Quinoline, isoquinoline and phthalazine derivatives as antagonists of the gonadotropin-releasing hormone

Description

Gonadotropin-releasing hormone (GnRH) is a hormone which is synthesized mainly, but not exclusively, in mammals by nerve cells of the hypothalamus, transported to the hypophysis via the portal vein and released in a regulated manner in the gonadotropic cells. By interaction with its receptor, which has 7 transmembrane domains, GnRH stimulates the production and the release of gonadotropic hormones by means of the second messenger inositol-1,4,5-trisphosphate and Ca^{2+} ions. The gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secreted by GnRH stimulate the production of sexual steroids and germ-cell maturation in both sexes. In addition to GnRH (also designated GnRH1), there are two further forms of GnRH, namely GnRH2 and 3.

The GnRH receptor is used as a pharmacological target in a number of diseases which are dependent on functioning sex hormone production, for example prostate cancer, premenopausal breast cancer, endometriosis and uterine fibroids. In these diseases, GnRH superagonists or superantagonists can be employed successfully. In particular, male fertility control in combination with a substitution dose of androgens forms a possible further indication.

An advantage of GnRH antagonists in comparison with superagonists is their immediate efficacy in blocking gonadotropin secretion. Superagonists initially bring about an overstimulation of the hypophysis, which leads to increased secretions of gonadotropin and sexual steroid.

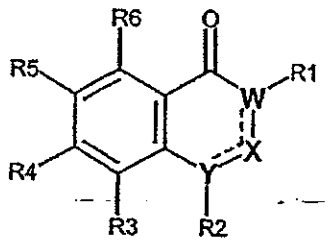
This hormonal reaction is ended only after a certain delay on account of desensitization and downregulation of the GnRH receptor concentrations. Possibly, GnRH superagonists, both on their own and in combination with testosterone, can therefore not effectively suppress sperm production in men and are thus not suitable for male fertility control. In contrast to this, peptide GnRH antagonists, in particular in combination with a substitution dose of androgens, are able to produce significant oligozoospermia in man.

Peptide GnRH antagonists, however, have a number of disadvantages. They for instance have a considerably lower activity than superagonists and must consequently be administered in considerably higher doses. Their oral bioavailability is also low, so that they need to be administered by injection. Repeated injections in turn lead to a lowering of compliance. Moreover, the synthesis of peptide GnRH antagonists in comparison with nonpeptide compounds is laborious and expensive.

Quinoline derivatives as nonpeptide GnRH antagonists are disclosed, for example, in WO97/14682. Up to now, however, no nonpeptide GnRH antagonists have been brought onto the market.

The object underlying the present invention consisted in making available novel GnRH antagonists which are superior to known peptide compounds and represent an effective alternative to known nonpeptide compounds. The novel GnRH antagonists should possess both a high activity and also a high oral bioavailability. Furthermore, they should be able to be synthesized simply and with costs which are as low as possible.

A first aspect of the invention provides a compound of the general formula (1):



(1)

in which

R^1 (a) is an acyl group -CO-R11 or CN, where R11 is a saturated, unsaturated, cyclic or/and (hetero)-aromatic organic radical, in particular a linear or branched alkyl chain having 1-10 C atoms, or a phenyl, furan or thiophene group optionally substituted by alkyl groups or halogen atoms, and

(b) a carboxylic acid ester group -CO-OR12 or carboxamide group -CO-NR12NR13 or a group $-SO_x$-R12 where X = 0, 1 or 2 or $-SO_2$-NR12NR13, where R12 is a saturated, unsaturated, cyclic or/and (hetero)-aromatic organic radical, in particular a linear or branched alkyl chain having 1-10 C atoms, an aralkyl group having 7-20 C atoms, where the aryl radical can optionally be substituted by alkyl groups or halogen atoms, or a phenyl radical optionally substituted by alkyl groups or halogen atoms and R13 can be a hydrogen atom or a linear or branched alkyl chain having 1-10 C atoms,

or

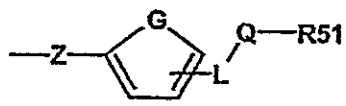
(c) is the group -A-NR14-CO-NR15R16, in which A is an alkylene group having 1-4 C atoms, in particular having 1 C atom, optionally substituted by a C_1-C_6-alkyl group, a carbonyl group, an oxygen atom or the group $-SO_x$- where X = 0, 1 or 2, R14 and R15 in each case independently are a hydrogen atom or a linear or branched alkyl chain having 1-10 C atoms and R16 is a linear or branched alkyl chain having 1-10 C atoms, a cycloalkyl group having 3-10 C atoms, a cycloalkylalkyl group having 7-20 C atoms, an aralkyl group having 7-20 C atoms, where the aryl radical can optionally be

substituted by alkyl groups or halogen atoms, a phenyl group optionally substituted by alkyl groups or halogen atoms, or a heterocyclic ring optionally substituted by alkyl groups or halogen atoms,

R2 is a group -CH(R21)R22, where R21 is a hydrogen atom, a C_1-C_{10}-alkyl group or an optionally substituted phenyl ring and R22 is an optionally substituted phenyl ring or naphthyl ring, or a group $-CH_2CH(R23)R24$, with R23 and R24 meaning an optionally substituted phenyl ring,

R3 and R4 in each case independently can be a hydrogen atom or an alkyl group having 1-10 C atoms and R3 can also be a halogen atom,

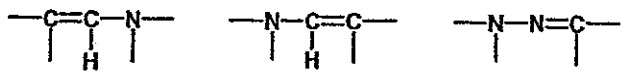
R5 is a group linked via the radical Z,



in which G is -C=C-, -C=N-, -N=C-, an oxygen or sulfur atom, Z is a direct bond, an oxygen or a sulfur atom, the group CH-R52 or -CHR52-CH-R53-, where R52 and R53 independently of one another have the meaning of a hydrogen atom or an alkyl group and n is the numbers 1 and 2, a -C≡C- triple bond or a group -CR52=CR53- or C=CR52R53 having the E or Z configuration, where R52 and R53 independently of one another have the meaning of a hydrogen atom or an alkyl group, L is a CH_2 or an NH group, Q is a carbonyl or $-SO_X$ group where X = 0, 1 or 2 and R51 is an amino group optionally substituted by an alkyl group, or a linear or branched alkyl group optionally substituted by halogen atoms, hydroxyl or alkoxy groups, or a cycloalkyl group having 3-7 ring members, optionally substituted by halogen atoms, hydroxyl or alkoxy groups,

R6 is the group CH_2-N(R61)R62, where R61 in each case independently is a hydrogen atom or an alkyl group and R62 is an alkyl group or an optionally substituted aralkyl group or heteroarylalkyl group having 7-20 C atoms and

—W=X=Y— can be the groups



in any orientation, and further all stereoisomers of the structures mentioned, and salts thereof with physiologically tolerable acids or bases.

In the compounds of the formula (1), by way of example

In R1 *Linear or branched alkyl chain:* means a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, n-pentyl, 2,2-dimethylpropyl or 3-methylbutyl group, an n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl group. The methyl or ethyl group is preferred.

A phenyl group optionally substituted by alkyl groups or halogen atoms: means a phenyl, an o-, m-, p-methyl-, ethyl-, propyl-, isopropylphenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-dimethyl- or -diethylphenyl group, an o-, m-, p-fluoro-, chloro-, bromo-, iodophenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-, difluoro-, dichloro-, dibromo-, or diiodophenyl group or a naphthyl group. A phenyl group is preferred.

An optionally substituted furan or thiophene group: means an unsubstituted 2- or 3-thienyl group or 2- or 3-furyl group or a 3-methyl-, 3-ethyl-, 3-fluoro-, 3-chloro-, 3-bromo-, 3-iodo-2-furyl or -2-thienyl group, a 4-methyl-, 4-ethyl-, 4-fluoro-, 4-chloro-,

4-bromo-, 4-iodo-2-furyl or -2-thienyl group, a 5-methyl-, 5-ethyl-, 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-2-furyl or -2-thienyl group, a 2-methyl-, 2-ethyl-, 2-fluoro-, 2-chloro-, 2-bromo-, 2-iodo-3-furyl or -3-thienyl group, a 4-methyl-, 4-ethyl-, 4-fluoro-, 4-chloro-, 4-bromo-, 4-iodo-3-furyl or -3-thienyl group, a 5-methyl-, 5-ethyl-, 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-3-furyl or -3-thienyl group. A 2-thienyl or 2-furyl group is preferred.

An aralkyl group having 7-20 C atoms: means a benzyl group, a 1-phenylethyl, -propyl, -butyl, -hexyl, -2-methlethyl, -2-ethylethyl, -2,2-dimethylethyl group, an o-, m-, p-methyl-, ethyl-, propyl-, isopropylbenzyl group, a 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, 3',5'-dimethyl- or -diethylbenzyl group, a 2'-, 3'-, 4'-fluoro-, chloro-, bromo-, iodobenzyl group, a 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, 3',5'-, difluoro-, dichloro-, dibromo-, or diiodobenzyl group or a 2- or 3-naphthylmethyl group, a 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl group.

