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Benævnelse: FREMGANGSMÅDE TIL OPRENSNING AF METHYL-[4,6-DIAMINO-2-[(2-FLUOROBENZYL)-1H-PYRAZOLO[3,4-B]PYRIDIN-3-YL]PYRIMIDIN-5-YL]METHYLCARBAMAT

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WO-A1-2005/095451
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CHEMMEDCHEM, Bd. 4, Nr. 5, Mai 2009 (2009-05), Seiten 853-865, XP002622814, ISSN: 1860-7179, DOI: DOI:10.1002/CMDC.200900014 in der Anmeldung erwähnt


Fortsættes...
The present invention relates to a process for purifying methyl \(4,6\text{-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}\)methylcarbamate of the formula (I)

![Chemical structure of (I)](image)

10 In the process for purifying the crude product of the compound of the formula (I) for use as a pharmaceutically active compound, methyl \(4,6\text{-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}\)methylcarbamate sulphonyldimethane (1:1), i.e. a compound of the formula (II)

![Chemical structure of (II)](image)

is isolated as intermediate or is generated as intermediate in this purification process, if appropriate present in a mixture.

20 The compound of the formula (I) acts as a stimulator of soluble guanylate cyclase and can be used as an agent for the
prophylaxis and/or treatment of cardiovascular disorders such as, for example, for the treatment of high blood pressure and of heart failure, stable and unstable angina pectoris, peripheral and cardiac vascular disorders, of arrhythmias, for the treatment of thromboembolic disorders and ischemias such as myocardial infarction, stroke, transitory and ischemic attacks, disturbances of peripheral blood flow, prevention of restenoses such as following thrombolysis therapies, percutaneous transluminal angioplasties (PTA), percutaneous transluminal coronary angioplasties (PTCA), bypass and for the treatment of arteriosclerosis, asthmatic disorders and diseases of the urogenital system such as, for example, prostate hypertrophy, erectile dysfunction, female sexual dysfunction, osteoporosis, glaucoma, pulmonary hypertension, gastroparesis and incontinence.

The preparation of the compound of the formula (I) and its purification are known in principle. WO 03/095451 describes the preparation of the compound of the formula (I) by the route below.

1. catalytic hydrogenation in the presence of Raney nickel
2. addition of hydrochloric acid

(III)

(IV)

(V)

(VI)
Here, initially 2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-[(E)-phenyldiazenyl]pyrimidine-4,6-diamine of the formula (III) is cleaved by catalytic hydrogenation, and the resulting trisamino compound is isolated as 2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-4,5,6-pyrimidinetriamine trihydrochloride of the formula (IV). This trihydrochloride is then reacted with methyl chloroformate of the formula (V) in the solvent pyridine to give methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinylcarbamate of the formula (VI). Alternatively, ChemMedChem 2009, 4, 853-865 describes that the trisamino compound is isolated as trihydrochloride and the HCl-free base is then generated by extraction with aqueous NaHCO₃ solution and the free base is reacted with methyl chloroformate of the formula (V) in the solvent pyridine to give the compound of the formula (VI). The compound of the formula (VI) is then reacted with methyl iodide of the formula (VII) in the presence of a base to give the crude product of the compound of the formula (I). The crude product of the compound of the formula (I) is purified according to the experimental procedure of Example 8 of WO 03/095451 and the comparable description in ChemMedChem 2009, 4, 853-865 by triturating the crude product with dichloromethane/THF, intermediate isolation of the product triturated with dichloromethane/THF by filtration, boiling the isolated solid with methanol, intermediate isolation of the solid boiled with methanol by filtration, dissolution of the solid in a mixture of dioxane,
dichloromethane and methanol in the presence of activated carbon, removal of the activated carbon by filtration through kieselguhr or Celite, concentration of the filtered solution to dryness, trituration of the solid concentrated to dryness with methanol, isolation of the solid triturated with methanol by filtration and (not described in WO 03/0945451 in Example 8 or ChemMedChem 2009, 4, 853-865, but objectively required) drying. Alternatively, a crude product of the compound of the formula (I) concentrated to dryness can be purified in poor yields by preparative chromatography (RP-HPLC).

This synthesis and the purifications have a number of disadvantages which are very unfavourable for an industrial realization on a large scale.

