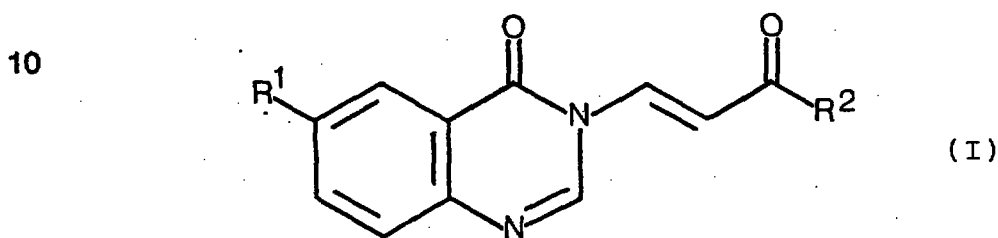


Trans-Quinazoline derivatives, processes for their preparation intermediates and medicaments containing these derivatives

5 The invention relates to trans-quinazoline derivatives of the general formula I



15 wherein R^1 represents lower alkyl, lower cycloalkyl, lower alkoxy, hydroxy, halogen, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O-, hydroxy-lower alkoxy, trifluoromethyl, nitro, amino, mono-lower alkylamino or di-lower alkyl-
20 amino, R^2 represents hydroxy, lower alkoxy, di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O- or di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -NH- and n represents an integer from 2 to 7 and
25 when R^2 represents hydroxy, salts thereof with pharmaceutically acceptable bases, and when R^1 represents amino, mono-lower alkylamino, di-lower alkylamino or di-(C_1 - C_7)-alkyl- $N(CH_2)_n$ -O- and/or R^2 represents di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O- or di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -NH-, salts thereof
30 with pharmaceutically acceptable acids.

35 The novel trans-3-(4-oxo-4H-quinazolin-3-yl)-2-propenoic acid derivatives of the general formula I are useful as agents in the treatment and prevention of allergic reactions.

As used in the present specification, the term "lower alkyl" means straight-chain and branched-chain alkyl groups with 1 to 7, preferably 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, neopentyl, n-pentyl and n-heptyl. The term "lower alkoxy", as used herein, means an alkoxy group in which the lower alkyl group is as described above, for example, methoxy, ethoxy, propoxy and pentoxy. The term "lower alkylthio" means an alkylthio group in which the lower alkyl group is as described above, for example, methylthio, ethylthio, propylthio and pentylthio. The term "lower alkylsulfinyl" means an alkylsulfinyl group in which the lower alkyl group is as described above, for example, methylsulfinyl and ethylsulfinyl. The term "lower alkylsulfonyl" means an alkylsulfonyl group in which the lower alkyl group is as described above, for example, methylsulfonyl and ethylsulfonyl. By the term "lower cycloalkyl", as used in this specification, is meant a cycloalkyl group with 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl and cyclohexyl. The term "halogen" means the four forms fluorine, chlorine, bromine and iodine.

The term "hydroxy-lower alkoxy" means a lower alkoxy group as described above in which one hydrogen atom is substituted by a hydroxy group, for example, 2-hydroxyethoxy or 2-hydroxypropoxy.

The term "mono-lower alkylamino" comprises residues, such as, methylamino, ethylamino and isopropylamino. The term "di-lower alkylamino" comprises residues, such as, dimethylamino, diethylamino, methyl-ethylamino and di-isopropylamino.

Exemplary of "di-(C₁-C₇)alkyl-N(CH₂)_n-O-" are residues, such as dimethylamino-ethoxy, diethylamino-ethoxy, diisopropylamino-butoxy and dipropylamino-ethoxy. Exemplary of "di-(C₁-C₇)alkyl-N(CH₂)_n-NH-" are residues,

such as, dimethylamino-ethylamino, diethylamino-ethylamino, ethyl-methylamino-ethylamino and diisopropylamino-ethylamino.

- 5 In a preferred aspect, the invention comprises compounds of the general formula I wherein R^1 represents lower alkyl, lower cycloalkyl, lower alkoxy or lower alkylthio.
- 10 Particularly preferred compounds of the general formula I are those wherein R^1 represents lower alkyl or lower alkylthio and R^2 represents hydroxy or di-(C_1-C_7)-alkyl- $N(CH_2)_n-NH-$. Other particularly preferred compounds of the invention are those, wherein R^1 represents
- 15 hydroxy or lower alkoxy and R^2 represents hydroxy. Compounds of the general formula I, wherein R^1 represents lower alkylsulfinyl and R^2 represents hydroxy, are also preferred. In another preferred aspect, the invention comprises compounds of the general formula I, wherein R^2
- 20 represents hydroxy.

Most preferred compounds of the invention are:

- 25 trans-3-(6-hydroxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid;
- trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid;
- trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid, 2-(diethylamino)ethyl amide hydrochloride;
- 30 trans-3-(6-isopropoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid;
- trans-3-(6-hydroxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid and
- trans-3-[6-(methylsulfinyl)-4-oxo-4H-quinazolin-3-yl]-
- 35 2-propenoic acid.

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Other preferred compounds of the invention are as follows:

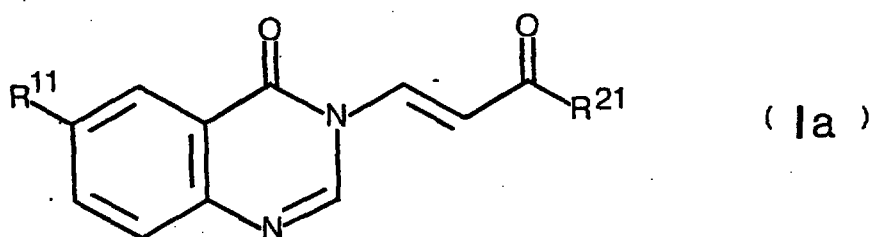
- trans-3-(6-ethoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic
5 acid;
trans-3-(6-n-propoxy-4-oxo-4H-quinazolin-3-yl)-2-
propenoic acid;
trans-3-(6-n-butoxy-4-oxo-4H-quinazolin-3-yl)-2-pro-
penoic acid;
10 trans-3-(6-methyl-4-oxo-4H-quinazolin-3-yl)-2-pro-
penoic acid;
trans-3-(6-ethyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic
acid;
trans-3-(6-n-propyl-4-oxo-4H-quinazolin-3-yl)-2-pro-
15 penoic acid;
trans-3-(6-n-butyl-4-oxo-4H-quinazolin-3-yl)-2-pro-
penoic acid;
trans-3-(6-bromo-4-oxo-4H-quinazolin-3-yl)-2-propenoic
acid;
20 trans-3-(6-fluoro-4-oxo-4H-quinazolin-3-yl)-2-pro-
penoic acid;
trans-3-(6-nitro-4-oxo-4H-quinazolin-3-yl)-2-propenoic
acid;
trans-3-(6-amino-4-oxo-4H-quinazolin-3-yl)-2-propenoic
25 acid;
trans-3-(6-dimethylamino-4-oxo-4H-quinazolin-3-yl)-2-
propenoic acid;
trans-3-(6-trifluoromethyl-4-oxo-4H-quinazolin-3-yl)-
2-propenoic acid;
30 trans-3-(6-t-butyl-4-oxo-4H-quinazolin-3-yl)-2-pro-
penoic acid;
trans-3-(6-isobutyl-4-oxo-4H-quinazolin-3-yl)-2-pro-
penoic acid and
trans-3-(6-sec-butyl-4-oxo-4H-quinazolin-3-yl)-2-
35 propenoic acid.