A C_1-C_6-alkyl group: means a linear or branched alkyl group having 1-6 C atoms such as a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, n-pentyl, 2,2-dimethylpropyl or 3-methylbutyl group.

A cycloalkyl radical: means a cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, decahydronaphthalene radical.

A cycloalkylalkyl radical: means a cyclopropyl-, cyclobutyl-, cyclopentyl-, cyclohexyl-, cycloheptylmethyl radical, a 1-cyclopropyl-, 1-cyclobutyl-, 1-cyclopentyl-,

1-cyclohexyl-, 1-cycloheptylethyl radical, a 2-cyclopropyl-, 2-cyclobutyl-, 2-cyclopentyl-, 2-cyclohexyl-, 2-cycloheptylethyl radical.

A heterocyclic ring: means an unsubstituted 2- or 3-thienyl or 2- or 3-furyl group or a 3-methyl-, 3-ethyl-, 3-fluoro-, 3-chloro-, 3-bromo-, 3-iodo-2-furyl or -2-thienyl group, a 4-methyl-, 4-ethyl-, 4-fluoro-, 4-chloro-, 4-bromo-, 4-iodo-2-furyl or -2-thienyl group, a 5-methyl-, 5-ethyl-, 3-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-2-furyl or -2-thienyl group, a 2-methyl-, 2-ethyl-, 2-fluoro-, 2-chloro-, 2-bromo-, 2-iodo-3-furyl or -3-thienyl group, a 4-methyl-, 4-ethyl-, 4-fluoro-, 4-chloro-, 4-bromo-, 4-iodo-3-furyl or -3-thienyl group, a 5-methyl-, 5-ethyl-, 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-3-furyl or -3-thienyl group, an unsubstituted 2-, 3- or 4-pyridyl group or a 3-methyl-, 3-ethyl-, 3-fluoro-, 3-chloro-, 3-bromo-, 3-iodo-2-pyridyl group, a 4-methyl-, 4-ethyl-, 4-fluoro-, 4-chloro-, 4-bromo-, 4-iodo-2-pyridyl group, a 5-methyl-, 5-ethyl-, 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-2-pyridyl group, a 2-methyl-, 2-ethyl-, 2-fluoro-, 2-chloro-, 2-bromo-, 2-iodo-3-pyridyl group, a 4-methyl-, 4-ethyl-, 4-fluoro-, 4-chloro-, 4-bromo-, 4-iodo-3-pyridyl group, a 5-methyl-, 5-ethyl-, 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-3-pyridyl group, a 2-, 4-, 5-, 6-pyrimidinyl group, a 3-, 4-, 5-, 6-pyridazinyl group or a 2- or 3-pyrazinyl group.

In R2 *An alkyl group:* means a linear or branched alkyl group having 1-6 C atoms such as a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, n-pentyl, 2,2-dimethylpropyl or 3-

methylbutyl group. A hydrogen atom is preferred.

An optionally substituted phenyl ring or naphthyl ring: means a phenyl, an o-, m-, p-methyl-, -ethyl-, -propyl-, -isopropylphenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-dimethyl- or -diethylphenyl group, an o-, m-, p-fluoro-, chloro-, bromo-, iodophenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-difluoro-, dichloro-, dibromo-, or diiodophenyl group, an o-, m-, p-trihalomethylphenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-ditrihalophenyl group, an o-, m-, p-methoxy-, -ethoxy-, -propoxy-, -isopropoxyphenyl group or a naphthyl group. A 2,5-difluorophenyl group is preferred.

In R3 and R4 *An alkyl group:* means a linear or branched alkyl group having 1-6 C atoms such as a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, n-pentyl, 2,2-dimethylpropyl or 3-methylbutyl group. A hydrogen atom is preferred.

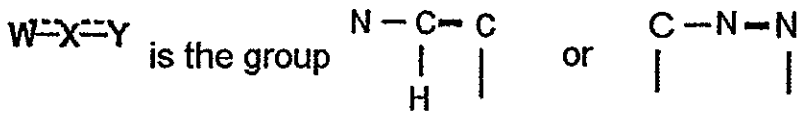
In R5 *An alkyl group:* means a linear or branched alkyl group having 1-6 C atoms such as a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, n-pentyl, 2,2-dimethylpropyl or 3-methylbutyl group. A hydrogen atom is preferred.

In R6 *An alkyl group:* means a linear or branched alkyl group having 1-6 C atoms such as a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, n-pentyl, 2,2-dimethylpropyl or 3-methylbutyl group. A methyl group is preferred.

An aralkyl group having 7-20 C atoms: means a benzyl group, a 1-phenylethyl, -propyl, -butyl, -hexyl, -2-methlethyl, -2-ethyl-ethyl, -2,2-dimethylethyl group, an o-, m-, p-methyl-, ethyl-, propyl-, isopropylbenzyl group, a 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, 3',5'-dimethyl- or -diethylbenzyl group, a 2'-, 3'-, 4'-fluoro-, chloro-, bromo-, iodobenzyl group, a 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, 3',5'-, difluoro-, dichloro-, dibromo-, or diiodobenzyl group or a 2- or 3-naphthylmethyl group, a 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl group.

A heteroaralkyl group having 7-20 C atoms: means a 2-, 3-, or 4-pyridylmethyl, -ethyl, or -propyl group, a 2- or 3-furylmethyl, -ethyl, or -propyl group, a 2- or 3-thienylmethyl, -ethyl, or -propyl group, a 2-, 3-, 4-, 5-, 6-, or 7-indolylmethyl, -ethyl or -propyl group. The benzyl group is preferred.

Preferred compounds of the formula (1) are those in which



If R1 is the group -CO-R11, then R11 has, for example, the preferred meaning methyl, ethyl, i-propyl, phenyl, 2-thienyl and 2-furyl. If R1 has the meaning -CO-OR12, then R12 can be, for example, preferably methyl, ethyl or i-propyl.

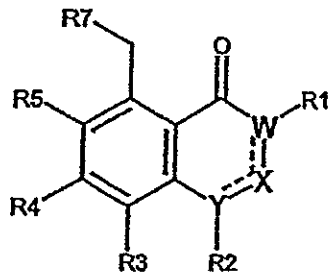
Compounds are furthermore preferred in which R2 is an aromatic group substituted on the aromatic ring by one or more halogen atoms, in particular fluorine atoms, e.g. a benzyl group, for example a 2',6'-difluorobenzyl

group. Compounds are likewise preferred in which at least one of R^3 and R^4, in particular both, are hydrogen atoms.

A preferred meaning of Z is a direct bond or an oxygen atom, while G is preferably a -C=C- group. L is preferably an NH group, while Q is preferably a carbonyl group and R51 is a C_1-C_6-alkyl group. Particularly preferred meanings for R61 are hydrogen atoms or C_1-C_3-alkyl groups, in particular methyl groups, and for R62 an aralkyl radical, e.g. a benzyl group.

A second aspect of the invention provides a process for the preparation of compounds of the general formula (1) by

(a) reaction of a compound of the general formula (2)



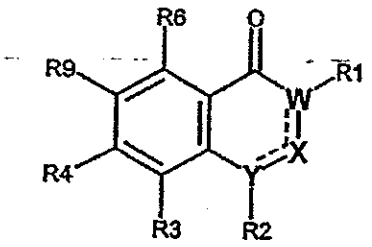
(2)

where R7 is a leaving group, e.g. a halogen atom or an alkyl-, perfluoroalkyl- or arylsulfonyl group and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (3)

R8-N(R61)R62 **(3)**

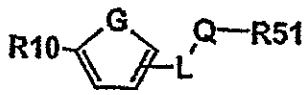
where R8 is a hydrogen atom or a metal atom, such as, for example, a lithium, sodium, potassium, cesium, calcium or barium atom and R61 and R62 have the meanings indicated in compound (1),

(b) reaction of a compound of the general formula (4)



(4)

in which R9 is the group $-OSO_2C_nF_{2n+1}$, a halogen atom, particularly a bromine or iodine atom or another leaving group, and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (5)

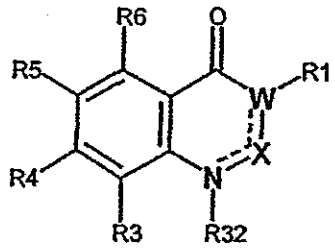


(5)

where R10 is a group containing a metal, such as a trialkyltin group, a halomagnesium group or a group containing a nonmetal, such as boron, silicon etc., group containing, a dialkoxyboron or a dihydroxyboron group, a hydroxyl or mercapto group optionally converted into a metal salt, such as, for example, a lithium, sodium, potassium, cesium, calcium, barium, silver or copper salt, the group -C≡C-R31 or a group -CR52=CR53R31 or -CR31=CR52R53 having the E or Z configuration, in which R31 is a group containing a metal or a nonmetal, such as boron, silicon etc., such as a trialkyltin group, a halomagnesium group, a dialkoxyboron group or a dihydroxyboron group, and all other radicals have the meaning indicated in compound (1), with or without participation of a catalyst, such as, for

example, copper, nickel, palladium, platinum or organic derivatives of the metals mentioned;

