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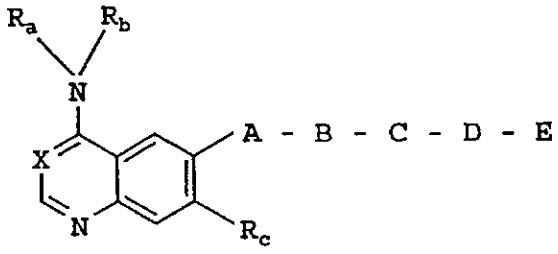
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[Fortsetzung auf der nächsten Seite]

(54) Title: BICYCLIC HETEROCYCLES, MEDICAMENTS CONTAINING THESE COMPOUNDS, THEIR USE AND METHODS FOR THE PRODUCTION THEREOF

(54) Bezeichnung: BICYCLISCHE HETEROCYCLEN, DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL, DEREN VERWENDUNG UND VERFAHREN ZU IHRER HERSTELLUNG



(I)

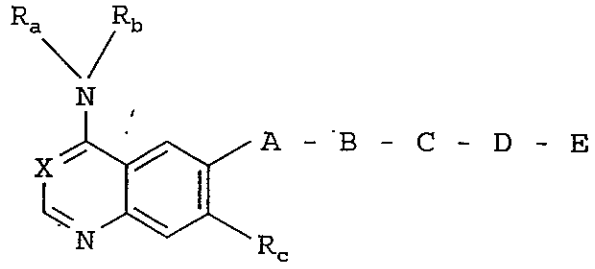
(57) Abstract: The invention relates to bicyclic heterocycles of general formula (I), in which R_a to R_c, A to E and X are defined as in Claim No. 1, to their tautomers, their stereoisomers and their salts, especially their physiologically compatible salts having inorganic or organic acids or bases. The inventive bicyclic heterocycles comprise valuable pharmacological properties, especially an inhibitory effect on the signal transduction procured by tyrosine kinases. The invention also relates to the use of the inventive bicyclic heterocycles for treating illnesses, especially tumor diseases, diseases of the lung and of the respiratory tract, and relates to the production of the inventive compounds.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft bicyclische Heterocyclen der allgemeinen Formel (I), in der R_a bis R_c, A bis E und X wie im Anspruch 1 definiert sind, deren Tautomeren, deren Stereoisomere und deren Salze, insbesondere deren physiologisch verträgliche Salze mit anorganischen oder organischen Säuren oder Basen, welche wertvolle pharmakologische Eigenschaften aufweisen, insbesondere eine Hemmwirkung auf die durch Tyrosinkinasen vermittelte Signaltransduktion, deren Verwendung zur Behandlung von Krankheiten, insbesondere von Tumorerkrankungen, von Erkrankungen der Lunge und der Atemwege und deren Herstellung.

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Bicyclic heterocycles, pharmaceutical compositions containing these compounds, their use and processes for preparing them

The present invention relates to bicyclic heterocycles of general formula



, (I)

the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, the use thereof for treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract, and the preparation thereof.

In the above general formula I

R_a denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, whilst

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, hydroxy, C_{1-4}-alkoxy, C_{3-6}-cycloalkyl, C_{4-6}-cycloalkoxy, C_{2-5}-alkenyl or C_{2-5}-alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3-5}-alkenyloxy or C_{3-5}-alkynyloxy group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, C_{1-4}-alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C_{1-4}-alkyl groups, wherein the substituents may be identical or different, or

R_1 together with R_2, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH or -CH=N-NH group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group,

X denotes a methyne group substituted by a cyano group or a nitrogen atom,

A denotes an imino group optionally substituted by a C_{1-4}-alkyl group,

B denotes a carbonyl or sulphonyl group,

C denotes a 1,3-allenylene, 1,1- or 1,2-vinylene group which may be substituted in each case by one or two methyl groups or by a trifluoromethyl group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group optionally substituted by 1 to 4 methyl groups or by a trifluoromethyl group,

D denotes an alkylene, -CO-alkylene or -SO_2-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms and additionally 1 to 4 hydrogen atoms in the alkylene moiety may be replaced by fluorine atoms, whilst the linking of the -CO-alkylene or -SO_2-alkylene group to the adjacent group C in each case must take place via the carbonyl or sulphonyl group,

a -CO-O-alkylene, -CO-NR_4-alkylene or -SO_2-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms, whilst the linking to the adjacent group C in each case must take place via the carbonyl or sulphonyl group, wherein

R_4 denotes a hydrogen atom or a C_{1-4}-alkyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group wherein the alkyl moieties may be identical or different,

a C_{2-4}-alkylamino group wherein the alkyl moiety is substituted in β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, whilst

R_5 denotes a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group,

a 4- to 7-membered alkyleneimino group optionally substituted by one or two methyl groups or

a 6- to 7-membered alkyleneimino group optionally substituted by one or two methyl groups wherein in each case a methylene group in position 4 is replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

an N-(C_{1-4}-alkyl)-N-(C_{2-4}-alkyl)-amino group wherein the C_{2-4}-alkyl moiety is substituted in β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, whilst R_5 is as hereinbefore defined,

a di-(C_{2-4}-alkyl)-amino group wherein the two C_{2-4}-alkyl moieties are substituted in each case in β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, whilst the substituents may be identical or different and R_5 is as hereinbefore defined,

a C_{3-7}-cycloalkylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkylamino group wherein in each case the nitrogen atom may be substituted by a further C_{1-4}-alkyl group,

an amino or C_{1-4}-alkylamino group wherein in each case the nitrogen atom is substituted by a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl, 1-(tetrahydrofuran-3-yl)-piperidin-4-yl, 1-(tetrahydropyran-3-yl)-piperidin-4-yl, 1-(tetrahydropyran-4-yl)-piperidin-4-yl,

3-pyrrolidinyl, 3-piperidinyl, 4-piperidinyl, 3-hexahydro-azepinyl or 4-hexahydro-azepinyl group optionally substituted by 1 to 3 C_{1-4}-alkyl groups,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 C_{1-2}-alkyl groups, which may be substituted by the group R_5 either at a cyclic carbon atom or at one of the alkyl groups, whilst R_5 is as hereinbefore defined,

a piperidino group substituted by a tetrahydrofuranyl, tetrahydropyranyl or tetrahydrofuranylmethyl group,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 C_{1-2}-alkyl groups wherein a methylene group in each case is replaced in the 4 position by an oxygen or sulphur atom, by an imino group substituted by the group R_6, or by a sulphinyl or sulphonyl group, whilst

R_6 denotes a hydrogen atom, a C_{1-4}-alkyl, 2-methoxy-ethyl, 3-methoxy-propyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl, formyl, C_{1-4}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_6, by a sulphinyl or sulphonyl group, whilst R_6 is as hereinbefore defined,

or D together with E denotes a hydrogen, fluorine or chlorine atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, heteroaryl, C_{1-4}-alkylcarbonyl or arylcarbonyl group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group or

a carbonyl which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group may be replaced in the 4 position by an oxygen or sulphur atom, by an imino group substituted by the group R_6, by a sulphinyl or sulphonyl group, whilst R_6 is as hereinbefore defined, and

R_c denotes a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-6}-alkoxy group wherein the cycloalkyl moiety in each case may be substituted by a C_{1-3}-alkyl, hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino, N-(C_{1-2}-alkyl)-piperazino, hydroxy-C_{1-2}-alkyl, C_{1-4}-alkoxy-C_{1-2}-alkyl, amino-C_{1-2}-alkyl, C_{1-4}-alkylamino-C_{1-2}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{1-2}-alkyl, pyrrolidino-C_{1-2}-alkyl, piperidino-C_{1-2}-alkyl, morpholino-C_{1-2}-alkyl, piperazino-C_{1-2}-alkyl or N-(C_{1-2}-alkyl)-piperazino-C_{1-2}-alkyl group, whilst the abovementioned monosubstituted cycloalkyl moieties may additionally be substituted by a C_{1-3}-alkyl group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuranylmethoxy group,

an C_{2-4}-alkoxy group substituted in the β-, γ- or δ-position with regard to the oxygen atom by an azetidin-1-yl, 4-methyl-homopiperazino or 4-ethyl-homopiperazino group,

a 3-pyrrolidinyloxy, 2-pyrrolidinyl-C_{1-4}-alkyloxy, 3-pyrrolidinyl-C_{1-4}-alkyloxy, 3-piperidinyloxy, 4-piperidinyloxy, 2-piperidinyl-C_{1-4}-alkyloxy, 3-piperidinyl-C_{1-4}-alkyloxy, 4-piperidinyl-C_{1-4}-alkyloxy, 3-hexahydro-azepinyloxy, 4-hexahydro-azepinyloxy, 2-hexahydro-azepinyl-C_{1-4}-alkyloxy, 3-hexahydro-azepinyl-C_{1-4}-alkyloxy or 4-hexahydro-azepinyl-C_{1-4}-alkyloxy group wherein in each case the cyclic nitrogen atom is substituted by the group R_6, where R_6 is as hereinbefore defined,

particularly those compounds of general formula I wherein R_a, R_b, A to C and X are as hereinbefore defined, (definition of E as in claim 1 of the priority text)

E denotes an amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group wherein the alkyl moieties may be identical or different,

a C_{2-4}-alkylamino group wherein the alkyl moiety is substituted from position 2 by the group R_5, whilst