According to the present invention, the compounds of the general formula I and their pharmaceutically acceptable salts with acids and bases are prepared by a process which comprises

5

a) for preparing a compound of the general formula Ia

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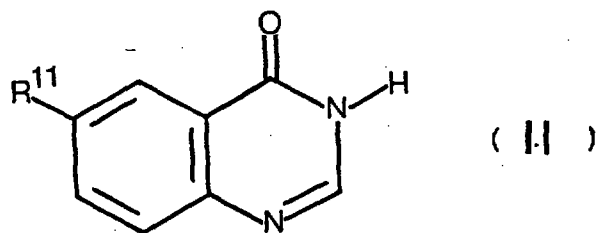
15

wherein R^{11} represents lower alkyl, lower cycloalkyl, lower alkoxy, nitro, halogen, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trifluoromethyl, di-lower alkylamino or di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O-, R^{21} represents lower alkoxy, di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O- or di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -NH- and n represents an integer from 2 to 7,

20

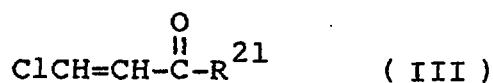
reacting a compound of the general formula II

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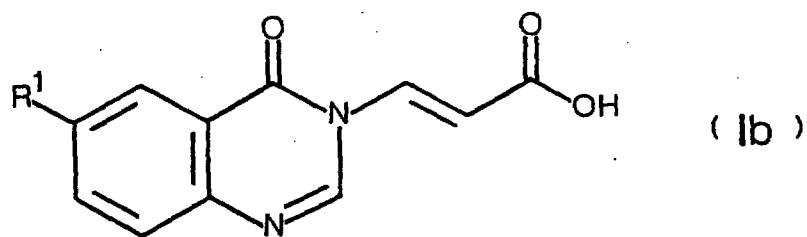
wherein R^{11} has the meaning indicated above, with a 3-chloroacrylic acid derivative of the general formula III



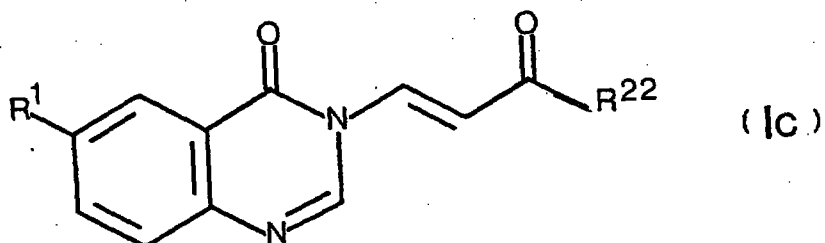
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wherein R^{21} has the meaning indicated above, or

b) for preparing a compound of the general formula Ib

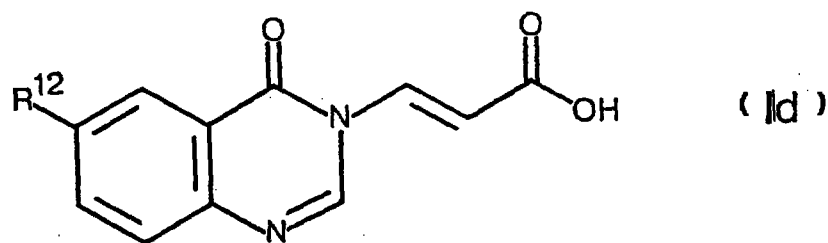


wherein R^1 has the meaning indicated above,
hydrolyzing a compound of the general formula Ic

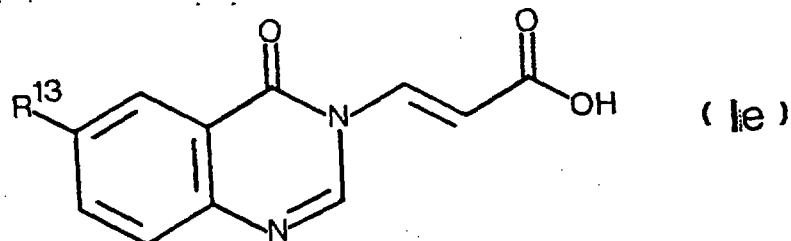


15
wherein R^{22} represents lower alkoxy and R^1 has the
meaning indicated above, or

c) for preparing a compound of the general formula Id

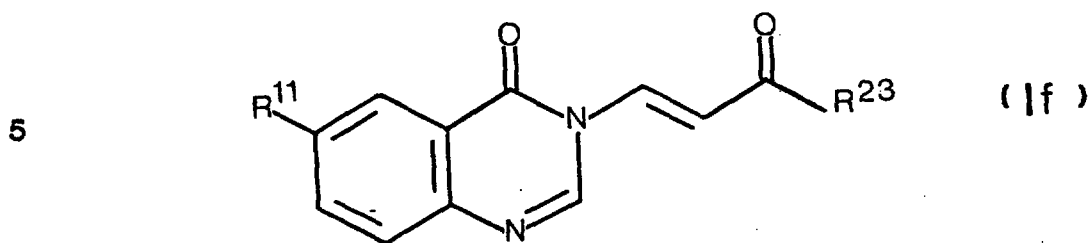


25
wherein R^{12} represents lower alkylsulfinyl or lower
alkylsulfonyl,
oxidizing a compound of the general formula Ie



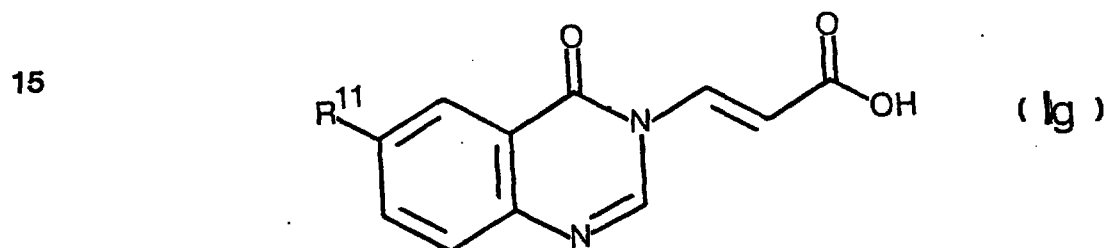
35
wherein R^{13} represents lower alkylthio, or

d) for preparing a compound of the general formula If

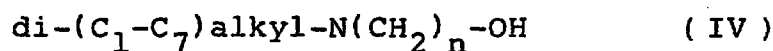


10 wherein R^{23} represents di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O- or di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -NH- and R^{11} and n have the meaning indicated above,

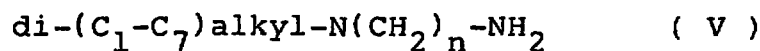
treating an active derivative of an acid of the general formula Ig



