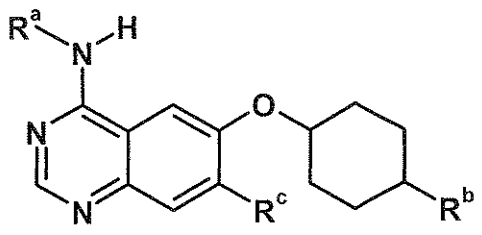
97430pct

Bicyclic heterocycles, pharmaceutical compositions containing these compounds, the use thereof and processes for the preparation thereof

The present invention relates to bicyclic heterocycles of general formula



(I),

their tautomers, their stereoisomers, their mixtures and their salts, in particular their physiologically acceptable salts with inorganic or organic acids and bases, which have valuable pharmacological properties, in particular an inhibitory action on the signal transduction mediated by tyrosine kinases, their use for the treatment of illnesses, in particular of tumoral diseases and of benign prostatic hyperplasia (BPH), of diseases of the lung and of the airways, and the preparation thereof.

In the above general formula (I)

R^a denotes a phenyl, 1-phenylethyl or indan-4-yl group, wherein the phenyl nucleus is substituted in each case by the groups R^1 to R^3, wherein

R^1 and R^2, which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

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

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a heteroaryl, heteroaryloxy, heteroarylmethyl or heteroarylmethoxy group,

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

a cyano, nitro or amino group, and

R^3 denotes a hydrogen, fluorine, chlorine or bromine atom or

a methyl or trifluoromethyl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-(C_{1-4}-alkyl-carbonyl)-piperazin-1-yl, 4-(C_{1-4}-alkyl-sulphonyl)-piperazin-1-yl, homopiperazin-1-yl, 4-(C_{1-4}-alkyl-carbonyl)-homopiperazin-1-yl or 4-(C_{1-4}-alkyl-sulphonyl)-homopiperazin-1-yl group which may be mono-, di- or trisubstituted by R^4 in each case, while the substituents may be identical or different and

R^4 denotes a fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl group,

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

an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)amino, C_{1-4}-alkyl-carbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-carbonylamino, C_{1-4}-alkyl-sulphonylamino or N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-sulphonylamino group,

an amino-C_{1-4}-alkyl, C_{1-4}-alkylamino-C_{1-4}-alkyl, di-(C_{1-4}-alkyl)amino-C_{1-4}-alkyl, C_{1-4}-alkyl-carbonylamino-C_{1-4}-alkyl, N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-carbonylamino-C_{1-4}-alkyl, C_{1-4}-alkyl-sulphonylamino-C_{1-4}-alkyl or N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-sulphonylamino-C_{1-4}-alkyl group,

a hydroxy, C_{1-4}-alkyloxy or C_{1-4}-alkyl-carbonyloxy group

a hydroxy-C_{1-4}-alkyl, C_{1-4}-alkyloxy-C_{1-4}-alkyl or C_{1-4}-alkyl-carbonyloxy-C_{1-4}-alkyl group,

a C_{1-4}-alkyl-carbonyl, cyano, C_{1-4}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-4}-alkyl-aminocarbonyl, di-(C_{1-4}-alkyl)amino-carbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, piperazin-1-yl-carbonyl, 4-C_{1-4}-alkyl-piperazin-1-yl-carbonyl or morpholin-4-yl-carbonyl group,

a C_{1-4}-alkylcarbonyl-C_{1-4}-alkyl, cyano-C_{1-4}-alkyl, C_{1-4}-alkyloxycarbonyl-C_{1-4}-alkyl, aminocarbonyl-C_{1-4}-alkyl, C_{1-4}-alkylaminocarbonyl-C_{1-4}-alkyl, di-(C_{1-4}-alkyl)aminocarbonyl-C_{1-4}-alkyl, pyrrolidin-1-yl-carbonyl-C_{1-4}-alkyl, piperidin-1-yl-carbonyl-C_{1-4}-alkyl, piperazin-1-yl-carbonyl-C_{1-4}-alkyl, 4-C_{1-4}-alkyl-piperazin-1-yl-carbonyl-C_{1-4}-alkyl or morpholin-4-yl-carbonyl-C_{1-4}-alkyl group,

a C_{1-4}-alkylsulphanyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, aminosulphonyl, C_{1-4}-alkyl-aminosulphonyl or di-(C_{1-4}-alkyl)amino-sulphonyl group,

a C_{1-4}-alkylsulphanyl-C_{1-4}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-4}-alkyl, C_{1-4}-alkylsulphonyl-C_{1-4}-alkyl, aminosulphonyl-C_{1-4}-alkyl, C_{1-4}-alkyl-aminosulphonyl-C_{1-4}-alkyl or di-(C_{1-4}-alkyl)amino-sulphonyl-C_{1-4}-alkyl group

and wherein the heterocycles mentioned under R^b above may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl group,

a C_{1-4}-alkyl group which is substituted by an R^5 group, where

R^5 denotes a hydroxy, C_{1-3}-alkyloxy, C_{3-6}-cycloalkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, bis-(2-methoxyethyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, 2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl, 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl, 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl, piperazin-1-yl, 4-C_{1-3}-alkyl-piperazin-1-yl, homopiperazin-1-yl or C_{1-3}-alkyl-homopiperazin-1-yl group or

a formylamino, C_{1-4}-alkylcarbonylamino, C_{1-3}-alkyloxy-C_{1-3}-alkyl-carbonylamino, C_{1-4}-alkyloxycarbonylamino, aminocarbonylamino, C_{1-3}-alkylaminocarbonylamino, di-(C_{1-3}-alkyl)aminocarbonylamino, pyrrolidin-1-ylcarbonylamino, piperidin-1-ylcarbonylamino, piperazin-1-ylcarbonylamino, 4-C_{1-3}-alkyl-piperazin-1-ylcarbonylamino, morpholin-4-ylcarbonylamino or a C_{1-4}-alkylsulphonylamino group,

a hydroxy group,

a C_{1-4}-alkyloxy group,

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

a C_{2-4}-alkyloxy group which is substituted by the group R^5, where R^5 is as hereinbefore defined,

a C_{3-7}-cycloalkyloxy or C_{3-7}-cycloalkyl-C_{1-4}-alkyloxy group,

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

a tetrahydrofuranyl-C_{1-4}-alkyloxy or tetrahydropyranyl-C_{1-4}-alkyloxy group,

a C_{1-4}-alkoxy group which is substituted by a pyrrolidinyl, piperidinyl or homopiperidinyl group substituted in the 1 position by the group R^6, where

R^6 denotes a hydrogen atom or a C_{1-3}-alkyl group,

or a C_{1-4}-alkoxy group which is substituted by a morpholinyl group substituted in the 4 position by the group R^6, where R^6 is as hereinbefore defined, and wherein the pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl groups mentioned above in the definition of the group R^c may each be substituted by one or two C_{1-3}-alkyl groups, and

wherein by the aryl groups mentioned in the definition of the foregoing groups is meant in each case a phenyl group which is mono- or disubstituted by R^7, wherein the substituents may be identical or different and

R^7 denotes a hydrogen atom, a fluorine, chlorine, bromine or iodine atom or a C_{1-3}-alkyl, hydroxy, C_{1-3}-alkyloxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy or cyano group, and

by the heteroaryl groups mentioned in the definition of the foregoing groups is meant a pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group, wherein the above-mentioned heteroaryl groups are mono- or disubstituted by the group R^7, wherein the substituents may be identical or different and R^7 is as hereinbefore defined, and

unless stated otherwise, the above-mentioned alkyl groups may be straight-chain or branched.

Preferred compounds of the above general formula I are those wherein

R^a denotes a phenyl, 1-phenylethyl or indan-4-yl group, wherein the phenyl nucleus is substituted in each case by the groups R^1 to R^3, wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl or ethynyl group,

a phenyloxy or phenylmethoxy group, wherein the phenyl moiety of the above-mentioned groups may optionally be substituted by a fluorine or chlorine atom, or

a pyridyloxy or pyridinylmethoxy group, wherein the pyridinyl moiety of the above-mentioned groups is optionally substituted by a methyl or trifluoromethyl group,

R^2 denotes a hydrogen, fluorine or chlorine atom or a methyl group and

R^3 denotes a hydrogen atom,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-piperazin-1-yl, 4-(C_{1-3}-alkyl-sulphonyl)-piperazin-1-yl, homopiperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-homopiperazin-1-yl or 4-(C_{1-3}-alkyl-sulphonyl)-homopiperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a fluorine atom,

a C_{1-3}-alkyl group,

an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group,

an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl, C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino-

C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl group,

a hydroxy, C_{1-3}-alkyloxy or C_{1-3}-alkyl-carbonyloxy group,

a hydroxy-C_{1-3}-alkyl, C_{1-3}-alkyloxy-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonyloxy-C_{1-3}-alkyl group,

a C_{1-3}-alkyl-carbonyl, cyano, C_{1-4}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl or di-(C_{1-3}-alkyl)amino-carbonyl-group,

a C_{1-3}-alkylcarbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, C_{1-4}-alkyloxycarbonyl-C_{1-3}-alkyl- group, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)aminocarbonyl-C_{1-3}-alkyl group,

a C_{1-4}-alkylsulphanyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl or di-(C_{1-3}-alkyl)amino-sulphonyl group,

a C_{1-4}-alkylsulphanyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphonyl-C_{1-3}-alkyl, aminosulphonyl-C_{1-3}-alkyl, C_{1-3}-alkyl-aminosulphonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-sulphonyl-C_{1-3}-alkyl group,

and wherein the heterocycles mentioned above under R^b - may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a hydroxy group,

a C_{1-3}-alkyloxy group,

a methoxy group which is substituted by one to three fluorine atoms,

an ethyloxy group which is substituted in the 2 position by an R^5 group, wherein

R^5 denotes a hydroxy, C_{1-3}-alkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, bis-(2-methoxyethyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl or a 4-C_{1-3}-alkyl-piperazin-1-yl group,

a propyloxy group which is substituted in the 3 position by the group R^5, wherein R^5 is as hereinbefore defined, or

a butyloxy group which is substituted in the 4 position by a group R^5, wherein R^5 is as hereinbefore defined, and

wherein, unless stated otherwise, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

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

R^a denotes a 1-phenylethyl, 3-ethynylphenyl, 3-bromo-2-fluoro-phenyl, 3-bromo-4-fluoro-phenyl, 3-chloro-2-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, 5-chloro-2-fluoro-phenyl, 2-fluoro-3-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 3-fluoro-5-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 2,4-difluoro-3-methyl-phenyl, 2,5-difluoro-3-methyl-phenyl, 3-chloro-2-methyl-phenyl or an indan-4-yl group,

a 3-chloro-4-benzyloxy-phenyl, 3-chloro-4-[(3-fluoro-benzyl)oxy]-phenyl, 4-(pyridin-3-yloxy)-phenyl, 4-[(6-methyl-pyridin-3-yl)oxy]-phenyl, 3-methyl-4-(pyridin-3-yloxy)-phenyl, 3-methyl-4-[(6-methyl-pyridin-3-yl)oxy]-phenyl, 3-chloro-4-(pyridin-3-yloxy)-phenyl or 3-chloro-4-[(6-methyl-pyridin-3-yl)oxy]-phenyl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-piperazin-1-yl or 4-(C_{1-3}-alkyl-sulphonyl)-piperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a fluorine atom,

a C_{1-3}-alkyl group,

an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group,

an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl, C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl group,

a hydroxy, C_{1-3}-alkyloxy or C_{1-3}-alkyl-carbonyloxy group,

a hydroxy-C_{1-3}-alkyl, C_{1-3}-alkyloxy-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonyloxy-C_{1-3}-alkyl group,

a C_{1-3}-alkyl-carbonyl, cyano, C_{1-4}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl or di-(C_{1-3}-alkyl)amino-carbonyl group,

a C_{1-3}-alkylcarbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, C_{1-4}-alkyloxycarbonyl-C_{1-3}-alkyl- group, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)aminocarbonyl-C_{1-3}-alkyl group,

a C_{1-4}-alkylsulphanyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl or di-(C_{1-3}-alkyl)amino-sulphonyl group,

a C_{1-4}-alkylsulphanyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphonyl-C_{1-3}-alkyl, aminosulphonyl-C_{1-3}-alkyl, C_{1-3}-alkyl-aminosulphonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-sulphonyl-C_{1-3}-alkyl group,

and wherein the heterocycles mentioned above under R^b may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a methoxy or ethyloxy group,

an ethyloxy group which is substituted in the 2 position by the group R^5, wherein

R^5 denotes a hydroxy, methoxy, ethoxy, amino, dimethylamino, diethylamino, bis-(2-methoxyethyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl or 4-ethylpiperazin-1-yl group,

a propyloxy group which is substituted in the 3 position by the group R^5, wherein R^5 is as hereinbefore defined, or
a butyloxy group which is substituted in the 4 position by the group R^5, wherein R^5 is as hereinbefore defined, and

wherein, unless stated otherwise, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

Most particularly preferred compounds of general formula I are those wherein

R^a denotes a 1-phenylethyl, 3-ethynylphenyl, 3-chloro-2-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, 5-chloro-2-fluoro-phenyl, 2-fluoro-3-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 3-fluoro-5-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 2,4-difluoro-3-methyl-phenyl, 2,5-difluoro-3-methyl-phenyl, 3-chloro-2-methyl-phenyl or an indan-4-yl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-piperazin-1-yl or 4-(C_{1-3}-alkyl-sulphonyl)-piperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a fluorine atom,

a C_{1-3}-alkyl group,

an amino, C_{1-2}-alkylamino, di-(C_{1-2}-alkyl)amino, C_{1-2}-alkyl-carbonylamino, N-(C_{1-2}-alkyl)-C_{1-2}-alkyl-carbonylamino, C_{1-2}-alkyl-sulphonylamino or N-(C_{1-2}-alkyl)-C_{1-2}-alkyl-sulphonylamino group,

an amino-C_{1-2}-alkyl, C_{1-2}-alkylamino-C_{1-2}-alkyl, di-(C_{1-2}-alkyl)amino-C_{1-2}-alkyl, C_{1-2}-alkyl-carbonylamino-C_{1-2}-alkyl, N-(C_{1-2}-alkyl)-C_{1-2}-alkyl-carbonylamino-C_{1-2}-alkyl, C_{1-2}-alkyl-sulphonylamino-C_{1-2}-alkyl or N-(C_{1-2}- alkyl)-C_{1-2}-alkyl-sulphonylamino-C_{1-2}-alkyl group,

a hydroxy, C_{1-2}-alkyloxy or C_{1-2}-alkyl-carbonyloxy group,

a hydroxy-C_{1-2}-alkyl, C_{1-2}-alkyloxy-C_{2-4}-alkyl or C_{1-2}-alkyl-carbonyloxy-C_{1-2}-alkyl group,

a C_{1-2}-alkyl-carbonyl, cyano, C_{1-2}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-2}-alkyl-aminocarbonyl or di-(C_{1-2}-alkyl)amino-carbonyl group,

a C_{1-2}-alkylcarbonyl-C_{1-2}-alkyl, cyano-C_{1-2}-alkyl, C_{1-2}-alkyloxycarbonyl-C_{1-2}-alkyl group, aminocarbonyl-C_{1-2}-alkyl, C_{1-2}-alkylaminocarbonyl-C_{1-2}-alkyl or di-(C_{1-2}-alkyl)aminocarbonyl-C_{1-2}-alkyl group,

a C_{1-2}-alkylsulphanyl, C_{1-2}-alkylsulphinyl or C_{1-2}-alkylsulphonyl group,

a C_{1-2}-alkylsulphanyl-C_{1-2}-alkyl, C_{1-2}-alkylsulphinyl-C_{1-2}-alkyl or C_{1-2}-alkylsulphonyl-C_{1-2}-alkyl group,

and wherein the heterocycles mentioned above under R^b may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a methoxy, ethyloxy or 2-(methoxy)-ethyloxy group,

a 2-(morpholin-4-yl)ethyloxy, 3-(morpholin-4-yl)propyloxy or 4-(morpholin-4-yl)butyloxy group,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.
Particularly preferred compounds of general formula I are those wherein

R^a denotes a 1-phenylethyl, 3-chloro-2-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, 5-chloro-2-fluoro-phenyl, 2-fluoro-3-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 3-fluoro-5-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 2,4-difluoro-3-methyl-phenyl, 3-chloro-2-methyl-phenyl or an indan-4-yl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl or 3-oxo-piperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a methyl, hydroxy, cyano, aminocarbonyl, methylamino-carbonyl or dimethylamino-carbonyl group, and

R^c denotes a methoxy group,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

Of the bicyclic heterocycles of general formula I described hereinbefore and the subgroups designated in each case as being preferred, particularly preferred, most particularly preferred and especially preferred, special emphasis should be placed in each case on those compounds wherein

R^a denotes a 3-chloro-2-fluoro-phenyl group,

a 2-fluoro-3-methyl-phenyl group,

a 2-fluoro-5-methyl-phenyl group or

a 3-chloro-2-methyl-phenyl group,

R^b denotes a 3-oxo-piperazin-1-yl group or

a 4-methyl-3-oxo-piperazin-1-yl group, and

R^c denotes a methoxy group,

wherein for R^a the 3-chloro-2-fluoro-phenyl group in particular, for R^b the 3-oxo-piperazin-1-yl or 4-methyl-3-oxo-piperazin-1-yl group and for R^c the methoxy group deserves special mention, and

wherein the *trans* arrangement of the substituents in the 1,4 position of the cyclohexane ring is preferred in each case.

The following particularly preferred compounds of general formula I deserve particular mention:

(a) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(b) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(c) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(d) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(e) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(f) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(g) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(h) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(i) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(j) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(k) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(l) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(m) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(n) 4-[(2-fluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(o) 4-[(2-fluoro-5-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

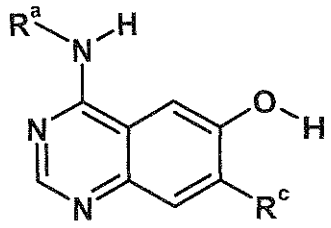
(p) 4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and

(q) 4-[(3-chloro-2-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

and the salts thereof.

