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wherein

R9 is hydrogen or lower alkyl,
X is oxo, thio, imino, N-tower alkyl-imiflo, hydroximino or 0-lower alkyl-hydroximino,
Y is oxygen or the group NH,
n isOorland

Rio is an aliphatic radical having at least 5 carbon atoms, or an aromatic, aromatic-
aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, heterocyclic or heterocyclic-aliphatic radical,
and the remaining radicals A4, R5, A6, R7 and A8 are each independently of the others
ID hydrogen, lower alkyl that is unsubstituted or substituted by free or alkylated amino, piperazinyl, piperidinyl, pyrrolidinyl or by morpholinyl, or tower alkanoyl, trifluoromethyt, free,
etherified or esterifed hydroxy, free, alkylated or acylated amino or free or esteritled
carboxy, or
a salt of such compounds having at least one salt-forming group.
Preferably, the definitions of the substituents given above have the meanings, especially
the preferred meanings, described in European Patent Application EP 0 564 409. Most preferred of these compounds is the compound of the formula Ill

H H

(NyN,N LN
(Ill)

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with the name 4-(4-methylpiperaziri-1 -ylmethyl)-N-[4-methy(-3-(4-pyridin-3-yl)pyrimidin-2-ylamirio)phenyljbenzamide, preferably in the form of the methane sulfonate salt as described in WO 99/03854, most preferably in the form of the methane sulfonate salt in the 3 -crystal form as described in WO 99/03854. This compound (the methane sulfonate salt form) is called ST1571 hereinafter.

An "organic compound capable of binding to a1 -acidic glycoprotein (AGP) is generally a basic or neutral drug, but also an acidic drug, especially selected from the group consisting of

alpha-blockers, especially Nicergoline or Prazosin;

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(acute lymphoblastic leukemia), or a solid tumor, especially selected from lung cancer, especially non-small cell lung cancer, and from cancer of the prostate, is meant; most
preferably, any of the diseases just mentioned that has become or is becoming resistant to
treatment with one or more of the mentioned tyrosine kinase inhibitors, or was resistant to
such treatment already before the treatment with any such tyrosine kinase inhibitor, espe-
cially due to higher AGP concentrations being present in the blood plasma of the individual
to be treated, is meant.

40 The pharmaceutical compositions comprise from approximately 0.0001 % to approximately 95 % of any component (a) and/or (b), dosage forms that are in single dose form preferably
comprising from approximately 10 % to approximately 90 % of component (a) or (b), and
dosage forms that are not in single dose form preferably comprising from approximately 10
% to approximately 60 % of each component. Unit dose forms, such as dragees, tablets,
ampoules or capsules, comprise from approximately 5 mg to approximately 1 g of com-
ponent (a) and/or component (b), preferably from 5 mg to approximately 1 g.

The pharmaceutical compositions are prepared in a manner known per Se, for example by
means of conventional mixing, granulating, confectioning, dissolving or lyophilising pro-
cesses, For example pharmaceutical compositions for oral administration can be obtained
by combining component (a) and/or (b) with one or more solid or liquid carriers, where
. necessary granulating a resulting mixture and processing the mixture or the granules, if desired or appropriate with the addition of further excipients, to form tablets or dragØe cores
or solutions, respectively.

Suitable carriers are especially fillers, such as sugars, e.g. lactose, saccharose, mannitol or
sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or
calcium hydrogen phosphate, and binders, such as starches, e.g. corn, wheat, rice or pota-
to starch, mothylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcelluloso and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, and also carboxymethyl starch, crosslinked polyvinylpyrrolidone or alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditio-ners and lubricants, e.g. silicic acid, talc, steanc acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

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are cured by the combined treatment; this value is significantly different (p<0,01) from the one (1/13) obtained in the ST1571 only group. Control groups receiving erythromycin alone
do not show any evidence of tumor regression (not shown).

