

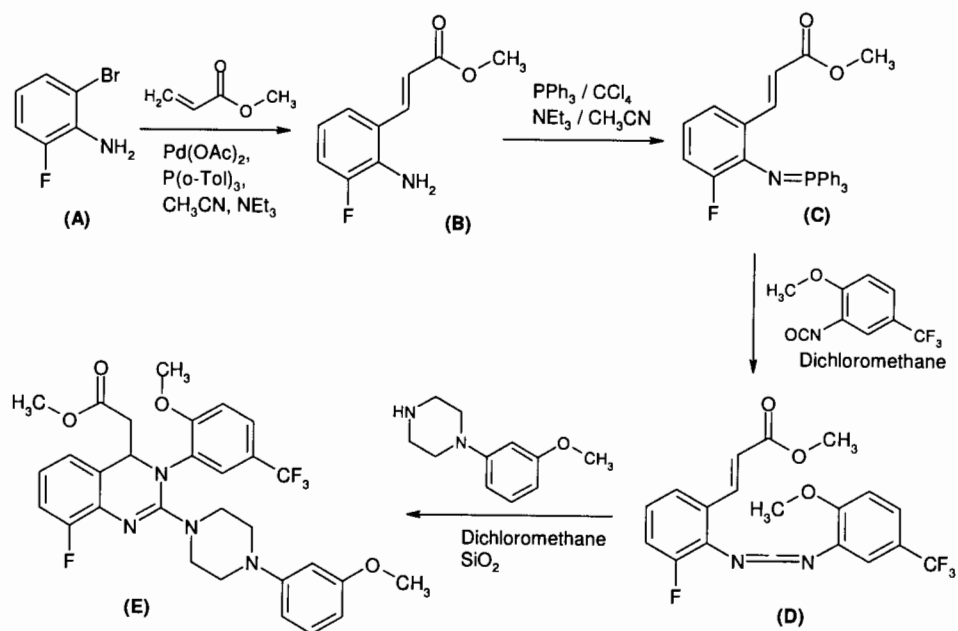
Method for the preparation of dihydroquinazolines

The present invention relates to a method for the preparation of dihydroquinazolines, which are used for the production of medicaments.

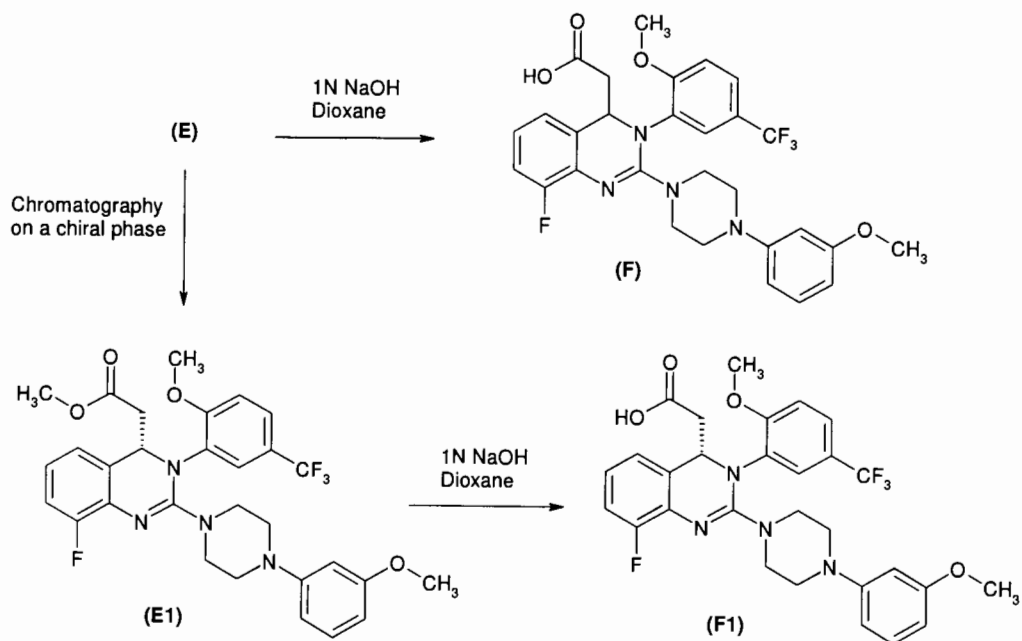
The compounds prepared according to the method of the invention are suitable for use as antiviral agents, in particular against cytomegaloviruses, as described in WO 04/072048 and WO 04/096778.

The synthesis of the dihydroquinazolines described there takes place starting with a 2-halo-substituted aniline (A), which is converted by means of a Heck coupling to a 2-aminocinnamic acid derivative (B). By reaction with triphenylphosphine in carbon tetrachloride, a phosphine imide (C) is prepared, which is subsequently reacted with an isocyanate with release of triphenylphosphine oxide to give a carbodiimide (D). By reaction of the carbodiimide (D) with an amine, the dihydroquinazoline methyl ester (E) is formed, which is separated into the enantiomers by chromatography on a chiral phase. Subsequently, the hydrolysis to the dihydroquinazoline acid (F1) takes place under standard conditions. The following schemes 1 and 2 illustrate the synthesis.

Scheme 1:



Scheme 2:



The reaction steps described above involve significant risks when carried out on an industrial scale, and by-products as well as stoichiometric amounts of organic waste products are formed. By using the phosphine imide (C) and the carbodiimide (D), intermediates having highly reactive functionalities are formed during the reaction sequence, which lead to by-products to a considerable extent. The by-products can only be separated by very laborious chromatographic purification or by a laborious extraction process.

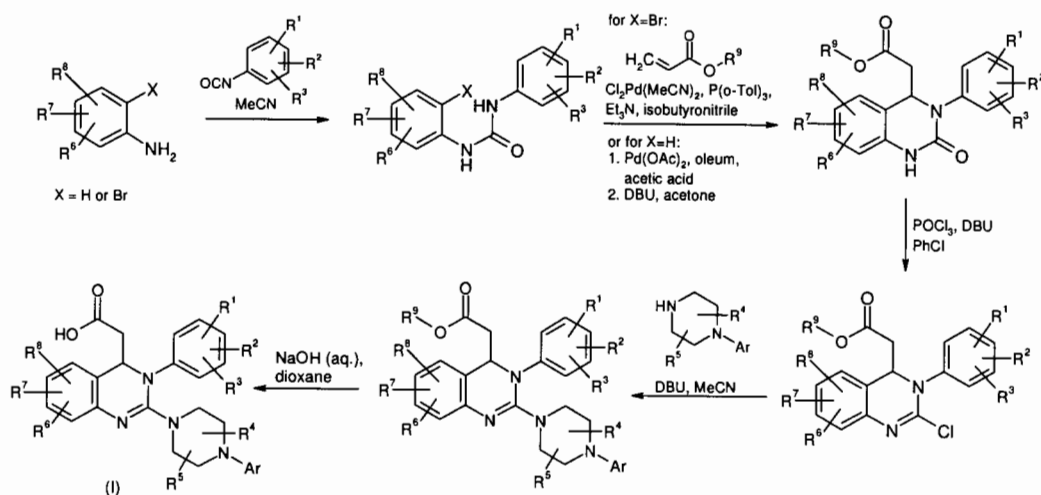
Furthermore, during the reaction of the compound of formula (C) to give the compound of formula (D), triphenylphosphine oxide is formed in stoichiometric amounts, which is separated from the desired product chromatographically in a laborious process. Chromatography is particularly disadvantageous in the synthesis of compounds on an industrial scale, since it is time-consuming and labour-intensive and consumes larger amounts of solvent.

The separation of the enantiomers of the compound of formula (E) takes place in a laborious process by chromatography on a chiral phase, with the undesired R-enantiomer being formed as a waste product.

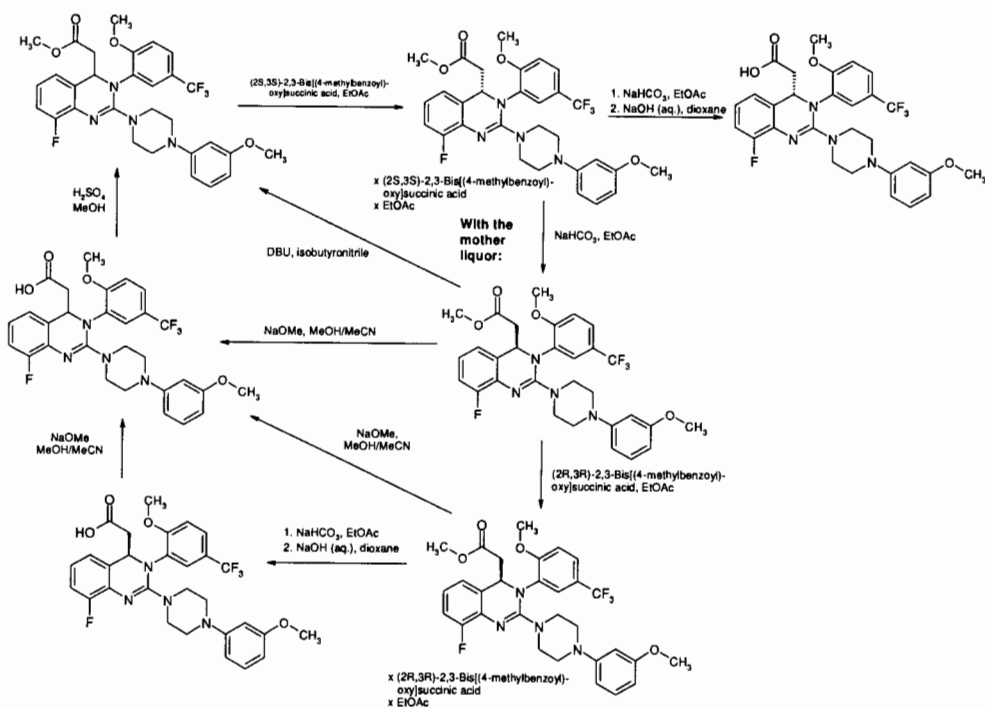
It is the object of the present invention to provide an industrially applicable method for the preparation of a dihydroquinazoline of formula (I), in particular of (S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl]acetic acid, in which the disadvantages of the above process steps known from the prior art are avoided, and in which no undesired R-enantiomer is formed as a waste product.

This object is achieved according to the present invention as follows. The following schemes 3 and 4 illustrate the individual reaction steps.

Scheme 3:



Scheme 4:



Surprisingly, it has now been found that compounds of formula (I) can be prepared by the method of the invention, i.e. by the reaction of the 2-halo-substituted aniline with an isocyanate and a subsequent Heck reaction with alkyl acrylate, preferably methyl acrylate, and that a phosphine imide and a carbodiimide as reactive intermediate and the formation of stoichiometric amounts of triphenylphosphine oxide respectively can thus be avoided.

In addition, it has surprisingly been found that the compounds of the intermediate stages form crystals and can be purified by crystallization without chromatography or extraction, whereby the industrial application of these process stages is made possible.

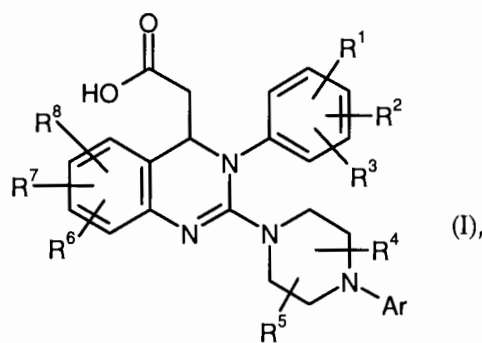
In addition, it has surprisingly been found that the building block methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate can be synthesized efficiently by means of an ortho-palladization. Here, N-(2-fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea is reacted with methyl acrylate and an oxidizing agent in the presence of an acid to give methyl (2E)-3-{3-fluoro-2-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenyl}acrylate. The ring closure to the tetrahydroquinazoline then takes place under basic reaction conditions.

In addition, it has surprisingly been found that the alkyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetates, preferably the methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, can be separated into the enantiomers by crystallization with (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid.