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

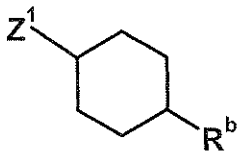
a) reacting a compound of general formula



,(II)

wherein

R^a and R^c are as hereinbefore defined, with a compound of general formula



,(III)

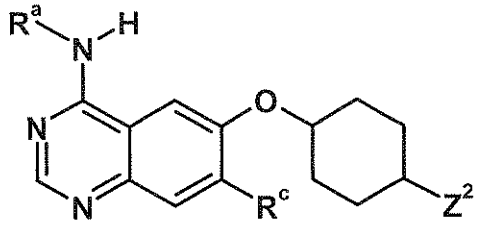
wherein

R^b is as hereinbefore defined and Z^1 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom, a sulphonyloxy group such as a methanesulphonyloxy or p-toluenesulphonyloxy group or a hydroxy group.

With a compound of general formula (III), wherein Z^1 denotes a halogen atom or a sulphonyloxy group, the reaction is expediently carried out in a solvent such as ethanol, isopropanol, acetonitrile, toluene, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulphoxide or N-methylpyrrolidinone, preferably in the presence of a base such as potassium carbonate, potassium-tert-butoxide, sodium hydride or N-ethyl-diisopropylamine, at temperatures in the range from 20°C to 160°C, for example at temperatures in the range from 80°C to 140°C.
With a compound of general formula III wherein Z^1 denotes a hydroxy group, the reaction is carried out in the presence of a dehydrating agent, preferably in the presence of a phosphine and an azodicarboxylic acid derivative such as e.g. Triphenylphosphine/ diethyl azodicarboxylate, conveniently in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, dioxane, toluene or ethyleneglycol

diethylether at temperatures between -50 and 150°C, but preferably at temperatures between -20 and 80°C.

b) reacting a compound of general formula



,(IV)

wherein

R^a and R^c are as hereinbefore defined, and Z^2 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom or a sulphonyloxy group such as a methanesulphonyloxy or p-toluenesulphonyloxy group, with a compound of general formula

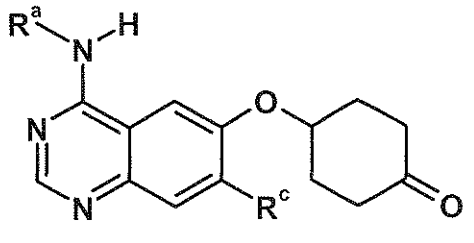
$$H\text{-}R^b \qquad ,(V)$$

wherein

R^b is as hereinbefore defined.

The reaction is preferably carried out in the presence of an organic or inorganic base such as potassium carbonate or N-ethyl-diisopropylamine, for example, in a solvent such as ethanol, isopropanol, acetonitrile, toluene, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulphoxide or N-methylpyrrolidinone at temperatures in the range from 0°C and 150°C.

c) reacting a compound of general formula


,(VI)

wherein

R^a and R^c are as hereinbefore defined, with a compound of general formula

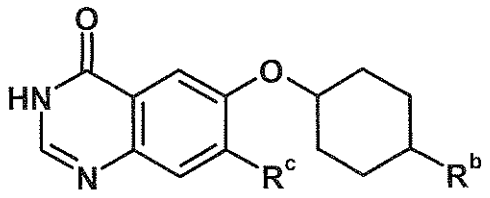
$$H\text{-}R^b \qquad ,(VII)$$

wherein

R^b is as hereinbefore defined, in the presence of a reducing agent.

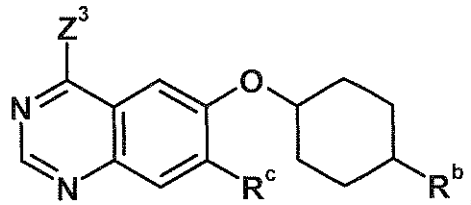
The reductive amination is carried out for example in a solvent such as dichloromethane, 1,2-dichloroethane, methanol, ethanol, tetrahydrofuran or dioxane in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride, optionally in the presence of acetic acid at temperatures between 0°C and 80°C. The reductive amination may also be carried out with hydrogen in the presence of a catalyst such as palladium on activated charcoal or platinum oxide. Another possibility is to form the enamine from the ketone of general formula VI and the amine of general formula VII while cleaving water, for example with titanium (IV) isopropoxide, and then to reduce this, for example with sodium borohydride or hydrogen/palladium on activated charcoal.

d) reacting a compound of general formula (VIII)



(VIII),

wherein R^b and R^c are as hereinbefore defined, with a halogenating agent, for example an acid halide such as thionyl chloride, thionylbromide, phosphorus trichloride, phosphorus pentachloride or phosphorus oxychloride, to obtain an intermediate compound of general formula (IX),



(IX),

wherein R^b and R^c are as hereinbefore defined and Z^3 denotes a halogen atom such as a chlorine or bromine atom,

and subsequently reacting with a compound of general formula (X),

R^a-NH_2 (X), wherein R^a is as hereinbefore defined, or the salts thereof.

The reaction with the halogenating agent is optionally carried out in a solvent such as methylene chloride, chloroform, acetonitrile or toluene and optionally in the presence of a base such as N,N-diethylaniline, triethylamine or N-ethyl-diisopropylamine at temperatures in the range from 20°C to 160°C, preferably 40°C to 120°C. However, the reaction is preferably carried out with thionyl chloride and catalytic amounts of dimethylformamide at the boiling temperature of the reaction mixture or with phosphorus oxychloride in acetonitrile in the presence of triethylamine at the boiling temperature of the reaction mixture.

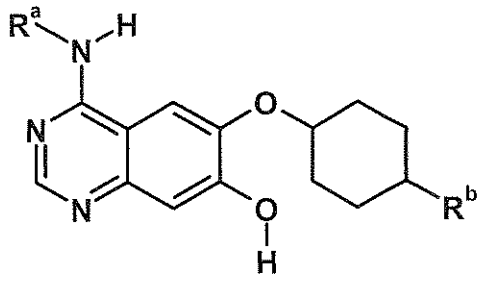
The reaction of the compound of general formula (IX) with the compound of general formula (X) or the salts thereof is conveniently carried out in a solvent such as

ethanol, isopropanol, acetonitrile, dioxane or dimethylformamide, optionally in the presence of a base such as potassium carbonate, triethylamine or N-ethyl-diisopropylamine, at temperatures in the range from 20°C and 160°C, preferably from 60°C to 120°C. However, the reaction is preferably carried out in isopropanol at the boiling temperature of the reaction mixture.

The reaction of a compound of general formula (VIII) to form a compound of general formula (I) may also be carried out as a one-pot reaction, for example in acetonitrile in the presence of triethylamine.

e) in order to prepare compounds of general formula I wherein R^c denotes one of the above-mentioned, optionally substituted alkyloxy groups:

reacting a compound of general formula



,(XI)

wherein R^a and R^b are defined as mentioned hereinbefore, with a compound of general formula

$$Z^4 - R^{c'} \qquad ,(XII)$$

wherein $R^{c'}$ denotes a C_{1-4}-alkyl group, a methyl or ethyl group substituted by 1 to 3 fluorine atoms, a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-4}-alkyl group, a tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl group, a tetrahydrofuranyl-C_{1-4}-alkyl or tetrahydropyranyl-C_{1-4}-alkyl group, a C_{2-4}-alkyl group substituted by R^7, wherein R^7 is as hereinbefore defined, a C_{1-4}-alkyl group which is substituted by a pyrrolidinyl,

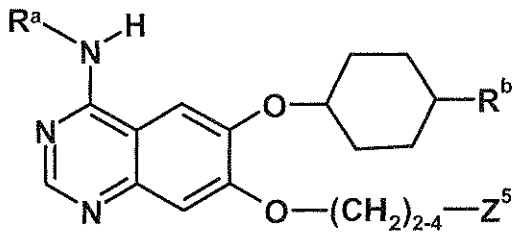
piperidinyl or homopiperidinyl group substituted in the 1 position by the group R^8, or a C_{1-4}-alkyl group which is substituted by a morpholinyl group substituted in the 4 position by the group R^8, wherein R^8 in each case is as hereinbefore defined, and

Z^4 denotes a leaving group such as a halogen atom, an alkylsulphonyloxy, arylsulphonyloxy or a hydroxy group.

If the leaving group is a halogen atom such as a chlorine, bromine or iodine atom or an alkylsulphonyloxy or arylsulphonyloxy group such as the methanesulphonyloxy or p-toluenesulphonyloxy group, the reaction is preferably carried out in the presence of an organic or inorganic base such as potassium carbonate, sodium hydride or N-ethyl-diisopropylamine. If the leaving group is a hydroxy group, the reaction is carried out in the presence of a dehydrating agent, preferably in the presence of a phosphine and an azodicarboxylic acid derivative such as e.g. Triphenylphosphine/diethyl azodicarboxylate.

f) in order to prepare compounds of general formula I wherein R^c denotes one of the above-mentioned alkyloxy groups which is substituted by an optionally substituted amino, alkylamino or dialkylamino group or by an optionally substituted heterocyclic group bound via an imino nitrogen atom:

reacting a compound of general formula



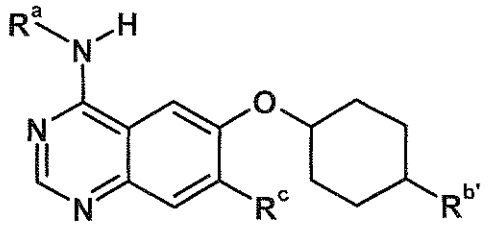
(XIII),

wherein R^a and R^b are as hereinbefore defined and Z^5 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom or a sulphonyloxy group such as a methanesulphonyloxy or p-toluenesulphonyloxy group, with

ammonia, a corresponding, optionally substituted alkylamine, dialkylamine or an imino compound or the suitable salts or derivatives thereof, such as morpholine, for example.

g) In order to prepare compounds of general formula I wherein R^b contains one or more hydroxy groups:

cleaving protective groups from a compound of general formula



(XIV),

wherein R^a and R^c are as hereinbefore defined and $R^{b'}$ contains one or more groups that can be converted into hydroxy groups, for example an optionally substituted benzyloxy group, a silyloxy, acetyloxy, benzoyloxy, methoxy, ethoxy, tert-butoxy or trityloxy group.

The protective groups are cleaved, for example, hydrolytically 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.

A benzyl or methoxybenzyl 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

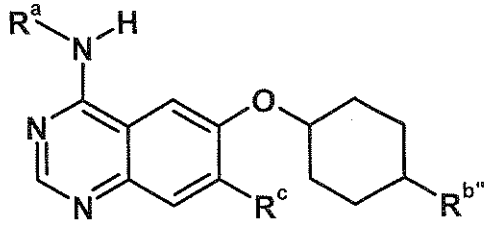
100°C, but preferably at ambient temperatures between 20 and 60°C, and under a hydrogen pressure of 1 to 7 bar, but preferably from 3 to 5 bar. A 2,4-dimethoxybenzyl group however is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.-butyl or benzyl group is cleaved for example by treating with an acid such as trifluoroacetic acid, hydrochloric acid or hydrobromic acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A silyloxy group, for example a tert.-butyl-dimethylsilyl group, is cleaved for example by treating with fluorides such as tetrabutylammonium fluoride, optionally using a solvent such as tetrahydrofuran or dioxane.

h) in order to prepare compounds of general formula I wherein R^b contains an –NH-group:

cleaving a protective group from a compound of general formula



(XV),

wherein R^a and R^c are as hereinbefore defined and $R^{b''}$ has the meanings given for R^b hereinbefore, with the proviso that $R^{b''}$ contains a protected nitrogen atom.

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

The protective group is 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.

A benzyl, methoxybenzyl or benzyloxycarbonyl group, however, is cleaved by hydrogenolysis, for example, 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 ambient temperatures between 20 and 60°C, and under a hydrogen pressure of 1 to 7 bar, but preferably from 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 treatment 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 carried out by treatment 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 treatment 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, *n*-butylamine or ethanolamine in a solvent

such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

If according to the invention a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I, wherein the acylating agents used may be, for example, carboxylic acid halides, carboxylic acid anhydrides and carboxylic acids with activating agents such as N,N'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide or O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate and the sulphonylating agents used may be sulphonylhalides, and/or

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

if a compound of general formula I is obtained which contains an alkoxycarbonyl group, this may be converted by ester cleavage into a carboxylic acid, and/or

if a compound of general formula I is obtained which contains an alkoxycarbonyl group, this may be converted by reaction with an amine into a carboxylic acid amide derivative, and/or

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

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

For example a protecting group for a hydroxy group might be the trimethylsilyl, acetyl, trityl, benzyl or tetrahydropyranyl group.

Protecting groups for an amino, alkylamino or imino group might be, for example, the formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, *tert.*-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group.

Any protective 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.

A benzyl, methoxybenzyl or benzyloxycarbonyl group, however, is cleaved by hydrogenolysis, for example, 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 ambient temperatures between 20 and 60°C, and under a hydrogen pressure of 1 to 7 bar, but preferably from 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 treatment 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 treatment 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 treatment with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

Other suitable protective groups and possible methods of introducing and cleaving them are described for example in "Protective Groups in Organic Synthesis" by Theodora W. Greene and Peter G. M. Wuts , Wiley-VCH.

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 obtained 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 or bases. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, phosphoric acid, fumaric acid, succinic acid, benzoic acid, salicylic acid, mandelic acid, lactic acid, malonic acid, citric acid, L-malic acid, L-tartaric acid or maleic acid. Suitable bases for this purpose include for example sodium hydroxide solution, potassium hydroxide solution, calcium hydroxide, diethanolamine or N-methyl-D-glucamine.

By the term "C_{1-4}-alkyl" (including where it is a component of other groups) are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl or *tert*-butyl. The abbreviations Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc. may optionally also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

By the term "C_{2-3}-alkenyl" (including where it is a component of other groups) are meant branched and unbranched alkenyl groups with 2 to 3 carbon atoms, provided that they have at least one double bond. Examples include: ethenyl or allyl.

By the term "C_{2-3}-alkynyl" (including where it is a component of other groups) are meant alkynyl groups with 2 to 3 carbon atoms meant, provided that they have at least one triple bond. Examples include: ethynyl or propargyl.

By the term "C_{3-7}-cycloalkyl" (including where it is a component of other groups) are meant cyclic alkyl groups with 3 to 7 carbon atoms. Examples include: cyclopropyl, cyclopentyl or cyclohexyl. Unless otherwise stated, the cyclic alkyl groups may be

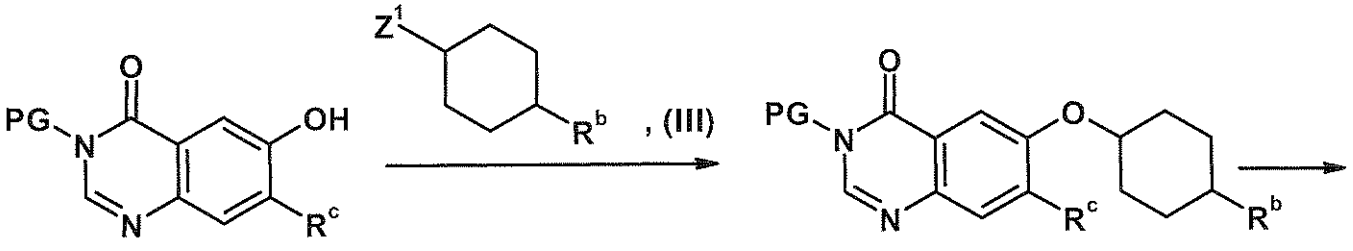
substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "aryl" (including where it is a component of other groups) are meant aromatic ring systems with 6, 10 or 14 carbon atoms. Examples include: phenyl or naphthyl, the preferred aryl group being phenyl. Unless stated otherwise, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

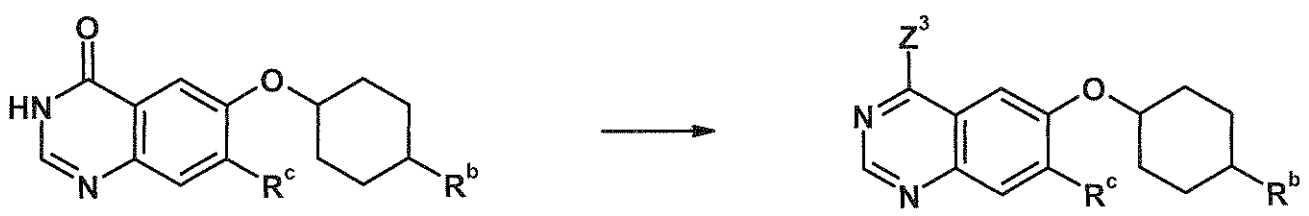
The compounds of general formulae II to XV used as starting materials are known from the literature to some extent or may be obtained by methods known from the literature (cf. Examples I to XVIII), optionally with the additional introduction of protecting groups.

Standard processes for preparing the starting materials are described for example in "March's Advanced Organic Chemistry" by Michael B. Smith and Jerry March, Wiley-VCH or in "Science of Synthesis/Houben-Weyl" published by Thieme.

For example the compounds of general formula (IX) may be obtained as follows:



(XVI) (XVII)



(VIII) (IX)

Scheme 1

Starting from a compound of general formula (XVI), wherein PG denotes a protective group such as benzyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl, for example, the reaction is carried out with a compound of general formula (III) analogously to process a) described hereinbefore to obtain a compound of general formula (XVII). The compounds of general formula (XVI) are known from the literature (cf e.g. WO 2004/108664 or WO 2007/003486) or may be obtained by methods known from the literature.

