Title: 2,4-SUBSTITUTED QUINAZOLINES AS LIPID KINASE INHIBITORS

Abstract: The invention relates to compounds of the formula (I), which are appropriate for the treatment of kinase, e.g. PI3K-related, diseases, such as proliferative diseases, inflammatory diseases, obstructive airways disorders and transplantation related diseases.
2,4-Substituted quinazolines as lipid kinase inhibitors

The invention relates to quinazolines substituted at least in the 4,6-position, the use of such a compound in the preparation of a pharmaceutical preparation or their use for the prophylactic and/or therapeutic treatment of one or more diseases selected from the group consisting of proliferative, inflammatory diseases, allergic diseases, obstructive airways diseases, and disorders commonly occurring in connection with transplantation, especially one or more diseases which respond to an inhibition of kinases of the PI3-kinase-related protein kinase family, especially lipid kinases and/or PI3 kinase (PI3K) and/or mTOR and/or DNA protein kinase and/or ATM and/or ATR and/or hSMG-1 activity, a compound of this type for use in the prophylactic and/or therapeutic treatment of one or more of the diseases just mentioned, a method for the preparation of a pharmaceutical formulation for use in one or more of the mentioned diseases, comprising mixing one of these compounds with at least one pharmaceutically acceptable carrier, and a method of treatment, comprising administering to a warm-blooded animal, including a human, especially in need of such treatment, a compound according to the invention, especially in an amount that is effective against a disease mentioned above; as well as to a process or method for the manufacture of a quinazoline substituted at least in the 4,6-position according to the invention; and to other aspects disclosed herein.

In a first aspect, the invention related to a compound of the formula I,

\[
\begin{array}{c}
\text{R}^4 \\
\text{R}^3 \\
\text{R}^2 \\
\text{R}^1 \\
\text{R}^5
\end{array}
\]

wherein

\( \text{R}^1 \) is hydrogen; or amino that is unsubstituted or monosubstituted with alkyl or cycloalkyl;

\( \text{R}^2 \) is an unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

\( \text{R}^3 \) is hydrogen, halogen, alkyl, alkoxy or cyano;
R^4 is unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl; and

R^5 is hydrogen, methyl or methyl substituted with halogen;

with the proviso that if R^4 is unsubstituted or substituted pyrazolyl then R^1 is amino that is unsubstituted or monosubstituted with alkyl (especially C_1-C_7, more especially Ci-C_4-alkyl) or cycloalkyl (especially C_3-C_8, more especially C_3-C_5-cycloalkyl) and R^2, R^3 and R^5 are as defined above;

and with the proviso that if R^2 is unsubstituted or substituted oxoindolyl, then R^1 is amino that is unsubstituted or monosubstituted with alkyl (especially CrC_7, more especially Ci-C_4-alkyl) or cycloalkyl (especially C_3-C_8, more especially C_3-C_5-cycloalkyl) and R^3, R^4 and R^5 are as defined above;

or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated, where more general terms whereever used may, independently of each other, be replaced by more specific definitions or remain, thus defining more preferred embodiments of the invention:

The prefix "lower" or "C_1-C_7" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Alkyl (also in alkoxy or the like) preferably has up to 12 carbon atoms and is more preferably lower alkyl, especially C_1-C_4-alkyl.

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or preferably methyl.
Cycloalkyl is preferably cycloalkyl with from and including 3 up to and including 10 carbon atoms in the ring; cycloalkyl is more preferably C_3-C_8-cycloalkyl, still more preferably C_3-C_5-cycloalkyl, especially cyclopentyl, cyclobutyl or cyclopentyl.

Alkyl (e.g. methyl) which is substituted by halogen is preferably fluoroalkyl wherein 1 or more, preferably all (then the alkyl is a perfluoroalkyl) hydrogen atoms are substituted by fluoro, such as difluoromethyl or trifluoromethyl.

Halogen, halogeno (or halo) is especially fluoro, chloro, bromo, or iodo, especially fluoro, chloro or bromo.

Aryl preferably has 6 to 18 carbon atoms and is a mono-, di- or polycyclic (preferably up to tricyclic, more preferably up to bicyclic) unsaturated carbocyclic moiety with conjugated double bonds in the ring, especially phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl. Naphthyl and preferably phenyl are especially preferred. Aryl is unsubstituted or substituted by one or more, e.g. one to three, substitutents preferably independently selected from the group consisting of C_1-C_r-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl; C_2-C_r-alkeny1; C_6-C_r-alkyl; C_6-C_r-aryl-C_r-alkyl in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by C_1-C_r-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidine by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_r-alkylamino, by halo, by C_r-alkoxy, such as methoxy, and/or by halo-C_r-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-C_r-alkyl wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by C_r-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_r-alkylamino, by halo, by C_r-alkoxy, such as methoxy, and/or by halo-C_r-alkyl, such as trifluoromethyl, for example pyrrolidino-C_r-alkyl, piperidino-C_r-alkyl, morpholino-C_r-alkyl, thiomorpholino-C_r-alkyl, N-C_r-alkyl-piperazinyl-C_r-alkyl, or N-mono- or N,N-di-(C_r-alkyl)-amino-substituted or unsubstituted pyrrolidino-C_r-alkyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-C_r-alkyl wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl,
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pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C-$\gamma$-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidine by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C-$\gamma$-alkylamino, by halo, by Ci-C-$\gamma$-alkoxy, such as methoxy, and/or by halo-C$_1$-$\gamma$-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinylo-carbonyl-Ci-C-$\gamma$-alkyl where in pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C-$\gamma$-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially pyrrolidino, by amino, by N-mono- and/or N,N-di-C-$\gamma$-alkylamino, by halo, by d-C-$\gamma$-alkoxy, such as methoxy, and/or by halo-C$_1$-$\gamma$-alkyl, such as trifluoromethyl; halo-C$_1$-$\gamma$-alkyl, such as trifluoromethyl; hydroxy-C$_1$-$\gamma$-alkyl; Ci-C$_1$-$\gamma$-alkoxy-C$_1$-$\gamma$-alkyl, such as 3-methoxypropyl or 2-methoxyethyl; C$_1$-$\gamma$-alkoxy-C$_1$-$\gamma$-alkoxy-C$_1$-$\gamma$-alkyl; phenox y- or nap thyl ox y-C$_1$-$\gamma$-alkyl; phenyl-C$_1$-$\gamma$-alkoxy- or nap thyl-C$_1$-$\gamma$-alkoxy-C$_1$-$\gamma$-alkyl; amino-Ci-C-$\gamma$-alkyl, such as aminomethyl; N-mono- or N,N-di-(Ci-C-$\gamma$-alkyl and/or mono-C$_1$-$\gamma$-alkoxy-C$_1$-$\gamma$-alkyl and/or (mono- or di-(Ci-C-$\gamma$-alkyl)-amino)-Ci-C-$\gamma$-alkyl; Cr$_1$-$\gamma$-alkoxy-C$_1$-$\gamma$-alkylamino-C$_1$-$\gamma$-alkyl; mono- or di-[C$_6$$_{18}$-aryl-C$_1$-$\gamma$-alkyl in which aryl is preferably phenyl, naphthyl, biphenyle nyl, indacenyl, acenaphth ylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by Cr$_1$-$\gamma$-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C$_1$-$\gamma$-alkylamino, by halo, by C$_1$-$\gamma$-alkylamino, such as methoxy, and/or by halo-C$_1$-$\gamma$-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-Ci-C-$\gamma$-alkyl wherein pyrrolidiny l, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C-$\gamma$-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C-$\gamma$-alkylamino, by halo, by Ci-C-$\gamma$-alkoxy, such as methoxy, and/or by halo-C$_1$-$\gamma$-alkyl, such as trifluoromethyl, for example pyrrolidino-C$_1$-$\gamma$-alkyl, piperidinyl-C$_1$-$\gamma$-alkyl, morpholino-C$_1$-$\gamma$-alkyl, thiomorpholino-C$_1$-$\gamma$-alkyl, N-d-C$_1$-$\gamma$-alkyl-piperazinyl-Cr$_1$-$\gamma$-alkyl, or N-mono- or N,N-di-(Ci-C-$\gamma$-alkyl)-amino-substituted or unsubstituted pyrrolidinyl-Ci-C-$\gamma$-alkyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-C$_1$-$\gamma$-alkyl wherein pyrrolidinyl, piperazinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazin yl are unsubstituted or substituted by Ci-C-$\gamma$-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C$_1$-$\gamma$-alkylamino, by halo, by d-
C Wenger, such as methoxy, and/or by halo-C<sub>7</sub>-alkyl, such as trifluoromethyl; and/or (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), pyrazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-carbonyl-C<sub>7</sub>-alkyl wherein pyrrolidinyl, piperidinyl, pyrazinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C<sub>7</sub>-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by Ci-C<sub>7</sub>-alkoxy, such as methoxy, and/or by halo-C<sub>7</sub>-alkyl, such as trifluoromethyl; especially naphthyl- or phenyl-C<sub>7</sub>-alkyl-amino-C<sub>7</sub>-alkyl; C<sub>7</sub>-alkanoylamino-Ci-C<sub>7</sub>-alkyl; carboxy-C<sub>7</sub>-alkyl; benzoyl- or naphthylamino-Ci-C<sub>7</sub>-alkyl; Ci-C<sub>7</sub>-alkylsulfonylamino-Ci-C<sub>7</sub>-alkyl; phenyl- or naphthylsulfonylamino-Ci-C<sub>7</sub>-alkyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, Ci-C<sub>7</sub>-alkyl moieties; phenyl- or naphthyl-C<sub>7</sub>-alkylsulfonylamino-C<sub>1</sub>-C<sub>7</sub>-alkyl; halo, especially fluoro (preferred), chloro (preferred) or bromo; hydroxy; Ci-C<sub>7</sub>-alkoxy; C<sub>6</sub>-C<sub>8</sub>-aryl-Ci-C<sub>7</sub>-alkoxy in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthelenyl, fluorenlyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by Ci-C<sub>7</sub>-alkyl, such as methyl or ethyl, by Ci-C<sub>7</sub>-alkoxy, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by d - C<sub>7</sub>-alkoxy, such as methoxy, and/or by halo-C<sub>1</sub>-C<sub>7</sub>-alkyl, such as trifluoromethyl; such as phe- nyl-Ci-C<sub>7</sub>-alkoxy wherein phenyl is unsubstituted or substituted by CrC<sub>7</sub>-alkoxy and/or halo; hal-C<sub>7</sub>-alkoxy, such as trifluoromethoxy; hydroxy-Ci-C<sub>7</sub>-alkoxy; Ci-C<sub>7</sub>-alkoxy-Ci-C<sub>7</sub>-alkoxy, such as 2-(methoxy)-ethoxy; amino-C<sub>1</sub>-C<sub>7</sub>-alkoxy, N-Ci-C<sub>7</sub>-alkanoylamino-Ci-C<sub>7</sub>-alkoxy; N-unsubstituted-, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>7</sub>-alkyl)carbamoyl-C<sub>1</sub>-C<sub>7</sub>-alkoxy; phenyl- or naphthyloxy; phenyl- or naphthyl-Ci-C<sub>7</sub>-alkyloxy; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-Ci-C<sub>7</sub>-alkoxy wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by d-C<sub>7</sub>-alkyl, such as methyl or ethyl; by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by Ci-C<sub>7</sub>-alkoxy, such as methoxy, and/or by halo-Ci-C<sub>7</sub>-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-Ci-C<sub>7</sub>-alkoxy wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C<sub>7</sub>-alkyl, such as methyl or ethyl; by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by C<sub>1</sub>-C<sub>7</sub>-alkoxy, such as methoxy, and/or by halo-Ci-C<sub>7</sub>-alkyl, such as trifluoromethyl; CrC<sub>7</sub>-
alkanoyloxy; benzoyl- or naphthoyloxy; Ci-C \( _{7} \)-alkylthio; halo-C\( _{7} \)-alkylthio, such as trifluoro-
romethylthio; C\( _{1} \)-C\( _{7} \)-alkoxy-C \( _{1} \)-C\( _{7} \)-alkylthio; phenyl- or naphthylthio; phenyl- or naphthyl-d-
C\( _{7} \)-alkylthio; Ci-C \( _{7} \)-alkanoylthio; benzoyl- or naphthoylthio; nitro; amino; mono- or di-(Ci-C \( _{7} \)
alkyl)-amino; mono- or di-(naphthyl- or phenyl-C \( _{1} \)-C\( _{7} \)-alkyl)-amino; C\( _{1} \)-Ci-C\( _{7} \)-alkanoylamino;
benzoyl- or naphthoylamino; Ci-C \( _{7} \)-alkylsulfonylamino; phenyl- or naphthylsulfonylamino
wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to
three, CrC \( _{7} \)-alkyl moieties; phenyl- or naphthyl-Ci-C \( _{7} \)-alkylsulfonylamino; CrC \( _{7} \)-alkanoyl;
C\( _{1} \)-C\( _{7} \)-alkoxy-C \( _{1} \)-C\( _{7} \)-alkanoyl; carboxyl (-COOH); C\( _{1} \)-Ci-C\( _{7} \)-alkoxy-carbonyl; phenoxy- or
naphthoxy carbonyl; phenyl- or naphthyl-Ci-C \( _{7} \)-alkoxycarbonyl; Ci-C\( _{7} \)-alkyl; especially C\( _{1} \)-Ci-C\( _{7} \)-alkylendioxy,
such as methylenedioxy or 1,2-ethylenedioxy; carbamoyl; N-mono- or N,N-di-(Cr
C\( _{7} \)-alkyl, naphthyl-Ci-C \( _{7} \)-alkyl, phenyl-Ci-C \( _{7} \)-alkyl, pyrrolidinyl(especially pyrrolidino)-Ci-C \( _{7}
alkyl, piperidinyl (especially piperidino)-C \( _{1} \)-C\( _{7} \)-alkyl, piperazinyl- or N-C\( _{1} \)-C\( _{7} \)-alkyl)piperazinyl
(especially piperazino or 4-Ci-C \( _{7} \)-alkylpiperazino)-Ci-C \( _{7} \)-alkyl, mono-Ci-C \( _{7} \)-alkoxy-Ci-C \( _{7} \)-alkyl
and/or (N'-mono- or N,N'-di-(Ci-C \( _{7} \)-alkyl)-amino-Ci-C \( _{7} \)-alkyl)-amino-carbonyl, such as N-
mono- or N,N-di-(Ci-C \( _{7} \)-alkyl)-amino-carbonyl; N-C\( _{7} \)-alkoxy-Ci-C \( _{7} \)-alkylcarbamoyl; pyro-
lidin-1-carbonyl; amino-N-pyrrolidin-1-carbonyl; N-mono- or N,N-di(C\( _{1} \)-C\( _{7} \)-alkyl)amino-
pyrrolidin-1-carbonyl; piperidin-1-carbonylmorpholin-4-carbonyl; thiomorpholin-4-carbonyl; S-
oxo-thiomorpholin-4-carbonyl; S,S-dioxothiomorpholin-4-carbonyl; piperazin-1-carbonyl; N-
Ci-C \( _{7} \)-alkyl-piperazin-1-carbonyl; N-C\( _{7} \)-alkoxycarbonyl-piperazin-1-carbonyl; N-mono- or
N,N-di-(C \( _{1} \)-C\( _{7} \)-alkyl)-amino-substituted or unsubstituted pyrrolidinyl-C \( _{1} \)-C\( _{7} \)-alkyl; cyano; C\( _{1} \)-Ci-
alkenylene or -alkylene; Ci-C \( _{7} \)-alkylsulfonyl; phenyl- or naphthylsulfonyl wherein phenyl or
naphthyl is unsubstituted or substituted by one or more, especially one to three, Ci-C \( _{7} \)-alkyl
moieties; phenyl- or naphthyl-Ci-C \( _{7} \)-alkylsulfonyl; sulamoyl; N-mono or N,N-di-(CrC \( _{7} \)-alkyl,
phenyl-, naphthyl-, phenyl-C \( _{1} \)-C\( _{7} \)-alkyl-, pyrrolidinyl(especially pyrrolidino)-C \( _{1} \)-C\( _{7} \)-alkyl,
piperidinyl(especially piperidino)-Ci-C \( _{7} \)-alkyl, piperazinyl(especially piperazino)-Ci-C \( _{7} \)-alkyl,
N-C\( _{7} \)-alkylpiperazinyl(especially 4-Ci-C \( _{7} \)-alkylpiperazino)-Ci-C \( _{7} \)-alkyl and/or naphthyl-d-
C\( _{7} \)-alkyl)-amino sulfonyle, pyrazolyl, pyrazolidinyl, pyrrolyl, pyridyl that is unsubstituted or
substituted by C\( _{1} \)-C\( _{7} \)-BikOxy, such as methoxy, and/or by halo-C\( _{1} \)-C\( _{7} \)-alkyl, such as trifluo-
romethyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-
dioxothiomorpholinyl, piperazinyl, N-C\( _{7} \)-alkyl-piperazinyl, 4-(phenyl-C\( _{7} \)-alkyl)-piper-
azinyl, 4-(naphthyl-C\( _{7} \)-alkyl)-piperazinyl, 4-(C\( _{1} \)-C\( _{7} \)-alkoxycarbonyl)-piperazinyl, 4-(phenyl-
C\( _{1} \)-C\( _{7} \)-alkoxycarbonyl)-piperazinyl and 4-(naphthyl-C \( _{1} \)-C\( _{7} \)-alkoxycarbonyl)-piperazinyl. Es-
pecially preferably aryl is phenyl or naphthyl, each of which is unsubstituted or substituted by
one or more, e.g. up to three, substituents independently selected from the group consisting
of 2-amino-pyrimidin-5-yl-C \( _{1} \)-C\( _{7} \)-alkyl, halo, hydroxy, CrC \( _{7} \)-alkoxy, CrC \( _{7} \)-alkoxy-CrC \( _{7} \)-
alkoxy, 4-Ci-C \(\gamma\)-alkyl-piperazin-1-carbonyl-Ci-C \(\gamma\)-alkoxy, 4-pyrolidino-piperidin-i-carbonyl-
Ci-C \(\gamma\)-alkoxy, 4-pyrolidino-piperidin-1-yl-Ci-C \(\gamma\)-alkoxy, 4-Ci-C \(\gamma\)-alkyl-piperazino-Ci-C \(\gamma\)-alkoxy,
pyridin (e.g.-2)-yloxy-Ci-C \(\gamma\)-alkoxy, pyrimidin(e.g. -4)-yloxy-Ci-C \(\gamma\)-alkoxy, amino, N-mono- or
N,N-di-(Ci-C \(\gamma\)-alkyl), phenyl-C \(\gamma\)-alkyl and/or naphthyl-C \(\gamma\)-alkyl)-amino, carboxy, Ci-C \(\gamma\-
alkoxycarbonyl, phenyl-Ci-C \(\gamma\)-alkoxycarbonyl, naphthyl-Ci-C \(\gamma\)-alkoxycarbonyl, phenoxy-
carbonyl, naphthoxycarbonyl, d-C 4-alkylendioxy, carbamoyl, N-mono- or N,N-di-(Ci-C \(\gamma\)-alkyl,
N,N'-di-(Ci-C \(\gamma\)-alkyl)amino-Ci-C \(\gamma\)-alkyl, pyrrolidino-Ci-C \(\gamma\)-alkyl and/or phenyl-Ci-C \(\gamma\)-alkyl-
carbamoyl, pipеридин-1-карбонил, пиридин-1-карбонил, 4-Ci-C \(\gamma\)-alkyl-piperazin-1-карбонил,
morpholin-4-карбонил, thiomorpholin-4-карбонил, S,S-dioxothiomorpholin-4-карбонил, S,S-
dioxothiomorpholin-4-карбонил, N,N-di(Ci-C \(\gamma\)-alkyl)amino-pyrrolidin-1-carbonyl, sulfa moyl, N-
mono- or N,N-di-(Ci-C \(\gamma\)-alkyl), N,N'-di-(Ci-C \(\gamma\)-alkyl)amino-Ci-C \(\gamma\)-alkyl, pyrrolidino-Ci-C \(\gamma\)-alkyl
and/or phenyl-C \(\gamma\)-alkyl)-sulfamoyl, pyrazolyl, especially pyrazole, pyrazolidinyl, especially
pyrazolidino, pyrrolyl, especially pyrroline-1-yl, (unsubstituted or Ci-C \(\gamma\)-alkoxy- and/or halo-de-
C \(\gamma\)-alkoxy-substituted pyridin(e.g. -3))-yl, pyrrolidinyl, especially pyrrolidine piperidiny,
especially piperidino, piperaziny, especially piperazino, 4-Ci-C \(\gamma\)-alkyl-piperaziny, especially
4-Ci-C \(\gamma\)-alkyl-piperazino, 4-(phenyl-C \(\gamma\)-alkyl)-piperaziny, especially 4-(phenyl-C \(\gamma\)
-alkyl)-piperazino, 4-(naphthyl-C \(\gamma\)-alkyl)-piperaziny, especially 4-(naphthyl-C \(\gamma\)-alkyl
-piperazino, 4-(Ci-C \(\gamma\)-alkoxycarbonyl)-piperaziny, especially 4-(Ci-C \(\gamma\)-alkoxycarbonyl
-piperazino, 4-(phenyl-Ci-C \(\gamma\)-alkoxycarbonyl)-piperaziny, especially 4-(phenyl-Ci-C \(\gamma\-
alkoxycarbonyl)-piperazin, 4-(naphthyl-Ci-C \(\gamma\)-alkoxycarbonyl)-piperaziny, especially 4-(naphthyl-
Ci-C \(\gamma\)-alkoxycarbonyl)-piperazino, morpholinyl, especially morpholinio, thiomorpholinyl, es-
especially thiomorpholino, S-oxothiomorpholino, especially S-oxothiomorpholino, and S,S-
dioxothiomorpholino, especially S,S-dioxothiomorpholino.

Heteroaryl is an unsaturated mono-, di- or polycyclic (preferably up to tricyclic, more prefer-
able up to bicyclic) ring, preferably with 3 to 20, more preferably 5 to 16 ring atoms, including
at least one, preferably up to 4, e.g. up to three ring heteroatoms selected from O, S, N and
NH, which carries the maximum possible number of conjugated double bonds in the ring
(that is, is unsaturated) and is unsubstituted or substituted by one or more, preferably up to
three, substituents independently selected from the substituents mentioned above for aryl.
Examples for preferred heteroaryl moieties are imidazolyl, thiophenyl, pyrrolyl, imidazolyl,
pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, 2H- or 4H-pyranyl, oxazolyl, thi-
azolyl, 5H-indazolyl, indolyl, isoindolyl, quinolyl, isoquinolinyl, phthalazinyl, 1,8-naphthyridinyl,
quinoxaliny, quinazoliny, cinnolinyl, indoliziny, 4H-quinoliniziny, pteridiny, puriny, carbazolyl,
beta-carbolinyl, acridiny, phenanthridiny, phenziny, 1,7-phenanthroliny, perimidinyl, ben-


zofuranyl, isobenzofuranyl, 2H-chromenyl, 4aH-isochromenyl, thianthrenyl, xanthenyl, phenoxathiinyl, phenoxazinyl or phenothiazinyl, each of which is unsubstituted or substituted as mentioned above; more preferably, pyrazolyl (especially as \( R^1 \)) and indolyl are excluded from the term "heteroaryl". Most preferably heteroaryl is pyrrolyl, thiophenyl, pyrazolyl (but only as \( R^2 \), not as \( R^1 \)), triazolyl, especially 1,2,4-triazolyl, pyridyl, quinolyl or quinoxalinyln, each of which is unsubstituted or substituted by one or more, especially up to three, substituents selected from the group consisting of halo, hydroxy, Ci-\( C_7 \)-alkoxy, Ci-\( C_7 \)-alkoxy-Ci-\( C_7 \)-alkoxy, amino, N-mono- or N,N-di-(Ci-\( C_7 \)-alkyl, phenyl-Ci-\( C_7 \)-alkyl and/or naphthyl-Ci-\( C_7 \)-alkyl)-amino, carboxy, Ci-\( C_7 \)-alkoxycarbonyl, phenyl-Ci-\( C_7 \)-alkoxycarbonyl, naphthyl-Ci-\( C_7 \)-alkoxycarbonyl, phenoxy carbonyl, naphthoxy carbonyl, Cl-\( C_{4,5} \)-alkylendioxy, carbamoyl, N-mono- or N,N-di-(Ci-\( C_7 \)-alkyl and/or phenyl-Ci-\( C_7 \)-alkyl)-carbamoyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-Ci-\( C_7 \)-alkyl-piperazin-1-carbonyl, morpholin-4-carbonyl, thiomorpholin-4-carbonyl, S-oxo-thiomorpholin-4-carbonyl, S,S-dioxothiomorpholin-4-carbonyl, sulfamoyl, N-mono- or N,N-di-(Ci-\( C_7 \)-alkyl and/or phenyl-Ci-\( C_7 \)-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-Ci-\( C_7 \)-alkyl-piperazinyl, 4-(phenyl-Ci-\( C_7 \)-alkyl)-piperazinyl, 4-(naphthyl-Ci-\( C_7 \)-alkyl)-piperazinyl, 4-(Ci-\( C_7 \)-alkoxy-carbonyl)-piperazinyl, 4-(phenyl-Ci-\( C_7 \)-alkoxycarbonyl)-piperazinyl, 4-(naphthyl-Ci-\( C_7 \)-alkoxy-carbonyl)-piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl.

An N-oxide derivative or pharmaceutically acceptable salt of each of the compounds of the formula I is also within the scope of this invention. For example, a nitrogen ring atom of the quinazole core or a nitrogen-containing heterocyclic (e.g. heteroaryl) substituent can form an N-oxide in the presence of a suitable oxidizing agent, e.g. a peroxide, such as m-chloroperoxy benzene acid or hydrogen peroxide.

Wherever a compound or compounds of the formula I are mentioned, this is further also intended to include N-oxides of such compounds, as well as tautomers of such compounds or N-oxides, also where not stated explicitly. Tautomerism may, for example, be present of the keto (or oxo/enol type, the imine/amine (e.g. imine/enamine) type, the lactim/lactame type or the like.

The term "an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof" especially means that a compound of the formula I may be present as such or in mixture with its N-oxide, as tautomer or in e.g. equilibrium reaction caused) mixture with its
tautomer, or as a salt of the compound of the formula I and/or any of these embodiments.

Compounds of the formula I can also be modified by appending appropriate functionalities to enhance selective biological properties. Modifications of this kind are known in the art and include those that increase penetration into a given biological system (e.g. blood, lymphatic system, central nervous system, testis), increase bioavailability, increase solubility to allow parenteral administration (e.g. injection, infusion), alter metabolism and/or alter the rate of secretion. Examples of this type of modifications include but are not limited to esterification, e.g. with polyethylene glycols, derivatisation with pivaloyloxy or fatty acid substituents, conversion to carbamates, hydroxylation of aromatic rings and heteroatom substitution in aromatic rings. Wherever compounds of the formula I, N-oxides and/or tautomers thereof are mentioned, this comprises such modified formulae, while preferably the molecules of the formula I, their N-oxides and/or their tautomers are meant.

In view of the close relationship between the novel compounds of the formula I in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the compounds or a compound of the formula I hereinbefore and hereinafter is to be understood as referring also to one or more salts, as appropriate and expedient, as well as to one or more solvates, e.g. hydrates.

Salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, malonic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-toluene sulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2- or 3-methylbenzenesulfonic acid, methylsulfuric acid,
ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In a preferred embodiment, the invention relates to a compound of the formula I wherein

R\(^1\) is hydrogen; or amino that is unsubstituted or monosubstituted with Ci-C\(^7\)-alkyl or C\(^3\)-C\(^8\) (preferably C\(^3\)-C\(^5\))-cycloalkyl;

R\(^2\) is unsubstituted or substituted aryl wherein aryl is selected from the group consisting of phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenlyl, phenalenyl, phenanthrenyl and anthracenyl, each of which is unsubstituted or substituted by one or more, preferably up to three, substituents independently selected from the group consisting of CrC\(^7\)-alkyl; C\(^2\)-C\(^7\)-alkenyl; C\(^2\)-C\(^7\)-alkyl; C\(^6\)-C\(^\alpha\)-aryl-C\(^1\)-C\(^7\)-alkyl in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenlyl, phenalenyl, phenanthrenyl or anthracenyl and is unsubstituted or substituted by CrC\(^7\)-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidine by pipazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C\(^1\)-C\(^7\)-alkylamino, by halo, by C\(^1\)-C\(^7\)-BkOXY, such as methoxy, and/or by halo-Ci-C\(^7\)-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), pipidinyl (especially piperidino), pipazinyl (especially piperazino), morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl or pyridazine)l-Ci-C\(^7\)-alkyl wherein pyrrolidinyl, pipidinyl, pipazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazine are unsubstituted or substituted by Ci-C\(^7\)-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pipazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-Ci-C\(^7\)-alkylamino, by halo, by d-C\(^7\)-alkoxy, such as methoxy, and/or by halo-Ci-C\(^7\)-alkyl, such as trifluoromethyl, for example pyrrolidino-C\(^1\)-C\(^7\)-alkyl, pipidinyl-C\(^1\)-C\(^7\)-alkyl, morpholino-C\(^1\)-C\(^7\)-alkyl, thiomorpholino-C\(^1\)-C\(^7\)-alkyl, N-Ci-C\(^7\)-alkyl-pipazinyl-Ci-C\(^7\)-alkyl, or N-mono- or N,N-di-(C\(^1\)+C\(^7\)-alkyl)-amino-substituted or unsubstituted pyrrolidino-Ci-C\(^7\)-alkyl; (pyrrolidinyl (especially pyrrolidino), pipidinyl (especially piperidino), pipazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazine)l-oxy-C\(^1\)-C\(^7\)-alkyl wherein pyrrolidinyl, pipidinyl, pipazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazine are unsubstituted or substituted by Ci-C\(^7\)-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pipazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C\(^7\)-alkylamino, by halo, by Ci-C\(^7\)-alkoxy, such as
methoxy, and/or by halo-C$_7$-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), piprazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-carbonyl-C$_7$-alkyl wherein pyrrolidinyl, piperidinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by d-C$_7$-alkoxy, such as methoxy, and/or by halo-C$_7$-alkyl, such as trifluoromethyl; halo-C$_7$-alkyl; hydroxy-C$_1$-C$_7$-alkyl; C$_1$-C$_7$-alkoxy-C$_1$-C$_7$-alkyl; C$_1$-C$_7$-alkoxy-C$_1$-C$_7$-alkyl; phenyloxy- or naphthoxy-C$_7$-alkyl; phenyl-C$_7$-alkoxy- or naphthyl-C$_7$-alkoxy-C$_7$-alkyl; amino-C$_7$-alkyl; N-mono- or N,N-di-(Cr$_7$-alkyl and/or mono-C$_7$-alkoxy-Cr$_7$-alkyl and/or (mono- or di-(Cr$_7$-alkyl)-amino-C$_7$-alkyl)-amino-C$_7$-alkyl; Ci-C$_7$-alkoxy-C$_1$-C$_7$-alkylamino-C$_1$-C$_7$-alkyl; mono- or di-[C$_6$-aryl-C$_1$-C$_7$-alkyl in which aryl is unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by Ci-C$_7$-alkoxy and/or by halo-C$_7$-alkyl; (pyrrolidinyl, piperidinyl, piprazinyl, pyrazinyl, morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-C$_1$-C$_7$-alkyl wherein pyrrolidinyl, piperidinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by Ci-C$_7$-alkoxy and/or by halo-C$_7$-alkyl; (pyrrolidinyl, piperidinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-C$_1$-C$_7$-alkyl wherein pyrrolidinyl, piperidinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by Ci-C$_7$-alkoxy and/or by halo-C$_7$-alkyl; (pyrrolidinyl, piperidinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-carbonyl-C$_1$-C$_7$-alkyl wherein pyrrolidinyl, piprazinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by Ci-C$_7$-alkoxy and/or by halo-C$_7$-alkyl; and/or (pyrrolidinyl, piperidinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-carbonyl-C$_1$-C$_7$-alkyl wherein pyrrolidinyl, piprazinyl, piprazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piprazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by Ci-C$_7$-alkoxy and/or by halo-C$_7$-alkyl; especially naphthyl- and/or phenyl-C$_1$-C$_7$-alkyl]-amino-C$_1$-C$_7$-alkyl; C$_1$-C$_7$-alkanoylamino-C$_1$-C$_7$-alkyl; carboxy-Ci-C$_7$-alkyl; benzoyl- or naphthoylamino-Ci-C$_7$-alkyl; Ci-C$_7$-alkylsulfonylamino-Ci-C$_7$-alkyl; phenyl- or naphthylsulfonylamino-Ci-C$_7$-alkyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, Ci-C$_7$-alkyl moieties, phenyl- or naphthyl-C$_1$-C$_7$-alkylsulfonylamino-C$_1$-C$_7$-alkyl, halo; hydroxy- C$_1$-C$_7$-alkoxy; C$_9$-aryl-C$_7$-alkoxy in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthlenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by Ci-C$_7$-alkyl, such as methyl or ethyl, by Ci-C$_7$-alkoxy, by
pyrrolidinyl, especially pyrrolidino, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by Ci-C<sub>7</sub>-alkoxy, such as methoxy, and/or by halo-Ci-C<sub>7</sub>-alkyl, such as trifluoromethyl; halo-Ci-C<sub>7</sub>-alkoxy; hydroxy-Ci-C<sub>7</sub>-alkoxy; CrC<sub>7</sub>-alkoxy-C<sub>1</sub>-C<sub>7</sub>-alkoxy; amino-C<sub>1</sub>-C<sub>7</sub>-alkoxy; N-C<sub>1</sub>-C<sub>7</sub>-alkanoylamino-C<sub>1</sub>-C<sub>7</sub>-alkoxy; N-unsubstituted-, N-mono- or N,N-di-(CrC<sub>7</sub>-alkyl)carbamoyl-Ci-C<sub>7</sub>-alkoxy; phenyl- or naphthyl- oxy; phenyl- or naphthyl-Ci-C<sub>7</sub>-alkoxy; (pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-Ci-C<sub>7</sub>-alkoxy wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by d-C<sub>7</sub>-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by Ci-C<sub>7</sub>-alkoxy and/or by halo-Ci-C<sub>7</sub>-alkyl; (pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-Ci-C<sub>7</sub>-alkoxy wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C<sub>7</sub>-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C<sub>7</sub>-alkylamino, by halo, by Ci-C<sub>7</sub>-alkoxy and/or by halo-Ci-C<sub>7</sub>-alkyl; Ci-C<sub>7</sub>-alkanoyloxy; benzylo- or naphthoxy; Ci-C<sub>7</sub>-alkylthio, halo-Ci-C<sub>7</sub>-alkylthio; Ci-C<sub>7</sub>-alkoxy-Ci-C<sub>7</sub>-alkylthio; phenyl- or naphthylthio; phenyl- or naphthyl-C<sub>1</sub>-C<sub>7</sub>-alkylthio; C<sub>1</sub>-C<sub>7</sub>-alkanoylthio; benzylo- or naphthylthio; nitro; amino; mono- or di-(Ci-C<sub>7</sub>-alkyl)-amino; mono- or di-(naphthyl- or phenyl-Ci-C<sub>7</sub>-alkyl)-amino; Ci-C<sub>7</sub>-alkanoylamino; benzylo- or naphthylamino; CrC<sub>7</sub>-alkylsulfonylamino; phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, Cr-C<sub>7</sub>-alkyl moieties; phenyl- or naphthyl-CrC<sub>7</sub>-alkylsulfonylamino; Ci-C<sub>7</sub>-alkanoyl; Ci-C<sub>7</sub>-alkoxy-Ci-C<sub>7</sub>-alkanoyl; carbonyl; Ci-C<sub>7</sub>-alkoxy-carbonyl; phenoxy- or naphthoxy carbonyl; phenyl- or naphthyl-Ci-C<sub>7</sub>-alkoxycarbonyl; C<sub>1</sub>-C<sub>7</sub>-o-, especially Ci-C<sub>4</sub>-alkylendioxy; carbamoyl; N-mono- or N,N-di-(Ci-C<sub>7</sub>-alkyl, naphthyl-CrC<sub>7</sub>-alkyl, pyrrolidinyl-CrC<sub>7</sub>-alkyl, piperidinyl -Ci-C<sub>7</sub>-alkyl, piperazinyl- or N-C<sub>1</sub>-C<sub>7</sub>-alkyl)-piperazinyl-Ci-C<sub>7</sub>-alkyl, phenyl-Ci-C<sub>7</sub>-alkyl, mono-Ci-C<sub>7</sub>-alkoxy-CrC<sub>7</sub>-alkyl and/or (N'-mono- or N,N'-di-(Ci-C<sub>7</sub>-alkyl)-amino-CrC<sub>7</sub>-alkyl)-amino-carbonyl; N-Ci-C<sub>7</sub>-alkoxy-CrC<sub>7</sub>-alkylcarbamoyl; pyrrolidin-1-carbonyl; amino-N-pyrrolidin-1-carbonyl; N-mono- or N,N-di(d-C<sub>7</sub>-alkyl)amino-pyrrolidin-1-carbonyl; piperidin-1-carbonyl; morpholin-4-carbonyl; thiomorpholin-4-carbonyl; S-oxo-thiomorpholin-4-carbonyl; S,S-dioxo-thiomorpholin-4-carbonyl; piperazin-1-carbonyl; N-Ci-C<sub>7</sub>-alkyl-piperazin-1-carbonyl; N-Ci-C<sub>7</sub>-alkoxycarbonyl-piperazin-1-carbonyl; N-mono- or N,N-di-(CrC<sub>7</sub>-alkyl)-amino-substituted or unsubstituted pyrrolidinyl-Ci-C<sub>7</sub>-alkyl; cyano; Ci-C<sub>7</sub>-alkenylene or -alkylene; Ci-C<sub>7</sub>-alkylsulfonyl; phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, Ci-C<sub>7</sub>-alkyl moieties; phenyl- or naphthyl-Ci-C<sub>7</sub>-alkylsulfonyl; sulfamoyl; N-mono or N,N-di-(Ci-C<sub>7</sub>-alkyl, phenyl-, naphthyl-, pyrrolidinyl(except
pyrrolidino)-C_7-alkyl, piperidinyl especially piperidino)-C_7-alkyl, piperazinyl especially piperazino)-C_7-alkyl, phenyl-C_7-alkyl- and/or naphthyl-C_7-alkyl)-aminosulfonyl; pyrazolyl; pyrazolidinyl; pyrrolyl; pyridyl that is unsubstituted or substituted by CrC_r-alkoxy, and/or by 1alo-C_r-C_r-alkyl, pyrrolidinyl; piperidinyl; morpholinyl; thiomorpholinyl; S-oxo-thiomorpholinyl; S,S-dioxothiomorpholinyl; piperazinyl; N-C_r-alkyl-piperazinyl; 4-(phenyl-C_r-alkyl)-piperazinyl; 4-(naphthyl-C_r-alkyl)-piperazinyl; 4-(Ci-C_r-alkoxycarbonyl)-piperazinyl; 4-(phenyl-C_r-C_r-alkoxycarbonyl)-piperazinyl and 4-(naphthyl-C_r-C_r-alkoxycarbonyl)-piperazinyl; or is unsubstituted or substituted heteroaryl where heteroaryl is selected from the group consisting of imidazolyl, thiophenyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyridazinyl, furyl, 2H- or 4H-pyranyl, oxazolyl, thiazolyl, 5H-indazolyl, isoindolyl, quinolyl, isoquinolinyl, phthalazinyl, 1,8-naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, indolizinyl, 4H-quinoliniziny, pteridinyl, purinyl, carbazolyl, beta-carbolinyl, acridinyl, phenanthridinyl, phenazine, 1,7-phenanthrolinyl, perimidinyl, benzofuranyl, isobenzofuranyl, 2H-chromenyl, 4aH-isochromenyl, thianthrenyl, xanthhenyl, phenoxathiinyl, phenoxazinyl or phenothiazinyl or preferably in an alternative embodiment - if R^1 is amino or amino monosubstituted with CrC_r (preferably C_4-alkyl or C_5-C_6 preferably C_5-C_6)-cycloalky, can also be pyrazolyl; each of which (= where each of the heteroaryl which are mentioned) is unsubstituted or substituted as mentioned above for aryl;

R^3 is hydrogen, halogen, Ci-C_r-alkyl, Ci-C_r-alkoxy or cyano;
R^4 is unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl, each independently selected from unsubstituted or substituted aryl as defined for R^2 and unsubstituted or substituted heteroaryl where heteroaryl is selected from the group consisting of imidazolyl, thiophenyl, pyrazolyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyridazinyl, furyl, 2H- or 4H-pyranyl, oxazolyl, thiazolyl, 5H-indazolyl, indolyl, soindolyl, quinolyl, isoquinolinyl, phthalazinyl, 1,8-naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, indolizinyl, 4H-quinoliniziny, pteridinyl, purinyl, carbazolyl, beta-carbolinyl, acridinyl, phenanthridinyl, phenazine, 1,7-phenanthrolinyl, perimidinyl, benzofuranyl, isobenzofuranyl, 2H-chromenyl, 4aH-isochromenyl, thianthrenyl, xanthhenyl, phenoxathiinyl, phenoxazinyl or phenothiazinyl, as defined for R^2; and
R^5 is hydrogen, methyl or methyl substituted with halogen;
or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof; as well as to its "use" as defined below.
In another preferred embodiment, the invention relates to a compound of the formula I wherein

R₁ is hydrogen, amino, N-alkylamino or C₃-C₅-cycloalkylamino,
R² is phenyl, naphthyl, pyrrolyl, thiophenyl, pyrazolyl, triazolyl, pyridyl, quinolyl or quinoxalinyl, or is pyrrolopyridinyl, especially H-pyrrolo[2,3-b]pyridin-5-yl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halo, hydroxy, Ci-C₇-alkoxy, Ci-C₇-alkoxy-Ci-C₇-alkoxy, amino, N-mono- or N,N-di-(CrC-alkyl), phenyl-CrC-alkyl and/or naphthyl-CrC-alkyl)-amino, carboxy, Ci-C₇-alkoxy-carbonyl, phenyl-Ci-C₇-alkoxy-carbonyl, naphthyl-Ci-C₇-alkoxy-carbonyl, phenoxy-carbonyl, naphthoxy-carbonyl, Ci-C₇-alkylendioxy, carbamoyl, N-mono- or N,N-di-(Ci-C₇-alkyl, . N',N'-di-(Ci-C₇-alkyl)amino-Ci-C₇-alkyl, pyrrolidino-Ci-C₇-alkyl and/or phenyl-Ci-C₇-alkyl)-carbamoyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-Ci-C₇-alkyl-piperazin-1-carbonyl, morpholin-4-carbonyl, thiomorpholin-4-carbonyl, S-oxothiomorpholin-4-carbonyl, S,S-dioxothiomorpholin-4-carbonyl, sulfamoyl, N-mono- or N,N-di-(Ci-C₇-alkyl, N',N'-di-(d-C₇-alkyl)amino-Ci-C₇-alkyl, pyrrolidino-Ci-C₇-alkyl and/or phenyl-Ci-C₇-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-Ci-C₇-alkyl-piperazinyl, 4-(phenyl-Ci-C₇-alkyl)-piperazinyl, 4-(naphthyl-Ci-C₇-alkyl)-piperazinyl, 4-(Ci-C₇-alkoxy-carbonyl)-piperazinyl, 4-(phenyl-Ci-C₇-alkoxy-carbonyl)-piperazinyl, 4-(naphthyl-Ci-C₇-alkoxy-carbonyl)-piperazinyl, morpholinyl, thiopiprolinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl, and/or from 2-amino-pyrimidin-5-yl-Ci-C₇-alkyl, 4-Ci-C₇-alkyl-piperazin-1-carbonyl-Ci-C₇-alkoxy, 4-pyrrolidinopiperazin-1-carbonyl-Ci-C₇-alkoxy, 4-pyrrolidinopiperidin-1-yl-Ci-C₇-alkoxy, 4-Ci-C₇-alkyl-piperazin-Ci-C₇-alkoxy, pyridin (e.g.: -2)-yloxy-Ci-C₇-alkoxy, pyrimidin(e.g.: -4)-yloxy-CrC₇-alkoxy, N,N-di(Ci-C₇-alkyl)amino-pyrrolidin-1-carbonyl and (unsubstituted or Ci-C₇-alkoxy- and/or halo-Ci-C₇-alkoxy-substituted pyridin(e.g.: -3))-yl; or alternatively or in addition selected from Ci-C₇-alkyl, halo-Ci-C₇-alkyl, such as trifluoromethyl, phenyl that is unsubstituted or substituted by one to three substituents independently selected from hydroxyl-Ci-C₇-alkyl, such as hydroxyl-methyl, d-C₇-alkoxy-Ci-C₇-alkyl, such as methoxymethyl, CrC₇-alkoxy, such as methoxy, amino and carbamoyl, Ci-C₇-alkanoylamino, such as acetylamino, cyano, 4-(Ci-C₇-alkanoyl)-piperazinyl, such as 4-acetyl-piperazin-1-yl, 4-(Ci-C₇-alkanesulfonyl)-piperazinyl, such as 4-methanesulfonyl-piperazin-1-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-azetidin-1-yl, 2-oxo-piperidin-1-yl and S-CrC₇-alkyl^-oxy-imidazolidin-i-yl, such as 3-methyl-2-oxo-imidazolidin-1-yl; 
R³ is hydrogen, or it is halo, preferably hydrogen;
R⁴ is phenyl, naphthyl, pyrrolyl, thiophenyl, triazolyl, pyridyl, quinoliny or quinoxalinyl, or is furanyl, such as furan-2-yl or 1H-pyrrolo[2,3-b]-pyridin-5-yl, (or, if R¹ is amino, N-CrC₄-
alkylamino or C₆-C₅-cycloalkylamino, can (preferably in an alternative embodiment) also (= in addition to the other moieties just mentioned) be pyrazolyl), each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halo, hydroxy, CrC alkyl, hydroxyl-C₆-alkyl, phenyl-C₆-alkyl and/or naphthyl-C₆-alkyl)-amino, carboxy, Ci-C₆-alkoxycarbonyl, phenyl-C₆-alkoxycarbonyl, naphthyl-C₆-alkoxycarbonyl, phenoxy carbonyl, naphthoxycarbonyl, CrC₆-alkylendioxy, carbamoyl, N-mono- or N,N-di-(C₆-alkyl), N,N-di-(C₆-alkyl)amino-C₆-alkyl, pyrrolidino-C₆-alkyl and/or phenyl-C₆-alkyl)-carbamoyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-Ci-C₆-alkyl-piperazin-1-carbonyl, morpholin-4-carbonyl, thiomorpholin-4-carbonyl, S-oxo-thiomorpholin-4-carbonyl, S,S-dioxothiomorpholin-4-carbonyl, sulfamoyl, N-mono- or N,N-di-(Ci-C₆-alkyl), N,N-di-(d-C₆-alkyl)amino-C₆-alkyl, pyrrolidino-C₆-alky and/or phenyl-C₆-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-Ci-C₆-alkyl-piperazinyl, 4-(phenyl-Ci-C₆-alkyl)-piperazinyl, 4-(naphthyl-Ci-C₆-alkyl)-piperazinyl, 4-(Ci-C₆-alkoxy-carbonyl)-piperazinyl, 4-(phenyl-Ci-C₆-alkoxy-carbonyl)piperazinyl, 4-(naphthyl-Ci-C₆-alkoxy-carbonyl)piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl, and/or from 2-amino-pyrimidin-5-yl-Ci-C₆-alkyl, 4-Ci-C₆-alkyl-piperazin-1-carbonyl-Ci-C₆-alkoxy, 4-pyrrolidino-piperidin-1-carbonyl-Ci-C₆-alkoxy, 4-pyrrolidino-piperidin-1-yl-Ci-C₆-alkoxy, 4-Ci-C₆-alkyl-piperazino-Ci-C₆-alkoxy, pyridin (e.g.-2)-yloxy-d-C₆-alkoxy, pyrimidin(e.g. -4)-yloxy-Ci-C₆-alkoxy, N,N-di(Ci-C₆-alkyl)amino-pyrrolidin-1-carbonyl and (unsubstituted or Ci-C₆-alkoxy- and/or halo-Ci-C₆-alkoxy-substituted pyridin(e.g. -3))-yl; or alternatively or in addition selected from the group consisting of halo-CrC alkyl, such as trifluoromethyl, amino-C₆-C₅-alkyl, such as aminomethyl, amino-C₆-C₅-alkyl, such as 3-amino propoxy or 2-aminoethoxy, phenyl-C₆-C₅-alkoxy, such as benzyloxy, Ci-C₆-alkanoyl, such as formyl and cyano; and R⁵ is hydrogen;
or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof; as well as to its "use" as defined below.

A more preferred embodiment of the invention relates to a compound of the formula I according to claim 1, wherein

R¹ is hydrogen, amino, methylamino, n-propylamino or cyclopropylamino;
R² is phenyl, 4-trifluoromethylphenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-ethoxy-3-methoxy-phenyl, 3,4-diethoxy-phenyl, 3-benzyllox-4-methoxyphenyl, 4-(2-methoxyethoxy)-3-methoxy-phenyl, 4-trifluormethoxyphenyl, 4-methoxy-3-trifluoromethoxyphenyl, 4-(3-tert-butoxycarbonylamino-propoxy)-3-methoxy-phenyl, 4-(2-tert-butoxycarbonylaminoethoxy)-3-methoxy-phenyl, 3,4,5-trimethoxyphenyl, 3-chloro-4-n-propoxy-phenyl, 4-acetylamino phenyl, 4-carboxy-3-methoxyphenyl, 4-methoxycarbonyl-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-cyanophenyl, 4-biphenyl, 4'-amino-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 4'-hydroxymethyl-biphenyl-4-yl, 4'-methoxymethyl-biphenyl-4-yl, 3',4'-dimethoxy-biphenyl-4-yl, 4'-carbamoyl-biphenyl-4-yl, 4-carbamoylphenyl, 4'-methoxy-4-carbamoylphenyl, 4-N-methylcarbamoyl-3-methoxyphenyl, 4-(N,N-dimethylcarbamoyl)-phenyl, 4-(N-methylcarbamoyl)-phenyl, 4-(N,N-dimethylcarbamoyl)-3-methoxy-phenyl, 4-(4-methylpiperazin-1-carbonyl)-3-methoxyphenyl, 4-(morpholin-4-carbonyl)-phenyl, 4-(4-morpholin-1-carbonyl)-3-methoxyphenyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 4-(piperazin-1-yl)-phenyl, 4-(2-oxo-pyrrolidin-1-yl)-phenyl, 4-(2-oxo-azetidin-1-yl)-phenyl, 4-(2-oxo-piperidin-1-yl)-phenyl, 4-(3-methyl-2-oxo-imidazolidin-1-yl)-phenyl, 4-methanesulfonyl-phenyl, 4-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoylphenyl, 4-pyrazol-phenyl, pyrrolyl, pyrazolyl, thiophenyl, especially thiophen-3-yl, 1,2,4-triazol-1-yl, 2-methoxy-pyridin-4-yl, 5-methoxy-pyridin-3-yl, 6-methoxy-pyridin-3-yl, 6-piperazino-pyridin-3-yl, 6-morpholin-4-yl-pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 4-[6-(4-methanesulfonyl)-piperazin-1-yl]-pyridin-3-yl, 5-(4-acetyl)piperazin-1-yl)-pyridin-3-yl or 2-[4-(tert-butoxycarbonyl)piperazin-1-yl]-pyridin-4-yl;

R³ is hydrogen,

R⁴ is 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-hydroxy-4-n-propoxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl, 3,4,5-trimethoxyphenyl, 3-ethoxy-4-methoxy-phenyl, 4-ethoxy-3-methoxyphenyl, 3-methoxy-4-(2-methoxy-ethoxy)-phenyl, 3-benzyllox-4-methoxyphenyl, 4-(3-aminoproxy)-3-methoxy-phenyl, 5-(3-aminoproxy)-3-methoxyphenyl, 4-(2-aminoethoxy)-3-methoxy-phenyl, 5-(2-aminoethoxy)-3-methoxy-phenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-n-propoxyphenyl, 4-(3-tert-butoxycarbonylamino-propoxy)-3-methoxy-phenyl, 4-(2-tert-butoxycarbonylaminoethoxy)-3-methoxy-phenyl, 4-formyl-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 3-carbamoyl-phenyl, 4-carbamoylphenyl, 4-carbamoyl-3-methoxy-phenyl, 3-sulfamoyl-phenyl, N,N-dimethyl-aminosulfonlyphenyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 6-
aminomethyl-pyridin-3-yl, pyridine-3-yl, 6-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3-yl, 2-methoxy-pyridin-4-yl, 2-amino-pyridin-4-yl, 6-amino-pyridin-3-yl, 6-amino-5-trifluoromethylpyridin-3-yl, 6-dimethylamino-pyridin-3-yl, 6-methylamino-pyridin-3-yl, 6-isobutylamino-pyridin-3-yl, 6-(2-methoxyethylamino)-pyridin-3-yl, 6-(piperazin-1-yl)-pyridin-3-yl, 6-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-3-yl, 2-(piperazin-1-yl)-pyridin-4-yl, 6-carbamoyl-pyridin-3-yl, 2-cyano-pyridin-5-yl, 5-cyano-pyridin-3-yl, 6-(2-hydroxyethyl-amino)-pyridin-3-yl, 2-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-4-yl, 6-morpholin-4-yl-pyridin-3-yl, furan-2-yl, furan-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, or quinolin-3-yl and

R^5 is hydrogen,
or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

A yet more preferred embodiment of the invention relates to a compound of the formula I wherein
R^1 is hydrogen, amino, methylamino, n-propylamino or cyclopropylamino;
R^2 is phenyl, 4-(2-amino-pyrimidin-5-ylmethyl)-phenyl, 3-(2-methoxy-6-trifluoromethyl)pyridin-3-yl-phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3-chloro-4-n-propoxy-phenyl, 4-carboxy-3-methoxyphenyl, 4-(2-pyridin-2-ylxyethoxy)-phenyl, 4-(2-pyrimidin-4-ylxyethoxy)-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-carbamoylphenyl, 4-N-methylcarbamoyl-3-methoxyphenyl, 4-(N,N-dimethyl-carbamoyl)-3-methoxy-phenyl, 4-(4-methylpiperazin-1-carbonyl)-3-methoxyphenyl, 4-(4-morpholin-1-carbonyl)-3-methoxyphenyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 4-[2-(4-pyrrolidino-piperidin-1-yl)-ethoxy]-phenyl, 4-(piperazin-1-yl)-phenyl, 4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl, 4-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-phenyl, 4-(4-methyl-piperazin-1-carbonylmethoxy)-phenyl, 4-(4-ethyl-piperazin-1-carbonylmethoxy)-phenyl, 4-(4-pyrrolidino-piperidin-1-carbonylmethoxy)-phenyl, 4-[N-(2-diethylaminoethyl)-N-methylcarbamoyl]-phenyl, 4-{[R, S or R,S)-3-dietilamino-pyrrolidin-1-carbonyl]-phenyl, 4-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoyl-phenyl, 4-[N-methyl-N-2-(pyrrolidino-ethyl)-sulfamoyl]-phenyl, 4-pyrazolyl-phenyl, pyrrolyl, pyrazolyl, thiophenyl, 1,2,4-triazol-1-yl, 6-methoxy-pyridin-3-yl or 6-piperazino-pyridin-3-yl;
R^3 is hydrogen,
R^4 is 4-(2-amino-pyrimidin-5-ylmethyl)-phenyl, 3-(2-methoxy-6-trifluoromethyl)pyridin-3-yl-phenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-hydroxy-4-n-
propoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 4-ethoxy-3-methoxyphenyl, 3-(2-methoxy-ethoxy)-4-methoxyphenyl, 3-methoxy-4-(2-methoxy-ethoxy)-phenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-n-propoxyphenyl, 4-(2-pyridin-2-yloxyethoxy)-phenyl, 4-(2-pyrimidin-4-yloxyethoxy)-phenyl, 4-[2-(4-pyrrolidino-piperidin-1 -yl)-ethoxy]-phenyl, 4-[2-(4-methyl-piperazin-1 -yl)-ethoxy]-phenyl, 4-[2-(4-ethyl-piperazin-1 -yl)-ethoxy]-phenyl, 4-(4-methyl-piperazin-1 -carbonylmethoxy)-phenyl, 4-(4-ethyl-piperazin-1 -carbonylmethoxy)-phenyl, 4-(4-pyrrolidino-piperidin-1 -carbonylmethoxy)-phenyl, 4-[(R,S)-3-diethylamino-pyrrolidin-1-carbonyl]-phenyl, 4-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoylphenyl, 4-[N-methyl-N-2-(pyrrolidino-ethyl)-sulfamoyl]-phenyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, pyridine-3-yl, 6-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3-yl, 2-amino-pyridin-4-yl, 6-amino-pyridin-3-yl, 6-(piperazin-1-yl)-pyridin-3-yl, 6-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-3-yl, 2-(piperazin-1-yl)-pyridin-4-yl or 2-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-4-yl, and

R⁵ is hydrogen, or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof; as well as to its "use" as defined below.