Particularly disadvantageous are the purification processes for the crude product of the formula (I). An effective purification is a conditio sine qua non for use as a pharmaceutically active compound. The described purification via RP HPLC, i.e. the chromatographic purification, is a laboratory method, the realization of which on an industrial scale is very expensive. In addition, the stated yield of only 29% for the synthesis step to the crude product of the formula (I) and its purification is very low. The alternative preparation and purification method is very complicated. It comprises a total of 5 isolations of solids (2 concentrations to dryness and 3 filtrations), and, as already mentioned above, concentrations to dryness on an industrial scale are very unfavourable. Altogether, when carrying out a chemical step, a number of 5 isolations of solids for the preparation and purification of a pharmaceutically active compound on an industrial scale is very disadvantageous. Accordingly, it was the object to provide a simplified process which is safe and can also be carried out advantageously on an industrial scale and which affords an active compound in high yield and high purity in pharmaceutically acceptable quality.

Surprisingly, we have now found a process for purifying methyl
{4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate of the formula (I)

\[
\text{H}_2\text{N} \quad \begin{array}{c}
\text{O} \\
\text{Me}
\end{array} \\
\text{N} \\
\text{N} \\
\text{F}
\]

for its use as a pharmaceutically active compound. This novel process differs from the processes known to date in the following point:
The purification of the crude product of the formula (I) for use as pharmaceutically active compound is carried out via the compound methyl \{4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl\}methylcarbamate sulphinyldimethane (1:1), i.e. a compound of the formula (II) as isolated intermediate or generated in a mixture

\[
\text{H}_2\text{N} \quad \begin{array}{c}
\text{O} \\
\text{CH}_3
\end{array} \\
\text{NH}_2 \\
\text{H}_2\text{C} \quad \begin{array}{c}
\text{S} \\
\text{CH}_3
\end{array} \\
\text{F}
\]

By virtue of this difference, it is possible to overcome the disadvantages of the processes known to date and to obtain an active compound in high yield and high purity and pharmaceutically acceptable quality.

The process according to the invention for purifying the
compound of the formula (I) via the intermediate of the formula (II) is described in detail below.

**Purification of the crude product of the compound of the formula (I)**

According to the invention, the crude product of the formula (I) is purified for use as pharmaceutically active compound. To this end, initially, a mixture is formed which contains high amounts of the compound of the formula (II) as intermediate.

![Chemical structures](image)

(I) (crude product)  
(II)

To this end, the crude product of the formula (I) is dissolved in DMSO, if appropriate in the presence of a pharmaceutically acceptable simple solvent from the class of the ketones, ethers, esters or alcohols. Examples of such solvents which may be mentioned are: methanol, ethanol, isopropanol, 1-butanol, 2-butanol, ethyl acetate, isopropyl acetate or propyl acetate, butyl acetate, tert-butyl methyl ether, diisopropyl ether, acetone, methyl ethyl ketone, methyl isobutyl ketone, etc. Preference is given to ethanol, isopropanol, ethyl acetate, isopropyl acetate, butyl acetate, methyl ethyl ketone, methyl isobutyl ketone; particular preference is given to ethyl acetate. It is also possible to use mixtures of these solvents.

DMSO is added in an amount of from 100 to 750% by weight,
preferably from 150 to 500% by weight, based on the amount of the crude product of the formula (I) employed.

If appropriate, activated carbon may be added to this mixture in an amount of from 0.25 to 35% by weight, preferably from 0.5 to 20% by weight, based on the amount of the crude product of the formula (I) employed.

To form a solution, the mixture is heated to 40-120°C, preferably 50-100°C.

To form a pharmaceutically acceptable product of the formula (I), the solution has to be filtered. The filtration has to be carried out independently of whether activated carbon was added or not.

The amount of the pharmaceutically acceptable solvent which, in addition to DMSO, is added to the solution of the crude product of the formula (I), i.e. used prior to the filtration, is from 25 to 200% by weight, preferably from 40 to 100% by weight, based on the DMSO.

The filtration is carried out hot, the temperatures are 40-120°C, preferably 50-100°C.

After the filtration, a pharmaceutically acceptable solvent, preferably the same solvent as above, is added to the hot filtrate. This results in a crystallization of the product of the formula (II).

The total amount of solvent added before and after the filtration is from 200 to 1500% by weight, preferably 400-1200% by weight, based on the DMSO.

The addition temperature is 30-110°C, preferably 35-90°C.

Prior to the isolation of the solid which contains high amounts of the compound of the formula (II), to bring the precipitation to completion, the mixture is cooled to a temperature range of 0-35°C, preferably to an ambient temperature of, for example, 20-30°C.
The isolation is carried out using customary isolation devices such as a nutsche filter or a centrifuge. To remove the mother liquor, the isolated material is, during isolation, washed with a pharmaceutically acceptable solvent, the same solvent as above being preferred.

