example, uncontrolled cell growth and reduced cell death. Stimulation of tumour-induced growth factors may also be the cause of overstimulation of kinases. Development of kinase modulators is therefore of particular interest for all pathogenic processes influenced by kinases.

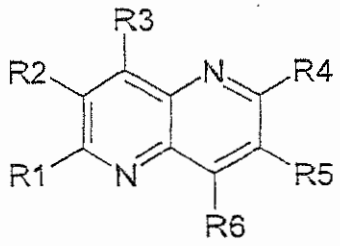
The disclosure~~invention~~ is therefore directed at generating novel compounds which are suitable as modulators of receptor tyrosine kinases and cytoplasmic tyrosine and serine/threonine kinases. Since not all kinases connected one behind the other in misdirected signal transduction cascades - such as, for example, in the case of Raf/Mek/Erk - have to be present as oncogenic kinases or as constitutively active enzymes, in this disclosure~~invention~~ the non-active kinases will also be considered to be therapeutic target proteins, i.e. the new compounds can bind both to active and also to non-active kinases and therefore influence the signal transduction.

Naphthyridine derivatives are finding many applications in pharmaceutical industry as pharmacodynamically active compounds and as building blocks for syntheses.

Naphthyridine derivatives are described in the document BMCL 2009, 19, 3568 as MCH1R inhibitors, in the patent WO2008/153752 as modulators of fatty acid amide hydrolase and in the patents DE 2650826, WO 00/21952, WO 00/43383, WO 01/07432, WO 02/056882, WO 02/08224 and WO2006/021448 as antibacterial agents. In the patents WO 99/58533, US 2007/0160538 and in the literature reference BMCL 2001, 11, 1907 naphthyridines are described as orexin-1 receptor antagonists. Substituted naphthyridines are described in the patent WO2000066583 as tyrosine kinase inhibitors and in the patent application WO2008150827 as PI3 kinase inhibitors.

Summary

In a first aspect, there is provided naphthyridine derivatives of the general formula I



Formula I

in which the substituents R1-R6 have the following meaning:

R1 can, be

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,
(iii) unsubstituted or substituted heterocyclyl,
(iv) unsubstituted or substituted aryl,
(v) unsubstituted or substituted heteroaryl,
(vi) halogen,
(vii) cyano,
(viii) alkoxy,
(ix) amino,
(x) carboxyl, alkoxycarbonyl, carboxyalkyl or alkoxycarbonylalkyl,
(xi) alkoxycarbonylamino, alkoxycarbonylaminoalkyl, and
(xii) NR7R8;

R2 can independently be

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,
(iii) unsubstituted or substituted heterocyclyl,

(iv) unsubstituted or substituted aryl,
(v) unsubstituted or substituted heteroaryl,
(vi) halogen,
(vii) cyano,
(viii) hydroxyl,
(ix) alkoxy,
(x) amino,
(xi) carboxyl, alkoxycarbonyl, carboxyalkyl or alkoxycarbonylalkyl,
(xii) alkoxycarbonylamino, alkoxycarbonylaminoalkyl, and
(xiii) NR7R8;

R3 can be independently be
(i) hydrogen,
(ii) unsubstituted or substituted, C_{1-12}-alkanyl or C_{2-12}-alkenyl,
(iii) unsubstituted or substituted saturated heterocyclyl,
(iv) unsubstituted or substituted aryl,
(v) halogen,
(vi) cyano,
(vii) hydroxyl,
(viii) alkoxy,
(ix) amino,
(x) carboxyl, alkoxycarbonyl, carboxyalkyl or alkoxycarbonylalkyl,
(xi) alkoxycarbonylamino, alkoxycarbonylaminoalkyl, and
(xii) NR7R8;

where at least one of the substituents R1-R3 has to be an NR7R8 and
where R7 can be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

and R8 may be:

-C(Y)NR9R10, where Y is O, S and R9 and R10 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iv) unsubstituted or substituted heterocyclyl,

(v) unsubstituted or substituted aryl,

(vi) or R9 and R10 together may be heterocyclyl,

-C(Y)NR11R12, where Y is NH and R11 and R12 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iv) unsubstituted or substituted heterocyclyl,

(v) unsubstituted or substituted aryl,

(vi) unsubstituted or substituted heteroaryl,

(vii) or R11 and R12 together may be heterocyclyl,

-C(NR13)R14 where R13 is H and R14 may be

(i) unsubstituted or substituted, saturated or unsaturated alkyl,

(ii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iii) unsubstituted or substituted heterocyclyl,

(iv) unsubstituted or substituted aryl,

(v) unsubstituted or substituted heteroaryl,

R4 may be:

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,
(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,
(iv) unsubstituted or substituted heterocyclyl,
(v) unsubstituted or substituted aryl,
(vi) unsubstituted or substituted heteroaryl,
(vii) halogen,
(viii) cyano,
(ix) alkoxy,
(x) NR15R16, where R15 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,
R16 can be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,
or R15 and R16 are together heterocyclyl, where heterocyclyl can, for their part, in turn be substituted,
and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;
(xi) OR17, where R17 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl,

cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalyl substituent can be saturated or unsaturated;

