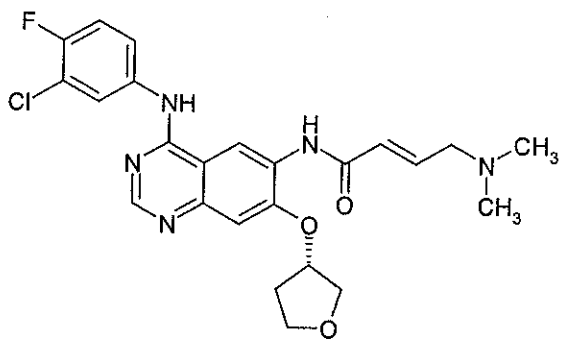
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Method for the production of amino crotonyl compounds

The invention relates to an improved process for preparing aminocrotonyl compounds such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline and the physiologically acceptable salts thereof, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, as well as 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate and the use thereof for preparing pharmaceutical compositions.

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]-amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline has the following structure:

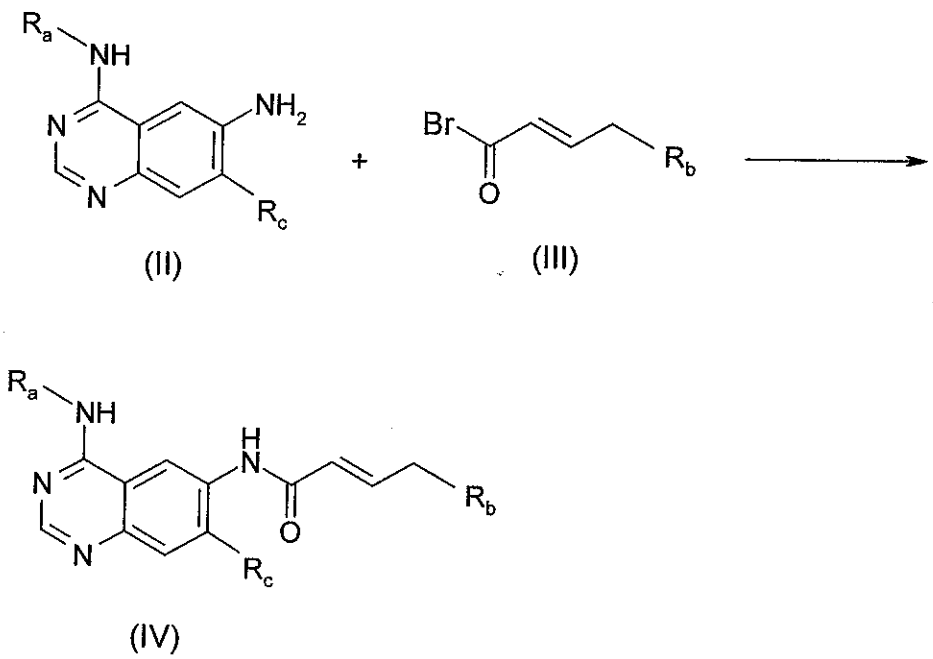


(I)

and is already known from WO 02/50043, which describes compounds with valuable pharmacological properties, including in particular an inhibiting effect on signal transduction mediated by tyrosinekinases and an inhibitory effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R). Therefore, compounds of this type are suitable for the treatment of diseases, particularly for the treatment of tumoral diseases, diseases of the lungs and respiratory tract and diseases of the gastrointestinal tract and bile duct and gall bladder.

WO 02/50043 discloses a method of preparation wherein aminocrotonyl compounds (IV) such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline are prepared in a one-pot reaction from the corresponding aniline component (II), bromocrotonic acid (III), oxalyl chloride and a secondary amine (see Diagram 1).

Diagram 1:



In this process the yield was at most 50 %. In addition, purification was generally carried out by column chromatography. Therefore, the method of preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline was not suitable on an industrial scale. Furthermore, the method had the disadvantage that bromocrotonic acid is not commercially available in large amounts and also the corresponding methyl bromocrotonate is only available in a purity of approx. 80 %. These circumstances also militate against the suitability of this process for the industrial production of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline.

In the light of the above disadvantages of the known method of production, the aim of the present invention is to provide a process which allows the production of aminocrotonylarylamides, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline, using highly pure starting materials which are readily available and without any great technical expenditure. This new process should therefore also be suitable for synthesis on an industrial scale and hence for commercial application.

