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(54) Benevnelse **PHARMACEUTICAL PREPARATION COMPRISING AN ANTIVIRAL DIHYDROQUINAZOLINE DERIVATIVE**

(56) Anførte publikasjoner

WO-A1-2006/133822
PT-E- 1 622 880
WO-A1-01/91751

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Pharmaceutical preparation containing an antivirally active dihydroquinazoline derivative

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

The invention further relates to methods for their preparation, their use for the treatment and/or prophylaxis of virus infections and their use for the preparation of medicaments for the treatment and/or prophylaxis of virus infections, in particular for the treatment of infections with the human cytomegalovirus (HCMV) or another member of the herpes viridae group.

{8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]- 3,4-dihydroquinazolin-4-yl}acetic acid, for example, is known from WO 2004/096778, whose disclosure is included in its entirety here by reference, and was developed by the applicant as a promising candidate for an antivirally active substance, in particular for combating infections with the human cytomegalovirus.

However, during development, problems emerged with the solubility of the substance and in particular it has proved complicated to produce stable formulations for intravenous administration or solid readily soluble preparations for the preparation of solutions for intravenous administration.

PT1 622 880 deals with PEG-containing injectable formulations whose active ingredient may be 2 ((4S)-8-fluoro-2-(4-(3-methoxyphenyl)piperazine-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 therefore a task of the invention to describe a pharmaceutical preparation, in particular for intravenous administration, containing {8-fluoro-2-(4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-di-

hydroquinazolin-4-yl}acetic acid which is stable and storable over a long period of time and also has a substantially physiological pH.

Another task of the invention is to describe a pharmaceutical preparation which can be used to easily and reliably prepare pharmaceutical preparations for intravenous administration containing {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid, which are then also stable for a sufficient period, e.g. more than 24 hours.

Within the context of the invention, “stability” means both the chemical stability of the ingredients of the pharmaceutical preparation and the stability of the solution itself. In particular, the preparation according to the invention shall be stable with respect to the precipitation of the ingredients.

In this context, the term “stability” for the inventive liquid pharmaceutical preparations at 2°C to 8°C, or at 25°C, or at 40°C, means a minimum content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)pheny1]-3,4-dihydroquinazolin-4-y1}acetic acid of > 90%, preferably > 95% for at least two, preferably at least three, most preferably for at least six weeks storage when said liquid pharmaceutical preparations are measured by means of one of the HPLC methods 1 - 3. This stability of the liquid pharmaceutical preparations is considered sufficient in the context of the invention.

The term “stability” for the inventive pharmaceutical preparations after dilution or reconstitution also means a final concentration of 0.8 – 10 mg/ml for infusion at 2°C to 8°C, a minimum content of {8-fluoro-2-[4-(3- methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid of > 90%, preferably > 95% for at least four hours, preferably at least six hours, most preferably at least 24 hours storage, if these liquid pharmaceutical preparations are measured after dilution or reconstitution by means of one of the HPLC methods 1 - 3. This stability of the pharmaceutical preparations after dilution or reconstitution is considered sufficient in the context of the invention.

Surprisingly, it was found that pharmaceutical preparations, especially for intravenous administration, which contain {8-fluoro-2-[4-(3-methoxyphenyl)piperazin-l-yl]-3-[2-methoxy-5-(trifluoromethy1)pheny1]-3,4-dihydroquinazolin-4-y1}acetic acid and water can be stabilised by adding at least one excipient selected from the cyclodextrins. It was also found that such preparations can be lyophilised to obtain a stable solid pharmaceutical preparation which can be easily reconstituted, for example by adding water for injection, which in turn can produce a stable pharmaceutical preparation, for example for intravenous administration.

The subject-matter of the invention is therefore pharmaceutical preparations, in particular for intravenous administration, which have the following features:

a) {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-y1]-3-[2-methoxy-5-(trifluoromethyl)pheny1]-3,4-dihydroquinazolin-4-yl) acetic acid or a salt, solvate or solvate of a salt thereof;
b) an excipient selected from the cyclodextrins; and
c) water.

The invention also relates to pharmaceutical preparations produced by lyophilising the above-mentioned pharmaceutical preparation.

