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(54) Benevnelse **PHARMACEUTICAL PREPARATION COMPRISING AN ANTIVIRAL DIHYDROQUINAZOLINE DERIVATIVE WITH S CONFIGURATION IN POSITION 4**

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PHARMACEUTICAL PREPARATION COMPRISING AN ANTIVIRAL DIHYDROQUINAZOLINE DERIVATIVE WITH S CONFIGURATION IN POSITION 4

The present invention relates to a pharmaceutical preparation, containing {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof.

The invention further relates to methods for the production thereof, their use for the treatment and/or prevention of viral infections, in particular for treating infections with the human cytomegalovirus (HCMV) or another representative of the Herpes viridae group.

{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid is known, for example, from WO 2004/096778, full disclosure of which is included herein by reference; it was developed by applicant as a promising candidate for an antivirally active substance, in particular for combating infections caused by the human cytomegalovirus. However, in the course of development it was discovered that problems occurred with the solubility of the substance, and in particular it proved complicated to produce stable formulations for intravenous administration or solid easily soluble preparations for producing solutions used for intravenous administration. PT1622880 deals with PEG-containing injectable formulations whose active ingredient is 2-((4S)-8-Fluoro-2-(4-(3-methoxyphenyl)-piperazin-1-yl)-3-(2-methoxy-5-(trifluoromethyl)phenyl)-4H-quinazolin-4-yl)acetic acid (also called letermovir). WO 2006/133822 relates to the production of dihydroquinazolines.

It is thus an object of the invention to describe a pharmaceutical preparation that is used in particular for intravenous administration, that contains {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, that has long-term stability and can be stored, and that in addition has a substantially physiological pH.

It is a further object of the invention to describe a pharmaceutical preparation with which it is possible, in a simple and reliable manner, to produce pharmaceutical preparations for intravenous administration which contain {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydro-quinazolin-4-yl}acetic acid and which also remain stable for an adequate period of time,

e.g. more than 24 hours.

Within the scope of the invention, the term “stability” is understood to mean not only the chemical stability of the constituents of the pharmaceutical preparation, but also the stability of the solution itself. In particular, the preparation according to the invention must be stable against precipitation of the constituents.

In this context, the term “stability” means that at 2°C to 8°C, or at 25°C or at 40°C the pharmaceutical preparations according to the invention contain a minimum proportion of 〉 90% and preferably 〉 95% {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid for a storage period of at least two, preferably at least three, and most preferred at least six weeks, when said liquid pharmaceutical preparations are measured using one of the HPLC methods 1-3. Said stability of the liquid pharmaceutical preparations is regarded as adequate within the scope of the invention.

Furthermore, the term “stability” means that, after they have been diluted or reconstituted to a final concentration of 0.8-10 mg/ml for infusion at 2°C to 8°C, the preparations according to the invention contain a minimum proportion of 90%, preferably at least 95%, of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid for a period of at least four hours, preferably at least six hours, and most preferred at least 24 hours in storage when, after dilution or reconstitution, said liquid pharmaceutical preparations are measured using one of the HPLC methods 1-3. Said stability of the pharmaceutical preparations after dilution or reconstitution is regarded as adequate within the scope of the invention.

It has surprisingly been discovered that pharmaceutical preparations, in particular those used for intravenous administration, that contain {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid as well as water can be stabilized by adding at least one excipient selected from cyclodextrins, lysine and arginine. It has further been discovered that such preparations can be lyophilized in order to obtain a stable, solid pharmaceutical preparation that can be reconstituted in a simple manner for injection purposes, e.g. by adding water, as a result of which, in turn, a stable pharmaceutical preparation, e.g. for intravenous administration, can be obtained.

The subject matter of the invention are thus pharmaceutical preparations, in

particular for intravenous administration, that have the following constituents, namely:

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

b) at least one excipient selected from the cyclodextrins, lysine and arginine, and

c) water.

In addition, subject matter of the invention are pharmaceutical preparations which are produced by lyophilization of the above-mentioned pharmaceutical preparation.

Within the scope of the invention, the term “salts” is understood to mean physiologically acceptable salts of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid. Physiologically acceptable salts of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid comprise acid addition salts of mineral acids, carbonic acids and sulfonic acids, for example of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid also comprise salts of usual bases, such as for example and preferably alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts), ammonium salts derived from ammonia or organic amines having 1 to 16 C-atoms, such as for example and preferably monoethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, 2-amino-2-methyl-1,3-propanediol, procaine, dibenzylamine, N-methylmorpholine, ethylene diamine and N-methylpiperidine as well as salts of alkaline amino acids.

Within the scope of the invention the term “solvates” refers to those forms of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid which form a complex through coordination with solvent molecules. Hydrates are a special form of solvates in which the coordination takes

place with water.

As is readily apparent to a skilled person, {8-fluoro-2-[4-(3-methoxyphenyl)-piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid has a stereocentre at the carbon in the 4-position in the dihydroquinazoline ring. Within the scope of the present invention, it is particularly preferable if this carbon has the S-configuration.

A cyclodextrin according to the invention is understood to be any modified or non-modified cyclodextrin. In this case, because of the size of the cavity in the ring, preference is given to β-cyclodextrins and in particular to modified β-cyclodextrins such as, for example, hydroxyalkyl-β-cyclodextrins, e.g. hydroxymethyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin or hydroxypropyl-β-cyclodextrin, alkyl-hydroxyalkyl-β-cyclodextrins, e.g. methyl-hydroxypropyl-β-cyclodextrins or ethyl-hydroxypropyl-cyclodextrins or sulfoalkyl-ether-β-cyclodextrins.

Within the scope of the invention, the water used for preparation purposes is normally water that is used for injections.

Within the scope of the present invention, the expression “have” or “having” denotes a non-exhaustive enumeration and, along with the explicitly mentioned components or steps, does not exclude any other components or steps.

Within the meaning of the present invention, the expression “consist of” or “consisting of” denotes an exhaustive enumeration and, apart from the explicitly mentioned components or steps, excludes any other components or steps.

Within the scope of the present invention, the expression “consist essentially of” or “consisting essentially of” denotes a partially exhaustive enumeration and denotes methods or preparations which, besides the mentioned components and steps, have only such other components and steps that do not materially modify the character of the preparation or of the method according to the invention, or which are present in quantities that do not materially modify the character of the preparation or of the method according to the invention.

If, within the scope of the present invention, a preparation or a method is described using the expression “have” or “having”, this explicitly includes preparations or methods that consist of the components or steps mentioned or that substantially consist of the components or steps mentioned.

Within the framework of the invention it is preferred if the pharmaceutical

preparation according to invention further has at least one buffer that is preferably selected from the phosphate buffers, the Tris buffers and the citrate buffers.

By adding the buffer it can, in particular, be ensured that the preparation always has a physiological pH. The buffers named are preferred, in particular due to the fact that they are well tolerated.

It is further preferable, within the scope of the invention, if the pharmaceutical preparation according to the invention further has at least one sugar, preferably selected from the group consisting of glucose, sucrose, lactose, maltose, trehalose, sorbitol and mannitol.

It has been found that the pharmaceutical preparation according to the invention can again be significantly stabilized by adding a sugar, and in particular one of the sugars explicitly mentioned above. Furthermore, it has been found that the addition of a sugar can facilitate the production of a solid preparation by lyophilization, as well as renewed reconstitution of such a solid preparation in order to produce a pharmaceutical preparation in particular for intravenous administration. Also, the addition of the at least one sugar serves to adjust the osmolality of the solution and to suppress any hemolysis that might occur.

Within the scope of the invention it is furthermore preferred that {8-fluoro-2-[4-β-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof is present in the pharmaceutical preparation in an amount corresponding to 1 to 100 mg, preferably 2 to 50 mg, more preferably 2 to 25 mg, and in particular to 5 to 20 mg of pure active compound per ml of preparation.

For the stability of the solution and also in the interest of simple storage it has proven advantageous if a quantity of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid is present in the above-mentioned ranges.

It is further preferred, within the scope of the invention, if the preparation has a pH in the range of 7.5 to 8.5.

The aforementioned pH range has proved advantageous because it is a pH in the range of a physiological pH. It has furthermore been found that the solubility of the pharmaceutical preparation according to the invention is again significantly better in the slightly alkaline range, i.e. in a range greater than 7.0, than at a pH value of 7.0 or less.

It is further preferred, within the scope of the invention, that the at least one excipient is present in the pharmaceutical preparation in an amount of 1 to 5 equivalents, preferably of 2 to 5 equivalents and more preferably of 2.5 to 4.5 equivalents in relation to the content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid.

It is further preferred within the scope of the invention, that said preparation, in relation to the content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, has 1 to 10 equivalents, preferably 2 to 7 equivalents, and in particular 2.5 to 5 equivalents of cyclodextrin as well as 0 to 2.0 equivalents, preferably 0.5 to 1.5 equivalents, and in particular 0.75 to 0.9 equivalents of NaOH.