(c) if Y in compound (1) is a nitrogen atom, by reaction of a compound of the general formula (6)



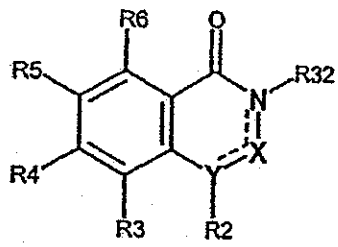
(6)

where R32 is a hydrogen atom or a metal atom, such as, for example, a lithium, sodium, potassium, cesium, calcium, barium, silver or copper atom, and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (7)

R33R2 **(7)**

where R33 is a leaving group, e.g. a halogen atom or an alkyl-, perfluoroalkyl- or aryl-sulfonyl group, and R2 has the meaning indicated in compound (1), or

(d) if W in compound (1) is a nitrogen atom, by reaction of a compound of the general formula (8)



(8)

where R32 is a hydrogen atom or a metal atom, such as, for example, a lithium, potassium, cesium, calcium, barium, silver or copper atom, and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (9)

R33-R1 **(9)**

where R33 is a leaving group, e.g. a halogen atom or an alkyl-, perfluoroalkyl- or arylsulfonyl group, and R1 has the meaning indicated in compound (1).

A third aspect of the invention provides the compounds as defined in the first aspect and its embodiments for use in therapy.

The compounds (1) as defined in the first aspect and its embodiments can be
employed as antagonists of gonadotropin-releasing hormone, for example for male fertility control, for hormone therapy, for the treatment of female sub- and infertility, for female contraception and for tumor control.

In male fertility control, the compounds as defined in the first aspect and its embodiments bring about a lowering of spermatogenesis. Preferably, combined administration with androgens takes place, e.g. testosterone or testosterone derivatives, such as, for example, testosterone esters. The administration of the testosterone derivatives can be carried out, for example, by injection, e.g. by intramuscular depot injection.

A fourth aspect of the invention provides a use of the compounds as defined in the first aspect and its embodiments for the manufacture of a medicament for treating endometriosis, uterine leiomyomas, and uterine fibroids, for controlling male fertility, for the treatment of female sub- and infertility, for female contraception and for tumor control.

In hormone therapy too, for example for the treatment of endometriosis, uterine leiomyomas and uterine fibroids, the compounds (1) can optionally be employed in combination with other hormones, e.g. estrogens or/ and progestins. Combinations of the GnRH antagonists according to the invention and tissue-selective partial estrogen agonists such as Raloxifene® are particularly preferred. Moreover, the compounds (1) as defined in the first aspect and its embodiments

can be employed for increasing female fertility, for example by inducing ovulation, and the treatment of sterility.

On the other hand, the compounds (1) are also suitable for contraception in women. Thus the GnRH antagonist can be administered on days 1 to 15 of the cycle together with estrogen, preferably with very low estrogen doses. On days 16 to 21 of the taking cycle, progestagen is added to the estrogen-GnRH antagonist combination. The GnRH antagonist can be administered continuously over the entire cycle period. In this way, a lowering of the hormone doses and thus a lowering of the side effects of nonphysiological hormone levels can be achieved. Furthermore, advantageous effects can be achieved in women who suffer from polycystic ovarian syndrome and androgen-dependent diseases such as acne, seborrhea and hirsutism. An improved cycle control compared with previous administration methods is also to be expected. Further indications are benign prostate hyperplasia, gonadal protection during chemotherapy, controlled ovarian stimulation/artificial reproduction techniques, early infantile developmental disorders, e.g. precocious puberty and polycystic ovaries.

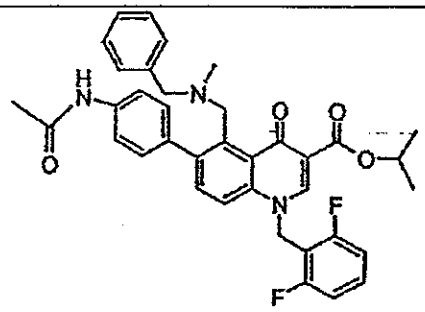
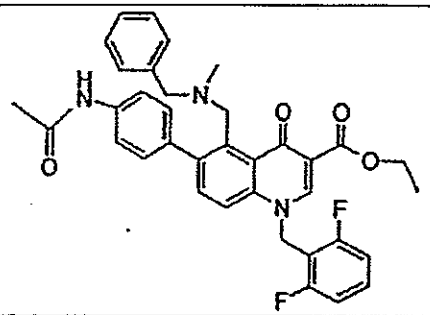
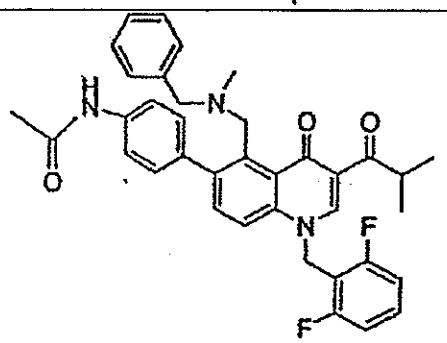
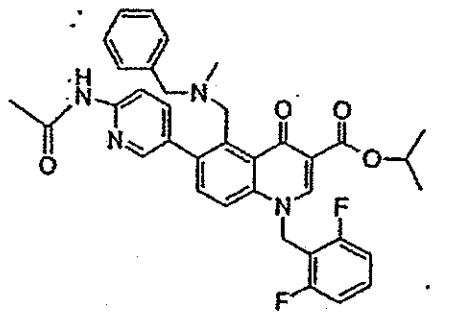
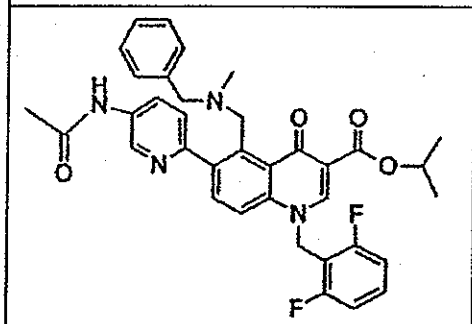
An embodiment may relate to the GnRH agonists being employed for the treatment of hormone-dependent oncoses, such as premenopausal breast cancer, prostate cancer, ovarian cancer and endometrial cancer in that they suppress the endogenous sexual steroid hormones.

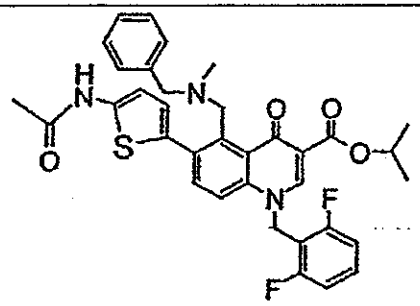
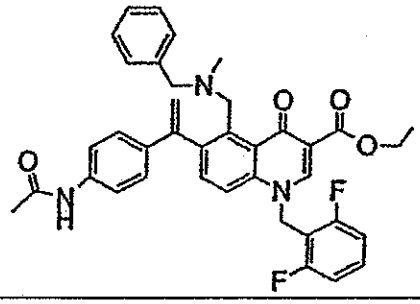
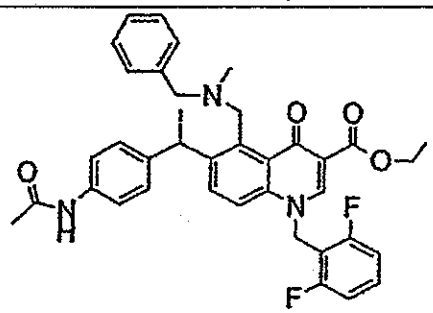
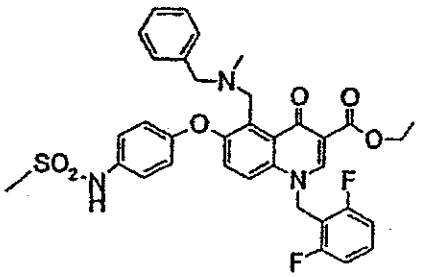
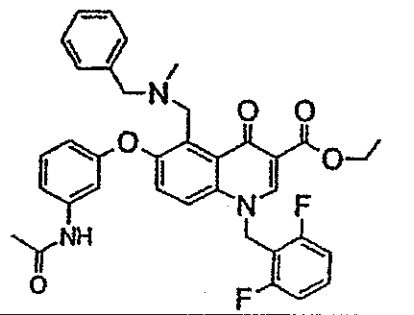
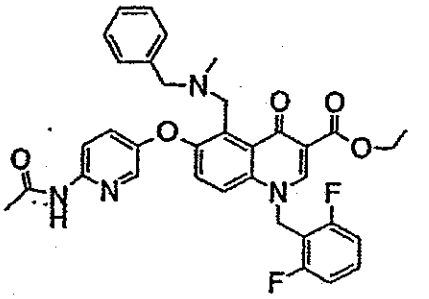
The compounds (1) as defined in the first aspect and its embodiments are
suitable as GnRH antagonists for administration to man, but also for veterinary medical purposes, e.g. in domestic and productive animals, but also in wild animals.