This aim is achieved by the process according to the invention for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline and other aminocrotonyl compounds. In addition to being industrially practicable with high yields the method of synthesis according to the invention also has the advantages of very good chemical purities and a low cis content of less than 0.1%.

In the process according to the invention the corresponding aminoaryl compound (V) is reacted with a di-(C_{1-4}-alkyl)-phosphonoacetic acid, preferably with diethylphosphonoacetic acid, in suitable solvents, after corresponding activation, preferably with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole or propanephosphonic anhydride, particularly preferably with 1,1-carbonyldiimidazole, according to Diagram 2. The solvent used may be for example tetrahydrofuran (THF) , dimethylformamide (DMF) or ethyl acetate.

The activation may be carried out by any possible method of amide linking, i.e. for example with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole, DCC (N,N-dicyclohexylcarbodiimide), EDC (N´-(dimethylaminopropyl)-N-ethylcarbodiimide), TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), thiazolidine-2-thione or by conversion into the corresponding acid chloride, possibly using thionyl chloride. If desired the activation may be carried out using organic bases such as triethylamine or pyridine, while DMAP (dimethylaminopyridine) may additionally be added. Suitable solvents include DMF, THF, ethyl acetate, toluene, chlorinated hydrocarbons or mixtures thereof.

In the formulae that follow

X denotes a methyne group or a nitrogen atom,

R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and

R^1 denotes a straight-chain or branched C_{1-4}-alkyl group.

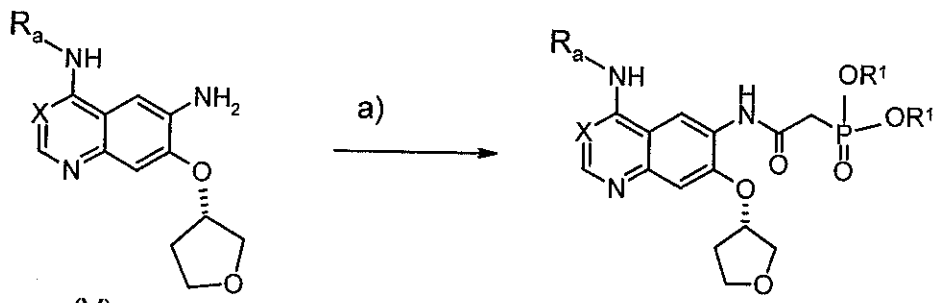
The process is preferably used for compounds wherein

X denotes a nitrogen atom,

R_a denotes a 3-chloro-4-fluorophenyl group and

R^1 denotes an ethyl group.

Diagram 2:

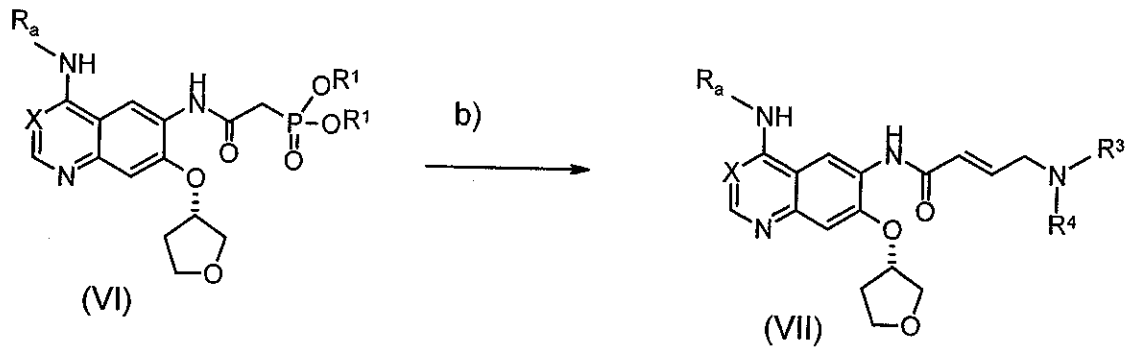


(V) (VI)

a) di-(C_{1-4}-alkyl)-phosphonoacetic acid, activating agent

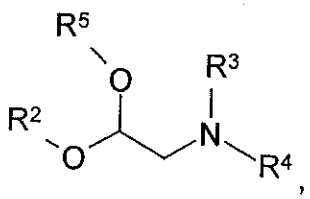
The arylamide (VI) thus obtained in a high yield and high purity is reacted with the corresponding 2-aminoacetaldehyde using suitable organic or inorganic bases in the sense of a Wittig-Horner-Emmons reaction (Diagram 3). This reaction may be carried out directly or after isolation of the compound (VI), for example by precipitation by the addition of tert-butylmethyl ether, for example. Suitable bases include for example DBU (1,5-diazabicyclo[4.3.0]non-5-ene), sodium hydroxide and potassium hydroxide, of which sodium hydroxide and potassium hydroxide are preferred and potassium hydroxide is particularly preferred. Instead of the aldehyde a corresponding equivalent, e.g. a hydrate or acetal, may be used, from which the aldehyde is released (beforehand or *in situ*).

