Title: CRYSTALLINE FORM OF A DIHYDROPTERIDIONE DERIVATIVE

Abstract: The present invention relates to a crystalline form of a dihydropoteridione derivative, namely a crystalline form of the free base N-[trans-4-[[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5, 6, 7, 8-tetrahydro -5-methyl -8 - (1-methylthethyl) - 6 - oxo - 2 - pteridinyl] amino]-3-methoxy-benzamide of structure (I), to a process for the manufacture thereof, and to the use thereof in a pharmaceutical composition.
CRYSTALLINE FORM OF A DIHYDROPTERIDIONE DERIVATIVE

The present invention relates to a crystalline form of a dihydropteridione derivative, namely a crystalline form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, to a process for the manufacture thereof, and to the use thereof in a pharmaceutical composition.

BACKGROUND TO THE INVENTION

A number of dihydropteridione derivatives are already known in the prior art. Thus, for example, International Patent Applications WO 03/020722 and WO 2004/076454 disclose dihydropteridione derivatives, a process for their manufacture and their use in a pharmaceutical composition to treat diseases connected with the activity of specific cell cycle kinases and characterised by excessive or abnormal cell proliferation.

The compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide and a process for its manufacturing are specifically disclosed in WO 2004/076454.

However, the above-mentioned patent applications do not disclose any specific crystal form of any of the compounds exemplified therein.

Although the pharmacologically valuable properties of the dihydropteridinone derivatives disclosed in the art and mentioned above constitute the basic prerequisite for effective use of the compounds as pharmaceutical compositions, an active substance must in any case satisfy additional requirements in order to be accepted for use as a drug. These parameters are largely connected with the physicochemical nature of the active substance. Hence, there continues to be a need for novel crystalline forms of active substances, which can be conveniently formulated for administration to patients and which are pure and highly crystalline in order to fulfil exacting pharmaceutical requirements and specifications.
Preferably, such compounds will be readily formed and have favourable bulk characteristics. Examples of favourable bulk characteristics are drying times, filterability, solubility, intrinsic dissolution rate, stability in general and especially thermal stability, and hygroscopicity.

An absence of breakdown products in the pharmaceutical composition being used is also favourable, since if breakdown products are present in the pharmaceutical composition the content of active substance present in the pharmaceutical formulation might be lower than specified.

Another critical parameter to be controlled is the hygroscopicity, since the absorption of moisture reduces the content of pharmaceutically active substance as a result of the increased weight caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, e.g. by the addition of suitable drying agents or by storing the drug in an environment where it is protected from moisture. In addition, the uptake of moisture may reduce the content of pharmaceutically active substance during manufacture if the pharmaceutical substance is exposed to the environment without being protected from moisture in any way. Preferably, therefore, the hygroscopicity of a pharmaceutically active substance should be well characterised, and possibly also stabilized.

As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances characterised by only slight polymorphism are preferred.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility and dissolution behaviour of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions) it is essential that the active
substance should be sufficiently soluble in physiologically acceptable solvents, particularly aqueous media. For drugs which are to be taken orally, it is in general very important that the active substance should be sufficiently soluble, readily dissolvable and bioavailable.

Decreased levels of organic solvents in the crystal lattice are also favourable, due in part to potential solvent toxicity to the recipient as a function of the solvent.

Under certain circumstances, it may be also favourable for drug development to use an anhydrous form than a hydrate form, since, for example, preparation and handling of hydrates might be sometimes difficult as reproducibility and stability of the hydrated forms may depend on external influences in complex manner, or some hydrates might tend to be less soluble with respect to homologous anhydrous forms, with potential detrimental effect also on the dissolution rate properties of the active compound per se and on its absorption profile through the gastrointestinal tract.

Furthermore, the process for preparing such a compound also needs to be conveniently carried out on commercial scale.

Hence, without being restrictive, examples of the parameters which needs to be controlled are the stability of the starting substance under various environmental conditions, the stability during production of the pharmaceutical formulation and the stability in the final compositions of the drug.

The pharmaceutically active substance used to prepare the pharmaceutical compositions should therefore have great stability which is ensured even under all kinds of environmental conditions.

Moreover, as it may be of further advantage for acceptance for use as a drug, it may be favourable that the active substance is suitable for oral administration. Likewise, it may be favourable that the active substance is useful for the manufacture of solid oral pharmaceutical forms, such as tablets and capsules, or liquid oral pharmaceutical forms, such as orally administered solutions and suspensions, whereby emphasis might be given to solid oral dosage forms.
The problem of the present invention is thus to provide a pharmaceutically active substance which is not only characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible.

SUMMARY OF THE INVENTION

Surprisingly, it has been found that the problem outlined above is solved by a crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[((7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, the structure of which compound is depicted below as formula (I).

Formula (I):

The crystalline anhydrous form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[((7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, which is described in greater detail herein, differs profoundly from the prior art and has surprising and particularly advantageous properties.

Hence, the crystalline form according to this invention is suitable for oral administration.

Thus, this crystalline form may be appropriate for use in an oral pharmaceutical administration form.

Further, this crystalline form is substantially pure, i.e. substantially devoid of other crystalline and/or amorphous forms.
Accordingly, this crystalline form may be useful for the manufacture of solid or liquid oral pharmaceutical dosage forms, such as tablets and capsules and orally administered solutions and suspensions.

Thus, a first object of the present invention is a crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide.

A further object of the present invention is a process for the manufacturing of a crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide.

A further object of the present invention is a pharmaceutical composition comprising a crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

A further object of the present invention is the use of a crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide in a method for treating diseases characterised by excessive or abnormal cell proliferation, or for preparing a pharmaceutical composition which is suitable for treating diseases characterised by excessive or abnormal cell proliferation.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the X-ray powder diffractogram of the crystalline free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to this invention, recorded using a STOE STADIP diffractometer fitted with a location-sensitive detector (OED) and a Cu anode as the x-ray source and a primary
monochromator eliminating CuKα2 radiation (CuKα radiation, λ = 1.54056 Å, 40 kV, 40 mA).