In addition, it has surprisingly been found that the R-enantiomer of the alkyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetates, preferably of methyl {8-fluoro-2-[4-(3-

methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluormethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetate, can be racemized under basic conditions at the stage of the acid after the hydrolysis of the alkyl or methyl ester and can be separated after renewed esterification by crystallization with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)-oxy]succinic acid, whereby the total yield of the *S*-enantiomer is increased.

In detail, the method of the invention for the preparation of a compound of formula (I)



in which

Ar represents aryl, wherein aryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of alkyl, alkoxy, formyl, carboxy, alkylcarbonyl, alkoxy carbonyl, trifluoromethyl, halogen, cyano, hydroxy, amino, alkylamino, aminocarbonyl and nitro,

wherein alkyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, amino, alkylamino, hydroxy and aryl,

or two of the substituents on the aryl, together with the carbon atoms to which they are bonded, form a 1,3-dioxolane, a cyclopentane ring or a cyclohexane ring and an optionally present third substituent is selected independently thereof from the group mentioned,

R¹ represents hydrogen, amino, alkyl, alkoxy, alkylamino, alkylthio, cyano, halogen, nitro or trifluoromethyl,

R² represents hydrogen, alkyl, alkoxy, alkylthio, cyano, halogen, nitro or trifluoromethyl,

R³ represents amino, alkyl, alkoxy, alkylamino, alkylthio, cyano, halogen, nitro, trifluoromethyl, alkylsulfonyl or alkylaminosulfonyl

or

one of the radicals R¹, R² and R³ represents hydrogen, alkyl, alkoxy, cyano, halogen, nitro or trifluoromethyl and the other two, together with the carbon atoms to which they are bonded, form a 1,3-dioxolane, a cyclopentane ring or a cyclohexane ring,

R⁴ represents hydrogen or alkyl,

R⁵ represents hydrogen or alkyl

or

the radicals R⁴ and R⁵ in the piperazine ring are bonded to carbon atoms directly opposing each other and form a methylene bridge which is optionally substituted with 1 to 2 methyl groups,

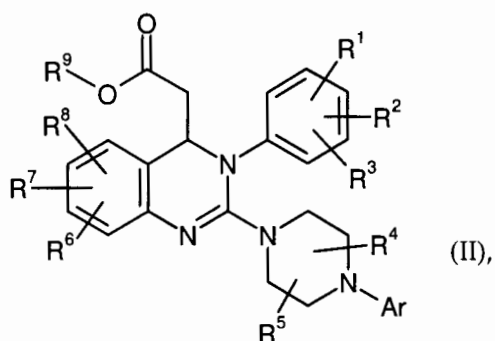
R⁶ represents hydrogen, alkyl, alkoxy, alkylthio, formyl, carboxy, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, trifluoromethyl, halogen, cyano, hydroxy or nitro,

R⁷ represents hydrogen, alkyl, alkoxy, alkylthio, formyl, carboxy, alkylcarbonyl, alkoxycarbonyl, trifluoromethyl, halogen, cyano, hydroxy or nitro

and

R⁸ represents hydrogen, alkyl, alkoxy, alkylthio, formyl, carboxy, alkylcarbonyl, alkoxy carbonyl, trifluoromethyl, halogen, cyano, hydroxy or nitro,

comprises the hydrolysis of the ester of a compound of formula (II)



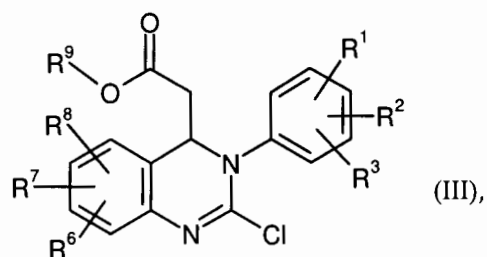
in which

Ar, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ have the meaning indicated above, and

R⁹ represents C₁-C₄-alkyl,

using a base or an acid.

The compound of formula (II) can be prepared by the reaction of a compound of formula (III)



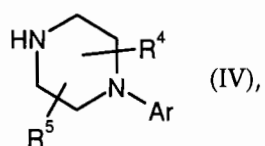
in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above, and

R^9 represents C_1 - C_4 -alkyl,

in the presence of a base

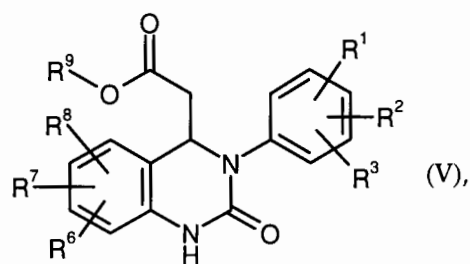
with a compound of formula (IV)



in which

Ar, R^4 and R^5 have the meaning indicated above.

The compound of formula (III) can be prepared by the reaction of a compound of formula (V)



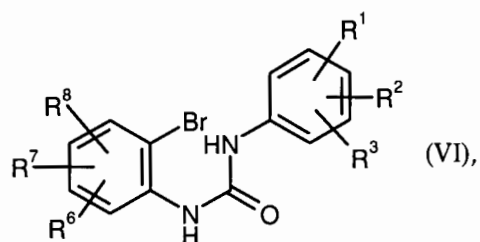
in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above, and

R^9 represents C_1 - C_4 -alkyl,

with phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride in the presence of a base.

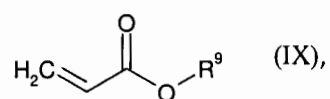
The compound of formula (V) can be prepared by the reaction of a compound of formula (VI)



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above,

with a compound of formula



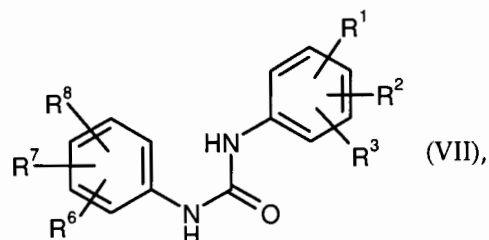
in which

R^9 represents C_1 - C_4 -alkyl,

in the presence of a palladium catalyst and a base.

Compounds of formulae (IV), (VI) and (IX) are known per se to the person skilled in the art or can be prepared by usual methods known from the literature.

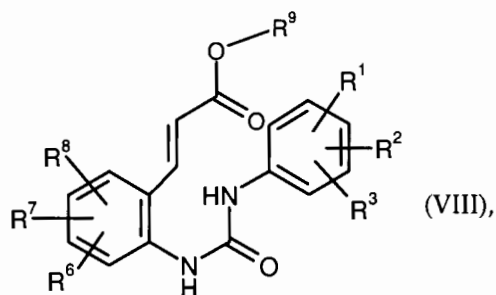
In an alternative method, a compound of formula (V) can be prepared by reacting a compound of formula (VII)



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above,

in the first stage with a compound of formula (IX) in acetic acid in the presence of a palladium catalyst, an oxidizing agent and an acid to give a compound of formula (VIII)



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above, and

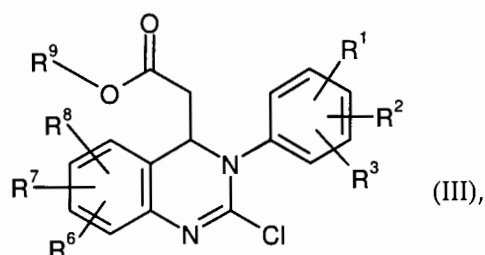
R^9 represents C_1 - C_4 -alkyl,

and in the second stage with a base to give a compound of formula (V).

Compounds of formula (VII) are known per se to the person skilled in the art or can be prepared by usual methods known from the literature.

According to a preferred embodiment of the present invention, in the synthesis method the radical R^9 in the compounds of formulae (II), (III), (V), (VIII) and (IX) represents methyl.

In addition, the present invention comprises compounds of formula (III)



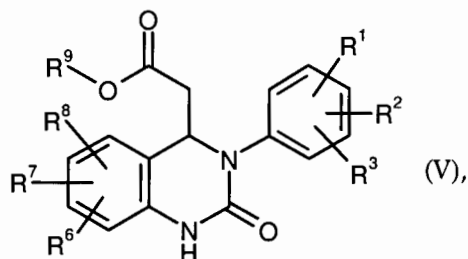
in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above, and

R^9 represents C_1 - C_4 -alkyl.

Compounds of formula (III) in which R^9 represents methyl are preferred.

In addition, the present invention comprises compounds of formula (V)



in which

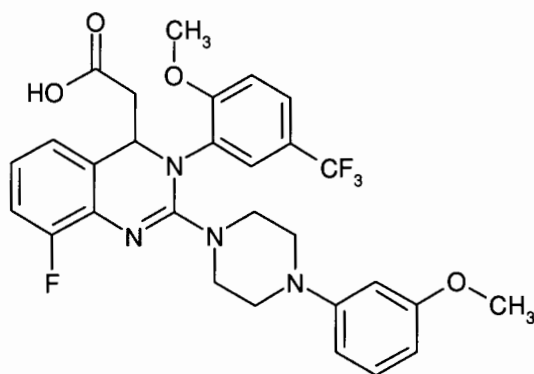
R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above, and

R^9 represents C_1 - C_4 -alkyl.

Compounds of formula (V) in which R^9 represents methyl are preferred.

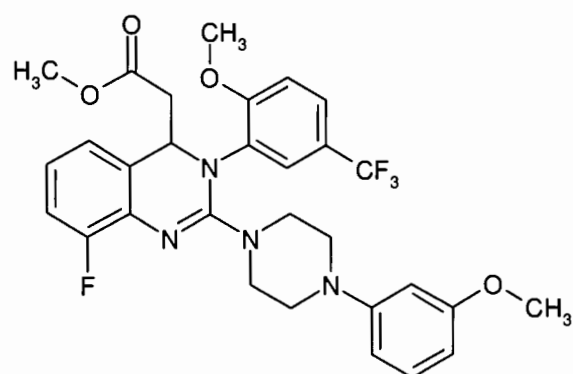
According to a particularly preferred embodiment of the present invention, the compound of formula (I) is the following compound:

{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid



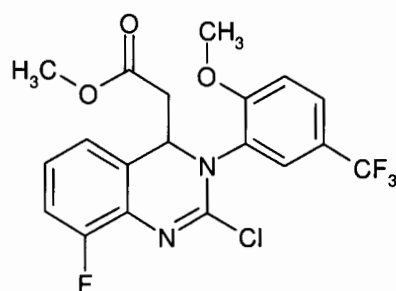
According to a particularly preferred embodiment of the present invention, the compound of formula (II) is the following compound:

methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate



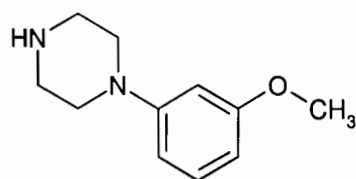
According to a particularly preferred embodiment of the present invention, the compound of formula (III) is the following compound:

methyl 2-chloro-8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]-acetate



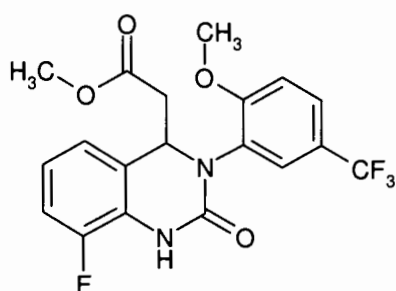
According to a particularly preferred embodiment of the present invention, the compound of formula (IV) is the following compound:

1-(3-methoxyphenyl)piperazine



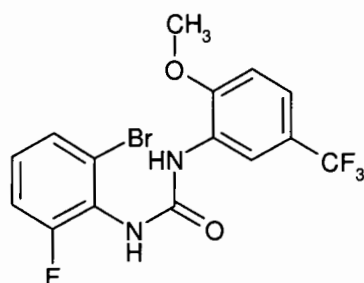
According to a particularly preferred embodiment of the present invention, the compound of formula (V) is the following compound:

methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate



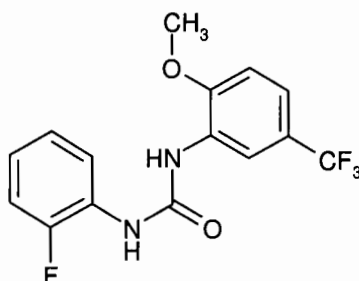
According to a particularly preferred embodiment of the present invention, the compound of formula (VI) is the following compound:

N-(2-bromo-6-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea



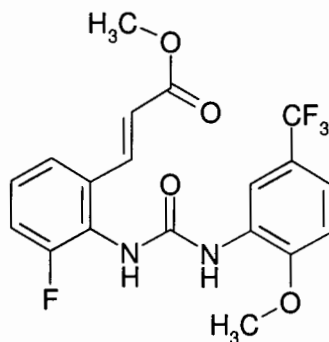
According to a particularly preferred embodiment of the present invention, the compound of formula (VII) is the following compound:

N-(2-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea



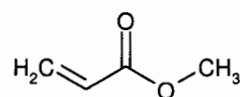
According to a particularly preferred embodiment of the present invention, the compound of formula (VIII) is the following compound:

methyl (2E)-3-((3-fluoro-2-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino)phenyl)acrylate



According to a particularly preferred embodiment of the present invention, the compound of formula (IX) is the following compound:

methyl acrylate



The hydrolysis of the ester of a compound of formula (II) to a compound of formula (I) takes place by reaction of a compound of formula (II) with a base in an inert solvent, in a temperature range from 18°C up to the reflux of the solvent, preferably

at 18 to 50°C, particularly preferably at 20 to 30°C, under atmospheric pressure within, for example, 0.5 to 10 hours, preferably within 1 to 5 hours.