The cleaving of the protective group from a compound of general formula (XVII) to obtain a compound of general formula (VIII) is carried out, if PG denotes benzyl, with hydrogen, for example, in the presence of a catalyst such as palladium/charcoal (e.g. analogously to Example IV). The cleaving of the protective group if PG denotes 4-methoxybenzyl or 2,4-dimethoxybenzyl may also be carried out oxidatively (e.g. with cerium(IV)-ammonium nitrate or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) or with acids (e.g. with trifluoroacetic acid in the presence of anisole).
A compound of general formula (VIII) may then be converted into a compound of general formula (IX), as described in the previous process d). The meanings for R^b, R^c, Z^1 and Z^3 in the compounds of Scheme 1 are defined as mentioned hereinbefore.

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

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 murine haematopoietic cell line is genetically modified so as to express functional human EGF-R. The proliferation of this cell line can therefore be stimulated by EGF.
The test is carried out as follows:

The cells are cultivated in RPMI/1640 medium. The proliferation is stimulated with 20 ng/ml of human EGF (Promega). To investigate the inhibitory activity of the compounds according to the invention these compounds are dissolved in 100% dimethylsulphoxide (DMSO) and added to the cultures in various dilutions, the maximum DMSO concentration being 1%. The cultures are 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 is measured in O.D. units using the Cell Titer 96TM AQueous Non-Radioactive Cell Proliferation Assay (Promega). The relative cell number is calculated as a percentage of the control and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC50) is derived therefrom.
The compounds of general formula I according to the invention exhibit IC50 values of < 10 micromolar, preferably < 1 micromolar, for example.

The following results are obtained, for example:

Compound (Example No.)	Inhibition of the EGFR-dependent proliferation IC_{50} [nM]
1 (*trans* compound)	1
1(1) (*trans* compound)	1
1(3) (*trans* compound)	1
1(5) (*trans* compound)	1

(36)	1
(44)	1

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

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

The compounds are also suitable for treating inflammatory 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 or polyps in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Ménétrier's disease, secreting adenomas and protein loss syndrome.

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

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

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

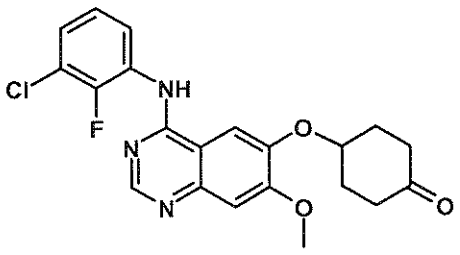
For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents,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

The Examples that follow are intended to illustrate the present invention in more detail without restricting it:

Preparation of the starting compounds:

Example I

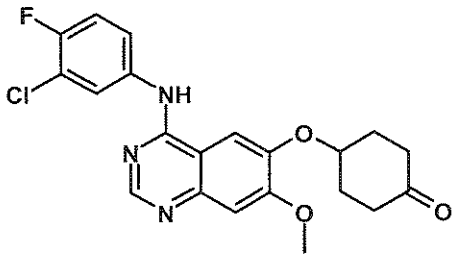
4-[(3-chloro-2-fluoro-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



25 ml 4M sulphuric acid are added to 9.0 g 4-[(3-chloro-2-fluoro-phenyl)amino]-6-(1,4-dioxa-spiro[4.5]decan-8-yl-oxy)-7-methoxy-quinazoline in 110 ml of tetrahydrofuran and the mixture is stirred for 18 hours at ambient temperature. The mixture is made alkaline with 4M sodium hydroxide solution and extracted several times with ethyl acetate. The combined organic phases are dried, evaporated down and stirred with diethyl ether. The solid is suction filtered and dried.
Yield: 7.4 g (90 % of theory)
Mass spectrum (ESI^+): m/z = 416, 418 $[M+H]^+$

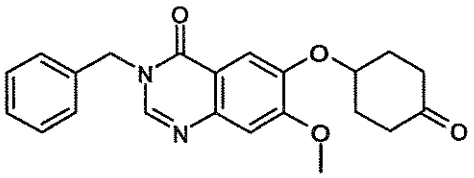
The following compounds are obtained analogously to Example I:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



Mass spectrum (ESI$^+$): m/z = 416, 418 $[M+H]^+$

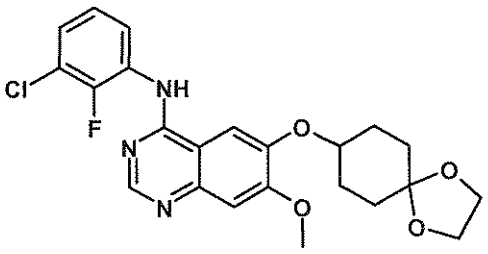
(2) 3-benzyl-3,4-dihydro-4-oxo-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



Mass spectrum (ESI$^+$): m/z = 379 $[M+H]^+$

Example II

4-[(3-chloro-2-fluoro-phenyl)amino]-6-(1,4-dioxa-spiro[4.5]decan-8-yl-oxy)-7-methoxy-quinazoline



At 50°C 12.5 g potassium carbonate and 16 g 8-methanesulphonyloxy-1,4-dioxa-spiro[4,5]decane (cf for example Journal of Medicinal Chemistry (1992), 35(12), 2243-7) are added to 18.1 g 4-[(3-chloro-2-fluoro-phenyl)amino]-6-hydroxy-7-methoxy-quinazoline (cf for example Bioorganic & Medicinal Chemistry Letters (2006), 16(18), 4908-4912) in 125 ml dimethylformamide and the mixture is stirred

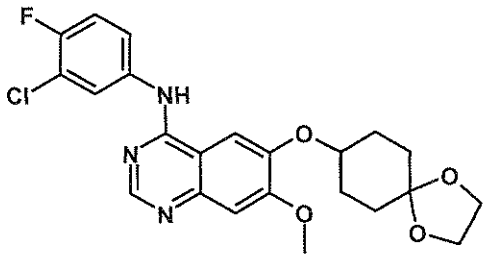
for 18 hours at 80°C. Another 4.7 g potassium carbonate and 4.0 g of 8-methanesulphonyloxy-1,4-dioxa-spiro[4,5]decane are added and the mixture is stirred for another 7 hours at 80°C. The reaction mixture is cooled, diluted with water and ethyl acetate and the precipitate formed is suction filtered and dried.

Yield: 12.2 g (47 % of theory)

Mass spectrum (ESI^+): m/z = 460, 462 $[M+H]^+$

The following is obtained analogously to Example II:

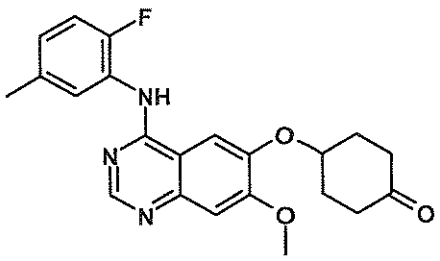
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline



Mass spectrum (ESI^+): m/z = 460, 462 $[M+H]^+$

Example III

4-[(2-fluoro-5-methyl-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline

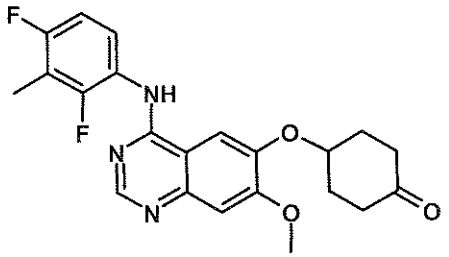


6 ml phosphorus oxychloride are added dropwise to 12.1 g 3,4-dihydro-4-oxo-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline in 120 ml acetonitrile and the mixture is heated to an internal temperature of 40°C. Then 9.3 ml triethylamine are added dropwise and the reaction mixture is refluxed for 3 hours. The mixture is

cooled to ambient temperature and after standing overnight half the solution of the intermediate product (4-chloro-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline, see Example IX) is combined dropwise with 2.7 ml of 2-fluoro-5-methylaniline in 5 ml acetonitrile. The reaction mixture is heated to 40°C for 3 hours, then cooled and evaporated down. The residue is mixed with water and stirred. The precipitate formed is suction filtered and divided between 1M sodium hydroxide solution and dichloromethane. The organic phase is separated off, dried, evaporated down and stirred with diisopropylether. The solid is suction filtered and dried.
Mass spectrum (ESI^+): m/z = 396 $[M+H]^+$

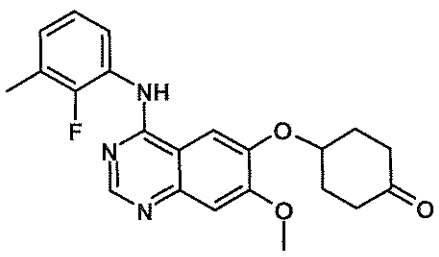
The following compounds are obtained analogously to Example III:

(1) 4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



For synthesis of 2,4-difluoro-3-methyl-aniline cf for example EP 28698
In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.
Mass spectrum (ESI^+): m/z = 414 $[M+H]^+$

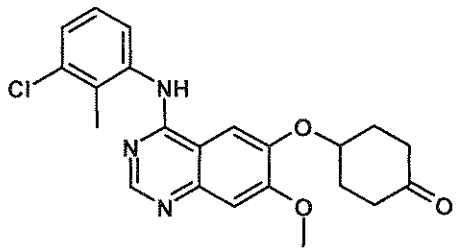
(2) 4-[(2-fluoro-3-methyl-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 396 $[M+H]^+$

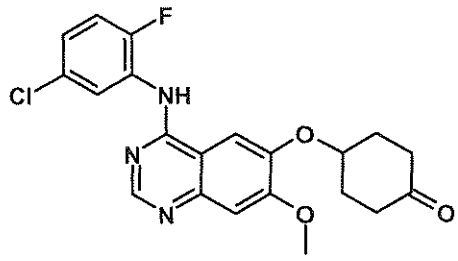
(3) 4-[(3-chloro-2-methyl-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 412, 414 $[M+H]^+$

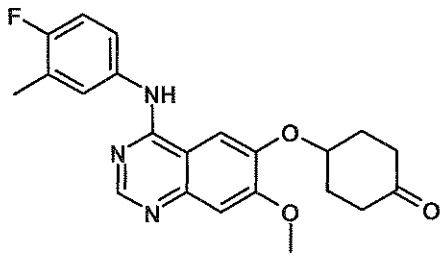
(4) 4-[(5-chloro-2-fluoro-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 416, 418 $[M+H]^+$

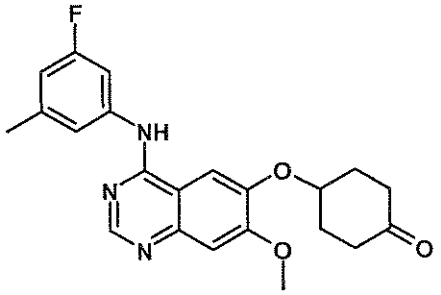
(5) 4-[(4-fluoro-3-methyl-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 396 $[M+H]^+$

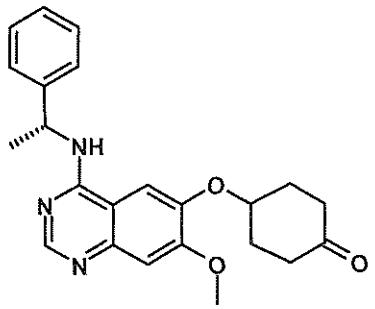
(6) 4-[(3-fluoro-5-methyl-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 396 $[M+H]^+$

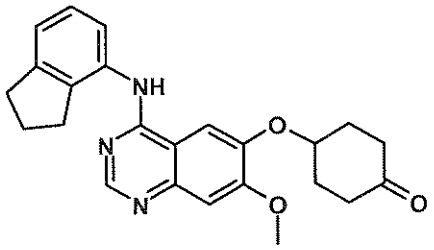
(7) (R)-4-[(1-phenylethyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 392 $[M+H]^+$

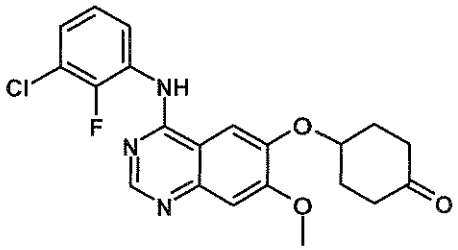
(8) 4-[(4-indanyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline



In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 404 $[M+H]^+$

(9) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline

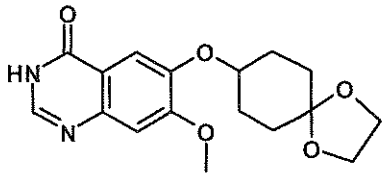


In order to cleave the ketal totally the crude product is also stirred with aqueous hydrochloric acid.

Mass spectrum (ESI^+): m/z = 416, 418 $[M+H]^+$

Example IV

3,4-dihydro-4-oxo-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline

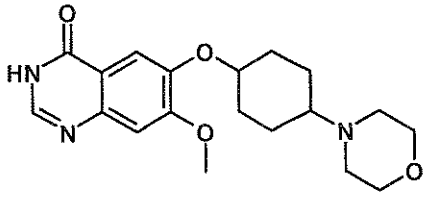


16.0 g 3-benzyl-3,4-dihydro-4-oxo-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline in 150 ml glacial acetic acid are hydrogenated in the presence of 1.6 g palladium on activated charcoal (10% Pd) at 60°C and at a hydrogen pressure of 50 psi. The catalyst is filtered off and the filtrate is evaporated down, combined with toluene and evaporated down again. The residue is mixed with water and made slightly alkaline with saturated sodium hydrogen carbonate solution. The precipitate is suction filtered and dried.

Mass spectrum (ESI^+): m/z = 333 $[M+H]^+$

The following compounds may be obtained analogously to Example IV:

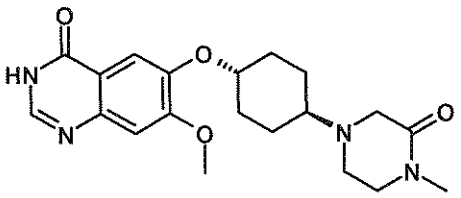
(1) 3,4-dihydro-4-oxo-6-[cis/trans-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline



Carried out at ambient temperature

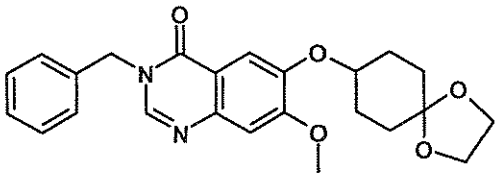
Mass spectrum (ESI^+): m/z = 360 $[M+H]^+$

(2) 3,4-dihydro-4-oxo-6-[trans-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



Example V

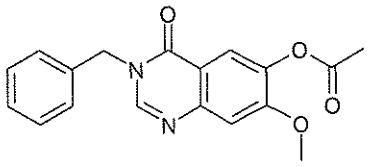
3-benzyl-3,4-dihydro-4-oxo-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline



At 50°C 16.0 g potassium carbonate and 20.0 g of 8-methanesulphonyloxy-(1,4-dioxa-spiro[4,5]decan are added to 20.0 g 3-benzyl-3,4-dihydro-4-oxo-6-hydroxy-7-methoxy-quinazoline in 150 ml N,N-dimethylformamide and the mixture is vigorously stirred for 18 hours at 80°C. To complete the reaction potassium carbonate and 8-methanesulphonyloxy-(1,4-dioxa-spiro[4,5]decane are each added three times more and in each case the mixture is stirred for several hours at 80°C. The reaction mixture is cooled and slowly combined with a total of 500 ml of water. The precipitate is suction filtered, washed with water and dried.

Mass spectrum (ESI^+): m/z = 423 $[M+H]^+$

Example VI



3-Benzyl-3,4-dihydro-4-oxo-6-acetyloxy-7-methoxy-quinazoline

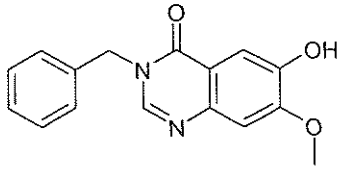
169 g 3,4-dihydro-4-oxo-6-acetyloxy-7-methoxy-quinazoline, 118.8 ml benzyl bromide and 138.2 g potassium carbonate are heated in 1600 ml acetone for 8 hours to 35-40°C. The mixture is stirred for 15 hours at ambient temperature and then combined with 2000 ml of water. The suspension is cooled to 0°C, the precipitate is

suction filtered, washed with 400 ml of water and 400 ml tert.-butylmethylether and dried at 50°C. The solid is dissolved in 4000 ml methylene chloride, filtered and evaporated down. The residue is suspended in tert.-butylmethylether, suction filtered and dried at 50°C. Yield: 203 g (86% of theory)

R_f value: 0.80 (silica gel, methylene chloride/ethanol = 9:1)

Mass spectrum (ESI^+): m/z = 325 $[M+H]^+$

Example VII



3-benzyl-3,4-dihydro-4-oxo-6-hydroxy-7-methoxy-quinazoline

Method A:

168.5 g 6-hydroxy-7-methoxy-benzo[d][1.3]oxazin-4-one are dissolved in 1200 ml of toluene and 74.7 ml benzylamine are added. The mixture is refluxed for 15 hours and then cooled to ambient temperature. The precipitate is filtered off and washed with tert.-butylmethylether.

Yield 124 g (72% of theory)

Method B:

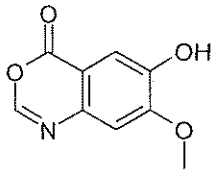
200 g 3-benzyl-3,4-dihydro-4-oxo-6-acetyloxy-7-methoxy-quinazoline are suspended in 200 ml of water and 1000 ml of ethanol. 300 ml 10N sodium hydroxide solution are added at ambient temperature and the mixture is heated to 30°C for 1 hour. After the addition of 172 ml acetic acid and 2000 ml of water the mixture is stirred for 20 hours at ambient temperature. The precipitate is suction filtered, washed with water and acetone and dried at 60°C.