R_5 denotes a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group,

a 4- to 7-membered alkyleneimino group optionally substituted by one or two methyl groups or

a 6- to 7-membered alkyleneimino group optionally substituted by one or two methyl groups wherein in each case a methylene group in position 4 is replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

an N-(C_{1-4}-alkyl)-N-(C_{2-4}-alkyl)-amino group wherein the C_{2-4}-alkyl moiety is substituted from position 2 onwards by the group R_5, where R_5 is as hereinbefore defined,

a di-(C_{2-4}-alkyl)-amino group wherein the two C_{2-4}-alkyl moieties are substituted in each case from position 2 onwards by the group R_5, whilst the substituents may be identical or different and R_5 is as hereinbefore defined,

a C_{3-7}-cycloalkylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkylamino group wherein in each case the nitrogen atom may be substituted by a further C_{1-4}-alkyl group,

an amino or C_{1-4}-alkylamino group wherein in each case the nitrogen atom is substituted by a 3-pyrrolidinyl, 3-piperidinyl, 4-piperidinyl, 3-hexahydro-azepinyl or 4-hexahydro-azepinyl group optionally substituted by 1 to 3 C_{1-4}-alkyl groups,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 C_{1-2}-alkyl groups, which may be substituted by the group R_5 either at a cyclic carbon atom or at one of the alkyl groups, whilst R_5 is as hereinbefore defined, or

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 C_{1-2}-alkyl groups wherein a methylene group in each case is replaced in the 4 position by an oxygen or sulphur atom, by an imino group substituted by the group R_6, or by a sulphinyl or sulphonyl group, whilst

> R_6 denotes a hydrogen atom, a C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, formyl, C_{1-4}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by

the group R_6, or by a sulphinyl or sulphonyl group, whilst R_6 is as hereinbefore defined,

or D together with E denotes a hydrogen, fluorine or chlorine atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, heteroaryl, C_{1-4}-alkylcarbonyl or arylcarbonyl group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylamino-carbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group or

a carbonyl which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups a methylene group may in each case be replaced in the 4 position by an oxygen or sulphur atom, by an imino group substituted by the group R_6, by a sulphinyl or sulphonyl group, whilst R_6 is as hereinbefore defined, and

R_c denotes a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-6}-alkoxy group wherein the cycloalkyl moiety in each case may be substituted by a C_{1-3}-alkyl, hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino, N-(C_{1-2}-alkyl)-piperazino, hydroxy-C_{1-2}-alkyl, C_{1-4}-alkoxy-C_{1-2}-alkyl, amino-C_{1-2}-alkyl, C_{1-4}-alkylamino-C_{1-2}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{1-2}-alkyl, pyrrolidino-C_{1-2}-alkyl, piperidino-C_{1-2}-alkyl, morpholino-C_{1-2}-alkyl, piperazino-C_{1-2}-alkyl or N-(C_{1-2}-alkyl)-piperazino-C_{1-2}-alkyl group, whilst the abovementioned monosubstituted cycloalkyl moieties may additionally be substituted by a C_{1-3}-alkyl group, or

a 3-pyrrolidinyloxy, 2-pyrrolidinyl-C_{1-4}-alkyloxy, 3-pyrrolidinyl-C_{1-4}-alkyloxy, 3-piperidinyloxy, 4-piperidinyloxy, 2-piperidinyl-C_{1-4}-alkyloxy, 3-piperidinyl-C_{1-4}-alkyloxy, 4-piperidinyl-C_{1-4}-alkyloxy, 3-hexahydro-azepinyloxy, 4-hexahydro-azepinyloxy, 2-hexahydro-azepinyl-C_{1-4}-alkyloxy, 3-hexahydro-azepinyl-C_{1-4}-alkyloxy or 4-hexahydro-azepinyl-C_{1-4}-alkyloxy group wherein in each case the cyclic nitrogen atom is substituted by the group R_6, where R_6 is as hereinbefore defined.

By the aryl moieties mentioned in the definition of the above-mentioned groups is meant a phenyl group which in each case may be monosubstituted by R_7, mono-, di- or trisubstituted by R_8 or monosubstituted by R_7 and additionally mono- or disubstituted by R_8, wherein the substituents may be identical or different and

R_7 denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group which is substituted by a 5- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group, and

R_8 denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_8, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group.

The heteroaryl groups mentioned in the definition of the abovementioned groups also include a 5-membered heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group which contains one, two or three nitrogen atoms,

whilst the abovementioned 5-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups and the abovementioned 6-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups or by a fluorine, chlorine, bromine or iodine atom or by a trifluoromethyl, hydroxy, methoxy or ethoxy group.

Preferred compounds of the above general formula I are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, whilst

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, hydroxy, C_{1-4}-alkoxy, C_{3-6}-cycloalkyl, C_{4-6}-cycloalkoxy, C_{2-5}-alkenyl or C_{2-5}-alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

a cyano or nitro group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group,

X denotes a methyne group substituted by a cyano group or a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl or sulphonyl group,

C denotes a 1,3-allenylene, 1,1- or 1,2-vinylene group,

an ethynylene or 1,3-butadien-1,4-ylene group,

D denotes an alkylene, -CO-alkylene or -SO_2-alkylene group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms and additionally 1 to 4 hydrogen atoms in the alkylene moiety may be replaced by fluorine atoms, whilst the linking of the -CO-alkylene or -SO_2-alkylene group to the adjacent group C in each case must take place via the carbonyl or sulphonyl group,

a -CO-O-alkylene, -CO-NR_4-alkylene or -SO_2-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, whilst the linking to the adjacent group C in each case must take place via the carbonyl or sulphonyl group, wherein

R_4 denotes a hydrogen atom or a C_{1-4}-alkyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond,

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes a di-(C_{1-4}-alkyl)-amino group wherein the alkyl moieties may be identical or different,

an N-(C_{1-4}-alkyl)-N-(C_{2-4}-alkyl)-amino group wherein the C_{2-4}-alkyl moiety is substituted in the β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, where

R_5 denotes a hydroxy, C_{1-4}-alkoxy or di-(C_{1-4}-alkyl)-amino group,

a 4- to 7-membered alkyleneimino group optionally substituted by one or two methyl groups or

a 6- to 7-membered alkyleneimino group optionally substituted by one or two methyl groups wherein in each case a methylene group in position 4 is replaced by an oxygen or sulphur atom, or by a sulphinyl, sulphonyl or N-(C_{1-4}-alkyl)-imino group,

a di-(C_{2-4}-alkyl)-amino group wherein the two C_{2-4}-alkyl moieties in each case are substituted in the β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, wherein the substituents may be identical or different and R_5 is as hereinbefore defined,

a C_{3-7}-cycloalkylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkylamino group wherein in each case the nitrogen atom is substituted by a further C_{1-4}-alkyl group,

a C_{1-4}-alkylamino group wherein the nitrogen atom is substituted by a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl, 1-(tetrahydrofuran-3-yl)-piperidin-4-yl, 1-(tetrahydropyran-3-yl)-piperidin-4-yl, 1-(tetrahydropyran-4-yl)-piperidin-4-yl, N-(C_{1-2}-alkyl)-3-pyrrolidinyl, N-(C_{1-2}-alkyl)-3-piperidinyl, N-(C_{1-2}-alkyl)-4-piperidinyl, N-(C_{1-2}-alkyl)-3-hexahydro-azepinyl or N-(C_{1-2}-alkyl)-4-hexahydro-azepinyl group,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups, which may be substituted either at a cyclic carbon atom or at one of the methyl groups by the group R_5, where R_5 is as hereinbefore defined,

a piperidino group substituted by a tetrahydrofuranyl, tetrahydropyranyl or tetrahydrofuranylmethyl group,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group is replaced in the 4 position by an oxygen or sulphur atom, by an imino group substituted by the group R_6 or by a sulphinyl or sulphonyl group, whilst

R_6 denotes a C_{1-4}-alkyl, 2-methoxy-ethyl, 3-methoxy-propyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl, formyl, C_{1-4}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_6, or by a sulphinyl or sulphonyl group, where R_6 is as hereinbefore defined,

or D together with E denotes a hydrogen, fluorine or chlorine atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, C_{1-4}-alkylcarbonyl or arylcarbonyl group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkyl-aminocarbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group or

a carbonyl group which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_6, or by a sulphinyl or sulphonyl group, where R_6 is as hereinbefore defined, and

R_c denotes a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-6}-alkoxy group wherein the cycloalkyl moiety in each case may be substituted by a C_{1-3}-alkyl, hydroxy, C_{1-4}-alkoxy, di-(C_{1-4}-alkyl)-amino, pyrrolidino, piperidino, morpholino, N-(C_{1-2}-alkyl)-piperazino, hydroxy-C_{1-2}-alkyl, C_{1-4}-alkoxy-C_{1-2}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{1-2}-alkyl, pyrrolidino-C_{1-2}-alkyl, piperidino-C_{1-2}-alkyl, morpholino-C_{1-2}-alkyl or N-(C_{1-2}-alkyl)-piperazino-C_{1-2}-alkyl group, whilst the abovementioned monosubstituted cycloalkyl moieties may additionally be substituted by a C_{1-3}-alkyl group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuranylmethoxy group,

an C_{2-4}-alkoxy group substituted in the β-, γ- or δ-position with regard to the oxygen atom by an azetidin-1-yl, 4-methyl-homopiperazino or 4-ethyl-homopiperazino group,

a 3-pyrrolidinyloxy, 2-pyrrolidinyl-C_{1-4}-alkyloxy, 3-pyrrolidinyl-C_{1-4}-alkyloxy, 3-piperidinyloxy, 4-piperidinyloxy, 2-piperidinyl-C_{1-4}-alkyloxy, 3-piperidinyl-C_{1-4}-alkyloxy, 4-piperidinyl-C_{1-4}-alkyloxy, 3-hexahydro-azepinyloxy, 4-hexahydro-azepinyloxy, 2-hexahydro-azepinyl-C_{1-4}-alkyloxy, 3-hexahydro-azepinyl-C_{1-4}-alkyloxy or 4-hexahydro-azepinyl-C_{1-4}-alkyloxy group wherein in each case the cyclic nitrogen atom is substituted by the group R_6, where R_6 is as hereinbefore defined, whilst

by the aryl moieties mentioned in the definition of the above-mentioned groups is meant a phenyl group which may in each case be monosubstituted by R_7, mono-, di- or trisubstituted by R_8 or monosubstituted by R_7 and additionally mono- or disubstituted by R_8, wherein the substituents may be identical or different and