Another more preferred embodiment of the invention relates to a compound of the formula I, wherein

R¹ is hydrogen, amino, methylamino, n-propylamino or cyclopropylamino;

R² is phenyl, 4-(2-amino-pyrimidin-5-ylmethyl)-phenyl, 3-(2-methoxy-6-trifluoromethyl)pyridin-3-yl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3-chloro-4-n-propoxy-phenyl, 4-carboxy-3-methoxyphenyl, 4-(2-pyridin-2-yloxyethoxy)-phenyl, 4-(2-pyrimidin-4-yloxyethoxy)-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-(4-methyl-piperazine-1-carbonyl)-3-methoxyphenyl, 4-(N,N-dimethyl-carbamoyl)-3-methoxyphenyl, 4-(4-methyl-piperazine-1-carbonyl)-3-methoxyphenyl, 4-(4-ethyl-piperazine-1-carbonyl)-3-methoxyphenyl, 4-(4-pyrrolidino-piperidin-1-carbonyl)-3-methoxyphenyl, 4-(2,3-dihydro-benzo[1,4]dioxin-6-yl), 4-[2-(4-pyrrolidino-piperidin-1-yl)-ethoxy]-phenyl, 4-(piperazin-1-yl)-phenyl, 4-(2-(4-ethyl-piperazine-1-yl)-ethoxy)-phenyl, 4-(2-(4-methyl-piperazine-1-yl)-ethoxy)-phenyl, 4-(4-ethyl-piperazine-1-carbonylmethoxy)-phenyl, 4-(4-pyrrolidino-piperidin-1-carbonylmethoxy)-phenyl, 4-(N-(2-dimethylamino-ethyl)-N-methyl-carbamoyl]-phenyl, 4-[(R,S)-3-diethylamino-pyrrolidin-1-carbonyl]-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-carbamoylphenyl, 4-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoylphenyl, 4-[N-methyl-N-2-(pyrrolidino-ethyl)-
sulfamoyl]-phenyl, 4-pyrazolyl-phenyl, pyrrolyl, pyrazolyl, thiophenyl, 1,2,4-triazol-1-yl, 6-methoxy-pyridin-3-yl, or 6-piperazino-pyridin-3-yl; 
R³ is hydrogen, 
R⁴ is 4-(2-amino-pyrimidin-5-ylmethyl)-phenyl, 3-(2-methoxy-6-trifluoromethyl)pyridin-3-yl-phenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-hydroxy-4-n-propoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 4-ethoxy-3-methoxyphenyl, 3-(2-methoxy-ethoxy)-4-methoxyphenyl, 3-methoxy-4-(2-methoxy-ethoxy)-phenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-n-propoxyphenyl, 4-(2-pyridin-2-yl)-oxyethoxy)-phenyl, 4-(2-pyrimidin-4-yl)-oxyethoxy)-phenyl, 4-[2-(4-pyrrolidino-piperidin-1-yl)-ethoxy]-phenyl, 4-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-phenyl, 4-(4-methyl-piperazin-1-yl)-carbonylmetoxy)-phenyl, 4-(4-ethyl-piperazin-1-yl)-carbonylmetoxy)-phenyl, 4-(4-pyrrolidino-piperidin-1-yl)-carbonylmetoxy)-phenyl, 4-[N-(2-dimethylamino-ethyl)-N-methylcarbamoyl]-phenyl, 4-[(R, S or R,S)-3-diethylamino-pyridin-1-carbonyl]-phenyl, 4-methoxy-carbonyl-3-methoxyphenyl, 4-carbamoylphenyl, N,N-dimethylamino-sulfonylphenyl, 4-[N-methyl-N-2-(pyrrolidino-ethyl)-sulfamoyl]-phenyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, pyridine-3-yl, 6-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3-yl, 2-amino-pyridin-4-yl, 6-amino-pyridin-3-yl, 6-(piperazin-1-yl)- pyridin-3-yl, 6-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-3-yl, 2-(piperazin-1-yl)-pyridin-4- yl or 2-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-4-yl, and 
R⁵ is hydrogen, 
or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

Especially preferred is a compound of the formula I as given in the Examples, as well as a way of its synthesis described therein, or a tautomer thereof or an N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof; as well as its "use" as defined below.

Very preferred are also embodiment of the invention represented in the claims which are therefore incorporated by reference herein.

Surprisingly, it has now been found that the compounds of formula I have advantageous pharmacological properties and inhibit the activity of the lipid kinases, such as the PI3-kinase and/or members of the PI3-kinase-related protein kinase family (also called PIKK and include
DNA-PK, ATM, ATR, hSMG-1 and mTOR), such as the DNA protein-kinase, and may be used to treat disease or disorders which depend on the activity of said kinases.

The phosphatidylinositol-3'-OH kinase (PI3K) pathway is one of the central signaling pathways that exerts its effect on numerous cellular functions including cell cycle progression, proliferation, motility, metabolism and survival. An activation of receptor tyrosine kinases causes PI3K to phosphorylate phosphatidylinositol-(4,5)-diphosphate, resulting in membrane-bound phosphatidylinositol-(3,4,5)-triphosphate. The latter promotes the transfer of a variety of protein kinases from the cytoplasm to the plasma membrane by binding of phosphatidylinositol-(3,4,5)-triphosphate to the pleckstrin-homology (PH) domain of the kinase. Kinases that are key downstream targets of PI3K include phosphoinositide-dependent kinase 1 (PDK1) and AKT (also known as Protein Kinase B). Phosphorylation of such kinases then allows for the activation or deactivation of numerous other pathways, involving mediators such as GSK3, mTOR, PRAS40, FKHD, NF-κB, BAD, Caspase-9, and the like. An important negative feedback mechanism for the PI3K pathway is PTEN, a phosphatase that catalyses the dephosphorylation of phosphatidylinositol-(3,4,5)-triphosphate to phosphorylate phosphatidylinositol-(4,5)-diphosphate. In more than 60% of all solid tumors, PTEN is mutated into an inactive form, permitting a constitutive activation of the PI3K pathway. As most cancers are solid tumors, such an observation provides evidence that a targeting of PI3K itself or individual downstream kinases in the PI3K pathway provide a promising approach to mitigate or even abolish the dysregulation in many cancers and thus restore normal cell function and behaviour. This, however, does not exclude that other mechanisms may be responsible for the beneficial effects of PI3K activity modifying agents such as those in the present invention.

Having regard to their inhibitory effect on phosphatidylinositol 3-kinase enzymes, compounds of formula (I) in free or pharmaceutically acceptable salt form, are useful in the treatment of conditions which are mediated by the activation (including normal activity or especially overactivity) of one or more of the members of the PI3 kinase family, especially PI3 kinase enzyme, such as proliferative, inflammatory or allergic conditions, obstructive airways diseases and/or disorders commonly occurring in connection with transplantation.

"Treatment" in accordance with the invention may be therapeutic, e.g. symptomatic, or prophylactic. Preferred is the treatment of warm-blooded animals, especially humans.
Preferred is a compound of formula I for use or the use thereof in the treatment of a proliferative disease selected from a benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, lymphomas, a mammary carcinoma or a leukemia. Other diseases include Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated.

Compounds according to the invention are also of use in the treatment of inflammatory or obstructive airways (respiratory tract) diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, e.g. mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome").

Prophylactic efficacy in the treatment of asthma can be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.
Compounds of the formula I can be of use for other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable and include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy.

The invention also to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoïd bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of the invention are also of use in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it affects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequent or concomitant to Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Compounds of the invention are also of use in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Compounds of the invention may also be used for the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca,
and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Furthermore, the invention provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof for the preparation of a medicament for the treatment of a proliferative disease, an inflammatory disease, an obstructive respiratory disease, or a disorder commonly occurring in connection with transplantation.

The invention especially relates to the use of a compound of the formula I (or a pharmaceutical formulation comprising a compound of the formula I) in the treatment of one or more of the diseases mentioned above and below where the disease(s) respond or responds (in a beneficial way, e.g. by partial or complete removal of one or more of its symptoms up to complete cure or remission) to an inhibition of one or more kinases of the PI3-kinase-related protein kinase family, most especially PI3 kinase (PI3K), especially where the kinase shows (in the context of other regulatory mechanisms) inadequately high or more preferably higher than normal (e.g. constitutive) activity.

Wherever the term "use" or "used" is mentioned, this is intended to include a compound of the formula I for use in the prophylactic and/or therapeutic treatment of a disease of a warm-blooded animal, especially a human, preferably of one or more diseases mentioned above or below, a method of use or a method of treatment comprising administering a compound of the formula I to a person in need of such treatment in an effective amount for the prophylactic and/or therapeutic treatment of a disease as mentioned above and below, the preparation or
a method or preparation of a pharmaceutical formulation/preparation for use in the prophylactic and therapeutic treatment of a disease mentioned above and below, especially involving mixing a compound of the formula I (as therapeutically active ingredient) with at least one pharmaceutically acceptable carrier material, including making it ready for use in such treatment (e.g. adding an instruction insert (e.g. package leaflet or the like), formulation, appropriate preparation, adaptation for specific uses, customizing and the like), and the use of a compound of the formula I for such preparation, and/or all other prophylactic or therapeutic uses mentioned hereinbefore or below. All these aspects are embodiments of the present invention.

The efficacy of the compounds of formula I and salts thereof as PI3 kinase inhibitors can be demonstrated as follows:

The kinase reaction is performed in a final volume of 50 µL per well of a half area COSTAR, 96 well plate. The final concentrations of ATP and phosphatidyl inositol in the assay are 5 µM and 6 µg/mL respectively. The reaction is started by the addition of PI3 kinase p110β. The components of the assay are added per well as follows:

- 10 µL test compound in 5% DMSO per well in columns 2-1.
- Total activity is determined by addition 10 µL of 5% vol/vol DMSO in the first 4 wells of column 1 and the last 4 wells of column 12.
- The background is determined by addition of 10 µM control compound to the last 4 wells of column 1 and the first 4 wells of column 12.
- 2 ml. 'Assay mix' are prepared per plate:
  - 1.912 ml. of HEPES assay buffer
  - 8.33 µL of 3 mM stock of ATP giving a final concentration of 5 µM per well
  - 1 µL of [33P]ATP on the activity date giving 0.05 µCi per well
  - 30 µL of 1 mg/mL PI stock giving a final concentration of 6 µg/mL per well
  - 5 µL of 1 M stock MgCl₂ giving a final concentration of 1 mM per well
- 20 µL of the assay mix are added per well.
- 2 mL 'Enzyme mix' are prepared per plate (x µL PI3 kinase p110β in 2 mL of kinase buffer). The 'Enzyme mix' is kept on ice during addition to the assay plates.
- 20 µL 'Enzyme mix' are added/well to start the reaction.
• The plate is then incubated at room temperature for 90 minutes.
• The reaction is terminated by the addition of 50 µl WGA-SPA bead (wheat germ agglutinin-coated Scintillation Proximity Assay beads) suspension per well.
• The assay plate was sealed using TopSeal-S (heat seal for polystyrene microplates, PerkinElmer LAS (Deutschland) GmbH, Rodgau, Germany) and incubated at room temperature for at least 60 minutes.
• The assay plate was then centrifuged at 1500 rpm for 2 minutes using the Jouan bench top centrifuge (Jouan Inc., Nantes, France).
• The assay plate was counted using a Packard TopCount, each well being counted for 20 seconds.

* The volume of enzyme is dependent on the enzymatic activity of the batch in use.

Some of the compounds show a certain level of selectivity against the different paralogs PI3K alpha, beta, gamma and delta.

Description of biochemical assay for DNA-PK:

The assay is conducted using the kit V7870 from Promega (SignaTECT® DNA-Dependent Protein Kinase Syste, comprises DNA-PK, biotinylated peptide substrate end further ingredients, Promega, Madison, Wisconsin, USA), that quantitates DNA-dependent protein kinase activity, both in purified enzyme preparations and in cell nuclear extracts. DNA-PK is a nuclear serine/threonine protein kinase that requires double-stranded DNA (dsDNA) for activity. The binding of dsDNA to the enzyme results in the formation of the active enzyme and also brings the substrate closer to the enzyme, allowing the phosphorylation reaction to proceed.

DNA-PK X5 reaction buffer (250 mM HEPES, 500 mM KCl, 50 mM MgCl₂, 1 mM EGTA, 0.5 mM EDTA, 5 mM DTT, pH to 7.5 with KOH) is diluted 1/5 in deionised water and BSA (stock = 10 mg/ml) is added to a final concentration of 0.1 mg/ml.

The activation buffer is made from 100 µg/ml of calf thymus DNA in control buffer (10 mM Tris-HCl (pH 7.4), 1 mM EDTA (pH 8.0)). Per tube, the reaction mix is composed of: 2.5 µl of activation or control buffers, 5 µl of X5 reaction buffer, 2.5 µl of p53-derived biotinylated
peptide substrate (stock= 4mM), 0.2 µl of BSA (stock at 10 mg/ml) and 5 µl of [γ-32P] ATP (5 µl of 0.5 mM cold ATP + 0.05 µl of Redivue [γ-32P] ATP = Amersham AA0068-250 µCi, 3000Ci/mmol, 10 µCi/µl (now GE Healthcare Biosciences AB, Uppsala, Sweden).

The DNA-PK enzyme (Promega V5811, concentration 00 U/µL) is diluted 1/10 in x1 reaction buffer and kept on ice until imminent use. 10.8 µl of the diluted enzyme is incubated with 1.2 µl of 100 µM compounds (diluted 1/100 in water from 10 mM stock in neat DMSO) for 10 minutes, at room temperature. During that time, 15.2 µl of the reaction mix is added to screw-capped tubes, behind Perspex glass. 9.8 µl of the enzyme is then transferred to the tubes containing the reaction mix and after 5 minutes incubation, at 30°C, the reaction is stopped by adding 12.5 µl of termination buffer (7.5 M guanidine hydrochloride).

After mixing well, a 10 µl aliquot of each tube is spotted onto a SAM2® biotin capture membrane (Promega, Madison, Wisconsin, USA), which is left to dry for a few minutes. The membrane is then washed extensively to remove the excess free [γ-32P] ATP and nonbiotinylated proteins: once for 30 seconds in 200 ml of 2M NaCl, 3 times for 2 minutes each in 200 ml of 2M NaCl, 4 times for 2 minutes each in 2M NaCl in 1% H3PO4 and twice for 30 seconds each in 100 ml of deionised water. The membrane is subsequently left to air-dry at room temperature for 30-60 minutes.

Each membrane square is separated using forceps and scissors and placed into a scintillation vial, after which 8 ml of scintillation liquid (Flo-Scint 6013547 from Perkin-Elmer) is added. The amount of 32P incorporated into the DNA-PK biotinylated peptide substrate is then determined by liquid scintillation counting. In this test system, compounds of the formula I can be shown to have IC50values in the range from 1 nM to 50 µM, e.g. from 1 nM to 10 µM.

The efficacy of the compounds of the invention in blocking the activation of the PI3K/PKB pathway can be demonstrated in cellular settings as follows:

Protocol for the detection of phospho-PKB in U87MG cells by Elisa:
U87MG cells (human glioblastoma, ATCC No. HTB-14) are trypsinized, counted in a CASY cell counter (Scharff systems, Gottingen, Germany), diluted in fresh complete DMEM high glucose medium to load ,per well ,150µl cell suspension containing 4x10⁴ cells, and test plates incubated for 18 hours. In parallel, 50 µl of coating antibody, at the desired concentration in PBS/O is loaded in each well of the ELISA plates, and plates are kept for 2 h at room temperature. This ELISA assays is performed in black flat-bottom 96-well plates
(Microtest™, Falcon Becton-Dickinson, Ref: 353941) sealed with Plate Sealers (Costar-Corning, Ref: 3095). Medium in plates is discarded and replaced by complete DMEM high glucose medium containing either 0.1% DMSO or 0.1% inhibitor at titters (7) between 10 nM and 0.156 mM in DMSO. After 30 minutes of contact, the medium is quickly removed by aspiration, plates are then placed on ice and immediately cells are lysed with 70 µL of Lysis buffer. In parallel, the 96 wells plates prepared with the coating antibody (1/250 diluted (in PBS/O) Anti-Akt1 C-20, goat, Santa-Cruz-1618, Santa Cruz Biotechnology, Inc., Santa Cruz, California, USA) are washed 3 times 1 min with PBS/O containing 0.05% Tween 20 and 0.1% Top-Block® (derivative of gelatine that blocks unspecific binding sites on surfaces; Sigma-Aldrich, Fluka, Buchs, Switzerland, Ref.: 37766), and remaining protein binding sites blocked to prevent non-specific interactions with 200 µL of PBS containing 3% Top Block®, for 2 h at room temperature. Well content is replaced with 50 µL of samples from treated cells, and plates are incubated for 3 h at 4°C. The ELISA assays are always done in parallel with the following controls, in 6 replicates: U87MG (untreated control) or Lysis buffer alone (LB). After 3 x 15 minutes washes, all wells received 50 µL of the secondary antibody (1/250 diluted (in 3% top block) Anti-S473P-PKB, rabbit, Cell Signaling-9271, Cell Signaling Technologies, Inc., Danvers, Massachusetts, USA), and are incubated for 16 h at 4°C. After three washes, plates are incubated with the third and conjugated antibody (1/1000 diluted (in 3% top block) anti rabbit (HRP) Jackson Immuno Research 111-035-144) for 2 hours at room temperature. Finally, the immune-complexes are washed 2 times 15 seconds with PBS/O/tween20/top block ,1 time with 200µl of water and finally 200µl of water are left in each test well before a for 45 min incubation in darkness. The plates are then assayed with (SuperSignal® ELISA pico Chemiluminescent substrate, Pierce, Ref: 27070, Pierce Biotechnology, Inc., Rockford, Illinois, USA). 100 µL of substrate are added, and plates shacked for 1 min. The luminescence is read immediately on a Top-Count NXT (Packard Bioscience) luminometer. Using this test system, IC₅₀ values in the range from 5 µM to 1 nM, more preferably from 1.5 µM to 5 nM, can be found for compounds of the formula

There are also experiments to demonstrate the antitumor activity of compounds of the formula (I) in vivo.

For example, female Harlan (Indianapolis, Indiana, USA) athymic nu/nu mice with s.c. transplanted human glioblastoms U87MG tumors can be used to determine the anti-tumor activity of PI3 kinase inhibitors. On day 0, with the animals under peroral Forene® (1-chloro-
2,2,2-trifluoroethyldifluormethylether, Abbot, Wiesbaden, Germany) narcosis, a tumor fragment of approximately 25 mg is placed under the skin on the animals' left flank and the small incised wound is closed by means of suture clips. When tumors reach a volume of 100 mm³, the mice are divided at random into groups of 6-8 animals and treatment commences. The treatment is carried out for a 2-3 weeks period with peroral, intravenous or intra-peritoneal administration once daily (or less frequently) of a compound of formula (I) in a suitable vehicle at defined doses. The tumors are measured twice a week with a slide gauge and the volume of the tumors is calculated.

As an alternative to cell line U87MG, other cell lines may also be used in the same manner, for example,

- the MDA-MB 468 breast adenocarcinoma cell line (ATCC No. HTB 132; see also In Vitro 14, 911-15 [1978]);
- the MDA-MB 231 breast carcinoma cell line (ATCC No. HTB-26; see also In Vitro 12, 331 [1976]);
- the MDA-MB 453 breast carcinoma cell line (ATCC No-HTB-131);
- the Colo 205 colon carcinoma cell line (ATCC No. CCL 222; see also Cancer Res. 38, 1345-55 [1978]);
- the DU145 prostate carcinoma cell line DU 145 (ATCC No. HTB 81; see also Cancer Res. 37, 4049-58 [1978]),
- the PC-3 prostate carcinoma cell line PC-3 (especially preferred; ATCC No. CRL 1435; see also Cancer Res. 40, 524-34 [1980]) and the PC-3M prostate carcinoma cell line;
- the A549 human lung adenocarcinoma (ATCC No. CCL 185; see also Int. J. Cancer 17, 62-70 [1976]),
- the NCI-H596 cell line (ATCC No. HTB 178; see also Science 246, 491-4 [1989]);
- the pancreatic cancer cell line SUIT-2 (see Tomioka et al., Cancer Res. 61_, 7518-24 [2001]).

Compounds of the invention exhibit T cell inhibiting activity. More particular the compounds of the invention prevent T cell activation and/or proliferation in e.g. aqueous solution, e.g. as demonstrated in accordance with the following test method. The two-way MLR is performed according to standard procedures (J. Immunol. Methods, 1973, 2, 279 and Meo T. et al., Immunological Methods, New York, Academic Press, 1979, 227-39). Briefly, spleen cells
from CBA and BALB/c mice (1.6 x 10^5 cells from each strain per well in flat bottom tissue culture microtiter plates, 3.2 x 10^5 in total) are incubated in RPMI medium containing 10% FCS, 100 U/ml penicillin, 100 µg/ml streptomycin (Gibco BRL, Basel, Switzerland), 50 µM 2-mercaptoethanol (Fluka, Buchs, Switzerland) and serially diluted compounds. Seven three-fold dilution steps in duplicates per test compound are performed. After four days of incubation 1 µCi 3H-thymidine is added. Cells are harvested after an additional five-hour incubation period, and incorporated 3H-thymidine is determined according to standard procedures. Background values (low control) of the MLR are the proliferation of BALB/c cells alone. Low controls are subtracted from all values. High controls without any sample are taken as 100% proliferation. Percent inhibition by the samples is calculated, and the concentrations required for 50% inhibition (IC_{50} values) are determined. In this assay, the compounds of the invention have IC_{50} values in the range of 1 nM to 5 µM, preferably from 5 nM to 500 nM.

A compound of the formula (I) may also be used to advantage in combination with other antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylamino(geldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-1 7-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (TEMODAL®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array PioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer, leucovorin, EDG binders, antileukemia compounds, ribonucleotide reductase inhibitors, S-adenosylmethionine decarboxylase inhibitors, antiproliferative antibodies or other chemotherapeutic compounds. Further, alternatively or in addition they may be used in com-
bination with other tumor treatment approaches, including surgery, ionizing radiation, photodynamic therapy, implants, e.g. with corticosteroids, hormones, or they may be used as radiosensitizers. Also, in anti-inflammatory and/or antiproliferative treatment, combination with anti-inflammatory drugs is included. Combination is also possible with antihistamine drug substances, bronchodilatory drugs, NSAID or antagonists of chemokine receptors.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in
the form as it is marketed, e.g. under the trademark ZOLADEX. Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophyllotoxines etoposide and teniposide. Etoposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark ETOPOPHER. Teniposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark VM 26- BRISTOL. Doxorubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark FARMORUBICIN. Idarubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g. in the form as it is marketed, e.g. under the trademark NOVANTRON.

The term "microtubule active compound" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochinine and epothilones and derivatives thereof, e.g. epothilone B or D or derivatives thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P.. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099. Also included are Epothilone derivatives which are disclosed in WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

The term "alkylating compound" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN.
lfosfamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially N-hydroxy-3-{4-[(2-hydroxyethyl)][2-(1 H-indol-3-yl)ethyl]-amino[methyl][phenyl]-2E-2-propenamide, N-hydroxy-3-{4-[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino[methyl][phenyl]-2E-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR.

The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity"; or a "protein or lipid phosphatase activity"; or "further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101, SU6668 and GFB-1 11;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599 or such as OSI906, or antibodies that target the extracellular domain of IGF-I receptor such as CP-
d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, e.g. imatinib;

h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g. imatinib;

i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825)

j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safinogol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor);

k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin.
A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzyldenedmalonitrile class or the S-aryldenedmalonitrile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-[[2,5-dihydroxyphenyl)methyl]amino]-benzoic acid adamantyl ester; NSC 680410, adaphostin);

l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as EP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541 ; and

m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g. okadaic acid or a derivative thereof.
Compounds which induce cell differentiation processes are e.g. retinoic acid, α-γ- or δ-tocopherol or α-γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylamino phenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylamino phenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates" as used herein includes, but is not limited to, etidronic, clodronic, tiludronic, pamidronic, alendronic, risedronic and zoledronic acid.

"Etidronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID. "Pamidronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

The term "biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.
The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. Bortezomib (Velcade™) and MLN 341.

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuranosylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, midostaurin, a staurosporine derivative, SU1 1248 and MLN518.

The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.
For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065, in particular, \( N \)-hydroxy-3-[4-[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and \( N \)-hydroxy-3-[4-[[2-hydroxyethyl][2-(1/-/-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

Somatostatin receptor antagonists as used herein refers to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230 (pasireotide). Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

The term "EDG binders" as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1/-/-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., Acta Oncologica, Vol. 33, No. 8, pp. 953-961 (1994).
The term "S-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is
not limited to the compounds disclosed in US 5,461,076.
Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF
disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a
pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495,
WO 00/27820, WO 00/59509, WO 98/1,1223, WO 00/27819 and EP 0 769 947; those as
described by Prewett et al, Cancer Res, Vol. 59, pp. 5209-5218 (1999); Yuan et al., Proc Natl
Acad Sci USA, Vol. 93, pp. 14765-14770 (1996); Zhu et al., Cancer Res, Vol. 58, pp. 3209-
3214 (1998); and Mordenti et al., Toxicol Pathol, Vol. 27, No. 1, pp. 14-21 (1999); in WO
00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., Cell, Vol. 79, pp.
315-328 (1994); ENDOSTATIN, described by O'Reilly et al., Cell, Vol. 88, pp. 277-285
(1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-
VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF
aptamer e.g. Macugen; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGl antibody,
Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

Photodynamic therapy as used herein refers to therapy which uses certain chemicals known
as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic
therapy includes treatment with compounds, such as e.g. VISUDYNE and porfimer sodium.
Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis,
such as, e.g., anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone,
17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and
dexamethasone.
Implants containing corticosteroids refers to compounds, such as e.g. fluocinolone,
dexamethasone.

"Other chemotherapeutic compounds" include, but are not limited to, plant alkaloids,
hormonal compounds and antagonists; biological response modifiers, preferably
lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA
or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of
action.

The compounds of the invention are also useful as co-therapeutic compounds for use in
combination with other drug substances such as anti-inflammatory, bronchodilatory or
antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445, WO 03/072592, non-steroidal glucocorticoid receptor agonists such as those described in WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195, WO 04/005229; LTB4 antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 and those described in US 5451700; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; A2a agonists such as those disclosed in EP 409595A2, EP 1052264, EP 1241176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO 04/039766, WO 04/045618 and WO 04/046083; A2b antagonists such as those
described in WO 02/42298; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula

![Chemical Structure](image)

and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula I of WO 04/16601, and also compounds of WO 04/033412.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424021, US 5171744, US 3714357, WO 03/33495 and WO 04/018422.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratadine, desloratadine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine as well as those disclosed in WO 03/099807, WO 04/026841 and JP 2004107299.

Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-{[4-[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-3-yl]carbonylamino}phenylo-3-methyltetrahydro-N,N-dimethylH-pyran-3-aminium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

The structure of the active compounds identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).
The above-mentioned compounds, which can be used in combination with a compound of
the formula (I), can be prepared and administered as described in the art, such as in the
documents cited above.

By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of
parts for the combined administration where a compound of the formula (I) and a combination
partner may be administered independently at the same time or separately within time intervals
that especially allow that the combination partners show a cooperative, e.g. synergistic effect.

The invention also provides a pharmaceutical preparation, comprising a compound of formu-
la I as defined herein, or an N-oxide or a tautomer thereof, or a pharmaceutically acceptable
salt of such a compound, or a hydrate or solvate thereof, and at least one pharmaceutically
acceptable carrier.

A compound of formula I can be administered alone or in combination with one or more other
therapeutic compounds, possible combination therapy taking the form of fixed combinations
or the administration of a compound of the invention and one or more other therapeutic
(including prophylactic) compounds being staggered or given independently of one another,
or the combined administration of fixed combinations and one or more other therapeutic
compounds. A compound of formula I can besides or in addition be administered especially
for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy,
phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally
possible as is adjuvant therapy in the context of other treatment strategies, as described
above. Other possible treatments are therapy to maintain the patient's status after tumor
regression, or even chemopreventive therapy, for example in patients at risk.