Yield: 172.2 g (98% of theory)

R_f value: 0.25 (silica gel, methylene chloride/ethanol = 19:1)

Mass spectrum (ESI^+): m/z = 283 $[M+H]^+$

Example VIII



6-hydroxy-7-methoxy-benzo[d][1,3]oxazin-4-one

1 g 2-amino-5-hydroxy-4-methoxy-benzoic acid (prepared by reacting methyl 2-nitro-4,5-dimethoxy-benzoate with potassium hydroxide solution to obtain the potassium salt of 2-nitro-5-hydroxy-4-methoxy-benzoic acid and subsequent catalytic hydrogenation in the presence of palladium on activated charcoal) and 20 ml triethyl orthoformate are heated to 100°C for 2.5 hours. After cooling to ambient temperature the precipitate is suction filtered and washed with diethyl ether.

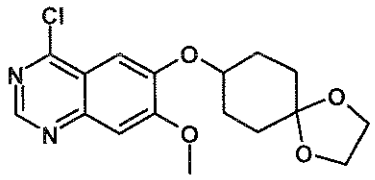
Yield: 0.97 g (93% of theory)

R_f value: 0.86 (silica gel, methylene chloride/methanol/acetic acid = 90:10:1)

Mass spectrum (ESI^+): m/z = 194 $[M+H]^+$

Example IX

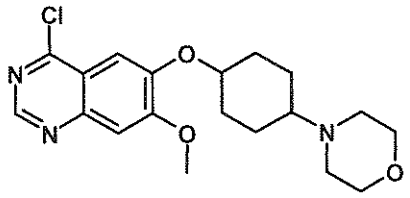
4-chloro-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline



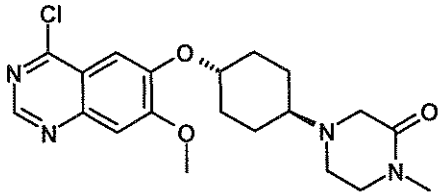
6 ml phosphorus oxychloride are added dropwise to 12.1 g 3,4-dihydro-4-oxo-6-(1,4-dioxa-spiro[4,5]decan-8-yl-oxy)-7-methoxy-quinazoline in 120 ml acetonitrile and the mixture is heated to an internal temperature of 40°C. Then 9.3 ml triethylamine are added dropwise and the reaction mixture is refluxed for 3 hours. The mixture is cooled to ambient temperature and left to stand overnight. The solution of the product is reacted further without any purification (see Example III).

The following compounds may be obtained analogously to Example IV:

(1) 4-chloro-6-[cis/trans-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline

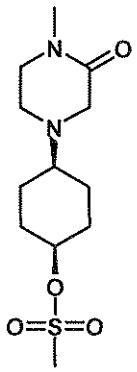


(2) 4-chloro-6-[trans-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



Example X

(cis)-1-methanesulphonyloxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane

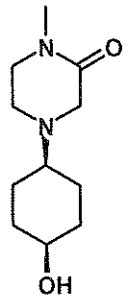


0.24 ml methanesulphonic acid chloride are added dropwise at 0°C to 500 mg (cis)-1-hydroxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane and 0.52 ml N,N-isopropyl-ethylamine in 10 ml dichloromethane and stirred for 1.5 hours at ambient temperature. The product is purified by column chromatography.

Mass spectrum (ESI^+): m/z = 291 $[M+H]^+$

Example XI

(cis)-1-hydroxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane

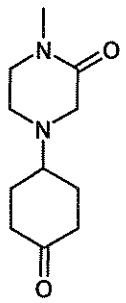


17 ml of a 1M L-Selctride solution (in tetrahydrofuran) are added dropwise at -78°C to 3.3 g 4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexan-1-one in 100 ml abs. tetrahydrofuran. After 5.5 hours 20 ml of methanol are added and the solution is evaporated down. The residue is purified by column chromatography. The mixture of *cis*- and *trans*-compound is separated by preparative HPLC.

Mass spectrum (ESI^+): m/z = 213 $[M+H]^+$

Example XII

4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexan-1-one

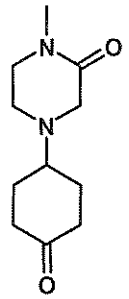


0.55 ml dimethylsulphoxide in 2 ml dichloromethane are added dropwise to 0.46 ml oxalyl chloride in 10 ml dichloromethane within two minutes at -60°C. After 5 minutes 1.0 g (trans)-1-hydroxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane in 8 ml dichloromethane are added within 5 min. After 20 minutes 3.3 ml triethylamine are added and the mixture is stirred for 70 minutes at ambient temperature. 15 ml of water are added and the mixture is extracted with dichloromethane. After evaporation of the solvent the residue contains the product.

Mass spectrum (ESI$^+$): m/z = 211 $[M+H]^+$

Example XIII

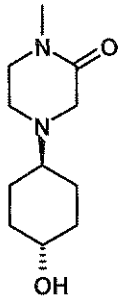
4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexan-1-one



2.3 g 8-(4-methyl-3-oxo-piperazin-1-yl)-1,4-dioxa-spiro[4,5]decane are stirred in 20 ml of 4M HCl for 48 hours at ambient temperature, for 7 hours at 50°C and for two hours at 70°C. The mixture is made alkaline with 4M sodium hydroxide solution and extracted five times with 40 ml dichloromethane. The organic phase is evaporated down and the product is purified by column chromatography.
Mass spectrum (ESI$^+$): m/z = 211 $[M+H]^+$

Example XIV

(trans)-1-hydroxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane



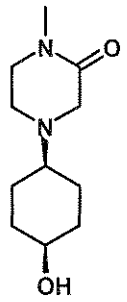
10.0 g (trans)-1-hydroxy-4-{[N-(2,2-dimethoxy-ethyl)-N-methyl-amino]-carbonylmethylamino}-cyclohexane are hydrogenated in a solution of 60 ml of water, 140 ml of methanol and 10.5 g methanesulphonic acid with 3.25 g platinum on charcoal (5% Pt) for 24 hours at 50°C. The solution is made alkaline with 50%

sodium hydroxide solution and evaporated down. The residue is extracted with dichloromethane. The organic phase is dried on magnesium sulphate and evaporated down.

Mass spectrum (ESI^+): m/z = 213 $[M+H]^+$

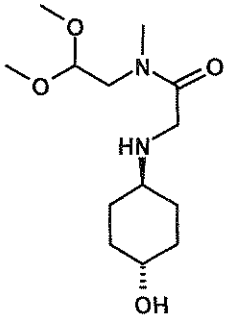
The following may be obtained analogously to Example XIV:

(cis)-1-hydroxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane



Example XV

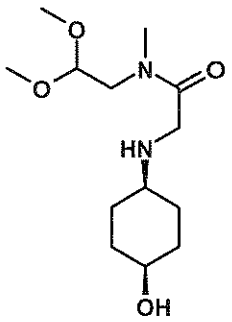
(trans)-1-hydroxy-4-{[N-(2,2-dimethoxy-ethyl)-N-methyl-amino]-carbonylmethylamino}-cyclohexane



15.0 g 2-chloro-N-(2,2-dimethoxy-ethyl)-N-methyl-acetamide in 80 ml acetonitrile are added dropwise within one hour to a suspension of 10.6 g (trans)-4-aminocyclohexanol, 16.25 g sodium carbonate and 0.64 g potassium iodide in 220 ml acetonitrile which has been warmed to 85°C. The mixture is stirred for one hour at 85°C and for 16.5 hours at ambient temperature. It is filtered off and the filtrate is evaporated down. The residue is purified by chromatography and then recrystallised from methyl-tert-butylether and cyclohexane.

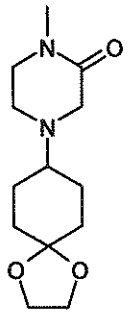
Mass spectrum (ESI^+): m/z = 275 $[M+H]^+$

The following may be obtained analogously to Example XV:
(cis)-1-hydroxy-4-{[N-(2,2-dimethoxy-ethyl)-N-methyl-amino]-carbonylmethylamino}-cyclohexane



Example XVI

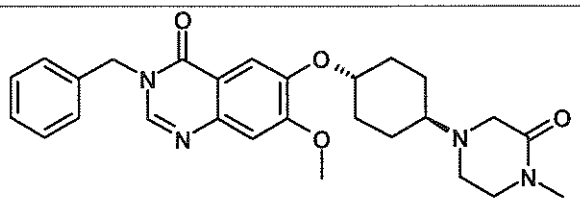
8-(4-methyl-3-oxo-piperazin-1-yl)-1,4-dioxa-spiro[4,5]decane



26.18 g Sodium triacetoxyborohydride are added at 5°C to a solution of 10.0 g 4-methyl-3-oxo-piperazine, 13.51 g 1,4-dioxa-spiro[4,5]decan-8-one, 5.65 ml acetic acid and 200 ml dichloromethane. After 23 hours stirring at ambient temperature 100 ml dichloromethane and 100 ml 4N sodium hydroxide solution are added. The phases are separated and the organic phase is evaporated down. The residue is purified by chromatography.
Mass spectrum (ESI^+): m/z = 255 $[M+H]^+$

Example XVII

3-benzyl-3,4-dihydro-4-oxo-6-[trans-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

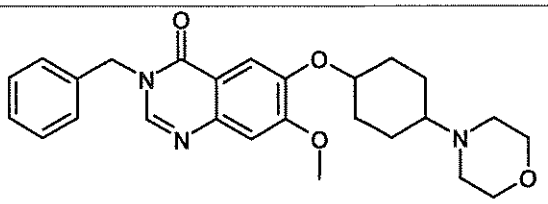


650 mg (cis)-1-methanesulphonyloxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane in 3 ml N-methyl-2-pyrrolidinone are added dropwise at 120°C over two hours to 632 mg 3-benzyl-3,4-dihydro-4-oxo-6-hydroxy-7-methoxy-quinazoline and 1.09 g caesium carbonate in 4 ml N-methyl-2-pyrrolidinone. The product is isolated by preparative HPLC.

Mass spectrum (ESI^+): m/z = 477 $[M+H]^+$

Example XVIII

3-benzyl-3,4-dihydro-4-oxo-6-[cis/trans-4-(4-morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline



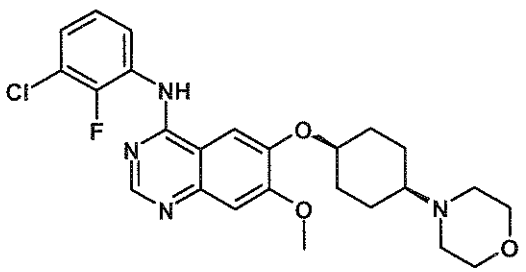
Prepared by reacting 3-benzyl-3,4-dihydro-4-oxo-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline with morpholine analogously to Example 1.

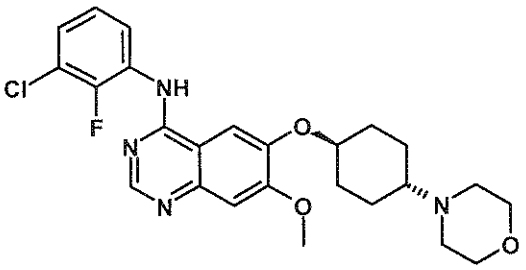
Mass spectrum (ESI^+): m/z = 450 $[M+H]^+$

Preparation of the end compounds:

Example 1

4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline





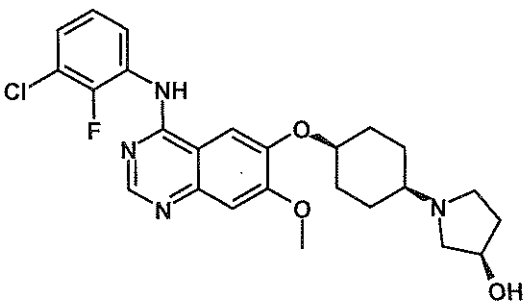
175 µl morpholine, 600 mg sodium-triacetoxyborohydride and 115 µl glacial acetic acid are added to 800 mg of 4-[(3-chloro-2-fluoro-phenyl)amino]-6-(4-oxo-cyclohexyloxy)-7-methoxy-quinazoline in 25 ml 1,2-dichloroethane and the mixture is stirred for 18 hours at ambient temperature under an argon atmosphere. Some more sodium-triacetoxyborohydride is added and stirring is continued for a further 3 hours. The reaction mixture is combined with 1M sodium hydroxide solution and briefly stirred, then extracted several times with dichloromethane. The combined organic phases are dried on magnesium sulphate and evaporated down. Purification through a silica gel column with dichloromethane/methanol (99:1 to 80:20) yields the two title compounds as a mixture. The cis/trans mixture is separated by preparative HPLC (xBridge™ C18 of Messrs. Waters; acetonitrile, water, aqueous ammonia). The isomers are attributed by 1H-NMR spectroscopy.

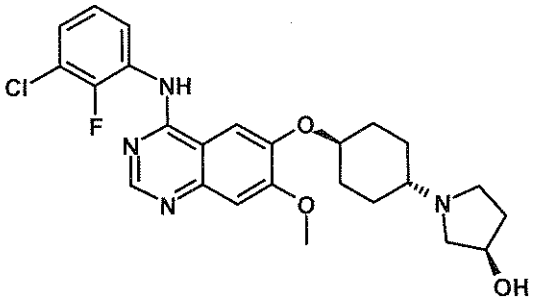
4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline:
Yield: 250 mg (25 % of theory)
Mass spectrum (ESI^+): m/z = 487, 489 $[M+H]^+$

4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline:
Yield: 320 mg (33 % of theory)
Mass spectrum (ESI^+): m/z = 487, 489 $[M+H]^+$

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



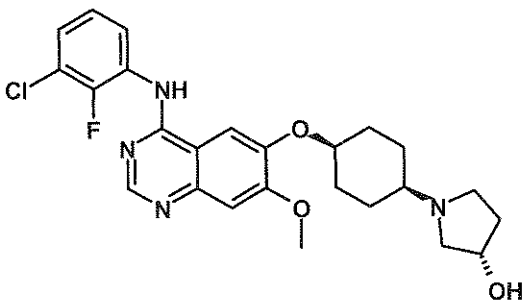
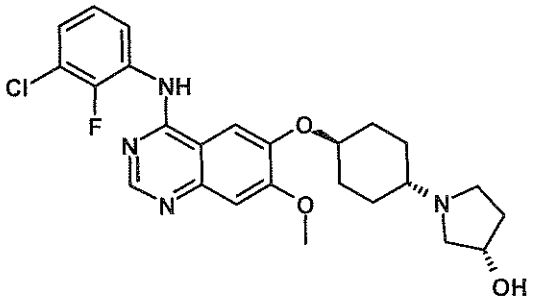


The reaction is carried out in tetrahydrofuran.

4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline
Mass spectrum (ESI^+): m/z = 487, 489 $[M+H]^+$

4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline
Mass spectrum (ESI^+): m/z = 487, 489 $[M+H]^+$

(2) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

The reaction is carried out in tetrahydrofuran.

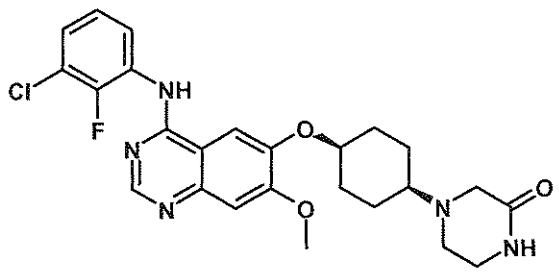
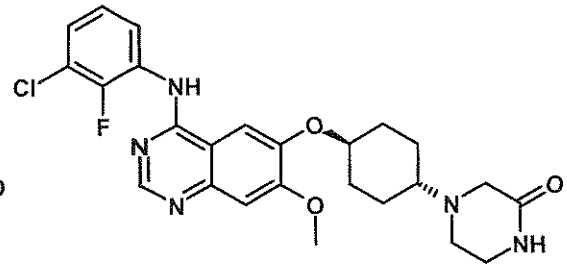
4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 487, 489 $[M+H]^+$

4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 487, 489 $[M+H]^+$

(3) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

The reaction is carried out in 1,2-dichloroethane.