Figure 2 shows the thermoanalysis and determination of the melting point (DSC/TG) of the crystalline free base N-prans^-^-^\text{-}^\text{-}cyclopropylmethyl]i-piperazinyljcyclohexyl]\text{-}^-[^{(7R)}-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to this invention, recorded using a DSC and evaluated by the peak onset (heating rate: 10°C/min). The value given is determined using a DSC 821 e made by Mettler Toledo.

DETAILED DESCRIPTION OF THE INVENTION

As already mentioned hereinbefore, the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide is specifically disclosed in WO 2004/076454, as well as a process for its preparation. For details on a process to manufacture this compound, reference is thus made to this patent application.

For an alternative process to manufacture this compound, reference is made to unpublished patent application PCT/EP2007/051 139 as well as to the following process.

Further, solid compound N-prans^-^-^\text{-}^\text{-}cyclopropylmethyl]i-piperazinyljcyclohexyl]\text{-}^-[^{(7R)}-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, which differs from the crystalline anhydrous form according to the present invention, is specifically disclosed in unpublished patent application PCT/EP2007/051 139, as well as a process for its preparation. For details on a process to manufacture this solid form, reference is thus made to this patent application as well as to the following process.

Further, the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide is specifically disclosed in unpublished patent application PCT/EP2007/051 139, as well as a process for its preparation. For
details on a process to manufacture this trihydrochloride salt, reference is thus made to this patent application as well as to the following process.

Abbreviations used.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TLC</td>
<td>Thin-Layer Chromatography</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential Scanning Calorimeter</td>
</tr>
<tr>
<td>TG</td>
<td>ThermoGravimetry</td>
</tr>
</tbody>
</table>

The starting materials trans-4-aminocyclohexanol I, 3-methoxy-4-nitrobenzoic acid 2, N-(cyclopropylmethyl)piperazine 12c, and 4-acetamido-cyclohexanone 18 are known compounds which are commercially available.

This process is a convergent process, which includes the steps of:

(i) synthesis of a compound of formula 15c

(ii) synthesis of a compound of formula 1_6

and (iii) reacting the compound of formula 15c with the compound of formula 1_6.
In the foregoing, the synthesis of a compound of formula \textbf{15c} and the synthesis of a compound of formula \textbf{16} are described.

(i) Synthesis of a compound of formula \textbf{15c}

\begin{equation}
\text{HO-C$_2$H$_5$NH$_2$} + \text{HO-C$_6$H$_4$NO$_2$} \rightarrow \text{HO-C$_2$H$_5$NCH$_2$C$_6$H$_4$NO$_2$}
\end{equation}

260g (1.32 mol) 3-methoxy-4-nitrobenzoic acid \textbf{2} are placed in 1.5 L toluene. 300 ml toluene are distilled off. 5 ml dimethylformamide are added to the residue and 123 ml (1.7 mol) thionyl chloride are added dropwise thereto. The reaction solution is refluxed for 2 hours. The solvent is concentrated by evaporation using the rotary evaporator under reduced pressure. The residue is dissolved in 500 ml tetrahydrofuran and added dropwise to a suspension of 202g (1.33 mol) trans-4-aminocyclohexanol \textbf{10} in 1.5 L tetrahydrofuran and 1.38 L of a 30% potassium carbonate solution, so that the temperature is maintained between 5° and 13°C. The mixture is stirred for 1 hour at 20°C and 5 L demineralised water are added. The precipitate is suction filtered and washed with demineralised water. The solid is dried at 70°C in the circulating air dryer. 380g (98% of theory) product H are obtained.

TLC (methylene chloride/ethanol = 9:1) \( R_f = 0.47 \)

\begin{equation}
\text{HO-C$_2$H$_5$NCH$_2$C$_6$H$_4$NO$_2$} \rightarrow \text{HO-C$_2$H$_5$NCH$_2$C$_6$H$_4$NO$_2$}
\end{equation}

1 g of finely powdered ruthenium(III)-chloride hydrate are added to 185g (0.63 mol) H and 234g N-methylmorpholine-N-oxide in 1.8 L acetonitrile and the mixture is refluxed for 1 hour. Under reduced pressure 1.6 L acetonitrile are evaporated off. 1.5 L demineralised water are added to the residue and the suspension is cooled to 5°C. The precipitate is suction filtered and washed with plenty of demineralised water. The solid
is dried at 70°C in the circulating air dryer. 168g (91% of theory) product 13 are obtained.

TLC (methylene chloride/ethanol = 9:1) \( R_f = 0.64 \)

112g (383 mmol) of product 13, 108g (770 mmol) N-(cyclopropylmethyl)piperazine 12c and 4.5 ml. methanesulphonic acid in toluene are refluxed for 3 hours using the water separator (approx. 76 ml. water are separated off). Under reduced pressure 900 ml toluene are evaporated off and the residue is suspended in 1.2 L ethanol. 15g sodium borohydride are added batchwise to this suspension at a temperature of 15° to 25°C within one hour. The mixture is stirred for 3 hours at 20°C and another 4g sodium borohydride are added. The mixture is stirred for 16 hours at 20°C. Under reduced pressure 650 ml. ethanol are evaporated off. 2 L demineralised water and 300 ml cyclohexane are added. The mixture is cooled to 5°C and the suspension is suction filtered. The residue is dissolved in 1 normal hydrochloric acid. 5g activated charcoal are added and the mixture is suction filtered. 400 ml. tert.-butylmethylether are added to the filtrate and it is made alkaline with ammonia solution. It is cooled to 4°C, the precipitate is suction filtered and washed with demineralised water. The residue is refluxed in 400 ml. tert.-butylmethylether. It is cooled, the solid is suction filtered and washed with tert.-butylmethylether. After drying in the circulating air dryer at 60°C 73g (46% of theory) product 14c is obtained.

TLC (methylene chloride/ethanol = 9:1) \( R_f = 0.2 \)

The compound 14c may alternatively also be prepared by the following method.
22g (142 mmol) 4-acetamido-cyclohexanone IS, 39.7g (283 mmol) N-cycloDroDylmethvlDiDerazine 12c and 0.71 ml. methanesulphonic acid in 175 ml toluene are refluxed using the water separator until no more water is precipitated. The mixture is left to cool and at 50°C 175 ml. ethanol are added and the resulting mixture is cooled to 20°C. 5.37g (142 mmol) sodium borohydride are added batchwise with thorough stirring and the mixture is stirred for 16 hours at 20°C. 200 ml. of 4 normal hydrochloric acid are added dropwise to the reaction mixture. Under reduced pressure 200 ml. solvent are evaporated off. 100 ml. saturated potassium carbonate solution and 200 ml. methylisobutylketone are added to the residue. The two-phase mixture is cooled to 5°C with thorough stirring. The product is suction filtered and dissolved at reflux temperature in 90 ml. methylisobutylketone. After the addition of activated charcoal it is filtered hot. The mixture is left to cool and the precipitate is removed by suction filtration. After drying, 16.2g (41% of theory) of trans compound 19 are obtained.

