances in each individual case. In general, for oral administration, a daily dose of about 0.3 mg to about 3 g, preferably about 1 mg to about 1 g, for example about 10 mg, per adult (70 kg), divided into preferably 1-3 individual doses which may, for example, be of equal size, may be appropriate, although the upper limit specified may also be exceeded if this should be found to be appropriate; typically, children receive a lower dose according to their age and body weight.

[0094] The following examples illustrate the present invention. All temperatures are stated in degrees Celsius, pressures in mbar. Unless mentioned otherwise, the reactions take place at room temperature. The abbreviation "Rf=xx(A)" means for example that the Rf is found in solvent system A to have the value xx. The ratio amounts of solvents to one another is always stated in proportions by volume. Chemical names of final products and intermediates were generated with the aid of the AutoNom 2000 (Automatic Nomenclature) program.

[0095] HPLC gradients on Hypersil BDS C-18 (5 μm); column: 4×125 mm

[0096] 95% water*/5% acetonitrile* to 0% water*/100% acetonitrile* in 10 minutes+2 minutes (1 ml/min).

[0097] * contains 0.1% trifluoroacetic acid

[0098] The following abbreviations are used:

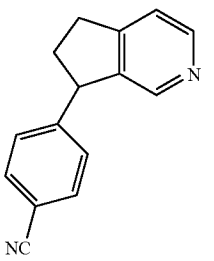
[0099] Rf ratio of the distance migrated by a substance to the distance of the solvent from the starting point in thin-layer chromatography

[0100] Rt retention time of a substance in HPLC (in minutes)

[0101] m.p. melting point (temperature)

EXAMPLE 1

[0102]



[0103] 4-(6,7-Dihydro-5H-[2]pyridin-2-yl)benzonitrile hydrochloride

[0104] A solution of 1.240 mmol of N-tert-butyl-4-(6,7-dihydro-5H-[2]pyridin-7-yl)benzamide and 1.0 ml of thionyl chloride in 30 ml of chloroform is stirred under reflux for 6 hours. The reaction mixture is cooled to room temperature and evaporated. The residue is taken up in dichloromethane and mixed with saturated aqueous sodium bicarbonate solution. The organic phase is separated off and the aqueous phase is extracted with dichloromethane (2×). The combined organic phases are dried with sodium sulphate and evaporated. The residue is dissolved in diethyl ether, and the title compound is converted into the hydrochloride salt by adding ethereal HCl solution (2 N). The solid is stirred in diethyl ether/acetone (1:1), filtered and dried. The title compound is obtained as a dark grey solid. Rf (free base)=0.36 (EtOAc); Rt=4.98.

[0105] The starting materials are prepared as follows:

[0106] a) N-tert-Butyl-4-(6,7-dihydro-5H-[2]pyridin-7-yl) benzamide

[0107] A solution of 1.250 mmol of N-tert-butyl-4-(5H-[2]pyridin-7-yl)benzamide in 10 ml of ethanol is mixed with 360 mg of 10% Pd/C, and the reaction mixture is then hydrogenated at 20-25° C. under atmospheric pressure for 6 hours. The reaction mixture is clarified by filtration and the filtrate is evaporated. The crude title compound is obtained as a brown oil from the residue.

[0108] b) N-tert-Butyl-4-(5H-[2]pyridin-7-yl)benzamide

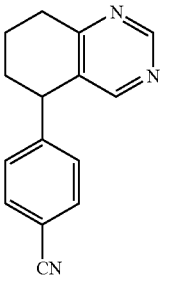
[0109] A solution of 1.260 mmol of N-tert-butyl-4-(7-hydroxy-6,7-dihydro-5H-[2]pyridin-7-yl)benzamide in 20 ml of 4 M HCl is stirred at 50° C. for 20 hours. The reaction mixture is cooled to room temperature and cautiously adjusted to pH 8 with saturated aqueous sodium bicarbonate solution. The aqueous phase is extracted with dichloromethane (3×)—the combined organic phases are dried with sodium sulphate and evaporated. The crude title compound is obtained as a yellow oil from the residue. Rt=5.47.