Bases are, for example, alkali metal hydroxides such as sodium hydroxide, lithium hydroxide or potassium hydroxide, or alkali metal carbonates such as caesium carbonate, sodium carbonate or potassium carbonate, or alkoxides such as sodium methoxide or potassium methoxide or sodium ethoxide or potassium ethoxide, with the base optionally being present in aqueous solution.

Inert solvents are, for example, ethers such as 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, or water, or mixtures of solvents.

Sodium hydroxide in water and dioxane is preferred.

The hydrolysis of the ester of a compound of formula (II) to a compound of formula (I) takes place by reaction of a compound of formula (II) with an acid in a solvent in the presence of water, in a temperature range from 18°C up to the reflux of the solvent, preferably at 18 to 50°C, particularly preferably at 20 to 30°C, under atmospheric pressure, within, for example, 0.5 to 48 hours, preferably within 5 to 24 hours.

Acids in a solvent are, for example, hydrochloric acid, sulfuric acid or phosphoric acid in dioxane or tetrahydrofuran.

Hydrochloric acid in dioxane is preferred.

The synthesis of a compound of formula (II) from a compound of formula (III) and a compound of formula (IV) in the presence of a base takes place in an inert solvent, in a temperature range from 40°C up to the reflux of the solvent, preferably under

reflux of the solvent, under atmospheric pressure, within, for example, 5 to 48 hours, preferably within 10 to 24 hours.

Bases are, for example, amides such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or amine bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1-(3-methoxyphenyl)piperazine or triethylamine, or other bases such as potassium tert.-butoxide or sodium hydride.

Inert solvents are, for example, chlorobenzene or ethers such as 1,2-dimethoxyethane, dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether.

DBU in dioxane is preferred.

The reaction of a compound of formula (V) to give a compound of formula (III) takes place by reaction of a compound of formula (V) with phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride, with phosphorus oxychloride being preferred, in the presence of a base in an inert solvent, in a temperature range from 40°C up to the reflux of the solvent, preferably under reflux of the solvent, under atmospheric pressure, within, for example, 5 to 48 hours, preferably within 10 to 24 hours.

Bases are, for example, amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine or triethylamine, or amides such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or other bases such as potassium tert.-butoxide.

Inert solvents are, for example, hydrocarbons such as benzene, xylene, toluene or chlorobenzene.

DBU in chlorobenzene is preferred.

The reaction of a compound of formula (VI) to give a compound of formula (V) takes place by reaction of a compound of formula (VI) with a compound of formula (IX) in the presence of a palladium catalyst and a base in an inert solvent, in a temperature range from 40°C up to the reflux of the solvent, preferably under reflux of the solvent, under atmospheric pressure, within, for example, 5 to 48 hours, preferably within 10 to 24 hours.

Palladium catalysts are, for example, bis(triphenylphosphine)palladium(II) chloride, tetrakis(triphenylphosphine)palladium(0), bis(tris(o-tolyl)phosphino)palladium(II) chloride or a palladium catalyst prepared from bis(acetonitrile)dichloropalladium or palladium(II) acetate and a ligand, for example, tris(o-tolyl)phosphine, triphenylphosphine or diphenylphosphinoferrocene.

Bases are, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine or diisopropylethylamine.

Inert solvents are, for example, ethers such as 1,2-dimethoxyethane, dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene or toluene, or other solvents such as isobutyronitrile, acetonitrile, nitrobenzene, dimethylformamide, dimethylacetamide, dimethyl sulfoxide or N-methylpyrrolidone.

A palladium catalyst prepared from bis(acetonitrile)dichloropalladium and tris(o-tolyl)phosphine and triethylamine in isobutyronitrile are preferred.

The reaction of a compound of formula (VII) to give a compound of formula (VIII) takes place by reaction of a compound of formula (VII) with a compound of formula (IX) in acetic acid in the presence of a palladium catalyst, an oxidizing agent and an acid, in a temperature range from 0°C to 50°C, preferably at room temperature, under atmospheric pressure, within, for example, 5 to 48 hours, preferably within 10 to 24 hours.

Palladium catalysts are, for example, palladium salts such as palladium(II) chloride, palladium(II) acetylacetonate, palladium(II) acetate or sodium tetrachloropalladate; palladium(II) acetate is preferred.

Oxidizing agents are, for example, p-benzoquinone or peroxides such as, for example, hydrogen peroxide, tert-butyl hydroperoxide or sodium perborate, or sulfur trioxide pyridine complex, manganese dioxide, 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ), sodium peroxodisulfate or oleum (fuming sulfuric acid); p-benzoquinone, sodium peroxodisulfate or oleum (fuming sulfuric acid) is preferred and oleum is particularly preferred.

Acids are, for example, methanesulfonic acid, trifluoromethanesulfonic acid or substituted benzenesulfonic acids, such as, for example, 4-methylbenzenesulfonic acid, 4-chlorobenzenesulfonic acid or 4-nitrobenzenesulfonic acid, or concentrated sulfuric acid in the form of oleum; trifluoromethanesulfonic acid or sulfuric acid in the form of oleum is preferred, oleum is particularly preferred.

The reaction of a compound of formula (VIII) to give a compound of formula (V) takes place by reaction of a compound of formula (VIII) with a base in an inert solvent, in a temperature range from 40°C up to the reflux of the solvent, preferably under reflux of the solvent, under atmospheric pressure, within, for example, 1 to 48 hours, preferably within 2 to 14 hours.

Bases are, for example, alkali metal carbonates such as caesium carbonate, sodium carbonate or potassium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine or diisopropylethylamine; potassium carbonate or DBU is preferred.

Inert solvents are, for example, ethers such as 1,2-dimethoxyethane, dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether, or hydrocarbons such as benzene, xylene or toluene, or ketones such as acetone or methyl isobutyl ketone (MIBK), or other solvents such as isobutyronitrile, acetonitrile, chlorobenzene,

nitrobenzene, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, N-methylpyrrolidone or tetrahydrothiophene-1,1-dioxide (sulfolane); acetone is preferred.

In addition, the present invention comprises a method for the separation of the enantiomers of (C₁-C₄)-alkyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate and the isolation of (C₁-C₄)-alkyl (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that the racemic ester is crystallized with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid. The crystallization takes place in a temperature range from 0 to 25°C in ethyl acetate. The salt of the S-enantiomer precipitates from the solution first.

A method for the separation of the enantiomers of methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate and the isolation of methyl (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that the racemic ester is crystallized with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid is preferred. The crystallization takes place in a temperature range from 0 to 25°C in ethyl acetate. The salt of the S-enantiomer precipitates from the solution first.

In addition, the present invention comprises the (C₁-C₄)-alkyl (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid salts.

In addition, the present invention comprises the methyl (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (2*S*,3*S*)-2,3 bis[(4-methylbenzoyl)oxy]succinic acid salt.

In addition, the present invention comprises a method for the racemization of (C₁-C₄)-alkyl (R)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that

in the first stage the alkyl ester is hydrolysed to the acid,

in the second stage the acid is racemized using sodium methoxide or sodium ethoxide and

in the third stage the acid is again converted into the alkyl ester.

A method for the racemization of methyl (R)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that

in the first stage the methyl ester is hydrolysed to the acid,

in the second stage the acid is racemized using sodium methoxide or sodium ethoxide and

in the third stage the acid is again converted into the methyl ester is preferred.

The hydrolysis in the first stage using an acid or a base takes place under the same reaction conditions as the hydrolysis of the ester of a compound of formula (II) to give a compound of formula (I).

The racemization in the second stage takes place by heating the acid with sodium methoxide or sodium ethoxide, with preferably at least 2 equivalents of base being used and with sodium methoxide or sodium ethoxide optionally being employed in an alcoholic solution, in a solvent under reflux, under atmospheric pressure, for, for example, 36 to 72 hours, preferably for 50 to 70 hours.

Solvents are, for example, ethers such as 1,2-dimethoxyethane, dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene or toluene, or other solvents such as isobutyronitrile, acetonitrile or dimethyl sulfoxide; acetonitrile is preferred.

The esterification in the third stage takes place, for example, by reaction of the acid with sulfuric acid in methanol or another alcohol under reflux, under atmospheric pressure, for, for example, 12 to 48 hours, preferably for 20 to 30 hours.

In addition, the present invention comprises a method for the racemization of (C₁-C₄)-alkyl (R)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that

the alkyl ester is reacted with a base in an inert solvent.

A method for the racemization of methyl (R)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that

the methyl ester is reacted with a base in an inert solvent is preferred.

The reaction takes place in a temperature range from 40°C up to the reflux of the solvent, preferably under reflux of the solvent, under atmospheric pressure, within, for example, 5 to 48 hours, preferably within 12 to 24 hours.

Bases are, for example, organic nitrogen bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or tetramethylguanidine; DBU is preferred.

Inert solvents are, for example, hydrocarbons such as benzene, xylene or toluene, or other solvents such as isobutyronitrile; isobutyronitrile is preferred.

The compounds described in the context of the method of the invention can also be present in the form of their salts, solvates or solvates of the salts.

The compounds described in the context of the method of the invention, depending on their structure, can exist in stereoisomeric forms (enantiomers, diastereomers). The method of the invention therefore also comprises the preparation and the use of the enantiomers or diastereomers and their respective mixtures. The stereoisomerically uniform constituents can be isolated from such mixtures of enantiomers and/or diastereomers in a manner known to the person skilled in the art.

The compounds described in the context of the method of the invention can also, depending on their structure, be present in the form of their tautomers.

Salts preferred in the context of the invention are physiologically acceptable salts of the compounds employed and prepared in the method of the invention.

Physiologically acceptable salts of the compounds employed and prepared in the method of the invention comprise acid addition salts of mineral acids, carboxylic acids and sulfonic acids, e.g. salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds employed and prepared in the method of the invention also comprise salts of usual bases, such as, by way of example and preferably, alkali metal salts (e.g. sodium salts and potassium salts), alkaline earth metal salts (e.g. calcium salts and magnesium salts) and ammonium salts, derived from ammonia or organic amines having 1 to 16 C atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiiso-

propylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

Solvates in the context of the invention refer to those forms of the compounds employed and prepared in the method of the invention which, in the solid or liquid state, form a complex by coordination with solvent molecules. Hydrates are a special form of the solvates, in which the coordination takes place with water.

In the context of the present invention racemic means that the compounds are not present in enantiomerically pure form, i.e. the compounds are present as mixtures of (S)- and (R)-enantiomers. The ratio of (S)-enantiomer to (R)-enantiomer is thereby variable. A mixture of (S)-enantiomer to (R)-enantiomer of 1:1 is preferred.