TLC (methylene chloride/ethanol/ammonia = 9:1:0.1) R_f = 0.39

A solution of 44g (157 mmol) of product 1j£ in 500 ml. 24% hydrochloric acid is refluxed for 6 hours. The solvent is concentrated by evaporation under reduced pressure and the residue is crystallised from 700 ml. isopropanol. The precipitate is suction filtered, washed with tert.-butylmethyl ether and dried at 60°C in the vacuum drying cupboard. 54.7g product 20 are obtained as the trihydrochloride (contains 5% water).
33g (90.4 mmol) 3-methoxy-4-nitrobenzoic acid are suspended in 80 mL toluene. 0.5 mL dimethylformamide and 16g (134 mmol) thionyl chloride are added. The mixture is refluxed for 1 hour. The solution is concentrated by evaporation under reduced pressure and the crude acid chloride is dissolved in 50 mL tetrahydrofurane. The solution is added dropwise to a suspension of 18.7g (94.9 mmol, 95%) of trihydrochloride and 49g (397 mmol) of diisopropylethylamine in 150 mL tetrahydrofurane while being cooled in the ice bath. TLC is used to check that the reaction is complete. After the reaction has ended water is added to the suspension and the pH is adjusted to 10 by the addition of sodium hydroxide solution. The organic phase is separated off and washed with saturated saline solution. The combined aqueous phases are extracted once with tetrahydrofurane. The combined organic phases are concentrated by evaporation under reduced pressure. The residue is refluxed in 300 mL tert.-butylmethylether. The mixture is left to cool to 20°C and the precipitate is suction filtered. After drying in the vacuum drying cupboard at 45°C, 31.3g (83% of theory) of product is obtained.

A solution of 72.5g (174 mmol) of product in 700 mL methanol and 145 mL dimethylformamide is hydrogenated in the presence of 10g Raney nickel at a temperature of 20°C and a hydrogen pressure of 50psi. The catalyst is filtered off and the methanol is evaporated under reduced pressure. 500 mL demineralised water are added to the residue and the suspension is cooled to 5°C. The precipitate is suction filtered and washed with demineralised water. After drying in the circulating air dryer at 60°C, 60.5g (90% of theory) of product is obtained.

TLC (methylene chloride/ethanol/ammonia = 9:1 :0.1) $R_f = 0.58$

(ii) Synthesis of a compound of formula
The synthesis of the 2-chloro-7-ethyl-7,8-dihydro-5-methyl-8-(1-methylethyl)-(7/?)-6(5/-/) -pteridinone 16 is described in general in WO 2004/076454, to which reference is made.

An alternative route of synthesis of the 2-chloro-7-ethyl-7,8-dihydro-5-methyl-8-(1-methylethyl)-(7/?)-6(5/-/) -pteridinone 16 is described in the following.

The following starting materials are known and commercially available: (R)-2-amino-butyrnic acid 21 and 2,4-dichloro-5-nitropyrimidine 5.

\[
\begin{align*}
\text{HOC} & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{Hz} & \quad \text{N} \\
\text{Hz} & \quad \text{N}
\end{align*}
\]

\(21\) \quad \rightarrow \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{Hz} & \quad \text{N} \\
\text{Hz} & \quad \text{N}
\]

\(22\)

A suspension of 25 g (242 mmol) (R)-2-amino-butyrnic acid 21 and 32 ml. (290 mmol) trimethylorthoformate in 150 mL methanol is heated to 50 °C. At this temperature 26.5 mL (364 mmol) of thionyl chloride are added in 30 minutes. Under evolution of gas the temperature increases to 60 °C. The reaction mixture is refluxed for 3 hours. 125 mL methanol are distilled off and 100 mL toluene are added. 75 mL of solvent are removed by distillation. A suspension of 77 g (364 mmol) sodium triacet oxyborohydride in 175 mL toluene is added to the reaction mixture at 60 °C. 22 mL acetone are added at 40 °C. The reaction mixture is stirred for 16 hours at room temperature. Under cooling 73 mL ammonia (25%) is added. After addition of 50 mL of demineralised water the mixture is heated to 50°C. The organic phase is separated and washed with demineralised water. 24 mL of a 10 molar solution of hydrogen chloride in ethanol is added. 125 mL of solvent are removed by distillation. 175 mL tetrahydrofurane is added and the suspension is cooled to 2 °C. The suspension is suction filtered and washed with cold tetrahydrofurane. After drying in a vacuum drying oven at 50°C, 42.9 g (90% of theory) of product 22 as hydrochloride is obtained.
9.3 ml. of a 50% aqueous sodium hydroxide solution is added to a stirred mixture of 33.3 g (170 mmol) 22 hydrochloride in 60 ml. cyclohexane and 60 ml. demineralised water. The aqueous phase is separated and the organic phase is added dropwise to a refluxed suspension of 30 g (155 mmol) 5 and 52 g (619 mmol) sodium hydrogen carbonate in 230 ml. cyclohexane. The suspension is refluxed for 5 hours using a water separator to remove the formed water. 75 ml. of solvent is destilled off. At 75 °C the suspension is suction filtered to remove the salts. The solvent is destilled off. The residue is dissolved in 240 ml. 2-propanol and 90 ml. of solvent is destilled of again. The solution is cooled slowly to 2 °C. The suspension is suction filtered and washed with cold 2-propanol. After drying in a vacuum drying oven at 50 °C, 38.9 g (79% of theory) of product 23 is obtained.

Lipophilic solvents such as e.g. cyclohexane, methylcyclohexane, toluene and the mixtures thereof are particularly suitable for achieving high regioselectivity in the nucleophilic substitution reaction with compound 5.