20 wherein R^{11} has the meaning indicated above, with an alkanol of the general formula IV

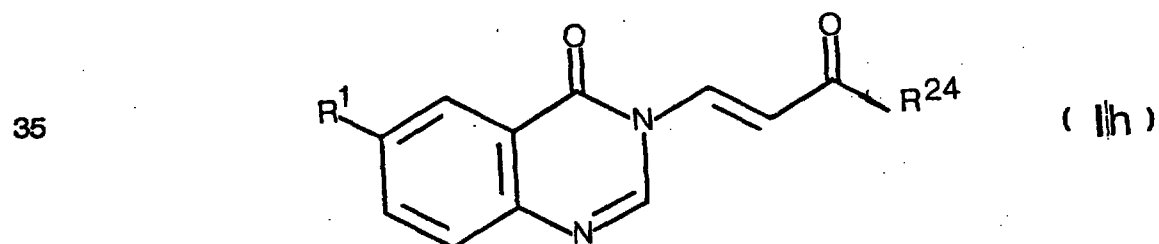


25 or with an amine of the general formula V

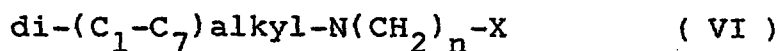


30 in which formulae n has the meaning indicated above, or

e) for preparing a compound of the general formula Ih

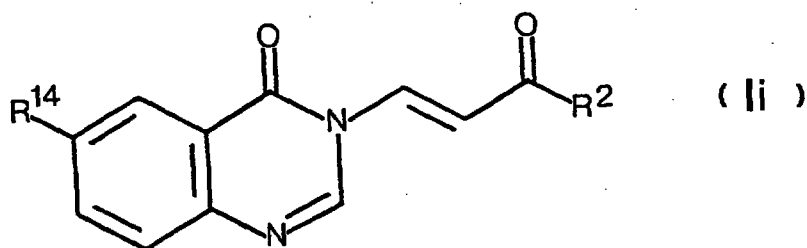


wherein R^{24} represents di-(C_1 - C_7)alkyl- $N(CH_2)_n$ -O- and R^1 and n have the meaning indicated above, treating an acid of the general formula Ib above with a halide of the general formula VI



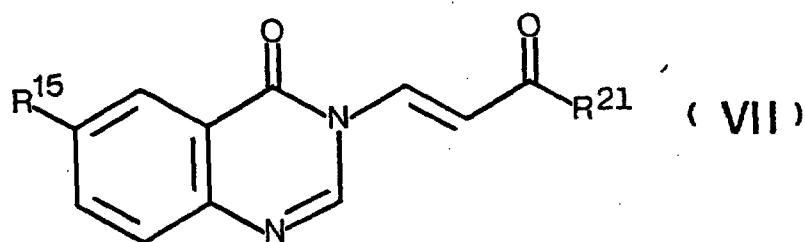
wherein X represents halogen and n has the meaning indicated above, or

f) for preparing a compound of the general formula II



wherein R^{14} represents amino, mono-lower alkylamino, hydroxy or hydroxy-lower alkoxy and R^{21} has the meaning indicated above,

splitting off a protecting group in a compound of the general formula VII



wherein R^{15} represents a protected amino-, mono-lower alkylamino-, hydroxy- or hydroxy-lower alkoxy-group and R^{21} has the meaning indicated above, and

g) if desired converting a compound of the general formula I, wherein R^2 represents hydroxy, into a pharmaceutically acceptable salt with a base, or converting a compound of the general formula I, wherein R^1 represents amino, mono-lower alkylamino, di-lower alkylamino or di-(C_1 - C_7)-

alkyl-N(CH₂)_n-O-, and/or R² represents di-(C₁-C₇)alkyl-N(CH₂)_n-O- or di-(C₁-C₇)alkyl-N(CH₂)_n-NH- and n has the meaning indicated above, into a pharmaceutically acceptable acid addition salt.

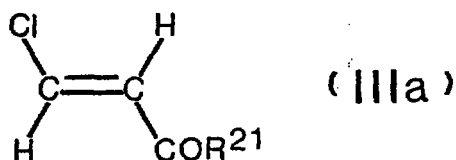
5

According to process embodiment a) a compound of the general formula Ia is prepared by reacting a compound of the general formula II with a 3-chloroacrylic acid derivative of the general formula III.

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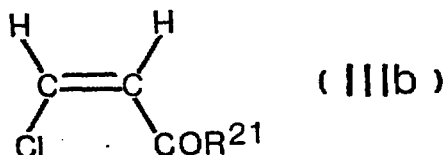
The N-3-alkylation of a compound of formula II with a compound of formula III, which may be in the trans configuration, i.e.,

15



or in the cis configuration, i.e.,

20



25

in which formulae R²¹ has the meaning indicated above, or a mixture thereof, can be carried out in the presence of a base, for example an alkali metal carbonate such as potassium carbonate, an alkali metal hydride such as sodium hydride, or an alkali metal alkoxide such as sodium methoxide. The N-3-alkylation can be carried out at a temperature in the range of from about 25° to about 100°C using a solvent such as dimethylformamide, acetone or dimethylsulfoxide. When sodium methoxide is the base, a lower alcohol such as methanol can also be used as the solvent. Preferably, the base is potassium carbonate, the solvent is acetone, and the reaction temperature is reflux temperature of the mixture. In another preferred embodiment the base is

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sodium hydride, the solvent is dimethylformamide and the reaction temperature may vary from about room temperature to 100°C, with about 50°C being preferred.

- 5 According to process embodiment b) a compound of the general formula Ib is prepared by hydrolyzing a compound of the general formula Ic. This reaction can be carried out with a mineral acid such as hydrochloric acid in a solvent such as water or acetic acid, preferably at
10 the reflux temperature of the chosen solvent.

 According to process embodiment c) a compound of the general formula Id is prepared by oxidizing a compound of the general formula Ie.

15

- More specifically, to obtain a compound of the general formula Id wherein R^{12} is lower alkylsulfinyl, the foregoing lower alkylthio compound of the general formula Ie is oxidized according to known methods, for example,
20 with an alkali metal metaperiodate such as sodium metaperiodate, preferably at room temperature. To obtain a compound of the general formula Id wherein R^{12} is lower alkylsulfonyl, a compound of
the general formula Ie is oxidized according to known
25 methods, for example, with hydrogen peroxide in the presence of a lower alkanolic acid such as acetic acid, preferably at a temperature in the range of from about 50° to about 100°C.

- 30 These oxidation steps can also be carried out according to other well known procedures, for example, with m-chloro-perbenzoic acid in a halogenated hydrocarbon, such as, methylene chloride or chloroform, or with peracetic acid preferably in acetic acid.

