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 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. For drugs which are to be taken orally, it is in general very important that the active substance should be sufficiently soluble and bioavailable.

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

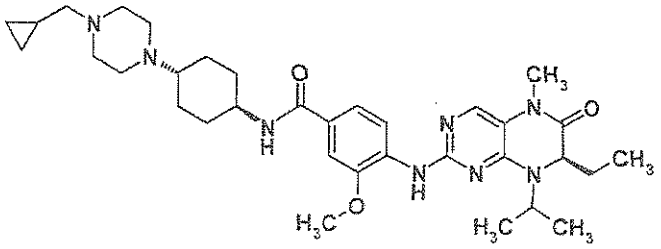
Hence, without being restrictive, examples of the parameters which needs to be controlled are the stability of the starting substance under various environmental conditions, the stability during production of the pharmaceutical formulation and the stability in the final compositions of the drug.

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.

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 the trihydrochloride salt and by the crystalline trihydrochloride hydrate 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 is depicted below in the form of the free base as formula (I).



(I)

The trihydrochloride salt and the crystalline trihydrochloride hydrate 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 offer numerous advantages over the free base and the anhydrous form of this compound. Hence, over the anhydrous form, the crystalline trihydrochloride hydrate form presents for example an advantage of stability under ambient conditions.

Furthermore, when compared to the base salt, the trihydrochloride salt presents an advantage of solubility in water, where the trihydrochloride is much more soluble than the free base.

Lastly, when compared to other common salt form builders, the trihydrochloride salt form presents also advantages as far as the yield, purity and reproducibility of the synthesis of the salt form are concerned.

Thus, a first aspect of the present disclosure refers to a crystalline, hydrated form of 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 wherein the hydrated form is mono-, di- or trihydrate or mixtures thereof.

A second aspect of the present disclosure refers to a crystalline, hydrated form of 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, wherein the hydrate contains up to three water molar equivalents.

A third aspect of the present disclosure refers to a pharmaceutical composition comprising the crystalline compound as defined above, together with a pharmaceutically acceptable carrier or diluent.

A fourth aspect of the present disclosure refers to the crystalline hydrated form of 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, having the following characteristic values d: 3.73 Å, 4.13 Å, 4.52 Å, 4.53 Å, 6.55 Å, 7.14 Å, 7.73 Å, 9.01 Å and 11.21 Å wherein the x-ray source is CuKα radiation, λ=1.54056 Å, 40 kV, 40 mA.

A fifth aspect of the present disclosure refers to a pharmaceutical composition comprising the crystalline compound as defined above, together with a pharmaceutically acceptable carrier or diluent.

A~~Thus, a~~ first embodiment~~object~~ of the present disclosure~~invention~~ is the trihydrochloride salt 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 embodiment~~object~~ of the present disclosure~~invention~~ is the trihydrochloride 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 embodiment~~object~~ of the present disclosure~~invention~~ are the crystalline trihydrochloride hydrate forms 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 embodiment~~object~~ of the present disclosure~~invention~~ is the crystalline trihydrochloride trihydrate 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 embodiment~~object~~ of the present disclosure~~invention~~ is an improved process for the manufacturing 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 embodiment~~object~~ of the present disclosure~~invention~~ is a process for the manufacturing 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.

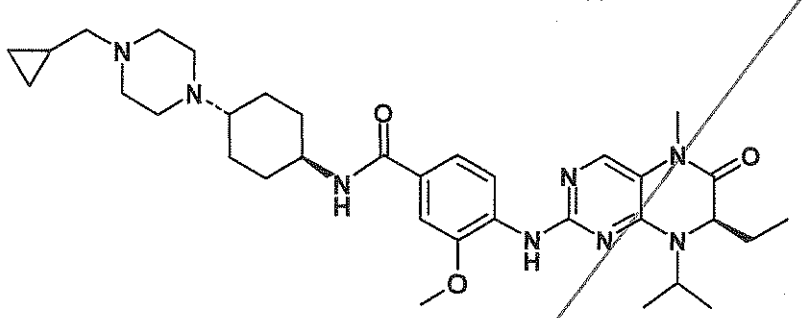
A further embodiment~~object~~ of the present disclosure~~invention~~ is a pharmaceutical composition comprising the trihydrochloride salt, a crystalline trihydrochloride hydrate form or the crystalline trihydrochloride trihydrate form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-me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

A further embodiment~~object~~ of the present disclosure~~invention~~ is the use of the trihydrochloride salt, a crystalline trihydrochloride hydrate form or the crystalline trihydrochloride trihydrate 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

CLAIMS

1. 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)



(I)

2. Crystalline trihydrochloride hydrated forms 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) in accordance with claim 1.

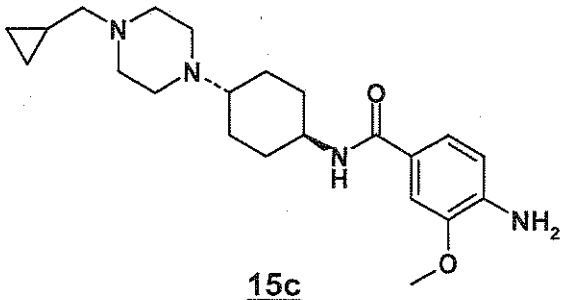
3. Crystalline trihydrochloride trihydrate form of the compound N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide of formula (I) in accordance with claim 1.

4. 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 of formula (I) in accordance with claim 1, said process comprising the steps of contacting 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 solvent mixtures, with hydrochloric acid or hydrogen chloride gas dissolved in an organic solvent, and collecting the precipitate formed.

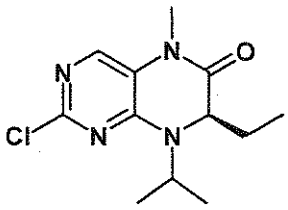
5. Process

in accordance with claim 4, said process additionally comprising reacting compound **15c**



15c

with the compound **16**



16

6. Process in accordance with claim 5, additionally comprising

suspending the compound of formula (I) as trihydrochloride in a suitable organic solvent;

heating the reaction medium to reflux;

adding water to the reaction medium;

collecting the precipitate, washing it and drying it.

7. Process for the manufacture of an hydrated crystal form of the trihydrochloride 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) in accordance with claim 1, said process comprising the steps of:

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

adding hydrochloric acid to the reaction medium;

cooling the reaction medium;

collecting the precipitate, washing the precipitate, and drying the precipitate.

8. Process in accordance with claim 7, wherein the hydrated crystal form is the trihydrate.

9. Pharmaceutical composition containing the trihydrochloride salt, a crystalline trihydrochloride hydrated form or the crystalline trihydrochloride trihydrate 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) in accordance with claim 1, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

10. Process for preparing a pharmaceutical composition according to claim 9, characterised in that the trihydrochloride salt, a crystalline trihydrochloride hydrated form or the crystalline trihydrochloride trihydrate 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) in accordance with claim 1 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

11. Use of the trihydrochloride salt, a crystalline trihydrochloride hydrated form or the crystalline trihydrochloride trihydrate 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) in accordance with claim 1 for preparing a pharmaceutical composition which is suitable for treating excessive or abnormal cell proliferation.

Claims:

1. A crystalline, hydrated form of 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 wherein the hydrated form is mono-, di- or trihydrate or mixtures thereof.

2. A crystalline, hydrated form of 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, wherein the hydrate contains up to three water molar equivalents.

3. A pharmaceutical composition comprising the crystalline compound in accordance with claim 1, together with a pharmaceutically acceptable carrier or diluent.

4. The crystalline hydrated form of 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, having the following characteristic values d: 3.73 Å, 4.13 Å, 4.52 Å, 4.53 Å, 6.55 Å, 7.14 Å, 7.73 Å, 9.01 Å and 11.21 Å wherein the x-ray source is CuKα radiation, λ=1.54056 Å, 40 kV, 40 mA.

5. A pharmaceutical composition comprising the crystalline compound in accordance with claim 4, together with a pharmaceutically acceptable carrier or diluent.