In the context of the invention, the term salts is understood to mean physiologically acceptable salts of {8-fluoro-2-(4-(3-methoxyphenyl)piperazine-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)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethy1)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid comprise acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluene-sulphonic acid, benzenesulphonic acid, naphthlialindisulphonic 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)piperazine-1-yl]- 3-(2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl) acetic acid also comprise salts of common 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 with 1 to 16 C atoms, such as exemplarily and preferably monoethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexyamine, dimethylaminoethanol, 2-amino-2-methy1-1,3-propandiol, procaine, dibenzylamine, N-methylmorpholine, ethylenediamine and N-methylpiperidine, as well as the salts of basic amino acids.

Surprisingly, it was found that pharmaceutical preparations, especially for intravenous administration, which contain {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-l-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid and water can be stabilised by adding at least one excipient selected from the cyclodextrins. It was also found that such preparations can be lyophilised to obtain a stable solid pharmaceutical preparation which can be easily reconstituted, for example by adding water for injection, which in turn can produce a stable pharmaceutical preparation, for example for intravenous administration.

In the context of the invention, solvates are those forms of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid which form a complex by coordination with solvent molecules. Hydrates are a special form of solvates in which coordination with water takes place.

As is readily obvious to an expert, {8-fluoro-2-[4-(3- methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid has a stereocentre on the carbon molecule in the 4-position of the dihydroquinazole ring. In the context of this invention, it is particularly preferred if this carbon has the S-configuration.

A cyclodextrin according to the invention is any modified or unmodified cyclodextrin. Due to the size of the cavity in the ring, β-cyclodextrins and in particular modified β-cyclodextrins such as 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-cyclodextrins are preferred.

Within the context of the invention, the water used in the preparation is usually water for injection.

In the context of the present invention, the term “exhibit” or “showing” refers to an open enumeration and does not exclude other components or steps in addition to the expressly mentioned components or steps.

The term “consist of” or “consisting of” means, in the context of this invention, a complete enumeration and excludes any other components or steps apart from those expressly mentioned.

The term “essentially consists of” or “essentially consisting of” in the context of the present invention designates a partially closed enumeration and designates methods or preparations which, in addition to the named components or steps, only have such other components or steps which do not materially change the character of the inventive preparation or method or which are present in quantities which do not materially change the character of the inventive preparation or method.

When in the context of the present invention a preparation or method is described using the expression “exhibit” or “having”, this explicitly includes preparations or methods consisting of or consisting essentially of the ingredients or steps mentioned.

It is preferred in the context of the invention if the pharmaceutical preparation according to the invention further comprises at least one buffer preferably selected from the phosphate buffers, the Tris buffers and the citrate buffers.

The addition of the buffer makes it possible, in particular, to ensure that the preparation always has a physiological pH, wherein the buffers mentioned are preferred, in particular because they are well tolerated.

It is further preferred in the context of the invention if the inventive pharmaceutical preparation further comprises at least one sugar preferably selected from the group consisting of glucose, sucrose, lactose, maltose, trehalose, sorbitol and mannitol.

It has been shown that the inventive pharmaceutical preparation can once again be clearly stabilised by the addition of a sugar and in particular the sugars explicitly mentioned above. It has also been shown that the addition of a sugar may facilitate the preparation of a solid preparation by lyophilisation and the reconstitution of such a solid preparation for the preparation of a pharmaceutical preparation, in particular for intravenous administration. The addition of at least one sugar also serves to adjust the osmolality of the solution and to suppress any haemolysis that may occur.

It is also preferred in the context of the invention if {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-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 5 to 20 mg of pure active substance per ml of preparation.

A content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-l-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid in the above-mentioned ranges has proved to be advantageous with regard to the stability of the solution as well as with regard to easy storage.

It is also preferred in the context of the invention if the preparation has a pH of 7.5 to 8.5.

The pH range mentioned above has proven to be advantageous due to the fact that it is a pH in the range of a physiological pH. It has also been shown that the solubility of the inventive pharmaceutical preparation in the slightly alkaline range, i.e. in a range greater than 7.0, is once again significantly better than at a pH value of 7.0 or less.

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

It is also preferred in the context of the invention if the preparation contains from 1 to 10 equivalents, preferably 2 to 7 equivalents and in particular 2.5 to 5 equivalents of cyclodextrin and 0 to 2.0 equivalents, preferably 0.5 to 1.5 equivalents and in particular 0.75 to 0.9 equivalents of NaOH in relation to the content of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid.

The term equivalents used within the scope of the invention are understood to be molar equivalents. It has been shown that the addition of less excipient than mentioned as the lower limit in the above areas leads to insufficient stabilisation of the solution. The addition of quantities of excipient greater than the upper limits does not provide further advantages in terms of the stability of the preparation. It is also feared that the addition of larger quantities of excipients will also lead to interactions with the active substance and thus to a reduction in the efficacy of the preparation.