Within the framework of the invention the term “equivalents” is understood to mean “molar equivalents”.

It has been found that adding less excipient than that given as the lower limit in the above-mentioned ranges causes inadequate stabilization of the solution. Adding amounts of excipient that exceed the aforementioned upper limits is not more advantageous in terms of the stability of the preparation. It is furthermore feared that adding larger amounts of excipient will also lead to interactions with the active substance and thus tend to reduce the effectiveness of the preparation.

Within the scope of the invention, particular preference is given to a pharmaceutical preparation having the following constituents based on 100 ml of preparation:

a) 0.25-2.0 g, preferably 0.5-1.25 g {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof,

b) 0.25-2.5 g, preferably 0.5 g-1.5 g of arginine,

c) 1.5-9.5 g, preferably 2.0-4.75 g of glucose,

d) 0.5-4.0 g, preferably 0.75-2.0 g of NaH_2PO_4, and

e) water,

wherein said preparation has a pH in the range of 7.5 to 8.5, preferably 7.7 to 8.0.

Furthermore, within the scope of the invention, particular preference is given to a pharmaceutical preparation having the following constituents based on 100 ml of

preparation:

a) 0.5-2.5 g, preferably 1.0-2.0 g {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof,

b) 10.0-30.0 g, preferably 12.5 g-22.5 g of HP-β-cyclodextrin,

c) 0.0-350 mg, preferably 75-225 mg, in particular 100-125 mg of NaOH, and

d) water,

wherein said preparation has a pH in the range of 7.5 to 8.5.

In the latter preparation the NaOH is used preferably in the form of an approx. 0.1M aqueous solution.

It has been found that pharmaceutical preparations constituted in this way are particularly advantageous both as regards clinical effectiveness and also stability.

The pharmaceutical preparations according to the invention are generally produced by first producing an aqueous solution of the excipient and then adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid to this solution, if necessarily followed by the addition of other additives, such as the at least one sugar and/or the at least one buffer. After adding all the constituents, the pH of the pharmaceutical preparation is adjusted to the desired value, with particular attention being paid to the fact that when the pH is adjusted from a value in the alkaline range towards the physiological pH value, by adding an acid or a buffer, this adjustment is carried out slowly and carefully to avoid any precipitation of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid resulting from an excessive local reduction in the pH value.

It is also possible to produce first of all individual solutions, with one solution containing the excipient and {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]3,4-dihydroquinazolin-4-yl}acetic acid and the other solution containing the other excipients, such as for example the at least one sugar and/or the at least one buffer, where in the next step the solutions are adjusted to the desired pH and then mixed with each other.

It is further possible to dissolve, at least partially, the {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-

dihydroquinazolin-4-yl}acetic acid in an aqueous alkaline solution, e.g. a solution of an alkali metal hydroxide, preferably an NaOH solution, and then to add the excipient as well as, if necessary, the other constituents to the solution and, if necessary, to adjust the solution to the desired pH value.

It is further possible to lyophilize the solutions obtained by the above-mentioned methods in order to obtain the solid pharmaceutical preparations according to the invention.

The subject matter of the invention is thus also a method to produce a pharmaceutical preparation according to the invention having the following steps:

A) Dissolving the at least one excipient in the water,

B) Adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof to the solution obtained in step A),

C) If necessary, adding at least one sugar and/or at least one buffer,

D) Adjusting the pH to the desired value in order to obtain a pharmaceutical preparation, and

E) Sterile-filtrating the solution obtained in step D) and filling into suitable containers.

F) If necessary, performing a final sterilization of the solution obtained in step E) under heat.

The subject matter of the invention is also a method to produce a pharmaceutical preparation according to the invention having the following steps:

I.) Dissolving the at least one excipient in a part of the water,

II.) Adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof to the solution obtained in step I.),

III.) If necessary, adjusting the pH of the solution obtained in step II.) to the desired value to obtain a first solution,

IV.) Dissolving at least one sugar and/or a buffer in a part of the water,

V.) If necessary, adjusting the pH of the solution obtained in step IV.) to the desired value to obtain a second solution,

VI.) Mixing the first and second solution to obtain a pharmaceutical preparation,

and

VII.) Sterile filtrating of the solution obtained in step VI.) and filling into suitable containers.

VIII.) If necessary, performing a final sterilization of the solution obtained in step VII.) under heat.

The subject matter of the invention is also a method to produce a pharmaceutical preparation according to the invention having the following steps:

a.) Adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, a solvate or a solvate of a salt to an aqueous NaOH solution, preferably an aqueous 0.1M NaOH solution to produce a solution or suspension,

b.) Adding water to the solution or suspension obtained in step a.),

c.) Adding cyclodextrin and NaCl to the solution or suspension obtained in step b.),

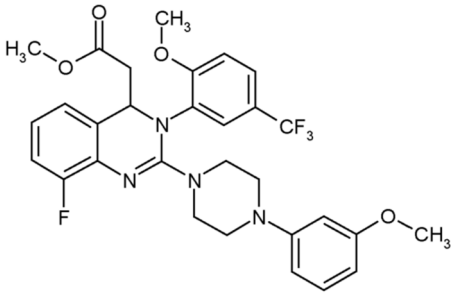
d.) Sterile filtrating of the solution obtained in step c.) and filling into suitable containers.

e.) If necessary, performing a final sterilization of the solution obtained in step d.) under heat.

The subject matter of the invention is in addition a method to produce a solid pharmaceutical preparation, wherein a pharmaceutical preparation produced according to the aforementioned methods is lyophilized.

The {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, or salts, solvates and solvates of the salts thereof, which are used to produce the pharmaceutical preparations according to the invention, are known and can be produced, for example, by the method described in WO 2006/133822.

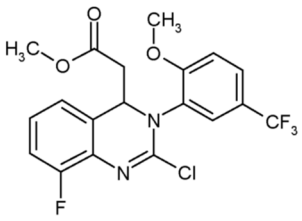
The production takes place in particular by the saponification of the ester of a compound having the formula (II)



(II),

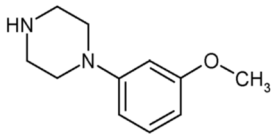
with a base.

The compound having the formula (II) can be produced by reacting a compound having the formula (III)



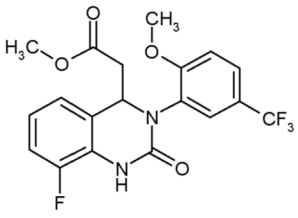
(III),

with a compound having the formula (IV) in the presence of a base.



(IV),

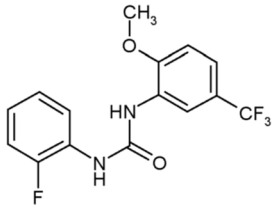
The compound having the formula (III) can be produced by reacting a compound having the formula (V)



(V),

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

The compound having the formula (V) can be produced by reacting a compound having the formula (VI)



(VI),

in the first step with acrylic acid methyl ester in the presence of a palladium catalyst and oleum, and in the second step with a base.

Compounds having the formulae (IV) and (VI) are in principle known to a skilled person or can be produced by customary methods known from the literature.

The saponification of the ester of a compound having the formula (II) to form {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid is achieved by reacting a compound having the formula (II) with a base in an inert solvent, in a temperature range from 18°C up to reflux of the solvent, preferably at 18 to 50°C, more preferably at 20 to 30°C, at normal pressure, within a period of, for example, 0.5 to 10 hours, preferably within 1 to 5 hours.

Bases are, for example, alkali hydroxides, such as sodium, lithium or potassium hydroxide, or alkali carbonates, such as caesium carbonate, sodium or potassium carbonate, or alcoholates such as sodium or potassium methanolate, or sodium or potassium ethanolate, where the base may be present in aqueous solution.

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

Sodium hydroxide in water and MTBE are preferred.

The synthesis of a compound having the formula (II) from a compound having the formula (III) and a compound having the formula (IV), in the presence of a base, takes place in an inert solvent, in a temperature range from 40°C up to reflux of the solvent, preferably at reflux of the solvent, at normal pressure, within for example 2 to 48 hours, preferably within 4 to 12 hours.

Bases are, for example, 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-butylate.

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 conversion of a compound having the formula (V) to a compound having the formula (III) takes place by reacting a compound having the 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 reflux of the solvent, preferably at reflux of the solvent, at normal pressure, within for example 1 to 48 hours, preferably within 2 to 12 hours.

Bases are, for example, amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine or triethylamine, or other bases such as potassium tert-butylate.

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

DBU in chlorobenzene is preferred.