The dosage of the active ingredient depends upon a variety of factors including type, spe-
cies, age, weight, sex and medical condition of the patient; the severity of the condition to be
treated; the route of administration; the renal and hepatic function of the patient; and the par-
ticular compound employed. A physician, clinician or veterinarian of ordinary skill can readily
determine and prescribe the effective amount of the drug required to prevent, counter or
arrest the progress of the condition. Optimal precision in achieving concentration of drug
within the range that yields efficacy requires a regimen based on the kinetics of the drug's
availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

The dose of a compound of the formula I or a pharmaceutically acceptable salt thereof to be administered to warm-blooded animals, for example humans of approximately 70 kg body weight, is preferably from approximately 3 mg to approximately 5 g, more preferably from approximately 10 mg to approximately 1.5 g per person per day, divided preferably into 1 to 3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

The compounds of the invention may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Topical administration is e.g. to the skin. A further form of topical administration is to the eye. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The invention relates also to pharmaceutical compositions comprising an effective amount, especially an amount effective in the treatment of one of the above-mentioned disorders, of a compound of formula I or an N-oxide or a tautomer thereof together with one or more pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parenteral administration and that may be inorganic or organic, solid or liquid. There can be used for oral administration especially tablets or gelatin capsules that comprise the active ingredient together with diluents, for example lactose, dextrose, mannitol, and/or glycerol, and/or lubricants and/or polyethylene glycol. Tablets may also comprise binders, for example magnesium aluminum silicate, starches, such as corn, wheat or rice starch, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorbents, dyes, flavorings and sweeteners. It is also possible to use the pharmacologically active compounds of the present invention in the form of parenterally administrable compositions or in the form of infusion solutions. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilisers, wetting compounds and/or emulsifiers, solubilisers, salts for
regulating the osmotic pressure and/or buffers. The present pharmaceutical compositions, which may, if desired, comprise other pharmacologically active substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes, and comprise approximately from 1% to 99%, especially from approximately 1% to approximately 20%, active ingredient(s).

Additionally, the present invention provides a compound of formula I or an N-oxide or a tautomer thereof, or a pharmaceutically acceptable salt of such a compound, for use in a method for the treatment of the human or animal body, especially for the treatment of a disease mentioned herein, most especially in a patient requiring such treatment.

The present invention also relates to the use of a compound of formula I or a tautomer thereof, or a pharmaceutically acceptable salt of such a compound, for the preparation of a medicament for the treatment of a proliferative disease, an inflammatory disease, or an obstructive airway disease, or disorders commonly occurring in connection with transplantation.

Furthermore, the invention relates to a method for the treatment of a proliferative disease which responds to an inhibition of lipid kinases and/or PI3-kinase-related protein kinases, in particular the PI3 kinase, and/or mTOR, and/or DNA protein kinase activity, which comprises administering a compound of formula I or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above, especially in a quantity effective against said disease, to a warm-blooded animal requiring such treatment.

Furthermore, the invention relates to a pharmaceutical composition for treatment of solid or liquid tumours in warm-blooded animals, including humans, comprising an antitumor effective dose of a compound of the formula I as described above or a pharmaceutically acceptable salt of such a compound together with a pharmaceutical carrier.

**Manufacturing Process:**

The invention relates also to a process for the manufacture of a compound of the formula I, an N-oxide thereof, a tautomer thereof and/or a salt thereof.

Compounds of the formula I can be prepared according to or in analogy to methods that, in principle and with other educts, intermediates and final products, are known in the art,
especially and according to the invention by a process comprising

a) for the manufacture of a compound of the formula I wherein \( R^4 \) is bound to the central quinazoline moiety in formula I via a carbon atom, reacting a compound of the formula NA,

\[
\text{halogen}^1
\]

\[
\begin{array}{c}
\text{halogen}^1 \\
\text{halogen}^2
\end{array}
\]

(IIA)

wherein \( R^1, R^2, R^3 \) and \( R^5 \) are as defined for a compound of the formula I and wherein halogen \(^1\) is halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, under cross-coupling conditions with a boronic acid or boronic acid ester of the formula III,

\[
R^4-D
\]

(III)

wherein \( R^4 \) is as defined for a compound of the formula I and is bound via a carbon atom to \( D \) and \( D \) is \(-\text{B(OH}_2\text{)}\) or a group of the formula A,

\[
\begin{array}{c}
\text{B} \\
\text{O} \\
\text{O}
\end{array}
\]

(A)

or

b) for the manufacture of a compound of the formula I wherein \( R^2 \) is bound to the central quinazoline moiety in formula I via a carbon atom, reacting a compound of the formula NB,
wherein \( R_1, R_3, R_4 \) and \( R_5 \) are as defined for a compound of the formula I and halogen\(^2\) is halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, under cross-coupling conditions with a boronic acid or boronic acid ester of the formula IV,

\[
R^2 \cdot D \quad \text{(IV)}
\]

wherein \( R^2 \) is as defined for a compound of the formula I and is bound via a carbon atom to \( D \) and \( D \) is \(-B(OH)_2\) or a group of the formula A given above; or

c) for the manufacture of a compound of the formula I wherein \( R^2 \) and \( R^4 \) are identical and are bound to the central quinazoline moiety in formula I via a carbon atom, reacting a compound of the formula NC,

\[
\text{(IIIC)}
\]

wherein \( R^1, R^3 \) and \( R^5 \) are as defined for a compound of the formula I and halogen\(^1\) and halogen\(^2\) are, independently of each other, halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, with a boronic acid or boronic acid ester of the formula V,

\[
R^{24} \cdot D \quad \text{(V)}
\]

wherein \( R^{24} \) is a moiety \( R^2 \) or \( R^4 \) bound via a carbon atom to \( D \) and is otherwise as defined for a compound of the formula I and \( D \) is \(-B(OH)_2\) or a group of the formula A given above; or

d) for the manufacture of a compound of the formula I wherein \( R^1 \) is amino, \( N\)-mono-d-Cio (preferably \( C_1-C_4 \))-alkyl-amino or \( N\)-mono-C\(_3\)-Ci\(_0\) (preferably \( C_3-C_5 \))~cycloalkylamino, reacting a compound of the formula ND.
wherein $R^2$, $R^3$, $R^4$, and $R^5$ are as defined for a compound of the formula I and wherein halogen* is haloo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, with an amine of the formula VI

$$R^1\cdot H$$

(VI)

wherein $R^1$ is amino, N-mono-C$_1$-C$_4$-alkyl-amino or N-mono-C$_3$-C$_{10}$ (preferably C$_3$-C$_5$)-cycloalkylamino;

or

e) for the manufacture of a compound of the formula I wherein $R^4$ is heteroaryl with at least one ring nitrogen and is bound to the central quinazoline moiety in formula I via a nitrogen atom, reacting a compound of the formula NA given above under a) with a compound of the formula VII,

$$R^4\cdot H$$

(VII)

wherein $R^{4\text{a}}$ is a nitrogen containing heteroaryl with at least one ring nitrogen and is bound to the hydrogen in formula VII via a nitrogen atom, under substitution conditions;

or

f) for the manufacture of a compound of the formula I wherein $R^2$ is heteroaryl with at least one ring nitrogen and is bound to the central quinazoline moiety in formula I via a nitrogen atom, reacting a compound of the formula NB given above under b) with a compound of the formula VIII,

$$R^2\cdot H$$

(VIII)
wherein \( R^6 \) is a nitrogen containing heteroaryl with at least one ring nitrogen and is bound to the hydrogen in formula VIII via a nitrogen atom, under substitution conditions; or

g) for the manufacture of a compound of the formula I wherein \( R^2 \) and \( R^4 \) are identical and are heteroaryl with at least one ring nitrogen and each of them is bound to the central quinazoline moiety in formula I via a nitrogen atom, reacting a compound of the formula IX,

\[
R^{2,4*}:\text{H} \quad \text{(IX)}
\]

wherein \( \textit{R}^{2,4*} \) is heteroaryl with at least one nitrogen atom and wherein \( \textit{R}^{24*} \) is a moiety \( \textit{R}^2 \) or \( \textit{R}^4 \) bound via a nitrogen atom to the hydrogen shown in formula IX and is otherwise as defined for a compound of the formula I, under substitution conditions with a compound of the formula N\( \textit{C} \) mentioned above; or

h) for the manufacture of a compound of the formula I wherein \( \textit{R}^4 \) is bound to the central quinazoline moiety in formula I via a carbon atom, reacting a boronic acid or boronic acid ester compound of the formula N\( \textit{A}^* \),

![Diagram](IIA*)

wherein \( \textit{R}^1, \textit{R}^2, \textit{R}^3 \) and \( \textit{R}^5 \) are as defined for a compound of the formula I and wherein \( \textit{D} \) is \( -\text{B(OH}_2 \) or a group of the formula A,

![Diagram](A)

under cross coupling conditions with compound of the formula III*,

\[
\textit{R}^4-\text{Hal} \quad \text{(III*)}
\]
wherein R⁴ is as defined for a compound of the formula I and is bound via a carbon atom to Hal and Hal is halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy;

where in any of the reactions represented under a) to h) functional groups in the starting materials can be present in protected form and in the obtainable compounds of the formula I carrying one or more protecting groups such protecting groups are removed;

and, if desired, a compound of the formula I obtainable according to a process variant selected from a) to g) is converted into a different compound of the formula I, an obtainable salt of a compound of the formula I is converted into a different salt thereof, an obtainable free compound of the formula I is converted into a salt thereof, and/or an obtainable isomer of a compound of the formula I is separated from one or more different obtainable isomers of the formula I.

Examples for preferred Reaction Conditions

In the following more detailed description of the processes, optional reactions and conversions, synthesis of starting materials and intermediates and the like, R¹, R², R³, R⁴ and R⁵ have the meanings given for a compound of the formula I or the compound mentioned specifically, while D is as defined for a compound of the formula (A), halogen¹ as for a compound of the formula NA, halogen² as for a compound of the formula NB, R²⁴ as for a compound of the formula IV, R¹⁰ as for a compound of the formula V, R⁴⁴ as for a compound of the formula VI, R² as for a compound of the formula VII, R²⁴ as for a compound of the formula VIII, Hal as for compound III°, in each case if not indicated otherwise, respectively.

Where useful or required, the reactions can take place under an inert gas, such as nitrogen or argon.

The reaction given under process variants a), b), c) and h), respectively, is preferably carried out under the conditions of a Suzuki-reaction, preferably in a mixture of a polar aprotic solvent, such as dimethylformamide (DMF) and water in the presence of a catalyst for the cross-coupling, especially a noble metal catalyst, preferably a palladium catalyst, such as palladium(II) complex, for example bis(triphenylphosphine)palladium (II) dichloride, in the presence of a base, such as potassium carbonate, sodium hydroxide or sodium
carbonate, at a preferred temperature in the range from 80 °C to 130 °C; or according to a another preferred method in a cyclic ether solvent, e.g. tetrahydrofuran, in the presence of a catalyst for the cross coupling, especially a noble metal catalyst, preferably a palladium (0) complex, for example tris(dibenzyldieneacetone)-dipalladium(0), in the presence of an appropriate ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos), at a preferred temperature in the range from 80 to 150 °C; if required conducting the reaction in a sealed vessel (e.g. a seal reactor) if the boiling point of the reaction mixture is exceeded and especially if (as is a preferred embodiment) the heating is effected by microwave excitation.

The reaction conditions for process variants d), e), f) and g) (substitution) are preferably chosen from customary conditions of a nucleophilic aromatic substitution, e.g. carrying out the reaction, preferably in a sealed vessel (e.g. a seal reaction), in a polar solvent, such as an alcohol, e.g. ethanol, or an aprotic solvent, such as 1-methyl-2-pyrrolidone, preferably at a temperature in the range from 120 to 180 °C; preferably, the energy for heating is provided by microwave excitation.

Protecting groups
If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a starting material, e.g. in any one or more starting materials of the formula NA, NA^+, NB, NC, ND, III, III^+ IV, V, VI, VII, VIII or IX, because they should not take part in the reaction or disturb the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars. Protecting groups are such groups that are no longer present in the final compounds once they are removed, while groups that remain as substitutents are not protecting groups in the sense used here which is groups that are added at a certain intermediate stage and removed to obtain a final compound. For example, tert-butoxy if remaining in a compound of the formula I is a substituent, while if it is removed to obtain the final compound of the formula I it is a protecting group.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by acetylation, protonolysis, solvolysis, reduction, photolysis or also
by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and below.


Optional Reactions and Conversions
A compound of the formula I may be converted into a different compounds of the formula I.

For example, in a compound of the formula I wherein the substituent R¹, R² or R⁴ comprises an esterified carboxy group, such as C⁰-C₇-alkoxycarbonyl, this esterified carboxy group may be hydrolysed to give the corresponding free carboxy group, e.g. in the presence of a base, such as an alkali metal hydroxide, e.g. lithium hydroxide, in an appropriate solvent, e.g. a cyclic ether, such as dioxane, water or a mixture thereof, e.g. at temperatures in the range from 0 to 50 °C.

In a compound of the formula I wherein the substituent R¹, R² or R⁴ comprises free carboxy group (e.g. obtainable by a preceding step as described in the last paragraph), this free carboxy group may be converted into a corresponding carbamoyl or N-mono or N,N-di-substituted carbamoyl group, e.g. by reaction with ammonia, N-mono- or N,N-di-(CrC₇-alkyl and/or phenyl-C₁-C₇-alkyl)-amine, piperidine, piperazine, 4-C₁-C₇-alkyl-piperazine, morpholine, thiomorpholine, S-oxo-thiomorpholine or S,S-dioxothiomorpholine; the reaction preferably takes place with the carboxy group in active form, more preferably under customary condensation conditions, where among the possible reactive derivatives of a carboxy group
reactive esters (such as the hydroxybenzotriazole (HOBT), pentafluorophenyl, 4-nitrophenyl or N-hydroxsuccinimide ester), acid halogenides (such as the acid chloride or bromide) or reactive anhydrides (such as mixed anhydrides with lower alkanoic acids or symmetric anhydrides) are preferred. Reactive carboxylic acid derivatives can preferably be formed in situ. The reaction is carried out by dissolving the corresponding compounds of the formula I carrying one or more carboxy substituents in a suitable solvent, for example a halogenated hydrocarbon, such as methylene chloride, \( \Lambda,\Lambda\)-dimethylformamide, \( \Lambda,\Lambda\)-dimethylacetamide, \( \Lambda\)-methyl-2-pyrrolidone, 4-(N,N-dimethylamino)-pyridine or acetonitrile, or a mixture of two or more such solvents, and by the addition of a suitable base, for example triethylamine, diisopropylethylamine (DIPEA) or \( \Lambda\)-methylmorpholine and, if the reactive derivative of the carboxyl substituent(s) is formed in situ, a suitable coupling agent that forms a preferred reactive derivative of the carboxyl group in situ, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBT); bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCI); O-(1,2-dihydro-2-oxo-1-pyridyl)-\( \Lambda,\Lambda,\Lambda,\Lambda\)-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU); (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), 0-(1 H-6-chlorobenzotriazole-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole (EDC/HOBT or EDC/HOAt) or HOAt alone, or with (1-chloro-2-methyl-propenyl)-dimethylamine. For review of some other possible coupling agents, see e.g. Klauser, Bodansky, *Synthesis* (1972), 453-463. The reaction mixture is preferably stirred at a temperature of between approximately -20 and 50 °C, especially between 0 °C and 30 °C, e.g. at room temperature.

A nitrogen ring atom of the quinazoline core or a nitrogen-containing heterocyclic (e.g. heteroaryl) substituent can form an N-oxide in the presence of a suitable oxidizing agent, e.g. a peroxide, such as m-chloro-perbenzoic acid or hydrogen peroxide.

Other reactions can be carried out as described, or in analogy to those mentioned, in the Examples.

Also in the optional process steps, carried out "if desired", functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove under "protecting groups". The protecting groups are then wholly or partly removed.
according to one of the methods described there.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known *per se*. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of formula I) may also be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from 130 to 170°C, one molecule of the acid being expelled per molecule of a compound of formula I.

Salts can usually be converted to free compounds, e.g. by treating with suitable basic compounds, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known *per se* by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates (and are thus useful in the preparation of corresponding starting materials).

**Starting materials:**

The starting materials of the formulae NA, NA⁻, NB, NC, ND, III, III⁺, IV, V, VI, VII, VIII or IX, as well as other starting materials mentioned herein, e.g. below, can be prepared according to or in analogy to methods that are known in the art, are known in the art and/or are commercially available. Novel starting materials, as well as processes for the preparation thereof, are likewise an embodiment of the present invention. In the preferred
embodiments, such starting materials are used and the reaction chosen are selected so as to enable the preferred compounds to be obtained.

For example, a compound of the formula $NA$, $NB$ or $NC$ (wherein the latter $R^1$ is amino or mono- or disubstituted amino as described for $R^1$ above) can be prepared from a compound of the formula $X$,

![Chemical structure](image)

wherein $R^3$ and $R^5$ are as defined under formula I and halogen$^1$, halogen$^2$ and halogen$^3$ are independently selected from halo, especially chloro, bromo or iodo, and from trifluoromethan-sulfonyloxy, by reacting it, in order to introduce C-bonded aryl or heteroaryl moieties, with a compound of formula III or IV in a cross-coupling (e.g. Suzuki) reaction, respectively, under preferred conditions as described above for the reaction variants a), b) or c) involving halogen$^1$ or halogen$^2$, respectively, or for the introduction of N-bound aryl or heteroaryl with a compound of the formula VII, VIII or IX or in the case of a compound of the formula $NC$ with a compound of the formula VI, in order to introduce the corresponding moiety $R^1$ other than hydrogen, in a nucleophilic aromatic substitution involving halogen$^1$, halogen$^2$ or halogen$^3$, respectively, in each case preferably under the reaction described as preferred for reaction variants e), f), g) or d) mentioned above, respectively; which can take place in a sequential manner with the regio-selectivity being controlled by the reactivity of the respective halogen according to the used reaction conditions. The nature of halogen$^1$, halogen$^2$ and halogen$^3$ are chosen such as to allow a certain level of selectivity for the given reaction to be performed with the chosen conditions, preferentially as described for the synthesis of a compound of the formula $NA$, $NB$ or $ND$. Two sequential Suzuki-reactions (as well as nucleophilic amination reactions) can be performed independently or in one-pot without isolation of the first reaction product.

For example, a compound of formula $NA$ or $NB$, wherein $R^1$ is hydrogen and $R^3$ and $R^5$ have the meanings as given under formula I, can be prepared from compound of the formula $XI$,
(which is also a compound of the formula NC wherein \( R^1 \) is hydrogen which thus can be obtained as illustrated below for the compound of the formula XI) wherein \( R^5 \) is as defined for a compound of the formula I and halogen \(^1\) and halogen \(^2\) are as defined for a compound of the formula X, by reacting with compound of formula III or IV, respectively, in a cross-coupling (preferably Suzuki) reaction involving halogen \(^1\) and halogen \(^2\), as described above under process variants a) or b), respectively, or with a compound of the formula VII or VIII under substitution conditions, preferably conditions as described under process variants e) and f) mentioned above.

A compound of the formula X or XI, wherein \( R^3 \) and \( R^5 \) have the meanings as given under formula I, is prepared by hydroxyl to halogeno exchange with suitable halogenation reagent, such as phosphoroxychloride, in the absence or presence of an appropriate tertiary nitrogen base, e.g. diethylamide, at preferred temperatures between 100°C and 140°C from the tautomeric carbonyl precursor of formula XII or XIII, respectively:

Alternatively, introduction of \( R^4 \) substituent by cross-coupling (preferably Suzuki-) reaction with a compound of the formula III mentioned above (preferably under reaction conditions as
described under process variants a) above) or nucleophilic substitution with a compound of the formula VII mentioned above (preferably under reaction conditions as described for process variant e) mentioned above) is carried out on an intermediate of the formula XII or XIII, followed by activation of the carbonyl intermediate to the halo intermediate, respectively, of formula XIV,

![Chemical Structure](XIV)

wherein $R^3, R^4$ and $R^5$ have the meanings as given under formula I and $Y$ is halogen or H.

This, if $Y$ is hydrogen, is also an intermediate of the formula NB wherein $R^1$ is hydrogen.

From the compound of the formula XIV, if $Y$ is halogen, a starting material of the formula ND wherein halogen $^3$ is halo is obtainable by cross-coupling (preferably under Suzuki conditions as described above for process variant b) it with a compound of the formula IV mentioned above or by nucleophilic substitution with a compound of the formula VIII (preferably under process conditions as described for process variant f) above) is accessible. The corresponding trifluoromethansulfonyl halogen $^3$ can be obtained from this compound by nucleophilic substitution or by other methods.

The bicyclic intermediates of the formulae XII and XIII can be obtained from the anthranilic type derivative of formula XV,

![Chemical Structure](XV)

wherein $R^3$ and $R^5$ have the meanings as given under formula I, using neat urea (that is, a melt in urea) at a temperature between 130°C and 160°C or neat formamide at a preferred temperature between 130°C and 180°C.
An anthranilic intermediate of the formula XVI,

\[
\begin{align*}
R^4 & \quad \text{carboxylic acid} \\
R^5 & \quad \text{amine}
\end{align*}
\]  

(XVI)

can be converted in the same manner to a compound of the formula XIV, and substituent \( R^4 \) is introduced prior to formation of the bicycle using a cross-coupling reaction with a compound of the formula III given above (specially Suzuki-reaction under conditions as for process variant a) described above) or nucleophilic substitution with a compound of the formula VII given above, especially under reaction conditions as described above for process variant e).

A compound of the formula \( \text{N} \) wherein \( R^1 \) is amino, N-mono-Ci-Ci \(_0\) (preferably Ci-Ci)\(_4\)-alkylamino or N-mono-Ci-Ci \(_0\) (preferably Cii-Ci)\(_3\)-cyloalkylamino as defined for a compound of the formula I can be obtained from a compound of the formula X given above by nucleophilic replacement with a compound of the formula VI wherein \( R^{11} \) is as defined under process variant d) and preferably the reaction conditions described for it.

Compounds of the formula \( \text{NA}^+ \) can be prepared from corresponding compounds of the formula \( \text{NA} \) by replacing halogen \(^1\) with the boronic or boronic ester group under conditions known in the art.

All remaining starting materials such as starting materials of the formula XII and III \(^*\) are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using processes as described or in analogy to those described in the Examples.

The following Examples serve to illustrate the invention without limiting its scope.

Temperatures are measured in degrees Celsius (°C). Unless otherwise indicated, the reactions take place at room temperature (rt).

Ratios of solvents (e.g. in eluents or solvent mixtures) are given in volume by volume (v/v).
HPLC linear gradient between A = H₂O/TFA 1000:1 and B = acetonitrile/TFA 1000:1
Grad 1: 2-100 % Bin 4.5 min and 1 min at 100 % B; column: Chromolith Performance 100 mm x 4.5 mm (Merck, Darmstadt, Germany); flow rate 2 ml/min. Detection at 215 nM.

The following further abbreviations are used:

Ac acetyl
brine (at rt) saturated sodium chloride solution
Celite Celite®, filtering aid based on diatomaceous earth (Celite Corp., Lompoc, USA)
DMA N,N-dimethylacetamide
DMAP 4-dimethylaminopyridine
ES-MS Electrospray Mass Spectrometry
Et ethyl
HPLC High Performance Liquid Chromatography
Isolute Isolute® (Biotage AB, Uppsala, Sweden)
JACS Journal of the American Chemical Society
LC-MS Liquid Chromatography-Mass Spectrometry
Me methyl
min minute(s)
NMP 1-methyl-2-pyrrolidone
NMR Nuclear Magnetic Resonance
Phe phenyl
PrOH n-propanol
RP-MPLC Reversed-Phase Medium-Pressure Liquid Chromatography
TFA trifluoroacetic acid
SPhos 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
THF tetrahydrofuran
TPTU O-(1',2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate
tret retention time

Example 1
4-(3,4-Dimethoxy-phenyl)-6-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline
113 mg (0.214 mmol) of 4-{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 1a) and 2 ml of TFA-H₂O (19:1) are stirred for 20 min. After this time, the reaction mixture is purified by preparative HPLC (H₂O-CH₃CN and 0.1 % TFA). The pure fractions are basified with NaHCO₃, concentrated and extracted with EtOAc (2x). The organic layers are washed with brine, dried over Na₂SO₄, filtered and evaporated to provide the title compound as a yellow solid. ES-MS: 428 (M+H)⁺; analytical HPLC: tᵣₑₐₗ = 52 min (Grad 1).

The starting materials are prepared as follows:

**Example 1a**

^[S^-S^-Dimethoxy-phenyO-quinazolin- 6-yll-pyridin^-y^-piperazine-i-carboxylic acid tert-butyl ester] (which is also a compound of the formula I according to the invention)

To 105 mg (0.41 mmol) of 6-bromo-4-chloro-quinazoline (Example 1c), 18 mg (0.025 mmol) of bis(triphenylphosphine)palladium (II) dichloride (Fluka, Buchs, Switzerland) and 75 mg (0.41 mmol) of 3,4-dimethoxyphenylboronic acid (Frontier Scientific, Logan, USA; B1) in 4 ml DMF under argon, 1 ml of a 1 M aqueous solution of K₂CO₃ is added. The mixture is
stirred for 20 min at 105°C (oil bath). LC-MS confirms the formation of desired intermediate 6-bromo-4-(3,4-dimethoxy-phenyl)-quinazoline (Example 1b). Then 192 mg (0.492) of 4-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-piperazine-1-carboxylic acid tert-butyl ester (CB Research & Development, New Castle, USA; B2), 18 mg (0.025 mmol) of bis(triphenylphosphine)palladium (II) dichloride and 1 ml of a 1 M aqueous solution of K₂CO₃ are added. The reaction mixture is stirred for 1.5 h at 105°C under argon. After this time, the mixture is quenched with sat. aqueous NaHCO₃ and extracted with EtOAc (2x). The organic layer is washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The residue is purified by flash chromatography (CH₂Cl₂-MeOH 1:0 to 24:1) to give the title compound as a yellow solid. ES-MS: 528 (M+H)+; analytical HPLC: t_ret. = 3.25 min (Grad 1).

**Example 1b**

6-Bromo-4-(3,4-dimethoxy-phenyl)-quinazoline

The intermediate compound in Example 1a can also be synthesized in a separate batch and then be subjected to the second (the Suzuki) reaction in the one-pot synthesis in Example 1a).

To 251 mg (1.03 mmol) of 6-bromo-4-chloro-quinazoline (Example 1c), 44 mg (0.062 mmol) of bis(triphenylphosphine)palladium (II) dichloride (Fluka, Buchs, Switzerland) and 187 mg (1.03 mmol) of 3,4-dimethoxyphenylboronic acid (B1) in 10 ml DMF under argon, 2.6 ml of a 1 M aqueous solution of K₂CO₃ is added. The mixture is stirred for 20 min at 105°C (oil bath). After this time, the reaction mixture is quenched with sat. aqueous NaHCO₃ and extracted with EtOAc (2x). The organic layers are washed with water and brine, are dried over Na₂SO₄, filtered and evaporated in vacuo. The residue is purified by flash chromatography (CH₂Cl₂-MeOH 1:0 to 49:1) to give the title compound as a yellow solid. ES-MS: 345, 347 (M+H)+, Br pattern; analytical HPLC: t_ret. = 3.63 min (Grad 1).
Example 1c

6-Bromo-4-chloro-quinazoline

![Chemical Structure](image)

A mixture of 0.5 g (2.2 mmol) of 6-bromo-3H-quinazolin-4-one (Example 1d), 0.7 ml (4.4 mmol) diethylamide and 4 ml POCl₃ is stirred for 3 h at 125°C. After this time, the reaction mixture is cooled to rt and dropped into icy water. The precipitate is filtered and dried in vacuo overnight to give the title compound as a violet solid. Analytical HPLC: tᵣₑₐₚ = 3.51 min (Grad 1, partial hydrolysis in HPLC conditions); ¹H-NMR (CDCl₃): δ 9.08/s (1H), 8.46/d (1H), 8.06/dd (1H), 7.97/d (1H).

Example 1d


6-Bromo-3H-quinazolin-4-one

![Chemical Structure](image)

5 g (23 mmol) of 2-amino-5-bromobenzoic acid (Aldrich, Buchs, Switzerland) in 12 ml of formamide in a seal reactor are heated with microwave excitation for 1 h at 170°C. The reaction mixture is triturated with hot methanol and cooled at 4°C. The solid is filtered to give the title compound as an off-white solid. ES-MS: 225, 227 (M + H)⁺, Br pattern; analytical HPLC: tᵣₑₚ = 2.53 min (Grad 1).