R_7 denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group which is substituted by a 5- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group may be replaced in the 4 position by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group, and

R_8 denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_8, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, stereoisomers and salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 and R_2, where

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl or methoxy group,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene group,

an ethynylene or 1,3-butadien-1,4-ylene group,

D denotes a C_{1-4}-alkylene group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond,

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl group,

E denotes a di-(C_{1-4}-alkyl)-amino group wherein the alkyl moieties may be identical or different,

an N-(C_{1-4}-alkyl)-N-(C_{2-4}-alkyl)-amino group wherein the C_{2-4}-alkyl moiety is substituted in the β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, whilst

R_5 denotes a hydroxy, C_{1-3}-alkoxy or di-(C_{1-3}-alkyl)-amino group,

a pyrrolidino, piperidino or morpholino group,

a di-(C_{2-4}-alkyl)-amino group wherein the two C_{2-4}-alkyl moieties in each case are substituted in the β-, γ- or δ-position with regard to the nitrogen atom of the amino group by the group R_5, wherein the substituents may be identical or different and R_5 is as hereinbefore defined,

an C_{1-4}-alkylamino group substituted at the nitrogen atom by a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl, 1-(C_{1-2}-alkyl)-pyrrolidin-3-yl, 1-(C_{1-2}-alkyl)-piperidin-3-yl, 1-(C_{1-2}-alkyl)-piperidin-4-yl, 1-(tetrahydrofuran-3-yl)-piperidin-4-yl, 1-(tetrahydropyran-3-yl)-piperidin-4-yl or 1-(tetrahydropyran-4-yl)-piperidin-4-yl group,

a C_{3-5}-cycloalkylamino or C_{3-5}-cycloalkyl-C_{1-3}-alkylamino group wherein in each case the nitrogen atom is substituted by a further C_{1-3}-alkyl group,

a 5- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups which may be substituted either at a cyclic carbon atom or at one or the methyl groups by the group R_5, where R_5 is as hereinbefore defined, or

a piperidino group substituted by a tetrahydrofuranyl, tetrahydropyranyl or tetrahydrofuranylmethyl group,

a piperidino group optionally substituted by 1 or 2 methyl groups wherein the methylene group is replaced in the 4 position by an oxygen or sulphur atom, by sulphinyl or sulphonyl group or by an imino group substituted by the group R_6, whilst

R_6 denotes a C_{1-3}-alkyl, 2-methoxy-ethyl, 3-methoxy-propyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl, C_{1-3}-alkylcarbonyl, C_{1-3}-alkylsulphonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

or D together with E denotes a hydrogen atom,

a C_{1-3}-alkyl group,

an aryl or C_{1-4}-alkylcarbonyl group or

a C_{1-4}-alkoxycarbonyl group,

R_c denotes a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group wherein the cycloalkyl moiety in each case may be substituted by a C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuranylmethoxy group,

an C_{2-4}-alkoxy group substituted in the β-, γ- or δ-position with regard to the oxygen atom by an azetidin-1-yl, 4-methyl-homopiperazino or 4-ethyl-homopiperazino group,

a 3-pyrrolidinyloxy, 2-pyrrolidinyl-C_{1-3}-alkyloxy, 3-pyrrolidinyl-C_{1-3}-alkyloxy, 3-piperidinyloxy, 4-piperidinyloxy, 2-piperidinyl-C_{1-3}-alkyloxy, 3-piperidinyl-

C_{1-3}-alkyloxy, 4-piperidinyl-C_{1-3}-alkyloxy, 3-hexahydro-azepinyloxy, 4-hexahydro-azepinyloxy, 2-hexahydro-azepinyl-C_{1-3}-alkyloxy, 3-hexahydro-azepinyl-C_{1-3}-alkyloxy or 4-hexahydro-azepinyl-C_{1-3}-alkyloxy group wherein in each case the cyclic nitrogen atom is substituted by a methyl or ethyl group, whilst

by the aryl moieties mentioned in the definition of the above-mentioned groups is meant a phenyl group which may be mono-, di- or trisubstituted by R_8, wherein the substituents may be identical or different and

R_8 denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group,

the tautomers, stereoisomers and salts thereof.

Most particularly preferred compounds of the above general formula I are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group, whilst the phenyl nucleus is substituted in each case by the radicals R_1 and R_2, whilst

R_1 and R_2, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene, ethynylene or 1,3-butadien-1,4-ylene group,

D denotes an C_{1-3}-alkylene group,

E denotes a Di-(C_{1-4}-alkyl)-amino group, wherein the alkyl moieties may be identical or different,

a methylamino or ethylamino group each substituted at the nitrogen atom by a 2-methoxy-ethyl, 1-methoxy-2-propyl, 2-methoxy-propyl, 3-methoxy-propyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, tetrahydrofuran-2-ylmethyl, 1-methyl-piperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(tetrahydrofuran-3-yl)-piperidin-4-yl, cyclopropyl or cyclopropylmethyl group,

a bis-(2-methoxyethyl)-amino group,

a pyrrolidino, piperidino or morpholino group each optionally substituted by one or two methyl groups,

a piperazino group substituted in 4-position by a methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-methoxy-ethyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl or tetrahydrofuran-2-ylmethyl group,

a thiomorpholino, S-oxido-thiomorpholino or S,S-dioxido-thiomorpholino group,

a 2-(methoxymethyl)-pyrrolidino, 2-(ethoxymethyl)-pyrrolidino, 4-hydroxy-piperidino, 4-methoxy-piperidino, 4-ethoxy-piperidino, 4-(tetrahydrofuran-3-yl)-piperidino or 4-morpholino-piperidino group

or D together with E denote a hydrogen atom, a methyl, phenyl, methoxycarbonyl or ethoxycarbonyl group and

R_c denotes a cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy group,

a cyclobutyloxy, cyclopentyloxy or cyclohexyloxy group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuran-2-ylmethoxy group,

a straight chained C_{2-4}-alkoxy group terminally substituted by an azetidin-1-yl, 4-methyl-homopiperazino or 4-ethyl-homopiperazino group,

a 1-methyl-piperidin-4-yloxy or 1-ethyl-piperidin-4-yloxy group,

a (1-methyl-piperidin-4-yl)-C_{1-3}-alkyloxy or (1-ethyl-piperidin-4-yl)-C_{1-3}-alkyloxy group,

especially those compounds wherein

R_a denotes a hydrogen atom,

R_b denotes a 1-phenylethyl group or a phenyl group wherein the phenyl nucleus is substituted by the radicals R_1 and R_2, whilst

R_1 and R_2, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene, ethynylene or 1,3-butadien-1,4-ylene group,

D denotes a methylene group,

E denotes a dimethylamino, diethylamino, Bis-(2-methoxy-ethyl)-amino, N-methyl-N-(2-methoxy-ethyl)-amino, N-ethyl-N-(2-methoxy-ethyl)-amino, N-methyl-N-cyclopropyl-amino, N-methyl-N-cyclopropylmethyl-amino, N-methyl-N-(1-methoxy-2-propyl)-amino, N-methyl-N-(2-methoxy-propyl)-amino, N-methyl-N-(3-methoxy-propyl)-amino-, N-methyl-N-(tetra-hydrofuran-3-yl)-amino, N-methyl-N-(tetrahydropyran-4-yl)-amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino or N-methyl-N-(1-methyl-piperidin-4-yl)-amino group,

a pyrrolidino, piperidino or morpholino group each optionally substituted by one or two methyl groups,

a piperazino group substituted in 4-position by a methyl, ethyl, cyclopropylmethyl or 2-methoxy-ethyl group,

a S-oxido-thiomorpholino group,

a 2-(methoxy-methyl)-pyrrolidino, 4-hydroxy-piperidino or 4-methoxy-piperidino group

or D together with E denote a hydrogen atom, a methyl, phenyl or ethoxycarbonyl group, and

R_c denotes a cyclopropylmethoxy, cyclobutyloxy or cyclopentyl-oxy group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetra-hydrofuran-2-ylmethoxy group,

a straight chained C_{2-4}-alkoxy group terminally substituted by an azetidin-1-yl or 4-methyl-homopiperazino group,

a 1-methyl-piperidin-4-yloxy group or

a (1-methyl-piperidin-4-yl)-C_{1-3}-alkyloxy group,

the tautomers, stereoisomers and salts thereof.