[0110] c) N-tert-Butyl-4-(7-hydroxy-6,7-dihydro-5H-[2] pyridin-7-yl)benzamide

[0111] 5.3 ml of n-butyllithium (1.6 M in hexane) are added dropwise to a solution of 4.250 mmol of 4-bromo-N-tert-butylbenzamide in 70 ml of tetrahydrofuran at −78° C. After 30 minutes, a solution of 3.270 mmol of 5,6-dihydro-[2]pyridin-7-one [51907-18-7] in 10 ml of tetrahydrofuran is added dropwise. The reaction mixture is stirred at −78° C. for 1 hour and at room temperature for 2 hours and then quenched with saturated aqueous ammonium chloride solution. The organic phase is separated off and the aqueous phase is extracted with ethyl acetate (2×). The combined organic phases are dried with sodium sulphate and evaporated. The title compound is obtained as a white foam from the residue by flash chromatography (SiO_2 60 F). Rf=0.29 (toluene:methanol=85:15), Rt=5.00.

Example 2

[0112]



[0113] 4-(5,6,7,8-Tetrahydroquinazolin-5-yl)benzonitrile

[0114] A solution of 0.480 mmol of 4-(7,8-dihydroquinazolin-5-yl)benzonitrile in 12 ml of ethanol is mixed with 33 mg of 10% Pd/C, and the reaction mixture is then hydrogenated at 20-25° C. under atmospheric pressure for 50 hours. The reaction mixture is clarified by filtration, and the filtrate is evaporated. The title compound is obtained as a yellow oil from the residue by flash chromatography (SiO_2 60 F). Rf=0.26 (dichloromethane:methanol=95.5); Rt=5.92.

[0115] The starting materials are prepared as follows:

[0116] a) 4-(7,8-Dihydroquinazolin-5-yl)benzonitrile

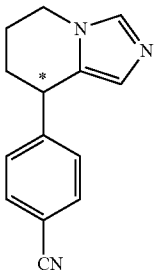
[0117] A solution of 0.500 mmol of 4-(5-hydroxy-5,6,7,8-tetrahydroquinazolin-5-yl)benzonitrile in 1.25 ml of 2 M HCl is stirred at 50° C. for 8 hours. The reaction mixture is cooled to room temperature and cautiously adjusted to pH 8 with saturated aqueous sodium bicarbonate solution. The aqueous phase is extracted with ethyl acetate (3×) and the combined organic phases are dried with sodium sulphate and evaporated. The crude title compound is obtained as a yellow oil from the residue. Rf=0.20 (toluene:methanol=85:15), Rt=6.21.

[0118] b) 4-(5-Hydroxy-5,6,7,8-tetrahydroquinazolin-5-yl)benzonitrile

[0119] 1.0 ml of isopropylmagnesium chloride (2.0 M in tetrahydrofuran) is added dropwise to a solution of 2.000 mmol of 4-iodobenzonitrile in 5 ml of tetrahydrofuran at −20° C. After 30 minutes, a solution of 1.000 mmol of 7,8-dihydro-6H-quinazolin-5-one [21599-28-0] in 2 ml of tetrahydrofuran is added dropwise. The reaction mixture is stirred at −20° C. for 30 minutes and at room temperature for 1 hour and then quenched with 0.1 M HCl. The organic phase is separated off and the aqueous phase is extracted with dichloromethane (2×). The combined organic phases are dried with sodium sulphate and evaporated. The title compound is obtained as a brown oil from the residue by flash chromatography (SiO_2 60 F). Rf=0.16 (toluene:methanol=85:15), Rt=5.15.

Example 3

[0120]



[0121] (S or R)-4-(5,6,7,8-Tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzonitrile

[0122] The preparative separation of the enantiomers of (rac)4-(5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzonitrile is performed with a Chiralpak AD-H column (5 μm, 250×20 mm) using 70:30:0.1 heptane/ethanol/diethylamine as the mobile phase at a flow rate of 50 ml/min. For analytical determinations of the optical purity, a Chiralpak AD-H column (5 μm, 250×4.6 mm) using 70:30:0.1 heptane/ethanol/diethylamine as the mobile phase at a flow rate of 1 ml/min is employed. The first eluting enantiomer is concentrated in vacuo to provide the title compound as a white solid. Rt=10.6.