In addition, within the scope of the invention, a pharmaceutical preparation which has the following characteristics in relation to 100 ml of preparation is particularly preferred:

a) a) 0.5-2.5 g, preferably 1.0-2.0 g {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-l-yl]-3-[2-methoxy-5-(trifluoromethyl)pheny1]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, solvate or 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 having a pH of from 7.5 to 8.5.

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

Pharmaceutical preparations containing these compounds have been shown to be particularly beneficial in terms of both clinical efficacy and stability.

The pharmaceutical preparations according to the invention are generally prepared by first preparing an aqueous solution of the excipient and then adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid to this solution, optionally followed by addition of other additives such as for example the at least one sugar and/or the at least one buffer. After all the ingredients have been added, the pH of the pharmaceutical preparation is then adjusted to the desired value, wherein it is particularly important to ensure that any adjustment of the pH is adjusted by adding an acid or a buffer from a value in the alkaline range in the direction of the physiological pH is carried out slowly and carefully to avoid precipitation of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-l-yl]-3- 2-methoxy-5-(trifluoromethyl) pheny1]-3,4-dihydroquinazolin-4-yl) acetic acid by a strong local lowering of the pH.

It is also possible to first prepare individual solutions, one solution containing the excipient and {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-2-methoxy-5-(trifluoromethyl)phenyl]-3,4 -dihydroquinazole in-4 -yl)acetic acid, and the other solution containing the other excipient such as at least one sugar and/or at least one buffer, the next step being to adjust the solutions to the weighted pH and then to mix them together.

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

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

It is also possible to lyophilise the solutions obtained by the above methods in order to obtain the inventive solid pharmaceutical preparations.

The object of the invention is thus also a method for the preparation of an inventive pharmaceutical preparation with the following steps:

A) dissolving at least one excipient in the water;
B) adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, solvate or solvate of a salt thereof to the solution obtained in step A);
C) if necessary, adding at least one sugar and/or buffer;
D) adjusting the pH to the desired value to obtain a pharmaceutical preparation, and
E) sterile-filtering 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) by heating.

The invention also relates to a method for producing an inventive pharmaceutical preparation using the following steps:

I.) dissolving the at least one excipient in a part of the water;
II.) adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluorinethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid or a salt, solvate or 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 solutions to obtain a pharmaceutical preparation, and

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

VIII.) if necessary, final sterilisation of the solution obtained in step VII.) by heating.

The invention also relates to a method for producing an inventive pharmaceutical preparation using the following steps:

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

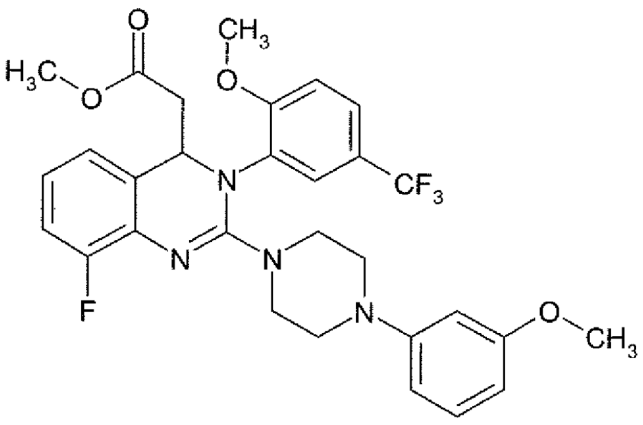
d.) sterile-filtering the solution obtained in step c.) and filling into suitable containers.

e.) if necessary, final sterilisation of the solution obtained in step d.) by heating.

The invention further comprises a method for producing a solid pharmaceutical preparation, wherein a pharmaceutical preparation prepared according to the above-mentioned processes is lyophilised.