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According to process embodiment d) a compound of the general formula If is prepared by treating an active derivative of an acid of the general formula Ig with an alkanol of the general formula IV or with an amine of the general formula V. The free acid of the general formula Ig can be activated by agents, such as dicyclohexylcarbodiimide, N,N-carbonyldiimidazole, trifluoroacetic acid anhydride, p-toluene sulfonic acid chloride or mesitylene-sulfonic acid chloride. A preferred active acid derivative is the corresponding acid chloride which may be prepared by treating the free acid of the general formula Ig with e.g. excess thionyl chloride, according to well known procedures. The corresponding acid chloride can then be treated with a compound of the general formula IV (e.g. 2-diethylamino-ethanol) or V (e.g. 2-diethylamino-ethylamine or 2-diisopropylamino-ethylamine) in an inert organic solvent, for example, in a hydrocarbon such as benzene or toluene, in an ether such as tetrahydrofuran or dimethoxyethane or in dimethylformamide, in a wide range of temperature, preferably at room temperature.

According to process embodiment e) a compound of the general formula Ih is prepared by treating an acid of the general formula Ib with a compound of the general formula VI. This reaction can be carried out by heating an acid of the general formula Ib and a halide of the general formula VI (e.g. 2-diethylamino-ethyl-chloride) in an inert organic solvent, for example in an alcohol such as isopropylalcohol, preferably at the reflux temperature of the chosen solvent.

According to process embodiment f) a compound of the general formula Ii is prepared by splitting off a protecting group in a compound of the general formula VII. Preferred protecting groups are those which can be removed under mild conditions, for example ethers such as tetrahydropyranylethers or methoxyethoxymethyl-ethers, or

silylethers such as trimethylsilyl-ether or t-butyl-dimethyl-silyl-ether.

The required reaction conditions for this process
5 embodiment, depending of course on the protecting group
used, are well known to those skilled in the art.

The above mentioned protecting groups can be split off,
for example, with a hydrohalic acid, such as hydrochloric
10 acid, at a temperature in the range of from about room
temperature to the reflux temperature, preferably at the
reflux temperature.

According to process embodiment g) the compounds of the
15 general formula I, wherein R^2 represents hydroxy, form
salts with pharmaceutically acceptable bases. Exemplary of
such bases are alkali metal hydroxides, such as sodium
hydroxide or potassium hydroxide, alkaline earth metal
hydroxides, such as calcium hydroxide or barium hydroxide,
20 alkali metal alkoxides, such as sodium ethanolate or
potassium ethanolate, organic bases such as piperidine,
diethylamine, N-methyl-glucamine and N-(2-aminoethyl)glycine.

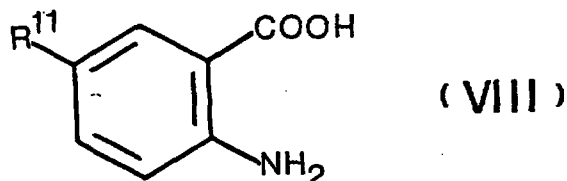
The compounds of the general formula I, wherein R^1
25 represents amino, mono-lower alkylamino, di-lower alkyl-
amino or $\text{di}(\text{C}_1\text{-C}_7)\text{alkyl-N}(\text{CH}_2)_n\text{-O-}$, and/or R^2 represents
 $\text{di}(\text{C}_1\text{-C}_7)\text{alkyl-N}(\text{CH}_2)_n\text{-O-}$ or $\text{di}(\text{C}_1\text{-C}_7)\text{alkyl-N}(\text{CH}_2)_n\text{-NH-}$
and n has the meaning indicated above, form salts with
30 pharmaceutically acceptable acids. Exemplary of such acids
are both pharmaceutically acceptable organic and inorganic
acids, such as methanesulfonic acid, p-toluenesulfonic
acid, maleic acid, acetic acid, hydrochloric acid, hydro-
bromic acid and sulfuric acid.

35 Such salts can be formed quite readily by those skilled
in the art, with the prior art and the nature of the com-
pound to be placed in salt form in view.

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A quinazolinone derivative of the general formula II which is used as starting material is prepared by reacting an anthranilic acid derivative of the general formula VIII

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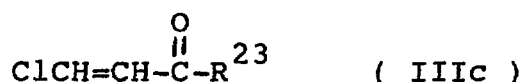
wherein R^{11} has the meaning indicated above, with formamide at a temperature in the range of from about 120° to about 180°C , preferably without added solvent.

15

The compounds of the general formula VIII are known compounds or can be prepared according to known procedures.

The 3-chloro-acrylic acid derivatives of the general formula III are known compounds or are prepared according to known procedures. The 3-chloro-acrylic acid derivatives of formula IIIc

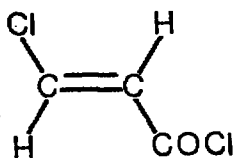
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wherein R^{23} has the meaning indicated above, for example, are prepared by treating an active derivative of 3-chloro-acrylic acid, for example, the anhydride, a mixed anhydride, the imidazolid or a halide, preferably the well known acid chloride of formula $\text{ClCH}=\text{CH}-\text{COCl}$, which may be in the trans configuration, i.e.

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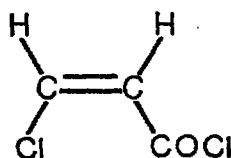


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or in the cis configuration, i.e.

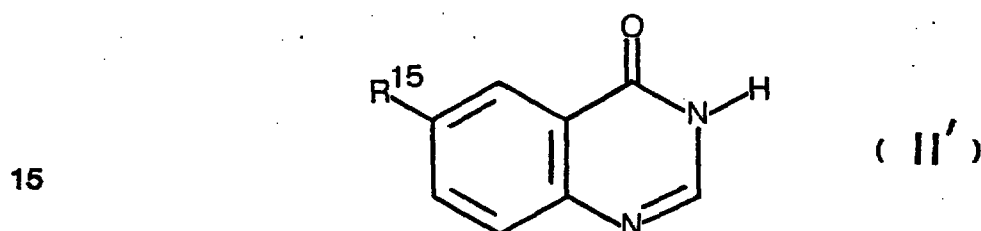
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- 14 -



5 or a mixture thereof, with an alkanol of the general formula IV or with an amine of the general formula V, respectively, according to process embodiment d).

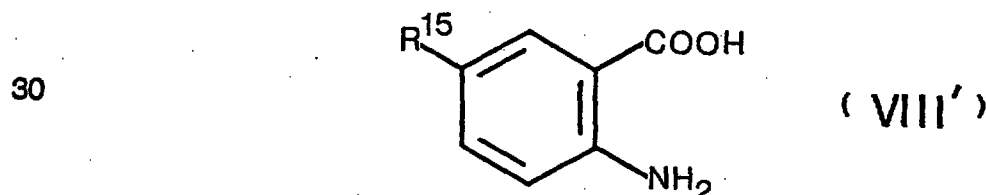
10 Compounds of the general formula VII are prepared according to process embodiment a) using protected quina-
zolinones of the general formula II'.



15 wherein R¹⁵ has the meaning indicated above,
and 3-chloro-acrylic acid derivatives of formula III as
20 starting materials.

Compounds of the general formula VII are novel and,
thus, also form part of the invention.