[0123] The starting materials are prepared as follows:

[0124] a) (rac)-4-(5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzonitrile

[0125] Analogously to Example 1, 1.74 mmol of N-tert-Butyl-4-(5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzamide hydrochloride are reacted. The title compound is obtained as a cream-colored solid. Rf=0.37 (toluene:methanol=85:15); Rt=4.88

[0126] b) N-tert-Butyl-4-(5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzamide hydrochloride

[0127] Analogously to Example 1a, 1.79 mmol of N-tert-Butyl-4-(5,6-dihydro-imidazo[1,5-a]pyridin-8-yl)-benzamide hydrochloride are reacted. The crude title compound is obtained as a brown solid. Rf=0.35 (toluene:methanol=85:15), Rt=5.54

[0128] c) N-tert-Butyl-4-(5,6-dihydro-imidazo[1,5-a]pyridin-8-yl)-benzamide hydrochloride

[0129] Analogously to Example 1b, 1.85 mmol of N-tert-Butyl-4-(8-hydroxy-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzamide are reacted. The crude title compound is obtained as a grey solid. Rt=5.54

[0130] d) N-tert-Butyl-4-(8-hydroxy-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-8-yl)-benzamide

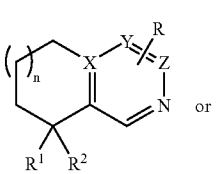
[0131] Analogously to Example 1c, 6.00 mmol of 6,7-dihydro-5H-imidazo[1,5-a]pyridin-8-one [51907-18-7] are reacted. The title compound is obtained as a yellow solid. Rf=0.16 (dichlormethane:methanol=95:5), Rt=4.96

[0132] The following compound is prepared in a manner analogous to the processes described in Examples 1-3.

Example

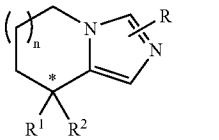
[0133] 4 4-(5,6,7,8-Tetrahydroisoguinolin-8-yl)benzonitrile starting from 6,7-dihydro-5H-isoquinolin-8-one [21917-88-4]

1. Compound of the general formula



(I)

or



(I*)

in which,

X is C;

Y is C or N;

Z is C;

R

a) is hydrogen; or

b) is C_1-C_8-alkyl, C_1-C_8-alkoxy, halogen or trifluoromethyl;

R^1 is aryl-C_0-C_4-alkyl or unsaturated heterocyclyl-C_0-C_4-alkyl, which radicals are unsubstituted or substituted by 1-4 C_1-C_8-alkoxy, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkyl, C_0-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, aryl-C_0-C_4-alkoxycarbonyl, aryl, cyano, halogen, heterocyclyl, oxo, trifluoromethoxy, trifluoromethyl or tri-C_1-C_4-alkylsilyl;

R^2

a) is hydrogen; or

b) is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, halogen, carboxy-C_1-C_4-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, C_0-C_4-alkylcarbonyl, aryl-C_0-C_4-alkyl or unsaturated heterocyclyl-C_1-C_4-alkyl, which radicals are unsubstituted or substituted by 1-4 C_1-C_8-alkoxy, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkyl, C_0-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, aryl-C_0-C_4-alkoxycarbonyl, aryl, cyano, halogen, heterocyclyl, oxo, trifluoromethoxy, trifluoromethyl or tri-C_1-C_4-alkylsilyl;

n is a number 0, 1 or 2;

whereby the term heterocyclyl stands for a saturated, partially saturated or unsaturated, 4-8-membered monocyclic ring system, for a saturated, partially saturated or unsaturated, 7-12-membered bicyclic ring system and also for a saturated, partially saturated or unsaturated, 7-12-membered tricyclic ring system, in each case comprising an N, O or S atom in at least one ring;