The conversion of a compound having the formula (VI) to a compound having the formula (V) takes place, in the first step, by reacting a compound of the formula (VI) with acrylic acid methyl ester in the presence of a palladium catalyst and oleum in a solvent, in a temperature range from 0°C to 40°C, preferably at room temperature, and in the second step by reaction with a base in an inert solvent, in a temperature range from 40°C up to reflux of the solvent, preferably at reflux of the solvent, at normal pressure, within for example 1 to 48 hours, preferably within 2 to 12 hours.

Palladium catalysts in the first step are, for example, palladium(II) acetate, bis(triphenylphosphine)palladium(II)chloride, tetrakis(triphenylphosphine)palladium(0), bis(tri(o-tolyl)phosphine)palladium-(II)-chloride, or a palladium catalyst produced from bis(acetonitrile)dichloropalladium or palladium(II) acetate and a ligand, for example tris(o-tolyl)phosphine, triphenylphosphine or diphenylphosphino ferrocene.

Solvents in the first step are, for example, organic acids such as acetic acid or propionic acid.

Palladium(II) acetate in acetic acid is preferred.

Bases in the second step are, for example, DBU, triethylamine or diisopropylethylamine.

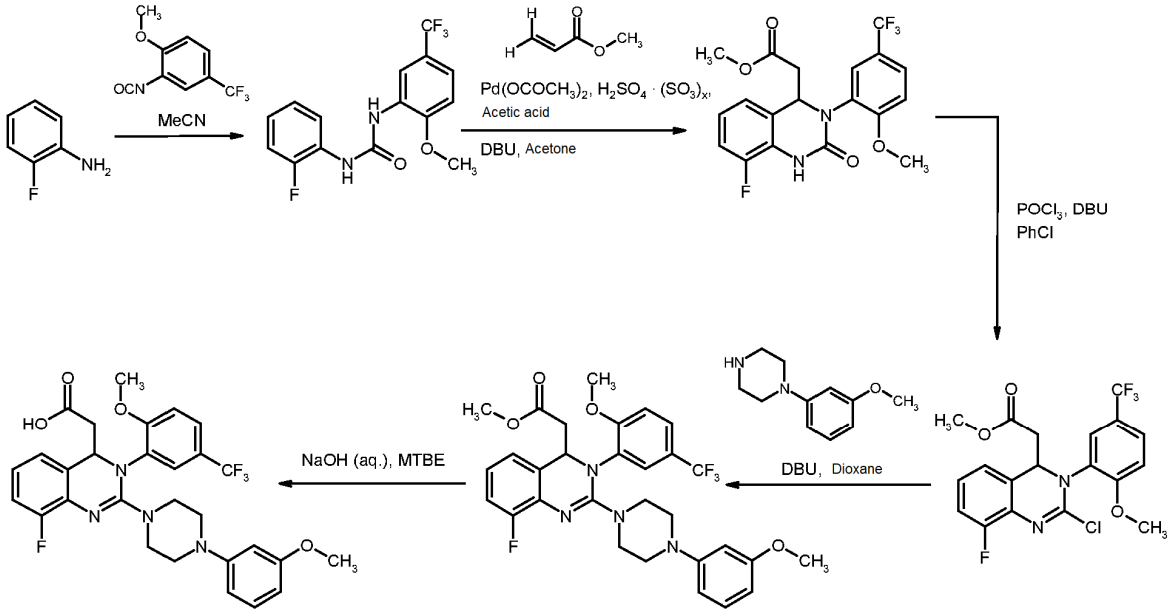
Inert solvents in the second step are, for example, ethers such as 1,2-dimethoxyethane, dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene or toluene, or other solvents such as isobutyronitrile, acetonitrile, acetone, nitrobenzene, dimethylformamide,

dimethylacetamide, dimethylsulfoxide or N-methylpyrrolidone.

DBU in acetone is preferred.

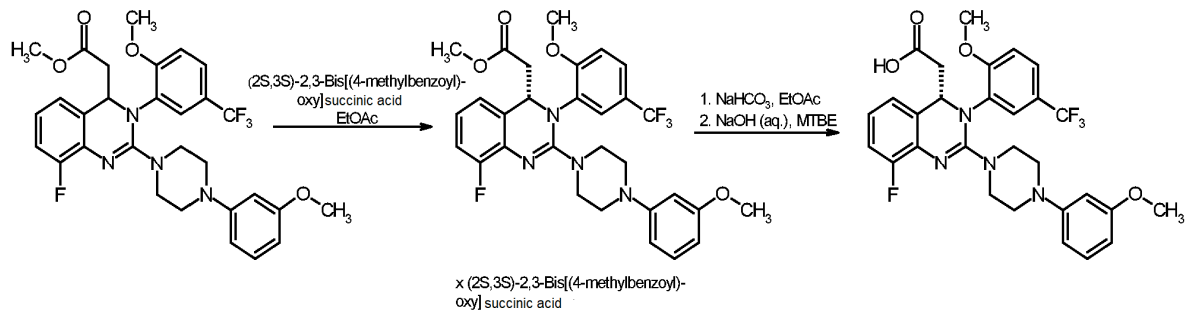
The production of the {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid used to produce the pharmaceutical preparation according to the invention is described in more detail, by way of example, in the following Synthesis Diagram 1. This synthesis diagram is nothing more than an example and should in no way be understood as restrictive.

Synthesis Diagram 1



As already mentioned further above, the {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid is used preferably in the form of the S-enantiomer. This S-enantiomer can be produced as shown, for example, in the following Synthesis Diagram 2.

Synthesis Diagram 2



The {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, as well as the salts, solvates, and solvates of the salts thereof contained in the pharmaceutical preparation exhibit an antiviral effect against representatives of the Herpes viridae group (herpes viruses), above all against the cytomegaloviruses (CMV), in particular against the human cytomegalovirus (HCMV). The pharmaceutical preparations according to the invention are thus suitable for use in methods of treating and/or preventing diseases, especially infections with viruses, in particular the viruses referred to herein and the infectious diseases caused by them. The term “viral infection” is understood to mean not only an infection with a virus but also a disease caused by infection with a virus.

Due to their properties and characteristics the pharmaceutical preparations according to the invention can be used to produce drugs that are suitable for use in methods of preventing and/or treating diseases, in particular viral infections.

The following areas of indication can be mentioned, by way of example:

1) Treatment and prevention of HCMV infections in AIDS patients (retinitis, pneumonitis, gastrointestinal infections).

2) Treatment and prevention of cytomegaloviral infections in bone marrow and organ transplant patients who often contract life-threatening HCMV pneumonitis or encephalitis, as well as gastrointestinal and systemic HCMV infections.

3) Treatment and prevention of HCMV infections in neonates and infants.

4) Treatment of acute HCMV infection in pregnant women.

5) Treatment of HCMV infection in immune-suppressed patients suffering from cancer and undergoing cancer therapy.

6) Treatment of HCMV-positive cancer patients with the aim of reducing HCMV-mediated tumour progression (cf. J. Cinatl, et al., FEMS Microbiology Reviews 2004, 28, 59-77).

The pharmaceutical preparations according to the invention are preferably used to produce drugs which are suitable for use in methods of preventing and/or treating infections with a representative of the Herpes viridae group, in particular a cytomegalovirus, in particular the human cytomegalovirus.

Due to their pharmacological properties and characteristics, the pharmaceutical preparations according to the invention can be used by themselves and, if needed, also in combination with other active substances, especially antiviral substances such as for example valganciclovir, ganciclovir, valacyclovir, acyclovir, foscarnet, cidofovir and related derivatives in methods of treating and/or preventing viral infections, in particular HCMV infections.

Further subject matter of the present invention is the use of the pharmaceutical preparations according to the invention in a method of treating and/or preventing diseases, preferably viral infections, in particular infections with the human cytomegalovirus (HCMV) or another representative of the Herpes viridae group.

Further subject matter of the present invention is the use of the pharmaceutical preparations according to the invention in a method of treating and/or preventing diseases, in particular the aforementioned diseases.

Further subject matter of the present invention is the use of the pharmaceutical preparations according to the invention to produce a drug for use in methods of treating and/or preventing diseases, in particular the aforementioned diseases.

Further subject matter of the present invention is a method of treating and/or preventing diseases, in particular the aforementioned diseases, using an antivirally effective amount of the pharmaceutical preparations according to the invention.

The term “antivirally effective amount” denotes the pharmaceutical preparations according to the invention in a dose of at least 0.001 mg/kg.

In general, it has proved to be advantageous to administer the pharmaceutical preparations in such a way that about 0.001 to 10 mg per kg, preferably 0.01 to 5 mg per kg body weight of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid is administered.

Nevertheless, it may be necessary to deviate from the stated amounts, namely depending on body weight, individual response to the active substance and the time and interval at which it is applied. For example, in certain cases it may be sufficient to get by

with less than the aforementioned minimum amount, while in other cases the stated upper limit has to be exceeded. When administering large amounts it may be recommendable to distribute these in several individual doses over the course of a day.

The invention will now be described in detail on the basis of non-restrictive examples.