Example 2

[4,6-Bis-(3,4-dimethoxy-phenyl)-quinazolin-2-yl]-n-propyl-amine
70 mg (0.16 mmol) of 2-chloro-4,6-bis-(3,4-dimethoxy-phenyl)-quinazoline (Example 2a) and 47 mg (0.80 mmol) of n-propylamine (Aldrich, Buchs, Switzerland; A1) in 0.4 ml NMP are heated in a seal reactor with microwave excitation for 10 min at 150°C. After this time, the reaction mixture is diluted with 4 ml water and the precipitate is filtered over Celite. The solid is washed with water, and the solid is then dissolved in CH₂Cl₂, washed with brine, dried over Na₂SO₄, filtered and evaporated. The crude product is purified by preparative HPLC (H₂O/CH₂CN and 3% n-propanol). The pure fractions are concentrated and extracted with CH₂Cl₂ (2x) to provide the title compound as a yellow solid. ES-MS: 460 (M + H)⁺; analytical HPLC: t_{ret}= 3.49 min (Grad 1).

The starting materials are prepared as follows:

**Example 2a**

2-Chloro-4,6-bis(3,4-dimethoxy-phenyl)-quinazoline
The title compound is obtained in a similar manner as in Example 1b starting from 2,4-dichloro-6-(3,4-dimethoxy-phenyl)-quinazoline (Example 2b); ES-MS: 437 (M + H)⁺, Cl pattern; analytical HPLC: \( t_{\text{ret}} = 3.99 \text{ min} \) (Grad 1).

**Example 2b**

2,4-Dichloro-6-(3,4-dimethoxy-phenyl)-quinazoline

![Chemical structure of 2,4-Dichloro-6-(3,4-dimethoxy-phenyl)-quinazoline](image)

1.81 g (6.1 mmol) of 6-(3,4-dimethoxy-phenyl)-1 H-quinazoline-2,4-dione (Example 2c) in 20 ml POCl₃ is stirred for 6.5 h at 125°C. The reaction mixture is evaporated to dryness and then treated with chilly sat. aqueous NaHCO₃. The precipitate is filtered. The solid is dissolved in CH₂Cl₂, washed with chilly water, dried over MgSO₄, filtered and evaporated. The solid is triturated in CH₂Cl₂ and filtered off (2x). The combined filtrates are evaporated to dryness to yield the title compound as a yellow solid. ES-MS: 335 (M + H)⁺, 2Cl pattern; analytical HPLC: \( t_{\text{ret}} = 4.03 \text{ min} \) (Grad 1).

**Example 2c**

6-(3,4-Dimethoxy-phenyl)-(7H, 3H)-quinazoline-2,4-dione

![Chemical structure of 6-(3,4-Dimethoxy-phenyl)-(7H, 3H)-quinazoline-2,4-dione](image)

The title compound is obtained in a similar manner as in Example 1b starting from 6-bromo-(7H,3H)-quinazoline-2,4-dione (Example 2d); ES-MS: 299 (M + H)⁺; analytical HPLC: \( t_{\text{ret}} = \)
2.73 min (Grad 1).

**Example 2d**
(following H. Liu et al., JACS 2004, 126, p.1108)

6-Bromo-(7H,3H>quinazoline-2,4-dione

![6-Bromo-(7H,3H>quinazoline-2,4-dione](image)

5 g (22.4 mmol) of 2-amino-5-bromobenzoic acid (Aldrich, Buchs, Switzerland) and 13.5 g (224 mmol) urea (Fluka, Buchs, Switzerland) are heated for 16 h at 150°C. The temperature is decreased to 100°C and one equivalent volume of water is added. The mixture is stirred 5 min and the resulting precipitate is filtered. The solid is trititated in glacial acetic acid, filtered and dried *in vacuo* to provide the title compound as an off-white solid. ES-MS: 241 (M + H)+, Br pattern; analytical HPLC: \( t_{R1} = 2.48 \) min (Grad 1).

**Example 3**

6-(6-Methoxy-pyridin-3-yl)-4-phenyl-quinazoline

![6-(6-Methoxy-pyridin-3-yl)-4-phenyl-quinazoline](image)

A mixture of 54 mg (0.20 mmol) of 4-chloro-6-(6-methoxy-pyridin-3-yl)-quinazoline (Example 3a), 36 mg (0.30 mmol) of phenylboronic acid (Fluka, Buchs, Switzerland, B3), 4.6 mg (0.008 mmol) of tris(dibenzylideneacetone)-dipalladium(0) (Across, Basel, Switzerland), 6.5 mg (0.016 mmol) SPhos (synthesized following T.E. Barder et al., JACS 2005, 127, p.4685) and 126 mg (0.595 mmol) \( \text{K}_3\text{PO}_4 \) in 2 ml THF under argon in a seal reactor is heated with microwave excitation at 110°C for 1 h. The reaction mixture is quenched with sat. aqueous
NaHCO₃ and extracted with EtOAc (2x). The organic layers are washed with brine, dried over Na₂SO₄, filtered and evaporated *in vacuo*. The residue is purified by flash chromatography (hexane-EtOAc 7:3 to 2:3) to give the title compound as a yellow solid. ES-MS: 314 (M + H)⁺; analytical HPLC: *t*ₚₑₓ= 3.74 min (Grad 1).

The starting materials are prepared as follows:

**Example 3a**

4-Chloro-6-(6-methoxy-pyridin-3-yl)-quazoline

![4-Chloro-6-(6-methoxy-pyridin-3-yl)-quazoline](image)

The title compound is obtained in a similar manner as in Example 2b starting from 6-(6-methoxy-pyridin-3-yl)-3H-quinazolin-4-one (Example 3b); ES-MS: 272 (M + H)⁺, Cl pattern; analytical HPLC: *t*ₚₑₓ= 3.51 min (Grad 1).

**Example 3b**

6-(6-Methoxy-pyridin-3-yl)-3H-quinazolin-4-one

![6-(6-Methoxy-pyridin-3-yl)-3H-quinazolin-4-one](image)

The title compound is obtained in a similar manner as in Example 1b starting from 6-bromo-3H-quinazolin-4-one (Example 1d) and 2-methoxy-5-pyridylboronic acid (Frontier Scientific, Logan, USA; B4); ES-MS: 254 (M + H)⁺; analytical HPLC: *t*ₚₑₓ= 2.50 min (Grad 1).
Example 4

3-[2-Amino-4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]phenol

The title compound is obtained in a similar manner as in Example 1b starting from 6-bromo4-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine (Example 4a) and 3-hydroxyphenylboronic acid (Aldrich, Buchs, Switzerland; B5); ES-MS: 374 (M + H)+; analytical HPLC: t\text{RT} = 2.88 min (Grad 1).

The starting materials are prepared as follows:

Example 4a

6-Bromo-4-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine

Two batches of 1.8 g (4.74 mmol) of 6-bromo-2-chloro-4-(3,4-dimethoxy-phenyl)-quinazoline (Example 4b) and 20 ml (40 mmol) of 2 M ammonia in EtOH (Aldrich, Buchs, Switzerland; A2)
are heated with microwave excitation in a seal reactor for 1 h at 170°C. The two batches are combined and evaporated to dryness. The residue is purified by flash chromatography (CH₂Cl₂-MeOH 1:0 to 97:3) to provide the title compound as a yellow solid. ES-MS: 360, 362 (M + H)+, Br pattern; analytical HPLC: t<sub>ret</sub> = 2.92 min (Grad 1).

**Example 4b**

6-Bromo-2-chloro-4-(3,4-dimethoxy-phenyl)-quinazoline

![Chemical Structure](image)

The title compound is obtained in a similar manner as in Example 1b starting from 6-bromo-2,4-dichloro-quinazoline (Example 4c); ES-MS: 374 (M + H)+; analytical HPLC: t<sub>ret</sub> = 2.88 min (GracM).

**Example 4c**

6-Bromo-2,4-dichloro-quinazoline

![Chemical Structure](image)

The title compound is obtained in a similar manner as in Example 1c starting from 6-bromo-1H-quinazoline-2,4-dione (Example 2d): analytical HPLC: t<sub>ret</sub> = 3.87 min (Grad 1).

Further commercially available boronic acids;
B6 4-hydroxyphenylboronic acid (Lancaster, Morecambe, UK);
B7 3-methoxyphenylboronic acid (Aldrich, Buchs, Switzerland);
B8 2-chlorophenylboronic acid (Aldrich, Buchs, Switzerland);
B9 4-methoxyphenylboronic acid (Aldrich, Buchs, Switzerland);
B10 2-thienylboronic acid (Aldrich, Buchs, Switzerland);
B11 4-((1 H-pyrazol-1-yl)phenyl)boronic acid (Anichem LLC, Monmouth Junction, USA);
B12 3-fluoro-4-methoxyphenylboronic acid (Aldrich, Buchs, Switzerland);
B13 3,4,5-trimethoxyphenylboronic acid (Aldrich, Buchs, Switzerland);
B14 S-methoxy^m-methoxycarbonylphenylboronic acid (Cuschem, Yonkers, USA);
B15 3,4-methylenedioxyphenylboronic acid (Aldrich, Buchs, Switzerland);
B16 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (Maybridge, Tintagel, UK);
B17 3-chloro-4-propoxyphenylboronic acid (Aldrich, Buchs, Switzerland);
B18 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Aldrich, Buchs, Switzerland);
B19 (4-aminocarbonylphenyl)boronic acid (Frontier Scientific, Logan, USA).
B20 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ylamine (Aldrich, Buchs, Switzerland)
B21 N,N-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide (Frontier Scientific, Logan, USA)
B22 2-methoxy-4-pyridylboronic acid (Combi-blocks, San Diego, USA)
B23 3-ethoxyphenylboronic acid (Aldrich, Buchs, Switzerland)
B24 3-chlorophenylboronic acid (Aldrich, Buchs, Switzerland)
B25 2-benzyloxy-1-methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzene (ABCR, Karlsruhe, Germany)
B26 4-methoxycarbonylphenylboronic acid (Aldrich, Buchs, Switzerland)
B27 3-quinoline boronic acid (Aros, Basel, Switzerland)
B28 5-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (Aldrich, Buchs, Switzerland)
B29 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide (Frontier Scientific, Logan, USA)
B30 2-benzyloxy-1-methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzene (ABCR, Karlsruhe, Germany)
B31 3-aminocarbonylphenylboronic acid (ABCR, Karlsruhe, Germany)
B32 4-chlorophenylboronic acid (Aldrich, Buchs, Switzerland)
B33 4-trifluoromethylphenylboronic acid (Aldrich, Buchs, Switzerland)
B34 3-chloro-4-methoxyphenylboronic acid (Aldrich, Buchs, Switzerland)
B35 3-thiopheneboronic acid (Aldrich, Buchs, Switzerland)
B36 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1 H-pyrrolo[2,3-b]pyridine (Alfa, Karlsruhe, Germany)
B37 furane-3-boronic acid (Aldrich, Buchs, Switzerland)
B38 4-cyanophenylboronic acid (Aldrich, Buchs, Switzerland)
B39 3-formyphenylboronic acid (Fluka, Buchs, Switzerland)
B40 4-biphenylboronic acid (Aldrich, Buchs, Switzerland)
B41 2-cyano-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (Frontier Scientific, Logan, USA)
B42 4-bromophenylboronic acid (Aldrich, Buchs, Switzerland)
B43 4-aminomethylphenylboronic acid, hydrochloride (Frontier Scientific, Logan, USA)
B44 4-hydroxymethylphenylboronic acid (Aldrich, Buchs, Switzerland)
B45 4-trifluoromethoxyphenylboronic acid (Aldrich, Buchs, Switzerland)
B46 4-fluorophenylboronic acid (Aldrich, Buchs, Switzerland)
B47 3-fluorophenylboronic acid (Aldrich, Buchs, Switzerland)
B48 3-methylsulfonylphenylboronic acid (Aldrich, Buchs, Switzerland)
B49 4-acetaminophenylboronic acid (Aldrich, Buchs, Switzerland)
B50 3-cyano-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine (Frontier Scientific, Logan, USA)
B51 1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]pyridine-2-yl)morpholine (Aldrich, Buchs, Switzerland)
B52 2-dimethylamino-pyridin-5-yl-boronic acid (Anichem, Monmouth Junction, USA)

Synthesized boronic acids:
The following boronic acids are synthesized according to standard etherification procedures using commercially available halo reagents:
B53 1-ethoxy-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]benzene using iodoethane (Fluka, Buchs, Switzerland)
B54  2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-4,4,5,5-tetramethyl-
[1,3,2]dioxaborolane using 2-bromoethyl methyl ether (Fluka, Buchs, Switzerland)

B55  [4-(3-tert-butoxycarbonylamino-propoxy)-3-methoxy-phenyl]-boronic
cacid using tert-butyl N-(3-bromopropyl)carbamate (Fluka, Buchs, Switzerland)

B56  [4-(2-tert-butoxycarbonylamino-ethoxy)-3-methoxy-phenyl]-boronic
cacid using tert-butyl N-(2-bromoethyl)carbamate (Fluka, Buchs, Switzerland)

The following boronic acid are prepared as follows:

B57  5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trifluoromethyl-pyridin-2-ylamine

8.04 g (31.7 mmol) of 5-Bromo-3-trifluoromethyl-pyridin-2-ylamine  (B57a), 10.5 g (41.2 mmol) of 4,4,5,5,4',4',5',4'-Octamethyl-[2,2']bi[(1,3,2)dioxaborolanyl]  (Aldrich, Buchs, Switzerland), 9.62 g (95.1 mmol) of KOAc in 100 ml dioxane are degassed with argon for 15 min. 776 mg (0.951 mmol) of bis(diphenylphosphino)ferrocene dichloror-palladium(II)dichloromethane are added and the mixture is degassed for 15 more minutes. The reaction mixture is heated at 115°C for 8 h. After that time, the reaction mixture is filtered and the solvent evaporated. The residue is purified by simple filtration on silicagel (solvent system: t-butyl-methyl ether-EtOAc-NEt₃ = 50:50:0.1) to yield the title compound as almost colorless solid. ES-MS 289 (M+H)⁺; analytical HPLC: tr = 1.68 min (Grad 1).

The starting material 5-Bromo-3-trifluoromethyl-pyridin-2-ylamine  (B57a) is prepared as follows:

To a solution of 5.37 g (32.8 mmol) of 3-trifluoromethyl-pyridin-2-ylamine  (Fluorochem, Derbyshire, UK) in 100 ml of dry CH3CN, 6.45 g of N-bromosuccinimide are added in 4 equal portions over a period of 1 h at 0-5°C under argon. The cooling bath is removed and stirring is continued for 3 h. The solvent is evaporated under vacuum, the residue is dissolved in EtOAc and washed with water and brine. The organic phase is dried over Na₂SO₄ and evaporated. The title compound is a reddish-yellow oil which is used after drying in the dark for 5 h at RT and under high vacuum in the next step without further purification. ES-MS: 241 (M-H)⁻.

B58  2-(3,4-diethoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound is synthesized in a similar manner as described in B57 starting with 3,4-diethoxybromobenzene  B58a: ES-MS: 293 (M + H)⁺; analytical HPLC: tr = 3.94 min (Grad 1).

The starting material 3,4-diethoxybromobenzene  (B58a) is prepared as follows:

The title compound is obtained according to standard etherification procedures using commercially available iodoethane (Fluka, Buchs, Switzerland) and 4-bromocatechol (ABCR,
Karlsruhe, Germany): analytical HPLC: \( t_{ret} = 3.79 \text{ min (Grad 1)} \).

**B59** 2-(3-trifluoromethoxy-4-methoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound is synthesized in a similar manner as **B58** starting from 4-bromo-2(trifluoromethoxy)phenol (Manchester, Runcorn, UK) and iodomethane (Fluka, Buchs, Switzerland): analytical HPLC: \( t_{ret} = 4.25 \text{ min (Grad 1)} \).

**B60** 2-isobutylamino-pyridin-5-ylboronic acid

The title compound is synthesized in a similar manner as **B57** starting from 5-bromo-2-isobutylamino-pyridine (**B60a**), the boronic pinacol ester being hydrolyzed during purification: ES-MS: 195 (M + H)^+; analytical HPLC: \( t_{ret} = 2.08 \text{ min (Grad 1)} \).

The starting material 5-bromo-2-isobutylamino-pyridine (**B60a**) is prepared as follows:

600 mg (3.12 mmol) of 5-bromo-2-chloropyridine (Aldrich, Buchs, Switzerland) in 3.13 ml (31.2 mmol) isobutylamine (Fluka, Buchs, Switzerland) is heated in a microwave oven for 2 h at 170°C. The reaction mixture is quenched with 50 ml water and extracted with EtOAc (2x). The combined organic layers are washed with water (5x), dried over Na₂SO₄, filtered and evaporated. The crude product is purified by flash chromatography (CH₂Cl₂) to give the title compound as a white solid. ES-MS: 229, 231 (M + H)^+, Br pattern; analytical HPLC: \( t_{ret} = 2.31 \text{ min (Grad 1)} \).

**B61** N-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl-amin

The title compound is synthesized in a similar manner as **B57** starting from 5-bromo-2-methylaminopyridine (**B61a**): ES-MS: 235 (M + H)^+; analytical HPLC: \( t_{ret} = 1.46 \text{ min (Grad 1)} \).

The starting material 5-bromo-2-methylaminopyridine (**B61a**) is prepared as follows:

The title compound is synthesized in a similar manner as **B60a** starting from A4: ES-MS: 187, 189 (M + H)^+, Br pattern; analytical HPLC: \( t_{ret} = 1.74 \text{ min (Grad 1)} \).

**B62** N-(2-hydroxyethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl-amine

The title compound is synthesized in a similar manner as **B57** starting from 2-(5-bromo-pyridin-2-ylamino)-ethanol (**B62a**): ES-MS: 265 (M + H)^+.

The starting material 2-(5-bromo-pyridin-2-ylamino)-ethanol (**B62a**) is prepared as follows:

The title compound is synthesized in a similar manner as **B60a** starting from A11: ES-MS: 217, 219 (M + H)^+, Br pattern; analytical HPLC: \( t_{ret} = 1.66 \text{ min (Grad 1)} \).

Commerially available amines:

A3 cycropropylamine (Fluka, Buchs, Switzerland);

A4 methylamine (8 M in EtOH (Fluka, Buchs, Switzerland));

A5 morpholine (Fluka, Buchs, Switzerland);
A6 N-methylpiperazine (Fluka, Buchs, Switzerland);
A7 dimethylamine 2 M in THF (Aldrich, Buchs, Switzerland).
A8 N-(2-methoxyethyl)methylamine (ABCR, Karlsruhe, Germany)
A9 N,N-dimethylethlenediamine (Fluka, Buchs, Switzerland)
A10 bis(2-methoxyethyl)amine (Fluka, Buchs, Switzerland)
A11 2-hydroxyethylamine (Fluka, Buchs, Switzerland)
A12 2-methoxyethylamine (Fluka, Buchs, Switzerland)

The following compounds (Table 1) are prepared in a similar manner as described in Example 1 by reacting 6-bromo-4-chloro-quinazoline (Example 1c) with the appropriate boronic acid(s) (Process A), or are prepared in a similar manner as described in Example 3 starting from 6-bromo-3H-quinazolin-4-one (Example 1d) and using the appropriate boronic acid(s) (Process B).

Table 1

<table>
<thead>
<tr>
<th>Example/ process</th>
<th>Boronic acids</th>
<th>Compound name</th>
<th>ES-MS (M+H)*</th>
<th>t&lt;sub&gt;ret&lt;/sub&gt; Grad 1 [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 / A</td>
<td>B1 B17</td>
<td>6-(3-Chloro-4-n-propoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>435</td>
<td>4.54</td>
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<tr>
<td>6 / A</td>
<td>B1 B18</td>
<td>4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenol</td>
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<tr>
<td>7 / A</td>
<td>B1 B16</td>
<td>6-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-4-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>401</td>
<td>3.74</td>
</tr>
<tr>
<td>8 / A</td>
<td>B1 B15</td>
<td>6-(Benzo[1,3]dioxol-5-yl)-4-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>387</td>
<td>3.75</td>
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<tr>
<td>9 / A</td>
<td>B1 B14</td>
<td>4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester</td>
<td>431</td>
<td>3.64</td>
</tr>
<tr>
<td>10 / A</td>
<td>B1 B13</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(3,4,5-trimethoxy-phenyl)-quinazoline</td>
<td>433</td>
<td>3.58</td>
</tr>
<tr>
<td>11 / B</td>
<td>B1 B12</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(3-fluoro-4-methoxy-phenyl)-quinazoline</td>
<td>391</td>
<td>3.80</td>
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<tr>
<td>12 / B</td>
<td>B1</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenyl]</td>
<td>431</td>
<td>3.68</td>
</tr>
<tr>
<td>Example/process</td>
<td>Boronic acids</td>
<td>Compound name</td>
<td>ES-MS (M+H)^+</td>
<td>t&lt;sub&gt;ret&lt;/sub&gt; Grad 1 [min]</td>
</tr>
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</tr>
<tr>
<td>13 / B</td>
<td>B1, B17</td>
<td>4-(3-Chloro-4-n-propoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
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<td>4.46</td>
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<tr>
<td>14 / B</td>
<td>B1, B13</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(3,4,5-trimethoxy-phenyl)-quinazoline</td>
<td>433</td>
<td>3.63</td>
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<tr>
<td>15 / B</td>
<td>B1, B16</td>
<td>4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
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<td>3.68</td>
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<td>16 / B</td>
<td>B1, B15</td>
<td>4-(Benzo[1,3]dioxol-5-yl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>387</td>
<td>3.67</td>
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<tr>
<td>17 / A</td>
<td>B2, B11</td>
<td>6-(6-Piperazin-1-yl-pyridin-3-yl)-4-(4-pyrazol-1-yl-phenyl)-quinazoline</td>
<td>434</td>
<td>2.66</td>
</tr>
<tr>
<td>18 / A</td>
<td>B1, B5</td>
<td>3-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-phenol</td>
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<td>3.27</td>
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<tr>
<td>19 / A</td>
<td>B1, B6</td>
<td>4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-phenol</td>
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<td>3.20</td>
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<tr>
<td>20 / A</td>
<td>B1, B19</td>
<td>4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-benzamide</td>
<td>386</td>
<td>3.00</td>
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<tr>
<td>21 / A</td>
<td>B1, B12</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(3-fluoro-4-methoxy-phenyl)-quinazoline</td>
<td>391</td>
<td>3.83</td>
</tr>
<tr>
<td>22 / B</td>
<td>B1, B3</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-phenyl-quinazoline</td>
<td>343</td>
<td>3.76</td>
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<tr>
<td>23 / B</td>
<td>B1, B10</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-thiophen-2-yl-quinazoline</td>
<td>349</td>
<td>3.74</td>
</tr>
<tr>
<td>24 / B</td>
<td>B1, B7</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(3-methoxy-phenyl)-quinazoline</td>
<td>373</td>
<td>3.80</td>
</tr>
<tr>
<td>25 / B</td>
<td>B1, B9</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(4-methoxy-phenyl)-quinazoline</td>
<td>373</td>
<td>3.71</td>
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<tr>
<td>26 / B</td>
<td>B1, B11</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(4-pyrazol-1-yl-phenyl)-quinazoline</td>
<td>409</td>
<td>3.80</td>
</tr>
<tr>
<td>27 / B</td>
<td>B1, B2</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline</td>
<td>428</td>
<td>2.79</td>
</tr>
<tr>
<td>Example/process</td>
<td>Boronic acids</td>
<td>Compound name</td>
<td>ES-MS (M+H)^+</td>
<td>t_{ret} Grad 1 [min]</td>
</tr>
<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>28 / A</td>
<td>B2 B19</td>
<td>4-[6-(6-Piperazin-1-yl-pyridin-3-yl)-quinazolin-4-yl]-benzamide</td>
<td>411</td>
<td>2.25</td>
</tr>
<tr>
<td>29 / A</td>
<td>B4 B11</td>
<td>6-(6-Methoxy-pyridin-3-yl)-4-(4-pyrazol-1-yl-phenyl)-quinazoline</td>
<td>380</td>
<td>3.70</td>
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<tr>
<td>30 / A</td>
<td>B4 B19</td>
<td>4-[6-(6-Methoxy-pyridin-3-yl)-quinazolin-4-yl]-benzamide</td>
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<td>2.95</td>
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<tr>
<td>31 / A</td>
<td>B2 B4</td>
<td>6-(6-Methoxy-pyridin-3-yl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline</td>
<td>399</td>
<td>2.67</td>
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<tr>
<td>32 / B</td>
<td>B1 B1</td>
<td>4,6-Bis(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>403</td>
<td>3.55</td>
</tr>
<tr>
<td>33 / B</td>
<td>B1 B19</td>
<td>4-(6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl)-benzamide</td>
<td>386</td>
<td>3.12</td>
</tr>
<tr>
<td>34 / B</td>
<td>B1 B4</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(6-methoxy-pyridin-3-yl)-quinazoline</td>
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<td>3.64</td>
</tr>
<tr>
<td>35 / A</td>
<td>B1 B4</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazoline</td>
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<tr>
<td>36 / A</td>
<td>B2 B4</td>
<td>4-(6-Methoxy-pyridin-3-yl)-6-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline</td>
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<td>B4 B10</td>
<td>6-(6-Methoxy-pyridin-3-yl)-4-thiophen-2-yl-quinazoline</td>
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<td>3.71</td>
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<td>38 / A</td>
<td>B4 B8</td>
<td>4-(2-Chloro-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazoline</td>
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<td>3.81</td>
</tr>
<tr>
<td>39 / B</td>
<td>B4 B4</td>
<td>4,6-Bis(6-methoxy-pyridin-3-yl)-quinazoline</td>
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<td>3.56</td>
</tr>
<tr>
<td>40 / B</td>
<td>B4 B9</td>
<td>4-(4-Methoxy-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazoline</td>
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<td>3.72</td>
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<td>41 / A</td>
<td>B1 B53</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-[4-ethoxy-3-methoxy-phenyl]-quinazoline</td>
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<td>3.79</td>
</tr>
<tr>
<td>42 / A</td>
<td>B1 B54</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinazoline</td>
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<td>3.58</td>
</tr>
<tr>
<td>43 / A</td>
<td>B1</td>
<td>5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-quinazoline</td>
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<td>2.59</td>
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<tr>
<td>Example/process</td>
<td>Boronic acids</td>
<td>Compound name</td>
<td>ES-MS (M+H)+</td>
<td>t&lt;sub&gt;ret&lt;/sub&gt; Grad 1 [min]</td>
</tr>
<tr>
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</tr>
<tr>
<td>44 / B</td>
<td>B1 B21</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-N,N-dimethyl-benzenesulfonamide</td>
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<td>3.70</td>
</tr>
<tr>
<td>45 / B</td>
<td>B1 B22</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(4-ethoxy-3-methoxy-phenyl)-quinazoline</td>
<td>417</td>
<td>3.74</td>
</tr>
<tr>
<td>46 / B</td>
<td>B1, B23</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinazoline</td>
<td>447</td>
<td>3.61</td>
</tr>
<tr>
<td>47 / A</td>
<td>B1 B22</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(2-methoxy-pyridin-4-yl)-quinazoline</td>
<td>374</td>
<td>3.37</td>
</tr>
<tr>
<td>48 / B</td>
<td>B1 B22</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(2-methoxy-pyridin-4-yl)-quinazoline</td>
<td>374</td>
<td>3.57</td>
</tr>
<tr>
<td>49 / A</td>
<td>B1 B55</td>
<td>(3-[4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy]-propyl)-carbamic acid tert-butyl ester</td>
<td>546</td>
<td>4.02</td>
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<tr>
<td>50 / B</td>
<td>B1 B55</td>
<td>(3-[4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenoxy]-propyl)-carbamic acid tert-butyl ester</td>
<td>546</td>
<td>3.99</td>
</tr>
<tr>
<td>51 / A</td>
<td>B1 B56</td>
<td>(2-[4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy]-ethyl)-carbamic acid tert-butyl ester</td>
<td>532</td>
<td>3.87</td>
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<tr>
<td>52 / B</td>
<td>B1 B56</td>
<td>(2-[4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenoxy]-ethyl)-carbamic acid tert-butyl ester</td>
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<td>3.89</td>
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<tr>
<td>53 / B</td>
<td>B1 B23</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(3-ethoxy-phenyl)-quinazoline</td>
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<td>3.97</td>
</tr>
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<td>54 / B</td>
<td>B1 B24</td>
<td>4-(3-Chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
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<td>4.07</td>
</tr>
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<td>55 / B</td>
<td>B1 B25</td>
<td>4-(3-Benzylxoy-4-methoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
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<td>4.12</td>
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<td>56 / B</td>
<td>B1 B26</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-benzoic acid methyl ester</td>
<td>401</td>
<td>3.82</td>
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<tr>
<td>Example/process</td>
<td>Boronic acids</td>
<td>Compound name</td>
<td>ES-MS (M+H)⁺</td>
<td>tₑᵣₑ Grad 1 [min]</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>57 / A</td>
<td>B1</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(5-methoxy-pyridin-3-yl)-quinazoline</td>
<td>374</td>
<td>2.73</td>
</tr>
<tr>
<td></td>
<td>B28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58 / A</td>
<td>B1</td>
<td>4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester</td>
<td>431</td>
<td>3.63</td>
</tr>
<tr>
<td></td>
<td>B14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59 / A</td>
<td>B1</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-quinolin-3-yl-quinazoline</td>
<td>394</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>B27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 / A</td>
<td>B19</td>
<td>4-[6-(5-Methoxy-pyridin-3-yl)-quinazolin-4-yl]-benzamide</td>
<td>357</td>
<td>2.39</td>
</tr>
<tr>
<td></td>
<td>B28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61 / A</td>
<td>B19</td>
<td>4-[6-(6-Amino-5-trifluoromethyl-pyridin-3-yl)-quinazolin-4-yl]-benzamide</td>
<td>410</td>
<td>2.71</td>
</tr>
<tr>
<td></td>
<td>B57</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>62 / A</td>
<td>B1</td>
<td>5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-3-trifluoromethyl-pyridin-2-ylamine</td>
<td>427</td>
<td>3.13</td>
</tr>
<tr>
<td></td>
<td>B57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63 / A</td>
<td>B1</td>
<td>3-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-benzenesulfonamide</td>
<td>422</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>B29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64 / A</td>
<td>B12</td>
<td>4-Benzo[1,3]dioxol-5-yl-6-(3-fluoro-4-methoxy-phenyl)-quinazoline</td>
<td>375</td>
<td>3.91</td>
</tr>
<tr>
<td></td>
<td>B15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 / B</td>
<td>B1</td>
<td>4-(3-Benzyloxy-4-methoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>479</td>
<td>4.10</td>
</tr>
<tr>
<td></td>
<td>B30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66 / A</td>
<td>B1</td>
<td>3-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-benzamide</td>
<td>386</td>
<td>3.01</td>
</tr>
<tr>
<td></td>
<td>B31</td>
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</tr>
<tr>
<td>67 / B</td>
<td>B1</td>
<td>4-(4-Chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>377</td>
<td>4.05</td>
</tr>
<tr>
<td></td>
<td>B32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 / B</td>
<td>B1</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(4-trifluoromethyl-phenyl)-quinazoline</td>
<td>411</td>
<td>4.10</td>
</tr>
<tr>
<td></td>
<td>B33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69 / A</td>
<td>B1</td>
<td>6-(3-Chloro-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>407</td>
<td>3.96</td>
</tr>
<tr>
<td></td>
<td>B34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 / B</td>
<td>B1</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-thiophen-3-yl-quinazoline</td>
<td>349</td>
<td>3.63</td>
</tr>
<tr>
<td></td>
<td>B35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71 / A</td>
<td>B1</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-quinazoline</td>
<td>383</td>
<td>2.95</td>
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<tr>
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<td>B36</td>
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</tr>
<tr>
<td>72 / A</td>
<td>B19</td>
<td>4-[6-(1H-Pyrrolo[2,3-b]pyridin-5-yl)-quinazolin-4-</td>
<td>366</td>
<td>2.59</td>
</tr>
<tr>
<td>Example/ process</td>
<td>Boronic acids</td>
<td>Compound name</td>
<td>ES-MS (M+H)^+</td>
<td>t&lt;sub&gt;ret&lt;/sub&gt; Grad 1 [min]</td>
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<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>73 / A</td>
<td>B19</td>
<td>4-[6-(6-Amino-pyridin-3-yl)-quinazolin-4-yl]-benzamide</td>
<td>342</td>
<td>2.30</td>
</tr>
<tr>
<td>74 / A</td>
<td>B1</td>
<td>6-(3-Benzyl-3-oxo-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>479</td>
<td>4.16</td>
</tr>
<tr>
<td>75 / B</td>
<td>B12</td>
<td>4-(4-Chloro-phenyl)-6-(3-fluoro-4-methoxy-phenyl)-quinazoline</td>
<td>365</td>
<td>4.31</td>
</tr>
<tr>
<td>76 / A</td>
<td>B19</td>
<td>4-[6-(4-Ethoxy-3-methoxy-phenyl)-quinazolin-4-yl]-benzamide</td>
<td>400</td>
<td>3.30</td>
</tr>
<tr>
<td>77 / A</td>
<td>B19</td>
<td>4-[6-(3,4-Diethoxy-phenyl)-quinazolin-4-yl]-benzamide</td>
<td>414</td>
<td>3.47</td>
</tr>
<tr>
<td>78 / A</td>
<td>B1</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-furan-3-yl-quinazoline</td>
<td>333</td>
<td>3.47</td>
</tr>
<tr>
<td>79 / A</td>
<td>B1</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-benzonitrile</td>
<td>368</td>
<td>3.65</td>
</tr>
<tr>
<td>80 / A</td>
<td>B20</td>
<td>4-[6-(6-Amino-pyridin-3-yl)-quinazolin-4-yl]-benzonitrile</td>
<td>324</td>
<td>2.62</td>
</tr>
<tr>
<td>81 / A</td>
<td>B1</td>
<td>4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-benzaldehyde</td>
<td>371</td>
<td>3.56</td>
</tr>
<tr>
<td>82 / B</td>
<td>B1</td>
<td>4-Biphenyl-4-yl-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>419</td>
<td>4.36</td>
</tr>
<tr>
<td>83 / B</td>
<td>B1</td>
<td>4-(3,4-Diethoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>431</td>
<td>3.84</td>
</tr>
<tr>
<td>84 / B</td>
<td>B1</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(4-methoxy-3-trifluoromethoxy-phenyl)-quinazoline</td>
<td>457</td>
<td>4.08</td>
</tr>
<tr>
<td>85 / A</td>
<td>B1</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(4-methoxy-3-trifluoromethoxy-phenyl)-quinazoline</td>
<td>457</td>
<td>4.08</td>
</tr>
<tr>
<td>86 / A</td>
<td>B1</td>
<td>5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-pyridine-2-carbonitrile</td>
<td>369</td>
<td>3.37</td>
</tr>
<tr>
<td>87 / B</td>
<td>B1</td>
<td>4-(4-Bromo-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>421</td>
<td>4.10</td>
</tr>
</tbody>
</table>
The following compounds (Table 2) are prepared in a similar manner as described in Example 2 by reacting 6-bromo-1 H-quinazoline-2,4-dione (Example 2d) with the appropriate boronic acids.
boronic acid(s) and ammonia or a primary amine (Process C), or are prepared in a similar manner as described in Example 4 starting from 6-bromo-2,4-dichloro-quinazoline (Example 4c) and using the appropriate boronic acid(s) and ammoniac or a primary amine (Process D):