In the context of the present invention, the substituents, have the following meaning, unless specified otherwise:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkylthio, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl and alkylaminosulfonyl represent a linear or branched alkyl radical generally having 1 to 6 ("C₁-C₆-alkyl"), preferably 1 to 4, particularly preferably 1 to 3 carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, tert.-butyl, n-pentyl and n-hexyl.

Alkoxy, by way of example and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert.-butoxy, n-pentoxy and n-hexoxy.

Alkylamino represents an alkylamino radical having one or two alkyl substituents (selected independently of one another), by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert.-butylamino, n-pentylamino, n-hexylamino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-

methyl-*N*-*n*-propylamino, *N*-isopropyl-*N*-*n*-propylamino, *N*-*t*-butyl-*N*-methylamino, *N*-ethyl-*N*-*n*-pentylamino and *N*-*n*-hexyl-*N*-methylamino. C₁-C₃-Alkylamino, for example, represents a monoalkylamino radical having 1 to 3 carbon atoms or a dialkylamino radical having 1 to 3 carbon atoms each per alkyl substituent.

Alkylthio, by way of example and preferably, represents methylthio, ethylthio, *n*-propylthio, isopropylthio, *tert*.-butylthio, *n*-pentylthio and *n*-hexylthio.

Alkylcarbonyl, by way of example and preferably, represents methylcarbonyl, ethylcarbonyl, *n*-propylcarbonyl, isopropylcarbonyl, *tert*.-butylcarbonyl, *n*-pentylcarbonyl and *n*-hexylcarbonyl.

Alkylsulfonyl, by way of example and preferably, represents methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *tert*.-butylsulfonyl, *n*-pentylsulfonyl and *n*-hexylsulfonyl.

Alkoxy carbonyl, by way of example and preferably, represents methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *tert*.-butoxycarbonyl, *n*-pentoxycarbonyl and *n*-hexoxycarbonyl.

Alkylaminosulfonyl represents an alkylaminosulfonyl radical having one or two alkyl substituents (selected independently of one another), by way of example and preferably methylaminosulfonyl, ethylaminosulfonyl, *n*-propylaminosulfonyl, isopropylaminosulfonyl, *tert*.-butylaminosulfonyl, *n*-pentylaminosulfonyl, *n*-hexylaminosulfonyl, *N,N*-dimethylaminosulfonyl, *N,N*-diethylaminosulfonyl, *N*-ethyl-*N*-methylaminosulfonyl, *N*-methyl-*N*-*n*-propylaminosulfonyl, *N*-isopropyl-*N*-*n*-propylaminosulfonyl, *N*-*tert*.-butyl-*N*-methylaminosulfonyl, *N*-ethyl-*N*-*n*-pentylaminosulfonyl and *N*-*n*-hexyl-*N*-methylaminosulfonyl. C₁-C₃-Alkylaminosulfonyl, for example, represents a monoalkylaminosulfonyl radical having 1 to 3 carbon atoms or a dialkylaminosulfonyl radical having 1 to 3 carbon atoms each per alkyl substituent.

Aryl represents a mono- or bicyclic aromatic, carbocyclic radical usually having 6 to 10 carbon atoms; by way of example and preferably phenyl and naphthyl.

Halogen represents fluorine, chlorine, bromine and iodine.

The present invention is described below by means of non-limiting preferred examples and comparative examples. If not stated otherwise, all quantitative data relate to percentages by weight.

Exemplary embodiments**Abbreviation index:**

ACN	acetonitrile
API-ES-pos.	atmospheric pressure ionization, electrospray, positive (in MS)
API-ES-neg.	atmospheric pressure ionization, electrospray, negative (in MS)
ca.	about
CI, NH ₃	chemical ionization (with ammonia)
conc.	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulfoxide
ESTD	external standardization
h	hour(s)
HPLC	high pressure liquid chromatography
MIBK	methyl isobutyl ketone
min.	minutes
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
R _T	retention time (in HPLC)
VDO	vacuum drying oven

General methods HPLC:

Method 1 (HPLC): Instrument: HP 1050 with multiple wavelength detection; column: Phenomenex-Prodigy ODS (3) 100A, 150 mm x 3 mm, 3 µm; eluent A: (1.0 g of KH₂PO₄ + 1.0 ml of H₃PO₄) / l of water, eluent B: acetonitrile; gradient: 0 min 10% B, 25 min 80% B, 35 min 80% B; flow: 0.5 ml/min; temp.: 45°C; UV detection: 210 nm.

Method 2 (HPLC): Instrument: HP 1050 with variable wavelength detection; column: Chiral AD-H, 250 mm x 4.6 mm, 5 μ m; eluent A: *n*-heptane + 0.2% diethylamine, eluent B: isopropanol + 0.2% diethylamine; gradient: 0 min 12.5% B, 30 min 12.5% B; flow: 1 ml/min; temp.: 25°C; UV detection: 250 nm.

For the S-enantiomer, positive e.e. values are reported, for the R-enantiomer negative e.e. values.

Method 3 (HPLC): Instrument: HP 1050 with variable wavelength detection; column: chiral AD-H, 250 mm x 4.6 mm, 5 μ m; eluent A: *n*-heptane + 0.2% diethylamine, eluent B: isopropanol + 0.2% diethylamine; gradient: 0 min 25% B, 15 min 25% B; flow: 1 ml/min; temp.: 30°C; UV detection: 250 nm.

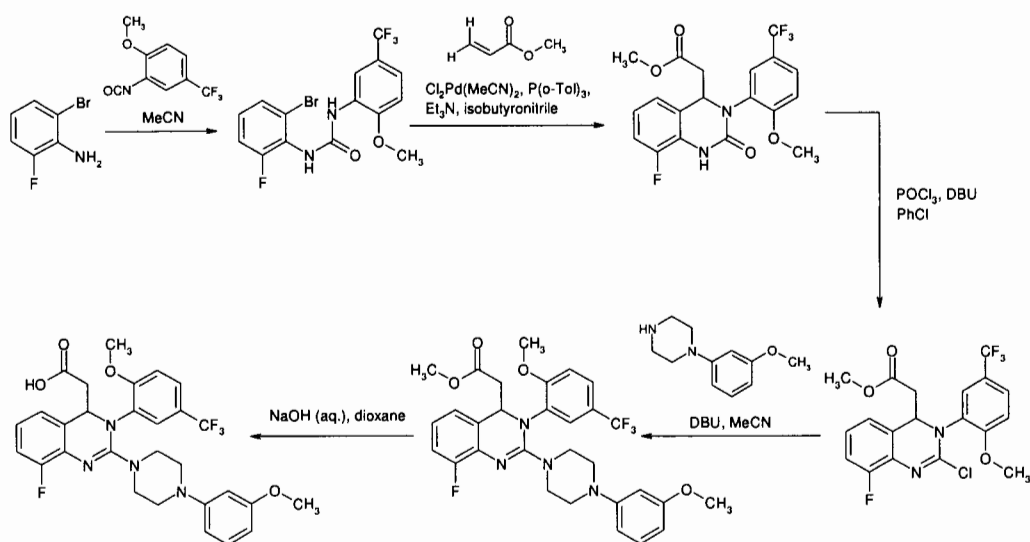
For the S-enantiomer, positive e.e. values are reported, for the R-enantiomer negative e.e. values.

Method 4 (HPLC): Instrument: HP 1100 with variable wavelength detection; column: Phenomenex-Prodigy C8, 150 mm x 3 mm, 5 μ m; eluent A: (1.36 g of KH_2PO_4 + 1.15 g of 85% H_3PO_4) / 1 of water, eluent B: acetonitrile; gradient: 0 min 10% B, 20 min 80% B, 30 min 80% B; flow: 0.5 ml/min; temp.: 40°C; UV detection: 210 nm.

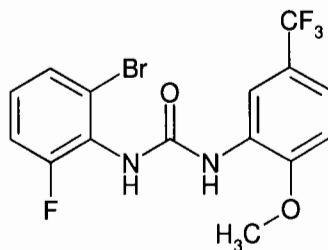
Yields reported are not corrected in terms of content.

Scheme 5:

Synthesis of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid

**Example 1**

N-(2-Bromo-6-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea



2-Methoxy-5-trifluoromethylphenyl isocyanate (274.3 g) is dissolved in acetonitrile (1 l), then 2-bromo-6-fluoroaniline (200 g) is added and rinsed with acetonitrile (50 ml). The resulting clear solution is stirred under reflux (ca. 85°C) for 38 h, then concentrated in vacuo at 40°C to a viscous magma. The solid is collected by suction

filtration, washed with acetonitrile (260 ml, cooled to 0-5°C) and dried overnight at 45°C in the VDO using entraining nitrogen. A total of 424.3 g of N-(2-bromo-6-fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea is thus obtained as a solid, corresponding to 99.2% of theory.

¹H NMR (300 MHz, d₆-DMSO): δ = 8.93 (s, 1H), 8.84 (s, 1H), 8.52 (d, ³J = 2,3, 2H), 7.55 (d, ²J = 7.7, 1H), 7.38-7.26 (m, 3H), 7.22 (d, ²J = 8.5, 1H), 4.00 (s, 3H) ppm;

MS (API-ES-pos.): m/z = 409 [(M+H)⁺, 100%];

HPLC (method 1): R_T = 22.4 and 30.6 min.

Example 2

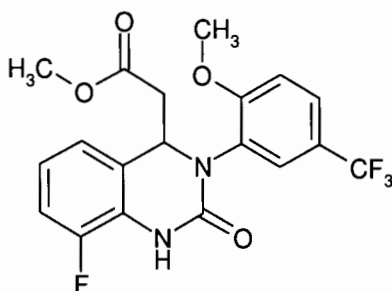
N-(2-Bromo-6-fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea (alternative synthesis)

2-Methoxy-5-trifluoromethylphenyl isocyanate (1.19 kg) is melted at about 35°C and dissolved in acetonitrile (4.2 l), then 2-bromo-6-fluoroaniline (870 g) is added and rinsed with acetonitrile (380 ml). The resulting clear solution is stirred at 74-88°C for 45 h, then concentrated in vacuo (200 mbar) at 50°C to give a viscous magma (amount of distillate 4.4 l). This is diluted at room temperature with diisopropyl ether (1.5 l), the solid is collected by suction filtration, washed with diisopropyl ether (1.15 l) and dried to constant mass (24 h) at 45°C in the VDO using entraining nitrogen. A total of 1.63 kg of N-(2-bromo-6-fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea is thus obtained as a solid, corresponding to 87.5% of theory.

HPLC (method 1): R_T = 22.6 and 30.8 min.

Example 3

Methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate



N-(2-Bromo-6-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea (300 g) is suspended in isobutyronitrile (1.2 l) under a nitrogen atmosphere, then triethylamine (210 ml), bis(acetonitrile)dichloropalladium (7.5 g), tris(*o*-tolyl)phosphine (18.0 g) and methyl acrylate (210 ml) are added in this order. The resulting suspension is stirred under reflux (ca. 102°C) for 16 h and then cooled to room temperature. Water (1.2 l) is added and the mixture is stirred at room temperature for 1 h, the solid is then collected by suction filtration and washed with water/methanol (1:1, 300 ml) and acetonitrile (100 ml). The residue is dried overnight at 45°C in the VDO using entraining nitrogen. A total of 208 g of *methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate* is thus obtained as a solid, corresponding to 68.5% of theory.

¹H NMR (300 MHz, d₆-DMSO): δ = 9.73 (s, 1H), 7.72 (d, ²J = 7.3, 1H), 7.71 (s, 1H), 7.33 (d, ²J = 9.3, 1H), 7.15 (dd, ²J = 9.6, ²J = 8.6, 1H), 7.01 (d, ²J = 7.3, 1H), 6.99-6.94 (m, 1H), 5.16 (t, ²J = 5.9, 1H), 3.84 (s, 3H), 3.41 (s, 3H), 2.81 (dd, ²J = 15.4, ²J = 5.8, 1H), 2.62 (dd, ²J = 15.4, ²J = 6.3, 1H) ppm;

MS (API-ES-pos.): m/z = 413 [(M+H)⁺, 100%], 825 [(2M+H)⁺, 14%];

HPLC (method 1): $R_T = 19.3$ min; Pd (ICP): 16 000 ppm.