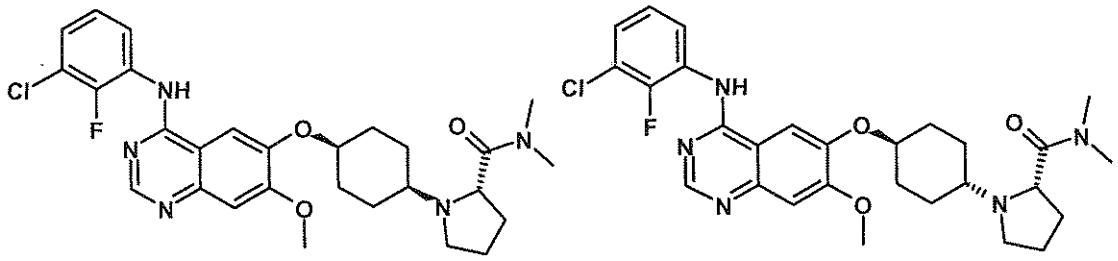
4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 500, 502 $[M+H]^+$

4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 500, 502 $[M+H]^+$

(4) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline and
4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

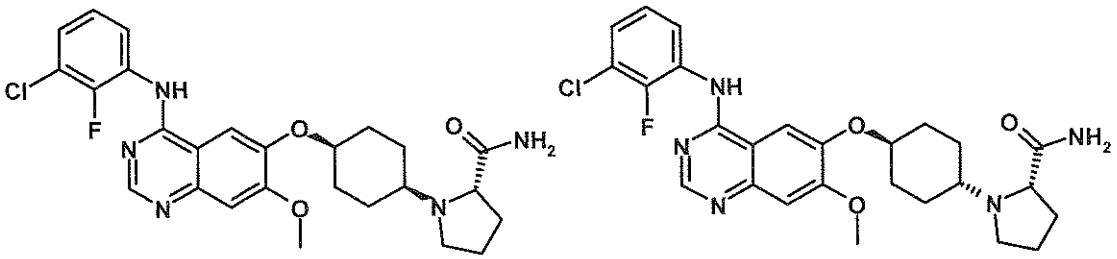
4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 542, 544 $[M+H]^+$

4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 542, 544 $[M+H]^+$

(5) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline and
4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

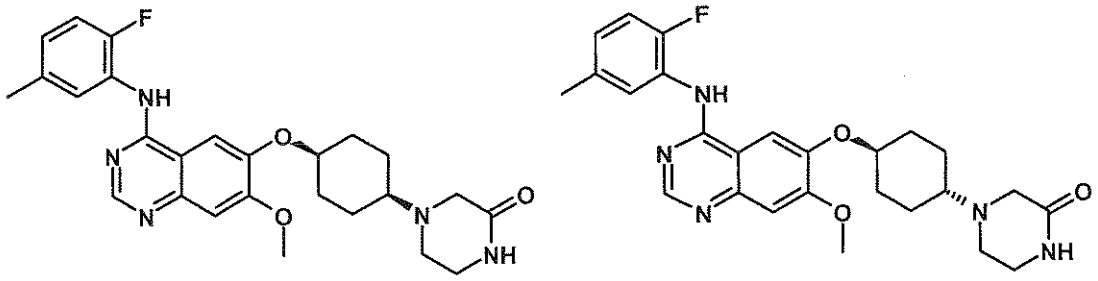
4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 514, 516 $[M+H]^+$

4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 514, 516 $[M+H]^+$

(6) 4-[(2-fluoro-5-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(2-fluoro-5-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

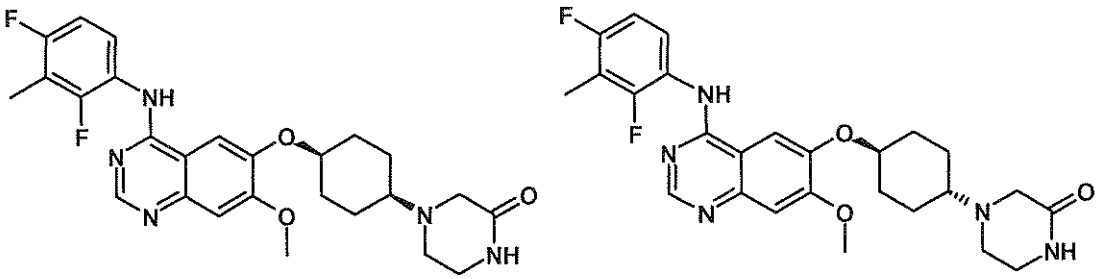
4-[(2-fluoro-5-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 480 $[M+H]^+$

4-[(2-fluoro-5-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 480 $[M+H]^+$

(7) 4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

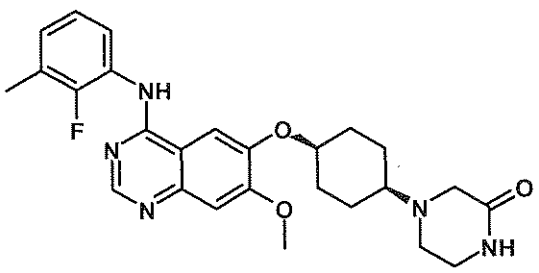
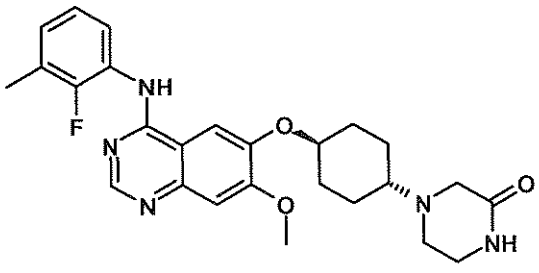
4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 498 $[M+H]^+$

4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 498 $[M+H]^+$

(8) 4-[(2-fluoro-3-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(2-fluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

The reaction is carried out in tetrahydrofuran.

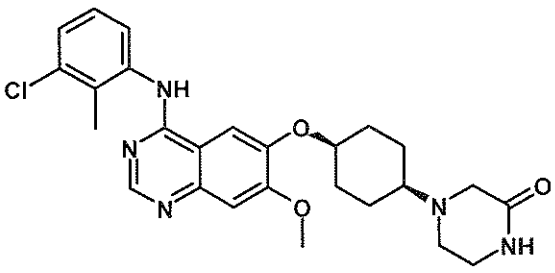
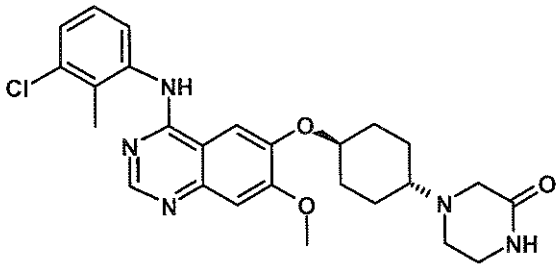
4-[(2-fluoro-3-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 480 $[M+H]^+$

4-[(2-fluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 480 $[M+H]^+$

(9) 4-[(3-chloro-2-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-chloro-2-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

The reaction is carried out in tetrahydrofuran.

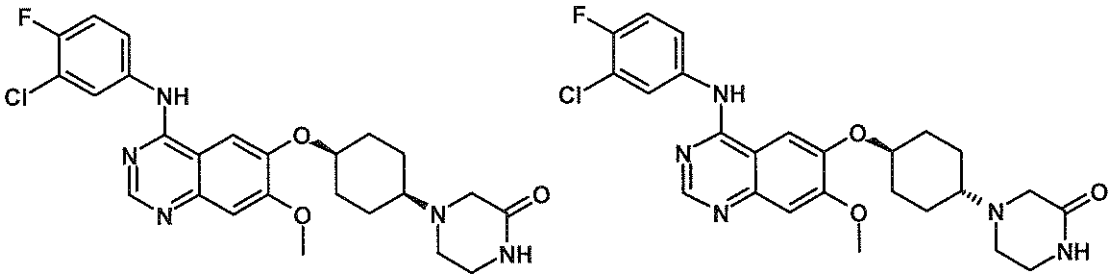
4-[(3-chloro-2-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 496, 498 $[M+H]^+$

4-[(3-chloro-2-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 496, 498 $[M+H]^+$

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

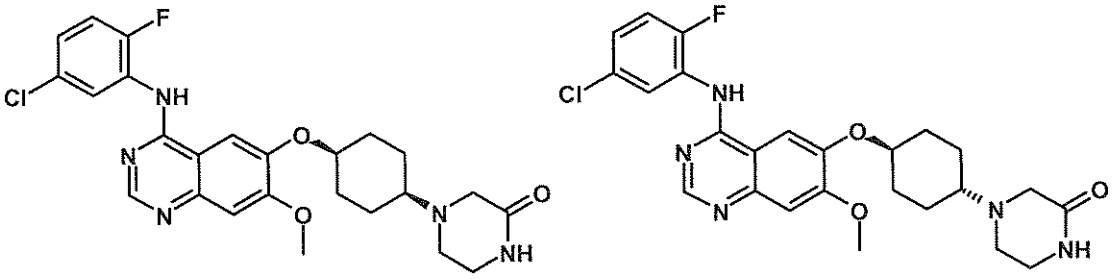
4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 500, 502 $[M+H]^+$

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI^+): m/z = 500, 502 $[M+H]^+$

(11) 4-[(5-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(5-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

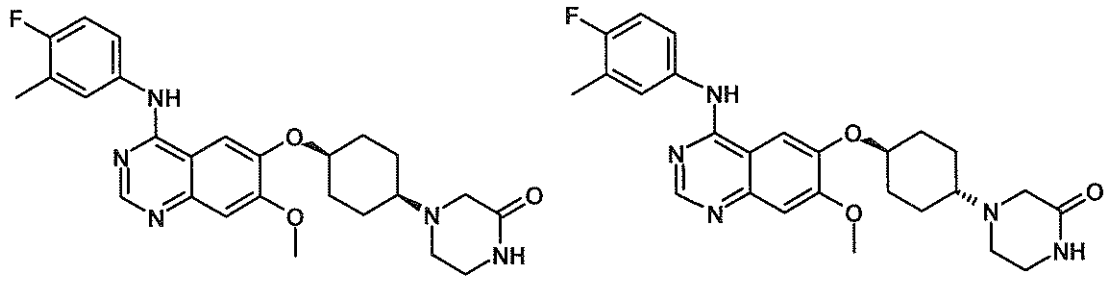
4-[(5-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 500, 502 $[M+H]^+$

4-[(5-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 500, 502 $[M+H]^+$

(12) 4-[(4-fluoro-3-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(4-fluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



The reaction is carried out in tetrahydrofuran.

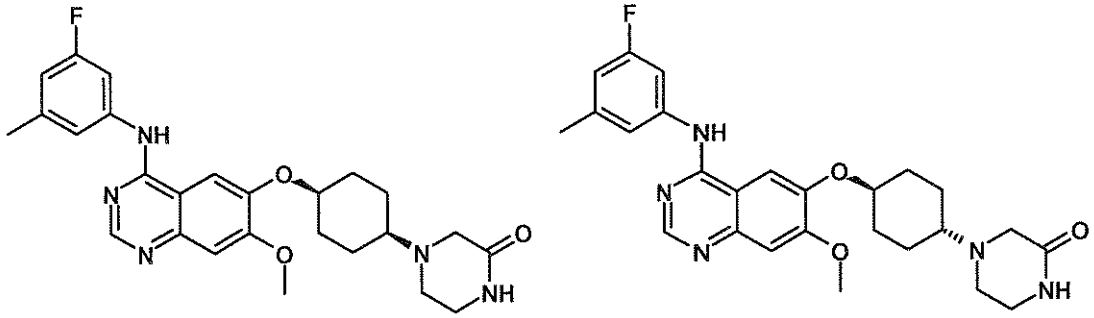
4-[(4-fluoro-3-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 480 $[M+H]^+$

4-[(4-fluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 480 $[M+H]^+$

(13) 4-[(3-fluoro-5-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and 4-[(3-fluoro-5-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline



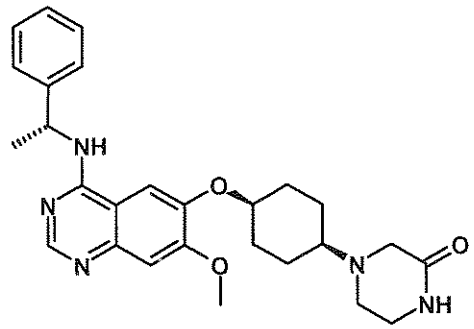
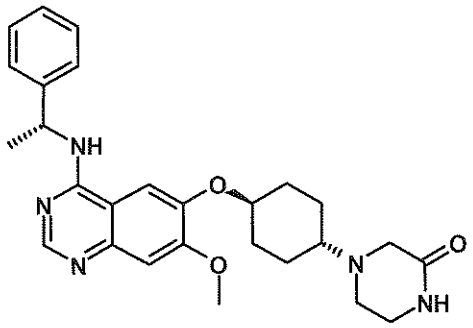
The reaction is carried out in tetrahydrofuran.

4-[(3-fluoro-5-methyl-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 480 $[M+H]^+$

4-[(3-fluoro-5-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

(14) (R)-4-[(1-phenylethyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and (R)-4-[(1-phenylethyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

The reaction is carried out in tetrahydrofuran.

(R)-4-[(1-phenylethyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 476 $[M+H]^+$

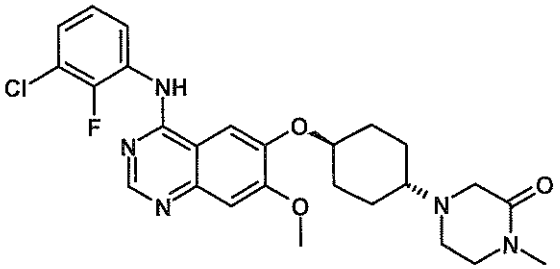
(R)-4-[(1-phenylethyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

Mass spectrum (ESI$^+$): m/z = 476 $[M+H]^+$

Example 2

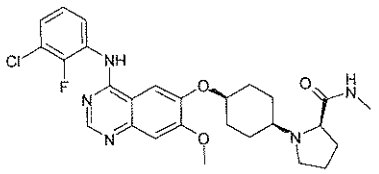
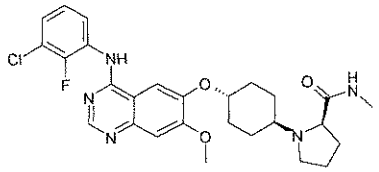
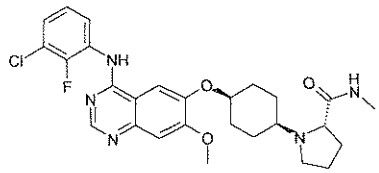
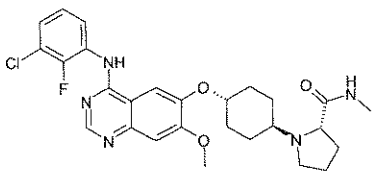
4-[(3-Chloro-2-fluoro-phenyl)amino]-6-[trans-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

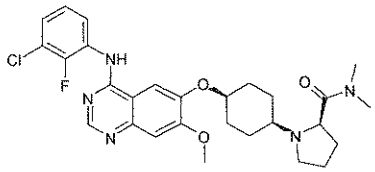
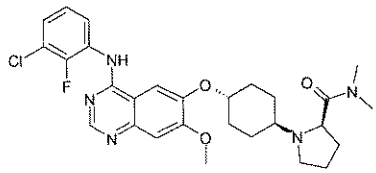
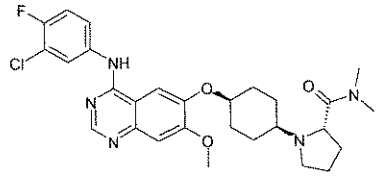
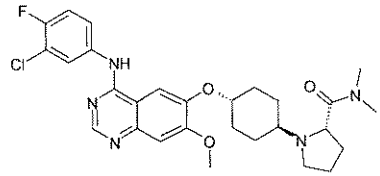
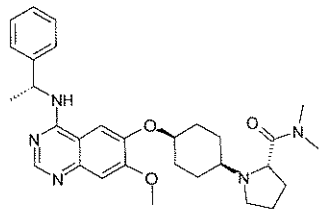
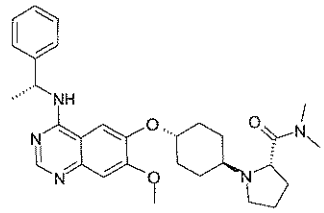
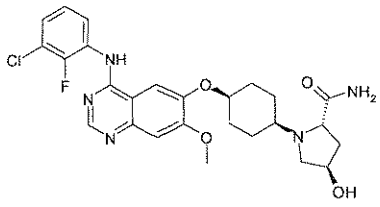
---

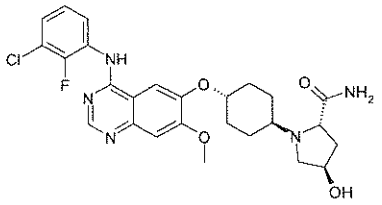
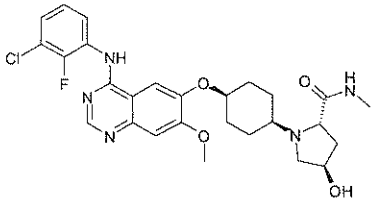
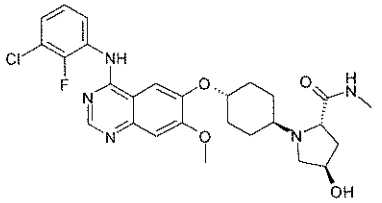
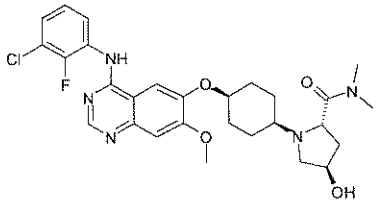
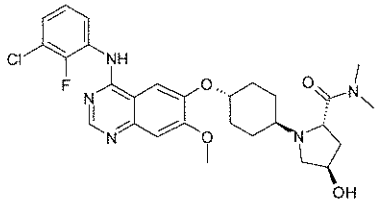
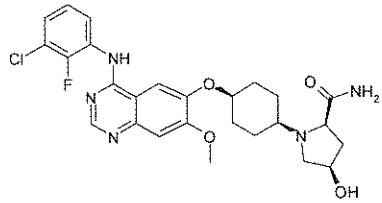
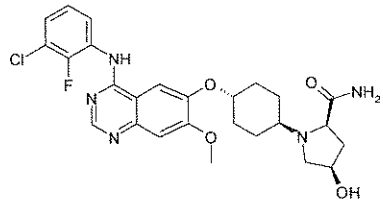


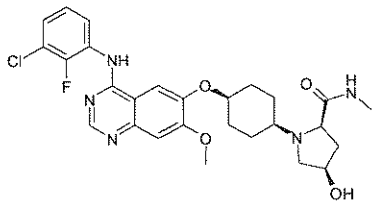
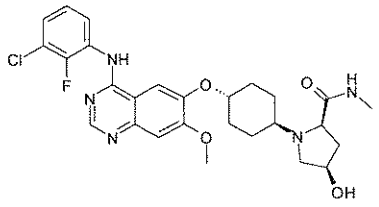
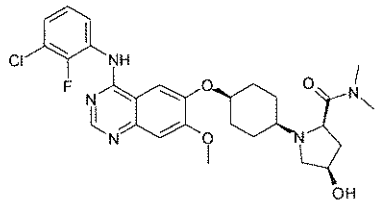
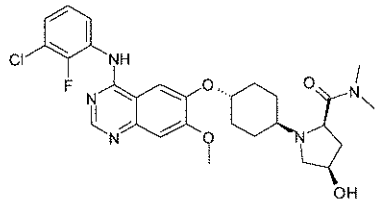
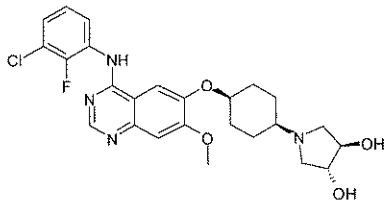
Prepared by reacting 4-[(3-chloro-2-fluoro-phenyl)amino]-6-hydroxy-7-methoxy-quinazoline with (cis)-1-methanesulphonyloxy-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexane in N-methyl-2-pyrrolidinone at 125°C in the presence of potassium carbonate.