50 g 23 in 375 ml. of tetrahydrofurane is hydrogenated in the presence of 5 g Platinum on Carbon (5%) at a hydrogen pressure of 3 bar and at 35 °C until no further hydrogen consumed. 2.5 g vanadyl acetylacetonate are added and the hydrogenation is continued. The suspension is filtered to remove the catalysts. The solvent is removed under reduced pressure. 150 ml. 2-propanol are added to the residue and heated to reflux. 300 ml of demineralised water are added. The suspension is cooled slowly to 2 °C. The suspension is suction filtered and washed with a cold mixture of 2-
propanol and demineralised water. After drying in a vacuum drying oven at 50°C, 36 g (90% of theory) of product 24 is obtained.

A suspension of 7 g (27.5 mmol) of product 25 and 5.7 g (41 mmol) potassium carbonate in 30 ml. dimethylcarbonate is heated to 130°C in an autoclave for 5 hours. The mixture is left to cool and 25 ml. demineralised water and 15 ml. ethyl acetate are added with stirring. The organic phase is distilled off under reduced pressure. A mixture of 25 ml. ethanol and 45 ml. demineralised water is added to the residue and heated to 60°C. The solution is left to cool to room temperature. The precipitate is suction filtered and washed with a mixture of demineralised water and ethanol (2:1). The product is dried at 50°C in the vacuum drying cupboard. 6 g (82% of theory) of product 16 are obtained.

(iii) Reaction of a compound of formula 15c with a compound of formula 16

A solution of 23g (59.5 mmol) of compound 15c, 16.8g (62.5 mmol) 2-chloro-7-ethyl-7,8-dihydro-5-methyl-8-(1-methylethyl)-(7R)-6(5H)-pteridinone 16 and 28.3g (149 mmol) para-toluenesulphonic acid hydrate in 350 ml. 2-methyl-4-pentanol is refluxed for 22 hours using the water separator. After the addition of 1g of compound 16 the mixture is refluxed for a further 2 hours. 300 ml. solvent are distilled off and the viscous oil is allowed to cool to 60°C. 300 ml. methylene chloride and 300 ml. demineralised water are added and the pH is raised by adding approx. 20 ml. of 10 normal sodium hydroxide solution to pH = 9. The organic phase is washed twice with demineralised
water and dried over sodium sulphate. The solvent is evaporated off under reduced pressure and the residue is dissolved at 65°C in 200 mL ethyl acetate. The mixture is left to cool slowly to 20°C, the precipitate is suction filtered and washed with cold ethyl acetate. After drying at 60°C in the vacuum drying cupboard 24.4g (66% of theory) of product (I) is obtained (m.p. = 182°C, DSC: 10 K/min, additional endothermic effects in the DSC diagram before melting).

Thus, it is provided a process for the manufacture of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I)

\[
\text{(I)}
\]

characterised in that a compound of formula 15c

\[
\text{15c}
\]

is reacted with a compound of formula 16.
wherein the compound of formula 1₆ is prepared by methylation of a compound of formula 8

in the presence of dimethylcarbonate.

It is further provided a process for the manufacture of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, said process comprising the steps of contacting, under elevated temperature or at room temperature, N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide dissolved in a suitable solvent or in a mixture of solvents, with hydrochloric acid or hydrogen chloride gas dissolved in an organic solvent, optionally in the presence of para-toluenesulfonic acid, and collecting the precipitate formed. Suitable solvents to dissolve N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide for performing the salt formation are alcohols like methanol, ethanol, 1- or 2-propanol, isomeric alcohols of butanol, isomeric alcohols of pentanol, isomeric alcohols of hexanol, like 2-methyl-4-pentanol, ketones like acetone, dialkylethers like tetrahydrofurane, acetic acid esters like ethyl acetate,
organic acids like acetic acid, amides like N-methylpyrrolidinone and nitriles like acetonitrile.

An alternative manufacturing process is illustrated by the following experiment, in which the trihydrochloride salt is obtained by addition of concentrated hydrochloric acid to the reaction medium after completion of the acid mediated nucleophilic aromatic substitution reaction of the compound 15c with the compound 16. The following example is illustrative and is not to be regarded as a limitation.

A suspension of 143 g (0.37 mol) 15c and 110 g (0.41 mol) 16 in 2 L 2-methyl-4-pentanol is heated up to 60 °C. 176 g (0.93 mol) para-toluenesulfonic acid monohydrate are added and the mixture is heated to reflux for 24 hours using a water separator. The solution is cooled to 100 °C. 183 g concentrated hydrochloric acid are added. At 60 °C 1.5 L acetone are added. The suspension is stirred for 16 hours at room temperature. The precipitate is suction filtered and washed with acetone. The product is dried at 60°C in the vacuum drying cupboard. 267 g of compound (I) as trihydrochloride are obtained.

It is further provided the following step of purification of the trihydrochloride salt via crystallization, wherein:

the compound (I) as trihydrochloride is suspended in a suitable organic solvent, such as ethanol;

the reaction medium is heated to reflux;

water is added;

after cooling the precipitate is collected, washed with a suitable solvent, such as ethanol, and dried.

The following example of purification via crystallization is illustrative and therefore is not to be regarded as a limitation:

Example of purification of the trihydrochloride salt of the compound of formula (I) via crystallization.

A suspension of 15.5 g of compound (I) as trihydrochloride in 160 ml. dry ethanol is heated to reflux. 5.5 ml. of demineralised water are added. The
solution is left to cool slowly to 20°C and stirred 16 hours at 20 °C. The precipitate is suction filtered and washed with ethanol. After drying at 50°C in the vacuum drying cupboard 13.3 g of compound (I) as trihydrochloride is obtained.

It is further provided a process for the manufacture of an hydrated crystal form of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I), said process comprising the steps of:

dissolving the compound (I) as base in a suitable organic solvent, such as ethanol, at room temperature or elevated temperature;

adding hydrochloric acid to the reaction medium;

cooling the reaction medium;

collecting the precipitate, washing the precipitate with e.g. ethanol, and drying.

The following example of manufacture of an hydrated crystal form of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I) is illustrative and therefore is not to be regarded as a limitation:

Example of manufacture of an hydrated crystal form of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I).