Diagram 3:



b) aldehyde, base, THF/water

The acetals used may be for example compounds of the following general type:



,

wherein R^2 to R^5 in each case represent a straight-chain or branched C_1-C_4-alkyl group, while the groups may be identical or different.

Preferably

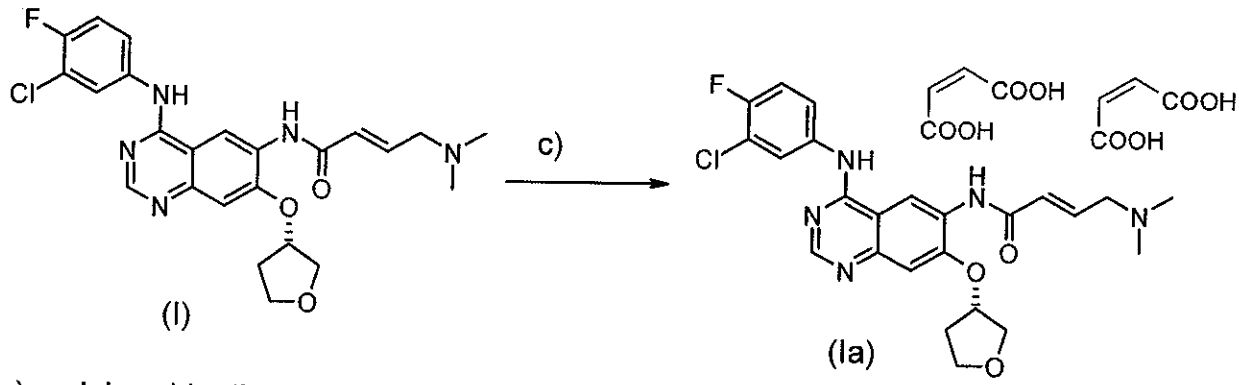
R^3 and R^4 in each case represent a methyl group and

R^2 and R^5 in each case represent an ethyl group.

The aminocrotonylarylamide of formula (VII) thus obtained, for example 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline of formula (I), may then be converted into the salts thereof, particularly the physiologically acceptable salts thereof, by methods known *per se*. Preferably they are converted into fumarates, tartrates or maleates. The dimaleate of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline of structural formula (Ia) and the conversion of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-

dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline into its dimaleate as shown in Diagram 4 are particularly preferred. To do this the compound (I) is dissolved in a suitable solvent, such as for example methanol, isopropanol, n-butanol or ethanol, optionally with the addition of water, preferably ethanol, and combined with crystalline maleic acid or a maleic acid solution, with heating. When ethanol is used as solvent the work is preferably done at a temperature of between 60 and 75 °C using an ethanolic maleic acid solution. The reaction conditions are preferably selected so that the desired salt crystallises out as quickly as possible. Preferably approx. 2 equivalents of maleic acid are used. After crystallisation has set in the mixture is cooled to ambient temperature, stirred and the crystals consisting of compound (Ia) are separated off.

Diagram 4:



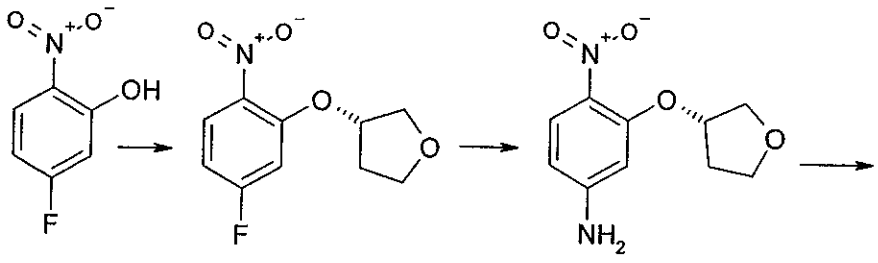
c) maleic acid, ethanol

The starting compound of formula (V) may for example be prepared as follows in accordance with methods known from the literature.