The following particularly valuable compounds of general formula I may be mentioned by way of example:

(a) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

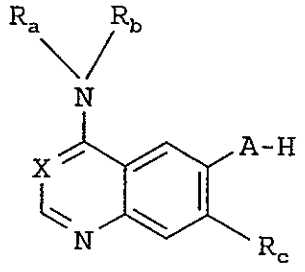
(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline and

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

as well as the salts thereof.

The compounds of general formula I may be prepared, for example, by the following processes:

a) reacting a compound of general formula



, (II)

wherein
R_a to R_c, A and X are as hereinbefore defined, with a compound of general formula

$$Z_1 - B - C - D - E \qquad , (III)$$

wherein
B to E are as hereinbefore defined and

Z_1 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom, or a hydroxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/-tetrahydrofuran or dioxane optionally in the presence of an inorganic or organic base and optionally in the presence of a dehydrating agent, expediently at temperatures between -50 and 150°C, preferably at temperatures between -20 and 80°C.

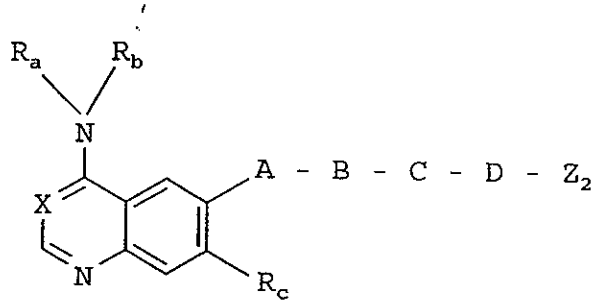
With a compound of general formula III wherein Z_1 denotes a leaving group, the reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig base), whilst these organic bases may simultaneously also act as solvent, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution expediently at temperatures between -50 and 150°C, preferably at temperatures between -20 and 80°C.

With a compound of general formula III wherein Z_1 denotes a hydroxy group, the reaction is preferably carried out in the presence of a dehydrating agent, e.g. in the presence of iso-butyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, hexamethyl-disilazane, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently in a solvent such as methylene chloride, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylsulphoxide, ethylene glycol

monomethylether, ethyleneglycol, diethylether or sulpholane and optionally in the presence of a reaction accelerator such as 4-dimethylaminopyridine at temperatures between -50 and 150°C, but preferably at temperatures between -20 and 80°C.

b) In order to prepare compounds of general formula I wherein the group E is linked to the group D via a nitrogen atom:

reacting a compound of general formula



, (IV)

wherein
R_a to R_c, A to D and X are as hereinbefore defined and Z_2 denotes a leaving group such as a halogen atom, a substituted hydroxy or sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group, with a compound of general formula

H - E´ , (V)

wherein
E´ denotes one of the groups mentioned for E hereinbefore, which is linked to the group D via a nitrogen atom.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethylsulphoxide, methylene chloride, ethylene glycol monomethylether, ethylene glycol diethylether or sulpholane, optionally in the presence of an inorganic or tertiary organic base, e.g. sodium carbonate or potassium hydroxide, a tertiary organic base,

e.g. triethylamine, or in the presence of N-ethyl-diisopropylamine (Hünig base), whilst these organic bases may simultaneously also serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide at temperatures between -20 and 150°C, but preferably at temperatures between -10 and 100°C. The reaction may, however, also be carried out without a solvent or in an excess of the compound of general formula V used.

If according to the invention a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I or

if a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I or

if a compound of general formula I is obtained which contains a carboxy or hydroxyphosphoryl group, this may be converted by esterification into a corresponding ester of general formula I or

if a compound of general formula I is obtained which contains a carboxy or ester group, this may be converted by reaction with an amine into a corresponding amide of general formula I.

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan or most advantageously in a corresponding alcohol, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionylchloride, trimethylchlorosilane,

sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent ester formation may also be carried out by reacting a compound which contains a carboxy or hydroxyphosphoryl group with a corresponding alkyl halide.

The subsequent acylation or sulphonylation is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with a corresponding acyl or sulphonyl derivative optionally in the presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexyl carbodiimide, N,N'-dicyclohexyl carbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an

alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethyl sulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, expediently at a pH of 6-7 and at ambient temperature or in the presence of a hydration catalyst, e.g. with hydrogen in the presence of palladium/charcoal, at a hydrogen pressure of 1 to 5 bar. The methylation can also be carried out in the presence of formic acid as reduction agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

The subsequent amide formation is carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding amine, optionally in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, whilst the amine used may simultaneously serve as solvent, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently at

temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, phosphono, O-alkyl-phosphono, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

protecting groups for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group,

protecting groups for a phosphono group may be an alkyl group such as the methyl, ethyl, isopropyl or n-butyl group, the phenyl or benzyl group, and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxan, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50°C.

A single alkyl group may be cleaved from an O,O'-dialkylphosphono group with sodium iodide, for example, in a solvent such as acetone, methylethylketone, acetonitrile or dimethylformamide at temperatures between 40 and 150°C, but preferably at temperatures between 60 and 100°C.

Both alkyl groups may be cleaved from an O,O'-dialkyl-phosphono group with iodotrimethylsilane, bromotrimethylsilane or chlorotrimethylsilane/sodium iodide, for example, in a solvent such as methyl chloride, chloroform or acetonitrile at temperatures between 0°C and the boiling temperature of the reaction mixture, but preferably at temperatures between 20 and 60°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst

the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy, hydroxyphosphoryl, sulpho or 5-tetrazolyl group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to V used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature (cf. Examples I to VII).

For example, a starting compound of general formula I is obtained by reacting a 7-fluoro-6-nitro compound correspondingly substituted in the 4 position with a corresponding alkoxide and subsequently reducing the nitro compound thus obtained or

a starting compound of general formula IV is obtained by reacting a 7-fluoro-6-nitro compound correspondingly substituted in the 4 position with a corresponding alkoxide, subsequently reducing the nitro compound thus obtained and then acylating with a corresponding compound.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R), whilst this may be achieved for example by inhibiting ligand bonding, receptor dimerisation or tyrosine kinase itself. It is also possible to block the transmission of signals to components located further down.

The biological properties of the new compounds were investigated as follows:

The inhibition of the EGF-R-mediated signal transmission can be demonstrated e.g. with cells which express human EGF-R and whose survival and proliferation depend on stimulation by EGF or TGF-alpha. A cell line of murine origin dependent on interleukin-3-(IL-3) which was genetically modified to express functional human EGF-R was used here. The proliferation of these cells known as F/L-HERc can therefore be stimulated either by murine IL-3 or by EGF (cf. von Rüden, T. et al. in EMBO J. 7, 2749-2756 (1988) and Pierce, J. H. et al. in Science 239, 628-631 (1988)).

The starting material used for the F/L-HERc cells was the cell line FDC-P_1, the production of which has been described by Dexter, T. M. et al. in J. Exp. Med. 152, 1036-1047 (1980). Alternatively, however, other growth-factor-dependent cells may also be used (cf. for example Pierce, J. H. et al. in Science 239, 628-631 (1988), Shibuya, H. et al. in Cell 70, 57-67 (1992) and Alexander, W. S. et al. in EMBO J. 10, 3683-

3691 (1991)). For expressing the human EGF-R cDNA (cf. Ullrich, A. et al. in Nature 309, 418-425 (1984)) recombinant retroviruses were used as described by von Rüden, T. et al., EMBO J. 7, 2749-2756 (1988), except that the retroviral vector LXSN (cf. Miller, A. D. et al. in BioTechniques 7, 980-990 (1989)) was used for the expression of the EGF-R cDNA and the line GP+E86 (cf. Markowitz, D. et al. in J. Virol. 62, 1120-1124 (1988)) was used as the packaging cell.

The test was performed as follows:

F/L-HERc cells were cultivated in RPMI/1640 medium (Bio-Whittaker), supplemented with 10 % foetal calf serum (FCS, Boehringer Mannheim), 2 mM glutamine (BioWhittaker), standard antibiotics and 20 ng/ml of human EGF (Promega), at 37°C and 5% CO_2. In order to investigate the inhibitory activity of the compounds according to the invention, 1.5 x 10^4 cells per well were cultivated in triplicate in 96-well dishes in the above medium (200 µl), the cell proliferation being stimulated with either EGF (20 ng/ml) or murine IL-3. The IL-3 used was obtained from culture supernatants of the cell line X63/0 mIL-3 (cf. Karasuyama, H. et al. in Eur. J. Immunol. 18, 97-104 (1988)). The compounds according to the invention were dissolved in 100% dimethylsulphoxide (DMSO) and added to the cultures in various dilutions, the maximum DMSO concentration being 1%. The cultures were incubated for 48 hours at 37°C.

In order to determine the inhibitory activity of the compounds according to the invention the relative cell number was measured in O.D. units using the Cell Titer 96™ AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). The relative cell number was calculated as a percentage of the control (F/LHERc cells without inhibitor) and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC_{50}) was derived therefrom. The following results were obtained:

Compound (Example No.)	Inhibition of EGF-dependent proliferation IC_{50} [nM]
1	<0.35
2(3)	0.35
1(7)	<0.5
3	5
3(1)	0.2

The compounds of general formula I according to the invention thus inhibit signal transduction by tyrosine kinases, as demonstrated by the example of the human EGF receptor, and are therefore useful for treating pathophysiological processes caused by hyperfunction of tyrosine kinases. These are e.g. benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and the abnormal proliferation of vascular endothelial cells (neoangiogenesis).

