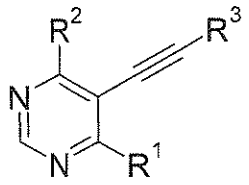
discovering mTOR inhibitors that bind to the ATP site and therefore target both mTORC2 and mTORC1. As a consequence, inhibition of the PI3K pathway, particularly mediated via Pi3Kα and mTOR, has emerged as an attractive target for cancer therapeutics.

5-Alkynyl-pyrimidines are described for example as protein kinases inhibiting compounds in WO2006044823.

Summary

In a first aspect, there is provided compounds of general formula (1),



(1),

wherein

wherein

$\mathbf{R}^3$ denotes pyridyl, optionally substituted by one or more identical or different $\mathbf{R}^4$; and

$\mathbf{R}^1$ denotes a group selected from among phenyl and pyridyl, optionally substituted by one or more identical or different $\mathbf{R}^5$ and

$\mathbf{R}^2$ denotes C_{1-4}alkyl, and

each $\mathbf{R}^4$ denotes a group selected from among methyl, ethyl, amino, methylamino, ethylamino; and

each $\mathbf{R}^5$ denotes a group selected from among $\mathbf{R}^m$ and $\mathbf{R}^n$; and

each $\mathbf{R}^m$ independently of one another denotes hydrogen or a group selected from among C_{1-4}alkyl, C_{4-6}cycloalkyl, methoxyethyl, cyclopropylmethyl, phenyl, naphthyl, benzyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, wherein $\mathbf{R}^m$ is optionally independently substituted by one or more identical or different $\mathbf{R}^n$ and/or $\mathbf{R}^{o4}$, and

each $\mathbf{R}^n$ denotes a suitable group and is selected independently of one another from among =O, -OH, -OCH_3, -OC_2H_5, –OCF_3, -$OCHF_2$, –SCH_3, =NOH, =$NOCH_3$, -NR^oR^{o1}, -F, -Cl, -Br, -CF_3, -CN, –NO_2, –N_3, –$S(O)R^o$, -$S(O)_2R^o$, –$C(O)R^o$, –$C(O)OR^o$, -$C(O)NR^oR^{o1}$, -$OC(O)R^o$, –$OC(O)OR^o$, –$OC(O)NR^oR^{o1}$, -$N(R^s)C(O)R^o$, –$N(R^s)S(O)R^o$, –$N(R^s)S(O)_2R^o$, -$N(R^s)S(O)_2NR^oR^{o1}$, –$N(R^s)C(O)OR^o$, -$N(R^s)C(O)NR^oR^{o1}$, and

each $\mathbf{R}^o$, $\mathbf{R}^{o1}$ and $\mathbf{R}^{o4}$ independently of one another denotes hydrogen or a group selected from among C_{1-4}alkyl, 2-6 membered heteroalkyl, C_{3-6}cycloalkyl, C_{4-10}cycloalkylalkyl, phenyl, benzyl, 5-6 membered

heteroaryl, C_{4-6}heterocycloalkyl, where R^o together with R^{o1} and/or R^s may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom, wherein $\mathbf{R^o}$, $\mathbf{R^{o1}}$ and $\mathbf{R^{o4}}$ is optionally independently substituted by one or more identical or different $\mathbf{R^p}$ and/or $\mathbf{R^{q4}}$, and

each $\mathbf{R^p}$ denotes a suitable group and is selected independently of one another from among =O, -OH, methoxy, ethoxy, isopropoxy, $-OCF_3$, - $OCHF_2$, $-SCH_3$, amino, methylamino, dimethylamino, ethylamino, isopropylamino, morpholine, piperidine, pyrrolidine, piperazine, N-methylpiperazine, acetyl, methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, methoxycarbonyl, ethoxycarbonyl, -F, -Cl, -Br, $-CF_3$, $-CN$,