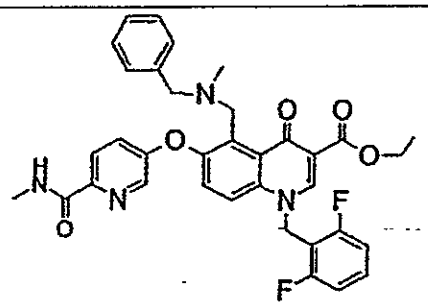
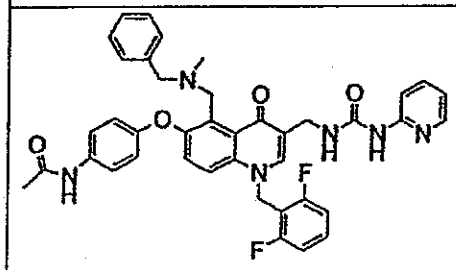
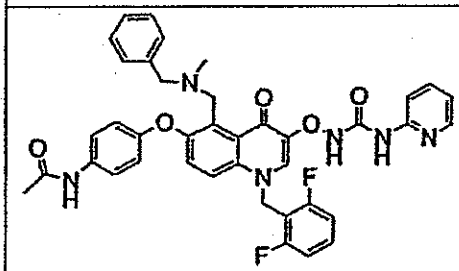
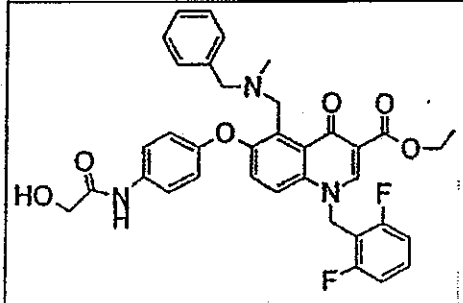
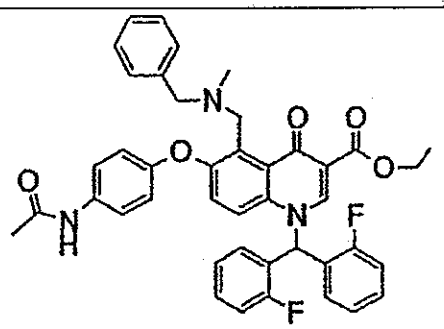
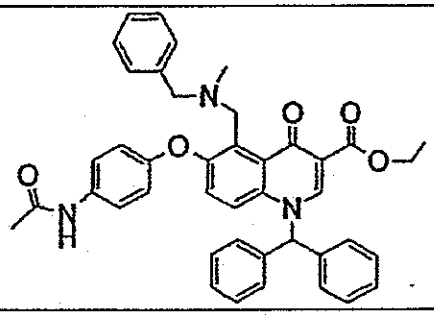
Administration can be carried out in a known manner, for example orally, topically, rectally, intravaginally, nasally or by injections. Oral administration is preferred. The compounds (1) are brought into a form capable of administration and optionally mixed with pharmaceutically acceptable vehicles and/or diluents. Oral administration can be carried out, for example, in solid form as tablets, capsules, coated tablets or powders, but also in the form of a drinkable solution. Nonoral administration can be carried out, for example, by means of intravenous, subcutaneous or intramuscular injection or by means of ointments, creams or suppositories. Optionally, it is also possible to carry out administration as a delayed-release form. The dose can vary depending on the type of indication, the severity of the disease, the age, sex, body weight and the sensitivity of the subject to be treated. Preferably, doses of 0.01 to 30 mg, particularly preferably of 0.1 to 3 mg and most preferably of 0.1 to 1 mg per kilogram of body weight per day are administered. Administration can be carried out in a single dose or a number of a separate doses.

A number of particularly preferred compounds (1) are listed below:

Particularly preferred compounds

	2-Propyl 6-(4-acetamidophenyl)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl 6-(4-acetamidophenyl)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	6-(4-Acetamidophenyl)-3-iso-butyryl-5-(N-benzyl-N-methyl-aminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline
	Isopropyl 6-(2-acetamido-5-pyridyl)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	2-Propyl 6-(3-acetamido-6-pyridyl)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate

	2-Propyl 6-(5-acetamido-2-thienyl)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl 6-[1-(4-acetamidophenyl)vinyl]-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl R- and S- and R,S-6-[1-(4-acetamidophenyl)ethyl]-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl 5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-6-(4-methanesulfonyl-amidophenoxy)-4-oxoquinoline-3-carboxylate
	Ethyl 6-(3-acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl 6-(2-acetamido-5-pyridyloxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate

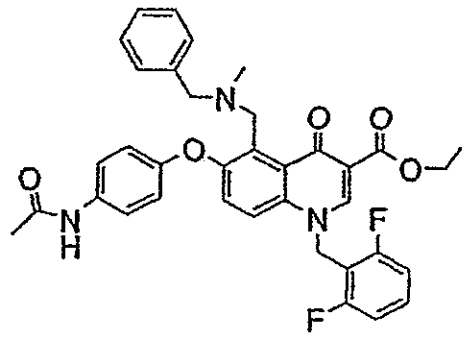
	Ethyl 6-(2-methylaminocarbonyl- 5-pyridyloxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	1-[6-(4-Acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinolin-3-yl)methyl]-3-pyridin-2-ylurea
	1-[6-(4-Acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinolin-3-yl)oxy]-3-pyridin-2-ylurea
	Ethyl 6-(4-hydroxyacetamido-phenoxy)-5-(N-benzyl-N-methyl-aminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl 6-(acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-[bis(2-fluorophenyl)methyl]-1,4-dihydro-4-oxoquinoline-3-carboxylate
	Ethyl 6-(acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-diphenylmethyl-1,4-dihydro-4-oxoquinoline-3-carboxylate

The invention will be furthermore illustrated by the following examples.

Working examples

Example 1

Ethyl 6-(4-acetamidophenoxy)-5-(N-benzyl-N-methyl-aminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate



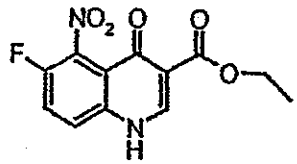
78 mg of etyl 6-(4-acetamidophenoxy)-5-(chloromethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate, dissolved in 3 ml of dimethylformamide, were treated at 0°C with 84 µl of N-methylbenzylamine and 84 µl of N,N-diisopropylethylamine and the mixture was stirred at room temperature for 20 hours. After addition of 20 ml of aqueous sodium bicarbonate solution, the precipitate was filtered off with suction, washed with water and then with n-hexane and dried at room temperature in vacuo. 70 mg of the title compound are obtained.

NMR: δ = 1.3 (t; 3H; CH_3); 1.9 (s; 3H; NCH_3); 2.05 (s; 3H; CH_3); 3.55 (s; 2H; NCH_2); 4.27 (q; 2H; OCH_2); 4.91 (s; 2H; NCH_2); 5.68 (s; 2H; NCH_2); 6.85 (d; 2H; ArCH); 7.1-7.22 (m; 7H; ArCH); 7.26 (d; 1H; ArCH); 7.42-7.6 (m; 4H; ArCH); 8.72 (s; 1H; NCH); 9.9 (s; 1H; NH)

MS: FAB: $M^{\oplus} + 1 = 526$ [M = 525]

The starting material, etyl 6-(4-acetamidophenoxy)-5-(chloromethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate, was obtained in the following way:

a. Ethyl 1,4-dihydro-6-fluoro-5-nitro-4-oxoquinoline-3-carboxylate

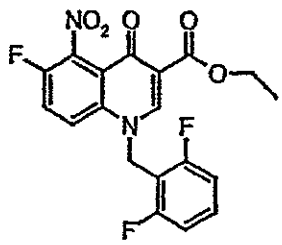


50 g of 4-fluoro-3-nitroaniline and 69 g of diethyl ethoxymethylenemalonate were heated at 120°C for 3 hours. The mixture was added to n-hexane, stirred for 2 hours and the crystalline material was filtered off with suction and dried in vacuo at room temperature. 93 g of diethyl N-(4-fluoro-3-nitrophenyl)amino-methylenemalonate are obtained. In 3 portions of 31 g, this is added to in each case 150 ml of a mixture of 26.5% diphenyl and 73.5% diphenyl ether (DOWTHERM A®), which has been preheated to 260°C, and the mixture is stirred at this temperature for 30 minutes. After cooling, it is diluted with 500 ml of n-hexane and the precipitate is filtered off with suction. A total of 64 g of a mixture of ethyl 1,4-dihydro-6-fluoro-5-nitro-4-oxoquinoline-3-carboxylate and of ethyl 1,4-dihydro-6-fluoro-7-nitro-4-oxo-quinoline-3-carboxylate is obtained.