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

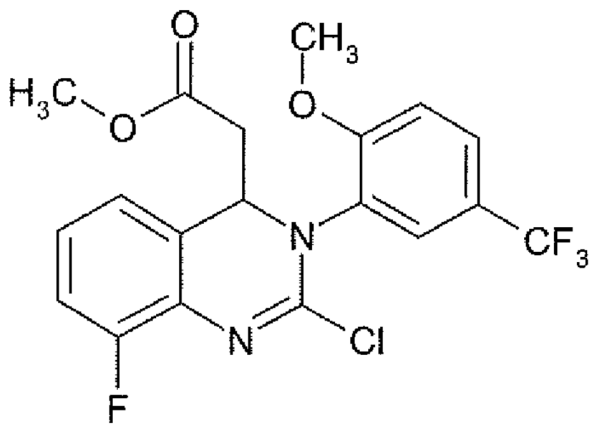
In particular, production is carried out through saponification of the ester of a compound with formula (II)



(II),

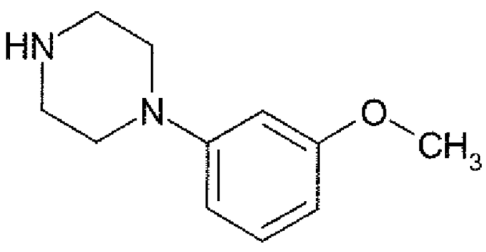
with a base.

The compound with formula (II) may be prepared by reacting a compound with formula (III)



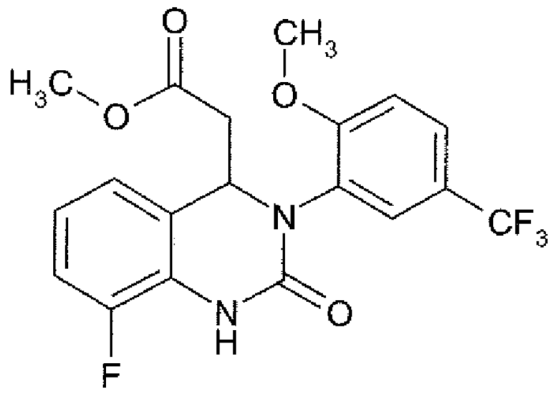
(III),

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



(IV),

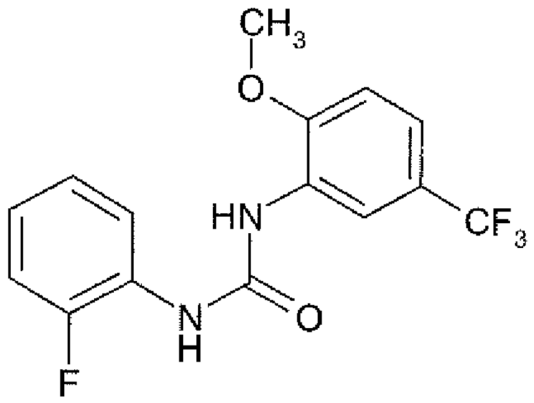
The compound of formula (III) may be prepared by reacting a compound of formula (V)



(V),

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

The compound of formula (V) may be prepared by reacting a compound of 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 of the formulae (IV) and (VI) are known to the expert or can be produced by conventional methods known in the literature.

The ester of a compound of formula (II) to {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid is saponified by reacting a compound of formula (II) with a base in an inert solvent in a

temperature range from 18°C to reflux of the solvent, preferably at 18 to 50°C, particularly preferably at 20 to 30°C, at normal pressure, within 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 alkoxides such as sodium or potassium methoxide or sodium or potassium ethoxides, wherein the base may be present in aqueous solution.

Inert solvents include 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, isopropanol, n-butanol or tert-butanol, or water, or mixtures of solvents, preferably sodium hydroxide in water and MTBE.

Sodium hydroxide in water and MTBE is preferred.

The synthesis of a formula (II) compound from formula (III) and formula (IV) compounds in the presence of a base takes place in an inert solvent, in a temperature range from 40°C to reflux of the solvent, preferably 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 include chlorobenzene or ethers such as 1,2-dimethoxyethane, dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether.

DBU in dioxane is preferred.

A formula (V) compound is converted to a formula (III) compound by reacting a formula (V) compound with phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride, preferably phosphorus oxychloride, in the presence of a base in a stable solvent, in a temperature range of 40°C until reflux of the solvent, preferably upon reflux of the solvent, at normal pressure, for example within 1 to 48 hours, preferably within 2 to 12 hours.

Bases, for example, are 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 include hydrocarbons such as benzene, xylene, toluene or chlorobenzene.

DBU in chlorobenzene is preferred.

The first stage of the conversion of a compound of formula (VI) to a compound of formula (V) occurs through the reaction of a compound of 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 the second stage by reaction with a base in an inert solvent in a temperature range from 40°C to reflux of the solvent, preferably upon 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 stage are for example palladium(II)acetate, 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 such as tris(o-tolyl)phosphine, triphenylphosphine or diphenylphosphinoferrocene.