1.1 g of concentrated hydrochloric acid are added to a solution of 2 g of the free base of (I) in 30 ml. ethanol. After stirring for 2 hours at 20 °C the suspension is cooled to 20°C. The precipitate is suction filtered and washed with ethanol. After drying in the vacuum drying cupboard 2.15 g of product (I) as trihydrochloride are obtained.

It is further provided a process for the manufacture of an anhydrous form of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I).
oxo-2-pteridinyl[amino]-3-methoxy-benzamide of formula (I), wherein a preparation of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]-cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl][amino]-3-methoxy-benzamide of formula (I) is dried at a temperature above 130°C and maintained under dry atmosphere.

In the solid state, the hydrated form of the trihydrochloride salt of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]-cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl][amino]-3-methoxy-benzamide of formula (I) appears as a white to off-white microcrystalline powder. The material crystallizes in rod like crystals.

The crystalline trihydrochloride trihydrate salt form of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]-cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl][amino]-3-methoxy-benzamide is characterised in that in the x-ray powder diagram has, inter alia, the characteristic values \( d = 3.73 \text{ A}, 4.13 \text{ A}, 4.52 \text{ A}, 4.53 \text{ A}, 6.55 \text{ A}, 7.14 \text{ A}, 7.73 \text{ A}, 9.01 \text{ A} \) and 11.21 \( \text{A} \) (most prominent peaks in the diagram, CuKa radiation, \( \lambda = 1.54056 \text{ A}, 40 \text{ kV}, 40 \text{ mA} \)).

Under standard conditions the crystalline trihydrochloride salt form of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]-cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl][amino]-3-methoxy-benzamide is present in the form of an hydrate and is obtainable after drying with a changing stoichiometry (1-3 water equivalents). The hydrate with a stoichiometry close to a trihydrate seems to be the stable hydrated form under ambient conditions and can be obtained after conditioning of the dried material. The crystal water is tightly bound. Lowering the humidity down to 10 % r.h. does not result in a significant weight loss.

The respective anhydrous form, obtained by heating a sample up to 140 °C, is not stable.

The crystalline trihydrochloride salt of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]-cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl][amino]-3-methoxy-benzamide is characterised by a melting point of
It is an object of the present invention to provide a process for the manufacture of crystalline free base of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, said process comprises the step of releasing said free base from an acid addition salt thereof.

As an embodiment of the aforementioned process, it is a further object of the present invention to provide a process for the manufacture of crystalline free compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I), said process comprising the following steps:

i) providing a two-phased mixture of water and a suitable substantially water immiscible organic solvent, such as ethyl acetate or isopropyl acetate, which mixture comprises a suitable acid addition salt of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I), in particular its trihydrochloride salt, in more particular its trihydrochloride trihydrate salt, and a neutralizing organic or inorganic base suitable to form the free compound of formula (I) from said acid addition salt, such as an alkali base, typically potassium carbonate,

ii) extracting the formed free compound of formula (I) into the organic phase,

iii) separating the organic phase from the aqueous phase,

iv) if required, removing residual (typically inorganic) salts from the organic phase (such as e.g. via desalting, or by precipitating and separating them off),

v) isolating the free compound of formula (I) from the organic phase (such as e.g. by crystallizing and collecting the crystalline free compound, or by evaporation of the solvent), and
vi) if required, further purifying of the obtained free compound of formula (I) (such as e.g. via recrystallization from an appropriate recrystallization solvent).

It is a further object of the present invention to provide a process for the manufacture of a crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, said process comprising the following steps:

i) forming at room temperature or at elevated temperature a two-phased mixture of water and a suitable substantially water immiscible organic solvent, such as isopropyl acetate, which mixture comprises the trihydrochloride salt of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, in particular its trihydrochloride trihydrate salt, and a neutralizing base, such as potassium carbonate, suitable to form the free compound from said salt,

ii) extracting the free compound into the organic phase at room temperature or at elevated temperature,

iii) separating the organic phase from the aqueous phase,

iv) concentrating the organic phase to precipitate residual (typically inorganic) salts,

v) eluting free compound from the precipitated salts with a suitable organic solvent, such as ethanol, or a mixture of solvents, such as ethanol / isopropyl acetate, at room temperature or, preferably, at elevated temperature,

vi) separating off the eluate from the remaining residual salts,

vii) inducing crystallization of the free compound from the eluate, e.g. by concentrating and/or cooling,

viii) collecting crystalline N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide, washing with a suitable solvent, such as isopropyl acetate, and drying.
The following example of manufacture of a crystalline free form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I) according to this invention from its trihydrochloride salt is illustrative and therefore is not to be regarded as a limitation:

Example of manufacture of a crystalline anhydrous form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I) from its trihydrochloride trihydrate salt.

70.7 g Potassium carbonate and 100 g N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide trihydrochloride trihydrate are stirred in 300 ml. purified water and 700 ml. isopropyl acetate for 1 hour at 50°C. The aqueous phase is separated and the organic phase is washed with 150 ml. of sodium chloride solution (15%) at 50°C. The aqueous phase is separated. 150 ml. of solvent are distilled from the organic phase under reduced pressure of 300 mbar and a bath temperature of 80°C. 50 ml. of anhydrous ethanol are added. The suspension is heated up to 70°C. To remove residual salts the suspension is suction filtered and the residue is washed with 200 ml. of isopropyl acetate. 400 ml. of solvent are distilled from the organic phase. The suspension is cooled to 20°C. The precipitate is filtered and washed with isopropyl acetate. After drying at 50°C 73.2 g free base of formula (I) are obtained.

Moreover, the present invention further includes the products obtainable from the processes indicated above.

The following solubility, dissolution and solid state characteristics of crystalline free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I), are relevant to the present invention.

Solubility and dissolution properties of the crystalline free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-
tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to this invention.