NMR: δ = 1.31 (t; 3H; CH_3); 4.25 (q; 2H; OCH_2); 7.88 (s; 1H; ArCH; isomer A); 7.92 (s; 1H; ArCH; isomer A); 8.1 (d; 1H; ArCH; isomer B); 8.45 (d; 1H; ArCH; isomer B); 8.59 + 8.69 (2s; each 1H; NCH; A + B)

MS: EI: $M^{\oplus}$ = 280 [M = 280]

b. Ethyl 1-(2',6'-difluorobenzyl)-1,4-dihydro-6-fluoro-5-nitro-4-oxoquinoline-3-carboxylate

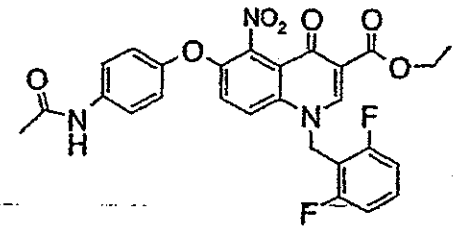


22 g of the mixture described above are stirred at room temperature for 5 hours with 16 g of potassium carbonate and 23.7 g of 2,6-difluorobenzyl bromide in 500 ml of dimethylformamide. The reaction mixture is added to 1 l of aqueous ammonium chloride solution and extracted three times with ethyl acetate. After drying with sodium sulfate and evaporating in vacuo, 500 ml of n-hexane are added and the mixture is stirred for 15 minutes. After decanting the hexane phase, the residue is recrystallized from ethyl acetate. 10.4 g of the title compound are obtained.

NMR: δ = 1.3 (t; 3H; CH_3); 4.25 (q; 2H; OCH_2); 5.84 (s; 2H; NCH_2); 7.15 - 7.25 (m; 2H; ArCH); 7.45 - 7.55 (m; 1H; ArCH); 7.92 (dd; 1H; ArCH); 8.04 - 8.14 (m; 1H; ArCH); 8.96 (s; 1H; NCH);

MS: EI: $M^{\oplus}$ = 406 [M = 406]

c. Ethyl 6-(4-acetamidophenoxy)-1-(2',6'-difluorobenzyl)-1,4-dihydro-5-nitro-4-oxoquinoline-3-carboxylate

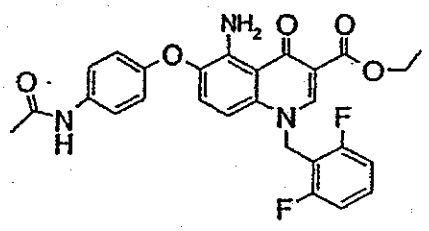


3.74 g of 4-acetamidophenol in 40 ml of dimethylformamide are treated with 733 mg of sodium hydride (80% in mineral oil) and the mixture is stirred at room temperature for 15 minutes. This solution is then added to 5 g of the compound described above, dissolved in 40 ml of dimethylformamide. After 5 hours at room temperature, the mixture is added to ice water and the precipitate is filtered off with suction. After chromatography on silica gel (eluent dichloromethane/2-propanol 95:5), 5.17 g of the title compound are obtained.

NMR: δ = 1.3 (t; 3H; CH_3); 2.03 (s; 3H; CH_3); 4.27 (q; 2H; OCH_2); 5.79 (s; 2H; NCH_2); 7.01 (d; 2H; ArCH); 7.13 - 7.23 (m; 2H; ArCH); 7.43 - 7.56 (m; 2H; ArCH); 7.61 (d; 2H; ArCH); 7.8 (d; 1H; ArCH); 8.93 (s; 1H; NCH); 9.97 (1H; S; NCH)

MS: EI: $M^{\oplus}$ = 537 [M = 537]

d. Ethyl 6-(4-acetamidophenoxy)-5-amino-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate

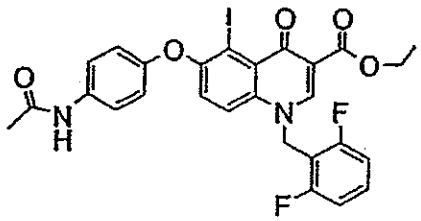


5.1 g of the aforementioned compound are hydrogenated using 510 mg of palladium/carbon (10%) in 650 ml of methanol. After filtering off the catalyst with suction and evaporating, 4.55 g of the title compound are obtained.

NMR: δ = 1.29 (t; 3H; CH_3); 2.02 (s; 3H; CH_3); 3.25 (s; 2H; NH_2); 4.25 (q; 2H; OCH_2); 5.55 (s; 2H; NCH_2); 6.55 (d; 1H; ArCH); 6.86 (d; 2H; ArCH); 7.07 (d; 1H; ArCH); 7.1 - 7.22 (m; 2H; ArCH); 7.4 - 7.55 (m; 3H; ArCH); 8.71 (s; 1H; NCH); 9.8 (s; 1H; NH);

MS: EI: $M^{\oplus}$ = 507 [M = 507]

e. Ethyl 6-(4-acetamidophenoxy)-1-(2',6'-difluorobenzyl)-1,4-dihydro-5-iodo-4-oxoquinoline-3-carboxylate



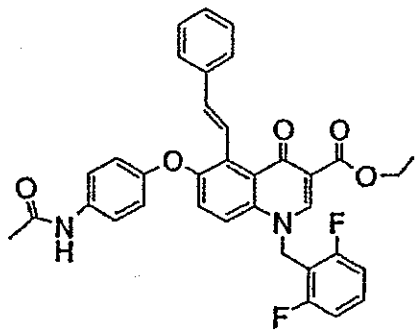
2 g of the aforementioned compound are dissolved in a mixture of 24 ml of concentrated sulfuric acid and 12 ml of water and the mixture is treated with 325 mg of sodium nitrite in 4 ml of water at 0°C. After 15 minutes, the mixture is adjusted to a pH of 3 using sodium bicarbonate solution and 100 mg of urea are added. 723 mg of potassium iodide in 0.5 ml of water are then added and the mixture is stirred at room temperature for one hour. After extraction with dichloromethane/methanol (95:5, v/v), the organic phase is washed with aqueous sodium thiosulfate solution, dried and evaporated. After chromatography on silica gel (eluent dichloromethane containing 0-15%

isopropanol), 697 mg of the title compound are obtained.

NMR: δ = 1.3 (t; 3H; CH_3); 2.02 (s; 3H; CH_3); 4.25 (q; 2H; OCH_2); 5.71 (s; 2H; NCH_2); 6.83 (d; 2H; ArCH); 7.1 - 7.2 (2H; m; ArCH); 7.3 (d; 1H; ArCH); 7.41 - 7.63 (m; 4H; ArCH); 8.83 (s; 1H; N-CH); 9.95 (s; 1H; NH)

MS: es: $M^{\oplus} + 1 = 493$ [M = 492]

f. Ethyl 6-(4-acetamidophenoxy)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxo-5-styrylquinoline-3-carboxylate



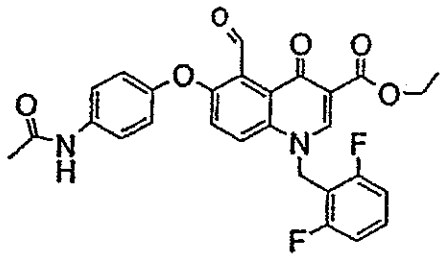
550 mg of the abovementioned iodo compound, 198 mg of styrylboronic acid, 55 mg of tetrakistriphenylphosphinepalladium(0), 1.1 ml of 2 molar sodium carbonate solution, 2.2 ml of ethanol and 22 ml of toluene are stirred at 80°C for 6 hours. Water is then added, the mixture is extracted with dichloromethane and the organic phase is washed with sodium chloride solution, dried and evaporated. The residue is purified by chromatography on silica gel (eluent dichloromethane containing 0-10% isopropanol). 902 mg of the title compound are obtained.