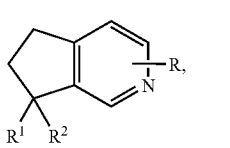
* designates an asymmetric carbon atom

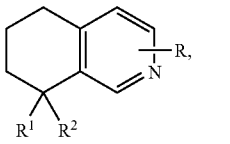
and its salt, prodrug or compound in which one or more atoms are replaced by their stable, nonradioactive isotopes, in particular pharmaceutically usable salt,

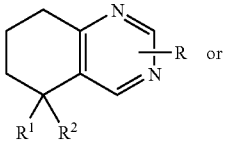
where, if X, Y and Z are C, R^1 is not an unsubstituted or alkoxy-substituted benzyl radical;

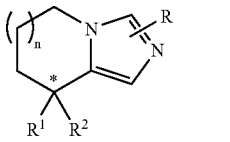
and excluding the compounds 5,6,7,8-tetrahydro-8-(4-pyridinyl)-isoquinoline and 5,6,7,8-tetrahydro-8-(4-pyridinyl)-isoquinoline.

2. Compound according to claim **1**, characterized in that it corresponds to the general formula


(Ia)


(Ib)


(Ic)


(I*)

where the meanings of R, R^1, R^2 and n are as indicated for compounds of the formula (I) or (I*) according to claim **1**.

3. Compound according to claim **1**, where R is hydrogen or C_1-C_8-alkyl, particularly preferably hydrogen or methyl.

4. Compound according to claim **1**, where R^1 is aryl or unsaturated heterocyclyl, very particularly preferably optionally mono- or disubstituted benzofuranyl, benzothiophenyl, indazolyl, indolyl, phenyl, pyrrolyl, thiazolyl, thiophenyl or oxazolyl.

5. Compound according to claim **1**, where R^2 is hydrogen, halogen, C_1-C_8-alkyl or aryl-C_1-C_4-alkyl.

6. Compound according to claim **1**, where n is a number 0 or 1.

7. Compound according to claim **2**, where

R is hydrogen or C_1-C_8-alkyl;

R^1 is aryl or unsaturated heterocyclyl, in each case optionally substituted by halogen, cyano, trifluoromethyl, heterocyclyl or C_1-C_8-alkylcarbonyl; and

R^2 is hydrogen, halogen, C_1-C_8-alkyl or aryl-C_1-C_4-alkyl.

8-9. (canceled)

10. Method for the prevention, for delaying the progression or for the treatment of a disease or condition which responds to aromatase inhibition where a therapeutically effective amount of a compound of the general formula (I) or (I*) according to claim **1** is used.

11. Pharmaceutical product comprising a compound of the general formula (I) or (I*) according to claim **1**, and conventional excipients.

12. Compound according to claim **2**, where R is hydrogen or C_1-C_8-alkyl, particularly preferably hydrogen or methyl.

13. Compound according to claim **2**, where R^1 is aryl or unsaturated heterocyclyl, very particularly preferably optionally mono- or disubstituted benzofuranyl, benzothiophenyl, indazolyl, indolyl, phenyl, pyrrolyl, thiazolyl, thiophenyl or oxazolyl.

14. Compound according to claim **2**, where R^2 is hydrogen, halogen, C_1-C_8-alkyl or aryl-C_1-C_4-alkyl.

15. Method for the prevention, for delaying the progression or for the treatment of a disease or condition which responds to aromatase inhibition, where a therapeutically effective amount of a compound of the general formula (Ia), (Ib), (Ic) or (Id) according to claim **2** is used.

16. Method for the prevention, for delaying the progression or for the treatment of a disease or condition which is a proliferative disease, where a therapeutically effective amount of a compound of the general formula (I) or (I*) according to claim **1** is used.

17. Method for the prevention, for delaying the progression or for the treatment of a disease or condition which is a proliferative disease, where a therapeutically effective amount of a compound of the general formula (Ia), (Ib), (Ic) or (Id) according to claim **2** is used.

18. Pharmaceutical product comprising a compound of the general formula (Ia), (Ib), (Ic) or (Id) according to claim **2**, and conventional excipients.

* * * * *