The compounds according to the invention are also useful for preventing and treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosine kinases, e.g. in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasis, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

The compounds are also suitable for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosine kinases, such as may be found e.g. in chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative

colitis, and ulcers in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Ménétrier's disease, secreting adenomas and protein loss syndrome.

In addition, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat other diseases caused by abnormal function of tyrosine kinases, such as e.g. epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of haematopoietic cells, etc.

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastine), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), antibodies, etc. For treating respiratory tract diseases, these compounds may be used on their own or in conjunction with other therapeutic agents for the airways, such as substances with a secretolytic, broncholytic and/or antiinflammatory activity. For treating diseases in the region of the gastrointestinal tract, these compounds may also be administered on their own or in conjunction with substances having an effect on motility or secretion. These combinations may be administered either simultaneously or sequentially.

These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intraperitoneal or intranasal route, by inhalation or transdermally or orally, whilst aerosol formulations are particularly suitable for inhalation.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it:

Preparation of the starting compounds:

Example I

6-Amino-4-[(3-bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxyl-quinazoline

1.00 g of 4-[(3-bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-6-nitro-quinazoline is dissolved in 16 ml of water, 35 ml of ethanol and 1.3 ml of glacial acetic acid and heated to boiling. Then 540 mg of iron powder are added with stirring. The reaction mixture is refluxed for about another 35 minutes. For working up the cooled reaction mixture is diluted with 15 ml of ethanol, made alkaline with 15 N sodium hydroxide solution, combined with 20 g of Extrelute and stirred for about 20 minutes. The precipitate formed is suction filtered and washed with 200 ml of warm ethanol. The filtrate is concentrated by evaporation, mixed with about 30 ml of water and extracted 3 x with 70 ml of methylene chloride/methanol (9:1) each time. The combined extracts are dried over

sodium sulphate and concentrated by evaporation, leaving a beige solid.
Yield: 716 mg (76 % of theory),
Melting point: 191-198°C
Mass spectrum (ESI^+): m/z = 470, 472 $[M+H]^+$

The following compounds are obtained analogously to Example I:

(1) 6-Amino-4-[(3-bromophenyl)amino]-7-[2-(1-methyl-piperidin-4-yl)ethoxy]-quinazoline
Melting point: 197°C
Mass spectrum (ESI^+): m/z = 456, 458 $[M+H]^+$

(2) 6-Amino-4-[(3-bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)methoxy]-quinazoline
Melting point: 207-208°C
Mass spectrum (ESI^+): m/z = 442, 444 $[M+H]^+$

(3) 6-Amino-4-[(3-bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)oxy]-quinazoline
Melting point: 170°C
Mass spectrum (ESI^+): m/z = 428, 430 $[M+H]^+$

(4) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropyl-methoxy-quinazoline
Melting point: 209°C
R_f value: 0.68 (silica gel, ethyl acetate)

(5) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclobutyl-oxy-quinazoline
R_f value: 0.32 (silica gel, cyclohexane/ethyl acetate = 3:4)
Mass spectrum (ESI^+): m/z = 359, 361 $[M+H]^+$

(6) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopentyl-oxy-quinazoline
R_f value: 0.33 (silica gel, cyclohexane/ethyl acetate = 1:1)
Mass spectrum (ESI^+): m/z = 373, 375 $[M+H]^+$

(7) 6-Amino-4-[(R)-(1-phenyl-ethyl)amino]-7-cyclobutyloxy-quinazoline
R_f value: 0.28 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 335 $[M+H]^+$

(8) 6-Amino-4-[(*R*)-(1-phenyl-ethyl)amino]-7-cyclopropylmethoxy-quinazoline
R_f value: 0.54 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 335 $[M+H]^+$

(9) 6-Amino-4-[(*R*)-(1-phenyl-ethyl)amino]-7-cyclopentyloxy-quinazoline
R_f value: 0.20 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 349 $[M+H]^+$

(10) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-quinazoline
R_f value: 0.12 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 444, 446 $[M+H]^+$

(11) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline
Melting point: 162-164°C
R_f value: 0.55 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 387, 389 $[M-H]^-$

(12) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(*S*)-(tetrahydrofuran-3-yl)oxy]-quinazoline
R_f value: 0.27 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 373, 375 $[M-H]^-$

(13) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydropyran-4-yl)oxy]-quinazoline
R_f value: 0.41 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 387, 389 $[M-H]^-$

(14) 6-Amino-4-[(*R*)-(1-phenyl-ethyl)amino]-7-[2-(azetidin-1-yl)-ethoxy]-quinazoline
R_f value: 0.37 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 364 $[M+H]^+$

(15) 6-Amino-4-[(*R*)-(1-phenyl-ethyl)amino]-7-[2-(4-methyl-perhydro-1,4-diazepin-1-yl)-ethoxy]-quinazoline
R_f value: 0.10 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)
Mass spectrum (ESI^+): m/z = 421 $[M+H]^+$

(16) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-methyl-perhydro-1,4-diazepin-1-yl)-propyloxy]-quinazoline
R_f value: 0.09 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 459, 461 $[M+H]^+$

(17) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(azetidin-1-yl)-propyloxy]-quinazoline
R_f value: 0.11 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 402, 404 $[M+H]^+$

Example II

4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-6-nitro-quinazoline

To a solution of 1.45 g of 3-(1-methyl-piperidin-4-yl)-propan-1-ol in 40 ml of tetrahydrofuran are added 360 mg of sodium hydride. The white suspension formed is stirred for 15 minutes at 65°C, cooled and mixed with 1.45 g of 4-[(3-bromophenyl)-amino]-7-fluoro-6-nitro-quinazoline, whereupon the mixture suddenly turns dark red. The reaction mixture is stirred first for 10 minutes at ambient temperature, then for 45 minutes at 65°C. As the reaction is not yet complete, a further 150 mg of

sodium hydride are added and the mixture is stirred for a further 45 minutes at 65°C. The solvent is distilled off using a rotary evaporator and the brown residue is stirred with 50 ml of ice water. The aqueous phase is extracted with methylene chloride. The combined extracts are washed with water, dried over sodium sulphate and concentrated by evaporation. The crude product is purified by chromatography over a silica gel column with methylene chloride/methanol/concentrated ammonia solution (90:10:0.05).
Yield: 1.30 g of (65 % of theory),
R_f value: 0.28 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI$^+$): m/z = 500, 502 $[M+H]^+$

The following compounds are prepared analogously to Example II:

(1) 4-[(3-Bromophenyl)amino]-7-[2-(1-methyl-piperidin-4-yl)-ethoxy]-6-nitro-quinazoline
Melting point: 152°C
Mass spectrum (ESI$^+$): m/z = 486, 488 $[M+H]^+$

(2) 4-[(3-Bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)-methoxy]-6-nitro-quinazoline
Melting point: 205-207°C
Mass spectrum (ESI$^+$): m/z = 472, 474 $[M+H]^+$

(3) 4-[(3-Bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)oxy]-6-nitro-quinazoline
Melting point: 219°C
Mass spectrum (ESI$^+$): m/z = 458, 460 $[M+H]^+$

(4) 4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxy-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
Melting point: 211-213°C
Mass spectrum (ESI$^+$): m/z = 389, 391 $[M+H]^+$

(5) 4-[(3-chloro-4-fluorophenyl)amino]-7-cyclobutyloxy-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
Melting point: 235°C
R_f value: 0.65 (silica gel, cyclohexane/ethyl acetate = 3:4)

(6) 4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopentyloxy-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
Melting point: 230°C
Mass spectrum (ESI$^+$): m/z = 403, 405 $[M+H]^+$

(7) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-cyclobutyloxy-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
Melting point: 108-110°C
R_f value: 0.54 (silica gel, ethyl acetate)

(8) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-cyclopropylmethoxy-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
Melting point: 155°C
R_f value: 0.24 (silica gel, cyclohexane/ethyl acetate = 1:1)

(9) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-cyclopentyloxy-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
R_f value: 0.24 (silica gel, petroleum ether/ethyl acetate = 1:1)
Mass spectrum (ESI$^+$): m/z = 379 $[M+H]^+$

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-quinazoline
R_f value: 0.30 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI$^+$): m/z = 474, 476 $[M+H]^+$

(11) 4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydrofuran-2-yl)methoxy]-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
R_f value: 0.47 (silica gel, ethyl acetate)
Mass spectrum (ESI^-): m/z = 417, 419 $[M-H]^-$

(12) 4-[(3-chloro-4-fluorophenyl)amino]-7-[(*S*)-(tetrahydrofuran-3-yl)oxy]-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
R_f value: 0.45 (silica gel, ethyl acetate)
Mass spectrum (ESI^-): m/z = 403, 405 $[M-H]^-$

(13) 4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydropyran-4-yl)oxy]-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
R_f value: 0.41 (silica gel, ethyl acetate)
Mass spectrum (ESI^-): m/z = 417, 419 $[M-H]^-$

(14) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-[2-(tetrahydropyran-2-yloxy)-ethoxy]-6-nitro-quinazoline
R_f value: 0.12 (silica gel, cyclohexane/ethyl acetate = 1:1)
Mass spectrum (ESI^+): m/z = 439 $[M+H]^+$

(15) 4-[(3-chloro-4-fluorophenyl)amino]-7-{3-[(tert.butyl-dimethylsilyl)oxy]-propyloxy}-6-nitro-quinazoline (carried out in dimethylformamide with potassium tert.butoxide as base)
R_f value: 0.87 silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 507, 509 $[M+H]^+$