NMR: δ = 1.28 (t; 3H; CH_3); 2.0 (s; 3H; CH_3); 4.24 (q; 2H; OCH_2); 5.7 (s; 2H; N-CH_2); 6.75 - 6.85 (m; 3H; ArCH; CH=CH); 7.08 - 7.28 (m; 3H; ArCH);

7.3 - 7.68 (m; 9H; ArCH); 7.86 (d; 1H; CH=CH); 8.75 (s; 1H; NCH); 9.72 (1H; S; NH)

MS: es: $M^{\oplus}$ + 1 = 595 [M = 594]

g. Ethyl 6-(4-acetamidophenoxy)-1-(2',6'-difluorobenzyl)-1,4-dihydro-5-formyl-4-oxoquinoline-3-carboxylate

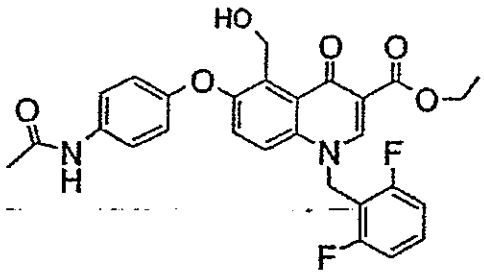


450 mg of the abovementioned styryl compound are dissolved in 25 ml of tetrahydrofuran and 7 ml of water and treated with 0.11 ml of a 2.5 percent solution of osmium tetroxide in tert-butanol. After stirring at room temperature for 15 minutes, 482 mg, after 20 and 22 hours 100 mg and after 24 hours a further 100 mg of sodium periodate, are added. After 26 hours, the mixture is diluted with water and extracted with ethyl acetate. After drying the organic phase using sodium sulfate, it is evaporated. 352 mg of the title compound are obtained as a foam.

NMR: δ = 1.29 (t; 3H; CH_3); 2.01 (s; 3H; CH_3); 4.27 (q; 2H; OCH_2); 5.71 (s; NCH_2); 7.12 - 7.22 (m; 2H; ArCH); 7.4 (d; 1H; ArCH); 7.43 - 7.64 (m; 3H; ArCH); 7.72 (d; 1H; ArCH); 9.0 (d; 1H; NCH); 9.97 (s; 1H; NH); 10.44 (s; 1H; CHO)

MS: FAB: $M^{\oplus}$ + 1 = 521 [M = 520]

h. Ethyl 6-(4-acetamidophenoxy)-1-(2',6'-difluorobenzyl)-1,4-dihydro-5-hydroxymethyl-4-oxoquinoline-3-carboxylate

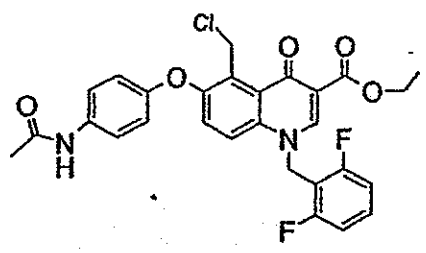


300 mg of the abovementioned aldehyde are dissolved in 13.8 ml of acetic acid and treated with 3 portions of 10 mg each of sodium borohydride at intervals of 10 minutes. After diluting with water, the mixture is extracted with ethyl acetate and the organic phase is washed neutral using sodium bicarbonate solution. After drying with sodium sulfate, it is evaporated. By chromatography on silica gel (eluent dichloromethane containing 0-10% isopropanol), 129 mg of the title compound are obtained as a foam.

NMR: δ = 1.31 (t; 3H; CH_3); 2.02 (s; 3H; CH_3); 4.27 (q; 2H; OCH_2); 4.86 (d; 2H; OCH_2); 5.12 (t; 1H; OH); 5.8 (s; 2H; NCH_2); 6.85 (d; 2H; ArCH); 7.12 - 7.22 (m; 2H; ArCH); 7.38 (d; 1H; ArCH); 7.42 - 7.59 (m; 3H; ArCH); 7.63 (d; 1H; ArCH); 8.94 (s; 1H; NCH); 9.5 (s; 1H; NH)

MS: FAB: $M^{\oplus}$ + 1 = 523 [M = 522]

i. Ethyl 6-(4-acetamidophenoxy)-5-chloromethyl-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylate



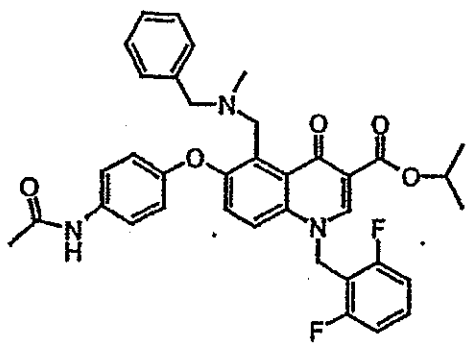
80 mg of the abovementioned alcohol are dissolved in 2 ml of dichloromethane and treated with 0.1 ml of thionyl chloride. After 20 minutes at room temperature, water is added, the mixture is extracted with dichloromethane and the organic phase is washed with sodium chloride solution. After drying with sodium sulfate, it is evaporated. 80 mg of the title compound are obtained as a foam.

NMR: δ = 1.33 (t; 3H; CH_3); 2.07 (s; 3H; CH_3); 4.3 (q; 2H; OCH_2); 5.66 (s; 2H; CH_2Cl); 5.75 (s; 2H; NCH_2); 6.98 (d; 2H; ArCH); 7.13 - 7.25 (m; 2H; ArCH); 7.3 (d; 1H; ArCH); 7.53 (t; 1H; ArCH); 7.61 (d; 2H; ArCH); 7.68 (d; 1H; ArCH); 8.82 (s; 1H; NCH); 9.98 (s; 1H; NH)

MS: es: $M^{\oplus}$ + 1 = 541/543 [M = 540/542]

Example 2

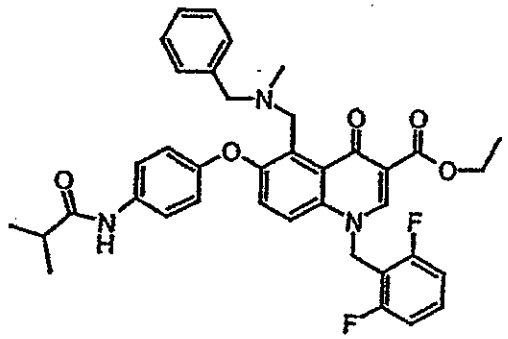
2-Propyl 6-(4-acetamidophenoxy)-5-(N-benzyl-N-methyl-aminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate



This compound is formed from ethyl 6-(4-acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate by heating with titanium tetraisopropoxide in isopropanol.

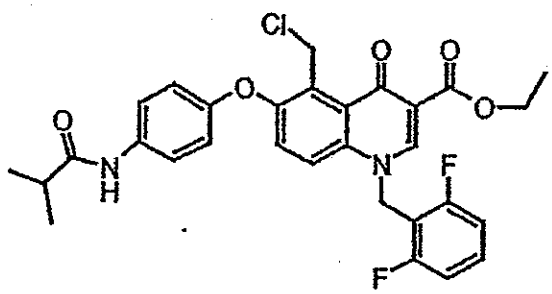
Example 3

Ethyl 5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-6-(4-isobutyramidophenoxy)-4-oxoquinoline-3-carboxylate



This compound is formed analogously to example 1 from etyl 5-(chloromethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-6-(4-isobutyramidophenoxy)-4-oxoquinoline-3-carboxylate and N-methylbenzylamine as a foam.

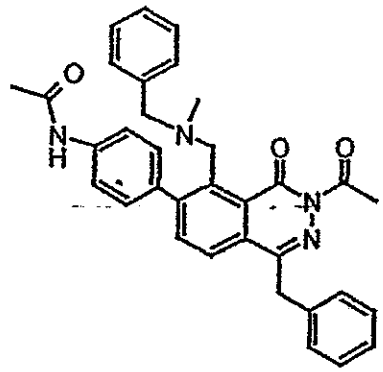
a. Etyl 5-(chloromethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-6-(4-isobutyramidophenoxy)-4-oxo-quinoline-3-carboxylate



This compound is obtained if 4-isobutyramidophenol is used instead of 4-acetamidophenol in example 1/c. and reacted further analogously to example 1/d. to example 1/i..

Example 4

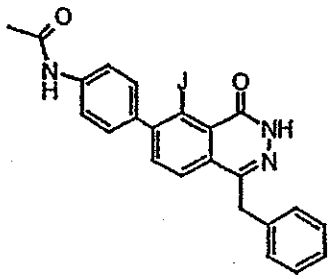
3-Acetyl-6-(4-acetamidophenyl)-1-benzyl-5-(N-benzyl-N-methylaminomethyl)phthalazin-4-one



The title compound is obtained by reacting 6-(4-acetamidophenyl)-1-benzyl-5-(N-benzyl-N-methylamino-methyl)phthalazin-4-one with acetyl chloride or acetic anhydride in the presence of a base such as sodium carbonate or sodium hydroxide.

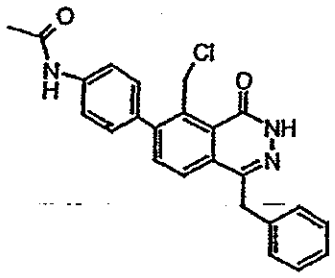
6-(4-Acetamidophenyl)-1-benzyl-5-(N-benzyl-N-methyl-aminomethyl)phthalazin-4-one is obtained in the following way:

a. 6-(4-Acetamidophenyl)-1-benzyl-5-iodophthalazin-4-one



1-Benzyl-5,6-diiodophthalazin-4-one (Indian J. Chem. 16B, 1978, 301-304) are reacted with 1 equivalent of 4-acetamidophenylboronic acid analogously to example 1/f.. The title compound is obtained pure by chromatography on silica gel.