Example 4

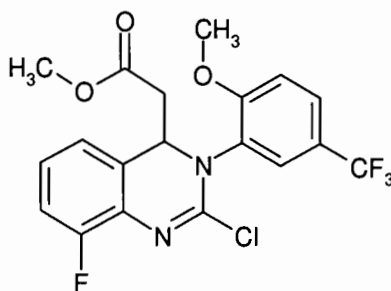
Methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate (alternative synthesis)

N-(2-Bromo-6-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea (2.5 kg) is suspended in isobutyronitrile (9 l) under a nitrogen atmosphere, then triethylamine (1.31 kg), bis(acetonitrile)dichloropalladium (64.9 g), tris(*o*-tolyl)phosphine (149 g) and methyl acrylate (1.59 kg) are added in this order. The resulting suspension is stirred at 90-100°C for 22 h, then cooled to room temperature. Water (9 l) is added and the mixture is stirred at room temperature for 1 h, the solid is then collected by suction filtration and washed with water/methanol (1:1, 2.5 l) and acetonitrile (850 ml). The residue is dried overnight at 45°C in the VDO to constant mass (21 h) using entraining nitrogen. A total of 1.90 kg of *methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate* is thus obtained as a solid, corresponding to 74.9% of theory.

HPLC (method 1): $R_T = 19.4$ min.

Example 5

Methyl {2-chloro-8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate/chlorination



A solution of 2.84 kg of methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate in 14.8 l of chlorobenzene is heated to reflux and the solvent is distilled off until water no longer separates. The mixture is cooled to 120°C. 3.17 kg of phosphorus oxychloride are added over the course of 10 min, and subsequently 2.10 kg of DBU are added within a further 10 min. The mixture is heated at reflux for 9 hours.

For the work-up, the mixture is cooled to 40°C, stirred overnight and the vessel contents are added onto 11.4 l of water which has previously been adjusted to 40°C. During the addition, an internal temperature of 40-45°C should be maintained. The mixture is allowed to cool to room temperature, 11.4 l of dichloromethane are added, the mixture is filtered through a Seitz filter plate and the phases are separated. The organic phase is washed with 11.4 l of water, 11.4 l of an aqueous saturated sodium hydrogencarbonate solution and again with 11.4 l of water. The organic phase is concentrated in vacuo on a rotary evaporator and the residue which remains (2.90 kg) is employed in the next stage without further treatment.

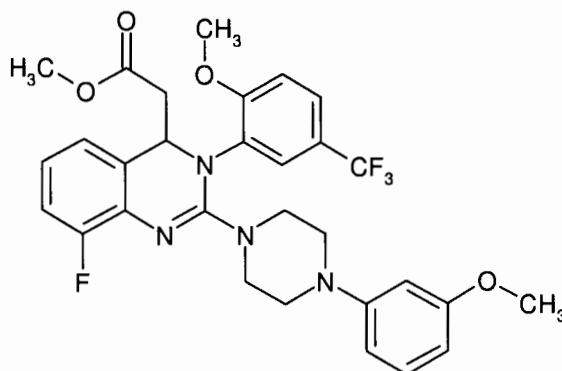
^1H NMR (300 MHz, d_6 -DMSO): δ = 7.93-7.82 (m, 2H), 7.38 (d, 2J = 8.9, 1H), 7.17 (m, 2H), 6.97-6.91 (m, 1H), 5.45 and 5.29 (m and t, 2J = 5.4, 1H), 3.91 and 3.84 (2s, 3H), 3.48 (s, 3H), 3.0-2.6 (m, 2H) ppm;

MS (CI, NH_3): m/z = 431 $[(M+H)^+]$, 100%];

HPLC (method 1): R_T = 23.5 min; typical Pd value (ICP): 170 ppm.

Example 6

Methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate/amination



Methyl {2-chloro-8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (52.5 g) is dissolved in 1,4-dioxane (100 ml), 3-methoxyphenyl-piperazine (25.8 g) and DBU (20.4 g) are then added at room temperature, whereby the temperature increases. The mixture is stirred under reflux for 22 h, then cooled to room temperature, diluted with ethyl acetate (500 ml) and water (200 ml) and the phases are separated. The organic phase is washed with 0.2N hydrochloric acid (three times 100 ml) and water (200 ml), dried over sodium sulfate and concentrated on a rotary evaporator. A total of 62.5 g of methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate is thus

obtained as a solidified foam, which is reacted as the crude product without further purification.

HPLC (method 1): R_T = 16.6 min.

Example 7

Methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate/one-pot chlorination + amination

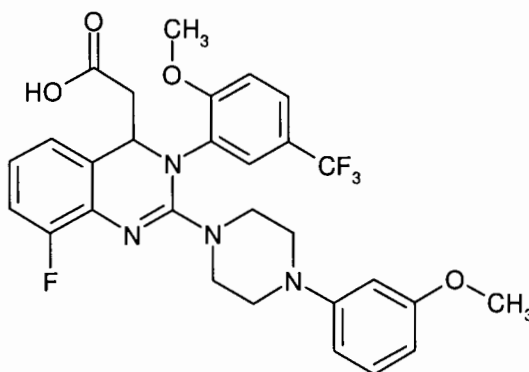
Methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate (50.0 g) is provided in chlorobenzene (300 ml), then chlorobenzene is partially distilled off (50 ml). The mixture is cooled to 120°C, DBU (36.9 g) is added, then phosphorus oxychloride (33.4 ml) is added at 120-128°C over the course of 10 min. The mixture is stirred under reflux (ca. 130°C) for 9 h. Subsequently, the mixture is cooled to 40°C, slowly at 40-45°C water (200 ml) is added, the mixture is cooled to room temperature and diluted with dichloromethane (200 ml), extracted with stirring and the phases are then separated. The organic phase is washed with water (200 ml), a saturated aqueous sodium hydrogencarbonate solution (200 ml) and again water (200 ml), dried over sodium sulfate, concentrated on a rotary evaporator and then dried at 50°C under high vacuum. The residue (48.1 g) is dissolved in chlorobenzene (20 ml), the solution is then diluted with 1,4-dioxane (80 ml) and 3-methoxyphenylpiperazine (23.6 g) and DBU (18.7 g) are added at room temperature, whereby the temperature increases. The mixture is stirred under reflux for 22 h, then cooled to room temperature, diluted with ethyl acetate (500 ml) and water (200 ml) and the phases are separated. The organic phase is washed with 0.2N hydrochloric acid (three times 100 ml) and water (200 ml), dried over sodium sulfate and concentrated on a rotary evaporator. A total of 55.6 g of *methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-*

dihydroquinazolin-4-yl]acetate is thus obtained as a solidified foam, which is reacted as the crude product without further purification.

HPLC (method 1): $R_t = 16.2$ min.

Example 8

(±)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl]acetic acid/hydrolysis of the racemate

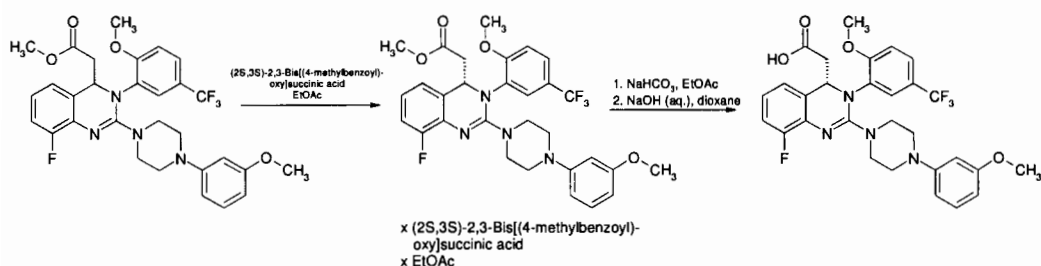


Methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetate (64 g) is dissolved in 1,4-dioxane (450 ml) and a 1N sodium hydroxide solution (325 ml) and stirred at room temperature for 2 h, then some of the solvent (400 ml) is distilled off at 30°C in vacuo. Subsequently, toluene (300 ml) is added and the phases are separated. The aqueous phase is washed with toluene (twice 150 ml), then the combined organic phases are extracted again with a 1N sodium hydroxide solution (50 ml). The pH of the combined aqueous phases is adjusted to 7.5 using 2N hydrochloric acid (ca. 150 ml), then MIBK (150 ml) is added. The phases are separated, the aqueous phase is extracted again with MIBK (150 ml), then the combined MIBK phases are dried over sodium sulfate and concentrated at 45°C. A total of 64 g of (±)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl]acetic acid is thus obtained in quantitative yield as an amorphous solid.

HPLC (method 1): $R_T = 14.9$ min.

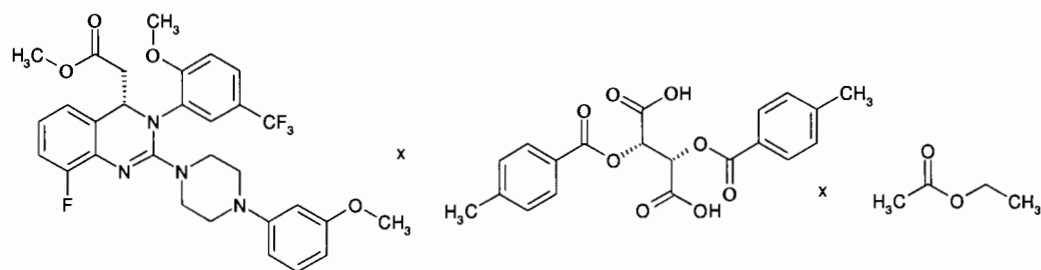
Scheme 6:

Separation of the enantiomers of methyl [8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetate



Example 9

(2S,3S)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl [8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetate (1:1-salt)/crystallization



Methyl [8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetate (62.5 g, crude product) is dissolved in ethyl acetate (495 ml) and filtered. (2S,3S)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid (42.0 g) is added to the filtrate, the mixture is stirred at room temperature for 30 min, then seeded with (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]-succinic acid –

methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (165 mg) and stirred at room temperature for 3 days, subsequently cooled to 0-3°C and stirred for a further 3 h. The suspension is collected by suction filtration and washed with cold ethyl acetate (0-10°C, 35 ml). The crystals are dried at 40°C for 18 h in the VDO using entraining nitrogen. A total of 37.1 g of the salt is thus obtained as a solid, corresponding to 30.4% of theory over three stages (chlorination, amination and crystallization) based on the racemate, or 60.8% based on the resulting S-enantiomer.

¹H NMR (300 MHz, d₆-DMSO): δ = 7.90 (d, ²J = 7.8, 4H), 7.56 (d, ²J = 8.3, 1H), 7.40 (d, ²J = 7.8, 4H), 7.28-7.05 (m, 4H), 6.91-6.86 (m, 2H), 6.45 (d, ²J = 8.3, 1H), 6.39-6.36 (m, 2H), 5.82 (s, 2H), 4.94 (m, 1H), 4.03 (q, ²J = 7.1, 2H), 3.83 (brs, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 3.47-3.36 (m, 8H and water, 2H), 2.98-2.81 (m, 5H), 2.58-2.52 (m, 1H), 2.41 (s, 6H), 1.99 (s, 3H), 1.18 (t, ²J = 7.2, 3H) ppm;

HPLC (method 1): R_T = 16.6 and 18.5 min.