Solubility in aqueous media

Table 1 shows the values of solubility of this crystalline free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide in different aqueous media.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Solubility [mg/ml]</th>
<th>pH of the saturated solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>0.11</td>
<td>9.6</td>
</tr>
<tr>
<td>0.1 N HCl</td>
<td>&gt; 10</td>
<td>1.1</td>
</tr>
<tr>
<td>0.01 N HCl</td>
<td>7.6</td>
<td>6.8</td>
</tr>
<tr>
<td>McIlvaine buffer pH 2.2</td>
<td>&gt; 10</td>
<td>2.8</td>
</tr>
<tr>
<td>McIlvaine buffer pH 3.0</td>
<td>&gt; 10</td>
<td>3.6</td>
</tr>
<tr>
<td>McIlvaine buffer pH 4.0</td>
<td>&gt; 10</td>
<td>4.6</td>
</tr>
<tr>
<td>McIlvaine buffer pH 5.0</td>
<td>&gt; 10</td>
<td>5.5</td>
</tr>
<tr>
<td>McIlvaine buffer pH 6.0</td>
<td>&gt; 10</td>
<td>6.3</td>
</tr>
<tr>
<td>McIlvaine buffer pH 7.0</td>
<td>&gt; 10</td>
<td>7.2</td>
</tr>
<tr>
<td>McIlvaine buffer pH 7.4</td>
<td>2.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Phosphate pH 6.0</td>
<td>&gt; 10</td>
<td>6.5</td>
</tr>
<tr>
<td>Phosphate pH 7.0</td>
<td>10</td>
<td>7.3</td>
</tr>
<tr>
<td>Phosphate pH 8.0</td>
<td>0.036</td>
<td>8.1</td>
</tr>
<tr>
<td>Sörensen pH 9.0</td>
<td>0.003</td>
<td>9.2</td>
</tr>
<tr>
<td>Sörensen pH 10</td>
<td>0.007</td>
<td>9.9</td>
</tr>
<tr>
<td>Sörensen pH 11</td>
<td>0.009</td>
<td>10.5</td>
</tr>
<tr>
<td>0.01 N NaOH</td>
<td>0.008</td>
<td>11.7</td>
</tr>
</tbody>
</table>
From the above results, it can be concluded that this crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide has a good solubility profile in aqueous media.

**Intrinsic dissolution rate in aqueous media**

The intrinsic dissolution rate of this crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide is determined in aqueous media covering a range of pH 1.1 - 7.4 using the rotating disc method which maintains a constant surface area. 5 mg drug substance is compressed to form a disc at 356.1 N for 60 s. These discs are mounted to specially designed sample holders which fit into a Sotax dissolution tester. The dissolution media (37°C) are stirred at 200 rpm. Samples are automatically withdrawn every second minute from the dissolution vessel and assayed via UV spectrophotometry. The intrinsic dissolution rate expressed in µg/cm²/min is calculated using the slope of the concentration versus time plot and from the linear portion of the slope of the dissolution curve, volume of dissolution medium (35ml) and area (diameter: 2 mm) of the exposed disk. Intrinsic dissolution rates in aqueous media are shown in Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>pH of aqueous medium</th>
<th>dissolution rate [µg/cm²/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>6600</td>
</tr>
<tr>
<td>3.1</td>
<td>2760</td>
</tr>
<tr>
<td>4.1</td>
<td>1810</td>
</tr>
<tr>
<td>5.0</td>
<td>1390</td>
</tr>
<tr>
<td>6.1</td>
<td>1180</td>
</tr>
</tbody>
</table>
Solid state properties of this crystalline form of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5, 6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide.

Crystallinity and polymorphism

This anhydrous crystal form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide is highly crystalline. The X-ray powder diffraction diagram is shown in Figure 1.

The X-ray powder reflection and intensities (normalized) are shown in the following Table 3 (wavelength: $\lambda = 1.54056$ Å).

<table>
<thead>
<tr>
<th>$2\theta$ [°]</th>
<th>$d_{hkl}$ [Å]</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,14</td>
<td>14,39</td>
<td>60</td>
</tr>
<tr>
<td>7,26</td>
<td>12,16</td>
<td>4</td>
</tr>
<tr>
<td>7,76</td>
<td>11,39</td>
<td>39</td>
</tr>
<tr>
<td>8,34</td>
<td>10,59</td>
<td>4</td>
</tr>
<tr>
<td>9,45</td>
<td>9,35</td>
<td>1</td>
</tr>
<tr>
<td>9,97</td>
<td>8,86</td>
<td>27</td>
</tr>
<tr>
<td>10,78</td>
<td>8,20</td>
<td>1</td>
</tr>
<tr>
<td>12,03</td>
<td>7,35</td>
<td>15</td>
</tr>
<tr>
<td>12,86</td>
<td>6,88</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>13,15</td>
<td>6.73</td>
<td></td>
</tr>
<tr>
<td>13,91</td>
<td>6.36</td>
<td></td>
</tr>
<tr>
<td>14,51</td>
<td>6.10</td>
<td></td>
</tr>
<tr>
<td>15,52</td>
<td>5.71</td>
<td></td>
</tr>
<tr>
<td>15,82</td>
<td>5.60</td>
<td></td>
</tr>
<tr>
<td>16,69</td>
<td>5.31</td>
<td></td>
</tr>
<tr>
<td>17,19</td>
<td>5.15</td>
<td></td>
</tr>
<tr>
<td>17,37</td>
<td>5.10</td>
<td></td>
</tr>
<tr>
<td>17,80</td>
<td>4.98</td>
<td></td>
</tr>
<tr>
<td>18,59</td>
<td>4.77</td>
<td></td>
</tr>
<tr>
<td>18,78</td>
<td>4.72</td>
<td></td>
</tr>
<tr>
<td>19,04</td>
<td>4.66</td>
<td></td>
</tr>
<tr>
<td>19,27</td>
<td>4.60</td>
<td></td>
</tr>
<tr>
<td>19,82</td>
<td>4.48</td>
<td></td>
</tr>
<tr>
<td>20,37</td>
<td>4.36</td>
<td></td>
</tr>
<tr>
<td>20,95</td>
<td>4.24</td>
<td></td>
</tr>
<tr>
<td>21,45</td>
<td>4.14</td>
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</tr>
<tr>
<td>21,61</td>
<td>4.11</td>
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</tr>
<tr>
<td>21,84</td>
<td>4.07</td>
<td></td>
</tr>
<tr>
<td>22,49</td>
<td>3.95</td>
<td></td>
</tr>
<tr>
<td>22,69</td>
<td>3.92</td>
<td></td>
</tr>
<tr>
<td>23,36</td>
<td>3.81</td>
<td></td>
</tr>
<tr>
<td>23,97</td>
<td>3.71</td>
<td></td>
</tr>
<tr>
<td>24,15</td>
<td>3.68</td>
<td></td>
</tr>
<tr>
<td>24,32</td>
<td>3.66</td>
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<tr>
<td>24,63</td>
<td>3.61</td>
<td></td>
</tr>
<tr>
<td>24,95</td>
<td>3.57</td>
<td></td>
</tr>
<tr>
<td>25,19</td>
<td>3.53</td>
<td></td>
</tr>
<tr>
<td>25,52</td>
<td>3.49</td>
<td></td>
</tr>
<tr>
<td>25,85</td>
<td>3.44</td>
<td></td>
</tr>
</tbody>
</table>
In Table II above the value “$2 \Theta [^\circ]$” denotes the angle of diffraction in degrees and the value “$d_{hk}$ [Å]" denotes the specified distances in Å between the lattice planes.