Example III

4-[(R)-(1-Phenyl-ethyl)amino]-6-nitro-7-fluoro-quinazoline
A solution of 74 ml of (*R*)-1-phenyl-ethylamine in 100 ml of dioxan is added dropwise to 108.8 g of 4-chloro-6-nitro-7-fluoro-quinazoline in 800 ml of methylene chloride with

cooling. The reaction mixture is washed with water after stirring overnight at room temperature, the organic phase is separated, dried and evaporated. The residue obtained is purified by chromatography over a silica gel column (petroleum ether/ethyl acetate = 1:1).
Yield: 52.9 g (35% of theory),
Melting point: 203°C
Mass spectrum (ESI$^+$): m/z = 313 $[M+H]^+$

Example IV

4-[(*R*)-(1-Phenyl-ethyl)amino]-7-[2-(azetidin-1-yl)-ethoxy]-6-nitro-quinazoline

221 mg of dried potassium carbonate and 50 mg of sodium iodide were added to 600 mg of 4-[(*R*)-(1-phenyl-ethyl)amino]-7-[2-methanesulphonyloxy-ethoxy]-6-nitro-quinazoline and 0.34 ml of azetidine in 5.0 ml of acetonitrile. The reaction mixture was heated to 70°C with stirring. Subsequently 3 ml of acetonitrile were added after one hour and the mixture was stirred for about another 40 hours at 70°C. The solvent was removed *in vacuo* and the residue obtained was mixed with ice water. The precipitate was suction filtered and dried. The aqueous phase was extracted with methylene chloride and evaporated. The combined precipitates were dissolved in ethyl acetate and stirred together with a little silica gel and 120 mg of charcoal for further purification. The suspension obtained was filtered and evaporated yielding a yellow resin.
Yield: 518 mg (95 % of theory),
R_f value: 0.40 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI$^+$): m/z = 394 $[M+H]^+$

The following compounds were obtained analogously to Example IV:

(1) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-[2-(4-methyl-perhydro-1,4-diazepin-1-yl)-ethoxy]-6-nitro-quinazoline
R_f value: 0.30 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 451 $[M+H]^+$

(2) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-methyl-perhydro-1,4-diazepin-1-yl)-propyloxy]-6-nitro-quinazoline
R_f value: 0.34 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 80:20:0.1)
Mass spectrum (ESI^+): m/z = 489, 491 $[M+H]^+$

(3) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(azetidin-1-yl)-propyloxy]-6-nitro-quinazoline
R_f value: 0.23 silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 432, 434 $[M+H]^+$

Example V

4-[(*R*)-(1-Phenyl-ethyl)amino]-7-[2-(methanesulphonyloxy)-ethoxyl-6-nitro-quinazoline

A solution of 1.79 ml methanesulphonic acid chloride in 10 ml of methylene chloride was added dropwise to a mixture of 8.08 g of 4-[(*R*)-(1-phenyl-ethyl)amino]-7-(2-hydroxy-ethoxy)-6-nitro-quinazoline and 4.53 ml of ethyl-diisopropylamine in 90 ml of methylene chloride while cooling with ice. The reaction mixture was stirred for about one hour at room temperature during which time a further 0.4 ml of methanesulphonic acid chloride and 0.5 ml of ethyl-diisopropylamine were added to complete the reaction. Subsequently the reaction mixture was mixed with ice water and stirred after the addition of saturated aqueous sodium carbonate solution. The organic phase was separated, washed with water, dried over magnesium sulphate and evaporated. The dark resinous residue obtained was crystallised by stirring with a little tert.butyl methylether, suction filtered and dried in a desiccator.

Yield: 9.72 g (99 % of theory),
Melting point: 128-134°C
Mass spectrum (ESI^-): m/z = 431 $[M-H]^-$

The following compound was obtained analogously to Example V:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(methanesulphonyl-oxy)-propyloxy]-6-nitro-quinazoline
R_f value: 0.75 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 471, 473 $[M+H]^+$

Example VI

4-[(*R*)-(1-Phenyl-ethyl)amino]-7-(2-hydroxy-ethoxy)-6-nitro-quinazoline

2 ml of concentrated hydrochloric acid were added to 8.05 g of 4-[(*R*)-(1-phenyl-ethyl)amino]-7-[2-(tetrahydropyran-2-yloxy)-ethoxy]-6-nitro-quinazoline in 120 ml of methanol. After stirring for 1.5 hours at 50°C the reaction mixture was worked up by neutralising it with saturated sodium carbonate solution and evaporating it. The solid residue was dissolved in ethyl acetate and the solution obtained was washed with water, with saturated sodium chloride solution, dried over magnesium sulphate and evaporated. The yellow residue obtained was stirred with 20 ml of tert.butyl methylether, suction filtered and dried in a desiccator.
Yield: 4.53 g (91 % of theory),
Melting point: 192-194°C
Mass spectrum (ESI^-): m/z = 353 $[M-H]^-$

Example VII

4-[(3-chloro-4-fluorophenyl)amino]-7-(3-hydroxy-propyloxy)-6-nitro-quinazoline

Prepared from 4-[(3-chloro-4-fluorophenyl)amino]-7-{3-[(tert.-butyl-dimethylsilyl)oxy]-propyloxy}-6-nitro-quinazoline by

splitting off the protective silyl group with tetrabutyl ammonium fluoride in tetrahydrofuran.
Yield: 94 % of theory,
R_f value: 0.61 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^-): m/z = 391, 393 $[M-H]^-$

Preparation of the end products:

Example 1

4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline

To a solution of 300 mg of 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-quinazoline in 7 ml of dichloromethane are added 0.28 ml of triethylamine. The reaction mixture is cooled to about -10°C in an ice/sodium chloride cooling bath. Then a solution of 59 µl of acrylic acid chloride in 1 ml of tetrahydrofuran is added dropwise within 10 minutes. The cooling bath is removed and the mixture is stirred for a further 15 minutes at ambient temperature. For working up, the reaction mixture is poured on to 20 ml of ice water and mixed with 2-3 ml of 2 N sodium hydroxide solution, whereupon a light-coloured precipitate is formed. The precipitate is suction filtered, washed with cold water and dissolved in dichloromethane. The solution is dried over sodium sulphate and concentrated by evaporation. The resin-like crude product is purified by chromatography over a silica gel column with methylene chloride/methanol/concentrated ammonia solution (90:10:0.5).
Yield: 118 mg (35 % of theory)
R_f value: 0.35 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 524, 526 $[M+H]^+$

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-Bromophenyl)amino]-7-[2-(1-methyl-piperidin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 129°C
Mass spectrum (ESI^+): m/z = 510, 512 $[M+H]^+$

(2) 4-[(3-Bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)methoxy]-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 174°C
Mass spectrum (ESI^+): m/z = 496, 498 $[M+H]^+$

(3) 4-[(3-Bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)oxy]-6-[(vinylcarbonyl)amino]-quinazoline
Melting point: 166°C
Mass spectrum (ESI^+): m/z = 482, 484 $[M+H]^+$

(4) 4-[(3-Bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)oxy]-6-[(1-oxo-2-buten-1-yl)amino]-quinazoline
R_f value: 0.67 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 40:10:0.5)
Mass spectrum (ESI^+): m/z = 496, 498 $[M+H]^+$

(5) 4-[(3-Bromophenyl)amino]-7-[(1-methyl-piperidin-4-yl)methoxy]-6-[(1-oxo-2-buten-1-yl)amino]-quinazoline
R_f value: 0.45 (aluminium oxide, activity III; ethyl acetate/methanol = 4:1)
Mass spectrum (EI): m/z = 509, 511 $[M]^+$

(6) 4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)-propyloxy]-6-[(3-ethoxycarbonyl-1-oxo-2-propen-1-yl)amino]-quinazoline
R_f value: 0.28 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 596, 598 $[M+H]^+$

(7) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline
R_f value: 0.33 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 498, 500 $[M+H]^+$

(8) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-[2-(azetidin-1-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline
R_f value: 0.60 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^-): m/z = 416 $[M-H]^-$

(9) 4-[(*R*)-(1-Phenyl-ethyl)amino]-7-[2-(4-methyl-perhydro-1,4-diazepin-1-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline
R_f value: 0.37 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^-): m/z = 473 $[M-H]^-$

(10) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-methyl-perhydro-1,4-diazepin-1-yl)-propyloxy]-6-[(vinylcarbonyl)-amino]-quinazoline
R_f value: 0.29 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^+): m/z = 513, 515 $[M+H]^+$

(11) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(azetidin-1-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline
R_f value: 0.39 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)
Mass spectrum (ESI^-): m/z = 454, 456 $[M-H]^-$

Example 2

4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-6-[(1-oxo-2,4-hexadien-1-yl)amino]-quinazoline

To 31 mg of sorbic acid in 1 ml of tetrahydrofuran are added 40 µl of isobutyl chloroformate followed by 45 µl of N-methylmorpholine whilst cooling with an ice bath. The white suspension is stirred for one minute, then a solution of 100 mg of 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)propyloxy]-quinazoline in 1.5 ml of pyridine is added. The ice bath is removed and the reaction mixture is stirred overnight. For working up, it is poured onto 20 ml of ice water, stirred for 30 minutes and adjusted to pH 9-10 with a few drops of 2 N sodium hydroxide solution. The aqueous phase is extracted with methylene chloride, the combined organic phases are dried over sodium sulphate and concentrated by evaporation. The resin-like crude product is purified by chromatography over an aluminium oxide column (activity III) with methylene chloride/methanol (99.5:0.5).
Yield: 62 mg (52 % of theory),
R_f value: 0.29 (aluminium oxide, activity III; methylene chloride/methanol = 98:2)
Mass spectrum (EI): m/z = 563, 565 $[M]^+$