Example 10

(2S,3S)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt)/recrystallization

(2S,3S)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (36.8 g) is suspended in ethyl acetate (370 ml) and dissolved by heating to reflux (77°C). The mixture is slowly cooled to room temperature. Spontaneous crystallization takes place over the course of this. The suspension is stirred at RT for 16 h, subsequently cooled to 0-5°C and stirred for a further 3 h. The suspension is collected by suction filtration and washed with cold ethyl acetate (0-10°C, two times 15 ml). The crystals are dried at 45°C for 18 h in the VDO using

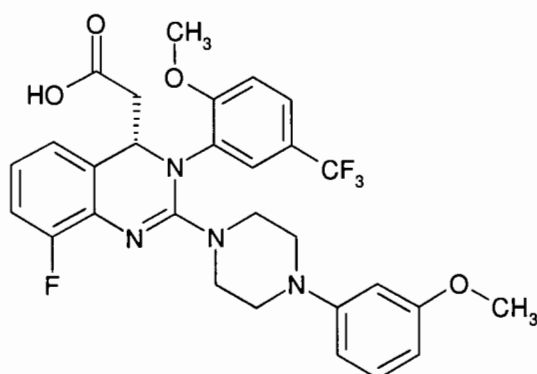
entraining nitrogen. A total of 33.6 g of the salt is thus obtained as a solid, corresponding to 91.3% of theory.

HPLC (method 1): R_T = 16.9 and 18.8 min.;

HPLC (method 3): 99.9% e.e.

Example 11

(*S*)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid



(2*S*,3*S*)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (10.1 g, containing 14 ppm of Pd) are suspended in ethyl acetate (100 ml) and shaken with a saturated aqueous sodium bicarbonate solution (100 ml) until both phases become clear. The phases are separated and the organic phase is concentrated on a rotary evaporator. The residue is dissolved in 1,4-dioxane (100 ml) and a 1N sodium hydroxide solution (31.2 ml) and stirred at room temperature for 3 h. Subsequently, the pH is adjusted to 7.5 using 1N hydrochloric acid (ca. 17 ml), MIBK (80 ml) is added, and the pH is then readjusted to 7.0 using 1N hydrochloric acid (ca. 2 ml). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated. The residue is dissolved in ethanol

(40 ml) and concentrated, then again dissolved in ethanol (40 ml) and concentrated and dried at 50°C under high vacuum. The solidified foam is dried at 45°C for 18 h in the VDO using entraining nitrogen. A total of 5.05 g of (*S*)-[8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl]acetic acid is thus obtained as an amorphous solid, corresponding to 85.0% of theory.

^1H NMR (300 MHz, $\text{d}_6\text{-DMSO}$): δ = 7.53 (d, 2J = 8.4, 1H), 7.41 (brs, 1H), 7.22 (d, 2J = 8.5, 1H), 7.09-7.01 (m, 2H), 6.86 (m, 2H), 6.45 (dd, 2J = 8.2, 3J = 1.8, 1H), 6.39-6.34 (m, 2H), 4.87 (t, 2J = 7.3, 1H), 3.79 (brs, 3H), 3.68 (s, 3H), 3.50-3.38 (m, 4H), 2.96-2.75 (m, 5H), 2.45-2.40 (m, 1H) ppm;

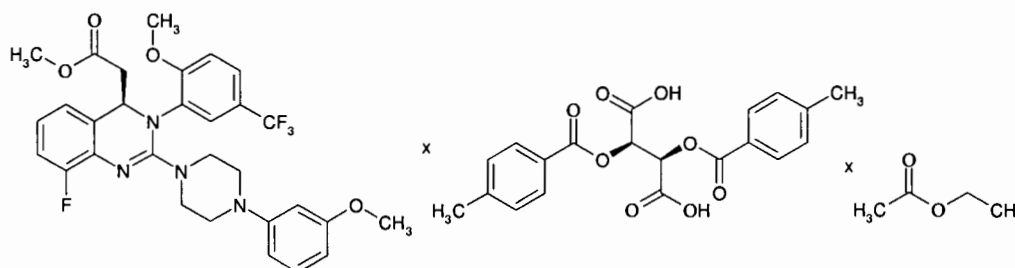
MS (API-ES-neg.): m/z = 571 [(M-H), 100%];

HPLC (method 1): R_T = 15.1 min;

HPLC (method 2): 99.8% e.e.; Pd (ICP): <1 ppm.

Example 12

(2*R*,3*R*)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl [8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetate (1:1 salt)/crystallization of the R isomer from mother liquor



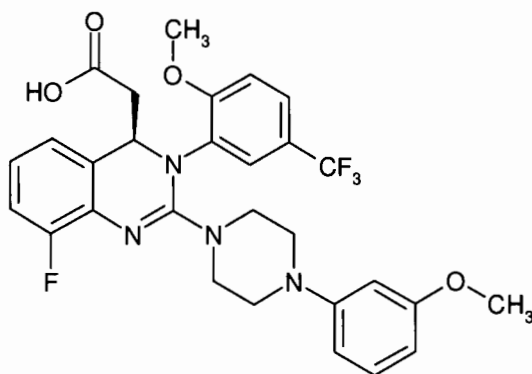
The mother liquor from a crystallization of (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) on a 279 g scale is shaken with a saturated aqueous sodium bicarbonate solution (1.5 l), the phases are separated and the organic phase is shaken with a semi-saturated aqueous sodium bicarbonate solution (1.5 l). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated on a rotary evaporator. The residue (188.4 g) is dissolved in ethyl acetate (1.57 l), then (2*R*,3*R*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid (121.7 g) is added and the mixture is stirred at room temperature for 10 min. Subsequently, the mixture is seeded with (2*R*,3*R*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (0.38 g) and stirred at room temperature for 18 h, subsequently cooled to 0-3°C and stirred for a further 3 h. The suspension is collected by suction filtration and washed with cold ethyl acetate (0-10°C, 500 ml). The crystals are dried at 40°C for 18 h in the VDO using entraining nitrogen. A total of 160 g of the salt is thus obtained as a solid.

HPLC (method 1): R_T = 16.6 and 18.5 min.;

HPLC (method 3): -99.0% e.e.

Example 13

(*R*)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid/preparation of the R-isomer



(2*R*,3*R*)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (170 g) are suspended in ethyl acetate (850 ml) and shaken with a saturated aqueous sodium bicarbonate solution (850 ml) until both phases become clear (ca. 5 min.). The phases are separated, and the solvent of the organic phase is replaced under atmospheric pressure with 1,4-dioxane up to a final temperature of 99°C (in portions a total of 2.55 l of solvent is distilled off and 2.55 l of 1,4-dioxane are employed). The mixture is cooled to room temperature and stirred at room temperature for 18 h with a 1N sodium hydroxide solution (525 ml). Subsequently, the pH is adjusted to 7.5 using concentrated hydrochloric acid (ca. 35 ml), MIBK (850 ml) is added, and the pH is then readjusted to 7.0 using concentrated hydrochloric acid (ca. 10 ml). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated. The residue is dissolved in ethanol (350 ml) and concentrated, then again dissolved in ethanol (350 ml) and concentrated at 50°C. A total of 91.6 g of (*R*)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid is thus obtained as an amorphous solid, corresponding to 91.6% of theory.

HPLC (method 1): $R_T = 14.8$ min.

Example 14

{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid/racemization of the R-enantiomer

(R)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid (50 g) is dissolved in acetonitrile (500 ml) and sodium methoxide (30% in methanol, 32.4 ml) is added and the mixture is then stirred under reflux for 60 h. After cooling to room temperature, the mixture is concentrated to one half in vacuo, then adjusted to pH 7.5 using hydrochloric acid (20%, ca. 20 ml), MIBK (200 ml) is added and the mixture is readjusted to pH 7 using hydrochloric acid (20%). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated on a rotary evaporator to give a hard foam. The residue is dissolved in ethanol (150 ml) and concentrated, then again dissolved in ethanol (150 ml) and concentrated. A total of 54.2 g of ($\pm$)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid is thus obtained as an amorphous solid in quantitative yield.

HPLC (method 1): R_t = 14.9 min.;

HPLC (method 4): 80.8% by weight.

Example 15

Methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate/esterification of the racemate

($\pm$)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid (54 g) is dissolved in methanol (540 g), then concentrated sulfuric acid (7.85 ml) is added. The mixture is stirred under reflux for 26 h, then cooled and concentrated in vacuo to ca. one third of the original volume. Water (150 ml) and dichloromethane (150 ml) are added, then the

phases are separated. The organic phase is extracted with a saturated sodium hydrogencarbonate solution (two times 140 ml), dried over sodium sulfate and concentrated to give a foamy residue. This is dissolved twice in succession in ethanol (150 ml each) and concentrated, and subsequently dried for 18 h in vacuo using entraining nitrogen. A total of 41.6 g of *methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate* is thus obtained as an amorphous solid, corresponding to 75.2% of theory.

HPLC (method 1): $R_T = 16.8$ min.;

HPLC (method 4): 85.3% by weight;

HPLC (method 3): -8.5% e.e.

Example 16

(2*S*,3*S*)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) /crystallization of the esterified racemate

Methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (41.0 g) is suspended in ethyl acetate (287 ml), then (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid (27.5 g) is added. The mixture is stirred at room temperature for 30 min, then seeded with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (0.08 g). The suspension is stirred at RT for 16 h, subsequently cooled to 0-5°C and stirred for a further 3 h, the solid is then collected by suction filtration and washed with cold ethyl acetate (0-10°C, four times 16 ml). The crystals are dried at 45°C for 18 h in the VDO using entraining nitrogen. A total of 25.4 g of the salt is thus obtained as a solid, corresponding to 37.4% of theory.

HPLC (method 1): R_T = 16.9 and 18.8 min.;

HPLC (method 4): 99.5% by weight;

HPLC (method 3): 99.3% e.e.

Example 17

(S)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid/hydrolysis of the crystallizate

(2S,3S)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (25.1 g) is suspended in ethyl acetate (250 ml) and shaken with a saturated aqueous sodium bicarbonate solution (250 ml) until both phases become clear. The phases are separated and the organic phase is concentrated on a rotary evaporator. The residue is dissolved in 1,4-dioxane (250 ml) and a 1N sodium hydroxide solution (77.4 ml) is added and stirred at room temperature for 18 h. Subsequently, the pH is adjusted to 7.5 using 1N hydrochloric acid (ca. 50 ml), MIBK (240 ml) is added, and the pH is then readjusted to 7.0 using 1N hydrochloric acid (ca. 15 ml). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated. The residue is dissolved in ethanol (90 ml) and concentrated, then again dissolved in ethanol (90 ml) and concentrated. The solidified foam is dried at 45°C for 18 h in the VDO using entraining nitrogen. A total of 12 g of (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid is thus obtained as an amorphous solid, corresponding to 81.2% of theory.

HPLC (method 1): R_T = 15.1 min;

HPLC (method 2): 97.5% e.e.; Pd (ICP): <20 ppm.

Alternative method for the racemization:

Example 18

(±)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid/hydrolysis of the concentrated R-isomer from the mother liquor after crystallization

The mother liquor from a crystallization of (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) on a 207 g scale is shaken with a saturated aqueous sodium bicarbonate solution (500 ml), the phases are separated and the organic phase is shaken with a semi-saturated aqueous sodium bicarbonate solution (500 ml). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated on a rotary evaporator. The residue is dissolved in ethanol (500 ml) and concentrated on a rotary evaporator to give a hard foam. This is dissolved in 1,4-dioxane (1,6 l) and a 1*N* sodium hydroxide solution (1.04 l) and stirred at room temperature for 18 h, then toluene (1.5 l) is added and the phases are separated. The aqueous phase is adjusted from pH 14 to pH 8 using hydrochloric acid (20%, ca. 155 ml), then MIBK (1.25 l) is added and the mixture is readjusted to pH 7 using hydrochloric acid (20% ca. 25 ml). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated on a rotary evaporator to give a hard foam. This is dried at 45°C for 18 h in the VDO using entraining nitrogen. A total of 150 g {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid is thus obtained as an (R/S) mixture as an amorphous solid.

HPLC (method 2): -14.6% e.e.

Example 19

(±)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid/racemization

{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid (150 g, R/S-mixture with -14.6% e.e.) is dissolved in acetonitrile (1.5 l) and sodium methoxide (30% in methanol, 97.2 ml) is added and the mixture is then stirred under reflux for 77 h. After cooling to room temperature, the mixture is concentrated to one half in vacuo, and then adjusted from pH 13 to pH 7.5 using hydrochloric acid (20%, ca. 80 ml), MIBK (0.6 l) is added and the mixture is readjusted to pH 7 using hydrochloric acid (20%, ca. 3 ml). The phases are separated, and the organic phase is dried over sodium sulfate and concentrated on a rotary evaporator to give a hard foam. The residue is dissolved in ethanol (500 ml) and concentrated, then again dissolved in ethanol (500 ml) and concentrated, then dried for 18 h at 45°C in the VDO using entraining nitrogen. A total of 148 g of (±)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid is obtained as an amorphous solid, corresponding to 98.7% of theory.