Table 2:

<table>
<thead>
<tr>
<th>Example/process</th>
<th>Boronic acids Amines</th>
<th>Compound name</th>
<th>ES-MS (M+H)’</th>
<th>( t_{\text{ret}} ) Grad. 1 [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>101 / C</td>
<td>B1, B1 A3</td>
<td>[4,6-Bis-(3,4-dimethoxy-phenyl)-quinazolin-2-yl]-cyclopropyl-amine</td>
<td>458</td>
<td>3.31</td>
</tr>
<tr>
<td>102 / C</td>
<td>B1, B19 A2</td>
<td>4-[2-Amino-6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-benzamide</td>
<td>401</td>
<td>2.66</td>
</tr>
<tr>
<td>103 / D</td>
<td>B1, B12</td>
<td>4-(3,4-Dimethoxy-phenyl)-6-(3-fluoro-4-methoxy-phenyl)-quinazolin-2-ylamine</td>
<td>406</td>
<td>3.25</td>
</tr>
<tr>
<td>104 / D</td>
<td>B1, B14 A2</td>
<td>4-[2-Amino-4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester</td>
<td>446</td>
<td>3.11</td>
</tr>
<tr>
<td>105 / D</td>
<td>B1, B13 A2</td>
<td>4-(3,4-Dimethoxyphenyl)-6-(3,4,5-trimethoxy-phenyl)-quinazolin-2-ylamine</td>
<td>448</td>
<td>3.10</td>
</tr>
<tr>
<td>106 / D</td>
<td>B1, B17 A2</td>
<td>6-(3-Chloro-4-n-propoxy-phenyl)-4-(3,4-dimethoxyphenyl)-quinazolin-2-ylamine</td>
<td>450</td>
<td>3.80</td>
</tr>
<tr>
<td>107 / D</td>
<td>B1, B6 A2</td>
<td>4-[2-Amino-4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-phenol</td>
<td>374</td>
<td>2.81</td>
</tr>
<tr>
<td>108 / D</td>
<td>B1, B16 A2</td>
<td>6-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-4-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine</td>
<td>416</td>
<td>3.20</td>
</tr>
<tr>
<td>109 / C</td>
<td>B1, B15 A2</td>
<td>4-(Benzo[1,3]dioxol-5-yl)-6-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine</td>
<td>402</td>
<td>3.15</td>
</tr>
<tr>
<td>110 / C</td>
<td>B1, B13 A2</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(3,4,5-trimethoxy-phenyl)-quinazolin-2-ylamine</td>
<td>448</td>
<td>3.11</td>
</tr>
<tr>
<td>111 / D</td>
<td>B1, B4 A2</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(6-methoxy-pyridin-3-yl)-quinazolin-2-ylamine</td>
<td>389</td>
<td>3.03</td>
</tr>
<tr>
<td>112 / C</td>
<td>B1, B1 A2</td>
<td>4,6-Bis(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine</td>
<td>418</td>
<td>3.08</td>
</tr>
</tbody>
</table>
Example 1

4,6-Bis(6-methoxy-pyridin-3-yl)-quinazolin-2-ylamine

Example 12

4-(3,4-Dimethoxy-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazolin-2-ylamine

Example 15

N-[4,6-Bis-(3,4-dimethoxy-phenyl)-quinazolin-2-yl]-N-methyl-amine

Example 16

4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine

Example 17

6-(6-Amino-pyridin-3-yl)-4-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine

Example 18

4-(3,4-Dimethoxy-phenyl)-6-quinolin-3-yl-quinazolin-2-ylamine

Example 119
4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid

107 mg (0.248 mmol) of 4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid methyl ester (Example 12) in 2 ml dioxane is treated with 0.50 ml 1 M aqueous LiOH. The reaction mixture is stirred for 2.5 h at rt. After this time, 0.50 ml 1 M aqueous HCl are added and the precipitate is filtered. The solid is dissolved in CH₂Cl₂ and washed with water (2x), dried over Na₂SO₄, filtered and evaporated to give the title compound as a yellow solid. ES-MS: 417 (M + H)⁺; analytical HPLC: tᵣₑᵣ = 3.30 min (Grad 1).

Example 120
4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid-N-methylamide

60 mg (0.143 mmol) of 4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid (Example 57), 62 µl (0.357 mmol) disopropylethylamine (Fluka, Buchs, Switzerland) and 42 mg (0.143 mmol) TPTU (Fluka, Buchs, Switzerland) in 1.5 ml DMA is stirred for 10 min at rt. The reaction mixture is added to a solution of 18 µl (0.143 mmol) A4 and 4.5 mg (0.036
mmol) DMAP in 1.5 ml DMA. The reaction mixture is stirred for 10 min at rt. After this time, the reaction mixture is diluted with water and extracted with EtOAc (2x). The organic layers are washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The residue is adsorbed on Isolute HM-N sorbent and purified by RP-MPLC ($H_2O/CH_3CN$ and 3% PrOH). The pure fractions are concentrated and the product precipitates to provide the title compound as an off-white solid. ES-MS: 430 (M + H)$^+$; analytical HPLC: $t_{ret}$ = 3.40 min (GracM).

The following compounds (Table 3) are prepared in a similar manner as described in Example 120 with the amine given:

Table 3

<table>
<thead>
<tr>
<th>Example</th>
<th>Amine</th>
<th>Compound Name</th>
<th>ES-MS (M+H)$^+$</th>
<th>$t_{ret}$ Grad. 1 [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>121</td>
<td>A2</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzamide</td>
<td>416</td>
<td>3.28</td>
</tr>
<tr>
<td>122</td>
<td>A7</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-N,N-dimethyl-amide</td>
<td>444</td>
<td>3.45</td>
</tr>
<tr>
<td>123</td>
<td>A6</td>
<td>{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenyl}-(4-methyl-piperazin-1-yl)-methanone</td>
<td>499</td>
<td>2.98</td>
</tr>
<tr>
<td>124</td>
<td>A5</td>
<td>{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenyl}~morpholin-4-yl-methanone</td>
<td>486</td>
<td>3.40</td>
</tr>
</tbody>
</table>

The following compounds (Table 4) are prepared in a similar manner as described in Example 120 starting with the amine given and 4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-benzoic acid, the hydrolysis side product of the synthesis of Example 56 (ES-MS: 387 (M + H)$^+$; analytical HPLC: $t_{ret}$ = 3.33 min (Grad 1)):

Table 4
The following compounds (Table 5) are prepared by Susuki coupling in a similar manner as described in Example 3 or in Example 1b starting with 4-(4-chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline (Example 67) or 4-(4-bromo-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline (Example 87) and the appropriate bornic acid:

<table>
<thead>
<tr>
<th>Example</th>
<th>Amine</th>
<th>Compound Name</th>
<th>ES-MS (M+H)^+</th>
<th>t\text{ret} Grad. 1 [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>A7</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-N,N-dimethyl-benzamide</td>
<td>414</td>
<td>3.40</td>
</tr>
<tr>
<td>126</td>
<td>A4</td>
<td>4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-N-methyl-benzamide</td>
<td>400</td>
<td>3.22</td>
</tr>
<tr>
<td>127</td>
<td>A6</td>
<td>{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone</td>
<td>469</td>
<td>2.92</td>
</tr>
<tr>
<td>128</td>
<td>A5</td>
<td>{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-morpholin-4-yl-methanone</td>
<td>456</td>
<td>3.36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example</th>
<th>Boronic acid</th>
<th>Compound Name</th>
<th>ES-MS (M+H)^+</th>
<th>t\text{ret} Grad. 1 [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>129</td>
<td>B43</td>
<td>C-[4'-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl]-methylamine</td>
<td>448</td>
<td>3.23</td>
</tr>
<tr>
<td>130</td>
<td>B9</td>
<td>6-(3,4-Dimethoxy-phenyl)-4-(4'-methoxy-biphenyl-4-yl)-quinazoline</td>
<td>449</td>
<td>4.33</td>
</tr>
<tr>
<td>131</td>
<td>B44</td>
<td>{4'-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl}-methanol</td>
<td>449</td>
<td>3.76</td>
</tr>
<tr>
<td>132</td>
<td>B6</td>
<td>4'-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-ol</td>
<td>435</td>
<td>3.76</td>
</tr>
<tr>
<td>133</td>
<td>B1</td>
<td>4-(3',4'-Dimethoxy-biphenyl-4-yl)-6-(3,4-dimethoxy-phenyl)-quinazoline</td>
<td>479</td>
<td>4.11</td>
</tr>
</tbody>
</table>
Example 136

6-(3,4-Dimethoxy-phenyl)-4-(4’-methoxymethyl-biphenyl-4-yl)-quinazoline

The title compound is obtained by standard etherification of 4’-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl]-methanol (Example 136) using iodomethane (Fluka, Buchs, Switzerland): ES-MS: 463 (M + H)+; analytical HPLC: t_{ret} = 4.29 min (Grad 1).

Example 137

3-{4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy}-propylamine

The title compound is obtained in a similar manner as described in Example 1 starting with (3-{4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy}-propyl)-carbamic acid tert-butyl ester (Example 49): ES-MS: 446 (M + H)+; analytical HPLC: t_{ret} = 2.93 min (Grad 1).

Example 138

2-{4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy}-ethylamine

The title compound is obtained in a similar manner as described in Example 1 starting with (2-{4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy}-ethyl)-carbamic acid tert-butyl ester (Example 51): ES-MS: 432 (M + H)+; analytical HPLC: t_{ret} = 2.81 min (Grad 1).

Example 139

3-{5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy}-propylamine

The title compound is obtained in a similar manner as described in Example 1 starting with 6-(3-benzyloxy-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline (Example 74): ES-MS: 446 (M + H)+; analytical HPLC: t_{ret} = 2.89 min (Grad 1).

Example 140

2-{5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy}-ethylamine

The title compound is obtained in a similar manner as described in Example 1 starting with 6-(3-benzyloxy-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline (Example 74) and using tert-butyl N-(2-bromoethyl)carbamate (Fluka, Buchs, Switzerland): ES-MS: 432 (M + H)+; analytical HPLC: t_{ret} = 2.81 min (Grad 1).

Example 141
4-(3,4-Dimethoxy-phenyl)-6-(3-ethoxy-4-methoxy-phenyl)-quinazoline
The title compound is obtained in a similar manner as described in Example 1 starting with 6-(3-benzylxy-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline (Example 74) and using iodoethane (Fluka, Buchs, Switzerland): ES-MS: 417 (M + H)⁺; analytical HPLC: t_ret = 3.74 min (Grad 1).

Example 142
4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid
The title compound is obtained in a similar manner as described in Example 120 using ammonia (A2) and starting with 4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid (Example 151a): ES-MS: 415 (M + H)⁺; analytical HPLC: t_ret = 3.15 min (Grad 1).

The starting material is prepared as follows:

Example 142a
4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid
The title compound is obtained in a similar manner as described in Example 119 starting with 4-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester (Example 58): ES-MS: 417 (M + H)⁺; analytical HPLC: t_ret = 3.22 min (Grad 1).

Example 143
5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-pyridine-2-carboxylic acid amide
A mixture of 80 mg (0.204 mmol) of 5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridine-2-carbonitrile (Example 86) in 2 ml dioxane and 0.51 ml (0.51 mmol) 1 M aqueous LiOH is stirred for 100 min at 100°C. The reaction mixture is quenched with 0.51 ml (0.51 mmol) 1 M aqueous HCl, diluted and extracted with EtOAc and CH₂Cl₂. The combined organic layer are dried over Na₂SO₄, filtered and evaporated in vacuo. The residue is purified by flash chromatography (CH₂Cl₂/MeOH 0% to 4%) to yield the title compound as a pale yellow solid. ES-MS: 387 (M + H)⁺; analytical HPLC: t_ret = 2.99 min (Grad 1).

Example 144
C-{5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-methylamine
A mixture of 95 mg (0.204 mmol) of 5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridine-2-carbonitrile (Example 86) in 5 ml MeOH, 0.25 ml concentrated aqueous ammonia and a spatula tip of Nickel Raney is shacked for 45 h at rt under 1 bar hydrogen. The catalyst is filtered off and washed with MeOH. The filtrate is evaporated in vacuo. The residue is purified
by preparative RP-HPLC (H₂O/ CH₃CN and 0.1% TFA). The pure fractions are basified with NaHCO₃, concentrated and extracted with EtOAC (3x). The combined organic layers are dried over Na₂SO₄, filtered and evaporated to provide the title compound as an orange solid. ES-MS: 373 (M + H)⁺; analytical HPLC: tₑᵣ = 2.53 min (Grad 1).

**Example 145**

6-(3,4-Dimethoxy-phenyl)-4-[6-(4-methanesulfonyl-piperazin-1-yl)-pyridin-3-yl]-quinazoline

A mixture of 45 mg (0.1 mmol) of 6-(3,4-dimethoxy-phenyl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline (Example 145a) in 1.5 ml pyridine and 17.4 mg (0.15 mmol) methanesulfonyl chloride (Fluka, Buchs, Switzerland) is stirred for 70 min at rt. The reaction mixture is diluted with water and extracted with EtOAc (2x). The combined organic layer is washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The residue is adsorbed on silica gel and purified by flash chromatography (CH₂Cl₂/MeOH 0% to 3%) to yield the title compound as a yellow solid. ES-MS: 506 (M + H)⁺; analytical HPLC: tₑᵣ = 3.13 min (Grad 1).

The starting material is prepared as follows:

**Example 145a**

6-(3,4-Dimethoxy-phenyl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline

The title compound is synthesized in a similar manner as in Example 1 starting with 4-{5-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 100): ES-MS: 428 (M + H)⁺; analytical HPLC: tₑᵣ = 2.79 min (Grad 1).

**Example 146**

1-(4-{5-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-pyridin-2-yl}-piperazin-1-yl)-ethanone

The title compound is synthesized in a similar manner as in Example 145 starting with 6-(3,4-dimethoxy-phenyl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline (Example 145a) and acetyl chloride (Fluka, Buchs, Switzerland): ES-MS: 470 (M + H)⁺; analytical HPLC: tₑᵣ = 2.98 min (Grad 1).

**Example 147**

1-{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-pyrrolidin-2-one

Under Ar, a mixture of 75 mg (0.174 mmol) of 4-(4-bromo-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline (Example 87), 1 mg (0.0009 mmol) bis(dibenzylideneacetone) palladium (II) (Fluka, Buchs, Switzerland), 1.6 mg (0.0027 mmol) of Xantphos (9,9-dimethyl-9H-xanthene-4,5-diy)bis[diphenylphosphine], Aldrich, Buchs, Switzerland) 81 mg (0.244 mmol) of cesium carbonate and 17.8 mg (0.209 mmol) 2-pyrrolidinone (Fluka, Buchs, Switzerland) in 0.18 ml
dioxane is stirred for 22 h at 100 °C. The reaction mixture diluted with EtOAc and washed with water and brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The residue is adsorbed on silica gel and purified by flash chromatography (CH₂Cl₂ZfMeOH 0% to 3%) to yield the title compound as a yellow solid. ES-MS: 426 (M + H)⁺; analytical HPLC: tᵣₑₜ = 3.55 min (Grad 1).

Commercially available cyclic aminocarbonyl starting materials:
L₁ 2-azetidinone (Fluka, Buchs, Switzerland)
L₂ 2-piperidinone (Fluka, Buchs, Switzerland)
L₃ 2-oxazolidinone (Fluka, Buchs, Switzerland)
L₄ 1-methyl-2-imidazolidinone (Acros, Basel, Switzerland)

The following compounds (Table 6) are prepared in a similar manner as described in Example 147 with the cyclic aminocarbonyl starting material given:

<table>
<thead>
<tr>
<th>Example</th>
<th>Amine</th>
<th>Compound Name</th>
<th>ES-MS (M+H)⁺</th>
<th>tᵣₑₜ Grad. 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>148</td>
<td>L₁</td>
<td>1-{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-azetidin-2-one</td>
<td>412</td>
<td>3.52</td>
</tr>
<tr>
<td>149</td>
<td>L₂</td>
<td>1-{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-piperidin-2-one</td>
<td>440</td>
<td>3.58</td>
</tr>
<tr>
<td>150</td>
<td>L₃</td>
<td>3-{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-oxazolidin-2-one</td>
<td>428</td>
<td>3.44</td>
</tr>
<tr>
<td>151</td>
<td>L₄</td>
<td>1-{4-[6-(3,4-Dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-3-methyl-imidazolidin-2-one</td>
<td>441</td>
<td>3.49</td>
</tr>
</tbody>
</table>

**Example 152**

6-(3,4-Dimethoxy-phenyl)-4-pyrazol-1-yl-quinazoline

A mixture of 64 mg (0.214 mmol) of 4-chloro-6-(3,4-dimethoxy-phenyl)-quinazoline (Example 152a) and 73 mg pyrazole (Fluka, Buchs, Switzerland) in 2 ml DMF is stirred at rt overnight.
The reaction mixture is quenched with water and extracted with EtOAc (2x). The organic layers are washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated in vacuo. The residue is adsorbed on Isolute sorbent (Isolute HM-N) and purified by RP-MPLC ($H_2O$/ CH$_3$CN and 3% PrOH). The pure fractions are concentrated and the product precipitates. The solid is filtered off, dissolved in CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered and evaporated to provide the title compound as an off-white solid. ES-MS: 333 (M + H)$^+$; analytical HPLC: $t_{ret} = 3.71$ min (Grad 1).

The starting material is prepared as follows:

**Example 152a**

4-Chloro-6-(3,4-dimethoxy-phenyl)-quinazoline

The title compound is synthesized in a similar manner as described in Example 3a using B$_1$; ES-MS: 301 (M + H)$^+$; analytical HPLC: $t_{ret} = 3.63$ min (Grad 1).

**Example 153**

6-(3,4-Dimethoxy-phenyl)-4-H,2,4triazol-1-yl-quinazoline

The title compound is synthesized in a similar manner as described in Example 152 using 1,2,4-triazole (Fluka, Buchs, Switzerland); ES-MS: 334 (M + H)$^+$; analytical HPLC: $t_{ret} = 3.41$ min (Grad 1).

**Example 154**

6-(3,4-Dimethoxy-phenyl)-4-pyrrol-1-yl-quinazoline

The title compound is synthesized in a similar manner as described in Example 152 using pyrrole (Fluka, Buchs, Switzerland) that is deprotonated beforehand with NaH; ES-MS: 332 (M + H)$^+$; analytical HPLC: $t_{ret} = 3.75$ min (Grad 1).

**Example 155**

4,6-Bis-(3,4-dimethoxy-phenyl)-5-fluoro-quinazoline

The title compound is obtained in a similar manner as described in Example 3 starting from 5-fluoro-3H-quinazolin-4-one (Example 155a) and using boronic acid B$_1$. ES-MS: 421 (M + H)$^+$; analytical HPLC: tret = 3.55 min (Grad 1).

**Example 155a**

5-Fluoro-3H-quinazolin-4-one
2.7 g (11.4 mmol) of 2-amino-6-fluorobenzamide (ABCR, Karlsruhe, Germany) in 50 ml triethylorthoformate (Fluka, Buchs, Switzerland) is heated for 46 h at 130°C. The reaction mixture is evaporated to dryness in vacuo. The residue is tritium in hexane/EtOAc and the solid is filtered and dry to give the title compound as an off-white solid. ES-MS: 243, 245 (M + H)+; analytical HPLC: $t_{ret} = 2.49$ min (Grad 1).

**Example 156**

4-[6-(3,4-Dimethoxy-phenyl)-5-fluoro-quinazolin-4-yl]-benzamide

The title compound is obtained in a similar manner as described in Example 3 starting from 5-fluoro-3H-quinazolin-4-one (Example 155a) and using boronic acid B19. ES-MS: 404 (M + H)+; analytical HPLC: $t_{ret} = 3.09$ min (Grad 1).

**Example 157**

{5-[4-(3,4-Dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-(2-methoxy-ethyl)-amine

The title compound is synthesized by Suzuki coupling in a similar manner as described in Example 1b starting from 4-(3,4-dimethoxy-phenyl)-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinazoline (Example 157a) and using (5-bromo-pyridin-2-yl)-(2-methoxy-ethyl)-amine (ES-MS: 231, 233 (M + H)+; analytical HPLC: $t_{ret} = 1.96$ min (Grad 1)) obtained in a similar manner as B60a using A12: ES-MS: 417 (M + H)+; analytical HPLC: $t_{ret} = 2.73$ min (Grad 1).

**Example 158**

4-(3,4-Dimethoxy-phenyl)-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinazoline

The title compound is synthesized in a similar manner as described in B57 starting with 6-Bromo-4-(3,4-dimethoxy-phenyl)-quinazoline (Example 1b): ES-MS: 393 (M + H)+; analytical HPLC: $t_{ret} = 2.50$ min (Grad 1).

**Example 159: Soft capsules**

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

<table>
<thead>
<tr>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
</tr>
<tr>
<td>Lauroglycol</td>
</tr>
</tbody>
</table>

Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propy-
lene glycol laurate, Gattefosse S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 µm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.
Claims:

1. A compound of the formula I,

\[ \text{formula I} \]

wherein

- \( R^1 \) is hydrogen; or amino that is unsubstituted or monosubstituted with alkyl or cycloalkyl;
- \( R^2 \) is an unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;
- \( R^3 \) is hydrogen, halogen, alkyl, alkoxy or cyano;
- \( R^4 \) is unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl; and
- \( R^5 \) is hydrogen, methyl or methyl substituted with halogen;

with the proviso that if \( R^4 \) is unsubstituted or substituted pyrazolyl then \( R^1 \) is amino that is unsubstituted or monosubstituted with alkyl or cycloalkyl and \( R^2, R^3 \) and \( R^5 \) are as defined above;
and with the proviso that if \( R^2 \) is unsubstituted or substituted oxoindolyl, then \( R^1 \) is amino that is unsubstituted or monosubstituted with alkyl or cycloalkyl and \( R^3, R^4 \) and \( R^5 \) are as defined above;

or a tautomer thereof or a N-oxide thereof, or a salt, or a hydrate or solvate thereof.