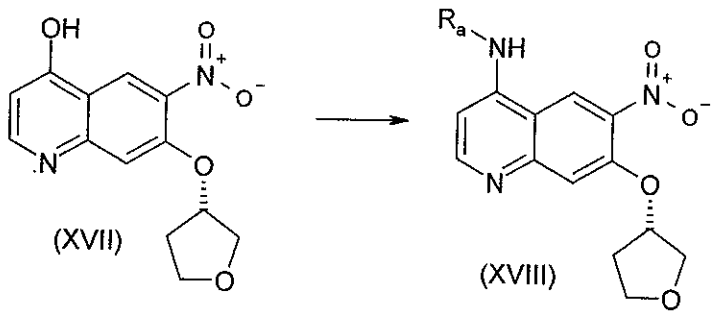
The quinoline components of formula (V), wherein X = CH, may be obtained starting from commercially obtainable 3-fluoro-6-nitrophenol (XIV) by alkylation, exchanging the fluorine atom for an amino group and reacting with ethoxyacrylic acid esters, ethoxymethylene-cyanoacetic acid esters or ethoxymethylene-malonic acid esters (Diagram 5a).

The compound thus obtained (XVII) is then converted into the compound (XVIII) as described in Diagram 6 for the quinazoline analogue

Diagram 5a:



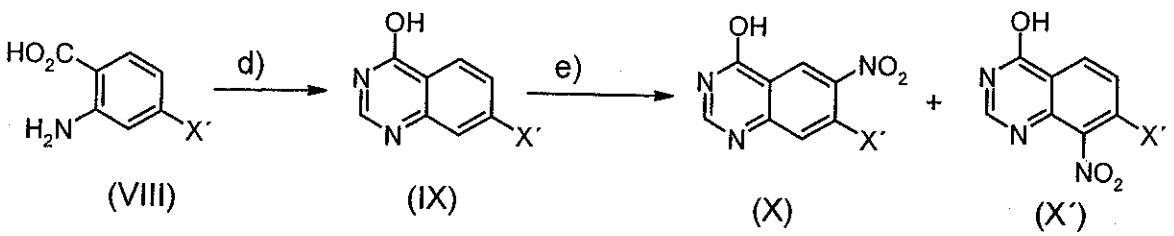
(XIV) (XV) (XVI)



(XVII) (XVIII)

To prepare the compound (V) wherein X = N the following procedure is used: Starting from commercially obtainable 4-chloro-anthranilic acid (VIII; X = Cl) the quinazolinone (IX) is obtained by reaction with formamidine-acetate, and is then nitrogenated using sulphuric acid and concentrated nitric acid (Diagram 5b). Alternatively, 4-fluoro-anthranilic acid may also be used as the starting material.

Diagram 5b:



(VIII) (IX) (X) (X')

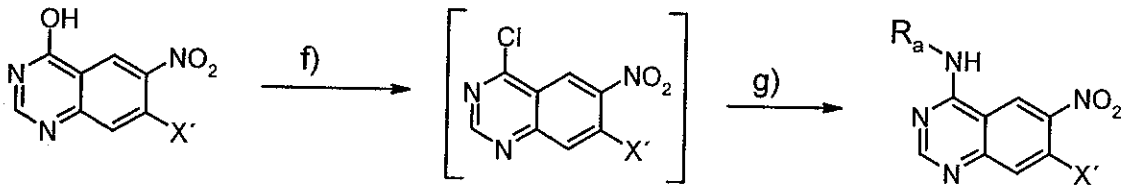
a: X' = Cl
b: X' = F

d) formamidine-acetate

e) H_2SO_4, HNO_3 conc.

The desired regioisomer (X) of the nitrogenation products thus obtained is then chlorinated, and the chlorination product (XI) is reacted *in situ* with the corresponding amine (Diagram 6).