(b) The biological effects of ST1571 pretreatment are also evaluated. Mice are pretreated or
not with ST1571 for 14 days, injected with KU812 cells and then treated with ST1571 (160
mg/kg every 8 hours for 11 days), starting 24 hours after leukemic cells injection. Under
these circumstances, 100% animals are expected to be cured by ST1571 The results are

40 present in Fig. 12. In the control group (non pretreated mice) 0/14 animals developed tumor
growth. In the group of pretreated mice, tumor growth occurs in 7/14 animals (p<0.05),
indicating that the AGP Increase associated with previous ST1571 treatment can also
produce a significant biological effect. These results, taken together, support experimental
evidence to the negative effects of AGP on the therapeutic activity of STI571; they also
suggest and provide partial experimental validation to a strategy aimed at bypassing in vivo
resistance mediated by AGP, using molecules able to bind to AGP in competition with ST1571.

Example 8: Tablets with 4-1(4-methyl-I -piperazin-1 -ylmethyO-N-f4-methyl-3-1t4-(3-pyridinyl)- 2yrimidinyl1amino1phenvl)benzamide methanesulfonate, 13 -crystal form
Tablets containing 100 mg of the active substance named in the title are usually prepared In the following composition:

Composition
Active ingredient 100 mg
Crystalline lactose 240 mg
Avicel 80 mg
PVPPXL 20 mg
Aerosil 2 mg
Magnesium stearate 5 mg

447 mg

Preparation: The active substance is mixed with carrier materials and compressed on a tableting machine (Korsch EKO, punch diameter 10 mm).

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possible to obtain 4-(4-methylpiperazin-1.ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl)benzamide methanesulfonate in a crystal form which is not needle-shaped. This form is described in the present text as

-crystal form.

The acrystal form of 4-(4-methylpiperazin-1.ylmethyl)-N-[4-methyl-3-(4-pyridifl-3-yl)pyrimidin-2-ylamino)phenylbenzamide methanesulfonate has the advantage that its flow properties are substantially more favourable than those of the a-crystal form. This crystal form has the further advantage of being thermodynamically more stable at temperatures below 140C. Finally, the -crystal form is less hygroscopic than the a-crystal form and thus also stores better and is easier to process.

The invention relates to an acid addition salt of a compound of formula I comprising non-needle-shaped crystals, especially the 3-crystal form of the methanesulfonic acid addition salt of the compound of formula I.

The invention relates especially to a particular, essentially pure crystal form, preferably that which is referred to hereinafter as the p-crystal form, of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1 -ylmethyl)-N-4-methyl-3-(4-pyrid-3-yl)pyrimidin-2-ylamino)phenyllbenzamide methanesulfonate of formula I

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Where the term methanesulfonic acid salt of a compound of formula I or of 4-(4-methyl-piperazin-1 -ylmethyl)-N-4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenylJbenzamide is used hereinbefore and hereinafter, this is especially taken to mean the methanesulfonic acid salt of formula II.

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One of the advantages of the 3-crystal form is especially its more compact crystal form, which results in substantially more beneficial flow properties and thus in better processability of the methanesulfonic acid addition salt of a compound of formula I in the 3-crystal form versus the -crystal form, for example in the manufacture of pharmaceutical preparations.

It is true to say that the a-crystal form of the methanesulfonic acid addition salt of a compound of formula I is metastable at room temperature. However, the 3-crystal form of the methanesulfonic acid addition salt of a compound of formula I is the thermodynamically stable form at room temperature. Greater stability is thus to be expected.

Finally, the 3-crystal form is less hygroscopic than the a-crystal form of the methanesulfonic acid addition salt of a compound of formula I, as can be shown by the following table:

On measurement of the crystal forms up to the point where equilibrium is reached (no further adsorption) in a glass climatic chamber at 25°C and at the humidities shown below, the following water content values are found (the % values for the final water content refer to dry weight):

Relative humidity Final water content on adsorption
(%) a-crystal form

-crystal form
(%) (molar) (%) (molar)
12 0.14 0.05 0.08 0.02
33 0.18 0.06 0.10 0.03
46 0.14 0.05
54 0.13 0.04 0.14 0.05
66 0.07 0.02 0.09 0.03
75 0,49 0.16
85 0.18 0.06 0.16 0.05
93 40 13.1 0.15 0.05
97 63 20.8 23 7.5
100