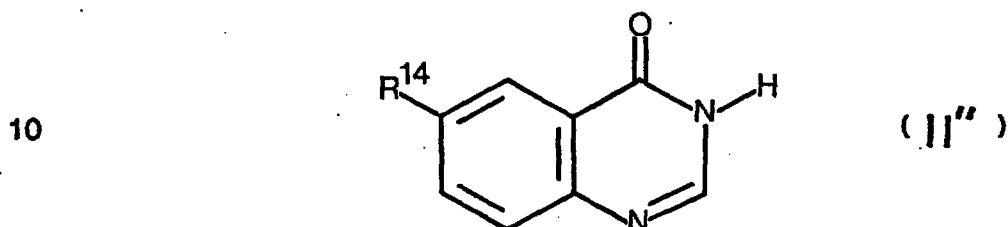
25 Compounds of the general formula II' are prepared
by reacting anthranilic acid derivatives of the general
formula VIII'



30
35 wherein R¹⁵ has the meaning indicated above,
with formamide as described earlier for the preparation of
quinazolinones of the general formula II from anthranilic
acid derivatives of the general formula VIII. The compounds

of the general formula VIII' are known compounds or are prepared according to known procedures.

In another aspect of the present invention quinazolinones of the general formula II' are prepared by introducing a protecting group into a compound of the general formula II"



wherein R^{14} has the meaning indicated above,
15 by treating it with a reagent, such as 3,4-dihydro-2H-pyran, trimethylchlorosilane or methyl-vinylether.

The compounds of the general formula I as well as their
20 pharmaceutically acceptable salts inhibit cutaneous anaphylaxis in rats, and are therefore useful in the prevention of allergic reactions, for example, they are useful in the prophylactic treatment of bronchial asthma. The antianaphylactic activity can be demonstrated by the
25 passive cutaneous anaphylaxis assay (PCA Test) in the rat. This test involves passive local sensitization of rats by intra-dermal injection of anti-sera. After a latent period of 24 hours, the test compound, in this case, a trans-3-(4-oxo-4H-quinazolin-3-yl)-2-propenoic acid derivative of
30 the invention is given intraperitoneally followed after 5 minutes by an intravenous injection of Reagen and Evans blue dye. The events associated with localized antigen-antibody reaction lead to the formation of skin wheals whose sizes are measured. The ability of the test compound to
35 decrease the size of the wheals compared to controls is taken as a measure of its activity.

When compounds of the present invention, such as e.g. trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid or trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid, are utilized as the test compounds at a
5 dose of 16 mg/kg intraperitoneally, the reduction in the wheal size is 100 and 87%, respectively.

The anti-allergic activity can also be demonstrated in the passively sensitized rat (IgE). In this test, a rat
10 is administered anti-sera intravenously 18 hours prior to the intravenous antigen (egg albumin) challenge. The antigen challenge originates the Immediate Hypersensitivity Reaction (IHR). When an anti-allergic compound is administered intravenously prior to the antigen challenge, it
15 inhibits IHR and prevents bronchospasm.

When trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid is utilized in the foregoing test at an oral dose of 0.02 mg/kg, the percent inhibition of broncho-
20 spasm is 50%.

The compounds of the general formula I and their pharmaceutically acceptable salts can be administered orally or parenterally as anti-allergic agents, for example
25 in the prophylactic treatment of bronchial asthma, with dosage adjustments for individual requirements. They can be administered therapeutically, for example, orally or parenterally, by incorporating a therapeutic dosage in a conventional dosage form, such as tablets, capsules,
30 elixirs, suspensions or solutions. They can be administered in mixture with conventional pharmaceutical carriers or excipients, such as, for example, corn starch, calcium stearate, magnesium carbonate, calcium silicate, dicalcium phosphate, talc or lactose. Moreover,
35 they can be administered in the presence of buffers, or agents used to adjust to isotonicity, and the pharmaceutical dosage forms can, if desired, be subjected to conventional pharmaceutical expedients such as, for example,

40

sterilization. As stated above, the dosage can be adjusted to individual requirements. They can also contain other therapeutically valuable substances.

5 The quantity of active ingredient which is present in any of the above-described dosage forms is variable. It is preferred, however, to provide capsules or tablets containing from about 1 mg to about 25 mg of the formula I base or an equivalent amount of a medicinally acceptable
10 salt thereof.

 The following examples further illustrate the invention but are not intended to limit the scope thereof.
15 All temperatures are given in degrees Centigrade.

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Example 1

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1.284 g of a 57% oil dispersion of sodium hydride was washed free of oil with pentane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 4.00 g of 6-methoxy-4(3H)-quinazolinone was added. The reaction mixture was stirred 10 minutes at room temperature and 30 minutes at 50°. After cooling to 30°, 3.02 g of methyl trans-3-chloroacrylate in 20 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 1 hour, cooled in an ice bath and 100 ml of water was added. The resultant solid was filtered and recrystallized from methylene chloride/methanol to yield 4.30 g, mp 184-186°, of pure trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

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Example 2

25 A mixture of 4.30 g of trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 110 ml of 6N hydrochloric acid was stirred and refluxed for 15 minutes. 100 ml of water was added and the reaction mixture was cooled in an ice bath and the resultant solid was
30 filtered to yield 3.13 g, mp 298-299°, of pure trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

Example 3

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To a suspension of 0.862 g of trans-3-(6-methoxy-4-oxo-

4H-quinazolin-3-yl)-2-propenoic acid in 15 ml of water was added 3.5 ml of 1.0N sodium hydroxide with stirring. After a few minutes, the mixture was filtered and 100 ml of pyridine was added to the filtrate. The solution was boiled to
5 remove most of the water and allowed to cool. Filtration gave 0.68 g, mp 329-330°, of pure trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid sodium salt hemihydrate.

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Example 4

15 To a solution of 0.513 g of trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 35 ml of pyridine was added 0.248 g of N-(2-aminoethyl)glycine dissolved in 5 ml of water. The solution was concentrated in vacuo and the residue was taken up in 150 ml of water containing
20 3 ml of pyridine. This solution was lyophilized to give trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid, N-(2-aminoethyl)glycine salt.

Example 5

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30 A suspension of 1.65 g of trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 100 ml of isopropyl alcohol was stirred and heated at reflux during the dropwise addition of 2.7 g of 2-(diethylamino)ethyl chloride in 30 ml of isopropyl alcohol. The reaction mixture was
35 stirred and refluxed for 8 hours and then allowed to cool to room temperature. The precipitate was filtered and then treated with 125 ml of saturated sodium bicarbonate solution and extracted with chloroform. The extract was dried over

magnesium sulfate and concentrated in vacuo to yield 2.3 g of solid. This solid was dissolved in 35 ml of methylene chloride and treated with 2.53 ml of 2.65N hydrochloric acid in methanol. Ether was added to turbidity and the solution was cooled overnight. Filtration gave 1.30 g, mp 217-218°, of pure trans-3-(6-methoxy-4-oxo-4H-quinazolin-3-yl)--2-propenoic acid (2-diethylaminoethyl)ester hydrochloride.