After the DMSO redissolution, the isolated material contains high amounts of the product of the formula (II). In addition, small amounts of the product of the formula (I) may also usually precipitate directly without forming a solvate with DMSO. Also possible is the formation of solvates of a different stoichiometry or the formation of solvent adducts with no fixed stoichiometry. Moreover, DMSO may also be present in unbound form as an adhering residual solvent. The content of DMSO in the isolated material is usually from 10 to 25% by weight, preferably 12-17%. According to the invention, the product of the formula (II) is particularly preferably formed in the form of this mixture and used for preparing the purified product of the formula (I).

The product of the formula (II) obtained in this manner can now be dried or, alternatively, be used in moist form comprising solvent residues, i.e. adhering DMSO and the precipitation solvent(s), for conversion into the purified product of the formula (I).

The compound of the formula (II) is novel. It can be prepared in pure form as described in the working examples below and be characterized analytically.

For pharmaceutical use, the DMSO has to be removed from the product of the formula (II) or the mixture comprising high amounts of the compound of the formula (II).
To this end, the product of the formula (II) or the isolated mixture comprising high amounts of the product of the formula (II) is boiled in a pharmaceutically acceptable solvent from the class of the ketones, ethers, esters or alcohols. Examples of such solvents which may be mentioned are: methanol, ethanol, isopropanol, 1-butanol, 2-butanol, ethyl acetate, isopropyl acetate or propyl acetate, butyl acetate, tert-butyl methyl ether, diisopropyl ether, acetone, methyl ethyl ketones, methyl isobutyl ketone, etc. Preference is given to ethanol, isopropanol, ethyl acetate, isopropyl acetate, butyl acetate, methyl ethyl ketone, methyl isobutyl ketone. It is also possible to use mixtures of these solvents. Particular preference is given to ethyl acetate or a mixture of ethyl acetate with ethanol.

Boiling takes place at reflux of the solvent in question or, if appropriate, at slightly elevated pressure. The temperature is 50-150°C, preferably 80-120°C.

The process according to the invention offers marked advantages compared to the prior art. Surprising was in particular that the purification of the crude product of the formula (I) for pharmaceutical use takes place in particular by redissolution in a DMSO-containing solvent mixture and that the novel compound of the formula (II) is obtained as an intermediate in this step, if appropriate in a mixture in high proportions. By this step, all impurities are removed except
for small residual amounts, so that, after the DMSO content has been removed by simple boiling, a highly pure solid of the formula (I) remains. This solid is generally colourless to very slightly yellow and the analytical purity (HPLC) is markedly above 98% by weight, which is very advantageous for pharmaceutical use.

The process can be carried out safely technically and allows a production on an industrial scale. It can be adapted flexibly to existing apparatus in the plant. In a particularly preferred embodiment, in the purification of the crude product of the formula (I), the intermediate isolation of the product of the formula (II) or of the mixture comprising high amounts of the compound of the formula (II) is carried out in a nutsche filter dryer. Subsequent removal of the DMSO from the product of the formula (II) isolated as an intermediate in the nutsche filter dryer is carried out by direct addition of solvent to the nutsche filter dryer with or without intermediate drying of the product of the formula (II). This avoids open handling of the solid of the product of the formula (II) with the associated risk of contamination.

**Experimental part**

**Abbreviations and acronyms:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>abs.</td>
<td>absolute</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization (in MS)</td>
</tr>
<tr>
<td>d</td>
<td>day(s)</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulphoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron-impact ionization (in MS)</td>
</tr>
<tr>
<td>ent</td>
<td>enantiomer/enantiomerically pure</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization (in MS)</td>
</tr>
<tr>
<td>GC-MS</td>
<td>gas chromatography-coupled mass</td>
</tr>
</tbody>
</table>
The examples below illustrate the invention, but the invention is not limited to the examples.

5 Reference

Example 1

Preparation of 2-[(1-(2-fluorobenzyl))-1H-pyrazolo[3,4-b]pyridin-3-yl]-4,5,6-pyrimidinetriamine (VIII)

In a pressure autoclave, 1100 g of the compound of the formula (III) were suspended in 5.4 l of DMF. 44 g of a conventional water-moist (about 50%) 5% Pd/carbon catalyst were added, and the sealed autoclave was, after inertization with nitrogen and application of hydrogen, hydrogenated at a hydrogen pressure of 65 bar and an internal temperature of about 60°C for about 18 h. After cooling to about 25°C, venting and inertization, the autoclave content was removed, rinsing with 650 ml of DMF.