Unless otherwise stated, the percentages given in the following tests and examples are weight percentages, parts are weight proportions, solvent ratios, dilution ratios and concentrations of liquid solutions relate, in each case, to the volume.

In certain embodiments, the present invention relates to subject matter, enumerated in the following points:

1. Pharmaceutical preparation, in particular for intravenous administration, comprising the following, namely:

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

b) at least an excipient selected from the cyclodextrins, lysine and arginine, and

c) water.

2. Pharmaceutical preparation according to point 1, further comprising at least one buffer selected from the phosphate buffers, the Tris buffers and the citrate buffers.

3. Pharmaceutical preparation according to point 1 or 2, further comprising at least one sugar,

wherein the sugar is preferably selected from the group consisting of glucose, sucrose, lactose, maltose, trehalose, sorbitol and mannitol.

4. Pharmaceutical preparation according to any one of points 1 to 3, characterized in that {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, or a salt, a solvate or a solvate of a salt thereof, is present in an amount corresponding to 1 to 100 mg, preferably 2 to 50 mg, most preferably 2 to 25 mg, and still most preferably 5 to 20 mg of pure active ingredient per mL of the preparation.

5. Pharmaceutical preparation according to any one of points 1 to 4, characterized in that the preparation has a pH of 7.5 to 8.5.

6. Pharmaceutical preparation according to any one of points 1 to 5, characterized in that the at least one excipient is present in an amount of 1 to 5 equivalents, preferably of 2 to 5 equivalents, and most preferably of 2.5 to 4.5 equivalents, in relation to the content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid.

7. Pharmaceutical preparation according to any one of points 1 to 6, characterized in that it has the following, in relation to 100 mL:

a) 0.2 - 2.0 g, preferably 0.5 - 1.25 g {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, or a salt, a solvate or a solvate of a salt thereof,

b) 0.25 - 2.5 g, preferably 0.5 - 1.5 g arginine,

c) 1.5 - 9.5 g, preferably 2.0 - 4.75 g glucose,

d) 0.6 - 4.0 g, preferably 0.75 - 2.0 g NaH_2PO_4, and

e) water,

wherein the preparation has a pH of 7.5 to 8.5, preferably of 7.7 to 8.0.

8. Pharmaceutical preparation according to any one of points 1 to 5, characterized in that the excipient is selected from cyclodextrins, preferably the β-cyclodextrins and the modified β-cyclodextrins, in particular the hydroxyalkyl-β-cyclodextrins, the alkyl-hydroxyalkyl-β-cyclodextrins and the sulfoalkylether-β-cyclodextrins.

9. Pharmaceutical preparation according to point 8, characterized in that the preparation, in relation to the content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, has 1 to 10 equivalents, preferably 2 to 7 equivalents and in particular 2.5 to 5 equivalents cyclodextrine, as well as 0 to 2.0 equivalents, preferably 0.5 to 1.5 equivalents and in particular 0.75 to 0.9 equivalents of NaOH.

10. Pharmaceutical preparation according to any one of points 1 to 5 or according to point 8 or 9, characterized in that it has the following in relation to 100 mL:

a) 0.5 - 2.5 g, preferably 1.0 - 2.0 g {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, or a salt, a solvate or a solvate of a salt thereof,

b) 10.0 - 30.0 g, preferably 12.5 g - 22.5 g HP-β-cyclodextrin,

c) 0.0 - 350 mg, preferably 75 - 225 mg, in particular 100 - 125 mg NaOH, and

d) water,

wherein the preparation has a pH of 7.5 to 8.5.

11. Solid pharmaceutical preparation produced by lyophilizing a pharmaceutical preparation according to any one of points 1 to 10.

12. Method for producing a pharmaceutical preparation according to any one of points 1 to 7, comprising the following steps, namely:

A) dissolving the at least one excipient in the water,

B) adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, or of a salt, a solvate or a solvate of a salt thereof to the solution obtained in step A),

C) if appropriate, adding at least one sugar and/or at least one buffer,

D) adjusting the pH to the desired value to obtain a pharmaceutical preparation, and

E) sterile filtering and filling the solution obtained in step D) into suitable containers.

F) if appropriate, end-sterilizing of the solution obtained in step E by heating.

13. Method for producing a pharmaceutical preparation according to any one of points 1 to 7, comprising the following steps, namely:

I.) dissolving the at least one excipient in a portion of the water,

II.) adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline4-yl}acetic acid, or of a salt, a solvate or a solvate of a salt thereof to the solution obtained in step I.),

III.) if appropriate, adjusting the pH of the solution obtained in step II.) to the desired value to obtain a first solution,

IV.) dissolving at least one sugar and/or buffer in a portion of the water,

V.) if appropriate, adjusting the pH of the solution obtained in step IV.) to the desired value to obtain a second solution,

VI.) mixing the first and second solution to obtain a pharmaceutical preparation, and

VII.) sterile filtering and filling the solution obtained in step VI.) into suitable containers.

VIII.) if appropriate, end-sterilizing the solution obtained in step VII.) by heating.

14. Method for producing a pharmaceutical preparation according to any one of points 1 to 5 or 8 to 10, comprising the following steps, namely:

a.) adding of {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline4-yl}acetic acid, or of a salt, a solvate or a solvate of a salt thereof to an aqueous NaOH solution, preferably an aqueous 0.1 M NaOH solution, for producing a solution or suspension,

b.) adding water to the solution or suspension obtained in step a.),

c.) adding cyclodextrin and NaCl to the solution or suspension obtained in step b.),

d.) sterile filtering and filling the solution obtained in step c.) into suitable containers.

e.) if appropriate, end-sterilizing the solution obtained in step d.) by heating.

15. Method for producing a solid pharmaceutical preparation according to point 11, comprising the production of a pharmaceutical preparation according to a method according to any one of points 12 to 14 followed by a step of lyophilizing the obtained pharmaceutical preparation to obtain a solid pharmaceutical preparation.

16. Pharmaceutical preparation according to any one of points 1 to 11, for use in a method for the treatment and/or prophylaxis of diseases, in particular of viral infections, preferably of infections with HCMV or another member of the Herpesviridae group.

17. Use of a pharmaceutical preparation according to any one of points 1 to 11, in a method for the treatment and/or prophylaxis of diseases, in particular of viral infections, preferably of infections with HCMV or another member of the Herpesviridae group.

18. Use of a pharmaceutical preparation according to any one of points 1 to 11, for the production of a medicament for the treatment and/or prophylaxis of diseases, in particular of viral infections, preferably of infections with HCMV or another member of the Herpesviridae group.

19. Method for combatting viral infections, preferably infections with HCMV or another member of the Herpesviridae group in humans and animals, which has the administration of a pharmaceutical preparation according to any one of points 1 to 11, or a pharmaceutical preparation produced according to any one of points 12 to 15 to a human or an animal, in need of such a treatment.

List of abbreviations.

ACN	Acetonitrile
API-ES-pos.	Atmospheric pressure ionization, electrospray, positive (in MS)
API-ES-neg.	Atmospheric pressure ionization, electrospray, negative (in MS)
ca.	circa
CI, NH_3	chemical ionization (with ammonia)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-Dimethylaminopyridine
DMSO	dimethyl sulfoxide
ESTD	external standardisation
h	hour(s)
HPLC	High pressure liquid chromatography
conc.	Concentrated
min.	Minutes
MS	Mass spectroscopy
MTBE	Methyl-*tert*-butylether
NMR	nuclear magnetic resonance spectroscopy
R_T	Retention time (in HPLC)
VTS	vacuum drying oven

HPLC general methods:

Method 1 (HPLC): Instrument: HP 1050 with variable wavelength detection; column: Phenomenex-Prodigy ODS (3) 100A, 150 mm x 3 mm, 3 µm; Eluent A: (1.0 g KH_2PO_4 + 1.0 mL H_3P0_4) / 1 Water, Eluent B: Acetonitrile; Gradient: 0 min 10% B, 25 min 80% B, 35 min 80% B; Flux: 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 km; Eluent A: *n*-Heptane + 0,2 % diethylamine, Eluent B: Isopropanol + 0,2 % diethylamine; Gradient: 0 min 12.5 % B, 30 min 12.5 % B; Flux: 1 ml/min; Temp.: 25°C; UV detection: 250 nm.

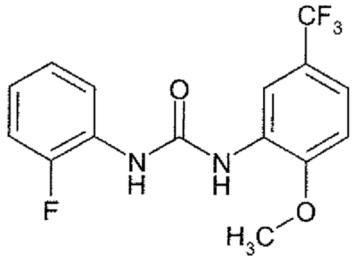
Method 3 (HPLC): Instrument: HP 1050 with variable wavelength detection; column: Chiral AD-H, 250 mm x 4.6 Min, 5µm Mmax; Eluent A: n-Heptane + 0.2 % diethylamine, Eluent B: Isopropanol + 0.2 % diethylamine; Gradient: 0 Min 25 % B, 15 min 25 % B, 1 ml/min; Temp.: 30°C; UV-Detection: 250 nm.