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

Palladium (II) acetate in acetic acid is preferred.

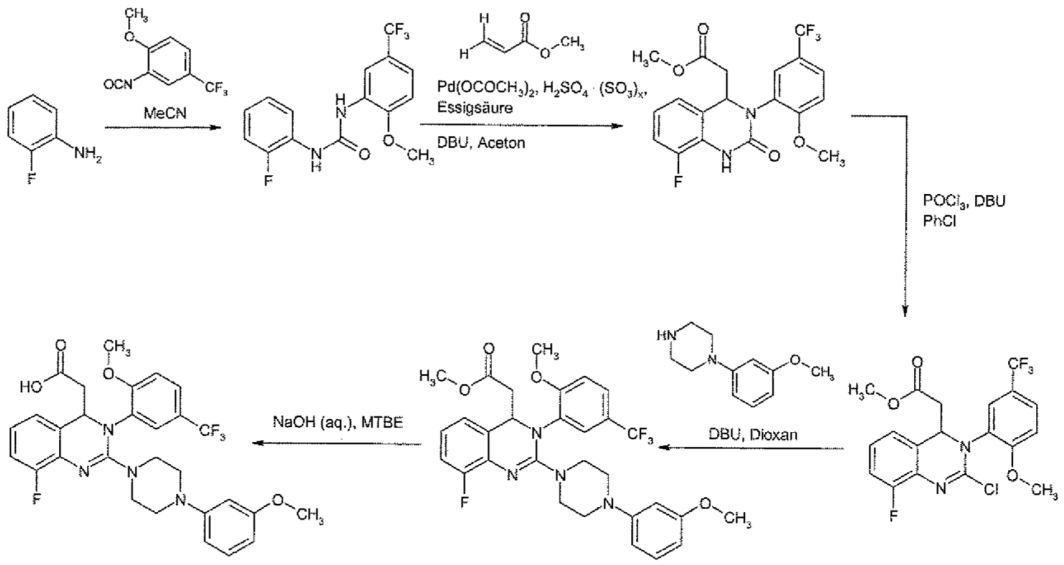
Bases in the second stage are for example DBU, triethylamine or diisopropylethylamine.

Inert solvents in the second stage 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)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid used for producing the inventive pharmaceutical preparation is described in more detail by way of example in the following synthesis schematic diagram 1. The synthesis schematic diagram is purely exemplary and in no way restrictive.

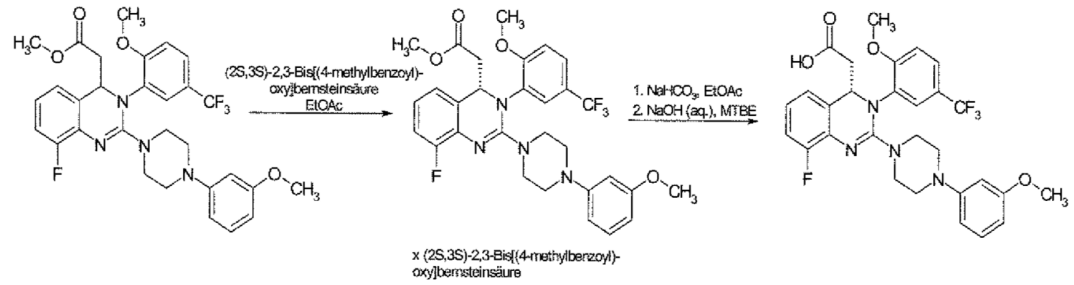
Synthesis schematic diagram 1



As previously mentioned, {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl)acetic acid is preferably

used in the form of the S-enantiomer. This S-enantiomer can be prepared as shown in synthesis schematic diagram 2 below.

Synthesis schematic diagram 2



The {8-fluoro-2- 4-(3- methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl) and its salts, solvates and solvates of the salts show an antiviral effect against representatives of the herpes viridae group (herpes viruses), especially against cytomegaloviruses (CMV), especially against the human cytomegalovirus (HCMV). The inventive pharmaceutical preparations are thus suitable for the treatment and/or prophylaxis of diseases, in particular of infections with viruses, in particular the viruses mentioned herein and the infectious diseases caused thereby. A viral infection is both an infection with a virus and a disease caused by an infection with a virus.

The inventive pharmaceutical preparations may, because of their properties, be used for the manufacture of medicinal products which are suitable for the prophylaxis and/or treatment of diseases, in particular viral infections.