Three of such reactions carried out in the same manner were combined, the old catalyst was filtered off, the filtercake was rinsed with 1.1 l of DMF and the filtrate was concentrated
under reduced pressure to about one third of its mass. Successively, 8.25 l of methanol and 8.25 l of water were metered into the residue of about 6.5 kg, to bring the crystallization to completion, the suspension was cooled to about 5°C and the solid was filtered off and washed with methanol/water (1:1 vol). The product was dried at 50°C under reduced pressure. The weight was 2415 g, which corresponds to 91.8% of theory. The content of the target product of the formula (VIII) (free base) was >98 area% or >97% by weight. The most significant impurities were DMF (about 0.8% by weight) and water (about 0.5% by weight).

Reference

Example 2

Preparation of methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinylcarbamate (VI)

3063 g of the compound of the formula (VIII) and 30.7 l of technical grade isopropanol were initially charged in a reaction vessel. With stirring, 1641 g of dimethyl dicarbonate were metered in at 20-25°C, and the mixture was stirred at this temperature for 22 h. The precipitated product was filtered off with suction, washed with industrial grade isopropanol and dried at 50°C under reduced pressure. The weight of the product obtained was 3748 g or 105.9% of theory. The product of the formula (I) contained, inter alia, about 4.7% of isopropanol virtually unremovable by drying (partially, an isopropanol solvate was present), and the analytical content was 89.5% by weight (HPLC). Based on this content, the yield was 94.8% of theory.

Reference

Example 3

Preparation of 2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-4,5,6-pyrimidinetriamine (VIII)

In a pressure autoclave, 300 g of the compound of the formula (III), 1600 ml of DMF and 60 g of water-moist Raney nickel
were initially charged and, after inertization, hydrogenated at an internal temperature of 60°C and a hydrogen pressure of 65 bar for about 18 h. After cooling and venting, the old catalyst was filtered off and rinsed with 100 ml of DMF. The filtrate was concentrated under reduced pressure to 534.5 g, and at 35-40°C, 750 ml of methanol and then, after cooling, at 0-5°C, 750 ml of water were metered into the residue. The solid was filtered off and dried at 50°C under reduced pressure. The weight was 219.7 g or 91.8% of theory.

Reference

Example 4

Preparation of methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinylcarbamate (VI)

In a reaction vessel, 1.50 kg of the compound of the formula (VIII) were initially charged in 14.25 l of isopropanol, and the mixture was heated with stirring to 35°C. 531 g of methyl chloroformate were, at a steady rate, metered in over a period of 30 min, rinsing with 750 ml of isopropanol, and the mixture was stirred at 35°C for 16 h. The mixture was then heated to 50°C and 3.85 l of methanol and 606 g of triethylamine were metered in with stirring at 50°C, rinsing with 450 ml of methanol. The mixture was then stirred at 50°C for 1 h, cooled to RT and stirred at RT for 1 h. The suspended solid was filtered off with suction, washed twice with in each case 3.0 l of isopropanol/methanol (4:1) and once with 3.0 l of isopropanol and sucked dry. The moist product was dried at 50°C for 1 h and then at 100°C for 22 h in a vacuum drying cabinet. The weight of the product obtained was 1.793 kg or 103.3% of theory. The product of the formula (VI) contained 6.45% of isopropanol virtually unremovable by drying (partially, an isopropanol solvate was present), and the analytical content was 87.9% by weight (HPLC). Based on this content, the yield was 90.8% of theory.

Comparative example 5
Preparation of methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate (I)

At 20-25°C, 1630 g of the compound of the formula (VI) was suspended in 16.3 l of THF. The suspension was cooled to from -6 to -4°C, and 3480 g of a 1M solution of bis(trimethylsilyl)sodium amide were metered in. The mixture was stirred, 596 g of methyl iodide were metered in, the mixture was stirred briefly and slowly allowed to warm to about 5°C. The mixture was stirred at this temperature until the reaction had ended (about 4 h). The reaction mixture was washed 4 times with 4.1 l of 15% strength ammonium chloride solution. The organic phase was concentrated by evaporation to a residue of about 6.4 kg, and the temperature was adjusted to about 25°C. The precipitated solid was filtered off, washed with a total of 3 l of THF and dried at 50°C under reduced pressure. This gave 1112 g of the crude product of the formula (I). This corresponded to a yield of 75.2% of theory.

Example 6

Preparation of a mixture consisting of methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate (I) and methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]methylcarbamate sulphinyldimethane (II) with high amounts of the product of the formula (II)

9.0 g of a crude product of the formula (I) which had been prepared in a manner comparable to Comparative Example 5 were dissolved in 16 ml of DMSO at 100°C. (The clarification by filtration which would have been required at this point to achieve a pharmaceutically acceptable product quality was dispensed within this laboratory experiment). The mixture was
then allowed to cool to 75°C, 110 ml of ethyl acetate were added and the mixture was cooled slowly to about 25°C. The precipitated solid was filtered off, washed with a total of 28 ml of ethyl acetate and dried at 50°C under reduced pressure. The weight was 9.6 g or 90.0% of theory.