2. A compound of the formula I according to claim 1, wherein

- \( R^1 \) is hydrogen; or amino that is unsubstituted or monosubstituted with \( C_1-C_7 \) (preferably \( C_1-C_4 \))-alkyl or \( C_3-C_8 \) (preferably \( C_3-C_5 \))-cycloalkyl;
R² is unsubstituted or substituted aryl wherein aryl is selected from the group consisting of phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylencyl, fluorenlyl, phenalenyl, phenanthrenyl and anthracenyl, each of which is unsubstituted or substituted by one or more, preferably up to three, substituents independently selected from the group consisting of C₁⁻C₇ -alkyl; C₂⁻C₇-alkenyl; C₂⁻C₇-alkynyl; C₆⁻C₈-aryl-Cᵣ-alkyl in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylencyl, fluorenlyl, phenalenyl, phenanthrenyl or anthracenyl and is unsubstituted or substituted by CrCᵣ-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidine by pipazazinyl, especially pipazazino, by amino, by N-mono- and/or N,N-di-Cᵣ-alkylalino, by halo, by Ci-Cᵣ-alkoxy, such as methoxy, and/or by halo-Cᵣ-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), pipazazinyl (especially pipazazino), morpholinol, thiomorpholinol, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-Cᵣ-Cᵣ-alkyl wherein pyrrolidinyl, piperidinyl, pipazazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-Cᵣ-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pipazazinyl, especially pipazazino, by amino, by N-mono- and/or N,N-di-Cᵣ-alkylalino, by halo, by d-Cᵣ-alkoxy, such as methoxy, and/or by halo-Cᵣ-Cᵣ-alkyl, such as trifluoromethyl, for example pyrrolidino-Cᵣ-Cᵣ-alkyl, pipazazin-Cᵣ-Cᵣ-alkyl, morpholinol-Cᵣ-Cᵣ-alkyl, thiomorpholinol-Cᵣ-Cᵣ-alkyl, N-Cᵣ-Cᵣ-alkyl-pipazazin-Cᵣ-Cᵣ-alkyl, or N-mono- or N,N-di-(Cᵣ-Cᵣ-alkyl)-amino-substituted or unsubstituted pyrrolidino-Cᵣ-Cᵣ-alkyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), pipazazinyl (especially pipazazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-Cᵣ-Cᵣ-alkyl wherein pyrrolidinyl, piperidinyl, pipazazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-Cᵣ-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pipazazinyl, especially pipazazino, by amino, by N-mono- and/or N,N-di-Cᵣ-Cᵣ-alkylalino, by halo, by CrCᵣ-alkoxy, such as methoxy, and/or by halo-Cᵣ-Cᵣ-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), piperidinyl (especially piperidino), pipazazinyl (especially pipazazino), pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-O-carbonyl-Cᵣ-Cᵣ-alkyl wherein pyrrolidinyl, piperidinyl, pipazazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-Cᵣ-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pipazazinyl, especially pipazazino, by amino, by N-mono- and/or N,N-di-Cᵣ-Cᵣ-alkylalino, by halo, by d-Cᵣ-alkoxy, such as methoxy, and/or by halo-Cᵣ-Cᵣ-alkyl, such as trifluoromethyl; halo-Cᵣ-Cᵣ-alkyl; hydroxy-Cᵣ-Cᵣ-alkyl; C₁⁻Cᵣ-alkoxy-Cᵣ-Cᵣ-alkyl; C₁⁻Cᵣ-alkoxy-Cᵣ-Cᵣ-alkoxy-Cᵣ-Cᵣ-alkyl; phenolxy- or naphtholxy-Cᵣ-Cᵣ-alkyl; phenol-Cᵣ-Cᵣ-alkoxy- or naphthol-Cᵣ-Cᵣ-alkoxy-Cᵣ-Cᵣ-alkyl; amino-Cᵣ-Cᵣ-alkyl; N-mono- or N,N-di-(CrCᵣ-Cᵣ-alkyl and/or mono-Cᵣ-Cᵣ-alkoxy-Cᵣ-Cᵣ-alkyl and/or (mono- or di-(CrCᵣ-Cᵣ-alkyl)-amino-Cᵣ-Cᵣ-alkyl)-amino-Cᵣ-Cᵣ-alkyl; Ci-Cᵣ-alkoxy-
Ci-C$_7$-alkylamino-Ci-C$_7$-alkyl; mono- or di-[C$_6$-Ci$_8$-aryl-Ci-C$_7$-alkyl in which aryl is unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by Ci-C$_7$-alkoxy and/or by halo-C$_7$-alkyl; (pyrrolidinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-CrC$_7$-alkyl wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by C$_7$-BikOxy and/or by halo-C$_7$-alkyl; (pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-CrC$_7$-alkyl wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by halo-C$_7$-alkylamino, by halo, by C$_7$-BikOxy and/or by halo-C$_7$-alkyl; and/or (pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-carbonyl-C$_7$-alkyl wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by CrC$_7$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C$_7$-alkylamino, by halo, by d$_C$-alkoxy and/or by halo-d$_C$-alkyl; especially naphthyl- and/or phenyl-C$_7$-alkyl]-amino-C$_7$-alkyl; d$_C$-alkanoylamino-d$_C$-alkyl; carboxy-C$_7$-alkyl; benzoyl- or naphthoylamino-CrC$_7$-alkyl; d$_C$-alkylsulfonylamino-CrC$_7$-alkyl; phenyl- or naphthylsulfonylamino-d$_C$-alkyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, d$_C$-alkyl moieties, phenyl- or naphthyl-d$_C$-alkylsulfonylamino-d$_C$-alkyl, halo; hydroxy; C$_1$-C$_7$-alkoxy; drd aryld$_d$-d-alkoxy in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by d$_C$-alkyl, such as methyl or ethyl, by d$_C$-alkoxy, by pyrrolidinyl, especially pyrrolidine by piperazinyl, especially piperazinyl, by amino, by N-mono- and/or N,N-di-d$_C$-alkylamino, by halo, by d$_C$-alkoxy, such as methoxy, and/or by halo-d$_C$-alkyl, such as trifluoromethyl; halo-d$_C$-alkoxy; hydroxy-d$_C$-alkoxy; C$_1$-C$_7$-alkoxy-d$_C$-alkoxy; amino-d$_C$-alkoxy; N-d$_C$-alkanoylamino-d$_C$-alkoxy; N-unsubstituted-, N-mono- or N,N-di-(C$_1$-C$_7$-alkyl)carbamoyl-C$_7$-alkoxy; phenyl- or naphthyl-oxo; phenyl- or naphthyl-d$_C$-alkoxy; (pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-d$_C$-alkoxy wherein pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by d$_C$-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-d$_C$-alkylamino, by halo, by d$_C$-alkoxy and/or by halo-d$_C$-alkyl; (pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl)-oxy-d$_C$-alkoxy wherein pyrrolidinyl,
piperidinyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl are unsubstituted or substituted by Ci-C₇-alkyl, by pyrrolidinyl, by piperazinyl, by amino, by N-monoo- and/or N,N-di-Ci-C₇-alkylamino, by halo, by Ci-C₇-alkoxy and/or by halo-Ci-C₇-alkyl; Ci-C₇-alkanoyloxy; benzoyl- or naphthoyloxy; C₇-C₉-alkythio, halo-C₇-C₉-alkthio; C₇-C₉-alkoxy-C₇-C₉-alkythio; phenyl- or naphthylthio; phenyl- or naphthyl-Ci-C₇-alkylthio; CrC₇-alkanoyloxy; benzoyl- or naphthylthio; nitro; amino; mono- or di-(Ci-C₇-alkyl)-amino; mono- or di-(naphthyl- or phenyl-Ci-C₇-alkyl)-amino; Ci-C₇-alkanoylamino; benzoyl- or naphthoylamino; Ci-C₇-alkylsulfonylamino; phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, Ci-C₇-alkyl moieties; phenyl- or naphthyl-Ci-C₇-alkylsulfonylamino; Ci-C₇-alkanoylamino; Ci-C₇-alkoxy-Ci-C₇-alkanoyl; carboxyl; Ci-C₇-alkoxy-carbonyl; phenoxy- or naphthoxycarbonyl; phenyl- or naphthyl-Ci-C₇-alkoxy-carbonyl; Ci-C₇-C₁₀, especially Ci-C₄-alkyleneoxy; carbamoyl; N-mono- or N,N-di-(Ci-C₇-alkyl, naphthyl-CrC₇-alkyl, pyrrolidinyl-CrC₇-alkyl, piperidinyl -CrC₇-alkyl, piperazinyl- or N-Ci-C₇-alkyl)-piperazinyl-CrC₇-alkyl, phenyl-d-C₄alkyl, mono-Ci-C₇-alkoxy-Ci-C₇-alkyl and/or (N'-mono- or N,N'-di-(Ci-C₇-alkyl)-amino-Ci-C₇-alkyl)-amino-carbonyl; N-CrC₇-alkoxy-CrC₇ alkylcarbamoyl; pyrrolidin-1-carbonyl; amino-N-pyrrolidin-1-carbonyl; N-mono- or N,N-di(Cr C₇-alkyl)amino-pyrrolidin-1-carbonyl; piperidin-1-carbonyl; morpholin-4-carbonyl; thiomorpholin-4-carbonyl; S-oxo-thiomorpholin-4-carbonyl; S,S-dioxothiomorpholin-4-carbonyl; piperazin-1-carbonyl; N-d-C₄alkyl-piperazin-i-carbonyl; N-CrC₇-alkoxy-carbonyl-piperazin-1-carbonyl; N-mono- or N,N-di-(Ci-C₇-alkyl)-amino-substituted or unsubstituted pyrrolidinyl-CrC₇-alkyl; cyan; CrC₇-alkenylenene or -alkinylenene; CrC₇-alkylsulfonyl; phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, CrC₇-alkyl moieties; phenyl- or naphthyl-Ci-C₇-alkylsulfonyl; sulfamoyl; N-mono or N,N-di-(Ci-C₇-alkyl, phenyl-, naphthyl-, pyrrolidinyl(especially pyrrolidino)-CrC₇-alkyl, piperidinyl(especially piperidino)-CrC₇-alkyl, piperazinyl(especially piperezino)-Ci-C₇-alkyl, N-CrC₄alkylpiperazin-1especially 4-CrC₇-alkylpiperazino)-CrC₇-alkyl, phenyl-CrC₇-alkyl- and/or naphthyl-CrC₇-alkyl-aminosulfonyl; pyrazolyl; pyrazolidinyl; pyrrolyl; pyridyl that is unsubstituted or substituted by C₇-C₁₀-alkyl, pyrrolidinyl; piperidinyl; morpholinyl; thiomorpholinyl; S-oxo-thiomorpholinyl; S,S-dioxothiomorpholinyl; piperazinyl; N-d-C₄alkyl-piperazinyl; 4-(phenyl-C₁-C₇-alkyl-piperazinyl; 4-(naphthyl-C₁-C₇-alkyl)-piperazinyl; 4-(C₁-C₇-alkoxy-carbonyl-piperazinyl; 4-(phenyl-C₁-C₇-alkoxy-carbonyl)-piperazinyl and 4-(naphthyl-C₁-C₇-alkoxy-carbonyl)-piperazinyl;

or is unsubstituted or substituted heteroaryl where heteroaryl is selected from the group consisting of imidazolyl, thiophenyl, pyrazolyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl,
pyridazinyl, furyl, 2H- or 4H-pyranyl, oxazolyl, thiazolyl, 5H-indazolyl, isoindolyl, quinolyl, isoquinolynyl, phthalazinyl, 1,8-naphthyridinyl, quinoxalinyln, quinazolinyl, cinnolinyl, indolizinyl, 4H-quinolizynyl, pteridinyl, purinyl, carbazolyl, beta-carbolinyl, acridinyl, phenanthridinyl, phenyrynyln, 1,7-phenanthrolinyl, perimidinyl, benzofuranyln, iso benzofuranyln, 2H-chromenyl, 4aH-isochromenyl, thianthrenyl, xanthenyln, phenoxathiyln, phenoxazinyln or phenothiazinyl, each of which is unsubstituted or substituted as mentioned above for aryl;

R³ is hydrogen, halogen, d-C γ-alkyl, C₆₋₇-BlkOXY or cyano;
R⁴ is unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl, independently selected from unsubstituted or substituted aryl as defined for R² and unsubstituted or substituted heteroaryl where heteroaryl is selected from the group consisting of imidazolyl, thio phenyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyln, pyridazinyl, furylko, 2H- or 4H-pyranyl, oxazolyl, thiazolyl, 5H-indazolyl, indolyl, isoindolyl, quinolynl, isoquinolynl, phthalazinyl, 1,8-naphthyridinyl, quinoxalinyln, quinazolinyl, cinnolinyl, indolizinyl, 4H-quinolizynyl, pteridinyl, purinyl, carbazolyl, beta-carbolinyl, acridinyl, phenanthridinyl, phenyrynyln, 1,7-phenanthrolinyl, perimidinyl, benzofuranyln, iso benzofuranyln, 2H-chromenyl, 4aH-isochromenyl, thianthrenyl, xanthenyln, phenoxathiyln, phenoxazinyln or phenothiazinyl, as defined for R²; or, if R⁴ is amino or amino monosubstituted with CrC γ (preferably Ci-C₄)-alkyl or C₃₋₇-C₈ (preferably C₃-C₅)-cycloalkyl, can also be ppyrazolyln, where each heteroaryl is unsubstituted or substituted as described above for aryl R²; and

R⁵ is hydrogen, methyl or methyl substituted with halogen;

or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

3. A compound of the formula I according to claim 1 wherein

R¹ is hydrogen, amino, N-mono-Ci-Ci₀ (preferably d-C₄)-alkylamino or C₃₋₇-C₈ (preferably C₃-C₅)-cycloalkylamino,

R² is phenyl, naphthyl, pyrrolyl, thiophenyl, pyrazolyl, triazolyl, pyridyl, quinolyl or quinoxalinyln, or is pyrrolopyridinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of CrC γ-alkyl, halo-d-Cγ-alkyl, phenyl that is unsubstituted or substituted by one to three substituents
independently selected from hydroxyl-CrC γ-alkyl, Ci-Cγ-alkoxy-Ci-C γ-alkyl, Ci-Cγ-alkoxy, amino and carbamoyl, halo, hydroxy, Ci-Cγ-alkoxy, Ci-Cγ-alkoxy-Ci-C γ-alkoxy, halo-Ci-Cγ-alkoxy, such as trifluoromethoxy, amino, N-mono- or N,N-di-(Ci-Cγ-alkyl, phenyl-Ci-Cγ-alkyl and/or naphthyl-C1-Cγ-alkyl)-amino, C1-Cγ-alkanoylamino, carboxy, C1-Cγ-alkoxycarbonyl, phenyl-Ci-Cγ-alkoxycarbonyl, naphthyl-Ci-Cγ-alkoxycarbonyl, phenoxy carbonyl, naphthoxy carbonyl, d-C4-alkylenedioxy, cyano, carbamoyl, N-mono- or N,N-di-(Ci-Cγ-alkyl, N′,N′-di-(Ci-Cγ-alkyl)-amino-Ci-Cγ-alkyl, pyrrolidino-Ci-Cγ-alkyl and/or phenyl-Ci-Cγ-alkyl)-carbamoyl, piperidin-1-carbonyl, pipercarin-1-carbonyl, 4-Cγ-Cγ-alkyl-piperazin-1-carbonyl, morpholin-4-carbonyl, thiomorpholin-4-carbonyl, S-oxo-thiomorpholin-4-carbonyl, S,S-dioxothiomorpholin-4-carbonyl, sulfamoyl, N-mono- or N,N-di-(CrC γ-alkyl, N′,N′-di-(C+Cγ-alkyl)amino-Ci-Cγ-alkyl and/or phenyl-Ci-Cγ-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-Cγ-Cγ-alkyl-pipercarin, 4-(phenyl-Ci-Cγ-alkyl)-pipercarin, 4-(naphthyl-Ci-Cγ-alkyl)-pipercarin, 4-(Ci-Cγ-alkanoyl)-pipercarin, 4-(Ci-Cγ-alkoxy carbonyl)-pipercarin, 4-(phenyl-Ci-Cγ-alkoxy carbonyl)-pipercarin, 4-(naphthyl-Ci-Cγ-alkoxycarbonyl)-pipercarin, 4-(Ci-Cγ-alkanesulfonyl)-pipercarin, 2-oxo-pyrrolidin-1-yl, 2-oxo-azetidin-1-yl, 2-oxo-piperidin-1-yl, 3-C1-Cγ-alkyl-2-oxo-imidazolidin-1-yl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl, and/or from 2-amino-pyrimidin-5-yl-Ci-C γ-alkyl, 4-Ci-Cγ-alkyl-pipercarin-1-carbonyl-Ci-Cγ-alkoxy, 4-pyrrolidino-piperidin-1-carbonyl-Ci-Cγ-alkoxy, 4-pyrrolidino-piperidin-1-yl-Ci-Cγ-alkoxy, 4-C1-Cγ-alkyl-pipercarin-1-carbonyl-Ci-Cγ-alkoxy, pyridin (e.g.-2)-yloxy-Cr Cγ-alkoxy, pyrimidin (e.g.-4)-yloxy-Ci-C γ-alkoxy, N,N-di(Ci-Cγ-alkyl)amino-pyrrolidin-1-carbonyl and (unsubstituted or Ci-Cγ-alkoxy- and/or halo-Ci-Cγ-alkoxy-substituted) pyridin(e.g.-3))-yl;  
R3 is hydrogen, or it is halo, preferably hydrogen,  
R4 is phenyl, napthyl, pyrrolyl, thiophenyl, triazolyl, pyridyl, quinolinyl, quinoxaliny, furanyl or 1H-pyrrolo[2,3-b]-pyridin-5-yl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halo-Ci-Cγ-alkyl, such as trifluoromethyl, amino-C1-Cγ-alkyl, such as aminomethyl, halo, hydroxy, CrC γ-alkoxy, C1-Cγ-alkoxy-CrC γ-alkoxy, amino-Ci-Cγ-alkoxy, phenyl-Ci-Cγ-alkoxy, amino, N-mono- or N,N-di-(Ci-Cγ-alkyl, hydroxy-Ci-Cγ-alkyl, phenyl-Ci-Cγ-alkyl and/or naphthyl-Ci-Cγ-alkyl)-amino, d-Cγ-alkanoyl, carboxy, Ci-Cγ-alkoxycarbonyl, phenyl-Ci-Cγ-alkoxycarbonyl, naphthyl-Ci-Cγ-alkoxycarbonyl, phenoxy carbonyl, naphthoxy carbonyl, Ci-C4-alkylenedioxy, cyano, carbamoyl, N-mono- or N,N-di-(Ci-Cγ-alkyl, N′,N′-di-(Ci-Cγ-alkyl)-amino-Ci-Cγ-alkyl, pyrrolidino-Ci-Cγ-alkyl and/or phenyl-Ci-Cγ-alkyl)-carbamoyl, piperidin-1-carbonyl, pipercarin-1-carbonyl, 4-d-Cγ-alkyl-pipercarin-1-carbonyl, morpholin-4-carbonyl, thiomorpholin-4-carbonyl, S-oxo-
thiomorpholin-4-carbonyl, S,S-dioxothiomorpholin-4-carbonyl, sulfamoyl, N-mono- or N,N-di-(C\(_i\)-C\(_7\)-alkyl), N'N'-di-(C\(_i\)-C\(_7\)-alkyl)amino, C\(_i\)-C\(_7\)-alkylamino, pyrrolidino-C\(_i\)-C\(_7\)-alkyl, pyrroldinyl, piperidinyl, piperazinyl, 4-C\(_7\)-alkyl-piperazinyl, 4-(phenyl-C\(_7\)-alkyl)-piperazinyl, 4-(naphthyl-C\(_7\)-alkyl)-piperazinyl, 4-(C\(_i\)-C\(_7\)-alkoxycarbonyl)-piperazinyl, 4-(phenyl-C\(_7\)-alkoxycarbonyl)-piperazinyl, 4-(naphthyl-C\(_7\)-alkoxycarbonyl)-piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl, and/or from 2-amino-pyrimidin-5-yl-d-C\(_7\)-alkyl, 4-C\(_7\)-alkyl-piperazin-1-carbonyl-C\(_7\)-alkoxy, 4-pyrrolidino-piperidin-1-carbonyl-C\(_7\)-alkoxy, 4-C\(_7\)-alkyl-piperazin-1-carbonyl-C\(_7\)-alkoxy, pyridin(e.g. -2)-yloxy-C\(_7\)-alkoxy, pyrimidin(e.g. -4)-yloxy-C\(_7\)-alkoxy, N,N-di(d-C\(_7\)-alkyl)amino-pyrrolidin-1-carbonyl and (unsubstituted or C\(_7\)-alkoxy- and/or halo-d-C\(_7\)-alkoxysubstituted) pyridin(e.g. -3))-yl; and R\(^5\) is hydroxyl; or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

4. A compound of the formula I according to claim 1 wherein

R\(^1\) is hydrogen, amino, N-OiOnO-C\(_i\)-C\(_10\) (preferably C\(_7\)-C\(_4\))-alkylamino or C\(_3\)-C\(_8\) (preferably C\(_3\)-C\(_5\))-cycloalkylamino,

R\(^2\) is phenyl, naphthyl, pyrrolyl, thiophenyl, pyrazolyl, triazolyl, pyridyl, quinolyl or quinoxalinyln, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halo, hydroxy, C\(_i\)-alkoxy, C\(_7\)-alkoxy-C\(_i\)-alkoxy, amino, N-mono- or N,N-di-(C\(_i\)-C\(_7\)-alkyl), phenyl-C\(_i\)-C\(_7\)-alkyl and/or naphthyl-C\(_i\)-alkyl)amino, carboxy, Cr\(_i\)-alkoxy-carbonyl, phenyl-d-C\(_7\)-alkoxycarboxy, naphthyl-d-C\(_7\)-alkoxycarboxy, phenoxy-carbonyl, naphthoxy-carbonyl, d-C\(_4\)-alkylendioxy, carbamoyl, N-mono- or N,N-di-(C\(_7\)-C\(_7\)-alkyl), N',N'-di-(C\(_7\)-C\(_7\)-alkyl)amino-C\(_7\)-alkyl, pyrrolidino-d-C\(_7\)-alkyl and/or phenyl-d-C\(_7\)-alkyl)-carbamoyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-d-C\(_7\)-alkyl-piperazin-1-carbonyl, morpholin-4-carbonyl, thiomorpholin-4-carbonyl, S-oxothiomorpholin-4-carbonyl, S,S-dioxothiomorpholin-4-carbonyl, sulfamoyl, N-mono- or N,N-di-(d-C\(_7\)-alkyl), N',N'-di-(d-C\(_7\)-alkyl)amino-d-C\(_7\)-alkyl, pyrrolidino-d-C\(_7\)-alkyl and/or phenyl-d-C\(_7\)-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-d-C\(_7\)-alkyl-piperazinyl, 4-(phenyl-d-C\(_7\)-alkyl)-piperazinyl, 4-(naphthyl-d-C\(_7\)-alkyl)-piperazinyl and/or phenyl-d-C\(_7\)-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-d-C\(_7\)-alkyl-piperazinyl, 4-(phenyl-d-C\(_7\)-alkyl)-piperazinyl, 4-(naphthyl-d-C\(_7\)-alkyl)-piperazinyl, 4-(naphthyl-d-C\(_7\)-alkyl)-piperazinyl.
alkyl)-piperazinyl, 4-(CrC 7-alkoxycarbonyl)-piperazinyl, 4-(phenyl-C 7-alkoxycarbonyl)-piperazinyl, 4-(naphthyl-C 7-alkoxycarbonyl)-piperazinyl, morpholiny1, thiomorpholinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl, and/or from 2-amino-pyrimidin-5-yl-C 7-alkyl, 4-C 7-alkyl-piperazin-1-carbonylC 7-alkoxy, 4-pyrrolidino-piperidin-1-yl-C 7-alkoxy, 4-C 7-alkyl-piperazino-C 7-alkoxy, pyridin (e.g.-2)-yloxy-C 7-alkoxy, pyrimidin(e,g. -4)-yloxy-C 7-alkoxy, N,N-di(d-d-alkyl)amino-pyrrolidin-1-carbonyl and (unsubstituted or C 7 -alkoxy- and/or halo-d-d-alkoxy-substituted) pyridin(e.g. -3))-yl; 
R 3 is hydrogen or halo, preferably hydrogen, 
R 4 is phenyl, naphthyl, pyrrolyl, thiophenyl, triazolyl, pyridyl, quinolinyl or quinoxalinyl each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halo, hydroxy, d-d-alkoxy, C 7-alkoxy-C 7-alkoxy, amino, N-mono- or N,N-di-(CrC 7-alkyl, phenyl-C 7-alkyl and/or naphthyl-C 7-alkyl)-amino, carboxy, Ci-C 7-alkoxycarbonyl, phenyl-d-d-alkoxycarbonyl, naphthyl-d-d-alkoxycarbonyl, phenoxy carbonyl, napthoxy carbonyl, Ci-C 4-alkylendioxy, carbamoyl, N-mono- or N,N-di-(Ci 7-alkyl, N,N-di-(Ci 7-alkyl)amino-C 1-C 7-alkyl, pyrrolidino-C 1-C 7-alkyl and/or phenyl-d-d-C 7-alkyl)-carbamoyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-Ci-C 7-alkyl-piperazin-1-carbonyl, morpholiny1-4-carbonyl, thiomorpholin4-carbonyl, S-oxo-thiomorpholin4-carbonyl, S,S-dioxothiomorpholin4-carbonyl, sulfamoyl, N-mono- or N,N-di-(Cl-C 7-alkyl, N,N-di-(d-C 7-alkyl)amino-C 1-C 7-alkyl, pyrrolidino-C 1-C 7-alkyl and/or phenyl-C 1-C 7-alkyl)-sulfamoyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-Ci-C 7-alkyl-piperazinyl, 4-(phenyl-Ci-C 7-alkyl)-piperazinyl, 4-(naphthyl-C 7-alkyl)-piperazinyl, 4-(Cl-C 7-alkoxycarbonyl)-piperazinyl, 4-(phenyl-Ci-C 7-alkoxycarbonyl)-piperazinyl, 4-(naphthyl-Ci-C 7-alkoxycarbonyl)-piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl and S,S-dioxothiomorpholinyl, and/or from 2-amino-pyrimidin-5-yl-C 7-alkyl, 4-Ci-C 7-alkyl-piperazin-1-carbonyl-C 7-alkoxy, 4-pyrrolidino-piperidin-1-carbonyl-C 7-alkoxy, 4-pyrrolidinopiperidin-1-yl-C 7-alkoxy, 4-Ci-C 7-alkyl-piperazino-C 7-alkoxy, pyridin (e.g.-2)-yloxy-C 7-alkoxy, pyrimidin(e.g. -4)-yloxy-C 7-alkoxy, N,N-di(Ci 7-alkyl)amino-pyrrolidin1-carbonyl and (unsubstituted or Ci-C 7-alkoxy- and/or halo-Ci-C 7-alkoxy-substituted) pyridin(e.g. -3))-yl; and 
R 5 is hydrogen; or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.
5. A compound of the formula I according to claim 1, wherein

$R^1$ is hydrogen, amino, methylamino, n-propylamino or cyclopropylamino;

$R^2$ is phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3-chloro-4-n-propoxy-phenyl, 4-carboxy-3-methoxyphenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-carbamoylphenyl, 4-N-methylcarbamoyl-3-methoxy-phenyl, 4-(N,N-dimethyl-carmamoyl)-3-methoxy-phenyl, 4-(4-methylpiperazin-1-carbonyl)-3-methoxyphenyl, 4-(4-morpholin-1-carbonyl)-3-methoxyphenyl, 4-(4-pyrazolyl-phenyl, 4-(piperazin-1-yl)-phenyl, 4-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoylphenyl, 4-pyrazolyl-phenyl, pyrrolyl, pyrazolyl, thiophenyl, 1,2,4-triazol-1-yl, 6-methoxy-pyridin-3-yl, or 6-piperazino-pyridin-3-yl;

$R^3$ is hydrogen,

$R^4$ is 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-hydroxy-4-n-propoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 4-ethoxy-3-methoxyphenyl, 3-(2-methoxy-ethoxy)-4-methoxyphenyl, 3-methoxy-4-(2-methoxy-ethoxy)-phenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-n-propoxyphenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-carbamoylphenyl, N,N-dimethyl-aminosulfonylphenyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 4-(piperazin-1-yl)-phenyl, 4-(pyrazolyl)-phenyl, pyrazolyl, thiophenyl, 1,2,4-triazol-1-yl, 6-methoxy-pyridin-3-yl, or 6-piperazino-pyridin-3-yl;