The following can be named as indications, for example:

1) Treatment and prophylaxis of HCMV infections in AIDS patients (retinitis, pneumonitis, gastrointestinal infections).
2) Treatment and prophylaxis of cytomegalovirus infections in bone marrow and organ transplant patients who often suffer from life-threatening HCMV pneumonitis, encephalitis, gastrointestinal and systemic HCMV infections.
3) Treatment and prophylaxis of HCMV infections in new-borns and infants.
4) Treatment of acute HCMV infection in pregnant women.

5) Treatment of HCMV infection in immunosuppressed patients with cancer and during 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 inventive pharmaceutical preparations are preferably used for producing medicinal products which are suitable for the prophylaxis and/or treatment of infectious diseases with a representative of the group Herpes viridae, in particular a cytomegalovirus, in particular the human cytomegalovirus.

Due to their pharmacological properties, the inventive pharmaceutical preparations may be used alone or, if necessary, in combination with other active substances, in particular antiviral active substances such as valganciclovir, ganciclovir, valacyclovir, acyclovir, foscarnet, cidofovir and related derivatives, for the treatment and/or prevention of viral infections, in particular HCMV infections.

Another object of the present invention is the use of the inventive pharmaceutical preparations in a process for the treatment and/or prophylaxis of diseases, preferably viral infections, in particular infections with the human cytomegalovirus (HCMV) or another member of the herpes viridae group.

Another object of the present invention is the use of the inventive pharmaceutical preparations for the treatment and/or prophylaxis of illnesses, in particular the aforementioned illnesses.

Another object of the present invention is the use of the inventive pharmaceutical preparations for producing a medicinal product for the treatment and/or prophylaxis of diseases, in particular the aforementioned diseases. Another subject of the present invention is a method for the treatment and/or prophylaxis of diseases, in particular the aforementioned diseases, using an antivirally active amount of the inventive pharmaceutical preparations.

The term “antivirally active amount” means the inventive pharmaceutical preparations in an administration quantity of at least 0.001 mg/kg.

In general, it has been found to be beneficial to administer the pharmaceutical preparations in such a way that approximately 0,001 to 10 mg per kg, preferably 0.01 to 5 mg per kg body weight of {8-fluoro-2-(4-(3-methoxyphenyl)piperazine-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 quantities mentioned, depending on body weight, individual behaviour with respect to the active substance and time or interval at which the application takes place. For example, in some cases it may be sufficient to manage with less than the minimum quantity mentioned above, while in other cases the upper limit mentioned must be exceeded. If larger quantities are to be applied, it may be advisable to distribute them in several individual doses throughout the day.

The invention is now explained in more detail below using non-restrictive examples.

The percentages given in the following tests and examples are, unless otherwise stated, weight percentages, parts are weight fractions, solvent ratio, dilution ratio and concentration of liquid solutions refer to volume.

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, NH3,	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.

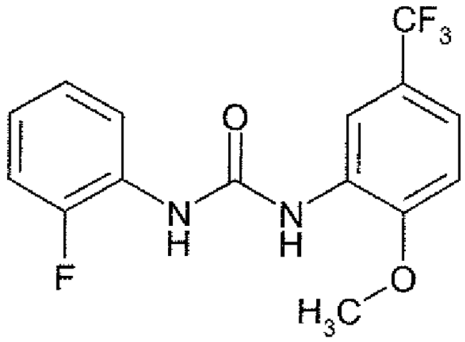
Method 3 (HPLC): Instrument: HP 1050 with variable wavelength detection; column: Chiral AD-H, 250 mm x 4.6 Min, 5µm Mmax; Eluent A: n-Heptane + 0.2 % diethylamine, Eluent B: Isopropanol + 0.2 % diethylamine; Gradient: 0 Min 25 % B, 15 min 25 % B, 1 ml/min; Temp.: 30°C; UV-Detection: 250 nm.

Examples

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

Example 1A:

N-(2-Fluoropheny1)-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.