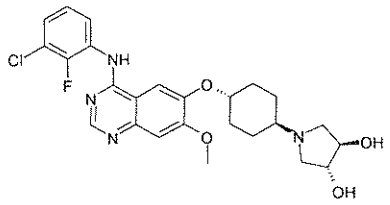
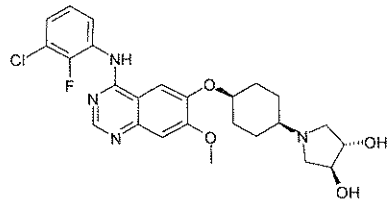
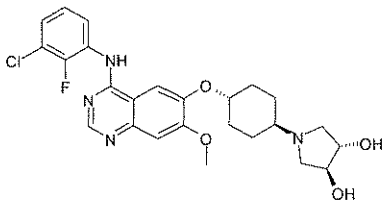
The following compounds may also be prepared analogously to the Examples described above and other methods known from the literature:

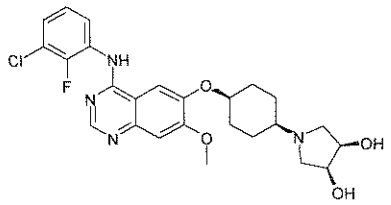
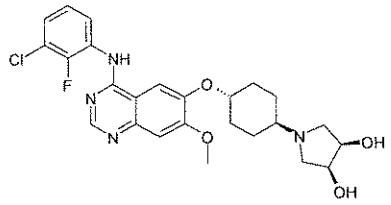
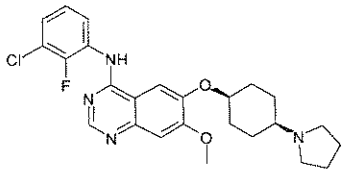
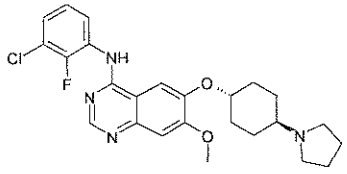
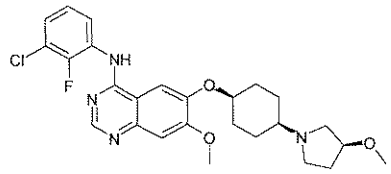
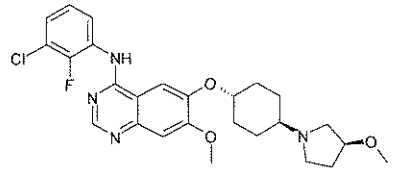
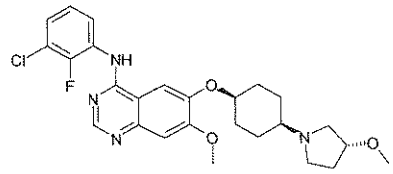
Example No.	Structure
(1)	
(2)	
(3)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI^+): m/z = 528, 530 $[M+H]^+$
(4)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI^+): m/z = 528, 530 $[M+H]^+$

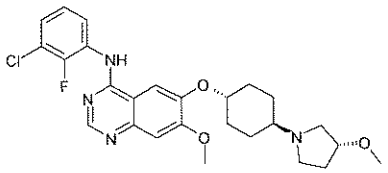
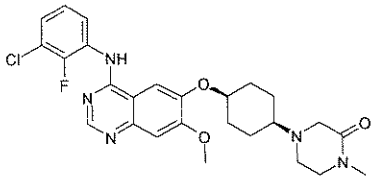
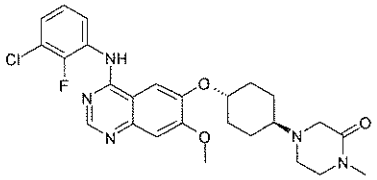
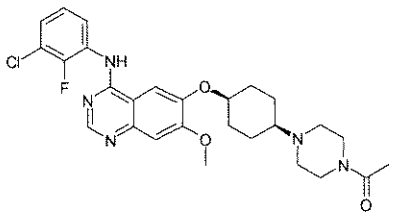
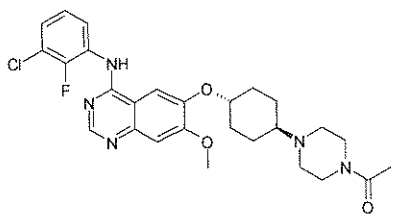
Example No.	Structure
(5)	
(6)	
(7)	
(8)	
(9)	
(10)	
(11)	

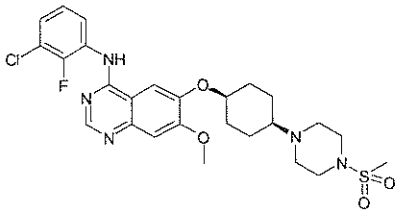
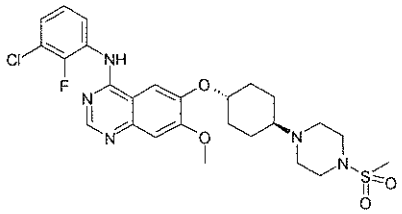
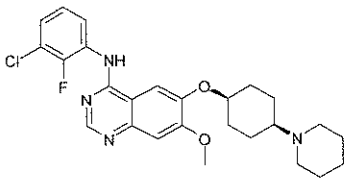
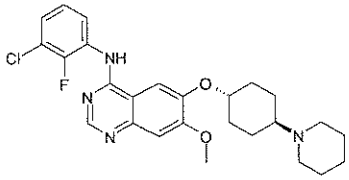
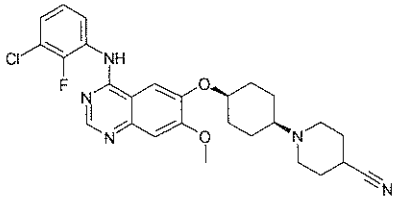
Example No.	Structure
(12)	
(13)	
(14)	
(15)	
(16)	
(17)	
(18)	

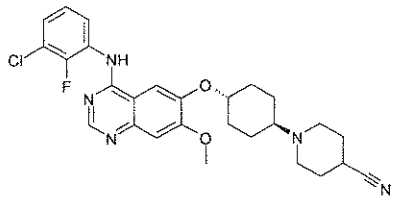
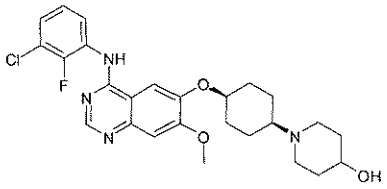
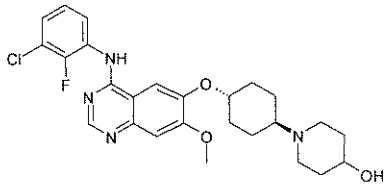
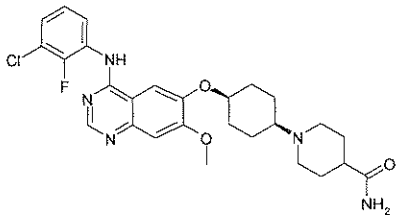
Example No.	Structure
(19)	
(20)	
(21)	
(22)	
(23)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI^+): m/z = 503, 505 $[M+H]^+$ (3R,4R)-3,4-dihydroxypyrrolidine: cf for example Tetrahedron, 63(5), 1243-1253; 2006

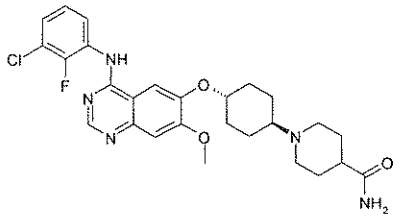
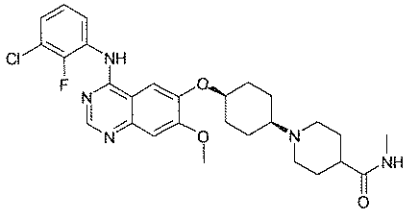
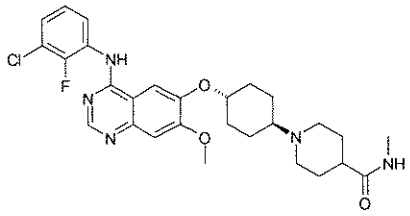
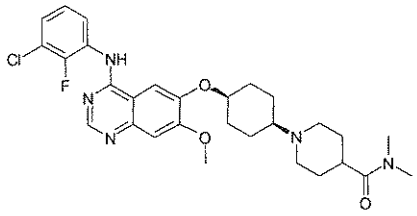
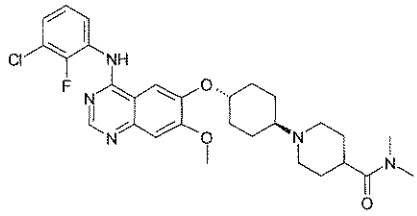
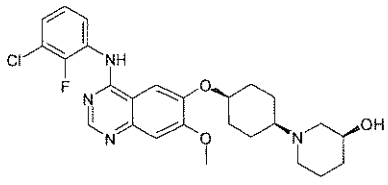
Example No.	Structure
(24)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI+): m/z = 503, 505 [M+H]+ (3R,4R)-3,4-dihydroxypyrrolidine: cf for example Tetrahedron, 63(5), 1243-1253; 2006
(25)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI+): m/z = 503, 505 [M+H]+ (3S,4S)-3,4-dihydroxypyrrolidine: cf for example Helvetica Chimica Acta, 87(12), 3167-3181; 2004
(26)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI+): m/z = 503, 505 [M+H]+ (3S,4S)-3,4-dihydroxypyrrolidine: cf for example Helvetica Chimica Acta, 87(12), 3167-3181; 2004

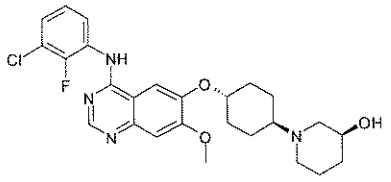
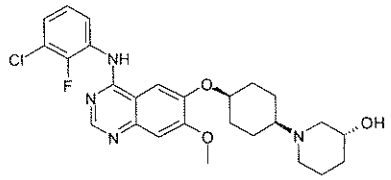
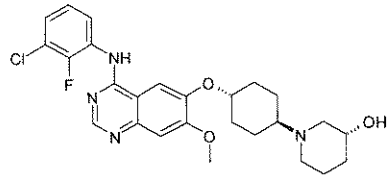
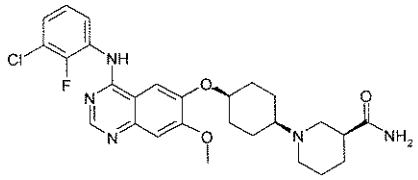
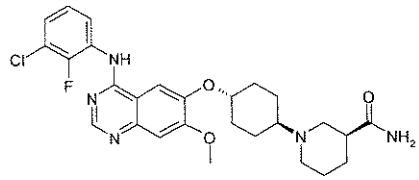
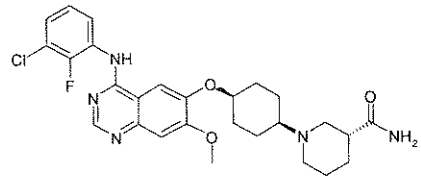
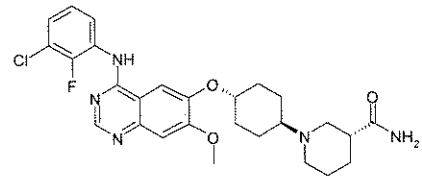
Example No.	Structure
(27)	
(28)	
(29)	
(30)	
(31)	
(32)	
(33)	

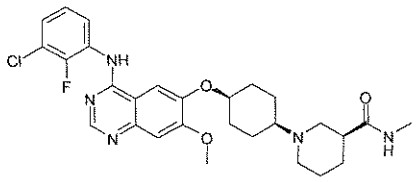
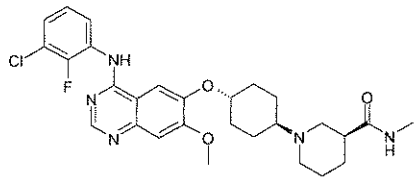
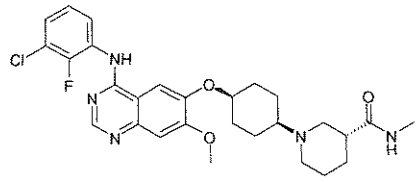
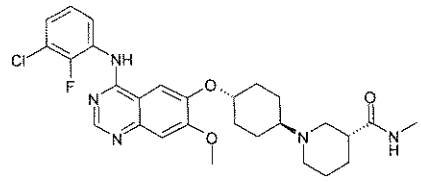
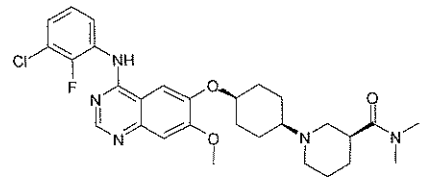
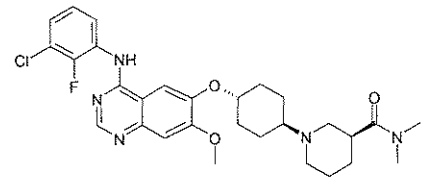
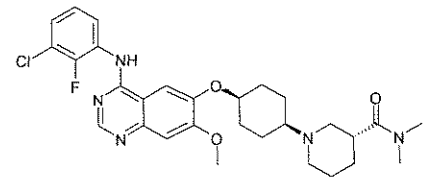
Example No.	Structure
(34)	
(35)	 Carried out according to Example 1 in tetrahydrofuran or 1,2-dichloroethane Mass spectrum (ESI^+): m/z = 514, 516 $[M+H]^+$
(36)	 Carried out according to Example 1 in tetrahydrofuran or 1,2-dichloroethane Mass spectrum (ESI^+): m/z = 514, 516 $[M+H]^+$
(37)	
(38)	

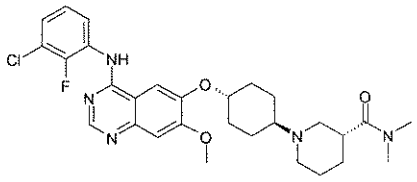
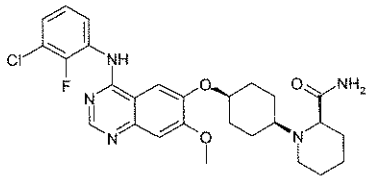
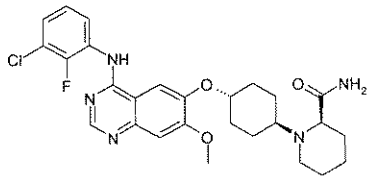
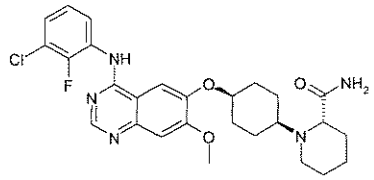
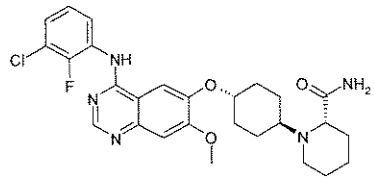
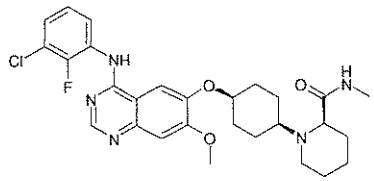
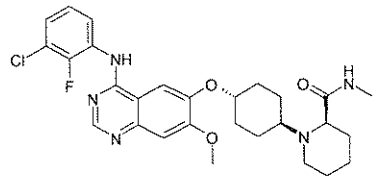
Example No.	Structure
(39)	
(40)	
(41)	
(42)	
(43)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI^+): m/z = 510, 512 $[M+H]^+$

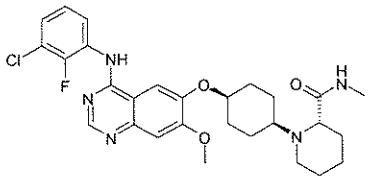
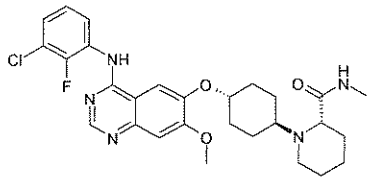
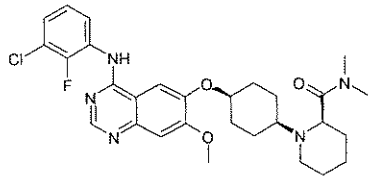
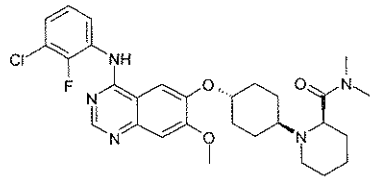
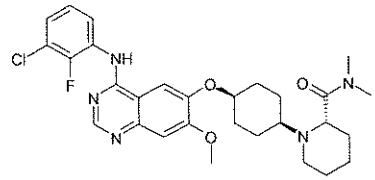
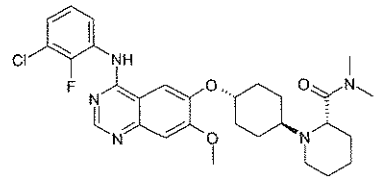
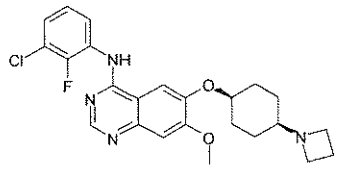
Example No.	Structure
(44)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI$^+$): m/z = 510, 512 $[M+H]^+$
(45)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI$^+$): m/z = 501, 503 $[M+H]^+$
(46)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI$^+$): m/z = 501, 503 $[M+H]^+$
(47)	