HPLC (method 2): 1.5% e.e.

Example 20

Methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (esterification)

(±)-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2-methoxy-5-trifluoromethylphenyl)-3,4-dihydroquinazolin-4-yl}acetic acid (148 g) is dissolved in methanol (1480 g), then concentrated sulfuric acid (21.5 ml) is added. The mixture is stirred under reflux for 6 h, then cooled and concentrated in vacuo to ca. one third of the

original volume. Water (400 ml) and dichloromethane (400 ml) are added, then the phases are separated. The organic phase is extracted with a saturated sodium hydrogencarbonate solution (two times 375 ml, diluted with 300 ml of water), dried over sodium sulfate and concentrated to give a foamy residue. This is dissolved twice in succession in ethanol (400 ml each) and concentrated, and subsequently dried in vacuo for 18 h using entraining nitrogen. A total of 124 g of *methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate* is thus obtained as an amorphous solid, corresponding to 81.9% of theory.

HPLC (method 1): $R_T = 16.9$ min.;

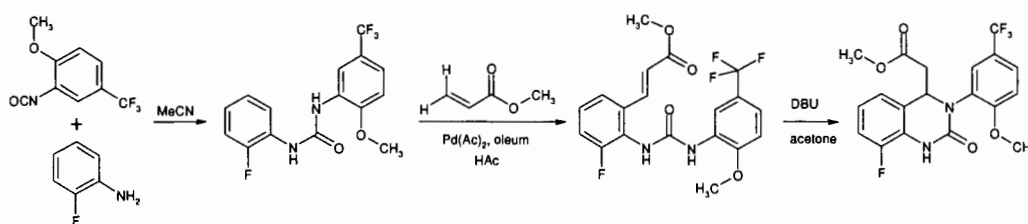
Example 21

(2*S*,3*S*)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1 salt)/crystallization of the esterified racemate

(2*S*,3*S*)-2,3-Bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (123 g, -14.4% e.e.) is suspended in ethyl acetate (861 ml) and filtered, then (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid (82.5 g) is added. The mixture is stirred at room temperature for 30 min, then seeded with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (0.24 g). The suspension is stirred at RT for 4 days, subsequently concentrated to ca. 600 ml and again seeded with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid – methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (1:1 salt) (0.24 g). The suspension is stirred at RT for 1 week, cooled to 0-5°C and stirred for a further 3 h, the solid is then collected by suction filtration and washed with cold

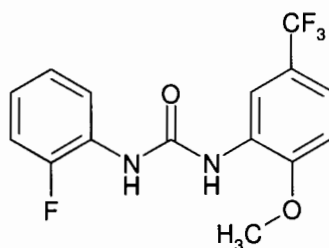
ethyl acetate (0-10°C, 4 x 40 ml). The crystals are dried at 45°C for 18 h in the VDO using entraining nitrogen. A total of 11.8 g of the salt is thus obtained as a solid, corresponding to 5.8% of theory.

Scheme 7:



Example 22

N-(2-Fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea



2-Methoxy-5-trifluoromethylphenyl isocyanate (1057.8 g) is dissolved in acetonitrile (4240 ml), then 2-fluoroaniline (540.8 g) is added and rinsed with acetonitrile (50 ml). The resulting clear solution is stirred under reflux (ca. 82°C) for 4 h, then seeded at ca. 78°C and stirred for ca. 15 min. The suspension is cooled to 0°C, and the product is collected by suction filtration and washed with acetonitrile (950 ml, cooled to 0-5°C). The product is dried overnight at 45°C in a vacuum drying oven using entraining nitrogen. A total of 1380.8 g of *N*-(2-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea is thus obtained as a solid, corresponding to 86.4% of theory.

^1H NMR (500 MHz, d_6 -DMSO): δ = 9.36 (s, 1H), 9.04 (s, 1H), 8.55 (d, 1.7Hz, 1H), 8.17 (t, 8.2Hz, 1H), 7.33 (d, 8.5Hz, 1H), 7.20 – 7.26 (m, 2H), 7.14 (t, 7.6Hz, 1H), 7.02 (m, 1H), 3.97 (s, 3H) ppm;

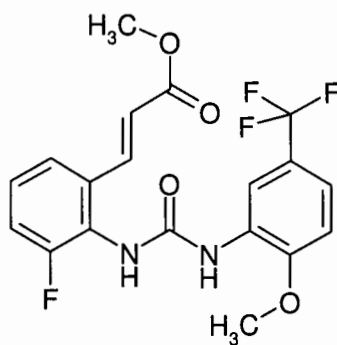
MS (API-ES-pos.): m/z = 329 $[(M+H)^+]$, 100%];

HPLC : R_T = 48.7 min.

Instrument: HP 1100 with multiple wavelength detection; column: Phenomenex-Prodigy ODS (3) 100A, 150 mm x 3 mm, 3 μm ; eluent A: (1.36 g of KH_2PO_4 + 0.7 ml of H_3PO_4) / 1 of water, eluent B: acetonitrile; gradient: 0 min 20% B, 40 min 45% B, 50 min 80% B, 65 min 80% B; flow: 0.5 ml/min; temp.: 55°C; UV detection: 210 nm.

Example 23

Methyl (2E)-3-{3-fluoro-2-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenyl}acrylate



N-(2-Fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea (0.225 kg) is dissolved in acetic acid (6.75 l) and palladium acetate (30.3 g) is added. 65% oleum (247.5 g) is then added and methyl acrylate (90 g) is subsequently added. The solution is stirred at room temperature overnight. Subsequently, acetic acid (3740 g) is distilled off at ca. 30°C and ca. 30 mbar. Water (2.25 l) is added to the suspension and the mixture is stirred for ca. 1 hour. The product is collected by suction filtra-

tion, washed twice with water (0.5 l) and dried at 50°C overnight in the vacuum drying oven using entraining nitrogen. A total of 210.3 g of *methyl (2E)-3-[3-fluoro-2-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenyl]acrylate* is thus obtained as a solid, corresponding to 72.2% of theory.

^1H NMR (300 MHz, d_6 -DMSO): δ = 9.16 (s, 1H), 8.84 (s, 1H), 8.45 (d, 1.7Hz, 1H), 7.73 (m, 2H), 7.33 (m, 3H), 7.22 (d, 8.6Hz, 1H), 6.70 (d, 16Hz, 1H), 3.99 (s, 3H), 3.71 (s, 3H) ppm;

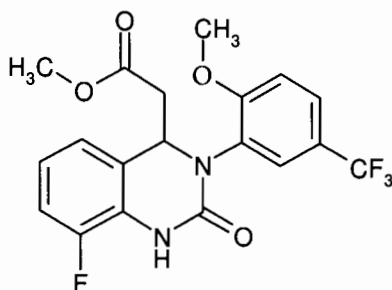
MS (API-ES-pos.): m/z = 429.9 [(M+NH₄)⁺]; 412.9 [(M+H)⁺]

HPLC : R_T = 46.4 min.

Instrument: HP 1100 with multiple wavelength detection; column: Phenomenex-Prodigy ODS (3) 100A, 150 mm x 3 mm, 3 μm ; eluent A: (1.36 g KH₂PO₄ + 0.7 ml H₃PO₄) / 1 of water, eluent B: acetonitrile; gradient: 0 min 20% B, 40 min 45% B, 50 min 80% B, 65 min 80% B; flow: 0.5 ml/min; temp.: 55°C; UV detection: 210 nm.

Example 24

Methyl [8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl]acetate



Methyl (2E)-3-[3-fluoro-2-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenyl]acrylate (50 g) is suspended in acetone (1.2 l) and 1,8-diazobi-

cyclo[5.4.0]undec-7-ene (3.7 g) is added. The suspension is warmed to reflux (ca. 56°C) and stirred for 4 h. The resulting clear solution is filtered warm through kieselguhr (5 g). The kieselguhr is rinsed with warm acetone (100 ml). Subsequently, acetone (550 g) is distilled off. The resulting suspension is cooled to 0°C over the course of 3 h and stirred. The product is collected by suction filtration, washed twice with cold acetone (50 ml) and dried at 45°C overnight in the vacuum drying oven using entraining nitrogen. A total of 44.5 g of *methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate* is thus obtained as a solid, corresponding to 89% of theory.

¹H NMR (300 MHz, d₆-DMSO): δ = 9.73 (s, 1H), 7.72 (d, ²J = 7.3, 1H), 7.71 (s, 1H), 7.33 (d, ²J = 9.3, 1H), 7.15 (dd, ²J = 9.6, ²J = 8.6, 1H), 7.01 (d, ²J = 7.3, 1H), 6.99-6.94 (m, 1H), 5.16 (t, ²J = 5.9, 1H), 3.84 (s, 3H), 3.41 (s, 3H), 2.81 (dd, ²J = 15.4, ²J = 5.8, 1H), 2.62 (dd, ²J = 15.4, ²J = 6.3, 1H) ppm;

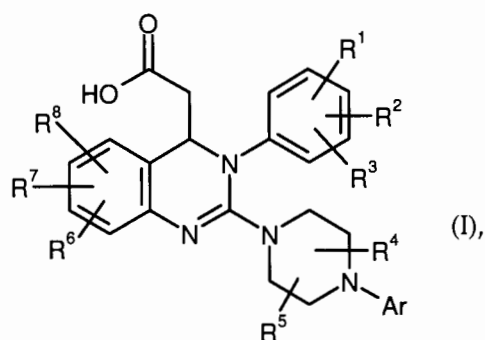
MS (API-ES-pos.): m/z = 413 [(M+H)⁺, 100%], 825 [(2M+H)⁺, 14%];

HPLC : R_T = 37.1 min.

Instrument: HP 1100 with multiple wavelength detection; column: Phenomenex-Prodigy ODS (3) 100A, 150 mm x 3 mm, 3 μm; eluent A: (1.36 g of KH₂PO₄ + 0.7 ml of H₃PO₄) / 1 of water, eluent B: acetonitrile; gradient: 0 min 20% B, 40 min 45% B, 50 min 80% B, 65 min 80% B; flow: 0.5 ml/min; temp.: 55°C; UV detection: 210 nm.