Example 6

A mixture of 5.38 g of 5-isopropylanthranilic acid and 4.82 ml of formamide was heated at 140-145° with stirring for 4 hours and then cooled to room temperature. The excess formamide was removed in vacuo and water was added. The precipitate was filtered and recrystallized from methylene chloride/hexane to yield 4.50 g, mp 147°, of pure 6-isopropyl-4(3H)-quinazolinone.

Example 7

1.15 g of a 57% oil dispersion of sodium hydride was washed free of oil with pentane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 3.86 g of 6-isopropyl-4(3H)-quinazolinone was added. The reaction mixture was stirred for 30 minutes at room temperature and 1 hour at 50°. After cooling to 30°, 2.68 g of methyl trans-3-chloroacrylate in 10 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 1.5 hours and concentrated in vacuo to remove most of the dimethylformamide. Water was added and the resultant solid was filtered and recrystallized from methylene chloride/methanol to give

2.73 g, mp 145°, of pure trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

Example 8

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A mixture of 2.995 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 175 ml of 6N hydrochloric acid was stirred and refluxed for 20 minutes. After cooling to room temperature, 175 ml of water was added and the reaction mixture was cooled overnight. Filtration gave 1.58 g, mp 245°, of pure trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

Example 9

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To a suspension of 1.29 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 20 ml of water was added 5.0 ml of 1.0N sodium hydroxide with stirring. After a few minutes, the mixture was filtered and 50 ml of water added to the filtrate. This solution was lyophilized to yield 1.40 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid sodium salt 0.25 molar hydrate.

Example 10

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To a solution of 0.774 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 50 ml of pyridine was added 0.354 g of N-(2-aminoethyl)glycine in 5 ml

of water. The solution was concentrated in vacuo, and the residue was taken up in 50 ml of water containing a few drops of pyridine. This solution was lyophilized to give
5 trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid, N-(2-aminoethyl)glycine salt.

Example 11

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A mixture of 1.77 g of 5-cyclopropyl-anthranilic acid and 1.6 ml of formamide was heated at 140-145° with stirring for 4 hours and then cooled to room temperature. The excess formamide was removed in vacuo and water was added. The
15 precipitate was filtered and recrystallized from methanol/ethyl acetate to yield 1.40 g, mp 201-202°, of pure 6-cyclopropyl-4(3H)-quinazolinone.

Example 12

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0.395 g of a 57% oil dispersion of sodium hydride was
25 washed free of oil with pentane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 1.40 g of 6-cyclopropyl-4(3H)-quinazolinone was added. The reaction mixture was stirred at room temperature for 15 minutes and at 50° for 30 minutes. After cooling
30 to 30°, 1.00 g of methyl trans-3-chloro-acrylate in 5 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 75 minutes and concentrated in vacuo to remove most of the dimethylformamide. Water was added and the resultant solid was filtered
35 and recrystallized from methylene chloride/methanol to give 1.24 g, mp 178°, of pure trans-3-(6-cyclopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

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Example 13

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A mixture of 1.18 g of trans-3-(6-cyclopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 50 ml of 6N hydrochloric acid was stirred and refluxed for 13 minutes. After cooling to room temperature, 150 ml of water was added and the reaction mixture was cooled. Filtration gave the crude product which was recrystallized from pyridine to give 0.38 g, mp 291-293°, of pure trans-3-(6-cyclopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

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Example 14

0.367 g of a 57% oil dispersion of sodium hydride was washed free of oil with pentane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 1.23 g of 6-chloro-4(3H)-quinazolinone was added. The reaction mixture was stirred at room temperature for 15 minutes and at 50° for 30 minutes. After cooling to 30°, 0.91 g of methyl trans-3-chloroacrylate in 5 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 75 minutes and concentrated in vacuo to remove most of the dimethylformamide. Water was added, and the resultant solid was filtered and recrystallized from methylene chloride/methanol to yield 0.95 g, mp 171-172°, of pure trans-3-(6-chloro-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

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Example 15

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A mixture of 0.92 g of trans-3-(6-chloro-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 30 ml of 6N hydrochloric acid was stirred and refluxed for 15 minutes. After cooling to room temperature, 200 ml of water was added and the reaction mixture was cooled. Filtration gave the crude product which was recrystallized from pyridine to give 0.31 g, mp 297-298°, of pure trans-3-(6-chloro-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

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Example 16

Preparation of 6-(methylthio)-4(3H)-quinazolinone

A mixture of 1.97 g of methyl 5-(methylthio)anthranilate and 1.6 ml of formamide was heated at 140-145° with stirring for 4 hours and then at 190° for 4 hours and then cooled to room temperature. The excess formamide was removed in vacuo and water was added. The precipitate was filtered and recrystallized from methanol/ethyl acetate to yield 0.73 g, mp 203-204.5°, of pure 6-(methylthio)-4(3H)-quinazolinone.

Example 17

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0.205 g of a 57% oil dispersion of sodium hydride was washed free of oil with pentane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 0.720 g of 6-(methylthio)-4(3H)-quinazolinone was added. The reaction mixture was stirred at room temperature for 10 minutes and at 50° for 30 minutes. After

cooling to 30°, 0.497 g of methyl trans-3-chloroacrylate in 5 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 1 hour and concentrated in vacuo to remove most of the dimethylformamide. Water was added and the resultant solid was filtered and recrystallized from methylene chloride/ methanol to yield 0.700 g, mp 170°, of pure trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

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Example 18

15 A mixture of 0.65 g of trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 30 ml of 6N hydrochloric acid was stirred and refluxed for 20 minutes. After cooling to room temperature, 100 ml of water was added and the reaction mixture was cooled. Filtration
20 gave the crude product which was recrystallized from pyridine to yield 0.47 g, mp 271-272°, of pure trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

Example 19

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 A mixture of 3.90 g of 5-isopropoxy-anthranilic acid and 3.2 ml of formamide was heated at 140-145° for 4 hours and then cooled to room temperature. The excess formamide was removed in vacuo and water was added. The precipitate was filtered and recrystallized from methanol to give 2.99 g, mp 206-208°, of pure 6-isopropoxy-4(3H)-quinazolinone.

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Example 20

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0.888 g of a 57% oil dispersion of sodium hydride was washed free of oil with pentane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 3.31 g of 6-isopropoxy-4(3H)-quinazolinone was added. The reaction mixture was stirred at room temperature for 10 minutes and at 50° for 45 minutes. After cooling to 30°, 2.150 g of methyl trans-3-chloroacrylate in 7 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was heated at 50° for 1 hour and concentrated in vacuo to remove most of the dimethylformamide. Water was added and the resultant solid was filtered and recrystallized from methylene chloride/methanol to yield 4.00 g, mp 156.5-157.5°, of pure trans-3-(6-isopropoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

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Example 21

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A mixture of 1.44 g of trans-3-(6-isopropoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 60 ml of 6N hydrochloric acid was stirred and refluxed for 5 minutes. After cooling to room temperature, 200 ml of water was added and the reaction mixture was cooled. Filtration gave the crude product which was recrystallized from acetic acid to give 0.37 g, mp 232.5-233.5°, of pure trans-3-(6-isopropoxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

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Example 22

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A mixture of 1.00 g of 5-(2-diethylamino-ethoxy)-anthranilic acid dihydrochloride and 1 ml of formamide was heated at 150° with stirring for 7 hours. The excess formamide was removed in vacuo and the residue was triturated
10 with methanol/ether to give 0.81 g of solid. Recrystallization from isopropyl alcohol/water gave 0.33 g, mp 233-234°, of pure 6-(2-diethylamino-ethoxy)-4(3H)-quinazolinone hydrochloride.