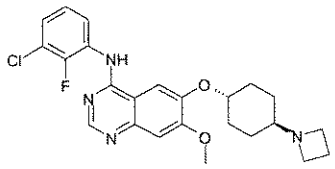
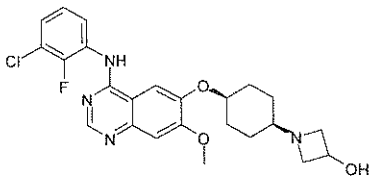
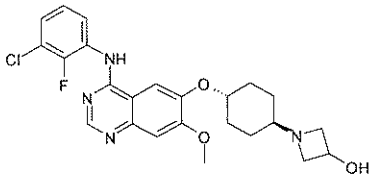
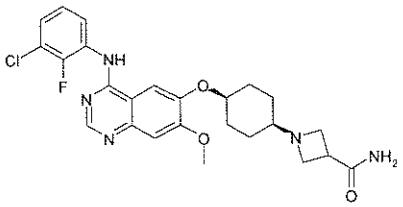
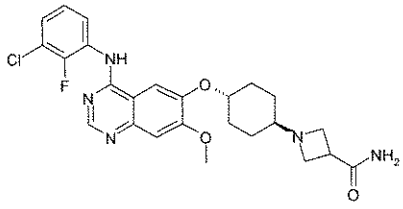
Example No.	Structure
(48)	
(49)	
(50)	
(51)	
(52)	
(53)	

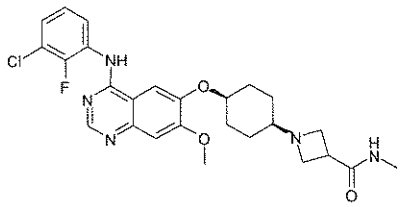
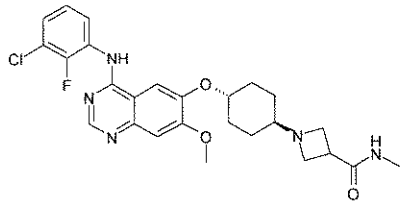
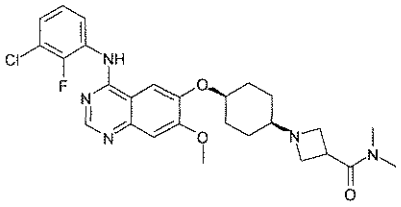
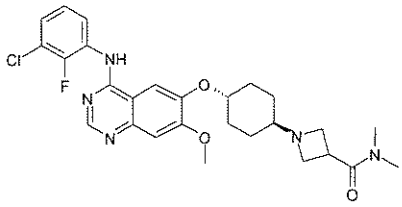
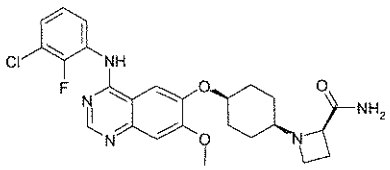
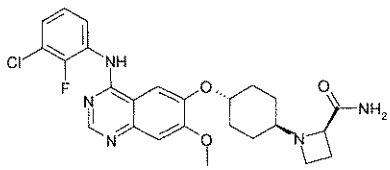
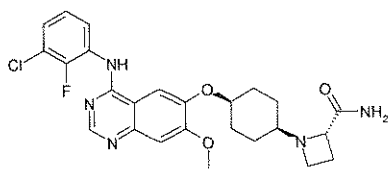
Example No.	Structure
(54)	
(55)	
(56)	
(57)	
(58)	
(59)	
(60)	

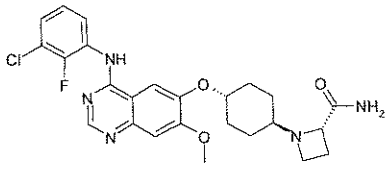
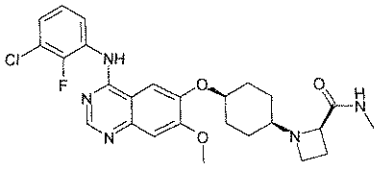
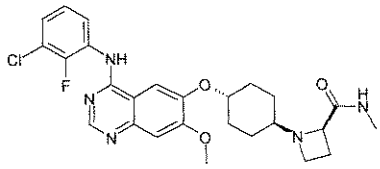
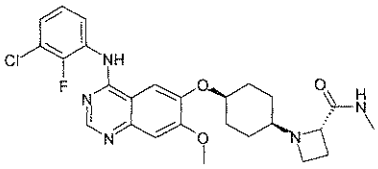
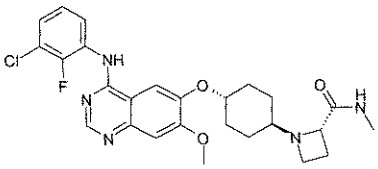
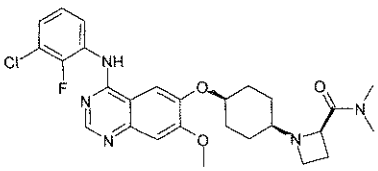
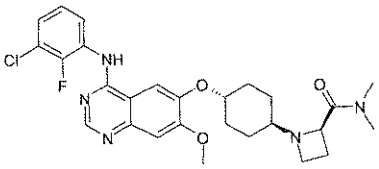
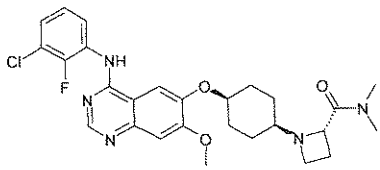
Example No.	Structure
(61)	
(62)	
(63)	
(64)	
(65)	
(66)	
(67)	

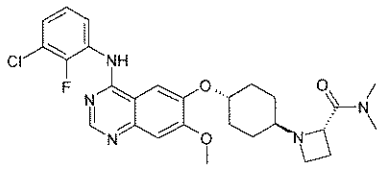
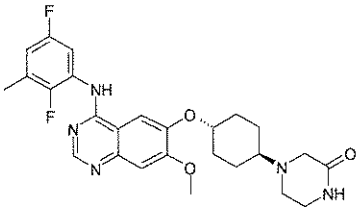
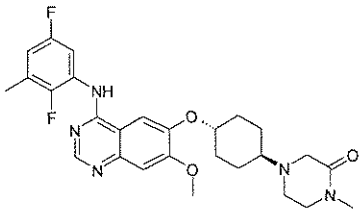
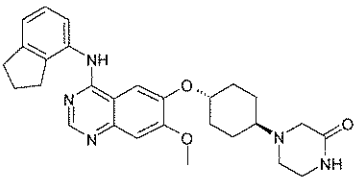
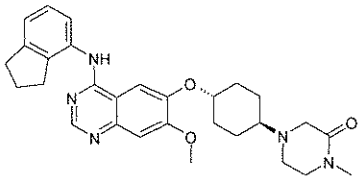
Example No.	Structure
(68)	
(69)	
(70)	
(71)	
(72)	
(73)	
(74)	

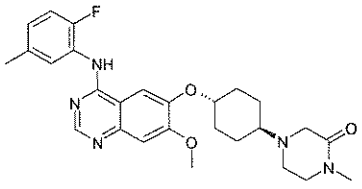
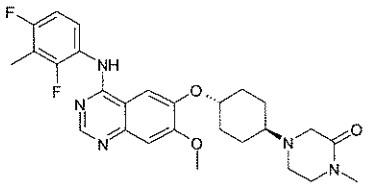
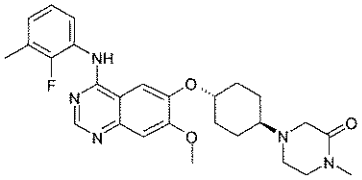
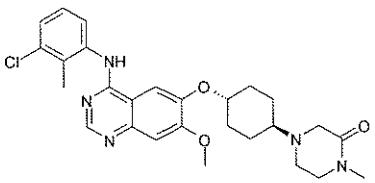
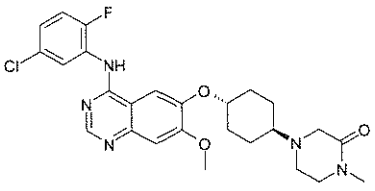
Example No.	Structure
(75)	
(76)	
(77)	
(78)	
(79)	
(80)	
(81)	

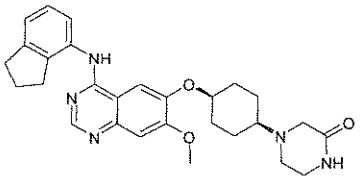
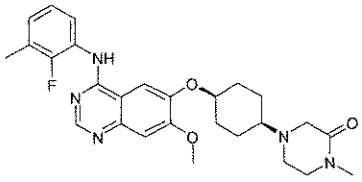
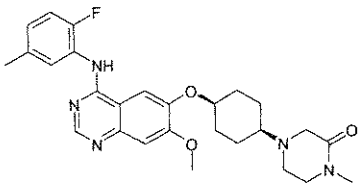
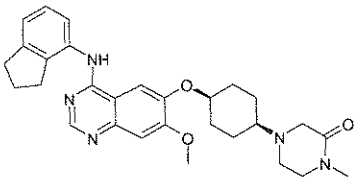
Example No.	Structure
(82)	
(83)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI$^+$): m/z = 473, 475 $[M+H]^+$
(84)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI$^+$): m/z = 473, 475 $[M+H]^+$
(85)	
(86)	

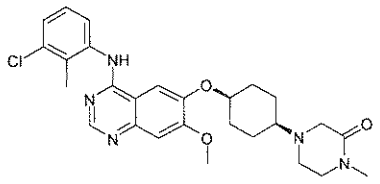
Example No.	Structure
(87)	
(88)	
(89)	
(90)	
(91)	
(92)	
(93)	

Example No.	Structure
(94)	
(95)	
(96)	
(97)	
(98)	
(99)	
(100)	
(101)	

Example No.	Structure
(102)	
(103)	
(104)	
(105)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI^+): m/z = 488 $[M+H]^+$
(106)	 Carried out according to Example 1 in dichloromethane Mass spectrum (ESI^+): m/z = 502 $[M+H]^+$

Example No.	Structure
(107)	 Carried out according to Example 1 in dichloromethane Mass spectrum (ESI^+): m/z = 494 $[M+H]^+$
(108)	
(109)	 Carried out according to Example 1 in 1,2-dichloroethane Mass spectrum (ESI^+): m/z = 494 $[M+H]^+$
(110)	 Carried out according to Example 1 in dichloromethane Mass spectrum (ESI^+): m/z = 510, 512 $[M+H]^+$
(111)	

Example No.	Structure
(112)	 Carried out according to Example 1 in tetrahydrofuran Mass spectrum (ESI$^+$): m/z = 488 $[M+H]^+$
(113)	 Carried out according to Example 1 in 1,2-dichloroethane Mass spectrum (ESI$^+$): m/z = 494 $[M+H]^+$
(114)	 Carried out according to Example 1 in dichloromethane Mass spectrum (ESI$^+$): m/z = 494 $[M+H]^+$
(115)	 Carried out according to Example 1 in dichloromethane Mass spectrum (ESI$^+$): m/z = 502 $[M+H]^+$

Example No.	Structure
(116)	 Carried out according to Example 1 in dichloromethane Mass spectrum (ESI^+): m/z = 510, 512 $[M+H]^+$

Example 2

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 3

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 4

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 5

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 6

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 7

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 8

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 9

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 10

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 11

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

1 spray contains:

active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid q.s.	
ethanol/water (50/50)	ad 15.000 mg

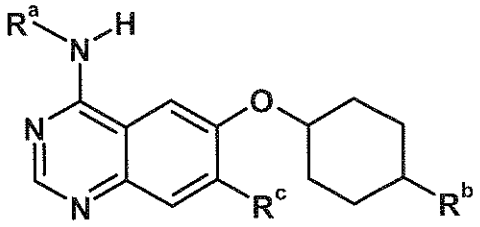
Preparation:

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

Contents of the container: 4.5 g

Patent Claims

1. Bicyclic heterocycles of general formula



(I),

wherein

R^a denotes a phenyl, 1-phenylethyl or indan-4-yl group, wherein the phenyl nucleus is substituted in each case by the groups R^1 to R^3, wherein

R^1 and R^2, which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

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

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a heteroaryl, heteroaryloxy, heteroarylmethyl or heteroarylmethoxy group,

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

a cyano, nitro or amino group, and

R^3 denotes a hydrogen, fluorine, chlorine or bromine atom or

a methyl or trifluoromethyl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-(C_{1-4}-alkyl-carbonyl)-piperazin-1-yl, 4-(C_{1-4}-alkyl-sulphonyl)-piperazin-1-yl, homopiperazin-1-yl, 4-(C_{1-4}-alkyl-carbonyl)-homopiperazin-1-yl or 4-(C_{1-4}-alkyl-sulphonyl)-homopiperazin-1-yl group which may be mono-, di- or trisubstituted by R^4 in each case, while the substituents may be identical or different and

R^4 denotes a fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl group,

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

an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)amino, C_{1-4}-alkyl-carbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-carbonylamino, C_{1-4}-alkyl-sulphonylamino or N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-sulphonylamino group,

an amino-C_{1-4}-alkyl, C_{1-4}-alkylamino-C_{1-4}-alkyl, di-(C_{1-4}-alkyl)amino-C_{1-4}-alkyl, C_{1-4}-alkyl-carbonylamino-C_{1-4}-alkyl, N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-carbonylamino-C_{1-4}-alkyl, C_{1-4}-alkyl-sulphonylamino-C_{1-4}-alkyl or N-(C_{1-4}-alkyl)-C_{1-4}-alkyl-sulphonylamino-C_{1-4}-alkyl group,

a hydroxy, C_{1-4}-alkyloxy or C_{1-4}-alkyl-carbonyloxy group

a hydroxy-C_{1-4}-alkyl, C_{1-4}-alkyloxy-C_{1-4}-alkyl or C_{1-4}-alkyl-carbonyloxy-C_{1-4}-alkyl group,

a C_{1-4}-alkyl-carbonyl, cyano, C_{1-4}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-4}-alkyl-aminocarbonyl, di-(C_{1-4}-alkyl)amino-carbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, piperazin-1-yl-carbonyl, 4-C_{1-4}-alkyl-piperazin-1-yl-carbonyl or morpholin-4-yl-carbonyl group,

a C_{1-4}-alkylcarbonyl-C_{1-4}-alkyl, cyano-C_{1-4}-alkyl, C_{1-4}-alkyloxycarbonyl-C_{1-4}-alkyl, aminocarbonyl-C_{1-4}-alkyl, C_{1-4}-alkylaminocarbonyl-C_{1-4}-alkyl, di-(C_{1-4}-alkyl)aminocarbonyl-C_{1-4}-alkyl, pyrrolidin-1-yl-carbonyl-C_{1-4}-alkyl, piperidin-1-yl-carbonyl-C_{1-4}-alkyl, piperazin-1-yl-carbonyl-C_{1-4}-alkyl, 4-C_{1-4}-alkyl-piperazin-1-yl-carbonyl-C_{1-4}-alkyl or morpholin-4-yl-carbonyl-C_{1-4}-alkyl group,

a C_{1-4}-alkylsulphanyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, aminosulphonyl, C_{1-4}-alkyl-aminosulphonyl or di-(C_{1-4}-alkyl)amino-sulphonyl group,

a C_{1-4}-alkylsulphanyl-C_{1-4}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-4}-alkyl, C_{1-4}-alkylsulphonyl- C_{1-4}-alkyl, aminosulphonyl-C_{1-4}-alkyl, C_{1-4}-alkyl-aminosulphonyl-C_{1-4}-alkyl or di-(C_{1-4}-alkyl)amino-sulphonyl-C_{1-4}-alkyl group

and wherein the heterocycles mentioned under R^b above may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl group,

a C_{1-4}-alkyl group which is substituted by an R^5 group, where

R^5 denotes a hydroxy, C_{1-3}-alkyloxy, C_{3-6}-cycloalkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, bis-(2-methoxyethyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, 2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl, 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl, 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl, piperazin-1-yl, 4-C_{1-3}-alkyl-piperazin-1-yl, homopiperazin-1-yl or C_{1-3}-alkyl-homopiperazin-1-yl group or

a formylamino, C_{1-4}-alkylcarbonylamino, C_{1-3}-alkyloxy-C_{1-3}-alkyl-carbonylamino, C_{1-4}-alkyloxycarbonylamino, aminocarbonylamino, C_{1-3}-alkylaminocarbonylamino, di-(C_{1-3}-alkyl)aminocarbonylamino, pyrrolidin-1-ylcarbonylamino, piperidin-1-ylcarbonylamino, piperazin-1-ylcarbonylamino, 4-C_{1-3}-alkyl-piperazin-1-ylcarbonylamino, morpholin-4-ylcarbonylamino or a C_{1-4}-alkylsulphonylamino group,

a hydroxy group,

a C_{1-4}-alkyloxy group,

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

a C_{2-4}-alkyloxy group which is substituted by the group R^5, where R^5 is as hereinbefore defined,

a C_{3-7}-cycloalkyloxy or C_{3-7}-cycloalkyl-C_{1-4}-alkyloxy group,

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

a tetrahydrofuranyl-C_{1-4}-alkyloxy or tetrahydropyranyl-C_{1-4}-alkyloxy group,

a C_{1-4}-alkoxy group which is substituted by a pyrrolidinyl, piperidinyl or homopiperidinyl group substituted in the 1 position by the group R^6, where

R^6 denotes a hydrogen atom or a C_{1-3}-alkyl group,

or a C_{1-4}-alkoxy group which is substituted by a morpholinyl group substituted in the 4 position by the group R^6, where R^6 is as hereinbefore defined, and wherein the pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl groups mentioned above in the definition of the group R^c may each be substituted by one or two C_{1-3}-alkyl groups, and

wherein by the aryl groups mentioned in the definition of the foregoing groups is meant in each case a phenyl group which is mono- or disubstituted by R^7, wherein the substituents may be identical or different and