Claims:

1. Method for the preparation of a compound of formula (I)



in which

Ar represents aryl, wherein aryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of alkyl, alkoxy, formyl, carboxy, alkylcarbonyl, alkoxycarbonyl, trifluoromethyl, halogen, cyano, hydroxy, amino, alkylamino, aminocarbonyl and nitro,

wherein alkyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, amino, alkylamino, hydroxy and aryl,

or two of the substituents on the aryl, together with the carbon atoms to which they are bonded, form a 1,3-dioxolane, a cyclopentane ring or a cyclohexane ring and an optionally present third substituent is selected independently thereof from the group mentioned,

R¹ represents hydrogen, amino, alkyl, alkoxy, alkylamino, alkylthio, cyano, halogen, nitro or trifluoromethyl,

R² represents hydrogen, alkyl, alkoxy, alkylthio, cyano, halogen, nitro or trifluoromethyl,

R³ represents amino, alkyl, alkoxy, alkylamino, alkylthio, cyano, halogen, nitro, trifluoromethyl, alkylsulfonyl or alkylaminosulfonyl

or

one of the radicals R¹, R² and R³ represents hydrogen, alkyl, alkoxy, cyano, halogen, nitro or trifluoromethyl and the other two, together with the carbon atoms to which they are bonded, form a 1,3-dioxolane, a cyclopentane ring or a cyclohexane ring,

R⁴ represents hydrogen or alkyl,

R⁵ represents hydrogen or alkyl

or

the radicals R⁴ and R⁵ in the piperazine ring are bonded to carbon atoms directly opposing each other and form a methylene bridge which is optionally substituted with 1 to 2 methyl groups,

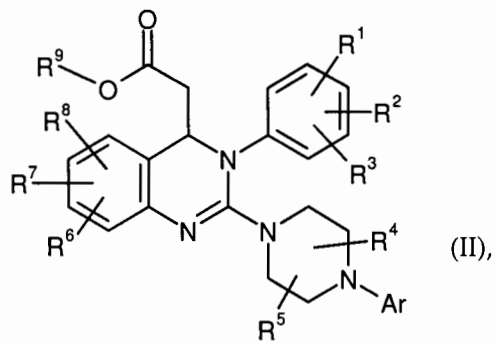
R⁶ represents hydrogen, alkyl, alkoxy, alkylthio, formyl, carboxy, amino-carbonyl, alkylcarbonyl, alkoxycarbonyl, trifluoromethyl, halogen, cyano, hydroxy or nitro,

R⁷ represents hydrogen, alkyl, alkoxy, alkylthio, formyl, carboxy, alkylcarbonyl, alkoxycarbonyl, trifluoromethyl, halogen, cyano, hydroxy or nitro

and

R⁸ represents hydrogen, alkyl, alkoxy, alkylthio, formyl, carboxy, alkylcarbonyl, alkoxy carbonyl, trifluoromethyl, halogen, cyano, hydroxy or nitro,

by hydrolysis of the ester of a compound of formula (II)

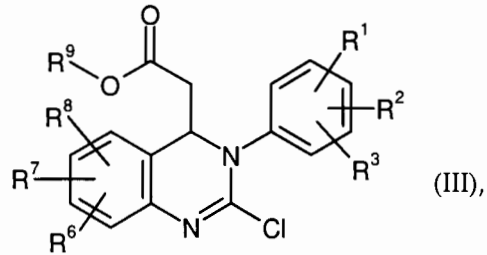


in which

Ar, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ have the meaning indicated above, and

R⁹ represents C₁-C₄-alkyl,

using a base or an acid, characterized in that the compound of formula (II) is prepared by the reaction of a compound of formula (III)



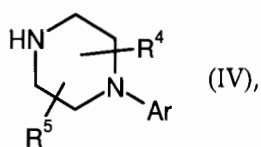
in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated above, and

R^9 represents C_1 - C_4 -alkyl,

in the presence of a base

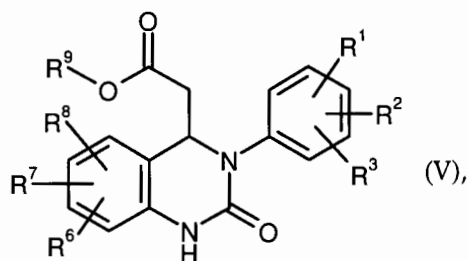
with a compound of formula (IV)



in which

Ar, R^4 and R^5 have the meaning indicated above.

2. Method according to claim 1, characterized in that the compound of formula (III), as defined in Claim 1, is prepared by the reaction of a compound of formula (V)



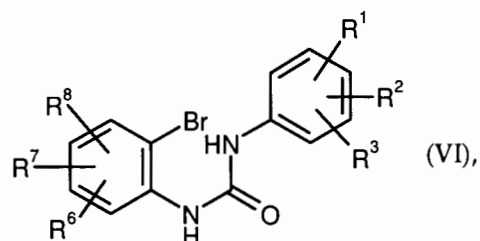
in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated in Claim 1, and

R^9 represents C_1 - C_4 -alkyl,

with phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride, in the presence of a base.

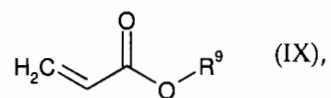
3. Method according to claim 2, characterized in that the compound of formula (V), as defined in Claim 2, is prepared by the reaction of a compound of formula (VI)



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated in Claim 2,

with a compound of formula

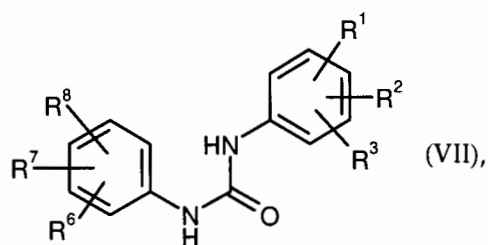


in which

R^9 represents C_1 - C_4 -alkyl,

in the presence of a palladium catalyst and a base.

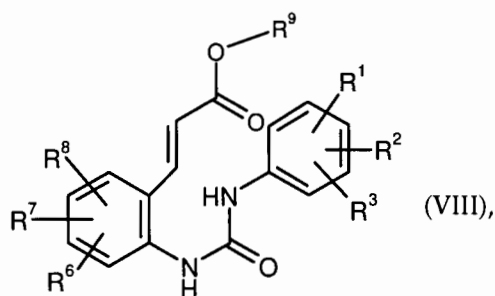
4. Method according to claim 2, characterized in that the compound of formula (V), as defined in Claim 2, is prepared by the reaction of a compound of formula (VII)



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated in Claim 2,

in the first stage with a compound of formula (IX) in acetic acid in the presence of a palladium catalyst, an oxidizing agent and an acid to give a compound of formula (VIII)



in which

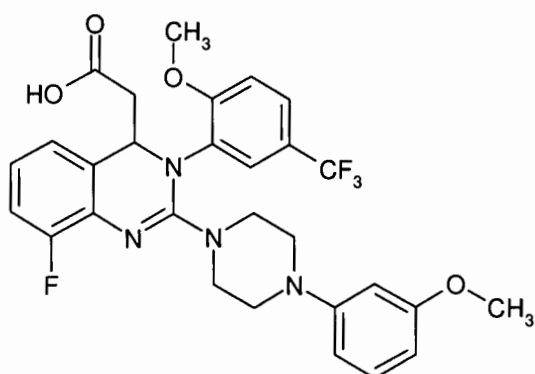
R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated in Claim 2, and

R^9 represents C_1 - C_4 -alkyl,

and in the second stage with a base to give a compound of formula (V).

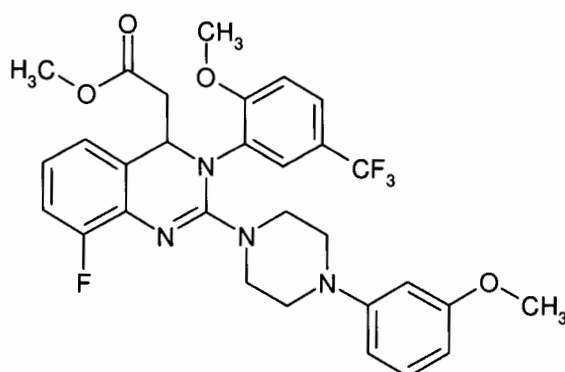
5. Method according to one of claims 1 to 4, characterized in that the compound of formula (I) is

{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid



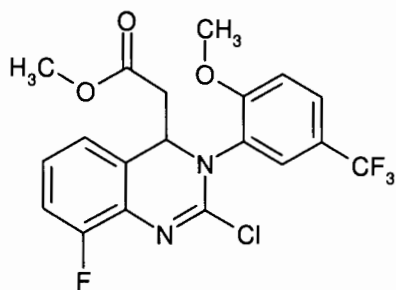
the compound of formula (II) is

methyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate



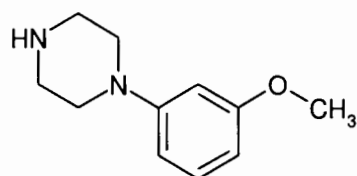
the compound of formula (III) is

methyl 2-chloro-8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate



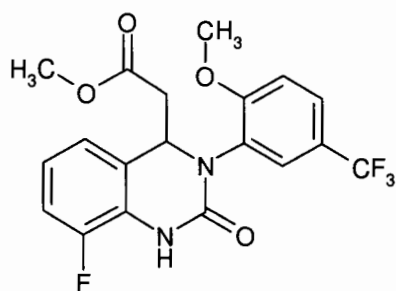
the compound of formula (IV) is

1-(3-methoxyphenyl)piperazine



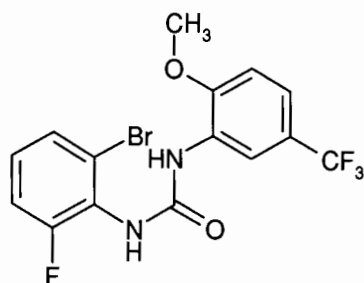
the compound of formula (V) is

methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate



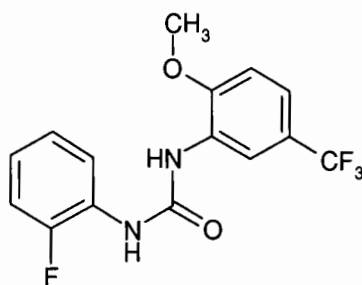
the compound of formula (VI) is

N-(2-bromo-6-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea



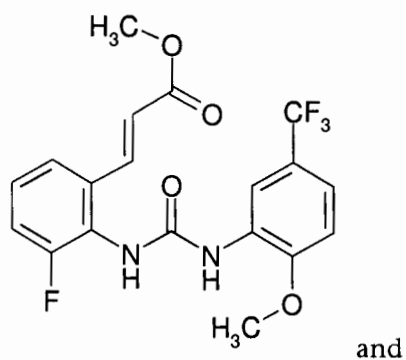
the compound of formula (VII) is

N-(2-fluorophenyl)-*N'*-[2-methoxy-5-(trifluoromethyl)phenyl]urea



the compound of formula (VIII) is

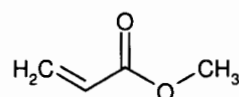
methyl (2*E*)-3-{3-fluoro-2-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenyl}acrylate



and

the compound of formula (IX) is

methyl acrylate



6. Method for the separation of the enantiomers of (C₁-C₄)-alkyl {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate and the isolation of (C₁-C₄)-alkyl (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that the racemic ester is crystallized with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid.
7. Methyl (S)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid salt.
8. Method for the racemization of (C₁-C₄)-alkyl (R)-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetate, characterized in that

in the first stage the alkyl ester is hydrolysed to the acid,

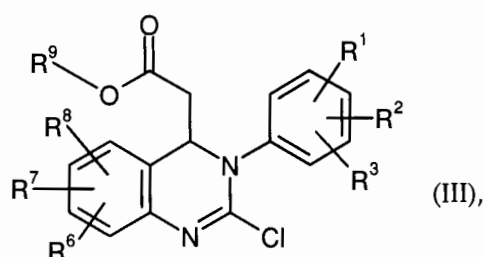
in the second stage the acid is racemized using sodium methoxide or sodium ethoxide and

in the third stage the acid is again converted into the alkyl ester.

9. Method for the racemization of (C₁-C₄)-alkyl (R)-(8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetate, characterized in that

the alkyl ester is reacted with a base in an inert solvent.

10. Compound of formula (III)

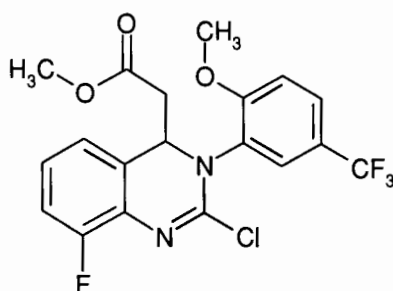


in which

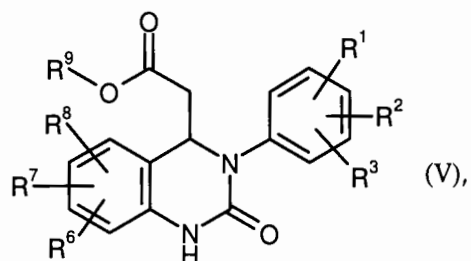
R¹, R², R³, R⁶, R⁷ and R⁸ have the meaning indicated in Claim 1, and

R⁹ represents C₁-C₄-alkyl.

11. Compound according to Claim 10, characterized in that the compound is methyl 2-chloro-8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetate



12. Compound of formula (V)



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 have the meaning indicated in Claim 1, and

R^9 represents C_1 - C_4 -alkyl.

13. Compound according to Claim 12, characterized in that the compound is methyl {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetate