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The invention relates also to a process for the treatment of warm-blooded animals suffering from said diseases, especially a tumour disease, wherein a quantity of the 3-crystal form of the methanesulfonic acid addition salt of a compound of formula I which is effective against the disease concerned, especially a quantity with antiproliferative and especially tumour-inhibiting efficacy, is administered to warm-blooded animals in need of such treatment. The invention relates moreover to the use of the 3-crystal form of the methanesulfonic acid addition salt of a compound of formula I for the inhibition of the above-mentioned tyrosine kinases, especially PDGF receptor kinase, v-abl kinase, and/or c-kit receptor kinase, or for the preparation of pharmaceutical compositions for use in treating the human or animal body, especially for the treatment of tumours, such as gliomas, ovarian tumours, prostate tumours, colon tumours, and tumours of the lung, such as especially small cell lung carcinoma, and tumours of the breast or other gynaecological tumours. Depending on species, age individual condition, mode of administration, and the clinical picture in question, effective doses, for example daily doses of about 1-2500 mg, preferably 1-1000 . mg, especially 5-500 mg, are administered to warm-blooded animals of about 70 kg bodyweight.

The invention relates also to pharmaceutical preparations which contain an effective amount, especially an effective amount for prevention or treatment of one of the said diseases, of the methanesulfonic acid addition salt of a compound of formula I in the - crystal form, together with pharmaceutically acceptable carriers which are suitable for topical, enteral, for example oral or rectal, or parenteral administration and may be inorganic or organic and solid or liquid. Especially tablets or gelatin capsules containing the active substance together with diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, and/or glycerin, and/or lubricants, for example silica, talc, stearic acid, or salts thereof, typically magnesium or calcium stearate, and/or polyethylene glycol, are used for oral administration, Tablets may likewise contain binders, for example magnesium aluminium silicate, starches, typically corn, wheat or rice starch, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if so desired, disintegrants, for example starches, agar, alginic acid, or a salt thereof, typically sodium alginate, and/or effervescent mixtures, or adsorbents, colouring agents, flavours, and sweetening
The pharmacologically active compounds of the present invention may further be used in the form of preparations for parenteral administration or infusion solutions. Such solutions

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are preferably isotonic aqueous solutions or suspensions, these possibly being prepared before use, for example in the case of lyophilised preparations containing the active substance either alone or together with a carrier, for example mannitol. The pharmaceutical substances may be sterilised and/or may contain excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubihsers, salts for the regulation of osmotic pressure, and/or buffers. The present pharmaceutical preparations which, if so desired, may contain further pharmacologically active substances, such as antibiotics, are prepared in a manner known per Se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes, and contain from about 1% to 100%, especially from about 1% to about 20%, of the active substance or substances.

The following Examples illustrate the invention without limiting the scope thereof. Ri-values are determined on TLC plates coated with silica gel (Merck, Darmstadt, Germany). The ratio of the solvents to one another in the solvent systems used is indicated by volume (v/v), and temperatures are given in degrees celsius (°C).

Eluents (gradients):
HPLC gradient:
0% b) in a) for 20 minutes, then 0% - 30% b) in a) for 10 minutes, then 30% b) in a) for 5

minutes.

Eluent a): Ion pairing reagent and methanol (420 ml + 580 ml)
Eluent b): Ion pairing reagent and methanol (40 ml + 960 ml)
Ion pairing reagent: 7.5 g 1-octanesulfonic acid dissolved in about 800 ml water, pH value adjusted to 2.5 with phosphoric acid, and diluted with water to 1000 ml.
Column: 150 x 3.9 mm, packed with Symmetry C18 51.1 (Waters), pre-equilibrated with eluent a).
Flow rate 1.2 ml/min, UV detection at 267 nm.

Examp

Example 1. Preparation of 3 -crystal form of 4-(4-methvlpiperazin-1 -ylmethvl)-N-14-methyl-3-4-pyridin-3-yl)pyrimmdin-2-ylamino1phenyl]benzamide methanesulfonate - Variant 1.
An 11% (w/w) suspension of 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)- pyrimidin-2-ylamino)phenyljbenzamide methanesulfonate in the a-crystal form is digested in

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

RadicaciOn No. 04-111533
Clasificación Internacional (IPC): A61 K9116, A61 K9/26
Concepto TØcnico No. 02832

Patente de Invenciôn P] Patente de Modelo de Utilidad D

Via Naciona(

Via PCT (fase nacional) E1 Cap.I F7 Cap. II D

No. Sol. Internacional PCT/EP03/04151
Fecha de Presentación Internal. 22 de Abril de 2003