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Example 23

20 0.20 g of a 57% oil dispersion of sodium hydride was washed free of oil with hexane and then suspended in 25 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 0.94 g of 6-(2-diethylamino-ethoxy)-4(3H)-quinazolinone was added. The reaction mixture was stirred for
25 15 minutes at room temperature and for 1 hour at 50°. After cooling to 30°, 0.48 g of methyl trans-3-chloroacrylate in 5 ml of anhydrous dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 1 hour 45 minutes and concentrated in vacuo to remove most of the di-
30 methylformamide. Water was added and the resultant solid was filtered to give 1.10 g, mp 131-133°, of pure trans-3-[6-(2-diethylamino-ethoxy)-4-oxo-4H-quinazolin-3-yl]-2-propenoic acid methyl ester.

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Example 24

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A mixture of 1.0454 g of trans-3-[6-(2-diethylamino-ethoxy)-4-oxo-4H-quinazolin-3-yl]-2-propenoic acid methyl ester and 25 ml of 6N hydrochloric acid was stirred and refluxed for 20 minutes. After concentration in vacuo to a yellow solid, this was recrystallized from isopropyl alcohol/water to yield 0.69 g, mp 227-230°, of pure trans-3-[6-(2-diethylamino-ethoxy)-4-oxo-4H-quinazolin-3-yl]-2-propenoic acid hydrochloride.

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Example 25

A mixture of 1.74 g of 5-(2-hydroxyethoxy)anthranilic acid and 2 ml of formamide was heated at 150° with stirring for 7.5 hours. Water was added and the product was filtered and crystallized from methanol to yield 1.24 g, mp 200-202°, of pure 6-(2-hydroxyethoxy)-4(3H)-quinazolinone.

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Example 26

To 2.0479 g of 6-(2-hydroxyethoxy)-4(3H)-quinazolinone in 60 ml of anhydrous dimethylformamide was added 1.52 ml of triethylamine followed by 1.40 ml of trimethylsilyl chloride added dropwise. After stirring at 25° for 1.5 hours, the precipitated triethylamine hydrochloride was removed by filtration. The filtrate was added to 0.6430 g of 57% sodium hydride which had previously been washed with hexane to remove the oil. After stirring for 5 minutes in an argon atmosphere, the reaction mixture was heated at

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50° for 45 minutes. On cooling to 30°, 1.3560 g of methyl trans-3-chloroacrylate in 2 ml of dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 75 minutes and concentrated in vacuo to remove most of the dimethylformamide. 50 ml of 6N hydrochloric acid was added and the mixture was stirred and refluxed for 15 minutes. After cooling, the resultant solid was filtered, washed well with water and dried to yield 0.9607 g, mp 247-248°, of pure trans-3-[6-(2-hydroxyethoxy)-4-oxo-4H-quinazolin-3-yl]-2-propenoic acid.

Example 27

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A suspension of 1.60 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 20 ml of thionyl chloride was stirred and refluxed for 3 hours. The reaction mixture was concentrated in vacuo, toluene was added, and it was concentrated again to remove traces of thionyl chloride. The acid chloride was dissolved in 50 ml of toluene and 1.08 g of 2-(diethylamino)ethyl amine in 15 ml of toluene was added dropwise. The reaction mixture was refluxed for 4 hours and concentrated in vacuo to remove the toluene. After partitioning between ethyl acetate and excess saturated sodium bicarbonate solution, the organic layer was dried over magnesium sulfate and concentrated to yield a dark oil. Crystallization from hexane gave a gray solid, which was dissolved in 10 ml of methylene chloride and treated with 2 ml of 4N hydrochloric acid in methanol. The solution was concentrated in vacuo and the residue was crystallized from isopropyl alcohol/ether to yield 0.90 g mp 179-180°, of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid, 2-(diethylamino)ethyl amide hydrochloride.

Example 28

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A suspension of 1.55 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 100 ml of isopropyl alcohol was stirred and heated at reflux during the drop-
10 wise addition of 2.71 g of 2-(diethylamino)ethyl-chloride in 30 ml of isopropyl alcohol. The reaction mixture was stirred at reflux for 8 hours, filtered, and the solid was washed well with isopropyl alcohol. The filtrate was concentrated to dryness in vacuo and the solid residue was partitioned between chloroform and saturated sodium bicarbonate
15 solution. The chloroform layer was dried over magnesium sulfate and concentrated in vacuo to yield 2.5 g of an oil. The oil was dissolved in 35 ml of methylene chloride and 4.0 ml of 1.77N hydrochloric acid in methanol was added.
20 Ether was added to turbidity and the resultant product was filtered to yield 1.88 g, mp 167-168°, of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid, 2-(diethylamino)ethyl ester hydrochloride.

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Example 29

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To a stirred solution of 4.00 g of trans-3-chloroacrylyl chloride in 10 ml of methylene chloride was added dropwise 3.78 g of 2-(diethylamino)ethanol in 5 ml of methylene chloride. The solution was stirred at room temperature for three days and then washed with saturated sodium
35 bicarbonate solution. After drying over magnesium sulfate, concentration in vacuo gave an oil which was distilled at 110-130° (1 mm) to give 1.63 g of trans-3-chloroacrylic acid, 2-(diethylamino)ethyl ester.

Example 30

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0.274 g of a 57% oil dispersion of sodium hydride was washed free of oil with pentane and then suspended in 10 ml of anhydrous dimethylformamide. While maintaining an argon atmosphere, 0.941 g of 6-isopropyl-4(3H)-quinazolinone was added. The reaction mixture was then stirred and heated at 50° for 30 minutes. After cooling to room temperature, 0.663 g of methyl cis-3-chloroacrylate in 5 ml of dimethylformamide was added dropwise. The reaction mixture was then stirred and heated at 50° for 75 minutes and concentrated in vacuo to remove most of the dimethylformamide. Water was added and the resultant solid was recrystallized from methylene chloride/methanol to give 0.58 g, mp 144-145°, of trans-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

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Example 31

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To 2.726 g of 6-hydroxy-4(3H)-quinazolinone in 110 ml of anhydrous dimethylformamide was added 2.6 ml of triethylamine followed by 2.6 ml of trimethylchlorosilane. After stirring at room temperature for 2 hours, the triethylamine hydrochloride was removed by filtration. The filtrate was added in one portion to 1.06 g of a 57% oil dispersion of sodium hydride which had previously been freed of oil by washing with pentane. The reaction mixture was stirred and heated at 50° for 90 minutes. After cooling to room temperature, 2.02 g of methyl trans-3-chloroacrylate in 10 ml of dimethylformamide was added dropwise. The reaction mixture was then heated at 50° for 2 hours. The dimethyl-

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formamide was removed in vacuo and water was added to yield a solid which was filtered. Recrystallization from ethyl acetate/methanol gave 2.725 g, mp 252-256°, of trans-3-(6-hydroxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester.

Example 32

A mixture of 8.35 g of trans-3-(6-hydroxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid methyl ester and 500 ml of 6N hydrochloric acid was stirred and refluxed for 15 minutes. After cooling, water was added and the resultant solid was filtered to yield 6.33 g, mp 294-296°, of trans-3-(6-hydroxy-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

Example 33

To a stirred suspension of 1.823 g of trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 80 ml of water and 7.7 ml of 1N sodium hydroxide at room temperature was added 1.827 g of sodium metaperiodate. After stirring at room temperature for 4.5 hours, 5 ml of acetic acid was added and the solid was filtered after stirring for 15 minutes. The crude product was recrystallized twice from acetic acid to give 1.102 g, mp 275-276°, of pure trans-3-(6-methylsulfinyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

Example 34

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To a stirred suspension of 1.8845 g of trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 100 ml of acetic acid was added 1.63 ml of 30% hydrogen peroxide. The reaction mixture was stirred and heated at 10 50° for 3 hours, cooled to room temperature and filtered. Recrystallization from acetic acid gave 0.8097 g, mp 284-290°, of pure trans-3-(6-methylsulfonyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid.

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Example 35

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A solution of 1.8120 g of trans-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid in 30 ml of thionyl chloride was stirred and refluxed for 2 hours. The excess thionyl chloride was removed in vacuo and dry toluene was added and again concentrated in vacuo to yield the solid acid chloride. 30 ml of anhydrous dimethylformamide was added followed by 2.4 ml of 2-(diisopropylamino)ethyl-amine at room temperature. The reaction mixture was stirred for 2 hours and left at room temperature for 16 hours. The solvent was removed on the oil pump to yield a dark oil which was dissolved in 20 ml of methanol and treated with 1.6 ml of 4.4N hydrogen chloride in methanol. After removal of the methanol in vacuo, the residue was triturated with isopropyl alcohol/ether and the resultant solid was removed by 30 filtration. Recrystallization from methylene chloride/ether gave 1.3037 g, mp 209-213°, of pure trans-N-[(2-diisopropylamino)ethyl]-3-(6-isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenamide hydrochloride. 35

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Example A

Tablets of the following composition are prepared:

5		<u>mg/tablet</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
	trans-3-(6-Isopropyl-4-oxo-4H-quinazolin-3-yl)-			
	2-propenoic acid	1	5	25
	Lactose	221	217	197
10	Microcrystalline Cellulose	45	45	45
	Modified Starch	30	30	30
	Magnesium Stearate	<u>3</u>	<u>3</u>	<u>3</u>
		300 mg	300 mg	300 mg

15 Procedure:

20 The active ingredient is well mixed with an equal amount of lactose. The microcrystalline cellulose, the modified starch and the remaining amount of lactose are added and well mixed. Then, the magnesium stearate is added and mixed for 3 minutes, and the mixture is compressed on a suitable press.

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Example B

Tablets of the following composition are prepared:

5		<u>mg/tablet</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
	trans-3-(6-Isopropyl-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid	1	5	25
	Lactose	202	198	223
10	Modified Starch	25	25	30
	Pregelatinized Starch	20	20	20
	Distilled Water	-	-	-
	Magnesium Stearate	<u>2</u>	<u>2</u>	<u>2</u>
		250 mg	250 mg	300 mg
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Procedure:

The first four ingredients are mixed in a suitable mixer, granulated with sufficient distilled water and dried in a suitable oven. The magnesium stearate is added and mixed well, and the mixture compressed on a suitable press.

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Example C

Capsules of the following composition are prepared:

	<u>mg/capsule</u>	<u>mg/capsule</u>	<u>mg/capsule</u>
5			
trans-3-(6-Isopropyl-4-oxo-4H-quinazolin-3-yl)-			
2-propenoic acid	1	5	25
Lactose	253	249	224
10 Starch	30	30	30
Talc	15	15	15
Magnesium Stearate	<u>1</u>	<u>1</u>	<u>1</u>
	300 mg	300 mg	300 mg

15 Procedure:

The first three ingredients are mixed in a suitable mixer. Talc and magnesium stearate are added and mixed for a short period of time, and the mixture encapsulated on an
20 an appropriate encapsulation machine.

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Example D

Tablets of the following composition are prepared:

5		<u>mg/tablet</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
	trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid	1	5	25
	Lactose	202	198	223
10	Modified Starch	25	25	30
	Pregelatinized Starch	20	20	20
	Distilled Water	-	-	-
	Magnesium Stearate	<u>2</u>	<u>2</u>	<u>2</u>
		250 mg	250 mg	300 mg

Procedure:

The first four ingredients are mixed in a suitable mixer, granulated with sufficient distilled water and dried in a suitable oven. The magnesium stearate is added and mixed well, and the mixture compressed on a suitable press.

Example E

Capsules of the following composition are prepared:

5		<u>mg/capsule</u>	<u>mg/capsule</u>	<u>mg/capsule</u>
	trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid	1	5	25
	Lactose	253	249	229
10	Starch	30	30	30
	Talc	15	15	15
	Magnesium Stearate	<u>1</u>	<u>1</u>	<u>1</u>
		300 mg	300 mg	300 mg

15 Procedure:

The first three ingredients are mixed in a suitable mixer. Talc and magnesium stearate are added and mixed for a short period of time, and the mixture encapsulated on an appropriate encapsulation machine.

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Example F

Tablets of the following composition are prepared:

5		<u>mg/tablet</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
	trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-2-propenoic acid	1	5	25
	Lactose	221	217	197
10	Microcrystalline Cellulose	45	45	45
	Modified Starch	30	30	30
	Magnesium Stearate	<u>3</u>	<u>3</u>	<u>3</u>
		300 mg	300 mg	300 mg

15 Procedure:

20 The active ingredient is well mixed with an equal amount of lactose. The microcrystalline cellulose, the modified starch and the remaining amount of lactose are added and well mixed. Then, the magnesium stearate is added and mixed for 3 minutes, and the mixture is compressed on a suitable press.

25 Claims

30 No English translation of the claims is provided herewith since the Letters Patent already contain an English version of the claims.

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Example F

Tablets of the following composition are prepared:

5		<u>mg/tablet</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
	trans-3-(6-methylthio-4-oxo-4H-quinazolin-3-yl)-			
	2-propenoic acid	1	5	25
	Lactose	221	217	197
10	Microcrystalline Cellulose	45	45	45
	Modified Starch	30	30	30
	Magnesium Stearate	<u>3</u>	<u>3</u>	<u>3</u>
		300 mg	300 mg	300 mg

15 Procedure:

20 The active ingredient is well mixed with an equal amount of lactose. The microcrystalline cellulose, the modified starch and the remaining amount of lactose are added and well mixed. Then, the magnesium stearate is added and mixed for 3 minutes, and the mixture is compressed on a suitable press.

25 Claims

30 No English translation of the claims is provided herewith since the Letters Patent already contain an English version of the claims.

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