Diagram 6:



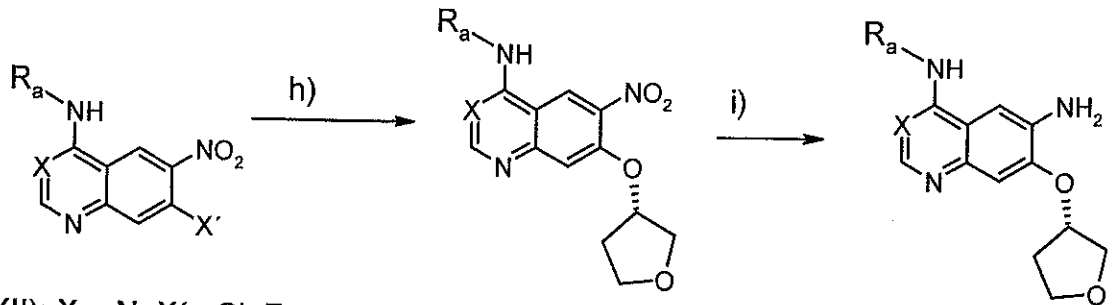
(X) (XI) (XII)

f) $SOCl_2$, acetonitrile

g) R_aNH_2

The compound of formula (XII) thus obtained is reacted with (*S*)-(+)-3-hydroxytetrahydrofuran to form compound (XIII). Hydrogenation of compound (XIII) or compound (XVIII) from Diagram 5a then yields the starting compound (V) (diagram 7).

Diagram 7:



(XII): X = N, X′= Cl, F

(XIII): X = N
(XVIII): X = CH

(V)

h) (*S*)-(+)-3-hydroxy-tetrahydrofuran

i) H_2

The invention also relates to 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate. This salt is particularly suitable for pharmaceutical use as it exists in only one crystalline modification, which is moreover anhydrous and very stable.

For pharmaceutical use an active substance not only has to exhibit the desired activity, but must also conform to additional requirements in order to be allowed to be used as a pharmaceutical composition. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restrictive, examples of these parameters are the stability of effect of the starting material under various environmental conditions, stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the pharmaceutical compositions should therefore have a high stability which must be guaranteed even under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in pharmaceutical formulations might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g. by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the medicament is exposed to the environment without being protected from damp in any way. Preferably a pharmaceutically active substance should therefore have only limited hygroscopicity.

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 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. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible.

This problem is solved by 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate has a melting point of 178°C (cf. the thermoanalysis shown in Figure 2). The crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate was investigated further by X-ray powder diffraction. The diagram obtained is shown in Figure 1.

The following Table lists the data obtained in this analysis:

Table: X-ray powder reflections and intensities (standardised) of the 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate

2-Θ [°]	**d-value [Å]**	**intensity I/I_o [%]**
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4

29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.467	1
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5

In the preceding Table the value "2 Θ [°]" denotes the angle of diffraction in degrees and the value "d_{hkl} [Å]" denotes the specified distances in Å between the lattice planes.

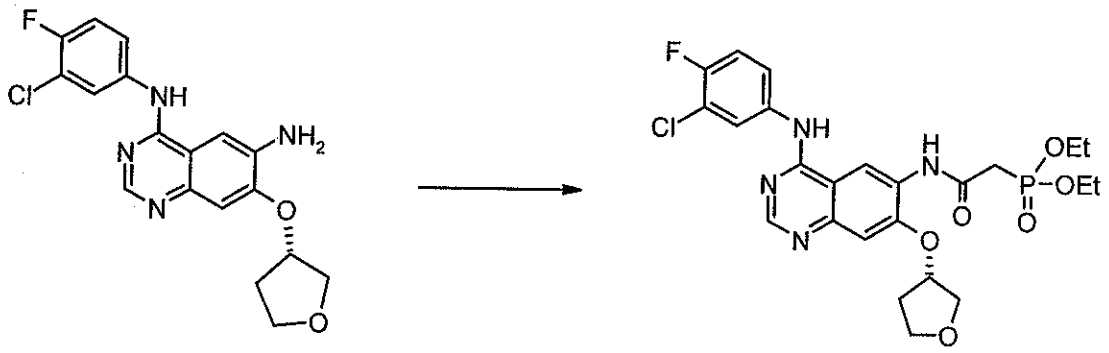
The x-ray powder diagrams were recorded, within the scope of the present invention, using a Bruker D8 Advanced diffractometer fitted with a PSD detector and a Cu anode as the x-ray source (CuK_{α_1} radiation, λ = 1.5418 Å, 40 kV, 40 mA).