Como resultado del examen de fondo, realizado con fundamento en el artIculo 48 de la SDecisiOn 486 de la ComisiOn de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 5 a 31 y 36 como se radicó inicialmente
Reivindicaciones: Folios 32 a 35 como se radicô inicialmente
Folios 79 a 82 modificaciones fase internacional
Folios 97 a 98 modificaciones fase nacional
Folios 118 a 119 modificaciones fase nacional
Folios 208 a 209 modificaciones fase nacional
Folios 241 a 242 modificaciones fase nacional
Prioridad: Folios: 01
23 de Abril de 2002, Reino Unido, 0209265.8
Respuesta del solicitante: Folios 113 y 117; Folios 199 a 207; Folios 235 a240

2. AnâIisis de la Prioridad

La fecha de prioridad del 23 de Abril de 2002 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

3. Modificaciones

Se acepta la preseritaciOri de la correspondiente solicitud divisional a este estudio de patentabilidad.

4. Objeto de la invención

Titulo de la solicitud: "Tableta con alta carga de fÆrmaco que comprende 4-(4-metilpiperazin-1 -ilmetil)-N-[4-metil-3-3(4-piridin-3-il)pirimidin-2-ilamino)fenil]- benzamida 0 las sales farmacØuticamente aceptables de la misma" Folio 1, En virtud de la respuesta presentada al oficio 10589, esta Oficina acepta el nuevo titulo, ya que el mismo cumple con los requisitos legales.

El objeto de la presente solicitud de patente de invenciOn consiste en una tableta del compuesto de fOrmula I.

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El problema planteado en esta solicitud es obtener una tableta de alta carga del fârmaco de fOrmula I con una proporciOn entre 30-80% en peso de la fracción activa. L

Para solucionar este problema tØcnico la solicitud en estudio proporciona una tableta del compuesto de fOrmula I o sus sales farmacØuticamente aceptables.

Clasificación Internacional de Patentes (IPC): A61K9/16, A61K9/26, A61K9/28, A61K47/32, A61K47/38, A61K31/505

5. De la solicitud de Patente

Reivindicaciones (artIculo 30 D 486)
La reivindicaciôn 3 se refiere al compuesto o su sal se encuentra en una cantidad entre 50 a 80% en peso de la fracción activa con base en el peso total de la tableta, intervalo de peso que no fue definido en la reivindicaciOn 1.

6. Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el Estado de la TØcnica es:

Fecha de presentación de la solicitud prioritaria: 23 de Abril de 2002

Considerando que la fecha de presentaciOn de la primera solicitud de patente de la cual se reivindica prioridad es: 23/04/2002 se encontraron los siguientes documentos del estado de la tØcnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

No Documento Titulo Fecha de

publicacion
Combinations of a receptor

Dl WO 01/47507 tyrosine kinase with an organic 05/07/2001 compound capable of binding to
a1-acidic_glycoprotein
Crystal modification of a N-phenyi-

WO 99/03854 2-pyrimidineamine derivative, 28/01/1999 L processes for its manufacture and

its use I

7. Respuesta a los argumentos del solicitante

El solicitante realiza modificaciones (Ver Folio 235) al capitulo reivindicatorio, el cual es aceptado por parte de esta oficina.

El solicitante se refiere en el Folio 236 y en adelante, a los documentos WO 01/47501 (Dl) y WO 99/03854 (D3), en cuanto al nivel inventivo y argumenta: "Dl no revela expresamente tabletas que contienen imatinib en cantidades superior al 30%, mientras que la presente invenciOn se refiere a tabletas que comprenderi entre un 30% y 80% del compuesto" y ademÆs argumenta ’No existe ninguna invitaciOn en el arte previo a producir tabletas con alta carga de imatinib" (peje.>40-65%)

Se remite al solicitante al ejemplo 8 (Ver pÆgina 18, compuestoIII, pÆgina31, lineas 7-12, pÆgina 47) de Dl, donde se ejempUfica la composiciOn en tabletas y en la pÆgina34, 21 pÆrrafoel documento sugiere concentraciones para el fÆrmacoentre 0.0001%-95% y donde las tabletas ademÆspueden tener una dosis de 5mg-1.5g.