Examples

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

Example 1A:

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

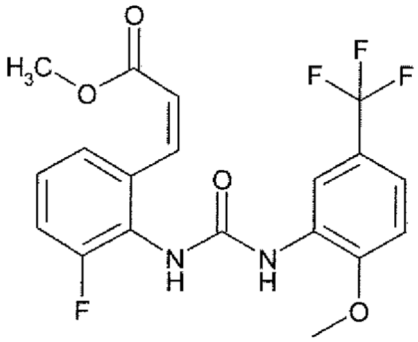


2-methoxy-5-trifluoromethylphenylisocyanate (78 kg) is melted at approx. 35 °C and dissolved in acetonitrile (total approx. 270 l), then 2-fluoroaniline (39.9 kg) is added and rinsed with acetonitrile (approx. 25 l). The resulting clear solution is stirred under reflux for 4 h and then cooled down to approx. 75°C. At this temperature the solution is inoculated with seed crystals of the desired final product (200 g), stirred for another 15 minutes and then cooled to 0°C for 3 hours. The crystalline product obtained is washed by centrifugation isolated with cold acetonitrile (twice approx. 13 l) and dried at 45°C in the VTS with entrained nitrogen (approx. 3.5 h). A total of 101.5 kg of *N-(2-fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea* is obtained as a solid, corresponding to 85.9 % of the theory.

^{1}H NMR (300 MHz, d_6-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 2A

Methyl-(2Z)-3-[3-fluor-2-({[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl}amino)-phenyl]acrylate



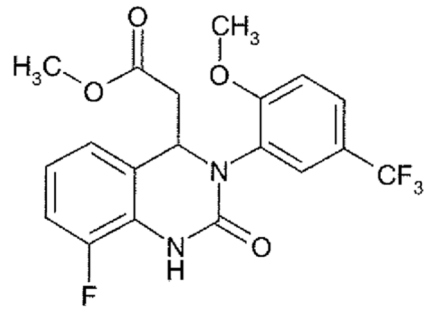
In a first reactor, N-(2-fluorophenyl)-N'-[2-methoxy-5-(trifluoromethyl)phenyl]urea (51 kg) is dissolved in acetic acid (approx. 430 1) under a nitrogen atmosphere. Methyl acrylate (20.1 kg) is added to the resulting solution and the resulting suspension is stirred until further use. In a second reactor, acetic acid (950 l) is introduced, oleum (57 kg) is carefully added and palladium (II) acetate (7 kg) is dissolved in the resulting mixture. The suspension formed in the first reactor is now added to the mixture contained in the second reactor for approx. 2 h, wherein the reaction mixture is overflowed with a mixture of 96% nitrogen and 4% oxygen and the resulting reaction mixture is stirred for approx. 18 h at room temperature. Then part of the acetic acid (approx. 900 1) is distilled off, water (approx. 500 l) is added to the remaining reaction mixture for approx. 1 h, and the suspension obtained is stirred for 1 h. The solids obtained are filtered off, washed once with a mixture of acetic acid and water (1:1) and twice with water and then dried at approx. 30 mbar and 50°C. Thus, a total of 44.8 kg of *methyl-(2Z)-3-[3-fluoro-2-({[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl}-amino)phenyl]acrylate* is obtained as a solid, corresponding to 65.0% of the theory.

^{1}H NMR (300 MHz, d_6-DMSO): 6 = 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 [$(M+NH_4)^+$]; 412.9 $(M+H)^+$]
HPLC : R_T = 46.4 min.

Instrument: HP 1100 with variable wavelength detection; column: Phenomenex-Prodigy ODS (3) 100A, 150 mm x 3 mm, 3 µm; Eluent A: (1.36 g KH_2PO_4 + 0.7 ml H_3PO_4)/l water, Eluent B: Acetonitrile; Gradient: 0 min 20% B, 40 min 45% B, 50 min 80% B, 65 min 80% B; Flux: 0.5 ml/min; Temp.: 55°C; UV-Detection: 210 nm.

Example 3A

{8-fluor-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydrochinazolin-4-yl}acetic acid methyl ester

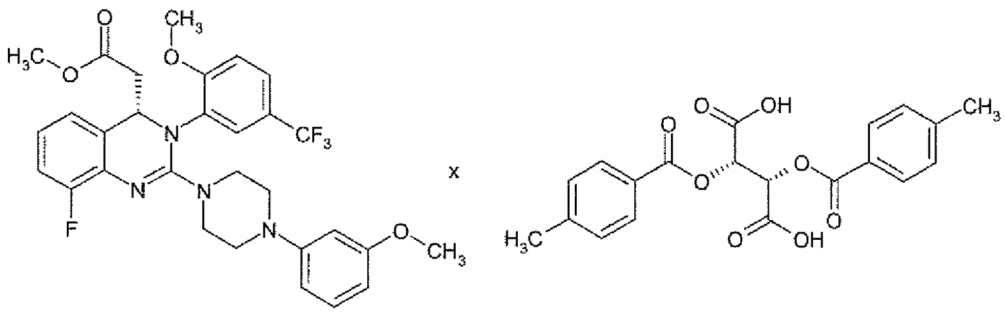


The compound of example 2A (75 kg) is suspended in acetone (1600 l) and DBU (5.7 kg) is added. The resulting suspension is heated to reflux and stirred for 4 h under reflux. The resulting solution is cooled to a shell temperature of 55°C and filtered over diatomaceous earth. A part of the solvent is removed from the reaction mixture by distillation (approx. 1,125 l) and the remaining residue is cooled down to 0°C for 2 hours. The resulting solid is separated by centrifugation and washed twice with cold acetone (approx. 15 l) and dried overnight at 45°C under reduced pressure with entraining nitrogen until mass constancy is achieved. A total of 58,3 kg *{8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl]acetic acid methyl ester* is obtained as a solid, corresponding to 84.1% of the theory.

HPLC (Method 1): R_T = 19.4 min.

Example 4A

(2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid ((4*S*)-8-fluoro-2-[4-(3-methoxy-phenyl)- piperazine-l-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)- methyl acetic acid (1:1 salt) chlorination/amination/crystallisation



A solution of {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetra-hydroquinazolin-4-yl)acetic acid methyl ester (Example 3A, 129.2 kg) in chlorobenzene (800 l) is heated to reflux and dried azeotropically. Phosphorus oxychloride (144 kg) is added and the reaction mixture is stirred under reflux for 3 hours. DBU (95 kg) and chlorobenzene (45 l) are then added and stirred under reflux for a further 9 hours. The reaction mixture is cooled to room temperature, hydrolysed by addition in water, diluted with chlorobenzene {80 l) and neutralised with aqueous ammonia solution (25%). The phases are separated and the organic phase is washed with water and the solvent distilled off. The remaining residue is dissolved in dioxane (170 l). 3-methoxyphenylpiperazine (66 kg), DBU (52 kg) and a further 90 litres of dioxane are added and the reaction mixture is heated under reflux for 4 hours. The reaction mixture is cooled to room temperature, add vinegar ester (1300 l) is added, and it is washed 1 x with water, 3 x with 0.2 N HCl, and 1 x with aqueous NaCl solution and the solvent is distilled off. The residue obtained is converted into vinegar esters 800 (l) and placed in a solution of (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid (121 kg) in acetic ester (600 l). The resulting mixture is stirred for about 60 minutes at room temperature, then inoculated with (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]- succinic acid ({4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5 (trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)methyl acetate and stirred for 3 days at room temperature. Then it is cooled to 0 - 5°C and stirred for another 3 hours. The suspension is suctioned off and washed in portions with ethyl acetate. Thus, a total of about 141 kg (calculated as dry) of the sediment is obtained as a solid, corresponding to about 46.2 % of the theory over three stages (chlorination, amination and crystallization) related to the racemate.

^{1}H NMR (300 MHz, d_6-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), 6.1 - 6.6 (m, 2H), 6.5 (d, 'J = 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, SH), 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 5A

(2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid-{(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydrochinazolin-4-yl}acetic acid methyl ester (1:1 salt) / recrystallization

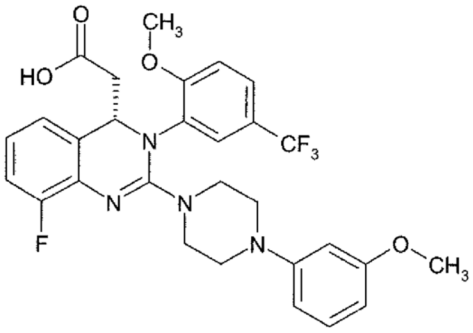
(2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid-(S){(4*S*)-8-fluoro-2-[4-(3-methoxy-phenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydrochinazolin-4-yl}acetic acid methyl ester (1:1 salt) (141 kg, calculated as dry) is suspended in ethyl acetate (1400 l) and dissolved by heating to reflux (77°C). The solution is filtered and slowly cooled to room temperature. Spontaneous crystallization takes place. The suspension is stirred for 16 hours at RT, then cooled to 0-5°C and stirred for a further 3 hours. The suspension is suctioned off and washed with cold ethyl acetate. The crystals are dried for 16 h in a vacuum at about 40 °C. A total of 131.2 kg of the salt is thus obtained as a solid, corresponding to 93.0 % of the theory.