According to the findings shown in Table 3 the present invention further relates to the crystalline anhydrous form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[{(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl}amino]-3-methoxy-benzamide, characterised in that in the x-ray powder diagram it has, inter alia, the characteristic values $d = 3.81$ Å, $3.92$ Å, $3.95$ Å, 4.24 Å, 4.48 Å, 4.72 Å, 4.77 Å, 5.15 Å, 6.10 Å, 6.73 Å, 6.88 Å, 8.86 Å, 11.39 Å and 14.39 Å (most prominent peaks in the diagram).

Further on, according to the findings shown in Table 3 the present invention further relates to the crystalline anhydrous form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[{(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl}amino]-3-methoxy-benzamide, characterised in that in the x-ray powder diagram it shows, inter alia, the characteristic values $d = 4.48$ Å, 4.77 Å, 5.15 Å, 6.10 Å, 11.39 Å and 14.39 Å with an intensity of more than about 40%.

Under standard conditions the crystalline form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[{(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl}amino]-3-methoxy-benzamide according to
the invention is present in an anhydrous form.

To study the hygroscopical behaviour of this material, sorption isotherms are registered on a DVS-1 water sorption monitor from Surface Measurement Systems. Adsorption and desorption isotherms are performed at 25°C with 10% r.h. step intervals ranging from 10% r.h. up to 90% r.h.

It is found that the crystalline form of the free base \(N-\text{[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide}\) according to the invention is not hygroscopic. Over the range 10 - 90% r.h. an uptake of approx. 0.7% of water is observed. The water-uptake is completely reversible. No hysteresis is observed which would indicate the existence of a stable hydrated form.

Thus, the present invention further relates to a crystalline form of the free base \(N-\text{[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide}\), characterised by a melting point of \(T_{\text{mp}} = 200 \pm 5°C\) (determined by DSC; evaluation using peak-maximum; heating rate: 10°C/min).

The thermoanalysis of the crystalline form of the free base \(N-\text{[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide}\) according to the invention shows only one sharp endothermic effect at approximately 200°C (DSC: 10 K-min\(^{-1}\) heating rate) \((\Delta H_{\text{ fus }} = 70 \pm 10 \text{ J/g})\), indicating melting of the compound. The DSC/TG diagram is shown in Figure 2. Weight loss on drying in a TG-experiment up to the melting point is small and usually in the range of less than 1.0% indicating an anhydrous form of the free base. Release of only small amounts of water is detected within a TG-IR coupling experiment within this temperature range.

Thus, the present invention further relates to a crystalline form of the free base \(N-\text{[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[7R]-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide}\), characterised by a melting point of \(T_{\text{mp}} = 200 \pm 5°C\) (determined by DSC; evaluation using peak-maximum; heating rate: 10°C/min).
From the above data, it can be concluded that the crystalline form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5, 6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I) according to this invention is characterized by its good solubility in aqueous media, its good thermal properties and its high crystallinity. The crystalline free form is distinguished by being neither a hydrate nor a solvate form. The crystalline polymorph form is characterized as an anhydrous form and is substantially not hygroscopic.

Further on, the crystalline form of the free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to this invention is substantially pure, i.e. substantially devoid of other crystalline and/or amorphous forms.

Likewise, this crystalline form of the free base may be suitable for the manufacture of commercially viable and pharmaceutically acceptable drug compositions or dosage forms.

In addition, it can be concluded from above data that the crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to this invention is suitable for oral administration.

Thus, this crystalline free base may be appropriate for use in an oral pharmaceutical administration form.

Accordingly, this crystalline free base may be useful for the manufacture of solid oral pharmaceutical forms, such as tablets and capsules, as well as liquid oral pharmaceutical forms, such as orally administered solutions and suspensions.

The present invention also relates to the metabolites of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I),
to prodrugs of this compound or of these metabolites obtained via, for example, chemical or non-chemical derivatization of the entire molecule or of one or more chemical groups on the molecule, to conjugates of this compound or of these metabolites with a natural or artificial polymer (for example an oligopeptide, a protein or a chemical polymer), and to the use thereof in a pharmaceutical composition.

"Metabolites" are intended to include compounds which are generated from the active parent drug according to formula (I) or other formulas or compounds of the present invention in vivo when such parent drug is administered to a mammalian subject.

Metabolites provide the same pharmacological effect and include compounds of the present invention wherein for example an alkyl-amino group is replaced by an unsubstituted amino group or the corresponding N-oxide, an ester group is replaced by the corresponding carboxylate, or a methyl group has been transformed into a hydroxymethyl or a carboxyl group.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) or other formulas or compounds of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the present invention, for example the compound of formula (I), are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound.

"Conjugates" are intended to include any covalently bonded natural or artificial polymer (for example an oligopeptide, a protein or a chemical polymer) which release the active parent drug according to formula (I) or other formulas or compounds of the present invention in vivo when such conjugate is administered to a mammalian subject. Conjugates of a compound of the present invention, for example formula (I), are prepared by attaching functional groups present in the compound to an oligopeptide, a protein or a polymer in such a way that the modifications are cleaved in vivo by a biomolecule, which usually is found in the vicinity of the target, to the parent compound.