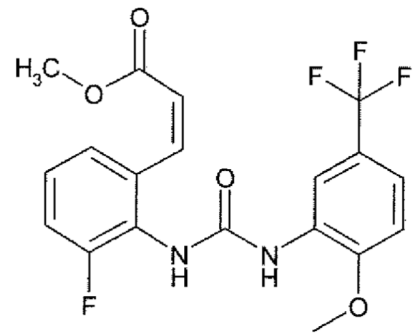
^{1}H NMR (300 MHz, d_6-DMSO): δ = 8.93 (s, 1H), 8.84 (s, 1H), 8.52 (d, ^3J = 2,3, 2H), 7.55 (d, ^2J = 7.7, 1H), 7.38 - 7.26 (m, 3H), 7.22 (d, ^2J = 8.5, 1H), 4.00 (s, 3H) ppm;

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;

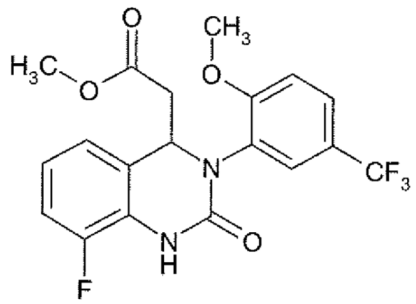
MS (API-ES-pos.): m/z — 429.9 [$(M+NH_4)^+$]; 412.9 $(M+H)^+$]

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



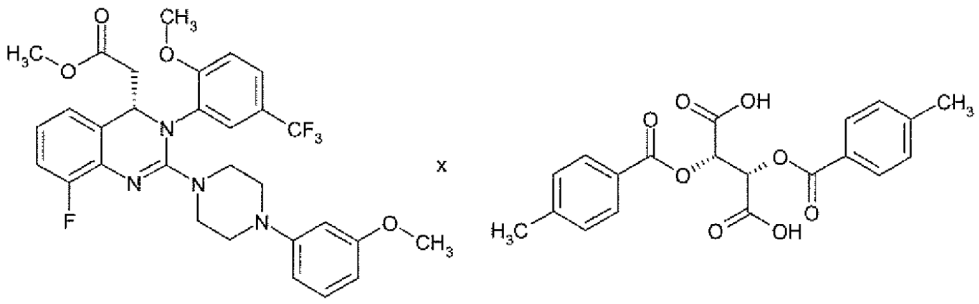
The compound of example 2A (75 kg) is suspended in acetone (1600 l) and DBU (5.7 kg) is added. The resulting suspension is heated to reflux and stirred for 4 h under reflux. The resulting solution is cooled to a shell temperature of 55°C and filtered over diatomaceous earth. A part of the solvent is 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-methoxypheny1)- piperazine-l-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-

dihydroquinazolin-4-yl)- methyl acetic acid (1:1 salt) chlorination/aminination/crystallisation



A solution of {8-fluoro-3-[2-methoxy-5-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-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)piperazine-l-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-methylbenzoy1)oxy]succinic acid — {(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy—5-(trifluoromethyl)phenyl]-3,4-dihydrochinazolin-4-yl}acetic acid methyl ester (1:1 salt) / recrystallization

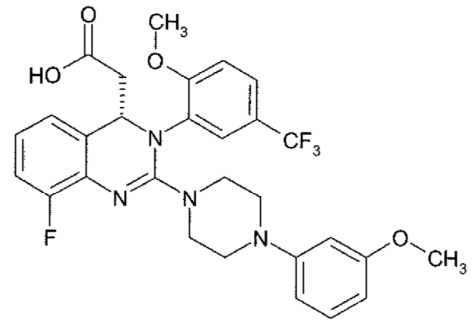
(2*S*,3*S*)-2,3-bis[(4-methy1benzoyl)oxy]succinic acid — (S) {(4*S*)-8-fluoro-2-[4-(3- methoxyphenyl)piperazine-1-yl]—3-[2-methoxy-5-(trifluoromethy1)phenyl]-3,4-dihydrochinazolin-4-y1}acetic acid methyl ester (1:1 salt) (141 kg, calculated as dry) is suspended in ethyl acetate (1400 l) and dissolved 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)piperazine-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)piperazine-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)piperazine-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.

Reference 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)piperazine-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)piperazine-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.

Reference 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)piperazine-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)piperazine-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.

Reference 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)piperazine-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)piperazine-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.

Reference 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)piperazine-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-y1)-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.

Reference 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.

Reference 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)piperazine-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.

Reference 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 dimethysulfoxide (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 eller et salt, et solvat eller et solvat av et salt derav,
b) en eksipiens valgt fra syklodekstrinene, og
c) vann.

2. Farmasøytisk preparat ifølge krav 1, som videre omfatter minst én buffer valgt fra fosfatbuffere, Tris-buffere og citratbuffere.

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

4. Farmasøytisk preparat ifølge krav 3, hvor 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-fluoro-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydrokinazolin-4-yl}eddiksyre eller et salt, et solvat eller et solvat av et salt derav er tilstede i en mengde tilsvarende 1 til 100 mg rent aktivt virksomt stoff per ml av preparatet.