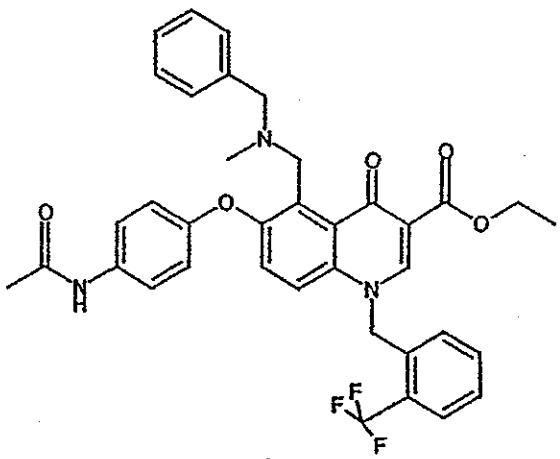
b. 6-(4-Acetamidophenyl)-1-benzyl-5-chloromethyl-phthalazin-4-one



6-(4-Acetamidophenyl)-1-benzyl-5-iodophthalazin-4-one is reacted further to give the title compound analogously to example 1/f.-i..

Example 5

Ethyl 6-(4-acetamidophenoxy)-5-(N-benzyl-N-methyl-aminomethyl)-1,4-dihydro-4-oxo-1-(2'-trifluoro-methylbenzyl)quinoline-3-carboxylate



130 mg (0.226 mmol) of ethyl 6-(4-acetamidophenoxy)-5-(chloromethyl)-1,4-dihydro-4-oxo-1-(2'-trifluoromethyl-benzyl)quinoline-3-carboxylate, dissolved in 5 ml of DMF, are treated with 125 µl of N,N-diisopropyl-ethylamine and 126 µl (0.97 mmol) of N-benzylmethyl-amine at -5°C. After warming to room temperature, the reaction mixture is stirred for 20 hours and then added to 50 ml of saturated sodium bicarbonate solution. The solid is filtered off with suction, washed with water and dried in vacuo. Further purification is carried out

by chromatography on silica gel using an eluent consisting of
90 parts of dichloromethane, 10 parts of ethanol and 1 part of conc. ammonia
(R_f : 0.38).2

45 mg of the title compound are obtained as a foam.
MS/molar peak, M^+ = 658
The starting material ethyl 6-(4-acetamidophenoxy)-5-(chloromethyl)-1,4-dihydro-4-oxo-1-(2'-trifluoromethylbenzyl)quinoline-3-carboxylate is prepared analogously to the route described in examples 1a to 1i using 2'-trifluoromethylbenzyl bromide instead of 2,6-difluoromethylbenzyl bromide.

Example 6
Ethyl 6-(4-methylaminocarbonylphenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate

35 mg (0.061 mmol) of ethyl 6-(4-methylaminocarbonylphenoxy)-5-(chloromethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate, dissolved in 1.3 µl of DMF, are treated with 35 µl of N,N-diisopropylethylamine and 35 µl (0.25 mmol) of N-methylbenzylamine at 0°C. After warming to room temperature, the reaction mixture is stirred for 20 hours and then added to 10 ml of saturated sodium bicarbonate solution. The solid formed is filtered off with suction, washed with water and hexane and dried over phosphorus pentoxide in vacuo.
27 mg of the title compound are obtained as a foam.

MS (esi): M^++1 = 626 [M = 625]

The starting material ethyl 6-(4-methylaminocarbonylphenoxy)-5-(chloromethyl)-1-(2',6'-difluorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate is prepared analogously to the route described in examples 1a to 1i

using 4-hydroxy-N-methylbenzamide instead of 4-acetamidophenol.

Example 7

Ethyl 6-(4-acetamidophenoxy)-5-(N-benzyl-N-methylaminomethyl)-1-(1-naphthylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate

45 mg (0.081 mmol) of ethyl 6-(4-acetamidophenoxy)-5-(chloromethyl)-1-(1-naphthylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate, dissolved in 1.7 ml of DMF, are treated with 46 µl of N,N-diisopropylethylamine and 46 µl (0.33 mmol) of N-methylbenzylamine at 0°C. After warming to room temperature, the reaction mixture is stirred for 20 hours and then added to 15 ml of saturated sodium bicarbonate solution. The solid formed is filtered off with suction, washed with water and hexane and dried over phosphorus pentoxide in vacuo.
32 mg of the title compound are obtained as a foam.

MS (esi): M^++1 = 639 [M = 638]

The starting material ethyl 6-(4-acetamidophenoxy)-5-(chloromethyl)-1-(naphthylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate is prepared analogously to the route described in examples 1a to 1i using 1-chloromethylnaphthalene instead of 2,6-difluoromethylbenzyl bromide.

Example 8

Demonstration of the antagonistic action

a) Materials

Buserelin was obtained from Welding (Frankfurt/Main, Germany). The compound was labelled with ^{125}I by use of the chloramine T method and $Na^{125}I$ (4000 Ci/mmol; Amersham-Buchler, Braunschweig, Germany). The labelled substance was purified by reverse phase HPLC on a Spherisorb ODS II column (250 x 4 mm, particle size

3 µm) by elution with 50% acetonitrile/0.15% trifluoroacetic acid at a flow rate of a 0.5 ml/min. The specific activity was 2000 Ci/mmol.

All other chemicals were obtained from a commercial source in the highest available degree of purity.

b) Cell culture

Alpha T3-1 cells (Bilezikjian et al., Mol. Endocinol 5 (1991), 347-355) were cultured on plastic tissue culture plates (Nunc, 245 x 245 x 20 mm) in DMEM medium (Gibco-BRL, Eggenstein-Leopoldshafen, Germany), containing penicillin (100 I.U./ml), streptomycin (0.1 mg/ml) and glutamine (0.01 mol/l) and 10% fetal calf serum (FCS; PAA Laboratories, Coelbe, Germany). CHO-3 cells (Schmid et al., J. Biol. Chem. 275 (2000), 9193-9200) were cultured under identical conditions, apart from the fact that Ham's F12 medium (Gibco-BRL) was used.

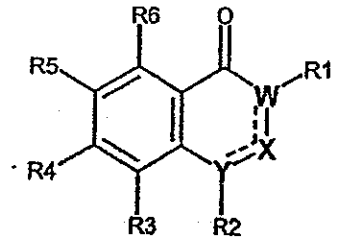
10 confluent cell culture plates were rinsed twice with 50 ml of phosphate-buffered saline solution (PBS). The cells were harvested in 5 ml of PBS by scraping off with a rubber scraper and sedimented by centrifugation at 800 rpm for 10 min in a laboratory centrifuge (Heraeus). The cell pellet was resuspended in 5 ml of 0.25 mol/l sucrose/0.01 mol/l triethanolamine, pH 7.4. The cells were lyzed by three cycles of freezing in dry ice/ethanol bath and thawing at room temperature. The lyzate was centrifuged at 900 rpm for 10 min and the sediment was discarded. The supernatant was centrifuged at 18,000 rpm in a Sorvall SS34 rotor for 30 min. The pellet (cell membranes) was suspended by pottering in 5 ml of assay buffer (0.25 mol/l sucrose, 0.01 mol/l triethanolamine, pH 7.5, 1 mg/ml ovalbumin) and stored at -20°C in 200 µl aliquots. The protein determination was carried out according to the method of Bradford (Anal. Biochem. 72 (1976), 248-254).

c. Receptor assay

Binding investigations for competition curves were carried out as triplicates. A test sample contained 60 µl of the cell membrane suspension (10 µg of protein for αT3-1 cells or 40 µg of protein for CHO3 cells), 20 µl of ^{125}I-labelled buserelin (100,000 Ipm per sample for competition curves and between 1500 and 200,000 Ipm for saturation experiments) and 20 µl of test buffer or test compound solution. The test compounds were dissolved in distilled water or 50% ethanol. Serial dilutions (5 x 10^{-6} mol/l to 5 x 10^{-12} mol/l) were prepared in test buffer. The nonspecific binding was determined in the presence of an excess of unlabelled buserelin (10^{-6} mol/l). The test samples were incubated at room temperature for 30 min. Bound and free ligand were separated by filtration (Whatman GF/C filters 2.5 cm diameter) using an Amicon 10x collection device and washed twice with 5 ml of 0.02 mol/l tris/HCl, pH 7.4. The filters were moistened with 0.3% polyethyleneimine (Serva; Heidelberg, Germany) for 30 min in order to reduce the nonspecific binding. The radioactivity retained by the filters was determined in a 5 channel gamma counter (Wallac LKB 1470 Wizard).