Like the dihydropteridinone derivatives mentioned in WO 2004/076454, the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5, 6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide
also has, in particular, an inhibiting effect on specific cell cycle kinases. Thus, this
compound may be used for example to treat diseases connected with the activity of
specific cell cycle kinases and characterised by excessive or abnormal cell
proliferation, and especially for treating diseases connected with the activity of the polo-
like kinase PLK-1. Such diseases include, for example: viral infections (e.g. HIV and
Kaposi's sarcoma); inflammatory and autoimmune diseases (e.g. colitis, arthritis,
Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or
parasitic infections; leukaemias, lymphoma and solid tumours; skin diseases (e.g.
psoriasis); bone diseases; cardiovascular diseases (e.g. restenosis and hypertrophy).
This compound is also suitable for protecting proliferating cells (e.g. hair, intestinal,
blood and progenitor cells) from damage to their DNA caused by radiation, UV
treatment and/or cytostatic treatment (Davis et al., 2001). It may be used for the
prevention, short-term or long-term treatment of the abovementioned diseases, also in
combination with other active substances used for the same indications, e.g.
cytoptastics.
Furthermore, the compounds in accordance with the present invention may be used on
their own or in conjunction with other pharmacologically active substances.

Suitable preparations for the pharmaceutical compositions in accordance with the
present invention include for example tablets, capsules, suppositories, solutions, -
particularly solutions for injection (s.c, i.v., i.m.) and infusion - elixirs, emulsions or
dispersible powders. The proportion of the pharmaceutically active compound(s)
should be in the range from 0.01 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the
composition as a whole, i.e. in amounts which are sufficient to achieve the dosage
necessary to achieve a therapeutic effect. If necessary the doses specified may be
given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with
known excipients, for example inert diluents such as calcium carbonate, calcium
phosphate or lactose, disintegrants such as maize starch or alginic acid, binders such
as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for
delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or
polyvinyl acetate. The tablets may also comprise several layers.
Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidine or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly, the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethylene glycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).
Physiologically acceptable solvents are known to the person skilled in the art and comprise, without limitation, for example isotonic salt or sugar containing solutions such as a 0.9% NaCl solution, a 5% glucose or mannitol solution, or a Ringer/lactate solution.

The preparations are administered by the usual methods, preferably by oral route, by injection or transdermally. For oral administration the tablets may of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

The dosage for intravenous use is from 1 - 1000 mg per hour, preferably between 5 and 500 mg per hour.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

The following examples of formulations illustrate the present invention without restricting its scope.

A) Tablets per tablet

<table>
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<tr>
<th>Active substance</th>
<th>100 mg</th>
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The finely ground active substance, lactose and some of the maize starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

<table>
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<th>Tablets</th>
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<tr>
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<td>active substance</td>
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<tr>
<td></td>
<td>lactose</td>
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<td></td>
<td>maize starch</td>
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<td></td>
<td>microcrystalline cellulose</td>
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<td>polyvinylpyrrolidone</td>
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<td>sodium-carboxymethyl starch</td>
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<tr>
<td></td>
<td>magnesium stearate</td>
<td>2 mg</td>
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</table>

400 mg

The finely ground active substance, some of the maize starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining maize starch and water to form a granulate which is dried and screened. The sodium carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

<table>
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<tr>
<td></td>
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<tr>
<td></td>
<td>sodium chloride</td>
</tr>
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<td></td>
<td>sodium hydroxide</td>
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The active substance is dissolved in water at its own pH and sodium chloride is added to make the solution isotonic. The pH is then adjusted to 4.0 by addition of sodium hydroxide 1N. The resulting solution is filtered to remove pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and heat-sealed. The ampoules may contain 5 mg, 25 mg or 50 mg of active substance.
CLAIMS


2. A crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to claim 1, characterised by a melting point of $T_{mp} = 199 \pm 5^\circ C$ (determined by DSC; evaluation using peak-maximum; heating rate: 10°C/min).

3. Crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to claim 1 or 2, characterised in that in the x-ray powder diagram it shows, inter alia, the characteristic values $d = 4.48 \text{ A}, 4.77 \text{ A}, 5.15 \text{ A}, 6.10 \text{ A}, 11.39 \text{ A} \text{ and } 14.39 \text{ A}$ with an intensity of more than about 40%.

4. Crystalline form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to any of the claims 1-3, characterised in that it is in an anhydrous form.

5. A process for the manufacture of crystalline free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to any of the claims 1-4, said process comprising the steps of:

i) forming at room temperature or at elevated temperature a two-phased mixture of water and a suitable substantially water immiscible organic solvent, which mixture comprises

a suitable acid addition salt of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide,
and

a neutralizing base suitable to form the free base from said salt,

ii) extracting the formed free base into the organic phase at room temperature or at elevated temperature,

iii) separating the organic phase from the aqueous phase,

iv) if required, removing residual salts from the organic phase,

v) inducing crystallization of the free base,

vi) collecting crystalline free base, washing with a suitable solvent, and drying.

6. The process according to claim 5 wherein said acid addition salt of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide used is its trihydrochloride.

7. The process according to claim 5 wherein said acid addition salt of N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide used is its trihydrochloride trihydrate.

8. The crystalline free base N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide obtainable from the process according to any one of claims 5 to 7.

9. The crystalline free compound according to any of the claims 1-4 and 8 characterized by being substantially pure.

10. Pharmaceutical composition containing the crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to any of the claims 1-4, 8 and 9, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

11. Oral pharmaceutical administration form comprising the crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-
[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to any of the claims 1-4, 8 and 9.

12. Process for preparing a pharmaceutical composition according to claim 10 or 11, characterised in that the crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to any of the claims 1-4, 8 and 9 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

13. Use of the crystalline anhydrous form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide according to any of the claims 1-4, 8 and 9 for preparing a pharmaceutical composition which is suitable for treating excessive or abnormal cell proliferation.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D475/00 A61K31/519 A61P35/00

According to International Patent Classification (IPC) and/or both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/018220 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; LINO) 23 February 2006 (2006-02-23) page 59; example 110; compound 17C</td>
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<td>WO 2004/076454 A (BOEHRINGER INGELHEIM PHARMA [DE]; HOFFMANN MATTHIAS [DE]; GRAUERT MATT) 10 September 2004 (2004-09-10) cited in the application examples 99, 110; table 1 page 54; example 212 page 56, line 7 - line 8</td>
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D. Further documents are listed in the continuation of Box C.

X See patent family annex.

Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed
'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'W' document member of the same patent family

Date of the actual completion of the international search: 30 October 2008

Date of mailing of the international search report: 06/11/2008

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (April 2005)
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