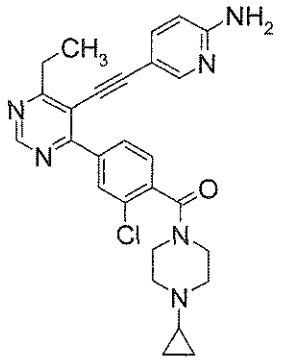
$-S(O)_2C_2H_5$, $-S(O)_2CH_3$, and

each $\mathbf{R^{q4}}$ denotes a suitable group and is independently of one another selected from among C_{1-4}alkyl, 4-6 membered heteroalkyl, C_{4-6}cycloalkyl, C_{4-7}cycloalkylalkyl, phenyl, benzyl, 5-6 membered heteroaryl, 6-8 membered heteroarylalkyl, 4-6 membered heterocycloalkyl and 4-7 membered heterocycloalkylalkyl, and

each $\mathbf{R^s}$ independently of one another denotes hydrogen or a group selected from among C_{1-4}alkyl, 2-6 membered heteroalkyl, C_{3-8}cycloalkyl, C_{4-10}cycloalkylalkyl, phenyl, benzyl, 5-6 membered heteroaryl, 6-12 membered heteroarylalkyl, 3-8 membered heterocycloalkyl and 4-10 membered heterocycloalkylalkyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

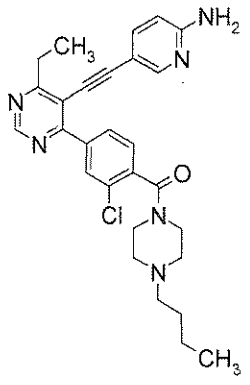
In a second aspect, there is provided a compound selected from:



D-28

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

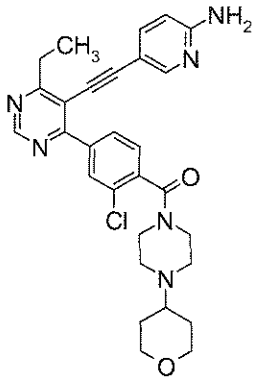
In a third aspect, there is provided a compound selected from:



D-29

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

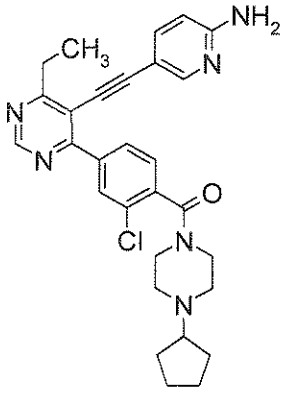
In a fourth aspect, there is provided a compound selected from:



D-31

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

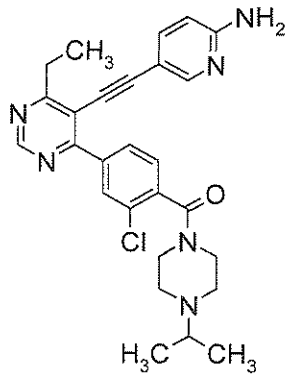
In a fifth aspect, there is provided a compound selected from:



D-38

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

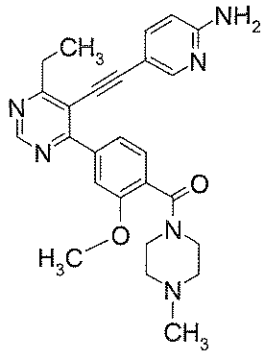
In a sixth aspect, there is provided a compound selected from:



D-42

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

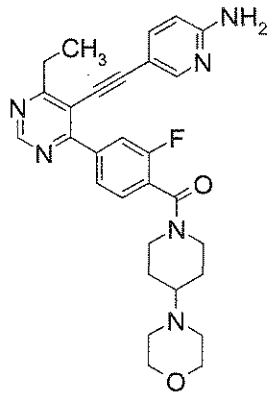
In a seventh aspect, there is provided a compound selected from:



D-58

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

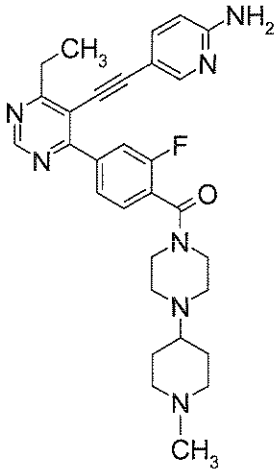
In an eighth aspect, there is provided a compound selected from:



D-63

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

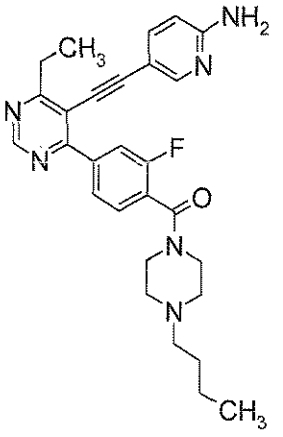
In a ninth aspect, there is provided a compound selected from:



D-64

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

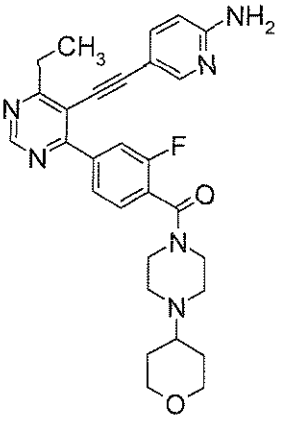
In a tenth aspect, there is provided a compound selected from:



D-83

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

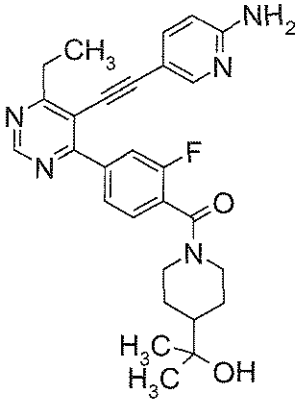
In an eleventh aspect, there is provided a compound selected from:



D-84

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

In a twelfth aspect, there is provided a compound selected from:

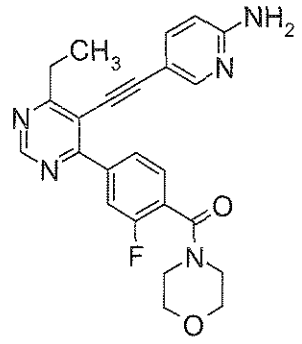


D-79

D-79

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

In a thirteenth aspect, there is provided a compound selected from:



D-239

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

In a fourteenth aspect, there is provided compounds, or the pharmacologically effective salts thereof, as defined above, as medicaments.

In a fifteenth aspect, there is provided compounds, or the pharmacologically effective salts thereof, as defined above, for preparing a medicament with an antiproliferative activity.

In a sixteenth aspect, there is provided pharmaceutical preparations, containing as active substance one or more compounds of general formula (1) as defined above or the pharmacologically effective salts thereof, optionally in combination with conventional excipients and/or carriers.

In a seventeenth aspect, there is provided compounds of general formula (1) as defined above for use in the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases

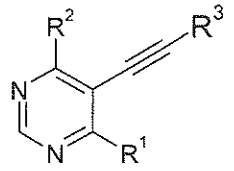
In an eighteenth aspect, there is provided the use of compounds of general formula (1) as defined above for preparing a medicament for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

In a nineteenth aspect, there is provided pharmaceutical preparation comprising a compound of general formula (1) as defined above and at least one other cytostatic or cytotoxic active substance, different from formula (1), optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, as well as optionally the pharmacologically acceptable salts thereof.

Detailed description of the invention

It has now surprisingly been found that compounds of general formula (1), wherein the groups R^1 to R^4 have the meanings given below, act as inhibitors of kinases. In particular, the compounds of the invention inhibit PI3Kα and mTOR kinases. Thus, the compounds according to the invention may be used for example for the treatment of diseases connected with the activity of kinases and characterised by excessive or abnormal cell proliferation, like for example cancer.

The present invention relates to compounds of general formula (1)



(1),

wherein

$\mathbf{R^3}$ denotes a group selected from among 3-8 membered heterocycloalkyl, $C_{6\text{-}10}$aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different $\mathbf{R^4}$; and

$\mathbf{R^1}$ denotes a group selected from among $C_{6\text{-}10}$aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different $\mathbf{R^5}$ and