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

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

8. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 7, karakterisert ved at den minst ene eksipiens er tilstede i en mengde på 2 til 5 ekvivalenter i forhold til innholdet av {8-fluoro-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 eksipienten er valgt fra β-cyclodekstriner og modifiserte β-cyclodekstrins, spesielt hydroksyalkyl-β-cyclodekstriner, alkyl-hydroksyalkyl-β-cyclodekstriner og sulfoalkyl-cyclodekstriner.

10. Farmasøytisk preparat ifølge krav 9, karakterisert ved at det nevnte preparat, i forhold til innholdet av {8-fluor-2-[4-(3-metoksyfenyl)piperazin-1-yl]-3-[2-metoksy-5-(trifluormetyl)fenyl]-3,4-dihydroquinazolin-4-yl}eddiksyre, inneholder 1 til 10 ekvivalenter cyklodekstrin så vel som 0 til 2,0 ekvivalenter NaOH.

11. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6 eller ifølge krav 9 eller 10, karakterisert ved at 100 ml av nevnte preparat omfatter følgende:
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 eller et salt, et solvat eller et solvat av et salt derav,
b) 10,0 - 30,0 g HP-β-cyklodekstrin,
c) 0,0 -350 mg, spesielt 100 - 125 mg NaOH, og
d) vann,
hvor nevnte preparat har en pH i området fra 7,5 til 8,5.

12. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 6 eller ifølge krav 9 til 11, karakterisert ved at 100 ml av nevnte preparat omfatter følgende:
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 eller et salt, et solvat eller et solvat av et salt derav,
b) fortrinnsvis 12,5 g - 22,5 g HP-β-cyklodekstrin,
c) fortrinnsvis 75 - 225 mg, spesielt 100 - 125 mg NaOH, og
d) vann,
hvor nevnte preparat har en pH i området fra 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 et hvilket som helst av kravene 1 til 8, ved anvendelse av de følgende trinn, nemlig:

A) oppløsning av 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 eller et salt, et solvat eller et solvat av et salt derav til løsningen oppnådd i trinn A),
C) om nødvendig, tilsetning av minst ett sukker og/eller minst én buffer,
D) justering av pH til ønsket verdi for å oppnå en farmasøytisk sammensetning, og
E) sterilfiltrering av løsningen oppnådd i trinn D) og fylling i passende beholdere,
F) om nødvendig, gjennomføring av en endelig sterilisering av løsningen oppnådd i trinn E) ved oppvarming.

15. Fremgangsmåte for fremstilling av et farmasøytisk preparat ifølge et hvilket som helst av kravene 1 til 8, ved anvendelse av de følgende trinn, nemlig:
I.) oppløsning av minst ett hjelpestoff 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 eller et salt, et solvat eller et solvat av et salt derav til løsningen oppnådd i trinn I.),
III.) om nødvendig, justering av pH i løsningen oppnådd i trinn II.) til ønsket verdi for å oppnå en første løsning,
IV.) oppløsning av minst ett sukker og/eller en buffer i en del av vannet,
V.) om nødvendig, justering av pH i løsningen oppnådd i trinn IV.) til ønsket verdi for å oppnå en andre løsning,
VI.) blanding av den første og den andre løsningen for å oppnå et farmasøytisk preparat, og
VII.) sterilfiltrering av løsningen oppnådd i trinn VI.) og fylling i passende beholdere,
VIII.) om nødvendig, gjennomføring av en endelig sterilisering 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 ved anvendelse av de 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 eller et salt, et solvat eller et solvat av et salt til en vandig NaOH-løsning, fortrinnsvis en vandig 0,1 M NaOH-løsning for å fremstille en løsning eller suspensjon,
b.) tilsetning av vann til løsningen eller suspensjonen oppnådd i trinn a.),
c.) tilsetning av cyklodekstrin og NaCl til løsningen eller suspensjonen oppnådd i trinn b.),
d.) sterilfiltrering av løsningen oppnådd i trinn c.) og fylling i passende beholdere,

e.) om nødvendig gjennomføring av en endelig sterilisering 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, fulgt 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 en behandling og/eller profylakse av virusinfeksjoner.

20. Farmasøytisk preparat ifølge hvilket som helst av kravene 1 til 13 for anvendelse i en behandling av HCMV-infeksjoner eller infeksjoner med et annet medlem av Herpes viridae gruppen.