$R^5$ is hydrogen,

or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

6. A compound of the formula I according to claim 1, wherein

$R^1$ is hydrogen, amino, methylamino, n-propylamino or cyclopropylamino;
R² is phenyl, 4-trifluoromethylphenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-
bromophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-
ethoxy-3-methoxy-phenyl, 3,4-diethoxy-phenyl, 3-benzyl-4-methoxyphenyl, 4-(2-
methoxyethoxy)-3-methoxy-phenyl, 4-trifluormethoxyphenyl, 4-methoxy-3-trifluoromethoxy-
phenyl, 4-(3-tert-butoxycarbonylamino-propoxy)-3-methoxy-phenyl, 4-(2-tert-butoxycarbonyl-
aminoethoxy)-3-methoxy-phenyl, 3,4,5-trimethoxyphenyl, 3-chloro-4-n-propoxy-phenyl, 4-
acetylaminophenyl, 4-carboxy-3-methoxyphenyl, 4-methoxycarbonyl-phenyl, 4-methoxycar-
bonyl-3-methoxyphenyl, 4-cyanophenyl, 4-biphenyl, 4'-amino-biphenyl-4-y1, 4'-methoxy-
biphenyl-4-yi, 4'-hydroxymethyl-biphenyl-4-y1, 4'-methoxymethyl-biphenyl-4-y1, 3',4'-dimetho-
xy-biphenyl-4-y1, 4'-carbamoyl-biphenyl-4-y1, 4-carbamoyl-phenyl, 4-N-methylcarbamoyl-3-
methoxy-phenyl, 4-(N,N-dimethylcarbamoyl)-phenyl, 4-(N-methylcarbamoyl)-phenyl, 4-(N,N-
dimethyl-carbamoyl)-3-methoxy-phenyl, 4-(4-methylpiperazin-1-carbonyl)-3-methoxyphenyl, 4-
(morpholin-4-carbonyl)-phenyl, 4-(4-morpholin-1-carbonyl)-3-methoxyphenyl, benzo[1 ,3]di-
oxol-5-y1, 2,3-dihydro-benzo[1 ,4]dioxin-6-y1, 4-(piperazin-1-y1)-phenyl, 4-(2-oxo-pyrrolidin-
1-y1)-phenyl, 4-(2-oxo-azetidin-1-y1)-phenyl, 4-(2-oxo-piperidine-1-y1)-phenyl, 4-(3-methyl-2-
oxo-imidazolidin-1-y1)-phenyl, 4-methanesulfonyl-phenyl, 4-sulfamoyl-phenyl, 4-N,N-
dimethyl-sulfamoylphenyl, 4-pyrazolyl-phenyl, pyrrolyl, pyrazolyl, thiophenyl, especially 
thiophen-3-y1, 1,2,4-triazol-1-y1, 2-methoxy-pyridin-4-y1, 5-methoxy-pyridin-3-y1, 6-methoxy-
pyridin-3-y1, 6-piperazino-pyridin-3-y1, 6-morpholin-4-y1-pyridin-3-y1, 1H-pyrrolo[2,3-
b]pyridin-5-y1, 4-[6-(4-methanesulfonyl)-piperazin-1 -y1]-pyridin-3-y1, 5-(4-acetyl-piperazin-1-
y1)-pyridin-3-y1 or 2-[4-(tert-butoxycarbonyl)-piperazin-1 -y1]-pyridin-4-y1; 

R³ is hydrogen, 

R⁴ is 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-hydroxy-4-n-
propoxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl, 3,4,5-
trimethoxyphenyl, 3-ethoxy-4-methoxy-phenyl, 4-ethoxy-3-methoxy-phenyl, 3-(methoxy-
ethoxy)-4-methoxyphenyl, 3-methoxy-4-(2-methoxy-ethoxy)-phenyl, 3-benzyl-4-
methoxyphenyl, 4-(3-aminopropoxy)-3-methoxy-phenyl, 5-(3-aminopropoxy)-3-methoxy-
phenyl, 4-(2-aminoethoxy)-3-methoxy-phenyl, 5-(2-aminoethoxy)-3-methoxy-phenyl, 3-
fluoro-4-methoxyphenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-n-propoxyphenyl, 4-(3-
tert-butoxycarbonylaminopropoxy)-3-methoxy-phenyl, 4-(2-tert-butoxycarbonylamino-ethoxy)-3-
methoxy-phenyl, 4-formyl-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 3-carbamoyl-phenyl, 4-
carbamoylphenyl, 4-carbamoyl-3-methoxy-phenyl, 3-sulfamoyl-phenyl, N,N-dimethyl-
aminosulfonylphenyl, benzo[1 ,3]dioxol-5-y1, 2,3-dihydro-benzo[1 ,4]dioxin-6-y1, 6-
aminomethyl-pyridin-3-yl, pyridine-3-yl, 6-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3-yl, 2-methoxy-pyridin-4-yl, 2-amino-pyridin-4-yl, 6-amino-pyridin-3-yl, 6-amino-5-trifluoromethylpyridin-3-yl, 6-dimethylamino-pyridin-3-yl, 6-methylamino-pyridin-3-yl, 6-isobutylamino-pyridin-3-yl, 6-(2-methoxyethylamino)-pyridin-3-yl, 6-(piperazin-1-yl)-pyridin-3-yl, 6-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-3-yl, 2-(piperazin-1-yl)-pyridin-4-yl, 6-carbamoyl-pyridin-3-yl, 2-cyano-pyridin-5-yl, 5-cyano-pyridin-3-yl, 6-(2-hydroxyethyl-amino)-pyridin-3-yl, 2-(4-tert-butoxycarbonyl-piperazin-1-yl)-pyridin-4-yl, 6-morpholin-4-yl-pyridin-3-yl, furan-2-yl, furan-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, or quinolin-3-yl and

R^5 is hydrogen,
or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

7. A compound of the formula I according to claim 1, selected from the group consisting of the following compounds:
4-(3,4-dimethoxy-phenyl)-6-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline,
4-{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester,
[4,6-bis-(3,4-dimethoxy-phenyl)-quinazolin-2-yl]-n-propyl-amine,
6-(6-methoxy-pyridin-3-yl)-4-phenyl-quinazoline,
3-[2-amino-4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-phenol,
6-(3-chloro-4-n-propoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline,
4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenol,
6-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-(3,4-dimethoxy-phenyl)-quinazoline,
6-(benzo[1,3]dioxol-5-yl)-4-(3,4-dimethoxy-phenyl)-quinazoline,
4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester,
4-(3,4-dimethoxy-phenyl)-6-(3,4,5-trimethoxy-phenyl)-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-(3-fluoro-4-methoxy-phenyl)-quinazoline,
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid methyl ester,
4-(3-chloro-4-n-propoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-(3,4,5-trimethoxy-phenyl)-quinazoline,
4-(benzo[1,3]dioxol-5-yl)-6-(3,4-dimethoxy-phenyl)-quinazoline,
6-(6-piperazin-1-yl-pyridin-3-yl)-4-(4-pyrazol-1-yl-phenyl)-quinazoline,
3-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-phenol,
4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-phenol,
4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-benzamide,
4-(3,4-dimethoxy-phenyl)-6-(3-fluoro-4-methoxy-phenyl)-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-phenyl-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-thiophen-2-yl-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-(3-methoxy-phenyl)-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-(4-methoxy-phenyl)-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-(4-pyrazol-1-yl-phenyl)-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline,
4-[6-(6-piperazin-1-yl-pyridin-3-yl)-quinazolin-4-yl]-benzamide,
6-(6-methoxy-pyridin-3-yl)-4-(4-pyrazol-1-yl-phenyl)-quinazoline,
4-[6-(6-methoxy-pyridin-3-yl)-quinazolin-4-yl]-benzamide,
6-(6-methoxy-pyridin-3-yl)-4-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline,
4,6-bis(3,4-dimethoxy-phenyl)-quinazoline,
4-(6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl)-benzamide,
6-(3,4-dimethoxy-phenyl)-4-(6-methoxy-pyridin-3-yl)-quinazoline,
4-(3,4-dimethoxy-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazoline,
6-(6-methoxy-pyridin-3-yl)-6-(6-piperazin-1-yl-pyridin-3-yl)-quinazoline,
6-(6-methoxy-pyridin-3-yl)-4-thiophen-2-yl-quinazoline,
4-(2-chloro-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazoline,
4,6-bis(6-methoxy-pyridin-3-yl)-quinazoline,
4-(4-methoxy-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazoline,
4-(3,4-dimethoxy-phenyl)-6-(4-ethoxy-3-methoxy-phenyl)-quinazoline,
[4,6-bis-(3,4-dimethoxy-phenyl)-quinazolin-2-yl]-cyclopropyl-amine,
4-[2-amino-6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-benzamide,
4-(3,4-dimethoxy-phenyl)-6-(3-fluoro-4-methoxy-phenyl)-quinazolin-2-ylamine,
4-[2-amino-4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester,
4-(3,4-dimethoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-quinazolin-2-ylamine,
6-(3-chloro-4-n-propoxy-phenyl)-4-(3,4-dimethoxyphenyl)-quinazolin-2-ylamine,
4-[2-amino-4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-phenol,
6-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine,
4-(benzo[1,3]dioxol-5-yl)-6-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine,
6-(3,4-dimethoxy-phenyl)-4-(3,4,5-trimethoxy-phenyl)-quinazolin-2-ylamine,
6-(3,4-dimethoxy-phenyl)-4-(6-methoxy-pyridin-3-yl)-quinazolin-2-ylamine,
4,6-bis(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine,
4,6-bis(6-methoxy-pyridin-3-yl)-quinazolin-2-ylamine,
4-(3,4-dimethoxy-phenyl)-6-(6-methoxy-pyridin-3-yl)-quinazolin-2-ylamine,
N-[4,6-bis-(3,4-dimethoxy-phenyl)-quinazolin-2-yl]-N-methyl-amine,
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid,
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzoic acid-N-methylamide,
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-benzamide,
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-N,N-dimethyl-amide,
{4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenyl}-(4-methyl-piperazin-1-yl)-methanone,
{4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenyl}-morpholin-4-yl-methanone,
4-(1,2,4-Triazol-1-yl)-6-(3,4-dimethoxy-phenyl)-quinazoline,
4-(3,4-dimethoxy-phenyl)-6-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinazoline,
5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-ylamine,
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-N,N-dimethyl-benzenesulfonamide,
6-(3,4-dimethoxy-phenyl)-4-pyrazol-1-yl-quinazoline,
6-(3,4-dimethoxy-phenyl)-4-[1,2,4]triazol-1-yl-quinazoline, and
6-(3,4-dimethoxy-phenyl)-4-pyrrol-1-yl-quinazoline;

or in each case an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof.

8. A compound of the formula I according to claim 1, wherein

R¹ is hydrogen, amino, methylamino, n-propylamino or cyclopropylamino;

R² is phenyl, 4-(2-amino-pyrimidin-5-ylmethyl)-phenyl, 3-(2-methoxy-6-trifluoromethyl)pyridin-3-yl-phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3-chloro-4-n-propoxy-phenyl, 4-carboxy-3-methoxyphenyl, 4-(2-pyridin-2-yloxyethoxy)-phenyl, 4-(2-pyrimidin-4-yloxyethoxy)-phenyl, 4-methoxycarbonyl-3-methoxyphenyl, 4-carbamoylphenyl, 4-N-methylcarbamoyl-3-methoxy-phenyl, 4-(N,N-di-methyl-carbamoyl)-3-methoxy-phenyl, 4-(4-methylpiperazin-1-carbonyl)-3-methoxyphenyl, 4-(4-morpholin-1-carbonyl)-3-methoxyphenyl, benzol[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 4-[2-(4-pyrrolidino-piperidin-1-yl)-ethoxy]-phenyl, 4-(piperazin-1-yl)-phenyl, 4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl, 4-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-phenyl, 4-[2-(4-
methyl-piperazin-1-carbonylmethoxy)-phenyl, 4-(4-ethyl-piperazin-1-carbonylmethoxy)-phenyl, 4-(4-pyrrolidino-piperidin-1-carbonylmethoxy)-phenyl, 4-[(R, S or R,S)-3-diethylamino-pyrrolidin-1-carbonyl]-phenyl, 4-sulfamoyl-phenyl, 4-N,N-dimethyl-sulfamoylphenyl, 4-[N-methyl-N-2-(pyrrolidino-ethyl)-sulfamoyl]-phenyl, 4-pyrazolyl-phenyl, pyrrolyl, pyrazolyl, thiophenyl, 1,2,4-triazol-1-yl, 6-methoxy-pyridin-3-yl or 6-piperazino-pyridin-3-yl; 

R³ is hydrogen, 

R⁴ is 4-(2-amino-pyrimidin-5-ylmethyl)-phenyl, 3-(2-methoxy-6-trifluoromethyl)pyridin-3-yl-phenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-hydroxy-4-n-propoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 4-ethoxy-3-methoxyphenyl, 3-(2-methoxy-ethoxy)-4-methoxyphenyl, 3-methoxy-4-(2-methoxy-ethoxy)-phenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-n-propoxyphenyl, 4-(2-pyridin-2-yloxyethoxy)-phenyl, 4-(2-pyrimidin-4-yloxyethoxy)-phenyl, 4-[2-(4-pyrrolidino-piperidin-1-yl)-ethoxy]-phenyl, 4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl, 4-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-phenyl, 4-(4-methyl-piperazin-1-carbonylmethoxy)-phenyl, 4-(4-ethyl-piperazin-1-carbonylmethoxy)-phenyl, 4-(4-pyrrolidino-piperidin-1-carbonyl)-phenyl, 4-[N-(2-dimethylamino-ethyl)-N-methylcarbamoyl]-phenyl, 4-

or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

9. A compound of the formula I according to claim 1, selected from the group consisting of the following compounds:
6-(3,4-dimethoxy-phenyl)-4-(4-ethoxy-3-methoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinazoline;
4-(3,4-dimethoxy-phenyl)-6-(2-methoxy-pyridin-4-yl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(2-methoxy-pyridin-4-yl)-quinazoline;
(3-[4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy]-propyl)-carbamic acid tert-butyl ester;
(3-[4-6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenoxy)-propyl)-carbamic acid tert-butyl ester;
(2-[4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxy]-ethyl)-carbamic acid tert-butyl ester;
(2-[4-6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-2-methoxy-phenoxy)-ethyl)-carbamic acid tert-butyl ester;
6-(3,4-dimethoxy-phenyl)-4-(3-ethoxy-phenyl)-quinazoline;
4-(3-chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
4-(3-benzyloxy-4-methoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-benzoic acid methyl ester;
4-(3,4-dimethoxy-phenyl)-6-(5-methoxy-pyridin-3-yl)-quinazoline
4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid methyl ester;
4-(3,4-dimethoxy-phenyl)-6-quinolin-3-yl-quinazoline;
4-[6-(5-methoxy-pyridin-3-yl)-quinazolin-4-yl]-benzamide;
4-[6-(6-amino-5-trifluoromethyl-pyridin-3-yl)-quinazolin-4-yl]-benzamide;
5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-3-trifluoromethyl-pyridin-2-ylamine;
3-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-benzenesulfonamide;
4-benzo[1,3]dioxol-5-yl-6-(3-fluoro-4-methoxy-phenyl)-quinazoline;
4-(3-benzyloxy-4-methoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
3-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-benzamide;
4-(4-chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(4-trifluoromethyl-phenyl)-quinazoline;
6-(3-chloro-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-thiophen-3-yl-quinazoline;
4-(3,4-dimethoxy-phenyl)-6-(1 H-pyrrolo[2,3-b]pyridin-5-yl)-quinazoline;
4-[6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-quinazolin-4-yl]-benzamide;
4-[6-(6-amino-pyridin-3-yl)-quinazolin-4-yl]-benzamide;
6-(3-benzyloxy-4-methoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline;
4-(4-chloro-phenyl)-6-(3-fluoro-4-methoxy-phenyl)-quinazoline;
4-[6-(4-ethoxy-3-methoxy-phenyl)-quinazolin-4-yl]-benzamide;
4-[6-(3,4-diethoxy-phenyl)-quinazolin-4-yl]-benzamide;
4-(3,4-dimethoxy-phenyl)-6-furan-3-yl-quinazoline;
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-benzonitrile;
4-[6-(6-amino-pyridin-3-yl)-quinazolin-4-yl]-benzonitrile;
4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-benzaldehyde;
4-biphenyl-4-yl-6-(3,4-dimethoxy-phenyl)-quinazoline;
4-(3,4-diethoxy-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(4-methoxy-3-trifluoromethoxy-phenyl)-quinazoline;
4-(3,4-dimethoxy-phenyl)-6-(4-methoxy-3-trifluoromethoxy-phenyl)-quinazoline;
5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridine-2-carbonitrile;
4-(4-bromo-phenyl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-diethoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(3,4-diethoxy-phenyl)-quinazoline;
6-(3,4-diethoxy-phenyl)-4-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(3,4-diethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(3,4-diethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(3,4-diethoxy-phenyl)-quinazoline;
5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-nicotinonitrile;
{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-isobutyl-amine;
6-(3,4-dimethoxy-phenyl)-4-(6-morpholin-4-yl-pyridin-3-yl)-quinazoline;
{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-dimethyl-amine;
{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-methyl-amine;
2-{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-ylamino}-ethanol;
4-{5-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid tert-
butyl ester;
4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-6-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine;
6-(6-amino-pyridin-3-yl)-4-(3,4-dimethoxy-phenyl)-quinazolin-2-ylamine;
4-(3,4-dimethoxy-phenyl)-6-quinolin-3-yl-quinazolin-2-ylamine;
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-N,N-dimethyl-benzamide;
4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-N-methyl-benzamide;
\{4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-phenyl\}-(4-methyl-piperazin-1-yl)-methanone;
\{4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-phenyl\}-morpholin-4-yl-methanone;
C-{4'-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl}-methylamine;
6-(3,4-dimethoxy-phenyl)-4-(3',4',5'-trimethoxy-biphenyl-4-yl)-quinazoline;
\{4'-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl\}-methanol;
\{4'-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl\}-biphenyl-4-ol;
4-(3',4'-dimethoxy-biphenyl-4-yl)-6-(3,4-dimethoxy-phenyl)-quinazoline;
6-(3,4-dimethoxy-phenyl)-4-(3',4',5'-trimethoxy-biphenyl-4-yl)-quinazoline;
\{4'-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-biphenyl-4-yl\}-carboxylic acid amide;
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3-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxoxy-propylamine;
2-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxoxy-ethylamine;
3-[5-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxoxy-propylamine;
2-[5-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-phenoxoxy-ethylamine;
4-(3,4-dimethoxy-phenyl)-6-(3-ethoxy-4-methoxy-phenyl)-quinazoline;
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4-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-2-methoxy-benzoic acid;
5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridine-2-carboxylic acid amide;
C-[5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl]-methylamine;
6-(3,4-dimethoxy-phenyl)-4-[6-(4-methanesulfonyl-piperazin-1-yl)-pyridin-3-yl]-quinazoline;
1-(4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-pyridin-2-yl)-piperazin-1-yl)-ethanone;
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3-{4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-oxazolidin-2-one;
1-{4-[6-(3,4-dimethoxy-phenyl)-quinazolin-4-yl]-phenyl}-3-methyl-imidazolidin-2-one;
4,6-bis-(3,4-dimethoxy-phenyl)-5-fluoro-quinazoline;
4-[6-(3,4-dimethoxy-phenyl)-5-fluoro-quinazolin-4-yl]-benzamide;
{5-[4-(3,4-dimethoxy-phenyl)-quinazolin-6-yl]-pyridin-2-yl}-(2-methoxy-ethyl)-amine;
and
4-(3,4-dimethoxy-phenyl)-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinazoline;
or a tautomer thereof or a N-oxide thereof, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof.

10. A compound of the formula 1, an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 9 for use in the treatment, including prophylactic treatment, of a warm-blooded animal, especially a human.

11. A compound of the formula 1, an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof, according to claim 10 where the use is against one or more diseases selected from the group consisting of proliferative, inflammatory diseases, allergic diseases, obstructive airways diseases, and disorders commonly occurring in connection with transplantation, especially one or more diseases which respond to an inhibition of kinases of the PI3-kinase-related protein kinase family, especially lipid kinases and/or PI3 kinase (PI3K) and/or mTOR and/or DNA protein kinase and/or ATM and/or ATR and/or hSMG-1 activity.

12. A pharmaceutical preparation, comprising a compound of the formula 1, an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 10 with at least

13. A method or process for the manufacture of a pharmaceutical preparation, comprising mixing a compound of the formula 1, an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 10 with at least
one pharmaceutically acceptable carrier material.

14. A process for the manufacture of a compound of the formula I according to any one of claims 1 to 8, comprising

a) or the manufacture of a compound of the formula I wherein \( R^4 \) is bound to the central quinazoline moiety in formula I via a carbon atom, reacting a compound of the formula NA,

\[
\text{halogen}^1 \quad \begin{array}{c} \text{N} \\ \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^5 \end{array}
\]

(wherein \( R^1, R^2, R^3 \) and \( R^5 \) are as defined for a compound of the formula I and wherein halogen \( ^1 \) is halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, under cross-coupling conditions with a boronic acid or boronic acid ester of the formula III,

\[
\text{R}^4\text{-D} \quad \text{(III)}
\]

(wherein \( R^4 \) is as defined for a compound of the formula I and is bound via a carbon atom to D and D is \(-\text{B(OH}_2\text{)}\) or a group of the formula A,

\[
\begin{array}{c} \text{B} \\ \text{O} \\ \text{O} \end{array}
\]

(A)

or

b) for the manufacture of a compound of the formula I wherein \( R^2 \) is bound to the central quinazoline moiety in formula I via a carbon atom, reacting a compound of the formula NB,
wherein $R_1$, $R_3$, $R_4$ and $R_5$ are as defined for a compound of the formula I and halogen$^2$ is halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, under cross-coupling conditions with a boronic acid or boronic acid ester of the formula IV,

$$R^2 \cdot D$$  \hspace{1cm} (IV)

wherein $R^2$ is as defined for a compound of the formula I and is bound via a carbon atom to $D$ and $D$ is -B(OH$_2$) or a group of the formula A given above; or

c) for the manufacture of a compound of the formula I wherein $R^2$ and $R^4$ are identical and are bound to the central quinazoline moiety in formula I via a carbon atom, reacting a compound of the formula NC,

$$R^{2,4} \cdot D$$  \hspace{1cm} (V)

wherein $R^{2,4}$ is a moiety $R^2$ or $R^4$ bound via a carbon atom to $D$ and is otherwise as defined for a compound of the formula I and $D$ is -B(OH$_2$) or a group of the formula A
given above;
or

d) for the manufacture of a compound of the formula I wherein \( R^1 \) is amino, N-mono-C\(_{1-6}\)-alkyl-amino or N-mono-C\(_{3-6}\)-cycloalkylamino, reacting a compound of the formula ND,

\[
\text{(IID)}
\]

wherein \( R^2, R^3, R^4 \) and \( R^5 \) are as defined for a compound of the formula I and wherein halogen is halato, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy, with an amine of the formula VI

\[
\text{R}^1'-\text{H} \quad \text{(VI)}
\]

wherein \( R^1' \) is amino, N-mono-C\(_{1-6}\)-alkyl-amino or N-mono-C\(_{3-6}\)-cycloalkylamino; or

e) for the manufacture of a compound of the formula I wherein \( R^4 \) is heteroaryl with at least one ring nitrogen and is bound to the central quinazoline moiety in formula I via a nitrogen atom, reacting a compound of the formula NA given above under a) with a compound of the formula VII,

\[
\text{R}^4'\text{-H} \quad \text{(VII)}
\]

wherein \( R^4' \) is a nitrogen containing heteroaryl with at least one ring nitrogen and is bound to the hydrogen in formula VII via a nitrogen atom, under substitution conditions; or

f) for the manufacture of a compound of the formula I wherein \( R^2 \) is heteroaryl with at least one ring nitrogen and is bound to the central quinazoline moiety in formula I via a nitrogen
atom, reacting a compound of the formula \( \text{NB} \) given above under b) with a compound of the formula \( \text{VIII} \),

\[
\text{R}^{2*}\cdot \text{H} \quad \text{(VIII)}
\]

wherein \( R^{6*} \) is a nitrogen containing heteroaryl with at least one ring nitrogen and is bound to the hydrogen in formula VIII via a nitrogen atom, under substitution conditions; or

g) for the manufacture of a compound of the formula I wherein \( R^2 \) and \( R^4 \) are identical and are heteroaryl with at least one ring nitrogen and each of them is bound to the central quinazoline moiety in formula I via a nitrogen atom, reacting a compound of the formula IX,

\[
\text{R}^{24*}\cdot \text{H} \quad \text{(IX)}
\]

wherein \( R^{24*} \) is heteroaryl with at least one nitrogen atom and wherein \( R^{24*} \) is a moiety \( R^2 \) or \( R^4 \) bound via a nitrogen atom to the hydrogen shown in formula IX and is otherwise as defined for a compound of the formula I, under substitution conditions with a compound of the formula \( \text{NC} \) mentioned above; or

h) for the manufacture of a compound of the formula I wherein \( R^4 \) is bound to the central quinazoline moiety in formula I via a carbon atom, reacting a boronic acid or boronic acid ester compound of the formula \( \text{NA}^* \),

\[
(\text{IIA}^*)
\]

wherein \( R^1, R^2, R^3 \) and \( R^5 \) are as defined for a compound of the formula I and wherein \( D \) is -B(OH\(_2\)) or a group of the formula A.
under cross coupling conditions with compound of the formula \( \text{III}^+ \),

\[
R^4\text{-Hal} \quad (\text{III}^+) 
\]

wherein \( R^4 \) is as defined for a compound of the formula \( \text{I} \) and is bound via a carbon atom to Hal and Hal is halo, preferably chloro, bromo or iodo, or is trifluoromethansulfonyloxy,

where in any of the reactions represented under a) to h) functional groups in the starting materials can be present in protected form and in the obtainable compounds of the formula \( \text{I} \) carrying one or more protecting groups such protecting groups are removed;

and, if desired, a compound of the formula \( \text{I} \) obtainable according to a process variant selected from a) to g) is converted into a different compound of the formula \( \text{I} \), an obtainable salt of a compound of the formula \( \text{I} \) is converted into a different salt thereof, an obtainable free compound of the formula \( \text{I} \) is converted into a salt thereof, and/or an obtainable isomer of a compound of the formula \( \text{I} \) is separated from one or more different obtainable isomers of the formula \( \text{I} \).

15. The use of a compound of the formula \( \text{I} \), an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 10 for the preparation of a pharmaceutical preparation for the treatment of a disease selected from the group consisting of proliferative, inflammatory diseases, allergic diseases, obstructive airways diseases, and disorders commonly occurring in connection with transplantation, especially one or more diseases which respond to an inhibition of kinases of the PI3-kinase-related protein kinase family, especially lipid kinases and/or PI3 kinase (PI3K) and/or mTOR and/or DNA protein kinase and/or ATM and/or ATR and/or hSMG-1 activity.

16. A method of treatment of a disease selected from the group consisting of proliferative, inflammatory diseases, allergic diseases, obstructive airways diseases, and disorders commonly occurring in connection with transplantation, especially one or more diseases which
respond to an inhibition of kinases of the PI3-kinase-related protein kinase family, especially lipid kinases and/or PI3 kinase (PI3K) and/or mTOR and/or DNA protein kinase and/or ATM and/or ATR and/or hSMG-1 activity, comprising administering a compound of the formula I, an N-oxide thereof, a tautomer thereof and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 10 in an amount that is effective against said disease to a patient in need of such treatment.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/74 C07D239/84 C07D401/04 C07D405/04 C07D401/14
C07D409/04 C07D403/04 A61K31/517 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. RELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2005/012241 A (TRIAD THERAPEUTICS INC.) 10 February 2005 (2005-02-10)</td>
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<td>WO 2004/099159 A (THE INSTITUTE FOR PHARMACEUTICAL DISCOVERY) 18 November 2004</td>
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Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on propriety claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
'S' document member of the same patent family

Date of the actual completion of the international search 12 November 2007

Date of mailing of the international search report 23/11/2007

Name and mailing address of the ISA/
European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer Helps, Ian
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<td>US 2004/014774 A1 (MYERS ET. AL.) 22 January 2004 (2004-01-22) page 1, paragraph 3 - paragraph 9; claims; examples</td>
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Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos: 16(part )
   because they relate to subject matter not required to be searched by this Authority, namely.
   see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos,
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos,
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos..

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

Remark on Protest  

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation

[ ] No protest accompanied the payment of additional search fees

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
Continuation of Box II.1

Although claim 16 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.I

Claims Nos.: 16(part)

Although claim 16 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
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