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

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

Example 6A

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



A mixture of (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid {(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid methyl ester (1:1 salt) (30.8 kg), sodium hydrogen carbonate (16.4 kg) and water (315 l) is mixed with MTBE (160 l). The phases are separated and the organic phase is treated with 35 l of an approximately seven per cent aqueous solution of sodium bicarbonate. The phases are separated and the organic phase

is mixed with 125 l of an approximately four percent aqueous sodium hydroxide solution. The reaction mixture is heated to reflux, the solvent is gently distilled until it dries up and the reactor contents are then stirred for a further 5 h at 55 - 60 °C. The reaction mixture is then mixed at about 22 °C with MTBE (160 l) and water (65 l) and stirred. Separate the phases and extract the organic phase with an aqueous sodium chloride solution (30 l) of about 6 %. Stir the combined aqueous phases with water (25 l) and MTBE (160 l) and adjust the pH to about 6.5 with about IN hydrochloric acid. The organic phase is separated, the solvent is gently distilled until it dries up and the residue is dissolved in acetone (approx. 75 l). A solvent exchange to acetone is carried out (6 distillation processes with approx. 130 l each). The target product is then filled by adding to water, isolated by centrifugation and dried in a vacuum dryer. Thus a total of 16.5 kg (*S)-[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 96.4 % of the theory.

^{1}H NMR (300 MHz, d_6-DMSO): δ = 7.53 (d, ^2J = 8.4, IH), 7.41 (brs, 1H), 7.22 (d, ^2J = 8.5, 1H), 7.09 - 7.01 (m, 2H), 6.86 (in, 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.

B) Examples of pharmaceutical preparations according to the invention

Example 1

Production of a pharmaceutical preparation using cyclodextrin:

30.03 g of hydroxypropyl-β-cyclodextrin HP5 (HPB Kleptose, Roquette) is mixed with 68.365 g of water for injection in a 250 ml three-necked flask and 6.6 g of 1 M sodium hydroxide solution is added to the mixture. After adding 5.005 g of the Example 6A compound, the mixture is heated to 50°C and stirred for 24 hours until a clear solution is formed. The solution is sterile-filtered (pore diameter 0.22 µm) and filled into sterile 20

ml glass containers under aseptic conditions. The filled glass containers are closed with infusion plugs and crimping caps.

Example 2

Production of a first pharmaceutical preparation using arginine as an excipient:

To produce a first stock solution, 262.38 mg of L-arginine is weighed into a 25 ml volumetric flask and dissolved in about 22 ml of water for injection. 504.51 mg of the Example 6A compound is added to the arginine solution obtained and the mixture is stirred for about 1 h until a clear solution is obtained. Finally, the volume is made up with water for injection.

To produce a second stock solution, 40.05 mg of sodium dihydrogen phosphate dihydrate is weighed out into a 50 ml volumetric flask and dissolved in about 48 ml of water for injection. The mixture is stirred until a clear solution is obtained and the volume is made up with water for injection.

To produce a solution with a concentration of 10 mg per ml of {8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-(2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid, 12.5 ml of the first stock solution is mixed with 10 ml of the second stock solution in a 25 ml volumetric flask and the pH is slowly and carefully adjusted to about 200 µl 1 M HCl. The volume is then made up with the second stock solution to obtain a mixture with a definitive pH of 7.9.

Using this protocol, preparations containing different concentrations of {8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid can be produced, wherein only the amount of the first stock solution used has to be varied. However, if necessary, care should be taken to ensure that the pH does not vary too much and, in particular, does not get into the acid range.

The resulting solutions are sterile-filtered (pore diameter 0.22 µm) and filled into sterilized containers under aseptic conditions. The containers are closed with infusion plugs and crimping caps.

Example 3

Production of a second pharmaceutical preparation using arginine as an excipient:

To produce a first stock solution, 2.1 g of L-arginine is dissolved in 88.8 g water for injection. 2 g of the Example 6A compound is added to the arginine solution obtained and the mixture is stirred for about 1 h until a clear solution is obtained. The pH value of the solution obtained is adjusted to 7.8 by adding 1 M HCl drop by drop, taking care to add it slowly so that the Example 6A compound does not precipitate. Finally, the volume of the solution is made up to 100 ml if necessary.

To produce a second stock solution, 3.1 g sodium dihydrogen phosphate dihydrate and 8.4 g glucose is weighed out into a suitable container and dissolved in about 74.5 g water for injection. The mixture is stirred until a clear solution is obtained and the pH of the solution obtained is adjusted to a pH of 7.8 with 1 M NaOH. Finally, the volume of the solution to 100 ml if necessary.

To produce a solution of a concentration of 10 mg per ml {8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid 50.5 g of the first stock solution is mixed with 53.0 g of the second stock solution and stirred for 5 minutes.

Using this protocol, preparations with different concentrations of {8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl)-3,4-dihydroquinazolin-4-yl]acetic acid may be prepared using only the amount of the first stock solution used.

The resulting solutions are sterile-filtered (pore diameter 0.22 µm) and filled into sterilized containers under aseptic conditions. The containers are closed with infusion plugs and crimping caps.

Example 4

Production of a third pharmaceutical preparation using arginine as an excipient:

To produce a first stock solution, 1.05 g of L- arginine and 1g of the Example 6A compound are dissolved in about 50.0 g of water for injection in a 100 ml volumetric flask, and the mixture is stirred until a clear solution is obtained. The pH value of the solution obtained is adjusted to 7.8 (approx. 43.5 ml) by adding 0.1 M HCl drop by drop, taking care to add it slowly so that the compound of example 6A does not precipitate. Finally, the volume of the solution is made up to 100 ml.

To produce a second stock solution, 1.56 g dihydrate of sodium dihydrogen phosphate and 4.18 g glucose are dissolved in approximately 80.0 g water for injection in a 100 ml volumetric flask. The mixture is stirred until a clear solution is obtained and the pH of the solution obtained is adjusted with 1 M NaOH to a pH of 7.8 (about 9.1 ml). Finally, the volume of the solution is made up to 100 ml.

To produce a solution at a concentration of 5 mg per ml {8-fluoro-2-[4-(3- methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid 50.24 g of the first stock solution is mixed with 51.35 g of the second stock solution and stirred for 5 min.

Using this protocol, preparations with different concentrations of {8-fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2-methoxy-5-(trifluorinethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid may be prepared, wherein only the amount of the first stock solution used has to be varied.

The resulting solutions are sterile-filtered (pore diameter 0,22 µm) and filled into sterilised containers under aseptic conditions. The containers are closed with infusion plugs and crimping caps.

Example 5

Production of a fourth pharmaceutical preparation using arginine as excipient:

To produce a first stock solution, 2.11 g of L- arginine and 2.01 g of the Example 6A compound are mixed in a 100 ml volumetric flask and the volume is made up with water for injection. The pH value of this first stock solution was 9.8.

To produce a second stock solution, 3.12 g of sodium dihydrogen phosphate dihydrate, 8.35 g of glucose and 0.50 g of NaCl are dissolved in approximately 80.0 g of water for injection in a 100 ml volumetric flask. The mixture is stirred until a clear solution is obtained and the pH of the solution obtained is adjusted with 1 M NaOH to a pH of 6.5 (about 9.7 ml). Finally, the volume of the solution is made up to 100 ml.

To produce a solution at a concentration of 10 mg per ml of {8-fluoro-2-(4-(3-methoxyphenyl) piperazin-1-yl)-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid, 50.50 g of the first stock solution is mixed with 52.65 g of the second stock solution and stirred for 5 min.

Using this protocol, preparations with different concentrations of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl)-3-(2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid can be prepared, wherein only the amount of the first stock solution used varies and the pH must be adjusted if necessary.

The solutions thus obtained are sterile-filtered (pore diameter 0,22 µm) and filled into sterilised containers under aseptic conditions. The containers are closed with infusion plugs and crimping caps.

Example 6

Production of a pharmaceutical composition using lysine as an excipient:

To produce a first stock solution, 217.24 mg of lysine is weighed out into a 25 ml volumetric flask and dissolved in 22 ml of water for injection. 500.71 mg of the Example 6A compound is added to the solution thus obtained and the mixture is stirred for about 1 h until a clear solution is obtained. The pH of the solution obtained is then set to pH 8 with approx. 460 µl 1 M HCl, wherein care must be taken again to avoid the excessive local

reduction of the pH value and the resulting precipitation of the compound in Example 6A. Finally, the volume is made up for injection in order to obtain a first stock solution.