The following Examples are intended to illustrate the invention:

Examples:

Example 1

Diethyl {[4-(3-chloro-4-fluoro-phenylamino)-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate



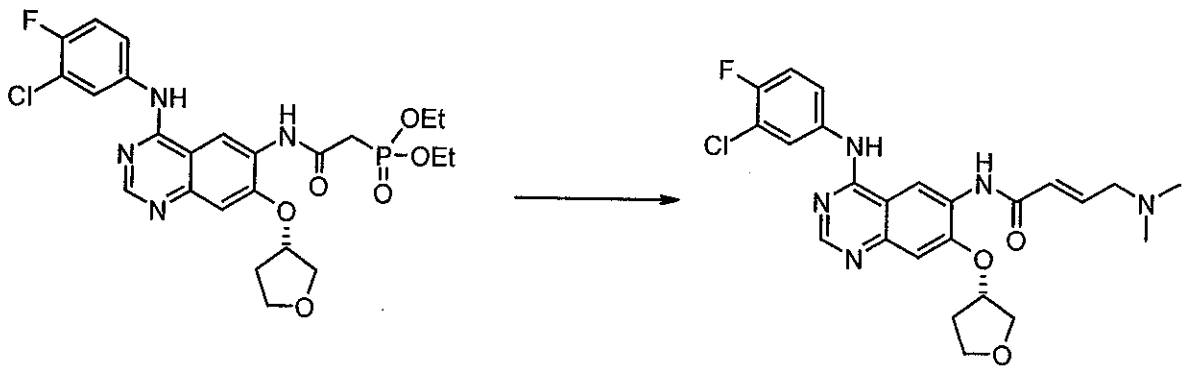
3.58 kg of 1,1-carbonyldiimidazole (22.16 mol) are placed in 12.8 litres of tetrahydrofuran and at 40 °C combined with 4.52 kg (22.16 mol) of diethylphosphonoacetic acid dissolved in 6.5 litres of tetrahydrofuran. The mixture is stirred for 30 minutes at 40 °C. The resulting solution is referred to as solution A.

6.39 kg (17.05 mol) of N^4-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine are placed in 26.5 litres of tetrahydrofuran and at 40°C combined with solution A and stirred for 2 hours at 30°C. 64 litres of tert.-butylmethylether are added to the suspension and after cooling to 20 °C the precipitate is removed by centrifuging. It is washed with a mixture of 16 litres of tetrahydrofuran and 16 litres of tert.-butylmethylether and then with 32 litres of water and dried at 50°C.

Yield: 6.58 kg (69.8%) of white crystals, content: HPLC 99.1 FI%

Example 2

(E)-4-dimethylamino-but-2-enoic acid-[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl]-amide



5.6 litres of 30 % hydrochloric acid (53.17 mol) are added to 4.4 litres of water. Then 4.28 kg of 95 % (dimethylamino)-acetaldehyde-diethylacetal (26.59 mol) are added dropwise within 20 minutes at 30°C. The reaction solution is stirred for 8 hours at 35°C stirred, cooled to 5 °C and stored under argon. This solution is referred to as solution B.

4.55 kg (68.06 mol) of potassium hydroxide are dissolved in 23.5 litres of water and cooled to –5°C. This solution is referred to as solution C.

5.88 kg (10.63 mol) of diethyl ((4-(3-chloro-4-fluoro-phenylamino)-7-(tetrahydrofuran-3-yloxy)-quinazoline-6-ylcarbamoyl)-methyl)-phosphonate and 0.45 kg of lithium chloride (10.63 mol) are placed in 23.5 litres of tetrahydrofuran and cooled to –7 °C. The cold solution C is added within 10 minutes. Then solution B is added at –7°C within 1 hour. After stirring for a further hour at –5 °C the reaction mixture is heated to 20°C and combined with 15 litres of water. After cooling to 3°C the suspension is suction filtered, the precipitate is washed with water and dried. Yield: 5.21 kg of crude product, 100 %, water content: 6.7 %

The crystallisation of the crude product is carried out with butyl acetate / methylcyclohexane

Yield: 78 % purity HPLC 99.4 FI%, water content 5.4 %

Example 3

(E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl)-amide dimaleate

6.0 kg (12.35 mol) of (E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-yl)-amide are placed in 84 litres of ethanol and heated to 70°C and combined with a solution of 2.94 kg (25.31 mol) of maleic acid in 36 litres of ethanol. After crystallisation has set in, first the mixture is cooled to 20 °C and stirred for 2 hours, then for 3 hours at 0 °C. The precipitate is suction filtered, washed with 19 litres of ethanol and dried in vacuo at 40°C .