(xii) SR18, where R18 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl subtituent can be saturated or unsaturated;

and R5 may independently be

(i) hydrogen,

(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iv) unsubstituted or substituted heterocyclyl,

(v) unsubstituted or substituted aryl,

(vi) unsubstituted or substituted heteroaryl,

(vii) halogen,

(viii) cyano,

(ix) hydroxyl,

(x) alkoxy,

(xi) NR15R16, where R15 and R16 can, independently of each other, be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,
or R15 and R16 are together heterocyclyl, where heterocyclyl can, for their part, in turn be substituted,
and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

(xii) OR17, where R17 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

(xiii) SR18, where R18 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl,

cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

and R6 may independently be

(i) hydrogen,

(ii) unsubstituted or substituted, C_{1-12}-alkanyl or C_{2-12}-alkenyl,

(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iv) unsubstituted or substituted saturated heterocyclyl,

(v) unsubstituted or substituted aryl,

(vi) halogen,

(vii) cyano,

(viii) hydroxyl,

(ix) alkoxy,

(x) NR15R16, where R15 and R16 can, independently of each other, be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

or R15 and R16 are together heterocyclyl, where heterocyclyl can, for their part, in turn be substituted,

and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

(xi) OR17, where R17 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

(xii) SR18, where R18 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

where at least one of the substituents R4-R6 has to be an unsubstituted or substituted (hetero)aryl or NR15R16,

their physiologically acceptable salts, hydrates, solvates, where the compounds of the general formula (I) and their salts, hydrates or solvates may be present in the form of their racemates, enantiomers and/or diastereomers, or in the form of mixtures of the enantiomers and/or diastereomers, in the form of the tautomers and their polymorphic forms.

In a second aspect, there is provided a pharmaceutical composition comprising a pharmacologically active amount of at least one compound as defined herein.

In a third aspect, there is provided a compound as defined herein for use as medicament.

In a fourth aspect, there is provided the use of the naphthyridine derivatives of the general Formula I as defined herein as therapeutic active ingredients for producing medicaments for the treatment of disorders which result from misdirected cellular signal transduction processes.

In a fifth aspect, there is provided a medicament for treating disorders which result from misdirected cellular signal transduction processes, comprising at least one naphthyridine derivative as defined herein.

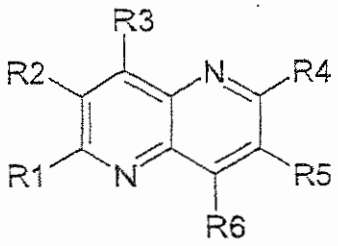
In a sixth aspect, there is provided a process for preparing a medicament as defined herein, characterized in that one or more naphthyridine derivatives as defined herein are processed to pharmaceutical preparations or converted into a therapeutically usable form with acceptable carriers and/or auxiliaries.

Description of the invention

The present invention relates to kinase modulators of the naphthyridine type and to the preparation and use thereof as medicaments for the modulation of misdirected cellular signal transduction processes, in particular for influencing the function of tyrosine and serine/threonine kinases and for the treatment of malignant or benign tumours and

Claims

1. Naphthyridine derivatives of the general formula I



Formula I

in which the substituents R1-R6 have the following meaning:

R1 can, ~~independently of each other,~~ be

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,
(iii) unsubstituted or substituted heterocyclyl,
(iv) unsubstituted or substituted aryl,
(v) unsubstituted or substituted heteroaryl,
(vi) halogen,
(vii) cyano,
(viii) alkoxy,
(ix) amino,
(x) carboxyl, alkoxycarbonyl, carboxyalkyl or alkoxycarbonylalkyl,
(xi) alkoxycarbonylamino, alkoxycarbonylaminoalkyl, and
(xii) NR7R8;

R2 can independently be

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,
(iii) unsubstituted or substituted heterocyclyl,

(x) carboxyl, alkoxycarbonyl, carboxyalkyl or alkoxycarbonylalkyl,

(xi) alkoxycarbonylamino, alkoxycarbonylaminoalkyl, and

(xii) NR7R8

where at least one of the substituents R1 or R3 has to be an NR7R8 and where R7 can be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted, and where the alkyl or cycloalkyl substituent can be saturated or unsaturated;

and R8 may be:

-C(Y)NR9R10, where Y is O, S and R9 and R10 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iv) unsubstituted or substituted heterocyclyl,

(v) unsubstituted or substituted aryl,

(vi) or R9 and R10 together may be heterocyclyl,

-C(Y)NR11R12, where Y is NH and R11 and R12 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

(iii) unsubstituted or substituted, saturated or unsaturated cycloalkyl,

(iv) unsubstituted or substituted heterocyclyl,

(v) unsubstituted or substituted aryl,

(vi) or R9 and R10 together may be heterocyclyl,

R2 can be

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

R4 may be

(i) hydrogen,
(ii) unsubstituted or substituted, saturated or unsaturated alkyl,

R6 may independently be

(i) hydrogen,
(ii) unsubstituted or substituted, C_{1-12}-alkanyl or C_{2-12}-alkenyl,

R5 may be:

(i) unsubstituted or substituted aryl,
(ii) unsubstituted or substituted heteroaryl,
(iii) NR15R16, where R15 and R16 can, independently of each other, be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and