Example 7

**Preparation of purified methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate (I)**

The entire amount of the product of the formula (II) prepared in the above Example 6 was stirred in 135 ml of ethyl acetate at reflux (about 78°C) for 1 h and cooled to about 25°C. The solid was filtered off with suction, washed with a total of 36 ml of ethyl acetate and dried under reduced pressure. The weight was 7.6 g or 93.8% of theory. The content of the product was markedly above 98% by weight (HPLC). As solvent, ethyl acetate was present in an amount of about 0.2%. The DMSO content was below 0.1%.

Example 8

**Preparation of purified methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate (I) with intermediate isolation of a mixture comprising high amounts of methyl [4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]methylcarbamate sulphonyldimethane (II) as moist product**

193.5 g of a crude product of the formula (I) which had been prepared in a manner comparable to Comparative Example 5 were dissolved in 344 ml of DMSO and 172 ml of ethyl acetate at about 96°C. 19.4 g of activated carbon and 172 ml of ethyl acetate were then added, and the hot mixture was stirred. The hot mixture was then filtered off to remove the activated carbon, rinsing with 172 ml of ethyl acetate. The temperature
of the filtrate was adjusted to 78°C, and 1850 ml of ethyl acetate were added slowly. Over about 2-3 h, the mixture was cooled to about 25°C, and the solid was filtered off and washed with a total of 772 ml of ethyl acetate. The moist product, which contained high amounts of the compound of the formula (II) in a mixture was suspended in 2900 ml of ethyl acetate, heated at reflux for 1 h and cooled to about 25°C. The solid was filtered off with suction, washed with a total of 774 ml of ethyl acetate and dried at 50°C under reduced pressure. The weight obtained was 155.1 g or 80.2% of the starting material. The content of the product was markedly above 98% by weight (HPLC). As solvents, virtually only ethyl acetate and DMSO were present in small amounts.

Example 9

Preparation and analytical characterization of methyl [4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]methylcarbamate sulphanyldimethane (II)

14.8 g of a crude product of the formula (I) which had been prepared in a manner comparable to Comparative Example 5 were dissolved in 28.9 g of DMSO and 11.85 g of ethyl acetate at about 94°C. 1.5 g of activated carbon Norit A-Supra and a further 11.85 g of ethyl acetate were then added, the mixture was stirred at reflux (88-90°C) for 1 h and the hot mixture was then filtered to remove the activated carbon. The solid, some of which had already precipitated, was re-dissolved by warming to about 78°C, and the solution was then allowed to cool slowly. The precipitated solid was filtered off with suction at RT, washed three times with in each case 50 ml of ethyl acetate and dried in a drying cabinet at 30°C for 18 h. This gave 9.2 g or 52.5% of theory of a slightly yellowish crystal powder of the compound of the formula (II).

HPLC: 99.90 area% (without taking the DMSO into account)
DMSO (GC): 14.7% by weight

¹H-NMR (400 MHz in DMF-d₇):
d = 2.59 (s, about 6H, 2 CH₃ at DMSO), 3.13 (s, 3H, N-CH₃),
3.58 + 3.67 (two s, 3H, hindered rotation at O-CH₃), 5.91
(s, 2H, -CH₂-), 6.53 (s, 4H, 2 -NH₂), 7.05-7.40 (m, 5H, 4
aromatic H at the o-fluorobenzyl substituent and 1H at the
pyrido ring meta to the pyrido nitrogen), 8.60 (dd, 1H, at the
pyrido ring ortho to the pyrido nitrogen), 9.12 (dd, 1H, at
the pyrido ring para to the pyrido nitrogen).
Elemental analysis:
found      C: 52.2% calculated      C: 52.79%
H: 4.9%      H: 5.03%
N: 22.7%      N: 22.39%
Patentkrav

1. Fremgangsmåde til oprensning af methyl-\{4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl\}methylcarbamat med formel (I),

   ![Molecule Formel](image)

   kendetegnet ved, at råproduktet af forbindelsen med formel (I) opløses i dimethylosulfoxid, og den i denne forbindelse opståede methyl-\{4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl\}methylcarbamatsulfinyldimethan med formel (II),

   ![Molecule Formel](image)

   isoleres, og dimethylosulfoxidet efterfølgende fjernes igen ved udkogning i et farmaceutisk acceptabelt opløsningsmiddel.

2. Methyl-\{4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl\}methylcarbamatsulfinyldimethan med formel
(II).