R^7 denotes a hydrogen atom, a fluorine, chlorine, bromine or iodine atom or a C_{1-3}-alkyl, hydroxy, C_{1-3}-alkyloxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy or cyano group, and

by the heteroaryl groups mentioned in the definition of the foregoing groups is meant a pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group, wherein the above-mentioned heteroaryl groups are mono- or disubstituted by the group R^7, wherein the substituents may be identical or different and R^7 is as hereinbefore defined, and

unless stated otherwise, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

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

R^a denotes a phenyl, 1-phenylethyl or indan-4-yl group, wherein the phenyl nucleus is substituted in each case by the groups R^1 to R^3, wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl or ethynyl group,

a phenyloxy or phenylmethoxy group, wherein the phenyl moiety of the above-mentioned groups may optionally be substituted by a fluorine or chlorine atom, or

a pyridyloxy or pyridinylmethoxy group, wherein the pyridinyl moiety of the above-mentioned groups is optionally substituted by a methyl or trifluoromethyl group,

R^2 denotes a hydrogen, fluorine or chlorine atom or a methyl group and

R^3 denotes a hydrogen atom,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-piperazin-1-yl, 4-(C_{1-3}-alkyl-sulphonyl)-piperazin-1-yl, homopiperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-homopiperazin-1-yl or 4-(C_{1-3}-alkyl-sulphonyl)-homopiperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a fluorine atom,

a C_{1-3}-alkyl group,

an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group,

an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl, C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl group,

a hydroxy, C_{1-3}-alkyloxy or C_{1-3}-alkyl-carbonyloxy group,

a hydroxy-C_{1-3}-alkyl, C_{1-3}-alkyloxy-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonyloxy-C_{1-3}-alkyl group,

a C_{1-3}-alkyl-carbonyl, cyano, C_{1-4}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl or di-(C_{1-3}-alkyl)amino-carbonyl-group,

a C_{1-3}-alkylcarbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, C_{1-4}-alkyloxycarbonyl-C_{1-3}-alkyl- group, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)aminocarbonyl-C_{1-3}-alkyl group,

a C_{1-4}-alkylsulphanyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl or di-(C_{1-3}-alkyl)amino-sulphonyl group,

a C_{1-4}-alkylsulphanyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphonyl-C_{1-3}-alkyl, aminosulphonyl-C_{1-3}-alkyl, C_{1-3}-alkyl-aminosulphonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-sulphonyl-C_{1-3}-alkyl group, and wherein the heterocycles mentioned above under R^b - may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a hydroxy group,

a C_{1-3}-alkyloxy group,

a methoxy group which is substituted by one to three fluorine atoms,

an ethyloxy group which is substituted in the 2 position by an R^5 group, wherein

R^5 denotes a hydroxy, C_{1-3}-alkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, bis-(2-methoxyethyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl or a 4-C_{1-3}-alkyl-piperazin-1-yl group,

a propyloxy group which is substituted in the 3 position by the group R^5, wherein R^5 is as hereinbefore defined, or

a butyloxy group which is substituted in the 4 position by a group R^5, wherein R^5 is as hereinbefore defined, and

wherein, unless stated otherwise, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

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

R^a denotes a 1-phenylethyl, 3-ethynylphenyl, 3-bromo-2-fluoro-phenyl, 3-bromo-4-fluoro-phenyl, 3-chloro-2-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, 5-chloro-2-fluoro-phenyl, 2-fluoro-3-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 3-fluoro-5-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 2,4-difluoro-3-methyl-phenyl, 2,5-difluoro-3-methyl-phenyl, 3-chloro-2-methyl-phenyl or an indan-4-yl group,

a 3-chloro-4-benzyloxy-phenyl, 3-chloro-4-[(3-fluoro-benzyl)oxy]-phenyl, 4-(pyridin-3-yloxy)-phenyl, 4-[(6-methyl-pyridin-3-yl)oxy]-phenyl, 3-methyl-4-(pyridin-3-yloxy)-phenyl, 3-methyl-4-[(6-methyl-pyridin-3-yl)oxy]-phenyl, 3-chloro-4-(pyridin-3-yloxy)-phenyl or 3-chloro-4-[(6-methyl-pyridin-3-yl)oxy]-phenyl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-piperazin-1-yl or 4-(C_{1-3}-alkyl-sulphonyl)-piperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a fluorine atom,

a C_{1-3}-alkyl group,

an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group,

an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl, C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino-C_{1-3}-alkyl group,

a hydroxy, C_{1-3}-alkyloxy or C_{1-3}-alkyl-carbonyloxy group,

a hydroxy-C_{1-3}-alkyl, C_{1-3}-alkyloxy-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonyloxy-C_{1-3}-alkyl group,

a C_{1-3}-alkyl-carbonyl, cyano, C_{1-4}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl or di-(C_{1-3}-alkyl)amino-carbonyl group,

a C_{1-3}-alkylcarbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, C_{1-4}-alkyloxycarbonyl-C_{1-3}-alkyl- group, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)aminocarbonyl-C_{1-3}-alkyl group,

a C_{1-4}-alkylsulphanyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl or di-(C_{1-3}-alkyl)amino-sulphonyl group,

a C_{1-4}-alkylsulphanyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-3}-alkyl, C_{1-4}-alkylsulphonyl-C_{1-3}-alkyl, aminosulphonyl-C_{1-3}-alkyl, C_{1-3}-alkyl-aminosulphonyl-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-sulphonyl-C_{1-3}-alkyl group,

and wherein the heterocycles mentioned above under R^b may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a methoxy or ethyloxy group,

an ethyloxy group which is substituted in the 2 position by the group R^5, wherein

R^5 denotes a hydroxy, methoxy, ethoxy, amino, dimethylamino, diethylamino, bis-(2-methoxyethyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl or 4-ethylpiperazin-1-yl group,

a propyloxy group which is substituted in the 3 position by the group R^5, wherein R^5 is as hereinbefore defined, or

a butyloxy group which is substituted in the 4 position by the group R^5, wherein R^5 is as hereinbefore defined, and

wherein, unless stated otherwise, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

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

R^a denotes a 1-phenylethyl, 3-ethynylphenyl, 3-chloro-2-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, 5-chloro-2-fluoro-phenyl, 2-fluoro-3-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 3-fluoro-5-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 2,4-difluoro-3-methyl-phenyl, 2,5-difluoro-3-methyl-phenyl, 3-chloro-2-methyl-phenyl or an indan-4-yl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C_{1-3}-alkyl-carbonyl)-piperazin-1-yl or 4-(C_{1-3}-alkyl-sulphonyl)-piperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a fluorine atom,

a C_{1-3}-alkyl group,

an amino, C_{1-2}-alkylamino, di-(C_{1-2}-alkyl)amino, C_{1-2}-alkyl-carbonylamino, N-(C_{1-2}-alkyl)-C_{1-2}-alkyl-carbonylamino, C_{1-2}-alkyl-sulphonylamino or N-(C_{1-2}-alkyl)-C_{1-2}-alkyl-sulphonylamino group,

an amino-C_{1-2}-alkyl, C_{1-2}-alkylamino-C_{1-2}-alkyl, di-(C_{1-2}-alkyl)amino-C_{1-2}-alkyl, C_{1-2}-alkyl-carbonylamino-C_{1-2}-alkyl, N-(C_{1-2}-alkyl)-C_{1-2}-alkyl-carbonylamino-C_{1-2}-alkyl, C_{1-2}-alkyl-sulphonylamino-C_{1-2}-alkyl or N-(C_{1-2}- alkyl)-C_{1-2}-alkyl-sulphonylamino-C_{1-2}-alkyl group,

a hydroxy, C_{1-2}-alkyloxy or C_{1-2}-alkyl-carbonyloxy group,

a hydroxy-C_{1-2}-alkyl, C_{1-2}-alkyloxy-C_{2-4}-alkyl or C_{1-2}-alkyl-carbonyloxy-C_{1-2}-alkyl group,

a C_{1-2}-alkyl-carbonyl, cyano, C_{1-2}-alkyl-oxycarbonyl, carboxy, aminocarbonyl, C_{1-2}-alkyl-aminocarbonyl or di-(C_{1-2}-alkyl)amino-carbonyl group,

a C_{1-2}-alkylcarbonyl-C_{1-2}-alkyl, cyano-C_{1-2}-alkyl, C_{1-2}-alkyloxycarbonyl-C_{1-2}-alkyl group, aminocarbonyl-C_{1-2}-alkyl, C_{1-2}-alkylaminocarbonyl-C_{1-2}-alkyl or di-(C_{1-2}-alkyl)aminocarbonyl-C_{1-2}-alkyl group,

a C_{1-2}-alkylsulphanyl, C_{1-2}-alkylsulphinyl or C_{1-2}-alkylsulphonyl group,

a C_{1-2}-alkylsulphanyl-C_{1-2}-alkyl, C_{1-2}-alkylsulphinyl-C_{1-2}-alkyl or C_{1-2}-alkylsulphonyl-C_{1-2}-alkyl group,

and wherein the heterocycles mentioned above under R^b may additionally be substituted by an oxo group,

R^c denotes a hydrogen atom,

a methoxy, ethyloxy or 2-(methoxy)-ethyloxy group,

a 2-(morpholin-4-yl)ethyloxy, 3-(morpholin-4-yl)propyloxy or 4-(morpholin-4-yl)butyloxy group,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

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

R^a denotes a 1-phenylethyl, 3-chloro-2-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, 5-chloro-2-fluoro-phenyl, 2-fluoro-3-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 3-fluoro-5-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 2,4-difluoro-3-methyl-phenyl, 3-chloro-2-methyl-phenyl or an indan-4-yl group,

R^b denotes an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl or 3-oxo-piperazin-1-yl group which may be mono- or disubstituted in each case by R^4, wherein the substituents may be identical or different and

R^4 denotes a methyl, hydroxy, cyano, aminocarbonyl, methylamino-carbonyl or dimethylamino-carbonyl group, and

R^c denotes a methoxy group,

the tautomers, the stereoisomers, the mixtures thereof and salts thereof.

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

(a) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(b) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(morpholin-4-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(c) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(d) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(R)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(e) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-cis-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(f) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[(S)-trans-4-(3-hydroxy-pyrrolidin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(g) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[cis-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(h) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(i) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(N,N-dimethylaminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(j) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(N,N-dimethylaminocarbonyl)- pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(k) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-cis-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(l) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-{(S)-trans-4-[2-(aminocarbonyl)-pyrrolidin-1-yl]-cyclohexyloxy]-7-methoxy-quinazoline,

(m) 4-[(3-chloro-2-fluoro-phenyl)amino]-6-[trans-4-(4-methyl-3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(n) 4-[(2-fluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(o) 4-[(2-fluoro-5-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline,

(p) 4-[(2,4-difluoro-3-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline and

(q) 4-[(3-chloro-2-methyl-phenyl)amino]-6-[trans-4-(3-oxo-piperazin-1-yl)-cyclohexyloxy]-7-methoxy-quinazoline

and the salts thereof.

7. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 6 with inorganic or organic acids or bases.

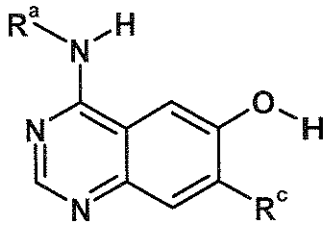
8. Pharmaceutical compositions, containing a compound according to at least one of claims 1 to 6 or a physiologically acceptable salt according to claim 7 optionally together with one or more inert carriers and/or diluents.

9. Use of a compound according to at least one of claims 1 to 7 for preparing a pharmaceutical composition which is suitable for the treatment of benign or malignant tumours, for the prevention and treatment of diseases of the airways and lungs and for the treatment of diseases of the gastro-intestinal tract and the bile duct and gall bladder.

10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

11. Process for preparing the compounds of general formula I according to claims 1 to 6, characterised in that

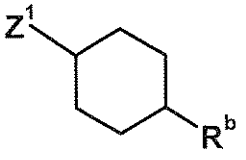
a) a compound of general formula



,(II)

wherein

R^a and R^c are as hereinbefore defined, is reacted with a compound of general formula

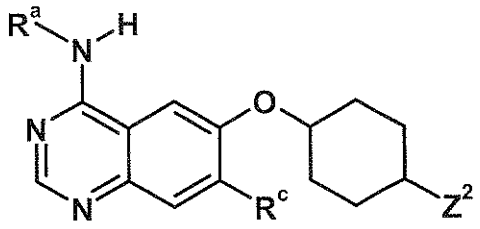


,(III)

wherein

R^b is as hereinbefore defined and Z^1 denotes a leaving group, or

b) a compound of general formula



,(IV)

wherein

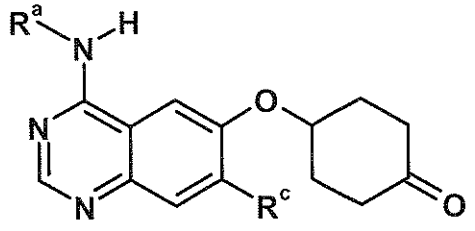
R^a and R^c are as hereinbefore defined, and Z^2 denotes a leaving group, is reacted with a compound of general formula

$$H\text{-}R^b \qquad ,(V)$$

wherein

R^b is as hereinbefore defined, or

c) a compound of general formula



,(VI)

wherein

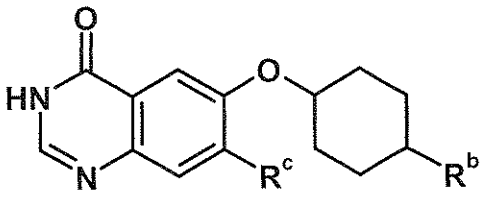
R^a and R^c are as hereinbefore defined, is reacted with a compound of general formula

$H\text{-}R^b$,(VII)

wherein

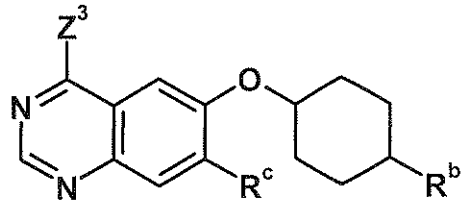
R^b is as hereinbefore defined, or

d) a compound of general formula (VIII)



(VIII),

wherein R^b and R^c are as hereinbefore defined, is reacted with a halogenating agent to form an intermediate compound of general formula (IX),



(IX),

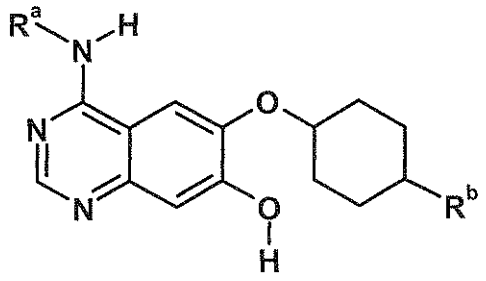
wherein R^b and R^c are as hereinbefore defined and Z^3 denotes a halogen atom, and this is then reacted with a compound of general formula (X),

$R^a\text{-}NH_2$ (X),

wherein R^a is as hereinbefore defined.

e) In order to prepare compounds of general formula I wherein R^c denotes one of the above-mentioned, optionally substituted alkyloxy groups,

a compound of general formula



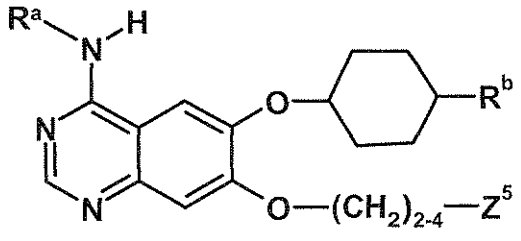
,(XI)

wherein R^a and R^b are as hereinbefore defined, is reacted with a compound of general formula

$$Z^4 - R^{c'} \qquad ,(XII)$$

wherein $R^{c'}$ is as hereinbefore defined and Z^4 denotes a leaving group, or

f) In order to prepare compounds of general formula I wherein R^c denotes one of the above-mentioned alkyloxy groups which is substituted by an optionally substituted amino, alkylamino or dialkylamino group or by an optionally substituted heterocyclic group bound via an imino nitrogen atom, a compound of general formula

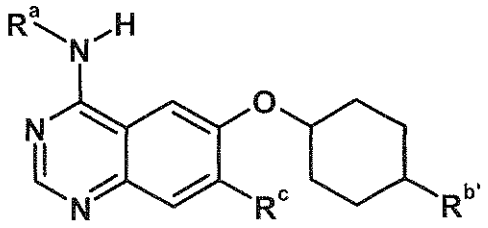


(XIII),

wherein R^a and R^b are as hereinbefore defined and Z^5 denotes a leaving group, is reacted with ammonia, a corresponding, optionally substituted alkylamine, dialkylamine or an imino compound or the suitable salts or derivatives thereof, or

g) In order to prepare compounds of general formula I wherein R^b contains one or more hydroxy groups,

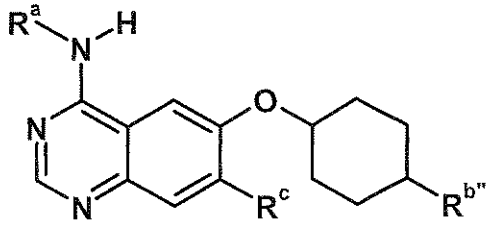
protective groups are cleaved from a compound of general formula


(XIV),

wherein R^a and R^c are as hereinbefore defined and $R^{b'}$ contains one or more groups that can be converted into hydroxy groups, or

h) In order to prepare compounds of general formula I wherein R^b contains an –NH-group:

a protective group is cleaved from a compound of general formula


(XV),

wherein R^a and R^c are as hereinbefore defined and $R^{b''}$ has the meanings given for R^b hereinbefore, with the proviso that $R^{b''}$ contains a protected nitrogen atom, and

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

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

a compound of general formula I which contains an alkoxycarbonyl group is converted by ester cleavage into a carboxylic acid, and/or

a compound of general formula I which contains an alkoxycarbonyl group is converted by reaction with an amine into a carboxylic acid amide derivative, and/or

a compound of general formula I which contains a carboxy group is converted by reaction with an amine into a carboxylic acid amide derivative, and/or

if necessary any protective group used in the reactions described above is cleaved again and/or

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

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