The following compounds are obtained analogously to Example 2:

(1) 4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)-propyloxy]-6-[(1-oxo-2-buten-1-yl)amino]-quinazoline
R_f value: 0.26 (aluminium oxide, activity III; methylene chloride/methanol = 98:2)
Mass spectrum (ESI^+): m/z = 538, 540 $[M+H]^+$

(2) 4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)-propyloxy]-6-[(3-phenyl-1-oxo-2-propen-1-yl)amino]-quinazoline
R_f value: 0.26 (aluminium oxide, activity III; methylene chloride/methanol = 98:2)
Mass spectrum (EI): m/z = 599, 601 $[M]^+$

(3) 4-[(3-Bromophenyl)amino]-7-[3-(1-methyl-piperidin-4-yl)-propyloxy]-6-[(1-oxo-2-butyn-1-yl)amino]-quinazoline

R_f value: 0.40 (aluminium oxide, activity III; methylene chloride/methanol = 98:2)
Mass spectrum (ESI^+): m/z = 536, 538 $[M+H]^+$

Example 3

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

To a solution of 640 mg of 4-bromo-2-butenoic acid in 10 ml of methylene chloride are added, at ambient temperature, 0.67 ml of oxalyl chloride and one drop of dimethylformamide. The reaction mixture is stirred for about another half hour at ambient temperature, until the development of gas has ceased. The acid chloride formed is substantially freed from solvent *in vacuo* using a rotary evaporator. Then the crude product is dissolved in 10 ml of methylene chloride and added dropwise, whilst cooling with an ice bath, to a mixture of 1.00 g of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxy-quinazoline and 1.60 ml of Hünig base in 50 ml of tetrahydrofuran. The reaction mixture is stirred for 1.5 hours in an ice bath and for a further 2 hours at ambient temperature. Then 2.90 ml of diethylamine are added and the mixture is stirred for 2.5 days at ambient temperature. To work it up, the reaction mixture is filtered and the filtrate is concentrated by evaporation. The filter residue is purified by chromatography over a silica gel column with ethyl acetate/methanol (19:1).
Yield: 550 mg (40 % of theory),
Melting point: 114°C
Mass spectrum (ESI^+): m/z = 498, 500 $[M+H]^+$

The following compounds are obtained analogously to Example 3:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.53 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 510, 512 $[M-H]^-$

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-ethyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.44 (silica gel, ethyl acetate/methanol/concentrated aqueous ammonia solution = 9:1:0.1)
Mass spectrum (EI): m/z = 538, 540 $[M]^+$

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2,6-dimethyl-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
Melting point: 160°C
Mass spectrum (ESI^+): m/z = 540, 542 $[M+H]^+$

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
Melting point: 137°C
Mass spectrum (ESI^+): m/z = 470, 472 $[M+H]^+$

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(1-oxido-thiomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
Melting point: 239°C
Mass spectrum (ESI^+): m/z = 544, 546 $[M+H]^+$

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline
R_f value: 0.45 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 512, 514 $[M+H]^+$

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline
Melting point: 143°C
R_f value: 0.45 (silica gel, ethyl acetate/methanol = 9:1)

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

Melting point: 111°C
R_f value: 0.21 (silica gel, ethyl acetate/methanol = 9:1)

(9) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline
Melting point: 105°C
R_f value: 0.23 (silica gel, ethyl acetate/methanol = 9:1)

(10) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline
R_f value: 0.33 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 488 $[M+H]^+$

(11) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.37 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 488 $[M+H]^+$

(12) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline
R_f value: 0.35 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 502 $[M+H]^+$

(13) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline
R_f value: 0.26 (silica gel, ethyl acetate/methanol = 4:1)
Mass spectrum (ESI$^+$): m/z = 474 $[M+H]^+$

(14) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline
R_f value: 0.31 (silica gel, ethyl acetate/methanol = 4:1)
Mass spectrum (ESI$^+$): m/z = 488 $[M+H]^+$

(15) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.15 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI$^+$): m/z = 474 $[M+H]^+$

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(1-methyl-piperidin-4-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.28 (silica gel, ethyl acetate/methanol/concentrated aqueous ammonia solution = 80:20:2)
Mass spectrum (ESI$^+$): m/z = 553, 555 $[M+H]^+$

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*R*)-2-methoxymethyl-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.33 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 540, 542 $[M+H]^+$

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*S*)-2-methoxymethyl-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
Melting point: 120°C
Mass spectrum (ESI$^+$): m/z = 540, 542 $[M+H]^+$

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.51 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 558, 560 $[M+H]^+$

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.33 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 528, 530 $[M+H]^+$

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.22 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI^+): m/z = 510, 512 $[M+H]^+$

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2-methyl-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.21 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 524, 526 $[M+H]^+$

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.10 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 496, 498 $[M+H]^+$

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-cyclopropyl-methyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
Melting point: 117°C
Mass spectrum (ESI^+): m/z = 565, 567 $[M+H]^+$

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2-methyl-pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
Melting point: 108-110°C
R_f value: 0.27 (silica gel, ethyl acetate/methanol = 9:1)

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.29 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 538, 540 $[M-H]^-$

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(cis-2,6-dimethyl-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.27 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 536, 538 $[M-H]^-$

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2,5-dimethyl-pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline
R_f value: 0.36 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 522, 524 $[M-H]^-$

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline
R_f value: 0.35 (silica gel, ethyl acetate/methanol/concentrated aqueous ammonia solution = 9:1:0.1)
Mass spectrum (ESI^-): m/z = 526, 528 $[M-H]^-$

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(*S*)-(tetrahydrofuran-3-yl)oxy]-quinazoline
Melting point: 119°C
Mass spectrum (ESI^-): m/z = 512, 514 $[M-H]^-$

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-diethylamino-methyl-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclo-propylmethoxy-quinazoline
R_f value: 0.20 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 593, 595 $[M-H]^-$

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-methyl-N-cyclopropylmethyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.73 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 510, 512 $[M+H]^+$

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxypropyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline (The N-methyl-N-(2-methoxypropyl)-amine used was prepared by reacting

2-methoxypropionic acid chloride with methylamine and subsequently reducing with lithium aluminium hydride)
Melting point: 123-125°C
R_f value: 0.66 (silica gel, methylene chloride/methanol = 9:1)

(34) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(3-methoxypropyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.66 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 528, 530 $[M+H]^+$

(35) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-methoxy-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline
Melting point: 129-130°C
R_f value: 0.20 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 538, 540 $[M-H]^-$

(36) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-hydroxy-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline
R_f value: 0.30 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 9:1:0.1)
Mass spectrum (ESI^-): m/z = 524, 526 $[M-H]^-$

(37) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)oxy]-quinazoline
R_f value: 0.47 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 528, 530 $[M-H]^-$

(38) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-yl-methyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
Melting point: from 145°C (decomposition)
R_f value: 0.23 (silica gel, methylene chloride/methanol = 15:1)
Mass spectrum (ESI^+): m/z = 540, 542 $[M+H]^+$

(39) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-3-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
(The starting N-methyl-N-(3-tetrahydrofuranyl)-amine was prepared by reaction of tetrahydrofuran-3-carboxylic acid with diphenyl phosphonate azide in benzyl alcohol and subsequent reduction of the 3-(benzyloxycarbonylamino)-tetrahydrofuran obtained with lithium aluminium hydride)
Melting point: 157-159°C
R_f value: 0.23 (silica gel, methylene chloride/methanol = 15:1)
Mass spectrum (ESI$^+$): m/z = 526, 528 $[M+H]^+$

(40) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(1-methoxy-2-propyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
(The starting N-methyl-N-(1-methoxy-2-propyl)-amine was prepared by reductive amination of methoxyacetone with methylamine hydrochloride and sodium triacetoxyborohydride in the presence of sodium acetate. The reaction was carried out in tetrahydrofuran)
R_f value: 0.38 (silica gel, ethyl acetate/methanol = 9:1)
Mass spectrum (ESI$^+$): m/z = 528, 530 $[M+H]^+$

The following compounds may also be obtained analogously to the above Examples and other methods known from the literature:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dibutylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(piperidin-1-yl)-

1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2,6-dimethyl-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-methyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-cyclopropylmethyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-cyclopropyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-methylsulphonyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(9) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-acetyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{4-[(N,N-dimethylamino)carbonyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)-amino]-7-cyclopropylmethoxy-quinazoline

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-methyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethyl-amino)-1-oxo-2-butyn-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethyl-amino)-1-oxo-2-butyn-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(piperidin-1-yl)-1-oxo-2-butyn-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-butyn-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-methyl-piperazin-1-yl)-1-oxo-2-butyn-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-methylsulphonyl-piperazin-1-yl)-1-oxo-2-butyn-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1,4-dioxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(3-N,N-dimethyl-amino-propan-1-yl)amino]-1,4-dioxo-2-buten-1-yl}amino]-7-cyclopropylmethoxy-quinazoline

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-({2-[(N,N-diethyl-amino)methyl]-1-oxo-2-propen-1-yl}amino]-7-cyclopropylmethoxy-quinazoline

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2-methoxymethyl-pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutylmethoxy-quinazoline

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentylmethoxy-quinazoline

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclohexylmethoxy-quinazoline

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(2-cyclopropyl-ethoxy)-quinazoline