To produce a second stock solution, 242.01 mg of sodium dihydrogen phosphate is weighed out into a 50 ml volumetric flask and dissolved in about 48 ml of water for injection. The mixture is stirred until a clear solution is obtained. The pH of the solution obtained is adjusted to a pH of 8 with approx. 1.825 µl 1 M NaOH and the volume is made up with water for injection.

To produce a solution with a concentration of 5 mg of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-l -yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid per ml of solution, 6.5 ml of the first stock solution is filled into a 25 ml volumetric flask and the volume is made up with the second stock solution to obtain a solution with a final pH of 8.

As already explained under Example 2, by varying the amount of the first stock solution, pharmaceutical preparations with other concentrations of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid can also be prepared.

The resulting solution is sterile-filtered (pore diameter 0.22 µm) and filled into sterilised containers under aseptic conditions.

Example 7

Production of a solid pharmaceutical preparation which can be reconstituted to prepare an infusion solution:

To produce a first stock solution, 261.16 mg of L-arginine is weighed out into a 25 ml volumetric flask and dissolved in 22 ml water for injection. 502.45 mg of the compound of example 6A is added to the solution obtained and the mixture is stirred for about 1 h until a clear solution is obtained. The pH of this solution is adjusted with approx. 660 µl 1 M HCl to a value of 7.8, wherein it must again be ensured that the compound of example 6A does not precipitate and the volume is made up with water for injection.

To produce a second stock solution, 240.05 mg of sodium dihydrogen phosphate is weighed out into a 50 ml volumetric flask and dissolved in about 48 ml of water for injection. The mixture is stirred until a clear solution is obtained. The pH of the solution obtained is adjusted to a value of 7.8 with approx. 1,850 µl l M NaOH and the volume is made up with water for injection.

To produce a solution with a concentration of {8-fluoro-2-[4-(3- methoxyphenyl) piperazin-1-yl]-3-(2-methoxy-5-(trifluoromethyl)phenyl]-3,4-di-hydroquinazolin-4-yl]acetic acid of 10 mg per ml, 12.5 ml of the first stock solution is placed in a 25 ml volumetric flask and the volume is made up with the second stock solution to obtain a solution with a final pH of 7.8.

1 ml each of the clear colourless solution is placed in 2 ml glass containers fitted with a suitable stopper and lyophilised in an EPSILON 2-4 D freeze dryer (Martin Christ GmbH, Germany) to obtain a colourless powder which can be easily converted into a solution suitable for intravenous use by adding 1 ml of water.

Example 8

Production of a solid pharmaceutical preparation which may be reconstituted to prepare an infusion solution:

To produce a first stock solution, 210.49 g of L-arginine is mixed with 9,665.8 g water for injection and stirred until a clear solution is obtained. 199.23 g of the Example 6A compound is added to the solution obtained, in small portions and with stirring and the mixture is stirred until a clear solution is obtained, but at least for 30 min.

To produce a second stock solution, 309.19 g of sodium dihydrogen phosphate dihydrate, 827.47 of glucose, 49.55 g of sodium chloride and 7,900.0 g of water for injection are stirred until a clear solution is obtained. The pH of the resulting solution is adjusted to 6.55 with 1 M NaOH and 1,418.29 g less the amount of NaOH solution used to adjust the pH is added to the resulting solution of water for injection.

To produce the desired solution, the second stock solution is added slowly and in small portions to the first stock solution while stirring gently and the solution obtained is sterilised. 15 ml of each clear colourless solution is poured into appropriate sterile glass containers fitted with a suitable stopper and lyophilised in a freeze dryer to obtain a colourless powder.

The lyophilisate thus obtained can be reconstituted without problems, e.g. by adding 30 ml of water for injection purpose, to a solution which can then be diluted again for use in infusions.

Example 9

Production of a second pharmaceutical preparation using cyclodextrin:

2.00 g of the Example 6A compound is weighed out and 30 g of a 0.1 M NaOH solution is added and the mixture obtained is stirred for 30 minutes (the Example 6A compound does not need to be completely dissolved). 57.7 g of water for injection, 15.0 g of hydroxypropyl β-cyclodextrin HP5 (Kleptose HPB, Roquette) and 0.31 g of NaCl are added to the resulting mixture which is stirred until a clear solution is obtained. The solution is sterile-filtered (pore diameter 0.22 µm) and filled under aseptic conditions into sterile 20 ml glass containers. The filled glass containers are closed with infusion plugs and crimping caps. The filled glass containers obtained in this way can be heat sterilised if necessary.

Example 10

Production of a third pharmaceutical preparation using cyclodextrin:

2.00 g of the Example 6A compound is weighed out and 30 g of a 0.1 M NaOH solution is added, then the mixture obtained is stirred for 30 minutes (the Example 6A compound does not need to be completely dissolved).

54.8 g of water for injection, 20.0 g of hydroxypropyl β-cyclodextrin HP5 (Kleptose HPB, Roquette) and 0.205 g of NaCl are added to the resulting mixture and stirred until a clear solution is obtained. The solution is sterile-filtered (pore diameter 0.22 µm) and filled under aseptic conditions into sterile 20 ml glass containers. The filled glass containers are

closed with infusion plugs and crimping caps. The filled glass containers obtained in this way can be heat sterilized if necessary.

Example 11

Production of a fourth pharmaceutical preparation using cyclodextrin:

0.5 g of the Example 6A compound is weighed out and 8.75 g of a 0.1 M NaOH solution is added and stir the mixture is stirred for 30 minutes (the compound of example 6A does not need to be completely dissolved). 12.45 g of water for injection and 5.0 g of 2-O-methyl-β-cyclodextrin (Crysmeb, Roquette) is added to the mixture obtained and stirred until a clear solution is obtained. The pH value of the solution is adjusted to pH 7.5 with 1M HC1, the solution is sterile-filtered (pore diameter 0.22 µm) and filled under aseptic conditions into sterile 20 ml glass containers. The filled glass containers are closed with infusion plugs and crimping caps.

The filled glass containers obtained in this way can be heat sterilised if necessary.

Example 12

Production of a fifth pharmaceutical preparation using cyclodextrin:

0.5 g of the Example 6A compound is weighed out and add 13.125 g of a 0.1 M NaOH solution is added and the resulting mixture is stirred for 30 minutes (the compound of Example 6A need not be completely dissolved). 8.075 g of water for injection and 5.0 g of sulfoalkylether-β-cyclodextrin (Captisol, CyDex Pharmaceuticals Inc.) are added to the resulting mixture and stirred until a clear solution is obtained. The pH value of the solution is adjusted to pH 7.5 with 500µl IM HCl, the solution is sterile-filtered (pore diameter 0.22 µm) and filled under aseptic conditions into sterile 20 ml glass containers. The filled glass containers are sealed with infusion plugs and crimping caps. The filled glass containers obtained in this way can be heat sterilized if necessary.

Before administration, the described solution can be diluted with an isotonic solution, e.g. an isotonic infusion solution.

C) Stability measurement

To measure stability, the solutions prepared in examples 1 to 6 were stored at 2 to 8°C, 25°C, 40°C and for two, three and six weeks, respectively, with all solutions showing sufficient stability.

Furthermore, the stability of a reconstituted solution prepared from the preparation of Example 7 was tested over 24 h at 2 to 8°C, 25°C and 40°C, wherein the solution was found to be stable under all conditions over 24 h.

D) Comparative trials for solid pharmaceutical preparations

To demonstrate the advantageous properties of the solid pharmaceutical preparation obtained in Example 7 over other solid preparations, the solid ingredients contained in the solution were mixed and reconstitution tests were then carried out.

It was not possible to obtain a clear solution in any of the cases investigated.

E) Evaluation of physiological efficacy

The in-vitro effect of the inventive preparations on replication of HCMV (human cytomegalovirus) can be demonstrated in the following antiviral assay:

F) HCMV Fluorescence Reduction Test

The Example 8 solution is used in the test without further dilution. For comparison, the compound of example 6A is used as 50 millimolar (mM) solutions in dimethyl sulfoxide (DMSO). Ganciclovir®, Foscarnet® or Cidofovir® can be used as reference compounds. One day prior to the test 1.5 x 10^4 human foreskin fibroblasts (NHDF cells)/well in 200 µl cell culture medium are seeded into the B2-G11 wells of 96-well plates (black with transparent bottom). The marginal wells of each 96-well plate are only filled with 200 µl medium to avoid marginal effects. On the test day, the cell culture medium of the Wells B2- G11 of each 96-well plate is aspirated and replaced by 100µl virus suspension. (Multiplicity of infection (MOI): 0.1 - 0.2). The virus used is a

recombinant HCMV which has integrated an expression cassette for the green fluorescence protein (GFP) into the virus genome. (HCMV AD 169 RV-HG (E. M. Borst, K. Wagner, A. Binz, B. Sodeik, and M. Messerle, 2008, *J. Virol*. **82**:2065-2078.). After an incubation period of 2h at 37°C and 5% CO_2, the virus inoculum is aspirated and all wells except the wells in column 3 are seeded with 200µl cell culture medium. Column 2 is not treated further and serves as a virus control. The wells in column 3 are each filled with 300 l preparation or solution of the test substance (the latter diluted in cell culture medium) in double determination. The concentration of the respective antiviral substance in column 3 is 27 times the concentration of the expected EC_{50} value. The test substance in column 3 is diluted in 8 steps 1:3 over the 96-well plate by transferring 100µl of each column into the right column and mixing it with the existing 200µl cell culture medium. In this way, three antiviral substances are tested in duplicate determinations.