Claims

1. A compound of the general formula (1):



(1)

in which

R^1 (a) is an acyl group -CO-R11 or CN, where R11 is a saturated, unsaturated, cyclic or/and (hetero)aromatic organic radical, in particular a linear or branched alkyl chain having 1-10 C atoms, or a phenyl, furan or thiophene group optionally substituted by alkyl groups or halogen atoms, and

(b) a carboxylic acid ester group -CO-OR12 or carboxamide group -CO-NR12NR13 or a group $-SO_x-$ R12 where X = 0, 1 or 2 or $-SO_2-$NR12NR13, where R12 is a saturated, unsaturated, cyclic or/and (hetero)aromatic organic radical, in particular a linear or branched alkyl chain having 1-10 C atoms, an aralkyl group having 7-20 C atoms, where the aryl radical can optionally be substituted by alkyl groups or halogen atoms, or a phenyl radical optionally substituted by alkyl groups or halogen atoms and R13 can be a hydrogen atom or a linear or branched alkyl chain having 1-10 C atoms,

or

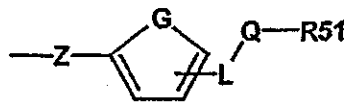
(c) is the group -A-NR14-CO-NR15R16, in which A is an alkylene group having 1-4 C atoms, in particular having 1 C atom, optionally substituted by a C_1-C_6-alkyl group, a carbonyl group, an oxygen atom or the group $-SO_x-$ where

X = 0, 1 or 2, R14 and R15 in each case independently are a hydrogen atom or a linear or branched alkyl chain having 1-10 C atoms and R16 is a linear or branched alkyl chain having 1-10 C atoms, a cycloalkyl group having 3-10 C atoms, a cycloalkylalkyl group having 7-20 C atoms, an aralkyl group having 7-20 C atoms, where the aryl radical can optionally be substituted by alkyl groups or halogen atoms, a phenyl group optionally substituted by alkyl groups or halogen atoms, or a heterocyclic ring optionally substituted by alkyl groups or halogen atoms,

R2 is a group -CH(R21)R22, where R21 is a hydrogen atom, a C_1-C_{10}-alkyl group or an optionally substituted phenyl ring and R22 is an optionally substituted phenyl ring or naphthyl ring, or a group $-CH_2CH(R23)R24$, where R23 and R24 have the meaning of an optionally substituted phenyl ring,

R3 and R4 in each case independently can be a hydrogen atom or an alkyl group having 1-10 C atoms and R3 can also be a halogen atom,

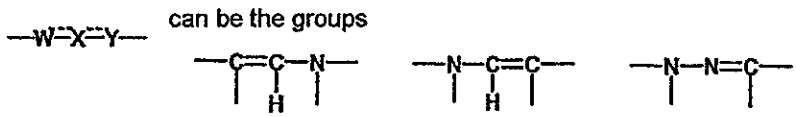
R5 is a group linked via the radical Z,



in which G is -C=C-, -C=N-, -N=C-, an oxygen or sulfur atom, Z is a direct bond, an oxygen or a sulfur atom, the group CH-R52 or -CHR52-CH-R53-, where R52 and R53 independently of one another have the meaning of a hydrogen atom or an alkyl group and n is the numbers 1 and 2, a -C≡C- triple bond or a group -CR52=CR53- or C=CR52R53 having the E or Z configuration, where R52 and R53 independently of one another

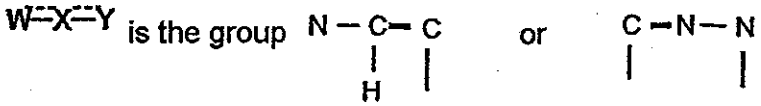
have the meaning of a hydrogen atom or an alkyl group, L is a CH_2 or an NH group, Q is a carbonyl or $-SO_X$ group where X = 0, 1 or 2 and R51 is an amino group optionally substituted by an alkyl group, or a linear or branched alkyl group optionally substituted by halogen atoms, hydroxyl or alkoxy groups or a cycloalkyl group having 3-7 ring members, optionally substituted by halogen atoms, hydroxyl or alkoxy groups,

R6 is the group CH_2-N(R61)R62, where R61 in each case independently is a hydrogen atom or an alkyl group and R62 is an alkyl group or an optionally substituted aralkyl group or hetero-arylalkyl group having 7-20 C atoms and



in any orientation, and further all stereoisomers of the structures mentioned, or salts thereof with physiologically tolerable acids or bases.

2. A compound as claimed in claims 1, **characterized in that**



3. A compound as claimed in claim 1 or 2, **characterized in that**

R1 is the group -CO-R11.

4. A compound as claimed in claim 3, **characterized in that**

R11 is selected from methyl, ethyl, i-propyl, phenyl, 2-thienyl and 2-furyl.

5. A compound as claimed in claim 1 or 2, **characterized in that** R1 is the group -CO-OR12.

6. A compound as claimed in claim 5, **characterized in that** R12 is selected from methyl, ethyl or i-propyl.

7. A compound as claimed in one of claims 1 to 6, **characterized in that** R2 is a 2',5'-difluorobenzyl group.

8. A compound as claimed in one of claims 1 to 7, **characterized in that** R3 and R4 are hydrogen atoms.

9. A compound as claimed in one of claims 1 to 8, **characterized in that** Z is a direct bond or an oxygen atom.

10. A compound as claimed in one of claims 1 to 9, **characterized in that** G is -C=C-.

11. A compound as claimed in one of claims 1 to 10, **characterized in that** L is an NH group.

12. A compound as claimed in one of claims 1 to 11, **characterized in that** Q is a carbonyl group and R51 is a C_1-C_6-alkyl group.

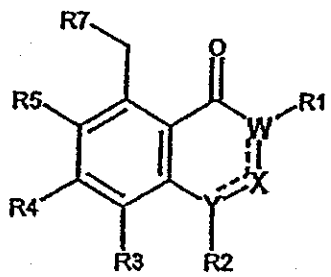
13. A compound as claimed in one of claims 1 to 12, **characterized in that** R61 is a hydrogen atom or a methyl group or/and R62 is a benzyl group.

14. The compounds as claimed in any of claims 1 to 13 for use in therapy.

15. Use of the compounds as claimed in any of claims 1 to 13 for the manufacture of a medicament for treating endometriosis, uterine leiomyonas, and uterine fibroids, for controlling male fertility, for the treatment of female sub- and infertility, for female contraception and for tumor control.

16. A process for the preparation of compounds of the general formula (1) by

(a) reaction of a compound of the general formula (2)



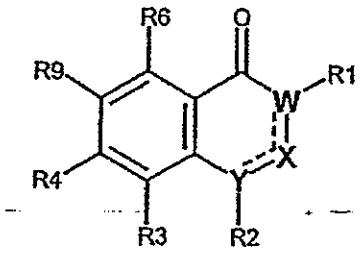
(2)

where R7 is a leaving group and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (3)

R8-N(R61)R62 (3)

where R8 is a hydrogen atom or a metal atom and R61 and R62 have the meanings indicated in compound (1),

(b) reaction of a compound of the general formula (4)



(4)

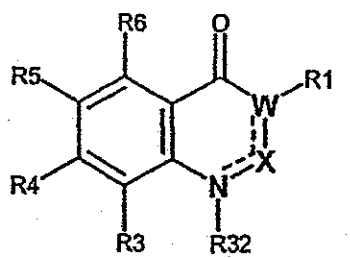
in which R9 is the group $-OSO_2C_nF_{2n+1}$, a halogen atom, particularly a bromine or iodine atom or another leaving group and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (5)



(5)

where R10 is a group containing a metal or a nonmetal, a hydroxyl or mercapto group optionally converted into a metal salt, the group -C≡C-R31 or a group -CR52=CR53R31 or -CR31=CR52R53 having the E or Z configuration, in which R31 is a group containing a metal or a nonmetal and all other radicals have the meaning indicated in compound (1), with or without participation of a catalyst;

(c) if Y in compound (1) is a nitrogen atom, by reaction of a compound of the general formula (6)



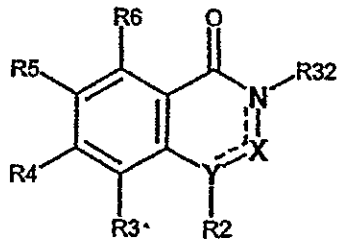
(6)

where R32 is a hydrogen atom or a metal atom and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (7)

R33R2 **(7)**

where R33 is a leaving group and R2 has the meaning indicated in compound (1), or

(d) if W in compound (1) is a nitrogen atom, by reaction of a compound of the general formula (8)



(8)

where R32 is a hydrogen atom or a metal atom and all other radicals have the meaning indicated in compound (1), with a compound of the general formula (9)

R33-R1 **(9)**

where R33 is a leaving group and R1 has the meaning indicated in compound (1).