$\mathbf{R^2}$ denotes a group selected from among hydrogen, $C_{1\text{-}4}$alkyl, $C_{3\text{-}8}$cycloalkyl, 3-8 membered heteroalkyl, 3-8 membered heterocycloalkyl, $-OR^v$, $-NR^vR^{vl}$, $-SR^v$, $-CF_3$, –CN, -NC and $-NO_2$, and

each $\mathbf{R^4}$ denotes a group selected from among $\mathbf{R^a}$ and $\mathbf{R^b}$; and

each $\mathbf{R^a}$ independently of one another denotes hydrogen or a group selected from among $C_{1\text{-}6}$alkyl, 2-6 membered heteroalkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}16}$cycloalkylalkyl,

~~, and~~

each $\mathbf{R^5}$ denotes a group selected from among $\mathbf{R^m}$ and $\mathbf{R^n}$; and

each $\mathbf{R^m}$ independently of one another denotes hydrogen or a group selected from among C_{1-4}alkyl, C_{4-6}cycloalkyl, methoxyethyl, cyclopropylmethyl, phenyl, naphthyl, benzyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, wherein $\mathbf{R^m}$ is optionally independently substituted by one or more identical or different $\mathbf{R^n}$ and/or $\mathbf{R^{o4}}$, and

each $\mathbf{R^n}$ denotes a suitable group and is selected independently of one another from among =O, -OH, -OCH_3, -OC_2H_5, –OCF_3, -$OCHF_2$, –SCH_3, =NOH, =$NOCH_3$, -NR^oR^{o1}, -F, -Cl, -Br, -CF_3, -CN,–NO_2, –N_3, –$S(O)R^o$, -$S(O)_2R^o$, –$C(O)R^o$, –$C(O)OR^o$, -$C(O)NR^oR^{o1}$, -$OC(O)R^o$, –$OC(O)OR^o$, –$OC(O)NR^oR^{o1}$, -$N(R^s)C(O)R^o$, –$N(R^s)S(O)R^o$,–$N(R^s)S(O)_2R^o$, -$N(R^s)S(O)_2NR^oR^{o1}$, –$N(R^s)C(O)OR^o$, -$N(R^s)C(O)NR^oR^{o1}$, and

each $\mathbf{R^o}$, $\mathbf{R^{o1}}$ and $\mathbf{R^{o4}}$ independently of one another denotes hydrogen or a group selected from among C_{1-4}alkyl, 2-6 membered heteroalkyl, C_{3-6}cycloalkyl, C_{4-10}cycloalkylalkyl, phenyl, benzyl, 5-6 membered heteroaryl, C_{4-6}heterocycloalkyl, where R^o together with R^{o1} and/or R^s may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom, wherein $\mathbf{R^o}$, $\mathbf{R^{o1}}$ and $\mathbf{R^{o4}}$ is optionally independently substituted by one or more identical or different $\mathbf{R^p}$ and/or $\mathbf{R^{q4}}$, and

each $\mathbf{R^p}$ denotes a suitable group and is selected independently of one another from among =O, -OH, methoxy, ethoxy, isopropoxy, –OCF_3, - $OCHF_2$, –SCH_3, amino, methylamino, dimethylamino, ethylamino, isopropylamino, morpholine, piperidine, pyrrolidine, piperazine, N-methylpiperazine, acetyl, methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, methoxycarbonyl, ethoxycarbonyl, -F, -Cl, -Br, –CF_3, –CN,

–$S(O)_2C_2H_5$, –$S(O)_2CH_3$, and

each $\mathbf{R^{q4}}$ denotes a suitable group and is independently of one another selected from among C_{1-4}alkyl, 4-6 membered heteroalkyl, C_{4-6}cycloalkyl, C_{4-7}cycloalkylalkyl, phenyl, benzyl, 5-6 membered heteroaryl, 6-8 membered heteroarylalkyl, 4-6 membered heterocycloalkyl and 4-7 membered heterocycloalkylalkyl, and

each $\mathbf{R^s}$ independently of one another denotes hydrogen or a group selected from among C_{1-4}alkyl, 2-6 membered heteroalkyl, C_{3-8}cycloalkyl, C_{4-10}cycloalkylalkyl, phenyl, benzyl, 5-6 membered heteroaryl, 6-12 membered heteroarylalkyl, 3-8 membered heterocycloalkyl and 4-10 membered heterocycloalkylalkyl,