The plates are incubated for 7 days at 37°C / 5% CO_2. Afterwards, all wells of a plate are washed 3 x with PBS (Phosphate Buffered Saline) and filled with 50 µl PBS. The GFP intensity of each well of a 96-well plate is then measured using a fluorescence reading device (FluoBox; Bayer Technology Services GmbH; filter settings): GFP, Ex 480nm, Em 520nm).

The EC_{50} of an anti-HCMV substance can be determined from the measured values obtained in this way:

EC_{50} (GFP-RA) = substance concentration in µM which reduces GFP fluorescence in infected cells by 50% compared to the untreated virus control.

Representative in-vitro active data for the inventive compounds are given in Table 1:

Table 1:

Virus stock	**Example 6A** **EC_{50} [µM]**	**Example 8** **EC_{50} [µM]**	**Ganciclovir** **EC_{50} [µM]**
AD169 RV-HG	0.0022 ± 0.0002	0.0026 ± 0.0005	2.5 ± 0.4

Patentkrav

1. Farmasøytisk preparat, for intravenøs administrering, omfattende følgende, nemlig:

a) {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre syre, karbonet i 4-posisjonen til dihydrokinazolringen med S-konfigurasjon, eller et salt, en oppløsning eller en oppløsning av et salt derav,
b) et hjelpestoff valgt fra syklodekstrinene, og
c) vann.

2. Farmasøytisk preparat ifølge krav 1, videre omfattende minst én buffer valgt fra fosfatbufferne, Tris-bufferne og sitratbufferne.

3. Farmasøytisk preparat ifølge krav 1 eller 2, videre omfattende minst ett sukker.

4. Farmasøytisk preparat ifølge krav 3, hvori sukkeret er valgt fra gruppen bestående av glukose, sukrose, laktose, maltose, trehalose, sorbitol og mannitol.

5. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 4, **karakterisert ved at** {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre, karbonet i 4-posisjonen til dihydrokinazolringen med S-konfigurasjon, eller et salt, en oppløsning eller en oppløsning av et salt derav, er tilstede i en mengde tilsvarende 1 til 100 mg ren aktiv bestanddel per ml av preparatet.

6. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 5, **karakterisert ved at** preparatet har en pH på 7,5 til 8,5.

7. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6, **karakterisert ved at** den minst ene hjelpestoffet er tilstede i en mengde på 1 til 5 ekvivalenter i forhold til innholdet av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre.

8. Den farmasøytiske formuleringen ifølge hvilket som helst av kravene 1 til 7, **karakterisert ved at** den minst ene hjelpestoffet er tilstede i en mengde på 2 til 5 ekvivalenter i forhold til innholdet av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre.

9. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6, **karakterisert ved at** hjelpestoffet er valgt fra β-syklodekstrinene og de modifiserte β-syklodekstrinene, spesielt hydroksyalkyl-β-syklodekstrinene, alkylhydroksyalkyl-β-syklodekstrinene og sulfoalkyleter-β-syklodekstrinene.

10. Farmasøytisk preparat ifølge krav 9, **karakterisert ved at** preparatet har 1 til 10 ekvivalenter av syklodekstrin og 0 til 2,0 ekvivalenter NaOH i forhold til innholdet av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre.

11. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6 eller ifølge krav 9 eller 10, **karakterisert ved at det har** følgende i forhold til 100 ml:

a) 0,5 - 2,5 g {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre, karbonet i 4-posisjonen

til dihydrokinazolringen med S-konfigurasjon, eller et salt, en oppløsning eller en oppløsning av et salt derav,
b) 10,0 - 30,0 g HP-β-syklodekstrin,
c) 0,0 - 350 mg, spesielt 100 - 125 mg NaOH, og
d) vann,

hvori preparatet har en pH på 7,5 til 8,5.

12. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6 eller ifølge kravene 9 til 11, **karakterisert ved at** det har følgende i forhold til 100 ml:

a) fortrinnsvis 1,0 - 2,0 g {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin- 4-yl}eddiksyre, karbonet i 4-posisjonen til dihydrokinazolringen med S-konfigurasjon, eller et salt, en oppløsning eller en oppløsning av et salt derav,
b) fortrinnsvis 12,5 g - 22,5 g HP-β-syklodekstrin,
c) fortrinnsvis 75 - 225 mg, spesielt 100 - 125 mg NaOH, og
d) vann,

hvori preparatet har en pH på 7,5 til 8,5.

13. Fast farmasøytisk preparat fremstilt ved lyofilisering av et farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 12.

14. Fremgangsmåte for fremstilling av et farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 8, omfattende følgende trinn, nemlig:

A) løse opp minst ett hjelpestoff i vannet,
B) tilsetning av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl} eddiksyre, karbonet i 4-posisjonen til dihydrokinazolringen med S-konfigurasjon, eller av et salt, en oppløsning eller en oppløsning av et salt derav til løsningen oppnådd i trinn A),
C) hvis det er hensiktsmessig, tilsette minst ett sukker og/eller minst en buffer,
D) justering av pH til ønsket verdi for å oppnå et farmasøytisk preparat, og
E) sterilfiltrering og fylling av løsningen oppnådd i trinn D) i egnede beholdere.
F) hvis det er hensiktsmessig, sluttsterilisering av løsningen oppnådd i trinn E ved oppvarming).

15. Fremgangsmåte for fremstilling av et farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 8, omfattende følgende trinn, nemlig:

I.) oppløsning av det minst ene hjelpestoffet i en del av vannet,
II.) tilsetning av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre, karbonet i 4-posisjonen til dihydrokinazolringen med S-konfigurasjon, eller av et salt, en oppløsning eller en oppløsning av et salt derav til løsningen oppnådd i trinn I.),
III.) hvis det er hensiktsmessig, justering av pH til løsningen oppnådd i trinn II.) til ønsket verdi for å oppnå en første løsning,
IV.) oppløsning av minst ett sukker og/eller buffer i en del av vannet,
V.) hvis det er hensiktsmessig, justering av pH til løsningen oppnådd i trinn IV.) til ønsket verdi for å oppnå en andre løsning,
VI.) blande den første og andre løsningen for å oppnå et farmasøytisk preparat, og
VII.) sterilfiltrering og fylling av løsningen oppnådd i trinn VI.) i egnede beholdere.
VIII.) hvis det er hensiktsmessig sluttsterilisering av løsningen oppnådd i trinn VII.) ved oppvarming.

16. Fremgangsmåte for fremstilling av et farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6 eller 9 til 12, omfattende følgende trinn, nemlig:

a.) tilsetning av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre, karbonet i 4-posisjonen til dihydrokinazolringen med S-konfigurasjon, eller av et salt, en oppløsning eller en oppløsning av et salt derav til en vandig NaOH-løsning, fortrinnsvis en vandig 0,1 M NaOH-løsning, for å produsere en løsning eller suspensjon,
b.) tilsetning av vann til løsningen eller suspensjonen oppnådd i trinn a.),
c.) tilsetning av syklodekstrin og NaCl til løsningen eller suspensjonen oppnådd i trinn b.),
d.) sterilfiltrering og fylling av løsningen oppnådd i trinn c.) i egnede beholdere.
e.) om hensiktsmessig sluttsterilisering av løsningen oppnådd i trinn d.) ved oppvarming.

17. Fremgangsmåte for fremstilling av et fast farmasøytisk preparat ifølge krav 13, omfattende fremstilling av et farmasøytisk preparat ifølge en fremgangsmåte ifølge hvilket som helst av kravene 14 til 16 etterfulgt av et trinn med lyofilisering av det oppnådde farmasøytiske preparat for å oppnå et fast farmasøytisk preparat.

18. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 13 for anvendelse i en fremgangsmåte for behandling og/eller profylakse av sykdommer.

19. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 13 for anvendelse i behandling og/eller profylakse av virusinfeksjoner.

20. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 13 for bruk i behandlingen av infeksjoner med HCMV eller en annen representant av Herpesviridae-gruppen.