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(3-cyclopropyl-propyloxy)-quinazoline

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[4-(tetrahydrofuran-3-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[4-(morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[4-(tetrahydrofuran-3-yl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(34) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[4-(tetrahydrofuran-2-yl-methyl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(35) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-methyl-N-[1-(tetrahydrofuran-3-yl)-piperidin-4-yl]-amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

(36) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*S*)-2-methoxymethyl-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(37) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*R*)-2-methoxymethyl-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(38) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(39) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(40) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*S*)-N-methyl-N-(1-methoxy-2-propyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(41) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*R*)-N-methyl-N-(1-methoxy-2-propyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(42) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(1-methoxy-2-propyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(43) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxypropyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(44) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(3-methoxypropyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(45) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-3-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(46) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*S*)-N-methyl-N-(tetrahydrofuran-3-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(47) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*R*)-N-methyl-N-(tetrahydrofuran-3-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(48) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(49) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(50) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-cyclopropyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(51) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-cyclopropylmethyl-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(52) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(53) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropylmethyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(54) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(55) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*R*)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxy-quinazoline

(56) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(*S*)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxy-quinazoline

(57) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(58) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2-methyl-pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(59) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2,5-dimethyl-pyrrolidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(60) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(61) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2-methyl-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(62) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2,6-dimethyl-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(63) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-hydroxy-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(64) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(4-methoxy-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(65) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxy-quinazoline

(66) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(3-methyl-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(67) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(3,5-dimethyl-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(68) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-3-yl-oxy)-quinazoline

(69) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydropyran-4-yl-oxy)-quinazoline

(70) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-2-yl-methoxy)-quinazoline

(71) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(azetidin-1-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline

(72) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-methyl-homopiperazin-1-yl)propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline

Example 4

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm

using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg
die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 5

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg
Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example 6

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	50.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg
die: 10 mm, flat

Example 7

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		50.0 mg
corn starch (dried)	approx.	80.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg
Capsule shell: size 1 hard gelatine capsule.

Example 8

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 9

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g

dist. water	ad	100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 10

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 11

Ampoules containing 50 mg of active substance

Composition:

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Example 12

Capsules for powder inhalation containing 5 mg of active substance

1 capsule contains:

active substance	5.0 mg
lactose for inhalation	15.0 mg
	20.0 mg

Preparation:
The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg).

weight of capsule: 70.0 mg
size of capsule = 3

Example 13

Solution for inhalation for hand-held nebulisers containing 2.5 mg active substance

1 spray contains:

active substance	2.500 mg
benzalkonium chloride	0.001 mg

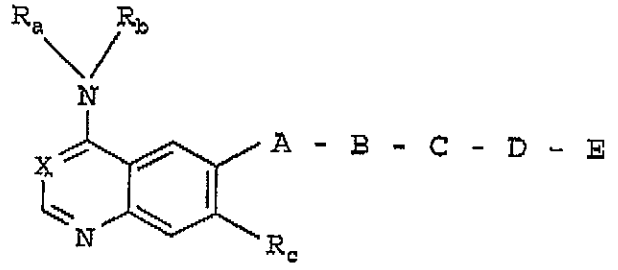
1N hydrochloric acid q.s.	
ethanol/water (50/50)	ad 15.000 mg

Preparation:
The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered and transferred into suitable containers for use in hand-held nebulisers (cartridges).

Contents of the container: 4.5 g

Patent Claims

1. Bicyclic heterocycles of general formula,



, (I)

wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group, whilst the phenyl nucleus is substituted in each case by the radicals R_1 and R_2, whilst

R_1 and R_2, which may be identical or different, each denotes a hydrogen, fluorine, chlorine or bromine atom,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene, ethynylene or 1,3-butadien-1,4-ylene group,

D denotes an C_{1-3}-alkylene group,

E denotes a Di-(C_{1-4}-alkyl)-amino group, wherein the alkyl moieties may be identical or different,

a methylamino or ethylamino group each substituted at the nitrogen atom by a 2-methoxy-ethyl, 1-methoxy-2-propyl, 2-methoxy-propyl, 3-methoxy-propyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, tetrahydrofuran-2-ylmethyl, 1-methyl-piperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(tetrahydrofuran-3-yl)-piperidin-4-yl, cyclopropyl or cyclopropylmethyl group,

a bis-(2-methoxyethyl)-amino group,

a pyrrolidino, piperidino or morpholino group each optionally substituted by one or two methyl groups,

a piperazino group substituted in 4-position by a methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-methoxy-ethyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl or tetrahydrofuran-2-ylmethyl group,

a thiomorpholino, S-oxido-thiomorpholino or S,S-dioxido-thiomorpholino group,

a 2-(methoxymethyl)-pyrrolidino, 2-(ethoxymethyl)-pyrrolidino, 4-hydroxy-piperidino, 4-methoxy-piperidino, 4-ethoxy-piperidino, 4-(tetrahydrofuran-3-yl)-piperidino or 4-morpholino-piperidino group, and

R_c denotes a cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy group,

a cyclobutyloxy, cyclopentyloxy or cyclohexyloxy group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuran-2-ylmethoxy group,

the tautomers, stereoisomers and salts thereof.

2. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a 1-phenylethyl group or a phenyl group wherein the phenyl nucleus is substituted by the radicals R_1 and R_2, whilst

R_1 and R_2, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

X denotes a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene, ethynylene or 1,3-butadien-1,4-ylene group,

D denotes a methylene group,

E denotes a dimethylamino, diethylamino, bis-(2-methoxy-ethyl)-amino, N-methyl-N-(2-methoxy-ethyl)-amino, N-ethyl-N-(2-methoxy-ethyl)-amino, N-methyl-N-cyclopropyl-amino, N-methyl-N-cyclopropylmethyl-amino, N-methyl-N-(1-methoxy-

2-propyl)-amino, N-methyl-N-(2-methoxy-propyl)-amino, N-methyl-N-(3-methoxy-propyl)-amino-, N-methyl-N-(tetrahydrofuran-3-yl)-amino, N-methyl-N-(tetrahydropyran-4-yl)-amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino or N-methyl-N-(1-methyl-piperidin-4-yl)-amino group,

a pyrrolidino, piperidino or morpholino group each optionally substituted by one or two methyl groups,

a piperazino group substituted in the 4-position by a methyl, ethyl, cyclopropylmethyl or 2-methoxy-ethyl group,

an S-oxido-thiomorpholino group,

a 2-(methoxy-methyl)-pyrrolidino, 4-hydroxy-piperidino or 4-methoxy-piperidino group, and

R_c denotes a cyclopropylmethoxy, cyclobutyloxy or cyclopentyloxy group,

a tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuran-2-ylmethoxy group,

the tautomers, stereoisomers and salts thereof.

3. The following compounds of general formula I according to claim 1:

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline and

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

as well as the salts thereof.

4. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 3 with inorganic or organic acids or bases.

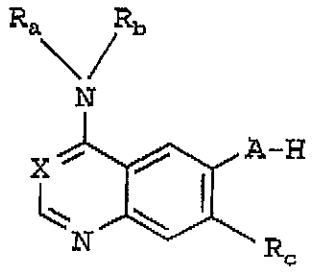
5. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 3 or a physiologically acceptable salt according to claim 4 optionally together with one or more inert carriers and/or diluents.

6. Use of a compound according to at least one of claims 1 to 4 for preparing a pharmaceutical composition which is suitable for treating benign or malignant tumours, for preventing and treating diseases of the airways and lungs and for treating diseases of the gastrointestinal tract and the bile duct and gall bladder.

7. Process for preparing a pharmaceutical composition according to claim 5, characterised in that a compound according to at least one of claims 1 to 4 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

8. Process for preparing the compounds of general formula I according to claims 1 to 5, characterised in that

a) a compound of general formula



, (II)

wherein

R_a to R_c, A and X are defined as in claims 1 to 3, is reacted with a compound of general formula

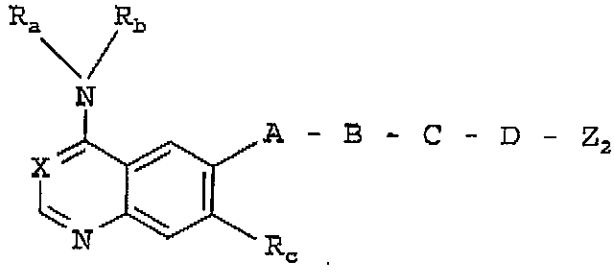
$$Z_1 - B - C - D - E \qquad , (III)$$

wherein

B to E are defined as in claims 1 to 3 and

Z_1 denotes a leaving group, or

b) in order to prepare compounds of general formula I wherein the group E is linked to the group D via a nitrogen atom, a compound of general formula



, (IV)

wherein

R_a to R_c, A to D and X are defined as in claims 1 to 3 and

Z_2 denotes a leaving group, is reacted with a compound of general formula

H - E´ , (V)

wherein
E´ denotes one of the groups mentioned for E in claims 1 to 3 which is linked to the group D via a nitrogen atom, and

if desired a compound of general formula I thus obtained which contains an amino, alkylamino or imino group is converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I and/or

a compound of general formula I thus obtained which contains an amino, alkylamino or imino group is converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy or hydroxyphosphoryl group is converted by esterification into a corresponding ester of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy or ester group is converted by reaction with a corresponding amine into a corresponding amide of general formula I and/or

if necessary any protecting group used during the above reactions is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof.