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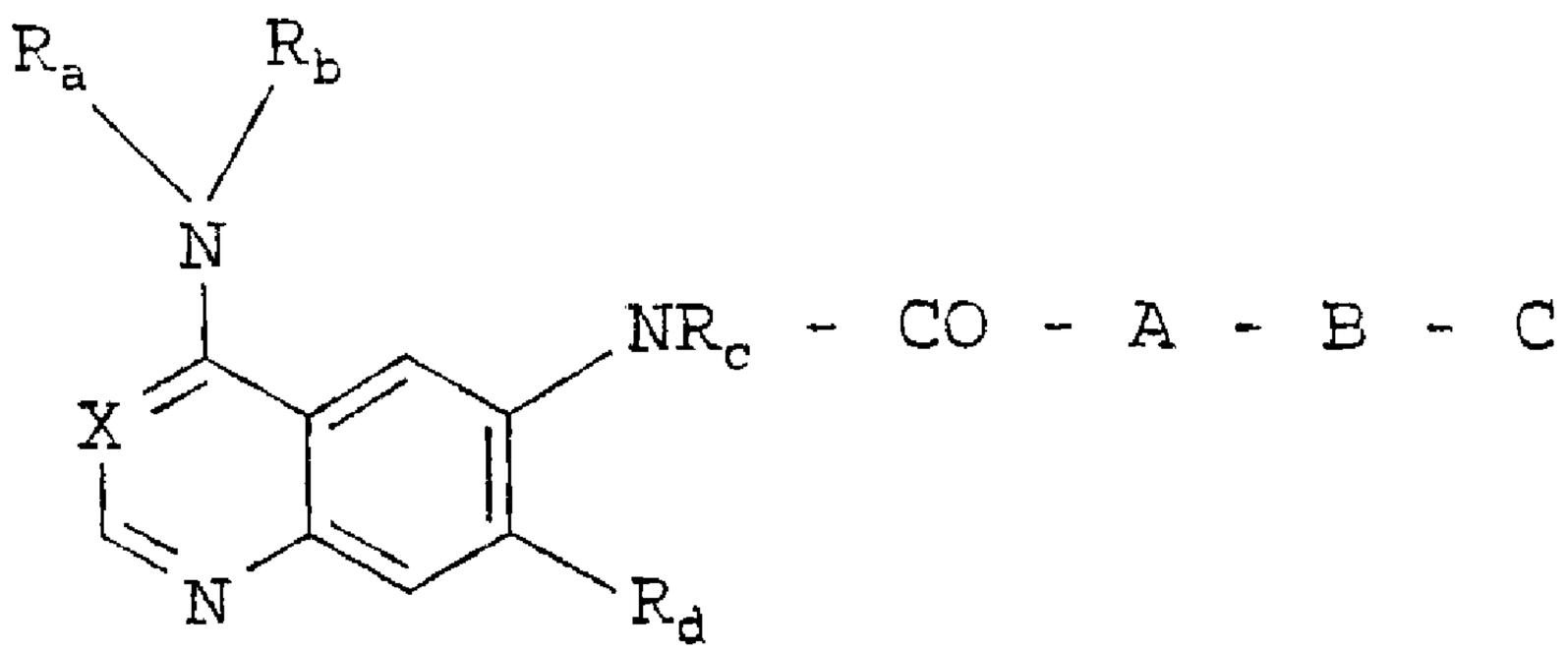
(54) Titre : HETEROCYCLES BICYCLIQUES, COMPOSITIONS PHARMACEUTIQUES CONTENANT CES COMPOSES, LEUR UTILISATION ET LEUR PROCEDE DE PREPARATION

(54) Title: BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS, THEIR USE AND PROCESSES FOR PREPARING THEM



(I)

(57) Abrégé/Abstract:
The invention relates to bicyclic heterocycles of the general formula (I), wherein R_a to R_d, A to C and X are defined as in claims 1 to 5. The invention further relates to the tautomers, stereoisomers and salts thereof, especially the physiologically salts with inorganic or organic acids or bases thereof, having valuable pharmacological properties, especially an inhibitory effect on tyrosine kinase mediated signal transduction. The invention further relates to the use of said compounds for treating diseases, especially tumor diseases, diseases of the lungs and the respiratory tract, and to the production of said compounds.

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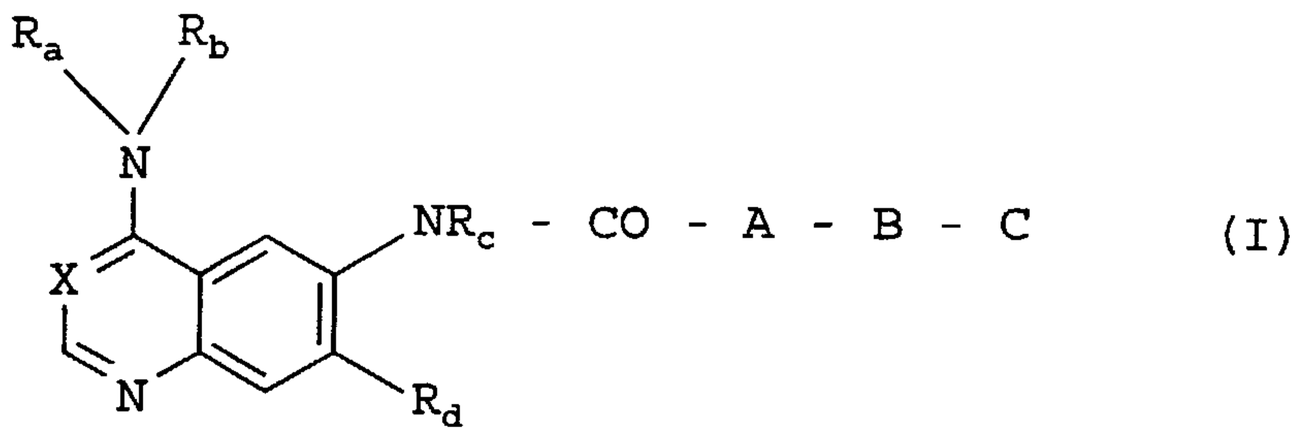
[Fortsetzung auf der nächsten Seite]

(54) Title: BICYCLIC HETEROCYLCES, MEDICAMENTS CONTAINING SAID COMPOUNDS, THE USE THEREOF AND METHOD FOR PRODUCING THEM

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



(57) Abstract: The invention relates to bicyclic heterocycles of the general formula (I), wherein R_a to R_d, A to C and X are defined as in claims 1 to 5. The invention further relates to the tautomers, stereoisomers and salts thereof, especially the physiologically salts with inorganic or organic acids or bases thereof, having valuable pharmacological properties, especially an inhibitory effect on tyrosine kinase mediated signal transduction. The invention further relates to the use of said compounds for treating diseases, especially tumor diseases, diseases of the lungs and the respiratory tract, and to the production of said compounds.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft bicyclische Heterocyclen der allgemeinen Formel (I), in der R_a bis R_d, A bis C und X wie in den Ansprüchen 1 bis 5 erwähnt definiert sind, deren Tautomeren, deren Stereoisomere und deren Salze, insbesondere deren physiologisch verträglichen 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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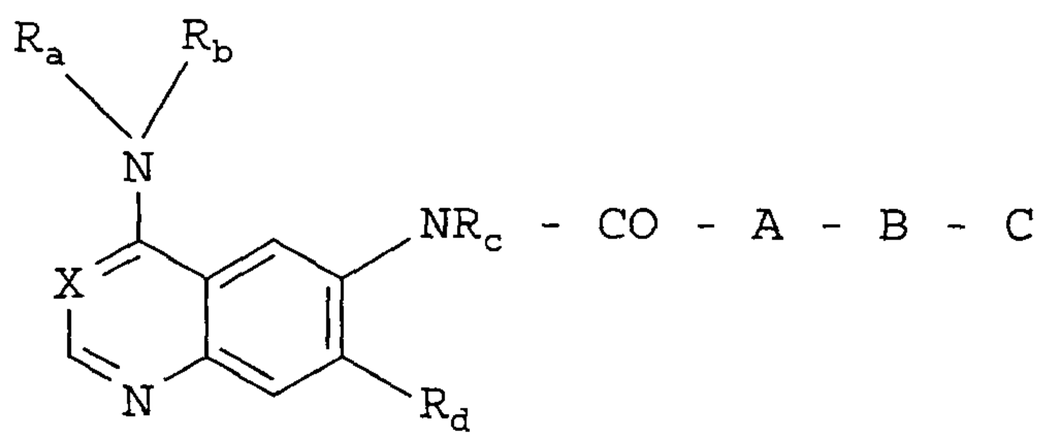
Bicyclic heterocycles, pharmaceutical compositions containing these compounds, their use and processes for preparing them

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

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

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 in each case is substituted 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, whilst 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,

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

R_d denotes a hydrogen atom, a C_{1-6}-alkoxy, C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group,

a C_{2-6}-alkoxy group, which is substituted from position 2 by a hydroxy, C_{1-4}-alkoxy, C_{4-7}-cycloalkoxy, C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, di-(C_{1-4}-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C_{1-4}-alkyl)-piperazino group, whilst the abovementioned cyclic imino groups may be substituted by one or two C_{1-2}-alkyl groups,

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

A denotes a 1,1- or 1,2-vinylene group optionally substituted by a methyl or trifluoromethyl group or by two methyl groups,

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

B denotes a C_{1-6}-alkylene group wherein one or two hydrogen atoms may be replaced by fluorine atoms, or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a pyrrolidino group wherein the two hydrogen atoms in the 2 position are replaced by a group D, wherein

D denotes a $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2-O-CO-CH_2CH_2-$, $-CH_2CH_2-O-CO-CH_2-$ or $-CH_2CH_2CH_2-O-CO-$ bridge optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group wherein the two hydrogen atoms in the 3 position are replaced by a group E, wherein

E denotes an $-O-CO-CH_2CH_2-$, $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-O-CO-CH_2CH_2CH_2-$, $-CH_2-O-CO-CH_2CH_2-$, $-CH_2CH_2-O-CO-CH_2-$,

$-CH_2CH_2CH_2-O-CO-$, $-O-CO-CH_2-NR_4-CH_2-$, $-CH_2-O-CO-CH_2-NR_4-$, $-O-CO-CH_2-O-CH_2-$ or $-CH_2-O-CO-CH_2-O-$ bridge optionally substituted by one or two C_{1-2}-alkyl groups,

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

a piperidino or hexahydroazepino group wherein the two hydrogen atoms in the 2 position are replaced by a group D, whilst D is as hereinbefore defined,

a piperidino or hexahydroazepino group wherein the two hydrogen atoms in the 3 position or in the 4 position are replaced by a group E, whilst E is as hereinbefore defined,

a piperazino or 4-(C_{1-4}-alkyl)-piperazino group wherein the two hydrogen atoms in the 2 position or in the 3 position of the piperazino ring are replaced by a group D, where D is as hereinbefore defined,

a pyrrolidino or piperidino group wherein two vicinal hydrogen atoms are replaced by an $-O-CO-CH_2-$, $-CH_2-O-CO-$, $-O-CO-CH_2CH_2-$, $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-O-CO-CH_2-NR_4-$ or $-O-CO-CH_2-O-$ bridge optionally substituted by one or two C_{1-2}-alkyl groups, whilst R_4 is as hereinbefore defined and the heteroatoms of the abovementioned bridges are not bound at the 2 or 5 position of the pyrrolidine ring and are not bound at the 2 or 6 position of the piperidino ring,

a piperazino or 4-(C_{1-4}-alkyl)-piperazino group wherein a hydrogen atom in the 2 position together with a hydrogen atom in the 3 position of the piperazino ring are replaced by a $-CH_2-O-CO-CH_2-$ or $-CH_2CH_2-O-CO-$ bridge optionally substituted by one or two C_{1-2}-alkyl groups,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a $-CO-O-CH_2CH_2-$ or $-CH_2-O-CO-CH_2-$ bridge optionally

substituted by one or two C_{1-2}-alkyl groups, whilst in each case the left-hand end of the abovementioned bridges is bound to the 3 position of the piperazino ring,

a pyrrolidino, piperidino or hexahydroazepino group substituted by the group R_5, wherein

R_5 denotes a 2-oxo-tetrahydrofuranyl, 2-oxo-tetrahydropyranyl, 2-oxo-1,4-dioxanyl or 2-oxo-4-(C_{1-4}-alkyl)-morpholinyl group optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group substituted in the 3 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two C_{1-2}-alkyl groups,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two C_{1-2}-alkyl groups,

a 4-(C_{1-4}-alkyl)-piperazino or 4-(C_{1-4}-alkyl)-homopiperazino group substituted at a cyclic carbon atom by R_5 , wherein R_5 is as hereinbefore defined,

a piperazino or homopiperazino group substituted in the 4 position by the group R_6, wherein

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group substituted in the 3 position by a (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group wherein R_4 and R_6 are as hereinbefore defined,

a pyrrolidino, piperidino or hexahydroazepino group substituted by a R_5-C_{1-4}-alkyl, (R_4NR_6)-C_{1-4}-alkyl, R_6O-C_{1-4}-alkyl, R_6S-C_{1-4}-alkyl, R_6SO-C_{1-4}-alkyl, R_6SO_2-C_{1-4}-alkyl or R_4NR_6-CO group wherein R_4 to R_6 are as hereinbefore defined,

a pyrrolidino group substituted in the 3 position by a R_5-CO-NR_4, R_5-C_{1-4}-alkylene-$CONR_4$, (R_4NR_6)-C_{1-4}-alkylene-$CONR_4$, R_6O-C_{1-4}-alkylene-$CONR_4$, R_6S-C_{1-4}-alkylene-$CONR_4$, R_6SO-C_{1-4}-alkylene-$CONR_4$, R_6SO_2-C_{1-4}-alkylene-$CONR_4$, 2-oxo-morpholino-C_{1-4}-alkylene-$CONR_4$, R_5-C_{1-4}-alkylene-Y or C_{2-4}-alkyl-Y group, whilst the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups, wherein

R_4 to R_6 are as hereinbefore defined and

Y denotes an oxygen or sulphur atom, an imino, N-(C_{1-4}-alkyl)-imino, sulphinyl or sulphonyl group,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by a R_5-CO-NR_4, R_5-C_{1-4}-alkylene-$CONR_4$, (R_4NR_6)-C_{1-4}-alkylene-$CONR_4$, R_6O-C_{1-4}-alkylene-$CONR_4$, R_6S-C_{1-4}-alkylene-$CONR_4$, R_6SO-C_{1-4}-alkylene-$CONR_4$, R_6SO_2-C_{1-4}-alkylene-$CONR_4$, 2-oxo-morpholino-C_{1-4}-alkylene-$CONR_4$, R_5-C_{1-4}-alkylene-Y or C_{2-4}-alkyl-Y group wherein Y is as hereinbefore defined, the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups and the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 to R_6 are as hereinbefore defined,

a 4-(C_{1-4}-alkyl)-piperazino or 4-(C_{1-4}-alkyl)-homopiperazino group substituted at a cyclic carbon atom by an R_5-C_{1-4}-alkyl,

(R_4NR_6)-C_{1-4}-alkyl, R_6O-C_{1-4}-alkyl, R_6S-C_{1-4}-alkyl, R_6SO-C_{1-4}-alkyl, R_6SO_2-C_{1-4}-alkyl or R_4NR_6-CO group, wherein R_4 to R_6 are as hereinbefore defined,

a piperazino or homopiperazino group substituted in the 4 position by an R_5-C_{1-4}-alkyl, R_5-CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO or R_6SO_2-C_{1-4}-alkylene-CO group wherein R_4 to R_6 are as hereinbefore defined,

a piperazino or homopiperazino group substituted in the 4 position by a C_{2-4}-alkyl group, wherein the C_{2-4}-alkyl group is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a pyrrolidino, piperidino or hexahydroazepino group substituted by a 2-oxo-morpholino-C_{1-4}-alkyl group, wherein the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group substituted in the 3 position by a C_{2-4}-alkyl-Y group, wherein Y is as hereinbefore defined and the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two C_{1-2}-alkyl groups,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by a C_{2-4}-alkyl-Y group wherein Y is as hereinbefore defined and the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two C_{1-2}-alkyl groups,

a 4-(C_{1-4}-alkyl)-piperazino or 4-(C_{1-4}-alkyl)-homopiperazino group substituted at a cyclic carbon atom by a 2-oxo-morpholino-C_{1-4}-alkyl group, wherein the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a piperazino or homopiperazino group substituted in the 4 position by a 2-oxo-morpholino-C_{1-4}-alkylene-CO group, wherein the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a piperazino or homopiperazino group substituted in the 4 position by a C_{2-4}-alkyl group, wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R_6, by an R_5-C_{1-4}-alkyl, R_5-CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO, R_6SO_2-C_{1-4}-alkylene-CO or 2-oxo-morpholino-C_{1-4}-alkylene-CO group wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by a C_{2-4}-alkyl group wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by the group R_6, by an R_5-C_{1-4}-alkyl, R_5-CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO, R_6SO_2-C_{1-4}-alkylene-CO or 2-oxo-morpholino-C_{1-4}-alkylene-CO group, wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by a C_{2-4}-alkyl group, wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a R_5-C_{1-4}-alkylene-NR_4 group wherein R_4 and R_5 are as hereinbefore defined, or

a C_{2-4}-alkyl-NR_4-group, wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups, while

by the abovementioned aryl moieties is meant a phenyl group which may in each case be mono- or disubstituted by R', while the substituents may be identical or different and

R' denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

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

Preferred compounds of the above general formula I are those wherein

X denotes a nitrogen atom,

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 methyl group or a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c denotes a hydrogen atom,

R_d denotes a hydrogen atom, a methoxy, ethoxy, C_{4-6}-cycloalkoxy, C_{3-6}-cycloalkylmethoxy, 2-methoxy-ethoxy, 2-(cyclobutyloxy)-ethoxy, 2-(cyclopentyloxy)-ethoxy, 2-(cyclohexyloxy)-ethoxy, 2-(cyclopropylmethoxy)-ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-2-ylmethoxy or tetrahydropyran-4-ylmethoxy group,

A denotes a 1,2-vinylene group,

B denotes a methylene or ethylene group or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a pyrrolidino group wherein the two hydrogen atoms in the 3 position are replaced by a group E, wherein

E denotes a $-O-CO-CH_2CH_2-$, $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2CH_2-O-CO-CH_2-$, $-O-CO-CH_2-NR_4-CH_2-$, $-CH_2-O-CO-CH_2-NR_4-$, $-O-CO-CH_2-O-CH_2-$ or $-CH_2-O-CO-CH_2-O-$ bridge optionally substituted by one or two methyl groups,

where R_4 denotes a methyl or ethyl group,

a piperidino group wherein the two hydrogen atoms in the 3 position or in the 4 position are replaced by a group E, where E is as hereinbefore defined,

a pyrrolidino or piperidino group wherein two vicinal hydrogen atoms are replaced by an -O-CO-CH_2-, -CH_2-O-CO-, -O-CO-CH_2-NR_4- or -O-CO-CH_2-O- bridge optionally substituted by one or two methyl groups, whilst R_4 is as hereinbefore defined and the heteroatoms of the abovementioned bridges are not bound at the 2 or 5 position of the pyrrolidine ring and are not bound at the 2 or 6 position of the piperidino ring,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a -CO-O-CH_2CH_2- or -CH_2-O-CO-CH_2- bridge optionally substituted by one or two methyl groups, whilst in each case the left-hand end of the abovementioned bridges is bound to the 3 position of the piperazino ring,

a pyrrolidino or piperidino group substituted by the group R_5, wherein

R_5 denotes a 2-oxo-tetrahydrofuranyl, 2-oxo-1,4-dioxanyl or 2-oxo-4-(C_{1-4}-alkyl)-morpholinyl group optionally substituted by one or two methyl groups,

a pyrrolidino group substituted in the 3 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two methyl groups,

a piperidino group substituted in the 3 or 4 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two methyl groups,

a piperazino group substituted in the 4 position by the group R_6, wherein

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydro-furan-4-yl group optionally substituted by one or two methyl groups,

a pyrrolidino group substituted in the 3 position by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a piperidino group substituted in the 3 or 4 position by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group substituted by an (R_4NR_6)-C_{1-2}-alkyl, HNR_6-CO or R_4NR_6-CO group, whilst R_4 and R_6 are as hereinbefore defined,

a pyrrolidino group substituted in the 3 position by an R_5-CO-NH or R_5-CO-NR_4 group, whilst R_4 and R_5 are as hereinbefore defined,

a piperidino group substituted in the 3 or 4 position by an R_5-CO-NH or R_5-CO-NR_4 group, whilst R_4 and R_5 are as hereinbefore defined,

a piperazino group substituted in the 4 position by an R_5-C_{1-2}-alkyl, R_5-CO, R_5-C_{1-2}-alkylene-CO, (R_4NR_6)-C_{1-2}-alkylene-CO, R_6O-C_{1-2}-alkylene-CO, R_6S-C_{1-2}-alkylene-CO, R_6SO-C_{1-2}-alkylene-CO or R_6SO_2-C_{1-2}-alkylene-CO group wherein R_4 to R_6 are as hereinbefore defined,

a piperazino group substituted in the 4 position by a C_{2-3}-alkyl group wherein the C_{2-3}-alkyl group is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, where R_4 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group substituted by a 2-oxo-morpholino-C_{1-2}-alkyl group wherein the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a piperazino group substituted in the 4 position by a 2-oxo-morpholino-C_{1-2}-alkylene-CO group wherein the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a piperazino group substituted in the 4 position by a C_{2-3}-alkyl group wherein the C_{2-3}-alkyl moiety is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two methyl groups,

a piperidinyl group substituted in the 1 position by the group R_6, by an R_5-C_{1-2}-alkyl, R_5-CO, R_5-C_{1-2}-alkylene-CO, (R_4NR_6)-C_{1-2}-alkylene-CO, R_6O-C_{1-2}-alkylene-CO, R_6S-C_{1-2}-alkylene-CO, R_6SO-C_{1-2}-alkylene-CO, R_6SO_2-C_{1-2}-alkylene-CO or 2-oxo-morpholino-C_{1-2}-alkylene-CO group, whilst R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a piperidinyl group substituted in the 1 position by a C_{2-3}-alkyl group wherein the C_{2-3}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by the group R_6, by an R_5-C_{1-2}-alkyl, R_5-CO, R_5-C_{1-2}-alkylene-CO, (R_4NR_6)-C_{1-2}-alkylene-CO, R_6O-C_{1-2}-alkylene-CO, R_6S-C_{1-2}-alkylene-CO, R_6SO-C_{1-2}-alkylene-CO, R_6SO_2-C_{1-2}-alkylene-CO or 2-oxo-morpholino-C_{1-2}-alkylene-CO group, wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups, or

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by a C_{2-3}-alkyl group, wherein the C_{2-3}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

the tautomers, the stereoisomers and the salts thereof.

Particularly preferred compounds of general formula I are those wherein

X denotes a nitrogen atom,

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, each denote a methyl group or a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c denotes a hydrogen atom,

R_d denotes a hydrogen atom, a methoxy, ethoxy, C_{4-6}-cycloalkoxy, C_{3-6}-cycloalkylmethoxy, 2-methoxy-ethoxy, 2-(cyclobutyloxy)-ethoxy, 2-(cyclopentyloxy)-ethoxy, 2-(cyclohexyloxy)-ethoxy, 2-(cyclopropylmethoxy)-ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-2-ylmethoxy or tetrahydropyran-4-ylmethoxy group,

A denotes a 1,2-vinylene group,

B denotes a methylene or ethylene group or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a piperidino group wherein the two hydrogen atoms in the 4 position are replaced by a $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2CH_2-O-CO-CH_2-$, $-O-CO-CH_2-NCH_3-CH_2-$ or $-O-CO-CH_2-O-CH_2-$ bridge,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a $-CO-O-CH_2-CH_2-$ or $-CH_2-O-CO-CH_2-$ bridge, whilst in each case the left-hand end of the above bridges is bound to the 3 position of the piperazino ring,

a piperidino group substituted by a 2-oxo-tetrahydrofuranyl group,

a piperidino group which is substituted in the 4 position by a 2-oxo-morpholino or 2-oxo-morpholinomethyl group, whilst the 2-oxo-morpholino moiety may in each case be substituted by one or two methyl groups,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

a piperidino group which is substituted in the 4 position by a CH_3NR_6 or R_6S group, whilst

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydro-furan-4-yl group,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuranylmethyl or 2-oxo-tetrahydrofuranyl-carbonyl group,

a piperazino group which is substituted in the 4 position by a straight-chained C_{2-3}-alkyl group, whilst the C_{2-3}-alkyl moiety is terminally substituted in each case by a 2-oxo-tetrahydrofuran-3-ylsulphenyl group,

a piperidin-4-yl group which is substituted in the 1 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

a piperidin-4-yl-NCH_3 group which is substituted at the cyclic nitrogen atom by a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl or 2-oxo-tetrahydrofuranylcarbonyl group,

the tautomers, the stereoisomers and the salts thereof.

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

X denotes a nitrogen atom,

R_a denotes a hydrogen atom,

R_b denotes a 1-phenylethyl group or a phenyl group substituted by the groups R_1 to R_3, wherein

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

R_3 denotes a hydrogen atom,

R_c denotes a hydrogen atom,

R_d denotes a hydrogen atom, a methoxy, ethoxy, 2-methoxy-ethoxy, cyclobutyloxy, cyclopentyloxy, cyclopropylmethoxy, cyclobutylmethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuran-2-ylmethoxy group,

A denotes a 1,2-vinylene group,

B denotes a methylene group or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a piperidino group in which the two hydrogen atoms are replaced in the 4 position by a $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2CH_2-O-CO-CH_2-$, $-O-CO-CH_2-NCH_3-CH_2-$ or $-O-CO-CH_2-O-CH_2-$ bridge,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a $-CO-O-CH_2-CH_2-$ or $-CH_2-O-CO-CH_2-$ bridge, while in each case the left-hand end of the abovementioned bridges is bound to the 3 position of the piperazino ring,

a piperidino group substituted by a 2-oxo-tetrahydrofuranyl group,

a piperidino group which is substituted in the 4 position by a 2-oxo-morpholino or 2-oxo-morpholinomethyl group, while the 2-oxo-morpholino moiety may in each case be substituted by one or two methyl groups,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

a piperidino group which is substituted in the 4 position by a CH_3NR_6 or R_6S group, where

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuranylmethyl or 2-oxo-tetrahydro-furanylcarbonyl group,

a piperazino group which is substituted in the 4 position by a [2-(2-oxo-tetrahydrofuran-3-ylsulphenyl)ethyl] group,

a piperidin-4-yl group which is substituted in the 1 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

a piperidin-4-yl-NCH_3 group which is substituted at the cyclic nitrogen atom by a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl or 2-oxo-tetrahydrofuranylcarbonyl group,

the tautomers, the stereoisomers and the salts thereof.

The following are mentioned as most particularly preferred compounds of general formula I:

(a) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-tetrahydrofuran-3-yl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

(b) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-tetrahydrofuran-4-yl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

(c) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{2-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-ethyl}-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(d) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(e) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(5-oxo-tetrahydrofuran-2-yl)carbonyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

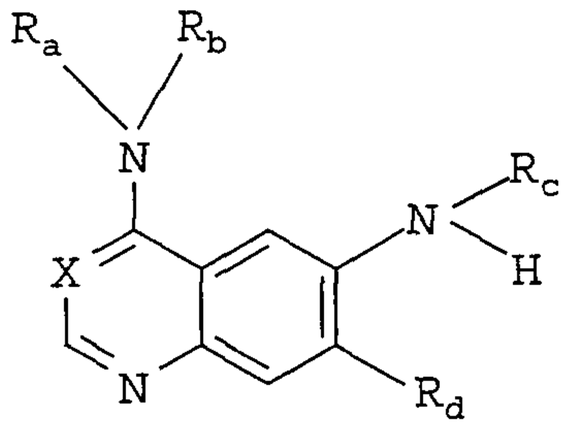
(f) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(1-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline and

(g) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

and the salts thereof.

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

a. reacting a compound of general formula



, (II)

wherein
R_a to R_d and X are as hereinbefore defined,

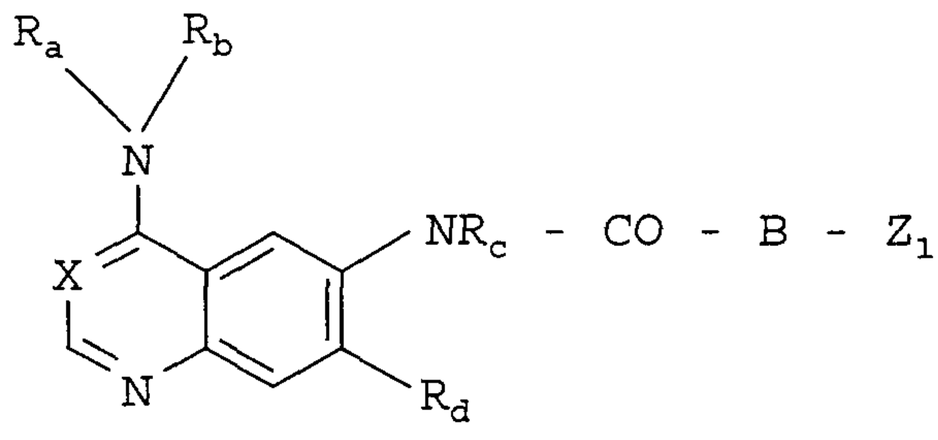
with a compound of general formula

HO-CO - A - B - C , (III)

wherein
A to C are as hereinbefore defined, or with the reactive derivatives thereof.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole, triphenylphosphine/carbon tetrachloride or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate or with a corresponding reactive derivative such as a corresponding ester, acid halide or anhydride, optionally with the addition of an inorganic or organic base, preferably with the addition of an organic base such as triethylamine, N-ethyl-diisopropylamine or 4-dimethylamino-pyridine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

b. reacting a compound of general formula



, (IV)

optionally formed in the reaction mixture, wherein R_a to R_d, A, B and X are as hereinbefore defined and Z_1 denotes an exchangeable group such as a halogen atom or a substituted sulphinyl or sulphonyl group, e.g. a chlorine or bromine atom, a methylsulphinyl, propylsulphinyl, phenyl-sulphinyl, benzylsulphinyl, methylsulphonyl, propylsulphonyl, phenylsulphonyl or benzylsulphonyl group,

with a compound of general formula

H - G , (V)

wherein
G denotes one of the groups mentioned for C hereinbefore which is linked to the group B via a nitrogen atom.

However, G may also denote a group which can be converted by lactonisation into one of the groups mentioned for C hereinbefore, which are linked to the group B via a nitrogen atom (e.g. a correspondingly substituted gamma- or delta-hydroxycarboxylic acid ester group).

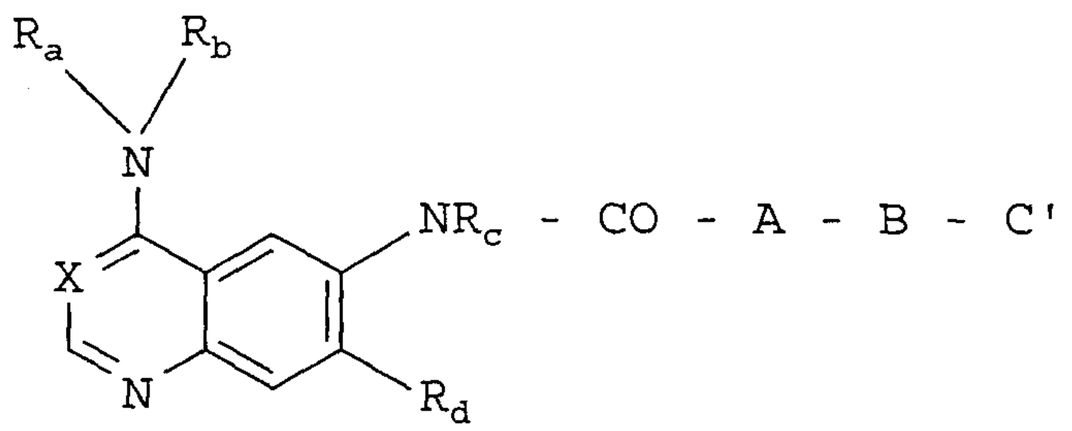
The reaction is conveniently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethylsulphoxide, methylene chloride, ethyleneglycol monomethylether, ethyleneglycol diethylether or sulpholane, optionally in the presence of an 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-diisopropyl-amine (Hünig base), whilst these organic bases may simultaneously serve as the 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 G denotes a group which can be converted by lactonisation into one of the groups mentioned for C hereinbefore which are linked to the group B via a nitrogen atom, cyclisation to form the corresponding lactone may optionally follow. The cyclisation to form the corresponding lactone is optionally carried out in a solvent such as acetonirile, methylene chloride, tetrahydrofuran, dioxane or toluene in the presence of an acid such as hydrochloric acid, p-toluenesulphonic acid

or trifluoroacetic acid at temperatures of between -10 and 120°C.

c. In order to prepare a compound of general formula I wherein C denotes one of the groups mentioned for C hereinbefore which contains an imino or HNR_4 group substituted by R_6 or by an R_5-C_{1-4}-alkyl group wherein R_4 to R_6 are as hereinbefore defined:

reacting a compound of general formula



, (VI)

wherein
R_a to R_d, A and B are as hereinbefore defined and
C' denotes one of the groups mentioned for C hereinbefore which contains a corresponding unsubstituted imino or HNR_4 group, where R_4 is as hereinbefore defined,

with a compound of general formula

$$Z_2 - U \qquad \text{, (VII)}$$

wherein
U denotes the group R_6 or a R_5-C_{1-4}-alkyl group, where R_5 and R_6 are as hereinbefore defined, and
Z_2 denotes an exchangeable group such as a halogen atom or a substituted sulphonyloxy group, e.g. a chlorine or bromine atom, a methylsulphonyloxy, propylsulphonyloxy, phenylsulphonyloxy or benzylsulphonyloxy group, or
Z_2 together with an adjacent hydrogen atom denotes another carbon-carbon bond which is attached to a carbonyl group.

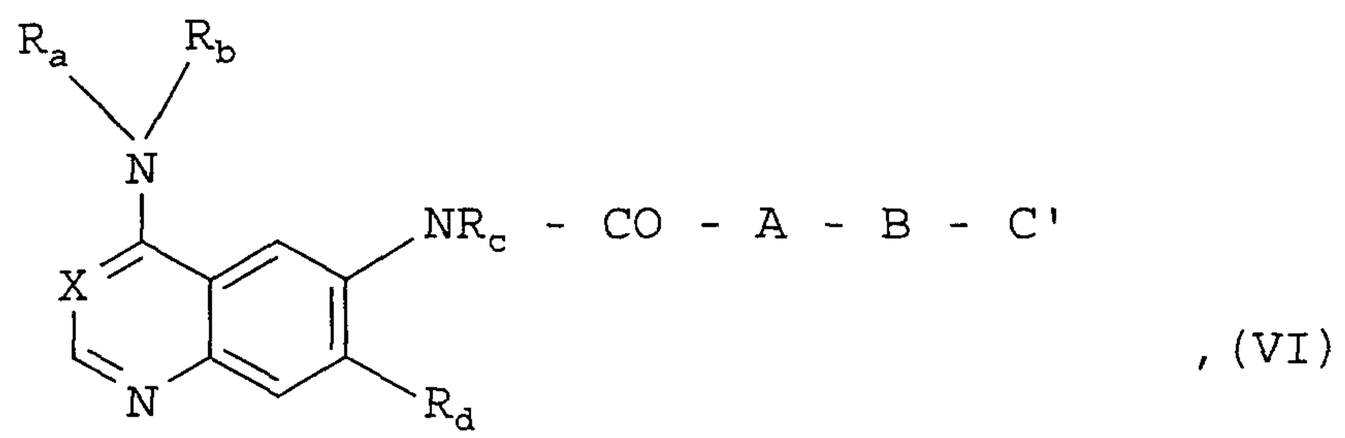
The reaction is conveniently carried out in a solvent such as methanol, ethanol, isopropanol or acetonitrile and optionally in the presence of a base such as triethylamine, N-ethyl-diisopropylamine or 2-dimethylamino-pyridine at temperatures between 0 and 100°C, but preferably at the boiling temperature of the reaction mixture.

If in a compound of general formula VII Z_2 denotes an exchangeable group, the reaction is preferably performed in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, sulpholane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, conveniently in the presence of a tertiary organic base such as triethylamine or N-ethyl-diisopropylamine (Hünig base), whilst these organic bases may simultaneously serve as the solvent, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution, conveniently at temperatures between -20 and 200°C, preferably at temperatures between 0 and 150°C, or

if in a compound of general formula VII Z_2 together with an adjacent hydrogen atom denotes another carbon-carbon bond attached to a carbonyl group, the reaction is preferably carried out in a solvent such as methanol, ethanol, isopropanol or acetonitrile at temperatures between 0 and 100°C, but preferably at temperatures between 20°C and the boiling temperature of the reaction mixture.

d. In order to prepare a compound of general formula I wherein C denotes one of the groups mentioned for C hereinbefore which contains an imino or HNR_4 group substituted by an R_5CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO, R_6SO_2-C_{1-4}-alkylene-CO or 2-oxo-morpholino-C_{1-4}-alkylene-CO group, where R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups:

reacting a compound of general formula



, (VI)

wherein
R_a to R_d, A and B are as hereinbefore defined and
C' denotes one of the groups mentioned for C hereinbefore which contains a corresponding unsubstituted imino or HNR_4 group, where R_4 is as hereinbefore defined,

with a compound of general formula

, (VIII)

wherein
W denotes the group R_5 or a R_5-C_{1-4}-alkyl, (R_4NR_6)-C_{1-4}-alkyl, R_6O-C_{1-4}-alkyl, R_6S-C_{1-4}-alkyl, R_6SO-C_{1-4}-alkyl, R_6SO_2-C_{1-4}-alkyl or 2-oxo-morpholino-C_{1-4}-alkyl group, wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide,
N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide,
N,N'-carbonyldiimidazole, triphenylphosphine/carbon tetrachloride or O-(benzotriazol-1-yl)-

N,N,N',N'-tetramethyluronium-tetrafluoroborate or with a corresponding reactive derivative such as a corresponding ester, acid halide or anhydride, optionally with the addition of an inorganic or organic base, preferably with the addition of an organic base such as triethylamine, N-ethyl-diisopropylamine or 4-dimethylamino-pyridine, conveniently 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, 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,

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 dioxane/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 room 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, dioxane, 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 dioxane at temperatures between 20 and 50°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 obtained 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.

The compounds of general formulae II to VIII 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 XV).

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 that the transmission of signals to components located further along is blocked.

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 (BioWhittaker), 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, 1.5×10^4 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™ AQueous 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	0.05
2	0.60
4	3
4(3)	10

The compounds of general formula I according to the invention thus inhibit the 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 of tyrosine kinases, e.g. in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, 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,

also for treating nasal polyps and polyps of the gastrointestinal tract of various origins, such as for example villous or adenomatous polyps of the large bowel, but also polyps in familial polyposis coli, intestinal polyps in Gardner's syndrome, polyps throughout the entire gastrointestinal tract in Peutz-Jeghers Syndrome, inflammatory pseudopolyps, juvenile polyps, colitis cystica profunda and pneumatosis cystoides intestinales.

Moreover, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat kidney diseases, particularly cystic changes as in cystic kidneys, for treating renal cysts which may be idiopathic in origin or which occur in syndromes such as e.g. tubercular sclerosis, in von-Hippel-Lindau Syndrome, in nephronophthisis and spongy kidney and other diseases caused by abnormal functioning of tyrosine kinases such as e.g. epidermal hyper-proliferation (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. vinblastin), 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 anti-inflammatory 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 or with anti-inflammatory substances. 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, intrarectal, 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/polyethyleneglycol, propyleneglycol, stearylalcohol, 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

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

5 ml of trifluoroacetic acid are added dropwise to 1.80 g of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(tert.-butyloxycarbonyl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline in 10 ml methylene chloride whilst cooling with an ice bath. After one hour the ice bath is removed and the reaction mixture is stirred overnight at ambient temperature. Then the mixture is evaporated to dryness, the flask residue is divided between 150 ml methylene chloride/methanol (9:1) and 100 ml of 1N sodium hydroxide solution. The aqueous phase is extracted twice more with the mixture of solvents, the combined organic phases are dried over magnesium sulphate and concentrated by evaporation. The brownish crude product reacted further without any more purification.

Yield: 1.32 g (88 % of theory),

R_f value: 0.60 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)

mass spectrum (ESI^+): m/z = 511, 513 $[M+H]^+$

The following compounds are obtained analogously to Example I:

(1) N-{2-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-ethyl}-piperazine x 2 trifluoroacetic acid

(The reaction mixture is concentrated by evaporation without aqueous working up.)

R_f value: 0.68 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-methylamino-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline
R_f value: 0.50 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)
mass spectrum (ESI^-): m/z = 537, 539 $[M-H]^-$

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[3-(piperidin-4-yl)-1-oxo-2-propen-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.50 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)
mass spectrum (ESI^-): m/z = 494, 496 $[M-H]^-$

(4) Perhydro-pyrazino[2,1-*c*][1,4]oxazin-3-one x 2 trifluoro-acetic acid
(The reaction mixture is concentrated by evaporation without aqueous working up.)
mass spectrum (ESI^+): m/z = 157 $[M+H]^+$

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[N-(piperidin-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropyl-methoxy-quinazoline
mass spectrum (ESI^-): m/z = 537, 539 $[M-H]^-$

(6) Perhydro-pyrazino[2,1-*c*][1,4]oxazin-1-one x 2 trifluoro-acetic acid
(The reaction mixture is concentrated by evaporation without aqueous working up.)
mass spectrum (ESI^+): m/z = 157 $[M+H]^+$

(7) 4-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-piperidine x 1 trifluoroacetic acid
(The reaction mixture is concentrated by evaporation without aqueous working up.)

R_f value: 0.57 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)
mass spectrum (ESI^+): m/z = 202 $[M+H]^+$

(8) 4-[(2-oxo-6,6-dimethyl-morpholin-4-yl)methyl]-piperidine x trifluoroacetic acid
(The starting material, 1-(tert.butyloxycarbonyl)-4-[N-(ethoxycarbonylmethyl)-N-((2-hydroxy-2-methyl-propyl)-aminomethyl]-piperidine, is obtained by reacting 1-(tert.butyloxycarbonyl)-4-(methanesulphonyloxymethyl)-piperidine with N-(ethoxycarbonylmethyl)-2-hydroxy-2-methyl-propylamine)
mass spectrum (ESI^+): m/z = 227 $[M+H]^+$

Example II

4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(tert.butyloxy-carbonyl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

4.7 ml of oxalyl chloride are added dropwise at ambient temperature to a solution of 4.51 g of 4-bromo-crotonic acid in 100 ml of methylene chloride. After the addition of one drop of N,N-dimethylformamide the reaction mixture is stirred for about another 45 minutes at ambient temperature until the development of gas has ceased. Then the solvent is distilled off from the resulting acid chloride *in vacuo*. In the meantime 7.00 g of 6-amino-4-[(3-chloro-4-fluoro-phenyl)amino]-7-cyclopropylmethoxy-quinazoline and 10.2 ml of diisopropylethylamine in 250 ml of tetrahydrofuran are cooled to 0°C in an ice bath. The crude acid chloride is taken up in 20 ml of methylene chloride and added dropwise within 5 minutes whilst cooling with an ice bath. The reaction mixture is stirred for 45 minutes at 0°C and for one hour at ambient temperature, then a suspension of 18.17 g of tert.butyl piperazine-1-carboxylate in 5 ml of N,N-dimethylformamide is added. After another 48 hours stirring at ambient temperature the solvent is distilled off *in vacuo* and the residue is

divided between water and ethyl acetate. The aqueous phase is extracted with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The crude product is purified by chromatography through a silica gel column with ethyl acetate/methanol (15:1 to 9:1).
Yield: 5.2 g (44 % of theory),
R_f value: 0.42 (silica gel, methylene chloride/methanol = 9:1)
mass spectrum (ESI^-): m/z = 609, 611 $[M-H]^-$

The following compounds are obtained analogously to Example II:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[N-(tert.-butyloxycarbonyl)-N-methylamino]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline
R_f value: 0.35 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 637, 639 $[M-H]^-$

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{N-[1-(tert.-butyloxycarbonyl)-piperidine-4-yl]-N-methyl-amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline
R_f value: 0.39 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 637, 639 $[M-H]^-$

Example III

6-amino-4-[(3-chloro-4-fluoro-phenyl)amino]-7-cyclopropyl-methoxy-quinazoline

30.00 g of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-cyclopropylmethoxy-6-nitro-quinazoline are suspended in a mixture of 900 ml of ethanol, 120 ml of glacial acetic acid and 300 ml of water. The suspension is refluxed, producing a clear solution. Then 17.24 g of iron powder are carefully added batchwise, whilst the reaction mixture effervesces each time. About 15 minutes after it has all been added, a precipitate is formed. The reaction mixture is stirred for a

further 15 minutes and then evaporated to dryness *in vacuo*. The residue in the flask is taken up in 1000 ml of methylene chloride/methanol (9:1) and combined with 30 ml of 33% aqueous ammonia solution. The iron slurry is filtered off and washed with methylene chloride : methanol (9:1). The brown filtrate is filtered through a silica gel pack and evaporated to dryness. The residue in the flask is stirred with 60 ml of diethylether, suction filtered and dried in the air.
Yield: 22.60 g (82 % of theory),
melting point: 208°C
mass spectrum (ESI^+): m/z = 359, 361 $[M+H]^+$

Example IV

4-[(3-chloro-4-fluoro-phenyl)amino]-7-cyclopropylmethoxy-6-nitro-quinazoline

66.66 g of potassium tert. butoxide are added batchwise to 47.07 ml of cyclopropylmethanol in 500 ml of N,N-dimethylformamide whilst cooling with an ice bath, while the temperature is not allowed to exceed 12°C. The reaction mixture is stirred for another 30 minutes in the cooling bath, then 50.00 g of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-fluoro-6-nitro-quinazoline are added batchwise, whereupon the reaction mixture turns dark red and the temperature rises to not more than 15°C. Then the cooling bath is removed and the reaction mixture is stirred for another hour at ambient temperature. To work it up the reaction mixture is poured onto 4000 ml of water and neutralised with about 210 ml of 2N hydrochloric acid. The precipitate formed is suction filtered, washed with water and dried at 40°C.
Yield: 60.47 g of crude product,
R_f value: 0.60 (silica gel, cyclohexane/ethyl acetate = 1:1)
mass spectrum (ESI^-): m/z = 387, 389 $[M-H]^-$

Example V

1-(tert.butyloxycarbonyl)-4-{2-[(2-oxo-tetrahydrofuran-3-yl)-sulphanyl]-ethyl}-piperazine

4.02 g of 1-(tert.butyloxycarbonyl)-4-[2-(methanesulphonyloxy)-ethyl]-piperazine dissolved in methylene chloride are added to a methanolic solution of 1.40 g of sodium-2-oxo-tetrahydrofuran-3-thiolate (prepared by treating 3-[(methylcarbonyl)sulphanyl]-tetrahydrofuran-2-one with sodium methoxide in methanol). Then 10 ml of N,N-dimethylformamide are added and the reaction mixture is stirred for 2.5 hours at 50°C. For working up 100 ml of ethyl acetate are added. The organic phase is separated off, washed with water and sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The red oily crude product is reacted without any further purification.
Yield: 3.50 g (96 % of theory)
R_f value: 0.48 (silica gel, methylene chloride/methanol = 9:1)
mass spectrum (ESI^-): m/z = 329 $[M-H]^-$

Example VI

3-(piperidin-4-yl)-dihydro-furan-2-one

3.60 g of 3-(1-benzyl-piperidin-4-ylidene)-dihydro-furan-2-one are dissolved in 40 ml of methanol, combined with 360 mg of palladium on active charcoal (10%) and hydrogenated at ambient temperature. After the calculated amount of hydrogen has been taken up, the catalyst is filtered off and the filtrate is concentrated by evaporation *in vacuo*. A colourless oil remains, which is reacted without any further purification.
R_f value: 0.16 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (EI): m/z = 169 $[M]^+$

The following compounds are obtained analogously to Example VI:

(1) 4-[N-(tert.Butyloxycarbonylmethyl)-N-(2-hydroxyethyl)-amino]-piperidine
Starting material: compound of Example XIV (1)
R_f value: 0.34 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 4:1:0.1)

(2) (*R*)-4-[N-(tert.Butyloxycarbonylmethyl)-N-(2-hydroxypropyl)-amino]-piperidine
Starting material: Compound of Example XIV (2)
Mass spectrum (ESI^+): m/z = 273 $[M+H]^+$

(3) 4-Hydroxy-4-[N-methyl-N-(ethoxycarbonylmethyl)-aminomethyl]-piperidine
Starting material: Compound of Example XVI
R_f value: 0.38 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 4:1:0.1)

Example VII

3-(1-benzyl-piperidin-4-ylidene)-dihydro-furan-2-one
24.00 g of diethyl (2-oxo-tetrahydrofuran-3-yl)-phosphonate are slowly added dropwise to 4.40 g of sodium hydride in 25 ml of toluene. Then 1-benzyl-9-piperidine-4-one is added and the reaction mixture is refluxed for 3 hours. After cooling to ambient temperature the supernatant solution is decanted off, diluted with toluene and washed with water and saturated sodium chloride solution. The organic phase is dried over magnesium sulphate, concentrated by evaporation and chromatographed over a silica gel column with ethyl acetate/methanol (95:5) as eluant.
Yield: 14.43 g (52 % of theory),
R_f value: 0.64 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 256 $[M-H]^-$

Example VIII

4-[(3-chloro-4-fluoro-phenyl)amino]-6-({3-[1-(tert.butyloxycarbonyl)-piperidin-4-yl]-1-oxo-2-propen-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

1.61 g of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({[(diethoxyphosphoryl)methyl]carbonyl}amino)-7-cyclopropylmethoxy-quinazoline are added to 127 mg of anhydrous lithium chloride in 20 ml of absolute tetrahydrofuran under argon. The mixture is stirred for 15 minutes at ambient temperature, then cooled to 0°C in an ice bath and 0.45 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene are added. After another 30 minutes at 0°C, 690 mg of 4-formyl-1-(tert.butoxycarbonyl)-piperidine are added. The reaction mixture is left overnight to come up to ambient temperature. For working up, the solvent is eliminated *in vacuo* and the residue in the flask is taken up with ethyl acetate/methanol (9:1). The solution is washed with water and saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The oily, brown crude product is purified by chromatography through a silica gel column with ethyl acetate as eluant.

Yield: 1.30 g (73 % of theory),

R_f value: 0.80 (silica gel, ethyl acetate)

mass spectrum (EI): m/z = 595, 597 $[M]^+$

Example IX

4-[(3-chloro-4-fluoro-phenyl)amino]-6-({[(diethoxyphosphoryl)-methyl]carbonyl}amino)-7-cyclopropylmethoxy-quinazoline

2.77 ml of triethylamine, 3.43 g of diethoxyphosphoryl-acetic acid and 5.62 g of benzotriazol-1-yl-N-tetramethyl-uronium-tetrafluoroborate are added successively to 5.00 g of 6-amino-4-[(3-chloro-4-fluoro-phenyl)amino]-7-cyclopropylmethoxy-quinazoline in 25 ml of N,N-dimethylformamide. The reaction mixture is stirred for one hour at ambient temperature. Then 250 ml of water are added and the mixture is extracted with

250 ml of ethyl acetate/methanol (10:1). The organic phase is washed with water and saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The residue in the flask is crystallised by stirring with diethylether.
Yield: 7.00 g (94 % of theory),
melting point: 186°C
mass spectrum (ESI^-): m/z = 535, 537 $[M-H]^-$

Example X

8-(tert.butyloxycarbonyl)-perhydro-pyrazino[2,1-c][1,4]oxazin-3-one

2.00 g of 1-(tert.butyloxycarbonyl)-4-[(ethoxycarbonyl)methyl]-3-hydroxymethyl-piperazine in 2.5 ml of acetonitrile are combined with 500 mg of p-toluenesulphonic acid monohydrate. The reaction mixture is refluxed for 3 hours until the reaction is complete. Then the solvent is distilled off *in vacuo*. The crude product is further reacted without additional purification.
R_f value: 0.80 (silica gel, ethyl acetate/methanol = 9:1)

The following compound is obtained analogously to Example X:

(1) 8-(tert.butyloxycarbonyl)-perhydro-pyrazino[2,1-c][1,4]-oxazin-1-one
R_f value: 0.60 (silica gel, methylene chloride/methanol = 95:5)
mass spectrum (ESI^+): m/z = 257 $[M+H]^+$

Example XI

1-(tert.butyloxycarbonyl)-4-[(ethoxycarbonyl)methyl]-3-hydroxymethyl-piperazine and 8-(*tert*-butyloxycarbonyl)-perhydro-pyrazino[2,1-c][1,4]oxazin-3-one

3.90 ml of ethyl bromoacetate are added to 5.80 g of 1-(tert.butyloxycarbonyl)-3-hydroxymethyl-piperazine and 4.50 ml of triethylamine in 60 ml of acetonitrile. The reaction

mixture is refluxed overnight, during which time two products are formed, according to thin layer chromatography. For working up the reaction mixture is concentrated by evaporation *in vacuo* and the residue is divided between ethyl acetate and water. The organic phase is dried over magnesium sulphate, concentrated by evaporation and chromatographed over a silica gel column with ethyl acetate/methanol (97:3). The following two products are obtained as yellowish oils:

8-(tert.butyloxycarbonyl)-perhydro-pyrazino[2,1-c][1,4]oxazin-3-one
Yield: 3.43 g (50 % of theory),
R_f value: 0.80 (silica gel, ethyl acetate/methanol = 9:1)

1-(tert.butyloxycarbonyl)-4-[(ethoxycarbonyl)methyl]-3-hydroxymethyl-piperazine
Yield: 2.08 g (26 % of theory),
R_f value: 0.58 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI$^+$): m/z = 303 $[M+H]^+$

The following compounds are obtained analogously to Example XI:

(1) 8-(tert.butyloxycarbonyl)-perhydro-pyrazino[2,1-c][1,4]-oxazin-1-one
R_f value: 0.60 (silica gel, methylene chloride/methanol = 95:5)
mass spectrum (ESI$^+$): m/z = 257 $[M+H]^+$

(2) 1-(tert.butyloxycarbonyl)-3-(ethoxycarbonyl)-4-(2-hydroxy-ethyl)-piperazine
R_f value: 0.50 (silica gel, methylene chloride/methanol = 95:5)
mass spectrum (EI): m/z = 302 $[M]^+$

Example XII

1-(tert.butyloxycarbonyl)-3-hydroxymethyl-piperazine

A solution of 8.00 g of 1-(tert.butyloxycarbonyl)-3-ethoxycarbonyl-piperazine in 10 ml of tetrahydrofuran is added dropwise to a suspension of 900 mg of lithium borohydride in 20 ml of tetrahydrofuran and then the mixture is refluxed for 3 hours. For working up the reaction mixture is concentrated by evaporation, adjusted to pH 4 with 10% aqueous citric acid solution and stirred for about 40 minutes whilst cooling with an ice bath. Then the mixture is made alkaline with concentrated sodium hydroxide solution and left to stand overnight. The next morning it is extracted with *tert*-butylmethylether. The organic phase is dried over magnesium sulphate and concentrated by evaporation. A clear oil is left, which slowly crystallises.

Yield: 5.80 g (87 % of theory),

R_f value: 0.28 (silica gel, ethyl acetate/methanol = 4:1)

mass spectrum (ESI^+): m/z = 217 $[M+H]^+$

Example XIII

1-(tert.butyloxycarbonyl)-3-ethoxycarbonyl-piperazine

21.80 g of di-tert.butyl pyrocarbonate are added to 15.80 g of 2-ethoxycarbonyl-piperazine in 400 ml of ethanol whilst cooling with an ice bath. The reaction mixture is stirred for another 3 hours at 0°C. Then it is concentrated by evaporation and the residue is divided between ethyl acetate and water. The organic phase is dried over magnesium sulphate, concentrated by evaporation and purified by chromatography through a silica gel column with ethyl acetate/methanol (95:5) as eluant.

Yield: 24.30 g (94 % of theory),

R_f value: 0.40 (silica gel, ethyl acetate/methanol = 9:1)

mass spectrum (ESI^+): m/z = 281 $[M+Na]^+$

Example XIV

1-tert.butyloxycarbonyl-4-methylamino-piperidine

25.50 g of methylamine hydrochloride are added to 15.00 g of 1-(tert.butyloxycarbonyl)-4-piperidinone and 31.20 g of sodium acetate in 300 ml of tetrahydrofuran. Then 19.00 g of sodium triacetoxyborohydride are added batchwise. The reaction mixture is stirred overnight at ambient temperature and the next day concentrated by evaporation. The residue is divided between 5% sodium hydrogen carbonate solution and methylene chloride. The aqueous phase is adjusted to about pH 11 with 4 N hydrochloric acid and extracted with ethyl acetate. The organic phase is dried over magnesium sulphate and concentrated by evaporation, leaving a colourless oil.
Yield: 12.74 g (79 % of theory),
R_f value: 0.22 (silica gel, ethyl acetate/methanol/concentrated aqueous ammonia solution = 90:10:1)
mass spectrum (ESI^+): m/z = 215 $[M+H]^+$

The following compounds are obtained analogously to Example XIV:

(1) 1-Benzyloxycarbonyl-4-[N-(tert.-butyloxycarbonylmethyl)-N-(2-hydroxyethyl)-amino]-piperidine
Mass spectrum (ESI^+): m/z = 393 $[M+H]^+$
R_f-value: 0.50 (silica gel, cyclohexane/ethyl acetate = 9:1)

(2) (*R*)-1-Benzyloxycarbonyl-4-[N-(tert.-butyloxycarbonylmethyl)-N-(2-hydroxypropyl)-amino]-piperidine
Mass spectrum (ESI^+): m/z = 407 $[M+H]^+$
R_f-value: 0.56 (silica gel, cyclohexane/ethyl acetate = 9:1)

Example XV

1-(tert.butyloxycarbonyl)-4-[(2-oxo-tetrahydrofuran-3-yl)-sulphanyl]-piperidine

2.73 g of potassium tert. butoxide are slowly added to 5.28 g of 1-(tert.butyloxycarbonyl)-4-mercapto-piperidine in 20 ml of N,N-dimethylformamide whilst cooling with an ice bath. The mixture is stirred for another 30 minutes whilst cooling with an ice bath, then a solution of 2.02 ml of 3-bromo-dihydro-furan-2-one in 20 ml of N,N-dimethylformamide is added dropwise. After the addition has finished, the reaction mixture is stirred for two hours at ambient temperature. Then it is neutralised with glacial acetic acid and concentrated by evaporation. The residue is divided between ethyl acetate and water. The organic phase is dried over magnesium sulphate and concentrated by evaporation. 7.60 g of a brownish-orange oil remain, which is reacted without further purification.

R_f value: 0.32 (silica gel, ethyl acetate/cyclohexane = 2:3)

mass spectrum (ESI^-): m/z = 300 $[M-H]^-$

Example XVI

1-Benzyloxycarbonyl-4-hydroxy-4-[N-methyl-N-(ethoxycarbonylmethyl)-aminomethyl]-piperidine

A mixture of 2.7 g of sarcosine ethyl ester and 3.09 g of 6-benzyloxycarbonyl-1-oxa-6-aza-spiro[2.5]octane in 20 ml of ethanol is heated to 90°C for 6 hours in a bomb tube. After cooling overnight the mixture is evaporated down and the residue is purified by chromatography over a silica gel column with cyclohexane/ethyl acetate (1:1).

Yield: 1.8 g (25% of theory)

Mass spectrum (ESI^+): m/z = 365 $[M+H]^+$

R_f-value: 0.35 (silica gel, cyclohexane/ethyl acetate= 1:1)

Preparation of the final compounds:

Example 1

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

0.42 ml of triethylamine are added to 608 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline in 3.0 ml of tetrahydrofuran. The mixture is cooled in the ice bath and a solution of 215 mg of 3-bromo-dihydro-furan-2-one in 1.0 ml of tetrahydrofuran is added dropwise and the mixture is stirred for one hour with cooling. Then the ice bath is removed and the mixture is stirred for about 48 hours at ambient temperature. The reaction mixture is chromatographed directly, without further processing, over a silica gel column, with methylene chloride/methanol (95:5 to 90:10) as eluant. The foamy crude product is crystallised by trituration with a little diethylether.
Yield: 393 mg (56 % of theory),
melting point: 130-131°C
mass spectrum (ESI^-): m/z = 593, 595 $[M-H]^-$

The following compounds are obtained analogously to Example 1:

(1) (R)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(5-oxo-tetrahydrofuran-2-yl)methyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline
(The reaction is carried out with (R)-5-mesyloxymethyl-2-oxo-tetrahydrofuran without a solvent)
melting point: 145-150°C
mass spectrum (ESI^-): m/z = 607, 609 $[M-H]^-$

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methylamino]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

R_f value: 0.22 (silica gel, ethyl acetate/methanol = 7:3)
mass spectrum (ESI^-): m/z = 621, 623 $[M-H]^-$

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{N-[1-(2-oxo-tetrahydrofuran-3-yl)-piperidin-4-yl]-N-methyl-amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline
R_f value: 0.73 (aluminium oxide, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 621, 623 $[M-H]^-$

Example 2

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

78 µl of 2(5H)-furanone are added to 500 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline in 2 ml of methanol. The reaction mixture is stirred for about 48 hours at ambient temperature and then evaporated to dryness *in vacuo*. The residue in the flask is purified by chromatography through a silica gel column with methylene chloride/methanol (95:5 to 90:10) as eluant. The product obtained is recrystallised from ethyl acetate.
Yield: 170 mg (29 % of theory),
R_f value: 0.43 (silica gel, methylene chloride/methanol = 9:1)
mass spectrum (ESI^-): m/z = 593, 595 $[M-H]^-$

The following compound is obtained analogously to Example 2:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({3-[1-(2-oxo-tetrahydrofuran-4-yl)-piperidin-4-yl]-1-oxo-2-propen-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
melting point: 138°C
mass spectrum (ESI^-): m/z = 578, 580 $[M-H]^-$

Example 3

(S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(5-oxo-tetrahydrofuran-2-yl)carbonyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

130 mg of (S)-5-oxo-tetrahydrofuran-2-carboxylic acid, 0.21 ml of triethylamine and 321 mg of benzotriazol-1-yl-N-tetramethyl-uronium-tetrafluoroborate are added to 500 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline in 3 ml of N,N-dimethylformamide. The reaction mixture is left to stand for about 48 hours at ambient temperature. Then 20 ml of water are added, whereupon a greasy precipitate is formed. This is suction filtered, washed with water and purified by chromatography through a silica gel column with methylene chloride/methanol (95:5 to 90:10) as eluant.
Yield: 330 mg (54 % of theory),
melting point: 155-157°C
mass spectrum (ESI^-): m/z = 621, 623 $[M-H]^-$

The following compound is obtained analogously to Example 3:

(1) 4-[(3-Chloro-4-fluoro-phenyl)amino]-6-{[4-(N-{1-[((*S*)-5-oxo-tetrahydrofuran-2-yl)carbonyl]-piperidin-4-yl}-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f-value: 0.36 (silica gel, ethyl acetate/methanol/concentrated aqueous ammonia solution = 9:1:0.2)
Mass spectrum (EI): m/z = 650, 652 $[M]^+$

Example 4

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{2-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-ethyl}-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

0.67 ml of oxalyl chloride are added dropwise at ambient temperature to a solution of 644 mg g of 4-bromo-crotonic acid

in 15 ml of methylene chloride. After the addition of one drop of N,N-dimethylformamide the reaction mixture is stirred for about another hour at ambient temperature, until the development of gas has ceased. Then the solvent is distilled off *in vacuo* from the acid chloride formed. In the meantime 1.00 g of 6-amino-4-[(3-chloro-4-fluoro-phenyl)amino]-7-cyclopropylmethoxy-quinazoline and 8.0 ml of diisopropylethylamine in 30 ml of tetrahydrofuran are cooled to 0°C in an ice bath. The crude acid chloride is taken up in 10 ml of methylene chloride and added dropwise within 5 minutes whilst cooling with an ice bath. The reaction mixture is stirred for another hour at 0°C and for two hours at ambient temperature. Then a suspension of 4.35 N-{2-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-ethyl}-piperazine in 5 ml of methylene chloride is added and the whole is stirred for another 48 hours at ambient temperature. The reaction mixture is concentrated by evaporation *in vacuo* and the residue in the flask is chromatographed through a silica gel column with ethyl acetate/methanol (95:5 to 90:10) as eluant.
Yield: 20 mg (1 % of theory),
R_f value: 0.32 (silica gel, methylene chloride/methanol = 9:1)
mass spectrum (ESI^-): m/z = 653, 655 $[M-H]^-$

The following compounds are obtained analogously to Example 4:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-tetrahydrofuran-3-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
R_f value: 0.17 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 592, 594 $[M-H]^-$

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-2-oxa-8-aza-spiro[4.5]dec-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
(The 2-oxa-8-aza-spiro[4.5]decan-3-one used is obtained from 8-benzyl-2-oxa-8-aza-spiro[4.5]decan-3-one by hydrogenolytic cleaving of the benzyl group)

R_f value: 0.37 (silica gel, methylene chloride/methanol = 9:1)
mass spectrum (EI): m/z = 579, 581 $[M]^+$

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.19 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 579, 581 $[M-H]^-$

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(1-oxo-2-oxa-8-aza-spiro[4.5]dec-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
R_f value: 0.48 (silica gel, methylene chloride/methanol = 9:1)
mass spectrum (EI): m/z = 579, 581 $[M]^+$

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(1-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-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 = 579, 581 $[M-H]^-$

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline
R_f value: 0.23 (silica gel, ethyl acetate/methanol = 9:1)
mass spectrum (ESI^-): m/z = 624, 626 $[M-H]^-$

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-6,6-dimethyl-morpholin-4-yl)methyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline
R_f value: 0.48 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0.2)
mass spectrum (ESI^-): m/z = 649, 651 $[M-H]^-$

(8) 4-((3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropyl-methoxy-quinazoline

prepared by lactonising the intermediate product (4-[(3-chloro-4-fluoro-phenyl)-amino]-6-({4-[4-[N-(tert.-butyloxycarbonylmethyl)-N-(2-hydroxyethyl)-amino]-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, melting point 114-117°C (with foaming), R_f-value: 0.46 (silica gel, methylene chloride/methanol = 9:1)) in the presence of 5 equivalents of trifluoracetic acid in acetonitrile under reflux
melting point: from 140°C (with foaming)
mass spectrum (ESI^+): m/z = 609, 611 $[M+H]^+$
R_f value: 0.26 (silica gel, ethyl acetate/methanol = 4:1)

(9) (R)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(6-methyl-2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
prepared by lactonising the intermediate product ((R)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-[N-(tert.-butyloxycarbonylmethyl)-N-(2-hydroxypropyl)-amino]piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, melting point: from 115°C (with foaming); R_f-value: 0.53 (silica gel, methylene chloride/methanol 9:1)) in the presence of 5 equivalents of trifluoroacetic acid in acetonitrile under reflux
melting point: from 126°C (with foaming)
mass spectrum (ESI^+): m/z = 623, 625 $[M+H]^+$
R_f value: 0.29 (silica gel, ethyl acetate/methanol 4:1)

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-([4-(4-methyl-2-oxo-1-oxa-4,9-diaza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
melting point: 125-130°C (with foaming)
mass spectrum (ESI^+): m/z = 609, 611 $[M+H]^+$
R_f value: 0.46 (silica gel, methylene chloride/methanol = 9:1)

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-3-oxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

mass spectrum (ESI^-): m/z = 592, 594 $[M+H]^-$
R_f value: 0.24 (silica gel, methylene chloride/methanol 9:1)
The starting material 2-oxo-3-oxa-9-aza-spiro[5.5]undecane is prepared as follows:
(a) 4,4-bis-(2-hydroxyethyl)-piperidine prepared by catalytic hydrogenation of 1-benzyl-4,4-bis-(2-hydroxyethyl)-piperidine in ethanol in the presence of palladium on activated carbon (10% Pd)
mass spectrum (ESI^+): m/z = 174 $[M+H]^+$

(b) 1-benzyloxycarbonyl-4,4-bis-(2-hydroxyethyl)-piperidine prepared by reaction of 4,4-bis-(2-hydroxyethyl)-piperidine with benzyl chloroformate in tetrahydrofuran in the presence of triethylamine
R_f value: 0.32 (silica gel, ethyl acetate/methanol = 9:1)

(c) 9-benzyloxycarbonyl-2-oxo-3-oxa-9-aza-spiro[5.5] undecane prepared by reaction of 1-benzyloxycarbonyl-4,4-bis-(2-hydroxyethyl)-piperidine with 4-methylmorpholine-N-oxide in methylene chloride/acetonitrile in the presence of tetrapropylammonium-perruthenate and pulverised molecular sieve
mass spectrum (ESI^-): m/z = 302 $[M+H]^-$

(d) 2-oxo-3-oxa-9-aza-spiro[5.5]undecane prepared by catalytic hydrogenation of 9-benzyloxycarbonyl-2-oxo-3-oxa-9-aza-spiro[5.5]undecane in ethanol in the presence of palladium on activated carbon (10% Pd) (the produkt must be reacted further immediately after careful evaporation)
mass spectrum (ESI^+): m/z 170 $[M+H]^+$

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

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(7-oxo-6-oxa-2,9-diaza-spiro[4.5]dec-2-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(7-oxo-6,9-dioxa-2-aza-spiro[4.5]dec-2-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-2-oxa-7-aza-spiro[4.4]non-7-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-1,4-dioxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-4-methyl-1-oxa-4,9-diaza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]-amino}-7-cyclopropylmethoxy-quinazoline

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-1-oxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-1,4-dioxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-oxo-perhydro-furo[3,4-b]pyrrol-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(6-oxo-perhydro-furo[3.4-b]pyrrol-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-perhydro-furo[2,3-c]pyrrol-5-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-4-methyl-perhydro-pyrrolo-[3,4-b][1.4]oxazin-6-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-perhydro-[1.4]dioxino[2,3-c]pyrrol-6-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-tetrahydrofuran-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(14) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-4-methyl-morpholin-3-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(15) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-4-methyl-morpholin-6-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(16) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[3-(2-oxo-6,6-dimethyl-morpholin-4-yl)-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}-amino)-7-cyclopropylmethoxy-quinazoline

(17) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-6,6-dimethyl-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(18) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-tetrahydrofuran-3-yl)oxy]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

(19) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{2-[(2-oxo-tetrahydrofuran-3-yl)oxy]ethyl}-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(20) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{[(2-oxo-tetrahydrofuran-3-yl)oxy]acetyl}-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(21) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]acetyl}-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(22) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[2-(2-oxo-6,6-dimethyl-morpholin-4-yl)ethyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

(23) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-6,6-dimethyl-morpholin-4-yl)acetyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

(24) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-6,6-dimethyl-morpholin-4-yl)methyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

(25) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-{1-[(5-oxo-tetrahydrofuran-2-yl)carbonyl]-piperidin-4-yl}-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(26) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(5-oxo-tetrahydrofuran-2-yl)carbonylamino]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline

(27) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{N-[(5-oxo-tetrahydrofuran-2-yl)carbonyl]-N-methyl-amino}-piperidin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(28) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutylmethoxy-quinazoline

(29) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline

(30) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline

(31) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)oxy]-quinazoline

(32) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclohexyloxy-quinazoline

(33) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)oxy]-quinazoline

(34) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-[2-(cyclobutyloxy)ethoxy]-quinazoline

(35) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino-[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-[2-(cyclopropylmethoxy)ethoxy]-quinazoline

(36) (R)-4-[(1-phenylethyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline

(37) (R)-4-[(1-Phenylethyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(38) (R)-4-[(1-phenylethyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinazoline

(39) (R)-4-[(1-phenylethyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-[2-(methoxy)ethoxy]-quinazoline

(40) (R)-4-[(1-phenylethyl)amino]-6-{[4-(3-oxo-perhydro-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-[3-(methoxy)propyloxy]-quinazoline

(41) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline

(42) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

(43) 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({4-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-quinazoline

(44) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(6-methyl-2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}-amino)-7-methoxy-quinazoline

(45) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(6-methyl-2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}-amino)-7-cyclopropylmethoxy-quinazoline

(46) 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({4-[4-(6-methyl-2-oxo-morpholin-4-yl)-piperidin-1-yl]-1-oxo-2-buten-1-yl}amino)-quinazoline

(47) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-3-oxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(48) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-3-oxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

(49) 4-[(*R*)-(1-phenyl-ethyl)amino]-6-{[4-(2-oxo-3-oxa-9-aza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline

(50) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-methyl-2-oxo-1-oxa-4,9-diaza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

(51) 4-[(*R*)-(1-Phenyl-ethyl)amino]-6-{[4-(4-methyl-2-oxo-1-oxa-4,9-diaza-spiro[5.5]undec-9-yl)-1-oxo-2-buten-1-yl]-amino}-quinazoline

(52) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline

(53) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-[(tetrahydropyran-4-yl)methoxy]-quinazoline

Example 5

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 6

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 7

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 8

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 9

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 10

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 11

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 12

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 13

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 14
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

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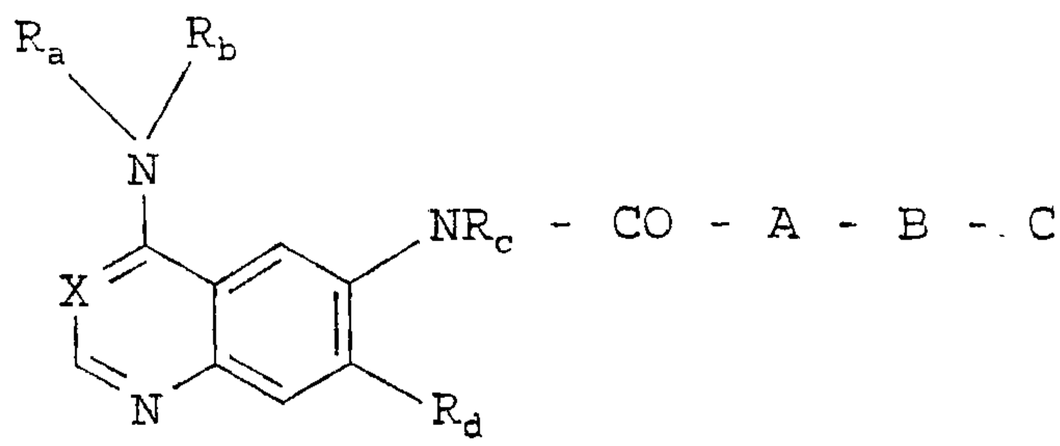
CLAIMS:

1. A bicyclic heterocycle of general formula



, (I)

or a tautomer, stereoisomer or salt thereof

wherein

X denotes a nitrogen atom,

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 in each case is substituted 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, whilst 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,

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

R_d denotes a hydrogen atom, a C_{1-6}-alkoxy, C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group,

a C_{2-6}-alkoxy group, which is substituted from position 2 by a hydroxy, C_{1-4}-alkoxy, C_{4-7}-cycloalkoxy, C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, di-(C_{1-4}-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C_{1-4}-alkyl)-piperazino group, whilst the abovementioned cyclic imino groups may be substituted by one or two C_{1-2}-alkyl groups,

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

A denotes a 1,1- or 1,2-vinylene group optionally substituted by a methyl or trifluoromethyl group or by two methyl groups, a 1,3-butadien-1,4-ylene group optionally substituted by a methyl or trifluoromethyl group or by two methyl groups, or an ethynylene group,

B denotes a C_{1-6}-alkylene group wherein one or two hydrogen atoms may be replaced by fluorine atoms, or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a pyrrolidino group wherein the two hydrogen atoms in the 2 position are replaced by a group D, wherein

D denotes a $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2-O-CO-CH_2CH_2-$, $-CH_2CH_2-O-CO-CH_2-$ or $-CH_2CH_2CH_2-O-CO-$ bridge optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group wherein the two hydrogen atoms in the 3 position are replaced by a group E, wherein

E denotes an $-O-CO-CH_2CH_2-$, $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-O-CO-CH_2CH_2CH_2-$, $-CH_2-O-CO-CH_2CH_2-$, $-CH_2CH_2-O-CO-CH_2-$, $-CH_2CH_2CH_2-O-CO-$, $-O-CO-CH_2-NR_4-CH_2-$, $-CH_2-O-CO-CH_2-NR_4-$, $-O-CO-CH_2-O-CH_2-$ or $-CH_2-O-CO-CH_2-O-$ bridge optionally substituted by one or two C_{1-2}-alkyl groups,

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

a piperidino or hexahydroazepino group wherein the two hydrogen atoms in the 2 position are replaced by a group D, whilst D is as hereinbefore defined,

a piperidino or hexahydroazepino group wherein the two hydrogen atoms in the 3 position or in the 4 position are replaced by a group E, whilst E is as hereinbefore defined,

a piperazino or 4-(C_{1-4}-alkyl)-piperazino group wherein the two hydrogen atoms in the 2 position or in the 3 position of the piperazino ring are replaced by a group D, where D is as hereinbefore defined,

a pyrrolidino or piperidino group wherein two vicinal hydrogen atoms are replaced by an -O-CO-CH_2-, -CH_2-O-CO-, -O-CO-CH_2CH_2-, -CH_2-O-CO-CH_2-, -CH_2CH_2-O-CO-, -O-CO-CH_2-NR_4- or -O-CO-CH_2-O- bridge optionally substituted by one or two C_{1-2}-alkyl groups, whilst R_4 is as hereinbefore defined and the heteroatoms of the abovementioned bridges are not bound at the 2 or 5 position of the pyrrolidine ring and are not bound at the 2 or 6 position of the piperidino ring,

a piperazino or 4-(C_{1-4}-alkyl)-piperazino group wherein a hydrogen atom in the 2 position together with a hydrogen atom in the 3 position of the piperazino ring are replaced by a -CH_2-O-CO-CH_2- or -CH_2CH_2-O-CO- bridge optionally substituted by one or two C_{1-2}-alkyl groups,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a -CO-O-CH_2CH_2- or -CH_2-O-CO-CH_2- bridge optionally substituted by one or two C_{1-2}-alkyl groups, whilst in each case the left-hand end of the abovementioned bridges is bound to the 3 position of the piperazino ring,

a pyrrolidino, piperidino or hexahydroazepino group substituted by the group R_5, wherein

R_5 denotes a 2-oxo-tetrahydrofuranyl, 2-oxo-tetrahydropyranyl, 2-oxo-1,4-dioxanyl or 2-oxo-4-(C_{1-4}-alkyl)-

morpholinyl group optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group substituted in the 3 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two C_{1-2}-alkyl groups,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two C_{1-2}-alkyl groups,

a 4-(C_{1-4}-alkyl)-piperazino or 4-(C_{1-4}-alkyl)-homopiperazino group substituted at a cyclic carbon atom by R_5 , wherein R_5 is as hereinbefore defined,

a piperazino or homopiperazino group substituted in the 4 position by the group R_6, wherein

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group substituted in the 3 position by a (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group wherein R_4 and R_6 are as hereinbefore defined,

a pyrrolidino, piperidino or hexahydroazepino group substituted by a R_5-C_{1-4}-alkyl, (R_4NR_6)-C_{1-4}-alkyl, R_6O-C_{1-4}-alkyl, R_6S-C_{1-4}-alkyl, R_6SO-C_{1-4}-alkyl, R_6SO_2-C_{1-4}-alkyl or R_4NR_6-CO group wherein R_4 to R_6 are as hereinbefore defined,

a pyrrolidino group substituted in the 3 position by a R_5-CO-NR_4, R_5-C_{1-4}-alkylene-$CONR_4$, (R_4NR_6)-C_{1-4}-alkylene-$CONR_4$, R_6O-C_{1-4}-alkylene-$CONR_4$, R_6S-C_{1-4}-alkylene-$CONR_4$, R_6SO-C_{1-4}-alkylene-$CONR_4$, R_6SO_2-C_{1-4}-alkylene-$CONR_4$, 2-oxo-morpholino-C_{1-4}-alkylene-$CONR_4$, R_5-C_{1-4}-alkylene-Y or C_{2-4}-alkyl-Y group, whilst the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups, wherein

R_4 to R_6 are as hereinbefore defined and

Y denotes an oxygen or sulphur atom, an imino, N-(C_{1-4}-alkyl)-imino, sulphinyl or sulphonyl group,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by a R_5-CO-NR_4, R_5-C_{1-4}-alkylene-$CONR_4$, (R_4NR_6)-C_{1-4}-alkylene-$CONR_4$, R_6O-C_{1-4}-alkylene-$CONR_4$, R_6S-C_{1-4}-alkylene-$CONR_4$, R_6SO-C_{1-4}-alkylene-$CONR_4$, R_6SO_2-C_{1-4}-alkylene-$CONR_4$, 2-oxo-morpholino-C_{1-4}-alkylene-$CONR_4$, R_5-C_{1-4}-alkylene-Y or C_{2-4}-alkyl-Y group wherein Y is as hereinbefore defined, the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups and the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 to R_6 are as hereinbefore defined,

a 4-(C_{1-4}-alkyl)-piperazino or 4-(C_{1-4}-alkyl)-homopiperazino group substituted at a cyclic carbon atom by an R_5-C_{1-4}-alkyl, (R_4NR_6)-C_{1-4}-alkyl, R_6O-C_{1-4}-alkyl, R_6S-C_{1-4}-alkyl, R_6SO-C_{1-4}-alkyl, R_6SO_2-C_{1-4}-alkyl or R_4NR_6-CO group, wherein R_4 to R_6 are as hereinbefore defined,

a piperazino or homopiperazino group substituted in the 4 position by an R_5-C_{1-4}-alkyl, R_5-CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO or R_6SO_2-C_{1-4}-alkylene-CO group wherein R_4 to R_6 are as hereinbefore defined,

a piperazino or homopiperazino group substituted in the 4 position by a C_{2-4}-alkyl group, wherein the C_{2-4}-alkyl group is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a pyrrolidino, piperidino or hexahydroazepino group substituted by a 2-oxo-morpholino-C_{1-4}-alkyl group, wherein the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidino group substituted in the 3 position by a C_{2-4}-alkyl-Y group, wherein Y is as hereinbefore defined and the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two C_{1-2}-alkyl groups,

a piperidino or hexahydroazepino group substituted in the 3 or 4 position by a C_{2-4}-alkyl-Y group wherein Y is as hereinbefore defined and the C_{2-4}-alkyl moiety of the C_{2-4}-alkyl-Y group is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two C_{1-2}-alkyl groups,

a 4-(C_{1-4}-alkyl)-piperazino or 4-(C_{1-4}-alkyl)-homopiperazino group substituted at a cyclic carbon atom by a 2-oxo-morpholino-C_{1-4}-alkyl group, wherein the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a piperazino or homopiperazino group substituted in the 4 position by a 2-oxo-morpholino-C_{1-4}-alkylene-CO group, wherein the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a piperazino or homopiperazino group substituted in the 4 position by a C_{2-4}-alkyl group, wherein the C_{2-4}-alkyl moiety is

substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R_6, by an R_5-C_{1-4}-alkyl, R_5-CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO, R_6SO_2-C_{1-4}-alkylene-CO or 2-oxo-morpholino-C_{1-4}-alkylene-CO group wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by a C_{2-4}-alkyl group wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by the group R_6, by an R_5-C_{1-4}-alkyl, R_5-CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO, R_6SO_2-C_{1-4}-alkylene-CO or 2-oxo-morpholino-C_{1-4}-alkylene-CO group, wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by a C_{2-4}-alkyl group, wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups,

a R_5-C_{1-4}-alkylene-NR_4 group wherein R_4 and R_5 are as hereinbefore defined, or

a C_{2-4}-alkyl-NR_4-group, wherein the C_{2-4}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two C_{1-2}-alkyl groups, while

by the abovementioned aryl moieties is meant a phenyl group which may in each case be mono- or disubstituted by R', while the substituents may be identical or different and

R' denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

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

2. A bicyclic heterocycle or a tautomer, stereoisomer or salt thereof according to claim 1, wherein

X denotes a nitrogen atom,

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 methyl group or a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c denotes a hydrogen atom,

R_d denotes a hydrogen atom, a methoxy, ethoxy, C_{4-6}-cycloalkoxy, C_{3-6}-cycloalkylmethoxy, 2-methoxy-ethoxy, 2-(cyclobutyloxy)-ethoxy, 2-(cyclopentyloxy)-ethoxy, 2-(cyclohexyloxy)-ethoxy, 2-(cyclopropylmethoxy)-ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-2-ylmethoxy or tetrahydropyran-4-ylmethoxy group,

A denotes a 1,2-vinylene group,

B denotes a methylene or ethylene group or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a pyrrolidino group wherein the two hydrogen atoms in the 3 position are replaced by a group E, wherein

E denotes a $-O-CO-CH_2CH_2-$, $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2CH_2-O-CO-CH_2-$, $-O-CO-CH_2-NR_4-CH_2-$, $-CH_2-O-CO-CH_2-NR_4-$, $-O-CO-CH_2-O-CH_2-$ or $-CH_2-O-CO-CH_2-O-$ bridge optionally substituted by one or two methyl groups,

where R_4 denotes a methyl or ethyl group,

a piperidino group wherein the two hydrogen atoms in the 3 position or in the 4 position are replaced by a group E, where E is as hereinbefore defined,

a pyrrolidino or piperidino group wherein two vicinal hydrogen atoms are replaced by an $-O-CO-CH_2-$, $-CH_2-O-CO-$, $-O-CO-CH_2-NR_4-$ or $-O-CO-CH_2-O-$ bridge optionally substituted by one or two methyl groups, whilst R_4 is as hereinbefore defined and the heteroatoms of the abovementioned bridges are not bound at the 2 or 5 position of the pyrrolidine ring and are not bound at the 2 or 6 position of the piperidino ring,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a $-CO-O-CH_2CH_2-$ or $-CH_2-O-CO-CH_2-$ bridge optionally substituted by one or two methyl groups, whilst in each case the left-hand end of the abovementioned bridges is bound to the 3 position of the piperazino ring,

a pyrrolidino or piperidino group substituted by the group R_5, wherein

R_5 denotes a 2-oxo-tetrahydrofuranyl, 2-oxo-1,4-dioxanyl or 2-oxo-4-(C_{1-4}-alkyl)-morpholinyl group optionally substituted by one or two methyl groups,

a pyrrolidino group substituted in the 3 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two methyl groups,

a piperidino group substituted in the 3 or 4 position by a 2-oxo-morpholino group, whilst the 2-oxo-morpholino group may be substituted by one or two methyl groups,

a piperazino group substituted in the 4 position by the group R_6, wherein

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetra-hydro-furan-4-yl group optionally substituted by one or two methyl groups,

a pyrrolidino group substituted in the 3 position by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a piperidino group substituted in the 3 or 4 position by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, whilst R_4 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group substituted by an (R_4NR_6)-C_{1-2}-alkyl, HNR_6-CO or R_4NR_6-CO group, whilst R_4 and R_6 are as hereinbefore defined,

a pyrrolidino group substituted in the 3 position by an R_5-CO-NH or R_5-CO-NR_4 group, whilst R_4 and R_5 are as hereinbefore defined,

a piperidino group substituted in the 3 or 4 position by an R_5-CO-NH or R_5-CO-NR_4 group, whilst R_4 and R_5 are as hereinbefore defined,

a piperazino group substituted in the 4 position by an R_5-C_{1-2}-alkyl, R_5-CO, R_5-C_{1-2}-alkylene-CO, (R_4NR_6)-C_{1-2}-alkylene-CO, R_6O-C_{1-2}-alkylene-CO, R_6S-C_{1-2}-alkylene-CO, R_6SO-C_{1-2}-alkylene-CO or R_6SO_2-C_{1-2}-alkylene-CO group wherein R_4 to R_6 are as hereinbefore defined,

a piperazino group substituted in the 4 position by a C_{2-3}-alkyl group wherein the C_{2-3}-alkyl group is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO or R_6SO_2 group, where R_4 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group substituted by a 2-oxo-morpholino-C_{1-2}-alkyl group wherein the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a piperazino group substituted in the 4 position by a 2-oxo-morpholino-C_{1-2}-alkylene-CO group wherein the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a piperazino group substituted in the 4 position by a C_{2-3}-alkyl group wherein the C_{2-3}-alkyl moiety is substituted in each case from position 2 by a 2-oxo-morpholino group optionally substituted by one or two methyl groups,

a piperidinyl group substituted in the 1 position by the group R_6, by an R_5-C_{1-2}-alkyl, R_5-CO, R_5-C_{1-2}-alkylene-CO, (R_4NR_6)-C_{1-2}-alkylene-CO, R_6O-C_{1-2}-alkylene-CO, R_6S-C_{1-2}-alkylene-CO, R_6SO-C_{1-2}-alkylene-CO, R_6SO_2-C_{1-2}-alkylene-CO or 2-oxo-morpholino-C_{1-2}-alkylene-CO group, whilst R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a piperidinyl group substituted in the 1 position by a C_{2-3}-alkyl group wherein the C_{2-3}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups,

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by the group R_6, by an R_5-C_{1-2}-alkyl, R_5-CO, R_5-C_{1-2}-alkylene-CO, (R_4NR_6)-C_{1-2}-alkylene-CO, R_6O-C_{1-2}-alkylene-CO, R_6S-C_{1-2}-alkylene-CO, R_6SO-C_{1-2}-alkylene-CO, R_6SO_2-C_{1-2}-alkylene-CO or 2-oxo-morpholino-C_{1-2}-alkylene-CO group, wherein R_4 to R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups, or

a pyrrolidin-3-yl-NR_4, piperidin-3-yl-NR_4 or piperidin-4-yl-NR_4 group substituted in each case at the cyclic nitrogen atom by a C_{2-3}-alkyl group, wherein the C_{2-3}-alkyl moiety is substituted in each case from position 2 by an (R_4NR_6), R_6O, R_6S, R_6SO, R_6SO_2 or 2-oxo-morpholino group, whilst R_4 and R_6 are as hereinbefore defined and the 2-oxo-morpholino moiety may be substituted by one or two methyl groups.

3. A bicyclic heterocycle or a tautomer, stereoisomer or salt thereof according to claim 1, wherein

X denotes a nitrogen atom,

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, each denote a methyl group or a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c denotes a hydrogen atom,

R_d denotes a hydrogen atom, a methoxy, ethoxy, C_{4-6}-cycloalkoxy, C_{3-6}-cycloalkylmethoxy, 2-methoxy-ethoxy, 2-(cyclobutyloxy)-ethoxy, 2-(cyclopentyloxy)-ethoxy, 2-(cyclohexyloxy)-ethoxy, 2-(cyclopropylmethoxy)-ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-2-ylmethoxy or tetrahydropyran-4-ylmethoxy group,

A denotes a 1,2-vinylene group,

B denotes a methylene or ethylene group or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a piperidino group wherein the two hydrogen atoms in the 4 position are replaced by a $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2CH_2-O-CO-CH_2-$, $-O-CO-CH_2-NCH_3-CH_2-$ or $-O-CO-CH_2-O-CH_2-$ bridge,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a $-CO-O-CH_2-CH_2-$ or $-CH_2-O-CO-CH_2-$ bridge, whilst in each

case the left-hand end of the above bridges is bound to the 3 position of the piperazino ring,

a piperidino group substituted by a 2-oxo-tetrahydrofuranyl group,

a piperidino group which is substituted in the 4 position by a 2-oxo-morpholino or 2-oxo-morpholinomethyl group, whilst the 2-oxo-morpholino moiety may in each case be substituted by one or two methyl groups,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

a piperidino group which is substituted in the 4 position by a CH_3NR_6 or R_6S group, whilst

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydro-furan-4-yl group,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuranylmethyl or 2-oxo-tetrahydrofuranyl-carbonyl group,

a piperazino group which is substituted in the 4 position by a straight-chained C_{2-3}-alkyl group, whilst the C_{2-3}-alkyl moiety is terminally substituted in each case by a 2-oxo-tetrahydro-furan-3-ylsulphenyl group,

a piperidin-4-yl group which is substituted in the 1 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

a piperidin-4-yl-NCH_3 group which is substituted at the cyclic nitrogen atom by a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetra-hydrofuran-4-yl or 2-oxo-tetrahydrofuranylcarbonyl group.

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4. A bicyclic heterocycle or a tautomer, stereoisomer or salt thereof according to claim 1, wherein

X denotes a nitrogen atom,

R_a denotes a hydrogen atom,

R_b denotes a 1-phenylethyl group or a phenyl group substituted by the groups R_1 to R_3, wherein

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

R_3 denotes a hydrogen atom,

R_c denotes a hydrogen atom,

R_d denotes a hydrogen atom, a methoxy, ethoxy, 2-methoxy-ethoxy, cyclobutyloxy, cyclopentyloxy, cyclopropylmethoxy, cyclobutylmethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuran-2-ylmethoxy group,

A denotes a 1,2-vinylene group,

B denotes a methylene group or, if B is bound to a carbon atom of group C, it may also denote a bond,

C denotes a piperidino group in which the two hydrogen atoms are replaced in the 4 position by a $-CH_2-O-CO-CH_2-$, $-CH_2CH_2-O-CO-$, $-CH_2CH_2-O-CO-CH_2-$, $-O-CO-CH_2-NCH_3-CH_2-$ or $-O-CO-CH_2-O-CH_2-$ bridge,

a piperazino group wherein a hydrogen atom in the 3 position together with the hydrogen atom in the 4 position are replaced by a $-CO-O-CH_2-CH_2-$ or $-CH_2-O-CO-CH_2-$ bridge, while in each case the left-hand end of the abovementioned bridges is bound to the 3 position of the piperazino ring,

a piperidino group substituted by a 2-oxo-tetrahydrofuranyl group,

a piperidino group which is substituted in the 4 position by a 2-oxo-morpholino or 2-oxo-morpholinomethyl group, while the 2-oxo-morpholino moiety may in each case be substituted by one or two methyl groups,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

a piperidino group which is substituted in the 4 position by a CH_3NR_6 or R_6S group, where

R_6 denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

a piperazino group which is substituted in the 4 position by a 2-oxo-tetrahydrofuranylmethyl or 2-oxo-tetrahydro-furanyl-carbonyl group,

a piperazino group which is substituted in the 4 position by a [2-(2-oxo-tetrahydrofuran-3-ylsulphenyl)ethyl] group,

a piperidin-4-yl group which is substituted in the 1 position by a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

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a piperidin-4-yl-NCH_3 group which is substituted at the cyclic nitrogen atom by a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl or 2-oxo-tetrahydrofuranyl-carbonyl group.

5. 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-tetrahydrofuran-3-yl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

6. 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[4-(2-oxo-tetrahydrofuran-4-yl)-piperazin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

7. 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(4-{2-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-ethyl}-piperazin-1-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

8. 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(3-oxo-perhydropyrazino [2,1-c] [1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

9. (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(5-oxo-tetrahydrofuran-2-yl)carbonyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

10. 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(1-oxo-perhydropyrazino [2,1-c] [1,4]oxazin-8-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

11. 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-{4-[(2-oxo-tetrahydrofuran-3-yl)sulphanyl]-piperidin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline, or a tautomer, stereoisomer or salt thereof.

12. A physiologically acceptable salt of a compound according to any one of claims 1 to 11 with an inorganic or organic acid or base.

13. A pharmaceutical composition comprising a bicyclic heterocycle as defined in any one of claims 1 to 11 or a physiologically acceptable salt according to claim 12 and a pharmaceutically acceptable carrier or diluent.

14. A pharmaceutical composition according to claim 13 for treatment of a benign or malignant tumor in a patient in need of the treatment.

15. A pharmaceutical composition according to claim 13 for treatment or prevention of a disease of the respiratory tract and lungs in a patient in need of the treatment.

16. A pharmaceutical composition according to claim 13 for treating a polyp, a disease of the gastro-intestinal tract, the bile duct, the gall bladder, kidneys and skin.

17. Use of a compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof in preparation of a pharmaceutical composition for treatment of a benign or malignant tumor in a patient in need of the treatment.

18. Use of a compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof in preparation of a pharmaceutical composition for treatment or prevention of a

disease of the respiratory tract and lungs in a patient in need of the treatment.

19. Use of a compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof in preparation of a pharmaceutical composition for treating a polyp, a disease of the gastro-intestinal tract, the bile duct, the gall bladder, kidneys and skin.

20. Use of a compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof for treatment of a benign or malignant tumor in a patient in need of the treatment.

21. Use of a compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof for treatment or prevention of a disease of the respiratory tract and lungs in a patient in need of the treatment.

22. Use of a compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof for treating a polyp, a disease of the gastro-intestinal tract, the bile duct, the gall bladder, kidneys and skin.

23. A compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof for treatment of a benign or malignant tumor in a patient in need of the treatment.

24. A compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof for treatment or prevention of a disease of the

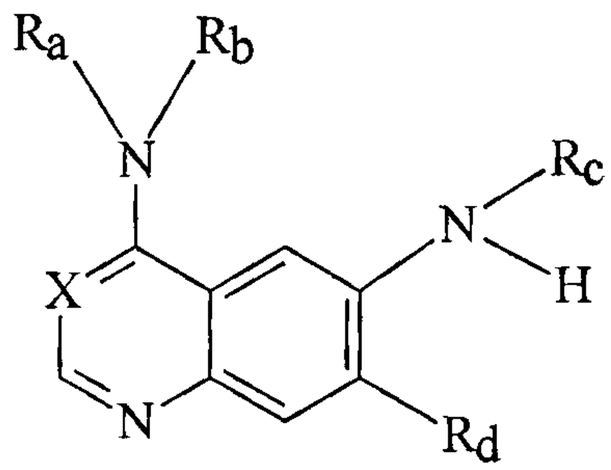
respiratory tract and lungs in a patient in need of the treatment.

25. A compound as defined in any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof for treating a polyp, a disease of the gastrointestinal tract, the bile duct, the gall bladder, kidneys and skin.

26. A process for preparing a pharmaceutical composition according to claim 13, wherein a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable tautomer, stereoisomer or salt thereof is admixed with a pharmaceutically acceptable carrier or diluent.

27. Process for preparing a compound of general formula I as defined in claim 1

a. a compound of general formula



, (II)

wherein

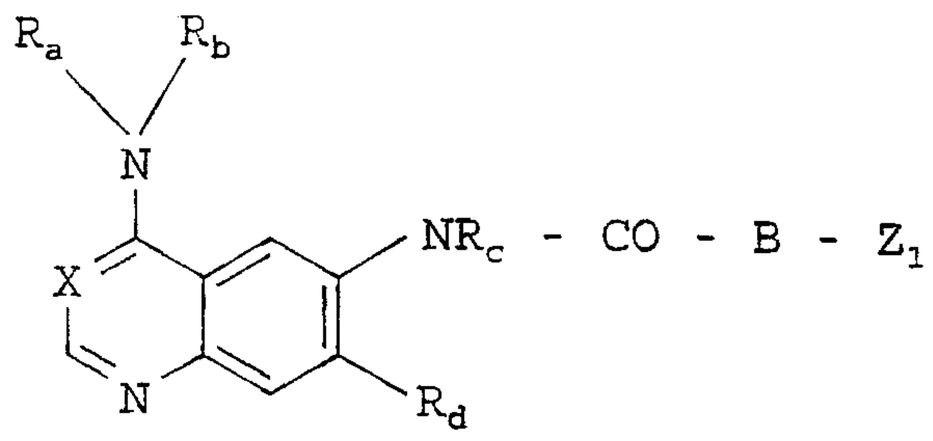
R_a to R_d and X are as defined in claim 1,

is reacted with a compound of general formula

HO-CO - A - B - C , (III)

wherein
A to C are as defined in claim 1, or with the reactive derivatives thereof

b. a compound of general formula



, (IV)

optionally formed in the reaction mixture
wherein
R_a to R_d, A, B and X are as defined in claim 1 and
Z_1 denotes an exchangeable group,

is reacted with a compound of general formula

H - G , (V)

wherein
G denotes one of the groups mentioned for C in claim 1, which is attached to the group B via a nitrogen atom, or

c. in order to prepare a compound of general formula I wherein C denotes one of the groups mentioned for C in claim 1, which comprises an imino or HNR_4 group substituted by R_6 or by an R_5-C_{1-4}-alkyl group, where R_4 to R_6 are as defined in claim 1, a compound of general formula

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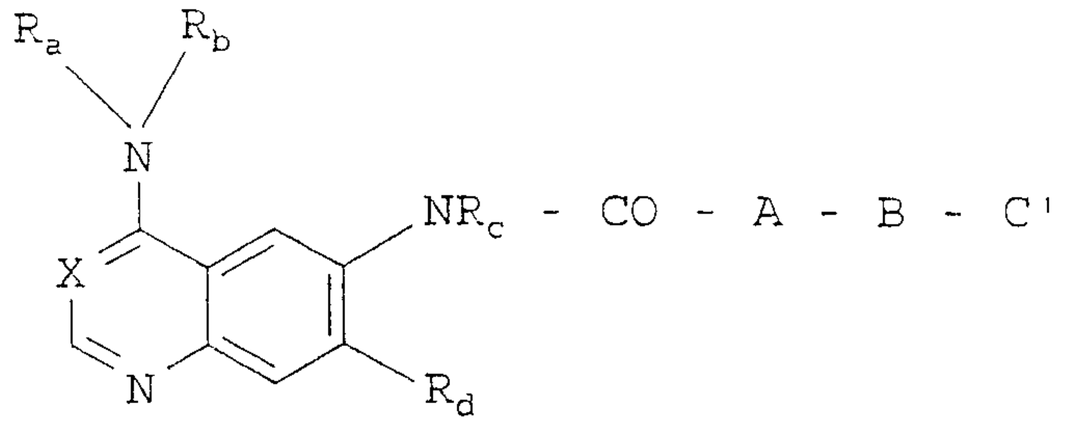


, (VI)

wherein
R_a to R_d, A and B are as defined in claim 1 and
C' denotes one of the groups mentioned for C in claim 1 which comprises a corresponding unsubstituted imino or HNR_4 group, where R_4 is as defined in claim 1,

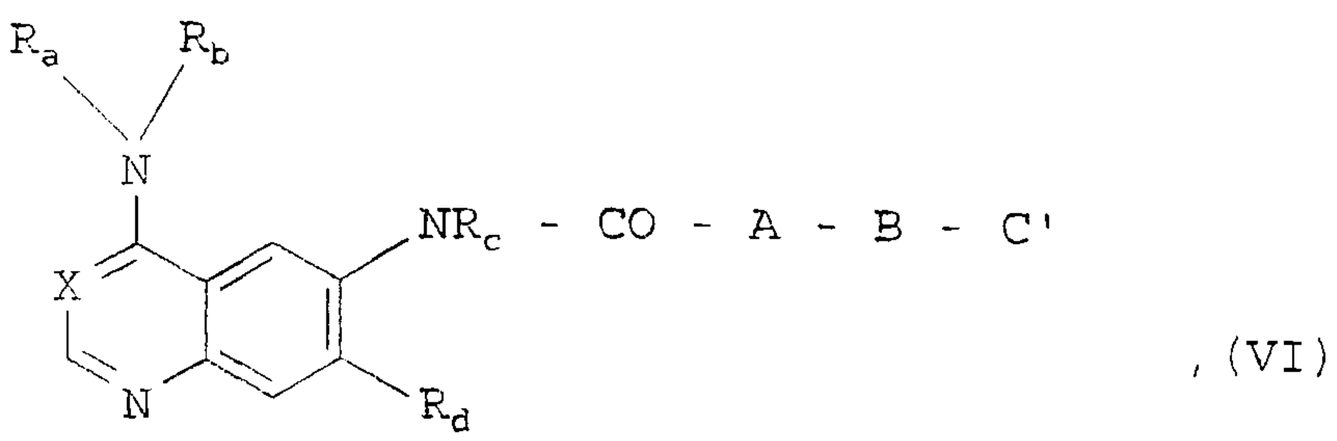
is reacted with a compound of general formula

, (VII)

wherein
U denotes the group R_6 or a R_5-C_{1-4}-alkyl group, where R_5 and R_6 are defined as in claims 1 to 5, and
Z_2 denotes an exchangeable group or
Z_2 together with an adjacent hydrogen atom denotes another carbon-carbon bond attached to a carbonyl group, or

d. in order to prepare a compound of general formula I wherein C denotes one of the groups mentioned for C in claim 1 which contains an imino or HNR_1 group substituted by an R_5CO, R_5-C_{1-4}-alkylene-CO, (R_4NR_6)-C_{1-4}-alkylene-CO, R_6O-C_{1-4}-alkylene-CO, R_6S-C_{1-4}-alkylene-CO, R_6SO-C_{1-4}-alkylene-CO, R_6SO_2-C_{1-4}-alkylene-CO or 2-oxo-morpholino-C_{1-4}-alkylene-CO group, where R_4 to R_6 are defined as in claim 1 and the 2-oxo-morpholino moiety is unsubstituted or substituted by one or two C_{1-2}-alkyl groups,

a compound of general formula



, (VI)

wherein
R_a to R_d, A and B are defined as in claim 1 and
C' denotes one of the groups mentioned for C in claim 1 which comprises a corresponding unsubstituted imino or HNR_4 group, where R_4 is defined as in claims 1 to 5,

is reacted with a compound of general formula

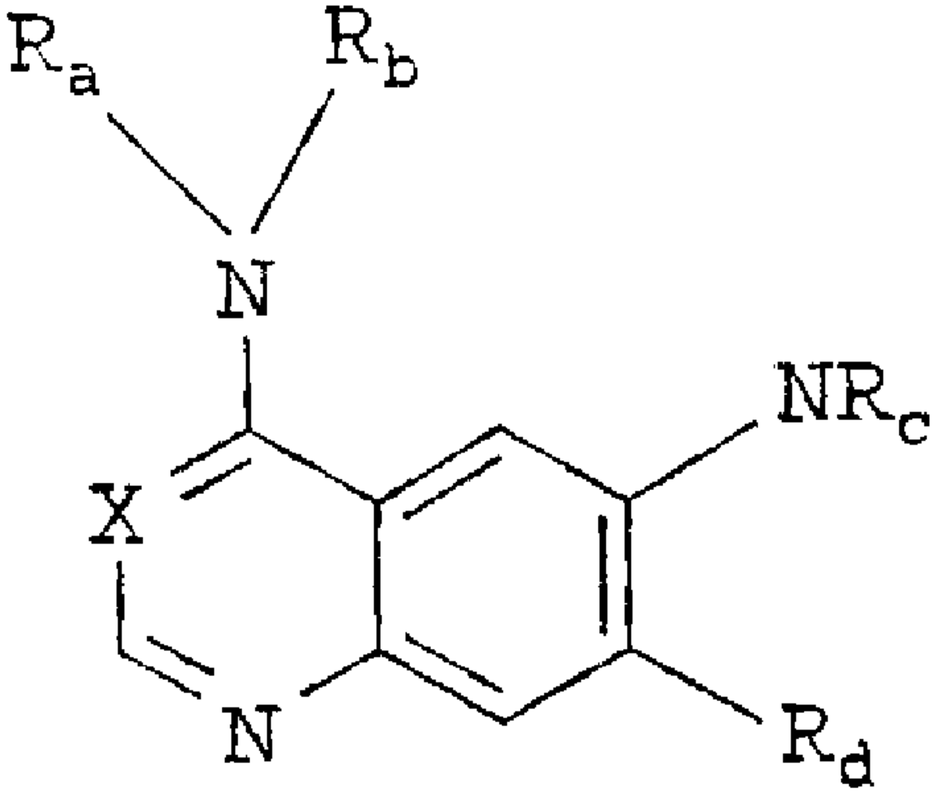
, (VIII)

wherein
W denotes the group R_5 or an R_5-C_{1-4}-alkyl, (R_4NR_6)-C_{1-4}-alkyl, R_6O-C_{1-4}-alkyl, R_6S-C_{1-4}-alkyl, R_6SO-C_{1-4}-alkyl, R_6SO_2-C_{1-4}-alkyl or 2-oxo-morpholino-C_{1-4}-alkyl group, wherein R_4 to R_6 are defined as in claim 1 and the 2-oxo-morpholino moiety is non-substituted or substituted by one or two C_{1-2}-alkyl groups, and

optionally, any protecting group used in the reactions described above is cleaved again or

optionally a compound of general formula I thus obtained is resolved into its stereoisomers or

optionally a compound of general formula I thus obtained is converted into a salt thereof.



(I)