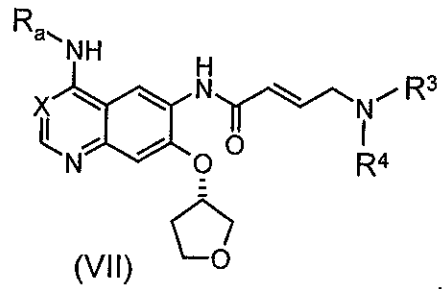
Yield: 8.11 kg (91.5%)

Melting point: 178 °C

^{1}H-NMR (CD_3OD): δ = 2.47 + 2.27 (m+m, 2H), 2.96 (s, 6H), 4.03 (m, 2H), 4.07 + 3.92 (m+m, 2H), 4.18 + 4.03 (m+m, 2H), 5.32 (m, 1H), 6.26 (s, 4H), 6.80 (m, 1H), 6.99 (m, 1H), 7.27(s, 1H), 7.30 (t, 1H), 7.66 (m, 1H), 7.96 (dd, 1H), 8.62 (s, 1H), 9.07 (s, 1H) ppm

Patent Claims

1. Process for preparing a compound of general formula (VII)

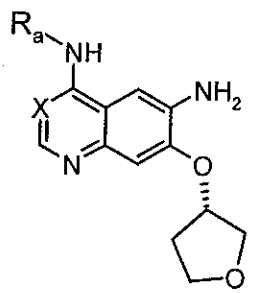


(VII)

wherein X denotes a methyne group or a nitrogen atom,
R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and
R^3 and R^4 denote a straight-chain or branched C_{1-4}-alkyl group,

comprising the following synthesis steps:

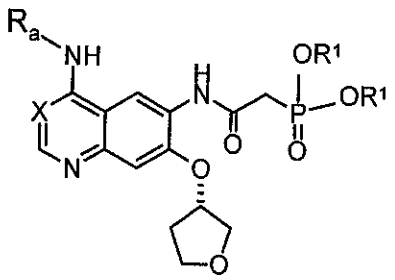
a) reacting a compound of general formula (V)



(V)

wherein X denotes a methyne group or a nitrogen atom and
R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group,
in suitable solvents after corresponding activation with di-(C_{1-4}-alkyl)-phosphonoacetic acid and

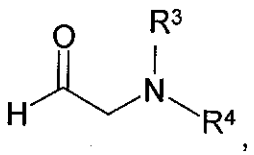
b) reacting the resulting compound of general formula (VI)



(VI)

wherein X denotes a methyne group or a nitrogen atom,
R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and
R^1 denotes a straight-chain or branched C_{1-4}-alkyl group,

with the aldehyde of formula



wherein R^3 and R^4 in each case represent a straight-chain or branched C_1-C_4-alkyl group, while the groups may be identical or different,

or a corresponding aldehyde equivalent, using suitable organic or inorganic bases.

2. Process for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising the following synthesis steps:

a) reacting N^4-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)-quinazoline-4,6-diamine in suitable solvents after corresponding activation with di-(C_{1-4}-alkyl)-phosphonoacetic acid and

b) reacting the resulting dialkylester {[4-(3-chloro-4-fluoro-phenylamino)-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate with

the aldehyde prepared *in situ* from the corresponding (dimethylamino)-acetaldehyde-dialkylacetal using suitable organic or inorganic bases.

3. Process according to claim 2, wherein as in step a) diethylphosphonoacetic acid is used as reagent.

4. Process according to claim 1 or 2, characterised in that in step b) DBU (1,5-diaza-bicyclo[4.3.0]non-5-ene), sodium hydroxide or potassium hydroxide is used as base.

5. Process according to claim 4, characterised in that in step b) potassium hydroxide is used as base.

6. Process for preparing the dimaleate of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline, comprising steps a and b according to claim 1 as well as the following step c):

c) converting the resulting 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline into the dimaleate by reacting with maleic acid in a suitable solvent, with heating.

7. Process according to claim 6, characterised in that ethanol or isopropanol is used as solvent, optionally with the addition of water.

8. Process according to claim 6 or 7, characterised in that at least 2 equivalents of maleic acid are used.

9. 4-[(3-Chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]-amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

10. Pharmaceutical compositions containing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-

quinazoline dimaleate optionally together with one or more inert carriers and/or diluents.

11. Use of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate for preparing a pharmaceutical composition which is suitable for the treatment of benign or malignant tumours, for preventing and treating diseases of the respiratory tract and lungs as well as for treating diseases of the gastro-intestinal tract and the bile duct and gall bladder.